University of California, Berkeley
U.C. Berkeley Division of Biostatistics Working Paper Series

Year 2008 *Paper* 232

The Construction and Analysis of Adaptive Group Sequential Designs

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http://biostats.bepress.com/ucbbiostat/paper232

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Abstract

In order to answer scientific questions of interest one often carries out an ordered sequence of experiments generating the appropriate data over time. The design of each experiment involves making various decisions such as 1) What variables to measure on the randomly sampled experimental unit?, 2) How regularly to monitor the unit, and for how long?, 3) How to randomly assign a treatment or drug-dose to the unit?, among others. That is, the design of each experiment involves selecting a so called treatment mechanism/monitoring mechanism/ missingness/censoring mechanism, where these mechanisms represent a formally defined conditional distribution of one of these actions (i.e., assignment of treatment/monitoring indicator/missingness indicators/ right censoring indicators), given observed data characteristics on the unit. The choice of these design mechanisms are typically made a priori, and, it is common that during the course of the ordered sequence of experiments the observed data suggests that the chosen design is ineffective in answering the scientific question of interest, or is dissatisfying from other perspectives, and that a much better design (i.e., choice of mechanisms) should have been selected. This naturally raises the question: Why not learn a user supplied optimal unknown choice of the controlled components of the design based on the data collected in the previously initiated experiments, and thereby adjust/adapt these controlled components of the design for future experiments during the course of the study? Although, certain basic types of so called ''response adaptive designs" in clinical trials have been proposed and studied from a frequentist perspective (Hu and Rosenberger (2006)), allowing treatment randomization probabilities to be a function of outcomes collected in previous experiments, by far most designs in practice are static and most of the adaptive design literature has focussed on adaptive stopping times based on sequential testing or other adaptive stopping rules. In spite of the results on

response adaptive clinical trial design as presented in Hu and Rosenberger (2006), among most practitioners there seems to be a widely accepted consensus that for formal frequentist statistical inference changing the design based on a look at the data in a clinical trial should be avoided even if it is not used for testing.

We present a general statistical framework which allows us to study adaptive designs and estimators based on data generated by these adaptive designs from a frequentist perspective in great generality. For each experimental unit we define a full data random variable and it is assumed that they are identically and independently distributed. For example, we can define the full data as the collection of setting-specific data structures which represents the data one would have observed on the unit if one had applied these particular settings in the design of this experiment, across all settings. In addition, one defines the observed data structure on an experimental unit as a specified many to one mapping of a choice of design setting and the full data random variable: this defines the observed data structure as a censored/missing data structure. The design settings (i.e., censoring variables) for experiment i are drawn from a conditional distribution, given the full data for the i-th unit, which satisfies the coarsening at random assumption (van der Laan and Robins (2003)) for the i-th censored data experiment. The choice of the conditional distribution of the design settings for the i-th experiment can be fully informed by the observed data collected in the previous i ? 1 experiments, and any external data sources. We refer to the collection of these i-specific design mechanisms as the adaptive design. In particular, we define and provide a template for constructing targeted adaptive designs, which aim to learn a particular unknown optimal fixed design from the incoming data during the trial. In particular, we propose easy to implement influence curve based targeted adaptive designs. We provide a variety of examples of such targeted adaptive designs targeting an optimal fixed design such as the fixed design maximizing asymptotic efficiency for a treatment effect in a clinical trial among all fixed designs.

Within this statistical framework we prove consistency and asymptotic linearity and corresponding normality results for the maximum likelihood estimator according to a correctly specified parametric model. We present new double robust targeted maximum likelihood estimators for semi-parametric models which are consistent if one either correctly specified a lower dimensional model for the common distribution or if one correctly specifies the design mechanisms, where the latter is always true in a controlled adaptive designs in which the selected design mechanisms are known. These targeted maximum likelihood estimators for adap-

tive designs generalize the targeted maximum likelihood estimator for independent experiments introduced and developed in (van der Laan and Rubin (2006)). We also propose a new class of relatively easy to implement (double robust) iterative inverse probability of censoring weighted reduced data targeted maximum likelihood estimators. Finally, we present estimators based on Martingale estimating functions generalizing estimating equation methodology for i.i.d. censored data structures as fully presented in (van der Laan and Robins (2003)). Our generalization martingale estimating function methodology includes Inverse Probability of Censoring Weighted Reduced Data martingale estimating functions, which represents a new approach (also for i.i.d. data) in which estimating functions are decomposed as an orthogonal sum and the inverse probability of censoring (IPC) weighting is applied to each component, thereby achieving additional robustness not obtained with standard IPC-weighting.

Our results show that one can learn an unknown user supplied definition of an optimal target fixed design during the course of the study, and thereby adapt/improve the design at any point in time based on the available data, and that statistical inference based on a normal limit distribution is still readily available. We illustrate the theory and resulting methods with various examples of practical interest.

In addition, we present a targeted empirical Bayesian learning methodology which allows one to specify a prior on the target parameter of interest, and it maps it into a posterior distribution, where the center and spread corresponds with the frequentist targeted maximum likelihood estimator. We also show how adaptive designs and sequential testing procedures can be combined.

The general contributions of this article can be listed as 1) general definition and practical constructions of adaptive, and, in particular, targeted adaptive group sequential designs targeting a particular user supplied definition of optimal fixed design, 2) presentation of a variety of possible design adaptations of great practical interest for which our theory applies, 3) presentation of maximum likelihood estimators, new robust (iterative) targeted maximum likelihood estimators, new (iterative) inverse probability of censoring weighted reduced data targeted maximum likelihood estimators, and estimators defined as solutions of Martingale estimating equations, based on the data collected in these general targeted adaptive designs, 4) establishing that the targeted adaptive designs asymptotically converge to the wished optimal unknown design (i.e., we can learn the optimal design), 5) presentation of formal statistical inference for the scientific parameter of interest

under general adaptive designs based on the above mentioned estimation methodologies, which shows, in particular, that the asymptotic efficiency of the targeted maximum likelihood estimator under targeted adaptive designs equals the asymptotic efficiency of the estimator under i.i.d. sampling from the unknown targeted optimal unknown fixed design, as learned during the study, 6) a new targeted empirical Bayesian learning methodology mapping a prior on parameter of interest into its posterior while enjoying the frequentist robust and efficiency properties of the targeted MLE in large semi-parametric models, and 7) sequential testing methods in general adaptive designs controlling the Type-I error at level alpha. In addition, we illustrate the results for a variety of examples of interest.

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March 19, 2008

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In order to answer scientific questions of interest one often carries out an ordered sequence of experiments generating the appropriate data over time. The design of each experiment involves making various decisions such as 1) What variables to measure on the randomly sampled experimental unit?, 2) How regularly to monitor the unit, and for how long?, 3) How to randomly assign a treatment or drug-dose to the unit?, among others. That is, the design of each experiment involves selecting a so called treatment mechanism/monitoring mechanism/missingness/censoring mechanism, where these mechanisms represent a formally defined conditional distribution of one of these actions (i.e., assignment of treatment/monitoring indicator/missingness indicators/right censoring indicators), given observed data characteristics on the unit. The choice of these design mechanisms are typically made a priori, and, it is common that during the course of the ordered sequence of experiments the observed data suggests that the chosen design is ineffective in answering the scientific question of interest, or is dissatisfying from other perspectives, and that a much better design (i.e., choice of mechanisms) should have been selected. This naturally raises the question: Why not learn a user supplied optimal unknown choice of the controlled components of the design based on the data collected in the previously initiated experiments, and thereby adjust/adapt these controlled components of the design for future experiments during the course of the study? Although, certain basic types of so called "response adaptive designs" in clinical trials have been proposed and studied from a frequentist perspective (Hu and Rosenberger (2006)), allowing treatment randomization probabilities to be a function of outcomes collected in previous experiments, by far most designs in practice are static and most of the adaptive design literature has focussed on adaptive stopping times based on sequential testing or other adaptive stopping rules. In spite of the results on response adaptive clinical trial design as presented in Hu and Rosenberger (2006), among most practitioners there seems to be a widely accepted consensus that for formal frequentist statistical inference changing the design based on a look at the data in a clinical trial should be avoided *even if it is not used for testing*.

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the unit if one had applied these particular settings in the design of this experiment, across all settings. In addition, one defines the observed data structure on an experimental unit as a specified many to one mapping of a choice of design setting and the full data random variable: this defines the observed data structure as a censored/missing data structure. The design settings (i.e., censoring variables) for experiment i are drawn from a conditional distribution, given the full data for the i-th unit, which satisfies the coarsening at random assumption (van der Laan and Robins (2003)) for the i-th censored data experiment. The choice of the conditional distribution of the design settings for the i-th experiment can be fully informed by the observed data collected in the previous $i-1$ experiments, and any external data sources. We refer to the collection of these i-specific design mechanisms as the adaptive design. In particular, we define and provide a template for constructing targeted adaptive designs, which aim to learn a particular unknown optimal fixed design from the incoming data during the trial. In particular, we propose easy to implement influence curve based targeted adaptive designs. We provide a variety of examples of such targeted adaptive designs targeting an optimal fixed design such as the fixed design maximizing asymptotic efficiency for a treatment effect in a clinical trial among all fixed designs.

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Key words: Adaptive design of sequence of experiments, causal inference, clinical trial, design of experiments, efficient influence curve/canonical gradient, efficiency theory, group sequential designs, influence curve/gradient, inverse probability of censoring weighting, local asymptotic normality of models, longitudinal studies, martingale central limit theorem, martingale estimating functions, maximum likelihood estimation, observational studies, pathwise differentiability, sequential testing, statistical inference for non independent and identically distributed data, targeted adaptive designs, targeted empirical Bayes learning, targeted maximum likelihood estimation.

1 The statistical framework for adaptive designs

This paper concerns statistical frequentist methods for designing and analyzing a series (e.g., ordered over time) of n experiments, in which each experiment provides information about the scientific parameter of interest, and the randomization probabilities for the settings in a particular experiment in this series of experiments are allowed to be a function of the data collected in the previous experiments. That is, one is allowed to adapt/adjust (i.e., set the design probabilities in) the next experiment based upon what one has learned from previous experiments. In spite of the fact that this adaptation results in dependence between the experiments, we will be able to provide robust and efficient estimation procedures, and statistical inference based on the martingale Central Limit Theorem under appropriate regularity conditions.

Data, Model, and Parameter.

Consider a series of n underlying independent experiments with common probability distribution P_0 resulting in $X_1, \ldots, X_n$ independent and identically distributed random variables, i.e., copies of a random variable X. Let $\mathcal{M}^F$ represent a model for P_0 in the sense that it is known that $P_0 \in \mathcal{M}^F$. Here X represents the wished full data structure, but our observed data will be a censored version of X. For example, X might represent the wished *full* data structure on a randomly sampled subject (e.g., cancer patient) from a particular population of interest defined by a set of baseline characteristics W, and a collection of treatment specific clinical outcomes $(Y(a) : a \in \mathcal{A})$ under a specified set $\mathcal{A}$ of drugs or dose-levels: $X = (W, (Y(a) : a \in \mathcal{A}))$. Typically, our interest lies in a Euclidean parameter $\Psi : \mathcal{M}^F \to \mathbb{R}^d$ defined on the model

$\mathcal{M}^F$ for the distribution of X, where $\psi_0 = \Psi(P_0)$ denotes the true parameter value. For example, if $X = (W, (Y(a) : a))$ as above, then the scientific parameter might be the marginal causal effect, $E(Y(a) - Y(0))$, of treatment choice a relative to control 0.

For the i-th experiment we observe $O_i = (A_i, L_i = X_i(A_i))$, where $X_i(A_i) = \Phi(A_i, X_i)$ for a specified many to one mapping Φ on X_i and a variable A_i, $i = 1, \ldots, n$. In this article we will often refer to A_i as the *design settings* used in experiment i, $i = 1, \ldots, n$, and A_i is a random draw from a set of possible settings $\mathcal{A}$. However, we note that the design settings A_i can also be viewed as a censoring variable which determines what part of X_i is observed. In many applications, as in the clinical trial example above, the full data structure can be represented as $X = (X(a) : a \in \mathcal{A})$, and denotes a collection of random variables indexed by certain design settings a ranging over a set $\mathcal{A}$ of possible design settings, so that $L = \Phi(A, X) = X(A)$ corresponds with a missing data structure in which one only observes the component of X as indicated by the actually assigned design settings A.

We assume that the ordering of the experiments $i = 1, \ldots, n$ is meaning-full since the adaptive designs proposed and studied in this article will allow that the assignment of A_i in experiment i is based on all available data $O_1, \ldots, O_{i-1}$ as collected in the first $i-1$ experiments, $i = 1, \ldots, n$. One application to keep in mind is that subjects are ordered by the entry time E_i of the subjects in the study, and one wishes to adapt the design for subject/experimental unit i to what one can learn from the data available at the time E_i of entry of subject i. In the case of a delayed response, the data available at the time E_i will correspond with right censored (by E_i) versions of longitudinal data structures $O_1, \ldots, O_{i-1}$ (see Chapter 3, van der Laan and Robins (2003)).

We note that this data structure $O_i = (A_i, L_i = X_i(A_i))$ is completely general, and includes any of the censored data structures analyzed in the literature (see van der Laan and Robins (2003)). As a consequence, our statistical framework, targeted adaptive designs, estimators and theorems are general and cover general longitudinal data structures and general adaptation schemes. For example, this includes the general longitudinal causal inference data structure as studied in the causal inference literature for the purpose of statistical inference regarding causal effects of time-dependent treatment (see e.g., Chapter 6 in van der Laan and Robins (2003)). In this case, $X = (L(a) : a \in \mathcal{A})$, where $L(a) = (L(a)(0), \ldots, L(a)(K+1))$ is the counterfactual time dependent data structure one would observe if the subject would have been assigned treatment regimen $a = (a(0), \ldots, a(K))$, and $\mathcal{A}$ is the set of possible treatment regimens. The temporal ordering assumptions states that this treatment specific process $L(a)$ at time j only depends on a through the previously assigned treatments

$\bar{a}(j-1) \equiv (a(1), \ldots, a(j-1))$: $L(a)(j) = L(\bar{a}(j-1))(j)$. In this setting

$$\begin{aligned} O_i &= (A_i, L_i(A_i)) \\ &= (L_i(0), A_i(0), \ldots, L_i(\bar{A}_i(k-1))(K), A_i(K), L_i(\bar{A}_i(K))(K+1), \end{aligned}$$

where $A_i(j)$ is the treatment assignment at time j taking place right after the the collection of $L_i(j) = L(\bar{A}_i(j-1))(j)$. We refer to chapter 6 in van der Laan and Robins (2003), where this representation of the observed data is also used to treat censoring/missingness/monitoring and treatment assignment in a unified manner: i.e., $A_i(j)$ now also includes missingness indicators, monitoring indicators, and right-censoring indicators, beyond a treatment assignment. In this longitudinal setting in which A_i is a time dependent process, adaptive designs as defined below allow that j-th treatment assignment $A_i(j)$ does not only depend on the observed past within the subject i (which is commonly referred to as the sequential randomization assumption in causal inference), but it can also depend on the observed data $O_1, \ldots, O_{i-1}$ on the previous $i-1$ subjects. In Section 18 we present an example of an adaptive design for sequentially randomized clinical trials in which treatment is time-dependent. In Section 19 we study adaptive designs for sequentially randomized clinical trials in which both treatment and right-censoring are controlled by the design.

For the sake of presentation, in this article most of our initial examples focus on the simplest case in which A_i simply denotes treatment assignment at a single point in time for subject i.

Adaptive Coarsening at Random (CAR) Assumption: Let $\mathbf{A} = (A_1, \ldots, A_n)$ and $\mathbf{X} = (X_1, \ldots, X_n)$ denote the n design settings and n full data random variables, respectively. We will use the short-hand notation, $\bar{\mathbf{X}}(i) = (X_1, \ldots, X_i)$ for the full data random variables for the first i subjects, and we use the same notation for other random variables such as $\bar{\mathbf{A}}(i) = (A_1, \ldots, A_i)$ and $\bar{\mathbf{O}}(i) = (O_1, \ldots, O_i)$. Let $\mathbf{g}(\cdot \mid \mathbf{X})$ denote the conditional probability distribution/density of the design settings $\mathbf{A}$, given the full data $\mathbf{X}$. In order to avoid technical details, we assume throughout this article that random variables have either discrete support or can be described by continuous Lebesgue densities. We have

$$\mathbf{g}(\mathbf{A} \mid \mathbf{X}) = \prod_{i=1}^{n} g_i(A_i \mid \bar{\mathbf{A}}(i-1), \mathbf{X}).$$

We assume

$$g_i(a \mid \bar{\mathbf{A}}(i-1), \mathbf{X}) = g_i(a \mid X_i, \bar{\mathbf{O}}(i-1)) = g_i(a \mid X_i(a), \bar{\mathbf{O}}(i-1)), \quad (1)$$

which we refer to as the adaptive CAR-assumption. In words, this states that A_i is conditionally independent of the full data $\mathbf{X}$ for all n experimental units, given the observed data $\bar{\mathbf{O}}(i-1)$ for the first i-1 experimental units, and the full data X_i for the i-th experimental unit, and, in addition, the probability of $A_i = a$, given the full data on unit i, X_i, and the observed data on the previous $i-1$ subjects, $\bar{\mathbf{O}}(i-1)$, only depends on the observed part $X_i(a)$ of the i-th unit, and $\bar{\mathbf{O}}(i-1)$. This assumption implies that the conditional probability $\mathbf{g}(\mathbf{A} \mid \mathbf{X})$ at $\mathbf{A}$, given $\mathbf{X}$, is only a function of the observed data $\mathbf{O}$, which proves that $\mathbf{g}$ satisfies the coarsening at random assumption (Heitjan and Rubin (1991), Jacobsen and Keiding (1995), Gill et al. (1997), van der Laan and Robins (2003)) w.r.t. to the full data $\mathbf{X}$ for all n units, and observed data $\mathbf{O} = (O_1, \ldots, O_n)$ for all n units. Since the design $\mathbf{g}$ is identified by the conditional distributions g_i of A_i, given $\bar{\mathbf{O}}(i-1), X_i$, $i = 1, \ldots, n$, we will also use the notation $\mathbf{g} = (g_1, \ldots, g_n)$.

Definition of adaptive design: We will refer to $\mathbf{g} = (g_1, \ldots, g_n)$ as the design of the study. In this article we will first consider the case that the design $\mathbf{g}$ is known in the sense that, given $O_1, \ldots, O_n$, the realized designs $g_i \in \mathcal{G}$ as used in experiment i are known (but, there is no need to know the actual mapping $(O_1, \ldots, O_{i-1}) \to g_i \in \mathcal{G}$ which resulted in this choice) for all $i = 1, \ldots, n$. In the case that the i-specific design choices g_i are unknown, given a model $\{g_{i,\eta} : \eta\}$ for g_i, $i = 1, \ldots, n$, one could estimate the unknown uncontrolled components of the adaptive design $\mathbf{g}$ with the maximum likelihood estimator

$$\eta_n = \arg\max_{\eta} \prod_{i=1}^{n} g_{i,\eta}(A_i \mid X_i, \bar{\mathbf{O}}(i-1)),$$

or regularized versions thereof, possibly using likelihood based cross-validation to select fine-tuning parameters or the model. In Section 26, we generalize our results for the known design case to the case in which the design g_i has a mixture of known and controlled components and unknown uncontrolled components modelled with a correctly specified model. If one or more of the conditional distributions $g_i(\cdot \mid X_i, \bar{\mathbf{O}}(i-1))$ is a function of $O_1, \ldots, O_{i-1}$, then we refer to $\mathbf{g}$ as an *adaptive design*. On the other hand, if $g_i(a \mid X_i, \bar{\mathbf{O}}(i-1)) = g_i(a \mid X_i)$ for all $i = 1, \ldots, n$, then $O_1, \ldots, O_n$ are independent (but not necessarily identical), in which case we will refer to $\mathbf{g}$ as a *fixed design*: note that this still allows that A_i is selected in response to observed baseline characteristics and time-dependent covariates of the i-th unit: i.e., in this case g_i is a conditional distribution of A_i, given X_i, satisfying the coarsening at random assumption so that O_i implies a coarsening at random for X_i (Chapter 1, van der Laan and Robins (2003)). We will denote the set of such CAR

conditional distributions of A, given X, with $\mathcal{G}$, and we will refer to $\mathcal{G}$ as the set of **fixed designs**:

$$\mathcal{G} \equiv \{g(\cdot \mid X) : g(A \mid X) = h(A, X(A)) \text{ for some measurable function } h\}.$$

Bound on adaptivity of adaptive designs: Our formal asymptotic normality results will restrict g_i to depend on $\bar{\mathbf{O}}(i-1)$ through a finite dimensional (common dimension in i) summary measure Z_i which, for $i \to \infty$, converges to a vector of fixed quantities. Therefore, g_i should be based on summary measures of $\bar{\mathbf{O}}(i-1)$ which should become stable/degenerate as $i \to \infty$. For example, as our results show, Z_i could include as components maximum likelihood estimators of parameters of the full data distribution P_0 of X based on $\bar{\mathbf{O}}(i-1)$, and the standard errors (or covariance matrix) of these maximum likelihood estimators.

Remark. Our results for adaptive designs include the fixed designs (possibly different across the experiments) as a special case, but, if one assumes a fixed design, then $O_1, \ldots, O_n$ are independent so that the analysis of estimators can be based on applications of Bernstein's inequality for sums of independent random variables and corresponding empirical process results in van der Vaart and Wellner (1996) for sums of independent random variables, and, as a consequence, it will be possible to obtain stronger uniform consistency and uniform CLT results than presented here based on the martingale CLT.

For notational convenience, we will from now on often use the notation $g_i(\cdot \mid X_i) = g_i(\cdot \mid X_i, \bar{\mathbf{O}}(i-1))$, thereby suppressing the dependence of g_i on $\bar{\mathbf{O}}(i-1)$, or, equivalently, suppressing that g_i is a random (through $\bar{\mathbf{O}}(i-1)$) conditional distribution of A_i, given X_i.

Factorization of the likelihood/density of observed data.

As a consequence of the coarsening at random assumption on the design $\mathbf{g}$, the density of $\mathbf{O}$ is given by (see Gill et al. (1997)):

$$P_{Q_0,\mathbf{g}}(o_1 = (a_1, l_1), \ldots, o_n = (a_n, l_n)) = Q_0((a_i, l_i), i = 1, \ldots, n)\mathbf{g}(\mathbf{a} \mid \mathbf{x}), \quad (2)$$

where, for a given $\mathbf{a} = (a_1, \ldots, a_n)$, $Q_0((a_i, l_i) : i = 1, \ldots, n)$ denotes the joint probability distribution/density of $(X_1(a_1), \ldots, X_n(a_n))$ at $(l_1, \ldots, l_n)$, which thus only depends on the common full data distribution P_0 of X. By independence of $X_1, \ldots, X_n$, we can conclude that the density factorizes in a Q_0-factor and the design g as follows:

$$P_{Q_0,\mathbf{g}}(o_1 = (a_1, l_1), \ldots, o_n = (a_n, l_n)) = \prod_{i=1}^{n} Q_0(a_i, l_i) \prod_{i=1}^{n} g_i(a_i \mid x_i, \bar{\mathbf{o}}(i-1)), \quad (3)$$

where $Q_0(a_i, l_i) = Pr(X(a_i) = l_i)$ denotes the probability distribution of $X(a_i)$ at l_i, which is a parameter of the full data distribution P_0 of X. Thus a model for the density of the observed data $O_1, \ldots, O_n$ can be denoted as $\{P_{Q,\mathbf{g}} : Q \in \mathcal{Q}\}$, where $\mathcal{Q}$ is the model for the true full data distribution parameter Q_0. Since Q_0 is the only identifiable part of the full data distribution of X this is typically the favorable modelling strategy (since it avoids modelling non-identifiable parameters of the distribution of X).

The model $\mathcal{Q}$ for Q_0 is allowed to be a semiparametric and thereby infinite dimensional model, but the parameter of interest $\psi_0 = \Psi(Q_0)$ will be assumed to be finite dimensional.

Description of data generating mechanism for adaptive design: Given the available data on $O_1, \ldots, O_{i-1}$ at the starting time for experiment i, one can calculate the conditional distribution $g_i(\cdot \mid X_i, O_1, \ldots, O_{i-1})$ of A_i, given X_i, and thereby carry out the i-th experiment $O_i = (A_i, L_i) \sim P_{Q_0,g_i}$, which involves drawing $X_i \sim P_0$, drawing A_i, given X_i, from g_i, and constructing $O_i = (A_i, L_i = X_i(A_i))$, $i = 1, \ldots, n$. Thus, the generation of $\mathbf{O}$ in an adaptive design only differs from generating $O_i \sim P_{Q_0,g_i}$ for a fixed conditional distribution $g_i(\cdot \mid X_i)$ of A_i, given X_i, $i = 1, \ldots, n$ (i.e., a fixed design), by the fact that one needs to order the experiments, and use the data generated in the previous $i-1$ experiments to define the CAR-censoring mechanism g_i used in the i-th experiment to generate A_i, given X_i.

The Maximum Likelihood Estimator for a correctly specified model.

At this stage, it is already of interest to note that the Q_0-factor in this density $P_{Q_0,\mathbf{g}}$ of the observed data $\mathbf{O}$ is identical to what it would have been for a fixed design in which $O_1, \ldots, O_n$ are independent. This means that for the sake of estimation one can proceed as if the design-mechanisms g_i, $i = 1, \ldots, n$ were a priori known, and thus ignore that g_i is adaptive. In particular, the maximum likelihood estimator Q_n of Q_0 according to a model $\mathcal{Q}$ is the same function of the data $O_1, \ldots, O_n$ as the maximum likelihood estimator of Q_0 for a fixed design:

$$Q_n = \arg\max_{Q \in \mathcal{Q}} \sum_{i=1}^{n} \log Q(A_i, L_i),$$

assuming that this maximum exists and can be uniquely defined.

The martingale scores/estimating functions:

In order to provide the reader with a basic understanding of how statistical inference for the maximum likelihood estimator based on a correctly specified model can be derived, we consider the case that $\mathcal{Q} = \{Q_\theta : \theta\}$ with θ finite dimensional. The score equation for the MLE θ_n is now given by

$$0 = \sum_{i=1}^{n} S(\theta_n)(O_i),$$

where $S(\theta)(O_i) = \frac{d}{d\theta} \log Q_\theta(A_i, L_i)$. As shown above and apparent from (3), conditional on the data $O_1, \ldots, O_{i-1}$ of the previous $i-1$ experiments, the density of O_i is given by

$$Q_{\theta_0}(A_i, L_i) g_i(A_i \mid X_i, \bar{\mathbf{O}}(i-1)).$$

As a consequence, under the usual regularity conditions required to show that a score has mean zero at the true parameter value, it follows that

$$E_{\theta_0, g_i}(S(\theta_0)(O_i) \mid O_1, \ldots, O_{i-1}) = 0, \ i = 1, \ldots, n. \tag{4}$$

This also implies that

$$E_0(S(\theta_0)(O_i) \mid S(\theta_0)(O_j), j = 1, \ldots, i-1)) = 0.$$

In general, we define Martingale estimating functions as follows.

Definition 1 *Consider a function $\theta \to D(\theta)(\bar{\mathbf{O}}(i))$ from a parameter space $\{\Theta(Q) : Q \in \mathcal{Q}\}$ for a Euclidean parameter $\Theta : \mathcal{Q} \to \mathbb{R}^d$ to functions of $O_1, \ldots, O_i$. Suppose that at the true parameter value $\theta_0 = \Theta(Q_0)$ of Q_0*

$$P_{Q_0, g_i} D(\theta_0) \equiv E(D(\theta_0)(\bar{\mathbf{O}}(i)) \mid O_1, \ldots, O_{i-1}) = 0 \text{ for all } i = 1, \ldots.$$

Then, we refer to $\theta \to D(\theta)$ as a Martingale estimating function for the parameter θ_0.

If we denote $M(n) = \sum_{i=1}^{n} S(\theta_0)(O_i)$, then for integer $m < n$

$$\begin{aligned} E(M(n) \mid M(m)) &= E\left(\sum_{i=1}^{m} S(\theta_0)(O_i) + \sum_{i=m+1}^{n} S(\theta_0)(O_i) \mid \sum_{i=1}^{m} S(\theta_0)(O_i)\right) \\ &= M(m) + \sum_{i=m+1}^{n} E(E(S(\theta_0)(O_i) \mid O_1, \ldots, O_{i-1}) \mid M(m)) \\ &= M(m). \end{aligned}$$

That is, the empirical mean of the scores at θ_0 over $O_1, \ldots, O_n$ is a discrete Martingale in n. This provides us with a framework for proving that the empirical mean of the scores, $M(n)$, converges to zero for $n \to \infty$ (as needed for consistency of the MLE) and for proving that the standardized mean of the score, $\sqrt{n}M(n)$, converges to a normal distribution (as needed to establish convergence in distribution of the standardized maximum likelihood estimator). This martingale structure is the essential building block for showing that, for all practical purposes, not only maximum likelihood estimation, but also statistical inference can be carried out as if the design mechanisms g_i were fixed and known a priori and all observations $O_1, \ldots, O_n$ are independent. This finding was established for a certain class of response adaptive designs in basic clinical trials (Chapters 2, 5, and 9 in Hu and Rosenberger (2006)).

We will also show how to compute fully efficient so called targeted Maximum Likelihood estimators based on Martingale estimating equations in general semiparametric models $\mathcal{Q}$ for the Q_0 factor. We show that the efficient influence curve based estimating functions for fixed designs, as in general presented in van der Laan and Robins (2003), have an analogue Martingale estimating function for the adaptive design, so that we can generalize targeted estimation methodology for semi-parametric models $\mathcal{Q}$ (i.e., targeted MLE and estimating function based estimation) to adaptive group sequential designs, while borrowing the closed form representations of efficient influence curves in i.i.d. censored data models from van der Laan and Robins (2003). In the targeted MLE methodology presented in this article, a parametric working model is used to obtain an initial (inconsistent) MLE for Q_0 which is then mapped through a targeted MLE procedure, analogue to van der Laan and Rubin (2006) for fixed designs, into a consistent and asymptotically normally distributed estimator of the Euclidean parameter of interest defined on the true (large) semi-parametric model.

1.1 Examples of adaptations of the design.

Above we provided the formal statistical framework for adaptive group sequential designs, involving defining the observed data structure as a missing data structure, the adaptive coarsening at random assumption on the adaptive design, the resulting factorization of the density of the data generating mechanism, corresponding parametric or semi-parametric models on the full data distribution factor Q_0 of the likelihood, and the martingale properties of scores of correctly specified parametric models. In this subsection, we hope to provide the reader with an illustration of the kind of adaptations of practical interest this statistical framework and our corresponding formal results pre-

sented later allow. For the sake of illustration, consider a clinical trial in which one wishes to study the effect of a few candidate drugs on the suppression of the HIV virus in a population of HIV infected subjects. The design of this trial involves various settings which can affect the success of the trial.

Adaptation of right-censoring mechanism/clinical outcome: Firstly, it involves setting the clinical outcome of interest. For example, one might define the clinical outcome as change in viral load over an eight week follow up period. Suppose now that after having observed a first group of subjects, it follows that some of the treatments are resulting in side effects towards the end of the eight week period, and one suddenly wonders if the presence of these toxicity effects will persist, start to occur more frequently, or worsen over longer follow up periods. For that purpose, one might wish to adapt the design by changing the follow up time from 8 to 12 weeks for the new recruits. This is an example of an adaptation of the right-censoring mechanism (one factor in $g_i(A_i \mid X_i)$). In order to also consider this 12 week clinical outcome as outcome of interest for approval of drugs one must have specified this potential alternative clinical outcome a priori (for sound statistical inference the choice of parameters of interest cannot be data adaptive, except if the introduction of an additional or new parameter is purely caused by external factors), and a multiple testing adjustment will need to be carried out to deal with the fact that 2 parameters are potentially considered. It should be noted that the test statistics for these two clinical outcomes will be heavily correlated so that a multiple testing adjustment based on the joint distribution of the two test statistics can be expected to be minor.

Adaptation of Missingness mechanism: During the trial, a new technique for genotyping the virus and or measuring the phenotype of the virus might become available which is shown to outperform the technology used in the current trial. Since reliable genotyping might advance the causal understanding of resistance of the virus to particular drugs, might improve the causal effect estimates of the treatments, and might result in detection of subgroups for which the treatment is particularly effective or ineffective, one might wish to apply these new techniques to the newly recruited subjects. This would be an example of an adaptation of the missingness mechanism on covariates: one starts out with collecting one particular set of covariates, but later on in the trial one starts replacing or augmenting a subset of these covariates by or with a new subset of covariates, where this new subset is purely defined by external factors (the occurrence of a new technology). As a consequence of the fact that the choice of new covariates are a product of external factors, one can redefine the full data X as including these different subsets of covariates, as if these potential covariate vectors were known before the trial, and define a

missingness mechanism on top of them. To summarize, the decision to change the missingness (i.e., to start using the new technology for genotyping) can be informed by the actual data collected on previously recruited subjects, but the choice of the alternative covariate needs to be a priori listed or be a product of pure external data sources. In general, during the trial one might decide to start collecting a new set of biomarkers of interest, where the potential sets of biomarkers were listed a priori or is a product of external factors such as the occurrence of an improved technology or scientific discoveries by other external scientists.

An example of this kind of adaptation is the following. A priori one listed two biomarkers. One starts the trial with biomarker number 1. During the trial one learns from the collected data that this biomarker is hardly predictive of the clinical outcome, and therefore is of no help for improving the efficiency of the treatment effect estimates. Therefore, based on these findings, it is decided to start using biomarker number 2. This is an example of an adaptation of the missingness mechanism on the two biomarkers. Since the parameter of interest is defined in terms of the full data (including the full data on both biomarkers) and does thus not change (as a distribution of the full data parameter) by adjusting the missingness mechanism, the adaptation of the missingness mechanism does not require a multiple testing adjustment.

Adaptations of monitoring and treatment mechanisms: Similarly, during the trial one might feel the need to change the monitoring intensity, the choice of time-dependent covariates collected at the monitoring times among a set of choices a priori specified or only influenced by external factors, and one might wish to change the randomization probabilities for the treatment assignment in response to the fact that certain treatment arms are more variable (w.r.t. outcome) than others, or because some treatments are obviously inferior and can be dropped. These adaptations would be examples of an adaptation of the monitoring mechanism, the treatment mechanism, and missingness mechanism (on a set of possible time-dependent covariates).

Introduction of additional "a priori listed" or "external factor based" intervention: During the trial one might note that the drop out rate needs to be improved by additional counselling and/or the administration of drugs which help the subject to deal with the toxicity symptoms while these drugs are known to have no effect on the counterfactual viral load and or CD4 counts. The administration of this additional intervention to newly incoming subjects would be an example of an adaptation of the assignment of compliance interventions: the original assignment was set at 0 (meaning no intervention is applied), and during the trial it was set at 1 for newly recruited subjects (meaning an a priori specified/external factor based intervention is

applied). Formally, the setting specific full data (counterfactual) process can be represented as $X(a_1a_2)$, where a_2 denotes the intervention indicator and a_1 denotes the other settings, and one assumes that $X(a_1a_2) = X(a_1)$ does not depend on the intervention level a_2. In general, one can introduce interventions which are known to not affect the counterfactual outcomes of interest defining the parameter of interest.

Introduction of improved questionnaire: During the trial it might become clear that subjects drop out time could be well predicted by a self-reported health measure, but it is noted that the currently used self-reported health questionnaire results in confusion and thereby measurement errors. Since informative drop out caused by unmeasured factors can result in bias for the effect estimates of interest, it is important to measure time-dependent covariates which are predictive of the drop out time. As a consequence, one might wish to make changes to the currently used questionnaire, by hiring an external consultant with the request to improve the current questionnaire, and use the new one for the newly recruited subjects. This adaptation in the design corresponds with an adaptation of the missingness mechanism, where the missingness indicator drawn from this mechanism indicates which of the two questionnaires is applied (the one a priori listed as the initial questionnaire or the one resulting from an external consultant).

Adaptation of entry intensity: During the trial one might determine that, based on the available data, the intensity at which new subjects should be recruited should be increased in order to keep the duration of the trial short enough. The entry time for experiment i is denoted with E_i and can be included as a component of A_i. An increased intensity would correspond with a denser pattern of entry times. This is an example of an adaptation of the entry intensity mechanism.

Issue to keep in mind when changing variables during design: Formally, one needs to a priori specify the definition of the full data $X = (X(a) : a \in \mathcal{A})$, and thereby the possible design settings $\mathcal{A}$ for the experimental units such as the monitoring times, treatments, potential additional interventions, potential additional covariates, and missingness indicators. However, there is an important exception to this which allows to adapt the set $\mathcal{A}$ and thereby the full data X, as long as this change is purely based on external data/information. In the previous paragraphs we hinted to some of such allowed adaptations such as the introduction of a new covariate to measure during the trial, which had not been a priori specified, but was only informed by a pure external source of data such as the occurrence of a new technology. In general, if a change during the trial of full data definition (e.g., including the set of possible baseline and time-dependent covariates which are poten-

tially measured on the unit), the possible settings $\mathcal{A}$, and even the choice of parameters of interest for which statistical inference is requested, is based on external factors (e.g., the request of a director who had zero access to the data collected in the trial), then one can make these changes and treat the statistical problem as if these definitions had been made a priori before the trial started. Off course, this could result in very dangerous practice if these choices are made by people who have also been informed by the data observed in the trial: this could result in target parameters which itself are a function of the internal data $O_1, \ldots, O_n$ and thereby are random (even after conditioning on external data sources) so that statistical inference about such random parameters will fail to be accurate.

1.2 The choice of design for experiment i can be fully informed by external factors.

In this article we will propose particular explicitly formulated so called targeted adaptive designs g_i which are defined a priori as a function of a maximum likelihood estimator based on $O_1, \ldots, O_{i-1}$ into an element of the set $\mathcal{G}$ of fixed designs. However, such a priori specified adaptive designs are not required for an application of our asymptotic results. We find this important to point out since in practice it is not hard to imagine that the preferred manner of adaptation might only become apparent during the trial and might be different for each experiment.

The choice of design $g_i \in \mathcal{G}$ for the i-th experiment can be an arbitrary function of external factors (i.e., factors independent of $O_1, \ldots, O_n$) and $O_1, \ldots, O_{i-1}$, and *this function does not need to be specified a priori and, in fact, does not need to be specified at all.* That is, to calculate the estimators and for formal asymptotic statistical inference we just need to know g_i as an element in the set of fixed designs $\mathcal{G}$, but it is not necessary to know the explicit mapping from $O_1, \ldots, O_{i-1}$ and external factors (say) F_i to this element $g_i \in \mathcal{G}$: i.e., we need to know the realization of g_i but not the explicit definition of g_i as random variable. For example, the following mechanism for generating g_i is allowed: at the i-th experiment, one has a group of experts sitting in a room, having access to $O_1, \ldots, O_{i-1}$ and the rest of the world, and this group's output is a choice of design $g_i \in \mathcal{G}_1$ which will be used to draw the settings A_i for experiment i.

The reason that the design g_i for the i-th experiment can be a random variable in $\mathcal{G}$ defined as some function on $O_1, \ldots, O_{i-1}$ *and* external data F_i is that we can apply our formal results for the estimators of the parameter

of interest *conditional on* $F_1, \ldots, F_n$. The conditional distribution of $\mathbf{O}$, given these external factors $F_1, \ldots, F_n$, equals the distribution of $\mathbf{O}$ in the case that $F_1, \ldots, F_n$ had been set by design a priori. As a consequence, the obtained results are the wished results of interest. That also means that our asymptotic stability condition for g_i in our CLT theorems (as required to obtain asymptotic normality of the estimators) only needs to hold conditional on $F_1, \ldots, F_n$, which thus only requires that for i converging to infinity g_i is approximately only random through external random factors (but will depend on asymptotically *consistent/degenerate* finite dimensional summary measures of of $O_1, \ldots, O_{i-1}$).

1.3 Adaptive designs targeting an optimal fixed design

In this subsection we provide a general example of so called targeted adaptive designs, which provides a particular class of targeted adaptive designs of interest we can handle with the theory presented in this article.

Hu and Rosenberger (2006) (Chapter 5) provide a presentation of a theory for response adaptive designs targeting a target allocation of treatment in clinical trials in which one only observes on each subject a treatment and outcome. This corresponds with our definition of adaptive designs in which g_i is just a marginal probability distribution on a set of possible treatments (chosen in response to the outcomes and treatments of the previous $i-1$ subjects). This excludes the case of targeted adaptive designs in clinical trials in which the randomization probabilities can depend on covariates. These authors state (page 158) "*Chapter 9 presents an overview of covariate-adaptive and CARA randomization procedures. Little is known about these procedures, and there are few papers regarding their theoretical properties in the literature.*" and they proceed mentioning that this represents an important area of future research. They also state "*We have discussed heterogeneity* (i.e., the use of covariates in adaptive designs) *very briefly in this book, and that is principally because there has been very little work in this area. Yet it is critical if these designs are to be used in clinical trials.*" Our article concerns this development of a theory for general targeted adaptive designs, and in this subsection we start out with providing a general definition and then discuss the implications of our general results for these targeted adaptive designs.

Suppose that, given the true probability distribution P_0 of X, we would know the optimal *fixed* design $g_i(\cdot \mid X)$ (i.e., the conditional distribution of A, given X) for experiment i in a user supplied subset of all allowed CAR fixed designs $\mathcal{G}$, where optimality is defined w.r.t. a particular criteria. That is, we

can define a mapping

$$\theta \to g_{i,\theta},$$

which maps a choice Q_θ of the identifiable part Q_0 of the distribution of X according to a (possibly misspecified) model $\mathcal{Q}^w = \{Q_\theta : \theta\}$ for Q_0 into the wished fixed design $g_{i,\theta}$ for A_i, given X_i, $i = 1, \ldots, n$. Let θ_0 denote the true parameter of Q_0 so that Q_{θ_0} either equals Q_0 or equals a specified known well defined (e.g., Kullback-Leibler projection) parameter of Q_0 defined onto the true (possibly semi-parametric) model $\mathcal{Q}$. For example, $g_{i,\theta} = g_\theta$ might be the fixed design minimizing the asymptotic variance of the maximum likelihood estimator of a real valued parameter ψ_0 (defined on the semiparametric model $\mathcal{Q}$) over all fixed designs $g \in \mathcal{G}$ based on sampling n i.i.d. observations from $P_{\theta,g} = P_{Q_\theta,g}$.

We can now define an adaptive design $\mathbf{g} = (g_1, \ldots, g_n)$ which learns this optimal fixed (unknown) design g_{θ_0} as $n \to \infty$, as shown by our general results under appropriate conditions. That is, our goal is to adapt the design (i.e., construct a $\mathbf{g} = (g_1, \ldots, g_n)$) in such a way that g_n or equivalently $\bar{g}_n = \frac{1}{n}\sum_{i=1}^n g_i$ converges to the fixed conditional probability distribution g_{θ_0} (of A, given X) in probability as $n \to \infty$. This can be achieved in the following manner.

Let θ_{i-1} be an estimator of the parameter θ_0 of Q_0 based on observations $O_1, \ldots, O_{i-1}$ Typically, one might make θ_i constant in i across blocks of experiments as in group sequential trials. Let θ_i, $i = 1, \ldots, n$, be such a sequence of estimators of θ_0. There are two strategies for selecting the adaptive design based on this sequence of estimators θ_i, $i = 1, \ldots$. Firstly, one could simply set $g_i = g_{\theta_{i-1}}$, $i = 1, \ldots, n$. Alternatively, one iteratively selects $g_1, \ldots, g_i$ so that $g_i = \arg\min_{g \in \mathcal{G}} \parallel \frac{1}{i}(\sum_{j=1}^{i-1} g_j + g) - g_{\theta_{i-1}} \parallel$, starting with an initial g_1, $i = 1, \ldots, n$. Here $\parallel g_1 - g_2 \parallel$ denotes some norm or dissimilarity between two fixed CAR-designs. The latter approach aims to chose g_n so that the average design $\bar{g}_n = 1/n \sum_i g_i$ is as close as possible to the wished g_{θ_n}.

The above two general forms of adaptive designs are just an example of adaptive design as analyzed in this article. Therefore, in particular, we can apply our results to analyze the estimator θ_n, where θ_n can either be a maximum likelihood estimator according to a correctly specified model (in case $\mathcal{Q}^w = \mathcal{Q}$), a targeted maximum likelihood estimator of θ_0 defined on the true semi-parametric model $\mathcal{Q} \supset \mathcal{Q}^w$, or a Martingale estimating equation based estimator of θ_0 of θ_0 defined on the true semi-parametric model $\mathcal{Q} \supset \mathcal{Q}^w$.

Firstly, we wish to establish that θ_n is consistent for the θ_0 parameter of Q_0. Our consistency theorems for adaptive designs indeed show that this typically holds for finite dimensional parameters without any need for convergence of

the design g_n to a fixed design. Therefore, without getting into a circular reasoning, we can establish that θ_n is consistent for a Euclidean parameter θ_0.

As a consequence of this consistency of θ_n we will have that the above adaptive design satisfies that $g_n = g_{\theta_{n-1}} \rightarrow g_{\theta_0}$ in probability as $n \rightarrow \infty$, or equivalently, that $\bar{g}_n \rightarrow g_{\theta_0}$, as $n \rightarrow \infty$. Given that the adaptive design g_n converges to a fixed design as the sample size converges to infinity, and thereby satisfies the asymptotic stability condition defined in our Central Limit Theorems, we are now in the situation that we can apply our central limit theorem for the maximum likelihood estimator, targeted maximum likelihood estimator or martingale estimating equation based estimator of the parameter of interest ψ_0 (e.g. including θ_0) based on data generated by adaptive group sequential designs. Application of these theorems shows, under regularity conditions, that $\sqrt{n}(\psi_n - \psi_0)$ converges in distribution to a normal distribution as $n \rightarrow \infty$, where the covariance matrix in this normal distribution is identical to what it would have been under i.i.d (i.e., fixed design) sampling from $P_{Q_0,g_{\theta_0}}$ (and if $Q_{\theta_0} = Q_0$, then this is the true wished optimal design). That is, under regularity conditions, we will have that the estimator ψ_n of the parameter of interest ψ_0 of Q_0 in the adaptive design is asymptotically equivalent with the estimator based on i.i.d. sampling using the optimal fixed CAR-design g_{θ_0} in case $Q_{\theta_0} = Q_0$ and "sub-optimal" fixed CAR design if the working model $\mathcal{Q}^w$ used to learn the optima fixed design was misspecified. Our examples will show a few rigorous illustrations of this result. In general, our theorems provide templates and conditions for establishing these results for general (e.g., targeted) adaptive designs.

Dealing with delayed response. Note that in the case that $O_j = (O_j(s) : s \geq 0)$, $j = 1, \ldots, n$, are longitudinal time dependent data structure collected over time, at the time E_i at which A_i needs to be drawn the data $O_1, \ldots, O_{i-1}$ for the first $i-1$ experiments might not have been observed yet. Thus the estimator θ_i in the targeted adaptive design $g_i = g_{\theta_{i-1}}$ will need to be based on the data available at time E_i at which A_i needs to be drawn in experiment i. In this case the estimator θ_{i-1} would be based on $i-1$ right censored versions $\bar{O}_1(E_i), \ldots, \bar{O}_{i-1}(E_i)$ of these $i-1$ observations $O_1, \ldots, O_{i-1}$, where $\bar{O}(t) \equiv (O(s) : s \leq t)$. If the entry times E_i satisfy the coarsening at random assumption again (just make E_i part of A_i and apply our definition of the adaptive coarsening at random assumption), then one could define θ_{i-1} as the (e.g.) maximum likelihood estimator based on $\bar{O}_j(E_i), j = 1, \ldots, i-1$, treating E_i as given, where the likelihood can be derived as if these $i-1$ observations are independent, as above in (3): see Chapter 3 van der Laan and Robins (2003)

for the Q_0-factor of the general likelihood of right censored data longitudinal data structures. If $A_i = A_i(0), \ldots, A_i(K)$ has K time dependent components drawn at subsequent times $E_i(0), \ldots, E_i(K)$, then the choice of mechanism for $A_i(j)$ can be based on the available data on $O_1, \ldots, O_{i-1}$ at time $E_i(j)$ at which $A_i(j)$ needs to be drawn in experiment i.

1.4 Sequential testing.

In Section 25 we will show that the sequential testing methods as typically used in clinical fixed design trials can be equally well applied on top of adaptive designs, as analyzed in this article. According to Hu and Rosenberger (2006): "*The basic statistical formulation of a sequential testing procedure requires determining the joint distribution of the sequentially computed test statistics. Under response-adaptive randomization, this is a difficult task. There has been little theoretical work done to this point, nor has there been any evaluation of sequential monitoring in the context of sequential estimation procedures (i.e., targeted adaptive designs) such as the double adaptive biased coin design.*" These authors end their book with the quote from Rosenberger (2002): "*Surprisingly, the link between response adaptive randomization and sequential analysis has been tenuous at best, and this is perhaps the logical place to search for open research topics.*" Indeed, in Section 25 we will determine the joint distribution of the sequentially computed test statistics based on our results, and provide a large class of sequential testing procedures whose asymptotic validity only relies on this joint distribution result.

1.5 Implications for FDA critical path initiative.

An important topic for the FDA critical path initiative is the streamlining of clinical trials. Specifically, we will list some of the items raised in their publications on the FDA critical path initiative as can be downloaded from the internet, and comment how the methods in this article affect some of these items.

Innovative and Efficient Clinical Trials: One item is the creation of innovative and efficient clinical trials. Our article provides targeted adaptive designs which target the design to optimize information in the data for a particular parameter of interest such as a causal effect of a treatment relative to control or the optimal dose of a drug. In general, our general framework allows statistical inference on a very general class of adaptive

designs, and therefore creates ample room for innovative and creative choices of adaptive designs.

Improved Clinical Endpoints: We show that if one lists a number of candidate clinical end points a priori, then one can adapt and target the design towards the best clinical end point by adjusting the design of future experiments based on data generated in previous experiments. In particular, one can decide to stop measuring certain clinical end points for next groups of experiments, or one can adjust the randomization probabilities to optimize the trial towards estimation of the causal effect of treatment on one of the clinical end points. The multiple testing adjustment should be based on the joint distribution of the test statistics for the different clinical end-points, in which case one can expect a relatively minor multiplicity adjustment due to the high correlation between the test statistics.

Enrichments Designs: Enrichment designs involve enrolling patients which are at higher risk or known to respond well to treatment. One can use initial groups to determine the higher risk patients and good responders, and subsequently only sample such patients, but, for the purpose of solid statistical inference w.r.t. to an a priori defined parameter of interest, estimators and inference cannot be based on these initial groups. Such kind of adaptations change the target parameter of interest and thus the corresponding null hypothesis of interest, and thereby make the parameter of interest and null hypothesis data driven. Nevertheless, in spite of the resulting loss of data (or more optimistically stated, that the data on these initial groups cannot be used for *both* parameter selection and estimation), such adaptations are very important and crucial to improve the success rate of clinical trials. It is an interesting statistical challenge to rationalize the use of the initial groups as well in the calculation of an estimator and test for a null hypothesis, under certain scenarios.

Data Driven Subgroups: Another similar issue raised in the Critical Path Initiative is "What types of retrospective subset analyses are valid. i.e. what can be reliably learned from subgroup analysis that were not prespecified in the original trial design?"" Again, if sub-group are a function of the data, then formal statistical inference for such a data adaptively selected sub-group cannot include the data which was used to select the subgroup.

Modification of Randomization Probabilities: In addition, the FDA Crit-

ical Path Initiative raises the question: "When is it valid to modify randomization probabilities based on results for example in phase 2/3 trial?". Clearly, our methods teach us that we can modify randomization probabilities in response to data generated in previous experiments, and, in fact, we should be doing this to obtain more efficient designs in answering the questions of interest.

Dose Response Curves and Optimal Dose: Most cancer trials identify and test the maximum tolerated dose to maximize efficacy. Such trials cannot answer key questions about dose response relationships such as "Do blood levels of drug relate to outcomes?" and "At what dose does the response plateau?" Therefore, it is necessary that we design trials which can find dose response curves. In Section 16 we provide such trials and, in particular, we provide a targeted adaptive design for finding the optimal dose, while still providing the whole dose response curve.

1.6 Organization of article.

In Section 2 we present and discuss a general class of targeted adaptive designs of the type presented in Subsection 1.3 to which our results can be applied. In particular, we present specific classes of targeted adaptive designs maximizing the information for a particular parameter of interest or number of significant findings for treatment effects in clinical trials. In Section 3 we highlight a class of particularly easy to implement *empirical influence curve based targeted adaptive designs*, and we illustrate it in the context of a clinical trial with baseline covariates.

In Section 4 we establish consistency and asymptotic normality of the maximum likelihood estimator based for the treatment effect in a clinical trial in which covariates are not exploited, based on our general asymptotic central limit theorem results established in later sections. The obtained results for the marginal unadjusted treatment effect estimate correspond with the results presented in Chapter 5 of Hu and Rosenberger (2006). In Section 5 we provide a general template for proving consistency of maximum likelihood estimators according to correctly specified parametric models.

Section 6 shows that, if one restricts the adaptive design for the i-th experiment to only respond to baseline covariates conditioned upon in the definition of the parameter of interest, but one still allows the settings of experiment i to depend in an arbitrary manner on the data generated in the previous $i-1$ experiments, then one can typically construct Martingale estimating functions which do not depend on the adaptive design (i.e., the g_i's). Although these

estimating functions are typically inefficient, they are attractive because of its simplicity and robustness w.r.t. the finite sample variability due to the variability of the adaptive design, which might out-weight their inefficiency. In Section 7 we present equally simple to implement Inverse Probability of Censoring Weighted estimators based on Martingale IPCW estimating functions, which can be inferred from the IPCW estimating functions for fixed designs as presented in van der Laan and Robins (2003), in general. These two sections 6 and 7 present ad hoc martingale estimating functions and corresponding easy to implement estimators, while in later sections we present the general methodology for deriving optimal (and non-optimal) martingale estimating functions based on the efficient influence curves for the corresponding fixed design models, and thereby corresponding estimating equation based estimators and targeted maximum likelihood estimators for adaptive group sequential designs.

In Section 8 we present methods for constructing Martingale estimating functions and corresponding estimating equations. Section 9 establishes consistency for estimators defined as solutions of Martingale estimating equations. Section 10 establishes the consistency for the adaptive design showing that adaptive designs will learn the targeted fixed design. In Section 11 we present and prove the asymptotic normality of the standardized maximum likelihood estimator and, in general, estimators defined as solutions of Martingale estimating equations.

Sections 12 and 13 presents 2 versions of the locally "efficient" robust targeted maximum likelihood estimator for adaptive designs. This generalizes the double robust locally efficient targeted maximum likelihood estimator for i.i.d. CAR censored data (i.e., fixed designs) as introduced and analyzed in van der Laan and Rubin (2006). In Section 14 we also establish the general consistency and asymptotic normality results for this (double) robust targeted maximum likelihood estimator.

Sections 15, and 16 are devoted to the application of our general consistency and asymptotic normality theorems for the maximum likelihood and targeted maximum likelihood estimator to targeted adaptive designs in clinical trials. In Section 15 we study targeted adaptive designs for clinical trials including covariates to improve efficiency of the estimate of the treatment effect, and to allow for adaptation of how treatment is assigned in response to covariates/subgroup-membership. In Section 16 we present targeted adaptive designs targeting the optimal dose level of a drug (and corresponding targeted maximum likelihood estimators), while still providing the causal dose response curve, where we show, in particular, that this targeted adaptive design exists in closed form.

In Section 17 we illustrate adaptive designs to adapt the covariate distribution for the purpose of estimating a regression function of these covariates. In Section 18 we present a number of examples of censored data structures and corresponding targeted adaptive designs, in order to provide some illustrations of the scope of our statistical framework and results, going beyond the basic data structure of a typical clinical trial. In particular, in Section 19 we illustrate the application of adaptive designs and our targeted MLE in the general context of a longitudinal study with time-dependent treatment and right-censoring.

In Sections 20 and 21 we provide an easy to implement and practically appealing Inverse Probability of Censoring Weighted Reduced Data Iterative Targeted MLE methodology and illustrate it by applying it to fitting causal effect models for time dependent treatments as represented by so called marginal structural models. Subsequently, in Section 22 we illustrate that this same methodology actually covers a whole range of double robust IPCW iterative targeted maximum likelihood estimation methodologies by allowing different degrees for the reduction of the data, where "no reduction" corresponds with the actual iterative targeted MLE as presented in Section 13. In these methods the estimators involve inverse probability of censoring weighting of each time-specific factor of the log-likelihood in such a manner that double robustness w.r.t. miss-specification of the design mechanism or the actual model for the likelihood is achieved.

In Sections 23 and 24 we present a targeted empirical Bayesian methodology which allows us to incorporate a prior distribution on the scientific parameter of interest and map it into a valid robust and targeted posterior distribution for the parameter of interest, by preserving the frequentist properties of the (iterative) targeted MLE.

In Section 25 we present sequential testing methods which can be applied in combination with the general adaptive group sequential designs. In Section 26 we generalize our results to adaptive design in which some of the components are unknown but modelled. Finally, in Section 27 we present our most general formulation of iterative targeted estimation, thereby including the iterative targeted likelihood based estimators as presented in this article as a special case, but also pointing to various generalizations of interest. We end this article with a discussion in Section 28. A number of technical results, required as building blocks for the consistency and CLT theorems, are deferred and proved in the two appendices.

1.7 Some relevant literature on adaptive designs for clinical trials

The literature on adaptive designs is vast (in particular, since it represents various statistical goals) and we apologize for not including all of it. To start with it is important to note that the word adaptive designs has also been used in the literature for sequential testing and, in general, on designs which allow data adaptive stopping times for the whole study or for treatment arms in the study, which achieve the wished control of the Type-I error for a test of a null hypothesis of interest. In this article, we have decided to completely separate the sequential testing problem and adaptive sample size formulas from the data adaptive determination of experimental settings in response to data collected in previous experiments. In a sense, stopping the trial corresponds with the extreme decision to not collect any data at all at the next experiment, which is not considered part of our definition of an adaptive design (stopping a treatment arm is). Instead, stopping and sequential testing will be considered a separate adaptation for which methods can be developed on top of the adaptive designs, as we do in Section 25. We believe that the separation of sequential testing and adaptive designs makes sense from a methodological point of view since valid sequential testing procedures typically rely on the determination of the asymptotic joint distribution of the sequentially computed test statistics in a trial which does not stop (but possibly still adapts) as in our definition of adaptive designs. The main literature on adaptive designs which corresponds with our general definition of an adaptive design has been called "response-adaptive randomization" (Hu and Rosenberger (2006)). Since we feel strongly that the conditional distribution $\mathbf{g}$ of the design settings $\mathbf{A}$, given $\mathbf{X}$, truly represents the design for the data generating experiment, we decided to refer to it as the adaptive design (instead of response adaptive randomization), and reserve names such as adaptive sample size formulas, adaptive stopping rules, and sequential testing for the additional adaptations one can put on top of the adaptive design, whose asymptotic theory cannot be developed without first developing the asymptotic theory for adaptive designs as sample size converges to infinity.

In order to illustrate the need for adaptive designs in clinical trials, we cite the following quote from a Pharmaceutical Executive Derek Lowe July 1, 2006, taken from an internet article: *A widely noted survey by Accenture provided some alarming figures a few years ago: Eighty-nine percent of all drug candidates from the initiation of Phase I through FDA approval failed in the clinic. Clearly, any techniques that could give an earlier read on these issues would be valuable. In too many cases , the chief result of a trial is to*

show that the trial itself was set up wrong, in ways that only became clear after the data were un-blinded. Did the numbers show that your dosage was suboptimal partway into a two year trial? Too bad- you probably weren't allowed to know that. Were several arms of your study obviously pointless from the start? Even if you know, what could you do about it without harming the validity of the whole effort? Over the last years, such concerns have stimulated an unprecedented amount of work on new approaches. Ideas have come from industry, academia, and regulatory agencies such as the FDA's critical path initiative. A common theme in these efforts has been to move toward adaptive clinical trials.

More of such quotes are easy to find reflecting the general feeling among many practitioners that drastic improvements in running trials should be possible and that adaptive designs hold the key to this.

The most familiar example of a simplistic adaptive trial is the phase I trial design for finding a maximum tolerated dose (MTD). In this case, patients are enrolled stage-wise. At the first stage a group of patients are enrolled in the lowest dose arm, and at subsequent stages patients are also enrolled to higher dose groups. This process of stage wise sampling and enrolling patients in higher dose groups proceeds till the dose results in toxicity effects. At that point, the next lower dose is declared to be the maximum tolerated dose.

Group sequential designs are typically used to monitor a study that unfolds over time at interim analysis times to assess whether there is enough evidence in support of the research hypothesis to warrant early termination of the study (Scharfstein et al. (1997)). In general, we refer to such a design as a group sequential testing study. In this setting a test statistic is computed at each analysis time and compared to a stopping boundary. Due to the repeated looks at the data, this boundary is adjusted to maintain some predetermined overall significance level. To determine this boundary, the joint distribution of the sequentially computed test statistics must be derived. We refer (Scharfstein et al. (1997)) for a general methodology for sequential testing and an overview of literature, and to (Scharfstein and Tsiatis (1998)) Tsiatis (2006) for information based group sequential testing studies. There is a rich literature on different ways to control the Type I error in group sequential trials involving sequential testing of the null hypothesis of interest (see e.g., Pampallona et al. (2001)).

A good reference for an overview of research on adaptive sample size determinations in clinical trials is the FDA/MIT workshop, October 19, 2004, "New Adaptive Trial Design: The evolution from group sequential trials to adaptive designs" which deals with the questions "How to preserve the Type-I error in an adaptive trial?" and "How much to increase the sample size issues

of trial management?"

In this case the adaptive designs considered are concerned with strategies for determining when to stop a trial, including the setting of the times at which one tests the null hypothesis of interest. In this FDA/MIT workshop of October 19, 2004, one distinguished between two approaches. Firstly, the group sequential design which starts out with a large up-front commitment of sample size, but uses sequential testing to allow early stopping. The second approach is (inconveniently) referred to as the adaptive design method, which starts out with a small commitment of sample size and extends it if necessary. We note that adaptivity of the design refers here only to the adaptive manner in which the sample size is determined (Tsiatis and Mehta (2003), Jennison and Turnbull (2003)).

In this workshop it is noted that some disadvantages of group sequential trials are that the sample size calculation requires a priori specification of a unique clinically meaningful alternative. It is noted that the theory does not support, changing your mind about this alternative after the trial is underway. On the other hand, the adaptive sample size formulas allows one to update the alternative and thereby the sample size calculation. It is noted in articles (e.g. Tsiatis and Mehta (2003)) that "Adaptive designs are theoretically less efficient than classical group sequential designs", but it is stated that "this loss of efficiency is compensated by the increased flexibility to change course of design". These statements for adaptive sample size determinations are due to multiple testing adjustments. They do not apply at all to our definition of adaptive designs in which adaptation can be used to heavily increase asymptotic efficiency of the estimator of the scientific parameter of interest relative to a fixed design (see also Hu and Rosenberger (2006)). It is also noted that the adaptive sample size formulas result in logistic problems: "Who in the organization will be permitted to view the un-blinded interim data and determine the sample size change" "What signal does a sample size increase send to the investigators!".

We provide the following references for work on adaptive sample size determination involving the sequential testing and thereby proper adjustment of the critical values: Tsiatis and Mehta (2003), Banerjee and Tsiatis (2006), Lokhnygina and Tsiatis (2006), Bauer and Kohne (1994), Cui et al. (1999), Jennison and Turnbull (2003), Koyama et al. (2004), Lan and Trost (1997), Li et al. (2002), Mehta and Tsiatis (2001), Mulle and Shafer (2001), Proschan and Hunsberger (1995), Shen and Fisher (1999), Wittes and Brittain (1999), L.M.Friedman et al. (1998).

We also provide the following references for adaptive treatment allocation in clinical trials: Bai et al. (2002); Andersen et al. (1994); Flournoy and Rosen-

berger (1995); Hu and Rosenberger (2000); Rosenberger (1996); Rosenberger et al. (1997); Rosenberger and Grill (1997); Rosenberger and Shiram (1997); Tamura et al. (1994); Wei (1979); Wei and Durham (1978); Wei et al. (1990); Zelen (1969); Cheng and Shen (2005).

The book Hu and Rosenberger (2006) is may be the most relevant reference for our article since it concerns asymptotical theory for maximum likelihood estimators based on adaptive designs in clinical trials, focussing on adaptation of the treatment randomization probabilities in response to observed responses in the previous experiments. One well known technique of response adaptive patient randomizations is the "Random play the winner", one of the "urn" methods- so called because they can be modelled after different ways of pulling various colored balls from an urn. Play the winner mathematically weight the treatment arms that have produced the fewest adverse events and/or the most positive data so that more patients are assigned to them. A similar "drop the loser" rule can be used, allowing for entire dosage groups or efficacy arms to be added or dropped as the data develop. These types of adaptive designs and targeted designs are studied in detail in the simple clinical trial setting in Hu and Rosenberger (2006).

We refer to this recent book Hu and Rosenberger (2006) for a representation of the literature on response adaptive randomization in clinical trials.

There is also a rich literature on the Bayesian approach to adaptive designs. Certain book references in this direction are Berry and Stangl (1996) and Spiegelalter et al. (2004). A basic overview of Bayesian adaptive designs is provided in Berry (2006). In the Bayesian approach, at certain time points, posterior probabilities are calculated given the observed history in the trial, where these calculations are, as usual, based on certain specified (e.g., parametric) models. Whatever decision rules based on these iteratively updated posterior probability distributions are implemented, the frequentist properties of the corresponding testing procedure are often simulated in extensive simulations. In this manner, these Bayesian adaptive designs aim to provide adaptive designs which still control the type I error as defined in the frequentist world. A concern is that these simulations are model based and that model misspecification can result in tests which fail to control the type I error. On the contrary, the asymptotic validity of our methods presented in this article (e.g. targeted maximum likelihood estimation) only relies on knowing (or being able to consistently estimate) the randomization probabilities for the various design settings such as treatment assignment probabilities, and mechanisms of other design settings. As a consequence, contrary to the standard Bayesian approach to adaptive designs, our method is able to use the knowledge about the design mechanism, and thereby obtain valid and locally efficient estima-

tors in large semi-parametric models. Our targeted empirical Bayesian still enjoys the same properties as our targeted robust estimators, but it now also allows the incorporation of a prior distribution on the parameter of interest, and maps it into a valid posterior distribution.

1.8 Notation.

Let $\mathcal{G}$ denote the set of conditional distributions of A, given X, satisfying CAR w.r.t. to the full data X for a single experimental unit and observed data $O = (A, L = X(A))$, which we will also refer to as the set of fixed designs. Thus $\mathcal{G}$ is the set of all conditional distributions of A, given X, satisfying $g(A \mid X) = h(A, X(A))$ for some measurable function h (Chapter 1, van der Laan and Robins (2003)). Let $\theta \rightarrow g_\theta$ represent a mapping from a Euclidean parameter space Θ into $\mathcal{G}$, which will often be referred to as a design function. Let g_i be the conditional distribution of A_i, given X_i and $O_1, \ldots, O_{i-1}$, $i = 1, \ldots, n$, but we find it useful to consider it as a conditional distribution of A_i, given X_i, depending on the random $O_1, \ldots, O_{i-1}$. That is, we will consider g_i as a random (through $\bar{O}(i-1)$) element of the set of fixed CAR-designs $\mathcal{G}$. A particular kind of adaptive design is the targeted adaptive design $g_i = g_{\theta_{i-1}}$, where θ_i is a sequence of estimators based on $\bar{\mathbf{O}}(i-1)$, $i = 1, \ldots$. Throughout this article, it will be assumed that g_i depends on $O_1, \ldots, O_{i-1}$ through a finite dimensional vector Z_i of fixed (in i) dimension. For convenience, we will also assume that g_i only depends on i through Z_i (*but this is not necessary for our results*): that is, $g_i = g_{Z_i} \in \mathcal{G}$ with probability 1, $i = 1, \ldots, n$. For a fixed or random conditional distribution g_i of A_i, given X_i, let P_{Q_0,g_i} denote the conditional probability distribution of O_i, given $O_1, \ldots, O_{i-1}$, which can be described as $O_i = (A_i, X_i(A_i) = \Phi(X_i, A_i))$, $X_i \sim P_0$, and $A_i \mid X_i \sim g_i(\cdot \mid X_i)$, as if g_i is a given conditional distribution of A_i, given X_i. For a function $D(O_i, Z_i)$ we define the corresponding conditional expectation operator $P_{Q_0,g_i} D = E_{Q_0,g_i}(D(O_i, Z_i) \mid O_1, \ldots, O_{i-1})$, which is thus still a random variable as a function of Z_i. For notational convenience, given a vector valued random variable $D(O, Z)$, we use the notation $P_{Q_0,g_i} D^2 \equiv P_{Q_0,g_i} D D^\top$, which is thus a matrix of conditional expectations w.r.t. O_i, given $O_1, \ldots, O_{i-1}$. In this article $\mathcal{Q}^w = \{Q_\theta : \theta \in \Theta\}$ denotes a parametric working model, while $\mathcal{Q}$ is the true (possibly semi-parametric) model for the Q_0-factor of the likelihood of the data. For the sake of defining the targeted MLE, given a $Q_\theta \in \mathcal{Q}^w \subset \mathcal{Q}$, $\{Q_\theta(\epsilon) : \epsilon\} \subset \mathcal{Q}$ denotes a submodel of $\mathcal{Q}$ through Q at $\epsilon = 0$ and indexed by a finite dimensional parameter ϵ. If this submodel is also indexed a choice of $g \in \mathcal{G}$, then we also denote it with $Q_{\theta,g}(\epsilon)$, and, typically, we set $g = g_\theta$ so that we obtain submodel

$\{Q_{\theta,g_\theta}(\epsilon) : \epsilon\}$. Let $\Psi : \mathcal{Q} \to \mathbb{R}^d$ denote the Euclidean parameter of interest, which is assumed to be path-wise differentiable at a fixed design distribution $P_{Q,g} \in \mathcal{M}(g) \equiv \{P_{Q_1,g} : Q_1 \in \mathcal{Q}\}$ in model $\mathcal{M}(g)$ for a single experimental unit O with efficient influence curve $D^*(Q,g)$, for all $Q \in \mathcal{Q}$ and $g \in \mathcal{G}$. For a function f, let $\| f \|_\infty = \sup_x \mid f(x) \mid$ denote the supremum norm, and, for a $p \geq 1$, let $\| f \|_{p,P_0} \equiv (E_{P_0} \mid f(X) \mid^p)^{1/p}$ denote the L^p-norm w.r.t. the distribution of X.

2 A general class of targeted adaptive designs

In this section we consider a general strategy for the formulation of a targeted adaptive design. Firstly, one specifies an optimal fixed design $g_{i,\theta_0} = \arg\max_{g \in \mathcal{G}_1} f_i(\theta_0, g)$ as a maximum over a user supplied class (e.g., finite set) of fixed designs $\mathcal{G}_1 \subset \mathcal{G}$ of some real valued criteria f_i applied to the parameters specifying the probability distribution $P_{\theta_0,g} = P_{Q_{\theta_0},g}$ of a single experimental unit $O = (A, X(A))$, given a working model $\mathcal{Q}^w = \{Q_\theta : \theta\}$ for Q_0. We will refer to g_{i,θ_0} as the design function. We note that instead of taking a maximum of the stated criterion in the definition of g_{i,θ_0} one might make other more ad hoc choices based on this criterion which do not necessarily correspond with a true maximum.

Given such a specified design function a corresponding targeted adaptive design is obtained by setting $g_i = g_{i,\theta_{i-1}}$, with θ_{i-1} an estimator of θ_0 based on $O_1, \ldots, O_{i-1}$, such as the MLE, $i = 1, \ldots, n$. Therefore, in this section we focus on proposing a number of interesting candidate criteria $g \to f_i(\theta_0, g)$. The criteria f_i is allowed to be indexed by i and $O_1, \ldots, O_{i-1}$. In many cases, such as the targeted adaptive designs considered in Section 1, the criteria f_i can be selected to not depend on $O_1, \ldots, O_{i-1}$ so that it is a fixed function f_i of θ_0, g. However, it is often more practical and convenient to define the wished *criteria* f_i for g_i in response to the observed $\bar{\mathbf{O}}(i-1)$. Adaptive designs which aim to respond to statistical significance against a null hypothesis $H_0(j)$ based on $O_1, \ldots, O_{i-1}$ will typically depend on a scaling factor $\sqrt{i}$.

We start out with some specific targeted adaptive designs for estimation of treatment effects in clinical trials. Subsequently, we discuss a variety of general targeted adaptive designs.

2.1 Targeted adaptive design in clinical trials with several treatment arms.

Let $Y(a)$ represent a treatment specific outcome one would observe if the randomly sampled patient would be assigned treatment $a \in \{0, 1, \ldots, d\}$ (e.g., representing different drugs or different doses), and let $X = (Y(0), Y(1), \ldots, Y(d)) \sim P_{X0}$ represent the collection of treatment specific outcomes on a randomly sampled patient. We will leave the probability distribution P_{X0} of X unspecified. Let $X_1, \ldots, X_n$ be n i.i.d. draws of X. The scientific parameter of interest is the causal effect of treatment j relative to treatment 0 defined as $\psi_0(j) = E_0(Y(j) - Y(0))$.

Let A_i be a treatment assignment for patient i, and let the observed data for patient i be $O_i = (A_i, Y_i(A_i))$, $i = 1, \ldots, n$. That is, for patient i, we observe the treatment and the corresponding clinical outcome. Let $\mathbf{g} = (g_1, \ldots, g_n)$ be an adaptive design satisfying CAR:

$$g_i(j \mid X_i, O_1, \ldots, O_{i-1}) = P(A_i = j \mid O_1, \ldots, O_{i-1}), i = 1 \ldots, n.$$

This CAR-assumption on the design requires A_i to be independent of the counterfactual outcomes $X_i = (Y_i(0), \ldots, Y_i(d))$, but, it is allows A_i to be dependent on the data collected on the previously recruited patients, $O_1, \ldots, O_{i-1}$. On the other hand, a fixed design g_i would not depend on $\bar{\mathbf{O}}(i-1)$, and would thus reduce to a simple marginal distribution on $\{0, 1 \ldots, d\}$.

Consider a model for the conditional distribution of Y, given A, indexed by parameter θ_0. Before we proceed, we provide a short "overview" of efficiency theory based on i.i.d. sampling. A regular estimator $\psi_n(j)$ of $\psi_0(j)$ based on i.i.d. sampling from $P_{Q_0,g}$, $g \in \mathcal{G}$, is asymptotically linear at $P_{Q_0,g}$ with influence curve $IC_j(Q_0, g)(O)$ if

$$\psi_n(j) - \psi_0(j) = \frac{1}{n} \sum_{i=1}^{n} IC_j(Q_0, g)(O_i) + o_P(1/\sqrt{n}).$$

A regular asymptotically linear estimator is asymptotically efficient at $P_{Q_0,g}$ if and only if it is asymptotically linear with influence curve equal to the so called efficient influence curve, where the latter is identified as the canonical gradient of the path-wise derivative at $P_{Q_0,g}$ of the parameter ψ_0. Under a common fixed design g (i.e., $g_i = g$) it is well known that the efficient influence curve of the parameter $\psi_0(j)$ at $P_{Q_0,g}$ is given by (e.g., van der Laan and Robins (2003)):

$$S_j(Q_0, g)(A, Y) = (Y - E_{Q_0}(Y \mid A)) \left(\frac{I(A = j)}{g(j)} - \frac{I(A = 0)}{g(0)}) \right).$$

The variance of this efficient influence curve is given by:

$$\mathrm{VAR}_{Q_0,g} S_j(Q_0,g)(A,Y) = \frac{\sigma^2(Q_0)(j)}{g(j)} + \frac{\sigma^2(Q_0)(0)}{g(0)},$$

where $\sigma^2(Q_0)(j) = \mathrm{VAR}_{Q_0}(Y \mid A = j)$ are the conditional variances of Y, given $A = j$, $j \in \{0,\ldots,d\}$. We define the covariance matrix of the vector efficient influence curve $S(Q_0,g)$ of the vector parameter ψ_0 as $\Sigma(Q_0,g) \equiv E_{Q_0,g} S(Q_0,g)(A,Y)S(Q_0,g)(A,Y)^\top$.

Thus, an estimator of ψ_0 is efficient if and only if it is asymptotically linear with influence curve equal to the efficient influence curve $S(Q_0,g)$. By the CLT, it follows that $\Sigma(Q_0,g)$ denotes the asymptotic covariance matrix of an efficient estimator. Therefore, the covariance matrix of the efficient influence curve of the scientific parameter of interest suggests important design functions such as:

$$g_{i,Q_0} = \arg\min_g \sum_{j=1}^{d} w_i(Q_0)(j)^2 \left(\frac{\sigma^2(Q_0)(j)}{g(j)} + \frac{\sigma^2(Q_0)(0)}{g(0)} \right), \tag{5}$$

where $w_i(Q_0)$ is a specified weight vector possibly depending on Q_0 and $O_1,\ldots,O_{i-1}$. Thus, g_{i,Q_0} is the fixed design which minimizes a weighted average over j of the variance of the efficient influence curve of treatment effect $\psi_0(j)$ under $P_{Q_0,g}$ over all fixed designs g, where it is allowed that the weights are updated in response to the observed data $\bar{\mathbf{O}}(i-1)$ and possibly depend on Q_0.

Writing $g(0) = 1 - \sum_{j=1}^{d} g(j)$, and setting the derivatives w.r.t. $g(j)$, $j = 1,\ldots,d$, equal to zero provides us with the following closed form solution for these design functions:

$$\begin{aligned} g_{i,Q_0}(0) &= \frac{\sigma(Q_0)(0)}{\sigma(Q_0)(0) + \sum_{j=1}^{d} w_i(Q_0)(j)\sigma(Q_0)(j)} \\ g_{Q_0}(j) &= w_i(Q_0)(j)\frac{\sigma(Q_0)(j)}{\sigma(Q_0)(0)} g(0). \end{aligned}$$

If $w_i = 1$ and $d = 2$, then this design equals the so called Neyman Allocation: see Chapter 1 Hu and Rosenberger (2006).

If one sets $w_i(Q_0)(j) = 1$ for all j, then this design $g_{i,Q_0} = g_{Q_0}$ corresponds with minimizing the sum over j of the variances of the efficient influence curve of the treatment effect $\psi_0(j)$. One could set $w_i(Q_0)(j) = w(Q_0)(j)$ equal to the probability under Q_0 that a patient exposed to treatment j has a successful clinical outcome, so that the resulting adaptive design g_i (based on an estimate $Q_{\theta_{i-1}}$ of Q_0 according to working model $\mathcal{Q}^w$) gives preference to treatment arms

which have been successful based on the previously collected data $O_1, \ldots, O_{i-1}$. Other possible interesting choices of $w_i(Q_0)(j) = w_i(j)$ are functions of p-values, and test-statistics for $H_0 : \psi_0(j) = 0$ based on $O_1, \ldots, O_{i-1}$.

Remark. We also wish to note that the criteria in (5) can be derived as a derivative of a general criteria based on the diagonal elements of the covariance matrix $\Sigma(Q_0, g)$. For example, consider the criteria

$$f : g \to \sum_{j=1}^{d} \bar{\Phi}\left(\frac{\psi_0(j)}{\sqrt{\sigma^2(Q_0)(j)/g(j) + \sigma^2(Q_0)(0)/g(0)}}\right),$$

where Φ is the standard normal cumulative distribution, and $\bar{\Phi} = 1 - \Phi$. The corresponding adaptive design g_i aims to adapt the design in order to maximize the average of transformed test-statistics based on $O_1, \ldots, O_{i-1}$ for the tests $H_0(j) : \psi_0(j) = 0$ of no-treatment effect. Firstly, consider this criteria as a function of $\Sigma(Q_0, g)(j, j) = \sigma^2(Q_0)(j)/g(j) + \sigma^2(Q_0)(0)/g(0)$. Now, the first order linear approximation of this function of $\Sigma(Q_0, g)(j, j)$ at $\Sigma(Q_0, g^0)$ is given by

$$\frac{1}{2}\sum_{j=1}^{d} w(Q_0)(j)\{\Sigma(Q_0, g)(j, j) - \Sigma(Q_0, g^0)(j, j)\},$$

where

$$w(Q_0)(j) = \frac{1}{2}\phi\left(\frac{\psi_0(j)}{\sqrt{\Sigma(Q_0, g^0)(j, j)}}\right)\frac{\psi_0(j)}{(\Sigma(Q_0, g^0)(j, j))^{1.5}}.$$

As a consequence, minimizing $g \to f(g)$ can be approximated by minimizing this first order Taylor expansion at an initial choice g^0, which is equivalent with minimizing

$$g \to \frac{1}{2}\sum_{j=1}^{d} w(Q_0)(j)\Sigma(Q_0, g)(j, j)$$

for which we derived a closed form solution above. This allows us to formulate fast minimization algorithms for minimizing f based on iteratively minimizing the derivative of the f.

2.2 Targeted design in clinical trials with various treatment arms and covariates.

Consider now the more general case that the full data $X_i = (W_i, Y_i(0), \ldots, Y_i(d))$ on a randomly sampled patient i consists of the treatment specific outcomes

and a vector of baseline covariates W_i, $i = 1, \ldots, n$. The observed data on the i-th patient is $O_i = (W_i, A_i, Y_i = Y_i(A_i))$ with $A_i \in \{0, \ldots, d\}$. For example, W_i might include an indicator of a subgroup where the subgroup membership is expected to be an important effect modifier for the effect of treatment. One common purpose of a clinical trial is to fully understand the effect of treatment for each of these subgroups. The CAR adaptive design g_i now represents a conditional distribution of A_i, given W_i and $O_1, \ldots, O_{i-1}$. In this case the set $\mathcal{G}$ of fixed designs consists of conditional distributions of A, given W.

Let $\psi_0(j) = E(Y(j) - Y(0))$, $j = 1, \ldots, d$ denote the causal effect of treatment j relative to the control 0. Let $\mathcal{Q}^w = \{Q_\theta : \theta\}$ be a working model for Q_0. The efficient influence curve of ψ_0 at $P_{\theta_0,g} = P_{Q_{\theta_0},g}$, $g \in \mathcal{G}$, under i.i.d. sampling is given by (see e.g., van der Laan and Robins (2003), van der Laan (2006a)):

$$\begin{aligned} S_j(\theta_0, g) &= (Y - E_{\theta_0}(Y \mid A, W)) \left(\frac{I(A = j)}{g(j \mid W)} - \frac{I(A = 0)}{g(0 \mid W)} \right) \\ &\quad + E_{\theta_0}(Y \mid A = j, W) - E_{\theta_0}(Y \mid A = 0, W). \end{aligned}$$

The variance of $S_j(\theta_0, g)$ under $P_{\theta_0,g}$ is given by:

$$\frac{\sigma^2(\theta_0)(j \mid W)}{g(j)} + \frac{\sigma^2(\theta_0)(0 \mid W)}{g(0)},$$

up till a term not depending on g. As in the previous subsection it follows that the optimal fixed design for estimation of treatment effect $\psi_0(j)$ among all conditional distributions of A, given W, (i.e., $\mathcal{G}$) minimizing the variance of the efficient influence curve $S_j(\theta_0, g)$ is given by:

$$g_{\theta_0}(j \mid W) = \frac{\sigma(\theta_0)(j \mid W)}{\sigma(\theta_0)(0 \mid W) + \sigma(\theta_0)(j \mid W)} \quad (6)$$

$$g_{\theta_0}(0 \mid W) = 1 - g_{\theta_0}(j \mid W). \quad (7)$$

That is, one would assign only treatments j and 0 and it would follow the so called Neyman Allocation conditional on W: see Chapter 1 Hu and Rosenberger (2006).

In order to generalize this optimal design-function, and thereby adaptive design, for the single treatment effect for a two arm trial to a multi-arm trial, analogue to the design function (5) for the marginal data structure, we now propose the design function

$$g_{i,\theta_0}(\cdot \mid W) \equiv \arg \min_{g(0),\ldots,g(d)} \sum_{j=1}^{d} w_i(\theta_0, W)(j)^2 \left(\frac{\sigma^2(\theta_0)(j \mid W)}{g(j)} + \frac{\sigma^2(\theta_0)(0 \mid W)}{g(0)} \right),$$

where $\sigma^2(\theta_0)(j \mid W) = \mathrm{VAR}_{\theta_0}(Y \mid A = j, W)$. Writing $g(0) = 1 - \sum_{j=1}^{d} g(j)$, and setting the derivatives w.r.t. $g(j)$, $j = 1, \ldots, d$, equal to zero provides us with the following closed form for g_{i,θ_0}:

$$\begin{aligned} g_{i,\theta_0}(0 \mid W) &= \frac{\sigma(\theta_0)(0 \mid W)}{\sigma(\theta_0)(0 \mid W) + \sum_{j=1}^{d} w_i(\theta_0, W)(j)\sigma(\theta_0)(j \mid W)} \\ g_{i,\theta_0}(j \mid W) &= w_i(\theta_0, W)(j)\frac{\sigma(\theta_0)(j \mid W)}{\sigma(\theta_0)(0 \mid W)} g_{i,\theta_0}(0 \mid W). \end{aligned} \tag{8}$$

In order to interpret this design function, let's consider the case that treatment is binary and that the weights are set equal to 1. If $A \in \{0, 1\}$ is binary, and $O = (W, A, Y) \sim P_{\theta_0,g}$, then the optimal fixed design g for estimation of the marginal treatment effect $E(Y(1) - Y(0))$ is given by $g_{\theta_0}(1 \mid W) = \frac{\sigma(\theta_0)(0|W)}{\sigma(\theta_0)(0|W)+\sigma(\theta_0)(1|W)}$, which equals g_{θ_0} (8). If $A \in \{0, 1\}$ is binary, W is discrete (e.g. indicating different subgroups of interest), and $O = (W, A, Y)$, then the optimal fixed design for estimation of the subgroup-specific effect $E_{\theta_0}(Y(1) - Y(0) \mid W = w)$ is also given by $g_{\theta_0}(1 \mid W = w)$: the corresponding adaptive design $g_i = g_{\theta_{i-1}}$ based on the MLE θ_{i-1} will thus be optimal for the purpose of simultaneous efficient estimation of all subgroup specific treatment effects. As a consequence, this design function g_{i,θ_0} has optimality properties for the two arm trial and aims to do an optimal job across all d treatment effects in a multi-arm trial with possibly preferences for certain effects as indicated by the weights $W_i(\theta_0, W)$.

2.3 Adaptive designs in clinical trials simultaneously targeting efficacy and safety.

In the definition of the design function (8) one can select the weight function $w_i(\theta, W)$ so that, if the value θ tells us that treatment j is harmful for patients with covariate $W = w$, then $w_i(\theta, w)(j) = 0$. Such a choice of weight function implies that the design function satisfies $g_{i,\theta^*}(j \mid W = w) = 0$ for such critical values θ^* so that in the corresponding adaptive design $g_i = g_{i,\theta_i}$ patients with $W = w$ will not be assigned the harmful treatment j anymore if θ_i is close enough to such a critical value θ^* so that $w_i(\theta_i, w)(j) = 0$. Thus, the weight function can be used to respond to safety concerns based on $O_1, \ldots, O_{i-1}$ regarding the treatment for certain sub-groups.

2.4 Influence curve based targeted adaptive designs

The adaptive designs defined above are examples of adaptive designs that are targeted towards a Euclidean parameter ψ_0 of θ_0. We will now present and discuss such information based adaptive designs in general.

Let $D(\theta_0, g)$ be a d-dimensional efficient influence curve of a certain d-dimensional parameter $\Psi(\theta_0)$ of θ_0 at $P_{\theta_0,g}$, $g \in \mathcal{G}$, based on i.i.d. sampling from $P_{\theta_0,g} = P_{Q_{\theta_0},g}$. Consider the $d \times d$ covariance matrix of this efficient influence curve:

$$\Sigma(\theta_0, g) \equiv P_{\theta_0,g} D^2(\theta_0, g).$$

An interesting class of targeted adaptive designs are defined by a design function

$$g_{i,\theta_0} = \arg\min_{g \in \mathcal{G}_1} f_i\left(\Sigma(\theta_0, g)\right),$$

for some real valued criteria f_i applied to $d \times d$ covariance matrices, and for a user supplied set of fixed CAR-designs $\mathcal{G}_1 \subset \mathcal{G}$.

The variance component $\Sigma(\theta_0, g)(j, j)$ represents the Cramer-Rao information bound for parameter $\psi_0(j)$ based on i.i.d sampling from $P_{\theta_0,g}$ in the sense that an estimator $\psi_{0n}(j)$ is efficient if and only if its standardized version $\sqrt{n}(\psi_{0n}(j) - \psi_0(j))$ is asymptotically normal with variance equal to $\Sigma(\theta_0, g)(j, j)$. Thus, a fixed design minimizing the j-th diagonal element $g \to \Sigma(\theta_0, g)(j, j)$ would be optimal for the purpose of estimation of $\psi_0(j)$, but it would typically be a very poor design for any of the other parameters $\psi_0(j')$ for $j' \neq j$. For example, if ψ_0 denotes a vector of differences between the mean of a treatment arm and control arm indexed by the d treatment arms, then the optimal design for one comparison is to only assign patients to the corresponding two arms in a manner identified in the previous subsection (i.e., the Neyman allocation conditional on baseline covariates), which would not even allow identification of the other comparisons between treatment arms.

One approach would be to set as goal to maximize the information bound for a particular real valued parameter of ψ_0 or a real valued parameter directly related to ψ_0 : For example, in a clinical trial this parameter could be defined as a weighted average of the treatment specific effects over the treatment arms, or the weighted average of the treatment specific means. Consider a weighted average $\lambda_0(c) = c^\top \psi_0$ of the components of ψ_0 indexed by a weight vector c. The Cramer-Rao lower bound for the asymptotic variance of any regular estimator is now given by $c^\top \Sigma(\theta_0, g) a$. The corresponding criteria is thus

$$g \to f_i(\Sigma(\theta_0, g)) \equiv c_i^\top \Sigma(\theta_0, g) a_i,$$

where the weight vector c_i can depend on i and $\bar{\mathbf{O}}(i-1)$.

Another possible interesting class of criteria are weighted averages of the diagonal elements of the covariance matrix:

$$g_{i,\theta_0} = \arg\min_{g\in\mathcal{G}_1} \sum_{j=1}^{d} a_i(j)\Sigma(\theta_0, g)(j,j),$$

where the weight vector a_i is a function of $O_1, \ldots, O_{i-1}$. If one uses constant equal weights, then this design would minimize the sum of the parameter specific information bounds/variances with no preference for particular parameters. However, one could imagine that there are situations in which one would prefer to invest more of the data into parameters with large (absolute) values (say representing treatment arms which are doing well). For that purpose, we could consider the following weight choices:

$$\begin{aligned} a_i(j) &= \psi_{i-1}(j) \\ a_i(j) &= \frac{\psi_{i-1}(j)}{\sqrt{\Sigma(\theta_{i-1}, g_{i-1})(j,j)}} \\ a_i(j) &= \Phi\left([\sqrt{i-1}]\frac{\psi_{i-1}(j)}{\sqrt{\Sigma(\theta_{i-1}, g_{i-1})(j,j)}}\right), \end{aligned}$$

where Φ is the standard normal cumulative distribution function, and we put the scaling factor between brackets to indicate that one could consider adding it to the weight or delete it. In these design functions one weights the information bound for each parameter by the estimated parameter or a monotonically transformed coefficient of variation of the estimated parameter so that the resulting adaptive design will aim to invest more into parameters with large estimated values or large t-statistics, respectively.

Our asymptotic normality results immediately apply to the design functions without the scaling factor inside the normal cumulative distribution function. However, the design function g_{i,θ_0} with the scaling factor is not a continuous function in θ_0 uniformly in i so that g_{i,θ_i} will not be asymptotically equivalent with a fixed design, which is one of the fundamental conditions in our asymptotic normality results. Therefore, it remains to be seen how adaptive designs based on g_{i,θ_0} with the scaling factor behave in practice and how one would determine the corresponding asymptotic limit distribution of the maximum likelihood estimator.

For example, the last choice results in the following design function:

$$g_{i,\theta_0} = \arg\min_{g\in\mathcal{G}_1} \sum_{j=1}^{d} \Phi\left([\sqrt{i-1}]\frac{\psi_{i-1}(j)}{\sqrt{\Sigma(\theta_{i-1}, g_{i-1})(j,j)}}\right)\Sigma(\theta_0, g)(j,j).$$

Let $\lambda(g, \theta_0)$ be the vector of eigenvalues of $\Sigma(g, \theta_0)$. A very sensible, but typically ambitious, approach is to define the design function as

$$g_{\theta_0} = \arg\min_{g \in \mathcal{G}_1} \sum_{j=1}^{d} \mid \lambda(g, \theta_0)(j) \mid .$$

This corresponds with minimizing the sum of Cramer-Rao lower bounds for a vector of d orthogonal parameters. Even though it might be computationally challenging to carry out this minimization problem over a continuous family $\mathcal{G}_1$ for high dimensional d, it will be easy to use this criteria to compare a finite set of candidate designs: that is, one might use other approaches to define candidate adaptations based on $O_1, \ldots, O_{i-1}$, and select the one which results in the smallest sum of absolute eigenvalues.

Another interesting design function focussing on maximizing the information is given by

$$g_{\theta_0} = \arg\min_{g \in \mathcal{G}_1} \sum_{j=1}^{d} \bar{\Phi}\left(\frac{\psi_0(j)}{\sqrt{\Sigma(\theta_0, g)(j, j)}}\right),$$

where $\bar{\Phi}$ denotes the standard normal survivor function. This design function is inspired by the design function presented in the next subsection.

2.5 Targeted adaptive designs maximizing number of significant findings.

Suppose now that we are interested in developing targeted adaptive designs which result in maximal number of rejections of the null hypotheses of interest $H_0(j) : \psi_0(j) = 0$, $j = 1, \ldots, d$, given a multiple testing procedure controlling the family wise error rate. In this case, if during the trial there is already plenty of statistical evidence that a particular parameter of interest is larger than the null value, then one should not invest more data into that parameter, but instead one should invest data in parameters which are borderline, but promising.

Important remark regarding scaling factors in design functions: Various possible adaptive designs aiming to maximize the number of correct rejections (i.e., a generalized definition of power) can be considered. However, all will be using a scaling factor $\sqrt{i-1}$ within a normal cumulative distribution function. Although, our consistency results for the MLE apply to such adaptive designs, the asymptotic stability condition of the adaptive design in our theorems for the asymptotic normality of maximum likelihood estimators

will now typically fail to hold. It remains to be investigated how robust our normal limiting distribution result are to such asymptotically random designs, so that this should be a future area of research. Because of this, we will state these adaptive designs with and without the scaling factor, and note that our asymptotic normality results immediately apply to the design functions without the scaling factor, or with the scaling factor replaced by a uniformly bounded sequence of scaling factors. That is, if one replaces $\sqrt{i-1}$ by a scaling factor c_i with $\limsup c_i < \infty$, then our asymptotic normality results for the maximum likelihood estimators will apply to these design functions.

The adaptive designs g_i we consider below are all concerned with maximizing a criteria involving the standardized quantity $[\sqrt{i-1}]\frac{\psi_{i-1}(j)}{\sqrt{\Sigma(\theta_{i-1},g)(j,j)}}$ over fixed designs g, simultaneously for all j. Note that this standardized quantity imitates the t-statistic for testing the null hypothesis $H_0(j) : \psi_0(j) = 0$ based on $O_1, \ldots, O_{i-1}$ assuming a fixed design g under i.i.d sampling from $P_{\theta_0,g}$.
Minimizing average p-value: Firstly, if one aims to minimize the average of p-values, then the following design function

$$g_{i,\theta_0} = \arg\min_{g\in\mathcal{G}_1} \sum_{j=1}^{d} \bar{\Phi}\left([\sqrt{i-1}]\frac{\psi_0(j)}{\sqrt{\Sigma(\theta_0,g)(j,j)}}\right)$$

is appropriate, and results in an adaptive design

$$g_i = \arg\min_{g\in\mathcal{G}_1} \sum_{j=1}^{d} \bar{\Phi}\left([\sqrt{i-1}]\frac{\psi_{i-1}(j)}{\sqrt{\Sigma(\theta_{i-1},g)(j,j)}}\right).$$

Maximizing number of rejections:

Under a fixed design $P_{\theta_0,g}$, we have that the expected number of rejections based on test statistics $T_{ni}(j) = \sqrt{i}\psi_i(j)/\sqrt{\Sigma(\theta_0,g)(j,j)}$ at cut-off c is approximately (for i large enough) given by

$$E_{\theta_0,g}\sum_{j=1}^{d} I\left(\sqrt{i}\frac{\psi_i(j)}{\sqrt{\Sigma(\theta_0,g)(j,j)}} > c\right) \;=\; \sum_{j=1}^{d}\bar{\Phi}\left(c-\sqrt{i}\frac{\psi_0(j)}{\sqrt{\Sigma(\theta_0,g)(j,j)}}\right),$$

where $\bar{\Phi}(t) = P(Z > t)$, with $Z \sim N(0,1)$. This suggests the following design function

$$g_{i,\theta_0} = \arg\max_{g\in\mathcal{G}_1} \sum_{j=1}^{d} \bar{\Phi}\left(Z_{1-\alpha/d} - [\sqrt{i-1}]\frac{\psi_0(j)}{\sqrt{\Sigma(\theta_0,g)(j,j)}}\right),$$

where $Z_{1-\alpha/d}$ is the $1-\alpha/d$ quantile of the standard normal distribution. The corresponding adaptive design is given by

$$g_i = \arg\max_{g\in\mathcal{G}_1} \sum_{j=1}^{d} \bar{\Phi}\left(Z_{1-\alpha/d} - [\sqrt{i-1}]\frac{\psi_{i-1}(j)}{\sqrt{\Sigma(\theta_{i-1},g)}} \right),$$

which aims to maximize the number of significant findings in a Bonferoni multiple testing procedure controlling the family wise error rate.

2.6 Adaptive design maximizing probability on finding significant treatment effect.

Let $\psi_0(j)$ denote a treatment effect relative to a control for treatment j, $j = 1,\ldots,d$. In the previous subsection we defined adaptive designs aiming to maximize the number of significant findings. In clinical trials one typically wishes to find a best treatment among the set of treatments. One might wish to maximize over all fixed designs g the probability under $P_{\theta_0,g}$ that the best performing treatment effect is significantly better than the control. For this purpose, we note that under i.i.d sampling from $P_{\theta_0,g}$ and for n large

$$\begin{aligned}
&Pr_{\theta_0,g}\left(\max_j \sqrt{n}\tfrac{\psi_n(j)}{\sqrt{\Sigma(\theta_0,g)(j,j)}} > z\right)\\
&\approx 1 - Pr_{\theta_0,g}\left(\max_j \left\{ Z(j) + \sqrt{n}\tfrac{\psi_0(j)}{\sqrt{\Sigma(\theta_0,g)(j,j)}} \right\} \le z\right)\\
&= 1 - Pr_{\theta_0,g}\left(Z(j) \le z - \sqrt{n}\tfrac{\psi_0(j)}{\sqrt{\Sigma(\theta_0,g)(j,j)}}, j=1,\ldots,d\right),
\end{aligned}$$

where $Z \sim N(0,\Sigma^*(\theta_0,g))$, and Σ^* denotes the correlation matrix corresponding with Σ.

This suggests the following design function

$$g_{i,\theta_0} = \arg\max_{g\in\mathcal{G}_1} 1 - Pr_{\theta_0,g}\left(Z(j) \le z_{1-\alpha/d} - \sqrt{i-1}\frac{\psi_0(j)}{\sqrt{\Sigma(\theta_0,g)(j,j)}}, j=1,\ldots,d \right),$$

where $Z \sim N(0,\Sigma^*(\theta_0,g))$, and $z_{1-\alpha/d}$ is the $1-\alpha/d$ quantile of the standard normal distribution. This results in an adaptive design

$$g_i = \arg\max_{g\in\mathcal{G}_1} 1 - Pr_{\theta_0,g}\left(Z(j) \le z_{1-\alpha/d} - \sqrt{i-1}\frac{\psi_{i-1}(j)}{\sqrt{\Sigma(\theta_{i-1},g)(j,j)}}, j=1,\ldots,d \right),$$

where θ_{i-1} and ψ_{i-1} are treated as given within the probability.

As noted above our consistency results apply to these adaptive designs, but our asymptotic normality results only apply if the scaling factor $\sqrt{i-1}$ is replaced by a uniformly bounded sequence c_i.

2.7 Combining targeted adaptive designs for real valued parameters into an adaptive design simultaneously targeting all parameters.

Let g_{j,θ_0} be a design function targeted at a particular real valued parameter $\psi_0(j)$, $j = 1, \ldots, d$. Let W denote the set of baseline co-variates we observe on an experimental unit, and let $(\Pi_{\theta_0}(j \mid W) : j = 1, \ldots, d)$ be a conditional probability distribution possibly indexed by the unknown θ_0. An adaptive design g_i could now be defined by a choice $\Pi_i = \Pi_{\theta_{i-1}}$ and $g_{j,i} = g_{j,\theta_{i-1}}$ in the sense that for the i-th experiment, one first draws a Δ from $\Pi_i = \Pi_{\theta_{i-1}}$, and one applies the targeted adaptive design $g_{\Delta,\theta_{i-1}}$, corresponding with this choice Δ for j, to the i-th experiment. In words, one first randomly decides which of the d designs $g_{j,i}$, $j = 1, \ldots, d$ to use for the i-th experiment, and then one applies the selected design. For example, in a clinical trial one might have formulated a targeted adaptive treatment mechanism which is targeted towards the effect of treatment on a clinical outcome for three different clinical outcomes, and for each newly recruited subject one randomly assigns one of these three treatment mechanisms.

3 Empirical Influence curve based targeted adaptive designs.

Above, in Subsection 2.4 we showed that an influence curve based targeted adaptive design involves computing the covariance matrix $\Sigma(Q_{\theta_0}, g)$ of a specified influence curve $D(\theta_0, g)(O)$ (at $P_{\theta_0,g}$) of the parameter of interest ψ_0, with $O \sim P_{\theta_0,g}$. Subsequently, one defines the design choice g_i as a minimizer over g of some real valued functional of this covariance matrix with Q_{θ_0} replaced by an estimate Q_{i-1} based on $O_1, \ldots, O_{i-1}$, and this real valued function can be indexed by $O_1, \ldots, O_{i-1}$ as well.

Although, in many applications the efficient influence curve, or at least, an inefficient influence curve, exists in closed form, obtaining a closed form formula for its variance and covariance elements is often challenging, and even if one succeeds it often involves numerically challenging integrals. Therefore, in this section we propose a modification of this previous definition of influence curve based targeted adaptive designs, in which we estimate $\Sigma(Q_0, g)$ based on $O_1, \ldots, O_{i-1}$ with an empirical variance estimate using inverse probability of censoring/design weighting to adjust for the fact that the data was generated by adaptive designs g_j, $j = 1, \ldots, i-1$. In this manner, we obtain an always

easy to implement and thereby very practical targeted adaptive design, which still satisfies the wished properties (namely that we learn the optimal fixed design when sample size increases).

For that purpose, we note that

$$\begin{aligned}\Sigma(\theta_0, g) &\equiv P_{\theta_0,g} D^2(\theta_0, g) \\ &= P_{\theta_0,g_i} D^2(\theta_0, g) \frac{g}{g_i}.\end{aligned}$$

Thus, if $P_{\theta_0,g_i} = P_{Q_0,g_i}$ for all i (i.e., the working model $\{Q_\theta : \theta\}$ is correctly specified), a natural estimate of $\Sigma(\theta_0, g)$ based on $O_1, \ldots, O_{i-1}$ is given by

$$\Sigma_{i-1}(g) = \frac{1}{i-1} \sum_{j=1}^{i-1} D(\theta_{i-1}, g)(O_j)^2 \frac{g}{g_j} - \left(\frac{1}{i-1} \sum_{j=1}^{i-1} D(\theta_{i-1}, g)(O_j) \frac{g}{g_j} \right)^2.$$

Here we note that the inverse probability of censoring (IPC) weighting is used to correct for fact that $O_j \mid O_1, \ldots, O_{j-1} \sim P_{Q_0,g_j}$, and thus that O_j was not sampled from $P_{Q_0,g}$. Clearly, this estimate $\Sigma_{i-1}(g)$ of $\Sigma(\theta_0, g)$ only requires having a closed form expression for $D(\theta_0, g)$ and is thus relatively easy to obtain.

The IPC-weighting we used can be refined as follows by applying it separately to each component of the influence curve $D(\theta_0, g)$, given an orthogonal decomposition $D = \sum_k D_k$ in the Hilbert space $L_0^2(P_{Q_{\theta_0},g})$. Such an orthogonal decomposition is often a natural consequence of factorization of the density $dP_{Q_0,g} = \prod_k Q_{0k} g$ so that tangent spaces of Q_{0k} and g are all pairwise orthogonal, giving an orthogonal decomposition of the tangent space at $P_{Q_0,g}$, and thereby also giving a corresponding orthogonal decomposition of the efficient influence curve $D^*(Q_0, g)$. In particular, one can apply this decomposition in the case that no models are assumed on Q_0 and g, giving an orthogonal decomposition of the whole $L_0^2(P_{Q_0,g})$, and thus, in particular, an orthogonal decomposition of any influence curve $D(Q_0, g)$. For example, many data generating densities can be represented as a product of conditional probability distributions, thereby giving a corresponding orthogonal decomposition of $L_0^2(P_{Q_0,g})$.

Given such an orthogonal composition, we know that

$$P_{Q_0,g} D(Q_0, g)^2 = \sum_k P_{Q_0,g} D_k(Q_0, g)^2.$$

As a consequence, we can apply the IPC-weighting to each D_k:

$$P_{Q_0,g} D(Q_0, g)^2 = \sum_k P_{Q_0,g_i} D_k(Q_0, g)^2 \frac{g}{g_i}.$$

Here it is important to note that if $D_k(O_i)$ only depends on A_i through some of its components, say $\bar{A}_i(j) = (A_i(0), \ldots, A_i(j))$, then one only needs to use the weights $g(\bar{A}_i(j) \mid X_i)/g_i(\bar{A}_i(j) \mid X_i)$ for these components $\bar{A}_i(j)$. As a consequence, one obtains in this manner a more stable estimate of the wished covariance $\Sigma(\theta_0, g)$. The resulting estimate is now given by:

$$\Sigma_{i-1}(g) = \frac{1}{i-1}\sum_{j=1}^{i-1}\sum_k D_k(\theta_{i-1}, g)(O_j)^2 \frac{g}{g_j} - \sum_k \left(\frac{1}{i-1}\sum_{j=1}^{i-1} D_k(\theta_{i-1}, g)(O_j)\frac{g}{g_j}\right)^2.$$

Recall, that in the previous Subsection 2.4 we defined $\Sigma(\theta_0, g) \equiv P_{\theta_0,g} D^2(\theta_0, g)$, and we then defined the adaptive design

$$g_i = \arg\min_{g \in \mathcal{G}_1} f_i\left(\Sigma(\theta_{i-1}, g)\right),$$

for some set $\mathcal{G}_1$ of fixed designs (possibly indexed by $O_1, \ldots, O_{i-1}$) and some real valued mapping f_i possibly depending on $O_1, \ldots, O_{i-1}$. Our proposed modification replaces $\Sigma(\theta_{i-1}, g)$ by the empirical covariance estimate $\Sigma_{i-1}(g)$ and we define

$$g_i = \arg\min_{g \in \mathcal{G}_1} f_i\left(\Sigma_{i-1}(g)\right).$$

However, by selecting $\mathcal{G}_1$ too large the resulting choice g_{i-1} would represent an over-fit based on $O_1, \ldots, O_{i-1}$ (which might represent a price to pay for using an empirical estimate of the variance instead of an expectation w.r.t. to the modeled Q_{θ_0}). Therefore, we wish to indicate natural variations one might employ. For example, one might let the set $\mathcal{G}_1$ be indexed by i and define it as a family of fluctuations through the previous choice g_{i-1}:

$$\mathcal{G}_i = \{g_{i-1,\epsilon} : \epsilon\}.$$

Alternatively, one fluctuates an average $\bar{g}_{i-1} = 1/(i-1)\sum_{j=1}^{i-1} g_j$.

In this way, at each next experiment one adjusts the previous choice by selecting the fluctuation parameter ϵ based on the criterion $\epsilon \to \Sigma_{i-1}(g_{i-1,\epsilon})$ in ϵ.

In addition, one might put an upper bound on the allowed fluctuations (by bounding the parameter space for ϵ) thereby only allowing for minor or controlled modifications of the design at each step. The latter is also important for obtaining more stable estimators since, although our estimators (e.g. targeted MLE and martingale estimating equation based estimators) are double robust, the finite sample variability of these double robust estimators will depend on the stability of the weights g/g_i for a carefully selected stabilizing fixed design g, in particular, if the working model for Q_0 is heavily misspecified. In

addition, even for establishing the CLT we need that the design g_i stabilizes as i converges to infinity, so that an adaptive design which is still fluctuating at a high rate at the time of analysis might result in too variable estimators if these estimators are not able to extrapolate according to an approximately correctly specified model for Q_0.

3.1 Application to construction of targeted adaptive design in clinical trial with covariates.

We will now illustrate this approach for construction of a targeted adaptive design with a clinical trial example with covariates. Thus, consider a clinical trial in which one samples a subject from a specified population and one collects (W, A, Y), where W denotes covariates, A denotes a binary treatment, and Y a clinical outcome. One wishes to construct an adaptive design g_i, $i = 1, \ldots$, where each g_i is a conditional distribution of A_i, given W_i, which itself is selected based on the previously collected data $O_1, \ldots, O_{i-1}$.

Firstly, we recall that the efficient influence curve for the additive causal effect $\Psi(Q) = E_Q(Y_1 - Y_0)$ is given by

$$D^*(Q_0, g) = D_1^*(Q_0, g) + D_2^*(Q_0, g),$$

where

$$\begin{aligned} D_1^*(Q_0, g)(O) &= (Y - Q_0(A, W)) \left\{ \frac{I(A = 1)}{g(1 \mid W)} - \frac{I(A = 0)}{g(0 \mid W)} \right\} \\ D_2^*(Q_0)(W) &= Q_0(1, W) - Q_0(0, W) - \Psi(Q_0), \end{aligned}$$

and $P_{Q_0,g} D_1^*(Q_0, g) D_2^*(Q_0) = 0$ (i.e., the two components are orthogonal in $L_0^2(P_{Q_0,g})$.

Given the realization of the first $i - 1$ experiments, $O_1, \ldots, O_{i-1}$ based on design choices $g_1, \ldots, g_{i-1}$, given an estimate Q_{i-1} of $Q_0(A, W) = E(Y \mid A, W)$, we estimate the variance $\Sigma(Q_0, g) = P_{Q_0,g} D^*(Q_0, g)^2$ as above:

$$\Sigma_{i-1}(g) = \frac{1}{i-1} \sum_{j=1}^{i-1} \left\{ D_1^*(Q_{i-1}, g)(O_j)^2 \frac{g(A_j \mid W_j)}{g_j(A_j \mid W_j)} + D_2^*(Q_{i-1})(W_j)^2 \right\},$$

where we, for simplicity, did not carry out the mean centering in this covariance estimate. Note that we did not need to IPC-weight the second component since it is not a function of treatment.

We could now define the adaptive design g_i as the minimizer of this variance over all fixed designs $\mathcal{G}$ or over a specified subset $\mathcal{G}_1$ of fixed designs:

$$g_i = \arg \min_{g \in \mathcal{G}_1} \Sigma_{i-1}(g).$$

Since the D_2^*-term in $\Sigma_{i-1}(g)$ does not depend on g, there is no need to include this term. So we can simplify this adaptive design as

$$g_i = \arg\min_{g \in \mathcal{G}_1} \frac{1}{i-1} \sum_{j=1}^{i-1} D_1^*(Q_{i-1}, g)(O_j)^2 \frac{g(A_j \mid W_j)}{g_j(A_j \mid W_j)},$$

or equivalently,

$$g_i = \arg\min_{g \in \mathcal{G}_1} \frac{1}{i-1} \sum_{j=1}^{i-1} (Y_j - Q(A_j, W_j))^2 \left\{ \frac{I(A_j = 1)}{g(A_j \mid W_j)} + \frac{I(A_j = 0)}{g(A_j \mid W_j)} \right\} \frac{1}{g_j(A_j \mid W_j)}.$$

As we showed earlier, closed form solutions of this minimization problem can be straightforwardly derived if $\mathcal{G}_1$ is class of all distributions of A, given V, for some discrete V. So this variational calculus is not repeated here.

4 Statistical analysis of treatment effect in targeted adaptive clinical trial, no covariates.

Let $Y(a)$ represent a treatment specific outcome one would observe if the randomly sampled patient would be assigned treatment $a \in \{0, 1\}$, and let $X = (Y(0), Y(1)) \sim P_{X0}$ represent the two treatment specific outcomes on a randomly sampled patient. We will leave P_{X0} unspecified. Let $X_1, \ldots, X_n$ be n i.i.d. draws of X. The scientific parameter is the causal effect of treatment defined as $\psi_0 = E_0(Y(1) - Y(0)) = E_0 Y(1) - E_0 Y(0)$.

Let A_i be a binary treatment assignment for patient i, $i = 1, \ldots, n$, and let the observed data on the n patients be $O_i = (A_i, Y_i = Y_i(A_i))$, $i = 1, \ldots, n$. Let $\mathbf{g} = (g_1, \ldots, g_n)$ be an adaptive design satisfying CAR:

$$g_i(1 \mid X_i, O_1, \ldots, O_{i-1}) = P(A_i = 1 \mid O_1, \ldots, O_{i-1}), i = 1 \ldots, n.$$

The CAR-assumption on the design requires A_i to be independent of the counterfactual outcomes $Y_i(0), Y_i(1)$, but, it is allowed that the probability distribution of A_i is a function of the data $O_1, \ldots, O_{i-1}$ collected on the previously recruited patients.

Firstly, we note that the likelihood of $O_1, \ldots, O_n$ for a model $\mathcal{Q} = \{Q_\theta : \theta\}$ factorizes as:

$$P_{\theta_0, \mathbf{g}}(O_1, \ldots, O_n) = \prod_{i=1}^{n} Q_{\theta_0}(Y_i \mid A_i) \prod_{i=1}^{n} g_i(A_i \mid \bar{\mathbf{O}}(i-1)),$$

where the conditional density of Y_i, given $A_i = a$, $Q_{\theta_0}(\cdot \mid a)$, equals the marginal density of $Y_i(a)$, $P_{\theta_0}(Y(a) = \cdot)$. In particular, it follows that for any CAR-adaptive design we have for each $i \in \{1, \ldots, n\}$

$$\psi_0 = E_0(Y_i \mid A_i = 1) - E_0(Y_i \mid A_i = 0).$$

Thus, ψ_0 is identifiable from the data and the nonparametric (or assuming a regression model for Y_i on A_i with (e.g.) normal errors) maximum likelihood estimator yields the following estimator

$$\psi_n = \frac{\sum_{i=1}^n I(A_i = 1)Y_i}{\sum_{i=1}^n I(A_i = 1)} - \frac{\sum_{i=1}^n I(A_i = 0)Y_i}{\sum_{i=1}^n I(A_i = 0)}. \tag{9}$$

Let's now aim to construct a particular targeted adaptive design $\mathbf{g}_n$. For that purpose we consider a fixed design in which (A_i, X_i) are i.i.d and $g_i(1 \mid X_i) = P(A_i = 1 \mid X_i) = \Pi \in (0, 1)$. The fixed design of this study is defined by the choice of Π. Under this fixed design it follows that ψ_n is consistent and asymptotically linear with efficient with influence curve given by:

$$S(\theta_0, \Pi)(A, Y) = (Y - E_{\theta_0}(Y \mid A)) \left(\frac{I(A = 1)}{\Pi} - \frac{I(A = 0)}{1 - \Pi}) \right).$$

The variance of this efficient influence curve is given by:

$$\mathrm{VAR}_{\theta_0,\Pi} S(\theta_0, \Pi)(A, Y) = \frac{\sigma^2(\theta_0)(1)}{\Pi} + \frac{\sigma^2(\theta_0)(0)}{1 - \Pi},$$

where $\sigma^2(\theta_0)(a) = \mathrm{VAR}_{\theta_0}(Y \mid A = a)$ are the conditional variances of Y, given $A = a$, $a \in \{0, 1\}$.

Let $\Pi(\theta_0) = \arg\min_\Pi \mathrm{VAR}_{\theta_0,\Pi} S(\theta_0, \Pi)(A, Y)$ be the design which minimizes the asymptotic variance of the estimator ψ_n under i.i.d. sampling from $P_{\theta_0,\Pi}$. We have

$$\Pi(\theta_0) = \frac{\sigma(\theta_0)(1)}{\sigma(\theta_0)(0) + \sigma(\theta_0)(1)} \in (0, 1), \tag{10}$$

which is known as the Neyman allocation (Hu and Rosenberger (2006)).

Thus the optimal fixed design requires knowing the variances of $Y(0)$ and $Y(1)$, or equivalently, the conditional variances of Y, given $A = 0$, and given $A = 1$, respectively. These variances are typically not known a priori. One might start out with an equal balance design, $\Pi = 0.5$, but during the course of the study it might become apparent that one of the treatment arms has much higher variance of the outcomes than the other. Based on that observation

one might wish to adapt the design by assigning more patients to the high variance treatment arm according to the mapping (10).

Let $\Pi_i^* = \frac{\sigma_{i-1}(1)}{\sigma_{i-1}(0)+\sigma_{i-1}(1)}$ be the estimator of Π_{θ_0} based on substitution of a maximum likelihood estimator θ_{i-1} based on $O_1, \ldots, O_{i-1}$. For $i \geq 3$, $\sigma_{i-1}^2(a)$ can be defined as the sample variance of Y_j among the observations with $A_j = a$, $j = 1, \ldots, i-1$. In particular, if $Y(a)$ is binary indicating a failure (0) or successful (1) response to treatment a, $a \in \{0, 1\}$, then we can set $\sigma_{i-1}^2(a) = p_{i-1}(a)(1 - p_{i-1}(a))$, where $p_{i-1}(a)$ is the proportion of successes among the observations (A_j, Y_j) with $A_j = a$, $j = 1, \ldots, i-1$.

Now, one could simply set $g_i(1) = \Pi_i^*$, or one could use the adaptive design $\Pi_i = g_i(1 \mid \bar{\mathbf{O}}(i-1))$ defined iteratively (starting at $i = 1$) by

$$\Pi_i = \arg \min_{\Pi \in [0,1]} \left(\frac{1}{i} \left(\sum_{j=1}^{i-1} g_j(1 \mid \bar{\mathbf{O}}(j-1)) + \Pi \right) - \Pi_i^* \right)^2, \ i = 1, \ldots, n. \quad (11)$$

Thus, at experiment i, one would set the next randomization probability Π_i so that the average of the previously used $i-1$ randomization probabilities Π_j, $j = 1, \ldots, i-1$, equals or approximates the estimated target balance $\Pi_i^* = \sigma_{i-1}(1)/(\sigma_{i-1}(0)+\sigma_{i-1}(1))$. Note also that in this manner, at experiment i, one obtains a balance between the two treatment arms which closely approximates the estimated target balance:

$$\frac{\sum_{j=1}^{i} I(A_j = 1)}{i} \approx \Pi_i^*.$$

In order to identify the treatment effect ψ_0 it is necessary that Π_i^* stays away from 0 and 1. Therefore, we propose to specify a priori a $\delta > 0$ so that if $\Pi_i^* < \delta$ or $\Pi_i^* > 1 - \delta$, then we set it equal to δ or $1 - \delta$, respectively. In this manner, one does never allow the adaptive design to stop a particular treatment arm due to a chance situation: e.g. $\sigma_{i-1}(1)$ one be equal to zero for small values of i.

It is also important to note (see also Chapter 2, Hu and Rosenberger (2006)) that a so called "favor the winner" design in which one selects with higher probability the currently most successful treatment arm might result in a very poor design w.r.t. to efficiency by not assigning enough observations to the highly variable arm. To look at this in more detail, let's consider the binary outcome case and assume that $Y = 1$ denotes a success. Suppose that the probability on a successful outcome is smaller than 0.5 in both treatment arms, and consider the case that $P(Y = 1 \mid A = 0) < P(Y = 1 \mid A = 1) < 0.5$ so that, in theory, the treatment arm is better than the control arm. This

implies that $P(Y = 1 \mid A = 1)(1 - P(Y = 1 \mid A = 1)) > P(Y = 1 \mid A = 0)(1 - P(Y = 1 \mid A = 0))$. Thus, if, as expected, during the trial indeed the treatment arm shows more successes than the control arm, then the targeted adaptive design will start assigning more patients to the successful treatment arm than to the control arm. However, if, for example, we are in the situation that a successful outcome is more likely than a failure, i.e., $0.5 < P(Y = 1 \mid A = 0) < P(Y = 1 \mid A = 1) < 1$, then the variance in the treatment arm is smaller than the variance in the control arm, so that the targeted adaptive designs will assign relatively more patients to the less performing control arm. This touches on an essential debate trading off the overall benefit for a population versus the individual benefit for each individual. Even from an ethical point of view following these fully efficient adaptive designs might not be a bad strategy since such a targeted design will be able to stop the trial earlier due to obtaining statistical significant evidence (that the treatment is better or worse than the control arm) at an earlier stage, thereby minimizing the total amount of time and subjects exposed to the inferior treatment while still obtaining a statistically significant result.

Maximum Likelihood Estimation: Consider a regression model $Y_i = \beta_0(0) + \beta_0(1)A_i + N(0, \sigma_0^2(A_i))$, $i = 1, \ldots, n$, or equivalently, $Y_i(a) = \beta_0(0) + \beta_0(1)a + Z_i$, where $Z_i \sim N(0, \sigma_0^2(a))$. Define $\theta_0 = (\mu_0(0), \mu_0(1), \mu_{20}(0), \mu_{20}(1))$, where $\mu_0(a) = E_0 Y(a)$, and $\mu_{20}(a) = E_0 Y^2(a)$. The MLE of θ_0 solves the empirical mean of the following estimating functions

$$\begin{aligned} D_1(\theta)(O_i) &= (Y_i - \mu(0))I(A_i = 0) \\ D_2(\theta)(O_i) &= (Y_i - \mu(1))I(A_i = 1) \\ D_3(\theta)(O_i) &= (Y_i^2 - \mu_2(0))I(A_i = 0) \\ D_4(\theta)(O_i) &= (Y_i^2 - \mu_2(1))I(A_i = 1). \end{aligned}$$

This defines a four dimensional estimating equation for the maximum likelihood estimator $\theta_n \in \mathbb{R}^4$ (according to a correctly specified model)

$$0 = \frac{1}{n} \sum_{i=1}^{n} D(\theta_n)(O_i),$$

where the solution exists in closed form and is given by the standard empirical means.

Definition of targeted adaptive design: Let $\delta > 0$ be a small number. Consider the adaptive design $g_i(1) = \Pi_i^*$, where $\Pi_i^* = \frac{\sigma_{i-1}(1)}{\sigma_{i-1}(0) + \sigma_{i-1}(1)}$ if this last number is between $(\delta, 1 - \delta)$, and else it is truncated at δ or $1 - \delta$ whichever bound it exceeds. Let $\Pi(\theta_0)$ be defined by (10), and let g_{θ_0} be the Bernoulli

probability distribution with $g_{\theta_0}(1) = \Pi(\theta_0)$. Let $P_0(\mid Y \mid < M) = 1$ for some $M < \infty$.

Application of our consistency Theorem 5 yields the following result.

Result 1 (Consistent estimation of treatment effect in randomized trial based on targeted adaptive design) *Assume that* $P(\mid Y \mid < M) = 1$ *for some* $M < \infty$. *Consider the adaptive design defined above. Let* θ_n *be the MLE. We have that* $\parallel \theta_n - \theta_0 \parallel \rightarrow 0$ *in probability as* $n \rightarrow \infty$. *As a consequence, we also have that the adaptive design converges to the optimal fixed design* g_{θ_0} *in the sense that*

$$g_n \rightarrow g_{\theta_0} \text{ and } \bar{g}_n = \frac{1}{n}\sum_{i=1}^{n} g_i \rightarrow g_{\theta_0},$$

in probability, as $n \rightarrow \infty$.

Proof. We note that $P_{\theta_0,g_i}D(\theta)$ equals the 4-dimensional vector

$$(\mu_0(0)-\mu(0))g_i(0), (\mu_0(1)-\mu(1))(1-g_i(0)), (\mu_{20}(0)-\mu_2(0))g_i(0), (\mu_{20}(1)-\mu_2(1))(1-g_i(0))).$$

Thus, if we can establish that $\frac{1}{n}\sum_{i=1}^{n} P_{\theta_0,g_i}D(\theta_n) \rightarrow 0$ in probability as $n \rightarrow \infty$, then that proves that $\theta_n - \theta_0 \rightarrow 0$ in probability as $n \rightarrow \infty$, under the assumption that there exists a $\delta > 0$ so that $Pr(\delta < 1/n\sum_{i=1}^{n} g_i(0) < 1-\delta) \rightarrow 1$ as $n \rightarrow \infty$. On the other hand, if the adaptive design stops a treatment arm with probability tending to 1, then naturally consistent estimation of the mean outcome in that arm cannot be achieved.

In order to establish this consistency result, we will apply Theorem 5. For that purpose, define $f_{\theta,1}(O_i, g_i(0)) = D_1(\theta)(O_i) - P_{\theta_0,g_i}D_1(\theta) = D_1(\theta)(O_i) - (\mu_0(0) - \mu(0))g_i(0)$, and, similarly, we define $f_{\theta,2}(O_i, g_i(0)) = D_2(\theta)(O_i) - (\mu_0(1)-\mu(1))(1-g_i(0))$, and $f_{\theta,j}$, $j = 3, 4$. This defines now the 4-dimensional function $f_\theta = (f_{\theta,j} : j = 1, \ldots, 4)$. Consider now the 4-dimensional martingale sum $M_n(f) = \frac{1}{n}\sum_{i=1}^{n} f(O_i, g_i(0))$ with $f \in \mathcal{F} = \{(a, y, g(0)) \rightarrow f_\theta(a, y, g(0)) : \theta\}$ with $a \in \{0, 1\}$, and $g(0) \in (0, 1)$. We assumed that $P(\mid Y = Y(A) \mid \leq M) = 1$ for some $M < \infty$ (and thereby that the parameters are within a bounded parameter set) so that the supremum norm of $f \in \mathcal{F}$ (in $a, y, g(0), \theta$) is bounded by a universal constant. Since the class of functions of (a, y, z) are parameterized by a four dimensional parameter θ, it follows that the covering number $N(\epsilon, \mathcal{F}, \parallel \cdot \parallel_\infty)$ of $\mathcal{F}$ w.r.t. to the supremum norm is bounded by a polynomial power ϵ^{-q} for some $q < \infty$ (van der Vaart and Wellner (1996)). Application of Theorem 5 now proves the consistency stating that the components $(\mu_0(0) - \mu_n(0))\bar{g}_n(0)$, $(\mu_0(1) - \mu_n(1))\bar{g}_n(1)$,

$(\mu_{20}(0) - \mu_{2n}(0))\bar{g}_n(0)$, and $(\mu_{20}(1) - \mu_{2n}(1))\bar{g}_n(1)$ converge to zero in probability, as $n \to \infty$, where $\bar{g}_n(0) = \frac{1}{n}\sum_{i=1}^n g_i(0)$. Finally, by selecting the randomization probabilities $g_i(0)$ to be between $(\delta, 1-\delta)$ for some $\delta > 0$, which is guaranteed by our assumption that Π_i^* is bounded away from 0 and 1 with probability 1, it follows that for any such adaptive design we have consistency of θ_n to θ_0. This completes the proof. □

Central Limit Theorem for MLE: Application of our Theorem 7 yields the wished asymptotic normality for the MLE.

Theorem 1 (Statistical Inference for Causal Effect in Targeted Adaptive Clinical Trial)

Assume $P(\mid Y \mid < M) = 1$ for some $M < \infty$. Consider the adaptive trial $g_n = g_{\theta_{n-1}}$ defined above, where θ_n is the maximum likelihood estimator of θ_0. We have

$$\sqrt{n}(\theta_n - \theta_0) = \frac{1}{\sqrt{n}}\sum_{i=1}^n D(\theta_0, g_{\theta_0})(O_i) + o_P(1),$$

where

$$\begin{aligned}
D_1(\theta, g)(O_i) &= (Y_i - \mu(0))\frac{I(A_i = 0)}{g(0)} \\
D_2(\theta, g)(O_i) &= (Y_i - \mu(1)\frac{I(A_i = 1)}{g(1)} \\
D_3(\theta, g)(O_i) &= (Y_i^2 - \mu_2(0))\frac{I(A_i = 0)}{g(0)} \\
D_4(\theta, g)(O_i) &= (Y_i^2 - \mu_2(1))\frac{I(A_i = 1)}{g(1)}.
\end{aligned}$$

In addition, $1/\sqrt{n}\sum_{i=1}^n D(\theta_0, g_{\theta_0})(O_i)$ is a discrete Martingale which converges to a normal distribution with mean zero and covariance matrix $\Sigma_0 = P_{Q_0, g_{\theta_0}} D(\theta_0, g_{\theta_0})D(\theta_0, g_{\theta_0})^\top$, where the latter covariance matrix can be consistently estimated with

$$\Sigma_n \equiv \frac{1}{n}\sum_{i=1}^n D(\theta_n, g_{\theta_n})D(\theta_n, g_{\theta_n})^\top(O_i).$$

By the delta-method, if $\theta \to f(\theta)$ is a Euclidean valued differentiable function, this also teaches us that

$$\sqrt{n}(f(\theta_n) - f(\theta_0)) = \frac{1}{\sqrt{n}}\sum_{i=1}^n \frac{d}{d\theta_0} f(\theta_0) D(\theta_0, g_{\theta_0})(O_i) + o_P(1),$$

with its corresponding normal limit distribution result.

This result is obtained as an application of Theorem 7. Since this is a simple example used to illustrate our results, we actually give the proof (following the general proof of Theorem 7) with some references to our building blocks.

Proof. We already proved that θ_n consistently estimates θ_0. In particular, this proves that g_{θ_n} (and $\bar{g}_n$) consistently estimates g_{θ_0}. For notational convenience, let $D(\theta) = D(\theta, g_\theta)$. We have $\sum_i D(\theta_n)(O_i) = 0$ and $P_{\theta_0,g_i} D(\theta_0) = 0$ for all i. As a consequence, we have that

$$\frac{1}{n}\sum_i \{D(\theta_n)(O_i) - D(\theta_0)(O_i)\} = -\frac{1}{n}\sum_i \{D(\theta_0)(O_i) - P_{\theta_0,g_i} D(\theta_0)\}.$$

Consider the left hand side. Firstly, note that $D(\theta_n)(O_i) - D(\theta_0)(O_i)$ equals

$$(\mu_0(0)-\mu_n(0))(1-A_i), (\mu_0(1)-\mu_n(1))A_i, (\mu_{20}(0)-\mu_{2n}(0))(1-A_i), (\mu_{20}(1)-\mu_{2n}(1))A_i).$$

Thus, $\frac{1}{n}\sum_{i=1}^n D(\theta_n)(O_i) - D(\theta_0)(O_i)$ equals

$$(\mu_0(0)-\mu_n(0))\bar{g}_n^e(0), (\mu_0(1)-\mu_n(1))\bar{g}_n^e(1), (\mu_{20}(0)-\mu_{2n}(0))\bar{g}_n^e(0), (\mu_{20}(1)-\mu_{2n}(1))\bar{g}_n^e(1)),$$

where

$$\bar{g}_n^e(0) = \frac{1}{n}\sum_{i=1}^n I(A_i = 0).$$

This shows that

$$\frac{1}{n}\sum_{i=1}^n D(\theta_n)(O_i) - D(\theta_0)(O_i) = A_n(\theta_n - \theta_0),$$

where A_n is a 4 by 4 diagonal matrix: $A_n = -diag(\bar{g}_n^e(0), \bar{g}_n^e(1), \bar{g}_n^e(0), \bar{g}_n^e(1))$. Thus, we have

$$(\theta_n - \theta_0) = -A_n^{-1}\frac{1}{n}\sum_{i=1}^n \left\{D(\theta_0)(O_i) - P_{\theta_0,g_i} D(\theta_0)\right\},$$

where $-A_n^{-1} = diag(1/\bar{g}_n^e(0), 1/\bar{g}_n^e(1), 1/\bar{g}_n^e(0), 1/\bar{g}_n^e(1)))$.

We now need to prove that A_n^{-1} converges to a fixed matrix A_0^{-1}. For this it suffices to prove that $\bar{g}_n^e(0) \to g_{\theta_0}(0)$. We have

$$\bar{g}_n^e(0) = \frac{1}{n}\sum_{i=1}^n (I(A_i = 0) - g_i(0)) + \frac{1}{n}\sum_{i=1}^n g_i(0).$$

Recall that $g_i(0) = P(A_i = 0 \mid O_1, \ldots, O_{i-1}) = P(A_i = 0 \mid \hat{\theta}_{i-1})$ depends on $O_1, \ldots, O_{i-1}$ through the MLE $\hat{\theta}_{i-1}$. By consistency of $\hat{\theta}_n$ to θ_0, we have

$\bar{g}_n = 1/n \sum_i g_i \to g_{\theta_0}$ in probability as $n \to \infty$. This shows that $\bar{g}_n^e(0) = M_n(f) + o_p(1)$, where $M_n(f) = \frac{1}{n}\sum_{i=1}^n f(O_i) - E(f(O_i) \mid O_1, \ldots, O_{i-1})$, and $f(O_i) \equiv I(A_i = 0)$. By the Law of Large numbers for martingales it follows that $M_n(f) \to 0$ in probability as $n \to \infty$. This proves that

$$-A_n^{-1} \to diag(1/g_{\theta_0}(0), 1/g_{\theta_0}(1), 1/g(\theta_0)(0), 1/g(\theta_0)(1)) \text{ in probability, as } n \to \infty.$$

The stated asymptotic normality theorem now follows from the Martingale central limit Theorem 17 applied to $1/\sqrt{n}\sum_{i=1}^n D(\theta_0)(O_i) - P_{\theta_0,g_i} D(\theta_0)$. Since we already showed that $\bar{g}_n \to g_{\theta_0}$ the conditions of this theorem holds trivially. In particular, $P_{\theta_0,g_i} D(\theta_0)^2$ converges to $P_{\theta_0,g_{\theta_0}} D(\theta_0)^2$ as $i \to \infty$ thereby giving the claimed covariance matrix Σ_0. Finally, the consistency of the estimate Σ_n as an estimate of Σ_0 follows from the consistency of θ_n and the martingale LLN applied to the estimate using θ_0 instead of θ_n: see Theorem 18. □

5 Consistency of MLE for correctly specified parametric model.

The uniform consistency result presented in Theorem 14 in the Appendix for the discrete martingale sum $M_n(f) = 1/n \sum_{i=1}^n f(\bar{\mathbf{O}}(i))$, uniformly in a class of functions $\mathcal{F}$ with polynomial covering number, allows us to prove consistency results for estimators based on $O_1, \ldots, O_n$. For example, we can establish the following consistency result for the MLE based on a correctly specified parametric model.

Theorem 2 *Consider the experiment generating* $\mathbf{O} = (O_1, \ldots, O_n) \sim P_{Q_0,\mathbf{g}_n}$ *as defined by (3). Let* θ_n *be the MLE over a parameter space* Θ *according to a correctly specified model* $\mathcal{Q} = \{Q_\theta : \theta \in \Theta\}$ *(i.e.,* $Q_0 \in \mathcal{Q}$*) based on* $O_1, \ldots, O_n$*:*

$$\theta_n = \arg\max_{\theta\in\Theta} \sum_{i=1}^n \log Q_\theta(O_i).$$

Let

$$\theta_0 = \arg\max_{\theta\in\Theta} \sum_{i=1}^n P_{Q_0,g_i} \log Q_\theta,$$

where we assume that these argmax can be uniquely defined. We note that θ_0 *is a fixed element in* Θ *satisfying* $Q_{\theta_0} = Q_0$.

Define the class of functions

$$\mathcal{F} \equiv \{(a, l, z) \to \log Q_{\theta_0}(a, l)/Q_\theta(g, l) - P_{Q_0,g_z} \log Q_{\theta_0}/Q_\theta : \theta \in \Theta\}.$$

Recall that P_{Q_0,g_z} denotes the conditional expectation operator of O_i, given $O_1,\ldots,O_{i-1}$ with $Z_i = Z_i(O_1,\ldots,O_{i-1}) = z$, and that g_i depends on $O_1,\ldots,O_{i-1}$ only through this finite dimensional $Z_i \in \mathcal{Z} \subset \mathbb{R}^d$ for some fixed d, $i = 1,\ldots,n$. Define the (random) Kullback-Leibler divergence

$$d_{KL,n}(\theta,\theta_0) \equiv \frac{1}{n}\sum_{i=1}^{n} P_{Q_0,g_i} \log Q_{\theta_0}/Q_\theta = P_{Q_0,\bar{g}_n} D(\theta_0,\theta),$$

where $\bar{g}_n = \frac{1}{n}\sum_{i=1}^n g_i$. Assume that $N(\epsilon,\mathcal{F},\|\cdot\|_\infty) = O(\epsilon^{-q})$ for some $q > 0$, where $N(\epsilon,\mathcal{F},\|\cdot\|_\infty$ denotes the covering number of $\mathcal{F}$ for balls of size ϵ w.r.t. to the supremum norm (van der Vaart and Wellner (1996)). Then, for all $p \geq 1$

$$E\left(d_{KL,n}(\theta_n,\theta_0)\right)^p \to 0,$$

as $n \to \infty$. In particular, $d_{KL,n}(\theta_n,\theta_0)$ converges to zero in probability as $n \to \infty$.

Discussion of conditions. If 1) the model $\mathcal{Q}$ is finite dimensional with bounded parameter space Θ, 2) the adaptive design g_i only depends on $O_1,\ldots,O_{i-1}$ through a finite dimensional summary measure Z_i of common and fixed dimension d, and 3) the data lives on a bounded set so that the likelihood ratios Q_θ/Q_{θ_0} are uniformly bounded, then this theorem provides the wished consistency of the maximum likelihood estimator according to a correctly specified parametric model $\mathcal{Q}$.

This consistency theorem puts hardly restrictions on the design $\mathbf{g}_n$ except that it can only depend on the past $O_1,\ldots,O_{i-1}$ through a finite (fixed in i) dimensional summary measure Z_i. For example, it is not required that g_n converges as $n \to \infty$ to some fixed design in $\mathcal{G}$.

The consistency result is in terms of a Kullback-Leibler divergence w.r.t. $P_{Q_0,\bar{g}_n}$. So if an adaptive design does not generate the data needed to identify a particular parameter of θ_0, then the consistency result will not result in consistency for that parameter. For example, if the design allows a particular treatment arm to be stopped, then consistent estimation of counterfactual mean outcome for that treatment arm is obviously not possible and that will be reflected by the resulting Kullback-Leibler divergence.

Proof of Theorem 2. For notational convenience, let $D(\theta_0,\theta) = \log Q_{\theta_0}/Q_\theta$. The two fundamental building blocks of this proof are that $\frac{1}{n}\sum_{i=1}^n D(\theta_0,\theta_n)(O_i) \leq 0$, and that, by definition of θ_0, for all $\theta \in \Theta$,

$$\frac{1}{n}\sum_{i=1}^{n} P_{Q_0,g_i} D(\theta_0,\theta) = P_{Q_0,\bar{g}_n} D(\theta_0,\theta) \geq 0.$$

For each θ we have

$$\begin{aligned} 0 &\leq \frac{1}{n}\sum_{i=1}^{n} P_{Q_0,g_i} D(\theta_0,\theta) \\ &= -\frac{1}{n}\sum_{i=1}^{n} (D(\theta_0,\theta)(O_i) - P_{Q_0,g_i} D(\theta_0,\theta)) \\ &\quad + \frac{1}{n}\sum_{i=1}^{n} D(\theta_0,\theta)(O_i) \\ &\equiv M_n(D(\theta_0,\theta)) + \frac{1}{n}\sum_{i=1}^{n} D(\theta_0,\theta)(O_i), \end{aligned}$$

where $-M_n(f) \equiv \frac{1}{n}\sum_{i=1}^{n} f(O_i, Z_i)$ with $f(O_i, Z_i) = f(O_i) - P_{Q_0,g_{Z_i}} f(O_i)$ is a martingale sum for each f.

Now, we use that $\frac{1}{n}\sum_{i=1}^{n} D(\theta_0,\theta_n)(O_i) \leq 0$ and

$$M_n(D(\theta_0,\theta))|_{\theta=\theta_n} \leq \sup_{\theta} \mid M_n(D(\theta_0,\theta)) \mid = \sup_{f\in\mathcal{F}} \mid M_n(f) \mid .$$

By Theorem 14, the latter random variable converges in p-th expectation to zero as $n \to \infty$ for all integers p. Thus, it follows that

$$0 \leq \frac{1}{n}\sum_{i=1}^{n} P_{\theta_0,g_i} D(\theta_0,\theta_n) \leq R(n),$$

where $E \mid R(n) \mid^p \to 0$ as $n \to \infty$ for all integers p. This proves that for all $p \geq 1$

$$E\left(\frac{1}{n}\sum_{i=1}^{n} P_{Q_0,g_i} D(\theta_0,\theta_n)\right)^p \to 0,$$

as $n \to \infty$. In particular,

$$E\frac{1}{n}\sum_{i=1}^{n} P_{Q_0,g_i} D(\theta_0,\theta_n) \to 0,$$

as $n \to \infty$. Since $1/n\sum_i P_{Q_0,g_i} D(\theta_0,\theta_n)$ is a positive random variable, this implies that $1/n\sum_i P_{Q_0,g_i} D(\theta_0,\theta_n)$ converges to zero in probability. This completes the proof of Theorem 2. □

6 Martingale estimating functions independent of adaptive design.

The following Theorem 3 shows that a class of estimating functions for fixed design data generating distributions $P_{Q_0,g}$ with g known to be an element of

a subset $\mathcal{G}_1 \subset \mathcal{G}$ of the set $\mathcal{G}$ of all CAR-fixed designs, where these estimating functions do not depend on the censoring/design mechanism, can also be used as Martingale estimating functions for adaptive designs g_i which fall with probability one in $\mathcal{G}_1$.

Theorem 3 *Suppose that there exist an estimating function $D(Q_0)(O)$, with $O = (A, L = X(A))$ a missing data structure on $X = (X(a) : a \in \mathcal{A})$, satisfying*

$$P_{Q_0,g} D(Q_0)(O) \;=\; 0 \text{ for any } g \in \mathcal{G}_1 \in \mathcal{G}.$$

If g_i is an adaptive design so that, $g_i \in \mathcal{G}_1$ for almost every $O_1, \ldots, O_{i-1}$, then $P_{Q_0,g_i} D(Q_0) = 0$ for all i.

Proof: Note

$$\begin{aligned} P_{Q_0,g} D(Q_0)(A, X(A)) &= E_{Q_0} \sum_a D(Q_0)(a, X(a)) g(a \mid X) \\ &= \sum_a \int D(Q_0)(a, X(a)) g(a \mid X) dQ_0(X), \quad (12) \end{aligned}$$

which equals zero for all $g \in \mathcal{G}_1$. Now, we note that

$$\begin{aligned} P_{Q_0,g_i} D(Q_0)(A_i, X_i(A_i)) &= E(D(Q_0)(A_i, X_i(A_i)) \mid \bar{\mathbf{O}}(i-1)) \\ &= E(\sum_a D(Q_0)(a, X_i(a)) g_i(a \mid X_i) \mid \bar{\mathbf{O}}(i-1)) \\ &= \sum_a \int D(Q_0)(a, X(a)) g_{Z_i}(a \mid X) dQ_0(X) \end{aligned}$$

where we use that X_i is independent of $\bar{\mathbf{O}}(i-1)$. Since $g_{Z_i} \in \mathcal{G}_1$ with probability 1, (12) implies that the latter random variable in Z_i is zero with probability 1. □

The following theorem is a special application of this result.

Theorem 4 *Suppose that there exist an estimating function $D(Q_0)(O)$, $O = (W, A, L = X(A))$, where W represents a set of baseline covariates, satisfying*

$$E(D(Q_0)(W, a, X(a)) \mid W) \;=\; 0 \text{ for all } a \in \mathcal{A}.$$

Then

$$P_{Q_0,g} D(Q_0)(O) = 0,$$

for any $g \in \mathcal{G}_1 = \{g \in \mathcal{G} : g(a \mid X) = g(a \mid W)\}$. As a consequence of Theorem 3, if g_i is an adaptive design so that, $g_i \in \mathcal{G}_1$ for almost every $O_1, \ldots, O_{i-1}$, then $P_{Q_0,g_i} D(Q_0) = 0$ for all i.

Proof: We have for $g \in \mathcal{G}_1$

$$P_{Q_0,g}D(Q_0)(W,A,X(A)) = E_{Q_0}\sum_a D(Q_0)(W,a,X(a))g(a \mid W).$$

Conditioning on W shows that this expectation equals zero so that the application of Theorem 3 completes the proof. □

We will now show the application of these general theorems to some censored data structures. In Section 17 we show, by applying the above theorem, that in the (e.g., clinical trial) context of $O = (W, A, Y = Y(A))$, $X = (W, (Y(a) : a))$, the estimating functions $D_h(\beta_0) = h(A)(Y(A) - m(A \mid \beta_0))$, indexed by arbitrary functions h, for a regression model $EY(a) = E(Y(A) \mid A = a) = m(a \mid \beta_0)$ are also Martingale estimating functions for adaptive designs $g_i(a \mid X_i) = g_i(a)$ which allow that A_i depends on $O_1, \ldots, O_{i-1}$.

A more general class of examples in which we can obtain such martingale estimating functions which do not depend on g_i are causal effect models for a possibly time-dependent treatment, conditional on a baseline covariate. Let $X = (X(a) : a \in \mathcal{A}) \sim P_{X0}$ be a collection of treatment regimen specific counterfactuals, and assume the temporal ordering assumption $X(a)(t) = X(\bar{a}(t-1))(t)$ which states that the counterfactual process at time t only depends on past treatment regimen $\bar{a}(t-1)$. Consider a so called marginal structural model $E(Y(a) \mid V) = m(a, V \mid \beta_0)$ for a user supplied finite dimensional model $\{m(\cdot \mid \beta) : \beta\}$, where V is a subset of the baseline covariates $X(0)$, and $Y(a)$ is a treatment specific outcome of interest which is a component of $X(a)$. Let $O = (A, L = X(A))$. A CAR-fixed design is a conditional distribution $g(A \mid X)$ (the so called treatment mechanism) satisfying:

$$g(A \mid X) = \prod_t g(A(t) \mid \bar{A}(t-1), X) = \prod_t g(A(t) \mid \bar{A}(t-1), \bar{L}(t)),$$

where $\bar{L}(t) = \bar{X}(A)(t)$. Consider the subset $\mathcal{G}_1$ of this set of all CAR fixed designs $\mathcal{G}$ defined as

$$\mathcal{G}_1 = \{g(A \mid X) \in \mathcal{G} : g(A \mid X) = g(A \mid V)\}.$$

That is, $g \in \mathcal{G}_1$ implies that $g(A(t) \mid \bar{A}(t-1), \bar{L}(t)) = g(A(t) \mid \bar{A}(t-1), V)$, which corresponds with A being randomized conditional on the baseline covariates V.

We can now consider the following class of estimating functions for β_0 indexed by a vector function h (such as $\frac{d}{d\beta_0}m(a, V \mid \beta_0)$):

$$D_h(\beta_0)(O) = h(A, V)(Y - m(A, V \mid \beta_0)).$$

It follows that $P_{Q_0,g}D_h(\beta_0) = 0$ for all $g \in \mathcal{G}_1$. As a consequence of Theorem 3, for any adaptive design $g_i(A_i \mid X_i) = g_i(A_i \mid V_i)$ so that $g_i \in \mathcal{G}_1$ with probability 1 (as a random variable of $\bar{\mathbf{O}}(i-1)$, so that we allow that treatment assignment probabilities for subject i are a function of the data collected on first $i-1$ subjects), we have

$$P_{Q_0,g_i}D_h(\beta_0) = 0,\ i = 1, \ldots, n.$$

So, for example, we can estimate β_0 in an adaptive group sequential design $g_i(A_i \mid X_i) = g_i(A_i \mid V_i)$ with the least squares estimator which corresponds with the Martingale estimating function $\frac{d}{d\beta}m(A, V \mid \beta)(Y - m(A, V \mid \beta))$:

$$\beta_n = \arg\min_{\beta} \sum_{i=1}^{n} (Y_i - m(A_i, V_i \mid \beta))^2.$$

Although these simple least squares estimators are inefficient by not using the additional covariate (including time-dependent covariate) information, they are attractive because of its simplicity and their independence of g_i.

One can also construct estimating function based estimators based on the corresponding double robust and efficient estimating functions, but now these estimating functions will depend on the adaptive design g_i: the general approach for constructing optimal (and non-optimal) martingale estimating functions is considered in detail in Section 8. As an illustration of this general methodology for construction of optimal martingale estimating functions and to contrast it to the above remarkably simple martingale estimation functions (independent of g_i), we now consider the point treatment case in which A represents treatment at a single time point after the collection of baseline covariates W. In this point treatment example the class of double robust estimating functions indexed by h are given by:

$$\begin{aligned} D_h(\beta_0, Q_0, g)(O) &= h(A,V)(Y - m(A, V \mid \beta_0)) \\ &\quad -h(A,V)(Q_0(A,W) - m(A, V \mid \beta_0)) \\ &\quad + \sum_a h(a,V)(Q_0(a,W) - m(a, V \mid \beta_0))g(a \mid V), \end{aligned}$$

and the optimal estimating function is defined by a particular choice h_{opt} (see van der Laan and Robins (2003)). Since g is considered known, one can treat Q as an index, i.e., $D_{h,Q}(\beta, g) = D_h(\beta, Q, g)$, since for all choices Q, h, we have $P_{Q_0,g}D_{h,Q}(\beta_0, g) = 0$. A corresponding class of Martingale estimating functions indexed by Q, g is given by $D_{h,Q}(\beta, g_i)$. Given a parametric model Q_θ, a corresponding index h_θ, a martingale estimating function $D(\theta)$ so that

θ_n solves $0 = \sum_i D(\theta_n)(O_i, Z_i) = 0$, we can estimate β with the solution of the corresponding double robust estimating equation

$$0 = \sum_i D_{h_{\theta_n}, Q_{\theta_n}}(\beta_n, g_i)(O_i) = 0.$$

Our theorem 7 can now be applied to the joint solution (θ_n, β_n) of the Martingale estimating function $D(\theta, \beta)(O_i, Z_i) = (D(\theta), D_{h_\theta, Q_\theta}(\beta, g_i))$, resulting in asymptotic normality of $\sqrt{n}(\beta_n - \beta_0)$ to a normal limit distribution equal to what it is under i.i.d sampling from P_{Q_0, g_0} where g_0 is the limit of the adaptive design g_i as $i \to \infty$. If components of the adaptive design g_i are unknown, then they can be modelled with models, and their parameters are then also solutions of martingale estimating equations, so that, again, our general theorem 7 can be applied. This estimating approach is the generalization of the estimating function approach presented in van der Laan and Robins (2003) for fixed designs to adaptive sequential designs. As an alternative of this estimating function based estimator (based on the efficient influence curve), in our article we consider in detail the targeted MLE of β_0, which is based on these double robust estimation functions, but differs by being a substitution estimator based on a maximum likelihood based estimator Q_n of Q_0.

We now consider an example in which $X = (W, (Y(a) : a \in \mathcal{A}))$, $A = (R, \Delta)$ represents a treatment R and missing indicator Δ, and $O = (W, R, \Delta, \Delta Y(R))$. Thus, this causal inference data structure allows now also missingness on the outcome $Y = Y(R)$. Suppose one assumes the causal (marginal structural) model $E(Y(r) \mid V) = m(r, V \mid \beta_0)$. Consider the fixed designs $\mathcal{G}_1 = \{g \in \mathcal{G} : g(A \mid X) = g(A \mid V)\}$ for which the conditional probability of treatment R and missingness indicator Δ only depend on X through V, while CAR allows that this conditional probability depends on W. Consider the class of estimating functions indexed by h:

$$D_h(\beta)(O) = h(R, V)(Y(R) - m(R, V \mid \beta_0))\Delta.$$

We have

$$P_{Q_0, g} D_h(\beta_0) = 0 \text{ for all } g \in \mathcal{G}_1.$$

As a consequence of Theorem 3, for any adaptive design g_i so that $g_i \in \mathcal{G}_1$ with probability 1, we have

$$P_{Q_0, g_i} D_h(\beta_0) = 0.$$

Thus, for example, in an adaptive design $g_i(A_i \mid X_i) = g_i(A_i \mid V_i)$, we can estimate β_0 with a least squares estimator

$$\beta_n = \arg\max_\beta \sum_{i=1}^n (Y_i - m(R_i, V_i \mid \beta))^2 \Delta_i.$$

The adaptive design g_i allows that the treatment assignment probabilities and the missing indicators are set in response to the data measured on the previous $i-1$ subjects.

The above examples are representative of general censored data structures. To understand the general derivation of martingale estimating functions independent of g_i, we need to note the following. In general, for many of the censored data structures and full data models treated in van der Laan and Robins (2003), there exists Inverse Probability of Censoring Weighted Estimating functions $D_{IPCW,h}(\psi_0, g)$, indexed by a class of indices $h \in \mathcal{H}$, for a full data parameter ψ_0, which have the property that there exists a subset $\mathcal{G}_1 \subset \mathcal{G}$ of conditional censoring distributions so that for any $g \in \mathcal{G}_1$, there exists a set $\mathcal{H}(g) \subset \mathcal{H}$ of indices so that for each choice $h \in \mathcal{H}(g)$ $D_{IPCW,h}(\psi_0, g)$ is constant in g (i.e. the choice h cancels out g). As a consequence, in all these cases we can define a class of Martingale estimating functions as $\{D_{IPCW,h}(\psi_0, g) : h \in \mathcal{H}(g)\}$, which does not depend on g by the above property, under the assumption that g_i falls with probability 1 in the set $\mathcal{G}_1$. This general statement is best illustrated with one of the above examples. For example, the class of Inverse Probability of Treatment (IPTW) (i.e., IPCW) weigthed estimating functions for a MSM $E(Y(a) \mid V) = m(a, V \mid \beta_0)$ is given by

$$D_{IPCW,h}(\beta_0, g) = \frac{h(A,V)}{g(A \mid X)}(Y - m(A, V \mid \beta_0)),$$

where h can vary over all functions $\mathcal{H}$ of A, V. Suppose that $\mathcal{G}_1$ consists of g with $g(a \mid X) = g(a \mid V)$. Then, for each $h \in \mathcal{H}(g) = \{g(A \mid V)h_1 : h_1 \in \mathcal{H}\}$ we have $D_{IPCW,h}(\beta_0, g) = h_1(A,V)(Y - m(A, V \mid \beta_0)$ so that it follows that $h_1(A,V)(Y - m(A, V \mid \beta_0)$ indexed by $h_1 \in \mathcal{H}$ is a class of Martingale estimating functions under the assumption that $g_i(\cdot \mid X_i) = g_i(\cdot \mid V_i)$.

To summarize, if one is willing to work with adaptive designs g_i, which still allow full dependence on $\bar{\mathbf{O}}(i-1)$, but which allow limited dependence on X_i (i.e., less than CAR), as in clinical trials in which treatment is typically randomized conditional on some baseline covariates, then it is typically possible to define a class of Martingale estimating functions which do not depend on g_i. We expect that such Martingale estimating functions are quite robust against finite sample variability of the adaptive design g_i: i.e., we expect that such estimating functions are more robust w.r.t. the asymptotic stability condition for the adaptive design as stated in our central limit theorems, than estimators based on estimating equations depending on g_i (e.g., through inverse weighting), so that the resulting estimators will achieve the normal limit distribution for smaller sample sizes.

7 Inverse probability of censoring weighted martingale estimating functions.

In this section we present Inverse Probability of Censoring Weighted (IPCW) martingale estimating functions, as another alternative of generating ad hoc simple to implement Martingale estimating functions and corresponding IPCW estimators, where the IPCW estimating functions are immediately implied by the IPCW estimating functions for fixed designs as in general presented in van der Laan and Robins (2003).

The IPCW estimating functions for fixed designs (see e.g., van der Laan and Robins (2003)) have an immediate analogue to adaptive designs. As a first example, we consider the case that $X = (Y(0), Y(1), W) \sim P_{X0}$ consists of treatment specific outcomes $(Y(0), Y(1))$ of interest, and a vector of baseline covariates. Let $\psi_0 = E(Y(1) - Y(0))$ be the effect of treatment on the mean outcome. Let $X_1, \ldots, X_n$ be n i.i.d. copies of X. Let $A_i = (\Delta_i, R_i)$ and $O_i = (W_i, R_i, \Delta_i, \Delta_i Y_i(R_i))$, $i = 1, \ldots, n$. Thus, we observe on the i-th subject, the vector of baseline covariates W_i, the treatment R_i the subject received, a missing indicator Δ_i indicating if we observe the outcome of interest, and if $\Delta_i = 1$, then we observe the outcome $Y_i(R_i)$ under treatment R_i. In an adaptive design we have that A_i is drawn from a CAR-conditional distribution $g_i(\cdot \mid X_i)$ of A_i, given X_i and $O_1, \ldots, O_{i-1}$, $i = 1, \ldots, n$. The adaptive design mechanism g_i can be factorized as

$$\begin{aligned} g_i(A_i \mid X_i) &= P(\Delta_i, R_i \mid X_i, O_1, \ldots, O_{i-1}) \\ &= g_1(R_i \mid X_i, \bar{\mathbf{O}}(i-1)) g_2(\Delta_i \mid R_i, X_i, \bar{\mathbf{O}}(i-1)) \\ &= P(R_i \mid W_i, \bar{\mathbf{O}}(i-1)) \\ &\quad \times P(\Delta_i \mid R_i, W_i, \bar{\mathbf{O}}(i-1)), \end{aligned}$$

where the first factor denotes a treatment mechanism, and the second factor a missingness mechanism.

A full data estimating function for ψ_0 is given by $D(\psi)(X) = Y(1) - Y(0) - \psi$. The IPCW-version of this full data estimating function is given by:

$$D_{IPCW}(\psi, g_i)(O_i) = Y_i \left\{ \frac{I(R_i = 1)}{g_{1i}(R_i \mid X_i)} - \frac{I(R_i = 0)}{g_{1i}(R_i \mid X_i)} \right\} \frac{\Delta_i}{g_{2i}(\Delta_i \mid R_i, X_i)} - \psi.$$

We note that indeed, under the assumption that g_{1i} has positive support on $R_i \in \{0, 1\}$ a.e., and that $g_{2i}(1 \mid R_i, X_i) > 0$ a.e., D_{IPCW} is a martingale estimating function

$$P_{Q_0, g_i} D_{IPCW}(\psi_0, g_i) = 0, \ i = 1, \ldots, n.$$

Such an estimating function can be used to construct an estimator given by the solution $\psi_{n,IPCW}$ of $\sum_i D_{IPCW}(\psi, g_i)(O_i) = 0$. This solution is given by:

$$\psi_{n,IPCW} = \frac{1}{n}\sum_{i=1}^{n} Y_i \left\{ \frac{I(R_i = 1)}{g_{1i}(R_i \mid X_i)} - \frac{I(R_i = 0)}{g_{1i}(R_i \mid X_i)} \right\} \frac{\Delta_i}{g_{2i}(\Delta_i \mid R_i, X_i)}.$$

It might be the case that the randomization probabilities of R_i are known, but that the missingness probabilities are not controlled by the experiment. It will typically be reasonable to assume that the conditional probability distribution of Δ_i only depends on R_i, and W_i, and is thus a fixed design. One can now estimate this conditional distribution with maximum likelihood estimation according to (say) a logistic regression model $\{g_{2\eta} : \eta\}$:

$$\eta_n = \arg\min_{\eta} \prod_{i=1}^{n} g_{2\eta}(\Delta_i \mid R_i, W_i).$$

As another example, we will consider right-censoring of a survival outcome instead of missingness of the outcome. Suppose that $X = (X_0, X_1) \sim P_{X0}$ consists of two treatment specific stochastic processes $X_0 = (X_0(t) : t \geq 0)$ and $X_1 = (X_1(t) : t \geq 0)$, where $X_j(0) = W$ is a vector of baseline covariates and $X_j(t)$ includes as component an indicator $I(T_j \leq t)$ of a treatment specific survival time T_j, $j = 1, 2$. The treatment specific processes are assumed to be truncated at T_j: $X_j(t) = X_j(\min(t, T_j))$, $j = 1, 2$. For example, if $X_j(t) = I(T_j \leq t)$, then X is equivalent with $X = (W, T_0, T_1)$. Let the survival risk difference $\psi_0 = P_{X0}(T_1 > t_0) - P_{X0}(T_0 > t_0)$ be the parameter of interest. Let $A_i(0) = R_i$ be the treatment indicator, and $A_i(t) = I(C_i \leq t)$ for $t > 0$ is the censoring process defined by a right-censoring time C_i. On the i-th unit we observe

$$O_i = (W_i, A_i = (R_i, (I(C_i \leq t) : t > 0)), \bar{X}_{R_i}(C_i) = (X_{R_i}(t) : t \leq C_i)),\ i = 1, \ldots, n.$$

We define $C_i = \infty$ if the failure time $T_i = T_{i,R_i}$ is observed. An adaptive design is defined by the conditional distribution of A_i, given X_i and $O_1, \ldots, O_{i-1}$. We have

$$\begin{aligned} g_i(A_i \mid X_i) &= g_{i1}(R_i \mid X_i) \prod_{0<t\leq \min(C_i, T_{R_i}))} g_{i2}(A_i(t) \mid \bar{A}_i(t-), R_i, X_i) \\ &= P(R_i \mid W_i, \bar{\mathbf{O}}(i-1)) \\ &\quad \times \prod_{t \leq \min(C_i, T_{R_i})} P(A_i(t) \mid R_i, \bar{A}_i(t-), \bar{X}_{R_i}(t), \bar{\mathbf{O}}(i-1)), \end{aligned}$$

where the first factor denotes the treatment mechanism, and the second product integral denotes the censoring mechanism. Thus, the adaptive design allows that the treatment is assigned in response to the baseline covariates of subject i, and the observed data on the first $i-1$ recruited subjects. In addition, it allows that the probability of being censored at time t is a function of the treatment arm R_i, the baseline covariates W_i, the observed history $\bar{X}_{i,R_i}(t)$ up till time t (e.g., including time-dependent covariates), and the data on the previously recruited subjects $\bar{\mathbf{O}}(i-1)$. It might be typical that the treatment mechanism is under control of the designer, but that the right-censoring mechanism cannot be fully controlled. In that case one would model (e.g., Cox proportional hazards model or logistic regression model) the right-censoring mechanism and estimate it with maximum likelihood estimation:

$$\eta_n = \arg\max_{\eta} \prod_{i=1}^{n} \prod_{t \leq \min(C_i, T_{R_i})} P_\eta(A_i(t) \mid R_i, \bar{A}_i(t-), \bar{X}_{R_i}(t), \bar{\mathbf{O}}(i-1)),$$

where one typically will be able to assume a model which assumes that the censoring probabilities are independent of $\bar{\mathbf{O}}(i-1)$.

We will now construct the IPCW-martingale estimating function for ψ_0. An IPCW-estimating function is given by

$$D_{IPCW}(\psi, g_i)(O_i) \equiv I(T_{R_i} > t_0) \left\{ \frac{I(R_i = 1, C_i > t_0)}{g_i(R_i, \bar{A}_i(t_0) = 0 \mid X_i)} - \frac{I(R_i = 0, C_i > t_0)}{g_i(R_i, \bar{A}_i(t_0) = 0 \mid X_i)} \right\} - \psi,$$

where

$$g_i(R_i, \bar{A}_i(t_0) = 0 \mid X_i) = g_{i1}(R_i \mid X_i) \prod_{0 < t \leq \min(t_0, T_{R_i})} g_{i2}(A_i(t) = 0 \mid \bar{A}_i(t-) = 0, R_i, X_i).$$

The corresponding IPCW-estimator of ψ_0 is the solution of $0 = \sum_i D_{IPCW}(\psi, g_i)(O_i)$ given by

$$\psi_{nIPCW} = \frac{1}{n} \sum_{i=1}^{n} I(T_{R_i} > t_0) \left\{ \frac{I(R_i = 1, C_i > t)}{g_i(R_i, \bar{A}_i(t_0) = 0 \mid X_i)} - \frac{I(R_i = 0, C_i > t_0)}{g_i(R_i, \bar{A}_i(t_0) = 0 \mid X_i)} \right\}.$$

If the treatment probabilities or censoring probabilities are unknown, then they can be replaced by maximum likelihood estimators according to (correctly specified) models.

Our theorems for solutions of Martingale estimating equations provide the corresponding statistical inference for these IPCW-estimators, where one of the fundamental conditions is the stability condition for the adaptive design g_i (i.e., g_i should depend on asymptotically consistent summary measures of

$\bar{\mathbf{O}}(i-1)$ as $i \to \infty$), and if g_i has unknown components which need to be estimated, then these components are correctly modelled.

A general type of IPCW martingale estimating function corresponding with a full data estimating function $D(X_i)$ is obtained as follows:

$$D_{IPCW}(g_i) = D(X_i)\frac{I(\Delta_i = 1)}{P_{g_i}(\Delta_i = 1 \mid X_i, \bar{\mathbf{O}}(i-1))},$$

where $\Delta_i = I(D(X_i)$ is observed) is the indicator of $D(X_i)$ being a function of O_i, and it is noted that the denominator probability is indeed determined by the conditional distribution of A_i, given X_i and $\bar{\mathbf{O}}(i-1)$.

To summarize, we note that any of the IPCW estimating functions for fixed CAR designs (i.e., CAR censoring mechanisms) as presented in general in van der Laan and Robins (2003) have an analogue for adaptive designs by simply replacing the fixed CAR design g by the adaptive CAR-design g_i.

8 Constructing Martingale estimating equations and corresponding estimators

Our consistency and central limit theorems apply to solutions of a Martingale estimating equations, assuming that the estimating equation identifies the true parameter. Below, we consider general approaches for constructing such martingale estimating equations and corresponding estimators of a particular parameter of Q_0, the P_{X0}-factor in the density of $O_1, \ldots, O_n$. In Sections 6 and 7 we showed how one can construct Inverse Probability of Censoring Weighted Martingale estimating functions and, under restrictions on the adaptive design, Martingale estimating functions which do not depend on the adaptive design. These are examples of ad hoc Martingale estimating functions. In this section we present the generalization of the fixed design estimating function methodology in van der Laan and Robins (2003) towards Martingale estimating functions for general adaptive designs. In the next subsection we first consider scores of correctly specified parametric models. Subsequently, we present the two estimating strategies for pathwise differentiable parameters in semiparametric models: estimating function based estimation and a targeted MLE. As we indicate, both rely on a nice behaving (i.e., Martingale based) estimator of a parameter in a possibly misspecified parametric working model for Q_0 and we show in the subsequent sections how such an estimator can be constructed.

8.1 MLE for correctly specified parametric model.

Consider a MLE according to a correctly specified parametric model $\mathcal{Q} = \{Q_\theta : \theta\}$

$$\theta_n = \arg\max_{\theta\in\Theta} \sum_{i=1}^{n} \log Q_\theta(O_i).$$

Under weak regularity conditions, this MLE solves the score equation:

$$0 = \sum_{i=1}^{n} D(\theta_n)(O_i),$$

where $D(\theta) \equiv \frac{d}{d\theta} \log Q_\theta$. In addition, under similar regularity conditions, the target parameter

$$\theta_0 = \arg\max_{\theta\in\Theta} \sum_{i=1}^{n} P_{Q_0,g_i} \log Q_\theta$$

should solve $0 = \sum_{i=1}^{n} P_{Q_0,g_i} D(\theta_0)$, and, in fact, satisfies $P_{Q_0,g_i} D(\theta_0) = 0$ for all $i = 1, \ldots, n$. Thus, $D(\theta_0)(O_i)$ denotes a Martingale estimating function, and the MLE θ_n solves the corresponding Martingale estimating equation $0 = \sum_{i=1}^{n} D(\theta_n)(O_i)$. The score of a correctly specified parametric model is a special Martingale estimating function since it is only a function of O_i and thus does not depend on the adaptive design g_i.

8.2 Martingale Estimating function based estimator of path-wise differentiable parameter.

Suppose that the parameter of interest is a path-wise Euclidean parameter $\Psi : \mathcal{Q} \to \mathbb{R}^m$ for a semi-parametric model $\mathcal{Q}$ for Q_0. Let $D^*(Q, g)$ be the efficient influence curve of this parameter at a fixed design distribution $P_{Q,g} \in \mathcal{M}(g) = \{P_{Q,g} : Q \in \mathcal{Q}\}$. Consider a parametric working model $\mathcal{Q}^w = \{Q_\theta : \theta \in \Theta\}$, which is allowed to be misspecified. Suppose that the efficient influence curve D^* can be represented as an estimating function for ψ_0 in the sense that $D^*(Q, g) = D^*(\Psi(Q), Q, g)$ for some mapping $(\psi, Q, g) \to D^*(\psi, Q, g)$. The efficient influence curve based Martingale estimating function is now given by

$$D^*(\psi, \theta)(O_i, Z_i) \equiv D^*(\psi, Q_\theta, g_{Z_i})(O_i),$$

or

$$D^*(\psi, Q_\theta, g_\theta)(O_i) g_\theta / g_{Z_i},$$

where g_θ is a design function supposed to approximate the actual adaptive design in the sense that $g_n \approx g_{\theta_{n-1}}$.

IPCW-weighting of efficient influence curve estimating function: We view $D^*(\psi, Q_\theta, g_\theta)g_\theta/g_i$ as IPCW-weighting of $D^*(\psi, Q_\theta, g_\theta)$. If D^* can be represented as a sum $D^* = \sum_j D_j^*$, and each $D_j^*(O_i)$ only depends on A_i through $\bar{A}(j^*(j)-1)$ for some integer mapping $j^*(j)$, then it is good practice (in line with our IPCW-R-TMLE introduced later) to weight each D_j^* with $g_\theta(\bar{A}_i(j^*(j)-1) \mid X_i)/g_i(\bar{A}_i(j^*(j)-1) \mid X_i)$ instead of using a common weight $g_\theta(A_i \mid X_i)/g_i(A_i \mid X_i)$. We can always determine such a decomposition of D^*. For example, if $Q_0 = \prod_j Q_{0j}$, where each $Q_{0j}(O)$ only depends on O through $\bar{A}(j^*(j))$, then we can decompose the efficient influence curve as an orthogonal sum $\sum_j D_j^*$, where each D_j^* is in the element of the tangent space generated by Q_{0j}. For example, if Q_{0j} denotes the conditional distribution of $L(j)$, given $\bar{A}(j-1), \bar{L}(j-1)$, then one defines $D_j^* = E(D^* \mid \bar{L}(j), \bar{A}(j-1)) - E(D^* \mid \bar{L}(j-1), \bar{A}(j-1))$. In the latter case, D_j^* has conditional mean zero, given $\bar{A}(j^*(j)-1), \bar{L}(j^*(j))$, which implies in particular a wished double robustness. For more details on the latter we refer to our IPCW-Reduced Data-TMLE section. This same IPCW weighting scheme applies to general estimating functions.

We need to augment this efficient influence curve based martingale estimating function for ψ_0 with a Martingale estimating function $D(\theta)(O_i, Z_i)$ for a finite dimensional parameter θ_0, defined by a nonparametric extension of the parametric working model $\mathcal{Q}^w$. That is, $P_{Q_0,g_i}D(\theta_0) = 0$ and $P_{Q_0,g_i}D^*(\psi_0, Q_{\theta_0}, g_i) = 0$. This results in a joint Martingale estimating function $D(\psi, \theta) = (D(\theta), D^*(\psi, \theta))$ for the joint parameter (ψ_0, θ_0) satisfying $P_{Q_0,g_i}D(\psi_0, \theta_0) = 0$. The estimator (ψ_n, θ_n) is now defined as a solution of $0 = \sum_i D(\psi_n, \theta_n)(O_i, Z_i)$. Our consistency results and CLT theorems can now be applied. The efficient influence curve based martingale estimating function can be replaced by inefficient gradient based martingale estimating functions (as in van der Laan and Robins (2003)) while still preserving the consistency and asymptotic normality, by application of our theorems.

If $P_{Q_0,g}D^*(\psi, Q, g)$ implies $\psi = \psi_0$ for all $Q \in \mathcal{Q}^w$, which holds in many censored data applications (see van der Laan and Robins (2003)), then it follows that ψ_n is consistent for ψ_0, *even if the working model is incorrectly specified.* Below, in Subsection 8.4 we present methods for constructing martingale estimating functions for the unknown parameter θ_0 of a possibly misspecified working model $\mathcal{Q}^w$.

8.3 Targeted MLE of path-wise differentiable parameter based on working model.

Suppose that the parameter of interest is a path-wise Euclidean parameter $\Psi : \mathcal{Q} \to \mathbb{R}^m$ for a semi-parametric model $\mathcal{Q}$ for Q_0. Let $D^*(Q, g)$ be the efficient influence curve of this parameter at a fixed design distribution $P_{Q,g} \in \mathcal{M}(g) = \{P_{Q,g} : Q \in \mathcal{Q}\}$. In Section 12 we define a targeted MLE of $\psi_0 = \Psi(Q_0)$ based on adaptive group sequential designs, which involves updating an initial estimator Q_{θ_n} of Q_0 according to a possibly misspecified parametric working model $\mathcal{Q}^w = \{Q_\theta : \theta \in \Theta\}$, so that the update maps into a consistent and asymptotically linear estimator of ψ_0.

We will show that our proposed one-step targeted ML procedure involves augmenting a Martingale estimating function $D(\theta)(O_i, Z_i)$ for the finite dimensional parameter θ_0, defined by a nonparametric extension of the parametric working model $\mathcal{Q}^w$, with the efficient influence curve based martingale estimating function $D^*(\theta, \epsilon)(O_i, Z_i) \equiv D^*(Q_\theta(\epsilon), g_{Z_i})(O_i)$, or $D^*(Q_\theta(\epsilon), g_\theta)g_\theta/g_i$ for a design function g_θ, where $Q_\theta(\epsilon) \subset \mathcal{Q}$ is a particular ϵ-fluctuation of Q_θ with $Q_\theta(0) = Q_\theta$. Given the estimator θ_n satisfying $\sum_i D(\theta_n)(O_i, Z_i) = 0$, the targeted MLE procedure defines ϵ_n as the solution of $\sum_i D^*(\theta_n, \epsilon_n)(O_i, Z_i) = 0$ and $Q_{\theta_n}(\epsilon_n)$ as the updated Q_{θ_n}. Multiple solutions for ϵ_n (and similarly selection among initial estimators Q_{θ_n}) is naturally handled by using the (minus) log likelihood of $Q_{\theta_n}(\epsilon_n)$ as loss function: so selection is either based on the log-likelihood or cross-validated log likelihood, in the case that one is comparing initial estimators based on different size working models. The target ϵ_0 of ϵ_n is the solution of $P_{Q_0,g_i}D^*(\theta_0, \epsilon_0) = E_0 D^F(Q_{\theta_0}(\epsilon_0)) = 0$, where D^F is the full data estimating function associated with the efficient influence curve, which is obtained by applying the conditional expectation operator, given X (see van der Laan and Robins (2003)). To establish consistency and asymptotic linearity of (θ_n, ϵ_n) for (θ_0, ϵ_0), and thereby consistency and asymptotic linearity of $\Psi(Q_{\theta_n}(\epsilon_n))$ as an estimator of $\Psi(Q_{\theta_0}(\epsilon_0))$, we then apply the consistency and CLT theorems to these estimators defined by the augmented/stacked estimating function $D(\theta, \epsilon) = (D(\theta), D^*(\theta, \epsilon))$. If $P_{Q_0,g}D^*(Q, g) = E_{Q_0}D^{*F}(Q) = 0$ implies $\Psi(Q) = \psi_0$ (which holds in many applications, by van der Laan and Robins (2003)), it then follows that $\Psi(Q_{\theta_n}(\epsilon_n))$ is consistent (and asymptotically linear) for ψ_0, *even if the working model is incorrectly specified*. For a detailed presentation of this one-step targeted MLE procedure, we refer to Section 12, which generalizes the targeted MLE for fixed designs as presented in van der Laan and Rubin (2006).

Below, we present methods for constructing martingale estimating functions for the unknown parameter of a possibly misspecified working model

$\mathcal{Q}^w$.

8.4 Weighted MLE and Martingale estimating functions for misspecified parametric working model.

Suppose that $\mathcal{Q}$ is a semi-parametric model so that, by the curse of dimensionality, a maximum likelihood estimator will require regularization. Consider a parametric sub-model/working model $\mathcal{Q}^w = \{Q_\theta : \theta \in \Theta\} \subset \mathcal{Q}$ of $\mathcal{Q}$.

Firstly, we wish to explain why the actual MLE for a misspecified working model targets a parameter of both Q_0 *and* the adaptive design, which therefore is harder to analyze, and might not necessarily be asymptotically normally distributed due to the dependencies and lack of martingale structure of the score under a misspecified model. Let θ_n^w be the MLE according to the working model $\mathcal{Q}^w = \{Q_\theta : \theta\}$, which solves the score equation $0 = \sum_{i=1}^n D(\theta_n^w)(O_i)$, where $D(\theta_n^w) = \frac{d}{d\theta} \log Q_\theta \Big|_{\theta=\theta_n^w}$. We note that this MLE targets the "parameter" $\arg\max_{\theta\in\Theta} \sum_{i=1}^n P_{Q_0,g_i} \log Q_\theta$, which equals $\Theta_{\bar{g}_n}(Q_0) \equiv \arg\max_{\theta\in\Theta} P_{Q_0,\bar{g}_n} \log Q_\theta$, where $\bar{g}_n = 1/n \sum_{i=1}^n g_i$. Thus, asymptotically it targets the parameter $\theta_0 = \Theta_{g_0}(Q_0)$, under the assumption that the design g_n converges to a fixed design $g_0 \in \mathcal{G}$, as $n \to \infty$. As a consequence, since g_0 itself can be a function of Q_0 and represents an unknown target fixed design, this is a more complex parameter to interpret and to analyze. In particular, the fundamental assumption that $P_{Q_0,g_i} D(\theta_0) = 0$ does not follow, so that the empirical mean of $D(\theta_0)$ does not represent a martingale sum (so that a CLT is not applicable). In addition, consistency of θ_n^w as an estimator of θ_0 now also requires consistency of g_n to g_0, and asymptotic normality will now also require that g_n converges at an appropriate rate to g_0. In other words, the target of a MLE for a misspecified parametric model represents a complex parameter whose statistical inference will rely on strong assumptions about the adaptive design. Therefore, we propose to not use maximum likelihood estimators according to misspecified parametric models.

Instead, firstly, we wish to target the parameter Θ_{g^*} for a fixed design $g^* \in \mathcal{G}$ for which we can define Martingale estimating functions so that we can analyze the resulting estimators with our theorems. Subsequently, we will also present a method allowing to estimate/update g^* sequentially during the course of the trial, while still obtaining an estimator which solves a Martingale estimating equation.

Firstly, we carefully define nonparametric extensions of θ_0 as defined under a correctly specified working model, and then consider efficient estimation of

that parameter. Define

$$\theta_0 = \Theta_{g^*}(Q_0) \equiv \arg\max_{\theta\in\Theta} P_{Q_0,g^*} \log Q_\theta \text{ for a fixed design } g^* \in \mathcal{G}.$$

Note that this defines Θ_{g^*} as a (smooth) parameter on the large (e.g., nonparametric) model $\mathcal{Q}$, and $\Theta_{g^*}(Q_0)$ would *not* depend on the choice g^* if $Q_0 \in \mathcal{Q}^w$. Thus Θ_{g^*} defines an extension of the true parameter for a model $\mathcal{Q}^w$ to a parameter defined on the true model $\mathcal{Q}$ containing $\mathcal{Q}^w$.

Let $D(Q, g)$ be the efficient influence curve of this parameter $\Theta_{g^*} : \mathcal{Q} \to \mathbb{R}^d$ at a fixed design $P_{Q,g} \in \mathcal{M}$. The results in van der Laan and Robins (2003) can be immediately applied to find and characterize this efficient influence curve, since O is a fixed design CAR censored data structure on a full data random variable X, and θ_0 is a path-wise differentiable parameter of the full data distribution. By the fact that D is an influence curve/gradient for a parameter of the full data distribution P_{X0} in a CAR censored data model, it follows (by Theorem 1.3, van der Laan and Robins (2003)) that $P_{Q_0,g}D(Q, g) = E_{Q_0}D^F(Q)(X)$ for a full data gradient D^F of the path-wise derivative of the parameter $\Theta_{g^*} : \mathcal{Q} \to \mathbb{R}^d$ at Q_0. A common property of a gradient applied to $D^F(Q)$ is that $E_{Q_0}D^F(Q) = 0$ for $Q \in \mathcal{Q}^w$ implies $\Theta_{g^*}(Q) = \Theta_{g^*}(Q_0)$. This teaches us that we can define $\theta_0 = \Theta_{g^*}(Q_0)$ as the solution in θ of

$$E_0 D^F(Q_\theta) = 0.$$

This implies that $D(Q_\theta, g_i)$ is a martingale estimating function for the parameter $\Theta_{g^*}(Q_0)$:

$$P_{Q_0,g_i} D(Q_{\theta_0}, g_i) = 0 \text{ for } i = 1, \ldots, n. \tag{13}$$

Let θ_n be the solution in Θ of

$$\frac{1}{n}\sum_{i=1}^{n} D(Q_\theta, g_i)(O_i) = 0 \text{ or } o_P(1/\sqrt{n}).$$

(As a side note, application of theorems in van der Laan and Robins (2003) and our CLT Theorem 7 shows, in particular, that this estimator θ_n of θ_0 is an asymptotically locally efficient estimator of θ_0 at fixed designs in the sense that it is always consistent and asymptotically linear and that it is efficient if $Q_0 \in \mathcal{Q}^w$.)

We can now define the estimating function $D(\theta)(O_i, Z_i) \equiv D(Q_\theta, g_{Z_i})(O_i)$ (or $D(Q_\theta, g_\theta)g_\theta/g_i$), which now indeed satisfies the Martingale property $P_{Q_0,g_i}D(\theta_0) = 0$, and θ_n solves the corresponding Martingale estimating equation $\sum_{i=1}^n D(\theta_n)(O_i, Z_i) = 0$, so that our consistency and CLT theorems can be applied to establish consistency of θ_n and asymptotic normality as an estimator of $\Theta_{g^*}(Q_0)$.

Above, we used the efficient influence curve of $\Theta_{g^*}(Q_0)$ as basis, but this can be replaced by any gradient of this parameter. In general, one can construct a Martingale estimating function and corresponding estimator θ_n of θ_0 as follows. Let $D(Q,g)$ be an influence curve/gradient of the parameter $\Theta_{g^*} : \mathcal{Q} \to \mathbb{R}^d$ at fixed design data generating distribution $P_{Q,g}$ in the model $\mathcal{M}(g) = \{P_{Q,g} : Q \in \mathcal{Q}\}$ with g known. For example, $D(Q_\theta, g) = S(\theta)g^*/g$, where $S(\theta) = \frac{d}{d\theta} \log Q_\theta$, or $D(Q,g)$ is the efficient influence curve of Θ_{g^*} as above. By the fact that D is an influence curve/gradient for a parameter of the full data distribution P_{X0} in a CAR censored data model, it follows (by Theorem 1.3, van der Laan and Robins (2003)) that $P_{Q_0,g}D(Q,g) = E_{Q_0}D^F(Q)(X)$ for a full data gradient D^F. Analogue to the derivation of (13)under the above mentioned natural property of a gradient, it follows that for $\theta_0 = \Theta_{g^*}(Q_0)$

$$P_{Q_0,g_i}D(Q_{\theta_0}, g) = E_0 D^F(Q_{\theta_0}) = 0.$$

Now, let θ_n be the solution in θ of

$$\frac{1}{n}\sum_{i=1}^{n} D(Q_\theta, g_i)(O_i) = 0 \text{ or } o_P(1/\sqrt{n}).$$

8.5 A sequentially data adaptively weighted MLE based on misspecified working model.

Above we defined an estimator θ_n of an extended parameter $\theta_0 = \Theta_{g^*}(Q_0)$ based on a working model $\mathcal{Q}^w$ and a user supplied choice of fixed design g^*. The targeted MLE or the estimating function based estimator ψ_n of ψ_0 based on this initial estimator Q_{θ_n} of Q_0 will thus also be indexed by this choice g^*. Although the choice g^* will not affect the consistency and asymptotic linearity of the targeted MLE ψ_n, and the convergence of the adaptive design $g_n = g_{\theta_{n-1}}$ to $g_{\theta_0} = g_{Q_{\theta_0}}$ (which is a working model based approximation of g_{Q_0}), it can affect the first order efficiency of ψ_n and it can also affect the limit design g_{θ_0}. That is, the first order efficiency is affected by the performance of Q_{θ_n} as an estimator of Q_0, and this estimator Q_{θ_n} depends on g^*. Therefore, it is worthwhile to investigate if we can also construct an estimator θ_n which is not indexed by such a user supplied arbitrary choice g^*.

Consider sample sizes $n_1 = p_1 n < n_2 = p_2 n < \ldots < n_k = p_k n$ for user supplied proportions $0 < p_1 < \ldots < p_k = 1$. We now propose the following sequential procedure for obtaining an estimator Q_n^0 based on the working model $\mathcal{Q}^w$. Let $\theta_n^0 = \theta^0 \in \Theta$ be a given parameter value so that $g^* = g_{\theta^0}$. Let

$\theta_n^1 = \arg\max_\theta \sum_{i=1}^{n_1} \log Q_\theta(O_i) g_{\theta_n^0}(A_i \mid X_i)/g_i(A_i \mid X_i)$, and, in general,

$$\theta_n^j = \arg\max_\theta \sum_{i=1}^{n_j} \log Q_\theta(O_i) \frac{g_{\theta_n^{j-1}}(A_i \mid X_i)}{g_i(A_i \mid X_i)},\ j = 1, 2, \ldots, k.$$

We now propose θ_n^k and corresponding estimator $Q_{\theta_n^k}$ of Q_0 as starting point for the targeted MLE estimator or estimating function based estimator. In order to apply our general theorems we will need to show that θ_n^k is a solution of a martingale estimating equation. Firstly, we note that θ_n^1 corresponds with Martingale estimating function $D^1(\theta, \theta^0)(O_i, Z_i) = I(i \leq n_1) S(\theta)(O_i) g_{\theta^0}(A_i \mid X_i)/g_{Z_i}(A_i \mid X_i)$ for the parameter $\theta_0^1 = \arg\max_\theta P_{Q_0, g_{\theta^0}} \log Q_\theta$. Secondly, we note that θ_n^2 corresponds with Martingale estimating function $D^2(\theta, \theta^1)(O_i, Z_i) = I(i \leq n_2) S(\theta)(O_i) g_{\theta^1}(A_i \mid X_i)/g_i(A_i \mid X_i)$ for parameter $\theta_0^2 = \arg\max_\theta P_{Q_0, g_{\theta^1}} \log Q_\theta$. In general, we note that θ_n^j corresponds with martingale estimating function $D^j(\theta, \theta^{j-1})(O_i, Z_i) = I(i \leq n_j) S(\theta)(O_i) g_{\theta^{j-1}}(A_i \mid X_i)/g_i(A_i \mid X_i)$ for parameter $\theta^j = \arg\max_\theta P_{Q_0, g_{\theta^{j-1}}} \log Q_\theta,\ j = 1, \ldots, k$. Thus, $\theta_0(k) = ((\theta_0^1, \ldots, \theta_0^k)$ corresponds with the stacked Martingale estimating function

$$D(\theta(k)) = D(\theta^1, \ldots, \theta^k) = (D^1(\theta^1, \theta^0), \ldots, D^k(\theta^k, \theta^{k-1})).$$

This estimating function indeed satisfies the Martingale property $P_{Q_0, g_i} D(\theta_0(k)) = 0$ for all i. Let $\theta_n(k)$ be the estimator of $\theta(k)$ solving the corresponding stacked Martingale estimating equation $\sum_{i=1}^n D(\theta_n(k))(O_i, Z_i) = 0$. In this way we succeeded to construct a martingale estimating function $D(\theta(k))$ for parameter $\theta(k)$ and corresponding estimator $\theta_n(k)$, while the MLE of interest will be the final estimator $Q_{\theta_n^k}$, which thus further ignores θ_n^j, $j = 1, \ldots, k-1$.

In this method we can replace the weighted scores $S_\theta g_{\theta_n^{j-1}}/g_i$ by $D(Q_\theta, g_{\theta_n^{j-1}}) g_{\theta_n^{j-1}}/g_i$, where $D(Q, g)$ is a gradient of Ψ at $P_{Q,g} \in \mathcal{M}(g) = \{P_{Q,g} : Q \in \mathcal{Q}\}$.

9 Consistency of solutions of Martingale estimating equations.

The following result establishes consistency of a solution of a Martingale estimating equation, assuming that the estimating equation identifies the true parameter.

Theorem 5 *Consider adaptive design experiment $O_1, \ldots, O_n \sim P_{Q_0, \mathbf{g}}$ as defined by (3). Given an estimating function $\theta \to D(\theta)$ on a parameter space Θ, suppose that θ_n is a Euclidean parameter estimate solving*

$$\frac{1}{n} \sum_{i=1}^n D(\theta_n)(O_i, Z_i) = 0.$$

Let $\theta_0 \in \Theta$ satisfy $P_{Q_0,g_i}D(\theta_0) = 0$, $i = 1,\ldots,n$, where $g_i(a \mid X_i) = g(a \mid O_1,\ldots,O_{i-1},X_i)$ depends on $O_1,\ldots,O_{i-1}$ only through a d-dimensional vector $Z_i = Z_i(O_1,\ldots,O_{i-1}) \in \mathcal{Z} \subset \mathbb{R}^d$ for some d, $i = 1,\ldots,n$. Let $\mathcal{F}$ be a class of functions $(a,l,z) \to f(a,l,z)$ defined as $\mathcal{F} \equiv \{(a,l,z) \to D(\theta)(a,l,z) - P_{Q_0,g_z}D(\theta) : \theta \in \Theta\}$ (recall $O_i = (A_i, L_i)$)

Assume that the covering number w.r.t. to supremum norm satisfies $N(\epsilon,\mathcal{F},\| \cdot \|_\infty) = O(\epsilon^{-q})$ for a $q > 0$. Then, for all $p \geq 1$

$$E\left(\frac{1}{n}\sum_{i=1}^{n} P_{Q_0,g_i}D(\theta_n)\right)^p \to 0,$$

as $n \to \infty$.

This consistency result for θ_n typically translates into a consistency result for θ_n, assuming that the data generating experiment allows identifiability of θ_0. For example, if $\Phi_{Q_0,g_i} : \theta \to P_{Q_0,g_i}D(\theta)$ is differentiable at θ_0 with derivative $\ddot{\Phi}_{Q_0,g_i}(\theta_0)$,

$$\frac{1}{n}\sum_{i=1}^{n} P_{Q_0,g_i}D(\theta_n) = \frac{1}{n}\sum_{i=1}^{n} \ddot{\Phi}_{Q_0,g_i}(\theta_0)(\theta_n - \theta_0) + o_P(\| \theta_n - \theta_0 \|),$$

and the linear mapping (i.e., matrix) $\frac{1}{n}\sum_{i=1}^{n} \ddot{\Phi}_{Q_0,g_i}(\theta_0)$ is invertible with an inverse which has a bounded norm uniformly in n, then this theorem provides the wished result $\| \theta_n - \theta_0 \| \to 0$ in probability as $n \to \infty$.

Proof of Theorem 5. Since θ_n solves the estimating equation $0 = \sum_i D(\theta_n)(O_i, Z_i)$ it follows that

$$\begin{aligned}\frac{1}{n}\sum_{i=1}^{n} P_{Q_0,g_i}D(\theta_n) &= -\frac{1}{n}\sum_{i=1}^{n}\left(D(\theta_n)(O_i,Z_i) - P_{Q_0,g_i}D(\theta_n)\right) \\ &\equiv -M_n(D(\theta_n)),\end{aligned}$$

where $M_n(f) \equiv \frac{1}{n}\sum_{i=1}^{n}\left(f(O_i,Z_i) - P_{Q_0,g_{Z_i}}f\right)$ is a martingale sum for each f. Now, we use that

$$M_n(D(\theta_n)) \leq \sup_\theta \mid M_n(D(\theta)) \mid = \sup_{f\in\mathcal{F}} \mid M_n(f) \mid .$$

By Theorem 14, the latter random variable converges in p-th expectation to zero for all $p \geq 1$.

Thus, it follows that for all $p \geq 1$

$$E\left(\frac{1}{n}\sum_{i=1}^{n} P_{Q_0,g_i}D(\theta_n)\right)^p \to 0,$$

as $n \to \infty$. This completes the proof of Theorem 5. □

10 Consistency of targeted adaptive design.

Consider a targeted adaptive design defined as $g_i = g_{\theta_{i-1}}$, with $\theta_i \in \Theta$ be a sequence of estimators of a Euclidean parameter θ_0 of Q_0 based on $O_1, \ldots, O_i$, where, for each $\theta \in \Theta$, $g_\theta \in \mathcal{G}$ is a CAR fixed design (i.e., a conditional distribution of A, given X, with $g(A \mid X)$ only a function A, L_A). Obviously, a consistency result of θ_n to θ_0, as one can obtain with the previously presented consistency theorems, implies asymptotic convergence of the adaptive design g_i to the fixed design g_{θ_0}, for $i \to \infty$, under a continuity condition on the mapping $\theta \to g_\theta$. We will state this useful result as a theorem.

Theorem 6 *Assume that $\theta \to g_\theta$ is continuous w.r.t to norms $\| \cdot \|$ on a space containing Θ, and $\| \cdot \|_1$ on a space containing the conditional distributions $\mathcal{G} = \{g(\cdot \mid X) : g(A \mid X) = h(A, X(A))$ for some $h\}$ in the sense that for any deterministic sequence $\theta'_n \in \Theta$ for which $\| \theta'_n - \theta_0 \| \to 0$, as $n \to \infty$, we have $\| g_{\theta_n} - g_{\theta_0} \|_1 \to 0$, as $n \to \infty$.*

If $\| \theta_n - \theta_0 \| \to 0$ in probability as $n \to \infty$, then $\| g_{\theta_n} - g_{\theta_0} \|_1 \to 0$ in probability as $n \to \infty$.

This is an immediate consequence of the continuous mapping theorem (van der Vaart and Wellner (1996)).

11 Asymptotic normality for solutions of Martingale estimating equations.

The previous Theorems 2 and 5 provide general tools for establishing consistency of an estimator θ_n of a parameter θ_0 of Q_0, which solve a Martingale estimating equation $0 = \sum_i D(\theta_n)(O_i, Z_i)$. Given such a consistency result, the following theorem provides a template and conditions for establishing the wished asymptotic normality of the standardized estimator $\sqrt{n}(\theta_n - \theta_0)$.

Theorem 7 *(CLT) Consider the adaptive design experiment generating $(O_1, \ldots, O_n) \sim P_{Q_0, \mathbf{g}_n} \in \{P_{Q,\mathbf{g}} : Q \in \mathcal{Q}\}$ as defined in (3). Let $\theta_n \in \Theta$ be a sequence of estimators of a Euclidean parameter $\theta_0 = \Theta(Q_0) \in \Theta$ of Q_0 for a parameter $\Theta : \mathcal{Q} \to \mathbb{R}^d$ solving the estimating equation*

$$0 = \frac{1}{n} \sum_{i=1}^{n} D(\theta_n)(O_i, Z_i) = 0,$$

where $Z_i = Z_i(O_1, \ldots, O_{i-1}) \in \mathcal{Z} \subset \mathbb{R}^k$ is a k-dimensional summary measure for some fixed k. Assume

Martingale unbiased estimating function: *Let* $\theta_0 \in \Theta$ *be so that* $P_{Q_0,g_i} D(\theta_0) = 0$ *for all* i*, and thus, in particular,* $\sum_{i=1}^n P_{Q_0,g_i} D(\theta_0) \equiv \sum_{i=1}^n E_{Q_0,g_i} D(\theta_0)(O_i, Z_i) \mid O_1, \ldots, O_{i-1}) = 0$*,* $i = 1, \ldots, n$*.*

Bounded estimating function: $\max_j \sup_{\theta \in \Theta} \parallel D_j(\theta) \parallel_\infty < \infty$*.*

Consistency: *Assume* $\parallel \theta_n - \theta_0 \parallel$ *converges to zero in probability as* $n \to \infty$ *w.r.t. to some norm.*

By Theorem 5 it suffices to assume that 1) $\mathcal{F} \equiv \{(a, l, z) \to D(\theta)(a, l, z) - P_{Q_0,g_z} D(\theta) : \theta \in \Theta\}$ *has a covering number* $N(\epsilon, \mathcal{F}, \| \cdot \|_\infty)$ *w.r.t. to supremum norm bounded by* $O(\epsilon^{-q})$ *for a* $q > 0$*, and 2) that,*

$$E \left(\frac{1}{n} \sum_{i=1}^n P_{Q_0,g_i} D(\theta_n) \right)^2 \to 0,$$

as $n \to \infty$*, implies* $\parallel \theta_n - \theta_0 \parallel \to 0$ *in probability, as* $n \to \infty$*.*

Asymptotic stable design: *Component wise,*

$$\frac{1}{n} \sum_{i=1}^n P_{Q_0,g_i} \{D(\theta_0)\}^2 - E \frac{1}{n} \sum_{i=1}^n P_{Q_0,g_i} \{D(\theta_0)\}^2 \to 0, \tag{14}$$

and

$$\frac{1}{n} \sum_{i=1}^n P_{Q_0,g_i} \frac{d}{d\theta_0} D(\theta_0) - E \frac{1}{n} \sum_{i=1}^n P_{Q_0,g_i} \frac{d}{d\theta_0} D(\theta_0) \to 0, \tag{15}$$

as $n \to \infty$ *a.s.*

If $D(\theta_0)(O_i, Z_i)$ *is only a function of* O_i *(e.g.,* $D(\theta_0)$ *is score at* θ_0 *of correctly specified parametric model* $\{Q_\theta : \theta\}$ *for* Q_0 *or a martingale estimating function as presented in Section 6), then (14) becomes*

$$P_{Q_0,\bar{g}_n - E\bar{g}_n} D(\theta_0)^2 \to 0 \tag{16}$$

in probability as $n \to \infty$*, where* $\bar{g}_n = \frac{1}{n} \sum_{i=1}^n g_i$*. Similarly, for* $\frac{d}{d\theta_0} D(\theta_0)$*.*

If the design is a targeted design, $g_i = g_{\theta_{i-1}}$*, then this "asymptotic stable design" condition can be concluded from the asymptotic convergence of* θ_n *to* θ_0 *as* $n \to \infty$*, and continuity of* $\theta \to g_\theta$*, by Theorem 6.*

Differentiability: *Assume*

$$\frac{1}{n} \sum_{i=1}^n \{D(\theta_n)(O_i, Z_i) - D(\theta_0)(O_i, Z_i)\} = \frac{1}{n} \sum_{i=1}^n \frac{d}{d\theta_0} D(\theta_0)(O_i, Z_i)(\theta_n - \theta_0)$$

up till (i.e., plus) a term $o_P(\| \theta_n - \theta_0 \|)$, *where* $\| \frac{d}{d\theta_0} D(\theta_0) \|_\infty < \infty$.

By the Kolmogorov Law of Large numbers for martingale sums, and by assumption (15), we have

$$\frac{1}{n}\sum_{i=1}^{n} \frac{d}{d\theta_0} D(\theta_0)(O_i, Z_i) - A_n \to 0$$

as $n \to \infty$ *a.s, where*

$$A_n \equiv E\frac{1}{n}\sum_{i=1}^{n} P_{Q_0,g_i} \frac{d}{d\theta_0} D(\theta_0).$$

Invertibility of A_n: *Assume* A_n^{-1} *exists, and* $\limsup_{n\to\infty} \| A_n^{-1} \| < \infty$. *If* $A_n \to A_0$ *for some fixed matrix* A_0, *as* $n \to \infty$, *then it suffices to assume* A_0^{-1} *exists.*

Positive Definite Covariance Matrix: *Let*

$$\Sigma(n) \equiv E\frac{1}{n}\sum_{i=1}^{n} P_{Q_0,g_i} \{D(\theta_0)\}^2 .$$

If $D(\theta_0)(O_i, Z_i) = D(\theta_0)(O_i)$, *then this reduces to* $\Sigma(n) \equiv= EP_{Q_0,\bar{g}_n} D(\theta_0)^2 = P_{Q_0,E\bar{g}_n} D(\theta_0)^2$.

Assume that for each $\lambda \in \mathbb{R}^d$ $\liminf_{n\to\infty} \lambda\Sigma(n)\lambda > 0$ *for all* λ, *or that* $\Sigma = \lim_{n\to\infty} \Sigma(n)$ *exists and is a positive definite covariance matrix.*

Then

$$\sqrt{n}(\theta_n - \theta_0) = \frac{1}{\sqrt{n}}\sum_{i=1}^{n} A_n^{-1} D(\theta_0)(O_i, Z_i) + o_P(1),$$

where $P_{Q_0,g_i} D(\theta_0) = 0$, *so that the sum is a multivariate Martingale satisfying the conditions of the Martingale central limit theorem. In particular,*

$$\Sigma(n)^{-1/2} A_n(\sqrt{n}(\theta_n - \theta_0)) \Rightarrow_d N(0, I), \text{ as } n \to \infty.$$

If $\Sigma(n) \to \Sigma$ *for some positive definite matrix* Σ *and* $A_n \to A_0$ *for an invertible matrix* A_0, *as* $n \to \infty$, *then this implies*

$$\sqrt{n}(\theta_n - \theta_0) \Rightarrow_d N(0, A_0^{-1}\Sigma A_0^{-1\top}).$$

A consistent estimate of the covariance matrix $\Sigma(n)$ *is given by*

$$\hat{\Sigma}(n) = \frac{1}{n}\sum_{i=1}^{n} \left(D(\theta_n)(O_i, Z_i) - \frac{1}{n}\sum_{i=1}^{n} D(\theta_n)(O_i, Z_i) \right)^2$$

satisfying

$$\hat{\Sigma}(n) - \Sigma(n) \to 0 \text{ in probability, as } n \to \infty.$$

Discussion of conditions. We already discussed the conditions needed for consistency of θ_n. Since θ is finite dimensional the covering number bound will hold in essentially each practical application, assuming that the estimating functions are uniformly bounded. As a consequence, the consistency of θ_n will hold whenever the design g_n allows identification of θ_0 as $n \to \infty$. The differentiability condition holds, for example, if $D(\theta)(O, Z)$ is differentiable in θ with a bounded derivative uniformly in (O, Z), and is therefore also a very mild regularity condition. The invertibility of A_0 and the positive definite matrix assumption correspond closely with simply assuming that the estimating function D identifies θ_0: $\sum_i P_{Q_0,g_i} D(\theta) = 0$ implies $\theta = \theta_0$. We conclude that, for most practical purposes, the important conditions are that the estimating function is uniformly bounded, and that the adaptive design g_n (g_n being a random conditional distribution of A_i, given X_i, in $\mathcal{G}$) is asymptotically non-random in the sense that $g_n - Eg_n$ converges, as a difference of random elements in $\mathcal{G}$, to the zero function in probability as $n \to \infty$. For example, this will hold if $g_i = g_{i,\theta_{i-1}}$ is a (possibly) i-specific deterministic function of an estimator θ_{i-1} based on $O_1, \ldots, O_{i-1}$. Thus, even if one keeps switching from one asymptotically stable targeted design to another asymptotically stable targeted design, this asymptotic stability assumption will still hold. For example, if half-way during the trial one suddenly decides that the adaptive design should be focussing on another target, then that will not violate the assumptions needed for honest asymptotic statistical inference. The important property of the adaptive design asymptotic statistical inference relies upon is that it responds to a finite number of summary measures which are asymptotically consistent, but switching between different ways of responding to these same summary measures is allowed.

Proof of Theorem 7. Because $\sum_i D(\theta_n)(O_i, Z_i) = \sum_i P_{Q_0,g_i} D(\theta_0) = 0$, we have

$$\frac{1}{n}\sum_{i=1}^{n}(D(\theta_n)(O_i, Z_i) - D(\theta_0)(O_i, Z_i)) = -\frac{1}{n}\sum_{i=1}^{n}\{D(\theta_0)(O_i) - P_{Q_0,g_i} D(\theta_0)\}.$$

By the consistency and differentiability assumption,

$$\frac{1}{n}\sum_{i=1}^{n}(D(\theta_n)(O_i) - D(\theta_0)(O_i)) = A_n(\theta_n - \theta_0) + o_P(\| \theta_n - \theta_0 \|)$$

for a uniformly (in n) invertible matrix A_n. Thus,

$$(\theta_n - \theta_0) = -A_n^{-1}\frac{1}{n}\sum_{i=1}^{n}\{D(\theta_0)(O_i, Z_i) - P_{Q_0,g_i} D(\theta_0)\} + o_P(\| \theta_n - \theta_0 \|). \quad (17)$$

The first term on the right hand side is a martingale sum. Because of the bounded estimating function, asymptotically stable design, and positive definite covariance matrix assumptions, we can apply Theorem 17 to $1/\sqrt{n}\sum_i\{D(\theta_0)(O_i,Z_i)-P_{Q_0,g_i}D(\theta_0)\}$, which gives us that the standardized version of this martingale sum converges to a standard multivariate normal distribution:

$$\Sigma(n)^{-0.5}\frac{1}{\sqrt{n}}\sum_{i=1}^{n}\{D(\theta_0)(O_i,Z_i)-P_{Q_0,g_i}D(\theta_0)\}\Rightarrow_d N(0,I). \tag{18}$$

Substitution of this result in (17) shows that $\parallel\theta_n-\theta_0\parallel=O_P(1/\sqrt{n})+o_P(\parallel\theta_n-\theta_0\parallel)$, which proves that $\parallel\theta_n-\theta_0\parallel=O_P(1/\sqrt{n})$. Therefore, the $o_P(\parallel\theta_n-\theta_0\parallel)$ in (17) can be replaced by $o_P(1/\sqrt{n})$, giving us

$$A_n(\sqrt{n}(\theta_n-\theta_0))=-\frac{1}{\sqrt{n}}\sum_{i=1}^{n}\{D(\theta_0)(O_i,Z_i)-P_{Q_0,g_i}D(\theta_0)\}+o_P(1).$$

By (18), this gives us the wished result:

$$\Sigma(n)^{-0.5}A_n(\sqrt{n}(\theta_n-\theta_0))\Rightarrow_d N(0,I).$$

The fact that $\hat{\Sigma}(n)$ consistently estimates $\Sigma(n)$ is a consequence of Theorem 18, the consistency of θ_n to θ_0, and the assumption that $P_{Q_0,g_n}D(\theta_0)\to 0$ in probability as $n\to\infty$. This completes the proof of Theorem 7. □

12 The One Step Targeted MLE.

Consider the Q_0-factor of the likelihood (3) of $(O_1,\ldots,O_n)\sim P_{Q_0,\mathbf{g}}$ with $O_i=(A_i,L_i=X_i(A_i))$ for an adaptive design $\mathbf{g}=(g_1,\ldots,g_n)$:

$$L_n(Q_0)=\prod_{i=1}^{n}Q_0(O_i).$$

Let $\psi_0=\Psi(Q_0)\in\mathbb{R}^d$ be the Euclidean parameter of interest for a parameter mapping $Q\to\Psi(Q)$ on a model $\mathcal{Q}$ for Q_0. It is assumed that Ψ is path-wise differentiable at any fixed design $P_{Q_0,g_0}\in\mathcal{M}(g_0)\equiv\{P_{Q,g}:Q\in\mathcal{Q}\}$, $g_0\in\mathcal{G}$, in the fixed design CAR-model $\mathcal{M}(g_0)$, and let $D^*(Q,g)$ denote the efficient influence curve/canonical gradient of the path-wise derivative at a fixed design distribution $P_{Q,g}\in\mathcal{M}(g)$. Recall that each density $p_{Q,g}$ in this fixed design model $\mathcal{M}(g)$ factorizes, by CAR: $p_{Q,g}(A,L)=Q(A,L)g(A\mid X)$. The goal is to construct a likelihood based estimator of ψ_0 under sampling $O_1,\ldots,O_n$ from an adaptive design data generating distribution $P_{Q_0,\mathbf{g}}$ (3) in the model

$\{P_{Q,\mathbf{g}} : Q \in \mathcal{Q}\}$. However, it is assumed that $\mathcal{Q}$ is a semi-parametric and high dimensional (e.g., nonparametric) model for Q_0 so that a standard MLE is not possible due to the curse of dimensionality.

Consider a parametric sub-model/working model $\mathcal{Q}^w = \{Q_\theta : \theta \in \Theta\} \subset \mathcal{Q}$ of $\mathcal{Q}$.

The standard MLE for the working model $\mathcal{Q}^w$ targets the "parameter" $\arg\max_{\theta\in\Theta} \sum_{i=1}^n P_{Q_0,g_i} \log Q_\theta$, which equals $\Theta_{\bar{g}_n}(Q_0) \equiv \arg\max_{\theta\in\Theta} P_{Q_0,\bar{g}_n} \log Q_\theta$, where $\bar{g}_n = 1/n \sum_{i=1}^n g_i$. Thus, a standard working model MLE does correspond with a data adaptive choice $\bar{g}_n$ for g^* in the Q_0-parameter $\Theta_{g^*}(Q_0) = \arg\max_{\theta\in\Theta} P_{Q_0,g^*} \log Q_\theta$, which heavily complicates the analysis of this estimator: in particular, it will become important how fast $\bar{g}_n$ converges to its unknown limit fixed design. Therefore we focussed in Section 8 on an estimator of $\Theta_{g^*}(Q_0)$ for a known fixed design g^* or sequentially estimated g^* so that the resulting estimator θ_n solves a martingale based estimating equation.

Specifically, in Subsection 8.4 we proposed estimators of $\Theta_{g^*}(Q_0)$ for a fixed known g^*. We showed that one can estimate Θ_{g^*} with a weighted MLE by assigning weights $w_i = g^*/g_i$, $i = 1, \ldots, n$, to the standard MLE. This weighted MLE corresponds with solving the Martingale estimating function $D(\theta)(O_i, Z_i) = S(\theta)g^*/g_{Z_i}$ for $\theta_0 = \Theta_{g^*}(Q_0)$, where $S(\theta)$ is the score at θ.

In addition, we also showed in Subsection 8.5 that one can empirically adjust the weighting g^*/g_i sequentially, based on a design function g_θ, so that the final and only used weighting will be g_{θ_n}/g_i, (e.g., $g_i = g_{\theta_{i-1}}$), which will likely result in more stable weights, and therefore represents our method of choice in practice. We also showed in Subsection 8.5 that this data adaptively weighted MLE θ_n can be viewed as a solution of a Martingale equation (along with other parameters not further used).

In general, in the following presentation of the one-step targeted MLE, θ_n can represent any estimator solving

$$\frac{1}{n}\sum_{i=1}^n D(\theta_n)(O_i, Z_i) = 0,$$

for some Martingale estimating function $D(\theta)$, and $\theta_0 \in \Theta$ represents a fixed (non-random) solution of $P_{Q_0,g_i} D(\theta_0) = 0$ for all i. The estimator Q_{θ_n} represents the initial estimator in the one-step targeted MLE update.

The (e.g., weighted ML) estimator Q_{θ_n} of Q_0 for a misspecified working model $\mathcal{Q}^w = \{Q_\theta : \theta \in \Theta\}$ (i.e., $Q_0 \notin \mathcal{Q}^w$) will typically map into a biased estimator $\Psi(Q_{\theta_n})$ of $\psi_0 = \Psi(Q_0)$: i.e., $\Psi(Q_{\theta_0}) \neq \Psi(Q_0)$. However, as shown in van der Laan and Rubin (2006) *for fixed designs*, one can select an ϵ-fluctuation $\{Q_{\theta_n}(\epsilon) : \epsilon\}$ of this estimator Q_{θ_n} with parameter ϵ so that maximum likelihood

estimation of ϵ results in a drastic reduction in asymptotic bias of $\Psi(Q_{\theta_n}(\epsilon_n))$ w.r.t. ψ_0: in fact, as shown in van der Laan and Rubin (2006) this one-step update or an iteration of this update maps an inconsistent estimator $\Psi(Q_{\theta_n})$ into a consistent and asymptotically normally distributed estimator of ψ_0. In this section we are concerned with constructing such a targeted MLE update of Q_{θ_n} and corresponding targeted MLE of ψ_0, as originally presented in van der Laan and Rubin (2006) for fixed CAR designs (i.e., $O_1, \ldots, O_n$ i.i.d. $P_{Q_0,g}$), for general adaptive CAR designs for $(O_1, \ldots, O_n) \sim P_{Q_0,\mathbf{g}}$ at $Q_0 \in \mathcal{Q}$.

For any $Q \in \mathcal{Q}$ and fixed design $g \in \mathcal{G}$, let $D^*(Q, g)$ be the efficient influence curve of Ψ at corresponding density $p_{Q,g} = Qg$ in the model $\mathcal{M}(g) = \{p_{Q,g} : Q \in \mathcal{Q}\}$. Before we proceed to provide the definition of the targeted MLE for adaptive designs, we wish to explain in general terms that D^* is an estimating function for densities targeted towards the parameter of interest ψ_0, since this will provide the fundamental motivation and robustness property of the targeted MLE w.r.t. misspecification of the working model $\mathcal{Q}^w$.

The (efficient) influence curve estimating function targets the parameter of interest: If the parameter Ψ is linear and the model is convex, then one will typically have for any $g \in \mathcal{G}$, and thus also for the random fixed design $g_{Z_i} \in \mathcal{G}$, $P_{Q_0,g}D^*(Q, g) = \Psi(Q_0) - \Psi(Q)$ for all $Q \in \mathcal{Q}$ (van der Laan (1998)), which makes D^* an estimating function fully targeted towards the parameter ψ_0: that is, $P_{Q_0,g}D^*(Q, g) = 0$ implies $\Psi(Q) = \psi_0$. In general, by the general representation theorem for the efficient influence curve as a Double robust Inverse Probability of Censoring Weighted mapping on a full data estimating function/gradient (Theorem 1.3, van der Laan and Robins (2003)), we have for any influence curve $D(Q, g)$ $P_{Q_0,g}D(Q, g) = E_0D^F(Q)(X)$ for a full data estimating function/gradient D^F of the path-wise derivative of Ψ in the full data model for ψ_0. Thus, if $P_{Q_0,g}D(Q, g) = 0$, then this implies $E_0D^F(Q)(X) = 0$. As a consequence, if $E_0D^F(Q)(X) = 0$ implies $\Psi(Q) = \psi_0$, then again the estimating function D, and, in particular, D^*, is fully targeted at ψ_0.

Even if Ψ is not linear or the model is not convex, and the latter identifiability property of the full data gradient does not fully (not for all $Q \in \mathcal{Q}$) apply, by the fact that D (or D^F) is a gradient of the path-wise derivative of Ψ (Chapter 1, van der Laan and Robins (2003)), the estimating function D will typically satisfy this relation up till a second order term, and therefore it is still an estimating function targeting ψ_0: $E_0D^F(Q)$ will behave like $\Psi(Q_0) - \Psi(Q)$ plus a second order difference between Q and Q_0. In particular, Q will at most need to correctly specify a nuisance parameter required to evaluate $D^F(Q)$.

In this section we present two one-step Targeted MLE's. These targeted MLE's generalize the one-step targeted MLE in van der Laan and Rubin (2006) for fixed designs. Our central limit theorem presented in Section 14 below applies to each of these targeted MLE's.

12.1 One step targeted MLE for adaptive designs.

In this subsection we will present two simple one step targeted MLE of ψ_0 based on the initial (e.g., ML) estimator Q_{θ_n} of Q_0 according to a working model $\mathcal{Q}^w = \{Q_\theta : \theta \in \Theta\}$.

For a given $Q \in \mathcal{Q}$, let $\{Q_g(\epsilon) : \epsilon\} \subset \mathcal{Q}$ be a path crossing Q at $\epsilon = 0$ (i.e., $Q(0) = Q$) indexed by a choice of fixed design $g \in \mathcal{G}$. It is recommended to satisfy

$$\frac{d}{d\epsilon} \log Q_g(\epsilon)(O)\Big|_{\epsilon=0} = D^*(Q, g)(O), \tag{19}$$

where $D^*(Q, g)$ is the efficient influence curve of Ψ at $P_{Q,g} \in \mathcal{M}(g) = \{P_{Q_1,g} : Q_1 \in \mathcal{Q}\}$. In this manner $Q_g(\epsilon)$ represents an optimal stretching strategy in which a small stretch of Q as measured by ϵ maximizes the change in the parameter of interest Ψ. This latter statement follows from the fact that for a path $Q(\epsilon)$ with score $s = \frac{d}{d\epsilon} \log Q(\epsilon)\Big|_{\epsilon=0}$ we have

$$\frac{d}{d\epsilon} \Psi(Q(\epsilon))\Big|_{\epsilon=0} = E_{Q,g} D^*(Q, g)(O) s(O),$$

and the Cauchy-Schwarz inequality (so that among all scores s with variance 1 the optimal score is $D^*(Q, g)$). (This latter property (19) is not required to establish consistency and asymptotic normality of the resulting estimator of ψ_0.) If the choice g is a targeted design choice g_Q corresponding with Q itself, then the latter condition gives:

$$\frac{d}{d\epsilon} \log Q(\epsilon)(O)\Big|_{\epsilon=0} = D^*(Q, g_Q)(O). \tag{20}$$

We will apply this path to Q_{θ_n} so that for a choice g such as $g = g_{\theta_n}$ condition (19) yields

$$\frac{d}{d\epsilon} \log Q_{\theta_n, g_{\theta_n}}(\epsilon)(O)\Big|_{\epsilon=0} = D^*(Q_{\theta_n}, g_{\theta_n})(O).$$

If the adaptive design g_n is itself a targeted design, $g_n = g_{\theta_{n-1}}$, then we recommend to set $g = g_\theta$ equal to the design function the actual adaptive design is based upon.

Although, the score condition (19) on this path $\{Q(\epsilon) : \epsilon\}$ is not necessary for the asymptotic normality and robustness of the targeted MLE of ψ_0, as is evident from our next CLT theorem, it does typically imply that our definition of one-step targeted-MLE update of the initial Q_{θ_n}, as defined in the next paragraph below, corresponds with maximizing or increasing the likelihood over ϵ, which is a nice property to have for finite sample performance. At the end of this subsection we present valid approaches in the context that the efficient influence curve $D^*(Q, g)$ is too complex to calculate, but ad hoc (and reasonably efficient) influence curves $D(Q, g)$ are available.

Let ϵ_n be a value, preferably so that the likelihood of $O_1, \ldots, O_n$ at $Q_{\theta_n}(\epsilon_n) = Q_{\theta_n, g_{\theta_n}}(\epsilon_n)$ (i.e., $\prod_i Q_{\theta_n}(\epsilon_n)(O_i)$) is larger than the likelihood at Q_{θ_n} (i.e., $\epsilon = 0$), either solving the equation

$$\frac{1}{n}\sum_{i=1}^{n} D^*(Q_{\theta_n}(\epsilon_n), g_{Z_i})(O_i) = 0 \text{ or } o_P(1/\sqrt{n}),$$

or solving the equation

$$\frac{1}{n}\sum_{i=1}^{n} D^*(Q_{\theta_n}(\epsilon_n), g_{\theta_n})(O_i)\frac{g_{\theta_n}(A_i \mid x_i)}{g_{Z_i}(A_i \mid X_i)} = 0 \text{ or } o_P(1/\sqrt{n}).$$

Given the resemblance of the one-step targeted MLE with the iterative targeted MLE in Section 13, it can be argued that this solution ϵ_n will typically correspond with increase in likelihood relative to $\epsilon = 0$, and in various of our examples ϵ_n happens to be equal to an actual weighted maximum likelihood estimator over ϵ.

If multiple solutions exist, then one selects the one which maximizes the likelihood of $O_1, \ldots, O_n$. If no solutions exists, one finds first an ϵ_n^1 increasing the likelihood, update the estimate of Q_0 with $Q_n^1 = Q_{\theta_n}(\epsilon_n^1)$, create the path $Q_n^1(\epsilon)$ as above, and one defines ϵ_n as the solution of one of these equations above with Q_{θ_n} replaced by the updated Q_n^1. If still no solution can be found, one iterates this process till a solution is found or till convergence. If the score condition (19) holds, then, under weak conditions, the sequence Q_n^k converges in k to a solution of the efficient influence curve equation (even if for each k no solution exists), as shown in van der Laan and Rubin (2006). We will not further repeat this modification, but proceed as if a solution ϵ_n can be found at the first try.

Let ϵ_0 be the asymptotic target of ϵ_n satisfying:

$$P_{Q_0,g_i} D^*(Q_{\theta_0}(\epsilon_0), g_i) = 0, \ i = 1, \ldots, n,$$

or

$$P_{Q_0,g_i}D^*(Q_{\theta_0}(\epsilon_0),g_{\theta_0})\frac{g_{\theta_0}}{g_i}=0,\ i=1,\ldots,n,$$

where $Q_{\theta_0}(\epsilon_0)=Q_{\theta_0,g_{\theta_0}}(\epsilon_0)$ corresponds with a choice $g_0=g_{\theta_0}\in\mathcal{G}$ fully identified by θ_0. Since, by the fact that D^* is an influence curve/gradient, $P_{Q_0,g}D^*(Q,g)=E_{Q_0}D^F(Q)$, as explained above, $P_{Q_0,g_i}D^*(Q_{\theta_0}(\epsilon_0),g_i)=E_{Q_0}D^F(Q_{\theta_0}(\epsilon_0))$ does not depend on i so that this condition follows if ϵ_0 is defined as solution of $E_{Q_0}D^F(Q_{\theta_0}(\epsilon_0))=0$. If $g_{\theta_0}/g_i<\infty$, then by the same argument

$$\begin{aligned}P_{Q_0,g_i}D^*(Q_{\theta_0}(\epsilon_0),g_{\theta_0})\frac{g_{\theta_0}}{g_i} &= P_{Q_0,g_{\theta_0}}D^*(Q_{\theta_0}(\epsilon_0),g_{\theta_0})\\ &= E_{Q_0}D^F(Q_{\theta_0}(\epsilon_0)),\end{aligned}$$

so that also for this choice of estimating function ϵ_0 is defined as the solution of $E_{Q_0}D^F(Q_{\theta_0}(\epsilon))=0$.

Given ϵ_n, our one step targeted (towards ψ_0) MLE (update of) Q_{θ_n} is defined as $Q_{\theta_n}(\epsilon_n)=Q_{\theta_n,g_{\theta_n}}(\epsilon_n)$, and our resulting one step targeted ML estimator of ψ_0 is given by the substitution estimator $\Psi(Q_{\theta_n}(\epsilon_n))$. The theorem below is concerned with the analysis of this estimator.

In our CLT Theorem 8 for this one-step targeted MLE presented in a later section, we assume the path $Q_{\theta,g_\theta}(\epsilon)$ for a choice g_θ. Then, we can define the Martingale estimating function

$$D(\theta,\epsilon)(O_i,Z_i)\equiv(D(\theta)(O_i,Z_i),D^*(Q_{\theta,g_\theta}(\epsilon),g_{Z_i})(O_i)),$$

or

$$D(\theta,\epsilon)(O_i,Z_i)\equiv\left(D(\theta)(O_i,Z_i),D^*(Q_{\theta,g_\theta}(\epsilon),g_\theta)(O_i)\frac{g_\theta(A_i\mid X_i)}{g_i(A_i\mid X_i)}\right).$$

Thus, $D(\theta,\epsilon)$ is the vector estimating function obtained by stacking the Martingale estimating function $D(\theta)$ for θ_0 onto the efficient influence curve based martingale estimating function $D^*(Q_\theta(\epsilon),g_i)$ or $D^*(Q_\theta(\epsilon),g_\theta)g_\theta/g_i$ for ϵ_0. We have

$$\begin{aligned}0 &= \frac{1}{n}\sum_{i=1}^n D(\theta_n,\epsilon_n)(O_i,Z_i)\\ 0 &= P_{Q_0,g_i}D(\theta_0,\epsilon_0),\ i=1,\ldots,n.\end{aligned}$$

As a consequence, we can apply Theorem 7 to this augmented Martingale estimating function $D(\theta,\epsilon)$, or equivalently, we can apply Theorem 8 to establish

consistency and asymptotic normality of $\psi_n = \Psi(Q_{\theta_n}(\epsilon_n))$ at $\sqrt{n}$-rate as an estimator of the parameter $\Psi(Q_{\theta_0}(\epsilon_0))$. It remains to show that $\Psi(Q_{\theta_0}(\epsilon_0)) = \psi_0$: i.e., that the ϵ_0-target is indeed providing the wished robustness.

Consider the second choice of Martingale estimating function for ϵ_0, given θ_0: the same argument applies to the first. Under the assumption that $g_{\theta_0}/g_i < \infty$, and that ϵ_0, θ_0 solve the expectation under P_{Q_0,g_i} of the martingale estimating function, we have

$$\begin{aligned} 0 &= P_{Q_0,g_i} D^*(Q_{\theta_0}(\epsilon_0), g_{\theta_0}) \frac{g_{\theta_0}}{g_i} = P_{Q_0,g_{\theta_0}} D^*(Q_{\theta_0}(\epsilon_0), g_{\theta_0}) \\ &= E_0 D^F(Q_{\theta_0}(\epsilon_0)). \end{aligned}$$

Thus, if $E_0 D^F(Q) = 0$ implies $\Psi(Q) = \psi_0$, then it follows that $\Psi(Q_{\theta_0}(\epsilon_0)) = \psi_0$. In this case, our CLT theorem proves that $\psi_n = \Psi(Q_{\theta_n}(\epsilon_n))$ is a consistent and asymptotically normally distributed estimator of ψ_0. Specifically, one can argue that it satisfies the Martingale asymptotic linearity result:

$$\psi_n - \psi_0 = \frac{1}{n} \sum_{i=1}^{n} D^*(Q_{\theta_0}(\epsilon_0), g_{\theta_0}) \frac{g_{\theta_0}}{g_i} + o_P(1/\sqrt{n}).$$

As a consequence, if $g_i = g_{\theta_{i-1}}$ is a targeted design based on design function $\theta \to g_\theta$, then ψ_n is asymptotically normally distributed with covariance matrix equal to the covariance matrix of the fixed design efficient influence curve $D^*(Q_{\theta_0}(\epsilon_0), g_{\theta_0})$ at $Q_{\theta_0}(\epsilon_0)$ and g_{θ_0} under sampling from fixed design $P_{Q_0,g_{\theta_0}}$. Thus, by using the adaptive design, the targeted ML estimator is able to achieve the performance one would have had with the unknown wished fixed design g_{θ_0}.

Remark: Generalization of one-step Targeted MLE of fixed designs. If $O_1, \ldots, O_n$ are actually i.i.d. P_{Q_0,g_0} for some fixed CAR design g_0, then $g_i = g_0$ and one would set $g_\theta = g_0$ so that $w_i = 1$. Indeed, in this case the two one-step targeted MLE's presented above are identical to the one-step targeted MLE as presented in van der Laan and Rubin (2006) for fixed designs.

Remark: Generalization to the use of any gradient instead of efficient influence curve in the ϵ-update. We can also define ϵ_n as solution of

$$0 = \sum_{i=1}^{n} D(Q_{\theta_n,g_{\theta_n}}(\epsilon_n), g_i)(O_i), \tag{21}$$

or

$$0 = \sum_{i=1}^{n} D(Q_{\theta_n,g_{\theta_n}}(\epsilon_n), g_{\theta_n}) \frac{g_{\theta_n}(A_i \mid X_i)}{g_i(A_i \mid X_i)}, \tag{22}$$

where $D(Q,g)$ is a gradient of the path-wise derivative of $\Psi : \mathcal{M} \to \mathbb{R}^d$ at $P_{Q,g}$ in the fixed design model $\mathcal{M}(g) = \{P_{Q_1,g} : Q_1 \in \mathcal{Q}\}$. That is, if the efficient influence curve D^* is not available in closed form, then one could decide to replace it by another influence curve/gradient which does exist in closed form. An example of this kind of targeted estimator is the Inverse Probability of Censoring Weighted Reduced Data Targeted MLE as presented in a later section.

In this case, application of Theorem 8 yields, under the stated regularity conditions, that the resulting estimator one-step targeted MLE ψ_n satisfies

$$\psi_n - \psi_0 = \frac{1}{n}\sum_{i=1}^{n} D(Q_{\theta_0}(\epsilon_0), g_{\theta_0})(O_i)\frac{g_{\theta_0}(A_i \mid X_i)}{g_i(A_i \mid X_i)} + o_P(1/\sqrt{n}).$$

As a consequence, if $g_i \to g_{\theta_0}$ as $i \to \infty$, then the asymptotic limit distribution of $\sqrt{n}(\psi_n - \psi_0)$ is now equivalent with the multivariate normal distribution of an asymptotically linear estimator of ψ_0 with influence curve $D(Q_{\theta_0}(\epsilon_0), g_{\theta_0})$ under a fixed design $P_{Q_0,g_{\theta_0}}$. Although, replacing the efficient influence curve by another influence curve negatively affects the efficiency of ψ_n, these kind of estimators will be practically appealing in models in which the efficient influence curve does not exist in closed form.

In this context in which the efficient influence curve is too complex, one will also need to decide what kind of paths $Q_{\theta,g}(\epsilon) \in \mathcal{Q}$ through Q_θ to use. A path with score $D(Q,g)$ at $\epsilon = 0$ will typically not be a valid submodel of $\mathcal{Q}$ since $D(Q,g)$ is not a score at $P_{Q,g}$: recall, that the efficient influence curve is the only influence curve which can be approximated by linear combinations of scores. We wish to select a path $Q_{\theta,g}(\epsilon)$ through Q_θ at $\epsilon = 0$, and which increases the likelihood at a solution ϵ_n of (22) (or, if one uses the first equation, then (21)). Natural extensions supported by the data might be available (e.g., adding a related covariate to the current regression model fit Q_{θ_n}), so that ϵ_n (which is targeted to obtain an unbiased improved fit for ψ_0) will typically result in an increased likelihood relative to $\epsilon = 0$. One could also define a user supplied class of extensions and maximize the information bound for ψ_0 at $\epsilon = 0$ for each of these extensions, so that the resulting proposed extension (identifies a good stretching strategy and) generalizes the efficient influence curve based extension (maximizing over all allowed extensions) provided above.

Targeted log-likelihood loss function for selection. As in van der Laan and Rubin (2006), we can view $-\log Q(\epsilon_0)$ as a new so called targeted log likelihood loss function for Q (compare with standard $-\log Q$ log likelihood loss), indexed by the nuisance parameter ϵ_0, where $E_{Q_0} D^F(Q(\epsilon_0)) = 0$ by definition

of ϵ_0. The corresponding targeted log likelihood and cross-validated targeted log-likelihood can now be used to select among different initial estimators Q_{θ_n} (i.e., working models) or to make other selections of fine tuning parameters.

Why not use a path indexed by adaptive design itself? The simplest generalization of the targeted MLE for fixed designs would be to replace the path $Q_{\theta,g}(\epsilon)$ describing the fluctuation of an initial Q_θ indexed by fixed design g, by a path $Q_{\theta,g_i}(\epsilon)$ and let ϵ_0 be solution of $\sum_i P_{Q_0,g_i} D^*(Q_{\theta_0,g_i}(\epsilon), g_i) = 0$. However, this latter equation reduces now to $E_{Q_0} D^F(Q_{\theta_0,g_i}(\epsilon)) = 0$ for the corresponding full data gradient D^F, which makes ϵ_0 a function of the g_i's and thereby random. This is the reason for using a path at $g = g_\theta$ as in our presentation of the one-step targeted MLE's above: either use $D(Q_{\theta,g_\theta}(\epsilon), g_i)$ or $D(Q_{g_\theta}(\epsilon), g_\theta) g_\theta / g_i$.

13 An iterative targeted MLE.

As in the previous section, for a given $Q \in \mathcal{Q}$ and $g \in \mathcal{G}$, consider a path $\{Q_g(\epsilon) : \epsilon\}$ with $Q_g(0) = Q$ and

$$\left. \frac{d}{d\epsilon} \log Q_g(\epsilon) \right|_{\epsilon=0} = D^*(Q, g), \tag{23}$$

where $D^*(Q, g)$ is the canonical gradient (i.e., efficient influence curve) of $\Psi : \mathcal{M} \to \mathbb{R}^k$ at a fixed design $P_{Q,g} \in \mathcal{M} = \{P_{Q,g} : Q \in \mathcal{Q}, g \in \mathcal{G}\}$. Let θ_n be a solution of a Martingale estimating equation $0 = \sum_i D(\theta)(O_i, Z_i) = 0$ based on a working model $\{Q_\theta : \theta \in \Theta\}$, where we recall that such estimators are discussed above, and presented in previous Section 8. The iterative targeted MLE represents takes an initial estimator Q_{θ_n} and maps it into an update.

The iterative Targeted MLE (update of Q_{θ_n}): Consider a mapping/design function $\theta \to g_\theta \in \mathcal{G}$. To maximize stability of the weighting in the targeted MLE presented below, one should try to select this mapping so that the actual adaptive design g_n is well approximated by g_{θ_n}: i.e., if g_n equals a targeted adaptive design $g_{\theta_{n-1}}$ based on design function $\theta \to g_\theta$, then we recommend this choice. Given this choice of $\theta \to g_\theta$, consider the MLE of ϵ

$$\epsilon_n^1 = \arg\max_\epsilon \sum_{i=1}^n \log Q_{\theta_n, g_{\theta_n}}(\epsilon)(O_i) w_i,$$

where $w_i = \frac{g_{\theta_n}(A_i|X_i)}{g_i(A_i|X_i)}$, $i = 1, \ldots, n$. For notational convenience, let $Q_n^0 \equiv Q_{\theta_n}$. The MLE ϵ_n^1 defines an update $Q_n^1 = Q_n^0(\epsilon_n^1)$ of Q_n^0. Note that $Q_n^1 = Q_{\theta_n}(\epsilon_n^1)$ is

defined by (θ_n, ϵ_n^1). We also note that under a standard regularity condition, ϵ_n^1 solves its score equation and is thus a solution of the estimating equation $0 = \sum_i D^0(\theta_n, \epsilon_n^1)(O_i, Z_i) = 0$, where

$$D^0(\theta_0, \epsilon_0^1) \equiv \frac{d}{d\epsilon_0^1} \log Q_{\theta_0 g_{\theta_0}}(\epsilon_0^1) \frac{g_{\theta_0}}{g_i}.$$

We now iterate this ML-step to define a sequence of updates $Q_n^{k+1} = Q_n^k(\epsilon_n^{k+1})$, starting with $Q_n^0 = Q_{\theta_n}$, where $Q_n^k(\epsilon) = Q_{n g_{\theta_n}}^k(\epsilon)$ is the path $Q_g(\epsilon)$ with $Q = Q_n^k$ and $g = g_{\theta_n}$ as defined above. Thus

$$\epsilon_n^k = \arg\max_{\epsilon} \sum_{i=1}^n \log Q_{n g_{\theta_n}}^{k-1}(\epsilon)(O_i) w_i, \ k = 1, \ldots,$$

where $w_i = g_{\theta_n}/g_i$ as above. We iterate this till $\epsilon_n^k \approx 0$, and the iterative targeted MLE update of Q_{θ_n} is defined as Q_n^k for this large enough k, and the corresponding targeted MLE of ψ_0 is defined as $\psi_n = \Psi(Q_n^k)$.

In the following subsection we show that one can still view this iterative targeted MLE update as a solution of a martingale estimating equation so that our CLT-theorem 8 can be applied. In particular, under the appropriate regularity conditions, it will satisfy the Martingale asymptotic linearity result:

$$\psi_n - \psi_0 = \frac{1}{n} \sum_{i=1}^n D^*(Q_0^{k+1}, g_{\theta_0}) \frac{g_{\theta_0}}{g_i} + o_P(1/\sqrt{n}),$$

where Q_0^{k+1} represents the target/limit of the $k+1$-th step targeted MLE update $Q_n^{k+1} = Q_n^k(\epsilon_n^{k+1})$. Statistical inference can now be based on this asymptotic linearity result. As a consequence, if $g_i = g_{\theta_{i-1}}$ is a targeted design based on design function $\theta \to g_\theta$, then ψ_n is asymptotically normally distributed with covariance matrix equal to the covariance matrix of the fixed design efficient influence curve $D^*(Q_0^k(\epsilon_0^{k+1}), g_{\theta_0})$ at $Q_0^k(\epsilon_0^{k+1})$ and g_{θ_0} under sampling from fixed design $P_{Q_0, g_{\theta_0}}$. Thus, by using the adaptive design, the iterative targeted ML estimator is able to achieve the performance one would have had with the unknown wished fixed design g_{θ_0}.

13.1 Martingale Estimating Function for the Iterative Targeted MLE:

We will now show that our Theorem 8 can indeed be applied to analyze this iterative targeted MLE.

The true value ϵ_0^1 is given by

$$\epsilon_0^1 = \epsilon_{g_{\theta_0}}^1(Q_0) \equiv \arg\min_{\epsilon} P_{Q_0,g_{\theta_0}} \log Q_{\theta_0}(\epsilon).$$

Thus, the joint parameter $(\theta_n^0, \epsilon_n^1)$ is a solution of a joint martingale estimating equation defined by the martingale estimating function $D^1(\theta_0, \epsilon_0^1) \equiv (D(\theta_0), D^0(\theta_0, \epsilon_0^1))$ for (θ_0, ϵ_0^1): $P_{Q_0,g_i} D^1(\theta_0, \epsilon_0^1) = 0$ for all i, and $\sum_i D^1(\theta_n, \epsilon_n^1)(O_i, Z_i) = 0$.

Similarly, since ϵ_n^k is a MLE, under a mild regularity condition it will solve its score equation

$$0 = \sum_i \frac{d}{d\epsilon_n^k} \log Q_{ng_{\theta_n}}^{k-1}(\epsilon_n^k)(O_i) w_i.$$

Thus, ϵ_n^k solves the estimating equation $\sum_i D^k(\theta_n, \epsilon_n^1, \ldots, \epsilon_n^{k-1}, \epsilon) = 0$ in ϵ, where $D^k(\cdot, \epsilon)(O_i, Z_i) = \frac{d}{d\epsilon} \log Q_\cdot(\epsilon) w_i$, $\cdot$ represents $(\theta_n, \epsilon_n^0, \ldots, \epsilon_n^{k-1})$ and we index $Q_n^k = Q_{\theta_n}(\epsilon_n^1, \ldots, \epsilon_n^k)$ by a vector $\theta_n^k = (\theta_n, \epsilon_n^0, \ldots, \epsilon_n^k)$. The joint estimate $\theta_n^k = (\theta_n, \epsilon_n^0, \ldots, \epsilon_n^k)$ is a solution of a Martingale estimating equation implied by a stacked Martingale estimating function

$$\mathbf{D}^k(\theta_n^k) = \mathbf{D}^k(\theta_n, \epsilon_n^1, \ldots, \epsilon_n^k) = (D(\theta_n), D^1(\theta_n, \epsilon_n^1), \ldots, D^k(\theta_n, \epsilon_n^1, \ldots, \epsilon_n^k)).$$

We have that $\mathbf{D}^k$ is the martingale estimating function for θ_n^k obtained by stacking the estimating functions for ϵ_n^j, given $\theta_n, \epsilon_n^1, \ldots, \epsilon_n^{j-1}$, $j = 0, \ldots, k-1$, on top of the estimating function for θ_n, as above. To summarize, we have $\sum_i \mathbf{D}^k(\theta_n^k)(O_i, Z_i) = 0$ and at the true values we have $P_{Q_0,g_i} D^k(\theta_0^k) = 0$, completely analogue as above for $k = 1$.

In addition, since the log-likelihood increases at each step, under a mild regularity condition (see also van der Laan and Rubin (2006)), we have $\epsilon_n^k \to 0$ as $k \to \infty$. By (23) and $\epsilon_n^k \to 0$ as $k \to \infty$, it is also a mild condition to assume that for k large enough ϵ_n^{k+1} solves approximately the score equation at 0

$$\sum_{i=1}^n D^*(Q_n^k(\epsilon_n^{k+1}), g_{\theta_n})(O_i) \frac{g_{\theta_n}}{g_i} = o_P(1/\sqrt{n}). \tag{24}$$

That is, this iterative algorithm will converge to a solution of $\sum_i D^*(Q, g_{\theta_n}) g_{\theta_n}/g_i = 0$ in Q as k converges to infinity. For this large enough k, we define $\theta_n^k = (\theta_n, \epsilon_n^1, \ldots, \epsilon_n^k)$ and denote Q_n^k with $Q_{\theta_n^k}$.

We have $\sum_{i=1}^n \mathbf{D}^k(Q_{\theta_n^k}) = 0$ and $\sum_i D^*(Q_{\theta_n^k}(\epsilon_n^{k+1}), g_{\theta_n}) g_{\theta_n}/g_i = o_P(1/\sqrt{n})$. In addition, we can define the true parameter values θ_0^k and ϵ_0^{k+1} as above, where θ_0^k solves $\sum_i P_{Q_0,g_i} \mathbf{D}^k(\theta_0^k) = 0$ and, given θ_0^k, ϵ_0^{k+1} solves $\sum_i D^*(Q_{\theta_0^k}(\epsilon_0^{k+1}), g_{\theta_0}) g_{\theta_0}/g_i = 0$. To summarize, we have $\sum_i \mathbf{D}^k(\theta_n^k)(O_i, Z_i) = 0$, $\sum_i D^*(Q_{\theta_n^k}(\epsilon_n^{k+1}), g_{\theta_0})(O_i) g_{\theta_0}(A_i \mid$

$X_i)/g_i(A_i \mid X_i) = 0$, $P_{Q_0,g_i}\mathbf{D}^k(\theta_0^k) = 0$, and $P_{Q_0,g_i}D^*(Q_{\theta_0^k}(\epsilon_0^{k+1}), g_{\theta_0})g_{\theta_0}/g_i$ for all i. Thus, we can apply Theorem 8 to establish consistency and asymptotic normality of $\psi_n = \Psi(Q_{\theta_n^k}(\epsilon_n^{k+1}))$ at $\sqrt{n}$-rate as an estimator of $\Psi(Q_{\theta_0^k}(\epsilon_0^{k+1}))$.

Under the assumption that $g_{\theta_0}/g_i < \infty$, we also have

$$\begin{aligned} 0 &= P_{Q_0,g_i}D^*(Q_{\theta_0^k}(\epsilon_0^{k+1}), g_{\theta_0})\frac{g_{\theta_0}}{g_i} = P_{Q_0,g_{\theta_0}}D^*(Q_{\theta_0^k}(\epsilon_0^{k+1}), g_{\theta_0}) \\ &= E_0 D^F(Q_{\theta_0^k}(\epsilon_0^{k+1})) = 0. \end{aligned}$$

Thus, if $E_0D^F(Q) = 0$ implies $\Psi(Q) = \psi_0$, then it follows that ψ_n is a consistent and asymptotically normally distributed estimator of ψ_0.

Remark I: First step Targeted MLE. Based on the results in van der Laan and Rubin (2006) and simulations for the targeted MLE in fixed designs, we suggest that most of the bias reduction of this iterative targeted MLE occurs in the first step, and that the crucial equation (24) might already hold for the first step targeted MLE, so that Theorem 8 is also applicable to this first step targeted MLE.

Remark II: Generalization of k-th step Targeted MLE of fixed designs. If $O_1, \ldots, O_n$ are actually i.i.d. P_{Q_0,g_0} for some fixed CAR design g_0, $g_i = g_0$ and one would set $g_\theta = g_0$ so that $w_i = 1$, then the k-th step targeted MLE is exactly the k-th step targeted MLE as presented in van der Laan and Rubin (2006) for fixed designs. This proves that this iterative targeted MLE generalizes the iterative targeted MLE for fixed designs in van der Laan and Rubin (2006).

14 Central Limit Theorem for Targeted MLE.

The theorem below can be used to prove asymptotic normality for an estimator $\psi_n = \Psi(Q_{\theta_n}(\epsilon_n))$, given an estimator Q_{θ_n} of Q_0 according to a working model $\mathcal{Q}^w$, where the path $Q_{\theta_0}(\epsilon)$ through Q_{θ_0} at $\epsilon = 0$, and the target parameter ϵ_0 for ϵ_n are chosen so that $\Psi(Q_{\theta_0}(\epsilon_0)) = \psi_0$. A possible choice for θ_n is the weighted MLE corresponding with the Martingale estimating function $D(\theta) = S(\theta)g^*/g_i$ for some fixed design $g^* \in \mathcal{G}$, where $S(\theta) = \frac{d}{d\theta}\log Q_\theta$. Other choices are obtained by letting $D(Q, g)$ be the efficient influence curve at $P_{Q,g}$ of an extended parameter $\Theta : \mathcal{Q} \to \mathbb{R}^d$: $\Theta(Q_0) = \arg\max_{\theta\in\Theta} P_{Q_0,g^*}\log Q_\theta$ indexed by a fixed design choice g^*, and to set $D(\theta)(O_i, Z_i) = D(Q_\theta, g_{Z_i})(O_i)$, or $D(\theta)(O_i, Z_i) = D(Q_\theta, g^*)(O_i)g^*/g_{Z_i}$. We also showed how to construct such

estimators based on an adaptively estimated g^* (with g_{θ_n}) corresponding with a stacked martingale estimating function: see Subsections 8.4 and 8.5. Above, in Section 13 we also showed how θ could play the role of an augmented parameter $\theta^k = (\theta, \epsilon^1, \ldots, \epsilon^k)$ solving a Martingale estimating function $\mathbf{D}^k(\theta^k)$ corresponding with the k-th step iterative targeted MLE.

Theorem 8 *Consider the adaptive design experiment generating* $(O_1, \ldots, O_n) \sim P_{Q_0,\mathbf{g}_n} \in \{P_{Q,\mathbf{g}_n} : Q \in \mathcal{Q}\}$, *as defined in (3). Here* $\mathbf{g}_n = (g_1, \ldots, g_n)$, $g_i = g_{Z_i} \in \mathcal{G}$ *with probability 1, where* $Z_i = Z_i(O_1, \ldots, O_{i-1}) \in \mathcal{Z} \subset \mathbb{R}^k$ *is a* k*-dimensional summary measure for some fixed* k, $i = 1, \ldots, n$. *Let* $\Psi : \mathcal{M} \to \mathbb{R}^m$ *be path-wise differentiable at each* $P_{Q,g} \in \mathcal{M}(g) = \{P_{Q,g} : Q \in \mathcal{Q}\}$ *for any* $g \in \mathcal{G}$, *with efficient influence curve/canonical gradient* $D^*(Q, g)$.

A working model and initial estimator: *Let* $\mathcal{Q}^w = \{Q_\theta : \theta \in \Theta \subset \mathbb{R}^d\} \subset \mathcal{Q}$ *be a working model. Let* θ_n *be a solution in* θ *of a Martingale estimating equation*

$$\frac{1}{n}\sum_{i=1}^{n} D(\theta_n)(O_i, Z_i) = 0 \text{ or } o_P(1/\sqrt{n}),$$

so that for a fixed element θ_0 *of* Θ

$$P_{Q_0,g_i} D(\theta_0) = 0 \text{ for } i = 1, \ldots, n. \tag{25}$$

Let $\theta \to g_\theta \in \mathcal{G}$ *be a mapping from* Θ *into the set of fixed designs. [It is recommended to chose this function* $\theta \to g_\theta$ *so that* $g_{\theta_{n-1}}$ *equals or approximately equals the design* g_n *as* $n \to \infty$.*]*

A targeted bias reduction path, and estimator: *Consider a set* $\mathcal{E} \subset \mathbb{R}^m$ *containing* 0. *For each* $\theta \in \Theta$, *let* $\{Q_{\theta,g}(\epsilon) : \epsilon \in \mathcal{E}\} \subset \mathcal{Q}$ *be a path so that* $Q_{\theta,g}(0) = Q_\theta \in \mathcal{Q}$ *for all* $g \in \mathcal{G}$. *Although not necessary for the conclusions of this theorem, we recommend it to also satisfy* $\frac{d}{d\epsilon} \log Q_{\theta,g}(\epsilon)(O)\Big|_{\epsilon=0} = D^*(Q_\theta, g)(O)$. *Given the function* $\theta \to g_\theta$, *let* ϵ_n *be a solution of*

$$\sum_{i=1}^{n} D^*(Q_{\theta_n,g_{\theta_n}}(\epsilon_n), g_i)(O_i) = 0 \text{ or } o_P(1/\sqrt{n}).$$

or

$$\sum_{i=1}^{n} D^*(Q_{\theta_n,g_{\theta_n}}(\epsilon_n), g_{\theta_n})(O_i) \frac{g_{\theta_n}(A_i \mid X_i)}{g_i(A_i \mid X_i)} = 0 \text{ or } o_P(1/\sqrt{n}).$$

Comment: *In the context that the efficient influence curve/canonical gradient* $D^*(Q, g)$ *is too complex too calculate, then one can replace* $D^*(Q, g)$ *by any gradient* $D(Q, g)$ *instead, and the results below apply with* $D^*(Q, g)$ *replaced by* $D(Q, g)$.

Given θ_0, let $\epsilon_0 \in \mathcal{E}$ be a fixed value satisfying

$$P_{Q_0,g_i} D^*(Q_{\theta_0,g_{\theta_0}}(\epsilon_0), g_i) = 0, \ \ i=1,\ldots,n.$$

Let $D^*(\theta,\epsilon)(O_i,Z_i) \equiv D^*(Q_\theta(\epsilon), g_{Z_i})(O_i)$, or $D^*(\theta,\epsilon)(O_i,Z_i) \equiv D^*(Q_\theta(\epsilon), g_\theta) g_\theta(A_i \mid X_i)/g_{Z_i}(A_i \mid X_i)$, $i = 1,\ldots,n$.

An Augmented Martingale Estimating function: *For each $(\theta,\epsilon) \in \Theta \times \mathcal{E}$, we define the $m+d$ dimensional estimating function*

$$D(\theta,\epsilon)(O_i,Z_i) = (D(\theta)(O_i,Z_i), D^*(\theta,\epsilon)(O_i,Z_i)).$$

By the above conditions, we have that $(\theta_n,\epsilon_n) \in \Theta \times \mathcal{E}$ solves

$$0 = \frac{1}{n}\sum_{i=1}^n D(\theta_n,\epsilon_n)(O_i,Z_i) = 0,$$

and $(\theta_0,\epsilon_0) \in \Theta \times \mathcal{E}$ solves

$$0 = P_{Q_0,g_i} D(\theta_0,\epsilon_0) \text{ for all } i.$$

Assume

Bounded estimating function: $\max_j \sup_{\theta\in\Theta,\epsilon\in\mathcal{E}} \parallel D_j(\theta,\epsilon) \parallel_\infty < \infty$.

Consistency: *Assume $\parallel (\theta_n,\epsilon_n) - (\theta_0,\epsilon_0) \parallel$ converges to zero in probability as $n \to \infty$.*

By Theorem 5 it suffices to assume that 1) $\mathcal{F} \equiv \{(o,z) \to D(\theta,\epsilon)(o,z) - P_{Q_0,g_z} D(\theta,\epsilon) : \theta \in \Theta, \epsilon \in \mathcal{E}\}$ has a covering number $N(\delta,\mathcal{F},\parallel\cdot\parallel_\infty)$ w.r.t. to supremum norm bounded by $O(\delta^{-q})$ for a $q > 0$, and 2) that,

$$E\left(\frac{1}{n}\sum_{i=1}^n P_{Q_0,g_i} D(\theta_n,\epsilon_n)\right)^2 \to 0,$$

as $n \to \infty$, implies $\parallel (\theta_n,\epsilon_n) - (\theta_0,\epsilon_0) \parallel \to 0$ in probability, as $n \to \infty$.

Asymptotic stable design: *Component wise*

$$\frac{1}{n}\sum_{i=1}^n P_{Q_0,g_i} D - E\frac{1}{n}\sum_{i=1}^n P_{Q_0,g_i} D \to 0, \text{ in probability, as } n \to \infty, \quad (26)$$

for the following choices of matrix functions D of (O_i,Z_i):

$$\begin{aligned} D &= \{D(\theta_0,\epsilon_0)\}^2 \\ D &= \frac{d}{d(\theta_0,\epsilon_0)} D(\theta_0,\epsilon_0). \end{aligned}$$

Comment: *If the design is a targeted design, $g_i = g_{\theta_{i-1},\epsilon_{i-1}}$, then this can be inferred from the asymptotic convergence of (θ_n, ϵ_n) to (θ_0, ϵ_0), as $n \to \infty$.*

Differentiability: *Assume*

$$\frac{1}{n}\sum_{i=1}^{n}\left(D(\theta_n,\epsilon_n)\right)(O_i,Z_i) - D(\theta_0,\epsilon_0)(O_i,Z_i))$$
$$= \frac{1}{n}\sum_{i=1}^{n}\frac{d}{d(\theta_0,\epsilon_0)}D(\theta_0,\epsilon_0)(O_i,Z_i)((\theta_n,\epsilon_n)-(\theta_0,\epsilon_0)) + o_P(\parallel(\theta_n,\epsilon_0)-(\theta_0,\epsilon_0)\parallel),$$

By the Kolmogorov LLN for martingale sums and the asymptotic stability (26) of the design, we have

$$\frac{1}{n}\sum_{i=1}^{n}\frac{d}{d(\theta_0,\epsilon_0)}D(\theta_0,\epsilon_0)(O_i,Z_i) - A_n \to 0 \quad a.s., \tag{27}$$

as $n \to \infty$, where $A_n \equiv \frac{1}{n}\sum_{i=1}^{n} E_0 \frac{d}{d(\theta_0,\epsilon_0)}D(\theta_0,\epsilon_0)(O_i,Z_i)$.

Invertibility of A_n: *A_n^{-1} exists, and $\limsup_n \parallel A_n^{-1} \parallel < \infty$.*

Positive Definite Covariance Matrix: *Let*

$$\Sigma(n) \equiv E\left(\frac{1}{n}\sum_{i=1}^{n} P_{Q_0,g_i}\left\{D(\theta_0,\epsilon_0)\right\}^2\right).$$

Assume that for each vector $\lambda \in \mathbb{R}^{d+m}$, we have $\liminf_{n\to\infty}\lambda\Sigma(n)\lambda > 0$, or that $\Sigma = \lim_{n\to\infty}\Sigma(n)$ exists and is a positive definite covariance matrix.

Then

$$\sqrt{n}((\theta_n,\epsilon_n)-(\theta_0,\epsilon_0)) = \frac{1}{\sqrt{n}}\sum_{i=1}^{n} A_n^{-1}D(\theta_0,\epsilon_0)(O_i,Z_i) + o_P(1),$$

where $P_{Q_0,g_i}D(\theta_0,\epsilon_0) = 0$ for all i, and the sum on the right hand side is a Martingale satisfying the conditions of the Martingale central limit theorem. In particular,

$$\Sigma(n)^{-1/2}A_n(\sqrt{n}((\theta_n,\epsilon_n)-(\theta_0,\epsilon_0)) \Rightarrow_d N(0,I), \text{ as } n \to \infty.$$

If $\Sigma(n) \to \Sigma$ for some positive definite matrix Σ, and $A_n \to A_0$, then this implies

$$\sqrt{n}((\theta_n,\epsilon_n)-(\theta_0,\epsilon_0)) \Rightarrow_d N(0, A_0^{-1}\Sigma A_0^{-1\top}).$$

We also have that $\Sigma(n)$ can be consistently estimated with

$$\hat{\Sigma}(n) = \frac{1}{n}\sum_{i=1}^{n}\left\{D(\theta_n,\epsilon_n)(O_i,Z_i) - \frac{1}{n}\sum_{i=1}^{n} D(\theta_n,\epsilon_n)\right\}^2.$$

Asymptotic equivalence with optimal fixed design: *If 1) $D(\theta_0,\epsilon_0)(O_i,Z_i) = D_1(\theta_0,\epsilon_0,g_{Z_i})(O_i)$ for some mapping $(\theta,\epsilon,g)\rightarrow D_1(\theta,\epsilon,g)$, 2) $g_{Z_i} = g_{\theta_{i-1}}$ converges to g_{θ_0} for $i\rightarrow\infty$ so that $A_n\rightarrow A_0 = P_{Q_0,g_{\theta_0}}\frac{d}{d(\theta_0,\epsilon_0)}D(\theta_0,\epsilon_0,g_{\theta_0})$ and $\Sigma(n)\rightarrow\Sigma_0\equiv P_{Q_0,g_{\theta_0}}D(\theta_0,\epsilon_0,g_{\theta_0})^2$ as $n\rightarrow\infty$, then the normal limit distribution of $\sqrt{n}((\theta_n,\epsilon_n)-(\theta_0,\epsilon_0))$ given $N(0,A_0^{-1}\Sigma_0A_0)$ equals the limit distribution under i.i.d. sampling from $P_{Q_0,g_{\theta_0}}$.*

Robustness w.r.t. ψ_0: *Suppose, $P_{Q_0,g_i}D^*(Q_{\theta_0}(\epsilon_0),g_i) = 0$ implies $\Psi(Q_{\theta_0}(\epsilon_0))-\Psi(Q_0) = 0$, $i = 1,\ldots,n$. Then, by the delta-method applied to $f(\theta,\epsilon) = \Psi(Q_\theta(\epsilon))$, the above result implies that the $\sqrt{n}(\Psi(Q_{\theta_n}(\epsilon_n))-\Psi(Q_0))$ converges in distribution to a multivariate normal distribution with mean zero, and specified covariance matrix in terms of the gradient of f and Σ.*

In particular, if $g_n = g_{\theta_n,\epsilon_n}$ is a targeted design so that $g_n\rightarrow g_{\theta_0,\epsilon_0}$ and A_n,Σ_n converge to the corresponding (with g_{θ_0,ϵ_0}) fixed limits A_0,Σ_0 specified above, then $\sqrt{n}(\Psi(Q_{\theta_n}(\epsilon_n)-\psi_0)$ converges to a multivariate normal $N(0,\Sigma_0)$, where Σ_0 is the covariance matrix of the efficient influence curve $D^*(Q_{\theta_0}(\epsilon_0),g_{\theta_0,\epsilon_0})$ under $P_{Q_0,g_{\theta_0,\epsilon_0}}$.

Remark. We also wish to present an alternative approach for analyzing the targeted MLE, which also explains the last statement. For the sake of illustration, let's consider the case that $-P_{Q_0,g_i}D^*(Q,g_i) = \Psi(Q)-\psi_0$ (in general, by the definition of pathwise differentiability, this holds up till a second order term). Combining the latter identity with $1/n\sum_i D^*(Q_{\theta_n}(\epsilon_n),g_i) = 0$ yields immediately

$$\Psi(Q_{\theta_n}(\epsilon_n))-\psi_0 = \frac{1}{n}\sum_{i=1}^{n}\{D^*(Q_{\theta_n}(\epsilon_n),g_i)(O_i) - P_{Q_0,g_i}D^*(Q_{\theta_n}(\epsilon_n),g_i)\}.$$

If one can now show that

$$\begin{aligned} o_P(1/\sqrt{n}) &= \frac{1}{n}\sum_{i=1}^{n}\{D^*(Q_{\theta_n}(\epsilon_n),g_i)(O_i) - D^*(Q_{\theta_0}(\epsilon_0),g_i)\} \\ &\quad -\frac{1}{n}\sum_{i=1}^{n} P_{Q_0,g_i}\{D^*(Q_{\theta_n}(\epsilon_n),g_i) - D^*(Q_{\theta_0}(\epsilon_0),g_i)\}, \end{aligned}$$

then one can conclude

$$\sqrt{n}(\Psi(Q_{\theta_n}(\epsilon_n))-\psi_0) = \frac{1}{\sqrt{n}}\sum_{i=1}^{n} D^*(Q_{\theta_0}(\epsilon_0),g_i)(O_i) + o_P(1),$$

where the right-hand side is a multivariate martingale converging to a multivariate normal distribution as $n \to \infty$. Although this approach immediately conjectures the asymptotic limit distribution of $\Psi(Q_{\theta_n}(\epsilon_n))$, showing that the empirical difference is $o_P(1/\sqrt{n})$ is not any easier than our proof of the theorem.

15 Statistical analysis of treatment effect in targeted adaptive clinical trial, including covariates.

We now generalize section 4 to the case that one also collects baseline covariates on each subject, and the outcome (e.g., including primary and secondary outcomes relevant for safety analysis) is allowed to be a vector.

Data and Parameter of Interest: Let $Y(a)$ represent a treatment specific outcome vector one would observe if the randomly sampled subject would be assigned treatment or dose-level $a \in \mathcal{A} = \{0, 1, \ldots, k\}$, and let $X = (W, (Y(a) : a \in \mathcal{A})) \sim P_{X0}$ represent the full data structure of interest consisting of the treatment specific outcomes, and baseline covariates W. We will leave P_{X0} unspecified. Let $X_1, \ldots, X_n$ be n i.i.d. draws of X. The scientific parameter is the causal effect of treatment on one particular outcome Y^* defined as $\psi_0(a) = E_0(Y^*(a) - Y^*(0)) = E_0(Y^*(a)) - E_0(Y^*(0))$, where $Y^*(a)$ is a component of $Y(a)$. Let $V \subset W \in \{1, \ldots, K\}$ be a discrete component of W indicating sub-group membership for a finite collection of subgroups of interest, and let

$$\psi_0(a, v) = E_0(Y^*(a) - Y^*(0) \mid V = v)$$

denote the causal effect of treatment a relative to treatment $a = 0$ for subgroup $V = v$, which represents another set of scientific questions of interest corresponding with sub-group analysis.

Adaptive Designs: Let A_i be the treatment assignment for subject i, $i = 1, \ldots, n$, and let the observed data on the n subjects be $O_i = (W_i, A_i, Y_i = Y_i(A_i))$, $i = 1, \ldots, n$. Let $\mathbf{g} = (g_1, \ldots, g_n)$ be a CAR adaptive design:

$$g_i(a \mid X_i, O_1, \ldots, O_{i-1}) = P(A_i = a \mid W_i, O_1, \ldots, O_{i-1}), i = 1 \ldots, n.$$

The CAR-assumption on the design requires A_i to be independent of the counterfactual outcomes $(Y_i(a) : a \in \mathcal{A})$, conditional on W_i, and the data on the previously recruited patients $O_1, \ldots, O_{i-1}$.

Likelihood and Identifiability: Firstly, we note that the likelihood of $(O_1, \ldots, O_n)$ factorizes as:

$$P_{Q_0,\mathbf{g}}(O_1, \ldots, O_n) = \prod_{i=1}^{n} Q_{10}(W_i) Q_{20}(Y_i \mid A_i, W_i) \prod_{i=1}^{n} g_i(A_i \mid W_i, \bar{\mathbf{O}}(i-1)),$$

where the conditional density of Y_i, given $A_i = a$, W_i, $Q_{20}(\cdot \mid a, W_i)$, equals the conditional density of $Y_i(a)$, given W_i, and Q_{10} denotes the marginal density of W. In particular, it follows that for any CAR-adaptive design for which $\liminf_{i\to\infty} g_i(a \mid W_i) g_i(0 \mid W_i) > 0$, we have that the marginal causal effect $\psi_0(a)$ is identified by the Q_0-factor of the likelihood by the following relation: for each $i \in \{1, \ldots, n\}$

$$\psi_0(a) = E_0\{E_0(Y_i^* \mid A_i = a, W_i) - E_0(Y_i^* \mid A_i = 0, W_i)\}.$$

In general, under this same condition,

$$\psi_0(a, v) = E_0\{E_0(Y_i^* \mid A_i = a, W_i) - E_0(Y_i^* \mid A_i = 0, W_i) \mid V_i = v\}.$$

Maximum Likelihood Estimation: Consider a model $Q_{2\theta}$ for the distribution of $Y(a)$, given W, and the corresponding maximum likelihood estimator θ_n:

$$\theta_n = \arg\max_{\theta} \sum_{i=1}^{n} \log Q_{2\theta}(Y_i \mid A_i, W_i).$$

We will leave the marginal distribution of W unspecified, so that this is estimated with the empirical probability distribution of $W_1, \ldots, W_n$. We will assume a separate model for each v for the conditional distribution of $Y(a)$, given W with $V = v$, so that $\theta = (\theta(v) : v)$, and the maximum likelihood estimator of $\theta_0(v)$ is

$$\theta_n(v) = \arg\max_{\theta} \sum_{i=1}^{n} I(V_i = v) \log Q_{2\theta}(Y_i \mid A_i, V_i = v, W_i).$$

For example, for each v value, $Q_{2v\theta(v)}$ might be a multivariate normal regression model with parameters $\theta(v)$ for the vector outcome Y, conditional on A, W with $V = v$, so that the maximum likelihood estimator will be a standard multivariate regression estimator.

Targeted adaptive designs for efficient estimation of subgroup specific causal effects: A variety of adaptive designs are of interest in this setting which includes covariates. In order to motivate a proposal we will present

here, we first note the following. Let $\psi_0(j) = E_0(Y^*(j) - Y^*(0))$, $j = 1, \ldots, d$ denote the marginal causal effect of treatment j relative to the control 0. The efficient influence curve of ψ_0 at $P_{\theta_0,g}$, $g \in \mathcal{G}$, under i.i.d. sampling is given by (see e.g., van der Laan and Robins (2003), van der Laan (2006a)):

$$\begin{aligned} S_j(\theta_0, g) &= (Y - E_{\theta_0}(Y \mid A, W)) \left(\frac{I(A=j)}{g(j \mid W)} - \frac{I(A=0)}{g(0 \mid W)} \right) \\ &\quad + E_{\theta_0}(Y \mid A = j, W) - E_{\theta_0}(Y \mid A = 0, W). \end{aligned}$$

The variance of $S_j(\theta_0, g)$ under $P_{\theta_0,g}$ is given by:

$$\frac{\sigma^2(\theta_0)(j \mid W)}{g(j \mid W)} + \frac{\sigma^2(\theta_0)(0 \mid W)}{g(0 \mid W)},$$

up till a term not depending on g. As in Section 2, it follows that the optimal fixed design among all conditional distributions of A, given V, minimizing the variance of the efficient influence curve $S_j(\theta_0, g)$ is given by:

$$g_{\theta_0}(j \mid V) = \frac{\sigma(\theta_0)(j \mid V)}{\sigma(\theta_0)(0 \mid V) + \sigma(\theta_0)(j \mid V)} \tag{28}$$

$$g_{\theta_0}(0 \mid V) = 1 - g_{\theta_0}(j \mid V), \tag{29}$$

where $\sigma^2(\theta_0)(j \mid V) = E_0(\sigma^2(\theta_0)(j \mid W) \mid V)$ is the conditional expectation, given V, of the conditional variance of Y, given $A = j$, W. This defines an optimal targeted adaptive design for estimation of $\psi_0(j)$ only.

This motivates us to consider the general design function which allows treatment A_i to be informed by the subgroup indicator V_i and the maximum likelihood estimator of θ_0 based on the previously $i-1$ recruited subjects:

$$g_{i,\theta_0}(\cdot \mid v) \equiv \arg \min_{g(0),\ldots,g(k)} \sum_{a=1}^{k} w_i(\theta_0, v)(a)^2 \left(\frac{\sigma^2(\theta_0)(a \mid v)}{g(a)} + \frac{\sigma^2(\theta_0)(0 \mid v)}{g(0)} \right),$$

where

$$\sigma^2(\theta_0)(a \mid v) \equiv E_{\theta_0}[\mathrm{VAR}_{\theta_0}(Y^* \mid a = a, W) \mid V = v].$$

Writing $g(0 \mid v) = 1 - \sum_{j=1}^{d} g(j \mid v)$, and setting the derivatives w.r.t. $g(j \mid v)$, $j = 1, \ldots, k$, equal to zero provides us with the following closed form expression for g_{i,θ_0}:

$$\begin{aligned} g_{i,\theta_0}(0 \mid v) &= \frac{\sigma(\theta_0)(0 \mid v)}{\sigma(\theta_0)(0 \mid v) + \sum_{a=1}^{k} w_i(\theta_0, v)(a) \sigma(\theta_0)(a \mid v)} \\ g_{\theta_0}(a \mid v) &= w_i(\theta_0, v)(a) \frac{\sigma(\theta_0)(a \mid v)}{\sigma(\theta_0)(0 \mid v)} g_{i,\theta_0}(0 \mid v). \end{aligned}$$

In order to provide some interpretation of this design function, consider the case that treatment is binary and that the weights are set equal to 1. If $A \in \{0,1\}$ is binary, and $O = (W, A, Y^*)$, then, for each subgroup $V = v$, the optimal fixed design, among fixed designs depending on W through V only, for estimation of the marginal treatment effect $E(Y^*(1) - Y^*(0) \mid V = v)$ is given by $g_{\theta_0}(1 \mid v) = \frac{\sigma(\theta_0)(0|v)}{\sigma(\theta_0)(0|v)+\sigma(\theta_0)(1|v)}$, which agrees with the above formula g_{θ_0}. The corresponding adaptive design $g_i = g_{\theta_{i-1}}$, based on an estimator θ_{i-1}, will thus be asymptotically optimal for the purpose of simultaneous efficient estimation of all subgroup specific treatment effects $\psi_0(1, v)$, $v = 1, \ldots, K$.

The corresponding adaptive design is thus defined as

$$\begin{aligned} g_i(0 \mid v) &= \frac{\sigma_{i-1}(0 \mid v)}{\sigma_{i-1}(0 \mid v) + \sum_{a=1}^{k} w_i(v)(a)\sigma_{i-1}(a \mid v)} \\ g_i(a \mid v) &= w_i(v)(a)\frac{\sigma_{i-1}(a \mid v)}{\sigma_{i-1}(0 \mid v)} g_i(0 \mid v), \end{aligned}$$

where $\sigma_{i-1}(a \mid v)$ is an estimator of $\sigma_0(a \mid v)$ based on $O_1, \ldots, O_{i-1}$. For example, if one assumes that the variance $\sigma_0^2(a, W)$ does only depend on V, then a natural estimator of $\sigma^2(a, v)$ is the standard sample variance for the subgroup indexed by v:

$$\sigma_n^2(a, v) = \frac{\sum_{i=1}^{n} I(V_i = v, A_i = a)(Y_i - m_n(a, v))^2}{\sum_{i=1}^{n} I(V_i = v, A_i = a)},$$

where $m_n(a, v) = \frac{\sum_{i=1}^{n} I(V_i=v, A_i=a)Y_i}{\sum_{i=1}^{n} I(V_i=v, A_i=a)}$.

Choosing the weights: The weights $w_i(v)(a)$ could be a function of $\psi_{i-1}(a, v)$ and corresponding standard error estimates. In addition, these weights could be chosen to indicate safety issues with treatment a for subgroup $V = v$, based on other asymptotically stable summary measures of $\bar{\mathbf{O}}(i-1)$. Such an example of interest is to make the weights $w_i(v)(a)$ a function of regression estimators of other (than Y^*) adverse clinical outcomes Y_j $(j > 1)$ on treatment and covariates, stratified by $V = v$. In particular, if the history $\bar{\mathbf{O}}(i-1)$ suggests that treatment a is not safe for subgroup v, then this might result in setting $w_i(a, v) = 0$ and thereby stopping the assignment of treatment a for subgroup v for future subjects: $g_i(a \mid v) = 0$.

15.1 MLE for correctly specified model.

Let's now discuss the MLE in more detail. Consider a model assuming $E_0(Y(a) \mid V = v, W) = m_v(a, W \mid \beta_0(v))$ for some parametrization $m_v(\cdot \mid \beta)$, which thus

also implies the same model for $E(Y_i \mid A_i = a, V_i = v, W_i)$, $i = 1, \ldots, n$. For example, if Y is univariate and continuous, then we assume that this model specifies that Y_i, given $A_i = a, V_i = v, W_i$, is normally distributed with mean $m(a, v, W_i \mid \beta_0(v))$ and variance $\sigma^2(a, v \mid \gamma(v))$ for some parametrization $\gamma \to \sigma^2(a, v \mid \gamma(v))$. If Y univariate and binary, then the model $m(a, v, W_i \mid \beta_0)$ already specifies the conditional distribution of Y_i, given $A_i = a$,$V_i = v$, W_i. If Y is univariate one typically either assumes a linear regression model or a linear logistic regression model: i.e., $m(a, v, W \mid \beta(v)) = \beta(v)(a, W)$ or $m(a, W \mid \beta(v)) = 1/(1 + \exp(-\beta(v)(a, w))$. Let $\{Q_{2\theta} : \theta\}$ denote this model for the conditional distribution of Y_i, given A_i, V_i, W_i. Note that, if Y is univariate, then either $\theta = (\beta(v), \gamma(v) : v)$ (linear) or $\theta = (\beta(v); v)$ (logistic).

We also wish to note that, if Y is multivariate, one could still only assume a model for the univariate Y^*, and work with the log-likelihood of the reduced data (W_i, A_i, Y_i^*), since our theorems for consistency and asymptotic normality will still apply to the MLE's for the reduced data or equivalently to the solutions of the corresponding Martingale score/estimating equations. These estimating equations derived from the log-likelihood of the reduced data will still be Martingale estimating equations (assuming the models are correctly specified), which ignore the information on the other outcomes, and thereby will be inefficient (but possibly more robust due to less modelling). These Martingale estimating equations result in consistent and asymptotically linear estimators, by application of our theorems.

The maximum likelihood estimator of θ according to this model is computed as in the standard i.i.d. case. For example, for the logistic regression model for a univariate outcome Y^*, the maximum likelihood estimator of β is given by

$$\beta_n(v) = \arg\max_{\beta} \sum_{i=1}^{n} I(V_i = v) \log \left\{ m(A_i, v, W_i \mid \beta)^{Y_i^*} (1 - m(A_i, v, W_i \mid \beta))^{1-Y_i^*} \right\}.$$

Given the maximum likelihood estimator γ_n of γ_0, the maximum likelihood estimator of β_0 for the linear regression model is the weighted least squares estimator defined as

$$\beta_n(v) = \arg\min_{\beta} \sum_{i=1}^{n} I(V_i = v) \frac{1}{\sigma^2(A_i, v \mid \gamma_n)} (Y_i^* - m(A_i, v, W_i \mid \beta))^2.$$

A particular estimator of $\sigma^2(a, v)$ is the standard sample variance $\sigma_n^2(a, v)$ for the subgroup indexed by v.

The MLE of parameter of interest: Given the MLE θ_n, the corresponding estimator of $\psi_0(a, v)$ is thus given by:

$$\psi_n(a, v) = E_n[E_{\theta_n}(Y^* \mid A = a, W) \mid V = v],$$

where $E_n(\cdot \mid V = v)$ denotes the conditional expectation over W, given $V = v$ w.r.t. to the empirical probability distribution of $W_1, \ldots, W_n$.

If the model $\mathcal{Q} = \{Q_\theta : \theta\}$ for Q_{20} is correctly specified, then application of our Theorems 5 and 7 for solutions of Martingale estimating equations (e.g., MLE) provides us with asymptotic consistency and asymptotic normality of $\psi_n(a, v)$, under the assumption that Y is uniformly bounded, $\liminf_{i \to \infty} g_i(a \mid v) g_i(0 \mid v) > 0$ (in other words, one needs to assume that the adaptive design keeps assigning subjects to treatment arm a and 0 in subgroup v), and some standard regularity/identifiability conditions on the regression model m as one would need in the i.i.d case.

15.2 The targeted MLE for a semi-parametric model.

We will now show that we can also construct a targeted maximum likelihood estimator $\psi_n(a, v)$ which is still consistent for $\psi_0(a, v)$ and asymptotically normally distributed in the nonparametric model $\mathcal{Q}$ for Q_0, even if the working model $\mathcal{Q}^w$ for Q_0 is misspecified. For this we apply our Theorem 8 for the targeted MLE as presented in Section 12 in general. The principle of targeted maximum likelihood estimation is to map an initial estimator Q_{θ_n} (representing the initial fit of the Q-factor of the likelihood representing both the marginal distribution of W and the conditional distribution of Y, given A, W) of a Q_{θ_0}, indexed by a parameter θ_0 of Q_0, into an asymptotically unbiased estimator of the parameter $\psi_0(a, v)$ in the actual (e.g.) nonparametric model $\mathcal{Q}$ for Q_0. Following the iterative targeted MLE as presented in Section 13, this can be done by maximizing a weighted log-likelihood over a fluctuation through this initial $Q_n^0 = Q_{\theta_n}$ with parameter ϵ which has score at $\epsilon = 0$ equal to the (double robust!) efficient influence curve of ψ_0 at fixed design $P_{Q_n^0, g_{\theta_n}}$. This type of targeted maximum likelihood estimation methodology was developed for i.i.d data structures in (van der Laan and Rubin (2006)) and it is extended to adaptive designs in Sections 12 and 13. We refer to this new update $Q_n^0(\epsilon_n)$ of an initial fit Q_n^0 as the targeted maximum likelihood estimator or update, and by our results, the corresponding substitution estimator $\psi_n(a, v)$ is now consistent and asymptotically linear in the large nonparametric model $\mathcal{Q}$ under appropriate regularity conditions, *even if the original working model* $\mathcal{Q}^w = \{Q_\theta : \theta \in \Theta\}$ *is misspecified*. The strategy presented here will compute the targeted maximum likelihood estimator for $\psi_0(a, v)$ separately for each choice (a, v), instead of targeting the maximum likelihood estimator for the vector parameter ψ_0 with one update, though both strategies result in the same asymptotic robustness against miss-specification of the working model, and asymptotic consistency and CLT results.

The true model $\mathcal{Q}$ for Q_0 is now the nonparametric model. Firstly, we note that, *in the nonparametric model* the efficient influence curve $S^*_{av}(Q,g)$ of $\psi_0(a,v)$ under i.i.d. sampling $P_{Q,g}(=Qg)$ (where the F_X-part of likelihood is denoted with Q), with $g \in \mathcal{G}_1 \subset \mathcal{G}$ being a fixed design only depending on W through V, is given by

$$\begin{aligned} S^*_{av}(Q,g)(O_i) &= I(V_i=v)(Y_i^* - Q_2(A_i,W_i))\left\{\frac{I(A_i=a)}{g(a \mid v)} - \frac{I(A_i=0)}{g(0 \mid v)}\right\} \\ &\quad + I(V_i=v)\left\{Q_2(a,W_i) - Q_2(0,W_i) - \psi(Q)(a,v)\right\}, \end{aligned}$$

divided by the constant $Q_1(v) = P_Q(V=v)$. Here Q includes both the marginal distribution Q_1 of W as well as the conditional distribution of Y^*, given A,W, while $Q_2(a,W)$ denotes the conditional *mean* of Y^*, given A,W, under Q (and $Q_1(v) = P_Q(V=v)$). In addition, Q_0 denotes the true F_X-factor of the density P_{Q_0,g_i} of O_i, given $\bar{\mathbf{O}}(i-1)$. In particular, $\psi_0(a,v) = \Psi(Q_0)(a,v)$. We denote the two components of S^*_{av} as presented in the two lines with S^*_{1av} and S^*_{2av}, respectively.

The important property of this efficient influence curve, our robustness result for the targeted MLE is based upon, is that for all Q

$$\frac{1}{n}\sum_i P_{Q_0,g_i} S^*_{av}(Q,g_i) = \frac{Q_0(v)}{Q(v)}\left(\Psi(Q_0)(a,v) - \Psi(Q)(a,v)\right).$$

In particular, if Q correctly specifies the marginal distribution of V (i.e, $Q(v) = Q_0(v)$), then the right-hand side equals $\psi_0(a,v) - \Psi(Q)(a,v)$.

To be specific, let's consider the case that Y^* is binary, and let (a,v) be given. The targeted MLE will be formulated separately for each combination (a,v) of treatment arm a and subgroup v. Consider the following v-specific logistic regression model for $P(Y^*=1 \mid A,W,V=v)$ with additional coefficient ϵ_1:

$$Q_{2\theta}(\epsilon_1)(Y_i^*=1 \mid A_i,W_i,V_i=v) = \frac{1}{1+\exp\left(-\beta(A_i,W_i) - \epsilon_1\left\{\frac{I(A_i=a)}{g_\theta(a|v)} - \frac{I(A_i=0)}{g_\theta(0|v)}\right\}\right)},$$

where the design function g_θ is chosen so that $g_{\theta_{n-1}}$ equals the actual adaptive design g_n or approximates this adaptive design g_n as $n \to \infty$, and $\beta(A_i,W_i)$ denotes a particular linear combination of variables extracted from (A_i,W_i) indexed by regression vector β.

Let β_n be an weighted MLE corresponding with this model $\{Q_{2\beta}(0) : \beta\}$ for $P(Y^*=1 \mid A,W,V=v)$, which corresponds with setting $\epsilon_1 = 0$, where the weights are

$$w_i = \frac{g^*(A_i \mid W_i)}{g_i(A_i \mid W_i)},\ i=1,\ldots,n$$

for a user supplied fixed design g^* (where in this case W_i can be replaced by V_i). This inverse weighting makes sure that, if the working model is misspecified, the asymptotic target of β_n corresponds with a parameter β_0 of Q_0 indexed by a known g^*, while without the weights the MLE targets a parameter of Q_0 indexed by a random $\bar{g}_n$ for which the theory is unclear (see Section 11). In particular, the weighting guarantees that the estimator solves a martingale estimating equation so that our theory can be applied. In Section 11 we also provide a method allowing sequential data adaptive estimation of g^* with g_{θ_n} and show that our theory also applies to this method. It remains to be seen if this fixed g^* weighting or sequential data adaptive weighting is also important in practice. In particular, we suggest that using $g^* = g_n$ or $g^* = \bar{g}_n$ might still result in appropriate estimators and statistical inference.

Let $Q_{2\theta_n} = Q_{2\theta_n}(0)$ be the fit of $P(Y^* = 1 \mid A, W, V = v)$ corresponding with this estimator β_n (and setting $\epsilon_1 = 0$). Here we suppressed the dependence on v of this model, the parameters, and the estimators of these parameters. We note that the score of ϵ_1 at $\epsilon_1 = 0$ at the maximum likelihood estimator β_n, i.e. $\frac{d}{d\epsilon_1} \log Q_{\theta_n}(\epsilon_1)(Y_i^* \mid A_i, W_i)$ at $\epsilon_1 = 0$, equals the first component $S_{1av}^*(Q_{2\theta_n}, g_{\theta_n})$ of the efficient influence curve

$$S_{1av}^*(Q_{2\theta_n}, g_{\theta_n}) = (Y_i - Q_{2\theta_n}(A_i, W_i))I(V_i = v)\left\{\frac{I(A_i = a)}{g_{\theta_n}(a \mid v)} - \frac{I(A_i = 0)}{g_{\theta_n}(0 \mid v)}\right\}.$$

Let the marginal distribution of W be estimated with the empirical distribution. By also augmenting this MLE for the marginal distribution of W with a parameter ϵ_2 with score $I(V_i = v)\{Q_{2\theta_n}(a, W_i) - Q_{2\theta_n}(0, W_i) - \Psi(Q_{\theta_n})(a, v)\}$ at $\epsilon_2 = 0$, we now obtain an extension $Q_{\theta_n}(\epsilon)$ of the original fit Q_{θ_n} of Q_0 with parameter $\epsilon = (\epsilon_1, \epsilon_2)$ so that the score of the likelihood of the O_i-factor at $\epsilon = 0$ equals $S_{av}^*(Q_{\theta_n}, g_{\theta_n})(O_i) = S_{1av}^*(Q_{\theta_n}, g_{\theta_n})(O_i) + S_{2av}^*(Q_{\theta_n})(O_i)$, where $Q_{\theta_n} = Q_{\theta_n}(0)$ includes the original fits of both the marginal distribution of W as well as the conditional distribution of Y^*, given A, W.

The one-step targeted MLE corresponds now with either setting ϵ_n be so that for both components

$$0 = \sum_{i=1}^{n} S_{jav}^*(Q_{\theta_n}(\epsilon_n), g_i)(O_i), \ j = 1, 2. \tag{30}$$

or setting ϵ_n so that

$$0 = \sum_{i=1}^{n} S_{jav}^*(Q_{\theta_n}(\epsilon_n), g_{\theta_n})(O_i)\frac{g_{\theta_n}(A_i \mid V_i)}{g_i(A_i \mid V_i)}, \ j = 1, 2. \tag{31}$$

If there are multiple solutions, then one can use the log-likelihood of $Q_{\theta_n}(\epsilon)$ as criteria to select the solution with the highest likelihood.

If no solution exists? If no solution ϵ_n of the equation exists, then we first determine a choice ϵ_n^1 which increases the log-likelihood relative to $\epsilon = 0$ (i.e. we increase the likelihood relative to Q_{θ_n}), update $Q_n^1 = Q_{\theta_n}(\epsilon_n^1)$, create the path $Q_n^1(\epsilon)$ through Q_n^1 as above, and find the solution of one of the above equations (30) or (31) with $Q_{\theta_n}(\epsilon)$ replaced by $Q_n^1(\epsilon)$, and, if still no solution can be found, then iterate this process till a solution can be found or till convergence. Below, we proceed as if a solution ϵ_n exists at the first try.

Since the MLE for the marginal distribution of W equals the empirical distribution of $W_1, \ldots, W_n$, it follows that $\epsilon_{2n} = 0$ gives $0 = 1/n \sum_i S^*_{2av}(Q_{\theta_n}(\epsilon_n))$ for each choice of ϵ_{1n}: i.e., the empirical distribution of W is not updated in this targeted MLE step. If we use (31), we have that ϵ_{1n} is chosen so that $0 = \sum_i S^*_{1av}(Q_{\theta_n}(\epsilon_n), g_{\theta_n}) w_i = 0$ with $w_i = w_i(\theta_n) = g_{\theta_n}(A_i \mid V_i)/g_i(A_i \mid V_i)$, or equivalently

$$\begin{array}{l} 0 = \sum_{i=1}^n w_i I(V_i = v) \left\{ \frac{I(A_i=a)}{g_{\theta_n}(a|v)} - \frac{I(A_i=0)}{g_{\theta_n}(0|v)} \right\} \\ \times \left(Y_i^* - \frac{1}{\exp(-\beta_n(A_i,W_i) - \epsilon_{1n} R_i(a,v))} \right), \end{array}$$

where

$$R_i(a, v) = \left\{ \frac{I(A_i = a)}{g_{\theta_n}(a \mid v)} - \frac{I(A_i = 0)}{g_{\theta_n}(0 \mid v)} \right\}.$$

(Similarly, for the case that ϵ_n is a solution of (30).) We note that the weighted MLE over ϵ_1 of the log likelihood for the model $\{Q_{2\beta_n}(\epsilon_1) : \epsilon_1\}$ at fixed β_n using weights w_i, $i = 1, \ldots, n$, solves this same score equation. This means that for this choice of targeted MLE, ϵ_{1n} is simply the MLE over ϵ_1 defined as

$$\epsilon_{1n} = \arg\max_{\epsilon_1} \sum_i w_i \log Q_{2\beta_n}(\epsilon_1)(Y_i^* \mid A_i, W_i). \tag{32}$$

This shows that we can compute ϵ_{1n} with standard logistic linear regression software by adding this additional covariate $R_i(a, v)$ to a logistic regression fit $Q_{2\theta_n}$ of $P(Y^*|A, W, V = v)$ and using weights w_i.

Statistical Inference: In order to formally understand the consistency and asymptotic linearity and normality of the targeted maximum likelihood estimator $\Psi(Q_{\theta_n}(\epsilon_n))(a, v)$ of $\psi_0(a, v)$, based on substitution of $Q_{\theta_n, g_{\theta_n}}(\epsilon)$, we will apply our general Theorem 8 for the analysis of the targeted MLE. For that purpose, we first define the stacked estimating equation:

$$D(\theta_n, \epsilon_n)(O_i, Z_i) \equiv (D(\theta_n)(O_i, Z_i), S^*_{1av}(Q_{\theta_n}(\epsilon_n), g_{Z_i}), S^*_{2av}(Q_{\theta_n}(\epsilon_n))),$$

or

$$D(\theta_n, \epsilon_n)(O_i, Z_i) \equiv (D(\theta_n)(O_i, Z_i), S^*_{1av}(Q_{\theta_n}(\epsilon_n), g_{\theta_n}) w_i(\theta_n), S^*_{2av}(Q_{\theta_n}(\epsilon_n))),$$

where $D(\theta)$ is the Martingale estimating function θ_n is based upon, identifying the asymptotic target θ_0 of θ_n. Consider the case that θ_n is the weighted MLE defined above, then $D(\theta)(O_i, Z_i) = \frac{d}{d\theta} \log Q_\theta \frac{g^*(A_i|W_i)}{g_i(A_i|W_i)}$. By definition of θ_n and ϵ_n we have that $\frac{1}{n}\sum_i D(\theta_n, \epsilon_n)(O_i, Z_i) = 0$. We have $\theta_0 = \arg\max_\theta P_{Q_0,g^*} \log Q_\theta$ so that indeed $P_{Q_0,g_i} D(\theta_0) = 0$ for all i as required for a Martingale estimating function: that is, θ_0 denotes the limit of the MLE θ_n under the possibly misspecified working model $\mathcal{Q}^w = \{Q_\theta : \theta\}$ for the true Q_0 (i.e., marginal distribution of W and conditional distribution of Y, given A, W). Let $\epsilon_0 = (\epsilon_{10}, 0)$ be the limit of ϵ_n: that is, it is the solution of

$$0 = P_{Q_0,g_i} S^*_{jav}(Q_{\theta_0}(\epsilon_0), g_i) = \psi_0 - \Psi(Q_{\theta_0}(\epsilon_0)),\ j = 1, 2.$$

In particular, we have $0 = 1/n \sum_i P_{Q_0,g_i} S^*_{1av}(Q_{\theta_0}(\epsilon_{10}), g_i)$ and $0 = 1/n \sum_i P_{Q_0,g_i} S^*_{1av}(Q_{\theta_0}(\epsilon_{10}), g_{\theta_0}) g_{\theta_0}/g_i$. We are now in the situation to apply the consistency Theorem 5, and the central limit Theorem 7, or apply Theorem 8 (which is in essence not much more than an application of Theorem 7) for the solution of the stacked estimating equation $\sum_i D(\theta_n, \epsilon_n)(O_i, Z_i) = 0$ based on the Martingale property $P_{Q_0,g_i} D(\theta_0, \epsilon_0) = 0$ for all i.

These theorems establish consistency of (θ_n, ϵ_n) as an estimator of (θ_0, ϵ_0), and establish asymptotic linearity and normality of $\sqrt{n}((\theta_n, \epsilon_n) - (\theta_0, \epsilon_0))$, under appropriate regularity conditions similar as required for the analysis of the MLE θ_n w.r.t to θ_0 based on the estimating equation $0 = \sum_i D(\theta_n)(O_i, Z_i)$. In particular, by the δ-method this implies that $\sqrt{n}(\Psi(Q_{\theta_n}(\epsilon_n))(a, v) - \Psi(Q_{\theta_0}(\epsilon_0)(a, v))$ is asymptotically linear and converges weakly to a normal distribution. Now, we use that $\Psi(Q_{\theta_0}(\epsilon_0))(a, v) = \psi_0(a, v)$ (!) due to 1) $0 = P_{Q_0,g_i} S^*_{av}(Q_{\theta_0}(\epsilon_0), g_i)$, and 2) $P_{Q_0,g_i} S^*_{av}(Q, g_i) = \psi_0(a, v) - \Psi(Q)(a, v)$ as noted above. As a consequence of Theorem 8, we have the following asymptotic linearity result for the targeted MLE $\Psi(Q_{\theta_n}(\epsilon_n))(a, v)$ of $\psi_0(a, v)$:

$$\Psi(Q_{\theta_n}(\epsilon_n))(a, v) - \psi_0(a, v) \approx \frac{1}{n} \sum_i S^*_{av}(Q_{\theta_0}(\epsilon_0), g_i) - P_{Q_0,g_i} S^*_{av}(Q_{\theta_0}(\epsilon_0), g_i),$$

or, if ϵ_n is based on (31), then $S^*_{av}(Q_{\theta_0}(\epsilon_0), g_i)$ is replaced by $S^*_{av}(Q_{\theta_0}(\epsilon_0), g_{\theta_0}) w(\theta_0)$. The combination of these (a, v)-specific asymptotic linearity results across all (a, v)-combinations provides us also with the asymptotic linearity of the estimator $\Psi(Q_{\theta_n}(\epsilon_n))$ as a vector estimator of $\psi_0 = (\psi_0(a, v) : a, v)$:

$$\Psi(Q_{\theta_n}(\epsilon_n)) - \psi_0 \approx \frac{1}{n} \sum_{i=1}^n S^*(Q_{\theta_0}(\epsilon_0), g_{\theta_0}) w_i(\theta_0) - P_{Q_0,g_i} S^*(Q_{\theta_0}(\epsilon_0), g_{\theta_0}) w_i(\theta_0),$$

where S^* now denotes a vector function $(S^*_{av} : a, v)$, and similarly for ϵ_n based on equation (30). Since, for each (a, v), $\sum_i P_{Q_0,g_i} S^*_{av}(Q_{\theta_0}(\epsilon_0), g_i) = 0$, this

teaches us that, regarding statistical inference, we can consistently estimate the covariance matrix of the asymptotic multivariate normal distribution of the targeted MLE $\psi_n = (\Psi(Q_{\theta_n}(\epsilon_n))(a,v) : a,v)$ with

$$\Sigma_n = \frac{1}{n}\sum_{i=1}^{n} S^*(Q_{\theta_n}(\epsilon_n), g_{\theta_n}) S_v^{*\top}(Q_{\theta_n}(\epsilon_n), g_{\theta_n}) w_i(\theta_n)^2,$$

or, if ϵ_n is based on (30)

$$\Sigma_n = \frac{1}{n}\sum_{i=1}^{n} S^*(Q_{\theta_n}(\epsilon_n), g_i) S_v^{*\top}(Q_{\theta_n}(\epsilon_n), g_i),$$

We note that this estimate is analogue of the estimate one would obtain in the fixed design case in which case g_i does not depend on a summary measure Z_i of $\bar{\mathbf{O}}(i-1)$, but is treated as a fixed (a priori set) design.

So, statistical confidence intervals for $\psi_0 = (\psi_0(a,v) : a,v)$ based on the targeted MLE $\psi_n = (\psi_n(a,v) : a,v)$ can be based on the multivariate normal distribution:

$$\psi_n \sim N(\psi_0, \Sigma_n).$$

For example, $\psi_n(a,v) \pm Z_{1-\alpha/2}\frac{\sqrt{\Sigma_n((a,v),(a,v))}}{\sqrt{n}}$ is an asymptotic $1-\alpha$ confidence interval for $\psi_0(a,v)$, where $\Sigma_n((a,v),(a,v))$ denotes the diagonal element of the covariance matrix Σ_n corresponding with the component (a,v) of ψ_n.

15.3 Formal theorem for consistency and asymptotic normality of causal effect sub-group specific targeted ML estimates in targeted adaptive clinical trial with covariates.

The previous subsection corresponds with the following formal theorem.

Theorem 9 *Let $Y(a)$ represent a treatment specific outcome vector one would observe if the randomly sampled subject would be assigned treatment or dose-level $a \in \mathcal{A} = \{0,1,\ldots,k\}$, and let $X = (W, (Y(a) : a \in \mathcal{A})) \sim P_{X0}$ represent the full data structure of interest consisting of the treatment specific outcomes, and baseline covariates W. Our model leaves P_{X0} unspecified. Let $X_1,\ldots,X_n$ be n i.i.d. draws of X. The scientific parameter is the causal effect of treatment on one particular outcome Y^* defined as $\psi_0(a) = E_0(Y^*(a) - Y^*(0)) = E_0(Y^*(a)) - E_0(Y^*(0))$, where $Y^*(a)$ is a component*

of $Y(a)$. Let $V \subset W \in \{1, \ldots, K\}$ be a discrete component of W indicating sub-group membership for a finite collection of subgroups of interest, and let

$$\psi_0(a, v) = E_0(Y^*(a) - Y^*(0) \mid V = v)$$

denote this causal effect of treatment a relative to treatment $a = 0$ for subgroup $V = v$.

Let A_i be the treatment assignment for subject i, $i = 1, \ldots, n$, and let the observed data on the n subjects be $O_i = (W_i, A_i, Y_i = Y_i(A_i))$, $i = 1, \ldots, n$. Let $\mathbf{g} = (g_1, \ldots, g_n)$ be an adaptive design satisfying CAR:

$$g_i(a \mid X_i, O_1, \ldots, O_{i-1}) = P(A_i = a \mid W_i, O_1, \ldots, O_{i-1}), i = 1 \ldots, n.$$

The CAR-assumption on the design requires A_i to be independent of the counterfactual outcomes $(Y_i(a) : a \in \mathcal{A})$, conditional on W_i, and the data on the previously recruited patients $O_1, \ldots, O_{i-1}$.

Maximum Likelihood Estimation: *Consider a working model $\{Q_{2\theta} : \theta\}$ for the true distribution Q_{20} of $Y(a)$, given W, or, equivalently, the conditional distribution Q_{20} of Y, given A and W. We will assume a separate model for each v for the conditional distribution of $Y(a)$, given W with $V = v$, so that $\theta = (\theta(v) : v)$, and the weighted maximum likelihood estimator of $\theta_0(v)$ is*

$$\theta_n(v) = \arg\max_{\theta} \sum_{i=1}^{n} I(V_i = v) \log Q_{2v\theta}(Y_i \mid A_i, V_i = v, W_i) w_i,$$

where $w_i = g^*(A_i \mid W_i)/g_i(A_i \mid W_i)$ for a user supplied g^*. We will leave the marginal distribution of W unspecified, and it is estimated with the empirical probability distribution of $W_1, \ldots, W_n$. For example, for each v value, $Q_{2v\theta(v)}$ might be a multivariate normal regression model with parameters $\theta(v)$ for the vector outcome Y, conditional on A, W with $V = v$, so that the maximum likelihood estimator will be a standard multivariate regression estimator.

Component Specific Maximum Likelihood Estimation: *Alternatively, for each component Y_j of Y, we consider a working model $\{Q_{2j\theta_j} : \theta_j\}$ for the true distribution Q_{20j} of $Y_j(a)$, given W, or, equivalently, the conditional distribution Q_{20j} of Y_j, given A and W. For each v, we will assume a separate model for the conditional distribution of $Y_j(a)$, given W with $V = v$, so that $\theta_j = (\theta_j(v) : v)$, and the weighted maximum likelihood estimator of $\theta_{j0}(v)$ is*

$$\theta_{jn}(v) = \arg\max_{\theta_j} \sum_{i=1}^{n} I(V_i = v) \log Q_{2vj\theta_j}(Y_{ji} \mid A_i, V_i = v, W_i) w_i,$$

where the weights w_i are defined as $w_i = g^*(A_i \mid W_i)/g_i(A_i \mid W_i)$, $i = 1, \ldots, n$, and g^* is a user supplied fixed design. We will leave the marginal distribution of W unspecified, so that this is estimated with the empirical probability distribution of $W_1, \ldots, W_n$. For example, for each j and v value, if Y_j is continuous, $Q_{2vj\theta_j(v)}$ is a univariate normal regression model with parameters $\theta_j(v)$, and if Y_j is binary, $Q_{2vj\theta_j(v)}$ is a logistic regression model with parameters $\theta_j(v)$. Let $Q^*_{2v\theta^*(v)}$ denote the a regression model for the conditional distribution of Y^*, given A, W and $V = v$.

In both cases, we define θ as the finite dimensional vector containing all these parameters as estimated with the weighted maximum likelihood estimator(s) θ_n using weights $w_i = g^*/g_i$. Let $D(\theta)(O_i, Z_i)$ be the stacked estimating function so that $\sum_i D(\theta_n)(O_i, Z_i) = 0$, and let θ_0 be its target satisfying $P_{Q_0,g_i} D(\theta_0) = 0$ for all i.

To be specific, let Y^* be binary and

$$Q^*_{2\theta}(\epsilon)(Y^*_i = 1 \mid A_i, W_i, V_i = v) = \frac{1}{1 + \exp\left(-\beta(a, W_i) - \epsilon\left\{\frac{I(A_i=a)}{g_\theta(a|v)} - \frac{I(A_i=0)}{g_\theta(0|v)}\right\}\right)}.$$

Let β_n be the weighted MLE corresponding with this model $\{Q_{2\beta}(0) : \beta\}$ for $P(Y^* = 1 \mid A, W, V = v)$ which corresponds with setting $\epsilon = 0$. Let $Q_{2\beta_n} = Q_{2\beta_n}(0)$ be the fit of $P(Y^* = 1 \mid A, W, V = v)$ corresponding with this estimator β_n (and setting $\epsilon_1 = 0$). For notational convenience, here we suppressed the dependence on v of this model, the parameters, and the estimators of these parameters.

Given θ_n, let ϵ_n be the solution of

$$\begin{aligned} 0 &= \sum_{i=1}^n w_i I(V_i = v)\left\{\frac{I(A_i = a)}{g_{\theta_n}(a \mid v)} - \frac{I(A_i = 0)}{g_{\theta_n}(0 \mid v)}\right\}\left(Y^*_i - \frac{1}{\exp\left(-\beta_n(A_i, W_i) - \epsilon_n R_i(a, v)\right)}\right), \\ &\equiv \sum_{i=1}^n S^*_{1av}(Q_{2\beta_n}(\epsilon_n), g_{\theta_n}) w_i, \end{aligned}$$

where

$$R_i(a, v) = \left\{\frac{I(A_i = a)}{g_{\theta_n}(a \mid v)} - \frac{I(A_i = 0)}{g_{\theta_n}(0 \mid v)}\right\},$$

and $w_i = g_{\theta_n}(A_i \mid X_i)/g_i(A_i \mid X_i)$. We have that ϵ_n is simply the weighted MLE over ϵ defined as

$$\epsilon_n = \arg\max_\epsilon \sum_i w_i I(V_i = v) \log Q_{2\beta_n}(\epsilon)(Y^*_i \mid A_i, W_i, V_i = v).$$

We define the stacked estimating equation:

$$D(\theta_n, \epsilon_n)(O_i, Z_i) \equiv (D(\theta_n)(O_i, Z_i), S^*_1(Q_{\theta_n}(\epsilon_n), g_{\theta_n}) g_{\theta_n}/g_i),$$

where $S_1^* = (S_{1av}^* : a, v)$ *and* $\epsilon_n = (\epsilon_n(a, v) : a, v)$ *denotes the stacked estimator whose components* $\epsilon_n(a, v)$ *are defined above for each* a, v*. By definition, we have that* $\frac{1}{n}\sum_i D(\theta_n, \epsilon_n)(O_i, Z_i) = 0$*. Let* θ_0 *be so that* $P_{Q_0,g_i} D(\theta_0) = 0$*: that is,* θ_0 *denotes a parameter of* Q_0 *(indexed by known* g^* *and it is the limit of* θ_n *under the possibly misspecified models* $\{Q_{v\theta(v)} : \theta\}$ *for the true* Q_0 *(i.e., marginal distribution of* W *and conditional distribution of* Y*, given* A, W*). Let* ϵ_0 *be the solution of*

$$0 = P_{Q_0,g_i} S_{1av}^*(Q_{\theta_0}(\epsilon_0), g_{\theta_0}) g_{\theta_0}/g_i = \psi_0 - \Psi(Q_{\theta_0}(\epsilon_0)).$$

In particular, we have $0 = 1/n \sum_i P_{Q_0,g_i} S_{1av}^*(Q_{\theta_0}(\epsilon_0), g_{\theta_0}) g_{\theta_0}/g_i$*.*

Assume the following regularity conditions:

Bounded estimating function: *Let* Θ *and* $\mathcal{E}$ *be bounded sets and* $\max_j \sup_{\theta\in\Theta,\epsilon\in\mathcal{E}} \parallel D_j(\theta, \epsilon) \parallel_\infty < M < \infty$*. It is assumed that* $(\theta_n, \epsilon_n) \in \Theta \times \mathcal{E}$ *with probability 1, and* $(\theta_0, \epsilon_0) \in \Theta \times \mathcal{E}$*.*

Consistency: *Assume* $\parallel (\theta_n, \epsilon_n) - (\theta_0, \epsilon_0) \parallel$ *converges to zero in probability as* $n \to \infty$*.*

A sufficient condition for this consistency is that

$$E\left(\frac{1}{n}\sum_{i=1}^n P_{Q_0,g_i} D(\theta_n, \epsilon_n)\right)^2 \to 0,$$

as $n \to \infty$*, implies* $\parallel (\theta_n, \epsilon_n) - (\theta_0, \epsilon_0) \parallel \to 0$ *in probability, as* $n \to \infty$*.*

Asymptotic stable design: *Component wise*

$$\frac{1}{n}\sum_{i=1}^n P_{Q_0,g_i} D - E\frac{1}{n}\sum_{i=1}^n P_{Q_0,g_i} D \to 0, \text{ in probability, as } n \to \infty, \quad (33)$$

for the following choices of matrix functions of (O_i, Z_i)*:*

$$\begin{aligned} D &= D(\theta_0, \epsilon_0)^2 \\ D &= \frac{d}{d(\theta_0, \epsilon_0)} D(\theta_0, \epsilon_0). \end{aligned}$$

If the design is a targeted design, $g_i = g_{\theta_i,\epsilon_i}$*, then this can be immediately inferred from the asymptotic consistency of* (θ_n, ϵ_n) *to* (θ_0, ϵ_0) *for* $n \to \infty$*.*

Differentiability: *Assume*

$$\frac{1}{n}\sum_{i=1}^{n}\left(D(\theta_n,\epsilon_n)\right)(O_i,Z_i) - D(\theta_0,\epsilon_0)(O_i,Z_i))$$
$$= \frac{1}{n}\sum_{i=1}^{n}\frac{d}{d(\theta_0,\epsilon_0)}D(\theta_0,\epsilon_0)(O_i,Z_i)((\theta_n,\epsilon_n)-(\theta_0,\epsilon_0)) + o_P(\parallel(\theta_n,\epsilon_0)-(\theta_0,\epsilon_0)\parallel),$$

where by the Kolmogorov LLN and (33)

$$\frac{1}{n}\sum_{i=1}^{n}\frac{d}{d(\theta_0,\epsilon_0)}D(\theta_0,\epsilon_0)(O_i,Z_i) - A_n \to 0$$

as $n\to\infty$ *a.s, where* $A_n \equiv \frac{1}{n}\sum_{i=1}^{n} E\frac{d}{d(\theta_0,\epsilon_0)}D(\theta_0,\epsilon_0)(O_i,Z_i)$.

Invertibility of A_n: A_n^{-1} *exists, and* $\limsup_n \parallel A_n^{-1}\parallel < \infty$.

Positive Definite Covariance Matrix: *Let*

$$\Sigma(n) \equiv E\left(\frac{1}{n}\sum_{i=1}^{n} P_{Q_0,g_i}\left\{D(\theta_0,\epsilon_0)\right\}^2\right).$$

Assume that for each vector $\lambda\in\mathbb{R}^{d+m}$, *we have* $\liminf_{n\to\infty}\lambda\Sigma(n)\lambda > 0$, *or that* $\Sigma = \lim_{n\to\infty}\Sigma(n)$ *exists and is a positive definite covariance matrix.*

If $g_i \to g_{\theta_0}\in\mathcal{G}$ *as* $i\to\infty$, *then this limit would be given by* $\Sigma = P_{Q_0,g_{\theta_0}}D(\theta_0,\epsilon_0,g_{\theta_0})^2$, *where* $D(\theta,\epsilon,g_{Z_i})(O_i)\equiv D(\theta,\epsilon)(O_i,Z_i)$ *so that* $D(\theta_0,\epsilon_0,g_{\theta_0})$ *is a function of* O_i *only obtained by replacing* g_i *in* $D(\theta_0,\epsilon_0)$ *by* g_{θ_0}.

Then

$$\sqrt{n}((\theta_n,\epsilon_n)-(\theta_0,\epsilon_0)) = \frac{1}{\sqrt{n}}\sum_{i=1}^{n} A_n^{-1}\{D(\theta_0,\epsilon_0)(O_i,Z_i) - P_{Q_0,g_i}D(\theta_0,\epsilon_0)\} + o_P(1),$$

where the sum on the right hand side is a Martingale satisfying the conditions of the Martingale central limit theorem. In particular,

$$\Sigma(n)^{-1/2}A_n(\sqrt{n}((\theta_n,\epsilon_n)-(\theta_0,\epsilon_0)) \Rightarrow_d N(0,I),\ \text{as } n\to\infty.$$

If $\Sigma(n)\to\Sigma$ *for some positive definite matrix* Σ, *and* $A_n\to A_0$, *as* $n\to\infty$, *then this implies*

$$\sqrt{n}((\theta_n,\epsilon_n)-(\theta_0,\epsilon_0)) \Rightarrow_d N(0,\Sigma_0\equiv A_0^{-1}\Sigma A_0^{-1\top}).$$

If $g_i \to g_{\theta_0}$ so that

$$\Sigma = P_{Q_0,g_{\theta_0}} D(\theta_0, \epsilon_0, g_{\theta_0})^2 \quad (34)$$

$$A_0 = P_{Q_0,g_{\theta_0}} \frac{d}{d(\theta_0,\epsilon_0)} D(\theta_0,\epsilon_0,g)\Big|_{g=g_{\theta_0}}, \quad (35)$$

then $\Sigma_0 = A_0^{-1}\Sigma A_0^{-1}$ equals the limit covariance matrix under i.i.d. sampling $O_1,\ldots,O_n$ of fixed design distribution $P_{Q_0,g_{\theta_0}}$. $\Sigma(n)$ can be consistently estimated with

$$\hat{\Sigma}(n) = \frac{1}{n}\sum_{i=1}^n \left\{ D(\theta_n,\epsilon_n)(O_i,Z_i) - \frac{1}{n}\sum_{i=1}^n D(\theta_n,\epsilon_n)(O_i,Z_i)\right\}^2.$$

Robustness w.r.t. ψ_0: *Since, $P_{Q_0,g}S^*(Q,g) = \Psi(Q) - \Psi(Q_0)$ for all $g \in \mathcal{G}$, it follows that $\Psi(Q_{\theta_0}(\epsilon_0)) = \Psi(Q_0)$, so that the above result implies that*

$$\sqrt{n}(\Psi(Q_{\theta_n}(\epsilon_n)) - \Psi(Q_0)) = \frac{1}{\sqrt{n}}\sum_{i=1}^n S^*(Q_{\theta_0,g_{\theta_0}}(\epsilon_0), g_{\theta_0})(O_i)\frac{g_{\theta_0}(A_i \mid V_i)}{g_i(A_i \mid V_i)} + o_P(1/\sqrt{n}),$$

so that it converges, by the Martingale Central Limit Theorem, in distribution to a multivariate normal distribution with mean zero and specified covariance matrix. In particular, if $g_n \to g_{\theta_0}$, $\Sigma(n) \to \Sigma$ and $A_n \to A_0$ with limits given by (34) and (35), then $\sqrt{n}(\Psi(Q_{\theta_n}(\epsilon_n) - \psi_0)$ converges to a multivariate normal $N(0,\Sigma_0)$, where $\Sigma_0 = P_{Q_0,g_{\theta_0}}\{S^*(Q_{\theta_0}(\epsilon_0), g_{\theta_0})\}^2$ is the covariance matrix of the fixed design efficient influence curve $S^*(Q_{\theta_0}(\epsilon_0), g_{\theta_0})$ under $P_{Q_0,g_{\theta_0}}$.

16 A targeted adaptive design for finding the dose response curve and optimal dose

We cite from the Critical Path Opportunities list of the FDA: "Most cancer trials identify and test the maximum tolerated dose, to maximize efficacy. Such trials cannot answer key questions about dose/response relationships: Do blood levels of drug relate to outcomes? At what dose does the response plateau?". In this section we describe a targeted adaptive design allowing efficient estimation of the dose response curve and, in particular, the optimal dose.

Dose response curve: Let $Y(a)$ represent a treatment specific outcome one would observe if the randomly sampled subject would be assigned a dose-level

$a \in \mathcal{A}$, and let $X = (W, (Y(a) : a \in \mathcal{A})) \sim P_{X0}$ represent the full data structure of interest on the randomly sampled subject consisting of the treatment specific outcomes, and baseline covariates W. Let $\mathcal{A}$ denote the set of dose levels, which could be an ordered discrete set of dose levels, or an interval. We will leave the full data distribution P_{X0} unspecified. Let $X_1, \ldots, X_n$ be n i.i.d. draws of X. A scientific parameter of interest is the causal dose response curve defined as $\psi_0(a) = E_0 Y(a)$. In addition, we are also concerned with the V-adjusted causal response curve for a $V \subset W$ defined as

$$\psi_0(a, v) = E_0(Y(a) \mid V = v),$$

where V represents a baseline characteristic which might potentially strongly affect the dose response curve, and, in particular, its optimal dose. Since the dose represents an ordered and many valued variable, we consider a working model $m(a, v \mid \beta)$ for $\psi_0(a, v)$, and define the target parameter as

$$\beta_0 = \arg\min_{\beta} E_{0V} \int_{a \in \mathcal{A}} (m(a, v \mid \beta) - \psi_0(a, v))^2 h(a, v) d\mu^*(a),$$

where h is a user supplied weight function, and $d\mu^*$ is either the counting measure on the finite set of dose levels or, if dose is continuous, it is the Lebesgue measure. The summary measure $\tilde{\psi}_0(a, v) = m(a, v \mid \beta_0)$ of ψ_0 implied by the working model $\{m(\cdot \mid \beta) : \beta\}$ provides now a model based approximation of the true dose response curve ψ_0. Note that β_0 is a parameter of ψ_0 and the marginal distribution P_{0V} of V. Although, we will consider the model for the full data distribution P_{X0} to be nonparametric and the working model as an approximation of the true causal response curve, our proposed estimators are valid if one actually assumes the working model to be correctly specified.

Optimal dose: We are also concerned with statistical inference for the optimal dose parameter for subgroup v

$$a^*(\beta_0)(v) = \arg\max_{a \in \mathcal{A}} m(a, v \mid \beta_0),$$

and, in case V is chosen to be the empty set, then this reduces to the marginal optimal dose

$$a^*(\beta_0) = \arg\max_{a \in \mathcal{A}} m(a \mid \beta_0).$$

For the sake of illustration, we will focus on a particular working model of interest given by a quadratic dose response model

$$m(a, v \mid \beta_0) = \beta_0(0)(v) + \beta_0(1)(v)a + \beta_0(2)(v)a^2,$$

where, for example, $\beta_0(j)(v) = \beta_0(j)(0) + \beta_0(j)(1)v$, $j = 0, 1, 2$. For this choice of working model we have that the optimal dose for subgroup $V = v$ is given by:

$$a^*(\beta_0)(v) = \frac{-\beta_0(1)(v)}{2\beta_0(2)(v)}.$$

In particular, the optimal marginal dose is given by

$$a^*(\beta_0) = \frac{-\beta_0(1)}{2\beta_0(2)}.$$

Below, we will formulate targeted adaptive designs which learn the design which is optimal for estimation of these optimal dose parameters.

Observed data: Let A_i be the treatment assignment for subject i, $i = 1, \ldots, n$, and let the observed data on the n subjects be $O_i = (W_i, A_i, Y_i = Y_i(A_i))$, $i = 1, \ldots, n$.

Adaptive Designs: Let $\mathbf{g} = (g_1, \ldots, g_n)$ be a CAR adaptive design:

$$g_i(a \mid X_i, O_1, \ldots, O_{i-1}) = P(A_i = a \mid W_i, O_1, \ldots, O_{i-1}), i = 1 \ldots, n.$$

The CAR-assumption on the design requires A_i to be independent of the counterfactual outcomes $(Y_i(a) : a \in \mathcal{A})$, conditional on W_i, and the data on the previously recruited subjects given by $O_1, \ldots, O_{i-1}$.

Likelihood and Identifiability: Firstly, we note that the likelihood of $(O_1, \ldots, O_n)$ factorizes as:

$$P_{Q_0,\mathbf{g}}(O_1, \ldots, O_n) = \prod_{i=1}^{n} Q_{10}(W_i) Q_{20}(Y_i \mid A_i, W_i) \prod_{i=1}^{n} g_i(A_i \mid W_i, \bar{\mathbf{O}}(i-1)),$$

where the conditional density of Y_i, given $A_i = a$, W_i, $Q_{20}(\cdot \mid a, W_i)$, equals the conditional density of $Y_i(a)$, given W_i, and Q_{10} denotes the marginal density of W. In particular, it follows that for any CAR-adaptive design for which $\liminf_{i\to\infty} g_i(a \mid W_i) > 0$, we have that the marginal causal dose response curve $\psi_0(a)$ is identified by the Q_0-factor of the likelihood by the following relation: for each $i \in \{1, \ldots, n\}$

$$\psi_0(a) = E_0 E_0(Y_i \mid A_i = a, W_i).$$

In general, under this same condition,

$$\psi_0(a, v) = E_0\{E_0(Y_i \mid A_i = a, W_i) \mid V_i = v\}.$$

Weighted Maximum Likelihood Estimation: Consider a model $Q_{2\theta}$ for the distribution of $Y(a)$, given W, and the corresponding weighted (or iteratively empirically weighted) maximum likelihood estimator θ_n:

$$\theta_n = \arg\max_\theta \sum_{i=1}^n \log Q_{2\theta}(Y_i \mid A_i, W_i) w_i,$$

indexed by weight vector (e.g.) $w_i = g^*(A_i \mid W_i)/g_i(A_i \mid W_i)$ for a user supplied choice g^*. We will leave the marginal distribution of W unspecified, so that this is estimated with the empirical probability distribution Q_{1n} of $W_1, \ldots, W_n$. This defines a working model $\mathcal{Q}^w$ for $Q_0 = (Q_{10}, Q_{20})$. Given an estimator θ_n, we will use the short-hand notation $Q_{\theta_n} = (Q_{1n}, Q_{2\theta_n})$. We wish to compute the targeted MLE for the nonparametric model targeting β_0, based on an initial maximum likelihood estimator based on this working model. For this purpose, we first need to know the efficient influence curve of β_0 in the nonparametric model and we will first define the targeted MLE for fixed designs, before generalizing it to adaptive designs.

Efficient influence curve for fixed design sampling: The efficient influence curve for β_0 at P_{Q_0,g_0} is, up till a normalizing matrix, given by

$$\begin{aligned} D^*(Q_0, g_0) &= \frac{h(A,V)\frac{d}{d\beta_0} m(A, V \mid \beta_0)}{g_0(A \mid X)}(Y - Q_{02}(A,W)) \\ &\quad + \int_a h(a,V)\frac{d}{d\beta_0} m(a, V \mid \beta_0)(Q_{02}(a,W) - m(a,V \mid \beta_0))d\mu^*(a) \\ &\equiv D_1^*(Q_0,g_0)(W,A,Y) + D_2^*(Q_0)(W), \end{aligned}$$

where we defined $Q_{02}(a,W) = E_{Q_0}(Y \mid A = a, W)$, and we note that $\beta_0 = \beta(Q_0)$ is a parameter of $Q_0 = (Q_{01}, Q_{02})$. Let

$$\begin{aligned} c(P_{Q_0,g_0}, g_0, \beta_0) &= P_{Q_0,g_0}\frac{h(A,V)}{g_0(A \mid X)}\frac{d}{d\beta_0} m(A,V \mid \beta_0)\frac{d}{d\beta_0} m(A,V \mid \beta_0)^\top \\ &= E_{Q_0}\int_a h(a,V)\frac{d}{d\beta_0} m(a,V \mid \beta_0)\frac{d}{d\beta_0} m(a,V \mid \beta_0)^\top d\mu^*(a). \end{aligned}$$

The efficient influence curve for β_0 is given by $c(P_{Q_0,g_0}, g_0, \beta_0)^{-1} D^*(Q_0, g_0)$. If Y is binary, then we would choose $h(a,V) = g_0(a \mid V)/m(a,V \mid \beta_0)(1 - m(a,V \mid \beta_0))$.

Targeted MLE for fixed design: Let $\{Q_{2\theta}(\epsilon) : \epsilon\}$ be a path through $Q_{2\theta}$ at $\epsilon = 0$ and satisfy the score condition $\frac{d}{d\epsilon}\log Q_{2\theta}(\epsilon)\big|_{\epsilon=0} = D_1^*(Q_{2\theta}, g_0)$. For example, if $Q_{2\theta}$ is a regression model of Y on A, W with normal errors, then

we can simply add the extension $\epsilon \frac{h(A,V)\frac{d}{d\beta_0}m(A,V|\beta_0)}{g_0(A|X)}$ to the regression model. Similarly, if $Q_{2\theta}$ is a logistic regression of a binary Y on A, W, then we simply add $\epsilon \frac{h(A,V)\frac{d}{d\beta_0}m(A,V|\beta_0)}{g_0(A|X)}$ to the logit of $Q_{2\theta}(1 \mid A, W)$. In both cases, these ϵ extensions have a score at $\epsilon = 0$ equal to $D_1^*(Q_{2\theta}, g_0)$. It is also important to note that by choosing $h(a, V) = g(a \mid V)/m(1-m)(A, V \mid \beta_0)$, in both cases the ϵ-fluctuation does not depend on β_0, but only on g_0, which is the reason that our one-step targeted MLE will also be the iterative targeted MLE (which converges in a single step). Let ϵ_n be the solution of

$$0 = \sum_i D_1^*(Q_{2\theta_n}(\epsilon_n), g_0)(O_i).$$

Identity: We note that for $\beta_0 = \beta(Q_0)$

$$\begin{aligned} 0 &= E_{0V} \int_a h(a, V) \frac{d}{d\beta_0} m(a, V \mid \beta_0)(m(a, V \mid \beta_0) - E_0(Y(a) \mid V)) d\mu^*(a) \\ &= E_{0W} \int_a h(a, V) \frac{d}{d\beta_0} m(a, V \mid \beta_0)(m(a, V \mid \beta_0) - Q_{02}(a, W))) d\mu^*(a). \end{aligned}$$

Let $\beta_n = \beta(Q_{1n}, Q_{2\theta_n})$, where Q_{1n} is the empirical probability distribution for the marginal distribution of W. Application of the above identity to $Q_n = (Q_{1n}, Q_{2\theta_n})$ implies

$$0 = \frac{1}{n} \sum_{i=1}^n h(a, V_i) \frac{d}{d\beta_n} m(a, V_i \mid \beta_n)(m(a, V \mid \beta_n) - Q_{2\theta_n}(a, W_i))) d\mu^*(a).$$

Application of this latter identity teaches us that for any $Q = (Q_1, Q_2)$ with Q_{1n} being the empirical probability distribution of $W_1, \ldots, W_n$, we have

$$0 = \sum_{i=1}^n D_2^*(Q)(O_i).$$

Thus, for all ϵ we have

$$0 = \sum_{i=1}^n D_2^*(Q_{\theta_n}(\epsilon)) = 0,$$

and, in particular,

$$0 = \sum_i D^*(Q_{\theta_n}(\epsilon_n), g_0)(O_i).$$

Targeted MLE Update as MLE over ϵ: In the case that $Q_{2\theta}$ is a normal error regression model, $Q_{2\theta}(\epsilon)$ is defined by adding the covariate extension

$\epsilon \frac{h(A,V)\frac{d}{d\beta_0}m(A,V|\beta_0)}{g_0(A|X)}$, and $d/d\beta m(A,V \mid \beta)$ does not depend on β (i.e., m is linear in β), one can show that

$$\epsilon_n = \arg\max_{\epsilon} \sum_{i=1}^{n} \log Q_{2\theta_n}(\epsilon)(Y_i \mid A_i, W_i)$$

is the MLE for ϵ for the parametric working model $\{Q_{2\theta_n}(\epsilon) : \epsilon\}$. Similarly, this applies to the logistic regression model under the modified choice of h.

The one-step targeted MLE is now defined as $Q_{\theta_n}(\epsilon - n)$ and the corresponding one-step targeted MLE of β_0 is defined as $\beta(Q_{\theta_n}(\epsilon_n)) = \beta(Q_{1n}, Q_{2\theta_n}(\epsilon_n))$. The iterative targeted MLE is defined similarly as outlined in Section 13, and in the above two linear and logistic regression model cases, so that ϵ_n is an MLE, these two targeted MLE procedures are identical.

Statistical Inference for targeted MLE in fixed design: Under regularity conditions, we have that the targeted MLE β_n is consistent and asymptotically linear with influence curve $c_0^{-1}D^*(Q_0, g_0)$, where $c_0 = c(P_{Q_0,g_0}, g_0, \beta_0)$ is the derivative matrix defined above:

$$\beta_n - \beta_0 = \frac{1}{n}\sum_{i=1}^{n} c_0^{-1}D^*(Q_0, g_0)(O_i) + o_P(1/\sqrt{n}).$$

Statistical inference can now be based on the central limit theorem and an estimate of the covariance matrix of the influence curve.

Targeted MLE in adaptive design: Let θ_n be a weighted MLE using weights $g^*(A_i \mid X_i)/g_i(A_i \mid X_i)$ for a user supplied choice g^*, $i = 1, \ldots, n$, or the sequentially adaptive weighted ML estimator as presented in detail in Section 8.

As above, let $Q_{2\theta,g}(\epsilon)$ be a path through $Q_{2\theta}$ at $\epsilon = 0$ satisfying the score condition $\frac{d}{d\epsilon}\log Q_{2\theta,g}(\epsilon)\Big|_{\epsilon=0} = D_1^*(Q_{2\theta}, g)$. For example, if $Q_{2\theta}$ is a regression model of Y on A, W with normal errors, then we can simply add $\epsilon \frac{h(A,V)\frac{d}{d\beta_0}m(A,V|\beta_0)}{g(A|X)}$ to the regression model. Similarly, if $Q_{2\theta}$ is a logistic regression of a binary Y on A, W, then we simply add $\epsilon \frac{h(A,V)\frac{d}{d\beta_0}m(A,V|\beta_0)}{g(A|X)}$ to the logit of $Q_{2\theta}(1 \mid A, W)$. In both cases, these ϵ extensions have a score at $\epsilon = 0$ equal to $D_1^*(Q_{2\theta}, g)$.

Let $\theta \to g_\theta$ be a given design function supposed to approximate the actual adaptive design in the sense that $g_i \approx g_{\theta_i}$: For example, if g_i is a targeted adaptive design $g_i = g_{\theta_{i-1}}$ based on design function $\theta \to g_\theta$, then we would select this particular choice of design function.

Let ϵ_n be a solution (if there are multiple solutions one selects the one with the maximum value of the likelihood of the data) of

$$0 = \sum_{i=1}^{n} D_1^*(Q_{\theta_n, g_{\theta_n}}(\epsilon_n), g_{\theta_n})(O_i) \frac{g_{\theta_n}(A_i \mid X_i)}{g_i(A_i \mid X_i)}.$$

An alternative is to define ϵ_n as solution of

$$0 = \sum_{i=1}^{n} D_1^*(Q_{\theta_n, g_{\theta_n}}(\epsilon_n), g_i)(O_i).$$

By the argument above, we also have (because the marginal of $Q_{\theta_n}(\epsilon_n)$ is the empirical Q_{1n})

$$0 = \sum_{i} D_2^*(Q_{\theta_n, g_{\theta_n}}(\epsilon_n))(O_i) = 0.$$

There is no need to weight this D_2^*-component with $g_{\theta_n}(A_i \mid X_i)/g_i(A_i \mid X_i)$, since $D_2^*(Q)(O_i)$ is only a function of Q and W_i so that $D_1^*(Q_{\theta_0}(\epsilon_0), g_{\theta_0}) g_{\theta_0}/g_i + D_2^*(Q_{\theta_0}(\epsilon_0))$ is a martingale estimating function.

In the case that $Q_{2\theta}$ is a normal error regression model, $Q_{2\theta}(\epsilon)$ is defined by adding the covariate extension $\epsilon \frac{h(A,V) \frac{d}{d\beta_0} m(A,V|\beta_0)}{g_{\theta_n}(A|X)}$, and $d/d\beta m(A, V \mid \beta)$ does not depend on β (i.e., m is linear in β), one can show that

$$\epsilon_n = \arg\max_{\epsilon} \sum_{i=1}^{n} \log Q_{2\theta_n}(\epsilon)(Y_i \mid A_i, W_i) w_i$$

is the weighted MLE for ϵ for the parametric model $\{Q_{2\theta_n}(\epsilon) : \epsilon\}$, where the weights are given by $w_i = g_{\theta_n}(A_i \mid X_i)/g_i(A_i \mid X_i)$, $i = 1, \ldots, n$. The same statement applies to the logistic regression model assuming the modification of $h(a, V) = g^*(a \mid V)/m(1-m)(a, V \mid \beta_n)$ so that the ϵ-fluctuation does not depend on β_n again.

The targeted MLE of β_0 is now defined as $\beta(Q_{\theta_n}(\epsilon_n)) = \beta(Q_{1n}, Q_{2\theta_n, g_{\theta_n}}(\epsilon_n))$. The iterative targeted MLE is defined similarly as outlined in Section 13 and the two procedures are identical in the the above mentioned cases in which ϵ_n happens to be a weighted MLE.

Statistical Inference for targeted MLE: Application of Theorem 8 shows that, under regularity conditions, the targeted MLE of β_0 is consistent, and asymptotically normally distributed, and if $g_i = g_{\theta_{i-1}}$ is a targeted adaptive design, then the limit covariance matrix is given by the covariance

matrix $P_{Q_0,g_0}\left\{D^*(Q_{\theta_0,g_{\theta_0}}(\epsilon_0),g_{\theta_0})\right\}^2$ of the locally efficient targeted MLE under fixed design sampling from $P_{Q_0,g_{\theta_0}}$. In addition, this covariance matrix can be estimated as

$$\Sigma_n = \frac{1}{n}\sum_{i=1}^{n}\left\{D^*(Q_{\theta_n,g_{\theta_n}}(\epsilon_n),g_{\theta_n})(O_i)w_i\right\}^2,$$

or one could only weight the D_1^* component of D^* as mentioned above.

Targeted adaptive design for determining optimal dose: Above we have not specified particular choices of adaptive designs g_i which target the optimal dose parameter, which we will do now. The optimal dose parameter represents a particular real valued parameter $f(\beta_0)$ of β_0. In this case the efficient influence curve of $f(\beta_0)$ at a fixed design data generating distribution P_{Q_0,g_0} is given by $\dot{f}(\beta_0)c_0^{-1}D^*(Q_0,g_0)$, where $\dot{f}(\beta_0) = \frac{d}{d\beta_0}f$ is the derivative (vector) of f. The corresponding variance is given by

$$\dot{f}(\beta_0)^\top c_0^{-1}P_{Q_0,g_0}D^*(Q_0,g_0)D^*(Q_0,g_0)^\top c_0^{-\top}\dot{f}(\beta_0).$$

Thus, for any selected parameter of interest $f(\beta_0)$, such as the optimal treatment dose $a^*(\beta_0)$ or the v-adjusted optimal treatment doses $a^*(\beta_0)(v)$, we can represent the variance of the efficient influence curve as

$$b(Q_0)^\top\Sigma(Q_0,g_0)b(Q_0),$$

for some specified vector $b(Q_0) \equiv c_0^{-\top}\dot{f}(\beta_0)$ where $\Sigma(Q_0,g_0) \equiv P_{Q_0,g_0}D^*(Q_0,g_0)^2$. For a $1\times m$ vector $b(Q_0)$ we have

$$b(Q_0)\Sigma(Q_0,g_0)b(Q_0)^\top = \sum_{j=1}^{m}\sum_{k=1}^{m}b(Q_0)(j)b(Q_0)(k)\Sigma(Q_0,g_0)(j,k). \tag{36}$$

Let $\sigma^2(Q_0,g_0)(v)$ be the variance of the efficient influence curve of the v-adjusted optimal dose defined by $f_v(\beta_0) = -\frac{\beta_0(1)(v)}{2\beta_0(2)(v)}$, and let $\sigma^2(Q_0,g_0)$ be the variance of the efficient influence curve of the marginal optimal dose defined by $f(\beta_0) = -\frac{\beta_0(1)}{2\beta_0(2)}$. These choices correspond with $1\times m$ vectors $b_v(Q_0) \equiv c_0^{-\top}\dot{f}_v(\beta_0)$ and $b(Q_0) \equiv c_0^{-\top}\dot{f}(\beta_0))$, respectively, in the above representation (36) of the variance of the efficient influence curve.

Let $\mathcal{G}_1 = \{g\in\mathcal{G} : g(\cdot\mid W) = g(\cdot\mid V)\}$ be the set of fixed designs in which the treatment decision is only based on $V\subset W$. We can now define the design function for the marginal optimal dose:

$$g_{Q_0} = \arg\min_{g\in\mathcal{G}_1}\sigma^2(Q_0,g).$$

Similarly, we can define the design function for the v-adjusted optimal dose:

$$g_{Q_0} = \arg\min_{g \in \mathcal{G}_1} \int_v \sigma^2(Q_0, g)(v) dR(v),$$

for a user supplied probability distribution R.

This defines now corresponding targeted adaptive designs $g_i = g_{Q_{i-1}}$, where Q_{i-1} is the estimator of Q_0 (i.e., empirical for marginal of W, and $Q_{2\theta_{i-1}}$ for the conditional distribution of Y, given A, W) based on $O_1, \ldots, O_{i-1}$). This adaptive design will learn the optimal design $g_{Q_{\theta_0}}$ for the purpose of estimation of the marginal optimal dose, or v-adjusted optimal dose for all v simultaneously.

We will now be concerned with the closed form implementation of this minimization problem required to calculate the targeted adaptive design $g_i = g_{Q_{i-1}}$. To start with, in order to implement this targeted adaptive design it is helpful to obtain an analytical expression for $\Sigma(Q_0, g_0) = P_{Q_0, g_0} D^*(Q_0, g_0)^2$. We note that the j, k-th element $\Sigma(Q_0, g_0)(j, k)$ of this covariance matrix is given by

$$E_{Q_0} \int_a \frac{h(a, V)}{g_0(a \mid V)} \frac{d}{d\beta_{0j}} m(a, V \mid \beta_{0j}) \frac{d}{d\beta_{0k}} m(a, V \mid \beta_{0k}) \sigma_0^2(a, V) d\mu^*(a),$$

plus an expectation of a function of W independent of g_0, where $\sigma_0^2(a, V) \equiv E((Y(a) - Q_{02}(a, W))^2 \mid V) = E(E((Y - Q_{02}(A, W))^2 \mid A = a, W) \mid V)$.

For the purpose of marginal optimal dose, we have to be able to minimize the following linear combination of these covariance elements over g_0:

$$\begin{aligned}
&\textstyle\sum_{j,k} b(Q_0)(j) b(Q_0)(k) E_{Q_0} \int_a \frac{h(a,V)}{g_0(a|V)} \frac{d}{d\beta_{0j}} m(a, V \mid \beta_0) \frac{d}{d\beta_{0k}} m(a, V \mid \beta_0) \sigma_0^2(a, V) d\mu^*(a) \\
&= E_{Q_0} \textstyle\int_a \frac{h(a,V)}{g_0(a|V)} \sigma_0^2(a, V) \left\{ \sum_{j,k} b(Q_0)(j) b(Q_0)(k) \frac{d}{d\beta_{0j}} m(a, V \mid \beta_0) \frac{d}{d\beta_{0k}} m(a, V \mid \beta_0) \right\} d\mu^*(a) \\
&\equiv E_{Q_0} \textstyle\int_a \frac{h(a,V)}{g_0(a|V)} \sigma_0^2(a, V) f_{marginal}(Q_0)(a, V) d\mu^*(a).
\end{aligned}$$

For the purpose of v-adjusted optimal dose, we have to be able to minimize over g_0

$$\begin{aligned}
&\textstyle\int_v dR(v) \sum_{j,k} b_v(Q_0)(j) b_v(Q_0)(k) \\
&\times \left\{ E_{Q_0} \textstyle\int_a \frac{h(a,V)}{g_0(a|V)} \frac{d}{d\beta_{0j}} m(a, V \mid \beta_0) \frac{d}{d\beta_{0k}} m(a, V \mid \beta_0) \sigma_0^2(a, V) d\mu^*(a) \right\} \\
&= E_{Q_0} \textstyle\int_a \frac{h(a,V)}{g_0(a|V)} \sigma_0^2(a, V) \\
&\left\{ \textstyle\int_v dR(v) \sum_{j,k} b_v(Q_0)(j) b_v(Q_0)(k) \frac{d}{d\beta_{0j}} m(a, V \mid \beta_0) \frac{d}{d\beta_{0k}} m(a, V \mid \beta_0) \right\} d\mu^*(a) \\
&\equiv E_{Q_0} \textstyle\int_a \frac{h(a,V)}{g_0(a|V)} \sigma_0^2(a, V) f_{adjusted}(Q_0)(a, V) d\mu^*(a).
\end{aligned}$$

So we can conclude that determining the design function g_{Q_0} will require minimizing a function

$$g_0 \rightarrow E_{Q_0} \int_{a \in \mathcal{A}} \frac{h(a,V)}{g_0(a \mid V)} \sigma_0^2(a,V) f(Q_0)(a,V) d\mu^*(a)$$

for some specified $f(Q_0)$ defined as either $f_{marginal}$ or $f_{adjusted}$. By approximating the possibly continuous valued set $\mathcal{A}$ by finite approximating subsets, we can arbitrarily well approximate the last expression with

$$g_0 \rightarrow \sum_{j=0}^{J} E_{Q_0} \frac{h(a_j,V) \sigma^2(Q_0)(a_j,V) f(Q_0)(a_j,V) d\mu^*(a_j)}{g_0(a_j \mid V)}.$$

So we can conclude that we need to be able to minimize expressions

$$g_0 \rightarrow \sum_{j=0}^{J} E_{Q_0} \frac{m(Q_0)(a_j,V)}{g_0(a_j \mid V)}$$

for some specified positive valued function
$m(Q_0)(a_j,v) \equiv h(a_j,V) \sigma^2(Q_0)(a_j,V) f(Q_0)(a_j,V) d\mu^*(a_j)$.

Setting $g_0(a_0 \mid V) = 1 - \sum_{j=1}^{J} g_0(a_j \mid V)$ and setting the derivatives w.r.t. $g_0(j \mid V)$ equal to zero, $j = 1, \ldots, J$, yields the solution

$$\begin{aligned} g_{Q_0}(a_j \mid v) &= \frac{\sqrt{\frac{m(Q_0)(a_j,v)}{m(Q_0)(a_0,v)}}}{1 + \sum_{j=1}^{J} \sqrt{\frac{m(Q_0)(a_j,v)}{m(Q_0)(a_0,v)}}} \\ & \qquad j = 1, \ldots, J \\ g_{Q_0}(a_0 \mid v) &= \frac{1}{1 + \sum_{j=1}^{J} \sqrt{\frac{m(Q_0)(a_j,v)}{m(Q_0)(a_0,v)}}}. \end{aligned}$$

So we can conclude that the design functions g_{Q_0} for a targeted adaptive design targeting the optimal dose exist in closed form.

We will state this result as a useful theorem.

Theorem 10 *(***Optimal fixed design for determining optimal dose:***)* **Dose response curve:** *Let $Y(a)$ represent a treatment specific outcome one would observe if the randomly sampled subject would be assigned a dose-level $a \in \mathcal{A}$, and let $X = (W, (Y(a) : a \in \mathcal{A})) \sim P_{X0}$ represent the full data structure of interest on the randomly sampled subject consisting of the treatment specific outcomes, and baseline covariates W. Let $\mathcal{A}$ denote the set of dose levels,*

which is assumed to be an ordered discrete set of dose levels. We will leave the full data distribution P_{X0} unspecified. Let $X_1, \ldots, X_n$ be n i.i.d. draws of X. The marginal causal dose response curve is defined as $\psi_0(a) = E_0 Y(a)$. The V-adjusted causal response curve for a $V \subset W$ is defined as

$$\psi_0(a, v) = E_0(Y(a) \mid V = v),$$

where V represents a baseline characteristic which might potentially strongly affect the dose response curve, and, in particular, its optimal dose. We consider a working model $m(a, v \mid \beta)$ for $\psi_0(a, v)$, and define the target parameter as

$$\beta_0 = \arg\min_{\beta} E_{0V} \int_{a \in \mathcal{A}} (m(a, v \mid \beta) - \psi_0(a, v))^2 h(a, v) d\mu^*(a),$$

where h is a user supplied weight function, and $d\mu^*$ is the counting measure on the finite set of dose levels. We are also concerned with targeted adaptive designs (and statistical inference) for the optimal dose parameter for subgroup v

$$a^*(\beta_0)(v) = \arg\max_{a \in \mathcal{A}} m(a, v \mid \beta_0),$$

and, in case V is chosen to be the empty set, then this reduces to the marginal optimal dose

$$a^*(\beta_0) = \arg\max_{a \in \mathcal{A}} m(a \mid \beta_0).$$

For the sake of illustration, we will focus on a particular working model of interest given by a quadratic dose response model

$$m(a, v \mid \beta_0) = \beta_0(0)(v) + \beta_0(1)(v)a + \beta_0(2)(v)a^2,$$

where, for example, $\beta_0(j)(v) = \beta_0(j)(0) + \beta_0(j)(1)v$, $j = 0, 1, 2$. For this choice of working model we have that the optimal dose for subgroup $V = v$ is given by:

$$a^*(\beta_0)(v) = \frac{-\beta_0(1)(v)}{2\beta_0(2)(v)}.$$

In particular, the optimal marginal dose is given by

$$a^*(\beta_0) = \frac{-\beta_0(1)}{2\beta_0(2)}.$$

The observed data is $O = (W, A, Y = Y(A)) \sim P_{Q_0, g_0}$, where $g_0(a \mid X) = P(A = a \mid X) = P(A = a \mid W)$. The efficient influence curve for β_0 at P_{Q_0, g_0}

is given by $c_0^{-1}D^*(Q_0,g_0)$*, where*

$$\begin{aligned} D^*(Q_0,g_0) &= \frac{h(A,V)\frac{d}{d\beta_0}m(A,V\mid\beta_0)}{g_0(A\mid X)}(Y-Q_{02}(A,W)) \\ &\quad + \int_a h(a,V)\frac{d}{d\beta_0}m(a,V\mid\beta_0)(Q_{02}(a,W)-m(a,V\mid\beta_0))d\mu^*(a) \\ &\equiv D_1^*(Q_0,g_0)(W,A,Y)+D_2^*(Q_0)(W), \end{aligned}$$

where $Q_{02}(a,W)=E_{Q_0}(Y\mid A=a,W)$*, and we note that* $\beta_0=\beta(Q_0)$ *is a parameter of* $Q_0=(Q_{01},Q_{02})$*. The normalizing matrix* $c_0=c(P_{Q_0,g_0},g_0,\beta_0)$ *is defined as*

$$\begin{aligned} c(P_{Q_0,g_0},g_0,\beta_0) &= P_{Q_0,g_0}\frac{h(A,V)}{g_0(A\mid X)}\frac{d}{d\beta_0}m(A,V\mid\beta_0)\frac{d}{d\beta_0}m(A,V\mid\beta_0)^\top \\ &= E_{Q_0}\int_a h(a,V)\frac{d}{d\beta_0}m(a,V\mid\beta_0)\frac{d}{d\beta_0}m(a,V\mid\beta_0)^\top d\mu^*(a). \end{aligned}$$

Let $\Sigma(Q_0,g_0)\equiv P_{Q_0,g_0}D^*(Q_0,g_0)^2$*. Let* $\sigma^2(Q_0,g_0)(v)$ *be the variance of the efficient influence curve of the* v*-adjusted optimal dose defined by* $f_v(\beta_0)=-\frac{\beta_0(1)(v)}{2\beta_0(2)(v)}$*, and let* $\sigma^2(Q_0,g_0)$ *be the variance of the efficient influence curve of the marginal optimal dose defined by* $f(\beta_0)=-\frac{\beta_0(1)}{2\beta_0(2)}$*. Consider the* $1\times m$ *vectors* $b_v(Q_0)\equiv c_0^{-\top}\dot{f}_v(\beta_0)$ *and* $b(Q_0)\equiv c_0^{-\top}\dot{f}(\beta_0)$*), respectively. We have*

$$\begin{aligned} \sigma^2(Q_0,g_0)(v) &= \sum_{j=1}^m\sum_{k=1}^m b_v(Q_0)(j)b_v(Q_0)(k)\Sigma(Q_0,g_0)(j,k) \\ \sigma^2(Q_0,g_0) &= \sum_{j=1}^m\sum_{k=1}^m b(Q_0)(j)b(Q_0)(k)\Sigma(Q_0,g_0)(j,k). \end{aligned}$$

Let $\mathcal{G}_1=\{g\in\mathcal{G}: g(\cdot\mid W)=g(\cdot\mid V)\}$ *be the set of fixed designs in which the treatment decision is only based on* $V\subset W$*. We can now define the design function for the marginal optimal dose (i.e., optimal fixed design minimizing variance of efficient influence curve for marginal optimal dose):*

$$g_{1,Q_0}=\arg\min_{g\in\mathcal{G}_1}\sigma^2(Q_0,g_0).$$

Similarly, we can define the design function for the v*-adjusted optimal dose:*

$$g_{2,Q_0}=\arg\min_{g\in\mathcal{G}_1}\int_v\sigma^2(Q_0,g_0)(v)dR(v),$$

for a user supplied probability distribution R*.*

Define

$$f_1(Q_0)(a,V) \equiv \sum_{j,k} b(Q_0)(j)b(Q_0)(k)\frac{d}{d\beta_{0j}}m(a,V \mid \beta_0)\frac{d}{d\beta_{0k}}m(a,V \mid \beta_0)$$

$$f_2(Q_0)(a,V) \equiv \int_v dR(v)\sum_{j,k} b_v(Q_0)(j)b_v(Q_0)(k)\frac{d}{d\beta_{0j}}m(a,V \mid \beta_0)\frac{d}{d\beta_{0k}}m(a,V \mid \beta_0).$$

We have

$$g_{s,Q_0} = \arg\min_{g\in\mathcal{G}_1}\sum_{a_j\in\mathcal{A}} E_{Q_0}\frac{m_s(Q_0)(a_j,V)}{g_0(a_j \mid V)}$$

for the specified function $m_s(Q_0)(a_j,v) \equiv h(a_j,V)\sigma^2(Q_0)(a_j,V)f_s(Q_0)(a_j,V)d\mu^*(a_j)$, $s=1,2$. *Assume that* $m_s(Q_0)(a_j,v) > 0$ *for all* $a_j \in \mathcal{A}$ *and* v *with* $dR(v) > 0$, $s=1,2$.

For $s \in \{1,2\}$, *we have*

$$\begin{aligned} g_{s,Q_0}(a_j \mid v) &= \frac{\sqrt{\frac{m_s(Q_0)(a_j,v)}{m_s(Q_0)(a_0,v)}}}{1+\sum_{j=1}^J\sqrt{\frac{m_s(Q_0)(a_j,v)}{m_s(Q_0)(a_0,v)}}} \\ & \quad j=1,\ldots,J \\ g_{s,Q_0}(a_0 \mid v) &= \frac{1}{1+\sum_{j=1}^J\sqrt{\frac{m_s(Q_0)(a_j,v)}{m_s(Q_0)(a_0,v)}}}. \end{aligned}$$

Application of our theorems for adaptive designs teach us that, under regularity conditions, the adaptive design $g_i = g_{s,Q_{\theta_{i-1}}}$ converges to its target fixed design $g_{s,Q_{\theta_0}}$ as $i \to \infty$.

17 Adaptive designs for regression.

Consider the case that one wishes to understand how the mean of an outcome is affected by a set of input variables. This function from the input variables to the mean is called a regression. The design settings for experiment i now corresponds with the settings of the input variables. An adaptive design allows now that we select the distribution of the settings in experiment i in response to what we have learned from the first $i-1$ experiments. In particular, we could aim to learn a design distribution which is optimal for a particular regression parameter of interest. Regression is one of the most common statistical applications in the practice of statistics. Therefore it is useful to point

out that adaptive designs can also be used to target and estimate regression parameters.

In the following two sub-sections we consider parametric and semi-parametric regression models.

17.1 Adaptive designs for parametric regression models.

Let $X = (Y(a) : a \in \mathcal{A}) \sim P_{X0}$, where a denotes now a vector of covariate values, and $Y(a)$ denotes the outcome under such a covariate-setting. Suppose that one assumes a regression model $E_0 Y(a) = m(a \mid \beta_0)$ for some regression model $\{m(\cdot \mid \beta) : \beta\}$.

Let $X_1, \ldots, X_n$ be n i.i.d copies of $X \sim P_{X0}$. We observe for experiment i $O_i = (A_i, Y_i = Y_i(A_i))$, $i = 1, \ldots, n$. An adaptive design corresponds with drawing the covariate settings A_i from a conditional distribution of A_i, given the data $O_1, \ldots, O_{i-1}$ observed in the previous $i-1$ experiments:

$$g_i(A_i \mid \mathbf{X}, A_1, \ldots, A_{i-1}) = P(A_i \mid \bar{\mathbf{O}}(i-1)),\ i = 1, \ldots, n.$$

The Q_0-factor of the likelihood of $O_1, \ldots, O_n$ is given by

$$\prod_{i=1}^{n} Q_0(Y_i \mid A_i),$$

where $Q_0(y \mid a) = P(Y(a) = y)$. Given a correctly specified parametric model $\mathcal{Q} = \{Q_\theta : \theta\}$ for Q_0, the maximum likelihood estimator of θ_0 is thus defined as:

$$\theta_n = \arg\max_\theta \prod_{i=1}^{n} Q_\theta(Y_i \mid A_i).$$

For example, if Y is continuous, one could assume normal and independent errors, and if Y is binary, then the regression model itself implies a model for Q_0. In both cases, θ_0 includes as component the regression components β_0.

Under weak regularity conditions, the maximum likelihood estimator solves the score equation $0 = \sum_i S(\theta_n)(O_i) = 0$, where $S(\theta)(O_i) = \frac{d}{d\theta} \log Q_\theta(Y_i \mid A_i)$. As shown by our Theorem 7, statistical inference can now be based on the Martingale Taylor expansion

$$\theta_n - \theta_0 = -A_n^{-1} \frac{1}{n} \sum_{i=1}^{n} S(\theta_0)(O_i) + o_P(1/\sqrt{n}),$$

where $A_n = \frac{1}{n} \sum_{i=1}^{n} \frac{d}{d\theta_0} S(\theta_0)(O_i)$.

We can also use a martingale estimating function based approach to construct estimators of β_0. The class of estimating functions for β_0 for fixed designs is given by

$$D_h(\beta_0)(A,Y) = h(A)(Y - m(A \mid \beta)),$$

with the optimal estimating function given by $h_{opt}(A) = \frac{d}{d\beta} m(A \mid \beta)/\text{VAR}(Y \mid A)$ (see Chapter 2, van der Laan and Robins (2003)). These estimating functions are also Martingale estimating functions as can be shown as follows. Firstly, we note that

$$\begin{aligned} P_{Q_0,g_i} h(A_i)(Y_i - m(A_i \mid \beta_0)) &= E(h(A_i)(Y_i(A_i) - m(A_i \mid \beta_0)) \mid O_1, \ldots, O_{i-1}) \\ &= E(\sum_a h(a)(Y_i(a) - m(a \mid \beta_0))g_i(a), \end{aligned}$$

where $g_i(a) = P(A_i = a \mid \bar{\mathbf{O}}(i-1))$. The latter random variable is a function of X_i and $O_1, \ldots, O_{i-1}$ (through $g_i(a)$). Since X_i is independent of $O_1, \ldots, O_{i-1}$, the conditional expectation, given $O_1, \ldots, O_{i-1}$, corresponds with taking the expectation w.r.t. the distribution of X:

$$\begin{aligned} &E(\textstyle\sum h(a)(Y_i(a) - m(a \mid \beta_0))g_i(a) \\ &= \textstyle\sum_a h(a)(E_0(Y_i(a)) - m(a \mid \beta_0))g_i(a) = 0. \end{aligned}$$

This proves that we can actually use as class of Martingale estimating functions $\{D_h(\beta) : h\}$, and estimate β_0, for example, with the solution of $0 = \sum_i \frac{d}{d\beta_n} m(A_i \mid \beta_n)(Y_i - m(A_i \mid \beta_n)) = 0$, or equivalently,

$$\beta_n = \arg\min_\beta \sum_i (Y_i - m(A_i \mid \beta))^2.$$

One can also use weights which are a function of A_i.

This teaches us that the approach of generalized estimating equations for fixed designs immediately generalizes to adaptive designs, and our theorems provide us with the corresponding statistical inference under the stability condition that the adaptive design g_i is asymptotically a fixed design. A nice property of these estimating functions is that they do not depend on g_i through inverse weighting, just as scores of correctly specified parametric models are martingale estimating functions.

In the above example, the class of estimating functions for fixed designs happen to also be Martingale estimating functions for adaptive designs g_i. The above class of Martingale estimating functions w.r.t. the adaptive design g_i, which are independent of g_i, represents an example of such classes of Martingale estimating functions (i.e., Martingale estimating functions independent of

g_i) for a large class of censored data structures and adaptive designs. That is, it is an application of the general Theorem 3 presented earlier.

Finally, we remark that the targeted adaptive designs $g_i = g_{Q_{i-1}}$ could be based on a design function g_Q minimizing the variance of the efficient influence curve at $P_{Q,g}$ of a particular real valued parameter of the regression vector-parameter β over a user supplied class of fixed designs, so that the adaptive design will be targeting this particular parameter.

17.2 Adaptive designs for semiparametric regression.

Let's now consider a semi-parametric regression model. Let $X = (Y(a_1, a_2) : (a_1, a_2) \in \mathcal{A}) \sim P_{X0}$. Consider a semi-parametric regression model $EY(a_1, a_2) - EY(0, a_2) = m(a_1, a_2 \mid \beta_0)$, or equivalently, $EY(a_1, a_2) = m(a_1, a_2 \mid \beta_0) + s(a_2)$ for an arbitrary function s and a parametric form $m(\cdot \mid \beta)$ satisfying $m(0, a_2 \mid \beta) = 0$ for all a_2 and β. The parameter of interest is β_0.

Let $O_i = (A_i = (A_{1i}, A_{2i}), Y_i = Y_i(A_i)),\ i = 1, \ldots, n$. In a sequentially adaptive design A_i is drawn from a conditional distribution of A_i, given $O_1, \ldots, O_{i-1}$:

$$g_i(A_i \mid X_1, \ldots, X_n, O_1, \ldots, O_{i-1}) = P(A_i \mid O_1, \ldots, O_{i-1}),\ i = 1, \ldots, n.$$

We have that β_0 is identifiable through the relation

$$E_0(Y_i \mid A_{1i}, A_{2i}) - E_0(Y_i \mid A_{1i} = 0, A_{2i}) = m(A_i \mid \beta_0).$$

The Q_0-factor of the density of $O_1, \ldots, O_n$ is given by:

$$\prod_{i=1}^{n} Q_0(Y_i \mid A_i),$$

where $Q_0(y \mid a) = P_{X0}(Y(a) = y)$. We are concerned with construction of a targeted maximum likelihood estimator of β_0.

Firstly, we consider a working regression model $\mathcal{Q}^w = \{Q_\theta : \theta \in \Theta\}$ for Q_0. For example, the working model assumes $E_\theta Y(a) = m(a_1, a_2 \mid \beta) + s_\theta(a)$, where β represents a component of θ and s_θ is a particular parametric form in θ. Let θ_n be an estimator based on a Martingale estimating function $D(\theta^*)(O_i, Z_i)$ satisfying $P_{Q_0,g_i} D(\theta_0^*) = 0$ for all i, where θ_0^* either equals θ_0 (as in the weighted maximum likelihood estimator using weights g^*/g_i) or includes θ_0 as a component (as in the sequentially weighted maximum likelihood estimator using weights $g_{\theta_{n_k}}/g_i$ at sample size n_k). Thus, θ_n^* is a solution of

$$0 = \sum_{i=1}^{n} D(\theta_n^*)(O_i, Z_i) = 0.$$

The efficient influence curve: In order to construct the targeted MLE we need to know the efficient influence curve of β_0 in the fixed design model. We note that the fixed design model is equivalent with the semi-parametric regression model $E(Y \mid A_1, A_2) - E(Y \mid A_1 = 0, A_2) = m(A_1, A_2 \mid \beta_0)$.

The orthogonal complement of the nuisance tangent space in the fixed design model is given by:

$$T_{nuis}^{\perp}(p) = \{D_h(p)(O) : h\} \subset L_0^2(P),$$

where

$$D_h(p)(O) \equiv h(p)(A_1, A_2)(Y - m(A_1, A_2 \mid \beta(p)) - E_p(Y \mid A_1 = 0, A_2),$$

and $h(p)(A_1, A_2) = h(A_1, A_2) - E_p(h(A_1, A_2) \mid A_2)$. The orthogonal complement of the nuisance tangent space corresponds with the set of gradients for $\beta(p)$ at p given by:

$$T_{nuis}^{\perp}(p)^* = \left\{-c(p)(h)^{-1} D_h(p)(O) : h = (h_1, \ldots, h_d)\right\},$$

where $c(p)(h) = \frac{d}{d\beta} E_p D_h(p, \beta)\Big|_{\beta=\beta(p)}$, and D_h now represents a vector function $(D_{h_1}, \ldots, D_{h_d})$. The efficient influence curve is identified by a closed form index $h^*(p)$ (see e.g., van der Laan (2006b)):

$$\begin{aligned} h^*(p)(A_1, A_2) &= \frac{1}{\sigma^2(A)} \frac{d}{d\beta(p)} m(A \mid \beta(p)) \\ &\quad - \frac{1}{\sigma^2(A)} \frac{E_p\left(\frac{d}{d\beta(p)} m(A \mid \beta(p))/\sigma^2(A) \mid A_2\right)}{E_p(1/\sigma^2(A) \mid A_2)}. \end{aligned} \tag{37}$$

This choice $h^*(p)$ corresponds with the efficient influence curve as provided and proved in Robins and Rotnitzky and Yu and van der Laan (2003). Let $D(p) = D_{h^*(p)}(p)$ be this efficient influence curve at p as identified by this index $h^*(p)$. We note that $D(p) = D(g(p), Q(p))$ depends on the conditional distribution $g(p)(A_1 \mid A_2)$ of A_1, given A_2, and the conditional distribution $Q(p)$ of Y, given A.

Let $g(p)$ be the marginal density of A under p, and let $Q(p)$ be the conditional distribution of Y, given A, under p. We note that the parameter $\beta(p)$ is only a function of $Q(p)$, and the density factorizes as $p(O) = g(p)(A)Q(p)(Y \mid A)$. As a consequence the elements $D_h(p)$ are orthogonal to the tangent space of the nuisance parameter $g(p)$. That is, we can decompose the efficient score $D(p)$ into two subcomponents as follows:

$$D(p) = D(p) - E_p(D(p) \mid A) + E_p(D(p) \mid A) - E_p D(p),$$

which corresponds with scores for $p(Y \mid A)$, $p(A)$, respectively, but $E_p(D(p) \mid A) - E_p D(p) = 0$. Thus the efficient influence curve $D(p)$ represents only a score for $Q(p)(Y \mid A)$, and indeed satisfies $E_p(D(p) \mid A) = 0$.

Let $Q_{\theta,g}(\epsilon)$ be a parametric extension through Q_θ at $\epsilon = 0$, satisfying $E_{Q_{\theta,g}(\epsilon)}(Y \mid A) - E_{Q_{\theta,g}(\epsilon)}(Y \mid A_1 = 0, A_2) = m(A \mid \beta(\epsilon))$ for some $\beta(\epsilon)$, and having score $D(Q_\theta, g)$ at $\epsilon = 0$. In the following paragraph we construct such a choice (see van der Laan and Rubin (2006)). We show that if $E_{Q_\theta}(Y \mid A) = m(A \mid \beta) + r(A_2)$ for some r and Y, given A, is normally distributed then, we can define the extension by just fluctuating the mean as $m(A \mid \beta + \epsilon) + r(A_2) + \epsilon r_1(A_2)$, where

$$r_1(p_{\theta,g})(A_2) = \frac{E_g\left(\frac{d/d\beta m(A|\beta)}{\sigma^2(A)} \mid A_2\right)}{E_p\left(\frac{1}{\sigma^2(A)} \mid A_2\right)}.$$

Let $\theta \to g_\theta$ be a design function for the marginal distribution of $A = (A_1, A_2)$ selected to approximate the actual adaptive design g_i in the sense that $g_i \approx g_{\theta_{i-1}}$. Let ϵ_n be a solution of

$$0 = \sum_{i=1}^{n} D^*(Q_{\theta_n, g_{\theta_n}}(\epsilon_n), g_{\theta_n})(O_i) \frac{g_{\theta_n}(A_i)}{g_i(A_i)}.$$

In the case that $\beta \to m(A \mid \beta)$ is linear, below it is shown that ϵ_n is a weighted MLE:

$$\epsilon_n = \arg\max_{\epsilon} \prod_{i=1}^{n} Q_{\theta_n, g_{\theta_n}}(\epsilon_n)(O_i) \frac{g_{\theta_n}(A_i)}{g_i(A_i)}. \tag{38}$$

Using our theorem for targeted MLE of Theorem 7, under appropriate regularity conditions, it follows that $\sqrt{n}(\beta(Q_{\theta_n}(\epsilon_n)) - \beta(Q_{\theta_0}(\epsilon_0)))$ converges in distribution. If $\beta \to m(\cdot \mid \beta)$ is linear, it follows immediately that $P_{Q_0,g} D(Q_{\theta_0}(\epsilon_0), g) = 0$ implies $\beta(Q_{\theta_0}(\epsilon_0)) = \beta_0$. The same robustness can be established in general. As a consequence of this result, the asymptotic normality of the targeted MLE as an estimator of β_0 is established.

We note that if the design only adapts A_{1i}, given A_{2i}, then the weights only involve $g_\theta(A_{1i} \mid A_{2i})/g_i(A_{1i} \mid A_{2i})$. The adaptive design could be targeted towards the estimation of a particular univariate summary measure or component of β_0.

Hardest parametric sub-model $Q_{\theta,g}(\epsilon)$.

Suppose that Q_θ is a normal distribution with mean $E_\theta(Y \mid A) = m(A \mid \beta) + r_\theta(A_2)$ and variance $\sigma^2(A) = \sigma^2(\theta)(A)$. Let $p_{\theta,g}$ denote the density of O

under Q_θ and marginal distribution g for A. Recall that $D(p) = (h(p)(A) - E_p(h(p)(A) \mid A_2))(Y - m(A \mid \beta(p)) - E_p(Y \mid A_1 = 0, A_2))$. For notational convenience, we will represent this function as $h(p)(A)(Y - E_p(Y \mid A))$, but now choosing $h(p)$ so that $E_p(h(p)(A) \mid A_2) = 0$. Consider the parametric sub-model defined as the normal density with conditional variance $\sigma^2(A)$ and conditional mean $m(A \mid \beta(\epsilon)) + r_\theta(\epsilon)(A_2)$. That is,

$$Q_\theta(\epsilon)(Y \mid A) = \frac{1}{\sigma(A)} f_0\left(\{Y - m(A \mid \beta(\epsilon)) - r_\theta(\epsilon)(A_2)\}/\sigma(A)\right),$$

where $\beta(0) = \beta$, $r_\theta(0) = r_\theta = E_\theta(Y \mid A_1 = 0, A_2)$, and f_0 is the standard normal density. We note that this is a valid sub-model through Q_θ at $\epsilon = 0$. Let $\beta(\epsilon) \equiv \beta + \epsilon$ and $r_\theta(\epsilon) = r_\theta + \epsilon r_1(A_2)$. It remains to find a function $r_1(A_2)$ so that the score of $Q_\theta(\epsilon)$ at $\epsilon = 0$ equals the efficient influence curve $D(Q_\theta, g)$ at $p_{\theta,g}$.

We have that the score $S(\epsilon)$ at ϵ is given by (note that $f_0'(x)/f_0(x) = x/\sigma^2$)

$$\begin{aligned} S(\epsilon) &= \frac{(Y - m(A \mid \beta(\epsilon)) - r_\theta(\epsilon)(A_2))}{\sigma^2(A)} \left\{ \frac{d}{d\epsilon} m(A \mid \beta(\epsilon)) - \frac{d}{d\epsilon} r_\theta(\epsilon)(A_2)) \right\} \\ &= \frac{\left\{ \frac{d}{d\beta(\epsilon)} m(A \mid \beta(\epsilon)) - r_1(A_2)) \right\} (Y - m(A \mid \beta(\epsilon)) - r_\theta(\epsilon)(A_2))}{\sigma^2(A)}. \end{aligned}$$

Thus $S(0)$ equals

$$\tfrac{1}{\sigma^2(A)} \left\{ \tfrac{d}{d\beta} m(A \mid \beta) - r_1(A_2) \right\} (Y - E_Q(Y \mid A)).$$

In order to have that this score equals $D_h = h(A)(Y - E_Q(Y \mid A))$ for a particular $h(A)$ with $E_p(h(A) \mid A_2) = 0$, we need

$$r_1(A_2) = r_1(p)(A_2) = \frac{E_p\left(\frac{d/d\beta m(A|\beta)}{\sigma^2(A)} \mid A_2 \right)}{E_p\left(\frac{1}{\sigma^2(A)} \mid A_2 \right)}.$$

We note that if m is linear in β, then $r_1(p) = r_1(g)$ only depends on g. This yields the following score for our sub-model $Q_\theta(\epsilon)$ at $\epsilon = 0$:

$$S(0) = h(p_{\theta,g})(A)(Y - m(A \mid \beta) - r_\theta(A_2)),$$

where

$$\begin{aligned} h(p_{\theta,g})(A) &= \frac{1}{\sigma^2(A)} \frac{d}{d\beta} m(A \mid \beta) \\ &\quad - \frac{1}{\sigma^2(A)} \frac{E_g\left(\frac{d}{d\beta} m(A \mid \beta)/\sigma_\theta^2(A) \mid A_2 \right)}{E_p(1/\sigma_\theta^2(A) \mid A_2)}. \end{aligned} \tag{39}$$

So we succeeded in finding a sub-model $Q_\theta(\epsilon)$ with a score at $\epsilon = 0$ equal to the efficient influence curve at $p_{\theta,g}$.

We will now show that ϵ_n as defined earlier can be viewed as a weighted MLE. Consider the weighted log-likelihood for $p_n^0(\epsilon)$ in ϵ:

$$l(\epsilon) \equiv \frac{1}{n}\sum_{i=1}^{n} \log f_0(Y_i - m(A_i, W_i \mid \beta_n^0 + \epsilon) - \{r_{\theta_n^0}(W) + \epsilon r_1(p_n^0)(W)\})w_i$$

with weights $w_i = g_\theta / g_i$. Let ϵ_n be the maximizer, which can thus be computed with standard weighted least squares regression:

$$\epsilon_n = \arg\min_\epsilon \sum_{i=1}^{n} w_i \frac{1}{\sigma^2(A_i, W_i)} \left(Y_i - m(A_i, W_i \mid \beta_n^0 + \epsilon) - r_{\theta_n^0}(W_i) - \epsilon r_1(p_n^0)(W_i)\right)^2 \quad (40)$$

The score equation $d/d\epsilon l(\epsilon) = P_n S(\epsilon) = 1/n \sum_i S(\epsilon)(O_i, Z_i)$ for ϵ_n is given by

$$\begin{aligned} 0 &= P_n w_i \frac{1}{\sigma^2(A,W)} \left\{ \frac{d}{\beta_n^0(\epsilon)} m(A, W \mid \beta_n^0(\epsilon)) - r_1(p_n^0)(W)) \right\} \\ &\quad \times (Y - m(A, W \mid \beta_n^0(\epsilon)) - r_{\theta_n^0}(W) - \epsilon r_1(p_n^0)(W)). \end{aligned}$$

In the sequel we consider the case that $m(A, W \mid \beta) = \beta^\top m_1(A, W)$ is linear in β for some specified covariate vector $m_1(A, W)$. In this case we have $d/d\beta m(A, W \mid \beta) = m_1(A, W)$ so that the score equation $P_n S(\epsilon) = 0$ reduces to:

$$\begin{aligned} 0 = P_n w_i \frac{1}{\sigma^2(A,W)} \left\{ m_1(A,W) - r_1(p_n^0)(W) \right\} \times \\ (Y - (\beta_n^0 + \epsilon_n) m_1(A,W) - r_{\theta_n^0}(W) - \epsilon_n r_1(p_n^0)(W)). \end{aligned} \quad (41)$$

Firstly, we note that ϵ_n exist in closed form:

$$\epsilon_n = C_n^{-1} P_n w_i \frac{\{m_1(A,W) - r(p_n^0)(W)\}(Y - \beta_n^0 m_1(A,W) - \theta_n^0(W))}{\sigma^2(A,W)},$$

where the $d \times d$ matrix C_n is given by

$$C_n \equiv P_n w_i \frac{1}{\sigma^2(A,W)} \left\{ m_1(A,W) - r(p_n^0)(W) \right\} (m_1(A,W) + r(p_n^0)(W))^\top.$$

Let $p_n^0(\epsilon_n)$ be the new density estimator. Recall that the distribution of A under $p_n^0(\epsilon_n)$ is still the same as under p_n^0, because $p_n^0(\epsilon)$ only updates the conditional distribution of Y, given A. We now wish to investigate when

this first step targeted MLE $p_n^1 \equiv p_n^0(\epsilon_n)$ solves the efficient score equation: $P_n w_i D(p_n^0(\epsilon_n)) = 0$. We have that $P_n w_i D(p_n^0(\epsilon_n))$ is given by

$$P_n w_i \frac{\{m_1 - r_1(p_n^0(\epsilon_n))\}\,(Y - (\beta_n^0 + \epsilon_n)m_1 - r_{\theta_n^0} - \epsilon_n r_1(p^0(\epsilon_n)))}{\sigma^2}.$$

Because $r_1(p_n^0(\epsilon)) = r_1(p_n^0)$, it follows that $P_n D(p^0(\epsilon_n))$ is given by

$$P_n w_i \frac{\{m_1 - r_1(p_n^0)\}\,(Y - (\beta_n^0 + \epsilon_n)m_1 - r_{\theta_n^0} - \epsilon_n r_1(p_n^0))}{\sigma^2},$$

but the latter equals zero by the fact that $P_n S(\epsilon_n) = 0$ (41). This proves that, if $m(A, W \mid \beta)$ is linear in β, then ϵ_n is indeed the weighted maximum likelihood estimator (38). For non-linear models $\beta \to m(A, W \mid \beta)$ the solution ϵ_n of (38) is not exactly equal to the weighted MLE.

18 Other examples of adaptive designs.

In this section we will present a number of other examples of adaptive designs to which our formal results can be applied.

18.1 Joint adaptation of the missingness indicators for auxiliary covariates and the treatment mechanism.

Suppose that on the i-th experimental unit we observe a J-dimensional vector of covariates $(\Delta_i(j)W_i(j), \Delta_i(j) : j = 1, \ldots, J)$ which are subject to missingness, a vector of covariates E_i which are always observed, a treatment R_i, and an outcome Y_i of interest. Here $\Delta_i(j)$ denotes a missing-ness indicator: if $\Delta_i(j) = 0$, then $W_i(j)$ is missing.

We define the full data on the i-th experimental unit as $X_i = (E_i, W_i, (Y_i(r) : r))$, where $Y_i(r)$ denotes the treatment specific counterfactual outcomes, and $W_i = (W_i(j) : j = 1, \ldots, J)$. The censoring variable is now defined as $A_i = (\Delta_i, R_i)$ and denotes both the missing-ness indicators as well as the treatment assignment R_i. The observed data can be represented as $O_i = (E_i, \Delta_i W_i, \Delta_i, R_i, Y_i = Y_i(R_i))$, and is thus a function of X_i and the censoring variable A_i, $i = 1, \ldots, n$.

It is assumed that the conditional probability distribution of Δ_i, R_i, given X_i and $O_1, \ldots, O_{i-1}$, only depends on X_i through the always observed covariates E_i. In this case, a choice of adaptive design is defined by the specification of the conditional distribution of Δ_i, R_i, given E_i and the data $O_1, \ldots, O_{i-1}$

observed on previous experiments,

$$g_i(\delta, r \mid E_i) \equiv g(\delta, r \mid E_i, O_1, \ldots, O_{i-1}).$$

We can factorize this conditional distribution into a treatment mechanism and missing-ness mechanism:

$$g_i(\delta, r \mid E_i) = g(\delta \mid E_i, O_1, \ldots, O_{i-1}) g(r \mid \delta, E_i, O_1, \ldots, O_{i-1}).$$

Note that this allows, beyond the previously studied adaptation of the randomization probabilities for treatment, to set the missing-ness indicators (and thereby the decision about what variables to measure) for experiment i in response to data collected in previous experiments.

We wish to consider some targeted adaptive designs $g_i = g_{\theta_i}$, where θ_i is an estimator of certain parameters θ_0 of the full data distribution based on $O_1, \ldots, O_{i-1}$.

Firstly, consider the case that one is interested in estimating a causal effect $\psi_0(r) = E_0(Y(r) - Y(0))$ of treatment level r relative to treatment level 0, or an adjusted causal effect $\psi(0)(r, V) = E_0(Y(r) - Y(0) \mid V)$ for a baseline co-variate $V \subset E$.

For the sake of illustration, let's consider the marginal causal effect parameter. Let $W^* = (W\Delta, \Delta)$ denote our observed data on the co-variate vector W. We have that A_i is conditionally independent of X_i, given W_i^*, E_i, and $O_1, \ldots, O_{i-1}$. As a consequence, we have that $\psi_0 = E_0(Y(r) - Y(0))$ is identified by the following parameter of the observed data distribution:

$$\psi_0 = E_0 E_0(Y_i \mid R_i = a, E_i, W_i^*) - E_0(Y_i \mid R_i = 0, W_i^*).$$

In addition, if one replaces $(W\Delta, \Delta)$ by any sub-vector, including the empty set this identifiability result still holds. We could estimate ψ_0 with the targeted MLE ψ_n as defined in previous section. The efficient influence curve of ψ_0 at a fixed design P_{Q_0, g_0}, $g_0 \in \mathcal{G}$, is given by:

$$\begin{aligned} D^*(Q_0, g_0) &= (Y - Q_0(R, E, W^*)) \left\{ \frac{I(R=1)}{g(1 \mid E, W^*)} - \frac{I(R=0)}{g(0 \mid E, W^*)} \right\} \\ &\quad + Q_0(1, E, W^*) - Q_0(0, E, W^*) - \psi_0. \end{aligned}$$

The variance of this efficient influence curve depends on the true marginal distribution of W^*, and on the treatment mechanism $g(r \mid E, W^*)$. The optimal design minimizing the variance of this efficient influence curve would be to allow for no missingness so that $W^* = W$, and the optimal randomization

probabilities for treatment are defined by the Neyman allocation probabilities conditional on (E, W):

$$g_{\theta_0}(1 \mid E, W) = \frac{\sigma(1 \mid E, W)}{\sigma(0 \mid E, W) + \sigma(1 \mid E, W)} \quad (42)$$

$$g_{\theta_0}(0 \mid E, W) = 1 - g_{\theta_0}(1 \mid E, W), \quad (43)$$

where $\sigma^2(j \mid E, W) = \mathrm{VAR}(Y \mid A = j, E, W)$. However, suppose that we are in the situation that the measurement of variable $W(j)$ costs $s(j)$ dollars on each subject, and that we wish to run a trial with n subjects. In addition, assume that their is only B dollars per patient available to spend on co-variate selection. So given a choice of missing indicator vectors $\Delta_1, \ldots, \Delta_n$ the average cost for covariate measurement per patient is given by

$$\frac{1}{n} \sum_{i=1}^{n} \sum_{j=1}^{J} \Delta_i(j) s(j).$$

The expected average cost per patient is thus given by:

$$\sum_{j=1}^{J} \Pi(j) s(j),$$

where $\Pi(j) = P(\Delta(j) = 1)$. In principle, one could now define an optimal fixed design $(g(Q_0, \Pi(Q_0))$ as the minimizer of the variance of the efficient influence curve under the constraint that the expected average cost is bounded by B:

$$(g(Q_0), \Pi(Q_0)) = \arg \min_{g, \Pi \in \{\sum_j \Pi(j) s(j) \leq B\}} \mathrm{VAR}_{Q_0, g, \Pi} D^*(Q_0, g).$$

One might also formulate a more ad hoc mapping from a candidate Q into a preferred choice of design $(g(Q), \Pi(Q))$. This defines now a design function and corresponding adaptive design $(g_i, \Pi_i) = (g(Q_{i-1}), \Pi(Q_{i-1}))$, where Q_{i-1} is an estimate of the marginal distribution of W and the conditional distribution of Y, given A, W, based on the first $i-1$ observations. As an example of a more ad hoc mapping $\Pi(Q_{i-1})$, given $O_1, \ldots, O_{i-1}$, one might estimate the marginal association of Y and W_j for each j, and set $\Pi_i(j) = 1$ for the top ranked variables, and set $\Pi_i(j) = 0$ for the remaining variables, while controlling the average cost $\sum_j \Pi_i(j) s(j) \leq B$. In the next subsection we study this example of adaptation in more generality in the case that the treatment mechanism is considered given.

18.2 Adapting the choice of auxiliary covariate information.

Let $X = ((Y(a) : a), W)$, W a vector of covariates, and $W(\Delta) = \Phi(\Delta, W)$ is a coarsening of W indexed by a censoring (possibly multivariate) variable Δ. For example, $\Delta = 0$ might correspond with the most precise and expensive measurement satisfying $W(0) = W$, while larger Δ values result in cheaper but more coarsened measurements of W. Let $\psi_0 = E(Y(r) - Y(0))$ be the parameter of interest. Let $O = (\Delta, W(\Delta), R, Y = Y(A))$. A fixed design is defined as the conditional distribution of (Δ, R), given X, which can be factorized as the conditional distribution Π of Δ, given X, and the conditional distribution $g(\cdot \mid \Delta, X)$ of R, given Δ, X. We consider CAR fixed designs for which this conditional distribution only depends on X through E, where E is always measured: i.e., E is a function of $W(\Delta)$. We denote this set of fixed CAR designs by $\mathcal{G}_1 \subset \mathcal{G}$. We have that $\psi_0 = E_0(Y(r) - Y(0))$ is identified by the following parameter of the observed data distribution:

$$\psi_0 = E_0 E_0(Y \mid R = r, W^*(\Delta)) - E_0(Y \mid R = 0, W^*(\Delta)),$$

where $W^*(\Delta) \equiv (\Delta, W(\Delta))$. In addition, if one replaces $W^*(\Delta)$ by any subvector including E, this identifiability result still holds. In particular,

$$\psi_0 = E_0(E(Y \mid R = r, E) - E_0(Y \mid R = 0, E)).$$

We could estimate ψ_0 with the targeted MLE ψ_n as defined in previous section. The efficient influence curve of ψ_0 at a fixed design data generating distribution P_{Q_0,g_0} is given by:

$$\begin{aligned} D^*(Q_0, g_0) &= (Y - Q_0(R, W^*(\Delta))) \left\{ \frac{I(R=1)}{g_0(1 \mid W^*(\Delta))} - \frac{I(R=0)}{g_0(0 \mid W^*(\Delta))} \right\} \\ &\quad + Q_0(1, W^*(\Delta)) - Q_0(0, W^*(\Delta)) - \psi_0, \end{aligned}$$

where $Q_0(R, W^*(\Delta)) = E_0(Y \mid R, W^*(\Delta))$.

We will now show that $Q_0(R, W^*(\Delta))$ is only a parameter of the distribution of X. Since Δ is conditionally independent of X, given E, we have

$$Q_0(R, W^*(\Delta)) = E[E[Y \mid R, \Delta, W] \mid R, \Delta, W(\Delta), E] = E(Q_0(R, W) \mid R, \Delta, W(\Delta)).$$

In addition, $E(Q_0(R, W) \mid R = r, \Delta, W(\Delta)) = E(Q_0(r, W) \mid \Delta, W(\Delta))$ so that the latter conditional expectation is w.r.t. the conditional density of W, given $\Delta, W(\Delta))$. By the fact that $(\Delta, W(\Delta))$ is a CAR missing data structure on W, the latter conditional density satisfies $P(W = w \mid W^*(\Delta) = w^*) =$

$p(W = w \mid W \in C(w^*))$, where $C(W^*(\Delta))$ is the coarsening for W implied by $W^*(\Delta) = (\Delta, W(\Delta))$ (see Gill et al. (1997) or Chapter 1 in van der Laan and Robins (2003)). Therefore, we can conclude that $E(Y \mid R, W^*(\Delta))$ is only a parameter of the distribution of X and does thus not depend on the conditional distribution g_0 of (Δ, A), given X.

For notational convenience, let $W^* = W^*(\Delta)$. The variance of the efficient influence curve $D^*(Q_0, g_0)$ under P_{Q_0,g_0} can be written as:

$$\begin{aligned}
V^2 &\equiv E(Y - Q_0(R, W^*))^2 \left(\frac{I(R=1)}{g_0^2(1 \mid W^*)} + \frac{I(R=0)}{g_0^2(0 \mid W^*)} \right) \\
&\quad + E\left(Q(1, W^*) - Q(0, W^*) - \psi_0\right)^2 \\
&= E\left(\frac{\sigma_0^2(1, W^*)}{g_0(1 \mid W^*)} + \frac{\sigma_0^2(0, W^*)}{g_0(0 \mid W^*)} \right) \\
&\quad + E\left(Q_0(1, W^*) - Q_0(0, W^*)\right)^2 - \psi_0^2 \\
&= E_W \sum_\delta \Pi(\delta \mid E) \left(\frac{\sigma_0^2(1, W^*(\delta))}{g_0(1 \mid \delta, E)} + \frac{\sigma_0^2(0, W^*(\delta))}{g_0(0 \mid \delta, E)} + \left(Q_0(1, W^*(\delta)) - Q_0(0, W^*(\delta))\right)^2 \right) \\
&\quad - \psi_0^2 \\
&= E_E \sum_\delta \Pi(\delta \mid E) \left(\frac{E(\sigma_0^2(1, W^*(\delta)) \mid E)}{g_0(1 \mid \delta, E)} + \frac{E(\sigma_0^2(0, W^*(\delta)) \mid E)}{g_0(0 \mid \delta, E)} \right) \\
&\quad + E_E \sum_\delta \Pi(\delta \mid E) E\left[\left(Q_0(1, W^*(\delta)) - Q_0(0, W^*(\delta))\right)^2 \mid E \right] - \psi_0^2 \\
&\equiv E_E \sum_\delta \Pi(\delta \mid E) \Phi(Q_0, g_0)(\delta, E) - \psi_0^2,
\end{aligned}$$

where $\sigma_0^2(r, W^*) = E_0((Y - Q_0(R, W^*))^2 \mid R = r, W^*)$ (which is only a function of the distribution of X by the same argument provided above for $Q_0(R, W^*)$).

Assume that the cost of measuring $W(\delta)$ equals $s(\delta)$. Then the average cost across n subjects is $1/n \sum_{i=1}^n s(\Delta_i)$. The expected cost per subject is thus $E_E \sum_\delta s(\delta)\Pi(\delta \mid E)$, and assume that we wish to bound the expected cost per subject by a number B. Given Q_0 and the treatment mechanism g_0, an optimal fixed design for Π would now be obtained by, for each E, minimizing

$$\sum_\delta \Pi(\delta \mid E) \Phi(Q_0, g_0)(\delta, E)$$

over $(\Pi(\delta \mid E) : \delta)$ under the constraint that $\sum_\delta \Pi(\delta \mid E) s(\delta) = B$. Thus for each E, this is a minimizer of a linear criteria under a linear constraint. This minimum can be obtained with standard constrained minimization algorithms (e.g., simplex algorithm). We denote this optimal choice with Π_{Q_0,g_0}.

A targeted adaptive design is given by $\Pi_i = \Pi_{Q_{i-1},g_i}$ with Q_{i-1} being an estimator based on $O_1, \ldots, O_{i-1}$, which only needs to be specified to result in an estimator of $\Phi(Q_0)$, and g_i the adaptive treatment mechanism used in the i-th data generating experiment.

18.3 Adapting the missingness mechanism for general CAR censored data structures.

Let X be the full data of interest with probability distribution P_{X0}. Assume that $O = \Phi(X, A)$ is a specified (by Φ) missing data structure on X with censoring variable A. Assume that $g_0(A \mid X)$ is a fixed CAR design in the set $\mathcal{G}$ of CAR designs. Let $D(Q_0)(X)$ be the full data efficient influence curve for a parameter ψ_0 of interest in the nonparametric full data model, where Q_0 denotes the F_X-factor of the density p_0 of O. In the case that X can be fully observed with positive probability, a general IPCW estimating function is given by:

$$D_{IPCW}(g_0, Q_0)(O) = \frac{D(X)\Delta}{\Pi_0(X)},$$

where $\Delta = I(D(X)$ is function of $O)$, and $\Pi_0(X) = P_0(\Delta = 1 \mid X)$ is determined by the censoring mechanism g_0. Here it needs to be assumed that there is a positive probability that $D(X)$ is observed. By CAR, we have that $\Pi_0(X)$ is a function of O only so that D_{IPCW} is indeed a function of O only. The efficient influence curve for ψ_0 is now defined as the projection of D_{IPCW} on the tangent space of Q_0 (see van der Laan and Robins (2003)). Therefore, in the case that the efficient influence curve is complex, one might use the simple D_{IPCW} (or another influence curve in the fixed design model with g_0 known) to define design functions of interest to generate adaptive designs.

From an efficiency point of view, the optimal design would be the one for which $\Pi_0(X) = 1$ for all X. However, measuring variables can be expensive so that part of the planning of a trial might be to consider the trade off between measuring variables and thereby increase the information in the data, and the cost of measuring these variables. For that purpose, we assume that the proportion of observations for which $D(X)$ can be measured is restricted by a upper bound δ completely determined by the maximal total cost the designer is willing to spend. We note that $P(\Delta = 1) = E_{Q_0} P(\Delta = 1 \mid X) = E_{Q_0}\Pi_0(X)$.

We now define as design function

$$g_{Q_0} = \arg \min_{g \in \mathcal{G}_1, E_{Q_0}\Pi_0(X) \leq \delta} \mathrm{VAR}_{g_0,Q_0} D^2_{IPCW}(g_0, Q_0)(O).$$

That is, we are interested to select a missing-ness mechanism which minimizes the variance of D_{IPCW} under the constraint that the missing-ness mechanism is less "expensive" than δ. In order to investigate if this kind of design function can be determined in closed form we investigate this minimization problem in more detail.

We note that the variance of D_{IPCW} is given by

$$E_X \frac{D^2(X)}{\Pi_0(X)} + \psi_0^2.$$

Treating X as discrete, the minimization problem over the missingness mechanism Π reduces to minimizing

$$\sum_x \frac{D^2(x)}{\Pi(x)} p_0(x),$$

over Π under the constraint that $\sum_x \Pi(x)p_0(x) = \delta$, where $p_0(x)$ denotes the probability distribution of X. We note that these summations/integrals w.r.t. $p_0(X)$ are identified by the P_X-factor Q_0, since the variance of the observable D_{IPCW} is obviously identified from the observed data distribution. If $\Pi_0(X)$ only depends on X through (say, baseline covariates) $W = \Phi(X)$ for some Φ, then we could write the criteria to be minimized as

$$\Pi \rightarrow E_0 \frac{E_0(D^2(X) \mid W)}{\Pi(W)}.$$

Thus, in this case we need to minimize $\Pi \rightarrow E_W \sigma_0^2(W)/\Pi(W)$ under the constraint that $E_W \Pi(W) = \delta$, where $\sigma_0^2(W) \equiv E_0(D^2(X) \mid W)$. The Lagrange multiplier global minimization problem corresponding with this constrained minimization problem is given by

$$\Pi \rightarrow \sum_w \frac{\sigma_0^2(w)p_0(w)}{\Pi(w)} - \lambda\{\sum \Pi(w)p_0(w) - \delta\}.$$

The solution to this minimization problem is given by

$$\delta \frac{\sigma_0(W)}{E_0\sigma_0(W)}.$$

This solution is not necessarily smaller than 1 for all W. However, it can easily be projected in a function between 0 and 1. For example, it does suggest the following design function:

$$\Pi_{Q_0}(W) = c_0(W) \min\left(1, \frac{\delta\sigma_0(W)}{E_0\sigma_0(W)}\right),$$

where $c_0(W)$ is a normalizing constant so that $E_{Q_0}\Pi_{Q_0}(W) = \delta$. This optimal fixed design now implies a targeted adaptive design $\Pi_i = \Pi_{Q_{i-1}}$, where Q_{i-1} needs to be specified till the degree that it maps into an estimator of $\sigma_0^2(W)$.

We will now present some examples of missing data structures for which we can determine this closed form targeted adaptive design.

For the sake of illustration we first consider a simple example. Suppose that the full data is $X = (Y, W)$, where Y is an outcome of interest and W is a vector of baseline covariates. Suppose we observe $O = (W, \Delta, \Delta Y)$, where Δ is a missing indicator which equals 1 if the outcome is observed, and 0 otherwise. Suppose that the parameter of interest is the mean, $\psi_0 = E_0 Y$, of Y. A CAR fixed design/censoring mechanism is a conditional distribution of Δ, given X, which is only allowed to depend on X through W. The efficient influence curve in the nonparametric full data model is given by $D(\psi_0)(X) = (Y - \psi_0)$. The IPCW-component of the efficient influence curve is given by:

$$D_{IPCW}(g_0, \psi_0)(O) = \frac{D(\psi_0)(Y)\Delta}{\Pi_0(W)}.$$

The variance of D_{IPCW} is expressed as

$$E_0 \frac{Y^2}{\Pi_0(W)} = E_W \frac{E_0(Y^2 \mid W)}{\Pi_0(W)}.$$

Thus, we need to minimize $\Pi \to E_W \sigma_0^2(W)/\Pi(W)$ under the constraint that $E_W \Pi(W) = \delta$, where $\sigma_0^2(W) \equiv E(Y^2 \mid W)$. The Lagrange multiplier global minimization problem corresponding with this constrained minimization problem is given by

$$\Pi \to \sum_w \frac{\sigma_0^2(w)p(w)}{\Pi(w)} - \lambda\{\sum \Pi(w)p(w) - \delta\}.$$

The solution to this minimization problem is given by

$$\delta \frac{\sigma_0(W)}{E_0\sigma_0(W)}.$$

This solution is not necessarily smaller than 1 for all W. However, it can easily be projected in a function between 0 and 1. For example, it does suggest the following design function:

$$\Pi_{Q_0}(W) = c_0(W) \min\left(1, \frac{\delta\sigma_0(W)}{E_0\sigma_0(W)}\right),$$

where $c_0(W)$ is a normalizing constant so that $E_{Q_0}\Pi_{Q_0}(W) = \delta$. Thus, this fixed design gives preference to measure the more variable Y in order to obtain more information for the marginal mean of Y.

This implies as adaptive design $\Pi_i = \Pi_{Q_{i-1}}$ with Q_{i-1} representing an estimator of $E(Y^2 \mid W)$, and the empirical distribution for the marginal of W, based on $O_1, \ldots, O_{i-1}$.

It is also of interest to compare this design function based on the IPCW estimating function with the design function one would obtain if one uses the actual efficient influence curve. The efficient influence curve is given by:

$$D^*(Q_0, g_0)(O) = \frac{(Y - E_0(Y \mid \Delta = 1, W))\Delta}{\Pi_0(W)} + E_0(Y \mid \Delta = 1, W) - \psi_0.$$

The variance of the efficient influence curve is thus given by

$$E_0 \frac{(Y - E_0(Y \mid \Delta = 1, W))^2}{\Pi_0(W)},$$

plus a term which does not depend on Π_0. Thus, in this case, we find the Lagrange multiplier solution

$$\delta \frac{\sigma_0^*(W)}{E\sigma_0^*(W)},$$

where $\sigma_0^{*2}(W) = E_0\{(Y - E_0(Y \mid \Delta = 1, W))^2 \mid W\}$. This results in the suggested design function:

$$\Pi^*_{Q_0}(W) = c_0^*(W) \min\left(1, \frac{\delta\sigma_0^*(W)}{E_0\sigma_0^*(W)}\right),$$

where $c_0(W)$ is a normalizing constant so that $E_{Q_0}\Pi^*_{Q_0}(W) = \delta$. In this particular example, there is no reason to give preference to Π_{Q_0}, but, instead, $\Pi^*_{Q_0}$ is the preferred design function, but in situations in which the efficient influence curve is too complex, the design function based on the IPCW component of the efficient influence curve might be more tractable.

18.4 Adapting the missingness mechanisms in a sequential design, and targeted MLE.

Let's now consider a missing data structure in which $X_i = (Y_i, E_i, W_i) \sim P_{X0}$, the effect of the variable E_i on Y_i is of interest, E_i is expensive to measure, but a surrogate $E_i^* \subset W_i$ is available for everybody. Here $X_1, \ldots, X_n$ are independent and identically distributed with common probability distribution P_{X0}.

The observed data structure is $O_i = (Y_i, \Delta_i, \Delta_i E_i, W_i)$, $i = 1, \ldots, n$. A CAR fixed design/missingness mechanism is a conditional probability distribution g_0 of Δ_i, given X_i, which only depends on $W_i^* \equiv (Y_i, W_i)$. On the other hand, an adaptive design $\mathbf{g} = (g_1, \ldots, g_n)$ is defined by conditional probability distributions g_i of Δ_i, given X_i, and $\bar{\mathbf{O}}(i-1)$, which only depends on X_i through W_i^*, $i = 1, \ldots, n$.

Let ψ_0 be a non-parametrically defined real valued effect of E on Y such as a pairwise correlation, or the regression coefficient in a marginal linear regression of Y on E. We wish to define a targeted adaptive design. For that purpose we will aim to minimize the variance of the efficient influence curve of ψ_0 over all fixed designs. Let $D(Q_0)(Y, E, W)$ be the full data efficient influence curve in the nonparametric full data model for this parameter ψ_0. The IPCW estimating function is given by:

$$D_{IPCW}(Q_0, g_0)(O) = \frac{D(Q_0)(X)\Delta}{\Pi(W^*)},$$

where $\Pi(W^*) = P(\Delta = 1 \mid X) = P(\Delta = 1 \mid W^*)$. The efficient influence curve of Ψ at p_{Q_0,g_0} is given by:

$$\begin{aligned} D^*(Q_0, g_0)(O) &= \frac{\{D(Q_0)(X) - E_0(D(Q_0)(X) \mid \Delta = 1, W^*)\}\Delta}{\Pi_0(W^*)} \\ &\quad + E_0(D(Q_0)(X) \mid \Delta = 1, W^*). \end{aligned}$$

It follows that the variance of the efficient influence curve is given by

$$E_0 \frac{\sigma_0^2(W^*)}{\Pi_0(W^*)},$$

plus a term not depending on the missingness mechanism g_0, where

$$\begin{aligned} \sigma_0^2(W^*) &= E_0(D_1(X)^2 \mid W^*), \\ D_1(X) &= D(Q_0)(X) - E_0(D(Q_0)(X) \mid \Delta = 1, W^*). \end{aligned}$$

Suppose we wish to minimize this variance over all fixed CAR designs Π under the constraint that $E_0\Pi(W^*) = \delta$. Thus, we need to minimize $\Pi \rightarrow E_{W^*}\sigma_0^2(W^*)/\Pi(W^*)$ under the constraint that $E_{W^*}\Pi(W^*) = \delta$. The Lagrange multiplier global minimization problem corresponding with this constrained minimization problem is given by

$$\sum_{w^*} \frac{\sigma_0^2(w^*)p(w^*)}{\Pi(w^*)} - \lambda\{\sum \Pi(w^*)p(w^*) - \delta\}.$$

The solution to this minimization problem is given by

$$\delta \frac{\sigma_0(W^*)}{E_0\sigma_0(W^*)}.$$

This solution is not necessarily smaller than 1 for all W^*. However, it can easily be projected in a function between 0 and 1. For example, it does suggest the following design function:

$$\Pi_{Q_0}(W^*) = c_0(W^*) \min\left(1, \frac{\delta\sigma_0(W^*)}{E_0\sigma_0(W^*)}\right).$$

This design function yields a targeted adaptive design $\Pi_i = \Pi_{Q_{i-1}}$, $i = 1, \ldots, n$, given a series of estimators $Q_1, \ldots, Q_n$ of Q_0. This targeted adaptive design prefers to measure subjects for which W_i^* corresponds with a more variable centered full data efficient influence curve $D_1(X)$. A special case of this targeted adaptive design is a two stage design in which one sets $\Pi_i = \pi$ for $i = 1, \ldots, n_1$, and one sets $\Pi_i = \Pi_{Q_{n_1}}$ for the remaining subjects $i = n_1 + 1, \ldots, n$, where Q_{n_1} is an estimator of the distribution Q_0 of $X = (E, W^*)$ based on the first n_1 observations.

Targeted MLE for fixed design: We will now consider the targeted MLE of ψ_0 for the fixed design and adaptive design, respectively. The density of O under a fixed design P_{Q_0,g_0} can be factorized as:

$$p_{Q_0,g_0}(O) = p_0(W^*)p_0(E \mid W^*)^{\Delta}g_0(\Delta \mid W^*).$$

We consider a parametric model $p_\theta(E \mid W^*)$ for the conditional distribution of E, given $W^* = (W, Y)$, and we leave the marginal distribution of $W^* = (W, Y)$ nonparametric. The maximum likelihood estimator for the marginal distribution of $W^* = (W, Y)$ is the empirical probability distribution of $W_i^* = (Y_i, W_i)$, $i = 1, \ldots, n$. The weighted maximum likelihood estimator for θ is defined as

$$\theta_n = \arg\max_\theta \sum_{i=1}^n \Delta_i \log p_\theta(E_i \mid W_i^*)w_i,$$

where the weights are set to 1 in the fixed design, and, if we have an adaptive design, then $w_i = g^*(1 \mid W_i^*)/g_i(1 \mid W_i^*)$ for a user supplied fixed design $g^* \in \mathcal{G}$. We note that this maximum likelihood estimator is identical to the standard weighted MLE for the parametric regression model of E on $W^* = (Y, W)$ as one would have used for uncensored data, but now restricted to all uncensored observations with $\Delta_i = 1$. As a consequence, θ_n can be computed with standard regression methodology and software, as long as one models the

conditional distribution of E, given W^*, with a standard regression model for which software is available. Let Q_n^0 denote the distribution of $X = (W^*, E)$ with marginal of W^* being the empirical probability distribution, and conditional of E, given W^*, be equal to p_{θ_n}.

Let's now consider the targeted MLE for the fixed design. Firstly, we note that the efficient influence curve $D^*(Q_0, g_0)$ can be written as a sum of two components $D_1^*(Q_0, g_0)$ and $D_2^*(Q_0)$, where

$$\begin{aligned} D_1^*(Q_0, g_0) &\equiv \frac{\{D(Q_0)(X) - E_0(D(Q_0)(X) \mid \Delta = 1, W^*)\}\Delta}{\Pi_0(W^*)} \\ D_2^*(Q_0) &\equiv E_0(D(Q_0)(X) \mid \Delta = 1, W^*). \end{aligned}$$

We note that $D_2(Q_0)$ is a function of $W^* = (Y, W)$ with mean zero so that it represents a score for the marginal distribution of W^*. Since we use the nonparametric maximum likelihood estimator for the marginal distribution of W^* there is no need to construct an ϵ-fluctuation of the MLE of the marginal distribution of W^*. Thus, in order to construct a targeted MLE it remains to construct an extension $p_{\theta_n}(\epsilon)$ so that $p_{\theta_n}(0) = p_{\theta_n}$, and $\frac{d}{d\epsilon} \log p_{\theta_n}(\epsilon)$ at $\epsilon = 0$ equals $D_1^*(Q_0, g_0)$. Below we present an easy to implement strategy for constructing such an ϵ-fluctuation. Let ϵ_n^1 be defined as

$$\epsilon_n^1 = \arg\max_{\epsilon} \prod_{i=1}^{n} p_{\theta_n}(\epsilon)(E_i \mid W_i^*)^{\Delta_i},$$

which defines the first step targeted MLE $Q_n^0(\epsilon_n^1)$ and corresponding $\psi_n^1 = \Psi(Q_n^0(\epsilon_n^1))$. Iteration of this updating step leads to the k-th step targeted MLE. Alternatively, we define the first step targeted MLE by a solution ϵ_n of

$$0 = \sum_{i=1}^{n} D(Q_n^0(\epsilon), g_0)(O_i).$$

In both cases we end up with a solution (or approximate solution) Q_n^* of the last equation, which is the single drive of the resulting robust asymptotics for the corresponding targeted MLE $\psi_n^* = \Psi(Q_n^*)$.

Constructing an ϵ-fluctuation: We will now present an approach for constructing the wished ϵ-fluctuation $Q_n^0(\epsilon)$ of Q_n^0. The model fit Q_n^0 for the conditional distribution of E, given W^*, and the marginal of W^* implies also a fit for the conditional distribution of $D(Q_n^0)$, given W^*. Let's denote this fit of $D(Q_n^0)$, given W^*, with $q_n^0(\cdot \mid W^*)$. The density of W^*, E under Q_n^0 can be represented as

$$Q_n^0(W^*, E) = p_n^0(W^*) q_{\theta_n}(D(Q_n^0)(W^*, E) \mid W^*),$$

where we assume that, given W^*, $E \to D(Q_0)(E, W^*)$ is 1-1, and we treat all random variables as discrete (otherwise, we have to include a Jacobian). As ϵ-fluctuation of Q_n^0, we now propose the ϵ-fluctuation

$$Q_n^0(\epsilon)(W^*, E) = p_n^0(W^*) q_{\theta_n}(\epsilon)(D(Q_n^0)(W^*, E) \mid W^*),$$

where $\frac{d}{d\epsilon} \log q_{\theta_n}(\epsilon)(D(Q_n^0)(W^*, E) \mid W^*)^{\Delta}\Big|_{\epsilon=0}$ is given by

$$\frac{\{D(Q_n^0)(W^*, E) - E_{\theta_n}(D(Q_n^0)(W^*, E) \mid \Delta = 1, W^*)\}\Delta}{\Pi_0(W^*)}.$$

If q_{θ_n} is a normal density with variance σ^2 and mean equal to a fitted regression $m_{\theta_n}(W^*)$, then $q_{\theta_n}(\epsilon)$ can be selected to be the normal density with variance σ^2 and mean $m_{\theta_n}(W^*) + \epsilon h(\Pi_0)(W^*)$, where the extra covariate is defined as:

$$h(\Pi_0)(W^*) = \frac{1}{\Pi_0(W^*)}.$$

Similarly, for other types of densities q_{θ_n} it will typically also be possible to augment its mean with a covariate $\epsilon h(W^*)$ so that the score equals $D_1(Q_n^0, g_0)$. Alternatively, if q_{θ_n} is not a normal density, one could simply redefine Q_n^0 by redefining its conditional distribution of $D(Q_n^0)$, given W^*, as a normal density with mean $E_{Q_n^0}(D(Q_n^0) \mid W^*) = m_{\theta_n}(W^*)$ and variance σ^2, and thereby proceed as above by augmenting this regression fit m_{θ_n} with $\epsilon h(W^*)$.

Targeted MLE for adaptive design: For adaptive designs, the targeted MLE requires the same extension $p_{\theta_n}(\epsilon)$ so that $p_{\theta_n}(0) = Q_{\theta_n}$, and $\frac{d}{d\epsilon} \log p_{\theta_n}(\epsilon)$ at $\epsilon = 0$ equals $D_1^*(Q_{\theta_n}, g)$, but where one now sets $g = g_{\theta_n}$ (i.e., $g_{Q_{\theta_n}}$), and g_i corresponds with the adaptive missingness probabilities $\Pi_{Q_{i-1}}$. One sets ϵ_n equal to the solution of

$$0 = \sum_{i=1}^{n} D_1(Q_{\theta_n}(\epsilon_n), g_{\theta_n})(O_i) \frac{g_{\theta_n}(1 \mid X_i)}{g_i(1 \mid X_i)}, \tag{44}$$

which corresponds with a weighted least squares estimator using weights $w_i = g_{\theta_n}(1 \mid X_i)/g_i(1 \mid X_i)$, $i = 1, \ldots, n$.

Thus, the targeted MLE in which one sets $g = g_{\theta_n}$ in the epsilon path $Q_{\theta_n, g}(\epsilon)$ can be constructed in exactly the same manner as for the fixed design above, with g_0 replaced by g_{θ_n} and by using weights w_i in the MLE-steps for ϵ. In particular, the extra covariate $h(\Pi_0)(W_i^*)$ for subject i is now replaced by $h(\Pi_{Q_{\theta_n}})(W_i^*)$, $i = 1, \ldots, n$. Thus this targeted MLE can be calculated with standard regression software.

Application of our CLT theorem for the targeted MLE in adaptive designs (and thus also for fixed designs) proves that, under regularity conditions, ψ_n^* is consistent and asymptotically normally distributed when $E_0 D(Q^*) = 0$ implies $\Psi(Q^*) = \psi_0$, where Q^* is the limit of $Q_n^* = Q_{\theta_n}(\epsilon_n)$ as $n \to \infty$. Its asymptotic normal distribution is the same as the normal limit distribution of the targeted MLE under a fixed design $P_{Q_0, g_{Q^*}}$, where g_{Q^*} is the stable limit of the adaptive design $g_i = g_{Q_i}$ as $i \to \infty$. Specifically, we have

$$\psi_n^* - \psi_0 = \frac{1}{n} \sum_{i=1}^{n} D^*(Q_{\theta_0}(\epsilon_0), g_{\theta_0})(O_i) \frac{g_{\theta_0}(A_i \mid X_i)}{g_i(A_i \mid X_i)} + o_p(1/\sqrt{n}),$$

so that statistical inference can be based on the Martingale CLT: see Theorem 8 for the precise statements.

18.5 Adaptive sequentially randomized clinical trials for time-dependent treatment.

Suppose that we observe on the i-th randomly sampled subject baseline covariates $L_i(0)$, a treatment $A_i(0)$, an intermediate outcome $L_i(1)$, a subsequent treatment $A_i(1)$, and a final outcome $Y_i = L_i(2)$: $O_i = (L_i(0), A_i(0), L_i(1), A_i(1), Y_i = L_i(2))$, $i = 1, \ldots, n$. Let $L_{\bar{a}} = (L(0), L_{a(0)}(1), L_{a(0)a(1)}(2))$ be the counterfactual process one would observe on a randomly sampled subject if the subject would have been assigned treatments $a(0), a(1)$. Let $X = (L_{\bar{a}} : \bar{a})$ be the collection of these treatment specific random variables, which represents the full data we would have liked to observe on each subject. The observed data on the randomly sampled subject can be represented as a missing data structure on X_i as follows:

$$O_i = (L_i(0), A_i(0), L_{A_i(0)}(1), A_i(1), Y_i = L_{\bar{A}_i(1)}(2)), \quad i = 1, \ldots, n.$$

It is assumed that X_i are i.i.d. random variables with common probability distribution P_{X0}. The adaptive design is defined by the distribution

$$g_i(a \mid X_i) = P(A_i = a \mid X_i, O_1, \ldots, O_{i-1}),$$

where $a = (a(0), a(1))$ represents a possible treatment strategy. Conditional on $O_1, \ldots, O_{i-1}$, it is assumed that g_i satisfies the sequential randomization assumption (SRA) which states:

$$\begin{aligned} g_i(a \mid X_i) &= \prod_{j=0}^{1} g_i(a(j) \mid \bar{A}_i(j-1) = \bar{a}(j-1), X_i) \\ &= \prod_{j=0}^{1} g_i(a(j) \mid \bar{A}_i(j-1), \bar{L}_i(j)) \text{ SRA}, \end{aligned} \tag{45}$$

where we used the notation $\bar{A}(j) = (A(0), \ldots, A(j))$, and the convention $\bar{A}(-1)$ being empty (similarly for L). That is, the randomization probabilities for treatment, $A_i(j)$, at time j for subject i can be a function of the observed past of the subject i as known at time j, and the data observed on all previously recruited subjects $1, \ldots, i-1$. The set of fixed designs $\mathcal{G}$ are all conditional probability distributions of A, given X, satisfying the SRA.

For example, consider a trial in which one wishes to investigate 4 drugs for the treatment of HIV-infected patients. For that purpose, one sequentially recruits blocks of patients over time. Each patient is initially randomized to one of the four drugs, and after a few months an intermediate outcome (e.g., success or failure) is collected. Subsequently, the patient is randomized again to a subset of these 4 drugs depending on the intermediate response, and a final outcome is collected: e.g., if the previously assigned treatment resulted in a good response the patient proceeds on the same treatment, but if it resulted in a poor response (e.g., side effects), then the patient is randomized to the remaining three drugs. In an adaptive design of the type above, one is allowed to make these randomization probabilities also a function of the data collected on the previously recruited patients. For example, during the trial one might determine that patients who fail on drug 1 almost always also fail on drug 3 (e.g., due to cross-resistance), and, as a consequence, one might stop switching patients from drug 1 to drug 3.

In this kind of trial one might be interested in comparing certain treatment rules. As a specific example, consider the rule $d(a) = d(a(0), a(1))$, which assigns treatment $a(0)$ at time 0, and, if the intermediate outcome is a success, then the patient stays on $a(0)$, but otherwise, the patient is switched to $a(1)$. We remind the reader that a dynamic treatment rule d applied at time points $0, 1$ are two functions $d(j)$ of the observed past as available right before time j, $j = 0, 1$. Here $a(0) \in \{1, 2, 3, 4\}$, and $a(1) \in \{1, 2, 3, 4\}/\{a(0)\}$ is any treatment different from $a(0)$. This describes 12 possible treatment rules. Suppose that we are interested in estimating $EY_{d(a)}$ for each of these 12 possible rules $d(a)$, where $Y_{d(a)}$ is the outcome one would observe on the randomly sampled patient if the patient follows rule $d(a)$. This counterfactual is a function of X and $a = (a(0), a(1))$: $L_{d(a)}(0) = L(0)$, $L_{d(a)}(1) = L_{a(0)}(1)$, $Y_{d(a)} = L_{d(a)}(2)$ equals $L_{a(0),a(0)}$ if $L_{a(0)}(1) = 1$, and else it equals $L_{a(0)a(1)}$.

Let $\mathcal{D} = \{d(a) : a\}$ denote the set of 12 possible dynamic rules $d(a)$. Suppose that the parameter of interest is $\psi_0 = EY_{d_1} - EY_{d_0}$ for two rules $d_0, d_1 \in \mathcal{D}$, and we leave the full data distribution unspecified. We will first define the efficient influence curve for the fixed design and the locally efficient targeted MLE of ψ_0 for the fixed and adaptive design. Subsequently, we will present a strategy for defining targeted adaptive designs.

Let $I(A = d(L))$ denote the indicator that the randomly sampled subject followed rule d: i.e., $A(0) = d_0(L(0))$, $A(1) = d_1(A(0), \bar{L}(1))$. The efficient influence curve can be represented as the projection of the IPTW estimating function on the tangent space of the P_{X0} factor Q_0 of the density of O: see van der Laan and Robins (2003). The IPTW estimating function for ψ_0 is given by

$$D_{IPTW}(O) = Y\left(\frac{I(A = d_1(L))}{g(A \mid X)} - \frac{I(A = d_0(L))}{g(A \mid X)}\right) - \psi_0.$$

The efficient influence curve for ψ_0 at a fixed design $p_0 = Q_0 g_0$ (Q_0 denotes the P_X-factor of the density of O, and $g_0 \in \mathcal{G}$ is the conditional density of A, given X) can be presented as

$$D^*(p_0)(O) \;=\; D_1(p_0)(0) + D_2(p_0)(0) + D_3(p_0)(O),$$

where

$$\begin{aligned}
D_1(Q_0, g_0)(O) &= E_0(D_{IPTW}(O) \mid L(0)) \\
D_2(Q_0, g_0)(O) &= E_0(D_{IPTW}(O) \mid \bar{L}(1), A(0)) - E_0(D_{IPTW}(O) \mid L(0), A(0)) \\
D_3(Q_0, g_0)(O) &= E_0(D_{IPTW}(O) \mid \bar{L}(2), \bar{A}(1)) - E_0(D_{IPTW}(O) \mid \bar{L}(1), \bar{A}(1)).
\end{aligned}$$

Let $p_n^0 = (g_n^0, Q_n^0)$ be an initial density estimator of $p_0 = (g_0, Q_0)$. For example, p_n^0 could be the maximum likelihood estimator based on a working model for Q_0. Note that Q_n^0 includes as components an estimator of the marginal distribution of $L(0)$, conditional distribution of $L(1)$, given $L(0), A(0)$, and conditional distribution of $Y = L(2)$, given $\bar{L}(1), \bar{A}(1)$. We will denote these 3 conditional distributions with Q_{0j}, $j = 0, 1, 2$. Let the marginal distribution of $L(0)$ be estimated with the empirical probability distribution of $L_i(0)$, $i = 1, \ldots, n$. If $L(1)$ is a simple indicator of having a successful response to treatment $A(0)$, we can estimate the conditional distribution of $L(1)$, given $L(0), A(0)$, with logistic regression software. Similarly, if Y is a 1-0 outcome, we can estimate the conditional distribution of Y with logistic regression, and, if Y is a continuous outcome, we can use linear regression with normal errors. In the case that $L(1)$ and or Y are categorical outcomes, then we can use multi-nomial logistic regression models to estimate these conditional distributions.

For concreteness and the sake of illustration, we assume that $L(1)$ and $Y = L(2)$ are both binary. Let $Q_{j\theta(j)}$ be a logistic regression working model for $L_i(j)$, given the past $\bar{L}_i(j-1), \bar{A}_i(j-1)$:

$$Q_{j\theta(j)}(1 \mid \bar{L}_i(j-1), \bar{A}_i(j-1)) = \frac{1}{1 + \exp\Big(-m_j(\bar{L}_i(j-1), \bar{A}_i(j-1) \mid \theta(j))\Big)}, \; j = 1, 2.$$

Let $Q_{jn}^0 = Q_{j\theta_n(j)}$ be the corresponding maximum likelihood estimator according to these working models, $j = 1, 2$:

$$\theta_n(j) = \arg\max_{\theta(j)} \sum_{i=1}^{n} \log \left\{ Q_{j\theta(j)}(L_i(j) \mid \bar{L}_i(j-1), \bar{A}_i(j-1)) \right\}^{L_i(j)} \quad j = 1, 2.$$

Targeted MLE in fixed design: We now proceed to map this maximum likelihood estimator Q_{θ_n} according to a possibly misspecified working model into the fully robust targeted maximum likelihood estimator. For that purpose, we now define the ϵ-fluctuation $Q_{jn}^0(\epsilon)(1 \mid \bar{L}_i(j-1), \bar{A}_i(j-1))$ of these fitted working models as

$$\frac{1}{1 + \exp\left(-m_j(\bar{L}_i(j-1), \bar{A}_i(j-1) \mid \theta_n(j)) + \epsilon h_j(\bar{L}(j-1), \bar{A}(j-1))\right)}.$$

The score of ϵ at $\epsilon = 0$ for observation i is given by:

$$S_j(0_i) = h_j(\bar{L}_i(j-1), \bar{A}_i(j-1))(L_i(j) - Q_{jn}^0(1 \mid \bar{L}_i(j-1), \bar{A}_i(j-1)), \ j = 1, 2,$$

and if we assume a common ϵ for the two working models, then the score of ϵ at $\epsilon = 0$ is given by the sum $S_1(O_i) + S_2(O_i)$ of these two scores. We need that this score S_j equals the efficient influence curve component $D_j(p_n^0)$. By the fact that, $D_j(p)(L(j), \bar{L}(j-1), \bar{A}(j-1))$ equals

$$\begin{aligned} &\left(D_j(p)(1, \bar{L}(j-1), \bar{A}(j-1)) - D_j(p)(0, \bar{L}(j-1), \bar{A}(j-1))\right) \\ &\times \left(L(j) - E_p(L(j) \mid \bar{L}(j-1), \bar{A}(j-1))\right), \end{aligned}$$

it follows that we should select $h_j(\bar{L}_i(j-1), \bar{A}_i(j-1))$ as

$$\left(D_j(p_n^0)(1, \bar{L}_i(j-1), \bar{A}_i(j-1)) - D_j(p_n^0)(0, \bar{L}_i(j-1), \bar{A}_i(j-1))\right), \ j = 1, 2.$$

Let ϵ_n^0 be the MLE of ϵ. Since the empirical marginal distribution of $L(0)$ is already a nonparametric MLE, there is no need to update the marginal distribution of $L(0)$ under Q_n^0. Given p_n^0, this MLE ϵ_n^0 can be fitted with standard logistic regression software. This yields now an updated fit $Q_n^1 = Q_n^0(\epsilon_n^0)$. This updating can be iterated to obtain a sequence of updates $Q_n^k = Q_n^{k-1}(\epsilon_n^k)$, $k = 1, 2, \ldots$. As shown in van der Laan and Rubin (2006), for k large enough, this results in an update so that

$$P_n D^*(g_0, Q_n^k) = o_P(1/\sqrt{n}).$$

In our experience, a few iterations already closely approximates a solution of the actual estimating equation $P_n D^*(g_0, Q) = 0$. In the sequentially randomized trial g_0 is known so that there is no need to estimate g_0: i.e., in

observational studies one replaces g_0 by an estimator g_n^0. The targeted MLE is defined as the substitution estimator $\Psi(Q_n^k)$ corresponding with the updated MLE Q_n^k. The consistency and asymptotic linearity of this targeted MLE of ψ_0 follows in essence from the fact that $P_0 D^*(g_0, Q) = -(\Psi(Q) - \psi_0)$ so that solutions of the estimating equation $P_n D^*(g_0, Q) = 0$ in Q result in consistent estimators of ψ_0, even if the original working model and thereby Q_n^0 is inconsistent.

Targeted MLE in adaptive design: The iterative targeted MLE for the adaptive design based on the $Q_{\theta,g_\theta}(\epsilon)$-path is similar, but $g_0(A_i \mid X_i)$ for observation O_i is now replaced by $g_{\theta_n}(A_i \mid X_i)$ and we use weights $w_i = g_{\theta_n}/g_i$ in the ML-steps for ϵ.

Thus, we now select the covariate extension $h_{ji}(\bar{L}_i(j-1), \bar{A}_i(j-1))$ as

$$\left(D_j(g_{\theta_n}, Q_n^0)(1, \bar{L}_i(j-1), \bar{A}_i(j-1)) - D_j(g_{\theta_n}, Q_n^0)(0, \bar{L}_i(j-1), \bar{A}_i(j-1))\right), \ j = 1, 2.$$

As above, this results in an update (for k large enough) so that

$$\frac{1}{n}\sum_{i=1}^{n} D^*(Q_n^k, g_{\theta_n})(O_i)\frac{g_{\theta_n}(A_i \mid X_i)}{g_i(A_i \mid X_i)} = o_P(1/\sqrt{n}).$$

The targeted MLE is defined as the substitution estimator $\Psi(Q_n^k)$ corresponding with the updated MLE Q_n^k.

The one-step targeted MLE as defined in Section 12 is based on the path $Q_{\theta,g_{\theta_n}}(\epsilon)$ for a targeted adaptive design $g_n = g_{\theta_{n-1}}$, where ϵ is estimated by a solution ϵ_n of

$$0 = \sum_{i=1}^{n} D^*(Q_{\theta_n,g_{\theta_n}}(\epsilon_n), g_{\theta_n})\frac{g_{\theta_n}}{g_i}.$$

If there are multiple solutions ϵ_n one can use the log likelihood of $Q_{\theta_n,g_n}(\epsilon)$ as criteria to select the one with the highest log-likelihood.

The consistency and asymptotic linearity of this targeted MLE of ψ_0 follows in essence from the fact that $P_{Q_0,g} D^*(Q, g) = -(\Psi(Q) - \psi_0)$ for all g so that solutions of the estimating equation $\frac{1}{n}\sum_{i=1}^{n} P_{Q_0,g_i} D^*(Q, g) g/g_i = 0$ in Q result in consistent estimators of ψ_0, even if the original working model and thereby Q_n^0 is inconsistent. Formally, our Theorem 8 provides the formal template for proving this consistency and asymptotic linearity, under the assumption that the adaptive design g_i is asymptotically stable (i.e., asymptotically g_i approximates a fixed design in $\mathcal{G}$), and some regularity conditions. In particular, under these regularity conditions, it shows that

$$\Psi(Q_{\theta_n,g_{\theta_n}}(\epsilon_n)) - \psi_0 = \frac{1}{n}\sum_{i=1}^{n} D^*(Q_{\theta_0,g_{\theta_0}}(\epsilon_0), g_{\theta_0})(O_i)\frac{g_{\theta_0}(A_i \mid X_i)}{g_i(A_i \mid X_i)} + o_P(1/\sqrt{n}),$$

where the sum is a Martingale so that statistical inference can proceed based on the Martingale CLT, as specified in Theorem 8.

Targeted adaptive design: In order to formulate a targeted adaptive design targeted at ψ_0, we propose the design function:

$$g_{Q_0} \equiv \arg\min_{g \in \mathcal{G}_1} P_{Q_0,g} D^2_{IPTW}(Q_0, g).$$

That is, g_{Q_0} is the fixed design which minimizes the variance of the IPTW component of the efficient influence curve among all fixed designs in a user supplied set $\mathcal{G}_1$. We suggest that this design function is more tractable than the design function minimizing the variance of the actual efficient influence curve of ψ_0, and that it still has nice properties since the actual efficient influence curve is defined as the projection of D_{IPTW} on the tangent space of Q_0.

Since the IPTW estimating function for ψ_0 is given by

$$D_{IPTW}(O) = Y \left(\frac{I(A = d_1(L))}{g(A \mid X)} - \frac{I(A = d_0(L))}{g(A \mid X)} \right) - \psi_0,$$

it follows that the variance of the IPTW estimating function is given by

$$\sigma^2(g, Q_0) \quad = \quad E \left\{ \frac{Y^2_{d_1}}{g(d_1(L_{d_1}) \mid X)} + \frac{Y^2_{d_0}}{g(d_0(L_{d_0}) \mid X)} \right\},$$

plus ψ_0^2. Treating l as discrete, and noting that we can ignore the ψ_0 term, this can be written as:

$$\begin{aligned} \sigma^2(g, Q_0) &= \sum_l \sum_a l(2)^2 \frac{I(d_1(l) = a) p_{d_1}(l) + I(d_0(l) = a) p_{d_0}(l)}{g(a \mid l)} \\ &\equiv \sum_l \sum_a \frac{\phi_0(a, l)}{g(a \mid l)}, \end{aligned}$$

where $p_d(l)$ denotes the density of the counterfactual process L_d under dynamic treatment rule d, and ϕ_0 is defined as the numerator in the integrand on the left-hand side summation. By the G-computation formula, this counterfactual density p_d is identified by the F_X-part Q_0 of p_0, and is given by

$$p_d(l) = Q_{00}(l(0)) Q_{01}(l(1) \mid l(0), a(0) = d(l(0))) Q_{02}(l(2) \mid \bar{l}(1), \bar{a} = d(\bar{l}(1)))$$

in which the treatment in the conditioning events is set at a value deterministically implied by the rule d and l. One now needs to minimize this variance expression over the conditional probability distribution $g(a \mid l) = g(a(0) \mid l(0)) g(a(1) \mid a(0), \bar{l}(1))$ among all $g \in \mathcal{G}_1$. In certain settings the optimal g_{Q_0}

exists in closed form in terms of ϕ_0 and can be derived analogue to our closed form derivations for the treatment mechanism in clinical trials.

This approach for generating candidate targeted adaptive designs can be generalized to a set of pairwise comparisons of dynamic treatment regimens, as in Section 2.

18.6 Adapting the monitoring mechanism: current status data.

Let the full data on an experimental unit be given by $X = (T, W)$, where T is a time till onset of disease, and W is a vector of baseline covariates. The observed data on an experimental unit is $O = (W, C, \Delta = I(T \leq C))$, where C is the monitoring time at which one determines the current status Δ of the unit. We refer to chapter 4 of van der Laan and Robins (2003) for an overview of literature and a detailed treatment of this data structure and its generalization to time-dependent covariates. A particular application are data collected in carcinogenicity experiments in which W are baseline characteristics of the mouse, and C is the time at which the mouse is sacrificed/monitored and the absence or presence of a tumor is determined. Suppose that one is concerned with estimation of a smooth parameter, $\psi_0(r) \equiv \int r(t)(1-F_{T0}(t))dt$, of the cumulative distribution function F_{T0} of the time till onset T, where the function r is user supplied. The set of fixed CAR designs are all conditional distributions of C, given X, for which C is conditionally independent of T, given W: $\mathcal{G} = \{g(\cdot \mid X) : g(\cdot \mid X) = g(\cdot \mid W)\}$. The variance of the efficient influence curve of this real valued parameter $\psi_0(r)$ at a distribution P_{g_0,Q_0} of O is given by

$$E_W \int \frac{r^2(c)}{g_0(c \mid W)} F_0(c \mid W)(1 - F_0(c \mid W))dc,$$

plus a term which does not depend on the monitoring density g. As shown in **?**, the optimal monitoring density minimizing this variance of the efficient influence curve is given by:

$$g_{Q_0}(c \mid W) = \frac{\mid r(c) \mid \sqrt{F_0(c \mid W)(1 - F_0(c \mid W))}}{K^*(W)},$$

where $K^*(W)$ is the normalizing constant so that the expression on the right hand side integrates over c till 1.

In general, for a parameter ψ_0 for which the full data efficient influence curve in the nonparametric full data model is given by $D(Q_0)(T, Z)$, we have

that the efficient influence curve of ψ_0 is given by

$$D^*(Q_0, g_0)(O) = \frac{D(Q_0)_1(C, W)}{g_0(C \mid W)}(F_0(C \mid W) - \Delta) + E_0(D(Q_0)(T, W) \mid W),$$

where $D(Q_0)_1(t, W) = \frac{d}{dt}D(Q_0)(t, W)$. Thus, the variance of the efficient influence curve, up till a term not depending on the monitoring density, is given by:

$$E_W \int_c \frac{D(Q_0)_1(c, W)^2}{g(c \mid W)} F_0(c \mid W)(1 - F_0(c \mid W)).$$

Thus, the optimal monitoring mechanism is given by

$$g_{Q_0}(c \mid W) = \frac{\mid D(Q_0)_1(c, W) \mid \sqrt{F_0(c \mid W)(1 - F_0(c \mid W))}}{K^*(W)},$$

where $K^*(W)$ is the normalizing constant so that the expression on the right hand side integrates over c till 1.

This optimal fixed design g_{Q_0} is unknown since it depends on the true conditional distribution function of T, given W. It implies a targeted adaptive design;

$$g_i(c \mid W) = g_{Q_i}(c \mid W),$$

where Q_i generates an estimator of $F_0(c \mid W)$ based on $O_1, \ldots, O_{i-1}$. For example, this estimator could be based on the following relation:

$$F_0(c \mid W) = P(\Delta = 1 \mid C = c, W),$$

a logistic regression model for $P(\Delta = 1 \mid C = c, W)$, and a corresponding maximum likelihood estimator of $F_0(c \mid W)$, which can be obtained with standard software.

Given a sequence $O_1, \ldots, O_n$ generated with this targeted adaptive design g_i, one can estimate the unknown parameter ψ_0 with the targeted MLE. In order to implement a targeted MLE for a particular parameter ψ_0 we note the following. Firstly, the P_X-factor of the density of $O_1, \ldots, O_n$ is given by:

$$L(Q) = \prod_{i=1}^{n} F(W_i)F(C_i \mid W_i)^{\Delta_i}(1 - F(C_i \mid W_i))^{1-\Delta_i}.$$

Consider an initial fit Q^0 representing the empirical distribution for the marginal distribution of W and a fit $F^0(\cdot \mid W) = \frac{1}{1+\exp(-h^0(c)-\beta^0 W)}$ of the conditional distribution of T, given W. Consider the ϵ-fluctuation:

$$F_{\epsilon,h}(c \mid W) = \frac{1}{1 + \exp(-(h^0(c) + \beta^0 W + \epsilon h(c, W)))}.$$

The score of ϵ at $\epsilon = 0$ is given by $h(C,W)(\Delta - F^0(C \mid W))$. Since the model for X is left unspecified, for a parameter ψ_0 with full data efficient influence curve $D(Q_0)(T,Z)$, the efficient influence curve for ψ_0 at P_{Q_0,g_0} is given by

$$D^*(Q_0,g_0)(O) = \frac{D(Q_0)_1(C,W)}{g_0(C \mid W)}(F_0(C \mid W) - \Delta) + E_0(D(Q_0)(T,W) \mid W),$$

where $D(Q_0)_1(t,W) = \frac{d}{dt}D(t,W)$. Thus the component of the efficient influence curve which represents a score of the conditional distribution of T, given W, part of the likelihood is given by $D(Q_0)_1/g_0(F_0 - \Delta)$.

This shows that, in order to obtain the targeted MLE for a fixed design, we should chose as additional covariate $h(C,W)$ the following choice:

$$h^*(g_0,Q^0)(C,W) \equiv -\frac{D(Q^0)_1(C,W)}{g_0(C \mid W)}.$$

Consider now data generated by an adaptive design. Let $F_{\theta_n}(\cdot \mid W)$ be a weighted maximum likelihood estimator of $F_0(\cdot \mid W)$ according to a working model with weights $g^*(C_i \mid W_i)/g_i(C_i \mid W_i)$ for a user supplied fixed monitoring design $g^* \in \mathcal{G}$. Consider the path $F_{\theta_n,h^*(g_{\theta_n},Q_{\theta_n})}(\epsilon)$ through F_{θ_n} defined above, but with g_0 replaced by g_{θ_n}, and let $Q_{\theta_n}(\epsilon)$ represent the corresponding path through Q_0 (where the marginal of W is set at the empirical probability distribution). Let ϵ_n be the solution of

$$0 = \sum_{i=1}^n D^*(Q_{\theta_n}(\epsilon_n), g_{\theta_n})w_i,$$

where $w_i = g_{\theta_n}(C_i \mid X_i)/g_i(C_i \mid X_i)$, $i = 1,\ldots,n$. It follows that

$$\epsilon_n = \arg\max_{\epsilon} \sum_{i=1}^n w_i \log\left\{F_{\theta_n,h^*(g_{\theta_n},Q_{\theta_n})}(\epsilon)(C_i \mid W_i)^{\Delta_i}(1 - F_{\theta_n,h^*(g_{\theta_n},Q_{\theta_n})}(C_i \mid W_i))^{1-\Delta_i}\right\},$$

which is obtained with standard logistic regression software. In the case that $h^*(g,Q)$ does not depend on Q, such as in the case that $\psi_0 = \int r(t)(1 - F_{T0})(t)dt$, it follows that the k-th step of this targeted MLE equals the first step targeted MLE.

As a consequence of our general CLT theorem for targeted MLE in adaptive designs $g_i = g_{Q_{i-1}}$, it follows that, under regularity conditions, the resulting targeted MLE of ψ_0 is always consistent and asymptotically linear (even if the working model is misspecified)

$$\Psi(Q_{\theta_n,g_{\theta_n}}(\epsilon_n)) - \psi_0 = \frac{1}{n}\sum_{i=1}^n D^*(Q_{\theta_0,g_{\theta_0}}(\epsilon_0), g_{\theta_0})(O_i)w_i + o_P(1/\sqrt{n}),$$

where the sum is a Martingale so that statistical inference can be based on the Martingale Central Limit Theorem, as specified in Theorem 8. That is, by using a targeted adaptive design and targeted MLE we adapt towards the optimal design $g(Q_0)$ (and we are consistent in doing so if $Q^* = Q_0$), and we achieve the asymptotic normal limit distribution corresponding with i.i.d. sampling from $P_{Q_0,g(Q^*)}$.

18.7 Adapting the monitoring mechanism: interval censored data.

Let the full data be given by $X = (T, W)$ again, where T is the time till onset of a disease which can only be observed by monitoring and testing the unit of study. Suppose that T is discrete on time points $t_0 < \ldots < t_J$. Let $A(1), \ldots, A(J)$ represent monitoring indicators, where $A(j) = 1$ if the subject is monitored at time t_j and is zero otherwise. The observed data on the i-th experimental unit is

$$O_i = (W_i, A_i(j), \Delta_i(j) \equiv A_i(j)I(T_i \leq t_j), j = 1, \ldots, J).$$

Thus, for each monitoring time we observe the indicator if the onset of the disease occurred or not. A fixed design is the conditional probability distribution of $A = (A(1), \ldots, A(J))$, given (T, W), and is assumed to satisfy the sequential randomization assumption:

$$g(A \mid X) = \prod_{j=1}^{J} g_j(A(j) \mid \bar{A}(j-1), \bar{\Delta}(j-1), W).$$

In words, the probability of being monitored at time t_j, past monitoring $\bar{A}(j-1)$ and X, only depends on the observed indicators $\Delta(1), \ldots, \Delta(j-1)$, and the baseline covariates W.

An adaptive design, on the other hand, will also allow that these monitoring probabilities at time t_j for experimental unit i are a function of the previously recruited $i-1$ subjects:

$$g_i(A_i \mid X_i) = \prod_{j=1}^{J} g_j(A_i(j) \mid \bar{A}_i(j-1), \bar{\Delta}_i(j-1), W_i, \bar{\mathbf{O}}(i-1)).$$

For example, during the course of the trial one might learn that for certain subgroups the onsets occur mostly in the first half of time window and other subgroups might only experience very few onsets. This kind of information could now be used to adapt the monitoring mechanism for the subsequent

experimental units in order to monitor with higher probability in time windows with reasonable onset intensity.

Analogue to Section 2 and the previous subsection, we could also define a design function as the minimizer of the variance of the IPCW estimating function for a particular parameter of interest over all fixed designs satisfying the SRA assumption, where the IPCW estimating function is defined in Chapter 6 of van der Laan and Robins (2003). Again, this is a more tractable approach than minimizing the variance of the efficient influence curve since the latter does not exist in closed form, although, almost efficient closed form influence curves are defined in chapter 6 of van der Laan and Robins (2003).

19 Adaptive designs for longitudinal data structures.

Let $L_a = (L_a(0), \ldots, L_a(\tau+1))$ be a a-specific process over time. Let T_a be a potentially random end of follow up time (e.g., survival) with support $[0, \tau+1]$, and $R_a(t) \equiv I(T_a \leq t)$ is assumed to be a component of $L_a(t)$. Let $L_a(t) = L_a(\min(t, T_a))$ be the process that stops observing $L_a(t)$ at this follow up time T_a in the sense that it stays constant after T_a. It is assumed that $L_a(t) = L_{\bar{a}(t-1)}(t)$ is only affected by the design settings $\bar{a}(t-1) = (a(0), \ldots, a(t-1))$, $t = 0, \ldots, \tau+1$, which is an assumption following from the time-ordering stating that treatment $A(t-1)$ is measured after $L(t-1)$ and before $L(t)$. Let $\mathcal{A}$ be a set of possible design settings $a = (a(0), \ldots, a(\tau))$. We will assume that each time-specific component $a(t) = (a_1(t), a_2(t))$ of the vector $a \in \mathcal{A}$ consists of two real valued components (typically binary or categorical), so that it will be clear for the readers how to immediately generalize our setting to more than 2 components for each setting $a(t)$ at time t. For example, $a_1(t)$ might denote treatment assignment at time t, and $a_2(t)$ might denote an indicator of being right censored at time t.

Let $X = (L_a : a \in \mathcal{A}) \sim P_{X0}$ be the full data structure. We will assume that the model for P_{X0} is nonparametric. It is assumed that $X_1, \ldots, X_n$ are n i.i.d. copies of X. Suppose that the observed data on each of the n experimental units is $O_i = (A_i, L_i = L_{A_i})$, where $A_i = (A_i(0), \ldots, A_i(\tau))$ and $A_i(t) = A_i(\min(t, \tilde{T}_i - 1))$ is truncated at $\tilde{T}_i - 1$ so that it is defined up till time τ, where $\tilde{T}_i = T_{i,A_i}$ is the follow up time under design A_i, $i = 1, \ldots, n$. Similarly, $L_{A_i}(t) = L_{A_i}(\min(t, \tilde{T}_i))$ is truncated at $\tilde{T}_i$. If $a_2(t)$ denotes a right-censoring indicator, then the set of possible designs $\mathcal{A}$ will have elements a so that $a_1(t) = a_1(t-1)$ for t larger than the first time point at which a_2 jumps to 1: that is, after right-censoring the unit, the settings for treatment do not

change anymore. In this manner, it is guaranteed that the observed A_i can be uniquely defined as an element of $\mathcal{A}$, and $L_i = L_{A_i}$.

As set of fixed designs we consider the conditional distribution of A, given X, satisfying the sequential randomization assumption:

$$
\begin{aligned}
g(a \mid X) &= \prod_{t=0}^{\tau} P(A(t) = a(t) \mid \bar{A}(t-1) = \bar{a}(t-1), X) \\
&= \prod_{t=0}^{T_a-1} P(A(t) = a(t) \mid \bar{A}(t-1) = \bar{a}(t-1), X) && (46) \\
&\quad \times \prod_{t=T_a}^{\tau} I(a(t) = a(t-1)) \\
&\overset{SRA}{=} \prod_{t=0}^{T_a-1} P(A(t) = a(t) \mid \bar{A}(t-1) = \bar{a}(t-1), \bar{L}_a(t)) && (47) \\
&\quad \times \prod_{t=T_a}^{\tau} I(a(t) = a(t-1)) && (48) \\
&= \prod_{t=0}^{T_a-1} P(A_1(t) = a_1(t) \mid \bar{A}(t-1) = \bar{a}(t-1), \bar{L}_a(t)) && (49) \\
&\quad \prod_{t=0}^{T_a-1} P(A_2(t) = a_2(t) \mid A_1(t) = a_1(t), \bar{A}(t-1) = \bar{a}(t-1), \bar{L}_a(t)) && (50) \\
&\quad \times \prod_{t=T_a}^{\tau} I(a(t) = a(t-1))) \\
&\equiv \prod_{t=0}^{T_a-1} g_1(a_1(t) \mid \bar{a}(t-1)l, \bar{L}_a(t)) && (51) \\
&\quad \prod_{t=0}^{T_a-1} g_2(a_2(t) \mid a_1(t), \bar{a}(t-1), \bar{L}_a(t)) \prod_{t=T_a}^{\tau} I(a(t) = a(t-1)),
\end{aligned}
$$

where we factorized the design in terms of an A_1 (say treatment assignment) mechanism and A_2 (say right-censoring assignment) mechanism.

Let $\mathcal{G}$ be the set of all conditional distributions of A, given X, satisfying the SRA. An adaptive CAR/SRA design is now a conditional distribution of

A_i, given X_i and $O_1, \ldots, O_{i-1}$, satisfying

$$
\begin{array}{l}
g_i(a \mid X_i, \bar{\mathbf{O}}(i-1)) = \prod_{t=0}^{\tau} P(A_i(t) = a(t) \mid \bar{A}_i(t-1) = \bar{a}(t-1), X_i, \bar{\mathbf{O}}(i-1)) \\
= \prod_{t=0}^{T_{ia}-1} P(A_i(t) = a(t) \mid \bar{A}_i(t-1) = \bar{a}(t-1), X_i, \bar{\mathbf{O}}(i-1)) \\
= \prod_{t=0}^{T_{ia}-1} P(A_i(t) = a(t) \mid \bar{A}_i(t-1) = \bar{a}(t-1), \bar{L}_{ia}(t), \bar{\mathbf{O}}(i-1)) \text{ SRA} \\
= \prod_{t=0}^{T_{ia}-1} P(A_{1i}(t) = a_1(t) \mid \bar{A}_i(t-1) = \bar{a}(t-1), \bar{L}_{ia}(t), \bar{\mathbf{O}}(i-1)) \\
\prod_{t=0}^{T_{ia}-1} P(A_{2i}(t) = a_2(t) \mid A_{1i}(t) = a_1(t), \bar{A}_i(t-1) = \bar{a}(t-1), \bar{L}_{ia}(t), \bar{\mathbf{O}}(i-1)) \\
\equiv \prod_{t=0}^{T_{ia}-1} g_{1i}(a_1(t) \mid \bar{a}(t-1)l, \bar{L}_{ia}(t), \bar{\mathbf{O}}(i-1)) \\
\prod_{t=0}^{T_{ia}-1} g_{2i}(a_2(t) \mid a_1(t), \bar{a}(t-1), \bar{L}_{ia}(t), \bar{\mathbf{O}}(i-1)),
\end{array}
$$

where we assumed that $a(t) = a(t-1)$ for $t > T_{ia} - 1$, and if the latter does not hold, then, as for the fixed design, $g_i(a \mid X_i) = 0$. Let $E_i(0), \ldots, E_i(\tau)$ be the chronological times at which $A_i(0), \ldots, A_i(\tau)$ are assigned, $i = 1, \ldots, n$. At time $E_i(t)$, the complete observations O_j might not be available yet for experiments $j = 1, \ldots, i-1$. Let $\bar{O}_j(E_i(t))$ represent the part of O_j which is available at chronological time $E_i(t)$, and, for notational convenience, let $\bar{\mathbf{O}}_{E_i(t)}(i-1)$ represent $(\bar{O}_j(E_i(t)) : j = 1, \ldots, i-1)$. Then,

$$
\begin{array}{rcl}
g_i(a \mid X_i, \bar{\mathbf{O}}(i-1)) & = & \prod_{t=0}^{T_{ia}-1} g_{1i}(a_1(t) \mid \bar{a}(t-1), \bar{L}_{ia}(t), \bar{\mathbf{O}}_{E_i(t)}(i-1)) \\
& & \prod_{t=0}^{T_{ia}-1} g_{2i}(a_2(t) \mid a_1(t), \bar{a}(t-1), \bar{L}_{ia}(t), \bar{\mathbf{O}}_{E_i(t)}(i-1)).
\end{array}
$$

The density of $O_1, \ldots, O_n$ under the adaptive design $\mathbf{g} = (g_1, \ldots, g_n)$ is given by:

$$
\begin{array}{rcl}
P_{Q_0,\mathbf{g}}(O_i : i = 1, \ldots, n) & = & \prod_{i=1}^{n} Q_0(A_i, L_i) g(A_i \mid X_i, \bar{\mathbf{O}}(i-1)) \\
& = & \prod_{i=1}^{n} \prod_{t=0} Q_{0t}(L_i(t) \mid \bar{L}_i(t-1), \bar{A}_i(t-1)) g(A_i \mid X_i, \bar{\mathbf{O}}(i-1)),
\end{array}
$$

where $Q_0(a, l) = P_{X0}(L_a = l)$, and $Q_{0t}(l(t) \mid \bar{l}(t-1), \bar{a}(t-1)) = P_{X0}(L_a(t) = l(t) \mid \bar{L}_a(t-1) = \bar{l}(t-1))$, which equals the conditional probability distribution $L_i(t)$ at $l(t)$, given $\bar{L}_i(t-1) = \bar{l}(t-1), \bar{A}_i(t-1) = \bar{a}(t-1)$, $i = 1, \ldots, n$. Given a working model $\mathcal{Q}^w = \{Q_\theta : \theta\}$ for Q_0 one can now construct a maximum likelihood estimator, possibly using likelihood based cross-validation to select certain fine tuning parameters. Let $Q_{\theta_n} = (Q_{t\theta_n} : t = 0, \ldots, \tau + 1)$ be this maximum likelihood estimator. We note that the non-degenerate part of Q_{0t} represents the conditional distribution of $L(t)$, given $\bar{A}(t-1), \bar{L}(t-1)$, where $\bar{L}(t-1)$ always implies $\tilde{T} \geq t$, while, if $\bar{L}(t-1)$ implies that $\tilde{T}$ already occurred,

then Q_{ot} is degenerate and thus known (recall that all processes are truncated after $\tilde{T}$).

Consider a particular parameter $\psi_0 = \Psi(Q_0)$ of interest. We now wish to focus on the targeted maximum likelihood estimator for the adaptive design, which maps this typically inconsistent Q_{θ_n} into a new updated $Q_{\theta_n}(\epsilon_n)$ which results in a consistent and asymptotically linear, and thereby asymptotically normally distributed estimator of ψ_0.

Firstly, let's consider a fixed design, since the targeted MLE for the adaptive design is a generalization of the targeted MLE for the fixed design. Let $D(Q_0) = \sum_{a \in \mathcal{A}} w(a, L(0)))D_a(Q_0)(L_a)$ be the efficient influence curve of ψ_0 in the full data model, where it is assumed that it can be represented as a weighted sum of a-specific functions of L_a. The IPCW component of the efficient influence curve can be given by (see chapter 6, van der Laan and Robins (2003)):

$$D_{IPCW}(Q_0, g)(O) = \frac{w(A, L(0))D_A(Q_0)(L)}{g(A \mid X)},$$

which indeed satisfies

$$E(D_{IPCW}(Q_0, g)(O) \mid X) = \sum_{a \in \mathcal{A}} w(a, L(0))D_a(Q_0)(L_a),$$

under the assumption that $\sup_{a \in \mathcal{A}} \frac{w(a,L(0))D_a(Q_0)(L_a)}{g(a|X)} < \infty$. The efficient influence curve of ψ_0 at fixed CAR design $P_{Q_0,g}$ can now be represented as the projection of $D_{IPCW}(Q_0, g)$ on the tangent space of Q_0:

$$\begin{aligned} D^*(Q_0, g)(O) &= \sum_{t=0}^{\tau+1} E_{Q_0,g}(D_{IPCW}(Q_0, g) \mid \bar{L}(t), \bar{A}(t-1)) \\ &\quad - \sum_{t=0}^{\tau+1} E_{Q_0,g}(D_{IPCW}(Q_0, g) \mid \bar{L}(t-1), \bar{A}(t-1)) \\ &\equiv \sum_{t=0}^{\tau+1} D_t^*(Q_0, g), \end{aligned}$$

where $D_t^*(Q_0, g)$ is a score of Q_{0t}, $t = 0, \ldots, \tau + 1$. Here we used that the tangent spaces of Q_0 is the orthogonal sum of the tangent spaces of Q_{0t}, and the latter tangent space is all functions of $\bar{L}(t), \bar{A}(t-1)$ which have conditional mean zero given $\bar{L}(t-1), \bar{A}(t-1)$. We also note that the sum over time t stops at $\tilde{T}$ since at and after this time point the two conditional expectations cancel each other (due to the fact that all observed processes are truncated at $\tilde{T}$).

Let $\{Q_{t\theta_n}(\epsilon) : \epsilon\}$ be a parametric extension satisfying $Q_{t\theta_n}(0) = Q_{t\theta_n}$ and that the linear span of the scores of $Q_{t\theta_n}(\epsilon)$ at $\epsilon = 0$ include the components of $D_t^*(Q_{\theta_n}, g)$, $t = 0, \ldots, \tau+1$: for example, ϵ is of the same dimension as ψ_0 and the score of ϵ of $Q_{t\theta_n}(\epsilon)$ equals $D_t^*(Q_{\theta_n}, g)$. Assuming a common parameter ϵ for all t, let ϵ_n^1 be defined as the MLE:

$$\epsilon_n^1 = \arg\max_{\epsilon} \prod_{i=1}^{n} \prod_{t=0}^{\tau+1} Q_{t\theta_n}(\epsilon)(L_i(t) \mid \bar{L}_i(t-1), \bar{A}_i(t-1)),$$

and iterate this procedure to obtain the $k-th$ step targeted MLE $Q_n^k = Q_n^{k-1}(\epsilon_n^k)$ with $Q_n^0 = Q_{\theta_n}$, or we simply select ϵ_n as the solution of

$$0 = \sum_{i=1}^{n} \sum_{t=0}^{\tau+1} D_t^*(Q_{\theta_n}(\epsilon), g)(O_i).$$

We focus on the latter approach, since also the iterative approach ends up with an approximate solution Q_n of this equation so that the same asymptotics apply (see Section 12). The targeted MLE of ψ_0 is now defined as $\psi_n = \Psi(Q_n) = \Psi(Q_{\theta_n}(\epsilon_n))$.

Consider now data generated in an adaptive design. Let $\{Q_\theta : \theta\}$ be a working model for Q_0, and let θ_n be the weighted MLE using weights $g^*(A_i \mid X_i)/g_i(A_i \mid X_i)$ for a user supplied fixed design $g^* \in \mathcal{G}$, which can be computed as above. Consider the path above $Q_{\theta_n,g}(\epsilon)$ with g replaced by g_{θ_n}, and let ϵ_n be the solution of $0 = \sum_{i=1}^n D^*(Q_{\theta_n,g_{\theta_n}}(\epsilon_n), g_{\theta_n})w_i$, where $w_i = g_{\theta_n}/g_i$, $i = 1, \ldots, n$. The targeted MLE of ψ_0 as analyzed in Section 12 is now given by $\Psi(Q_{\theta_n}(\epsilon_n))$.

Thus, ϵ_n is defined as the solution of

$$0 = \sum_{i=1}^{n} \sum_{t=0}^{\tau+1} D_t^*(Q_{\theta_n}(\epsilon), g_{\theta_n})(O_i)w_i,$$

and the targeted MLE of ψ_0 is defined as $\psi_n = \Psi(Q_{\theta_n}(\epsilon_n))$ again.

In order to provide an explicit demonstration of this targeted MLE, consider the case that $L(t)$ for $t = 1, \ldots, \tau+1$ is binary. Suppose that $Q_{t,\theta}$ is modelled with a logistic regression model for the binary $L(t)$, given $\bar{L}(t-1), \bar{A}(t-1)$, where we only need to model it for histories which imply that $\tilde{T} \geq t$. One could assume a separate logistic regression model for each $t \geq 1$, or one could assume models with common parameters. By adding a covariate $h(t, \bar{L}(t-1), \bar{A}(t-1))$ to the logistic regression model with parameter ϵ, we obtain a model $Q_{t,\theta_n}(\epsilon)$ whose score at $\epsilon = 0$ equals $h(t, \bar{L}(t-1), \bar{A}(t-1))(L(t) - Q_{t,\theta}(1 \mid \bar{L}(t-1), \bar{A}(t-1))$. We can represent $D_t^*(Q, g)(L(t), \bar{L}(t-1), \bar{A}(t-1))$ as

$$(D_t^*(1, \bar{L}(t-1), \bar{A}(t-1)) - D_t^*(0, \bar{L}(t-1), \bar{A}(t-1))(L(t) - Q_t(1, \bar{L}(t-1), \bar{A}(t-1))).$$

Thus, for the fixed design we should select $h^*(Q_{\theta_n}, g)(t, \bar{L}_i(t-1), \bar{A}_i(t-1))$ as

$$(D_t^*(Q_{\theta_n}, g)(1, \bar{L}_i(t-1), \bar{A}_i(t-1)) - D_t^*(Q_{\theta_n}, g)(0, \bar{L}_i(t-1), \bar{A}_i(t-1)).$$

For the adaptive design we select $h^*(Q_{\theta_n}, g_{\theta_n})(t, \bar{L}_i(t-1), \bar{A}_i(t-1))$, $t = 1, \ldots, \tau+1$, $i = 1, \ldots, n$. As above, ϵ is selected to solve the efficient influence curve equation $0 = \sum_i D^*(Q_{\theta_n}(\epsilon_n), g_{\theta_n}) w_i = 0$. The iterative targeted MLE involves iteratively applying weighted maximum likelihood estimation for logistic regression, which can thus be carried out with standard logistic regression software.

If $L(t) = (L(t)(1), \ldots, L(t)(k))$ is a vector of k binary variables, then we can further factorize Q_{0t} as a product of k conditional probabilities Q_{0tj} of $L(t)(j)$, given $L(t)(1), \ldots, L(t)(j-1))$ and $\bar{L}(t-1), \bar{A}(t-1)$, and model each of these k conditional probability distributions with logistic regression. The (iterative) targeted MLE can in this case be computed in exactly the same manner as above: In the above presentation of the targeted MLE for binary $L(t)$ replace $L(1), \ldots, L(\tau+1)$ by the sequence of binary variables $L(1)(1), \ldots, L(1)(k_1), \ldots, L(\tau+1)(1), \ldots, L(\tau+1)(k_{\tau+1}))$, rename this last sequence as $L'(0), \ldots, L'(\tau'+1)$ and apply the above targeted MLE.

Since any categorical variable can be coded with 1-0 variables, this manner of computing targeted MLE, by adding explicit covariates to the logistic regression models, provides a general manner for computing the targeted MLE for fixed and adaptive designs.

As a consequence of our general CLT Theorem 8 for the targeted MLE in adaptive designs $g_i = g_{\theta_{i-1}}$, it follows that, under regularity conditions, the targeted MLE of ψ_0 is always consistent and asymptotically linear (even if working model $\mathcal{Q}^w$ for Q_0 is misspecified):

$$\Psi(Q_{\theta_n, g_{\theta_n}}(\epsilon_n)) - \psi_0 = \frac{1}{n} \sum_{i=1}^{n} D^*(Q_{\theta_0, g_{\theta_0}}(\epsilon_0), g_{\theta_0})(O_i) w_i + o_P(1/\sqrt{n}),$$

where the sum is a Martingale satisfying the conditions of the Martingale CLT so that statistical inference follows. That is, by using an adaptive design g_i which learns a fixed design $g_{\theta_0} \in \mathcal{G}$ as $i \to \infty$, and applying the targeted MLE we adapt towards the design g_{θ_0} (and this design is optimal if $Q_{\theta_0} = Q_0$), and we achieve the asymptotic normal limit distribution corresponding with i.i.d. sampling from $P_{Q_0, g_{\theta_0}}$. As is evident from our CLT theorem for the targeted MLE in adaptive designs, the asymptotic consistency and linearity under a misspecified working model relies on $P_{Q_0, g_i} D^*(Q^*, g_i) = E_{Q_0} D^F(Q^*) = 0$ implying that $\Psi(Q^*) = \psi_0$. Thus, if the full data efficient influence curve does rely on some nuisance parameters of Q_0, then $Q_{\theta_n}(\epsilon_n)$ needs to correctly specify

these nuisance parameters. In many examples, the full data efficient influence curve does only depend on Q_0 through ψ_0 so that this result is automatically true.

19.1 Example: Adaptive randomized trial with right censored survival outcome.

The full data of interest consists of baseline covariates W, and a set of treatment specific survival times $T_{a(0)}$ with support $\{0, 1, \ldots, \tau + 1\}$ indexed by a set of possible single time points treatments $a(0)$ assigned at baseline. Let $a = (a(0), a(1), \ldots, a(\tau))$ with $a(t) = I(c = t)$, $t = 1, 2, \ldots, \tau$ for some set censoring time c: thus, $a(t)$ has only a single 1 at most, and after this 1 it stays zero. If $a(1) = \ldots = a(\tau) = 0$, then we will also refer to this as $c = \infty$. Let $L(0) = W$, $L_a(t) = (I(T_{a(0)c} \leq t)$, $t = 1, \ldots$, where $T_{a(0)c} \equiv \min(T_{a(0)}, c)$. The full data is $X = (L_a : a \in \mathcal{A})$. The observed data on each experimental unit is $O_i = (A_i, L_{A_i})$, where A_i identifies the assigned treatment $A_i(0)$ and the right-censoring time C_i, where $C_i \equiv \infty$ if $T_i \leq C_i$. Equivalently, $O_i = (W_i, A_i, \tilde{T}_i = T_{A_i})$. Let

$$\psi_0(t) = P(T_{a(0)} > t) - P(T_0 > t) = P(T_{a(0)0} > t) - P(T_{00} > t),$$

where $T_{a(0)0} = T_{a(0)}$ is the follow up time if censoring is set at $c = \infty$, which thus equals the treatment specific survival time $T_{a(0)}$.

A CAR fixed design is a conditional distribution of A, given X, satisfying

$$\begin{aligned} g(a \mid X) &= \prod_{t=0}^{\tau} g(a(t) \mid \bar{A}(t-1) = \bar{a}(t-1), X) \\ &\stackrel{CAR}{=} \prod_{t=0}^{\min(c(a), T_{a(0)}-1)} g(a(t) \mid \bar{A}(t-1) = \bar{a}(t-1), \bar{L}_A(t)) \prod_{t=T_a}^{\tau} I(a(t) = 0), \end{aligned}$$

where the first factor at $t = 0$ denotes a treatment mechanism, and the other factors represent the censoring mechanism, where censoring is set at ∞ after the failure time $T_{a(0)}$. An adaptive CAR design $\mathbf{g} = (g_1, \ldots, g_n)$ consists of n conditional distributions of A_i, given X_i and $O_1, \ldots, O_{i-1}$, satisfying

$$g_i(a \mid X_i) = g_i(a \mid X_i, \bar{\mathbf{O}}(i-1)) = \prod_{t=0} g_{it}(a(t) \mid \bar{A}_i(t-1) = \bar{a}(t-1), \bar{L}_i(t), \bar{\mathbf{O}}(i-1)).$$

The density of $O_1, \ldots, O_n$ is given by:

$$p_{Q_0,\mathbf{g}}(O_1, \ldots, O_n) = \prod_{i=1}^{n} Q_0(A_i, L_i) g_i(A_i \mid X_i)$$

$$
\begin{aligned}
&= \prod_{i=1}^{n} \prod_{t=0}^{\tau+1} Q_{0t}(L_i(t) \mid \bar{L}_i(t-1), \bar{A}_i(t-1)) \prod_{i=1}^{n} g_i(A_i \mid X_i, \bar{\mathbf{O}}(i-1)) \\
&= \prod_{i=1}^{n} \prod_{t=0}^{\tilde{T}_i = \min(T_{iA_i(0)}, C_i)} Q_{0t}(L_i(t) \mid \bar{L}_i(t-1), \bar{A}_i(t-1)) \\
&\quad \prod_{i=1}^{n} \prod_{t=0}^{\tilde{T}_i} g_{it}(A_i(t) \mid \bar{A}_i(t-1), \bar{L}_i(t), \bar{\mathbf{O}}(i-1)),
\end{aligned}
$$

where $Q_{0t}(l(t) \mid \bar{l}(t-1), \bar{a}(t-1))$ denotes the conditional probability distribution of $L_a(t)$ at $l(t)$ given $\bar{L}_a(t-1) = \bar{l}(t-1)$, so that $Q_0(a, l) = P(L_a = l)$. As discussed earlier, if at time $E_i(t)$, the observation $O_1, \ldots, O_{i-1}$ are not yet fully observed, then g_{it} will only depend on $O_1, \ldots, O_{i-1}$ through right-censored versions of these $i-1$ data structures. Note that Q_{0t} models the hazard of survival time $T_i = T_{A_i(0)}$, given T_i has not happened yet, baseline covariates W_i, and treatment $A_i(0)$.

We could model Q_{0t} with a logistic regression model:

$$
Q_{t\theta}(dL(t) = 1 \mid \bar{L}(t-1), L(0), \bar{A}(t-1), A(0)) = I(\tilde{T} \geq t) \frac{1}{1 + \exp(-\theta(t) f(L(0), A(0)))},
$$

where $f(L(0), A(0))$ is a vector valued summary measure of $(L(0), A(0))$. Note that this logistic function at $\bar{A}(t-1) = \bar{a}(t-1)$ is actually modelling

$$
P(dL(t) = 1 \mid \bar{L}(t-1), \bar{A}(t-1) = \bar{a}(t-1), \tilde{T} \geq t) = P(T_{a(0)} = t \mid T_{a(0)} \geq t, L(0)),
$$

which is the hazard of the treatment specific survival time $T_{a(0)}$ indexed by baseline treatment $a(0)$, conditional on $L(0)$. Let $\mathcal{Q}^w = \{Q_\theta : \theta\} = \{(Q_{t\theta(t)} : t) : \theta\}$ be this model for Q_0. The maximum likelihood estimator of $\theta = (\theta(t) : t)$ can be computed with standard logistic regression software. If the survival time is continuous (e.g.,, the time scale is chosen fine enough so that no ties occur at the same time), then one could also model Q_{0t} with a multiplicative intensity model:

$$
P(dL(t) = 1 \mid \bar{L}(t-), \bar{A}(t-)) = I(\tilde{T} \geq t) \lambda_0(t) \exp(\theta f_t(L(0), A(0))),
$$

where $f_t(L(0), A(0))$ is a time dependent covariate defined as a function of $t, L(0), A(0)$. In particular, one could assume a Cox-proportional hazards model for T conditional on $L(0), A(0)$. Again, the maximum likelihood estimator for the multiplicative intensity model can be fitted with standard software (e.g., Coxph() in R).

We now wish to consider the targeted maximum likelihood estimator of ψ_0 based on this maximum likelihood estimator for this working model $\mathcal{Q}^w$.

Firstly, we consider the fixed design case. An inverse probability of censoring weighted estimating function for $\psi_0(t_0)$ is given by:

$$\begin{aligned} D_{IPCW}(Q_0,g)(O) &= I(T>t_0)I(C\geq t_0)\left\{\frac{I(A(0)=a(0))}{g(a(0)\bar{0}(t_0)\mid X)}-\frac{I(A(0)=0)}{g(0\bar{0}(t_0)\mid X)}\right\} \\ &\quad -\Psi(Q_0)(t_0), \end{aligned}$$

where

$$g(a(0)\bar{0}(t_0)\mid X)=g(a(0)\mid L(0))\prod_{t=1}^{t_0}P(A(t)=0\mid A(0)=a(0),A(t-1)=0,L(0))$$

is the conditional probability of having $a(0)$ assigned and being uncensored up till and including time t_0. The efficient influence curve $D^*(Q_0,g)$ at a fixed design data generating distribution $P_{Q_0,g}$ can be represented as the projection of D_{IPCW} onto the tangent space of Q_0:

$$\begin{aligned} D^*(Q_0,g) &= \Pi(D_{IPCW}(Q_0,g)\mid T(Q_0)) \\ &= \sum_{t=0}^{\tau+1}E_{Q_0,g}(D_{IPCW}(Q_0,g)\mid \bar{L}(t),\bar{A}(t-1)) \\ &\quad -\sum_{t=0}^{\tau+1}E_{Q_0,g}(D_{IPCW}(Q_0,g)\mid \bar{L}(t-1),\bar{A}(t-1)) \\ &= \sum_{t=0}^{\tilde{T}}E_{Q_0,g}(D_{IPCW}(Q_0,g)\mid L(0),A(0),dL(t),\tilde{T}=\min(T,C)\geq t) \\ &\quad -\sum_{t=0}^{\tilde{T}}E_{Q_0,g}(D_{IPCW}(Q_0,g)\mid L(0),A(0),\tilde{T}=\min(T,C)\geq t), \end{aligned}$$

where we recall that $dL(t)=I(\tilde{T}=t,C\geq t)$ equals 1 if a failure $T=t$ occurs at time t (but $dL(t)=0$ if $C=t$ but $T\neq t$). We define $h^*(Q_0,g)(t,L(0),A(0))$ as

$$\begin{aligned} &E_{Q_0,g}(D_{IPCW}(Q_0,g)\mid L(0),A(0),dL(t)=1,\tilde{T}=\min(T,C)\geq t) \\ &-E_{Q_0,g}(D_{IPCW}(Q_0,g)\mid L(0),A(0),dL(t)=0,\tilde{T}=\min(T,C)\geq t), \end{aligned}$$

and we note that

$$\begin{aligned} D^*(Q_0,g) &= \sum_{t=0}^{\tilde{T}}D_t^*(Q_0,g) \\ &= \sum_{t=0}^{\tilde{T}}h^*(Q_0,g)(t,L(0),A(0))(dL(t)-Q_{0t}(1\mid \bar{L}(t-1),\bar{A}(t-1))). \end{aligned}$$

Let $Q_{t\theta_n}(\epsilon)$ be a 1-dimensional extension parameter ϵ so that $Q_{t\theta_n}(0) = Q_{t\theta_n}$ and the score of ϵ at $\epsilon = 0$ for observation O_i equals $D_t^*(Q_{\theta_n}, g) = h^*(Q_{\theta_n}, g)(t, L_i(0), A_i(0))(dL_i(t) - Q_{t\theta_n}(1 \mid \bar{L}_i(t-1), \bar{A}_i(t-1)))$. This can be achieved by adding to the logistic regression model $Q_{t\theta_n}(1 \mid \bar{L}_i(t-1), \bar{A}_i(t-1))$ a covariate $h^*(Q_{\theta_n}, g)(t, L_i(0), A_i(0))$ with coefficient ϵ. Similarly, one can add this covariate to the multiplicative intensity model. Let ϵ_n be the maximum likelihood estimator of ϵ for this one dimensional parametric model

$$\epsilon_n = \arg\max_{\epsilon} \prod_{i=1}^{n} \prod_{t} Q_{t\theta_n}(\epsilon)(L_i(t) \mid \bar{L}_i(t-1), \bar{A}_i(t-1)).$$

Computing ϵ_n corresponds with fitting a logistic regression model based on a pooled (across time) sample with a single regression coefficient ϵ and can thus be done with standard software. Let $Q_{\theta_n}(\epsilon_n) = (Q_{t\theta_n}(\epsilon_n) : t)$. The first step targeted maximum likelihood estimator of ψ_0 for the fixed design is now defined as $\psi_n = \Psi(Q_{\theta_n}(\epsilon_n))$. The k-th step targeted MLE is defined by iterating this process. One can also simply define ϵ_n as the solution of $0 = \sum_i D^*(Q_{\theta_n}(\epsilon), g) = 0$.

Application of results in van der Laan and Rubin (2006) or the CLT Theorem 8 for the k-th step targeted MLE or this latter one step targeted MLE shows that ψ_n is consistent and asymptotically linear at $P_{Q_0,g}$ with influence curve $D^*(Q^*, g)$, where Q^* is the limit of $Q_{\theta_n}(\epsilon_n)$. In particular, if $Q^* = Q_0$, i.e., if $\mathcal{Q}$ is correctly specified, then ψ_n is asymptotically efficient. In other words, the targeted MLE is locally efficient.

The targeted maximum likelihood estimator for the adaptive design is now defined by replacing g by g_{θ_n} in the path $Q_\theta(\epsilon)$, and estimate θ_0 with the weighted maximum likelihood estimator using weights $w_i = g^*(A_i \mid X_i)/g_i(A_i \mid X_i)$, where we also showed that g^* can be adaptively and sequentially estimated. In addition, one uses weights $w_i = g_{\theta_n}/g_i$ in the equations for ϵ_n.

Specifically, let $Q_{t\theta_n}(\epsilon)$ be a 1-dimensional extension parameter ϵ so that $Q_{t\theta_n}(0) = Q_{t\theta_n}$ and the score of ϵ at $\epsilon = 0$ for observation O_i equals $D_t^*(Q_{\theta_n}, g_{\theta_n}) = h^*(Q_{\theta_n}, g_{\theta_n})(t, L_i(0), A_i(0))(dL_i(t) - Q_{t\theta_n}(1 \mid \bar{L}_i(t-1), \bar{A}_i(t-1)))$. This can be achieved by adding to the logistic regression model $Q_{t\theta_n}(1 \mid \bar{L}_i(t-1), \bar{A}_i(t-1))$ a covariate $h^*(Q_{\theta_n}, g_{\theta_n})(t, L_i(0), A_i(0))$ with coefficient ϵ. Similarly, one can add this covariate to the multiplicative intensity model.

One estimates ϵ with a solution ϵ_n of $0 = \sum_i D^*(Q_{\theta_n}(\epsilon), g_{\theta_n})w_i = 0$ where $w_i = g_{\theta_n}/g_i$. Consider the case that the adaptive design $g_i = g_{\theta_{i-1}}$. Application of our central limit theorem for a targeted MLE shows that the targeted MLE ψ_n is consistent and asymptotically linear for ψ_0 with normal limit distribution identical to the normal limit distribution for an asymptotically linear estimator

with influence curve $D^*(Q^*, g_{\theta_0})$ under a fixed design data generating distribution $P_{Q_0,g_{\theta_0}}$, where Q^* is the limit of $Q_{\theta_n}(\epsilon_n)$ and $g_{\theta_0} \in \mathcal{G}$ is the stable fixed design limit of the adaptive design $g_i = g_{\theta_{i-1}}$ for $i \to \infty$. In other words, ψ_n is asymptotically equivalent with the locally efficient targeted MLE at $P_{Q_0,g_{\theta_0}}$ with an unknown fixed design g_{θ_0}.Specifically, under regularity conditions,

$$\Psi(Q_{\theta_n,g_{\theta_n}}(\epsilon_n)) - \psi_0 = \frac{1}{n}\sum_{i=1}^{n} D^*(Q_{\theta_0,g_{\theta_0}}(\epsilon_0), g_{\theta_0})(O_i)\frac{g_{\theta_0}(A_i \mid X_i)}{g_i(A_i \mid X_i)} + o_P(1/\sqrt{n}),$$

where the right hand side sum is a Martingale satisfying the conditions of the Martingale CLT so that the limit distribution is normal with mean zero and covariance matrix which can be consistently estimated with

$$\Sigma_n = \frac{1}{n}\sum_{i=1}^{n}\{D^*(Q_{\theta_n,g_{\theta_n}}(\epsilon_n), g_{\theta_n})w_i\}^2.$$

We refer to Theorem 8 for precise statements.

The fundamental identity this robustness of the targeted MLE is based upon is that $P_{Q_0,g_i}D^*(Q, g_i)(= -(\Psi(Q) - \psi_0)) = 0$ implies $\Psi(Q) - \psi_0 = 0$ so that a solution Q_n, such as the targeted MLE Q_n, solving $\frac{1}{n}\sum_i D^*(Q_n, g_{\theta_n})w_i = 0$ will result in an estimator $\Psi(Q_n)$ consistent for ψ_0.

20 IPCW-Reduced Data Targeted MLE for fixed and adaptive designs

As is apparent from our presentation of the targeted MLE for longitudinal data structures with time dependent covariates in the previous Section 19, the (iterative) targeted MLE can be quite involved for complex longitudinal data structures. Therefore, it is of interest to also provide easy to compute statistical estimation procedures which still inherit many of the nice features of the iterative targeted MLE. For that purpose we propose a general class of so called Inverse Probability of Censoring Weighted-Reduced Data-Targeted MLE, which can be chosen to be much simpler by only requiring computation of the targeted MLE for a user supplied reduced (simplified) data structure, while weighting the log-likelihoods in this procedure with inverse probability of censoring weights, thereby still preserving consistency under general adaptive or fixed designs only satisfying CAR/SRA for the complete data structure. The following applies also to fixed design by letting the design mechanism g_{0i} for experiment i be equal to a common g_0 for all $i = 1, \ldots, n$.

Let $X = (L_a : a = (a(0), \ldots, a(K)) \in \mathcal{A})$ be a collection of action/design specific random variables L_a indexed by action/design regimen a, and let the observed data structure for one experimental unit be given by

$$O = (A, L = L_A) = (L(0), A(0), \ldots, L_A(K), A(K), L_A(K+1)).$$

The latter represents the time ordering which implies that $L_a(t) = L_{\bar{a}(t-1)}(t)$ and thus $L_A(t) = L - \bar{A}(t-1)(t)$. Typically, $L_a(t)$ includes a component $R_a(t) = I(T_a \leq t)$ for a failure/end of follow up time T_a, and $L_a(t) = L_a(\min(t, T_a))$ becomes degenerate after this time variable T_a. The action process $A(t)$ can have various components describing censoring as well as treatment actions at time t, and for certain values of $A(t-1)$, such as values implying right-censoring, the future process $A(t), \ldots, A(K)$ will be a deterministic function of $\bar{A}(t-1) = (A(0), \ldots, A(t-1))$. In addition, typically, certain values of the observed history $\bar{L}(t), \bar{A}(t-1)$, such as one implying the failure time event $T_A = t$, will determine the future values $A(t), \ldots, A(K)$.

We assume the adaptive sequential randomization assumption on the conditional distribution of A_i, given X_i and $\bar{\mathbf{O}}(i-1)$

$$g_i(a \mid X_i) = \prod_t g_{ti}(a(t) \mid \bar{A}_i(t-1) = \bar{a}(t-1), X_i) \stackrel{SRA}{=} \prod_t g_{ti}(a(t) \mid \bar{A}_i(t-1) = \bar{a}(t-1), L_{\bar{A}(t-1),i}(t)),$$

where the conditional distributions g_i and g_{ti} are allowed to be deterministic functions of $\bar{\mathbf{O}}(i-1)$. By support restrictions on $\mathcal{A}$ and the possibly deterministic relation between an observed history $\bar{A}_i(t-1), \bar{L}_i(t)$ and the future action process $A_i(t), \ldots, A_i(K)$, this product over time t can often be represented as

$$g_i(a \mid X_i) = \prod_{t=0}^{\min(T_{ai}-1, c_a)} g_{ti}(a(t) \mid \bar{A}_i(t-1) = \bar{a}(t-1), \bar{L}_i(t)) \prod_{t=\min(T_{ai}-1, C_a)+1}^{K} I(a(t+1) = a(t)),$$

where c_a denotes the censoring/end of follow up time implied by action regimen a.

Under this CAR/SRA, the probability distribution of the observed data random variable $O_i = (A_i, L_{Ai})$ for the single experimental unit i, given $O_1, \ldots, O_{i-1}$, factorizes in a factor Q_0 implied by the full data distribution of X and a factor $g_i(\cdot \mid X)$.

$$\begin{aligned} dP_{Q_0,g_i}(O_i) &= \prod_{t=0}^{K+1} P_{Q_0}(L_i(t) \mid \bar{L}_i(t-1), \bar{A}_i(t-1)) g_i(A_i \mid X_i) \\ &\equiv \prod_{t=0}^{K+1} Q_{0t}(L_i(t) \mid \bar{L}_i(t-1), \bar{A}_i(t-1)) g_i(A_i \mid X_i), \end{aligned}$$

where, by CAR we have $Q_{0t}(l(t) \mid \bar{l}(t-1), \bar{a}(t-1)) = P(L_a(t) = l(t) \mid \bar{L}_a(t-1) = \bar{l}(t-1))$ so that indeed Q_0 represents the identifiable part of the full data distribution of X.

Consider a particular model $\mathcal{M}(g) = \{P_{Q,g} : Q \in \mathcal{Q}\}$ for a single experimental unit O implied by a model $\mathcal{Q}$ for Q_0 and a fixed design/censoring mechanism g contained in the set $\mathcal{G}$ of all SRA-conditional distributions of A, given X. Consider also a particular parameter $\Psi : \mathcal{Q} \to \mathbb{R}^d$ defined on this model $\mathcal{Q}$ for Q_0, and let $\psi_0 = \Psi(Q_0)$ denote the true parameter value. Since Q_0 is identifiable, one can also view Ψ as a parameter on the model $\mathcal{M}(g)$ of possible data generating distributions of O.

In this article we provide a class of so called Inverse Probability of Censoring Weighted-Reduced Data- Targeted Maximum Likelihood estimators (IPCW-R-TMLE), obtained by applying the iterative targeted MLE for to reduced data structures O_i^r or O_i, but using inverse probability of censoring weighted log-likelihoods at each step. The general targeted MLE methodology is proposed and developed in van der Laan and Rubin (2006) for fixed designs, and can thus also be applied to the complete longitudinal data structures O_i. The advantage of the IPCW-R-TML estimators is mainly of a practical nature. That is, the IPCW-R-TMLE is often far less complex (and thereby much easier to implement with standard software packages implementing maximum likelihood procedures for the reduced data) than the actual targeted MLE for the actual observed longitudinal data structure which includes time-dependent covariate processes, while the IPCW-R-TMLE still preserves and improves upon important efficiency and robustness properties of the targeted MLE for the reduced data structure. Specifically, an IPCW-R-TML estimator is defined by the following steps.

Specify Reduced Data Structure for single experimental unit: Determine a reduction $O^r = (A, L_A^r)$ (i.e., O^r is a function of O), where L_A^r is a measurable function of L_A, where the reduction needs to be so that it is still possible to identify the parameter of interest ψ_0 from the probability distribution of O_r under the under the SRA assumption for the reduced full data structure $X^r = (L_a^r : a \in \mathcal{A})$. For example, $O = (W = L(0), A, \bar{L}(K), Y = L(K+1))$ consists of baseline covariates W, treatment regimen $A = (A(0), \ldots, A(K))$, time dependent covariate process $\bar{L}(K)$, and a final outcome Y, while one defines $O^r = (W, A, Y)$, which is obtained from O by deleting all time-dependent covariates.

Reduced Data Model for single experimental unit. Consider the corresponding reduced data SRA model $\mathcal{M}^r(g^r) = \{dP^r_{Q^r,g^r} = Q^r g^r : Q^r \in$

$\mathcal{Q}^r\}$ for a $g^r \in \mathcal{G}^r$ (as described above in general) for $O^r = (A, L_A^r)$, where $\mathcal{G}^r$ is a set of conditional distributions of A, given $X^r = (L_a^r : a \in \mathcal{A})$, satisfying the SRA assumption for the reduced data structure O^r, and $\mathcal{Q}^r$ is a model for the identified component Q_0^r of the full data distribution of X^r. Since Q_0^r is a function of Q_0, it follows that the model $\mathcal{Q}^r = \{Q^r : Q \in \mathcal{Q}\}$ for Q_0^r is implied by model $\mathcal{Q}$ for Q_0. Let $\Psi^r : \mathcal{Q}^r \to \mathbb{R}^d$ be such that $\Psi^r(Q^r) = \Psi(Q)$ for all $Q \in \mathcal{Q}^r$, and, in particular, $\Psi^r(Q_0^r) = \Psi(Q_0)$.

Factorization of Q^r: Suppose $dP_{Q_0^r, g_0^r} = \prod_j Q_{j0}^r g_0^r$ factors in various terms Q_{j0}^r, $j = 1, \ldots, J$ (e.g., $J = K + 1$). Suppose that $Q_{j0}^r(O^r)$ depends on O^r only through $((A(0), \ldots, A(j^r - 1), \bar{L}^r(j^r))$, $j = 1, \ldots, J$. In a typical scenario, we have that Q_{j0}^r denotes the conditional distribution of $L^r(j^r)$, given $(A(0), \ldots, A(j^r - 1)$ and $\bar{L}^r(j^r - 1)$. For notational convenience, we used the short-hand notation $j^r = j^r(j)$, suppressing its deterministic dependence on j.

Determine Q_j^r-components of efficient influence curve for reduced data model: Let $D^r(P^r)$ be the efficient influence curve at $dP^r = dP_{Q^r, g^r}^r = Q^r g^r$ for the parameter Ψ^r in the model $\mathcal{M}^r(g^r)$ for the reduced data structure O^r. This efficient influence curve can be decomposed as:

$$D^r(P^r) = D^r(Q^r, g^r) = \sum_{j=1}^{J} D_j^r(P^r),$$

where $D_j^r(P^r)$ is an element of the tangent space generated by the j-th factor Q_j^r of $Q^r = \prod_j Q_j^r$ at P^r, $j = 1, \ldots, J$.

Determine hardest Q_j^r-fluctuation functions: Given a Q^r construct submodels $\{Q_j^r(\epsilon) : \epsilon\}$ through Q_j^r at $\epsilon = 0$, with score at $\epsilon = 0$ equal to $D_j^r(Q^r, g^r)$:

$$\frac{d}{d\epsilon} \log Q_j^r(\epsilon)\Big|_{\epsilon=0} = D_j^r(Q^r, g^r),\ j = 1, \ldots, J.$$

Construct IPCW-weights for each Q_j^r-factor: For each j construct weight-function

$$w_{ji} = \frac{g^r(\bar{A}_i(j^r) \mid X^r)}{g_i(\bar{A}_i(j^r) \mid X_i)},\ j = 1, \ldots, J.$$

In short, we will often represent the weights $g^r(\bar{A}_i(j^r) \mid X^r)/g_i(\bar{A}(j^r) \mid X)$ as g^r_j/g_{ji}. We note

$$\begin{aligned} Q^r_{j0} &= \arg\max_{Q^r_j \in \mathcal{Q}^r_j} P_{Q_0,g_i} \log Q^r_j w_{ji} \\ &= \arg\max_{Q^r_j \in \mathcal{Q}^r_j} P_{Q^r_0,g^r_0} \log Q^r_j, \ j = 1, \ldots, J, \end{aligned}$$

so that it follows that the IPCW log-likelihood loss function $\sum_j \log Q^r_j w_j$ is a valid loss function for Q^r_0.

IPCW-(Iterative) Targeted MLE based on reduced data at specified g^r: We will now compute the iterative targeted MLE under i.i.d sampling $O^r_1, \ldots, O^r_n$ from $P^r_{Q^r_0,g^r}$, treating g^r as known (e.g., estimated a priori), but assigning IPCW-weights, as follows. Let Q^{r0} be an initial estimator of Q^r_0 such as a weighted-MLE according to a working model $\mathcal{Q}^r_j$:

$$Q^{r0}_j = \arg\max_{Q^r_j \in \mathcal{Q}^r_j} \sum_i \log Q^r_j(O^r_i) w_{ji}.$$

Compute the overall amount of fluctuation with weighted maximum likelihood estimation:

$$\epsilon^1_n = \arg\max_{\epsilon} \sum_i \sum_j \log Q^{r0}_j(\epsilon)(O^r_i) w_{ji},$$

and compute the corresponding first step targeted ML update $Q^{r1}_j = Q^{r0}_j(\epsilon^1_n)$, $j = 1, \ldots, J$, and thereby the overall update $Q^{r1} = Q^{r0}(\epsilon^1_n)$. Iterate this process till convergence (i.e., $\epsilon^k_n \approx 0$) and denote the final update with $Q^r_n = (Q^r_{jn} : j = 1, \ldots, J)$.

Let $D(Q^r, g^r, g_i) = \sum_j D^r_j(Q^r, g^r) \frac{g^r_j}{g_{ji}}$. Under a weak regularity condition we have (see proof in van der Laan and Rubin (2006))

$$0 = \sum_i D(Q^r_n, g^r, g_i)(O_i) = \sum_i \sum_j D^r_j(Q^r_n, g^r)(O^r_i) w_{ji}. \tag{52}$$

Substitution estimator: Our estimator of ψ_0 is given by $\Psi^r(Q^r_n)$.

The IPCW-R-TMLE is an estimator Q^r_n solving an IPCW-reduced data efficient influence curve equation (52). Firstly, we establish that this IPCW-reduced data efficient influence curve is an "estimating function" for the target parameter with nice robustness properties w.r.t its nuisance parameters Q^r_0 and

g_0. Subsequently, we discuss the corresponding implications on the statistical properties of the IPCW-R-TMLE.

Robustness properties of IPCW-Reduced Data Efficient Influence Function: Recall that $D^r(Q^r, g^r)$ denotes the efficient influence curve for the reduced data $O^r \sim P_{Q^r,g^r}$ for model $\mathcal{M}^r$ and parameter Ψ^r. It follows from general results in van der Laan and Robins (2003) that $P_{Q_0^r,g_0^r} D^r(Q^r, g^r) = 0$ if either $Q^r = Q_0^r$ or $\Psi(Q^r) = \Psi(Q_0^r)$ and $g^r = g_0^r$. This double robustness result for D^r is exploited/inherited by the estimating function

$$D(Q^r, g^r, g_0) \equiv \sum_j D_j^r(Q^r, g^r) g_j^r / g_{ji},$$

whose corresponding estimating equation is solved by our IPCW targeted MLE, in the following manner. We have

$$\begin{aligned} P_{Q_0,g_{0i}} D(Q^r, g^r, g_i) &= P_{Q_0,g_{0i}} \sum_j D_j^r(Q^r, g^r) \frac{g_j^r}{g_{ji}} \\ &= P_{Q_0,g^r} \sum_j D_j^r(Q^r, g^r) \frac{g_{0ji}}{g_{ji}}. \end{aligned}$$

This implies that if $g_{ji} = g_{0ji}$ (i.e., the action mechanism is correctly specified), then $P_{Q_0,g_{0i}} D(Q^r, g^r, g_i) = 0$ for all choices of Q^r, g^r with $\Psi(Q^r) = \Psi(Q_0^r)$. In a typical scenario, we have that Q_{j0}^r denotes the conditional distribution of $L^r(j^r)$, given $A(0), \ldots, A(j^r - 1)$ and $\bar{L}^r(j^r - 1)$. In this case, if g_{0j} is only a function of O^r, then if $Q^r = Q_0^r$, it follows that $P_{Q_0,g^r} D_j^r(Q_0^r, g^r) \frac{g_{0j}}{g_j} = 0$ for all g_j only being a function of O^r (by using that the conditional expectation of a score $D_j^r(Q_0^r, g^r)$ of Q_{j0}^r, given $(A(0), \ldots, A(j^r - 1)$ and $\bar{L}^r(j^r - 1)$, equals zero), and as a consequence, $P_{Q_0,g_{0i}} D(Q_0^r, g^r, g) = 0$ for such misspecified g. That is, in the case that the true g_{0i} and its asymptotic fit are only functions of the reduced data structure, we have the double robustness of the estimating function $D(Q^r, g^r, g)$ in the sense that $P_{Q_0,g_{0i}} D(Q^r, g^r, g_i) = 0$ if $\Psi(Q^r) = \Psi(Q_0^r)$ and, either $Q^r = Q_0^r$ or $g_i = g_{0i}$, for all g^r.

Statistical Properties of IPCW-Reduced Data Targeted MLE: The above mentioned robustness property of the estimating equation $\sum_i D(Q_n^r, g_n^r, g_{ni}) = 0$, g_{ni} an estimator of g_{0i}, as solved by the IPCW-R-TMLE Q_n^r translates under regularity conditions in the following statistical properties of the substitution estimator $\psi_n = \Psi^r(Q_n^r)$. Firstly, under appropriate regularity conditions, if g_{ni} consistently estimates g_{0i}, then ψ_n will be a consistent and asymptotically linear estimator of ψ_0. In addition, if $g_{ni}(A \mid X)$ and its target $g_{0i}(A \mid X)$ are only functions of the reduced data structure O_i^r for each i (beyond being functions of $\bar{\mathbf{O}}(i-1)$), then 1) ψ_n is consistent and asymptotically linear if

either Q_n^r consistently estimates Q_0^r or g_{ni} consistently estimates g_{0i}, and if both estimates are consistent, then the estimator ψ_n is more efficient than an efficient estimator based on n i.i.d. observations of the reduced data structure O^r only.

Off course, in adaptive of fixed designs the design mechanism g_{0i} is typically known so that in that case the IPCW-R-TMLE is always a consistent and asymptotically linear estimator.

Remark: Special IPC-weighting. We note that an important feature of the IPCW-R-TMLE is that we apply the IPC-weighting to the log of each time-dependent dependent factor Q_t^r separately ($Q^r = \prod_t Q_t$). In this manner, we guarantee that the weights are only functions of the conditioning data of the conditional distribution of Q_t^r so that the wished double robustness is achieved. It shows that the manner of applying IPC-weighting is important to achieve the wished double robustness and it also provides a more stable weighting scheme than applying a single IPC-weight to the whole log likelihood of Q_0.

21 IPCW-Reduced Data-Targeted-MLE for Marginal Structural Models for fixed and adaptive designs.

In this section we apply the IPCW-R-TMLE presented in the previous section to estimate causal effects in fixed or adaptive designs.

Let $O_i = (W_i = L_i(0), A_i(0), \ldots, L_i(K), A_i(K), Y_i = L_i(K+1))$, where $L_i(0)$ are baseline co-variates, $A_i(j) = (A_{1i}(j), A_{2i}(j))$, $A_{1i}(j)$ denotes a treatment at time j, $A_{2i}(j) = I(C_i \leq j)$ indicates a censoring event/drop out at time j, $L_i(j)$ are time dependent co-variates collected after $A_i(j-1)$ and before $A_i(j)$, and Y_i is a final outcome of interest collected at time $K+1$, $i = 1, \ldots, n$. The chronological ordering of the data implies that $L_i(j) = L_{i\bar{A}_i(j-1)}(j)$ is affected by past action history $\bar{A}_i(j-1)$. Let the full data structure be $X_i = (L_{ia} : a \in \mathcal{A})$, $L_{ia}(t) = L_{i\bar{a}(t-1)}(t)$, so that the observed data structure O_i for the i-th experimental unit can be presented as a missing data structure $O_i = (A_i, L_{iA_i})$. It is assumed that X_i, $i = 1, \ldots, n$, are n i.i.d. copies of a random variable X. We assume the sequential randomization assumption $g_{0i}(A_i(j) \mid \bar{A}_i(j-1), X_i) = g_{0i}(A_i(j) \mid \bar{A}_i(j-1), \bar{L}_i(j))$, $j = 0, \ldots, K$, where g_{0i} is a conditional distribution indexed by a function of $\bar{\mathbf{O}}(i-1)$. Conditional on $O_1, \ldots, O_{i-1}$, we have $O_i \sim dP_{Q_0,g_{0i}}(A_i, L_i) = Q_0(A_i, L_i) g_{0i}(A_i \mid X_i)$, where $Q_0(a, l) = P(L_a = l)$, under the assumption that $g_{0i}(a \mid X) > 0$ for all $a \in \mathcal{A}$.

Consider a marginal structural working model $E_0(Y_{a_10} \mid V) = m(a_1, V \mid \beta_0)$ for a user supplied working model $\{m(\cdot \mid \beta) : \beta\}$ for the counterfactual mean of Y_{a_10} under treatment regimen $a_1 = (a_1(0), \ldots, a_1(K))$ and no censoring (i.e., $a_2 = 0$), conditional on baseline covariates V included in the set of baseline covariates $W = L(0)$. Our goal is to estimate β_0 defined non-parametrically as

$$\beta_0 = \Psi(Q_0) \equiv \arg\min_{\beta} E_{Q_0} \sum_{a_1} h(a_1, V)(m(a_1, V \mid \beta) - E_{Q_0}(Y_{a_10} \mid V))^2$$

for some user supplied weight function $h(a_1, V)$. A typical choice is $h(a_1, V) = g^*(a_1 \mid V)$, where g^* is a conditional distribution of A_1, given V, representing the limit of an estimate of the true conditional distribution of A_1, given V according to a possibly misspecified working model. Equivalently,

$$\beta_0 = \Psi(Q_0) = \arg\min_{\beta} E_{Q_0} \sum_{a_1} h(a_1, V)(Q_0(a_1, W) - m(a_1, V \mid \beta))^2,$$

where we define $Q_0(a_1, W) = E_0(Y_{a_10} \mid W)$.

Conditional on $O_1, \ldots, O_{i-1}$, the model for the observed data structure $O_i \sim dP_{Q_0, g_{0i}} = Q_0 g_0$ can be written as $\mathcal{M}(g_{0i}) = \{P_{Q, g_{0i}} : Q\}$, where Q can be arbitrary.

Data reduction: Let the reduced data be obtained by excluding all the time-dependent co-variates $O_i^r = (W_i, A_i = (A_i(0), \ldots, A_i(K)), Y_{iA_i})$. Let $X^r = (W, (Y_a : a \in \mathcal{A}))$, so that $O_i^r = (W_i, A_i, Y_{iA_i})$ is a missing data structure on X_i^r, $i = 1, \ldots, n$.

SRA for reduced data: Consider an action mechanism g^r satisfying $g^r(A \mid X) = g^r(A \mid X^r) = g^r(A \mid W)$. We consider a choice g^r so that $P(A_2 = 0) = 1$ under g^r.

Reduced Data Model: In the reduced data model for O_i^r one assumes $g^r(A_i \mid X^r) = g^r(A_i \mid W_i)$, so that, conditional on $O_1^r, \ldots, O_{i-1}^r$, $O_i^r \sim p_{Q_0^r, g^r} = Q_0^r g^r$, $Q_0^r = Q_{01}^r * Q_{02}^r$, where Q_{01}^r is a marginal distribution of W_i, Q_{02}^r is a conditional distribution of Y_i, given A_i, W_i, and g^r is the conditional distribution of A_i, given X_i^r. We have $Q_{02}^r(y \mid a, w) = P(Y_a = y \mid W = w)$. We note that Q_0^r is a function of Q_0, and both are identified as counterfactual distributions: $Q_0^r(w, a, y) = P(W = w, Y_a = y)$ is a sub-distribution of $Q_0(a, l) = P(L_a = l)$.

Consider the parameter

$$\beta_0^r = \Psi^r(Q_0^r) \equiv \arg\min_{\beta} E_0 \sum_{a_1} h(a_1, V)\{Q_0^r(a_1, W) - m(a_1, V \mid \beta)\}^2,$$

where $Q_0^r(a_1, W) = E_0(Y_{a_10} \mid W)$. It follows that $\beta_0^r = \beta_0$. In general, $\Psi^r(Q^r) = \Psi(Q)$ for any Q and corresponding Q^r.

Efficient influence curve of Ψ^r in fixed design reduced data model: The efficient influence curve of Ψ^r at $p_{Q_0^r,g^r} \in \mathcal{M}^r(g^r)$ is given by

$$\begin{aligned} D^r &= \frac{h(A_1,V)}{g^r(A_10 \mid W)} \frac{d}{d\beta_0} m(A_1,V \mid \beta_0)(Y - Q_0^r(A_1,W))I(A_2=0) \\ &\quad + \sum_{a_1} h(a_1,V) \frac{d}{d\beta_0} m(a_1,V \mid \beta_0)(Q_0^r(a_1,W) - m(a_1,V \mid \beta_0)) \\ &\equiv D_1^r(Q_0^r,g^r) + D_2(Q_0^r), \end{aligned}$$

where $Q_0^r(a_1,W) = E_0(Y_{a_10} \mid W)$. We also note that g^r can be factored as

$$\begin{aligned} g^r(A_10 \mid W) &= \prod_{j=0}^{K} g_1^r(A_1(j) \mid A_2(j)=0, \bar{A}_1(j), W) \\ &\quad \prod_{j=1}^{K} g_2^r(A_2(j)=0 \mid \bar{A}_1(j-1), A_2(j-1)=0, W), \end{aligned}$$

where g_1^r represents a treatment mechanism and g_2^r a censoring mechanism.

IPCW-Weighted Reduced Data Efficient Influence Curve: By weighting the first component D_1^r with g^r/g_{0i}, we obtain

$$D_1(Q_0^r,g^r)(O_i^r)g^r(A_i \mid X_i^r)/g_{0i}(A_i \mid X_i) = D_1(Q_0^r,g^r)(O_i^r)g^r(A_{1i}0 \mid X_i^r)/g_{0i}(A_{1i}0 \mid X_i),$$

which yields the following IPCW-Weighted Reduced Data Efficient Influence Curve:

$$\begin{aligned} D(Q_0,g_{0i})(O_i) &= \frac{h(A_{1i},V_i)}{g_{0i}(A_{1i}0 \mid X_i)} \frac{d}{d\beta_0} m(A_{1i},V_i \mid \beta_0)(Y_i - Q_0^r(A_{1i},W_i))I(A_{2i}=0) \\ &\quad + \sum_{a_1} h(a_1,V_i) \frac{d}{d\beta_0} m(a_1,V_i \mid \beta_0)(Q_0^r(a_1,W_i) - m(a_1,V_i \mid \beta_0)) \\ &\equiv D_1(Q_0^r,g_0)(O_i) + D_2(Q_0^r)(W_i). \end{aligned}$$

IPCW-R-Targeted MLE solving IPCW-Reduced Data Efficient Influence Curve Equation: We will now compute the iterative targeted MLE based on $O_1^r,\ldots,O_n^r$ from $P^r_{Q_0^r,g^r}$, treating g^r as known, but assigning IPCW-weights, as follows. Firstly, we estimate the marginal distribution Q_{01}^r of W with the empirical probability distribution of $W_1,\ldots,W_n$. Let Q_2^{r0} be an initial estimator of the conditional distribution Q_{20}^r of Y_{a_10}, given W, such as a weighted-MLE according to a working model for Y, given A,W:

$$Q_2^{r0} = \arg\max_{Q_2^r \in \mathcal{Q}_2^r} \sum_i \log Q_2^r(Y_i \mid A_i,W_i)w_i,$$

where

$$w_i = I(A_{2i} = 0)\frac{g_n^r(A_{1i}0 \mid W_i)}{g_{0i}(A_{1i}0 \mid X_i)}.$$

For example, if one assumes a normal error regression model for Y on A, W, then this corresponds with weighted least squares regression, and if Y is binary, and one assumes a logistic regression model for Y, given A, W, then this corresponds with weighted logistic linear regression.

Subsequently, we extend the current fit Q_2^{r0} with an ϵ-fluctuation so that the score at $\epsilon = 0$ equals $D_1(Q^{r0}, g^r)$. As shown previously, in the normal regression model case, this corresponds with adding a covariate-extension

$$\epsilon\frac{h(A_{1i}, V_i)}{g^r(A_{1i}0 \mid W_i)}\frac{d}{d\beta_0}m(A_{1i}, V_i \mid \beta_0)$$

and, in the logistic regression case, one adds the covariate extension

$$\epsilon\frac{h(A_{1i}, V_i)}{g^r(A_{1i}0 \mid W_i)}\frac{\frac{d}{d\beta_0}m(A_{1i}, V_i \mid \beta_0)}{m_{\beta_0}(1 - m_{\beta_0})(A_{1i}, V_i)}$$

to the logit. We now compute the amount of fluctuation with weighted maximum likelihood

$$\epsilon_n^1 = \arg\max_{\epsilon} \sum_i \sum_j \log Q_2^{r0}(\epsilon)(O_i^r)w_i,$$

which corresponds with univariate weighted least squares regression or univariate weighted logistic regression, and can thus be done with standard software.

We now compute the corresponding first step targeted ML update $Q_2^{r1} = Q_2^{r0}(\epsilon_n^1)$ of Q^{r0}. We iterate this process till convergence (i.e., $\epsilon_n^k \approx 0$) and denote the final update with Q_{2n}^r. If $m(\cdot \mid \beta)$ is linear in β or if it is a logistic linear model, then it follows that the ϵ-fluctuations mentioned above do not depend on the updates Q_2^{rk}, and, as a consequence, convergence occurs in one single update step: $Q_2^{rk} = Q_2^{r1}$, $k = 2, 3, \ldots$.

Let $Q_n^r = (Q_{1n}^r, Q_{2n}^r)$ be the corresponding estimate of the true $Q_0^r = (Q_{01}^r, Q_{02}^r)$. Under a weak regularity condition we have that the IPCW-R-TMLE Q_n^r of Q_0^r solves the IPCW-R-Efficient influence curve equation

$$0 = \sum_i D(Q_n^r, g_{0i})(O_i).$$

Substitution estimator: The IPCW-R-TML estimator of $\beta_0 = \Psi(Q_0)$ is given by $\Psi^r(Q_n^r)$.

Estimation of Treatment and Censoring mechanism: In the case that g_{0i} is unknown, when estimating $g_{0i}(A \mid X)$ it is a good strategy to give

preference to the baseline covariates W, so that the time-dependent covariates are only entered if they provide significant improvement relative to a fit based on the baseline covariates only. In this manner, one obtains relatively stable weights $w_i = g_0^r(A_i \mid X_i)/g_{0i}(A_i \mid X_i)$. In addition, as point out above, it exploits maximally the double robust property of the IPCW-R-Efficient influence curve function w.r.t. the baseline covariates. Application of the central limit theorem for martingale estimating equations provides the wished statistical inference.

22 DR-IPCW-Iterative Targeted MLE for adaptive designs

This section is till a large degree a copy of the previous Section 20, but we now point out that the reduction of the data is optional and that thereby the resulting class of iterative targeted MLE's covers the whole range of iterative targeted MLE's as presented in this article so far (including the iterative targeted MLE of Section 13).

Let $X = (L_a : a = (a(0), \ldots, a(K)) \in \mathcal{A})$ be a collection of action/design specific random variables L_a indexed by action/design regimen a, and let the observed data structure for one experimental unit be given by

$$O = (A, L = L_A) = (L(0), A(0), \ldots, L_A(K), A(K), L_A(K+1)).$$

The latter represents the time ordering which implies that $L_a(t) = L_{\bar{a}(t-1)}(t)$ and thus $L_A(t) = L_{\bar{A}(t-1)}(t)$. Typically, $L_a(t)$ includes a component $R_a(t) = I(T_a \leq t)$ for a failure/end of follow up time T_a, and $L_a(t) = L_a(\min(t, T_a))$ becomes degenerate after this time variable T_a. The action process $A(t)$ can have various components describing censoring as well as treatment actions at time t, and for certain values of $A(t-1)$, such as values implying right-censoring, the future process $A(t), \ldots, A(K)$ will be a deterministic function of $\bar{A}(t-1) = (A(0), \ldots, A(t-1))$. In addition, typically, certain values of the observed history $\bar{L}(t), \bar{A}(t-1)$, such as one implying the failure time event $T_A = t$, will determine the future values $A(t), \ldots, A(K)$.

We assume the adaptive sequential randomization assumption on the conditional distribution of A_i, given X_i and $\bar{\mathbf{O}}(i-1)$

$$g_i(a \mid X_i) = \prod_t g_{ti}(a(t) \mid \bar{A}_i(t-1) = \bar{a}(t-1), X_i) \stackrel{SRA}{=} \prod_t g_{ti}(a(t) \mid \bar{A}_i(t-1) = \bar{a}(t-1), L_{\bar{A}(t-1),i}(t)),$$

where the conditional distributions g_i and g_{ti} are allowed to be deterministic functions of $\bar{\mathbf{O}}(i-1)$. By support restrictions on $\mathcal{A}$ and the possibly determin-

istic relation between an observed history $\bar{A}_i(t-1), \bar{L}_i(t)$ and the future action process $A_i(t), \ldots, A_i(K)$, this product over time t can often be represented as

$$g_i(a \mid X_i) = \prod_{t=0}^{\min(T_{ai}-1, c_a)} g_{ti}(a(t) \mid \bar{A}_i(t-1) = \bar{a}(t-1), \bar{L}_i(t)) \prod_{t=\min(T_{ai}-1, C_a)+1}^{K} I(a(t+1) = a(t)),$$

where c_a denotes the censoring/end of follow up time implied by action regimen a.

Under this CAR/SRA, the probability distribution of the observed data random variable $O_i = (A_i, L_{Ai})$ for the single experimental unit i, given $O_1, \ldots, O_{i-1}$, factorizes in a factor Q_0 implied by the full data distribution of X and a factor $g_i(\cdot \mid X)$.

$$\begin{aligned} dP_{Q_0, g_i}(O_i) &= \prod_{t=0}^{K+1} P_{Q_0}(L_i(t) \mid \bar{L}_i(t-1), \bar{A}_i(t-1)) g_i(A_i \mid X_i) \\ &\equiv \prod_{t=0}^{K+1} Q_{0t}(L_i(t) \mid \bar{L}_i(t-1), \bar{A}_i(t-1)) g_i(A_i \mid X_i), \end{aligned}$$

where, by CAR we have $Q_{0t}(l(t) \mid \bar{l}(t-1), \bar{a}(t-1)) = P(L_a(t) = l(t) \mid \bar{L}_a(t-1) = \bar{l}(t-1))$ so that indeed Q_0 represents the identifiable part of the full data distribution of X.

Our goal is estimation of a parameter $\Psi : \mathcal{Q} \to \mathbb{R}^d$. For fixed CAR-designs/CAR censoring mechanisms, in van der Laan and Rubin (2006) we introduced an iterative targeted maximum likelihood estimator of $\psi_0 = \Psi(Q_0)$. In this section we show that this iterative targeted MLE estimator can be generalized to adaptive designs by applying time-dependent IPCW-weights for the corresponding time-specific log-likelihoods for Q_{0t}. The resulting IPCW iterative targeted MLE will now be double robust in the sense that if either the censoring/design mechanism is known or the working model for Q_0 is correct, then the estimator of ψ_0 is consistent and asymptotically normally distributed. This result implies, in particular, that even in the case that the design is unknown, this IPCW-iterative targeted MLE is still more robust than the MLE based on the working model. In addition, if the working model is correctly specified, it can be expected that the finite sample and asymptotic efficiency of the IPCW-iterative targeted MLE is very close to the finite sample and asymptotic efficiency of the MLE for the correctly specified working model.

In addition, one can also start out reducing the data structure, and again apply the iterative targeted maximum likelihood estimator for the reduced data but with the appropriate time-dependent IPCW-weights for the corresponding time-specific log-likelihoods for the time-dependent factors Q_{0j}^r in

the Q_0^r-factor of the reduced data likelihood, where Q_0^r denotes the identified component of Q_0 in the reduced data CAR model (i.e., after the reduction of the data). In this manner, the IPCW-iterative targeted MLE provides us with a very large class of double robust targeted maximum likelihood estimators, where the level of robustness, complexity, and asymptotic efficiency depends on the degree of data reduction applied: no reduction gives maximal potential (achieved when the working model for Q_0 is correctly specified) asymptotic efficiency and maximal double robustness (i.e., the estimator is consistent if the working model for Q_0 is correctly specified, even if there is time-dependent censoring/treatment assignment, and even if the model for censoring/design mechanism is completely misspecified), but reduction of the data can make the estimator much easier to implement and can provide important finite sample robustness gains.

Consider the model $\mathcal{M}(g) = \{P_{Q,g} : Q \in \mathcal{Q}\}$ for a single experimental unit O implied by a model $\mathcal{Q}$ for Q_0 and a fixed design/censoring mechanism g contained in the set $\mathcal{G}$ of all SRA-conditional distributions of A, given X. We note that, since Q_0 is identifiable based on i.i.d. sampling from an element in $\mathcal{M}(g)$, one can also view Ψ as a parameter on the model $\mathcal{M}(g)$ of possible data generating distributions of O.

We will now provide the class of so called Double Robust Inverse Probability of Censoring Weighted (Reduced Data) Iterative Targeted Maximum Likelihood estimators (DR-IPCW-(R)-TMLE), obtained by applying the iterative targeted MLE for fixed designs, as developed in van der Laan and Rubin (2006), to adaptive designs, but using inverse probability of censoring weighted time-dependent log-likelihoods at each step. In our abbreviation we put "Reduced Data" between parentheses in order to indicate that reducing the data is an optional step, which can be skipped. Specifically, the DR-IPCW-(R)-TML estimator is defined by the following steps.

(Optional) Specify Reduced Data Structure for single experimental unit:
Determine a reduction $O^r = (A, L_A^r)$ (i.e., O^r is a function of O), where L_A^r is a measurable function of L_A, where the reduction needs to be so that it is still possible to identify the parameter of interest ψ_0 from the probability distribution of O_r under the under the SRA assumption for the reduced full data structure $X^r = (L_a^r : a \in \mathcal{A})$. For example, $O = (W = L(0), A, \bar{L}(K), Y = L(K+1))$ consists of baseline covariates W, treatment regimen $A = (A(0), \ldots, A(K))$, time dependent covariate process $\bar{L}(K)$, and a final outcome Y, while one defines $O^r = (W, A, Y)$, which is obtained from O by deleting all time-dependent covariates. One option is to not reduced the data in which case $O^r = O$.

Reduced Data Model for single experimental unit. Consider the corresponding reduced data SRA model $\mathcal{M}^r(g^r) = \{dP^r_{Q^r,g^r} = Q^r g^r : Q^r \in \mathcal{Q}^r\}$ for a $g^r \in \mathcal{G}^r$ (as described above in general) for $O^r = (A, L^r_A)$, where $\mathcal{G}^r$ is a set of conditional distributions of A, given $X^r = (L^r_a : a \in \mathcal{A})$, satisfying the SRA assumption for the reduced data structure O^r, and $\mathcal{Q}^r$ is a model for the identified component Q^r_0 of the full data distribution of X^r. Since Q^r_0 is a function of Q_0, it follows that the model $\mathcal{Q}^r = \{Q^r : Q \in \mathcal{Q}\}$ for Q^r_0 is implied by model $\mathcal{Q}$ for Q_0. Let $\Psi^r : \mathcal{Q}^r \to \mathbb{R}^d$ be such that $\Psi^r(Q^r) = \Psi(Q)$ for all $Q \in \mathcal{Q}^r$, and, in particular, $\Psi^r(Q^r_0) = \Psi(Q_0)$.

In particular, if the data is not reduced in the previous step, then $O^r = O$, $Q^r = Q$, $g^r = g$, $\mathcal{M}^r(g^r) = \mathcal{M}(g)$, $\mathcal{G}^r = \mathcal{G}$, $\Psi^r = \Psi$.

Factorization of Q^r: Suppose $dP_{Q^r_0,g^r_0} = \prod_j Q^r_{j0} g^r_0$ factors in various terms Q^r_{j0}, $j = 1, \ldots, J$ (e.g., $J = K + 1$). Suppose that $Q^r_{j0}(O^r)$ depends on O^r only through $((A(0), \ldots, A(j^r - 1), \bar{L}^r(j^r))$, $j = 1, \ldots, J$. In a typical scenario, we have that Q^r_{j0} denotes the conditional distribution of $L^r(j^r)$, given $(A(0), \ldots, A(j^r - 1)$ and $\bar{L}^r(j^r - 1)$. For notational convenience, we used the short-hand notation $j^r = j^r(j)$, suppressing its deterministic dependence on j.

In particular, if the data is not reduced, then $dP_{Q_0,g_0} = \prod_t Q_{t0} g_0$, $t = 1, \ldots, K + 1$ where Q_{t0} denotes the conditional distribution of $L(t)$, given $\bar{L}(t - 1), \bar{A}(t - 1)$, so that $Q_{t0}(O)$ depends on O only through $(A(0), \ldots, A(t - 1))$, $t = 1, \ldots, K + 1$.

Determine Q^r_j-components of efficient influence curve for reduced data model: Let $D^r(P^r)$ be the efficient influence curve at $dP^r = dP^r_{Q^r,g^r} = Q^r g^r$ for the parameter Ψ^r in the model $\mathcal{M}^r(g^r)$ for the reduced data structure O^r. This efficient influence curve can be decomposed as:

$$D^r(P^r) = D^r(Q^r, g^r) = \sum_{j=1}^{J} D^r_j(P^r),$$

where $D^r_j(P^r)$ is an element of the tangent space generated by the j-th factor Q^r_j of $Q^r = \prod_j Q^r_j$ at P^r, $j = 1, \ldots, J$.

In particular, if the data was not reduced and the model for Q_0 is nonparametric, then the efficient influence curve $D(P) = \sum_{t=1}^{K+1} D_t(P)$ with

$$D_t(P) = E_P(D(P)(O) \mid \bar{A}(t-1), \bar{L}(t)) - E_P(D(P)(O) \mid \bar{A}(t-1), \bar{L}(t-1))$$

being the projection of $D(P)$ on the tangent space generated by the conditional distribution Q_{0t} of $L(t)$, given $\bar{L}(t - 1), \bar{A}(t - 1)$.

Determine hardest Q_j^r-fluctuation functions: Given a Q^r construct sub-models $\{Q_j^r(\epsilon) : \epsilon\}$ through Q_j^r at $\epsilon = 0$, with score at $\epsilon = 0$ equal to $D_j^r(Q^r, g^r)$:

$$\frac{d}{d\epsilon} \log Q_j^r(\epsilon)\Big|_{\epsilon=0} = D_j^r(Q^r, g^r),\ j = 1, \ldots, J.$$

In particular, if the data is not reduced, then, given a $Q \in \mathcal{Q}$ construct sub-models $\{Q_t(\epsilon) : \epsilon\}$ through Q_t at $\epsilon = 0$, with score at $\epsilon = 0$ equal to $D_t(Q, g)$:

$$\frac{d}{d\epsilon} \log Q_t(\epsilon)\Big|_{\epsilon=0} = D_t(Q, g),\ t = 1, \ldots, K+1.$$

Construct IPCW-weights for each j-specific Q_j^r-factor: For each j construct weight-function

$$w_{ji} = \frac{g^r(\bar{A}_i(j^r) \mid X^r)}{g_i(\bar{A}_i(j^r) \mid X_i)},\ j = 1, \ldots, J.$$

In short, we will often represent the weights $g^r(\bar{A}_i(j^r) \mid X^r)/g_i(\bar{A}(j^r) \mid X)$ as g_j^r/g_{ji}. We note

$$\begin{aligned} Q_{j0}^r &= \arg\max_{Q_j^r \in \mathcal{Q}_j^r} P_{Q_0, g_i} \log Q_j^r w_{ji} \\ &= \arg\max_{Q_j^r \in \mathcal{Q}_j^r} P_{Q_0^r, g_0^r} \log Q_j^r,\ j = 1, \ldots, J, \end{aligned}$$

so that it follows that the IPCW log-likelihood loss function $\sum_j \log Q_j^r w_j$ is a valid loss function for Q_0^r.

In particular, if the data is not reduced, then, for each time t construct weight function

$$w_{ti} = \frac{g^r(\bar{A}_i(t-1) \mid X_i)}{g_i(\bar{A}_i(t-1) \mid X_i)},\ t = 1, \ldots, K+1.$$

IPCW-(Iterative) Targeted MLE based on reduced data at specified g^r: We will now compute the iterative targeted MLE under i.i.d sampling $O_1^r, \ldots, O_n^r$ from $P_{Q_0^r, g^r}^r$, treating g^r as known (e.g., estimated a priori), but assigning IPCW-weights, as follows. Let Q^{r0} be an initial estimator of Q_0^r such as a weighted-MLE according to a working model $\mathcal{Q}_j^r$:

$$Q_j^{r0} = \arg\max_{Q_j^r \in \mathcal{Q}_j^r} \sum_i \log Q_j^r(O_i^r) w_{ji}.$$

Compute the overall amount of fluctuation with weighted maximum likelihood estimation:

$$\epsilon_n^1 = \arg\max_{\epsilon} \sum_i \sum_j \log Q_j^{r0}(\epsilon)(O_i^r) w_{ji},$$

and compute the corresponding first step targeted ML update $Q_j^{r1} = Q_j^{r0}(\epsilon_n^1)$, $j = 1, \ldots, J$, and thereby the overall update $Q^{r1} = Q^{r0}(\epsilon_n^1)$. Iterate this process till convergence (i.e., $\epsilon_n^k \approx 0$) and denote the final update with $Q_n^r = (Q_{jn}^r : j = 1, \ldots, J)$.

Let $D(Q^r, g^r, g_i) = \sum_j D_j^r(Q^r, g^r) \frac{g_j^r}{g_{ji}}$. Under a weak regularity condition we have (see proof in van der Laan and Rubin (2006))

$$0 = \sum_i D(Q_n^r, g^r, g_i)(O_i) = \sum_i \sum_j D_j^r(Q_n^r, g^r)(O_i^r) w_{ji}. \tag{53}$$

In particular, if the data is not reduced, then Q_n solves the equation

$$0 = \sum_i \sum_t D_t(Q_n, g^r)(O_i) w_{ti}.$$

Substitution estimator: Our estimator of ψ_0 is given by $\Psi^r(Q_n^r)$.

In particular, if the data is not reduced, then ψ_0 is estimated with $\Psi(Q_n)$.

The DR-IPCW-R-TMLE is an estimator Q_n^r solving an IPCW-reduced data efficient influence curve equation (53). Firstly, we establish that this IPCW-reduced data efficient influence curve is an "estimating function" for the target parameter with nice robustness properties w.r.t its nuisance parameters Q_0^r and g_0. Subsequently, we discuss the corresponding implications on the statistical properties of the DR-IPCW-R-TMLE.

Robustness properties of IPCW-Reduced Data Efficient Influence Function: Recall that $D^r(Q^r, g^r)$ denotes the efficient influence curve for the reduced data $O^r \sim P_{Q^r, g^r}$ for model $\mathcal{M}^r$ and parameter Ψ^r. It follows from general results in van der Laan and Robins (2003) that $P_{Q_0^r, g_0^r} D^r(Q^r, g^r) = 0$ if either $Q^r = Q_0^r$ or $\Psi(Q^r) = \Psi(Q_0^r)$ and $g^r = g_0^r$. This double robustness result for D^r is exploited/inherited by the estimating function

$$D(Q^r, g^r, g_0) \equiv \sum_j D_j^r(Q^r, g^r) g_j^r / g_{ji},$$

whose corresponding estimating equation is solved by our IPCW targeted MLE, in the following manner. We have

$$\begin{aligned} P_{Q_0,g_{0i}} D(Q^r, g^r, g_i) &= P_{Q_0,g_{0i}} \sum_j D_j^r(Q^r, g^r) \frac{g_j^r}{g_{ji}} \\ &= P_{Q_0,g^r} \sum_j D_j^r(Q^r, g^r) \frac{g_{0ji}}{g_{ji}}. \end{aligned}$$

This implies that if $g_{ji} = g_{0ji}$ (i.e., the action mechanism is correctly specified), then $P_{Q_0,g_{0i}} D(Q^r, g^r, g_i) = 0$ for all choices of Q^r, g^r with $\Psi(Q^r) = \Psi(Q_0^r)$. In a typical scenario, we have that Q_{j0}^r denotes the conditional distribution of $L^r(j^r)$, given $A(0), \ldots, A(j^r - 1)$ and $\bar{L}^r(j^r - 1)$. In this case, if g_{0j} is only a function of O^r, then if $Q^r = Q_0^r$, it follows that $P_{Q_0,g^r} D_j^r(Q_0^r, g^r) \frac{g_{0j}}{g_j} = 0$ for all g_j only being a function of O^r (by using that the conditional expectation of a score $D_j^r(Q_0^r, g^r)$ of Q_{j0}^r, given $(A(0), \ldots, A(j^r - 1)$ and $\bar{L}^r(j^r - 1)$, equals zero), and as a consequence, $P_{Q_0,g_{0i}} D(Q_0^r, g^r, g) = 0$ for such misspecified g. That is, in the case that the true g_{0i} and its asymptotic fit are only functions of the reduced data structure, we have the double robustness of the estimating function $D(Q^r, g^r, g)$ in the sense that $P_{Q_0,g_{0i}} D(Q^r, g^r, g_i) = 0$ if $\Psi(Q^r) = \Psi(Q_0^r)$ and, either $Q^r = Q_0^r$ or $g_i = g_{0i}$, for all g^r.

In particular, if the data is not reduced, then we have

$$P_{Q_0,g_{0i}} D(Q, g, g_i) = 0 \text{ if } \Psi(Q) = \psi_0 \text{ and either } Q = Q_0 \text{ or } g_i = g_{0i},$$

for all $g \in \mathcal{G}$.

Statistical Properties of IPCW-R-TMLE: The above mentioned robustness property of the estimating equation $\sum_i D(Q_n^r, g_n^r, g_{ni}) = 0$, g_{ni} an estimator of g_{0i}, as solved by the IPCW-R-TMLE Q_n^r translates under regularity conditions in the following statistical properties of the substitution estimator $\psi_n = \Psi^r(Q_n^r)$. Firstly, under appropriate regularity conditions, if g_{ni} consistently estimates g_{0i}, then ψ_n will be a consistent and asymptotically linear estimator of ψ_0. In addition, if $g_{ni}(A \mid X)$ and its target $g_{0i}(A \mid X)$ are only functions of the reduced data structure O_i^r for each i (beyond being functions of $\bar{\mathbf{O}}(i-1)$), then 1) ψ_n is consistent and asymptotically linear if either Q_n^r consistently estimates Q_0^r or g_{ni} consistently estimates g_{0i}, and if both estimates are consistent, then the estimator ψ_n is more efficient than an efficient estimator based on n i.i.d. observations of the reduced data structure $O^r \sim P_{Q_0^r,g^r}^r$ only.

In particular, if the data is not reduced, and Q_n is solution of $0 = \sum_i D(Q_n, g_n, g_{ni})(O_i)$, then, under regularity conditions, if either g_{ni} consistently estimates g_{0i}, or Q_n

consistently estimates Q_0, then the substitution estimator $\psi_n = \Psi(Q_n)$ is consistent and asymptotically normally distributed. In addition, if $g_n/g_{ni} \to 1$ and g_n converges to some fixed design $g_0 \in \mathcal{G}$, then, if Q_n is consistent for Q_0, then the substitution estimator ψ_n is at least as efficient than an efficient estimator based on n i.i.d. observations of $O \sim P_{Q_0,g_0}$.

Off course, in adaptive of fixed designs the design mechanism g_{0i} is typically known so that in that case the DR-IPCW-R-TMLE is always a consistent and asymptotically linear estimator.

22.1 Example: Causal effect of treatment in presence of baseline covariates.

Consider the case that in each experiment we observe baseline covariates W_i, a treatment assignment A_i, and an outcome of interest Y_i, $i = 1, \ldots, n$. Suppose that the parameter of interest is the marginal causal effect of treatment on outcome, formally defined as $\psi_0 = EY_1 - EY_0 = E_0\{E_0(Y \mid A = 1, W) - E_0(Y \mid A = 0, W)\}$. Consider a fixed design g^r representing a fixed conditional distribution of A, given W. The Q_0-factor of the density of O_i, given $O_1, \ldots, O_{i-1}$, is given by the product of the marginal probability distribution of W_i and the conditional probability distribution of Y_i, given A_i, W_i. Consider initial estimators $Q_n^0(W)$ and $Q_n^0(Y \mid A, W)$ of these two factors such as maximum likelihood estimators according to working models for the marginal distribution of W and the conditional distribution of Y, given A, W. Let $Q_n^0(\epsilon)(W)$ be a fluctuation with score $D_1(Q_n^0)(W) = Q_n^0(1, W) - Q_n^0(0, W) - \Psi(Q_n^0)$ and let $Q_n^0(\epsilon)(Y \mid A, W)$ be a fluctuation with score $D_2(g^r, Q_n^0) = (Y - Q_n^0(A, W))\{I(A = 1)/g^r(1 \mid W) - I(A = 0)/g^r(0 \mid W)\}$. The latter fluctuation can be achieved by adding an ϵ covariate extension

$$\epsilon h(A, W) = \epsilon \{I(A = 1)/g^r(1 \mid W) - I(A = 0)/g^r(0 \mid W)\}$$

to an initial linear or logistic regression fit, as presented earlier. The joint fluctuation $(Q_n^0(\epsilon)(W), Q_n^0(\epsilon)(Y \mid A, W))$ defines now a fluctuation of the Q_n^0 factor of the probability distribution of the data with score at $\epsilon = 0$ equal to efficient influence curve $D(Q_n^0, g^r)$. We now estimate ϵ with the IPCW-maximum likelihood estimator:

$$\epsilon_n^0 = \arg\max_{\epsilon} \sum_i \log Q_n^0(\epsilon)(W_i) + \log Q_n^0(\epsilon)(Y_i \mid A_i, W_i) w_i,$$

where $w_i = g^r(A_i \mid W_i)/g_i(A_i \mid W_i)$. Note that we do not need to weight the first factor $Q_n^0(\epsilon)(W)$ since this one does not depend on A. In the special, but

natural case, that Q_n^0 is the empirical distribution of $W_1, \ldots, W_n$, then one could replace $Q_n^0(\epsilon)(W)$ by $Q_n^0(W)$ and thus only fluctuate the conditional distribution of Y, given A, W.In addition, it is also an option to use a bivariate fluctuation $Q_n^0(\epsilon_1)(W)$ and $Q_n^0(\epsilon_2)(Y \mid A, W)$, but this is not necessary. This defines now an update $Q_n^1 = Q_n^0(\epsilon_n^0)$. We can now iterate this process of updating. However, we note that the ϵ-extension of $Q_n^1(\epsilon)(Y \mid A, W)$ corresponds typically with adding $\epsilon_n^0 h(A, W) + \epsilon h(A, W)$ to $Q_n^0(Y \mid A, W)$ or its logit. Thus, in the special case that $Q_n^0(W)$ is the empirical distribution and or that we use a bivariate fluctuation, convergence occurs in the first step for the conditional distribution of Y, given A, W, so that $Q_n^k = Q_n^1$, $k = 1, 2, \ldots$.

At convergence, we have that the final solution Q_n^k solves

$$0 = \sum_{i=1}^{n} D_1(Q_n^k)(W_i) + D_2(Q_n^k, g^r)(O_i) \frac{g^r(A_i \mid W_i)}{g_i(A_i \mid W_i)},$$

which can also be written as

$$\Psi(Q_n^k) = \frac{1}{n} \sum_{i=1}^{n} Q_n^k(1, W_i) - Q_n^k(0, W_i) + D_2(Q_n^k, g^r)(O_i) \frac{g^r(A_i \mid W_i)}{g_i(A_i \mid W_i)}.$$

Conservative statistical inference can now be based on the asymptotically linear martingale expansion

$$\Psi(Q_n^k) - \psi_0 = \frac{1}{n} \sum_{i=1}^{n} Q(1, W_i) - Q(0, W_i) - \psi_0 + D_2(Q, g^r)(O_i) \frac{g^r(A_i \mid W_i)}{g_i(A_i \mid W_i)},$$

where Q denotes the limit of Q_n^k.

23 Targeted Empirical Bayesian Learning for i.i.d. sampling

The iterative targeted maximum likelihood estimation methodology in van der Laan and Rubin (2006) for i.i.d. sampling, resulting in a sequence of updated density estimators converging to a solution of the efficient influence curve equation, can be generalized to a targeted empirical Bayesian learning method in which one assumes a prior distribution on the parameter of interest and ends up with a targeted posterior distribution of this parameter of interest. In addition, we can extend this further to adaptive designs. In this section, we first present targeted empirical Bayesian learning for i.i.d. sampling, and its generalization to adaptive designs is handled in the next section.

Consider the setting in which we observe n i.i.d. observations $O_1, \ldots, O_n$ of a random variable $O \sim P_0$, which is known to be an element of a model $\mathcal{M}$, and let $\Psi : \mathcal{M} \to \mathbb{R}^d$ be the target parameter mapping of interest. A special case is that $O = \Phi(A, X)$ is modelled by a CAR censored data model $calM = \{dP_{Q,g} = Qg : Q \in \mathcal{Q}, g \in \mathcal{G}_1\}$ for some submodel $\mathcal{G}_1$ of all CAR censoring mechanisms, thereby including the fixed designs, and some model $\mathcal{Q}$ for the factor Q_0 representing the identifiable part of the distribution of X.

Step 1, Determine Prior Distribution on Parameter of Interest: Specify a prior distribution Π of the parameter ψ_0. Let f_Π be the density of Π.

Step 2, Determine targeted (frequentist) estimator of distribution P_0: Consider a targeted estimated probability distribution $\hat{P}$ in the model $\mathcal{M}$. This estimator is recommended to be a targeted estimator itself such as the iterative targeted MLE (van der Laan and Rubin (2006)).

Step 3, Determine targeted optimal ϵ-fluctuation function: Let $\{\hat{P}(\epsilon) : \epsilon\} \subset \mathcal{M}$ be a fluctuation through $\hat{P}$ at $\epsilon = 0$ with score at $\epsilon = 0$ equal to the efficient influence curve $D^*(\hat{P})$ at $\epsilon = 0$.

Step 4, Derive prior distribution on fluctuation parameter ϵ equivalent with prior on ψ_0: Determine a prior distribution on ϵ that yields the assumed prior distribution on the true parameter ψ_0 of interest. For this purpose one notes that a prior distribution on a set $\mathcal{E}$ of ϵ-values implies a prior distribution on $\{\Psi(\hat{P}(\epsilon)) : \epsilon \in E\}$ (and thus on ψ_0) through the mapping $f(\hat{P}) : \epsilon \to \Psi(\hat{P}(\epsilon))$. As a consequence, one can choose the prior distribution of ϵ as the probability distribution of $f(\hat{P})^{-1}(X)$ with $X \sim \Pi$, assuming $f(\hat{P})$ is invertible. This corresponds with a random variable E defined by drawing from Π and applying $f(\hat{P})^{-1}$ to it. Let Π^* be this prior distribution of ϵ. The density of Π^* is given by

$$f_{\Pi^*}(\epsilon) = f_\Pi(f(\hat{P})(\epsilon))J(\epsilon),$$

where $J(\epsilon) = \mid \frac{d}{d\epsilon} f(\hat{P})(\epsilon) \mid$ is the Jacobian corresponding with transformation $\psi = f(\hat{P})(\epsilon)$.

Step 5, Determine (targeted) posterior distribution of ϵ, given data, treating $\hat{P}$ as fixed/non random: Since, from a Bayesian perspective, the conditional density of $O_1, \ldots, O_n$, given ϵ, is given by $\prod_{i=1}^n d\hat{P}(\epsilon)(O_i)$, by Bayes formula, the posterior density of ϵ, given the data $O_1, \ldots, O_n$, treating $\hat{P}$ as fixed and given, is given by (up till normalizing constant)

$$\propto \prod_{i=1}^n d\hat{P}(\epsilon)(O_i) f_{\Pi^*}(\epsilon).$$

One can use standard Bayesian methodology such as Monte-Carlo Markov Chain sampling to sample a large number of draws, say, $E_1, \ldots, E_B$, from this posterior distribution of ϵ, given $O_1, \ldots, O_n$.

Step 6, Output targeted posterior distribution of ψ_0, given data, treating $\hat{P}$ as fixed/non random: The posterior distribution of ψ_0 is now described by the sample $f(\hat{P})(E_b) = \Psi(\hat{P}(E_b))$, $b = 1, \ldots, B$.

Optional: Iterate. If $\hat{P}$ was not a targeted estimator, then one could compute the posterior mean of ϵ, given $O_1, \ldots, O_n$, and compute the updated distribution $P^1 = \hat{P}(E(\epsilon \mid O_1, \ldots, O_n))$ by substituting the posterior mean of ϵ into the fluctuation function $\hat{P}(\epsilon)$ for ϵ. One now carries out Step 3-5 (thus with the same a priori specified prior distribution on ψ_0) and one iterates this process till the posterior mean of ϵ converges to zero at which point we have achieved our wished targeted estimator of P_0. One now finalizes the procedure with Step 6, by outputting the posterior distribution of ψ_0.

We refer to this methodology as *empirical* targeted Bayesian because we treat the (initial) frequentist estimator $\hat{P}$ in the model $\{\hat{P}(\epsilon) : \epsilon\}$ for the data generating distribution as fixed so that only ϵ is treated as a parameter on which we put a prior distribution, and we calculate its posterior distribution accordingly.

Rational behind the targeted posterior distribution on parameter of interest: The rational of this methodology for generating a posterior distribution of ψ_0 is as follows. To evaluate the posterior distribution of ψ_0 we need to be concerned about its bias w.r.t to ψ_0 and its spread needs to be representative of the actual standard error of the posterior mean. Regarding the bias, because $\hat{P}$ is a targeted estimator of the data generating distribution such as the iterative targeted MLE, $\Psi(\hat{P})$ is a robust and locally efficient estimator of ψ_0. Consequently, also the posterior mean of the outputted posterior distribution of ψ_0 will be centered closely around $\Psi(\hat{P})$ and will thus represent a robust and locally efficient estimator w.r.t to frequentist theory. Regarding the spread, one needs to know that $\{P_0(\epsilon) : \epsilon\}$, whose score at $\epsilon_0 = 0$ equals the efficient influence curve of $\Psi : \mathcal{M} \to \mathbb{R}^d$ at P_0, is a so called hardest submodel for estimation of ψ_0 (e.g., see Bickel et al. (1997) or van der Laan and Robins (2003)) in the sense that estimation of the parameter $\psi_0 = \Psi(P_0(\epsilon_0))$ of ϵ_0 in this hardest sub-model of $\mathcal{M}$ (treating P_0 as known so that only ϵ_0 is the unknown parameter) is asymptotically as hard as it is to estimate ψ_0 in the actual model $\mathcal{M}$. As a consequence, statistical inference (i.e., asymptotic

covariance matrix, and information matrix) for a maximum likelihood estimator of $\psi_0 = \Psi(P_0(\epsilon_0))$ in this sub-model (in which $\epsilon_0 = 0$ is the only unknown parameter) will be representative of the statistical inference of the estimator $\Psi(\hat{P})$ of ψ_0 in the actual model $\mathcal{M}$.

To make this point more specific, we consider statistical inference of the ML estimator $\Psi(\hat{P}(\epsilon_n))$ of $\Psi(\hat{P}(\epsilon_0))$, $\epsilon_0 = 0$, in the model $\{\hat{P}(\epsilon) : \epsilon\}$ treating $\hat{P}$ as given. We have that ϵ_n solves its score equation $0 = \sum_i D^*(\hat{P}(\epsilon_n))$, and because $\hat{P}$ is already a targeted estimator such as the iterative targeted MLE we have that $\epsilon_n \approx 0$. In addition, we have the identity $\frac{d}{d\epsilon_0}\Psi(\hat{P}(\epsilon_0)) = \frac{d}{d\epsilon_0}E_{\hat{P}}D^*(\hat{P}(\epsilon_0))$ is the identity matrix (Lemma 1.2, page 59, van der Laan and Robins (2003)). As a consequence, the standard delta-method applied to the MLE ϵ_n as an estimator of ϵ_0 yields the asymptotic linearity

$$\Psi(\hat{P}(\epsilon_n)) - \Psi(\hat{P}(\epsilon_0)) \approx \frac{1}{n}\sum_{i=1}^{n} D^*(\hat{P})(O_i).$$

That is, under this hardest sub-model we would estimate the asymptotic variance $\mathrm{VAR}_{\hat{P}}D^*(\hat{P})$ of $\sqrt{n}(\Psi(\hat{P}(\epsilon_n)) - \psi_0)$ as $1/n\sum_i D^*(\hat{P})(O_i)^2$, which is typically the right estimate in the actual model. So this shows that indeed statistical inference of the MLE $\Psi(\hat{P}(\epsilon_n))$ of $\Psi(\hat{P}(\epsilon_0))$ for the hardest submodel provides the right statistical inference for this MLE $\Psi(\hat{P}(\epsilon_n))$ as an estimator of ψ_0 in the actual model. By the asymptotic equivalence of posterior means of posterior distributions and MLE, this also argues for the appropriateness of Bayesian inference based on the hardest working model, as carried out by our proposed Targeted empirical Bayesian methodology.

23.1 Example: Targeted Bayesian learning of Survival function.

We now illustrate this completely general empirical targeted Bayesian analogue of the iterative targeted MLE methodology with a simple example. Suppose, we wish to estimate a survival function at a point, $\psi_0 = P_0(O > x_0)$, based on n i.i.d. observations $O_1, \ldots, O_n \sim P_0$ in a nonparametric model for P_0.

Prior distribution: Consider a prior distribution on ψ_0 such as a uniform distribution on $[a_0, b_0] \subset [0, 1]$ for some numbers $0 \leq a_0 < b_0 \leq 1$. Let π be its density.

Targeted density estimator: Consider a targeted ML density estimator $\hat{p} = p^0(\epsilon^0)$ of the density p_0, given an initial density estimator p^0, a one-

dimensional fluctuation function $\epsilon \to p^0(\epsilon)$ (into valid densities), and

$$\epsilon^0 = \arg\max_{\epsilon} \prod_{i=1}^{n} p^0(\epsilon)(O_i),$$

satisfying $0 = \sum_i D^*(p^0(\epsilon^0))(O_i)$, where $D^*(p) = I(O \leq x_0) - \int_{x_0}^{\infty} p(x)dx$ is the efficient influence curve of Ψ at p. In van der Laan and Rubin (2006) we showed that indeed the first step targeted MLE's can be constructed to already solve the efficient influence curve estimating equation: e.g. choose $p^0(\epsilon) = (1 + \epsilon D^*(p^0)(O))p^0$.

Targeted fluctuation of targeted density estimator: Let $\hat{p}(\epsilon) = (1 + \epsilon D^*(\hat{p}))\hat{p}$ be the targeted fluctuation function of $\hat{p}$ whose score at $\epsilon = 0$ indeed equals $D^*(\hat{p})$.

Evaluate prior distribution for ϵ implied by prior of ψ_0: We have $\epsilon \to f(\hat{P})(\epsilon) = \Psi(\hat{p}(\epsilon)) = \int_{x_0}^{\infty}(1 + \epsilon D^*(\hat{P})(x))\hat{p}(x)dx$. The inverse of $\epsilon \to f(\hat{P})(\epsilon)$ is given by

$$g(\psi) \equiv f(\hat{P})^{-1}(\psi) = \frac{\psi - \Psi(\hat{p})}{E_{\hat{p}} D^{*2}(\hat{p})},$$

which shows that $f(\hat{P})$ is invertible. In particular, this shows that we can choose the prior distribution of ϵ as the distribution of $g(X)$ with $X \sim \Pi$, where Π is the prior distribution on ψ_0 specified initially.

Targeted posterior density of ϵ: The derivative of $f(\hat{P})$ at ϵ is given by $\sigma^2 \equiv E_{\hat{p}} D^{*2}(\hat{P})$ so that the Jacobian is given by a constant $J(\epsilon) = \sigma^2$. The univariate posterior density of ϵ, given $O_1, \ldots, O_n$, is thus given by

$$\pi(\epsilon \mid O_1, \ldots, O_n) = \frac{\prod_{i=1}^{n} \hat{p}(\epsilon)(O_i)\pi(f(\hat{P}(\epsilon))}{\int_{\epsilon} \prod_{i=1}^{n} \hat{p}(\epsilon)(O_i)\pi(f(\hat{P}(\epsilon))}, \tag{54}$$

where we recall that π is the density of the prior distribution on ψ_0.

Targeted posterior density of survival function: The posterior density of ϵ implies the posterior distribution of $f(\hat{P}(\epsilon)) = \Psi(\hat{P}(\epsilon))$, i.e. the survival function at x_0. In this example, one can even pursue analytic calculation of this posterior density of the survival function since it only involves univariate density calculations. The Monte Carlo simulation approach would be to sample $E_1, \ldots, E_B$ from the posterior density $\pi(\cdot \mid O_1, \ldots, O_n)$ specified in (54), and evaluate the corresponding $\Psi(\hat{P}(E_b))$, $b = 1, \ldots, B$, which gives us a random sample from the posterior distribution of the survival function at x_0, given the observed data $O_1, \ldots, O_n$.

Properties of targeted posterior distribution of survival function and comparison with standard Bayesian learning: A standard Bayesian approach would involve specifying a parametric model, specifying a prior distribution on all the parameters of this parametric model, calculating the corresponding posterior distribution involving sampling from a high dimensional multivariate density (since there are many parameters), and model selection (e.g.) based on the posterior density so that these calculations will have to be carried out for lots of candidate parametric models. In spite of the computational challenges and effort of this standard Bayesian approach, the resulting estimator of the survival function will typically be too biased due to model miss-specification. Model selection using a likelihood or Bayesian criteria would generally not reduce the bias at the wished rate of $o(1/\sqrt{n})$, since the selection is in essence based on a bias variance trade off for the purpose of estimating the whole density. As a consequence, the relative efficiency of the simple empirical survival probability and such a standard Bayesian estimator (e.g posterior mean) would converge to infinity in favor of the empirical survival function. The same criticism would apply to a sieve based (frequentist) maximum likelihood estimator using (say) likelihood based cross-validation to select models or other fine tuning parameters. The problem of both the Bayesian and maximum likelihood estimation methodology is that the estimation and model selection are not targeted towards the nice smooth parameter being the survival probability, so that the resulting estimation procedure involves the wrong bias variance trade off.

On the other hand, the targeted empirical posterior Bayesian distribution is centered at the efficient empirical survival probability (recall $\Psi(\hat{P}) = 1/n \sum_i I(O_i > x_0)$), and the spread of the posterior distribution is asymptotically completely driven by the variance of this efficient empirical survival function estimate (and by the prior distribution for small samples). In addition, the calculations for establishing this targeted posterior distribution only involve sampling from a univariate posterior density and is therefore easy and fast from a computational point of view.

24 Targeted Empirical Bayesian Learning in adaptive designs.

Consider a sequential adaptive design in which we observe $O_i = (A_i, L_i = X_i(A_i))$ sequentially over time, and the data generating distribution $dP_{Q_0,\mathbf{g}_n} = \prod_i Q_0(A_i, L_i)\mathbf{g}(\mathbf{A} \mid \mathbf{X})$ of $O_1, \ldots, O_n$ is described by (3). Here $Q_0(a, l) = P(X(a) = l)$ is the identifiable component of the common distribution of the

full data structure $X = (X(a) : a \in \mathcal{A})$, and design $\mathbf{g}$ is the conditional probability distribution of $\mathbf{A} = (A_1, \ldots, A_n)$, given $\mathbf{X} = (X_1, \ldots, X_n)$ satisfying the sequential adaptive CAR assumption. We are concerned with statistical inference for a Euclidean parameter of interest $\Psi : \mathcal{Q} \to \mathbb{R}^d$, where $\mathcal{Q}$ denotes a model for Q_0. Let $\psi_0 = \Psi(Q_0)$ denote the true parameter value. Let $D^*(Q, g)$ be the efficient influence curve of Ψ in the fixed design model $\mathcal{M}(g) = \{dP_{Q,g} = Qg : Q \in \mathcal{Q}\}$. Below, we describe the steps defining targeted empirical Bayesian learning in adaptive designs.

Step 1, Determine Prior Distribution on Parameter of Interest: Specify a prior distribution Π of the parameter ψ_0. Let f_Π be the density of Π.

Step 2, Determine targeted (frequentist) estimator of distribution P_0: Consider a targeted estimated probability distribution $\hat{P} = \hat{P}_{\hat{Q},\mathbf{g}}$ in the model $\mathcal{M} = \{dP_{Q,\mathbf{g}} : Q \in \mathcal{Q}\}$. This estimator is recommended to be a *targeted* estimator such as the iterative targeted MLE as presented in Section 13.

Step 3, Determine targeted optimal ϵ-fluctuation function: Let $\{dP_{\hat{Q}(\epsilon),\mathbf{g}} : \epsilon\} \subset \mathcal{M}$ be a fluctuation through $\hat{P} = P_{\hat{Q},\mathbf{g}}$ at $\epsilon = 0$ with score at $\epsilon = 0$ equal to the fixed design efficient influence curve $D^*(\hat{Q}, g_{\hat{Q}})$ for some fixed design $g_{\hat{Q}}$ possibly indexed by $\hat{Q}$.

Step 4, Derive prior distribution on fluctuation parameter ϵ equivalent with prior on ψ_0: Determine a prior distribution on ϵ that yields the assumed prior distribution on the true parameter ψ_0 of interest. For this purpose one notes that a prior distribution on a set $\mathcal{E}$ of ϵ-values implies a prior distribution on $\{\Psi(\hat{Q}(\epsilon)) : \epsilon \in E\}$ (and thus on ψ_0) through the mapping $f(\hat{Q}) : \epsilon \to \Psi(\hat{Q}(\epsilon))$. As a consequence, one can choose the prior distribution of ϵ as the probability distribution of $f(\hat{Q})^{-1}(X)$ with $X \sim \Pi$, assuming $f(\hat{Q})$ is invertible. This corresponds with a random variable E defined by drawing from Π and applying $f(\hat{Q})^{-1}$ to it. Let Π^* be this prior distribution of ϵ. The density of Π^* is given by

$$f_{\Pi^*}(\epsilon) = f_\Pi(f(\hat{Q})(\epsilon))J(\epsilon),$$

where $J(\epsilon) = \mid \frac{d}{d\epsilon} f(\hat{Q})(\epsilon) \mid$ is the Jacobian corresponding with transformation $\psi = f(\hat{Q})(\epsilon)$.

Step 5, Determine (targeted) posterior distribution of ϵ, given data, treating $\hat{Q}$ as fixed/non random: Since, from a Bayesian perspective,

the conditional density of $O_1, \ldots, O_n$, given ϵ, is given by $\prod_{i=1}^n \hat{Q}(\epsilon)(O_i)\mathbf{g}(\mathbf{A} \mid \mathbf{X})$, by Bayes formula, the posterior density of ϵ, given the data $O_1, \ldots, O_n$, treating $\hat{Q}$ as fixed and given, is given by (up till normalizing constant)

$$\begin{aligned} p(\epsilon \mid O_1, \ldots, O_n) &= \propto \prod_{i=1}^n \hat{Q}(\epsilon)(O_i)\mathbf{g}(\mathbf{A} \mid \mathbf{X}) f_{\Pi^*}(\epsilon) \\ &= \propto \prod_{i=1}^n \hat{Q}(\epsilon)(O_i) f_{\Pi^*}(\epsilon). \end{aligned}$$

One can use standard Bayesian methodology such as Monte-Carlo Markov Chain sampling to sample a large number of draws, say, $E_1, \ldots, E_B$, from this posterior distribution of ϵ, given $O_1, \ldots, O_n$.

Step 6, Output targeted posterior distribution of ψ_0, given data, treating $\hat{P}$ as fixed/non random: The posterior distribution of ψ_0 is now described by the sample $f(\hat{P})(E_b) = \Psi(\hat{P}(E_b))$, $b = 1, \ldots, B$.

We refer to this methodology as *empirical* targeted Bayesian because we treat the (initial) frequentist estimator $\hat{P}$ in the model $\{\hat{P}(\epsilon) : \epsilon\}$ for the data generating distribution as fixed so that only ϵ is treated as a parameter on which we put a prior distribution, and we calculate its posterior distribution accordingly using our general representation (3) of the data generating distribution in the sequential adaptive design.

Rational behind the targeted posterior distribution on parameter of interest: The rational of this methodology for generating a posterior distribution of ψ_0 is as follows. To evaluate the posterior distribution of ψ_0 we need to be concerned about its bias w.r.t to ψ_0 and its spread needs to be representative of the actual standard error of the posterior mean. Regarding the bias, because $\hat{P}$ is a targeted estimator of the data generating distribution such as the iterative targeted MLE for adaptive designs as presented in Section 13, $\Psi(\hat{P})$ is a robust and locally efficient estimator of ψ_0. Consequently, also the posterior mean of the outputted posterior distribution of ψ_0 will be centered closely around $\Psi(\hat{P})$ and will thus represent a robust and locally efficient estimator w.r.t to frequentist theory. Regarding the spread, one needs to know that $\{P_0(\epsilon) : \epsilon\}$, whose score at $\epsilon_0 = 0$ equals the efficient influence curve of $\Psi : \mathcal{M} \to \mathbb{R}^d$ at P_0, is a so called hardest submodel for estimation of ψ_0 (e.g., see Bickel et al. (1997) or van der Laan and Robins (2003)) in the sense that estimation of the parameter $\psi_0 = \Psi(P_0(\epsilon_0))$ of ϵ_0 in this hardest sub-model of $\mathcal{M}$ (treating P_0 as known so that only ϵ_0 is the unknown parameter) is asymptotically as hard as it is to estimate ψ_0 in the actual model

$\mathcal{M}$. As a consequence, as shown in the previous section, statistical inference (i.e., asymptotic covariance matrix, and information matrix) for a maximum likelihood estimator of $\psi_0 = \Psi(\hat{P}(\epsilon_0))$ (parameter of only unknown parameter ϵ_0) in this sub-model will be representative of statistical inference for the (targeted) maximum likelihood estimator $\Psi(\hat{P}(\epsilon_n))$ of ψ_0 in the model $\mathcal{M}$.

24.1 Example: Targeted Bayesian learning of causal effect on survival function in adaptive design.

We now illustrate this completely general empirical targeted Bayesian analogue of the iterative targeted MLE methodology with a simple example. Suppose, we wish to estimate a difference of survival function at a point, $\psi_0 = P_0(T_1 > t_0) - P_0(T_0 > t_0)$, based on observations $O_i = (W_i, A_i, T_i = T_i(A_i))$, $i = 1, \ldots, n$, in a sequential adaptive design, where W_i are baseline covariates, A_i is treatment, and T_i is the measured survival time. The i-th randomization probability $g_i(1 \mid X_i = (T_{0i}, T_{1i}, W_i)$ is only a function of $O_1, \ldots, O_{i-1}$ and W_i. Let $Q \to g_Q$ be a design function so that, for example, $g_i = g_{\hat{Q}_{i-1}}$ for a sequence of estimators $\hat{Q}_{i-1}$ based on $O_1, \ldots, O_{i-1}$. In general, we wish to have that g_i/g_{Q_n} converges to 1 for i and n large. The fixed design efficient influence curve of ψ_0 is given by:

$$D^*(Q,g)(A,T) = (Y - Q(A,W)) \left\{ \frac{I(A=1)}{g(1)} - \frac{I(A=0)}{g(0)} \right\} + Q(1,W) - Q(0,W) - \Psi(Q),$$

where $Q_0(1,W) = E(Y \mid A=1,W)$, $Q_0(0,W) = E(Y \mid A=0,W)$, $Y = I(T > t_0)$, $g_0(1) = P(A=1)$, and $\Psi(Q) = Q(1) - Q(0)$.

Prior distribution on causal effect of treatment on survival: Consider a prior distribution on the univariate parameter ψ_0 such as a uniform distribution on $[a_0, b_0] \subset [0,1]$ for some numbers $0 \leq a_0 < b_0 \leq 1$. Let π be its density.

Targeted ML density estimator: Consider an iterative targeted ML density estimator $Q_n(Y \mid A)$ based on $O_1, \ldots, O_n$ so that either

$$0 = \sum_i D^*(Q_n, g_i)(O_i), \text{ or } 0 = \sum_i D^*(Q_n, g_{Q_n})(O_i) \frac{g_{Q_n}(A_i)}{g_i(A_i)}.$$

In the marginal case in which there are no baseline covariates, these two efficient influence curve estimating equations are identical and result in the following targeted ML estimator of ψ_0:

$$\psi_n = \frac{\sum_i Y_i I(A_i=1)/g_i(1)}{\sum_i I(A_i=1)/g_i(1)} - \frac{\sum_i Y_i I(A_i=0)/g_i(0)}{\sum_i I(A_i=0)/g_i(0)}.$$

In general, a slight modification in which only the $Y \mid A, W$ component of the efficient influence curve is inverse weighted, we have the following expression for the estimator:

$$\psi_n = \frac{1}{n}\sum_{i=1}^{n}(Y_i - Q_n(A_i, W_i))\left\{\frac{I(A_i = 1)}{g_i(1 \mid W_i))} - \frac{I(A_i = 0)}{g_i(0 \mid W_i)}\right\} + Q_n(1, W_i) - Q_n(0, W_i).$$

Targeted fluctuation of targeted density estimator: Let $Q_n(\epsilon)(T \mid A, W)$ be so that $Q_n(0) = Q_n$, and $\frac{d}{d\epsilon}\log Q_n(\epsilon)\Big|_{\epsilon=0} = D^*(Q_n, g_{Q_n})$. For example, if one reduces the data $O_i = (W_i, A_i, T_i)$ to (W_i, A_i, Y_i), then this can be arranged by modelling $Q_n(\epsilon)(1 \mid A_i, W)$ with a logistic regression with an extra covariate extension $\epsilon h(A_i, W_i)$ so that

$$h(A_i, W_i) = \frac{\{I(A_i = 1)/g_{Q_n}(1 \mid W_i) - I(A_i = 0)/g_{Q_n}(0 \mid W_i)\}}{Q_n(1 \mid A_i, W_i)(1 - Q_n(1 \mid A_i, W_i))}.$$

Evaluate prior distribution for ϵ implied by prior of ψ_0: We have $\epsilon \to f(Q_n)(\epsilon) = \Psi(Q_n(\epsilon)) = \frac{1}{n}\sum_i Q_n(\epsilon)(1 \mid A_i = 1, W_i) - Q_n(\epsilon)(1 \mid A_i = 0, W_i)$, where $Q_n(1 \mid A_i, W_i)$ denotes the estimate of $P(Y_i = 1 \mid A_i, W_i)$. We can choose the prior distribution of ϵ as the distribution of $g(X)$ with $X \sim \Pi$, where Π is the prior distribution on ψ_0 specified initially and g denotes the inverse of $\epsilon \to f(Q_n)(\epsilon)$, which is easy to work out in each application.

Targeted posterior density of ϵ: Denote the derivative of $f(Q_n)$ at ϵ with $\sigma^2(\epsilon)$ so that the Jacobian is given by $J(\epsilon) = \sigma^2(\epsilon)$. In particular we can work this out with the logistic regression fluctuation function. The univariate posterior density of ϵ, given $O_1, \ldots, O_n$, is thus given by

$$\propto \pi(\epsilon \mid O_1, \ldots, O_n) = \prod_{i=1}^{n} Q_n(\epsilon)(Y_i \mid A_i, W_i)\pi(f(Q_n(\epsilon))\sigma^2(\epsilon), \qquad (55)$$

where we recall that π is the density of the prior distribution on ψ_0.

Targeted posterior density of causal effect on survival: The posterior density of ϵ implies the posterior distribution of $f(Q_n(\epsilon)) = \Psi(Q_n(\epsilon))$, i.e. the causal effect of treatment on survival function at t_0. In this example, one can even pursue analytic calculation of this posterior density of the survival function difference since it only involves univariate density calculations. The Monte Carlo simulation approach would be to sample $E_1, \ldots, E_B$ from the posterior density $\pi(\cdot \mid O_1, \ldots, O_n)$ specified in (55), and evaluate the corresponding $\Psi(Q_n(E_b))$, $b = 1, \ldots, B$, which gives us a random sample from the posterior distribution of the survival function differences at t_0, given the observed data $O_1, \ldots, O_n$.

Properties of targeted posterior distribution of causal effect of treatment on survival function, and comparison with standard Bayesian learning: A standard Bayesian approach would involve specifying a parametric model, specifying a prior distribution on all the parameters of this parametric model, calculating the corresponding posterior distribution involving sampling from a high dimensional multivariate density (since there are many parameters), and model selection (e.g.) based on the posterior density so that these calculations will have to be carried out for lots of candidate parametric models. In spite of the computational challenges and effort of this standard Bayesian approach, the resulting estimator of the causal effect of treatment on survival function will typically be too biased due to model miss-specification. Model selection using a likelihood or Bayesian criteria would generally not reduce the bias at the wished rate of $o(1/\sqrt{n})$, since the selection is in essence based on a bias variance trade off for the purpose of estimating the whole density. The same criticism would apply to a sieve based (frequentist) maximum likelihood estimator using (say) likelihood based cross-validation to select models or other fine tuning parameters. The problem of both the Bayesian and maximum likelihood estimation methodology is that the estimation and model selection are not targeted towards the *smooth* parameter being the causal effect of treatment on survival probability, so that the resulting estimation procedure involves the wrong bias variance trade off.

On the other hand, the targeted empirical posterior Bayesian distribution of the causal effect on survival is centered at the locally efficient iterative targeted MLE $\Psi(Q_n)$, and the spread of the posterior distribution is asymptotically completely driven by the variance of this efficient influence curve under Q_n at g_{Q_n}, where g_i/g_{Q_n} converges to 1 for i large. In addition, the calculations for establishing this targeted posterior distribution only involve sampling from a univariate posterior density and is therefore easy and fast from a computational point of view.

24.2 Discussion regarding targeted empirical Bayesian learning in adaptive designs.

The proposed targeted empirical Bayesian learning allows us to use 1) the frequentist framework and its corresponding targeted maximum likelihood estimators for sequential adaptive designs with good and well understood frequentist properties, as needed for hypothesis testing and inference in general, while 2) augmenting this framework with a simple straightforward calculation of a posterior distribution for the scientific parameter of interest given a prior

distribution on the scientific parameter of interest. In addition, one can use the targeted empirical posterior distribution based on $O_1, \ldots, O_{i-1}$ to adapt the design g_i for experiment i, $i = 1, \ldots, n$. This is particularly important in cases in which prior studies provide important evidence about the scientific parameter, which now can be incorporated to get more precise estimates for small sample sizes, in particular, allowing for more reliable adaptations early on in the design.

25 Sequential testing in an adaptive design

In this section we show that sequential testing, as exists in the current literature on group sequential testing in fixed designs (i.e., g_i are fixed a priori specified elements in $\mathcal{G}$, $i = 1, \ldots, n$), can be generalized to our general definition of adaptive designs for which the central limit theorems as presented in this article apply. Specifically, analogue to the current literature on sequential testing in (fixed) group sequential designs, we propose a class of sequential testing procedures based on a fixed number K of sequential testing times which control the Type-I error at level alpha as n converges to infinity for general adaptive designs. We will distinguish between the case in which the K subsequent sample sizes (i.e., times) at which one tests the null hypothesis are given a priori and thus non-random, and the case in which the k-th sample size at which one tests the null hypothesis is set in response to the data collected as was available at the $k-1$-th testing sample size, $k = 1. \ldots, K$. We will refer to these two scenarios as "Sequential Testing at Fixed Sample Sizes" and "Sequential Testing at Random Sample Sizes".

25.1 Sequential testing at fixed sample sizes.

Consider a univariate test statistic $T(n)$ based on $O_1, \ldots, O_n$ for testing the null hypothesis $H_0 : \psi_0 = 0$ for a univariate parameter ψ_0. Suppose that one tests the null hypothesis at sample sizes $n_1 = p_1 n, \ldots, n_k = p_k n$ based on $T(n_1), \ldots, T(n_k)$, respectively, where $0 < p_1 < \ldots < p_k \leq 1$ are fixed a priori set proportions. We wish to use a sequential testing procedure based on the sequential test "if $T(n_j) > c_j$, then reject H_0", $j = 1, \ldots, k$, (thus, it stops at the first j for which $T(n_j) > c_j$), with the cut-offs c_j chosen so that the probability of falsely rejecting H_0 in this sequential testing procedure is smaller or equal than α. We note that the probability of falsely rejecting H_0 can be decomposed as:

$$P(\text{Reject } H_0) = P(T(n_1) > c_1) + P(T(n_2) > c_2, T(n_1) < c_1)$$

$$
\begin{aligned}
&+ \ldots + P(T(n_k) > c_k, T(n_l) < c_l, l = 1 \ldots, k-1) \\
= &\sum_{j=1}^{k} P(T(n_j) > c_j, T(n_l) < c_l, l = 1, \ldots, j-1).
\end{aligned}
$$

Consider now a vector $(\alpha_1, \ldots, \alpha_k)$ of positive numbers so that $\sum_{j=1}^{k} \alpha_j = \alpha$. Each such a vector of α_j-values defines now a sequential testing procedure controlling the Type-I error at level α, by sequentially setting c_j so that

$$
P(T(n_j) > c_j, T(n_l) < c_l, l = 1, \ldots, j-1) = \alpha_j, \ j = 1, \ldots, k.
$$

Such a sequential testing procedure requires knowing the marginal distribution of $T(n_1)$ at the first test, the bivariate distribution of $(T(n_1), T(n_2))$ at the second test, and, in general, it requires knowing the joint distribution of $(T(n_1), \ldots, T(n_j))$ at the j-th test, $j = 1, \ldots, k$. A variety of such sequential testing procedures have been proposed in the literature based on such a specification of α_j-values. For example, a simple choice is to set the cut-offs c_j and α^* so that $\alpha^* = P(T(n_1) > c_1)$, $P(T(n_2) > c_2 \mid T(n_1) < c_1) = \alpha^*$, ..., $P(T(n_k) > c_k \mid T(n_j) \leq c_j, j = 1, \ldots, k-1) = \alpha^*$, and

$$
\sum_{j=1}^{k} \alpha_j = \alpha, \text{ where } \alpha_j = (1 - \textstyle\sum_{l=1}^{j-1} \alpha_l)\alpha^*.
$$

Other popular choices can be found in the literature.

To conclude, the only requirement for an asymptotically valid class of sequential testing procedure is that we can establish the k-variate normal limit distribution of $(T(n_1), \ldots, T(n_k))$ as $n \to \infty$. For that purpose, we assume that the test statistic $T(n)$ is such that, if $H_0 : \psi_0 = 0$ is true, then

$$
T(n) = \frac{1}{\sqrt{n}} \sum_{i=1}^{n} D(O_i, Z_i)/\sigma_n + o_p(1),
$$

where Z_i is a function of $O_1, \ldots, O_{i-1}$, $\sum_i D(O_i, Z_i)$ is a univariate discrete martingale and σ_n^2 is a consistent estimator of the variance of $1/\sqrt{n} \sum_i D(O_i, Z_i)$ (under H_0): e.g., $\sigma_n^2 = \frac{1}{n} \sum_{i=1}^{n} D(O_i, Z_i)^2$). Specifically, if $\psi_0 = 0$, then $E(D(O_i, Z_i) \mid O_1, \ldots, O_{i-1}) = 0$, $i = 1, \ldots, n$. This linear approximation of the test-statistic can be established by applying our general central limit Theorems 7 and 8 under the assumption that the null hypothesis $H_0 : \psi_0 = 0$ is true. That gives that ψ_n is a Martingale asymptotically linear estimator of ψ_0 so that the corresponding "t-statistic" $T(n) = \sqrt{n}\psi_n/\sigma_n$ is approximately a discrete univariate martingale: $T(n) = \frac{1}{\sqrt{n}} \sum_{i=1}^{n} D(O_i, Z_i)/\sigma_n + o_P(1)$ for some D specified in our theorems.

By the multivariate martingale central limit Theorem 17 it follows that, if H_0 is true, then $(T(n_1), \ldots, T(n_k))$ is multivariate normal with mean zero and a certain covariance matrix. Since $T(n_j)$ converges to a marginal normal distribution with mean zero and variance 1 it follows that the diagonal elements of the covariance matrix are all equal to 1. In addition, the covariance elements of the covariance matrix follow from the fact that for $l < m$, we have

$$\begin{aligned} E(T(n_l)T(n_m)) &= \frac{1}{\sigma_{n_l}\sigma_{n_m}\sqrt{n_l}\sqrt{n_m}} \sum_{i=1}^{n_l} ED(O_i, Z_i)^2 \\ &\approx \frac{1}{\sigma_{n_l}\sigma_{n_m}\sqrt{n_l}\sqrt{n_m}} n_l\sigma^2 \\ &\approx \sqrt{n_l/n_m} = \sqrt{p_l}/\sqrt{p_m}. \end{aligned}$$

So, $(T(n_1), \ldots, T(n_k))$ converges to a multivariate normal distribution with mean vector 0 and covariance matrix Σ with $\Sigma(j,j) = 1$ and $\Sigma(l,m) = \sqrt{p_l/p_m}$.

We will state this result as a theorem.

Theorem 11 *(***Sequential testing at fixed sample sizes***) Consider the sequence in n of data generating mechanisms for $(O_1, \ldots, O_n) \sim P_{Q_0,\mathbf{g}}$ in an adaptive design defined by $\mathbf{g} = (g_1, \ldots, g_n)$, where the density $p_{Q_0,\mathbf{g}_n}$ is defined in (3). Consider a corresponding sequence of test statistics $T(n)$ based on $O_1, \ldots, O_n$ for testing the null hypothesis $H_0 : \psi_0 = \Psi(Q_0) = 0$ for a univariate parameter ψ_0. Suppose that one tests the null hypothesis at sample sizes $n_1 = p_1 n, \ldots, n_k = p_k n$ based on $T(n_1), \ldots, T(n_k)$, respectively, where $0 < p_1 < \ldots < p_k \leq 1$ are fixed a priori set proportions. Assume that the test statistic $T(n)$ is such that, if $H_0 : \psi_0 = 0$ is true, then*

$$T(n) = \frac{1}{\sqrt{n}} \sum_{i=1}^{n} D(O_i, Z_i)/\sigma_n + o_p(1),$$

where $\sum_i D(O_i, Z_i)$ is a univariate discrete martingale and σ_n^2 (e.g., $\sigma_n^2 = \frac{1}{n}\sum_{i=1}^n D(O_i, Z_i)^2$)) is a consistent estimator of the variance of $1/\sqrt{n}\sum_i D(O_i, Z_i)$ as $n \to \infty$ (under H_0). Specifically, if $\psi_0 = 0$, then $E(D(O_i, Z_i) \mid O_1, \ldots, O_{i-1}) = 0$, $i = 1, \ldots, n$. This martingale linear approximation of the test-statistic can be established by applying our general central limit Theorems 7 and 8 under the assumption that the null hypothesis $H_0 : \psi_0 = 0$ is true: thus the conditions of these theorems provide sufficient conditions.

Then, $(T(n_1), \ldots, T(n_k))$ converges to a multivariate normal distribution with mean vector 0 and covariance matrix Σ with $\Sigma(j,j) = 1$ and $\Sigma(l,m) = \sqrt{p_l/p_m}$.

Consider now a vector $(\alpha_1, \ldots, \alpha_k)$ *of positive numbers so that* $\sum_{j=1}^k \alpha_j = \alpha$. *Each such a vector of* α_j*-values defines now a sequential testing procedure asymptotically controlling the Type-I error at level* α, *by sequentially setting* c_j *so that*

$$P(Z_j > c_j, Z_l > c_l, l = 1, \ldots, j-1) = \alpha_j, \ j = 1, \ldots, k,$$

where $Z \sim N(0, \Sigma)$, *and using the sequential testing procedure "if* $T(n_j) > c_j$ *reject* H_0, $j = 1, \ldots, k$".

The above result can be easily generalized to the case that at n_j a j-specific test statistic $T_j(n_j)$ is used. For example, if the data $O_1, \ldots, O_{n_j}$ is right-censored by a fixed censoring variable E_j (i.e., the time at which the n_j-th experiment is carried out or finalized). This generalization is obtained by assuming that the j-th test statistic $T_j(n_j)$ is such that, if $H_0 : \psi_0 = 0$ is true, then

$$T_j(n_j) = \frac{1}{\sqrt{n}} \sum_{i=1}^{n} D_j(O_i, Z_i)/\sigma_{jn} + o_p(1),$$

where $\sum_i D_j(O_i, Z_i)$ is a univariate discrete martingale and σ_{nj}^2 (e.g., $\sigma_{nj}^2 = \frac{1}{n}\sum_{i=1}^n D_j(O_i, Z_i)^2$)) is a consistent estimator of the variance of $1/\sqrt{n}\sum_i D_j(O_i, Z_i)$ as $n \to \infty$ (under H_0), $j = 1, \ldots, k$. Again, the derivation of the influence curves D_j would be implied by our general asymptotic linearity Theorems 7 and 8 for an estimator ψ_{jn_j} of ψ_0 based on (e.g., the right-censored by E_j versions) of $O_1, \ldots, O_{n_j}$.

25.2 Sequential testing at random sample sizes.

Consider a univariate test statistic $T(n)$ being a specified function of $O_1, \ldots, O_n$, such as a standardized t-statistic $T(n) = \sqrt{n}\psi_n/\sigma_n$ based on an estimator ψ_n of a univariate parameter ψ_0, for testing the null hypothesis $H_0 : \psi_0 = 0$. Suppose that one wishes to test the null hypothesis at k random sample sizes $0 < N_1, \ldots, N_k \leq n$ between 0 and n. It is assumed that 1) $N_j = n_j(\bar{\mathbf{O}}(N_{j-1}), n)$ is a deterministic function of the data $O_1, \ldots, O_{N(j-1)}$ available at the previous testing sample size $N(j-1)$ and n, $j = 1, \ldots, k$, and 2) $N_1 = n_1$ is non-random. In addition, these deterministic functions are such that with probability 1 $N_j > N_{j-1}$ for $j = 2, \ldots, k$, and $\limsup_{n\to\infty} N_1/n > 0$: i.e., the random sample sizes N_j converge to infinity at the same rate as n converges to infinity.

We wish to use a sequential testing procedure based on the sequential test "if $T(N_j) > c_j$, then reject H_0", $j = 1, \ldots, k$, (thus, it stops at the first j

for which $T(N_j) > c_j$ or it stops at N_k), with the cut-offs c_j chosen so that the probability of falsely rejecting H_0 in this sequential testing procedure is smaller or equal than α. We note that the probability of falsely rejecting H_0 can be decomposed as:

$$\begin{aligned} P(\text{Reject } H_0) &= P(T(N_1) > c_1) + P(T(N_2) > c_2, T(N_1) < c_1) \\ &\quad + \ldots + P(T(N_k) > c_k, T(N_l) < c_l, l = 1 \ldots, k-1) \\ &= \sum_{j=1}^{k} P(T(N_j) > c_j, T(N_l) < c_l, l = 1, \ldots, j-1). \end{aligned}$$

Consider now a vector $(\alpha_1, \ldots, \alpha_k)$ of positive numbers so that $\sum_{j=1}^{k} \alpha_j = \alpha$. Each such a vector of α_j-values defines now a sequential testing procedure controlling the Type-I error at level α, by sequentially setting c_j so that

$$P(T(N_j) > c_j, T(N_l) < c_l, l = 1, \ldots, j-1) = \alpha_j, \ j = 1, \ldots, k.$$

Such a sequential testing procedure requires knowing the marginal distribution of $T(N_1)$ at the first test, the bivariate distribution of $(T(N_1), T(N_2))$ at the second test, and, in general, it requires knowing the joint distribution of $(T(N_1), \ldots, T(N_j))$ at the j-th test, $j = 1, \ldots, k$. A variety of such sequential testing procedures have been proposed in the literature based on such a specification of α_j-values. For example, a simple choice is to set the cut-offs c_j and α^* so that $\alpha^* = P(T(N_1) > c_1)$, $P(T(N_2) > c_2 \mid T(N_1) < c_1) = \alpha^*$, ..., $P(T(N_k) > c_k \mid T(N_j) \leq c_j, j = 1, \ldots, k-1) = \alpha^*$, and

$$\sum_{j=1}^{k} \alpha_j = \alpha, \text{ where } \alpha_j = (1 - \textstyle\sum_{l=1}^{j-1} \alpha_l)\alpha^*.$$

To conclude, the requirement for an asymptotically valid class of sequential testing procedure is that we can establish the k-variate limit distribution of $(T(N_1), \ldots, T(N_k))$ as $n \to \infty$.

Assume that the test statistic $T(n)$ is such that, if $H_0 : \psi_0 = 0$ is true, then $T(n) = Z(n) + R(n)$, with $R(n) = o_P(1)$, where

$$Z(n) = \frac{\frac{1}{\sqrt{n}} \sum_{i=1}^{n} D(O_i, Z_i)}{\sqrt{\frac{1}{n} \sum_{i=1}^{n} D(O_i, Z_i)^2}},$$

and $E(D(O_i, Z_i) \mid O_1, \ldots, O_{i-1}) = 0$, $i = 1, \ldots, n$, so that $\sum_i D(O_i, Z_i)$ is a univariate discrete martingale.

This linear approximation of the test-statistic can be established by applying our general central limit Theorems 7 and 8 under the assumption

that the null hypothesis $H_0 : \psi_0 = 0$ is true. That yields that ψ_n is an asymptotically linear estimator of ψ_0 so that the corresponding "t-statistic" $T(n) = \sqrt{n}\psi_n/\sigma_n$ is approximately a discrete univariate martingale: $T(n) = \frac{1}{\sqrt{n}} \sum_{i=1}^{n} D(O_i, Z_i)/\sigma_n + R(n)$ with $R(n) = o_P(1)$, and for some D specified in our theorems.

We now note that

$$T(N_j) = \frac{1}{\sqrt{N_j}} \sum_{i=1}^{N_j} D(O_i, Z_i)/\sigma_{N_j} + R(N_j).$$

We have $\delta n < N_j < n$ with probability 1. Thus $\lim_{n\to\infty} \mid R(n) \mid = 0$ a.s. implies $\lim_{n\to\infty} \mid R(N_j) \mid = 0$ a.s. As a consequence of the almost sure representation theorem applied to $R(n) = o_P(1)$, this implies now that, if H_0 is true, then $R(N_j) = o_P(1)$. This proves that, if $\psi_0 = 0$, then $(T(N_1), \ldots, T(N_k)) = (Z(N_1), \ldots, Z(N_k)) + o_P(1)$.

It remains to establish and characterize the multivariate normal distribution of $(Z(N_1), \ldots, Z(N_k))$. We define

$$M_j(n) = \sum_{i=1}^{n} I(i \leq N_j) D(O_i, Z_i) \; j = 1, \ldots, k.$$

We note that the weak convergence of the random vector $(M_j(n) : j)$ implies the wished weak convergence of $(Z(N_j) : j)$. Given $O_1, \ldots, O_{i-1}$, for each j, the indicator $I(i \leq N_j)$ is known. Therefore,

$$E(I(i \leq N_j) D(O_i, Z_i) \mid O_1, \ldots, O_{i-1}) = I(i \leq N_j) E(D(O_i, Z_i) \mid O_1, \ldots, O_{i-1}) = 0.$$

This shows that $M_j(n)$ is a discrete univariate martingale. Let $D_j(O_i, Z_i) \equiv I(i \leq N_j) D(O_i, Z_i)$ so that $M_j(n) = \sum_{i=1}^{n} D_j(O_i, Z_i)$. Define $M(n) = (M_1(n), \ldots, M_k(n)) = \sum_{i=1}^{n} \vec{D}(O_i, Z_i)$ as the multivariate martingale with j-th component $M_j(n)$, $j = 1, \ldots, k$.

Let $\Sigma(n)^2 = E \frac{1}{n} \sum_{i=1}^{n} \vec{D}^2(O_i, Z_i)$. Application of the multivariate martingale Theorem 17 shows that, if $\| \vec{D} \|_\infty < \infty$, $\liminf \lambda \Sigma(n)^2 \lambda > 0$ for all λ (or that $\Sigma^2 = \lim_{n\to\infty} \Sigma(n)^2$ exists and is a positive definite covariance matrix), and that component wise

$$\frac{1}{n} \sum_{i=1}^{n} P_{Q_0, g_i} \vec{D}^2 - E \frac{1}{n} \sum_{i=1}^{n} P_{Q_0, g_i} \vec{D}^2 \to 0 \tag{56}$$

in probability as $n \to \infty$, then

$$\sqrt{n} \Sigma(n)^{-1} M_n \Rightarrow_D N(0, I), \text{ as } n \to \infty,$$

and, if $\Sigma^2(n) \to \Sigma^2$ for some positive definite covariance matrix Σ^2, then

$$\sqrt{n}M_n \Rightarrow_D N(0, \Sigma^2), \text{ as } n \to \infty.$$

In addition, application of Theorem 18 teaches us that, under these same conditions, we have that

$$\frac{1}{n}\sum_{i=1}^{n} \vec{D}(O_i, Z_i)^2 - \Sigma(n)^2 \to 0 \text{ in probability, as } n \to \infty,$$

and, if $\Sigma^2(n) \to \Sigma^2$, as $n \to \infty$, for a positive definite matrix Σ^2, then this also implies $\frac{1}{n}\sum_{i=1}^{n} \vec{D}(O_i, Z_i)^2 \to \Sigma^2$ in probability, as $n \to \infty$.

We note that the only substantial condition is the asymptotic stability condition for the adaptive design g_i defined by (56), as we assume in each of our central limit theorems. That is, this condition is not adding any additional restrictions as required for the analysis of the MLE or solutions of estimating equations.

Thus, the covariance element $\Sigma(n)^2(l, m)$, $l \leq m$, of the multivariate martingale $M(n)$ can be consistently estimated with

$$\widehat{\Sigma(n)}^2(l, m) = \frac{1}{n}\sum_{i=1}^{N_l} D(O_i, Z_i)^2,$$

and the corresponding correlations $\Sigma(n)^{*2}(l, m)$ are consistently estimated as:

$$\begin{aligned}
\widehat{\Sigma(n)}^{*2}(l, m) &= \frac{\sum_{i=1}^{N_l} D(O_i, Z_i)^2}{\sqrt{\sum_{i=1}^{N_l} D^2(O_i, Z_i)}\sqrt{\sum_{i=1}^{N_m} D^2(O_i, Z_i)}} \\
&= \sqrt{N_l/N_m}\sqrt{\frac{\sum_{i=1}^{N_l} D_i^2/N_l}{\sum_{i=1}^{N_m} D_i^2/N_m}} \\
&\approx \sqrt{N_l/N_m}.
\end{aligned}$$

We conclude that $(Z(N_1), \ldots, Z(N_k))$ approximates in distribution $N(0, \Sigma^{*2}(n))$ as $n \to \infty$, where $\Sigma^{*2}(n)$ is the correlation matrix corresponding with $\Sigma^2(n)$, and the (l, m)-off diagonal elements of $\Sigma^{*2}(n)$ can be consistently estimated with $\sqrt{N_l/N_m}$. As a consequence, $(T(N_1), \ldots, T(N_k))$ approximates in distribution $N(0, \Sigma^{*2}(n))$ as $n \to \infty$.

We will state this result as a theorem.

Theorem 12 *(**Sequential testing at random sample sizes**) Consider the sequence in n of data generating mechanisms for $(O_1, \ldots, O_n) \sim P_{Q_0,\mathbf{g}}$ in an*

adaptive design defined by $\mathbf{g} = (g_1, \ldots, g_n)$*, where the density* $p_{Q_0,\mathbf{g}_n}$ *is defined in (3).*

Consider a corresponding sequence of test statistics $T(n)$ *based on* $O_1, \ldots, O_n$ *for testing the null hypothesis* $H_0 : \psi_0 = \Psi(Q_0) = 0$ *for a univariate parameter* ψ_0*. Suppose that one wishes to test the null hypothesis at* k *random sample sizes* $0 < N_1, \ldots, < N_k \leq n$ *between* 0 *and* n*. It is assumed that* $N_j = n_j(\bar{\mathbf{O}}(N_{j-1}), n)$ *is a deterministic function of* $O_1, \ldots, O_{N(j-1)}$ *and* n*,* $j = 1, \ldots, k$*, and* $N_1 = n_1$ *is non-random. In addition, these deterministic functions are such that with probability 1,* $N_j > N_{j-1}$ *for* $j = 2, \ldots, k$*, and* $\limsup_{n\to\infty} N_1/n > 0$*: i.e., the random sample sizes* N_j *converge to infinity at the same rate as* n *converges to infinity.*

Assume that the test statistic $T(n)$ *is such that, if* $H_0 : \psi_0 = 0$ *is true, then* $T(n) = Z(n) + o_P(1)$*, where*

$$Z(n) = \frac{\frac{1}{\sqrt{n}} \sum_{i=1}^n D(O_i, Z_i)}{\sqrt{\frac{1}{n} \sum_{i=1}^n D(O_i, Z_i)^2}},$$

and $E(D(O_i, Z_i) \mid O_1, \ldots, O_{i-1}) = 0$*,* $i = 1, \ldots, n$*, so that* $\sum_i D(O_i, Z_i)$ *is a univariate discrete martingale. Define* $D_j(O_i, Z_i) \equiv I(i \leq N_j) D(O_i, Z_i)$*,* $\vec{D} \equiv (D_1, \ldots, D_k)$*, and the covariance matrix* $\Sigma(n)^2 = E \frac{1}{n} \sum_{i=1}^n \vec{D}^2(O_i, Z_i)$*. Assume* $\| \vec{D} \|_\infty < \infty$*,* $\liminf \lambda \Sigma(n)^2 \lambda > 0$ *for all* λ *(or that* $\Sigma^2 = \lim_{n\to\infty} \Sigma(n)^2$ *exists and is a positive definite covariance matrix), and that component wise*

$$\frac{1}{n} \sum_{i=1}^n P_{Q_0,g_i} \vec{D}^2 - E \frac{1}{n} \sum_{i=1}^n P_{Q_0,g_i} \vec{D}^2 \to 0 \tag{57}$$

in probability as $n \to \infty$*.*

We have, if $\psi_0 = 0$*, then* $(T(N_1), \ldots, T(N_k))$ *approximates a multivariate normal distribution* $N(0, \Sigma^{*2}(n))$ *as* $n \to \infty$*, where* $\Sigma^{2*}(n)$ *is the correlation matrix of* $\Sigma^2(n)$*.*

We also have that

$$\frac{1}{n} \sum_{i=1}^n \vec{D}(O_i, Z_i)^2 - \Sigma(n)^2 \to 0 \text{ in probability, as } n \to \infty,$$

and, if $\Sigma^2(n) \to \Sigma^2$*, as* $n \to \infty$*, for a positive definite matrix* Σ^2*, then this also implies* $\frac{1}{n} \sum_{i=1}^n \vec{D}(O_i, Z_i)^2 \to \Sigma^2$ *in probability, as* $n \to \infty$*.*

Thus, the covariance elements $\Sigma(n)^2(l, m)$*,* $l \leq m$*, can be consistently estimated with*

$$\widehat{\Sigma(n)}^2(l, m) = \frac{1}{n} \sum_{i=1}^{N_l} D(O_i, Z_i)^2,$$

and the corresponding correlations $\Sigma(n)^{*2}(l,m)$ *are consistently estimated as:*

$$\begin{aligned}\widehat{\Sigma(n)}^{*2}(l,m) &= \frac{\sum_{i=1}^{N_l} D(O_i,Z_i)^2}{\sqrt{\sum_{i=1}^{N_l} D^2(O_i,Z_i)}\sqrt{\sum_{i=1}^{N_m} D^2(O_i,Z_i)}} \\ &= \sqrt{N_l/N_m}\sqrt{\frac{\sum_{i=1}^{N_l} D_i^2/N_l}{\sum_{i=1}^{N_m} D_i^2/N_m}} \\ &\approx \sqrt{N_l/N_m}.\end{aligned}$$

Consider now a vector $(\alpha_1,\ldots,\alpha_k)$ *of positive numbers so that* $\sum_{j=1}^k \alpha_j = \alpha$. *Each such a vector of* α_j*-values defines now a sequential testing procedure asymptotically controlling the Type-I error at level* α, *by sequentially setting* c_j *so that*

$$P(Z_j > c_j, Z_l > c_l, l = 1,\ldots,j-1) = \alpha_j,\ \ j = 1,\ldots,k,$$

where $Z \sim N(0,\Sigma^{*2}(n))$, *and carrying out the sequential testing procedure "Reject* H_0 *if* $T(N(j)) > c_j$, $j = 1,\ldots,k$*".*

26 Generalization to adaptive designs with uncontrolled (unknown) components.

In the methods presented so far it was assumed that the design mechanism g_i for experiment i, i.e., the conditional distribution of the design settings A_i for experiment i, given X_i and $O_1,\ldots,O_{i-1}$, is known, $i = 1,\ldots,n$. In many applications certain components of the mechanism g_i are known (e.g., treatment assignment) but other components (e.g., right censoring mechanism) are not fully controlled by the design and thus unknown. We will assume that the unknown controlled components of the mechanism g_i can be correctly modelled and thereby estimated with maximum likelihood estimation methodology. For example, it might be known that the right-censoring for experiment i is independent of the previous experiments, but depends on some covariates collected in experiment i, and we might assume a logistic regression type of model.

Therefore, it is important to present the extension of our methodology for unknown but modelled adaptive designs. Consider a model $\{g_{\eta,Z_i} : \eta\} \subset \mathcal{G}$ so that

$$g_i(A_i \mid X_i) = g_{\eta_0,Z_i}(A_i \mid X_i)$$

for an unknown parameter η_0. For example, consider the case that A_i has two components (A_{1i}, A_{2i}), where A_{1i} represents treatment assignment, and

A_{2i} represents a missing indicator (e.g., of the outcome), and we factorize the design mechanism for experiment i as follows

$$g_i(A_i \mid X_i) = g_{i1}(A_{1i} \mid X_i) g_{i2}(A_{2i} \mid A_{1i}, X_i).$$

Suppose now that the treatment mechanism g_{1i} is fully controlled by the experimenter so that g_{1i} is a known conditional distribution of A_{1i}, given $\bar{\mathbf{O}}(i-1), X_i$, but that g_{i2} is a missingness mechanism ruled by actions of the subject under study not controlled by the experimenter (such as dropping out of the study). With respect to modelling of this uncontrolled missingness mechanism, suppose that there is no reason that the missingness for subject i is related to the data collected in the previous $i-1$ experiments, in which case we can assume $g_{i2}(A_{2i} \mid A_{1i}, X_i) = g_2(A_{2i} \mid A_{1i}, X_i)$ is a fixed design. One might now propose a model for this missingness mechanism: $g_2 = g_{2\eta_0}$ for some parametric model $\{g_{2\eta} : \eta\}$. This implies now a model for g_i given by: $g_i = g_{i1} g_{2\eta_0}$, where g_{i1} is a known adaptive treatment mechanism (i.e., it responds to $\bar{\mathbf{O}}(i-1)$ in a specified manner), and $g_{2\eta_0}$ is a missingness mechanism indexed by an unknown parameter η_0. One could also imagine situations in which one expects that the missingness in experiment i might be influenced on data from experiments $1, \ldots, i-1$, and that one would model this dependence, in which case g_{2i} is a *adaptive* missingness mechanism indexed by an unknown parameter η_0.

The likelihood for η_0 is given by

$$\eta \to \prod_{i=1}^{n} g_{\eta, Z_i}(A_i \mid X_i)$$

so that the maximum likelihood estimator of the unknown parameters in the adaptive design is given by

$$\eta_n = \arg\max_{\eta} \prod_{i=1}^{n} g_{\eta, Z_i}(A_i \mid X_i),$$

but regularized MLE of η_0 (e.g., using likelihood based cross-validation) can be considered as well. In our example above in which g_{1i} is known and g_{2i} is an unknown fixed design, this likelihood factors in two likelihoods with only one depending on unknown parameter η, so that we have

$$\eta_n = \arg\max_{\eta} \prod_{i=1}^{n} g_{2\eta}(A_{2i} \mid A_{1i}, X_i).$$

The score equation for η_n is thus given by

$$0 = \sum_{i=1}^{n} S(\eta_n)(O_i, Z_i),$$

where

$$S(\eta)(O_i, Z_i) = \frac{d}{d\eta} \log g_{\eta, Z_i}(A_i \mid X_i).$$

Again, in our example above, we would have that

$$S(\eta)(O_i) = \frac{d}{d\eta} \log g_{2\eta}(A_{2i} \mid A_{1i}, X_i)$$

is only a function of O_i.

We have

$$\begin{aligned} P_{Q_0, g_{\eta_0}, Z_i} \frac{\frac{d}{d\eta} g_{\eta, Z_i}(A_i \mid X_i)\Big|_{\eta=\eta_0}}{g_{\eta_0, Z_i}(A_i \mid X_i)} &= \frac{d}{d\eta} P_{Q_0, g_{\eta, Z_i}} 1 \Big|_{\eta=\eta_0} \\ &= 0, \end{aligned}$$

where $P_{Q_0, g_{\eta_0, Z_i}}$ denotes the conditional expectation operator, given $O_1, \ldots, O_{i-1}$, which shows that $S(\eta)$ is a Martingale estimating function: $P_{Q_0, g_{\eta_0, Z_i}} S(\eta_0) = 0$ for all $i = 1, \ldots$.

Targeted adaptive designs in the presence of unknown components: Let's now discuss how to construct targeted adaptive designs, since this will require a slight generalization of our previously described methods for constructing targeted adaptive designs. The construction of a targeted adaptive design involves first defining an optimal fixed design for the controlled components of the adaptive design, which one aims to learn during the trial. This optimal fixed design for the controlled components will depend on the Q_0-factor of the likelihood, but it can also easily depend on the unknown components of the design. As a consequence, the design function used to construct an adaptive design for the controlled components will be a function of both Q_0 and the unknown parameters η_0.

To be specific, consider the example above. In this example, one only aims to adapt the treatment mechanism g_{1i}. A fixed design data generating distribution $P_{Q_0, g_1, g_{2\eta_0}}$ is now indexed by a choice of treatment mechanism g_1 and the unknown missingness mechanism $g_{2\eta_0}$. One might now define an optimal fixed design for g_1 by minimizing a criteria $R(P_{Q_0, g_1, g_{2\eta_0}})$ (e.g., the variance of the efficient influence curve under fixed design data generating distribution $P_{Q_0, g_1, g_{2\eta_0}}$ for the causal effect of interest) over a set of fixed designs $\mathcal{G}_1$ for the treatment mechanism:

$$g_{1\eta_0 Q_0} \equiv \arg \min_{g_1 \in \mathcal{G}_1} R(P_{Q_0, g_1, g_{2\eta_0}}).$$

We note that this optimal fixed design for the treatment mechanism is now indexed by both Q_0 and the unknown parameter η_0 of the missingness mechanism. This design function $(Q_0, \eta_0) \rightarrow g_{1Q_0\eta_0}$ defines now an adaptive design $g_{1i} = g_{1\eta_{i-1}Q_{i-1}}$ for the treatment mechanism by replacing Q_0 and η_0 by their estimators based on the data $O_1, \ldots, O_{i-1}$ collected on the previous $i-1$ experiments. This corresponds with an adaptive design

$$g_i = g_{\eta_0\eta_{i-1}Q_{i-1}} = g_{1\eta_{i-1}Q_{i-1}}g_{2\eta_0}$$

indexed by an unknown η_0 required to specify the missingness mechanism g_2. Therefore, in general, our design functions used to define a targeted adaptive design for the whole g_i will now be indexed by an unknown η_0, and they represent a mapping from both Q_0 and some or all of the unknown parameters η_0:

$$(\eta, Q) \rightarrow g_{\eta_0,\eta,Q}.$$

Generalizing the targeted MLE: We wish to also generalize the targeted MLE of a parameter $\Psi(Q_0)$ as presented in Sections 12 and 13 to the case that the adaptive design $g_{\eta_0 i}$ is unknown and thereby estimated. Firstly, we recall that the targeted MLE $\psi_n = \Psi(Q_{\theta_n}(\epsilon_n))$ for known adaptive designs required solving a Martingale estimating equation $0 = \sum_i D(\theta_n, g_{Z_i})(O_i)$ in θ_n and, given θ_n, solving $0 = \sum_i D(\epsilon_n, \theta_n, g_{Z_i})(O_i)$ in ϵ_n, where we previously suppressed in the notation the dependence of the estimating functions on the adaptive design g_{Z_i} since it was known. We now replace these two estimating equations by three Martingale estimating equations 1) solving $0 = \sum_i S(\eta_n)(O_i, Z_i) = 0$ in η_n, 2) given η_n, solving $0 = \sum_i D(\theta_n, g_{\eta_n,Z_i})(O_i) = 0$ in θ_n, and, 3) given η_n, θ_n, solving $0 = \sum_i D(\epsilon_n, \theta_n, g_{\eta_n,Z_i})(O_i)$ in ϵ_n. These three estimating functions stacked on top of each other correspond with a single Martingale estimating function $D(\eta, \theta, \epsilon)$ satisfying $P_{Q_0,g_{\eta_0,Z_i}}D(\eta_0, \theta_0, \epsilon_0) = 0$ for all i, while the estimators solve $\sum_i D(\eta_n, \theta_n, \epsilon_n)(O_i, Z_i) = 0$. As a consequence, we can apply our Theorem 7 for estimators defined as solutions of Martingale estimating equations, including the targeted MLE's.

The resulting consistency and asymptotic linearity of the estimator $\psi_n = \Psi(Q_{\theta_n,\eta_n}(\epsilon_n))$ (in which the path $Q_\theta(\epsilon)$ in ϵ is now also indexed by η_0, as specified below!) will rely on correct specification of the model $g_i = g_{\eta_0,Z_i}$, $i = 1, \ldots$, but, given this assumption, similar conclusions are achieved, with the modification taking place in the limit covariance matrix of the normal limit distribution of $\sqrt{n}(\psi_n - \psi_0)$ due to the estimation of η_0. The next Theorem 13 presents the generalization of Theorem 8 to adaptive designs $g_i = g_{\eta_0,i}$ indexed by unknown parameters, typically factored in terms of controlled and uncontrolled unknown components.

Theorem 13 *Consider the adaptive design experiment generating* $(O_1, \ldots, O_n) \sim P_{Q_0, \mathbf{g}_n} \in \{P_{Q,\mathbf{g}_n} : Q \in \mathcal{Q}\}$, *as defined in (3). Here* $\mathbf{g}_n = (g_1, \ldots, g_n)$, $g_i = g_{Z_i} \in \mathcal{G}$ *with probability 1, where* $Z_i = Z_i(O_1, \ldots, O_{i-1}) \in \mathcal{Z} \subset \mathbb{R}^k$ *is a* k*-dimensional summary measure for some fixed* k, $i = 1, \ldots, n$. *Let* $\Psi : \mathcal{M} \to \mathbb{R}^m$ *be path-wise differentiable at each* $P_{Q,g} \in \mathcal{M} = \{P_{Q,g} : Q \in \mathcal{Q}, g \in \mathcal{G}\}$ *with efficient influence curve/canonical gradient* $D^*(Q, g)$.

Modelling and estimation of the adaptive design: *Consider a model* $\{g_{\eta,Z_i} : \eta \in \Gamma\} \subset \mathcal{G}$ *so that*

$$g_i(A_i \mid X_i) = g_{\eta_0,Z_i}(A_i \mid X_i)$$

for an unknown parameter $\eta_0 \in \Gamma$. *Let* η_n *be an estimator of* η_0 *solving a martingale estimating equation* $0 = \sum_{i=1}^n S(\eta_n)(O_i, Z_i) = 0$ *so that* $P_{Q_0,g_{\eta_0,Z_i}} S(\eta_0) = 0$ *for all* $i = 1, \ldots$. *For example,* $S(\eta)(O_i, Z_i) = \frac{d}{d\eta} \log g_{\eta,Z_i}(A_i \mid X_i)$.

A working model and initial estimator: *Let* $\mathcal{Q}^w = \{Q_\theta : \theta \in \Theta \subset \mathbb{R}^d\} \subset \mathcal{Q}$ *be a working model. Let* θ_n *be a solution in* θ *of a Martingale estimating equation*

$$\frac{1}{n} \sum_{i=1}^n D(\eta_n, \theta_n)(O_i, Z_i) = 0 \text{ or } o_P(1/\sqrt{n}),$$

so that for a fixed element θ_0 *of* Θ

$$P_{Q_0,g_{\eta_0,i}} D(\eta_0, \theta_0) = 0 \text{ for } i = 1, \ldots, n. \tag{58}$$

Design function: *Let* $(\eta, \theta) \to g_{\eta_0,\eta,\theta} \in \mathcal{G}$ *be a mapping into the set of fixed designs possibly indexed by the unknown* η_0. *It is recommended to chose this design function* $(\eta, \theta) \to g_{\eta_0,\eta,\theta}$ *so that* $g_n = g_{\eta_0,\eta_{n-1},\theta_{n-1}}$ *or that* g_n *is approximated by* $g_{\eta_0,\eta_{n-1},\theta_{n-1}}$ *as* $n \to \infty$.

A targeted bias reduction path, and estimator: *Consider a set* $\mathcal{E} \subset \mathbb{R}^m$ *containing* 0. *For each* $\theta \in \Theta$, *let* $\{Q_{\theta,g}(\epsilon) : \epsilon \in \mathcal{E}\} \subset \mathcal{Q}$ *be a path so that* $Q_{\theta,g}(0) = Q_\theta \in \mathcal{Q}$ *for all* $g \in \mathcal{G}$. *Although not necessary for the conclusions of this theorem, we recommend it to also satisfy* $\frac{d}{d\epsilon} \log Q_{\theta,g}(\epsilon)(O)\Big|_{\epsilon=0} = D^*(Q_\theta, g)(O)$. *Given the design function* $(\eta, \theta) \to g_{\eta_0,\eta,\theta}$, *and estimators* η_n, θ_n, *let* ϵ_n *be a solution of*

$$\sum_{i=1}^n D^*(Q_{\theta_n,g_{\eta_n,\eta_n,\theta_n}}(\epsilon_n), g_{\eta_n,Z_i})(O_i) = 0 \text{ or } o_P(1/\sqrt{n}).$$

or

$$\sum_{i=1}^n D^*(Q_{\theta_n,g_{\eta_n,\eta_n,\theta_n}}(\epsilon_n), g_{\eta_n,\eta_n,\theta_n})(O_i) \frac{g_{\eta_n,\eta_n,\theta_n}(A_i \mid X_i)}{g_{\eta_n,Z_i}(A_i \mid X_i)} = 0 \text{ or } o_P(1/\sqrt{n}).$$

In the context that the efficient influence curve/canonical gradient $D^*(Q,g)$ is too complex too calculate, then one can replace $D^*(Q,g)$ by any gradient $D(Q,g)$ instead, and the results below apply with $D^*(Q,g)$ replaced by $D(Q,g)$.

Given η_0, θ_0, let $\epsilon_0 \in \mathcal{E}$ be a fixed value satisfying

$$P_{Q_0,g_{\eta_0,i}} D^*(Q_{\theta_0,g_{\eta_0,\eta_0,\theta_0}}(\epsilon_0), g_{\eta_0,i}) = 0, \ \ i=1,\ldots,n.$$

Let $D^*(\eta,\theta,\epsilon)(O_i,Z_i) \equiv D^*(Q_{\theta,g_{\eta,\eta,\theta}}(\epsilon), g_{\eta,Z_i})(O_i)$, or $D^*(\eta,\theta,\epsilon)(O_i,Z_i) \equiv D^*(Q_{\theta,g_{\eta,\eta,\theta}}(\epsilon), g_{\eta,\eta,\theta}) g_{\eta,\eta,\theta}(A_i \mid X_i)/g_{\eta,Z_i}(A_i \mid X_i)$, $i = 1,\ldots,n$.

A Martingale Estimating function: *For each $(\eta,\theta,\epsilon) \in \Gamma \times \Theta \times \mathcal{E}$, we define the martingale estimating function*

$$D(\eta,\theta,\epsilon)(O_i,Z_i) = (S(\eta)(O_i,Z_i), D(\eta,\theta)(O_i,Z_i), D^*(\eta,\theta,\epsilon)(O_i,Z_i)).$$

By the above conditions, we have that $(\eta_n,\theta_n,\epsilon_n) \in \Gamma \times \Theta \times \mathcal{E}$ solves

$$0 = \frac{1}{n}\sum_{i=1}^n D(\eta_n,\theta_n,\epsilon_n)(O_i,Z_i) = 0,$$

and $(\eta_0,\theta_0,\epsilon_0) \in \Theta \times \mathcal{E}$ solves

$$0 = P_{Q_0,g_{\eta_0,i}} D(\eta_0,\theta_0,\epsilon_0) \text{ for all } i.$$

Assume

Bounded estimating function: $\max_j \sup_{\eta\in\Gamma,\theta\in\Theta,\epsilon\in\mathcal{E}} \parallel D_j(\eta,\theta,\epsilon) \parallel_\infty < \infty$.

Consistency: *Assume $\parallel (\eta_n,\theta_n,\epsilon_n) - (\eta_0,\theta_0,\epsilon_0) \parallel$ converges to zero in probability as $n \to \infty$.*

By Theorem 5 it suffices to assume that 1) $\mathcal{F} \equiv \{(o,z) \to D(\eta,\theta,\epsilon)(o,z) - P_{Q_0,g_{\eta,z}} D(\eta,\theta,\epsilon) : \eta \in \Gamma, \theta \in \Theta, \epsilon \in \mathcal{E}\}$ has a covering number $N(\delta,\mathcal{F},\parallel \cdot \parallel_\infty)$ w.r.t. to supremum norm bounded by $O(\delta^{-q})$ for a $q > 0$, and 2) that,

$$E\left(\frac{1}{n}\sum_{i=1}^n P_{Q_0,g_{\eta_0,i}} D(\eta_n,\theta_n,\epsilon_n)\right)^2 \to 0,$$

as $n \to \infty$, implies $\parallel (\eta_n,\theta_n,\epsilon_n) - (\eta_0,\theta_0,\epsilon_0) \parallel \to 0$ in probability, as $n \to \infty$.

Asymptotic stable design: *Component wise*

$$\frac{1}{n}\sum_{i=1}^n P_{Q_0,g_{\eta_0,i}} D - E\frac{1}{n}\sum_{i=1}^n P_{Q_0,g_{\eta_0,i}} D \to 0, \text{ in probability, as } n \to \infty, \quad (59)$$

for the following choices of matrix functions D of (O_i, Z_i):

$$\begin{aligned} D &= \{D(\eta_0, \theta_0, \epsilon_0)\}^2 \\ D &= \frac{d}{d(\eta_0, \theta_0, \epsilon_0)} D(\eta_0, \theta_0, \epsilon_0). \end{aligned}$$

Comment: *If the design is a targeted design, $g_i = g_{\eta_0, \eta_{i-1}, \theta_{i-1}, \epsilon_{i-1}}$, then this can be inferred from the asymptotic convergence of $(\eta_n, \theta_n, \epsilon_n)$ to $(\eta_0, \theta_0, \epsilon_0)$, as $n \to \infty$.*

Differentiability: *Assume*

$$\begin{aligned} &\tfrac{1}{n}\textstyle\sum_{i=1}^n (D(\eta_n, \theta_n, \epsilon_n))(O_i, Z_i) - D(\eta_0, \theta_0, \epsilon_0)(O_i, Z_i)) \\ &= \tfrac{1}{n}\textstyle\sum_{i=1}^n \frac{d}{d(\eta_0, \theta_0, \epsilon_0)} D(\eta_0, \theta_0, \epsilon_0)(O_i, Z_i)((\eta_n, \theta_n, \epsilon_n) - (\eta_0, \theta_0, \epsilon_0)) \\ &\qquad + o_P(\| \, (\eta_n, \theta_n, \epsilon_n) - (\eta_0, \theta_0, \epsilon_0) \, \|), \end{aligned}$$

By the Kolmogorov LLN for martingale sums and the asymptotic stability (59) of the design, we have

$$\frac{1}{n}\sum_{i=1}^n \frac{d}{d(\eta_0, \theta_0, \epsilon_0)} D(\eta_0, \theta_0, \epsilon_0)(O_i, Z_i) - A_n \to 0 \quad a.s., \tag{60}$$

as $n \to \infty$, where $A_n \equiv \frac{1}{n}\sum_{i=1}^n E_0 \frac{d}{d(\eta_0, \theta_0, \epsilon_0)} D(\eta_0, \theta_0, \epsilon_0)(O_i, Z_i)$.

Invertibility of A_n: *A_n^{-1} exists, and* $\limsup_n \| \, A_n^{-1} \, \| < \infty$.

Positive Definite Covariance Matrix: *Let*

$$\Sigma(n) \equiv E\left(\frac{1}{n}\sum_{i=1}^n P_{Q_0, g_{\eta_0, i}} \{D(\eta_0, \theta_0, \epsilon_0)\}^2\right).$$

Assume that for each vector $\lambda \in \mathbb{R}^{d+m}$, we have $\liminf_{n\to\infty} \lambda \Sigma(n) \lambda > 0$, or that $\Sigma = \lim_{n\to\infty} \Sigma(n)$ exists and is a positive definite covariance matrix.

Then

$$\sqrt{n}((\eta_n, \theta_n, \epsilon_n) - (\eta_0, \theta_0, \epsilon_0)) = \frac{1}{\sqrt{n}}\sum_{i=1}^n A_n^{-1} D(\eta_0, \theta_0, \epsilon_0)(O_i, Z_i) + o_P(1), \tag{61}$$

where $P_{Q_0, g_{\eta_0, i}} D(\eta_0, \theta_0, \epsilon_0) = 0$ for all i, so that the sum on the right hand side is a Martingale satisfying the conditions of the Martingale central limit theorem. In particular,

$$\Sigma(n)^{-1/2} A_n(\sqrt{n}((\eta_n, \theta_n, \epsilon_n) - (\eta_0, \theta_0, \epsilon_0)) \Rightarrow_d N(0, I), \text{ as } n \to \infty.$$

If $\Sigma(n) \to \Sigma$ *for some positive definite matrix* Σ*, and* $A_n \to A_0$*, then this implies*

$$\sqrt{n}((\eta_n, \theta_n, \epsilon_n) - (\eta_0, \theta_0, \epsilon_0)) \Rightarrow_d N(0, A_0^{-1}\Sigma A_0^{-1\top}). \tag{62}$$

We also have that $\Sigma(n)$ *can be consistently estimated with*

$$\hat{\Sigma}(n) = \frac{1}{n}\sum_{i=1}^{n}\left\{D(\eta_n, \theta_n, \epsilon_n)(O_i, Z_i) - \frac{1}{n}\sum_{i=1}^{n} D(\eta_n, \theta_n, \epsilon_n)\right\}^2.$$

Robustness w.r.t. ψ_0**:** *Suppose,*

$$P_{Q_0,g_i} D^*(Q, g_i) = 0 \text{ implies } \Psi(Q) - \Psi(Q_0) = 0,\ i = 1, \ldots, n, \tag{63}$$

or simply assume $\Psi(Q_{\theta_0}(\epsilon_0)) = \psi_0$*. Then, the delta-method applied to* $f(\eta, \theta, \epsilon) \equiv \Psi(Q_{\theta, g_{\eta,\eta,\theta}}(\epsilon))$*, and the weak convergence (62) imply that* $\sqrt{n}(\Psi(Q_{\theta_n, g_{\eta_n,\eta_n,\theta_n}}(\epsilon_n)) - \Psi(Q_0))$ *converges in distribution to a multivariate normal distribution with mean zero, and specified covariance matrix* Σ_0^* *in terms of the gradient of* f *and* $A_0^{-1}\Sigma_0 A_0$*.*

Asymptotic equivalence with optimal fixed design: *Represent*

$$D(\eta_0, \theta_0, \epsilon_0)(O_i, Z_i) = \left(\frac{d}{d\eta_0}\log g_{\eta_0, Z_i}(A_i \mid X_i), D_1(\eta_0, \theta_0, \epsilon_0, g_{\eta_0, Z_i})(O_i)\right)$$

for some mapping $(\eta, \theta, \epsilon, g) \to D_1(\eta, \theta, \epsilon, g)$*. Given the design function* $(\eta, \theta) \to g_{\eta_0,\eta,\theta}$ *used to define a targeted adaptive design* $g_{\eta_0 i} = g_{\eta_0,\eta_{i-1},\theta_{i-1}}$*, let* $D^\infty(\eta_0, \theta_0, \epsilon_0)(O_i) = (\frac{d}{d\eta_0}\log g_{\eta_0,\eta_0,\theta_0}(A_i \mid X_i), D_1(\eta_0, \theta_0, \epsilon_0, g_{\eta_0,\eta_0,\theta_0})(O_i))$*. Suppose that the adaptive design is a targeted adaptive design, i.e.,* $g_{\eta_0,Z_i} = g_{\eta_0,\eta_{i-1},\theta_{i-1}}$*, and that it converges to the fixed design* $g_{\eta_0,\eta_0,\theta_0} \in \mathcal{G}$ *for* $i \to \infty$ *so that*

$$\begin{aligned} A_n &\to A_0 = P_{Q_0, g_{\eta_0,\eta_0,\theta_0}} \frac{d}{d(\eta_0, \theta_0, \epsilon_0)} D^\infty(\eta_0, \theta_0, \epsilon_0) \\ &\text{and} \\ \Sigma(n) &\to \Sigma_0 \equiv P_{Q_0, g_{\eta_0,\eta_0,\theta_0}} D^\infty(\eta_0, \theta_0, \epsilon_0)^2, \end{aligned} \tag{64}$$

as $n \to \infty$*. Then*

$$\sqrt{n}((\eta_n, \theta_n, \epsilon_n) - (\eta_0, \theta_0, \epsilon_0)) \Rightarrow N(0, A_0^{-1}\Sigma_0 A_0), \tag{65}$$

where the latter normal limit distribution equals the limit distribution of the targeted MLE under i.i.d. sampling from fixed design data generating distribution $P_{Q_0, g_{0\eta_0}}$ *with* η_0 *in* $g_{0\eta_0} = g_{\eta_0,\eta_0,\theta_0}$ *estimated with* $\eta_n = \arg\max_\eta \prod_i g_{0\eta}(A_i \mid X_i)$*.*

Conservative asymptotic inference: The last statement teaches us that we can also derive the asymptotic covariance matrix of the targeted MLE $\Psi(Q_{\theta_n,g_{\eta_n,\eta_n,\theta_n}}(\epsilon_n))$ of ψ_0 by deriving its limit distribution under i.i.d. sampling from the fixed design data generating distribution $P_{Q_0,g_{0\eta_0}}$ where $g_{0\eta_0} = g_{\eta_0,\eta_0,\theta_0}$ denotes the limit of the adaptive design $g_n = g_{\eta_0,\eta_{n-1},\theta_{n-1}}$ as $n \to \infty$, and $\{g_{0\eta} = g_{\eta,\eta_0,\theta_0} : \eta\}$ is a correctly specified model for $g_{0\eta_0}$. By results in van der Laan and Robins (2003) (Theorem 2.5) and van der Laan and Rubin (2006), it follows that under i.i.d. sampling we would have that this targeted MLE ψ_n is asymptotically linear with influence curve given by:

$$D^*(Q_{\theta_0,g_{0\eta_0}}(\epsilon_0), g_{0\eta_0}) - \Pi(D^*(Q_{\theta_0,g_{0\eta_0}}(\epsilon_0), g_{0\eta_0}) \mid T(g_{0\eta_0})),$$

where $\Pi(\cdot \mid T(g_{0\eta_0}))$ is the projection operator onto the tangent space of $\{g_{\eta,\eta_0,\theta_0} : \eta\}$ at η_0 (i.e., the closure of the linear span of the scores of η at η_0) in the Hilbert space $L_0^2(P_{Q_0,g_{0\eta_0}})$ endowed with inner product $\langle f_1, f_2\rangle = E_{P_{Q_0,g_{0\eta_0}}} f_1(O)f_2(O)$. In particular, this teaches us that a conservative influence curve under i.i.d. sampling is given by $D^*(Q_{\theta_0,g_{0\eta_0}}(\epsilon_0), g_{0\eta_0})$. As a consequence, we can base our statistical inference on the conservative Martingale asymptotic linear approximation given by

$$\psi_n - \psi_0 = \frac{1}{n}\sum_{i=1}^n D^*(Q_{\theta_0,g_{0\eta_0}}(\epsilon_0), g_{0\eta_0})\frac{g_{0\eta_0}(A_i \mid X_i)}{g_{\eta_0,i}(A_i \mid X_i)} + o_P(1/\sqrt{n}).$$

Thereby, we can consistently conservatively estimate the covariance matrix of the normal limit distribution of ψ_n with

$$\Sigma_n = \frac{1}{n}\sum_{i=1}^n \left\{ D^*(Q_{\theta_n,g_{\eta_n,\eta_n,\theta_n}}(\epsilon_n), g_{\eta_n,\eta_n,\theta_n})\frac{g_{\eta_n,\eta_n,\theta_n}(A_i \mid X_i)}{g_{\eta_n,i}(A_i \mid X_i)} \right\}^2.$$

Thus, for the sake of statistical inference we can work with the normal (conservative) approximation $\psi_n \sim N(\psi_0, \Sigma_n/n)$ to construct corresponding asymptotically conservative confidence intervals and test-statistics. To conclude, statistical inference for adaptive designs $g_i = g_{\eta_0,i}$, which are indexed by an unknown parameter η_0, can proceed as if η_0 is known (and is given by the maximum likelihood estimator η_n), just as in our presentation in the previous sections for the case that g_i is known, but by doing this one will obtain *conservative (first order)* statistical inference. In order to carry out *asymptotically exact* statistical inference, one will have to work with the limit covariance matrix specified in the Theorem, which will take into account that one has estimated η_0.

27 General Iterative Targeted Estimation.

In this section we present our most general presentation of iterative targeted learning and estimation methodology. Let $O_1, \ldots, O_n$ be a data set of n observations with some probability distribution $P_0^n \in \mathcal{M}^n$, where $\mathcal{M}^n$ denotes a model for this probability distribution P_0^n of $(O_1, \ldots, O_n)$.

Let Q_0 represent a fixed (typically infinite dimensional) parameter of P_0^n in the sense that there exists a mapping $A^n : \mathcal{M}^n \to \mathcal{Q}$ and $A^n(P_0^n) = Q_0$ for all $n = 1, \ldots,$. For example, the data generating distribution $P_0^n = P_{Q_0,\mathbf{g}}^n$ for an adaptive design is determined by a Q_0 representing the identifiable component of the full data distribution, and a censoring mechanisn/design mechanism $\mathbf{g} = (g_1, \ldots, g_n)$, so that we can indeed represent Q_0 as a fixed quantity in this data generating experiment. In words, Q_0 represents a fixed (in n) quantity the true probability distribution of our data set $O_1, \ldots, O_n$ behaves in accordance with.

Let $\mathcal{Q}$ be a fixed (typically infinite dimensional) model for Q_0. For example, the model for adaptive designs is of the form $\mathcal{M}^n = \{P_{Q,\mathbf{g}}^n : Q \in \mathcal{Q}\}$. In many cases, $\mathcal{Q}$ consists of elements representing one or more probability distributions: e.g. in censored data models such as the sequential adaptive design we have that $Q_0(a, l) = P(L_a = l)$ so that $Q(a, \cdot)$ represents indeed a probability distribution for each a.

Let $\Psi : \mathcal{Q} \to \mathbb{R}^d$ be a target feature mapping so that $\psi_0 = \Psi(Q_0)$ represents the target feature of the true Q_0 we wish to estimate.

Consider now user supplied 1) empirical criteria for a candidate $Q \in \mathcal{Q}$ measuring overall performance w.r.t. Q_0, and 2(an empirical equation in Q measuring a performance of $\Psi(Q)$ w.r.t. ψ_0. Specifically, let $L_n : \mathcal{Q} \to \mathbb{R}$ be the empirical criterion in Q. Thus $L_n(Q) = L(Q \mid O_1, \ldots, O_n)$ is a deterministic function of Q and the data $O_1, \ldots, O_n$. Let $F_n(Q) = F(Q \mid O_1, \ldots, O_n)$ be a vector valued function, typically chosen to have the same dimension d as the target feature mapping, so that $F_n(Q) = 0$ represents an empirical equation in Q whose solutions Q are considered targeted towards the target feature: that is, given an overall good empirical performance of a solution Q of $F_n(Q) = 0$, the estimator $\Psi(Q)$ is a good estimator of ψ_0.

For example, $F_n(Q)$ might have the property that its expectation $E_0 F_n(Q) = \Psi(Q) - \Psi(Q_0)$ so that solutions of $F_n(Q) = 0$ are clearly targeted towards fitting $\Psi(Q_0)$. Off course, for a Euclidean norm $\| \cdot \|$, one can also view $\| F_n(Q) \|$ as an empirical criterion for Q targeted towards the target feature. We will refer to the equation $F_n(Q) = 0$ or its corresponding empirical criterion $\| F_n(Q) \|$ as a target feature empirical equation or target feature empirical criterion, respectively.

Next, we wish to construct a mapping from a candidate Q, such as an initial estimator $\hat{Q}$ of Q_0, into a targeted version $Q_n^*(Q)$ which solves the target feature empirical equation $F_n(Q_n^*(Q)) = 0$. Thus, for any $Q \in \mathcal{Q}$, we have that $Q_n^*(Q)$ solves $F_n(Q_n^*(Q)) = 0$. We also wish that the empirical performance of the modified $Q_n^*(Q)$ is better than the empirical performance of Q:

$$L_n(Q) \leq L_n(Q_n^*(Q)) \text{ for all } Q \in \mathcal{Q}.$$

Given such a mapping, one can now carry out a sieve based estimation methodology for estimating Q_0. That is, given sub-models $\mathcal{Q}_k \subset \mathcal{Q}$, one can define candidate targeted estimators $Q_n^{*k} = Q_n^*(Q_n^k)$, where

$$Q_n^k = \arg \max_{Q \in \mathcal{Q}_k} L_n(Q_n^*(Q)),$$

or, in general, one could define Q_n^k as the solution of an algorithm based on criterion $Q \rightarrow L_n(Q_n^*(Q))$ and a sub-model $\mathcal{Q}_k$. Note that these candidate targeted estimators Q_n^{*k}, $k = 1, \ldots$, are all targeted in the sense that they solve $F_n(Q_n^{*k}) = 0$.

Secondly, one needs to define a criterion for selecting k. For that purpose, one might use the cross-validated empirical criterion

$$k \rightarrow E_{B_n} L_{B_n=1}(Q_{B_n=0}^{*k})),$$

which is obtained by splitting the sample $O_1, \ldots, O_n$ in a training sample $\{j : B_n(j) = 0\}$ and validation sample $\{j : B_n(j) = 1\}$, one computes the candidate estimators $Q_{B_n=0}^k$ based on the training sample, one computes the corresponding targeted versions $Q_{B_n=0}^{*k}$ based on the training sample, one evaluates the empirical criterion of the obtained targeted estimator over the validation sample (i.e., $L_{B_n=1}(Q_{B_n=0}^{*k})$), and finally, one averages the obtained results across a number of splits in training and validation sample.

Finally, one selects the best among the targeted candidate estimators indexed by:

$$k_n = \arg \max_k E_{B_n} L_{B_n=1}(Q_{B_n=0}^{*k})).$$

The final estimator of Q_0 is now given by

$$Q_n = Q_n^{k_n},$$

and the corresponding estimator of the target feature ψ_0 is given by

$$\psi_n = \Psi(Q_n).$$

It remains to determine the targeted mapping $Q \to Q_n^*(Q)$. For this purpose, we consider a stretching function $Q(\epsilon)$ so that $\{Q(\epsilon) : \epsilon\} \subset \mathcal{Q}$ is a sub-model and $Q(0) = 0$. We wish to select the stretching function in such a way so that

$$\frac{d}{d\epsilon} L_n(Q(\epsilon))\Big|_{\epsilon=0} = F_n(Q), \tag{66}$$

and, for that purpose, we assume that the choice of L_n and F_n is indeed such that such a stretching function and corresponding sub-model exists. Given this condition (66), we are now ready to present the iterative targeted estimation algorithm in terms of an initial Q, the global criterion $L_n(\cdot)$, the targeted function and criterion $F_n()$, and the with $F_n(\cdot)$ corresponding stretching function. Firstly, let $Q_n^0 = Q$, and $Q_n^1 = Q_n^0(\epsilon_n^0)$, where

$$\epsilon_n^0 = \arg\max_{\epsilon} L_n(Q_n^0(\epsilon)),$$

or ϵ_n^0 is chosen in another way but so that $L_n(Q_n^0(\epsilon_n^0)) \geq L_n(Q_n^0)$. One now, iterates this process, by setting $k = 0$, $Q_n^{k+1} = Q_n^k(\epsilon_n^k)$, where

$$\epsilon_n^k = \arg\max_{\epsilon} L_n(Q_n^k(\epsilon)),$$

or ϵ_n^k is chosen in another way but so that

$$L_n(Q_n^k(\epsilon_n^k)) \geq L_n(Q_n^k), k = 1, 2, \ldots.$$

Under the assumption that $\epsilon_n^k \to 0$ for $k \to \infty$ (e.g., $Q \to L_n(Q)$ is bounded from above), it follows that $Q_n^*(Q) = Q_n^K$ for K large enough solves (just use that $\epsilon_n^K \approx 0$ and that ϵ_n^K solves the derivative of $L_n(Q_n^{K-1}(\epsilon))$ w.r.t. ϵ)

$$F_n(Q_n^*(Q)) = 0$$

up till user supplied precision. Note that indeed $L_n(Q_n^*(Q)) \geq L_n(Q)$ and $F(Q_n^*(Q)) = 0$.

It should be noted that, given an empirical criterion $Q \to L_n(Q)$ on model $\mathcal{Q}$, and a target feature function $Q \to F_n(Q)$ on $\mathcal{Q}$, we can not always construct a path $\{Q(\epsilon) : \epsilon\} \subset \mathcal{Q}$, through Q at $\epsilon = 0$, so that the derivative of $\epsilon \to L_n(Q(\epsilon))$ at $\epsilon = 0$ equals $F_n(Q)$? For example, if $L_n(Q)$ is the log-likelihood at Q, then $F_n(Q)$ needs to be in the so called tangent space at Q defined as the closure of the linear span of all scores $\frac{d}{d\epsilon} L_n(Q(\epsilon))\Big|_{\epsilon=0}$ generated by all possible paths $\{Q(\epsilon) : \epsilon\} \subset \mathcal{Q}$ through Q at $\epsilon = 0$. In general, $F_n(Q)$ needs to be an element of the closure of the linear span of all functions one can generate as $\frac{d}{d\epsilon} L_n(Q(\epsilon))\Big|_{\epsilon=0}$.

Strategy for deriving path and target feature equation: Therefore one particular sensible strategy is the following in which we constructively derive a choice for the path $Q(\epsilon)$ and the corresponding target feature function $F_n(Q)$. Firstly, one determines a path-wise derivative of $\Psi : \mathcal{Q} \to \mathbb{R}^d$ in the sense that for any path $Q_h(\epsilon)$ indexed by or implying an element $h \in H$ so that

$$\frac{d}{d\epsilon}\Psi(Q_h(\epsilon))\Big|_{\epsilon=0} = \langle D(Q,g), h\rangle_{Q,g},$$

for some inner product $\langle .,. \rangle_{Q,g}$ defined on Hilbert space $H(Q,g)$, $h \in H \subset H(Q,g)$, and element $D(Q,g) \in H(Q,g)$, where these spaces and elements are indexed by Q and a censoring/design mechanism $g \in \mathcal{G}$. Typically, $H(Q,g) = L_0^2(P_{Q,g})$ for some distribution $P_{Q,g}$ of a possibly reduced data structure O^r of O. We can call $D(Q,g)$ a gradient of the path-wise derivative. We define the sub-Hilbert space $T(Q,g)$ of $H(Q,g)$ generated by the closure and linear span of H, i.e. the closure of the linear span of all elements h indexing the paths $Q_h()$. We will refer to $T(Q,g)$ as a tangent space at Q. Let $D^*(Q,g) \in T(Q,g)$ be the unique gradient which is also an element of the tangent space $T(Q,g)$ at Q. This inner product representation of the path-wise derivative (as known to exist by Riesz-Representation theorem, under weak conditions) of $\Psi : \mathcal{Q} \to \mathbb{R}^d$ teaches us that:

$$\begin{aligned}\frac{\left(\frac{d}{d\epsilon}\Psi(Q_h(\epsilon))\Big|_{\epsilon=0}\right)^2}{\langle h,h\rangle_{Q,g}} &= \frac{\langle D^*(Q,g),h\rangle_{Q,g}^2}{\langle h,h\rangle_{Q,g}} \leq \frac{\langle D^*(Q,g),D^*(Q,g)\rangle_{Q,g}\langle h,h\rangle_{Q,g}}{\langle h,h\rangle_{Q,g}} \\ &= \langle D^*(Q,g),D^*(Q,g)\rangle_{Q,g}.\end{aligned}$$

Thus, the path which maximizes a normalized change in the target parameter is given by a $\{Q_h(\epsilon) : \epsilon\}$ with $h = D^*(Q,g)$. Let $\{Q^*(\epsilon) : \epsilon\}$ be this optimal stretching/fluctuation function. We note that this optimal path is indexed by the class of paths $Q_h(\epsilon)$ indexed by $h \in \mathcal{H}$, and the choice of inner product $\langle \cdot,\cdot \rangle_{Q,g}$, so that this strategy corresponds with a class of such optimal stretching/fluctuation functions.

Given the empirical criterion $L_n(Q)$, we now simply define the target feature function at any Q as follows

$$F_n(Q) = \frac{d}{d\epsilon}L_n(Q^*(\epsilon))\Big|_{\epsilon=0}.$$

We note that $L_n(\cdot)$ might itself be indexed by the same g as used in the optimal path derivation above.

One now carries out the iterative targeted estimator described above involving, given current fit Q^k, constructing optimal stretching function $Q^{k*}(\epsilon)$,

maximizing the wished global empirical criterion $\epsilon \rightarrow L_n(Q^{k*}(\epsilon))$ over ϵ to determine the wished stretching amount ϵ_n^k, and updating the current fit Q^k accordingly with $Q^{k*}(\epsilon_n^k)$, $k = 1, \ldots$.

We will now illustrate that our previously general iterative targeted estimation methods can be shown to follow the last general approach.

IPCW-R-TMLE: We consider the IPCW-R-TMLE estimator of the target feature for fixed CAR designs/censoring mechanisms. Let $O = (A, L = L_A) \sim P_{Q_0,g_0}$ be the observed data on a single experimental unit, and let $\Psi : \mathcal{Q} \rightarrow \mathbb{R}^d$ be the target parameter, so that $\Psi(Q_0)$ denotes the true target parameter. One observes n i.i.d. copies of O.

Let $O^r = (A, L_A^r) \sim P^r_{Q_0^r,g^r}$ be the reduced data structure under a CAR-mechanism for this reduced data structure. Let $\Psi^r : \mathcal{Q}^r \rightarrow \mathbb{R}^d$ represent the target parameter in the sense that $\Psi(Q) = \Psi^r(Q^r)$ for all $Q \in \mathcal{Q}$, so that $\Psi^r(Q_0^r)$ denote the true value of target parameter. As before we note that Q^r is a deterministic function of Q so that $\mathcal{Q}^r$ is implied by the model $\mathcal{Q}$ for Q_0. We can represent the path-wise derivative of Ψ^r at Q^r along a path $Q^r(\epsilon)$ as

$$\frac{d}{d\epsilon}\Psi^r(Q^r(\epsilon))\Big|_{\epsilon=0} = \langle D^{*F}(Q^r)), s\rangle_{Q^r} = \langle D^{*r}(Q^r, g^r), A^r_{Q^r}(s)\rangle_{Q^r,g^r},$$

where D^{*F} is canonical gradient in the full data model for X^r, while $D^{*r}(Q^r, g^r)$ is the canonical gradient of Ψ^r viewed as parameter on $\mathcal{M}^r(g^r)$ at data generating distribution $P^r_{Q^r,g^r}$. Thus, we observe that each choice of fixed design/censoring mechanism $g^r \in \mathcal{G}^r$ gives a new representation of the path-wise derivative of the target parameter in terms of an inner product in $L_0^2(P^r_{Q^r,g^r})$. (Recall that the classical path-wise derivative in efficiency theory requires that the path-wise derivative at Q_0 is expressed in terms of inner product in $L_0^2(P_0)$ with P_0 representing the actual true data generating distribution)

Thus each choice g^r defines now an optimal path $Q^r_{g^r}(\epsilon)$ through Q^r with the property that

$$\frac{d}{d\epsilon}\log Q^r_{g^r}(\epsilon)\Big|_{\epsilon=0} = D^{*r}(Q^r, g^r).$$

A particular type of optimal path is to make the choice g^r a function of the data or a function of Q^r. Consider an optimal path $Q^r_{g^r}(\epsilon) \in \mathcal{Q}^r$ through Q^r at $\epsilon = 0$

Our next step is to determine a sensible empirical criterion for evaluating the performance of a candidate $Q^r \in \mathcal{Q}^r$ w.r.t the true Q_0^r. As we have shown

such a criterion is given by the IPCW-reduced data log likelihood:

$$Q^r \to L_n^r(Q^r) \equiv \sum_{i=1}^n \log Q^r(O_i^r) \frac{g^r(A_i \mid X_i^r)}{g_0(A_i \mid X_i)}.$$

The optimal path $Q_{g^r}^r(\epsilon)$ for any $Q^r \in \mathcal{Q}^r$, and the empirical criterion $Q^r \to L_n^r(Q^r)$ now defines the iterative targeted estimator (i.e., the iterative-IPCW-reduced data targeted MLE) of $\psi_0^r = \psi_0$. The estimating equation this estimator aims to solve is now given by:

$$\begin{aligned} 0 &= F_{ng^r}(Q^r) \\ &\equiv \sum_{i=1}^n D^{*r}(Q^r, g^r)(O_i^r) \frac{g^r(A_i \mid X_i^r)}{g_0(A_i \mid X_i)}. \end{aligned}$$

If one selects g^r as a function of the data or as a function of the current fit Q^r (or both), then the iterative targeted estimator would solve $F_{ng_n^r}(Q_n^r) = 0$ or $F_{ng_{nQ_n^r}}(Q_n^r) = 0$.

Iterative T-MLE for Adaptive CAR Designs: Let $O_1, \ldots, O_n \sim P_{Q_0,\mathbf{g}}^n$ be data generated by a sequential CAR design. Let $\Psi : \mathcal{Q} \to \mathbb{R}^d$ be the target parameter mapping, and let $\Psi(Q_0)$ denote the true target feature.

Let $O^r \sim P_{Q_0,g}^r$ be the data structure under a fixed design CAR-mechanism g so that $(O_1^r, \ldots, O_n^r) \sim P_{Q_0,g}^n$ are i.i.d. with common distribution $P_{Q_0,g}$.

We can represent the path-wise derivative as

$$\begin{aligned} \frac{d}{d\epsilon}\Psi(Q(\epsilon))\Big|_{\epsilon=0} &= \langle D^{*F}(Q)), s\rangle_Q \\ &= \langle D^*(Q,g), A_Q(s)\rangle_{Q,g}, \end{aligned}$$

where D^{*F} is canonical gradient in full data model, while $D^*(Q,g)$ is the canonical gradient of Ψ viewed as parameter on $\mathcal{M}(g)$ at $P_{Q,g}$. Thus, we observe that each choice of fixed design $g \in \mathcal{G}$ gives a new representation of the path-wise derivative of the target parameter in terms of an inner product in $L_0^2(P_{Q,g})$. (The classical path-wise derivative in efficiency theory requires that the path-wise derivative at Q_0 is expressed in terms of inner product in $L_0^2(P_0^n)$ with P_0^n representing true data generating distribution of $O_1, \ldots, O_n$)

Thus each fixed design $g \in \mathcal{G}$ defines now an optimal path $Q_g(\epsilon)$ through Q with the property that

$$\frac{d}{d\epsilon} \log Q_g(\epsilon)\Big|_{\epsilon=0} = D^*(Q,g).$$

A particular type of optimal path is to make the choice g a function of the data and/or a function of Q such as $g = g_Q$. Consider an optimal path $Q_g(\epsilon)$ through $Q \in \mathcal{Q}$ at $\epsilon = 0$.

Our next step is to determine a sensible empirical criterion for evaluating the performance of a candidate Q w.r.t the true Q_0. As we have shown such a criteria is given by the IPCW-log likelihood:

$$Q \to L_n(Q) \equiv \sum_{i=1}^{n} \log Q(O_i) \frac{g(A_i \mid X_i)}{g_i(A_i \mid X_i)}.$$

The optimal path $Q_g(\epsilon)$ for any $Q \in \mathcal{Q}$, and the empirical criterion $Q \to L_n(Q)$ now defines the iterative targeted maximum likelihood estimator for adaptive designs (i.e., the iterative-IPCW-reduced data targeted MLE) of ψ_0.

The estimating equation this estimator will solve in Q is now given by:

$$\begin{aligned} 0 &= F_{ng}(Q) \\ &\equiv \sum_{i=1}^{n} D^*(Q, g)(O_i) \frac{g(A_i \mid X_i)}{g_i(A_i \mid X_i)}. \end{aligned}$$

If one adapts the choice g to the data and/or the current fit Q, then the iterative targeted MLE would converge to a solution Q_n satisfying $F_{ng_n}(Q_n) = 0$ or $F_{ng_{nQ_n}}(Q_n) = 0$.

Our general methodology can be applied to many other empirical criterions $L_n(Q)$ of interest such as empirical criterions indexed by other loss functions than the log-likelihood of a reduced or complete data structure, including partial log-likelihoods, log-likelihood of marginal distributions, loss functions for parameters of Q such as loss functions for regressions implied by Q, and so on.

28 Discussion.

In this article we considered a sequence of n experiments whose starting points are ordered over time and in which the underlying data of interest, X, is drawn independently from a common probability distribution. One is concerned with estimation and statistical inference for a scientific parameter of this common probability distribution. The settings in the i-th experiment, as denoted with A_i, determine what one observes about X_i, or, in other words, determines the censoring/missingness of X_i, $i = 1, \ldots, n$. The design for experiment i is defined as the conditional probability distribution of A_i, given X_i, and the previously collected observations $O_1, \ldots, O_{i-1}$, and an adaptive design for the

n ordered experiments is defined by the collection of n of these conditional distributions. We show that under a general coarsening at random assumption the data generating distribution factorizes in the adaptive design and the likelihood factor only depending on the distribution of X and this latter likelihood factor is identical to what it would have been in a fixed design in which A_i, given X_i, has to satisfy CAR for X_i, and A_i is independent (just like X_i) of the previous experiments. As a consequence, the maximum likelihood estimator is identical to what it would have been in the classical fixed design case. These design distributions g_i could be completely known, but, more generally, one will typically be able to factorize g_i into controlled and unknown uncontrolled components. In this article we defined a large class of targeted adaptive designs which target optimal designs for the controlled components of the design mechanism, only known if the full data distribution of X would be known. These adaptive designs use the previously collected data to estimate the unknown parameters of the full data distribution according to a working model and set the design for the next experiment equal to the optimal target design according to this working model at these estimated parameters. That is, our proposed adaptive designs learn during the course of the trial the optimal design according to the working model. We prove generally applicable theorems showing that the maximum likelihood estimator, targeted maximum likelihood estimators, and, in general, estimators solving Martingale estimating equations are consistent and asymptotically normally distributed with a limit distribution corresponding with the target the adaptive design converges to as sample size n converges to infinity. As a consequence, our methods allows one to learn from data the optimal design (e.g. for the purpose of estimating the scientific parameter of interest) as well the parameter of interest.

We also presented a variety of adaptations one wishes to and should pursue in clinical trials for which our theory and estimators apply, but we also made clear that adaptations changing the scientific parameter of interest (e.g., changing sampling population) have to be treated with the utmost suspicion and a safe way to still allow for them is to simply throw away the data used to generate the wished scientific parameter (as has been common practice moving from phase II to phase III trials).

We believe that this general toolbox for defining targeted adaptive designs and the corresponding statistical tools for efficient and robust (i.e., targeted maximum likelihood) estimation, and inference for the scientific parameter, provides new powerful methods for designing, running, and analyzing clinical trials. In our work we distinguished between 1) looks at data for the purpose of testing and thereby possibly stopping the trial versus 2) looks at the data which only serve the purpose of adapting the design. Our work shows that looking

at the data (as in 2) during the trial is not wrong, but, on the contrary, it is required to learn the wished optimal design: for example, if one targets a design which maximizes the information in the data for the scientific parameter, then the learning of the optimal design can result in much more precise estimators.

Beyond iterative targeted maximum likelihood estimators generalizing the targeted maximum likelihood estimators for fixed designs (van der Laan and Rubin (2006)), we also provided relatively simple to compute IPCW-Reduced Data targeted MLE so that our targeted estimators are relatively easy to implement even for complex longitudinal data structures involving time dependent design settings $A_i = (A_i(t) : t)$. We also provided a whole new targeted empirical Bayesian learning methodology which allows on to be a Bayesian w.r.t. the parameter of interest without having to give up on the wished robustness and efficiency properties of the frequentist targeted estimators.

One can put a sequential testing procedure (as in 1) on top of an adaptive design, where the sample sizes at which testing occurs are either a specified subset or random subset of the sample sizes at which one potentially adapts the trial. We provided a class of such sequential testing procedures controlling the type I error at level α, based on a simple to estimate multivariate normal distribution of the vector of subsequent test statistics.

In future work we will implement various of the proposed targeted adaptive designs, and corresponding proposed estimators, and establish their practical performance and benefits based on simulated data imitating adaptive designs the FDA is interested in.

Finally, we remark that we have not formally addressed efficiency of our proposed estimators in this article: we addressed that targeted adaptive designs can be used to achieve the efficiency of the optimal fixed (unknown) design, but we have not shown that the targeted-MLE based on such a targeted adaptive design or any other adaptive design is in fact asymptotically efficient. We could use the efficiency theory for local asymptotic normal (LAN) log-likelihoods (see, Chapter 8 Andersen et al. (1993)). The LAN-property of the log-likelihood for adaptive designs follows from the fact that the scores of our likelihood of the data $\mathbf{O}_n$ are asymptotically normally distributed, by the Martingale CLT. Now, using the efficiency theory as nicely laid out in Chapter 8 of Andersen et al. (1993), we could define an efficient estimator and prove that the MLE for a correctly specified parametric model, under the conditions of our CLT Theorem 7, is asymptotically efficient. Similarly, we could prove that our targeted MLE based on a parametric working model $\mathcal{Q}^w$ within a semi-parametric model $\mathcal{Q}$ for Q_0, under the conditions of Theorem 8 is locally efficient in the sense that it is asymptotically efficient if $Q_0 \in \mathcal{Q}^w \subset \mathcal{Q}$, while it remains consistent and asymptotically linear for any $Q_0 \in \mathcal{Q}$.

APPENDIX I: Basic building blocks for consistency results.

In order to prove convergence of the discrete martingale sum $M_n(f) = 1/n \sum_{i=1}^n f(O_1, \ldots, O_i)$ for a given function f satisfying $E(f(O_1, \ldots, O_i) \mid O_1, \ldots, O_{i-1}) = 0$ we can apply Kolmogorov Strong Law of Large Numbers for martingales (e.g., Theorem 2.4.2 in Sen and Singer (1993)). This theorem states that if $T(n) = \sum_{i=1}^n X_i$, $E \mid X_i \mid^p$ exists for all i with $1 \leq p \leq 2$, and $b(n)$ is an increasing sequence of positive numbers such that $b_n \to \infty$ so that $\sum_n b_n^{-p} E(\mid X_n \mid^p \mid X_1, \ldots, X_{n-1}) < \infty$ a.s., then $b_n^{-1} T(n) \to 0$ a.s. Application of this result to $b(n) = n$, $T(n) = \sum_{i=1}^n f(O_1, \ldots, O_i)$, $p = 2$ yields that $M_n(f) \to 0$ a.s. for any uniformly bounded function f.

In order to prove consistency of maximum likelihood estimators or estimators defined as solutions of estimating equations based on $O_1, \ldots, O_n$ we need a uniform consistency result for $M_n(f)$ uniformly in a class of functions $\mathcal{F}$. Specifically, we will rely on the following result.

Notation: $\| f \|_p \equiv (E \mid f(O) \mid^p)^{1/p}$. We need in proof below that $\mathcal{A}$ is finite. $P_{Q_0,g_i} f_{\theta_n} = P_{Q_0,g_i} f(\theta)|_{\theta=\theta_n}$. $\mathcal{G} = \{g(\cdot \mid X) : g(A \mid X) = h(A, X(A)) \text{ for some } h\}$

Theorem 14 *Consider a set of functions $\mathcal{F}$ so that $M_n(f) = 1/n \sum_i f(O_i, Z_i)$ with $E(f(O_i, Z_i) \mid O_1, \ldots, O_{i-1}) = 0$ for all $i = 1, \ldots,$ and $Z_i = Z_i(O_1, \ldots, O_{i-1}) \in \mathbb{R}^d$ is a d-dimensional summary measure of $O_1, \ldots, O_{i-1}$. Assume that this class $\mathcal{F}$ of functions on (A, L, Z) satisfies $\sup_{f \in \mathcal{F}} \| f \|_\infty < \infty$, and that the covering number $N(\epsilon, \mathcal{F}, \| \cdot \|_\infty)$ w.r.t. supremum norm is bounded by $C \frac{1}{\epsilon^V}$ for some $V < \infty$ and constant $C < \infty$, uniformly in $\epsilon > 0$. Then, for even $p > q$,*

$$\| \sup_{f,g \in \mathcal{F}} \mid M_n(f) - M_n(g) \mid \|_p \leq \frac{K}{n^{1/p}} \int_0^{diam(\mathcal{F})} \epsilon^{-q/p} d\epsilon = O(n^{-1/p}),$$

where $diam(\mathcal{F})$ is the diameter of $\mathcal{F}$ w.r.t. to the supremum norm.

In particular, for such classes it follows that for any $p \geq 1$, we have

$$\| \sup_{f \in \mathcal{F}} \mid M_n(f) \mid \|_p \to 0,$$

and thus also

$$\sup_{f \in \mathcal{F}} \mid M_n(f) \mid \to 0 \text{ in probability, as } n \to \infty.$$

In order to prove this theorem we need the following lemma.

Lemma 1 *Let* $M_n(f) = \frac{1}{n}\sum_{i=1}^n f(O_i, Z_i)$, *where* $Z_i = Z_i(O_1, \ldots, O_{i-1}) \in \mathbb{R}^d$ *for some fixed dimension* d. *Let* $\mathcal{Z} \subset \mathbb{R}^d$ *be such that* $P(Z_i \in \mathcal{Z}, i = 1, \ldots, n) = 1$. *Assume* $E(f(O_i, Z_i) \mid O_1, \ldots, O_{i-1}) = 0$, $\| f \|_\infty < M < \infty$. *Then for integer* $p < n$, *we have*

$$EM_n(f)^p \leq C_1 \frac{1}{n} \| f \|_{p,Q_0}^p,$$

where

$$\| f \|_{p,Q_0} \equiv \left(\sum_{a \in \mathcal{A}} E_{Q_0} \sup_{z \in \mathcal{Z}} \mid f(a, X(a), z) \mid^p \right)^{1/p}$$

and C_1 *is a finite constant only depending on* p. *In particular, for even* $p < n$, *we have*

$$E \mid M_n(f) \mid^p \leq C_1 \frac{1}{n} \| f \|_{p,Q_0}^p .$$

Thus, if we define the norm $\| M_n(f) \|_p \equiv (E \mid M_n(f) \mid^p)^{1/p}$, *and norm* $d(f,g) \equiv \| f - g \|_{p,Q_0}$, *then there exists a* $C < \infty$ *only depending on* p *so that for even integers* $p < n$

$$\| M_n(f) \|_p \leq C \| \frac{f}{n^{1/p}} \|_{p,Q_0} = \frac{C}{n^{1/p}} \| f \|_{Q_0,p} .$$

Proof. For a given n-dimensional integer valued vector $m \in \{0, 1, \ldots, p\}^n$, let $j^* = j^*(m) = \max\{j : m(j) > 0, m(i) = 0, i > j\}$ be the index of the last non-zero component, and $m^* = m^*(m) \equiv m(j^*)$ be the corresponding component of m. Let $\mathcal{B} = \{m \in \{0, \ldots, p\}^n : \sum_j m(j) = p\}$. Firstly, we note that, if $m^* = 1$, then

$$E \prod_{j=1}^n f(O_j, Z_j)^{m(j)} = E \left(\prod_{j=1}^{j^*-1} f(O_j, Z_j) E(f(O_{j^*}, Z_{j^*}) \mid O_1, \ldots, O_{j^*-1}) \right) = 0.$$

As a consequence,

$$\begin{aligned} EM_n(f)^p &= E \frac{1}{n^p} \sum_{m \in \mathcal{B}} \prod_{j=1}^n f(O_j, Z_j)^{m(j)} \\ &= E \frac{1}{n^p} \sum_{m \in \mathcal{B}, m^* > 1} \prod_{j=1}^n f(O_j, Z_j)^{m(j)} \\ &\leq \frac{1}{n^p} \sum_{m \in \mathcal{B}, m^* > 1} E \prod_{j=1}^n f^*(O_j)^{m(j)}, \end{aligned}$$

where

$$f^*(O_j) \equiv \sup_{z \in \mathcal{Z}} \mid f(O_j, z) \mid .$$

We also have

$$\begin{aligned}
&E_{Q_0,\mathbf{g}_n} \textstyle\prod_{j=1}^n f^*(A_j, X_j(A_j))^{m(j)} \\
&= \textstyle\sum_a \int_x \prod_{j=1}^n f^*(a_j, x_j(a_j))^{m(j)} \prod_{j=1}^n g_j(a_j \mid x_j, \bar{\mathbf{a}}(j-1), \bar{\mathbf{x}}(j-1)) dF_0(x_j) \\
&= \textstyle\sum_{\{a_i, x_i : m(i)>0\}} \prod_{j=1}^n f^*(a_j, x_j(a_j))^{m(j)} \times \\
&\qquad \left(\textstyle\sum_{\{a_i, x_i : m(i)=0\}} \prod_{j=1}^n g_j(a_j \mid x_j, (a_l, x_l), l \leq j-1) dF_0(x_j) \right).
\end{aligned}$$

Now, we note that

$$\begin{aligned}
&\textstyle\sum_{\{a_i, x_i : m(i)=0\}} \prod_{j=1}^n g_j(a_j \mid x_j, (a_l, x_l), l \leq j-1) dF_0(x_j) \\
&= P((x_i, a_i : m_i > 0)) \\
&= P((a_i : m_i > 0) \mid (x_i : m_i > 0)) \textstyle\prod_{i : m_i > 0} dF_0(x_i) \\
&\leq \textstyle\prod_{i : m_i > 0} dF_0(x_i),
\end{aligned}$$

where $P((x_i, a_i : m_i > 0))$ denotes the marginal probability/density of the subvector $(x_i, a_i : m_i > 0)$ of $(x_i, a_i : i = 1, \ldots, n)$. As a consequence,

$$\begin{aligned}
&E_{Q_0,\mathbf{g}_n} \textstyle\prod_{j=1}^n f^*(A_j, X_j(A_j))^{m(j)} \\
&\leq \textstyle\sum_{\{(a_i, x_i) : m_i > 0\}} \prod_{j=1}^n f^*(a_j, x_j(a_j))^{m(j)} \prod_{j=1 : m(j)>0}^n dF_0(x_j) \\
&= \textstyle\prod_{i=1, m(i)>0}^n \left(\sum_{a_i} \int_{x_i} f^*(a_i, x_i(a_i))^{m(i)} dF_0(x_i) \right) \\
&= \textstyle\prod_{i=1 : m(i)>0}^n \sum_{a \in \mathcal{A}} E_{Q_0} \mid f^*(a, X(a)) \mid^{m(i)} .
\end{aligned}$$

Now, we can use that for $r \leq p$ and a measure $Q \parallel g \parallel_r = (\int \mid g \mid^r dQ)^{1/r} \leq C \parallel g \parallel_p = (\int \mid g \mid^p dQ)^{1/p}$ for some $C < \infty$ only depending on p. Applying this inequality to the Q representing the product measure of $dF_0(x) d\mu(a)$ with $d\mu$ being the counting measure on the finite set $\mathcal{A}$ yields

$$\begin{aligned}
\prod_{i=1 : m(i)>0}^n \sum_{a \in \mathcal{A}} E_0 \mid f^*(a, X(a)) \mid^{m(i)} &= \prod_{i=1 : m(i)>0}^n \parallel f^* \parallel_{Q_0, m(i)}^{m(i)} \\
&\leq C \prod_{i=1 : m(i)>0}^n \parallel f^* \parallel_{Q_0, p}^{m(i)} \\
&= C \parallel f^* \parallel_{Q_0, p}^p \\
&= C \left(\sum_{a \in \mathcal{A}} E_{Q_0} \mid f^*(a, X(a)) \mid^p \right)
\end{aligned}$$

for some $C < \infty$.

So we have now shown that

$$EM_n(f)^p \leq C\frac{1}{n^p}\sum_{m\in\mathcal{B},m^*(m)>1} \parallel f^* \parallel^p_{Q_0,p} \leq \frac{C_1}{n} \parallel f^* \parallel^p_{Q_0,p}.$$

This completes the proof of Lemma 1. □

Proof of Theorem 14. We will apply Theorem 2.2.4 in van der Vaart and Wellner (1996) with $\psi(x) = x^p$, p an even integer, so that $\| \cdot \|_\psi = (E \mid f \mid^p)^{1/p}$. Lemma 1 proves

$$\parallel M_n(f) - M_n(g) \parallel_\psi \leq C\frac{1}{c(n)} \parallel f - g \parallel_{p,Q_0},$$

with $c(n) = n^{1/p}$. This Theorem 2.2.4 concludes that there exists a $K < \infty$ only depending on C so that

$$\parallel \sup_{f,g\in\mathcal{F}} \mid M_n(f) - M_n(g) \mid\mid\mid_\psi \quad \leq \quad K\int_0^{diam_n(\mathcal{F})} \psi^{-1}(N(\epsilon,\mathcal{F},\| \cdot \|_{p,Q_0}/c(n)))d\epsilon,$$

where the diameter of $\mathcal{F}$ is measured w.r.t. to the norm $\|\|\|_{p,Q_0}/c(n)$. Let $diam(\mathcal{F})$ be the diameter measured w.r.t. to $\| \cdot \|_{p,Q_0}$, which is thus bounded by a constant times the diameter w.r.t to the supremum norm. We have $diam_n(\mathcal{F}) = diam(\mathcal{F})/c(n)$. We also have that $N(\epsilon,\mathcal{F},\| \cdot \|/c(n)) = N(\epsilon c(n),\mathcal{F},\| \cdot \|)$. Thus,

$$\begin{aligned}\int_0^{diam_n(\mathcal{F})} \psi^{-1}(N(\epsilon,\mathcal{F},\| \cdot \|_{p,Q_0}/c(n)))d\epsilon &= \int_0^{diam(\mathcal{F})/c(n)} \psi^{-1}(N(\epsilon c(n),\mathcal{F},\| \cdot \|_{p,Q_0}))d\epsilon \\ &= \frac{1}{c(n)}\int_0^{diam(\mathcal{F})} \psi^{-1}(N(\epsilon,\mathcal{F},\| \cdot \|_{p,Q_0}))d\epsilon.\end{aligned}$$

As a consequence, we can state the following result: for all even integers $p < n$ we have

$$\parallel \sup_{f,g\in\mathcal{F}} \mid M_n(f) - M_n(g) \mid\mid\mid_p \leq \frac{K}{n^{1/p}}\int_0^{diam(\mathcal{F})} (N(\epsilon,\mathcal{F},\| \cdot \|_{p,Q_0}))^{1/p}\, d\epsilon.$$

Consider a class $\mathcal{F}$ of functions on (A, L, Z) so that the covering number $N(\epsilon,\mathcal{F},\| \cdot \|_\infty)$ w.r.t. supremum norm is bounded by $C\frac{1}{\epsilon^q}$ for some $q < \infty$ and constant $C < \infty$. Then, for even integers $p > q$,

$$\parallel \sup_{f,g\in\mathcal{F}} \mid M_n(f) - M_n(g) \mid\mid\mid_p \leq \frac{K}{n^{1/p}}\int_0^{diam(\mathcal{F})} \epsilon^{-q/p}d\epsilon = O(n^{-1/p}).$$

In particular, for such classes it follows that for any $p \geq 1$, we have

$$\| \sup_{f \in \mathcal{F}} \mid M_n(f) \mid \|_p \rightarrow 0,$$

as $n \rightarrow \infty$, and thus also

$$\sup_{f \in \mathcal{F}} \mid M_n(f) \mid \rightarrow 0 \text{ in probability, as } n \rightarrow \infty.$$

This completes the proof of Theorem 14. □

APPENDIX II: Basic building blocks for central limit theorem for solutions of martingale estimating equations.

28.1 Central limit theorem for univariate martingale sum.

We have the following result.

Theorem 15 *Let* $M(n) = \sum_{i=1}^n D(O_i, Z_i)$, $Z_i = f_1(O_1, \ldots, O_{i-1})$, $E(D(O_i, Z_i) \mid O_1, \ldots, O_{i-1}) = 0$. *Let* $s(n)^2/n = \frac{1}{n}\sum_{i=1}^n ED(O_i, Z_i)^2$, *and* $w(n)^2/n = \frac{1}{n}\sum_{i=1}^n E(D(O_i, Z_i)^2 \mid O_1, \ldots, O_{i-1}) = \frac{1}{n}\sum_{i=1}^n P_{Q_0,g_i} D^2$, *where* $g_i(A_i \mid X_i) \equiv g_i(A_i \mid X_i, O_1, \ldots, O_{i-1})$ *only depends on* $\mathbf{O}(i-1)$ *through* Z_i, $i = 1, \ldots, n$.

Assume $\| D \|_\infty < \infty$, $\liminf s(n)^2/n > 0$, *and*

$$\frac{1}{n}\sum_{i=1}^n P_{Q_0,g_i} D^2 - E\frac{1}{n}\sum_{i=1}^n P_{Q_0,g_i} D^2 \rightarrow 0 \tag{67}$$

in probability as $n \rightarrow \infty$.

Then $w(n)^2/s(n)^2 \rightarrow 1$ *in probability as* $n \rightarrow \infty$, *and*

$$\frac{M(n)}{s(n)} \Rightarrow_D N(0,1),$$

or equivalently, if we define $\sigma_n = \sqrt{s(n)^2/n}$,

$$\frac{\sqrt{n}M(n)}{\sigma_n} \Rightarrow_D N(0,1).$$

The condition $\liminf_n s(n)^2/n > 0$ holds if there exists a $\delta > 0$ so that $\liminf_{i \rightarrow \infty} ED(O_i, Z_i)^2 > \delta$. The condition (67) essentially requires that the variance of Z_i converges to zero for $i \rightarrow \infty$.

28.2 Estimation of variance of martingale sum:

Note that the natural estimator of $s(n)^2/n = E\frac{1}{n}\sum_{i=1}^n P_{Q_0,g_i}D^2$ is given by $1/n\sum_{i=1}^n D(O_i,Z_i)^2$. The following result proves that this estimator is asymptotically consistent.

Theorem 16 *Under the conditions stated in Theorem 15, we have that*

$$\frac{1}{n}\sum_{i=1}^n D(O_i,Z_i)^2 - \frac{s(n)^2}{n} \to 0$$

in probability as $n \to \infty$.

This result teaches us that we can estimate the limiting distribution of $\sqrt{n}M(n)$ by treating $O_1,\ldots,O_n$ as independent draws from P_{Q_0,g_i}, treating g_i as a given fixed design in $\mathcal{G}$, $i = 1,\ldots,n$. In particular, one will have that the parametric or nonparametric bootstrap method ignoring the dependence structure of $O_1,\ldots,O_n$ consistently estimates the limiting variance $s(n)^2/n$.

Proof of Theorem 16. Firstly, we note that

$$\frac{1}{n}\sum_{i=1}^n D(O_i,Z_i)^2 = \frac{1}{n}\sum_{i=1}^n (D^2(O_i,Z_i) - P_{Q_0,g_i}D^2) + \frac{1}{n}\sum_{i=1}^n P_{Q_0,g_i}D^2.$$

Now note that the first term

$$M_1(n) \equiv \frac{1}{n}\sum_{i=1}^n (D^2(O_i,Z_i) - E(D^2(O_i,Z_i) \mid O_1,\ldots,O_{i-1}))$$

is a Martingale. As a consequence of Kolmogorov LLN for martingales, if $\| D \|_\infty < \infty$, we have $M_1(n) \to 0$ almost surely as $n \to \infty$. Thus, it remains to show that $\frac{1}{n}\sum_{i=1}^n P_{Q_0,g_i}D^2 - \frac{1}{n}\sum_{i=1}^n EP_{Q_0,g_i}D^2$ converges to zero, as $n \to \infty$, but that is guaranteed by assumption (67). This completes the proof. □

28.3 Proof of Theorem 15.

We will apply the following Central Limit Theorem for discrete martingales (Theorem 3.3.7. in Sen and Singer (1993)).

Lemma 2 *Let* $T(n) = \sum_{i=1}^n D(X_i)$, $E(D(X_i) \mid X_1,\ldots,X_{i-1}) = 0$, $\| D \|_\infty < \infty$. *Let* $\sigma^2(i) = ED(X_i)^2$, $v^2(i) \equiv E(D(X_i)^2 \mid X_1,\ldots,X_{i-1})$, $i = 1,\ldots,n$. *Let* $s^2(n) \equiv \sum_{i=1}^n \sigma^2(i)$, *and* $w^2(n) \equiv \sum_{i=1}^n v^2(i)$.

Assume

$$(A)\ w^2(n)/s^2(n) \to 1 \text{ in probability as } n \to \infty,$$

and

$$(B)\ \textit{for every } \epsilon > 0\ \frac{1}{s^2(n)} \sum_{i=1}^{n} E\left(D(X_i)^2 I(\mid D(X_i) \mid > \epsilon s(n))\right) \to 0\ \textit{as } n \to \infty.$$

Then $T(n)/s(n)$ *converges in distribution to* $N(0,1)$ *as* $n \to \infty$.

We apply this theorem with $X_i = (O_i, Z_i)$. Let's first consider condition (B). We assumed that $\liminf_n s^2(n)/n > 0$. Then (we assumed $\| D \|_\infty < M < \infty$), $s^2(n)$ converges to infinity at rate n. Thus, in this case we need to verify that for every $\epsilon > 0$, $\frac{1}{n}\sum_{i=1}^{n} E\left[D(O_i, Z_i)^2 I(\mid D(O_i, Z_i) \mid > \epsilon\sqrt{n})\right] \to 0$. We assumed that $\| D \|_\infty < M < \infty$. Thus for $n > M^2/\epsilon^2$, we have that $I(\mid D(O_i, Z_i) \mid > \epsilon\sqrt{n}) = 0$ for all $i = 1, \ldots, n$ with probability 1. Thus this proves condition (B) under the condition that $\| D \|_\infty < \infty$ and $\liminf_n s^2(n)/n > 0$. The latter condition is clearly not necessary, but in most applications it is a condition which will hold.

We will state this as a lemma.

Lemma 3 *Let* $M(n) = \sum_{i=1}^{n} D(O_i, Z_i)$, $Z_i = Z_i(O_1, \ldots, O_{i-1})$, $E(D(O_i, Z_i) \mid O_1, \ldots, O_{i-1}) = 0$, $s^2(n) = \sum_{i=1}^{n} ED(O_i, Z_i)^2$. *If* $\| D \|_\infty < M < \infty$, *and* $\liminf s^2(n)/n > 0$, *then*

$$(B)\ \textit{for every } \epsilon > 0\ \frac{1}{s^2(n)} \sum_{i=1}^{n} E\left(D(O_i, Z_i)^2 I(\mid D(O_i, Z_i)) \mid > \epsilon s(n))\right) \to 0\ \textit{as } n \to \infty.$$

Regarding condition (A), we have

$$v^2(i) \;=\; E(D(O_i, Z_i)^2 \mid O_1, \ldots, O_{i-1}) = P_{Q_0, g_i} D^2.$$

Thus,

$$\frac{w^2(n)}{n} = \frac{1}{n}\sum_{i=1}^{n} v^2(i) = \frac{1}{n}\sum_{i=1}^{n} P_{Q_0, g_i} D^2.$$

Since $\sigma^2(i) = Ev^2(i) = EP_{Q_0, g_i} D^2$, we have $\frac{s(n)^2}{n} = E\frac{1}{n}\sum_{i=1}^{n} P_{Q_0, g_i} D^2$. So to prove that $w(n)^2/n - s(n)^2/n$ converges to zero as $n \to \infty$ is equivalent with condition (67).

Finally, we note that

$$\frac{w(n)^2}{s(n)^2} - 1 = \frac{w(n)^2/n}{s(n)^2/n} - 1 = \frac{w(n)^2/n - s(n)^2/n}{s(n)^2/n}.$$

So if we also assume that $\liminf_{n\to\infty} s(n)^2/n > 0$, then condition (A) is proved. We state this as a lemma.

Lemma 4 *Let* $M(n) = \sum_{i=1}^{n} D(O_i, Z_i)$, $E(D(O_i, Z_i) \mid O_1, \ldots, O_{i-1}) = 0$, $Z_i = Z_i(O_1, \ldots, O_{i-1})$. *If* $\| D \|_\infty < M < \infty$, $\liminf s^2(n)/n > 0$, $\frac{1}{n}\sum_{i=1}^{n} P_{Q_0,g_i} D^2 - E\frac{1}{n}\sum_{i=1}^{n} P_{Q_0,g_i} D^2 \to 0$ *in probability, as* $n \to \infty$, *then* $w(n)^2/s(n)^2 \to 1$ *in probability,.*

28.4 Multivariate Central Limit Theorem for martingale sum

The following theorem proves that the multivariate $M_n(D) = 1/\sqrt{n}\sum_{i=1}^{n} D(O_i, Z_i)$ converges to a multivariate normal distribution with covariance matrix

$$\Sigma^2 \equiv \lim_{n\to\infty} \Sigma^2(n) \equiv \lim_{n\to\infty} E\frac{1}{n}\sum_{i=1}^{n} P_{Q_0,g_i} DD^\top,$$

if one assumes this limit exists. If the latter does not hold, then one still obtains that $\Sigma(n)^{-1} M_n(D) \Rightarrow_D N(0, I)$.

Theorem 17 *Let* $M_n(D) = \sum_{i=1}^{n} D(O_i, Z_i)$, $D = (D_1, \ldots, D_d)$, $E(D(O_i, Z_i) \mid O_1, \ldots, O_{i-1}) = 0$, *and* $Z_i = Z_i(O_1, \ldots, O_{i-1})$. *Let* $\Sigma_i^2 \equiv ED(O_i, Z_i)^2 \equiv ED(O_i, Z_i)D(O_i, Z_i)^\top$ *and* $V_i^2 \equiv E\left(D(O_i, Z_i)^2 \mid O_1, \ldots, O_{i-1}\right) = P_{Q_0,g_i} D^2$. *Let* $\Sigma^2(n) \equiv \frac{1}{n}\sum_{i=1}^{n} \Sigma_i^2 = E\frac{1}{n}\sum_{i=1}^{n} P_{Q_0,g_i} D^2$ *and* $W^2(n) \equiv \frac{1}{n}\sum_{i=1}^{n} V_i^2 = \frac{1}{n}\sum_{i=1}^{n} P_{Q_0,g_i} D^2$.

Assume $\max_j \| D_j \|_\infty < M < \infty$, $\liminf \lambda\Sigma(n)^2\lambda > 0$ *for all* λ *(or that* $\Sigma^2 = \lim_{n\to\infty} \Sigma(n)^2$ *exists and is a positive definite covariance matrix), and that component wise*

$$\frac{1}{n}\sum_{i=1}^{n} P_{Q_0,g_i} D^2 - E\frac{1}{n}\sum_{i=1}^{n} P_{Q_0,g_i} D^2 \to 0 \tag{68}$$

in probability as $n \to \infty$.

Then

$$\sqrt{n}\Sigma(n)^{-1} M_n(D) \Rightarrow_D N(0, I), \text{ as } n \to \infty,$$

and, if $\Sigma^2(n) \to \Sigma^2$, *as* $n \to \infty$, *for some positive definite covariance matrix* Σ^2, *then*

$$\sqrt{n} M_n(D) \Rightarrow_D N(0, \Sigma^2), \text{ as } n \to \infty.$$

28.5 Estimation of limit covariance matrix of multivariate martingale sum.

Note that the natural estimator of $\Sigma^2(n) = E\frac{1}{n}\sum_{i=1}^{n} P_{Q_0,g_i} D^2$ is given by $\hat{\Sigma}^2(n) = \frac{1}{n}\sum_{i=1}^{n} D(O_i, Z_i)^2$. The following results proves that this estimator of the covariance matrix of the multivariate margingale $1/n\sum_i \{D(O_i, Z_i) - P_{Q_0,g_i} D\}$ is indeed asymptotically consistent.

Theorem 18 *Under the conditions stated in Theorem 17, we have that*

$$\frac{1}{n}\sum_{i=1}^{n} D(O_i, Z_i)^2 - \Sigma(n)^2 \to 0 \text{ in probability, as } n \to \infty,$$

and, if $\Sigma^2(n) \to \Sigma^2$, *as* $n \to \infty$, *for a positive definite matrix* Σ^2, *then this also implies* $\frac{1}{n}\sum_{i=1}^{n} D(O_i, Z_i)^2 \to \Sigma$ *in probability, as* $n \to \infty$.

This result teaches us that we can estimate the limiting distribution of $\sqrt{n}M(n)$ by treating $O_1, \ldots, O_n$ as independent draws from P_{Q_0,g_i}, treating g_i as a given fixed design in $\mathcal{G}$), $i = 1, \ldots, n$. In particular, one will have that the parametric or nonparametric bootstrap method ignoring the dependence structure of $O_1, \ldots, O_n$ consistently estimates the covariance matrix $\Sigma^2(n)$.

Proof of Theorem 18. Firstly, we note that

$$\frac{1}{n}\sum_{i=1}^{n} D(O_i, Z_i)^2 = \frac{1}{n}\sum_{i=1}^{n}(D^2(O_i, Z_i) - P_{Q_0,g_i}D^2) + \frac{1}{n}\sum_{i=1}^{n} P_{Q_0,g_i}D^2.$$

Now note that the first term

$$M_1(n) \equiv \frac{1}{n}\sum_{i=1}^{n}(D^2(O_i, Z_i) - E(D^2(O_i, Z_i) \mid O_1, \ldots, O_{i-1}))$$

is a multivariate Martingale. As a consequence of Kolmogorov LLN for martingales, if $\max_j \parallel D_j \parallel_\infty < \infty$, we have $M_1(n) \to 0$ almost surely as $n \to \infty$. Thus, it remains to show that $\frac{1}{n}\sum_{i=1}^{n} P_{Q_0,g_i}D^2 - \frac{1}{n}\sum_{i=1}^{n} EP_{Q_0,g_i}D^2$ converges to zero, as $n \to \infty$, but that is guaranteed by assumption (16). This completes the proof of Theorem 18. □

28.6 Proof of Theorem 17

We can prove this result as follows (see page 123, Sen and Singer (1993)). Firstly, for each $\lambda \in \mathbb{R}^d$, we can define the univariate Martingale $M_n(\lambda) \equiv \lambda^\top M_n = \sum_{i=1}^{n} \lambda^\top D(O_i, Z_i) \equiv \sum_{i=1}^{n} D_\lambda(O_i, Z_i)$. Now, we note that $M_n(\lambda)$ is also a Martingale and the conditions of Theorem 15 apply to prove that $\sqrt{n}M_n(\lambda)$ converges to $N(0, \lambda^\top\Sigma\lambda)$. Thus, we can state the following lemma to establish the CLT for $\lambda^\top M(n)$ for each λ.

Lemma 5 *Let* $M_n(D) = \sum_{i=1}^{n} D(O_i, Z_i)$, $D = (D_1, \ldots, D_d)$, $Z_i = Z_i(O_1, \ldots, O_{i-1})$, $E(D(O_i, Z_i) \mid O_1, \ldots, O_{i-1}) = 0$. *Let* $\Sigma_i^2 \equiv ED(O_i, Z_i)^2 \equiv ED(O_i, Z_i)D(O_i, Z_i)^\top$ *and* $V_i^2 \equiv E\left(D(O_i, Z_i)^2 \mid O_1, \ldots, O_{i-1}\right)$. *Let* $\Sigma^2(n) \equiv \frac{1}{n}\sum_{i=1}^{n} \Sigma_i^2$ *and* $W(n)^2 \equiv$

$\frac{1}{n}\sum_{i=1}^n V_i^2$. *For each* $\lambda \in \mathbb{R}^d$, *let* $s(n,\lambda)^2/n = 1/n\sum_{i=1}^n \lambda^\top \Sigma_i^2 \lambda = \lambda^\top \Sigma^2(n)\lambda$, $w(n,\lambda)^2/n = \frac{1}{n}\sum_{i=1}^n \lambda^\top V_i^2 \lambda = \lambda^\top W^2(n)\lambda$.

Assume, $\max_j \parallel D_j \parallel_\infty < M < \infty$, $\liminf_n s(n,\lambda)^2/n = \liminf_n \lambda^\top \Sigma^2(n)\lambda > 0$, *and*

$$\lambda^\top \left(\frac{1}{n}\sum_{i=1}^n P_{Q_0,g_i} D^2 - E\frac{1}{n}\sum_{i=1}^n P_{Q_0,g_i} D^2 \right) \lambda \to 0 \tag{69}$$

in probability as $n \to \infty$.

Then $w(n,\lambda)^2/s(n,\lambda)^2 \to 1$ *in probability, and*

$$\frac{\lambda^\top M(n)}{s(n,\lambda)} \Rightarrow_D N(0,1).$$

Secondly, we apply the Cramér-Wold theorem (Theorem 3.2.4 in Sen and Singer (1993)) which states that $\sqrt{n}M_n \Rightarrow_D Z$ in $\mathbb{R}^d$ if and only if for every fixed $\lambda \in \mathbb{R}^d$, we have $\lambda^\top \sqrt{n} M_n \Rightarrow_D \lambda^\top Z$. This proves Theorem 17.

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