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Statistical Learning of Origin-Specific Statically Optimal Individualized Treatment Rules

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Abstract

Consider a longitudinal observational or controlled study in which one collects chronological data over time on n randomly sampled subjects. The time-dependent process one observes on each randomly sampled subject contains time-dependent covariates, time-dependent treatment actions, and an outcome process or single final outcome of interest. A statically optimal individualized treatment rule (as introduced in van der Laan, Petersen & Joffe (2005), Petersen & van der Laan (2006)) is a (unknown) treatment rule which at any point in time conditions on a user-supplied subset of the past, computes the future static treatment regimen that maximizes a (conditional) mean future outcome of interest, and applies the first treatment action of the latter regimen. In particular, Petersen & van der Laan (2006) clarified that, in order to be statically optimal, an individualized treatment rule should not depend on the observed treatment mechanism. Petersen & van der Laan (2006) further developed estimators of statically optimal individualized treatment rules based on a past capturing all confounding of past treatment history on outcome. In practice, however, one typically wishes to find individualized treatment rules responding to a user-supplied subset of the complete observed history, which may not be sufficient to capture all confounding. The current article provides an important advance on Petersen & van der Laan (2006) by developing locally efficient double robust estimators of statically optimal individualized treatment rules responding to such a user-supplied subset of the past. However, failure to capture all confounding comes at a price; the static optimality of the resulting rules becomes origin-specific. We explain origin-specific static optimality, and discuss the practical importance of the proposed methodology. We further present the results of a data analysis in which we estimate a statically optimal rule for switching antiretroviral therapy among patients infected with resistant HIV virus.

1 Introduction.

Consider a longitudinal observational or controlled study in which one collects data over time on n randomly sampled subjects. The time-dependent process one observes on each randomly sampled subject contains time-dependent covariates, time-dependent treatment actions, and either an outcome process or a single final outcome of interest. This time-dependent process is a random variable defined by the experiment which randomly samples a subject and subsequently measures this time-dependent process. In statistical learning one refers to this random variable as the experimental unit. The statistical question we are concerned with can be stated as follows: Can we use data consisting of n such time-dependent processes to estimate a treatment rule that responds to a user-supplied subset of a subject's measured history in such a way that it aims to maximize the mean outcome of interest? Treatment rules of this type, which respond to individual covariates, are called individualized treatment rules or dynamic treatment regimes.

In order to address the question of interest, we focus on estimation of statically optimal individualized treatment rules. A statically optimal individualized treatment rule is an (unknown) treatment rule which at any point in time conditions on a user-supplied subset of the past, computes the future static treatment regimen maximizing a (conditional) mean future outcome of interest, and applies the first treatment action of the latter regimen. We refer to this treatment rule as a *statically-optimal individualized treatment rule*, to distinguish it from an optimal dynamic treatment regime as modelled in Murphy (2003) and Robins (2003).

We first introduced statically optimal individualized treatment rules in our article van der Laan et al. (2005) in which we introduced (observed) history-adjusted marginal structural models (HA-MSM). However, as made explicit in Petersen et al. (2006), the optimality of rules estimated by HA-MSM can depend on the treatment mechanism of the observed data, and as a result, the HA-MSM-derived rule can fail to select the optimal future treatment plan (given individual covariate values) if applied to an equivalent population with a different observed treatment mechanism. Dependence on observed treatment mechanism implies, in particular, that the rule can fail to select the statically optimal treatment at each time point in the setting where the rule itself has been applied to the population beginning at baseline (as, for example, would occur if the rule were tested in a clinical trial). As a result, Petersen et al. (2006) refine the definition of static optimality to specify that a statically optimal rule must not depend on observed treatment mechanism. They further point out that HA-MSM-derived rules are only truly statically optimal if the covariates in the history-adjusted marginal structural model are sufficient to capture all confounding of past treatment on outcome.

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The statically optimal rules discussed by Petersen et al. (2006) have the attractive property that they select the optimal future treatment plan *regardless* of how past treatment has been assigned. As a result, these rules will retain their static optimality if applied to an exchangeable population that has been following the rule in question (as would occur in the context of a clinical trial) or if applied to an exchangeable population that has been following some unknown treatment mechanism (as could occur in the course of clinical practice). In order to achieve this generality, however, the statically optimal rules must incorporate sufficient covariate history to control for confounding of past treatment history on outcome.

Due to limited resources, practical sensibility, and reliability, clinical trials will be forced to focus on candidate individualized treatment rules which only respond to a small number of user-supplied bio-markers or other relevant measurements. The current article provides an important advance by presenting models and corresponding locally efficient double robust estimators of individualized treatment rules responding to a *user-supplied* subset of a subject's past. However, failure to incorporate sufficient covariates to control for confounding has a price: the static optimality of the resulting rules is *origin-specific*. In other words, the individualized treatment rules described in this paper retain their optimality only in settings where the population has been following the rule itself beginning at baseline (or in other words, a since a specified origin). Thus the origin-specific statically optimal rules described in this paper are appropriate for evaluation in the context of a clinical trial, but not for application to an individual who has been following an unknown past treatment mechanism, as may occur in the context of clinical practice.

1.1 Organization of article.

In Section 2 we define the observed data and a statistical framework/model for the data generating distribution in which we formally state the statistical learning problem to be addressed. In particular, we define the origin-specific statically optimal treatment rule. We introduce a novel parameter, the counterfactual history-adjusted mean outcome, which represents a mean outcome conditional on a user-supplied subset of the past in the counterfactual world in which each subject follows a particular static treatment regimen. We then show that the counterfactual history-adjusted mean implies our desired origin-specific statically optimal rule. We further demonstrate the identifiability of the statically optimal individualized treatment rule. Our model corresponds with only modelling the counterfactual history-adjusted mean outcome, while leaving all nuisance parameters unspecified. In Section 3 we derive the class of all estimating functions in this model for the data generating distribution, which are orthogonal to the nuisance parameters and thereby result in robust

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estimation procedures. These estimating functions for the parameter of interest are indexed by nuisance parameters: the treatment mechanism, and the conditional distributions of the covariates given the past. However, due to the orthogonality property of these estimating functions, they remain unbiased if one (not both) of these two nuisance parameters is misspecified. In the literature these estimating functions are referred to as double robust inverse probability of treatment weighted (IPTW) estimating functions (van der Laan and Robins (2003)). By assuming models for these two nuisance parameters, which represent factors in the likelihood of the observed data, and estimating them accordingly with maximum likelihood procedures, we obtain double robust IPTW estimators of the origin-specific statically optimal individualized treatment rules. In Section 4 we discuss statistical inference. In Section 5 we review conditions under which the origin-specific statically optimal treatment rule estimated using the counterfactual history-adjusted mean parameter, as presented in this paper, is equivalent to the statically optimal rule defined by Petersen et al. (2006). Section 6 presents the results of a data analysis drawn from the treatment of patients infected with resistant HIV. We estimate origin-specific statically optimal individualized rules for deciding when to switch antiretroviral therapy regimen among patients with incomplete virologic suppression due to resistant virus. Section 7 discusses various generalizations of practical interest.

2 The origin-specific statically optimal individualized treatment rule and counterfactual history-adjusted mean.

We adopt the counterfactual causal inference framework in order to formally define the origin-specific statically optimal individualized treatment rule, and the counterfactual history-adjusted mean outcome on which it is based, as parameters of the data generating distribution.

2.1 The statistical framework.

The observed data structure on a randomly sampled subject is defined as a missing data structure on the set of treatment-specific time-dependent processes, where each treatment-specific process represents the counterfactual data we would have observed on the subject, if, possibly contrary to the fact, the subject would have followed that particular treatment regimen. In addition, we make the sequential randomization assumption (defined below), allowing us to identify the probability distribution of the counterfactual processes, and

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thereby allowing us to learn causal parameters of interest from the observed data.

Representation of the observed data as a missing data structure. The chronological data structure observed on a randomly sampled subject/ experimental unit is given by

$$O = (L(0), A(0), L(1), A(1), \ldots, L(T-1), A(T-1), L(T)),$$

where $L(t)$ is data collected at time t, $A(t)$ is treatment at time t assigned after $L(t)$, $T \leq K+1$ is a fixed end-point or a random end-point such as death and $K+1$ denotes a maximal follow up time. It is assumed that for each subject and each possible treatment regimen $\bar{a} = (a(0), \ldots, a(K)) \in \mathcal{A}$ there exists a process $L_{\bar{a}} = L_{\bar{a}}(0), \ldots, L_{\bar{a}}(T_{\bar{a}})$, and that the observed process L on the subject is the treatment-specific process indexed by the treatment regimen the subject actually took: $L = L_{\bar{A}}$. Here $\mathcal{A}$ denotes the support of the random treatment process $\bar{A} = (A(0), \ldots, A(K))$. Thus, we define a collection of treatment-specific time-dependent processes $(L_{\bar{a}}(t) : 0 \leq t \leq T_{\bar{a}})$, stopped by some possibly random stopping time $T_{\bar{a}}$, and indexed by a treatment regimen $\bar{a} = (a(0), \ldots, a(K))$.

We assume that there is an experiment resulting in the observation of all these random processes, and we denote this random variable with $X = (L_{\bar{a}} : \bar{a} \in \mathcal{A})$ (in the censored data literature, X is often referred to as the full data). Let P_{X0} denote the probability distribution of this collection X of treatment-specific processes. It is assumed that $L_{\bar{a}}(t) = L_{\bar{a}(t-1)}(t)$, where we use the notation $\bar{a}(t) = (a(0), \ldots, a(t))$. The latter assumption is implied by the time-ordering assumption that $A(t)$ occurs after $L(t)$ and before $L(t+1)$. We make the convention that $L_{\bar{a}}(t) = L_{\bar{a}}(\min(t, T_{\bar{a}}))$ and $A(t) = A(\min(t, T-1))$, so that these processes are also defined after the stopping time. Let $Y_{\bar{a}}(t)$ be a treatment-specific outcome process, and $S_{\bar{a}}(t)$ denote the components of $L_{\bar{a}}(t)$ on which the individualized treatment rule is based. It is assumed that $S_{\bar{a}}(t)$ includes the stopping time indicator process $I(T_{\bar{a}} \leq t)$. To conclude, the observed data structure O on a randomly sampled subject can be represented as

$$O = (\bar{A}, L_{\bar{A}}),$$

or equivalently,

$$O = (L(0), A(0), L_{A(0)}(1), A(1), \ldots, L_{\bar{A}(T-2)}(T-1), A(T-1), L_{\bar{A}(T-1)}(T)),$$

where $T = T_{\bar{A}}$. Thus the observed random process O is a missing data structure on the full data structure X.

Let $G_0(\cdot \mid X)$ denote the conditional probability distribution of $\bar{A}$ given X, which is called the treatment mechanism since it determines how treatment is assigned. We note that the observed data structure O is a random variable

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with a probability distribution P_{P_{X0},G_0} implied by P_{X0} and $G_0(\cdot \mid X)$. We assume that we observe n i.i.d. copies $O_1, \ldots, O_n$ of this random variable $O \sim P_{P_{X0},G_0}$.

Sequential randomization assumption. In order to be able to identify parameters of the probability distribution of X from the probability distribution of O, we assume the coarsening at random assumption on the missingness/ treatment mechanism $G_0(\cdot \mid X)$. That is,

$$\begin{aligned} g_0(\bar{a}(T_{\bar{a}}-1) \mid X) &\equiv \prod_{t=0}^{T_{\bar{a}}-1} \Pr(A(t)=a(t) \mid \bar{A}(t-1)=\bar{a}(t-1), X) \\ &= \prod_{t=0}^{T_{\bar{a}}-1} \Pr(A(t)=a(t) \mid \bar{A}(t-1), \bar{L}_{\bar{A}}(t)). \end{aligned}$$

In the context of causal inference this is often referred to as the sequential randomization assumption.

In the following sections we first define the origin-specific statically optimal treatment rule. We then show that this rule identified by the counterfactual history-adjusted mean, a parameter of P_{X0}.

2.2 The origin-specific statically optimal individualized treatment rule.

We begin by defining counterfactuals indexed by individualized treatment rules. For a given rule d with treatment assignment at time t a function of $\bar{L}(t)$, the corresponding counterfactual process L_d is a random variable defined by the deterministic function of the collection of treatment-specific processes $X = (L_{\bar{a}} : \bar{a})$ and the rule d given by $L_d \equiv L_{\bar{a}(d,X)}$, where $\bar{a}(d, X)$ is the treatment vector assigned by rule d for a subject with full data structure X. Thus, counterfactual processes/random variables L_d indexed by any individualized treatment rule d are also well defined, given our definition of static treatment regimen-specific processes $L_{\bar{a}}$ for all $\bar{a}$.

Using this definition of a counterfactual covariate process indexed by an individualized treatment rule, we provide the following definition of an origin-specific statically optimal treatment rule. $Y_d(t, m)$ is a future rule-specific (counterfactual) outcome such as, for example, $Y_d(t+m)$ for some user-supplied integer $m \geq 0$. In order to keep some generality, we allow this outcome $Y_d(t, m)$ to be any function of the future outcome process $(Y_d(s) : s \geq t)$ starting at time t, indexed by a scalar m. We let d_t denote the function assigning the treatment decision under rule d at time t, $\bar{d}_t = (d_0, d_1, \ldots, d_t)$ and $\underline{a}(t)$ denote a future static treatment regimen beginning at time t, $\underline{a}(t) = (a(t), a(t+1), \ldots, a(K))$. We use $K(m)$ to denote the last time point t for which $Y(t, m)$ is defined.

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For example, if $Y(t,m) = Y(t+m)$, then $Y(t,m)$ is only defined for $t = 0, ..., K(m) = K + 1 - m$.

Note that T represents a stopping time that defines the end of the full data of interest, rather than simply a censoring event acting as an additional missingness mechanism on the full data. For example, T may represent death or a specific failure time of interest; in such cases T will generally be incorporated explicitly in the outcome. For example, if T represents death, the outcome of interest may be survival; i.e. $Y(t,m) = I(T > t+m)$. Alternatively, the outcome of interest might include both T and a covariate process. For example, a researcher interested in disease progression might consider an outcome that reflects both whether a patient is still alive, and if so, whether a biomarker of interest (W) has crossed a given threshold (th); i.e. $Y(t,m) = I(T > t+m)I(W(t+m) > th)$. Note that if T represents death, then defining the outcome using only a covariate process, without incorporating T explicitly, will result in a covariate outcome defined for time points following a patient's death (specifically, an outcome reflecting the last measurement of the covariate prior to death). In most cases such an outcome will not be of interest. An alternative incorporation of T into the parameter of interest is presented in the data example in Section 6.

Definition 1 *Below we define an* origin-specific statically optimal dynamic treatment rule

$$\bar{d}_K \equiv \bar{d}_K(\bar{S}_d(K)) = (d_0(S(0)), d_1(\bar{S}_d(1)), \ldots, d_K(\bar{S}_d(K))),$$

where each function $\bar{S}_d(t) \rightarrow d_t(\bar{S}_d(t))$ *describes how* $A(t)$ *is assigned in response to* $\bar{S}_d(t)$ *for all* $t = 0, \ldots, K$.

This rule d *is defined by the following algorithm:*

$$\begin{aligned}
\underline{a}^*(0 \mid S(0)) &= \arg\max_{\underline{a}(0)} E(Y_{0,\underline{a}(0)} \mid S(0)) \\
d_0 &\equiv \underline{a}^*(0 \mid S(0))(1) \\
\underline{a}^*(1 \mid \bar{S}_{d_0}(1)) &= \arg\max_{\underline{a}(1)} E(Y_{d_0,\underline{a}(1)} \mid \bar{S}_d(1)) \\
d_1 &\equiv \underline{a}^*(1 \mid \bar{S}_d(1))(1) \\
\underline{a}^*(t \mid \bar{S}_d(t)) &= \arg\max_{\underline{a}(t)} E(Y_{\bar{d}_{t-1},\underline{a}(t)} \mid \bar{S}_d(t)) \\
d_t &= \underline{a}^*(t \mid \bar{S}_d(t))(1),\ t = 2, \ldots, K(m),
\end{aligned}$$

where $Y_{\bar{d}_{t-1},\underline{a}(t)} \equiv Y_{\bar{d}_{t-1},\underline{a}(t)}(t,m)$ *is the counterfactual random variable corresponding to following the treatment rule* d *from time* 0 *to time* $t-1$, *and then static treatment regimen* $\underline{a}(t)$. *Similarly,* $\bar{S}_d(t) \equiv \bar{S}_{\bar{d}_{t-1}}(t)$ *is the counterfactual*

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random variable corresponding to following the treatment rule d from time point 0 to time $t-1$. $\underline{a}^*(t \mid \bar{S}_d(t))(1)$ is used to denote the first component of the optimal static treatment regimen $\underline{a}^*(t \mid \bar{S}_d(t))$.

For time points $t = K(m)+1, ..., K$, the rule d_t assigns the next action of the static regimen

$$\underline{a}^*(K(m) \mid \bar{S}_d(K(m))) = \arg \max_{\underline{a}(K(m))} E(Y_{\bar{d}_{K(m)-1}, \underline{a}(K(m))} \mid \bar{S}_d(K(m)))$$

Note that the origin-specific statically optimal rule must assign treatment deterministically at every time point. Thus, while in many settings there may be several choices of $\underline{a}(t|\bar{S}_d(t))$ that optimize the expected outcome (i.e. the $\arg\max_{\underline{a}(t)}$ is not unique), in this case the user must specify a deterministic way of choosing between these choices. Further, note that the rule defines a treatment decision for each time point up till time K for each subject, even though the full data of interest for some subjects may end at time T. However, as T denotes the end of the full data for a subject, treatment decisions occurring after T will not be relevant for the counterfactuals of interest.

The origin-specific statically optimal treatment rule of Definition 1 satisfies the following property: it selects, at each time point t, the initial treatment of the future *static* regimen ($\underline{a}(t)$) which optimizes the expected outcome $Y(t,m)$, given the history $\bar{S}(t)$, *in the world* where treatment up till that time point corresponds to following the statically optimal treatment rule d (and thus $\bar{S}(t) = \bar{S}_d(t)$ and the counterfactual outcome is also indexed by $\bar{d}_{t-1}$). We specify that the rule is *origin-specific* to clarify that, if applied to a population with an identical full data generating distribution, the rule will assign the optimal future static regimen at each time point if past treatment (beginning at baseline, or the origin) has been assigned according to the rule itself. Thus the rule is appropriate for evaluation in the context of a clinical trail, where the rule itself is applied beginning at enrollment. The origin-specific statically optimal rule can be distinguished from the statically optimal rule defined by Petersen et al. (2006), in that the latter selects the optimal future static regimen at each time point *regardless* of how past history has been assigned.

2.3 The counterfactual history-adjusted mean outcome and corresponding treatment rule.

In this section, we show that the origin-specific statically optimal treatment rule is a function of the counterfactual history-adjusted mean outcome. We first define the counterfactual history-adjusted mean outcome as a parameter of the full data generating distribution, and define an individualized treatment rule based on this parameter. Next, we show that this treatment rule is equivalent to the origin-specific statically optimal treatment rule, and thus that the counterfactual history-adjusted mean outcome identifies the rule of interest.

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The counterfactual history-adjusted mean outcome is defined as

$$E(Y_{\bar{a}(t-1),\underline{a}(t)}(t,m) \mid \bar{S}_{\bar{a}(t-1)}(t)), \tag{1}$$

This counterfactual history-adjusted mean outcome provides us with the following individualized treatment rule:

Definition 2 *Define*

$$\theta_0(t,\underline{a}(t) \mid \bar{a}(t-1),\bar{s}(t)) \equiv E(Y_{\bar{a}(t-1),\underline{a}(t)} \mid \bar{S}_{\bar{a}(t-1)}(t)=\bar{s}(t)).$$

We define the following treatment rule:

$$\bar{d}_K(\theta_0)(\bar{S}(K)) = (d_0(S(0)), d_1(\bar{S}(1)), \ldots, d_K(\bar{S}(K))),$$

where each function $\bar{S}(t) \rightarrow d_t(\bar{S}(t))$ describes how $A(t)$ is assigned in response to $\bar{S}(t)$ for all $t = 0, \ldots, K$.

This rule $\bar{d}_K(\theta_0)$ is defined by the following algorithm applied to $\bar{S}(K) = (S(0), \ldots, S(K))$:

$$\begin{aligned}
\underline{a}^*(0 \mid S(0)) &= \arg\max_{\underline{a}(0)} \theta(0,\underline{a}(0) \mid S(0)) \\
d_0(S(0)) &\equiv \underline{a}^*(0 \mid S(0))(1) \\
\underline{a}^*(1 \mid \bar{S}(1)) &= \arg\max_{\underline{a}(1)} \theta(1,\underline{a}(1) \mid d_0(S(0)), \bar{S}(1)) \\
d_1(\bar{S}(1)) &\equiv \underline{a}^*(1 \mid \bar{S}(1))(1) \\
\underline{a}^*(t \mid \bar{S}(t)) &= \arg\max_{\underline{a}(t)} \theta(t,\underline{a}(t) \mid \bar{d}_{t-1}(\bar{S}(t-1)), \bar{S}(t)) \\
d_t(\bar{S}(t)) &= \underline{a}^*(t \mid \bar{S}(t))(1),\ t = 2, \ldots, K(m).
\end{aligned}$$

Here we use the notation $\bar{d}_{t-1}(\bar{S}(t-1)) \equiv (d_0(S(0)), d_1(\bar{S}(1)), \ldots, d_{t-1}(\bar{S}(t-1)))$ for the first $t-1$ components of the dynamic treatment rule d applied to $\bar{S}(t-1)$, where we note that $\bar{d}_t(\bar{S}(t))$ corresponds to a specific $\bar{a}(t)$. As above, $\underline{a}^*(t \mid \bar{S}(t))(1)$ denotes the first component of the optimal static treatment regimen $\underline{a}^*(t \mid \bar{S}(t))$. And as above, for time points $t = K(m)+1, ..., K$, the rule d_t assigns the next action of the static regimen

$$\underline{a}^*(K(m) \mid \bar{S}(K(m))) = \arg\max_{\underline{a}(K(m))} \theta(t,\underline{a}(K(m)) \mid \bar{d}_{K(m)-1}(\bar{S}(K(m)-1)), \bar{S}(K(m)))$$

We now show that, once we condition on the covariates on which the treatment rule depends, $E(Y_{\bar{a}(t-1),\underline{a}(t)} \mid \bar{S}_{\bar{a}(t-1)}(t) = \bar{s}(t))$ is equal to $E(Y_{\bar{d}_{t-1},\underline{a}(t)} \mid \bar{S}_d(t) = \bar{s}(t))$ at a particular $\bar{a}(t-1)$, and thus the origin-specific statically optimal regimen of interest (Definition 1) is identified by applying Definition 2 to the counterfactual history-adjusted mean (1). This is because, as shown in Definition 1, given $\bar{s}(t)$, the origin-specific statically optimal treatment rule applied at time t corresponds to a deterministic choice of $a(t)$, $t = 0, ..., K$. We presents these results formally as a Lemma:

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Lemma 1 *Define*

$$\theta_0(t, \underline{a}(t) \mid \bar{a}(t-1), \bar{s}(t)) \equiv E(Y_{\bar{a}(t-1),\underline{a}(t)}(t, m) \mid \bar{S}_{\bar{a}(t-1)}(t) = \bar{s}(t)),$$

Given a dynamic treatment rule $\bar{S}(K) \rightarrow d(\bar{S}(K))$*, we have*

$$E(Y_{\bar{d}_{t-1}\underline{a}(t)}(t, m) \mid \bar{S}_d(t) = \bar{s}(t)) = \theta(t, \underline{a}(t) \mid \bar{a}_{\bar{d}_{t-1}}(t-1), \bar{s}(t)), \qquad (2)$$

where $Y_{\bar{d}_{t-1}\underline{a}(t)}(t, m)$ *is the counterfactual random variable corresponding with following rule* d *from time* 0 *till* $t-1$*, and subsequently, following the static treatment regimen* $\underline{a}(t)$*. Note that* $Y_{\bar{d}_{t-1}\underline{a}(t)}(t, m)$ *is a random variable defined as a deterministic function of* X*, the rule* d*, and static treatment* $\underline{a}(t)$*. We use* $\bar{a}_{\bar{d}_{t-1}}$ *to denote the treatment history (through time* t*) corresponding to applying rule* d *to* $\bar{s}(t-1)$*.*

Proof Given $\bar{S}_d(t) = \bar{S}_{\bar{d}_{t-1}}(t) = \bar{s}(t)$, we have that $\bar{d}_{t-1} = (a(0), \ldots, a(t-1))$ for some fixed $\bar{a}_{\bar{d}_{t-1}}(t-1)$ defined by $\bar{s}(t)$. Thus, given $\bar{S}_d(t) = \bar{s}(t)$, with probability equal to 1 we have $Y_{\bar{d}_{t-1}\underline{a}(t)}(t, m) = Y_{\bar{a}_{\bar{d}_{t-1}}(t-1)\underline{a}(t)}(t, m)$ and $\bar{S}_d(t) = \bar{S}_{\bar{a}_{\bar{d}_{t-1}}(t-1)}(t)$: that is, counterfactuals indexed by dynamic treatment regimens are identical to counterfactuals indexed by a corresponding static treatment regimen, which proves the result (2). □

Origin-specific static optimality of $d(\theta_0)$**.** The importance of this identity (2) is established as follows. Suppose that the treatment decisions $A(0), \ldots, A(t-1)$ have been assigned according to the treatment rule $d = d(\theta_0)$ so that $A(0) = d_0(S(0)), A(1) = d_1(\bar{S}_d(1)), \ldots, A(t-1) = d_{t-1}(\bar{S}_d(t-1))$, and that we are now confronted with making a treatment decision at time t: thus, we are given the treatment past $\bar{A}(t-1) = \bar{d}_{t-1}(\bar{S}_d(t-1))$ and covariate past $\bar{S}_d(t)$ in the world in which we have been applying rule $d = d(\theta_0)$. We want to show that the origin-specific statically optimal treatment decision at time t, given $\bar{S}_d(t)$, is now precisely given by $d_t(\bar{S}_d(t))$ with $d = d(\theta_0)$. The origin-specific statically optimal treatment decision at time t, given $\bar{S}_d(t)$, is defined by optimizing the wished expected outcome $E(Y_{\bar{d}_{t-1}\underline{a}(t)}(t, m) \mid \bar{S}_d(t) = \bar{s}(t))$ over all static future treatment regimens $\underline{a}(t)$, and carrying out the first component of this latter treatment regimen. By the previous lemma applied to $d = d(\theta_0)$, it follows that at time t, optimizing the wished expected outcome $E(Y_{\bar{d}_{t-1}\underline{a}(t)}(t, m) \mid \bar{S}_d(t) = \bar{s}(t))$ over all statically future treatment regimens $\underline{a}(t)$ is equivalent with optimizing $\theta_0(t, \underline{a}(t) \mid \bar{a}_d(t-1), \bar{s}(t))$ over $\underline{a}(t)$. This proves that indeed the origin-specific statically optimal treatment decision at time t, given $\bar{S}_d(t)$, is now precisely given by $d_t(\bar{S}_d(t))$. Thus, if treatment decisions are assigned deterministically according to rule $d(\theta_0)$, then it follows that at each point in time t, given the observed $\bar{S}(t) = (\bar{S}_d(t)) = \bar{s}(t)$, our treatment decision at time t equals the first treatment in the future treatment

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regimen maximizing the mean outcome of $Y_{\bar{d}_{t-1}\underline{a}(t)}(t,m)$, given $\bar{S}(t) = \bar{s}(t)$, over all future static treatment regimens $\underline{a}(t)$. This proves that indeed the rule $d(\theta_0)$ is an origin-specific statically optimal treatment rule, and thus that estimates of this rule $d(\theta_0)$ are potential candidates for treatment regimens to be evaluated in clinical trials.

In this section we have established that the counterfactual history-adjusted mean θ_0 identifies the origin-specific statically optimal dynamic treatment rule, and illustrated why such a rule is of interest. In the next section we discuss estimation of θ_0, and thus estimation of the origin-specific statically optimal dynamic treatment rule $d(\theta_0)$.

2.4 A model for the counterfactual history-adjusted mean.

In order to deal with the curse of dimensionality, we will assume a model for our parameter of interest $\theta(P_X)(t, \underline{a}(t) \mid \bar{a}(t-1), \bar{s}(t)) = E_{P_X}(Y_{\bar{a}(t-1)\underline{a}(t)}(t,m) \mid \bar{S}_{\bar{a}(t-1)}(t) = \bar{s}(t))$ of P_X:

$$\theta_{P_X}(t, \underline{a}(t) \mid \bar{a}(t-1), \bar{s}(t)) = m_{\beta(P_X)}(t, \underline{a}(t) \mid \bar{a}(t-1), \bar{s}(t)) \tag{3}$$

for some parametrization $(m_\beta : \beta)$ indexed by a Euclidean parameter β. Let $\beta_0 = \beta(P_{X0})$ denote the true parameter value of β. Note that we could also extend the definition of this parameter to the nonparametric model consisting of all full data distributions P_X so that, if this model (3) is wrong, then β_0 can be interpreted as a summary measure of interest of the true θ_0, in the same manner as we might interpret a linear regression fit as a summary measure of the true underlying regression curve.

2.5 Model for observed data.

Because of the sequential randomization assumption, the density of the data structure O can be factorized into a P_{X0}-part and G_0-part as follows:

$$p_{P_{X0},G_0}(O) = Q_{X0}(O) g_0(\bar{A}(T-1) \mid X),$$

where the P_{X0}-part of the density is defined as

$$Q_0(O) = Q_{X0}(O) \equiv \prod_{t=0}^{T} Pr(L(t) \mid \bar{L}(t-1), \bar{A}(t-1)).$$

Our approach is to derive the class of estimating functions for β in the model for the observed data structure O only assuming (3). This results in a class of double robust inverse probability of treatment weighted estimating functions for β indexed by nuisance parameters g_0 and Q_0, where the estimating functions remain unbiased at β_0 if one (but not both) of these two nuisance

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parameters is misspecified. That is, it is not possible to construct consistent estimators of β_0 without either consistently estimating Q_0 or consistently estimating the treatment mechanism g_0. As a consequence, beyond the sequential randomization assumption and the model for θ_0, we either need a model $\mathcal{G}$ for g_0, or a model $\mathcal{Q}$ for Q_{X0}. (Alternatively, we can assume the union model which states that either $g_0 \in \mathcal{G}$ or $Q_{X0} \in \mathcal{Q}$.) Given these models, we assume that valid estimators g_n of g_0 according to model $\mathcal{G}$ and Q_n of Q_0 according to model $\mathcal{Q}$ are provided. For example, in the case that the models are small enough, g_n and Q_n could be maximum likelihood estimators:

$$g_n = \arg\max_{g \in \mathcal{G}} \sum_{i=1}^{n} \log g(\bar{A}_i \mid X_i)$$

$$Q_n = \arg\max_{Q \in \mathcal{Q}} \sum_{i=1}^{n} \log Q(O_i).$$

If the models are large, then it is typically necessary to use a sieve-based maximum likelihood estimator which involves selection of sub-models of $\mathcal{Q}$ and/or $\mathcal{G}$.

2.6 Identifiability of the statically optimal individualized treatment regimen.

In order to identify the statically optimal individualized treatment regimen $d(\theta_0)$ from the observed data probability distribution we need to be able to identify $\theta_0(t, \underline{a}(t) \mid \bar{a}(t-1), \bar{s}(t)) \equiv E_0(Y_{\bar{a}(t-1),\underline{a}}(t, m) \mid \bar{S}_{\bar{a}(t-1)}(t) = \bar{s}(t))$, for all $\bar{a} \in \mathcal{A}$. Thus, it suffices to identify the joint distribution $(Y_{\bar{a}}, S_{\bar{a}})$ for all treatment regimens $\bar{a} \in \mathcal{A}$. This requires the so called experimental treatment assignment assumption (ETA) given by: for all $\bar{a} \in \mathcal{A}$

$$g(\bar{a}(T_{\bar{a}} - 1 \mid X) > 0 \ P_{X0}\text{-a.e.} \tag{4}$$

Equivalently, at each time $t \leq T-1$, we need that for all possible observed histories $\bar{A}(t-1) = \bar{a}(t-1), \bar{L}(t) = \bar{l}(t)$

$$P(A(t) = a(t) \mid \bar{A}(t-1) = \bar{a}(t-1), \bar{L}_A(t) = \bar{l}(t)) > 0 \text{ for all } a(t)$$

compatible with $\bar{a}(t-1)$ in the sense that $\bar{a}(t)$ is a possible regimen: that is, $\bar{a}(t)$ is in the support of $\bar{A}(t)$. Under the ETA, we have that the probability distribution of the treatment-specific counterfactual process $L_{\bar{a}}$ is given by

$$P(L_{\bar{a}} = l) = \prod_{t=0}^{T} Pr(L(t) = l(t) \mid \bar{L}(t-1) = \bar{l}(t-1), \bar{A}(t-1) = \bar{a}(t-1)). \tag{5}$$

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This formula (5) for the probability distribution of $X_{\bar{a}}$ was named the G-computation formula by Robins (Robins (2000)). That is, the $\bar{a}$-specific marginal distribution of X is identified by a simple intervention on the Q_X-part of the density of O. One can evaluate this probability distribution by simulating many realizations from this $\bar{a}$-specific density of a time-dependent process $(L(0), \ldots, L(K+1))$, which, in particular, provides us with a Monte-Carlo approximation of the probability distribution of $(Y_{\bar{a}}, S_{\bar{a}})$. Given our model (3), a large collection of realizations $(Y_{\bar{a}}, S_{\bar{a}})$ can now also be used to obtain the corresponding approximation for β_0. Application of this Monte-Carlo approach to a maximum likelihood-based estimate of Q_{X0} results in a likelihood-based estimator of β_0.

The disadvantage of likelihood-based estimation of β_0 is that a misspecified model for Q_0 immediately implies a biased representation of β_0 so that, for example, testing a null hypothesis $H_0 : \beta_0 = 0$ based on this likelihood-based estimator will practically fail to control the probability on a false rejection of the null hypothesis. We are concerned with constructing maximally robust estimators of β_0. In particular, we are interested in estimating β_0 based on data generated in a clinical trial such as a sequentially randomized trial, in which case the treatment mechanism g_0 is known. The knowledge about g_0 is not of any help for the likelihood-based approach so that, in particular, the likelihood-based estimator still fails to provide a valid test of the null hypothesis when g_0 is known. On the other hand, the inverse probability of treatment weighted (IPTW) and double robust(DR)-IPTW estimators of β_0, presented in the next section, are known to be consistent and asymptotically linear if g_0 is known. In this case, the latter estimators yield an asymptotically valid test of a null hypothesis $H_0 : \beta_0 = 0$, and yield root-n consistent estimators of our origin-specific statically optimal individualized treatment regimen $d(\theta_0)$ accompanied by valid confidence intervals.

3 Double robust inverse probability of treatment weighted estimating functions.

As presented in van der Laan and Robins (2003) (e.g. Chapter 6), given the model m_β, the class of all estimating functions can be represented in terms of a class of double robust IPTW estimating functions, derived by orthogonalizing a class of IPTW estimating functions with respect to the treatment mechanism.

3.1 IPTW estimating functions.

In the next result we provide the class of IPTW estimating functions, and thereby the corresponding class of IPTW estimators of β_0.

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Result 1 *Consider the following class of IPTW-estimating functions for* β_0 *in the model for* O *only assuming* $\theta_0(t, \underline{a}(t) \mid \bar{a}(t-1), \bar{s}(t)) = m_{\beta_0}(t, \underline{a}(t) \mid \bar{a}(t-1), \bar{s}(t))$*:*

$$D_{h,IPTW}(O \mid \beta, g) \equiv \frac{1}{g(\bar{A} \mid X)} \sum_{t=0}^{K(m)} h(t, \bar{A}, \bar{S}(t))(Y(t,m) - m_\beta(t, \underline{A}(t) \mid \bar{A}(t-1), \bar{S}(t))).$$

If (4) holds, then

$$E_0 D_{h,IPTW}(O \mid \beta_0, g_0) = 0.$$

Proof. The conditional expectation of $D_{h,IPTW}(O \mid \beta_0, g_0)$, given X, is given by

$$\sum_{\bar{a}} \sum_{t} h(t, \bar{a}, \bar{S}_{\bar{a}}(t))(Y_{\bar{a}}(t,m) - m_{\beta_0}(t, \underline{a}(t) \mid \bar{a}(t-1), \bar{S}_{\bar{a}}(t)).$$

Now, move the expectation operator within the sums and condition on $\bar{S}_{\bar{a}}(t)$, giving us the term $E(Y_{\bar{a}}(t,m) \mid \bar{S}_{\bar{a}}(t)) - m_{\beta_0}(t, \underline{a}(t) \mid \bar{a}(t-1), \bar{S}_{\bar{a}}(t))$, which equals zero. This completes the proof. □

As a particular choice for the IPTW-estimating function we propose $D_{h^*,IPTW}$ with

$$h^*(t, \bar{A}, \bar{S}(t)) \equiv g(\bar{A} \mid \bar{S}(t)) \frac{d}{d\beta_0} m_{\beta_0}(t, \underline{A}(t) \mid \bar{A}(t-1), \bar{S}(t)),$$

where

$$g(\bar{A} \mid \bar{S}(t)) = \prod_{j=0}^{T-1} g(A(j) \mid \bar{A}(j-1), \bar{S}(\min(j,t)).$$

If the model m_β is linear in β, then h^* does not depend on β and is thus known up to the stabilizing factor $g(\bar{A} \mid \bar{S}(t))$. The advantage of this choice is that the solution $\beta_{n,IPTW}$ of the estimating equation $\sum_{i=1}^n D_{h^*(\beta),IPTW}(O_i \mid \beta, g_n) = 0$ corresponds with a weighted least squares estimator:

$$\beta_{n,IPTW} = \arg\min_\beta \sum_{i=1}^{n} \sum_{t=0}^{K(m)} w_i(t) \left\{ Y_i(t,m) - m_\beta(t, \underline{A}_i(t) \mid \bar{A}_i(t-1), \bar{S}_i(t)) \right\}^2$$

with weights given by

$$w_i(t) \equiv \frac{g_n(\bar{A}_i \mid \bar{S}_i(t))}{g_n(\bar{A}_i \mid X_i)}.$$

This estimator can be calculated with standard regression software applied to a pooled sample in which each subject contributes $K(m)$ lines of data, using the weight option.

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3.2 Double robust IPTW estimating functions for β_0.

In the next result we present the class of double robust IPTW estimating functions

Result 2 *Consider the following class of DR-IPTW-estimating functions for β_0 in the model for O only assuming $\theta_0(t, \underline{a}(t) \mid \bar{a}(t-1), \bar{s}(t)) = m_{\beta_0}(t, \underline{a}(t) \mid \bar{a}(t-1), \bar{s}(t))$:*

$$D_{h,DR}(O \mid g, Q, \beta) \equiv D_{h,IPTW}(O \mid g, \beta) - D_{h,SRA}(O \mid g, Q),$$

where

$$\begin{aligned} D_{h,SRA}(O \mid g, Q) \equiv & \sum_{t=0}^{K(m)} E_{g,Q}(D_{h,IPTW}(O \mid g, \beta(Q)) \mid \bar{A}(t), \bar{L}(t)) \\ & - \sum_{t=0}^{K(m)} E_{g,Q}(D_{h,IPTW}(O \mid g, \beta(Q)) \mid \bar{A}(t-1), \bar{L}(t)). \end{aligned}$$

We have that

$$E_{g_0,Q_0}(D_{h,DR}(O \mid g, Q, \beta_0) = 0,$$

if g satisfies (4), and either $g = g_0$ or $Q = Q_0$.

Given estimators g_n, Q_n, corresponding likelihood-based estimator $\beta(Q_n)$ of β_0 (i.e., the G-computation estimator), and a possibly estimated index h_n, the double robust IPTW estimator $\beta_{n,DR}$ is defined as the solution in β of the estimating equation

$$0 = \sum_{i=1}^{n} D_{h_n,DR}(O_i \mid g_n, Q_n, \beta).$$

If $\beta \to m_\beta$ is linear, then this estimating equation in β is linear in β so that the solution $\beta_{n,DR}$ exists in closed form.

3.3 Special case of counterfactuals indexed by restricted treatment history.

We note that, in the special case that $Y_{\bar{A}}(t, m) = Y_{\bar{A}(t^*(m))}(t, m)$, so that the counterfactuals of interest are only indexed by treatment up till time $t^*(m)$, then the IPTW and DR estimating equations can be altered so that $g(\bar{A}|X) = g(\bar{A}(t^*(m))|X)$ and $h(t, \bar{A}, \bar{S}(t)) = h(t, \bar{A}(t^*(m)), \bar{S}(t))$. Such a situation occurs, for example, if the outcome of interest is $Y(t+m)$, so that the counterfactuals are indexed by treatment only until the outcome is measured

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at time $\bar{A}(t+m-1)$. In this case, the IPTW estimating function can be written as:

$$D_{h,IPTW}(O \mid \beta, g) \equiv \sum_{t=0}^{K(m)} \frac{h(t, \bar{A}(t^*(m)), \bar{S}(t))}{g(\bar{A}(t^*(m)) \mid X)}$$
$$(Y(t,m) - m_\beta(t, \underline{A}(t, t^*(m)) \mid \bar{A}(t-1), \bar{S}(t))),$$

where $\underline{A}(t, t^*(m)) = (A(t), A(t+1), ..., A(t^*(m)))$ denotes future treatment until the outcome is measured. We modify h^* accordingly to

$$h^*(t, \bar{A}(t^*(m))), \bar{S}(t)) \equiv g(\bar{A}(t^*(m) \mid \bar{S}(t)) \frac{d}{d\beta_0} m_{\beta_0}(t, \underline{A}(t, t^*(m)) \mid \bar{A}(t-1), \bar{S}(t)),$$

where

$$g(\bar{A}(t^*(m)) \mid \bar{S}(t)) = \prod_{j=0}^{t^*(m)} g(A(j) \mid \bar{A}(j-1), \bar{S}(\min(j,t))).$$

The corresponding DR-IPTW estimating function is derived simply by subtracting off

$$\begin{aligned} D_{h,SRA}(O \mid g, Q) \equiv & \sum_{t=0}^{K(m)} E_{g,Q}(D_{h,IPTW}(O \mid g, \beta(Q)) \mid \bar{A}(t), \bar{L}(t)) \\ & - \sum_{t=0}^{K(m)} E_{g,Q}(D_{h,IPTW}(O \mid g, \beta(Q)) \mid \bar{A}(t-1), \bar{L}(t)). \end{aligned}$$

4 Statistical inference.

Under appropriate conditions, and the assumption that either g_n converges to g_0 or Q_n converges to Q_0, it can be shown that these estimators of β_0 are asymptotically linear with specified influence curve (see van der Laan and Robins (2003) chapter 2). For example, if g_n converges to g_0, and Q_n converges to a possibly misspecified Q_1, then under regularity conditions, we have that $\beta_{n,DR}$ is a consistent and asymptotically linear estimator of β_0 with influence curve

$$IC(O) \equiv -c(\beta_0)^{-1} D_{h,DR}(O \mid g_0, Q_1, \beta_0) - \Pi(-c(\beta_0)^{-1} D_{h,DR} \mid T_G(P_0)),$$

where

$$c(\beta) = \frac{d}{d\beta} E_0 D_{h,DR}(O \mid g_0, Q_1, \beta)$$

is the usual derivative matrix of the estimating equation, $T_G(P_0)$ is the tangent space of the nuisance parameter g at P_0 under model $\mathcal{G}$, and $\Pi(\cdot \mid T_G(P_0))$

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is the projection operator onto this tangent space within the Hilbert space $L_0^2(P_0)$ endowed with covariance inner product $\langle f_1, f_2 \rangle = E_0 f_1(O) f_2(O)$. As a consequence, conservative inference can be based upon the following influence curve, which is simple to calculate:

$$IC^*(O) \equiv -c(\beta_0)^{-1} D_{h,DR}(O \mid g_0, Q_1, \beta_0).$$

In particular, in the case that $\mathcal{G}$ is correctly specified, a conservative asymptotic 0.95 confidence interval for $\beta_0(j)$ is given by

$$\beta_{n,DR}(j) \pm 1.96\sigma_n/\sqrt{n},$$

where

$$\sigma_n^2 \equiv \frac{1}{n}\sum_{i=1}^{n}\left(IC_n^*(O_i) - \frac{1}{n}\sum_{i=1}^{n} IC_n^*(O_i)\right)^2,$$

and IC_n^* is an estimator of the function IC^* obtained by substituting the estimators g_n, Q_n, and estimating the derivative matrix $c(\beta_0)$ with its empirical counterpart.

Since influence curve inference is heavily based on the first-order behavior of the estimator, in the case that g_n and Q_n are highly data-adaptive estimators we suggest the bootstrap method as a more honest method for establishing the true variability of $\beta_{n,DR}$ and obtaining corresponding confidence intervals.

Regarding inference for the individualized treatment rule $d(\theta_0) = d(\beta_0)$, we propose to use an estimate of the sampling distribution of β_{nDR}. For example, one could use as estimate of this sampling distribution the distribution $\beta_{nDR}^{\#} \sim N(\beta_{nDR}, \sigma_n^2/n)$ or the bootstrap distribution of β_{nDR} defined by the distribution of the double robust IPTW estimator when applied to samples of n i.i.d. observations from the empirical distribution. In this manner, one can obtain the sampling distribution of $d_t(\beta_{nDR}^{\#})(\bar{S}(t))$ for treatment assignment at time t for any given history $\bar{S}(t)$. That is, the estimate $d(\beta_{nDR})$ of the statically optimal individualized treatment rule will be accompanied with a measure of uncertainty when applied at any time t and history $\bar{S}(t)$.

5 Comparison with statically optimal treatment rules.

In the preceding sections, we have illustrated how an origin-specific statically optimal treatment rule can be estimated based on the counterfactual history-adjusted mean outcome. The results of Petersen et al. (2006) demonstrate that this treatment rule is also statically optimal in a more general sense when the following equality holds:

$$E(Y_{\bar{A}(t-1)\underline{a}(t)} | \bar{A}(t-1) = \bar{a}(t-1), \bar{S}(t) = \bar{s}(t)) = E(Y_{\bar{a}(t-1)\underline{a}(t)} | \bar{S}_{\bar{a}}(t) = \bar{s}(t)). \quad (6)$$

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Specifically, when the counterfactual history-adjusted mean outcome equals the observed history-adjusted mean outcome (as estimated using the history-adjusted marginal structural models of van der Laan et al. (2005)) then the static optimality of the individualized treatment given by Definition 2 is no longer origin-specific. That is, if equality (6) holds, then the resulting rule chooses the future static treatment plan expected to optimize outcome, regardless of how past treatment has been assigned. The rule thus retains its optimality properties not only if applied to a population that has been following the rule of interest, but also if applied to a population that has been following some other treatment mechanism.

There are several practical implications of this finding. If $\bar{S}(t)$ is chosen so that equality (6) holds, the individualized treatment rules estimated using the counterfactual history-adjusted mean will gain an additional property; they will be generally statically optimal rather than origin-specific statically optimal, and thus will be appropriate for application in contexts where the past treatment mechanism is unknown. This suggests that, if general static optimality is desirable, the researcher may wish to choose the covariates to be included in the rule accordingly.

Petersen et al. (2006) provide criteria for $\bar{S}$ sufficient to ensure (general) static optimality. Specifically, equality (6) will hold if the covariates on which the rule depends are sufficient to control for confounding of past treatment history on future outcome. More formally,

$$\begin{aligned}
&\text{If } P(\bar{A}(t-1) = \bar{a}(t-1) | Y_{\bar{a}} = y, \bar{S}_{\bar{a}}(t) = \bar{s}(t)) \\
&= P(\bar{A}(t-1) = \bar{a}(t-1) | \bar{S}_{\bar{a}}(t) = \bar{s}(t)) \\
&\text{then } E(Y_{\bar{A}(t-1)\underline{a}(t)} | \bar{A}(t-1) = \bar{a}(t-1), \bar{S}(t) = \bar{s}(t)) = E(Y_{\bar{a}(t-1)\underline{a}(t)} | \bar{S}_{\bar{a}}(t) = \bar{s}(t)).
\end{aligned}$$

Petersen et al. (2006) point out that if past treatment assignment is only a function of the covariates of interest $\bar{S}(t)$, or if the covariates of interest $\bar{S}_{\bar{a}}(t)$ *d-separate* $\bar{A}(t-1)$ from $Y_{\bar{a}}(t, m)$, then this identity will hold, and estimation of either the observed history-adjusted parameter or the counterfactual history-adjusted parameter will estimate the (general) statically optimal treatment rule.

Inclusion of sufficient covariates in the rule to ensure that past treatment assignment is only a function of $\bar{S}(t)$ may be undesirable or unpractical. In the case where this condition is not met, the question may still arise as to whether the static optimality of a rule based on the counterfactual history-adjusted mean is origin-specific. The *d-separation* criteria provides one means to evaluate the claim of general vs. origin-specific static optimality; however, this aproach relies on background knowledge sufficient to inform the underlying causal graph. Alternatively, the observed history-adjusted parameter, as described in van der Laan et al. (2005), can be estimated, and the null hypothesis that the counterfactual history-adjusted parameter is equal to the

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observed history-adjusted parameter (i.e. that equality 6 holds) can be tested, using, for example, a chi-square statistic.

6 Data example: When to switch antiretroviral therapy?

This section describes a data example focused on making treatment decisions for individuals infected with resistant HIV. While antiretroviral regimens are generally able to suppress HIV replication, viral drug resistance frequently emerges. Resistance allows HIV replication to resume, resulting in an increase in the amount of virus detectable in a patient's blood (plasma HIV RNA level or viral load), and potentially accelerating immunologic decline (reflected in a falling CD4 T cell count) and disease progression. Ideally, a patient infected with resistant virus will be switched to a new regimen to which the virus remains susceptible (DHHS (2004)). However, a limited number of antiretroviral regimens are available, and alternative regimens may be more toxic or difficult to adhere to than a patient's current regimen. Given evidence that some antiretroviral regimens continue to confer immunologic benefits in the presence of viral resistance, it is unclear how long the clinician should wait before switching a patient who has lost viral suppression to a new antiretroviral regimen (Deeks (2003). Switching too early risks prematurely depleting future treatment options, while switching too late risks accelerating disease progression, as well as allowing the virus to evolve new resistance mutations. We applied the method described in this paper to estimate an origin-specific statically optimal treatment rule for deciding when to switch therapy among HIV-infected individuals who have lost virologic suppression due to the emergence of resistant virus.

6.1 Data.

The data are drawn from the Study of the Consequences of the Protease Inhibitor Era (SCOPE), an observational clinical cohort of HIV-infected individuals in San Francisco, California. Subjects were followed longitudinally over time, and data were collected on all antiretroviral drug use, AIDS-defining illnesses, use of recreational drugs, adherence to prescribed antiretroviral therapies, homelessness, presence of hepatitis C virus antibody, CD4 and CD8 T cell counts, and plasma HIV RNA levels. In addition, baseline data were collected on demographics (age, sex, income, race), sexual orientation, and treatment history. We denote these covariates $\bar{L}$.

We identified all episodes of virologic failure among patients followed in SCOPE between 2000 and 2004. Virologic failure (t=0) was defined as at

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least 2 detectable and no undetectable plasma HIV RNA levels in either 1) the first 6 months after starting a new regimen; or 2) over a 4 month period on a stable regimen. The outcome of interest for a given time t was CD4 T cell count $m = 8$ months in the future ($Y(t+8) \subset L(t+8)$). The treatment of interest was time until treatment modification (switch), where treatment modification was defined as change or interruption of at least 1 drug in the failing regimen. At each time point during follow up, treatment was defined using a binary variable (A) indicating whether a subject remained on his original non-suppressive therapy ($A = 1$ until a subject switched, after which $A = 0$).

The analysis focused on the 8 months following loss of viral suppression ($t = 0, ..., 8$, and thus $K+1 = 16$, and $K(m) = 8$). However, because a subject could only switch therapy once, counterfactual outcomes of interest were only defined for time points up till the point that a subject switched treatment. If we denote this switching time R (a function of $\bar{A}$), then the full data for a given individual were thus $\bar{L}_{\bar{a}}(T)$, where $T \equiv \min((R + 8 - 1), 16)$.

In the absence of censoring, the observed data thus would have consisted of n i.i.d. copies of

$$O^* = (L(0), A(0), L(1), A(1), ...L(K), A(K), L(K + 1)) = (\bar{A}(T - 1), \bar{L}_{\bar{A}}(T))$$

We note that this observed data, in the absence of censoring, can also be considered a time-dependent process:

$$O^*(t) = (\bar{A}(t - 1), \bar{L}_{\bar{A}}(t)),$$

where $t = 0, ...T$.

However, subjects were further subject to two distinct censoring processes; the full data on a subject could be censored 1)when follow-up ended in 2004, or 2) as a result of death or loss to follow-up (here, we consider death a censoring process rather than an outcome of interest). We denote the time at which censoring occurred due to the end of follow-up as C_1, and the time at which censoring occurred due to death or loss to follow-up as C_2. $C = min(C_1, C_2)$ denotes a subject's censoring time, and we define $\tilde{T} = min(T, C)$. We further define a censoring process over time:

$$\bar{C}(t) = (\bar{C}_1(t), \bar{C}_2(t)) = (I(C_1 \leq t), I(C_2 \leq t))$$

The observed data thus consisted of n i.i.d. copies of

$$O = (O^*(\tilde{T}), \bar{C}(\tilde{T}), \tilde{T})$$

In all, 133 subjects (167 episodes of failure) were evaluated. Of these, 66 episodes were censored due to the end of follow-up in 2004, and 18 were censored due to death or loss to follow-up (3 deaths and 15 losses to follow

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up). In total, 116 episodes (100 subjects) had at least one outcome available (corresponding to $t = 0$). Of these subjects, median time to switch was 6 months (IQR=4,11). The study population was primarily male (86%), and primarily men who have sex with men (49%). Subjects were heavily treatment experienced; 49% were treated with antiretroviral drugs prior to the availability of protease inhibitors in 1996. Petersen et al. (2005) describe the sample in greater detail.

6.2 Parameter of interest.

We aimed to identify the origin-specific statically optimal rule for deciding when to modify treatment, given a specific set of covariates $\bar{S}(t)$. In other words, we estimated for each time point the future switch time expected to maximize CD4 T cell count 8 months later, given covariate values, among individuals who had not yet modified treatment. Following, at each time point, the first action (switch or not) of this optimal treatment plan provided an individualized treatment rule. The static optimality of the rule was *origin-specific* because it identified, for each time point, the optimal future switch time given that subjects had followed the statically optimal rule itself up till that time point.

Specifically, we considered treatment rules based on current CD4 T cell count and an indicator of viral re-suppression prior to switching regimens. The later covariate was included because our goal was to identify rules for switching among individuals who were infected with resistant HIV. Individuals who achieved viral re-suppression without switching regimens almost certainly did not initially lose suppression due to the presence of resistant virus. Thus, $\bar{S}(t) = (CD4(t), Sup(t))$ where $CD4(t)$ denoted CD4 T-cell count at time t, and $Sup(t)$ denoted an indicator that re-suppression of the virus had occurred by time t.

As demonstrated in Lemma 1, the origin-specific statically optimal treatment rule for deciding when to switch (among individuals who have not already switched, i.e. $\bar{a}(t-1) = 1$) is identified by the parameter

$$\begin{aligned}&\theta(t, \underline{a}(t)|\bar{a}(t-1) = 1, Sup_{\bar{a}}(t) = 0, CD4_{\bar{a}}(t))\\ &= E(Y_{\bar{a}(t-1)=1,\underline{a}(t)}(t+8)|Sup_{\bar{a}}(t) = 0, CD4_{\bar{a}}(t)).\end{aligned}$$

We further note that, as the outcome is measured at time $t + 8$, the counterfactuals of interest are in fact indexed only by treatment up till time $t^* = t + 8 - 1$ ($Y_{\bar{a}(t-1)\underline{a}(t)} = Y_{\bar{a}(t-1)\underline{a}(t,t^*)}$), where we remind the reader that $\underline{a}(t, t^*) = (a(t), a(t+1), ..., a(t^*))$.

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6.3 Model for counterfactual history-adjusted mean.

We assumed the following model on the parameter $\theta(t, \underline{a}(t, t^*)|\bar{a}(t-1), \bar{s}(t)) = m_\beta(t, \underline{a}(t, t^*)|\bar{a}(t-1)\bar{s}(t))$, where

$$m_\beta(t, \underline{a}(t, t^*)|\bar{a}(t-1) = 1, Sup(t) = 0, CD4(t)) =$$
$$\beta_0 + \beta_1 \sum_{j=t}^{t^*} a(j) + \beta_2 CD4(t) + \beta_3 t + \beta_4 \sum_{j=t}^{t^*} a(j) \times CD4(t) + \beta_5 \sum_{j=t}^{t^*} a(j) \times t +$$
$$\beta_6 CD4(t) \times t + \beta_7 \sum_{j=t}^{t^*} a(j) \times CD4(t) \times t,$$

where $\sum_{j=t}^{t^*} a(j)$ is the residual amount of time until either treatment is modified or the outcome is measured, under treatment regimen $\underline{a}(t, t^*)$.

6.4 Model for observed data.

Treatment mechanism. As defined in Subsection 2.1, we assumed sequential randomization; in other words, we assumed that the decision whether to switch treatment or not at each time point only depended on covariates measured prior to that time point. In addition, as defined in Subsection 2.6, we assumed experimental treatment assignment; namely that an individual who had not already switched had some positive probability of both switching treatment and not switching, regardless of her observed past.

Censoring mechanism. We assumed that the probability of being censored at every time point, given that censoring had not already occurred, only depended on the observed past (censoring at random):

$$g(\bar{C}(T) = 0|O^*) \equiv \prod_{t=0}^{T} Pr(C > t|\bar{C}(t-1) = 0, O^*)$$
$$= \prod_{t=0}^{T} Pr(C_1 > t|\bar{C}(t-1) = 0, \bar{A}(t-1), \bar{L}(t-1))$$
$$\prod_{t=0}^{T} Pr(C_2 > t|C_1 > t, \bar{C}(t-1) = 0, \bar{A}(t-1), \bar{L}(t-1))$$

We also made two additional identifiability assumptions (counterpart to the experimental treatment assignment assumption). For each type of censoring and every time point, we assumed that, given that censoring had not already occurred, an individual had some positive probability of not being censored regardless of his observed past:

$$Pr(C_1 > t|\bar{C}(t-1) = 0, \bar{A}(t-1), \bar{L}(t-1)) > 0, t = 0, ..., T$$

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and

$$Pr(C_2 > t | C_1 > t, \bar{C}(t-1) = 0, \bar{A}(t-1), \bar{L}(t-1)) > 0, t = 0, ..., T$$

We note that censoring due to the end of follow-up in 2004 (C_1)is not necessarily non-informative, as calender time at baseline ($t = 0$) in the current data analysis is itself a random variable that deterministically predicts censoring due to end of follow-up in 2004, and could also potentially be related to outcome (due to differences in the characterstics of subjects that lose virologic suppression at different calender times).

6.5 IPTW estimation.

In the absence of censoring, the IPTW estimating function would be

$$D_{h,IPTW}(O|\beta, g) \equiv \sum_{t=0}^{K(m)} \frac{h(t, \bar{A}(t^*), \bar{S}(t))}{g(\bar{A}(t^*)|X)}$$
$$I(\bar{A}(t-1) = 1) I(Sup(t) = 0) \{Y(t+8) - m_\beta(t, \underline{A}(t, t^*) | \bar{A}(t-1) \bar{S}(t))\}.$$

We chose h as

$$h^*(t, \bar{A}(t^*) \bar{S}(t)) \equiv g(\bar{A}(t^*)|\bar{S}(t)) \frac{d}{d\beta} m_\beta(t, \underline{A}(t, t^*) | \bar{A}(t-1), \bar{S}(t))$$

where $g(\bar{A}(t^*)|\bar{S}(t) = \prod_{j=0}^{t^*} g(A(j)|\bar{A}(j-1), \bar{S}(\min(j, t)))$.

However, in the presence of censoring, we use the following estimating function, which incorporates an additional inverse probability of censoring component:

$$D_{h,IPTW}(O|\beta, g) \equiv \sum_{t=0}^{K(m)} \frac{I(C > t+8) g(\bar{C}(t+8) = 0 | \bar{A}(t^*), \bar{S}(t))}{g(\bar{C}(t+8) = 0 | O^*)} \frac{h(t, \bar{A}(t^*), \bar{S}(t))}{g(\bar{A}(t^*)|X)}$$
$$I(\bar{A}(t-1) = 1) I(Sup(t) = 0) \{Y(t+8) - m_\beta(t, \underline{A}(t, t^*) | \bar{A}(t-1) \bar{S}(t))\}.$$

The estimator was implemented using weighted least squares, as described in Section (3). Specifically, each subject contributed one weighted line of data for each time point $t \leq K(m)$ for which censoring did not occur before the outcome was measured ($t+8 < C$), and for which the subject had not already switched treatments ($I(A(t-1) = 1) = 0$), or achieved re-suppression of the virus ($I(Sup(t-1) = 0) = 0$). In this pooled dataset, we regressed the observed CD4 T cell count 8 months in the future ($Y(t+8)$) on future time until switching treatment ($\underline{a}^*(t, t^*)$), elapsed time t since failure, and current CD4 T cell count ($CD4(t)$), according to the model m_β.

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For a given time point t, the weight was estimated as the product of a treatment component,

$$\frac{g(\bar{A}(t^*)|\bar{S}(t))}{g(\bar{A}(t^*)|X)},$$

and a censoring component,

$$\frac{g(\bar{C}(t+8)=0|\bar{A}(t^*),\bar{S}(t))}{g(\bar{C}(t+8)=0|O^*)}.$$

Note that there is flexibility in choosing a numerator for these weights. Given fits of the treatment mechanism and censoring mechanism, one generally selects a numerator with the purpose of making the weights minimally variable (i.e. of making the weights as close to 1 as possible). Several approaches are available to do this; one general strategy involves simply using the treatment/censoring mechanism selected, but setting all terms not included in $\bar{S}(t), \bar{A}(t^*)$ equal to zero.

By factorizing the censoring component, it can be further rewritten as a product of a weight for censoring mechanism 1 (end of follow-up in 2004),

$$\frac{\prod_{j=0}^{t+1} Pr(C_1>j|\bar{C}(j-1)=0,\bar{A}(j-1),\bar{S}(j-1)) \prod_{j=t+2}^{t+8} Pr(C_1>j|\bar{C}(j-1)=0,\bar{A}(j-1),\bar{S}(t))}{\prod_{j=0}^{t+8} Pr(C_1>j|\bar{C}(j-1)=0,\bar{A}(j-1),\bar{L}(j-1))}$$

and a weight censoring mechanism 2 (death or loss to follow-up),

$$\frac{\prod_{j=0}^{t+1} Pr(C_2>j|C_1>j,\bar{C}(j-1)=0,\bar{A}(j-1),\bar{S}(j-1)) \prod_{j=t+2}^{t+8} Pr(C_2>j|C_1>j,\bar{C}(j-1)=0,\bar{A}(j-1),\bar{S}(t))}{\prod_{j=0}^{t+8} Pr(C_2>j|C_1>j,\bar{C}(j-1)=0,\bar{A}(j-1),\bar{L}(j-1))}$$

Similarly, the treatment component of the weights can be written as:

$$\frac{\prod_{j=0}^{t} g(A(j)|\bar{S}(j),\bar{A}(j-1)=1) \prod_{j=t+1}^{t^*} g(A(j)|\bar{S}(t),\bar{A}(j-1)=1)}{\prod_{j=0}^{t^*} g(A(j)|\bar{L}(j),\bar{A}(j-1)=1)}$$

Implementation of the IPTW estimator, then, relied on estimation of the following nuisance parameter models:

1. **Treatment mechanism:**

$$\prod_{j=0}^{t^*} g(A(j)|\bar{L}(j),\bar{A}(j-1)=1)$$

We used the Deletion/Substitution/Addition algorithm (Sinisi and van der Laan (2004)) and 5-fold cross validation to fit a pooled logistic regression model of the probability of switching treatment given the observed past. Note that the model was fit only among those who had not already been censored or switched, as these were the only subjects at risk of switching.

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Estimation of the treatment mechanism employed inverse probability of censoring weights for each time point j ($\frac{I(C>j)}{g(\bar{C}(j)=0|O*)}$). In modelling the treatment mechanism, we assumed that treatment assignment at time j was independent of covariates at time $j-1$ given covariates at time j. In other words,

$$g(A(j)|\bar{L}(j), \bar{A}(j-1)=1) = g(A(j)|L(j), \bar{A}(j-1)=1).$$

2. **Numerator for treatment weight:** In calculating the numerator of the treatment weights, for $j <= t$ we made the similar assumption that $g(A(j)|\bar{S}(j), \bar{A}(j-1)=1) = g(A(j)|S(j), \bar{A}(j-1)=1)$. For time points $j > t$, a different model had to be adopted, as the latest available covariates were measured at time t. To avoid the need to fit a separate model for each time point after t (e.g., $g(A(j)|S(j-1), \bar{A}(j-1) = 1)$, $g(A(j)|S(j-2), \bar{A}(j-1))$, etc.), for $j > t$ we used the model $g(A(j)|\bar{S}(t), \bar{A}(j-1) = 1) = g(A(j)|S(0), \bar{A}(j-1) = 1)$. Thus, the numerator of the treatment weight consisted of

$$\prod_{j=0}^{t} g(A(j)|S(j), \bar{A}(j-1)=1) \prod_{j=t+1}^{t^*} g(A(j)|S(0), \bar{A}(j-1)=1),$$

Estimates of $g(A(j)|S(j), \bar{A}(j-1)=1)$ and $g(A(j)|S(0), \bar{A}(j-1)=1)$ were fit using logistic regression of the probability of switching on most recent or baseline CD4 T cell count, respectively, and suppression history.

3. **Censoring mechanisms:**

$$\prod_{j=0}^{t+8} Pr(C_1 > j|\bar{C}(j-1)=0, \bar{A}(j-1), \bar{L}(j-1))$$

$$\prod_{j=0}^{t+8} Pr(C_2 > j|C_1 > j, \bar{C}(j-1)=0, \bar{A}(j-1), \bar{L}(j-1))$$

As with the treatment mechanism, we used the D/S/A algorithm to fit, for each censoring mechanism, a pooled logistic regression model of the probability of being censored given that censoring had not already occurred and the observed past. As in modelling the treatment mechanism, we assumed that censoring probability at time j was independent of covariates at time $j-1$ given covariates at time j. In other words,

$$Pr(C_1 > j|\bar{C}(j-1)=0, \bar{A}(j-1), \bar{L}(j-1)) = Pr(C_1 > j|\bar{C}(j-1)=0, \bar{A}(j-1), L(j-1)),$$

and similarly for C_2

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4. **Numerators for censoring weight:** In estimating the numerator for the censoring weight, we made equivalent assumptions as when estimating the numerator for the treatment weight. The numerators of the censoring weights consisted of:

$$\prod_{j=0}^{t+1} Pr(C_1 > j|\bar{C}(j-1) = 0, \bar{A}(j-1), S(j-1))$$
$$\prod_{j=t+2}^{t+8} Pr(C_1 > j|\bar{C}(j-1) = 0, \bar{A}(j-1), S(0))$$

$$\prod_{j=0}^{t+1} Pr(C_2 > j|C_1 > j, \bar{C}(j-1) = 0, \bar{A}(j-1), S(j-1))$$
$$\prod_{j=t+2}^{t+8} Pr(C_2 > j|C_1 > j, \bar{C}(j-1) = 0, \bar{A}(j-1), S(0))$$

The resulting estimates β_n of β provided a origin-specific statically optimal treatment rule according to Definition (2). Standard error estimates and confidence intervals for the parameter β, and variability in the resulting decision rule, were calculated by applying the entire estimation algorithm to 100 non–parametric bootstrap samples.

6.6 Results.

The D/S/A algorithm and cross-validation selected a treatment mechanism with 8 main terms. The corresponding odds ratios are reported in Table (1). The same algorithm applied to the censoring mechansims selected an intercept-only model for each of the censoring mechanisms; thus, the censoring component of the weights was estimated as 1. Both prior work (Petersen et al. (2006)) and background knowledge suggest that CD4 T cell count may be the most important potential source of bias due to informative censoring. To address this concern, we performed a sensitivity analysis, in which we fit a model of censoring due to loss to follow-up/death (C_2) based on most recent CD4 T cell count and used this model in the estimation of the censoring component of the weights. Changes in the causal coefficients estimated using this censoring model were minimal (relative change or 3% or less), supporting the presence of minimal bias due to informative censoring.

IPTW estimation relying on these fits yielded the following estimate of the counterfactual history-adjusted parameter of interest:

$$m_\beta(t, \underline{a}(t, t^*)|\bar{a}(t-1) = 1, Sup(t) = 0, CD4(t)) =$$

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Table 1: Odds ratios for switching treatment based on data-adaptive fit of treatment mechanism

Covariate	Odds Ratio
Current diagnosis with an opportunistic disease	1.21
Number of protease inhibitor drugs experienced	1.11
Most recent HIV RNA level undetectable	0.44
Percent average adherence (per 10%)	0.92
Most recent CD4 T cell count (per 100 CD4 T cells)	0.92
Nadir CD4 T cell count (per 100 CD4 T cells)	1.06
Most recent HIV RNA level more than one month prior	0.90
Age (per 5 years)	0.80

$$92.8 - 9.4 \times \sum_{j=t}^{t^*} a(j) + 0.48 \times CD4(t) - 16.12 \times t + 0.05 \times \sum_{j=t}^{t^*} a(j) \times CD4(t)$$
$$+1.46 \times \sum_{j=t}^{t^*} a(j) \times t + 0.07 \times CD4(t) \times t - 0.009 \times \sum_{j=t}^{t^*} a(j) \times CD4(t) \times t,$$

This model yields the following origin-specific statically optimal treatment rule:

$$d_t = I(\{-9.4 \times \sum_{j=t}^{t^*} a(j) + 0.05 \times \sum_{j=t}^{t^*} a(j) \times CD4(t)$$
$$+1.46 \times \sum_{j=t}^{t^*} a(j) \times t - 0.009 \times \sum_{j=t}^{t^*} a(j) \times CD4(t) \times t\} < 0),$$

where, d_t is the treatment decision at time t (if $d_t = 1$ then switch, if $d_t = 0$ then wait). The coefficients which contribute to this rule, together with their 95% confidence intervals, are provided in Table 2.

Table 2: Coefficients contributing to origin-specific statically optimal rule for when to switch therapy, based on model $m_\beta(t, \underline{a}(t, t^*)|\bar{a}(t-1) = 1, Sup(t) = 0, CD4(t))$

Term	Coefficient	95% CI
$\sum_{j=t}^{t^*} a(j)$	-9.4	-17.8, -0.9
$\sum_{j=t}^{t^*} a(j) \times CD4(t)$	0.05	0.02, 0.08
$\sum_{j=t}^{t^*} a(j) \times t$	1.46	-0.5, 3.4
$\sum_{j=t}^{t^*} a(j) \times t \times CD4(t)$	-0.009	-0.02, -0.002

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In addition to providing confidence intervals for estimates of the coefficients that contribute to the individualized treatment rule, bootstrap sampling provides a means to judge the variability of the treatment decision provided by the rule. Figure 1 shows the proportion of bootstrap samples in which the origin-specific statically optimal treatment rule indicated a switch, plotted for each month following loss of viral suppression, and for four different CD4 T cell counts.

Thus the results of these analyses can be summarized as follows:

- Immediately following loss of suppression, individuals with high CD4 T-cell counts can wait to switch, while individuals with low CD4 T cell counts should switch immediately.

- At later time points, an individual's current CD4 T cell count is less important to the decision whether to wait to switch. Thus at later time points, the decision whether to switch or not is less clear, and should likely depend on additional considerations.

It is interesting to compare these results with the results reported in Petersen et al. (2005). Petersen et al. (2005) reported estimates of the observed HA-MSM parameter, using the same SCOPE dataset, same $\bar{S}(t)$, and same model m_β, but estimating the observed history-adjusted parameter:

$$E[Y_{\bar{A}(t-1),\underline{a}(t,t^*)}|\bar{S}(t), \bar{A}(t-1)).$$

The coefficients contributing to the resulting individualized treatment rule are reported in Table 3. The similarity between the estimate of the counterfactual history-adjusted mean (Table 2) and the estimate of the observed history-adjusted mean (Table 3) supports the claim of Petersen et al. (2006) that in this dataset, the choice $\bar{S}(t) = (CD4(t), Sup(t))$ is sufficient to control confounding of the effect of past treatment history (up till time $t-1$) on the outcome. Such a finding suggests that the static optimality of the treatment rule presented here is not origin-specific; the rule should remain statically optimal if applied to individuals remaining on their original non-suppressive therapy at a given time point, regardless of how the decision whether to switch therapy up till that time point has been made.

7 Discussion.

This paper has presented a new parameter of the full data-generating distribution, together with corresponding estimating equations, and demonstrated that this parameter directly identifies an origin-specific statically optimal individualized treatment rule. The proposed individualized treatment rule is

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Table 3: Estimated effect of each additional month waiting to switch on CD4 T cell count 8 months later, based on observed history-adjusted parameter (Petersen et al. (2005))

Term	Coefficient	95% CI
$\sum_{j=t}^{t^*} a(j)$	-9.2	-17.6, -7.6
$\sum_{j=t}^{t^*} a(j) \times CD4(t)$	0.05	0.02, 0.08
$\sum_{j=t}^{t^*} a(j) \times t$	1.5	-0.4, 3.4
$\sum_{j=t}^{t^*} a(j) \times t \times CD4(t)$	-0.009	-0.02, -0.004

relatively easy to estimate with standard software. We have further shown that, applied to a data example, the method can provide both practical and interpretable results.

If these methods are applied to data generated in a sequentially randomized trial, in which the treatment mechanism is known, then the DR-IPTW estimator is known to be asymptotically consistent and asymptotically linear under the assumption that the model for the counterfactual history-adjusted mean is correct. In particular, since our model $\{m_\beta : \beta\}$ for the counterfactual history-adjusted mean always contains the null hypothesis $H_0 : \beta = 0$, it follows that the IPTW or DR-IPTW estimator provide a valid test of the null hypothesis under no conditions when applied to data generated by randomized trials.

As clarified in the discussion of van der Laan et al. (2005) our model for the counterfactual history-adjusted mean of the outcome $Y_{\bar{a}}(t, m)$ can be replaced by a model for a counterfactual history-adjusted parameter of the conditional distribution $P_{Y_{\bar{a}}(t,m)|\bar{S}_{\bar{a}}(t))}$ such as the conditional median, or conditional survival function of $Y_{\bar{a}}(t, m)$. In this manner, our models yield estimators of origin-specific statically optimal individualized treatment rules which are optimal w.r.t. any user-supplied parameters of the distribution of the future outcome. For example, in the case that the outcome process of interest is an indicator process jumping from 0 to 1 at a survival time (e.g., time till recurrence of cancer) our methods can be used to estimate individualized treatment rules which at each point in time, conditional on a user-supplied subset of the observed history, select the treatment action (statically) optimizing the survival probability at (e.g.) 5 additional years.

Finally, as illustrated in the data example, the general estimating function methodology (van der Laan and Robins (2003)) for censored data can be used to map the estimating functions based on observing $(\bar{A}, L_{\bar{A}})$ presented in this article into estimating functions for the censored longitudinal causal inference data structure $O = (C, \bar{A}(C), \bar{L}_{\bar{A}}(C))$ for a right-censoring variable C (Chapter 3, van der Laan and Robins (2003)).

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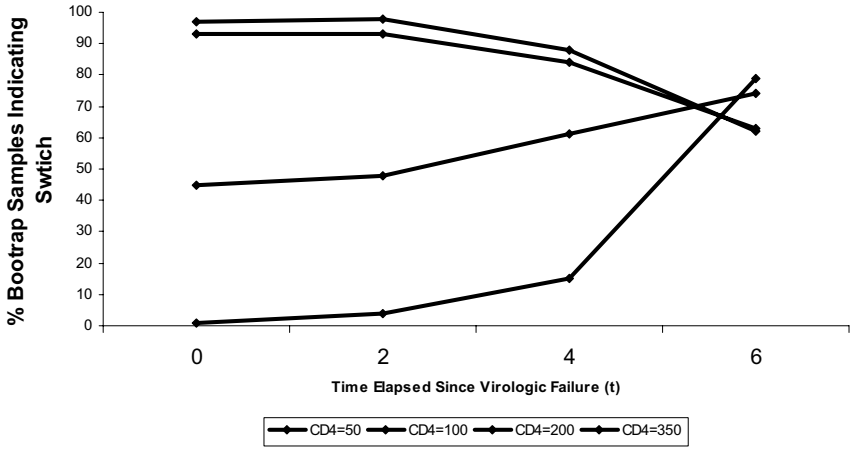
Figure 1: Variability in statically optimal decision whether to switch therapy, depending on current CD4 T cell count and elapsed time since failure



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8 Appendix.

8.1 An alternative derivation of DR-IPTW estimating functions.

It is interesting to note the link between the DR-IPTW estimating functions presented in the previous section and the estimating functions for the observed history-adjusted mean presented in van der Laan et al. (2005). Consider a treatment mechanism $g^*(\bar{A} \mid X)$ so that

$$E_{P_{X0}}(Y_{\bar{a}(t-1),\underline{a}(t)}(t,m) \mid \bar{S}_{\bar{a}}(t) = \bar{s}(t))$$
$$= E_{P_{X0},g^*}(Y_{\bar{a}(t-1),\underline{a}(t)}(t,m) \mid \bar{S}(t) = \bar{s}(t), \bar{A}(t-1) = \bar{a}(t-1)).$$

For example, any treatment mechanism $g^*(\bar{A} \mid X) = \prod_{t=0}^{T-1} g(A(t) \mid \bar{A}(t-1), \bar{S}(t))$ satisfies this condition: that is, if treatment assignment is only based on the $S(t)$ process, then the counterfactual history-adjusted mean equals the observed history-adjusted mean. Thus, our model (3) can also be viewed as the following model:

$$E_{P_{X0},g^*}(Y_{\bar{a}(t-1),\underline{a}(t)}(t,m) \mid \bar{S}(t) = \bar{s}(t), \bar{A}(t-1) = \bar{a}(t-1)) = m_{\beta_0}(t, \underline{a}(t) \mid \bar{a}(t-1), \bar{s}(t)). \quad (7)$$

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However, the latter kind of model is the HA-MSM introduced in van der Laan et al. (2005), and in the latter article we also derived the corresponding class of DR-IPTW estimator of β_0 based on sampling from P_{P_{X0},g^*}. Let's denote the latter DR-IPTW estimating functions with $D_{h,g^*,Q}(O \mid \beta)$ indexed by arbitrary functions h, g^*, Q. Thus, we have

$$E_{P_{P_{X0},g^*}} D_{h,g^*,Q}(O \mid \beta_0) = 0 \text{ for all } h, g^*, Q.$$

The choice $Q = 0$ corresponds with the class of IPTW-estimating functions for the HA-MSM (7) based on sampling from P_{P_{X0},g^*}. The latter IPTW estimating functions are given by

$$D_{h,g^*}(O \mid \beta) = \sum_{t=0}^{K(m)} \frac{h(t, \bar{A}, \bar{S}(t))}{g^*(\underline{A}(t) \mid \bar{A}(t-1), X)} \{Y(t,m) - m_\beta(t, \underline{A}(t) \mid \bar{A}(t-1), \bar{S}(t))\},$$

where

$$g^*(\underline{A}(t) \mid \bar{A}(t-1), X) = \prod_{j=t}^{T-1} g^*(A(j) \mid \bar{A}(j-1), \bar{S}(j)).$$

The typical choice we recommend is

$$h^*(t, \bar{A}, \bar{S}(t)) \equiv \frac{d}{d\beta} m_\beta(t, \underline{A}(t) \mid \bar{A}(t-1), \bar{S}(t)) g^*(\underline{A}(t) \mid \bar{A}(t-1), \bar{S}(t)), \quad (8)$$

where

$$g^*(\underline{A}(t) \mid \bar{A}(t-1), \bar{S}(t)) \equiv \prod_{j=t}^{T-1} g^*(A(j) \mid \bar{A}(j-1), \bar{S}(t)).$$

This implies now the following class of IPTW-estimating functions based on sampling from the actual true probability distribution P_{P_{X0},g_0} of O:

$$D_{b=(h,g^*,Q),IPTW}(O \mid g, \beta) \equiv D_{h,g^*,Q}(O \mid \beta) \frac{g^*(\bar{A} \mid X)}{g(\bar{A} \mid X)}. \quad (9)$$

This class of IPTW-estimating functions is indexed by arbitrary functions $b = (h, g^*, Q)$. If we set $Q = 0$, then we obtain the following class of IPTW estimating functions indexed by (h, g^*)

$$D_{b=(h,g^*),IPTW}(O \mid g, \beta) = \sum_{t=0}^{K(m)} \frac{h(t, \bar{A}, \bar{S}(t))}{g^*(\underline{A}(t) \mid \bar{A}(t-1), X)} \{Y(t,m) - m_\beta(t, \underline{A}(t) \mid \bar{A}(t-1), \bar{S}(t))\} \frac{g^*(\bar{A} \mid X)}{g(\bar{A} \mid X)}.$$

If we choose $h = h^*$ (8), then the corresponding IPTW-estimator defined as the solution of $0 = \sum_{i=1}^n D_{h,g_n^*,IPTW}(O \mid g_n, \beta) = 0$ is the following weighted least squares estimator:

$$\beta_{n,IPTW} = \arg\min_\beta \sum_{i=1}^n \sum_{t=0}^{K(m)} w_i(t) \left\{ Y_i(t,m) - m_\beta(t, \underline{A}_i(t) \mid \bar{A}_i(t-1), \bar{S}_i(t)) \right\}^2$$

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with weights given by

$$w_i(t) \equiv \frac{g_n^*(\bar{A}_i \mid X_i)}{g_n(\bar{A}_i \mid X_i)} \frac{g_n^*(\underline{A}_i(t) \mid \bar{A}_i(t-1), \bar{S}_i(t))}{g_n^*(\underline{A}_i(t) \mid \bar{A}_i(t-1), X_i)}.$$

Note, however, that this weight can be re-written:

$$\begin{aligned} w_i(t) &\equiv \frac{g_n^*(\bar{A}_i \mid \bar{S}_i)}{g_n(\bar{A}_i \mid X_i)} \frac{g_n^*(\underline{A}_i(t) \mid \bar{A}_i(t-1), \bar{S}_i(t))}{g_n^*(\underline{A}_i(t) \mid \bar{A}_i(t-1), \bar{S}_i)} \\ &= \frac{g_n(\bar{A}_i \mid \bar{S}_i(t))}{g_n(\bar{A}_i \mid X_i)}. \end{aligned}$$

Thus this alternative mapping gives back the original IPTW estimating function, given in section 3.1. In the special case that $\bar{S}$ is such that $g^* = g$, then this estimator reduces to the IPTW-estimator proposed in van der Laan et al. (2005) for HA-MSM models (the first ratio now equals 1 in $w_i(t)$).

As in the previous subsection, these IPTW estimating functions can be mapped into DR-IPTW estimating functions.

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