Optimal Dynamic Treatment Regimes: Regret-Regression Method With Myopic Strategies

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I wish to dedicate this thesis to my late mother, Anis Hamzah. Her pure love, dedication and determination have been missed over the last five years.

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Abstract

Optimal dynamic treatment strategies provide a set of decision rules that are based on a patient's history. We assume there are a sequence of decision times $j = 1, 2, \ldots, K$. At each time a measurement of the state of the patient S_j is obtained and then some action A_j is decided. The aim is to provide rules for action choice so as to maximise some final value Y.

In this thesis we will focus on the regret-regression method described by Henderson et al. (2009), and the regret approach to optimal dynamic treatment regimes proposed by Murphy (2003). The regret-regression method combines the regret function with regression modelling and it is suitable for both long term and myopic (short-term) strategies.

We begin by describing and demonstrating the current theory using the Murphy and Robins G-estimation techniques. Comparison between the regret-regression method and these two methods is possible and it is found that the regret-regression method provides a better estimation method than Murphy's and Robins G-estimation.

The next approach is to investigate misspecification of the Murphy and regret-regression models. We consider the effect of misspecifying the model that is assumed for the actions, which is required for the Murphy method, and of the model for states, which is required for the regret-regression approach. We also consider robustness of the fitting algorithms to starting values of the parameters. Diagnostic tests are available for model adequacy.

An application to anticoagulant data is presented in detail. Myopic one and two-step ahead strategies are studied. Further investigation involves the use of Generalised Estimating Equations (GEEs) and Quadratic Inference Functions (QIF) for estimation. We also assess the robustness of both methods. Finally we consider the influence of individual observations on the parameter estimates.

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Chapter 1

An Overview of Optimal Dynamic Treatment Regimes.

1.1 Thesis Outline

Dynamic treatment methodology has had considerable attention in recent years. It has become an important tool for making decisions in many research areas. It also provides an ethical and flexible set of formal rules to study the treatment effects that can vary over time. Murphy (2003) introduced dynamic treatment regimes to the mainstream statistics literature. She defined it as a list of decision rules over time intervals, when the level of treatment can depend on the response of a patient so far.

The regret-regression method introduced by Henderson et al. (2009) provides an alternative method in order to improve the optimal dynamic treatment regimes. It provides quicker estimation and allows diagnostics which can be used to compare a variety of candidate models. We begin the thesis with an introduction to causal inference to understand the effect of various covariates and responses to treatment. Then, in Chapter 2, we will demonstrate the theory behind the optimal dynamic treatment regimes using Murphy and Robins G-estimation methods. We will make comparison between the regret-regression method with these two methods using simulations.

An investigation of misspecification of the regret-regression method and the Murphy method will be described in Chapter 3 to discover the sensitivity of the methods. We will test the sensitivity of the methods by misspecifying the initial values for the action model for the Murphy method while for the regret-regression method we misspecify the state model. We extend our investigation of the regret-regression method by introduce some covariates into the model in Chapter 4. Using simulations, we will make comparison between the models and diagnostics using the residual plot and wild bootstrap test. In Chapter 5, we apply the regret-regression method to data on anticoagulation. We extend the method to myopic decision rules in Chapter 6 which is the main idea of this thesis.

Chapter 7 and Chapter 8 demonstrate the use of Generalised Estimating Equations (GEE) and Quadratic Inference Function (QIF) in myopic regret-regression for estima-

tion via simulation and application. The possibility of influential observations in myopic regret-regression is investigated using the anticoagulation data in Chapter 9. Conclusions are presented in the closing chapter.

1.2 Causal Inference

Causal inference has been the subject of study for many years. It is focused into the main areas of:

- Non parametric structural equations
- Graphical models
- Counterfactual Analysis

Causal inference is rooted in empirical research which motivates much research especially in health, social and behavorial sciences. For example, what is the efficiency of a medicine when applied to a certain population? In order to express causal assumptions mathematically, some extensions in statistical theory are required. Previous work includes advances in graphical models (Pearl, 1988; Lauritzen, 1995) and (Cowell et al., 1999), counterfactual or potential outcome analysis (Rosenbaum & Rubin, 1983; Robins, 1986; Manski, 1995; Angrist et al., 1996; Greenland, 1990), structural equation models (Heckerman & Shachter, 1995) and (Pesaran & Smith, 1998). More recent work has attempted to combines these approaches into a single interpretation (Pearl, 1995a) and (Pearl, 2000).

There are three major types of causal models for health-sciences research: graphical models (causal diagrams), potential-outcome (counterfactual) models and sufficient-component cause models. Graphical models can illustrate qualitative population assumptions and sources of bias not easily seen with other approaches. The sufficient-component cause models can illustrate specific hypotheses about the treatment action. The potential-outcome and structural-equations models provide a basis for quantitative analysis of effects.

1.2.1 Graphical Models

The following is a brief summary of concepts and causal diagrams. For further explanations refer to Greenland (1999) and Robins (2001). For example, if $X \longrightarrow Y$ where there is an arrow from a variable X to another variable Y it means that variable X is a parent of Y, and Y is called a child of X.

A sequence of arcs connecting X and Y is a path between two variables X and Y. A path whose first arc is an arrow pointing to X is a back-door path from X to Y. In Figure 1.1(a), there is no back-door path from X to Y. The path $X-U-Y$ in Figure 1.1(c) is a back-door path from X to Y. The paths of $X - U - Z - Y$ and $X - Z - V - Y$

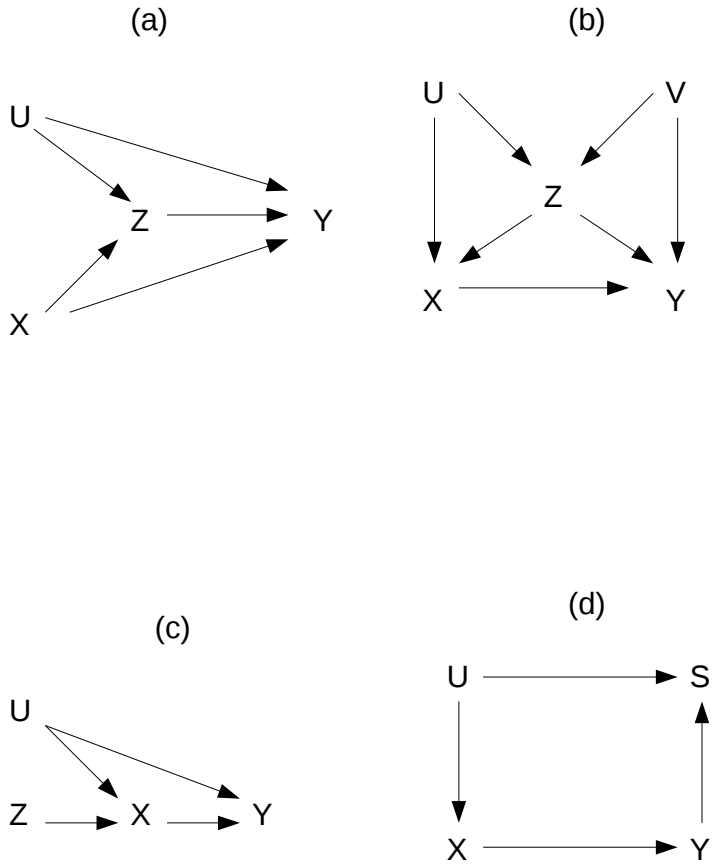

Figure 1.1: Four causal diagrams. The variables S, U, V, X and Z are the exposures and Y is the outcome variable.

in Figure 1.1(b) are open paths, whereas $X - U - Z - V - Y$ is closed or blocked path because $U - Z - V$ is a parent-child-parent sequence. A directed path is a sequence of arrows such that the child in the sequence is the parent in the next step. The variable X is called an ancestor of Y and Y is called a descendant of X if there is a directed path from X to Y.

A graph is acyclic if no directed path forms a closed loop or if there is no node which is both ancestor and descendant. A graph which is both directed and acyclic is a called *directed acyclic graphs* or DAGs which is shown in Figure 1.1 where each graph is a DAGs. A graph is causal if every arrow represents the presence of an effect of the parent (causal) variable on the child (affected) variable. Each graph in Figure 1.1 shows causal relationships within a population of individuals, where each variable represents the states or events among individuals in that population. For example, if X is a treatment variable, then the value of X represents the level of treatment received by the individual. Missing direct paths from X to Y indicates that the causal null hypothesis has no alteration to the distribution of X which could change the distribution of Y.

Suppose in Figure 1.1, part (a): the variable X represents a 6-month weight loss programme that is randomly chosen for a cohort of cardiovascular patients. A patient who is assigned the programme has, $X = 1$ and we set $X = 0$ for not assigned. The variable Z represents a set of clinical CHD (Coronary Heart Disease) risk factors (serum lipids, blood pressure) measured upon completion. The variable Y represents death within the year following completion and U represents a set of unmeasured genes that affect death risk both directly and through the clinical factors Z.

Although U does affect Y it is not a confounder of the $X - Y$ association because it is independent of X. A common approach to analysing effects of weight on health is to adjust for serum lipids and blood pressure. The reason of Z is a child of both U and X, either U or X should be associated with Z. Consequently, U can become a confounder with Z, although it was not the variable to begin with.

The variable Z generates confounding where Z and Y share the same causes besides X. The association of Z with Y is confounded, and often the estimated indirect effect of X on Y. The four plots in Figure 1.1 represent four of the sets of assumptions we might make.

1.2.2 Potential Outcomes or Counterfactual Models

A graphical display provides a visualisation of the qualitative assumptions about the independence and causal directions in a population. Meanwhile a quantitative model specifies in detail the assumptions on the effects of exposures. The quantitative models from Neyman (1923) and Fisher (1925) are in later terminology counterfactual or potential-outcome models. These models formalise the cause and effect interpolation which is widely found in philosophy and epidemiology studies.

Counterfactual (potential) outcomes are the outcome of the model under conditions

contrary to fact; that is in reality, not all subjects follow a given exposure history. Models for counterfactual outcomes are sometimes known as structural or causal models (Hernán, 2005). A counterfactual is a potential outcome, prior to the actual outcome being observed. If a person had followed a particular treatment regime it is defined as a person's outcome which is possibly different from the regime that he or she was actually observed to follow. The causal effect of a regime may be seen as the difference in outcomes if he had followed the regime when compared to a placebo or a standard treatment.

1.2.3 Structural-Equation Models

Structural-equations modelling (SEM) was initially developed from the informal use of graphs where the network of causation is modelled by a system of equations and independence assumptions Fornell & Larcker (1981) and Anderson & Gerbing (1988). Each equation shows how an individual response variable changes as its direct (parent) causal variables change. Similar to causal diagrams, the individual may be the unit of interest.

A variable may appear once in equation as a response variable, but may appear in any other equation as a causal variable in the system. A response variable in the system is said to be endogenous (within the system), otherwise it is exogenous.

The qualitative schematic for a structural-equations models is a causal graph (Pearl, 1998; Loehlin, 2012) and (Greenland & Brumback, 2002). For example, Figure 1.1(a) is a schematic for the linear system

$$\begin{aligned} Z &= \alpha_Z + \beta_{UZ}u + \beta_{XZ}x \\ Y &= \alpha_Y + \beta_{UY}u + \beta_{XY}x + \beta_{ZY}z \end{aligned} \tag{1.1}$$

in which u, x, z are specific values of U, X, Z. The intercepts, α_Z and α_Y are unmeasured random disturbances of Z and Y, and α_Z, α_Y, U and X are assumed to be jointly independent between each other. A different linear system but referring to the same schematic Figure 1.1(a) is

$$\begin{aligned} Z &= \alpha_Z + \beta_{UZ}u + \beta_{XZ}x + \beta_{UXZ}ux \\ ln(Y) &= \alpha_Y + \beta_{UY}u + \beta_{XY}x + \beta_{ZY}z \end{aligned} \tag{1.2}$$

where α_Z, α_Y, U and X again are assumed to be jointly independent. The system in Equation (1.1) is different from the system in Equation (1.2) since the product term has been added to the Z equation, and the Y equation has changed to log-linear instead of linear. Otherwise both systems share the same properties from the schematic Figure 1.1(a).

The variables U and X are the two exogenous variables which directly affect two endogenous variables Z and Y, and Z directly affects Y, indicated by the arrows from U and X to Z and Y, and also straight from Z to Y. The exogenous variables and random disturbances are jointly independent of one another which means there are no connections

among these variables.

1.3 Causal Effects

Although the definition for cause is difficult and complex, the concept of the causal effect of a treatment in empirical research seems to be more straightforward and practically useful (Roderick & Rubin, 2000). The idea of explaining the causal effects is through potential outcomes.

The comparisons of potential outcomes provides causal effects. Let us consider the case of two treatments, numbered 0 and 1. The i^{th} of the N units under study has a response $Y_i(1)$ that would have resulted if it had received treatment 1, and a response $Y_i(0)$ if it had received treatment 0.

Causal effects are based on comparisons between $Y_i(1)$ and $Y_i(0)$, for example $Y_i(1) - Y_i(0)$ or $Y_i(1)/Y_i(0)$. Since each unit receives only one treatment, either $Y_i(1)$ or $Y_i(0)$ is observed, but not both so comparisons of $Y_i(1)$ and $Y_i(0)$ will bring speculation.

Nevertheless, estimating the causal effects of treatments is a missing data problem, since either $Y_i(1)$ or $Y_i(0)$ is missing Fisher (1951) and Kempthorne (1952) followed by (Rubin, 1974, 1977, 1978) and (Rubin, 1980). Hamilton (1979) also had similar approach. The structure would not be adequate if the response of unit i treatment depends on the treatment given to unit j. Rosenbaum & Rubin (1983) estimated the average treatment effects as

$$E[Y_i(1)] - E[Y_i(0)]$$

where $E[.]$ denotes the expectation in the population and N units are viewed as a simple random sample from that population.

The target of estimation, is defined as the average difference between treated and untreated for all units in a population or in some subpopulation. For example the population of males and females. This approach is commonly used in statistics and epidemiology (Efron & Feldman, 1991) and (Greenland & Robins, 1986). This approach is known as the *Rubin Causal Model*, RCM by Holland (1986). The RCM provides a link between various approaches (Hearst et al., 1986; Holland, 1988; Permutt & Hebel, 1989; Sommer & Zeger, 1991) and (Imbens & Angrist, 1994).

1.4 Longitudinal Data

Longitudinal data is defined as a set of repeated measurements of an outcome and a set of covariates for each of many units. The aim of statistical analysis is to model and estimate the marginal expectation of the response variable as a function of the covariates while accounting for the correlation among the repeated observations for a given unit (Zeger & Liang, 1986).

Longitudinal data have repeated observations on the same subject over time. In clinical trials, each patient's response to a treatment will be recorded at each decision point. We do not always have interest only in how the mean response differs across treatment, but as sometimes we wish to see the change in mean outcome over time and other issues regarding the relationship between response and time. Thus it is necessary to represent the situation through a statistical model that acknowledges the way in which the data were collected.

Specialised methods of analysis are required to complement the models. Although repeated measurements most often take place over time, that is not only way that measurements are taken repeatedly on the same unit. For example human subjects may be taken as units. For each subject, reduction in diastolic blood pressure is measured in several occasions with each occasion involving administration of a different dose of an anti hypertensive medication. Thus, the subject is measured repeatedly over dose (Davidian et al., 2008).

1.4.1 Observational Studies, Randomised Trials and Causal Effects

In a randomised trial, each subject is randomly assigned to a treatment group or control group before the start of treatment. *Sequential ignorability* is required when we wish to compare the effects of dynamic treatment regimes from a sample treatments and outcomes. This depends on the assumption that new treatment is assigned independently of potential future responses to treatment, conditional on the history of treatments and response to date. The assumption of sequential ignorability must be assumed in longitudinal observational studies for randomisation (Lavori & Dawson, 2004).

Individuals are randomly assigned to a treatment and control group in randomised trials. If the groups are found significantly different after treatment, then the treatment is assumed to cause the difference. Meanwhile in observational studies, more assumptions are needed before we can conclude a treatment have a causal effect.

Definition *Let A_i be a binary (random) treatment variable for unit i where $i = 1, 2, \ldots, n$. Consider fixed (non random) but possibly unknown potential outcomes, $Y_i(1)$ and $Y_i(0)$, for each i. Then the following sample average causal effects of interest can be defined by $\frac{1}{n}\sum_{i=1}^{n}(Y_i(1) - Y_i(0))$.*

Definition *The treatment is said to be randomised if the treatment variable A_i is independent of all potential outcomes, $Y_i(a)$, for all units, i.e.,$Y_i(a) \perp A_i$ for all a and all i.* (Dawid, 1979)

1.4.2 Time-Varying Treatment

A time-varying variable obviously is a variable that changes over time. These are commonly used in survival analysis. In our context the dose of a drug is a time-varying covariate, if a person is treated at many time points with different doses.

Treatment policies where the type of treatment or the level of treatment changes over time are known as time-varying treatment regimes. When there are fixed care policies, the same dose is maintained over time. For example, a patient taking the same dose twice a day at the same time for 4 weeks. Meanwhile a patient who takes different types of drugs over four weeks is considered as following a time-varying regime. A time-varying regime can be dynamic or non-dynamic. A dynamic treatment regime is one in which the level of treatment received depends on time-varying patient diagnosis. Consider the following example for a dynamic treatment regime: Varying doses are needed for each patient treated with Warfarin for anticoagulation. There can be severe bleeding if dose is too high while too little can cause blood clots. Classical methods cannot predict how much of the drug a person will need. To measure how fast the blood clots, physicians measure the patient's International Normalised Ratio (INR) continuously and estimate the dose of Warfarin that should be given to the patient. The next example is of a non-dynamic time-varying regime; The control of the side effects from Chemotherapy for cancer treatment.

1.4.3 Assumptions for Causal Inference

Three assumptions for causal inference are usually needed (Rosenbaum & Rubin, 1984). First, let us introduce some notation

- a_j be a possible treatment decision at time point j;
- A_j be the observed decision at time point j, where A_j is selected from all possible decisions $\{a_j\}$;
- $\bar{A}_j = (A_1, \ldots, A_j)$ denote all past decisions up to and including A_j;
- S_j be the status (possibly a vector) at the beginning of time interval j. Generally S_j contains predictors of the response;
- $\bar{S}_j = (S_1, \ldots, S_j)$ denotes all past states up to and including S_j;
- Y be the response at the end of a final time interval K.

Assumption 1 *No interference between units.* Let A be an N dimensional vector of treatment assignment, where the i^{th} element represents the treatment value of unit i for $i = 1, 2, \ldots, N$. Let $Y_i(A)$ be the potential outcome of unit i given the treatment assignment for all units A. Then, the assumptions implies that $Y_i(A = x) = Y_i(A = y)$ whenever $x = y$. This assumption is sometimes called the *stable unit treatment value assumption* (SUTVA) (Rubin, 1978) also known as *consistency assumption* (Rosenbaum & Rubin, 1984). The results of a subject's allocation are not affected by other subjects' treatment allocation.

Assumption 2 *No unmeasured confounders.* The treatment received in any interval is allowed to be conditional on history, but is independent of any future potential outcomes meaning that $Y_a \perp A|S = s$ for each possible value a of A and s of S. This assumption is sometimes called *conditional exchangeability*. It holds in a randomised experiment in which treatment is randomly assigned (Robins & Wasserman, 1997).

Assumption 3 *Positivity.* When the treatment is not deterministically allocated within level s of covariates S, not all source population subjects with a given value s of S are assigned to be treated or untreated (Hernán & Robins, 2006). If $P(S = s) \neq 0$ (the population marginal probability that S takes the value s) then $P(A = a|S = s) > 0$ (the conditional probability that A takes the value a among the subjects in the population with S equal to s). The above assumed S and A to be discrete variables.

The optimal regime might be estimated from among the set of feasible regimes without any additional assumptions (Robins, 1994) as will be described in the next chapter.

1.5 Conclusions

The problem of estimating the treatment effects from observational studies is a multistage decision problem. Dynamic treatment regimes are designed to deal with this problem. There are defined as a set of decision rules which are tailored through time to suit individual conditions and history. The regime is optimised when the mean response is maximised at the end of a final interval.

In the next chapter we will explain in detail the optimal dynamic treatment regimes method introduced by Murphy (2003).

Chapter 2

Estimation Techniques for Optimal Dynamic Treatment Regimes

2.1 An Overview of Dynamic Treatment Regimes

A dynamic treatment regime is defined as a set of decision rules which are based on the observation or history of the patients at the decision time point. The set of decision rules or actions forms the treatment regime Murphy (2003). Since it depends on time-varying measurements, it may be influenced by earlier treatments and patient responses.

Optimal dynamic treatment regimes provide optimal decision rules over a time interval, aimed at for example producing the highest mean response at the end of the time period. The structure of optimal dynamic treatment regimes consists of multistage decision points. Suppose only one decision is made at every time interval. At interval j in $\{1, 2, \ldots, K\}$, A_j denotes the treatment decision while S_j denotes the status of the patient at the beginning of the time interval. The response at the end of time interval time K is denoted Y. The sequence is $S_1, a_1, S_2, \ldots, a_K, Y$.

2.1.1 Notation

Finding the optimal dynamic treatment regimes is a sequential or multistage decision problem. We consider the treatment regime to be a set of decision rules with one rule per time interval. At each time point $j \in \{1, 2, \ldots, K\}$, let

- a_j be a possible treatment decision at time point j;
- A_j be the observed decision at time point j, where A_j is selected from all possible decisions $\{a_j\}$;
- $\bar{A}_j = (A_1, \ldots, A_j)$ denote all past decisions up to and including A_j;
- S_j be the status (possibly a vector) at the beginning of time interval j. Generally S_j contains predictors of the response;

- $\bar{S}_j = (S_1, \ldots, S_j)$ denotes all past states up to and including S_j;
- d_j be the decision rule for time point j and $\underline{d}_j = (d_j, d_{j+1}, \ldots, d_K)$ is the vector of decision rules from j onward;
- $\underline{d}_j^{opt}$ be the collection of best possible decision from time point j onward (unknown);
- Y be the response at the end of time interval K. So the order of occurrence is $(S_1, A_1, S_2, \ldots, A_K, Y)$.

In summary, lower case is a possible action and will be used usually as the argument of a function. Upper case A is the action actually chosen. We use d to imply rules, S for observational states, and Y for the final response. In the above, we have distinguished decision rules from actions. The rule is a policy or algorithm to be followed in deciding upon an action.

Suppose, we consider the HIV data from Moodie et al. (2007). In Figure 2.1, Moodie et al. (2007) only considered two-time intervals, $j = 2$. The first interval, t_1 is from 0 to 6 months while the second interval, t_2 is from 6 to 12 months. The status variables, S_1 and S_2 are the $CD4$ cell counts and the $CD4$ count is also used to determine the optimal rule for AZT (*Zidovudine*) dose at each interval. The $CD4$ is the *T-cells* in the white blood cell that play an important role to the immune system. The larger values of Y or high $CD4$ cell counts is aimed at the end of study.

The $CD4$ cell counts for S_1, S_2 and Y are at, 0 (baseline), 6 and 12 months respectively. A patient who received AZT treatment at first interval is denoted as $A_1 = 1$ and equivalently $A_2 = 1$ for second interval. Meanwhile $A_j = 0$ at $j = 1, 2$ is for patient who did not received the AZT treatment.

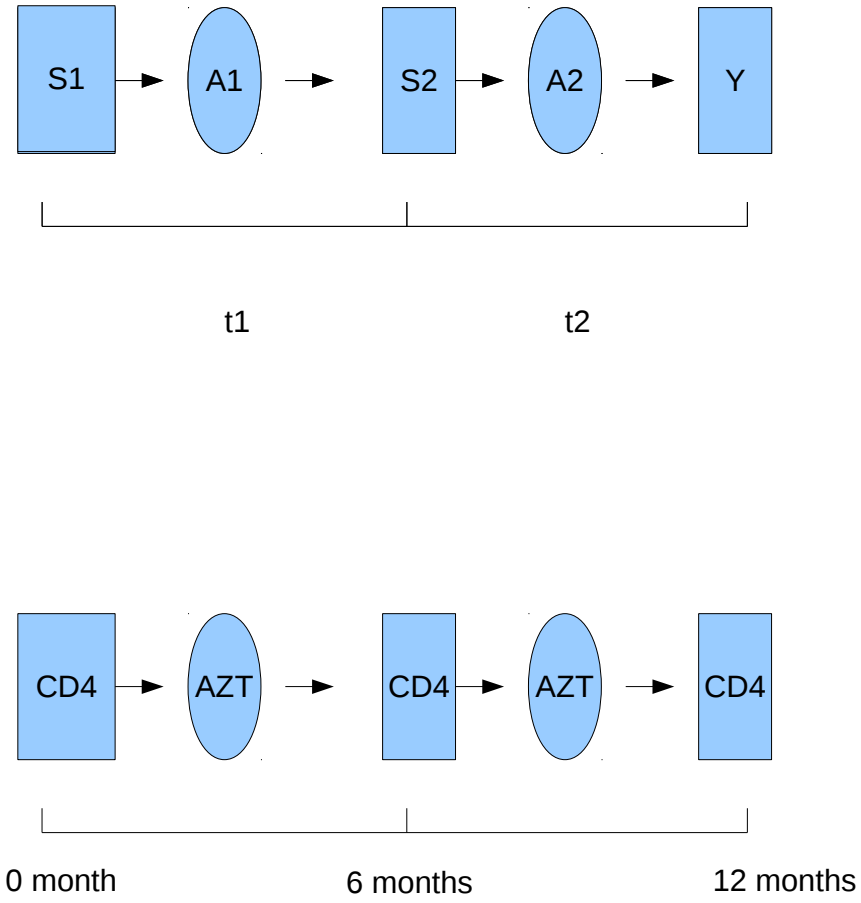

Figure 2.1: Illustration of data for two intervals.(a)The structure of the dynamic treatment regime and (b) The order of occurrence of HIV data

2.1.2 Assumptions

We make the following assumptions:

1. Consistency: If the regime is followed, the potential outcomes under any particular treatment or action correspond to the actual outcomes.
2. No unmeasured confounder: The action, A_j cannot depend on the potential outcomes except through the observed history $(\bar{S}_j, \bar{A}_{j-1})$.
3. Positive probability of treatment occurring in the data.
4. Finite second moment for Y.
5. Between-subject independence

Assumptions (1) and (2) are the standard assumptions for causal inference. Assumption (3) is adopted when the treatment is discrete and non-parametric methods are used, or when we have parametric models for treatment effects in the simulation or application data. The final assumptions, that are the assumption (4) and (5) are to make sure that the least squares estimators to introduced later will work correctly.

2.2 Murphy Method

2.2.1 The Murphy Regret Function

Murphy (2003) introduced a method to estimate optimal decision rules with the aim of producing the highest mean response at the end of the study. Murphy's method uses experimental or observational data to construct the estimator.

One approach is to model the multivariate distribution of $(\bar{S}_K, \bar{A}_K, Y)$ and then apply a dynamic programming method. Dynamic programming is a backward induction method which is used to find the decision rules that maximise the mean response. It can be impractical computationally for realistic problems.

Murphy's contribution is to show how dynamic programming can be avoided through the introduction of *regret functions* combined with an iterative estimation method. This method is semi-parametric because it only parametrises the regret function and then estimates it rather than parametrising the conditional density of Y, $E[Y|\bar{S}_j, \bar{A}_{j-1}]$.

$Y(\underline{d}_j^{opt})$ is defined as the response under the best possible decisions from time j and we define the regret functions for each $j = 1, \ldots, K$ as

$$\mu_j(a_j|\bar{S}_j, \bar{A}_{j-1}; \psi) = E[Y(\underline{d}_j^{opt})|\bar{S}_j, \bar{A}_{j-1}] - E[Y(a_j, \underline{d}_{j+1}^{opt})|\bar{S}_j, \bar{A}_{j-1}] \qquad (2.1)$$

where the first term is the best expected value of Y at time point j given the past whilst the second term is the best expected value of Y from time point j choosing decision a_j given the past but still under optimal future decisions.

Thus, the loss in expected response is measured by the regret when comparing a_j with the best action at time point j, with both cases following the optimal regime later. Each μ_j defined in Equation (2.1) must satisfy the constraint,

$$\inf_{a_j} \left\{ \mu_j(a_j|\bar{S}_j, \bar{A}_{j-1}; \psi) \right\} = 0$$

This constraint ensures the regret should be equal to zero when the optimal decision is chosen at time j or equal to positive values since our target is to maximise the response, Y.

Murphy (2003) shows that the mean of Y given $(\bar{S}_K, \bar{A}_K)$ can be written in terms of the regrets as

$$E[Y|\bar{S}_K, \bar{A}_K] = \beta_0(S_1) + \sum_{j=1}^{K} \phi_j(\bar{S}_{j-1}, \bar{A}_{j-1}, S_j) - \sum_{j=1}^{K} \mu_j(A_j|\bar{S}_j, \bar{A}_{j-1}) \tag{2.2}$$

where

$$\phi_j(\bar{S}_{j-1}, \bar{A}_{j-1}, S_j) = E[Y(\underline{d}_j^{opt}|\bar{S}_{j-1}, \bar{A}_{j-1}, S_j)] - E[Y(\underline{d}_j^{opt}|\bar{S}_{j-1}, \bar{A}_{j-1})]. \tag{2.3}$$

From Equation (2.3) we see that the function ϕ_j compares the expected response under the optimal rule *after* S_j is revealed with the expected optimal rule response *before* S_j.

The optimal response Y is influenced by β_0, chosen actions A_j and the states S_j. We see that the states S_j enter through the ϕ terms and the chosen actions A_j enter through the regrets μ. The β_0 term is the initial condition and also the expected maximal mean response at optimal decisions, since each ϕ_j has expectation zero (over S_j) by definition.

Thus, the expression of the maximal mean response is

$$\beta_0(S_1) = E[Y|\bar{S}_K, \bar{A}_K] + \sum_{j=1}^{K} E(\mu_j(A_j|\bar{S}_j, \bar{A}_{j-1}))$$

where the ϕ-function is considered as type of noise and $\sum_{j=1}^{K} E(\phi_j(\bar{S}_{j-1}, \bar{A}_{j-1}, S_j)) = 0$, for $j = 1, \ldots, K$.

The combination of parametrising the regret function and the estimation method will lead to real practical advantages, as discussed by Murphy (2003). Besides that, this method can be useful in testing whether particular features of the past information are needed in the optimal decision rule.

2.2.2 Murphy Estimation Procedure

The model for the regrets, $\mu_j(\bar{S}_j, \bar{A}_j; \psi)$ is developed with a p-dimensional unknown parameter ψ so that $\inf_a\{\mu_j(\bar{S}_j, \bar{A}_{j-1}, a; \psi)\} = 0$. The estimation is based on a sum of squares which contain the observed responses and the regret functions for estimation of

the unknown parameter $\psi \subseteq \mathbb{R}^P$ and $c \subseteq \mathbb{R}$ an unknown scalar. Murphy considers

$$\sum_{j=1}^{K} \mathbb{P}_n \left\{ Y + c + \sum_{l=1, l\neq j}^{K} \mu_l(\bar{S}_l, \bar{A}_l; \hat{\psi}_n) + \mu_j(\bar{S}_j, \bar{A}_j; \psi) - \hat{E}_j(\mu_j(a|\bar{S}_j, \bar{A}_j; \psi)) \right\}^2 . \tag{2.4}$$

Here $\mathbb{P}$ is an average over the sample data defined as $\mathbb{P}\{f(X)\} = (\frac{1}{n}) \sum_{i=1}^{n} f(X_i)$ (assuming that the sample observations are drawn independently from a distribution) and

$$\hat{E}_j(\mu_j(a|\bar{S}_j, \bar{A}_j; \psi)) = \sum_a \mu_j(a|\bar{S}_j, \bar{A}_j; \psi) p_j(a|\bar{S}_j, \bar{A}_j).$$

We assume at least to begin with the conditional probability, $p_j(a|\bar{S}_j, \bar{A}_j)$ is known. This assumption can be relaxed by for instance estimating the density of actions using say maximum likelihood. For example, $\hat{\alpha}$ can be estimated from the model $p_j(a|\bar{S}_j, \bar{A}_j; \alpha)$ with unknown α by maximising the log-likelihood

$$\mathbb{P}(\sum_{j=1}^{K} \log p_j(A_j|\bar{S}_j, \bar{A}_{j-1}; \alpha)).$$

Murphy's method will be described later. The method is based on the following relationship, which Murphy proved:

$$\begin{aligned} \sum_{j=1}^{K} \mathbb{P}_n \left\{ Y + \hat{c}_n + \sum_{l=1}^{K} \mu_l(\bar{S}_l, \bar{A}_l; \hat{\psi}_n) - \sum_a \mu_j(a|\bar{S}_j, \bar{A}_j; \hat{\psi}_n) p_j(a|\bar{S}_j, \bar{A}_j; \hat{\alpha}_n) \right\}^2 \\ \leq \sum_{j=1}^{K} \mathbb{P}_n \left\{ Y + c + \sum_{l=1, l\neq j}^{K} \mu_l(\bar{S}_l, \bar{A}_l; \hat{\psi}_n) + \mu_j(\bar{S}_j, \bar{A}_j; \psi) \right. \\ \left. - \sum_a \mu_j(a|\bar{S}_j, \bar{A}_j; \psi) p_j(a|\bar{S}_j, \bar{A}_j; \hat{\alpha}_n) \right\}^2 \end{aligned} \tag{2.5}$$

Introducing the scalar c was suggested by Murphy as a way to stabilise her estimation routine and Murphy showed that the scalar c does not affect its consistency.

2.2.3 Murphy Simulation Scenario

We will follow the simulation procedure taken by Murphy (2003) based on a hypothetical educational programme for children. The data are simulated as follows. As a start, we choose a sample size, $n = 1000$, and $K = 10$ time points.

For each interval there are two possible actions, where the first action (A_1) is binary $1 = \text{yes}; 0 = \text{no}$. This first action is about whether the child should receive special education. If the child requires special education, level 1 will be assigned otherwise level 0 for not receiving special education. This simulation is a sequentially randomised experiment where the actions about whether the child should receive special education

are uniformly distributed {0,1}, i.e equally likely.

The second action (A_2) is about the amount of the appropriate treatment to be decided. The treatment amount if receiving special education $(A_1 = 1)$ is uniform on {1,2,3} and treatment amount for not receiving special education $(A_1 = 0)$ is uniform on {0,1,2,3}.The conditional density of Y given $(\bar{S}_K, \bar{A}_K)$ is normally distributed with variance 0.64 and mean

$$E[Y|\bar{S}_K, \bar{A}_K] = \beta_0(S_1) + \sum_{j=1}^{K} \phi_j(\bar{S}_{j-1}, \bar{A}_{j-1}, S_j) - \sum_{j=1}^{K} \mu_j(A_j|\bar{S}_j, \bar{A}_{j-1}) \tag{2.6}$$

where $\beta_0 = 30$ and $\phi_j(\bar{S}_j, \bar{A}_{j-1}) = -5(S_j - E(S_j|\bar{S}_{j-1}, \bar{A}_{j-1}))$. The marginal density of S_1 is Normal with mean$_1 = 0.5$ and variance=0.01. The conditional density of each S_j given $(\bar{S}_{j-1}, \bar{A}_{j-1})$ for $j > 2$ is Normal with mean $m_j = 0.5 + 0.2S_{j-1} - 0.07A_{j-1}A_{j-2} - 0.01A_{j-1}(1 - A_{j-2})$ and variance=0.01.

The true regret function $\mu_j(\bar{A}_j|\bar{S}_j, \bar{A}_{j-1}, \psi)$ for this simulation is defined to be

$$\begin{aligned}\mu_j(\bar{A}_j|\bar{S}_j, \bar{A}_{j-1}, \psi) = &\sum_{j=1}^{K} \psi_1(A_{1j} - I(S_j > \psi_2))^2 \\ &+ \left[\sum_{j=1}^{K} \psi_4(A_{1j}) \times (A_{2j} - (\psi_3 + \psi_5 S_j))^2\right] \\ &+ \psi_7(1 - A_{1j})(A_{2j} - (\psi_6 + \psi_8 S_j))^2\end{aligned}$$

Note that β_0 is the optimal mean response if the regrets are equal to zero.

For estimation, Murphy proposed an iterative procedure based on the right hand side of the Equation (2.5). Let

$$\begin{aligned}S(\psi^{(1)}, \psi^{(2)}, c) = \sum_{j=1}^{K} \mathbb{P}\Bigg\{ Y + c + \sum_{l=1, l\neq j}^{K} \mu_l(\bar{S}_l, \bar{A}_l; \psi^{(1)}) + \mu_j(\bar{S}_j, \bar{A}_j; \psi^{(2)}) \\ - \sum_{a} \mu_j(a|\bar{S}_j, \bar{A}_{j-1}; \psi^{(2)}) p_j(a|\bar{S}_j, \bar{A}_{j-1}) \Bigg\}^2\end{aligned} \tag{2.7}$$

The function has two versions of the parameter vector ψ, say $\psi^{(1)}$ and $\psi^{(2)}$, together with a constant, c. Murphy's method is as follows:

1. Set the initial estimates of $\psi^{(1)}$. In this simulation, our initial estimates of $\psi^{(1)}$ is the true value of ψ. Therefore $\psi^{(1)} = \{6, 5/9, 0, 1.5, 2, 0, 1.5, 5.5\}$.

2. Fix $\psi^{(1)}$. Minimise $S(\psi^{(1)}, \psi^{(2)}, c)$ with respect to $\psi^{(2)}$ and c using the Newton-Raphson method:

$$\psi^{(2)new} = \psi^{(2)old} - \left(\frac{\partial^2 S}{\partial \psi^{(2)} \partial \psi^{(2)T}}\right)^{-1} \frac{\partial S}{\partial \psi^{(2)}}$$

3. Set $\psi^{(1)} = \psi^{(2)}$.

4. Test for convergence. If $|\psi^{(1)} - \psi^{(2)}| \leq \epsilon$, then stop. Otherwise return to Step 2.

Murphy also approximates the non-smooth function $I(S_j > \psi_2)$ for the first action (A_1) in her estimation of the *yes-no* special education decision.

Theorem 2 from Murphy (2003) justifies this procedure as providing consistent estimates of the regret parameter, ψ. Below is an example of minimisation of $S(\psi^{(1)}, \psi^{(2)}, c)$ at Step 2. We are going to show how to derive the first derivative and second derivative of $\psi_1^{(2)}$ and *c* from the true regret function. Suppose the regret function is,

$$\begin{aligned}\mu_j(\bar{S}_j, \bar{A}_j, \psi^{(2)}) = \psi_1^{(2)}(A_{1j} - I(S_j > \psi_2^{(2)}))^2 + \psi_4^{(2)}(A_{1j})(A_{2j} - (\psi_3^{(2)} + \psi_5^{(2)} S_j))^2 \\ + \psi_7^{(2)}(1 - A_{1j})(A_{2j} - (\psi_6^{(2)} + \psi_8^{(2)} S_j))^2. \end{aligned} \tag{2.8}$$

We differentiate the sum of squares from Equation (2.7) with respect to *c* and $\psi_1^{(2)}$. The first derivative with respect to *c* is

$$\begin{aligned}\frac{\partial S}{\partial c} = 2\sum_{j=1}^{K} \mathbb{P}\Bigg\{ Y + c + \sum_{l=1, l\neq j}^{K} \mu_l(\bar{S}_l, \bar{A}_l; \psi^{(1)}) + \mu_j(\bar{S}_j, \bar{A}_j; \psi^{(2)}) \\ - \sum_a \mu_j(a|\bar{S}_j, \bar{A}_{j-1}; \psi^{(2)}) p_j(a|\bar{S}_j, \bar{A}_{j-1}) \Bigg\}.\end{aligned}$$

The second derivative with respect to *c* is

$$\frac{\partial^2 S}{\partial c \partial c^T} = 2.$$

We continue to differentiate the sum of squares $S(\psi^{(1)}, \psi^{(2)}, c)$ with respect to $\psi_1^{(2)}$

$$\begin{aligned}\frac{\partial S}{\partial \psi_1^{(2)}} = 2\sum_{j=1}^{K} \mathbb{P}\Bigg\{ Y + c + \sum_{l=1, l\neq j}^{K} \mu_l(\bar{S}_l, \bar{A}_l; \psi^{(1)}) + \mu_j(\bar{S}_j, \bar{A}_j; \psi^{(2)}) \\ - \sum_a \mu_j(a|\bar{S}_j, \bar{A}_{j-1}; \psi^{(2)}) p_j(a|\bar{S}_j, \bar{A}_{j-1}) \Bigg\} \times \frac{\partial}{\partial \psi_1^{(2)}} \Bigg[\mu_j(\bar{S}_j, \bar{A}_j; \psi^{(2)}) \\ - \sum_a \mu_j(a|\bar{S}_j, \bar{A}_{j-1}; \psi^{(2)}) p_j(a|\bar{S}_j, \bar{A}_{j-1}) \Bigg]\end{aligned}$$

where

$$\frac{\partial}{\partial \psi_1^{(2)}}(\mu_j(\bar{S}_j, \bar{A}_j; \psi^{(2)})) = (A_{1j} - I(S_j > \psi_2^{(2)}))^2.$$

Note that this is equal to 1 if $A_{1j} = 1$ and $I(S_j > \psi_2^{(2)}) = 0$ or $A_{1j} = 0$ and $I(S_j > \psi_2^{(2)}) = 1$, otherwise $\frac{\partial}{\partial \psi_1^{(2)}}(\mu_j(\bar{S}_j, \bar{A}_j; \psi^{(2)}))$ is equal to 0. The probability $p_j(A_{1j}|\bar{S}_j, \bar{A}_{j-1})$

is always $\frac{1}{2}$ for $A_{1j} = \{0, 1\}$ and so

$$\hat{E}_j(\mu_j(a|\bar{S}_j, \bar{A}_j; \psi^{(2)})) = \sum_a \mu_j(a|\bar{S}_j, \bar{A}_{j-1}; \psi^{(2)}) p_j(a|\bar{S}_j, \bar{A}_{j-1}) = (0 \times \frac{1}{2}) + (1 \times \frac{1}{2}) = \frac{1}{2}.$$

Hence

$$\frac{\partial S}{\partial \psi_1^{(2)}} = 2 \sum_{j=1}^{K} \mathbb{P} \left\{ Y + c + \sum_{l=1, l \neq j}^{K} \mu_l(\bar{S}_l, \bar{A}_l; \psi^{(1)}) + \mu_j(\bar{S}_j, \bar{A}_j; \psi^{(2)}) - \sum_a \hat{E}_j(\mu_j(a|\bar{S}_j, \bar{A}_j; \psi^{(2)})) \right\} \times \left\{ (A_{1j} - I(S_j > \psi_2^{(2)}))^2 - \frac{1}{2} \right\}$$

Furthermore, the second derivatives with respect to $\psi_1^{(2)}$ are:

$$\frac{\partial S}{\partial \psi_1^{(2)} \partial (\psi_1^{(2)})^T} = 2 \sum_{j=1}^{K} \mathbb{P} \left\{ (A_{1j} - I(S_j > \psi_2^{(2)}))^2 - \frac{1}{2} \right\}^2$$

and

$$\frac{\partial S}{\partial \psi_1^{(2)} \partial c} = 2 \sum_{j=1}^{K} \mathbb{P} \left\{ (A_{1j} - I(S_j > \psi_2^{(2)}))^2 - \frac{1}{2} \right\}$$

Other than $\psi_2^{(2)}$, which appears in the indicator function, the derivatives of S with respect to all the other parameters can be calculated in a similar way, though the terms involved are more complicated. Details are omitted.

2.3 Robins Method

2.3.1 The Blip Function Model

Robins (2004) introduced blip functions as a route to find an optimal regime. The blip function is based on the idea of structural nested mean models (SNMM). An SNMM is defined as an expected difference between a person's counterfactual response on a specific treatment regime from $j+1$ onward and on another specific regime from j conditional on history.

Suppose H_j is the history of the treatment decision and status up to the beginning of time j but not including the treatment decision at time j, so $H_j = (S_1, A_1, S_2, A_2, \ldots, S_j)$. The *optimal blip-to-reference function* is defined as the difference between expected outcome using a reference regime $d_j^{\text{ref}} = d_j^{\text{ref}}(H_j)$ rather than a_j at time j. The *optimal blip-to-reference function* is

$$\gamma_j^{d_j^{\text{ref}}}(a_j|\bar{S}_j, \bar{A}_{j-1}) = E\left[Y(a_j, \underline{d}_{j+1}^{\text{opt}})|\bar{S}_j, \bar{A}_{j-1}\right] - E\left[Y(d_j^{\text{ref}}, \underline{d}_{j+1}^{\text{opt}})|\bar{S}_j, \bar{A}_{j-1}\right] \tag{2.9}$$

Another version of the blip function is the *blip-to-zero* function which is also suggested by Robins (2004). This *blip-to-zero* function replaces the reference regime d_j^{ref} with 'zero' at time j. This 'zero' action means the standard treatment or placebo in the medical case. Then,

$$\gamma_j^{d_j^{\text{ref}}=0}(a_j|\bar{S}_j, \bar{A}_{j-1}) = E\left[Y(a_j, \underline{d}_{j+1}^{\text{opt}})|\bar{S}_j, \bar{A}_{j-1}\right] - E\left[Y(d_j^{\text{ref}} = 0, \underline{d}_{j+1}^{\text{opt}})|\bar{S}_j, \bar{A}_{j-1}\right] \tag{2.10}$$

The optimal blip is,

$$\gamma_j(a_j|\bar{S}_j, \bar{A}_{j-1}) = E\left[Y(a_j, \underline{d}_{j+1}^{\text{opt}})|\bar{S}_j, \bar{A}_{j-1}\right] - E\left[Y(\underline{d}_{j+1}^{\text{opt}})|\bar{S}_j, \bar{A}_{j-1}\right] \tag{2.11}$$

The regret function from Murphy (2003) defined at (2.1) is the negative of the optimal blip.

$$\mu_j(a_j|\bar{S}_j, \bar{A}_{j-1}) = E\left[Y(\underline{d}_j^{\text{opt}})|\bar{S}_j, \bar{A}_{j-1}\right] - E\left[Y(a_j, \underline{d}_{j+1}^{\text{opt}})|\bar{S}_j, \bar{A}_{j-1}\right] \tag{2.12}$$

2.3.2 G-Estimation

Robins (2004) introduced *g-estimation* and has produced a number of estimating equations using structural nested mean models (SNMM). G-estimation estimates the parameter ψ either from the optimal blip-to-zero or the regret function. The *h-function* is defined as,

$$h_j(\psi) = Y + \sum_{m=j}^{K}\left[\gamma_m(d_m^{\text{opt}}|\bar{S}_m, \bar{A}_{m-1}; \psi) - \gamma_m(A_m|\bar{S}_m, \bar{A}_{m-1}; \psi)\right] \tag{2.13}$$

Substituting the observed values $(\bar{S}_j, \bar{A}_j)$ into $h_j(\psi)$ will give a patient's actual outcome, Y added to the expected difference between the outcome for someone who received a_j treatment with someone who was given the reference regime such as placebo or control treatment at time j, and were treated optimally when both had the same treatment and history to that interval.

Thus, returning to the blip function

$$\begin{aligned} h_j(\psi) &= Y + \sum_{m=j}^{K} \big\{ E\left[Y(d_m^{\text{opt}}, d_{m+1}^{\text{opt}})|\bar{S}_m, \bar{A}_{m-1}; \psi\right] - E\left[Y(d_{m+1}^{\text{opt}})|\bar{S}_m, \bar{A}_{m-1}; \psi\right] \\ &\quad - E\left[Y(A_m, d_{m+1}^{\text{opt}})|\bar{S}_m, \bar{A}_{m-1}; \psi\right] + E\left[Y(d_{m+1}^{\text{opt}})|\bar{S}_m, \bar{A}_{m-1}; \psi\right] \big\} \\ &= Y + \sum_{m=j}^{K} \big\{ E\left[Y(\underline{d}_m^{\text{opt}})|\bar{S}_m, \bar{A}_{m-1}; \psi\right] - E\left[Y(A_m, d_{m+1}^{\text{opt}})|\bar{S}_m, \bar{A}_{m-1}; \psi\right] \big\} \end{aligned} \tag{2.14}$$

For example, if we have K=2 then the *h-functions* will be

$$\begin{aligned} h_2(\psi) &= Y + E\left[Y(\underline{d}_2^{\text{opt}})|\bar{S}_2, A_1; \psi\right] - E\left[Y(A_2)|\bar{S}_2, A_1; \psi\right] \\ h_1(\psi) &= Y + E\left[Y(\underline{d}_1^{\text{opt}})|S_1; \psi\right] - E\left[Y(A_1, \underline{d}_1^{\text{opt}})|S_1; \psi\right] \\ &\quad + E\left[Y(\underline{d}_2^{\text{opt}})|\bar{S}_2, A_1; \psi\right] - E\left[Y(A_2)|\bar{S}_2, A_1; \psi\right] \end{aligned}$$

The difference in Equation (2.14) is equivalent to the regret function defined at Equation (2.12) and therefore,

$$h_j(\psi) = Y + \sum_{m=j}^{K} \mu_m(\bar{A}_m|\bar{S}_m, \bar{A}_{m-1}). \tag{2.15}$$

Let $\nu_j(A_j)$ be an arbitrary vector with length $\dim(\psi)$ determined by states and actions to time j. Specifying the functions $h_j(\psi)$ and $\nu_j(A_j)$ for estimation, we define

$$U(\psi) = \sum_{j=1}^{K} h_j(\psi) \left\{ \nu_j(A_j) - E[\nu_j(A_j)|\bar{S}_j, \bar{A}_{j-1}] \right\}. \tag{2.16}$$

Setting $U(\psi) = 0$ defines an unbiased estimating equations and we can estimate ψ by the value for which $U(\hat{\psi}) = 0$. By construction, $h_j(\psi)$ is the expected value of response Y with optimal decision taken at time j onward rather than the actual decision A_j, conditional on $(\bar{S}_j, \bar{A}_{j-1})$. This means that h_j is dependent on previous actions, $\bar{A}_{j-1} = (A_1, A_2, \ldots, A_{j-1})$ but independent of the future actions $\underline{A}_j = (A_j, A_{j+1}, \ldots, A_k)$. We define

$$\begin{aligned} E[U(\psi)] &= \sum_{j=1}^{K} E\left[h_j(\psi) \left\{ \nu_j(A_j) - E[\nu_j(A_j)|\bar{S}_j, \bar{A}_{j-1}] \right\} \right] \\ &= \sum_{j=1}^{K} E\left[h_j(\psi)\right] E\left\{ \nu_j(A_j) - E\left[\nu_j(A_j)|\bar{S}_j, \bar{A}_{j-1}\right] \right\} \\ &\quad + \text{cov}\left[h_j(\psi), \left\{ \nu_j(A_j) - E\left[\nu_j(A_j)|\bar{S}_j, \bar{A}_{j-1}\right] \right\} \right] \end{aligned}$$

Previously we have mentioned that $h_j(\psi)$ depends on A_{j-1} given the past but is inde-

pendent of A_j given its earlier history so that $E\left\{\nu_j(A_j) - E[\nu_j(A_j)|\bar{S}_j, \bar{A}_{j-1}]\right\} = 0$ and $\text{cov}[h_j(\psi), \left\{\nu_j(A_j) - E[\nu_j(A_j)|\bar{S}_j, \bar{A}_{j-1}]\right\}] = 0$. Thus we have $E[U(\psi)] = 0$ and so an unbiased estimating equation, as stated.

The estimators are not efficient however, Robins (2004) has refined the equation (2.16) to gain efficiency. Let

$$U^t(\psi) = \sum_{j=1}^{K} (h_j(\psi) - E[h_j(\psi)|\bar{S}_j, \bar{A}_{j-1}]) \times \{\nu_j(A_j) - E[\nu_j(A_j)|\bar{S}_j, \bar{A}_{j-1}]\} \quad (2.17)$$

Introducing the $E[h_j(\psi)|\bar{S}_j, \bar{A}_{j-1}]$ gives estimation which can be shown to be more efficient than found in Equation (2.16) even if the model is misspecified. However, obtaining $E[h_j(\psi)|\bar{S}_j, \bar{A}_{j-1}]$ is problematic in practice. Therefore, we prefer the Equation (2.16).

2.3.3 Relating the Two Methods

As seen Robins uses *blip* models while Murphy uses *regret* functions, but both are mathematically equivalent. Moodie et al. (2007) demonstrated the similarities between these methods. For estimation of model parameters, Robins uses *g-estimation* whilst Murphy uses the *iterative minimisation for optimal regimes (IMOR)* described above. Moodie et al. (2007) have related these two methods together by using the *h-function* which is found in *g-estimation*. To relate these two methods, first, we consider the regret function:

$$\begin{aligned}
\mu_j(a_j|\bar{S}_j, \bar{A}_{j-1}) &= E[Y(\underline{d}_j^{\text{opt}}|\bar{S}_j, \bar{A}_{j-1})] - E[Y(a_j, \underline{d}_{j+1}^{\text{opt}}|\bar{S}_j, \bar{A}_{j-1})]. \\
&= E[Y(\underline{d}_j^{\text{opt}}|\bar{S}_j, \bar{A}_{j-1})] - E[Y(d_j^{\text{ref}}, \underline{d}_{j+1}^{\text{opt}}|\bar{S}_j, \bar{A}_{j-1})] \\
&- \left\{E[Y(a_j, \underline{d}_{j+1}^{\text{opt}}|\bar{S}_j, \bar{A}_{j-1})] - E[Y(d_j^{\text{ref}}, \underline{d}_{j+1}^{\text{opt}}|\bar{S}_j, \bar{A}_{j-1})]\right\}
\end{aligned}$$

Hence,

$$\mu_j(a_j|\bar{S}_j, \bar{A}_{j-1}) = \gamma_j^{\text{ref}}(\underline{d}_j^{\text{opt}}|\bar{S}_j, \bar{A}_{j-1}) - \gamma_j^{\text{ref}}(a_j|\bar{S}_j, \bar{A}_{j-1}).$$

Then, we consider the blip function:

$$\begin{aligned}
\gamma_j^{\text{ref}} &= E[Y(a_j, \underline{d}_{j+1}^{\text{opt}}|\bar{S}_j, \bar{A}_{j-1})] - E[Y(d_j^{\text{ref}} = 0, \underline{d}_{j+1}^{\text{opt}}|\bar{S}_j, \bar{A}_{j-1})] \\
&= E[Y(a_j, \underline{d}_{j+1}^{\text{opt}}|\bar{S}_j, \bar{A}_{j-1})] - E[Y(\underline{d}_j^{\text{opt}}|\bar{S}_j, \bar{A}_{j-1})] \\
&- \left\{E[Y(\underline{d}_j^{\text{opt}}|\bar{S}_j, \bar{A}_{j-1})] - E[Y(d_j^{\text{ref}}, d_{j+1}^{\text{opt}}|\bar{S}_j, \bar{A}_{j-1})]\right\}.
\end{aligned}$$

We can write this as

$$\begin{aligned}
\gamma_j^{\text{ref}} &= E[Y(\underline{d}_j^{\text{opt}}|\bar{S}_j, \bar{A}_{j-1})] - E[Y(\underline{d}_j^{\text{ref}}, d_{j+1}^{\text{opt}}|\bar{S}_j, \bar{A}_{j-1})] \\
&- \left\{E[Y(\underline{d}_j^{\text{opt}}|\bar{S}_j, \bar{A}_{j-1})] - E[Y(a_j, \underline{d}_{j+1}^{\text{opt}}|\bar{S}_j, \bar{A}_{j-1})]\right\}
\end{aligned}$$

Thus

$$\gamma_j^{\text{ref}} = \mu_j(d_j^{\text{ref}}|\bar{S}_j, \bar{A}_{j-1}) - \mu_j(a_j|\bar{S}_j, \bar{A}_{j-1}).$$

Recall the Murphy's regret function from Equation (2.8) and re-write it in shorter notation as

$$\begin{aligned}\mu_j &= \psi_1(A_{j1} - I((S_j) > \psi_2))^2 + \psi_4 A_{j1}(A_{j2} - \psi_3 - \psi_5 S_j)^2 \\ &\quad + \psi_7(1 - A_{j1})(A_{j2} - \psi_6 - \psi_8 S_j)^2 \\ &= \psi_1 v_{j1} + \psi_4 v_{j4} + \psi_7 v_{j7} \end{aligned} \tag{2.18}$$

From Equation (2.15) above, we get,

$$\begin{aligned} h_j(\psi) &= Y + \sum_{m=j}^{K} \mu_m(\bar{A}_m|\bar{S}_m, \bar{A}_{m-1}) \\ &= Y + \psi_1 \sum_{m=j}^{K} v_{m1} + \psi_4 \sum_{m=j}^{K} v_{m4} + \psi_7 \sum_{m=j}^{K} v_{m7}. \end{aligned} \tag{2.19}$$

Next, we define $d_{j1} = v_{j1} - E_j[v_{j1}]$, $d_{j4} = v_{j4} - E_j[v_{j4}]$ and $d_{j7} = v_{j7} - E_j[v_{j7}]$. We will use these to obtain the estimating equations for ψ_1, ψ_4, ψ_7 conditional on $\psi_2, \psi_3, \psi_5, \psi_6, \psi_8$. Since, as seen $h_j(\psi)$ is independent of actions after time j, it follows that

$$\sum_{j=1}^{K} h_j d_{j1} = 0$$

is an unbiased estimating equation. Expanding the h_j function from Equation (2.19) to get,

$$\sum_{j=1}^{K} \left\{ Y + \psi_1 \sum_{m=j}^{K} v_{m1} + \psi_4 \sum_{m=j}^{K} v_{m4} + \psi_7 \sum_{m=j}^{K} v_{m7} \right\} d_{j1} = 0$$

and so

$$-\sum_{j=1}^{K} Y d_{j1} = \left(\sum_{j=1}^{K} \sum_{m=j}^{K} v_{m1} d_{j1} \right) \psi_1 + \left(\sum_{j=1}^{K} \sum_{m=j}^{K} v_{m4} d_{j1} \right) \psi_4 + \left(\sum_{j=1}^{K} \sum_{m=j}^{K} v_{m7} d_{j1} \right) \psi_7$$

Similarly, for the other two coefficients ψ_4 and ψ_7, we use

$$\sum_{j=1}^{K} h_j d_{j4} = 0$$

$$\sum_{j=1}^{K} h_j d_{j7} = 0,$$

leading to,

$$-\sum_{j=1}^{K} Y d_{j4} = \left(\sum_{j=1}^{K}\sum_{m=j}^{K} v_{m1} d_{j4}\right)\psi_1 + \left(\sum_{j=1}^{K}\sum_{m=j}^{K} v_{m4} d_{j4}\right)\psi_4 + \left(\sum_{j=1}^{K}\sum_{m=j}^{K} v_{m7} d_{j4}\right)\psi_7$$

and

$$-\sum_{j=1}^{K} Y d_{j7} = \left(\sum_{j=1}^{K}\sum_{m=j}^{K} v_{m1} d_{j7}\right)\psi_1 + \left(\sum_{j=1}^{K}\sum_{m=j}^{K} v_{m4} d_{j7}\right)\psi_4 + \left(\sum_{j=1}^{K}\sum_{m=j}^{K} v_{m7} d_{j7}\right)\psi_7$$

We can write these three equations in general form as,

$$-\sum_{j=1}^{K} Y d_{ji} = \left(\sum_{j=1}^{K}\sum_{m=j}^{K} v_{m1} d_{ji}\right)\psi_1 + \left(\sum_{j=1}^{K}\sum_{m=j}^{K} v_{m4} d_{ji}\right)\psi_4 + \left(\sum_{j=1}^{K}\sum_{m=j}^{K} v_{m7} d_{ji}\right)\psi_7 \tag{2.20}$$

for $i = 1, 4, 7$. It is also possible to write these equations collectively in vector form as

$$Z = B \times \psi_r$$

where B is a symmetric matrix which we require to be invertible, $\psi_r = (\psi_1, \psi_4, \psi_7)$ and Z is the vector of left hand sides of the above. Therefore, a closed form for $\hat{\psi}(\bar{S}_j, \bar{A}_{j-1}) = (\hat{\psi}_1, \hat{\psi}_4, \hat{\psi}_7)$ conditional on $\psi_2, \psi_3, \psi_5, \psi_6, \psi_8$ is

$$\hat{\psi}_r = B^{-1} Z \tag{2.21}$$

For the other parameters $\psi_3, \psi_5, \psi_6, \psi_8$ excluding ψ_2 we use a Newton-Raphson method:

1. Set the initial estimates of ψ. In this simulation, our initial estimates of ψ are the values of $\psi_3, \psi_5, \psi_6, \psi_8$.

2. Fix ψ_2. Estimate ψ_1, ψ_4 and ψ_7 using Equation (2.21). Then solve using Equation (2.19) for the other parameters $\psi_3, \psi_5, \psi_6, \psi_8$ using Newton-Raphson:

$$\psi^{new} = \psi^{old} - \left(\frac{\partial^2 U(\psi)}{\partial\psi\partial\psi^T}\right)^{-1} \frac{\partial U(\psi)}{\partial\psi}$$

   The parameter ψ_2 is more awkward, as will be discussed later. For the moment we assume that ψ_2 is known.

3. Set $\psi^{new} = \psi^{old}$

4. Test for convergence. If $|\psi^{old} - \psi^{new}| \leq \epsilon$, then stop. Otherwise return to Step 2.

2.4 Regret-Regression Method

Henderson et al. (2009) proposed another method for determining optimal dynamic treat-

ment regimes from observational data that follow all the assumptions above. This method, which they called regret-regression, was applied to an anticoagulant dataset in order to choose the best potentially time-varying dose for patients on long term treatment. Rosthøj et al. (2006) applied the Murphy (2003) regret function to estimate the optimal decision from the anticoagulant data but they were only able to fit a very simplified model.

From Equations (2.1), (2.2) and (2.3), we have

$$\begin{aligned}\phi_j(\bar{S}_{j-1}, \bar{A}_{j-1}, S_j) &= E[Y(\underline{d}_j^{opt}|\bar{S}_{j-1}, \bar{A}_{j-1}, S_j)] - E[Y(\underline{d}_j^{opt}|\bar{S}_{j-1}, \bar{A}_{j-1})] \\ &= E[Y(\underline{d}_j^{opt}|\bar{S}_{j-1}, \bar{A}_{j-1}, S_j)] - E_{S_j|\bar{S}_{j-1},\bar{A}_{j-1}}\left\{E[Y(\underline{d}_j^{opt}|\bar{S}_{j-1}, \bar{A}_{j-1}, S_j)]\right\}\end{aligned} \tag{2.22}$$

and we note $E_{S_j|\bar{S}_{j-1},\bar{A}_{j-1}}\left[\phi_j(\bar{S}_{j-1}, \bar{A}_{j-1}, S_j)\right] = 0$.

Henderson et al. (2009) suggests to parametrise the $\phi_j(\bar{S}_{j-1}, \bar{A}_{j-1}, S_j)$ function from Equation (2.2) rather than avoiding it. Besides that, they model $\phi_j(\bar{S}_{j-1}, \bar{A}_{j-1}, S_j; \beta)$ as a linear combination of residuals between S_j and their respective conditional expectations given $(\bar{S}_{j-1}, \bar{A}_{j-1})$. Let $Z_j = S_j - E[S_j|\bar{S}_{j-1}, \bar{A}_{j-1}]$ and assume,

$$E[Y|\bar{S}_K, \bar{A}_K] = \beta_0(S_1) + \sum_{j=2}^{K} \beta_j^T(\bar{S}_{j-1}, \bar{A}_{j-1})Z_j - \sum_{j=1}^{K} \mu_j(A_j|\bar{S}_j\bar{A}_{j-1}; \psi) \tag{2.23}$$

Notice here that $\beta_j(\bar{S}_{j-1}, \bar{A}_{j-1})$ is a coefficient vector which measures the effect of S_j *after* $(\bar{S}_{j-1}, \bar{A}_{j-1})$ is observed and supposing that the best actions have been chosen from time point j onwards.

2.4.1 Regret-Regression Estimation Procedure

The regret-regression method is a full parametric model where it parameterise the conditional density of Y, $E[Y|\bar{S}_K, \bar{A}_K]$. We use the linear regression method to model $\phi(\bar{S}_{j-1}, \bar{A}_{j-1})$ term by defining the residuals between S_j which depend on previous history, $Z_j = S_j - E[S_j|\bar{S}_{j-1}, \bar{A}_{j-1}]$. Then, we follow the Murphy method to parameterise the regret function, $\mu_j(a_j|\bar{S}_j, \bar{A}_{j-1})$. Suppose Equation (2.23) is always true and $\beta_j(\bar{S}_{j-1}, \bar{A}_{j-1})$ depends on $(\bar{S}_{j-1}, \bar{A}_{j-1})$. We minimise the sum of squares function

$$\begin{aligned}SSE &= \sum_{i=1}^{n}(Y_i - E[Y_i|\bar{S}_{iK}, \bar{A}_{iK}])^2 \\ &= \sum_{i=1}^{n}\left(Y_i - \beta_0(S_{1i}) - \sum_{j=2}^{K}\beta_j^T(\bar{S}_{j-1,i}, \bar{A}_{j-1,i})Z_{ji} - \sum_{j=1}^{K}\mu_j(A_{ji}|\bar{S}_{ji}, \bar{A}_{j-1,i}; \psi)\right)^2\end{aligned} \tag{2.24}$$

to obtain the estimated parameter $\hat{\beta}$ and $\hat{\psi}$. The bootstrap method is used to estimate the variance, including re-estimation of the residuals Z_{ji} at each resample. Henderson et al.

(2009) propose diagnostic checking to examine the residuals between observed and fitted value of Y, which is not possible under the Murphy or Robins estimation methods.

2.5 Simulations

2.5.1 Murphy Simulation

In this section we discuss results obtained from the simulation scenario proposed by Murphy. Based on the results, we examine estimation accuracy using different sample sizes n with 1000 repetitions and make a comparison between the estimated parameter $\hat{\psi}$ with true ψ and recall we have fixed ψ_2 for the most part.

Sample Size	Percentage of successful convergences,(%)
250	89.8
500	94.0
1000	98.8

Table 2.1: Successful convergence rates for different sample sizes based on Murphy's method with 1000 repetitions

We begin the estimation procedure by fixing $\psi^{(1)}$. We set $\psi^{(1)}$ to be an initial estimates. In this simulation we consider the initial estimates to be the true value of ψ. Murphy has set the true value of ψ as $(6, 5/9, 0, 1.5, 2, 0, 1.5, 5.5)$. Then, we minimise the least squares, $S(\psi^{(1)}, \psi^{(2)}, c)$ in Equation (2.7) using the Newton-Raphson method to obtain $\psi^{(2)}$. We then set $\psi^{(1)} = \psi^{(2)}$ and test for convergence, $|\psi^{(1)} - \psi^{(2)}| \leq \epsilon$ by comparing the initial estimates, $\psi^{(1)}$ with the new estimates, $\psi^{(2)}$. If the differences is small, i.e. $\epsilon = 0.001$, we stop the process otherwise we continue until it converged.

One immediate problem we found in this simulation is that the Murphy iterative routine did not always converge even though our initial parameter estimates are in fact the true values. We notice that the estimation procedure is not a standard estimation procedure. Murphy method is found sensitive to the starting value (Rosthøj et al., 2006). Rosthøj et al. (2006) also has tested many different starting values using the one search root-finding algorithm.

Table 2.1 shows the convergence rate improves as we increase the sample size. We start the simulation with sample size 250 and we found 89.8% of simulations converged. This percentage has increase to 94% as we increased the sample size to 500. Sample size 1000 leads to a very impressive 98.8% convergence. We are not considering the sample size smaller than 250 where there will be a convergence problem if sample size is too low (Rosthøj et al., 2006).

Table 2.2 shows that on average the parameter estimates $\hat{\psi}$ are close to the true values ψ as sample size increases when ψ_2 is fixed based on successfully converged samples. The standard error (SE) and the root mean square error (RMSE) decreases as sample size increases as we expected. We will drop the sample size 250 in future analysis because

		Sample Size,(n)		
	Parameter	250	500	1000
Mean	$\psi_1 = 6.000$	5.987	6.011	5.994
	$\psi_3 = 0.000$	0.004	-0.006	-0.013
	$\psi_4 = 1.500$	1.521	1.493	1.495
	$\psi_5 = 2.000$	2.001	1.997	2.017
	$\psi_6 = 0.000$	0.000	0.006	0.004
	$\psi_7 = 1.500$	1.495	1.498	1.504
	$\psi_8 = 5.500$	5.510	5.494	5.488
SE	ψ_1	0.132	0.088	0.063
	ψ_3	0.178	0.122	0.084
	ψ_4	0.130	0.087	0.064
	ψ_5	0.264	0.188	0.129
	ψ_6	0.112	0.079	0.061
	ψ_7	0.062	0.044	0.033
	ψ_8	0.256	0.177	0.141
RMSE	ψ_1	0.143	0.093	0.069
	ψ_3	0.217	0.124	0.085
	ψ_4	0.146	0.096	0.064
	ψ_5	0.294	0.199	0.131
	ψ_6	0.119	0.083	0.061
	ψ_7	0.066	0.044	0.034
	ψ_8	0.272	0.192	0.145

Table 2.2: The Mean, standard error (SE) and root mean square error (RMSE) of the estimated parameters obtained from Murphy's method with different sample sizes and 1000 simulations.

we found that it gives poor estimates when compared with the other two sample sizes, as well as having the convergence issues.

2.5.2 Murphy Smooth Function

The regret function of the first action, A_1 is,

$$\mu_{j1}(a_{j1}|\bar{S}_K, \bar{A}_{j-1}; \psi) = \psi_1(a_{j1} - I(S_j > \psi_2))^2 \tag{2.25}$$

As suggested by Murphy (2003), we replace the *non-smooth* function $I(S_j > \psi_2)$ with the *smooth* function

$$\exp\{30(S_j - \psi_2)\}/[1 + \exp\{30(S_j - \psi_2)\}]$$

Thus, our new approximate regret function for the first action, A_1 is,

$$\mu_{j1}(a_{j1}|\bar{S}_K, \bar{A}_{j-1}; \psi) = \psi_1(a_{j1} - (\exp\{30(s_j - \psi_2)\}/[1 + \exp\{30(s_j - \psi_2)\}]))^2 \tag{2.26}$$

Table 2.3 compares the convergence rate when we estimate ψ_2 using the smooth function with what happens when we assume ψ_2 is fixed. We found using the smooth function

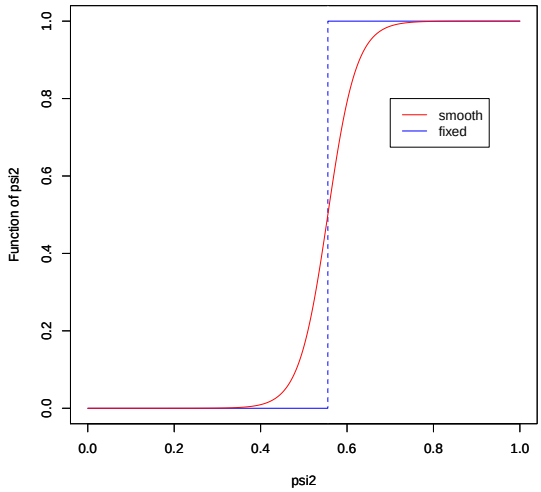

Figure 2.2: The smooth function approximation to indicator function.

Samples(n)	Percentage of successful convergences,(%)	
	Smooth Function(estimated $\hat{\psi}_2$)	Fixed ψ_2
500	52.6	93.9
1000	41.4	98.8

Table 2.3: The percentage of successful convergences between the smooth and fixed functions for the estimated $\hat{\psi}_2$ at sample size 500 and 1000. This simulated study is repeated 1000 times.

to estimate ψ_2 has lower convergence rate almost by half than the convergence rate for fixed ψ_2. When sample size increases, the convergence rate also increases for fixed ψ_2 but not for the smooth function where the convergence rate is poorer at just 41.4% at sample size 1000 due to the random simulation noise.

Table 2.4 shows the mean, SE and RMSE using both methods at sample size $n = 500$ and $n = 1000$. As we can see the mean, SE and RMSE when using the smooth function give poor estimates of ψ for all the parameters, often far away from the true ψ even at the large sample size $n = 1000$. The bias is huge especially for the parameters ψ_1 and ψ_8. This is in contrast to the fixed ψ_2 function where the simulations provided very good estimates with a very small bias. This fixed ψ_2 works best at sample size $n = 1000$.

Since our main concern is with the general performance and not the difficulty of incorporating non-differential functions, for the remainder of this work we shall regard ψ_2 as fixed.

2.5.3 Comparison Between All Three Methods

We have described the Murphy simulation scenario in the previous section and have related the Murphy method to the *g-estimation* procedure of Robins. It is also possible to link the Murphy method with the regret-regression method. We begin with the mean from

Samples(n)	Parameter	Smooth approximation			Fixed ψ_2		
		Mean	SE	RMSE	Mean	SE	RMSE
500	$\psi_1 = 6.000$	7.524	0.409	1.578	6.011	0.088	0.093
	$\psi_2 = 0.556$	0.556	0.005	0.005	0.556	0.000	0.000
	$\psi_3 = 0.000$	0.429	0.281	0.513	-0.006	0.122	0.124
	$\psi_4 = 1.500$	1.573	0.152	0.169	1.493	0.087	0.096
	$\psi_5 = 2.000$	1.435	0.388	0.686	1.997	0.188	0.199
	$\psi_6 = 0.000$	0.174	0.148	0.228	0.006	0.079	0.083
	$\psi_7 = 1.500$	1.600	0.086	0.132	1.498	0.044	0.044
	$\psi_8 = 5.500$	5.018	0.366	0.605	5.494	0.177	0.192
1000	$\psi_1 = 6.000$	7.533	0.306	1.622	5.994	0.063	0.069
	$\psi_2 = 0.556$	0.556	0.004	0.004	0.556	0.000	0.000
	$\psi_3 = 0.000$	0.466	0.111	0.480	-0.004	0.084	0.085
	$\psi_4 = 1.500$	1.574	0.127	0.156	1.500	0.064	0.064
	$\psi_5 = 2.000$	1.422	0.281	0.693	2.004	0.129	0.131
	$\psi_6 = 0.000$	0.179	0.110	0.230	0.002	0.061	0.061
	$\psi_7 = 1.500$	1.598	0.068	0.123	1.501	0.033	0.034
	$\psi_8 = 5.500$	5.005	0.256	0.600	5.496	0.141	0.145

Table 2.4: Parameter estimates between the smooth approximation and fixed ψ_2 at sample size 500 and 1000. This simulated study is repeated 1000 times.

Murphy simulation:

$$E[Y|\bar{S}_K, \bar{A}_K] = \beta_0 + \beta_1 \sum_{j=1}^{K}(S_j - m_j) - \sum_{j=1}^{K}\{\psi_1(a_{j1} - I\{S_j > \psi_2\})^2 - \psi_4(a_{j2} - \psi_3 - \psi_5 S_j)^2 + \psi_7(a_{j2} - \psi_6 - \psi_8 S_j)^2\}. \quad (2.27)$$

It seems that the Equation (2.27) is equivalent to Equation (2.23). The Murphy procedure models the potential outcomes or counterfactual potential outcomes, $E[Y|(\bar{S}_K, \bar{A}_K)]$ semiparametrically and works only on the regret functions μ_j found in Equation (2.2). The initial values β_0 and the ϕ term are treated as nuisance parameters.

This is in contrast to the regret-regression method where the potential outcomes are treated as full parametric model. The method parameterises the ϕ term as well as the μ term from Equation (2.2). The regret-regression method models the ϕ term as a linear combination of residuals between S_j and the expected of S_j given the past. This is defined as $Z_j = S_j - m_j$ found in Equation (2.27).

The Murphy estimation procedure requires the actions and previous history $(\bar{S}_{j-1}, \bar{A}_{j-1})$ in order to find expected regrets over all possible decisions. In contrast the regret-regression method models the states given history to obtain the residuals. We discovered that the estimation in the regret-regression method is more direct than the Murphy estimation in addition to being less challenging in computation compared to the Murphy method. This can supported by simulation which will be discussed in detail later.

Simulation using Fixed ψ_2 for All Methods

Methods	Percentage of successful convergences,(%)	
	n=500	n=1000
Murphy	93.9	98.8
Regret-Regression	100.0	100.0
Robins	81.1	96.6

Table 2.5: Percentage of successful convergences between methods when ψ_2 is fixed with sample size, $n = 500$ and $n = 1000$

Table 2.5 shows the rate of convergence for the different methods. We compared these methods at two different sample sizes, $n = 500$ and $n = 1000$. From all the methods, the regret-regression method shows the highest percentage of successful convergence with 100% convergence at both sample sizes. This is followed by the Murphy procedure. The Robins method has the poorest convergence rate especially at $n = 500$ with 81.1%, though this increased to 96.6% when sample size, $n = 1000$. We continue our investigation of these three methods by looking at mean, SE and RMSE given in Table 2.6.

From the simulations, we found that the regret-regression method works very well for parameter estimation followed by the Murphy method and then Robins. We also found that the regret regression estimates have small bias compared to Murphy and Robins. There is also less bias when the sample is large, $n = 1000$. Robins method has poor performance in the parameter estimates where the mean values are often far away from the true ψ and the RMSE can be very large.

Sample size	Parameter	True,ψ	Methods							
			Murphy			Regret-regression			Robins	
			Mean	SE	RMSE	Mean	SE	RMSE	Mean	SE	RMSE
500	$\psi_1 = 6.000$	6.00	6.011	0.088	0.093	6.001	0.063	0.064	6.037	0.910	0.910
	$\psi_3 = 0.000$	0.000	-0.006	0.122	0.124	0.003	0.087	0.090	0.093	0.899	0.904
	$\psi_4 = 1.500$	1.50	1.493	0.087	0.096	1.499	0.056	0.057	1.726	0.802	0.833
	$\psi_5 = 2.000$	2.00	1.997	0.188	0.199	1.998	0.095	0.097	1.756	1.237	1.261
	$\psi_6 = 0.000$	0.00	0.006	0.079	0.083	0.000	0.020	0.020	0.044	0.453	0.455
	$\psi_7 = 1.500$	1.50	1.498	0.044	0.044	1.501	0.013	0.014	1.498	0.351	0.351
	$\psi_8 = 5.500$	5.50	5.494	0.177	0.192	5.499	0.056	0.057	5.568	0.957	0.96
1000	$\psi_1 = 6.000$	6.00	5.994	0.063	0.069	6.001	0.022	0.023	6.000	0.607	0.607
	$\psi_3 = 0.000$	0.00	-0.004	0.084	0.085	0.000	0.028	0.028	-0.017	0.600	0.600
	$\psi_4 = 1.500$	1.50	1.500	0.064	0.064	1.501	0.022	0.023	1.596	0.551	0.560
	$\psi_5 = 2.000$	2.00	2.004	0.129	0.131	2.000	0.036	0.036	1.922	0.856	0.860
	$\psi_6 = 0.000$	0.00	0.002	0.061	0.061	0.000	0.012	0.013	-0.001	0.307	0.307
	$\psi_7 = 1.500$	1.50	1.501	0.033	0.034	1.500	0.009	0.009	1.491	0.251	0.251
	$\psi_8 = 5.500$	5.50	5.496	0.141	0.145	5.501	0.029	0.030	5.585	0.695	0.700

Table 2.6: Parameter estimates for Murphy, regret-regression and Robins methods. This simulation is based on sample sizes 500 and 1000 with 1000 repetitions.

Simulation using Smooth Approximation of ψ_2 between Murphy and Regret-Regression Methods

Samples(n)	Percentage of successful convergences,(%)	
	Murphy's smooth approximation	Regret-regression smooth approximation
500	52.6	100.0
1000	41.4	100.0

Table 2.7: The convergences rate for the Murphy and regret-regression methods using smooth approximation to estimate the parameters based on sample sizes 500 and 1000 with 1000 repetitions.

Samples(n)	Parameter	Murphy's			Regret-regression		
		Mean	SE	RMSE	Mean	SE	RMSE
500	$\psi_1 = 6.000$	7.524	0.409	1.578	5.997	0.127	0.127
	$\psi_2 = 0.556$	0.556	0.005	0.005	0.556	0.001	0.001
	$\psi_3 = 0.000$	0.429	0.281	0.513	-0.009	0.193	0.193
	$\psi_4 = 1.500$	1.573	0.152	0.169	1.509	0.215	0.215
	$\psi_5 = 2.000$	1.435	0.388	0.686	1.999	0.017	0.017
	$\psi_6 = 0.000$	0.174	0.148	0.228	0.003	0.065	0.065
	$\psi_7 = 1.500$	1.600	0.086	0.132	1.490	0.227	0.227
	$\psi_8 = 5.500$	5.018	0.366	0.605	5.499	0.024	0.024
1000	$\psi_1 = 6.000$	7.533	0.306	1.622	6.001	0.039	0.039
	$\psi_2 = 0.556$	0.556	0.004	0.004	0.556	0.000	0.000
	$\psi_3 = 0.000$	0.466	0.111	0.480	0.002	0.043	0.043
	$\psi_4 = 1.500$	1.574	0.127	0.156	1.497	0.054	0.054
	$\psi_5 = 2.000$	1.422	0.281	0.693	2.000	0.009	0.009
	$\psi_6 = 0.000$	0.179	0.110	0.230	0.000	0.032	0.032
	$\psi_7 = 1.500$	1.598	0.068	0.123	1.503	0.051	0.051
	$\psi_8 = 5.500$	5.005	0.256	0.600	5.500	0.013	0.013

Table 2.8: Parameter estimates for Murphy and regret-regression methods using the smooth approximation. This simulation is based on sample sizes 500 and 1000 and repeated 1000 times.

We repeat the experiment of Section 2.5.2 using the smooth approximation to estimate ψ_2 and apply it to the regret-regression method. The purpose of this test is to see whether the regret-regression method still provides consistency in the parameter estimates and better efficiency compared to Murphy procedure with smooth estimation. Robins methods will not be considered here due to its poor performance compared to the other two methods in the previous simulation (see Table 2.5 and Table 2.6).

The regret-regression method successfully converged with 100% convergence using the smooth approximation which is far better than Murphy at both sample sizes in Table 2.7. Table 2.8 shows that the parameter estimates are consistent with means that are close to the true parameter values and greatly improved efficiency as sample size increases. In each sample, we found the regret-regression method has less bias and smaller standard error than the Murphy procedure with smooth estimation.

In Murphy's method, the parameters are estimated using the Newton-Raphson method except ψ_2. The parameter ψ_2 is possible to estimate by replacing the indicator variable in $\mu(a_j|\bar{S}_{j-1}, \bar{A}_{j-1})$ with the smooth approximation function which is discussed in the previous section. In contrast the regret-regression method is feasible with or without changing the function in $\mu(a_j|\bar{S}_{j-1}, \bar{A}_{j-1})$. This gives greatly improved efficiency compared to Murphy method and also provide a quicker estimation procedure compared to the other two methods.

2.6 Conclusions

In this chapter we have shown that the regret-regression method can provide excellent performance in estimating optimal dynamic treatment regimes where in our simulations it always provide a good estimates with smaller standard error in the simulations. We found that the regret-regression estimates have less bias than Murphy or Robins. Estimation for ψ_2 is possible with or without the smooth approximation to estimate the parameters. The regret-regression method estimates the parameter more directly than the Murphy or Robins techniques and it is less challenging in computation than the other two methods.

Chapter 3

Misspecification and Sensitivity

3.1 Sensitivity Analysis Under Murphy Method

A misspecification of a model means it provides an incorrect description of the data. In this chapter we will investigate performance of the Murphy and the regret-regression techniques when the model is misspecified, or when the initial values for the estimation method are not taken to be the true values. In the previous section we assumed them to be equal to the true values which is evidently unrealistic. Using uncertain initial values is not of course a misspecification. This part is included to assess sensitivity. We begin with the Murphy method.

We start the simulation with the initial parameter vector, ψ, which has seven elements since ψ_2 is fixed. Then, for each $\hat{\psi}_j$ we find the estimated standard deviation, $\hat{\sigma}_j$, from simulations. These are given in Table 3.1.

n	ψ_1	ψ_3	ψ_4	ψ_5	ψ_6	ψ_7	ψ_8
250	0.132	0.178	0.130	0.264	0.112	0.062	0.256
500	0.088	0.122	0.087	0.188	0.079	0.044	0.177
1000	0.063	0.084	0.0647	0.129	0.061	0.033	0.141

Table 3.1: The estimated standard deviation, $\hat{\sigma}_j$ at different sample sizes n when ψ_2 is fixed

In each simulation we first generate $Z_j \sim N(0, \sigma_j^2)$ to form a vector Z with seven elements. We will assume that the initial values for the simulations are taken as

$$\psi_0 = \psi + kZ$$

and where appropriate we constrain elements of ψ_0 to be positive and ψ is a true value from Murphy simulation found in Chapter 2. Here ψ takes the values of $(6, 0, 1.5, 2, 0, 1.5, 5.5)$ where $\psi_2 = 5/9$ is fixed and k is a scalar with values chosen from $k = 0, 0.5, 1, 2, 5, 6, 7$. In this way the error in the chosen initial value is meaningfully scaled.

We will consider cases where either just one parameter has an incorrect starting value, or all parameters are initialised wrongly.

Secondly, we will investigate misspecification of the action model. Recall that we assumed that our model has equal probabilities for all the actions for both A_1 and A_2. To investigate, we will add unequal probabilities of the action into the model, when generating the data but will falsely assume equal probability when estimating.

Investigation is divided into several parts:-

- Part(a). All initial values are not set at the true values, with the same scale factor, k.
- Part(b). The initial values are not the true values for one parameter at a time, i.e. $Z = kZ_j$ where Z_j is a vector of zero everywhere except the element j which is $N(0, \sigma_j^2)$ and k is a scalar. For example $k = 5$ and Z_1 is simulated with $k\hat{\sigma}_1^2 = 5 \times (0.088)^2$. In this case only ψ_1 has been allocated a wrong initial value whilst the other parameters are initialised at their true values.
- Part(c). Generate data with unequal probabilities for the first action, A_1 and the second actions, $A_2|(A_1 = 0)$ and $A_2|(A_1 = 1)$ in the model but falsely assume these probabilities are equal in estimation.
- Part(d). Allow the action probabilities to depend on state S_j at time j when generating data. Assume the action probabilities are independent of state when fitting the model.

Besides of investigating the sensitivity analysis in Murphy method, we extend our investigation by misspecifying the model using the regret-regression method. The misspecification is devided into three different parts:

- Part(I). We fit the model using the correct state model.

$$E[S_j|\bar{S}_{j-1}, \bar{A}_{j-1}] = \beta_0 + \beta_1 S_{j-1} + \beta_2 A_{j-1} A_{j-2} + \beta_3 A_{j-1}(1 - A_{j-2}).$$

- Part(II). We extend our analysis by fitting the model using the wrong state model, which does not depend on previous actions, i.e. we falsely assume

$$E[S_j|\bar{S}_{j-1}, \bar{A}_{j-1}] = \beta_0 + \beta_1 S_{j-1}.$$

- Part(III). Again, we fit the model using the wrong state model by ignoring the previous states. The assumed model is

$$E[S_j|\bar{S}_{j-1}, \bar{A}_{j-1}] = \beta_0 + \beta_1 A_{j-1} A_{j-2} + \beta_2 A_{j-1}(1 - A_{j-2}).$$

In this study, we only investigate the parameters ψ_6, ψ_7 and ψ_8. These parameters appear in the regret function for the second action of A_2 given $A_1 = 0$. In the Murphy simulation, the second action A_2 has a greater range of possible values than the first binary action A_1. Hence parameters have more scope for high influence than the other parameters in the regret function.

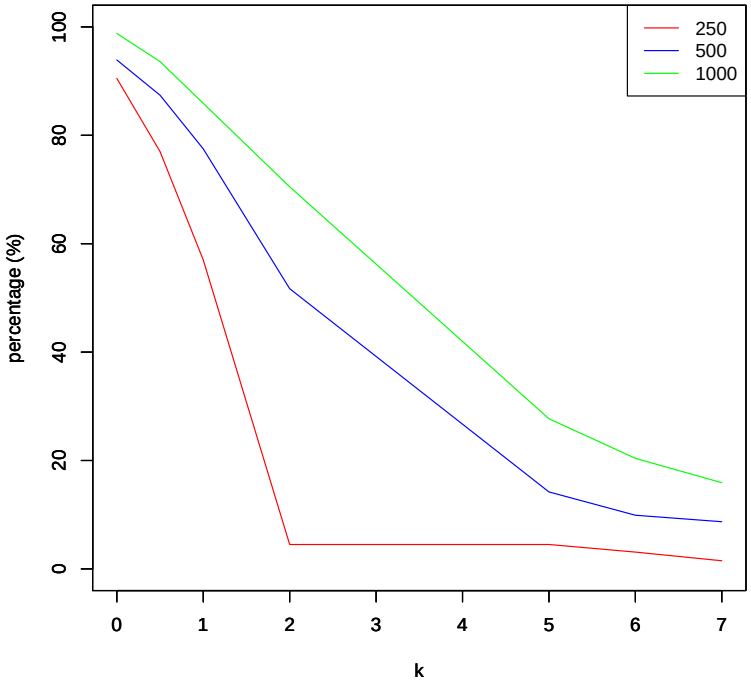

Figure 3.1: Convergence rates for different sample sizes and different value of k.

3.1.1 Murphy Sensitivity Analysis: Part(a)

Table 3.2 and Figure 3.1 show the percentage of successfully converged simulations when using the Murphy estimation method and all parameters may have initial values which differ from the true ones. We increase the scale factor k from 0 to 7 standard errors.

We simulated 1000 data sets as described earlier and for each simulation the algorithm was stopped after 100 iterations of the outer loops or if converged (Table 3.2).

Percentage of successful convergences, %							
	k						
n	0	0.5	1	2	5	6	7
250	90.5	77.0	57.0	4.5	4.5	3.1	1.5
500	93.9	87.4	77.5	51.7	14.2	9.9	8.7
1000	98.8	93.6	85.9	70.5	27.7	20.4	15.9

Table 3.2: Convergence rates using different sample sizes n and various scalar k with 1000 repetitions

Sample size 250 has the poorest convergence rate. This can be seen most obviously in Figure 3.1. It shows that at sample size 250 there is a dramatic reduction starting at $k = 0$. Sample size 500 and 1000 have slower reductions in the percentage converged though even at sample size 1000 the convergence rate is very poor once initial values are in the region of 5 standard errors from the true values.

		k						
Parameter	n	0	0.5	1	2	5	6	7
Mean								
$\psi_6 = 0$	250	0.00	0.00	0.01	0.00	0.04	0.01	0.14
	500	0.00	0.00	0.00	0.00	0.01	0.13	0.07
	1000	0.00	-0.01	0.00	0.00	0.01	0.02	0.02
$\psi_7 = 1.5$	250	1.50	1.50	1.50	1.50	1.46	1.54	1.41
	500	1.50	1.50	1.50	1.50	1.50	1.39	1.43
	1000	1.50	1.50	1.50	1.50	1.49	1.48	1.48
$\psi_8 = 5.5$	250	5.50	5.51	5.47	5.48	5.29	5.40	4.79
	500	5.51	5.50	5.49	5.50	5.48	4.95	5.16
	1000	5.51	5.51	5.51	5.51	5.45	5.42	5.38
Standard Error, SE								
$\psi_6 = 0.0$	250	0.12	0.12	0.19	0.13	0.36	0.14	0.49
	500	0.08	0.08	0.10	0.08	0.09	0.53	0.26
	1000	0.06	0.06	0.06	0.06	0.11	0.17	0.21
$\psi_7 = 1.5$	250	0.07	0.07	0.11	0.07	0.31	0.07	0.51
	500	0.04	0.04	0.09	0.04	0.04	0.47	0.39
	1000	0.03	0.03	0.03	0.03	0.17	0.22	0.23
$\psi_8 = 5.5$	250	0.27	0.27	0.55	0.31	1.39	0.36	2.26
	500	0.19	0.18	0.35	0.20	0.24	2.11	1.42
	1000	0.14	0.14	0.14	0.14	0.62	0.80	0.95
Root Mean Square Error, RMSE								
$\psi_6 = 0.0$	250	0.12	0.12	0.19	0.13	0.37	0.14	0.51
	500	0.08	0.08	0.10	0.08	0.09	0.54	0.27
	1000	0.06	0.06	0.06	0.06	0.11	0.17	0.21
$\psi_7 = 1.5$	250	0.07	0.07	0.11	0.07	0.31	0.08	0.51
	500	0.04	0.04	0.09	0.04	0.04	0.48	0.40
	1000	0.03	0.03	0.03	0.03	0.17	0.22	0.23
$\psi_8 = 5.5$	250	0.27	0.27	0.55	0.31	1.41	0.37	2.37
	500	0.19	0.18	0.36	0.20	0.24	2.18	1.46
	1000	0.14	0.14	0.14	0.14	0.62	0.80	0.96

Table 3.3: Parameter estimates using different sample sizes and different value of k.

Table 3.3 summarises the mean, standard error (SE) and the root mean square error (RMSE) of the estimates for the simulated samples where we successfully obtained convergence. The mean indicates that even for these successfully converged samples there can be biased parameter estimates when the initial values for the procedure are not close to the true values. There is a lot of uncertainty in the data because of the small number of convergences in places and also because there were occasionally highly extreme but converged estimates. Nonetheless the patterns are clear. We have positive bias, which increases with k, for ψ_6 and negative bias for ψ_7 and ψ_8. There is less bias at the larger sample sizes.

There are occasional very unusual values, caused by highly extreme estimates in some samples, but overall a pattern of increasing uncertainty as k increases is clear. Again, the sample size has an effect, with more reliable results, as expected, for larger samples. The same conclusions can be drawn for RMSE which combines both bias and variability.

Overall it is clear that there needs to be accuracy in the initial values if the Murphy estimation method is to be recommended. This is supported by Rosthøj et al. (2006) where she found the Murphy method is sensitive to the starting values. For example, this is the simple four parameter model taken from Rosthøj et al. (2006) paper. Rosthøj et al. (2006) define the regret function as

$$\mu_j(a_j|\bar{S}_j, \bar{A}_{j-1}) \;=\; \begin{cases} I(a_j \neq 0)\big(\beta_1 + \beta_2 a_j^2\big) & S_j = 0 \\ \beta_3\big(a_j - \beta_4 S_j\big)^2 & S_j \neq 0 \end{cases} \tag{3.1}$$

for $j = 1, 2, \ldots, K$ and the parameters β_2, β_3 and β_4 should be non-negative since the regret function is non-negative. Rosthøj et al. (2006) has fixed two of the parameters, $\beta_1 = 5.89$ and $\beta_2 = 1.59$ as well as $c = -59.23$ and estimated β_3 and β_4 using the grid search for the initial values. The parameter β_3 varies between $(0.01, 0.80)$ and β_4 between $(-5, 3)$.

The Figure 3.2 show how the Murphy iterative method is performed. The grey dots indicate that the values of β_3 and β_4 which algorithm is converged while the red dots represent the values that the algorithm did not converged. The black dot is the solution for the regret function. Although the simulation study is limited, we have shown enough evidence to support the conclusion that the Murphy estimation method is sensitive to the initial values.

3.1.2 Murphy Sensitivity Analysis: Part(b)

The question now arises as to whether some of the parameters are more robust to initial values than the others. In this part, we will vary the initial values, one at a time using only sample size 500.

Table 3.4 and Figure 3.3 show how the convergence rate is affected when just one parameter has an incorrect initial value. The parameter ψ_7, which is the scale factor in the

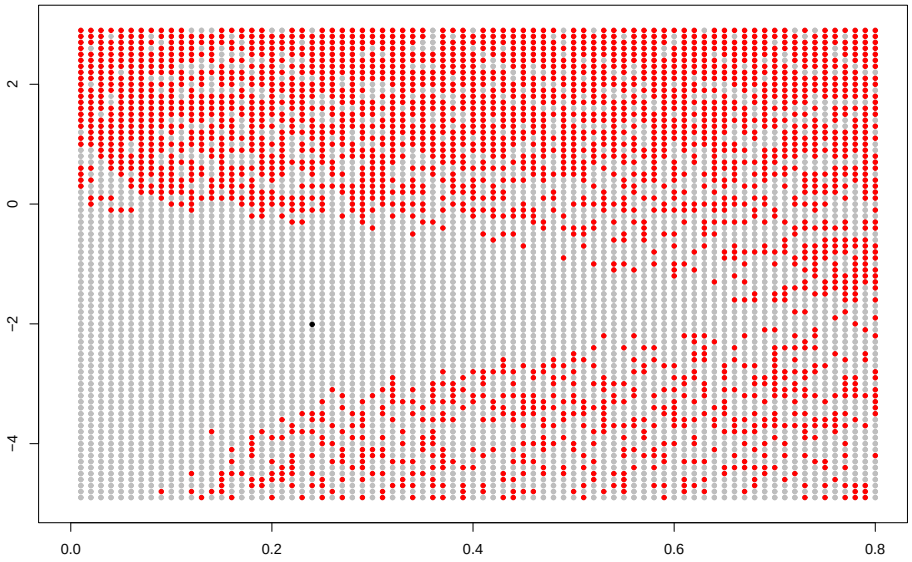

Figure 3.2: A plot for starting values for Murphy iterative procedure. The x-axis represent the value of the parameter β_3 and the y-axis represent the value for β_4.

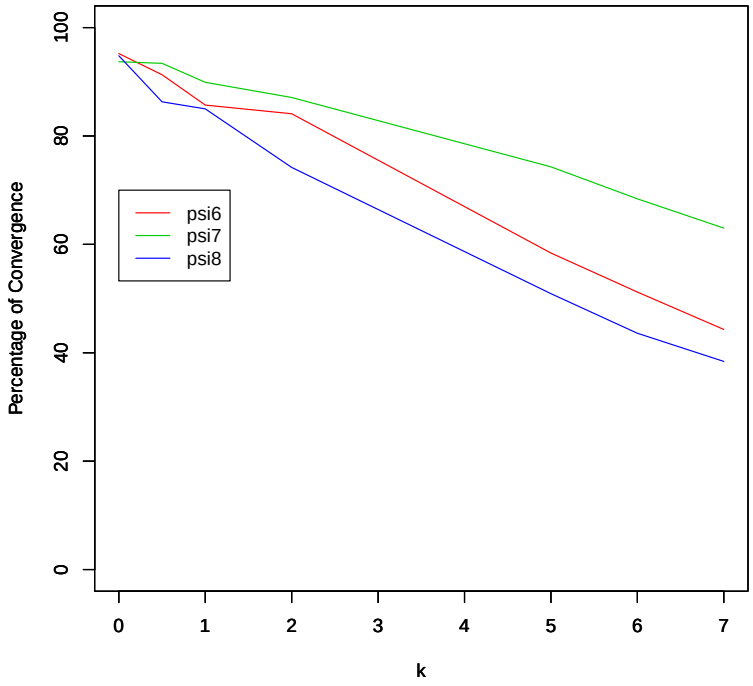

Figure 3.3: Successful convergence rate plot when only one parameter has an incorrect initial value using sample size $n = 500$

Percentage of successful convergences, %							
	k						
Parameter	0	0.5	1	2	5	6	7
ψ_6	95.2	91.3	85.7	84.1	58.4	51.2	44.3
ψ_7	93.7	93.4	89.9	87.1	74.3	68.4	63.0
ψ_8	94.8	86.3	85.0	74.2	50.9	43.6	38.4

Table 3.4: Percentage of successful convergences using different value of k at sample size $n = 500$

regret function at (2.27) is more robust than the other two parameters ψ_6 and ψ_8.

Table 3.5: Estimation of mean, $\hat{\psi}$

		k						
Parameter with incorrect initial value	Parameter	0	0.5	1	2	5	6	7
ψ_6	$\psi_6 = 0.0$	-0.01	0.00	0.00	0.00	0.00	0.01	0.01
	$\psi_7 = 1.5$	1.50	1.50	1.50	1.50	1.50	1.50	1.50
	$\psi_8 = 5.5$	5.52	5.51	5.50	5.50	5.49	5.44	5.48
ψ_7	$\psi_6 = 0.0$	0.00	0.00	0.00	0.00	0.00	0.01	0.00
	$\psi_7 = 1.5$	1.50	1.50	1.50	1.50	1.50	1.50	1.50
	$\psi_8 = 5.5$	5.50	5.50	5.50	5.49	5.50	5.49	5.50
ψ_8	$\psi_6 = 0.0$	0.00	0.00	0.00	0.02	0.01	0.00	0.02
	$\psi_7 = 1.5$	1.49	1.49	1.50	1.49	1.50	1.50	1.48
	$\psi_8 = 5.5$	5.52	5.51	5.51	5.44	5.48	5.50	5.40

Table 3.6: Estimation of standard error (SE), $\hat{\psi}$

		k						
Parameter with incorrect initial value	Parameter	0	0.5	1	2	5	6	7
ψ_6	$\psi_6 = 0.0$	0.08	0.08	0.08	0.09	0.08	0.11	0.08
	$\psi_7 = 1.5$	0.04	0.04	0.04	0.05	0.04	0.13	0.05
	$\psi_8 = 5.5$	0.19	0.19	0.19	0.20	0.19	0.45	0.19
ψ_7	$\psi_6 = 0.0$	0.08	0.08	0.09	0.09	0.08	0.08	0.08
	$\psi_7 = 1.5$	0.04	0.04	0.05	0.05	0.04	0.05	0.04
	$\psi_8 = 5.5$	0.19	0.18	0.20	0.20	0.19	0.19	0.18
ψ_8	$\psi_6 = 0.0$	0.08	0.09	0.08	0.15	0.08	0.08	0.17
	$\psi_7 = 1.5$	0.04	0.04	0.04	0.15	0.04	0.05	0.20
	$\psi_8 = 5.5$	0.19	0.20	0.18	0.57	0.18	0.19	0.84

Table 3.7: Estimation of root mean square error (RMSE), $\hat{\psi}$

		k						
Parameter with incorrect initial value	Parameter	0	0.5	1	2	5	6	7
ψ_6	$\psi_6 = 0.0$	0.08	0.08	0.08	0.09	0.08	0.11	0.08
	$\psi_7 = 1.5$	0.04	0.04	0.04	0.05	0.04	0.13	0.05
	$\psi_8 = 5.5$	0.19	0.19	0.19	0.20	0.19	0.45	0.19
ψ_7	$\psi_6 = 0.0$	0.08	0.08	0.09	0.09	0.08	0.08	0.08
	$\psi_7 = 1.5$	0.04	0.04	0.05	0.05	0.04	0.05	0.04
	$\psi_8 = 5.5$	0.19	0.18	0.20	0.20	0.19	0.19	0.18
ψ_8	$\psi_6 = 0.0$	0.08	0.09	0.08	0.15	0.08	0.08	0.17
	$\psi_7 = 1.5$	0.04	0.05	0.04	0.15	0.04	0.05	0.20
	$\psi_8 = 5.5$	0.19	0.20	0.18	0.57	0.18	0.19	0.84

Table 3.5, 3.6 and 3.7 provide the mean, standard error and root mean square error for the successfully converged samples. The left column indicates which parameter has an incorrect initial value. Table 3.5 shows that using a single incorrect initial value has little effect on the mean results provided convergence can be obtained, except perhaps for ψ_8. There is some evidence of increased variability when ψ_6 or ψ_8 have incorrect initial values (Table 3.6 and Table 3.7). It is perhaps worth noting that the estimation routine does not necessarily converge to a unique value. There is no theorem to the effect that the converged value is unique. Recall also that the method is very unusual, in that we are not attempting to minimise the sum of squares defined at (2.7).

3.1.3 Murphy Sensitivity Analysis: Part(c)

We now turn to the action probability model. In estimation based on (2.7) we assume that $p_j(a_j|\bar{S}_j, \bar{A}_{j-1})$ is known. In simulating the data and subsequent estimation we have taken actions to be equally likely (uniformly) over possible values. To investigate, we now simulate with alternative action models but fit assumed equally likely actions. We will consider in turn:

1. Action 1, (A_1)
2. Action 2, $(A_2|A_1 = 0)$
3. Action 3, $(A_2|A_1 = 1)$

Action 1, (A_1)

Action 1 is binary with values 0 and 1. The default is equally likely values. We investigated using alternative data generating models, denoted $(P_1, 1-P_1)$, where $P_1 = P(A_1 = 0)$.

	$P(A_1)$						
Sample Size,(n)	(0.2,0.8)	(0.3,0.7)	(0.4,0.6)	(0.5,0.5)	(0.6,0.4)	(0.7,0.3)	(0.8,0.2)
250	84.9	82.6	87.9	88.4	92.9	95.6	96.5
500	85.2	85.4	90.7	94.9	97.9	99.4	99.7
1000	85.7	86.7	94.2	97.5	99.8	100.0	99.7

Table 3.8: Percentage of successful number of convergences when action A_1 has different probabilities and for various sample sizes n.

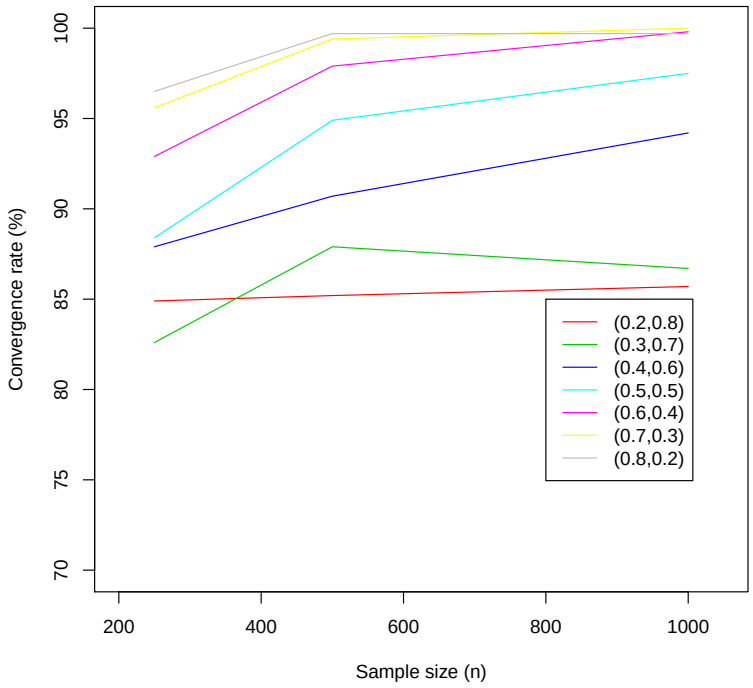

Figure 3.4: Percentage of successful convergences plot when action A_1 has different probabilities and for various sample sizes n.

Table 3.8 and Figure 3.4 show the convergence rates for the different sample sizes for a variety of choices. Each result is based on 1000 repetitions. Results show that the convergence rate decreases if a false value of P_1 is mistakenly assumed, though not dramatically. We note here that in principle the action model is obtainable from the observed data, and hence in this simple example at least we would not expect gross misspecification.

Note here we found that $P_1 = 0.2$ gives poorer convergence than $P_1 = 0.8$. This is because the action $A_2|A_1 = 0$ has greater range than $A_2|A_1 = 1$ and hence high influence in the regret function. Therefore the probability P_1 indirectly affects the estimation and the convergence rates in this simulation.

Table 3.9: Results when action A_1 has different probabilities P_1 for various sample sizes. This simulation is based on 1000 repetitions.

		$P(A_1) = (P_1, 1 - P_1)$						
n	Parameter	(0.2,0.8)	(0.3,0.7)	(0.4,0.6)	(0.5,0.5)	(0.6,0.4)	(0.7,0.3)	(0.8,0.2)
Mean								
250	ψ_6	0.01	0.01	0.00	0.00	0.00	0.00	-0.01
	ψ_7	1.51	1.51	1.50	1.49	1.50	1.50	1.50
	ψ_8	5.46	5.47	5.49	5.51	5.51	5.52	5.52
500	ψ_6	0.01	0.01	0.00	0.00	0.00	-0.01	-0.01
	ψ_7	1.50	1.50	1.50	1.50	1.50	1.50	1.49
	ψ_8	5.47	5.49	5.49	5.51	5.51	5.52	5.52
1000	ψ_6	0.02	0.01	0.01	0.00	0.00	0.00	-0.01
	ψ_7	1.51	1.51	1.50	1.50	1.50	1.50	1.50
	ψ_8	5.46	5.47	5.48	5.50	5.50	5.51	5.52
Standard Error, SE								
250	ψ_6	0.12	0.11	0.12	0.12	0.11	0.12	0.11
	ψ_7	0.07	0.06	0.06	0.06	0.06	0.06	0.06
	ψ_8	0.28	0.27	0.27	0.27	0.27	0.27	0.27
500	ψ_6	0.08	0.08	0.08	0.08	0.08	0.08	0.08
	ψ_7	0.05	0.05	0.05	0.05	0.05	0.05	0.04
	ψ_8	0.19	0.19	0.19	0.19	0.19	0.19	0.19
1000	ψ_6	0.06	0.06	0.06	0.06	0.06	0.06	0.06
	ψ_7	0.03	0.03	0.03	0.03	0.03	0.03	0.03
	ψ_8	0.14	0.14	0.13	0.14	0.14	0.13	0.13
Root Mean Square Error, RMSE								
250	ψ_6	0.12	0.12	0.12	0.12	0.11	0.12	0.12
	ψ_7	0.07	0.06	0.06	0.06	0.06	0.06	0.06
	ψ_8	0.28	0.27	0.27	0.27	0.27	0.27	0.27
500	ψ_6	0.08	0.08	0.08	0.08	0.08	0.08	0.08
	ψ_7	0.05	0.05	0.05	0.05	0.05	0.05	0.04
	ψ_8	0.19	0.19	0.19	0.19	0.19	0.19	0.19
1000	ψ_6	0.06	0.06	0.06	0.06	0.06	0.06	0.06
	ψ_7	0.03	0.03	0.03	0.03	0.03	0.03	0.03
	ψ_8	0.15	0.14	0.14	0.14	0.14	0.13	0.13

Table 3.9 shows the mean, SE and RMSE of successfully converged estimates. There is no real evidence of systematic bias or increased uncertainty for parameter estimates if

the action model is wrong in the described way. Hence it appears there is some robustness to this misspecification for the simulation scenario under consideration.

Action 2, $(A_2|A_1 = 1)$

We now turn to the second action: choice of treatment amount for those subjects with $A_1 = 1$ where three possible values are taken from $\{1, 2, 3\}$ with possible probabilities $(1/3, 1/3, 1/3)$ by default. In this case, each probability is $P(A_2 = 1|A_1 = 1) = 1/3$, $P(A_2 = 2|A_1 = 1) = 1/3$ and $P(A_2 = 3|A_1 = 1) = 1/3$. There are four models to consider. We will label these as Q_1, Q_2, Q_3, Q_4 and Q_5. The three probabilities just mentioned are taken to be:

1. Q1:$(0.4, 0.2, 0.4)$
2. Q2:$(0.167, 0.333, 0.5)$
3. Q3:$(0.333, 0.333, 0.333)$
4. Q4:$(0.5, 0.333, 0.167)$
5. Q5:$(0.111, 0.778, 0.111)$

Note that Q_1 gives high probability to the extreme actions. Choices Q_2 and Q_4 are skew, and choice Q_5 gives low probability to the extremes.

	$P(A_2\|A_1 = 1)$				
Number of Samples,(n)	Q1	Q2	Q3	Q4	Q5
250	89.7	90.7	88.4	99.4	85.4
500	94.6	85.1	94.9	100.0	95.4
1000	97.7	81.9	97.5	100.0	98.6

Table 3.10: Percentage of successful convergences when action, $A_2|(A_1 = 1)$ has different probabilities for various sample sizes n.

Table 3.11: Estimation of the parameters when action, $A_2|(A_1 = 1)$ has different probabilities from various sample sizes n which based from 1000 repetitions.

		$P(A_2\|A_1 = 1)$				
n	Parameter	Q1	Q2	Q3	Q4	Q5
Mean						
250	$\psi_6 = 0.0$	0.00	0.00	0.00	-0.01	0.01
	$\psi_7 = 1.5$	1.50	1.50	1.49	1.50	1.50
	$\psi_8 = 5.5$	5.49	5.50	5.51	5.52	5.49

Continued on next page

		$P(A_2\|A_1=1)$				
n	Parameter	Q1	Q2	Q3	Q4	Q5
500	$\psi_6 = 0.0$	0.00	0.00	0.00	0.00	0.00
	$\psi_7 = 1.5$	1.49	1.50	1.50	1.50	1.50
	$\psi_8 = 5.5$	5.51	5.51	5.51	5.51	5.51
1000	$\psi_6 = 0.0$	0.01	0.00	0.00	0.00	0.00
	$\psi_7 = 1.5$	1.50	1.50	1.50	1.50	1.50
	$\psi_8 = 5.5$	5.49	5.49	5.50	5.49	5.49
Standard Error, SE						
250	$\psi_6 = 0.0$	0.08	0.12	0.12	0.08	0.08
	$\psi_7 = 1.5$	0.05	0.07	0.06	0.05	0.05
	$\psi_8 = 5.5$	0.19	0.28	0.27	0.19	0.19
500	$\psi_6 = 0.0$	0.08	0.08	0.08	0.08	0.08
	$\psi_7 = 1.5$	0.04	0.05	0.05	0.05	0.05
	$\psi_8 = 5.5$	0.18	0.19	0.19	0.19	0.19
1000	$\psi_6 = 0.0$	0.06	0.06	0.06	0.06	0.06
	$\psi_7 = 1.5$	0.03	0.03	0.03	0.03	0.03
	$\psi_8 = 5.5$	0.13	0.14	0.14	0.14	0.13
Root Mean Square Error, RMSE						
250	$\psi_6 = 0.0$	0.08	0.12	0.12	0.08	0.08
	$\psi_7 = 1.5$	0.05	0.07	0.06	0.05	0.05
	$\psi_8 = 5.5$	0.19	0.28	0.27	0.19	0.19
500	$\psi_6 = 0.0$	0.08	0.08	0.08	0.08	0.08
	$\psi_7 = 1.5$	0.05	0.05	0.05	0.05	0.05
	$\psi_8 = 5.5$	0.19	0.19	0.19	0.19	0.19
1000	$\psi_6 = 0.0$	0.06	0.06	0.06	0.06	0.06
	$\psi_7 = 1.5$	0.03	0.03	0.03	0.03	0.03
	$\psi_8 = 5.5$	0.13	0.14	0.14	0.14	0.13

Table 3.10, 3.11 and Figure 3.5 show the effect of generating data with unequal probabilities, but mistakenly assuming equality in estimation. Convergence is generally good, though affected to some extent at the smaller sample size. The optimal decision for $A_2|A_1 = 1$ is usually near $A_2 = 1$ where states tend to be near 0.5. Note that convergence is worst under Q2 where there is high probability of choosing $A_2 = 3$ which is far away from the optimum. There is no obvious effect on the mean, SE or RMSE of the estimates.

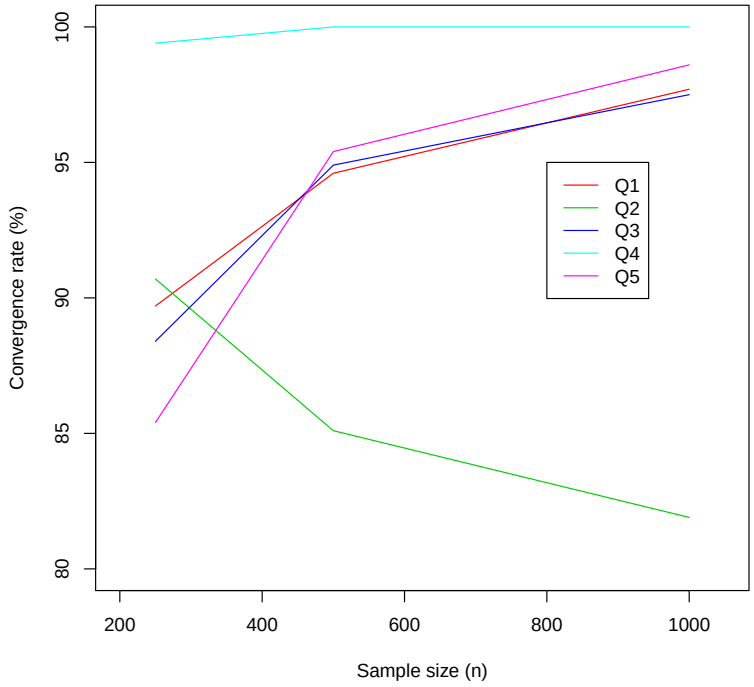

Figure 3.5: Convergence rates when action $A_2|(A_1 = 1)$ has different probabilities for various sample sizes n.

Action 2, $(A_2|A_1 = 0)$

We repeat the above form of investigation, this time for the second type of treatment, without special education, $A_1 = 0$. Now four values are allowed, $\{0, 1, 2, 3\}$, with by default equal probabilities $(1/4, 1/4, 1/4, 1/4)$ meaning $P(A_2 = 0|A_1 = 0) = 1/4$, $P(A_2 = 1|A_1 = 0) = 1/4$, $P(A_2 = 2|A_1 = 0) = 1/4$ and $P(A_2 = 3|A_1 = 0) = 1/4$. We simulate with seven possibilities of different distributions with, in an obvious notation:

1. R1:$(1/4, 1/4, 1/4, 1/4)$, equal probabilities;
2. R2:$(3/7, 1/7, 1/7, 2/7)$, skewed towards small values;
3. R3:$(4/7, 1/7, 1/7, 1/7)$, skewed towards small values;
4. R4:$(2/7, 1/7, 1/7, 3/7)$, skewed towards large values;
5. R5:$(1/7, 1/7, 1/7, 4/7)$, skewed towards large values;
6. R6:$(3/8, 1/8, 1/8, 3/8)$, extreme values more likely, higher variance;
7. R7:$(1/8, 3/8, 3/8, 1/8)$, extreme values less likely, smaller variance.

	$A_2\|(A_1=0)$						
Sample Size,(n)	R1	R2	R3	R4	R5	R6	R7
250	88.4	90.2	83.8	90.7	59.4	99.4	85.4
500	94.9	96.1	87.7	94.7	48.5	96.5	94.5
1000	97.5	98.4	91.9	98.6	36.0	98.4	97.5

Table 3.12: Rate of convergence when action, $A_2|(A_1=0)$ has different probabilities for various sample sizes n

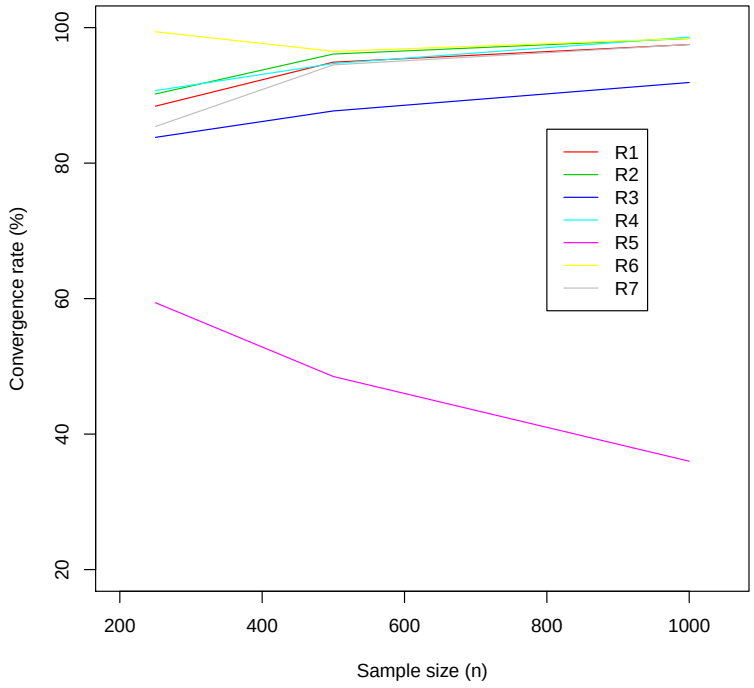

Figure 3.6: Convergence rates when action, $A_2|(A_1=0)$ has different probabilities for various sample sizes n

Table 3.13: Parameter estimates based on 1000 simulations when action, $A_2|(A_1=0)$ has different types of probabilities in various sample sizes.

		$P(A_2\|A_1=0)$						
n	Parameter	R1	R2	R3	R4	R5	R6	R7
Mean								
250	$\psi_6=0.0$	0.00	-0.02	-0.41	0.00	0.68	-0.01	0.01
	$\psi_7=1.5$	1.49	1.50	1.80	1.50	1.32	1.50	1.50
	$\psi_8=5.5$	5.51	5.55	5.74	5.49	4.58	5.52	5.49
500	$\psi_6=0.0$	0.00	-0.02	-0.40	0.01	0.67	-0.01	0.00
	$\psi_7=1.5$	1.50	1.49	1.79	1.48	1.30	1.49	1.51
	$\psi_8=5.5$	5.51	5.55	5.75	5.51	4.60	5.54	5.48
	$\psi_6=0.0$	0.00	-0.02	-0.40	0.01	0.66	0.00	0.01
1000								

Continued on next page

		$P(A_2\|A_1=0)$						
n	Parameter	R1	R2	R3	R4	R5	R6	R7
	$\psi_7=1.5$	1.50	1.50	1.79	1.49	1.30	1.49	1.51
	$\psi_8=5.5$	5.50	5.53	5.74	5.49	4.65	5.52	5.47
Standard Error, SE								
	$\psi_6=0.0$	0.12	0.12	0.10	0.08	0.18	0.08	0.08
250	$\psi_7=1.5$	0.06	0.07	0.08	0.05	0.12	0.05	0.05
	$\psi_8=5.5$	0.27	0.28	0.25	0.19	0.46	0.19	0.19
	$\psi_6=0.0$	0.08	0.08	0.07	0.08	0.12	0.08	0.08
500	$\psi_7=1.5$	0.05	0.05	0.06	0.05	0.11	0.05	0.05
	$\psi_8=5.5$	0.19	0.19	0.17	0.19	0.40	0.19	0.19
	$\psi_6=0.0$	0.06	0.06	0.05	0.06	0.09	0.06	0.06
1000	$\psi_7=1.5$	0.03	0.03	0.04	0.03	0.05	0.03	0.03
	$\psi_8=5.5$	0.14	0.14	0.12	0.14	0.22	0.14	0.14
Root Mean Square Error, RMSE								
250	$\psi_6=0.0$	0.12	0.12	0.42	0.08	0.71	0.08	0.08
	$\psi_7=1.5$	0.06	0.07	0.31	0.05	0.22	0.05	0.05
	$\psi_8=5.5$	0.27	0.28	0.34	0.19	1.03	90.19	0.19
	$\psi_6=0.0$	0.08	0.09	0.41	0.08	0.68	0.08	0.08
500	$\psi_7=1.5$	0.05	0.05	0.29	0.05	0.22	0.05	0.05
	$\psi_8=5.5$	0.19	0.20	0.30	0.19	0.98	0.19	0.19
	$\psi_6=0.0$	0.06	0.06	0.40	0.06	0.66	0.06	0.06
1000	$\psi_7=1.5$	0.03	0.03	0.29	0.03	0.21	0.03	0.03
	$\psi_8=5.5$	0.14	0.14	0.27	0.14	0.88	0.14	0.14

From Table 3.12, 3.13 and Figure 3.6, almost all of the samples provide a good percentage of convergence except for $R3$ and $R5$. Obviously we found the probability $R5$ has low convergence rate compared to others especially when the sample size is small followed by $R3$. Again, we see there is an effects on the mean for $R3$ and $R5$ where all the estimates are far away from the true values with large effects on errors and biases. This is because the probability of choosing $A_2 = 0|A_1 = 0$ is $4/7$ for $R3$ which is far away from the optimal decisions where A_2 should be around 1 when S_j near to 0.5. Similar to $R5$ where we choose $A_2 = 3|A_1 = 0$ with probability $4/7$.

Overall when we test the sensitivity of the Murphy method using the unequal probabilities for the first action A_1, we found P_1 less than 0.5 will have slightly low convergence rate and estimates than P_1 greater than 0.5. This is because $A_2|A_1 = 0$ has greater range and high influence in the regret function than $A_2|A_1 = 1$.

The probability of choosing the second actions, either $A_2|A_1 = 0$ or $A_2|A_1 = 1$ which is far away from the optimal decisions will give poor estimates with large biases and very large in errors where the optimal decisions for the second actions suppose to be $A_2 = 1$ when the states is near to 0.5.

3.1.4 Murphy Sensitivity Analysis: Part(d)

In the previous parts we investigated the Murphy method with misspecification for the action models. We have assumed that the actions did not depend on states for estimation and have estimated the marginal probabilities for all actions.

In this part we further our investigation by allowing the action model to depend on states, S_j. The misspecification for the first binary action was discussed in Rosthøj et al. (2006) but we also will look into misspecification for the second action.

The first binary action, $A_1 = (0, 1)$ has equal probability where $P(A_1 = 1) = P(A_1 = 0) = 0.5$ by default. We now change it to

$$p = P(A_1 = 0|S_j > 0.5)$$

so

$$1 - p = P(A_1 = 1|S_j > 0.5).$$

The second action A_2 depends on the first. In this work we will investigate the effect of second action when the first takes the value $A_1 = 0$. In this case there are four possible values for A_2 i.e. 0, 1, 2 or 3. The default in generating data and the assumption in estimation, is that these values are equally likely. Let q be the probabilities for the four values, so $q = (1/4, 1/4, 1/4, 1/4)$ by default. Similar to Section 3.1.3, the equal probabilities $q = (1/4, 1/4, 1/4, 1/4)$ indicate that $P(A_2 = 0|A_1 = 0, S_j > 0.5) = 1/4$, $P(A_2 = 1|A_1 = 0, S_j > 0.5) = 1/4$, $P(A_2 = 2|A_1 = 0, S_j > 0.5) = 1/4$ and $P(A_2 = 3|A_1 = 0, S_j > 0.5) = 1/4$. We will also vary q as described below.

We have 8 misspecification models to investigate. The first four models, $T1$ to $T4$ use the misspecification on the first actions while models $T5$ to $T8$ have the misspecification for the second action given $A_1 = 0$. The model $T0$ is the true model with equal probabilities for first and second actions.

1. T0: $p = 0.5$, $1 - p = 0.5$; $q = (1/4, 1/4, 1/4, 1/4)$
2. T1: $p = 0.3$, $1 - p = 0.7$
3. T2: $p = 0.7$, $1 - p = 0.3$
4. T3: $p = 0.4$, $1 - p = 0.6$
5. T4: $p = 0.6$, $1 - p = 0.4$
6. T5: $q = (0, 1/3, 1/3, 1/3)$

7. T6: $q = (1/3, 1/3, 1/3, 0)$

8. T7: $q = (0, 0, 1/2, 1/2)$

9. T8: $q = (1/2, 1/2, 0, 0)$

The model $T5$ is skewed toward higher values of A_2 whilst T6 is skewed towards smaller values. The model $T7$ allows only higher values and model $T8$ allows only lower values of A_2.

Percentage successfully converged									
	Model								
n	T0	T1	T2	T3	T4	T5	T6	T7	T8
500	94.7	48.7	5.3	83.3	47.1	87.9	87.7	87.6	86.8
1000	97.9	42.9	6.0	79.5	44.6	86.4	91.0	89.4	90.5

Table 3.14: Number of times in 1000 simulations in which the estimation algorithm converged for different sample sizes n

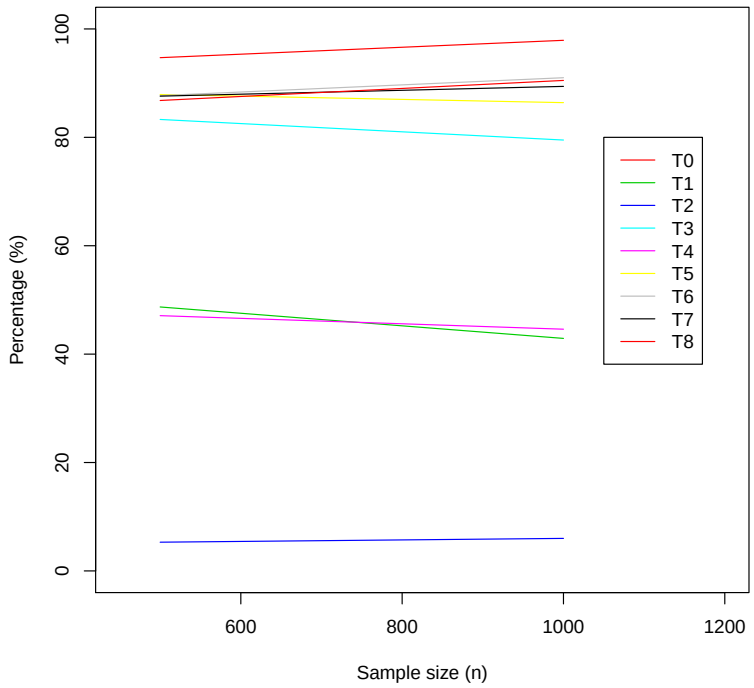

Figure 3.7: Percentage for estimation algorithm converged plot for two sample sizes (500 and 1000).

The first four models ($T1$ to $T4$) represent the misspecification for first action model that depends on state while the last four models ($T5$-$T8$) correspond to misspecification for the second action that depend on state. From Table 3.14 and Figure 3.7 we see that the misspecification of the second model leads to higher convergence rates than the misspecification for first action except for model $T3$. As sample size increases, the convergence

rate does not always improve due we presume to simulation noise. Model $T2$ has very poor convergence rate.

Table 3.15: Estimated parameters from 1000 simulations when action $A_2|(A_1 = 0)$ which depend on states S_{j-1} for sample size 500 and 1000.

		Model								
n	Parameter	T0	T1	T2	T3	T4	T5	T6	T7	T8
$n = 500$										
Mean	$\psi_6 = 0.0$	0.00	0.36	-0.41	0.19	-0.21	0.15	-0.10	0.14	-0.10
	$\psi_7 = 1.5$	1.50	1.64	1.34	1.58	1.41	0.86	1.51	0.86	1.51
	$\psi_8 = 5.5$	5.50	4.53	6.55	5.0	6.06	6.32	5.76	6.34	5.77
SE	$\psi_6 = 0.0$	0.08	0.08	0.10	0.09	0.09	0.15	0.08	0.16	0.08
	$\psi_7 = 1.5$	0.05	0.06	0.05	0.05	0.04	0.04	0.03	0.04	0.04
	$\psi_8 = 5.5$	0.19	0.20	0.28	0.20	0.21	0.28	0.18	0.28	0.19
RMSE	$\psi_6 = 0.0$	0.08	0.37	0.42	0.21	0.23	0.22	0.12	0.21	0.13
	$\psi_7 = 1.5$	0.05	0.15	0.16	0.09	0.10	0.64	0.04	0.64	0.04
	$\psi_8 = 5.5$	0.19	0.99	1.08	0.54	0.60	0.87	0.32	0.89	0.33
$n = 1000$										
Mean	$\psi_6 = 0.0$	0.00	0.36	-0.40	0.19	-0.21	0.15	-0.10	0.15	-0.10
	$\psi_7 = 1.5$	1.50	1.64	1.33	1.58	1.41	0.86	1.51	0.86	1.51
	$\psi_8 = 5.5$	5.50	4.53	6.57	4.99	6.06	6.32	5.76	6.33	5.76
SE	$\psi_6 = 0.0$	0.06	0.06	0.04	0.06	0.06	0.10	0.05	0.10	0.05
	$\psi_7 = 1.5$	0.03	0.04	0.02	0.04	0.03	0.03	0.02	0.03	0.02
	$\psi_8 = 5.5$	0.14	0.14	0.07	0.14	0.14	0.19	0.13	0.18	0.12
RMSE	$\psi_6 = 0.0$	0.06	0.22	0.40	0.20	0.36	0.18	0.11	0.17	0.11
	$\psi_7 = 1.5$	0.03	0.09	0.17	0.09	0.15	0.64	0.03	0.64	0.03
	$\psi_8 = 5.5$	0.14	0.58	1.08	0.53	0.98	0.84	0.29	0.85	0.28

Table 3.15 shows as usual the mean, standard error and root mean square error (RMSE) for these misspecification. We see that the estimates are generally very sensitive to the assumed action model, and large biases with high variability that can occur if the assumptions are false.

3.2 Misspecification and the Regret-Regression Method.

In this section, we investigate the effect of incorrect initial values with the same scale factor k as in Part(a), but now using the regret-regression method.

3.2.1 Regret-Regression Misspecification: Part(I)

We use the correct state model

$$E[S_j|(\bar{S}_{j-1}, \bar{A}_{j-1})] = \beta_0 + \beta_1 S_{j-1} + \beta_2 A_{j-1}A_{j-2} + \beta_3 A_{j-1}(1 - A_{j-2})$$

This is obtained because the conditional density of $S_j|(\bar{S}_{j-1}, \bar{A}_{j-1})$ for $j > 2$ is normally distributed with mean $0.5 + 0.2S_{j-1} - 0.07A_{j-1}A_{j-2} - 0.01A_{j-1}(1 - A_{j-2})$ and variance 0.01 in Murphy's simulation scenario. The simulation is repeated 1000 times.

		k						
Parameter	n	0	0.5	1	2	5	6	7
Mean								
$\psi_6 = 0.0$	250	-0.01	0.00	0.00	-0.01	0.01	0.00	-0.01
	500	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	1000	0.00	0.00	0.00	0.00	0.00	0.00	0.03
$\psi_7 = 1.5$	250	1.51	1.50	1.51	1.50	1.51	1.50	1.50
	500	1.50	1.50	1.50	1.50	1.50	1.50	1.50
	1000	1.50	1.50	1.50	1.50	1.50	1.50	1.43
$\psi_8 = 5.5$	250	5.50	5.50	5.50	5.53	5.47	5.51	5.51
	500	5.49	5.50	5.49	5.50	5.50	5.50	5.50
	1000	5.50	5.50	5.47	5.50	5.50	5.50	5.52
Standard Error, SE								
$\psi_6 = 0.0$	250	0.02	0.02	0.02	0.02	0.03	0.02	0.02
	500	0.02	0.02	0.02	0.02	0.02	0.02	0.02
	1000	0.01	0.01	0.05	0.01	0.01	0.01	0.25
$\psi_7 = 1.5$	250	0.01	0.01	0.01	0.02	0.02	0.01	0.02
	500	0.01	0.01	0.01	0.01	0.01	0.01	0.01
	1000	0.01	0.01	0.03	0.01	0.01	0.01	0.66
$\psi_8 = 5.5$	250	0.04	0.06	0.04	0.06	0.06	0.04	0.06
	500	0.04	0.04	0.04	0.04	0.04	0.04	0.04
	1000	0.03	0.03	0.25	0.03	0.03	0.03	0.18
Root Mean Square Error, RMSE								
$\psi_6 = 0.0$	250	0.02	0.02	0.02	0.03	0.03	0.02	0.02
	500	0.02	0.02	0.02	0.02	0.02	0.02	0.02
	1000	0.01	0.01	0.05	0.01	0.01	0.01	0.25
$\psi_7 = 1.5$	250	0.01	0.01	0.01	0.02	0.02	0.01	0.02
	500	0.01	0.01	0.01	0.01	0.01	0.01	0.01
	1000	0.01	0.01	0.03	0.01	0.01	0.01	0.66
$\psi_8 = 5.5$	250	0.04	0.06	0.04	0.07	0.07	0.04	0.06
	500	0.04	0.04	0.04	0.04	0.04	0.04	0.04
	1000	0.03	0.03	0.25	0.03	0.03	0.03	0.18

Table 3.16: Estimation of ψ using regret-regression method

Table 3.16 shows that the the estimates are generally good with the means quite close to the true values with very small error.

3.2.2 Regret-regression misspecification: Part(II)

We going to follow the misspecification in the previous part (3.2.1) but fitting the model using the wrong state model. In estimation we assume the model

$$E[S_j|(\bar{S}_{j-1}, \bar{A}_{j-1})] = \beta_0 + \beta_1 S_{j-1}.$$

So that the previous actions are falsely assumed not to influence current state given previous state.

		k						
Parameter	n	0	0.5	1	2	5	6	7
Mean								
$\psi_6 = 0.00$	250	-0.16	0.00	0.01	-0.01	0.05	0.00	0.01
	500	-0.12	0.01	0.48	0.00	0.00	-0.02	-0.04
	1000	0.00	0.00	0.00	0.00	0.00	0.00	0.00
$\psi_7 = 1.50$	250	1.51	1.52	1.50	1.51	1.49	1.51	1.51
	500	1.49	1.50	1.50	1.50	1.50	1.50	1.49
	1000	1.50	1.50	1.50	1.50	1.50	1.50	1.50
$\psi_8 = 5.5$	250	5.86	5.49	5.46	5.50	5.38	5.49	5.47
	500	5.49	5.47	4.87	5.51	5.51	5.50	5.52
	1000	5.50	5.51	5.5	5.50	5.50	5.50	5.50
Standard Error, SE								
$\psi_6 = 0.0$	250	1.55	0.13	0.12	0.03	0.47	0.02	0.03
	500	1.16	0.13	4.82	0.02	0.02	0.21	0.45
	1000	0.01	0.01	0.01	0.01	0.01	0.01	0.01
$\psi_7 = 1.50$	250	0.13	0.16	0.02	0.02	0.15	0.02	0.02
	500	0.09	0.07	0.02	0.01	0.01	0.06	0.15
	1000	0.01	0.01	0.01	0.01	0.01	0.01	0.01
$\psi_8 = 5.5$	250	3.56	0.35	0.35	0.06	1.22	0.06	0.07
	500	0.17	0.33	6.30	0.04	0.04	0.07	0.38
	1000	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Root Mean Square Error, RMSE								
$\psi_6 = 0.0$	250	1.56	0.13	0.12	0.03	0.48	0.03	0.03
	500	1.17	0.13	4.85	0.02	0.02	0.21	0.45
	1000	0.01	0.01	0.01	0.01	0.01	0.01	0.01
$\psi_7 = 1.50$	250	0.13	0.16	0.02	0.02	0.15	0.02	0.02
	500	0.10	0.07	0.02	0.01	0.01	0.06	0.15
	1000	0.01	0.01	0.01	0.01	0.01	0.01	0.01
$\psi_8 = 5.5$	250	3.58	0.35	0.36	0.06	1.22	0.06	0.07
	500	0.17	0.33	6.34	0.04	0.04	0.07	0.38
	1000	0.03	0.03	0.03	0.03	0.03	0.03	0.03

Table 3.17: Estimation of ψ using misspecified regret-regression model

Table 3.17 shows that although we fit the misspecified the state model we still find the estimates are good at sample size $n = 1000$. At sample size $n = 250$ we found there is some unreliability. When $n = 500$, the estimates for ψ_6 are a little far away from the true values at $k = 1$ but generally the estimates are still good with small error and bias

especially when we increase the sample size, n. We believe the occasional evidence of the poor performance is due to a small number of simulations where the estimates converge, but to the very extreme values. We suggest that in practice this type of odd behaviour would be noted, especially if the diagnostics we will describe later are applied.

		k						
Parameter	n	0	0.5	1	2	5	6	7
Mean								
$\psi_6 = 0.00$	250	1.46	2.27	0.25	1.93	-3.06	1.06	0.01
	500	-0.88	-0.15	0.19	-0.43	4.35	-2.27	-0.82
	1000	-1.25	-0.01	-0.02	0.20	0.96	0.03	0.52
$\psi_7 = 1.50$	250	1.36	0.73	1.27	1.25	-9.01	1.38	1.53
	500	1.23	1.26	1.22	1.42	1.20	1.14	1.07
	1000	1.28	1.48	1.36	0.60	1.30	0.92	1.18
$\psi_8 = 5.5$	250	2.73	2.84	4.47	1.30	11.19	6.61	5.40
	500	6.23	6.57	4.31	6.48	-2.65	8.51	5.59
	1000	8.13	5.52	5.73	6.30	4.97	3.67	3.94
Standard Error, SE								
$\psi_6 = 0.0$	250	3.86	3.19	0.56	11.46	8.22	13.37	0.02
	500	3.39	0.51	2.46	0.99	11.37	9.10	1.44
	1000	3.29	0.04	0.18	0.56	2.01	5.29	1.35
$\psi_7 = 1.50$	250	1.11	2.46	0.69	0.58	33.25	0.75	0.03
	500	0.60	0.55	0.62	0.38	1.24	0.93	0.74
	1000	0.57	0.12	0.33	2.70	2.89	0.82	0.63
$\psi_8 = 5.5$	250	6.65	7.75	2.40	18.63	18.41	31.25	0.06
	500	5.26	2.53	5.40	3.04	20.12	14.14	0.68
	1000	6.27	0.29	0.54	2.19	1.13	8.38	3.60
Root Mean Square Error, RMSE								
$\psi_6 = 0.0$	250	4.13	3.91	0.61	11.62	8.77	13.41	0.02
	500	3.51	0.54	2.47	1.08	12.18	9.38	1.66
	1000	3.52	0.04	0.18	0.59	2.23	5.29	1.45
$\psi_7 = 1.50$	250	1.12	2.58	0.73	0.63	34.87	0.76	0.04
	500	0.66	0.60	0.68	0.39	1.28	1.00	0.85
	1000	0.61	0.12	0.36	2.85	2.90	1.00	0.71
$\psi_8 = 5.5$	250	7.21	8.20	2.61	19.10	19.27	31.27	0.12
	500	5.31	2.75	5.53	3.19	21.70	14.46	0.69
	1000	6.80	0.29	0.58	2.33	1.25	8.58	3.92

Table 3.18: Estimation of ψ using misspecified regret-regression model

3.2.3 Regret-Regression Misspecification: Part(III)

In Section 3.2.2, we fitted a misspecified state model but we found the estimates are reasonable using the regret-regression method. In this section, we investigate a misspecification by fitting a different misspecified state model which now only considers the previous actions. The model is

$$E[S_j|(\bar{S}_{j-1}, \bar{A}_{j-1})] = \beta_0 + \beta_1 A_{j-1}A_{j-2} + \beta_2 A_{j-1}(1 - A_{j-2})$$

Table 3.18 shows that the estimates are very poor when we fit this misspecified model. We also see that there are very large errors and biases as k increases. The bias and errors improves as we increase the sample size n. When we compared the results in Section 3.2.2 and 3.2.3, we found the previous states is more important than the previous actions in the

state model. However, the combination of both previous states and actions gives good estimates for the state model using the regret-regression method.

3.3 Conclusions

In this chapter we have investigated the sensitivity and misspecification to the initial values for the Murphy and the regret-regression techniques. To begin with we looked at the role of initial values. We furthered our investigation by using unequal action probabilities or by allowing the action probabilities to depend on state at time j when generating the data but falsely assuming equal probabilities when fitting the model in both cases. In general, we found Murphy estimates are quite sensitive to the assumed action model with large biases and very large in errors.

For regret-regression method we found that misspecifying the state model might or might not make a difference. In Section 3.2.2 we ignored previous actions and found good results. However, in Section 3.2.3, where we ignored previous state, the results were poor. Just as for the Murphy action model, we note that the state model is fit to the observed data and so gross misspecification should be seen.

Chapter 4

Further Investigation of the Regret-Regression Method

4.1 Regret-Regression Method with Inclusion of Covariates

The regret-regression method incorporates the regret functions of Murphy (2003) into a regression model for observed responses. We found that this method is more straightforward to implement than the Murphy or Robins techniques. Besides providing direct estimates of the parameters, the method also allows diagnostics and model comparisons as will be illustrated later.

In this chapter we will allow the regret function to depend on covariates. There have been no previous investigations of this method in the presence of subject-specific covariate effects. To explore, we will focus on simulations using one type of action.

4.2 Simulation using Regret-Regression

In this section we use an example to illustrate the regret regression procedure. The ordinary least squares method is chosen for parameter estimation and bootstrap variance estimation is used. There are no distributional assumptions on Y because we only model the mean response.

4.2.1 Regret-Regression Simulation Procedure

We follow a simulation scenario similar to Murphy (2003). We again take $K = 10$ time points but this time have just a single action type chosen randomly from $0, 1, 2, 3$ with equal probabilities. Each individual starts with first states simulated as

$$S_1 \sim N(0.5, 0.01)$$

and then for $j = 2, \ldots, 10$

$$S_j \sim N(m_j, 0.01)$$

where $m_j = 0.5 + 0.2S_{j-1} - 0.07A_{j-1}$. Associated with each individual is a single covariate, x distributed as

$$x \sim N(0, 0.25).$$

We suppose the final response Y has the optimal mean value of 30. The regret function at each time point is

$$\mu_j(A_j|\bar{S}_j, \bar{A}_{j-1}) = e^{\psi_1+\psi_2 x}(A_j - \psi_3 - \psi_4 S_j - \psi_5 x)^2.$$

This regret function has been modified from the regret function found in Equation (2.27). The mean final response follows as

$$E[Y|\bar{S}_j, \bar{A}_j] = 30 - 5\sum_{j=1}^{10}(S_j - m_j) - \sum_{j=1}^{10} e^{\psi_1+\psi_2 x}(A_j - \psi_3 - \psi_4 S_j - \psi_5 x)^2$$

We then generate Y as a normally distributed with variable mean $E[Y|\bar{S}_j, \bar{A}_j]$ defined above and variance 0.64. As stated, in estimation we do not assume normality as we only model the mean response Y.

4.3 Regret-Regression Estimation

The regret at time point j is

$$\mu_j = \mu_j(A_j|\bar{S}_j, \bar{A}_{j-1}) = e^{\psi_1+\psi_2 x}(A_j - \psi_3 - \psi_4 S_j - \psi_5 x)^2$$

The aim of having no regret is achieved if action j follows the optimal rule

$$d_j^{opt} = \psi_3 + \psi_4 S_j + \psi_5 x.$$

We will use the regret-regression method to estimate when the regret function is correctly or incorrectly specified. As stated, the true model is

$$M_0 : \mu_j = e^{\psi_1+\psi_2 x}(A_j - \psi_3 - \psi_4 S_j - \psi_5 x)^2.$$

Next, we propose fitting a misspecified model. We consider five alternatives:

1. Model $M_1 : \mu_j = e^{\psi_1}(A_j - \psi_3 - \psi_4 S_j - \psi_5 x)^2$
2. Model $M_2 : \mu_j = e^{\psi_1+\psi_2 x}(A_j - \psi_3 - \psi_5 x)^2$

Parameter ψ	Models						
	True ψ	M_0	M_1	M_2	M_3	M_4	M_5
ψ_1	0.5000	0.5005	0.5366	0.6531	0.4282	0.7161	0.6323
ψ_2	0.5000	0.5000	-	0.7715	0.7149	0.6098	-
ψ_3	0.1000	0.1007	0.1432	3.1053	0.2082	3.0062	3.2489
ψ_4	5.5000	5.4975	5.4749	-	5.4966	-	-
ψ_5	0.3000	0.3000	0.9650	-0.2041	-	-	-

Table 4.1: Mean of the parameter estimates of $\hat{\psi}$ for all the models M_0-M_5.

3. Model $M_3 : \mu_j = e^{\psi_1+\psi_2 x}(A_j - \psi_3 - \psi_4 S_j)^2$

4. Model $M_4 : \mu_j = e^{\psi_1+\psi_2 x}(A_j - \psi_3)^2$

5. Model $M_5 : \mu_j = e^{\psi_1}(A_j - \psi_3)^2$.

The first misspecified model M_1 is similar to the true model but with missing ψ_2. The purpose of introducing this model is to assess the impact of missing the covariate x term from the scale factor in the model. Model M_2 has missing ψ_4 which is related to the states while model M_3 with missing ψ_5 is again related to the covariate x term. The models M_4 and model M_5 are created to see the effects of missing both states and covariates x.

The optimal decision which leads to zero regret is given below for each model.

1. Model $M_1 : d_j^{opt} = \psi_3 + \psi_4 S_j + \psi_5 x$

2. Model $M_2 : d_j^{opt} = \psi_3 + \psi_5 x$

3. Model $M_3 : d_j^{opt} = \psi_3 + \psi_4 S_j$

4. Model $M_4 : d_j^{opt} = \psi_3$

5. Model $M_5 : d_j^{opt} = \psi_3$.

The optimal decision for the first misspecification model, M_1 is identical to the optimal decision for the true model M_0. The optimal decisions for the last two models M_4 and M_5 are the same, i.e $d_j^{opt} = \psi_3$.

The data are generated from the simulation procedure described earlier. Then, all the models are fitted using the built-in function, *optim* in R to estimate the parameters β, ψ in Equation (2.23). After each simulation, we generate new datasets with sample size 1000 and 1000 repetitions. We obtained the optimal decisions using the estimated, $\hat{\psi}$ from the fitted models. We also estimate the mean, SE and RMSE of $\hat{\psi}$ as well as the maximum achieved response, Y under the assumed optimal rules and the standard deviation of that response for all models.

Tables 4.1 and 4.2 show the mean, SE and RMSE of the estimates of ψ for all the models. We found that model M_0 leads to parameter estimates which are quite close to the true values of ψ as expected with smaller standard error and bias. Model M_1 with

	Parameter ψ	Models					
		M_0	M_1	M_2	M_3	M_4	M_5
SE	ψ_1	0.0044	0.0313	0.0380	0.0137	0.0568	0.1476
	ψ_2	0.0040	-	0.1369	0.0051	0.0163	-
	ψ_3	0.0084	0.0613	0.0972	0.0284	0.0677	0.2591
	ψ_4	0.0223	0.1428	-	0.0646	-	-
	ψ_5	0.0054	0.0148	0.1920	-	-	-
RMSE	ψ_1	0.0045	0.0482	0.1577	0.0731	0.2235	0.1982
	ψ_2	0.0040	-	0.3040	0.2149	0.1110	-
	ψ_3	0.0084	0.0750	3.0069	0.1118	2.9070	3.1596
	ψ_4	0.0225	0.1450	-	0.0647	-	-
	ψ_5	0.0054	0.6652	0.5394	-	-	-

Table 4.2: SE and RMSE of $\hat{\psi}$ for all the models M_0-M_5.

	Model	
	Gold	Random
Mean	29.9338	-32.9823
Standard Deviation	1.7700	38.7552

Table 4.3: The achieved response, Y when using gold standard and completely random actions

missing ψ_2 provide a good estimates for ψ_1, ψ_3 and ψ_4 but poorly estimate for ψ_5. We found the SE and RMSE for ψ_4 in Model M_1 is slightly higher than the others except for ψ_5 with large bias. Model M_2 with missing ψ_4 poorly estimates the parameter of ψ. We found ψ_2 and ψ_5 have slightly higher in standard errors while the bias for ψ_3 is quite large. Model M_3 closely estimates ψ_1 and ψ_4 but poorly estimates ψ_2 and ψ_3. The last two models M_4 and M_5 produced poor estimates for ψ_3 in particular with large in bias.

Table 4.3 show the optimal response Y when using the gold standard and completely random actions. The gold standard happens when there are zero regrets in the model. We found the mean for gold standard is quite close to the optimal mean response Y with smaller in standard deviation. A negative optimal mean response Y with large errors was obtained when we have a model with completely random actions with equal probabilities with higher variability.

Table 4.4 gives the mean achieved Y and standard deviation. As expected, if the correct model M_0 is used in estimation and the basis for future decisions, then the response is maximised. If a misspecified model is assumed however then there is a price to be paid. Models M_2, M_4 and M_5 would lead to severe reduction in response. The correct model

	Model					
	M_0	M_1	M_2	M_3	M_4	M_5
Mean	29.9923	27.8664	8.6145	29.5267	12.7918	-0.8370
Standard Deviation	1.7677	4.3711	7.3200	1.8564	5.2383	7.8683

Table 4.4: The achieved response, Y when actions are selected using assumed optimal decisions

formulation thus seems to be crucial. We found the optimal mean response for model M_0 is almost similar to the gold standard with small standard deviation. The model M_1 which has similar optimal decision as M_0 also provide a good optimal mean response with small standard deviation but model M_3 has better optimal mean response with smaller standard deviation than model M_1 although model M_3 has different optimal decision than the correct model M_0.

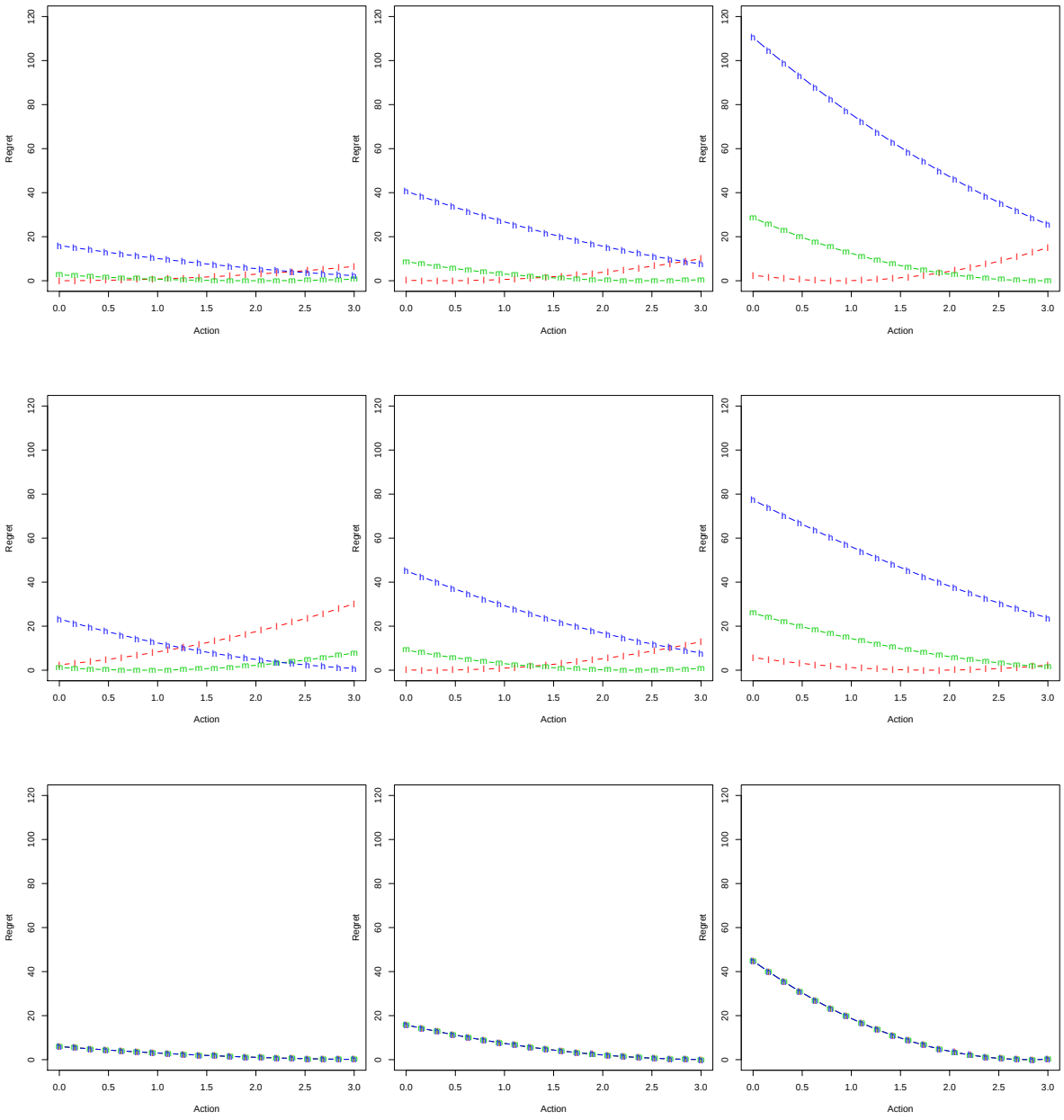

Figure 4.1: Estimated regret function for model M_0, M_1 and M_2. The first row is for model M_0, second row is the model M_1 and the third row represents model M_2. Each subplot consists of different levels of the single covariate. We indicate high states as the h line, medium states as the m line and the l line as low states.

Figure 4.1 shows the estimated regrets at mean parameter values for models M_0, M_1 and M_2. The first row is for model M_0, second row is the model M_1 and the third row represents model M_2. The left plot is for a subject with a low covariate. The middle plot is for a subject with a medium covariate while the right plot is for a subject with high covariate. Each plot shows regret at three levels of states: low states, l; medium m; and high states, h. The states and covariates are continuous variables and so we categorise the states and covariates into three different levels to simplify the analysis and help with interpretation of results.

The top row of Figure 4.1 corresponds to M_0, the true model. Consider the regrets at medium state. As the covariate increases the optimal action also increases, though generally within the range of actions shown the regrets can be quite low. At high state there is a very obvious effect of covariate, and all regrets are very high. The regret pattern for low states changes with covariate, with optimal action increasing as x does.

The middle row corresponds to M_1, a misspecified model. The pattern in the centre plot is similar to M_0 where the true regret is used. At low or high x however there are some marked differences. The optimal action at low x is reduced, and the regret seems to increase more rapidly. At high x the optimal action is higher than if the true regret function is used.

Model M_2 is the misspecified model with the regret function $\mu_j = e^{\psi_1+\psi_2 x}(A_j - \psi_3 - \psi_5 x)^2$. In Figure 4.1 we see that there are no differences between states. This is because the regrets and the actions do not depend on states in this misspecified model. If we choose low actions the regrets will be high at all levels of the covariates x. The regret goes very high especially at higher covariates. To achieve zero regret we need to choose high actions at all levels of the covariate.

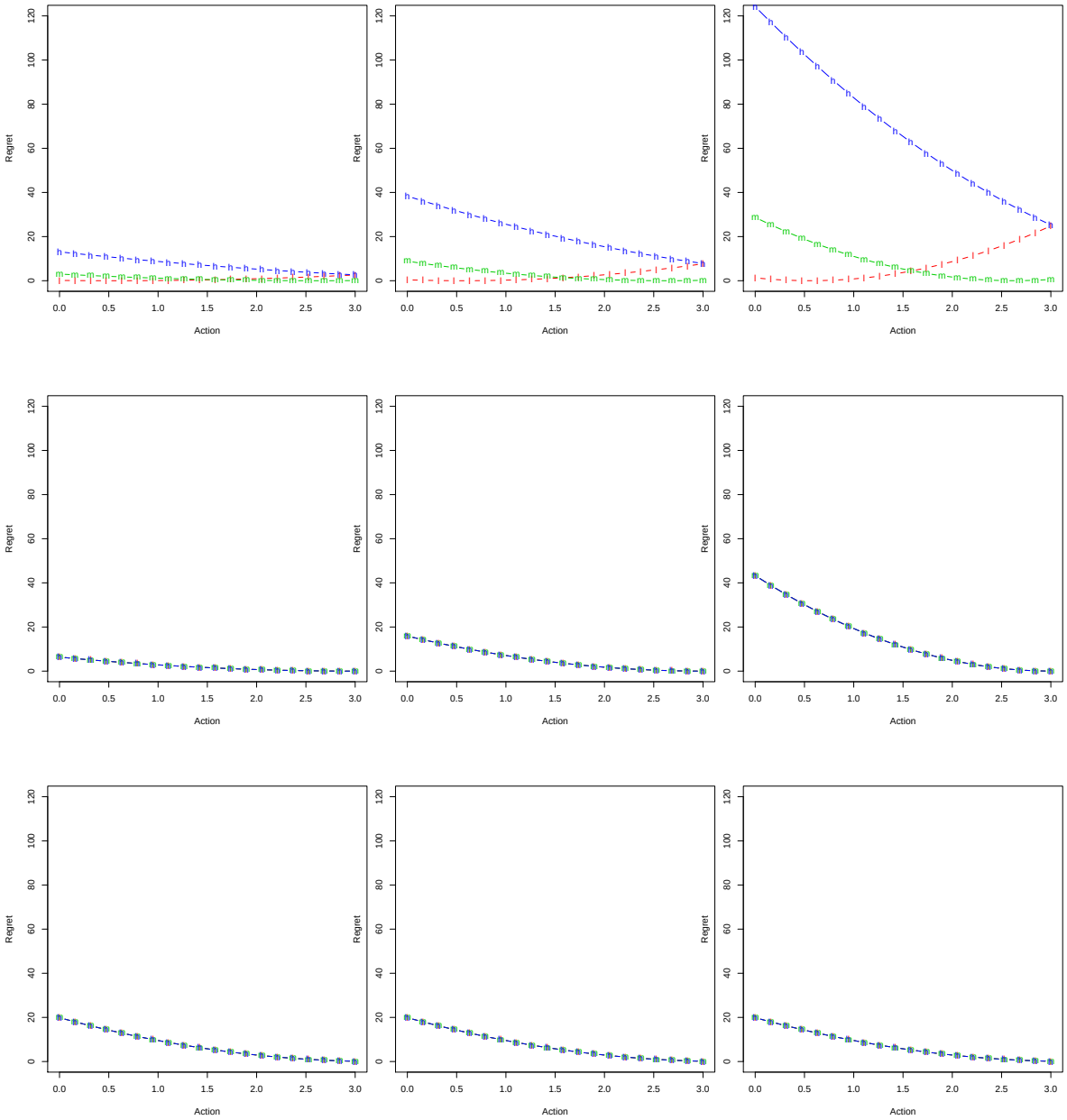

Figure 4.2: Estimated regret function for model M_3, M_4 and M_5. The first row represent the model M_3, second row for the model M_4 and the third row represent model M_5.

The fourth model M_3 in Figure 4.2 is the misspecified model with the regret function of the form $\mu_j = e^{\psi_1+\psi_2 x}(A_j - \psi_3 - \psi_4 S_j)^2$. To minimise or obtain zero regret, we need to choose the optimal action as $d_j^{opt} = \psi_3 + \psi_4 S_j$.

From Figure 4.2 (first row) we see model M_3 has a similar pattern to model M_0 where low actions at higher states will have higher regrets at all levels of the covariate. Either low actions at low states or high actions at medium states will have low regrets at all levels of the covariate. The main difference is in the right plot with high covariates, where low actions in high states reach the highest regret.

Model M_4 in the second row in Figure 4.2 has assumed the regret function $\mu_j = e^{\psi_1+\psi_2 x}(A_j - \psi_3)^2$. The patterns are quite similar to model M_2. To minimise or achieve zero regret, we choose the optimal action, $d_j^{opt} = \psi_3$. We see that there is no effect of state and the actions do not depend on covariate x. Low actions have higher regrets whilst higher actions minimise the regrets at all levels of the covariate.

Our last model M_5 is the misspecified model with regret function of $\mu_j = e^{\psi_1}(A_j - \psi_3)^2$. We choose the optimal action, $d_j^{opt} = \psi_3$ to achieve zero regret as shown the third row in Figure 4.2. We see similarity to model M_4 with a decreasing pattern as the actions increase though the regret function now does not vary with covariates. Low actions give higher regrets whilst higher actions minimise the regret at any covariate level regardless of the effects of the states.

We have seen the effects of the estimated regrets with different types of actions. We next extend our analysis by comparing the true regrets with the estimated regrets for all our models. If the estimated regrets of the chosen model are close to the true regrets then in practice the model is effective, even if misspecified.

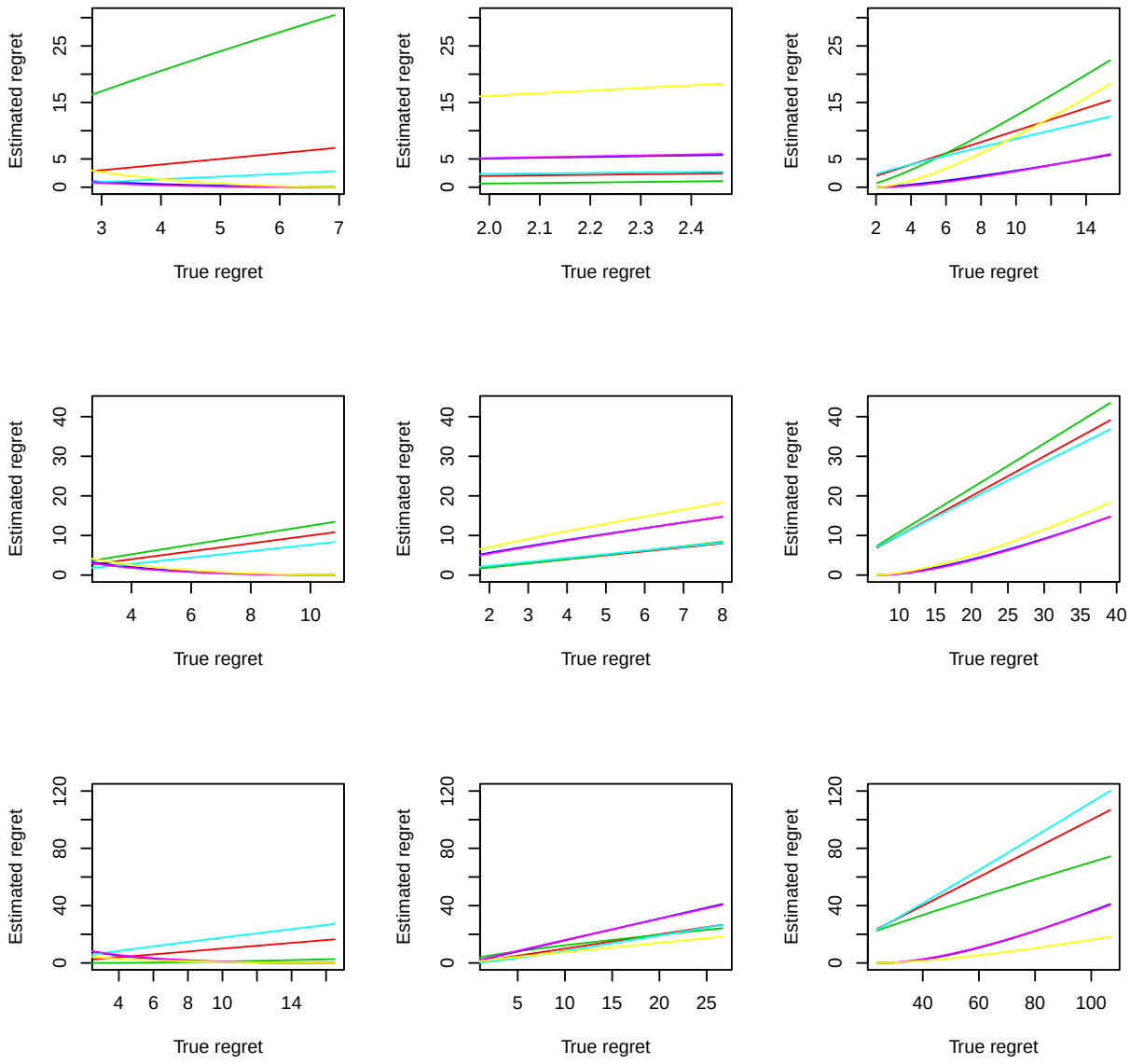

Figure 4.3: Comparison between true regret and the estimated regret for all the models. Each row of the subplot represents different levels of covariate x with low, medium and high covariates while each column represents different level of states with low states, medium and high states. The colours in each subplot indicate the estimated regret function for all the models. We represent red line for model M_0, the green line for model M_1, the dark blue line for model M_2, the light blue line for model M_3, the purple line for model M_4 and the yellow line for model M_5.

Figure 4.3 shows the true regrets against the estimated regrets for all the models, $M_0 - M_5$. The plot consists of 9 subplots where rows represent different levels of the covariates x while columns represent different level of states. The first row represents low covariate, the second row for medium levels and the third row is the high level covariates. The first column for the plot is for low states, the second column for medium states and third column is for high states. As mentioned earlier we categorise the states and covariates to simplify the analysis and interpret the results.

The x-axis represents the true regret function while the y-axis represents the estimated regret function. The colours in the subplots represent the estimated regret function for all the models, $M_0 - M_5$. The red line shows the regret function for model M_0, the green line model M_1, dark blue line for model M_2, light blue line for model M_3, purple line, model M_4 and yellow line for model M_5.

Note that the y-axis is not on the same scale as the x-axis for every plot. This is because the fitted regret was sometimes much higher than the true regret. This is particularly true for the final row, where we needed to have much wider range on the y-axis than on the x-axis.

From these subplots, there are no obvious patterns. The first subplot shows that at the low covariate x and low level of states, the estimated regret function for model M_1 is very high with the green line well above the red line. The other models are under the red line which indicates under estimation of regrets. The second row represents the medium covariate x with different levels of states. At medium states, we see that models M_1 and M_3 have similar estimated regrets to model M_0, with the three lines overlapping each other. The estimated regrets in the final column, high state, are often high. We note that this is true for the true model also.

4.4 Diagnostic Assessment in the Regret-Regression Method

Diagnostic methods are used to examine whether model assumptions are valid and to identify any unusual characteristics of the data that may influence the conclusions (Cook & Weisberg, 1983). Graphical procedures are often found useful in validating the model assumptions followed by statistical tests. Residual plots are often useful for assessing the fit of a model to the data and to check whether the model is useful.

4.4.1 Regret-Regression Residual Plots

Residuals can be used to assess model adequacy. A residual plot is particularly useful for identifying patterns in the data which may suggest heterogeneity of variance or bias due to misspecification (Mansfield & Conerly, 1987). Nevertheless, in this analysis we have not assumed a constant variance in our model. As previously stated we only model the mean response and we have not assumed normality for the model.

If the model is a correct model, the residuals should have zero mean for all states, regrets and covariates x. However, to define a pattern in a residual plot due to misspecification or natural variation can be challenging (Johnston & So, 2003).

The residual is defined as the difference between the observed data and the fitted values. For each model, we follow the simulation procedure which we described earlier to obtain the parameters $\hat{\beta}$ and $\hat{\psi}$. The residuals of states Z_j are obtained from the linear model of S_j given history $\bar{S}_{j-1}, \bar{A}_{j-1}$. From Equation (2.23), the fitted Y is

$$\hat{Y} = \hat{\beta}_1 S_1 + \sum_j \hat{\beta}_j Z_j - \sum_j \mu_j(a_j|\bar{S}_j, \bar{A}_{j-1}; \hat{\psi}).$$

Then, the residual between the observed data and fitted Y is

$$Y - \hat{Y} = Y - \hat{\beta}_1 S_1 - \sum_j \hat{\beta}_j Z_j + \sum_j \mu_j(a_j|\bar{S}_j, \bar{A}_{j-1}; \hat{\psi}).$$

Note that residuals would not be obtained if the Murphy or Robins method are used, as no model for $E[Y|\bar{S}_K, \bar{A}_K]$ is specified. We can plot the residuals against the states, actions or covariate x. It is possible to plot at each time point. To illustrate, we begin by pooling over the the time points in order to see if there any trends or unusual pattern in our models. If the model is correctly specified, the mean residual should always be zero.

We simulate with sample size $n = 1000$. To combine all 10 time points, we replicate the residuals and pool together the regrets at each time point. We will have 10000 residuals and 10000 regrets for all time points. We repeat the same procedure for the states function.

Figure 4.4 shows the residuals plotted against the regret for the models $M_0 - M_5$. The smooth trend in the plot for M_0 is almost perfectly straight at value zero. Thus, as required, there is no evidence against the model. There is some evidence of trend for M_1, M_3 and perhaps M_2, though the later decrease towards the right may simply reflect more sparse data.

The mean residual is almost constant at zero for model M_4. The smooth line also looks perfectly straight for model M_5 but this does not mean that there is no evidence against the fitted model. The model M_5 only contains the actions values $A_j = \{0, 1, 2, 3\}$ in the regret function. This is the reason why the residual against regret plot for this model does not look like those for other models.

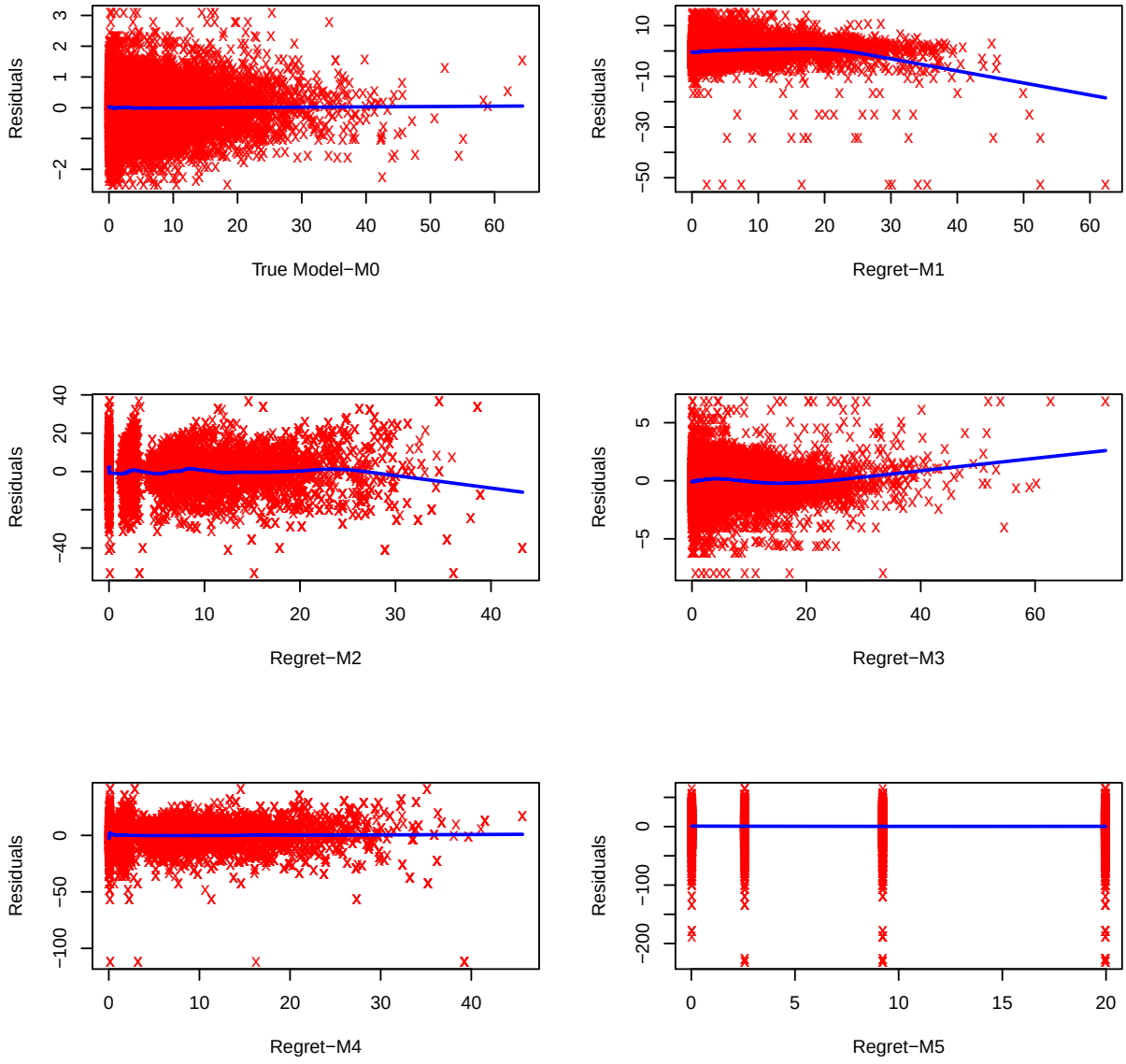

Figure 4.4: Residuals plotted against fitted regrets for all models. In each plot, all the time points are pooled together, i.e. each residual is replicated 10 times and plotted against the 10 estimated regrets. The line represents a smooth trend through the data.

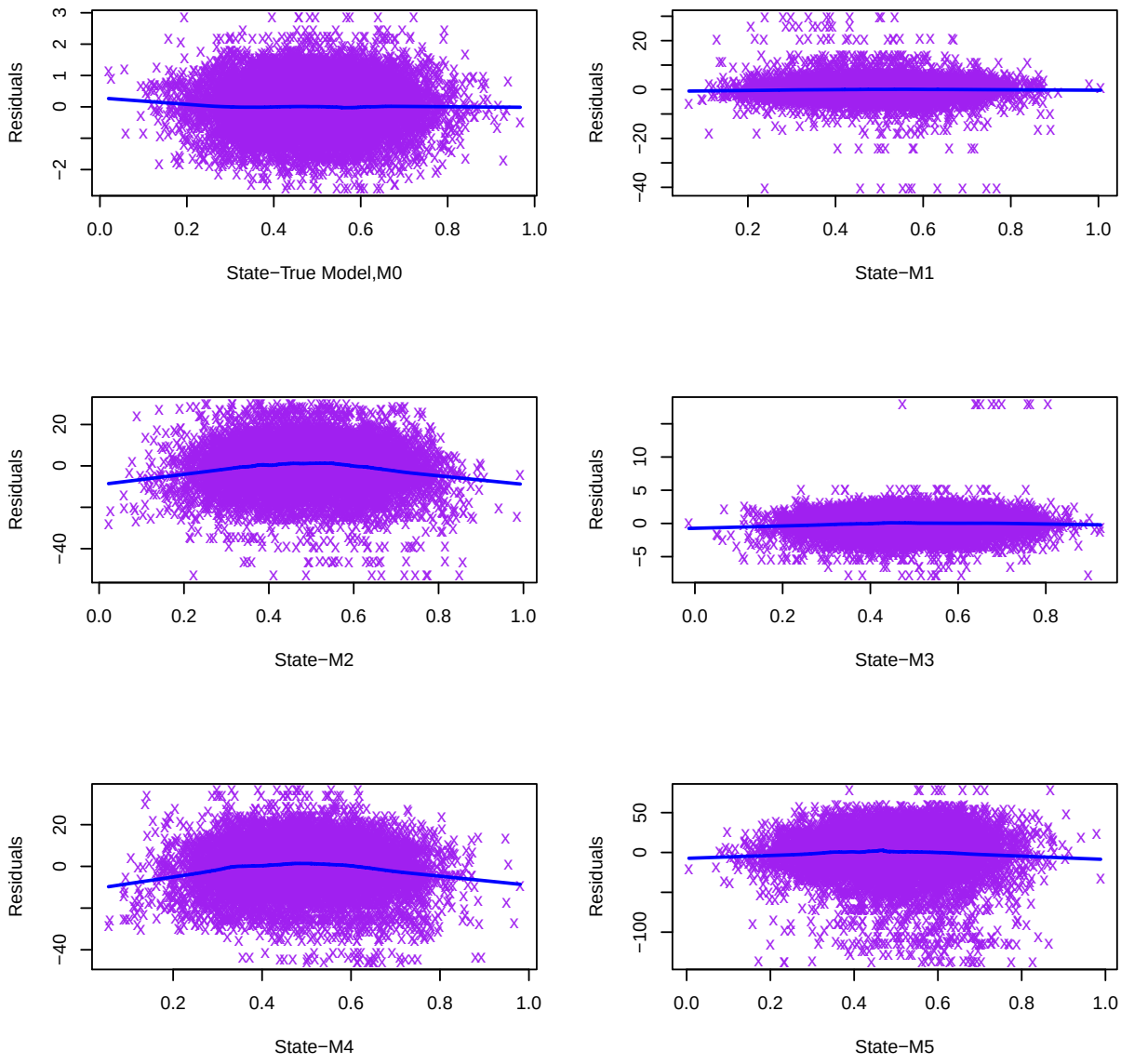

Figure 4.5: Residuals plotted against states for all models. In each plot, all the time points are pooled together, i.e. each residual is replicated 10 times and plotted against the 10 states. The line represents a smooth trend through the data.

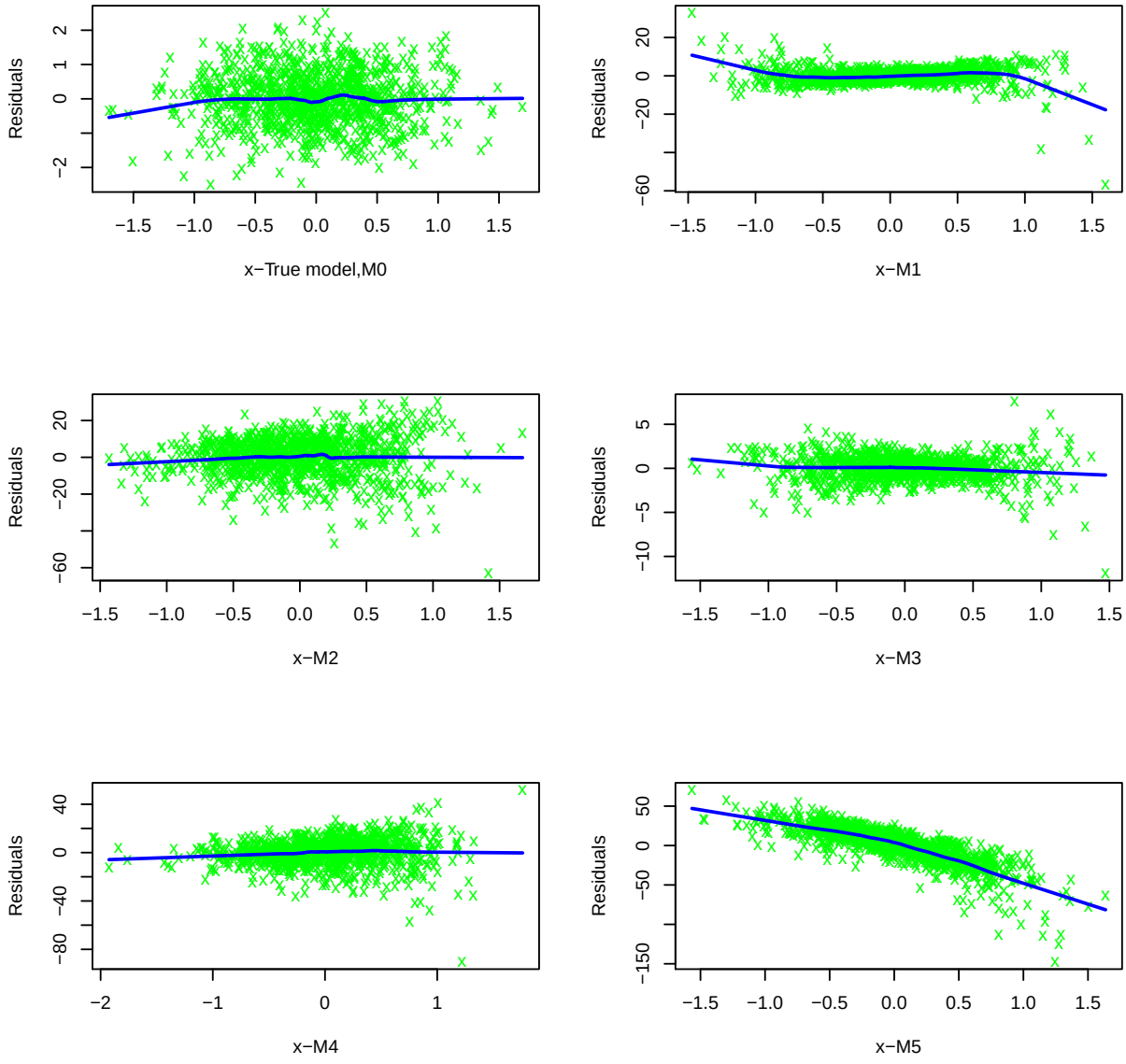

Figure 4.6: Residuals plotted against covariate x for all models. The line represents a smooth trend through the data.

Figure 4.5 shows the residuals against states, again all time points are pooled in each plot. There is some evidence against the fitted model for M_2 and M_4 but overall no strong trends occur in all the models.

Figure 4.6 shows plots of residuals against the covariate x. This time there is strong evidence against the model M_1 and M_5 but no trends occur for the other models.

Instead of combining all the time points, it is possible to examine whether there are trends at individual time points. We further our investigation by looking at the residuals against the states or the regrets at every single time point. Several residual plots for all the models can be found in Appendix 11.1 and Appendix 11.2.

We found similar results combining the time points for residuals versus the regrets with no trend for models M_0, M_4 and M_5 but there are some trends for models M_1, M_2 and M_3. Model M_5 only contains the actions with the range of values of $\{0, 1, 2, 3\}$. Also for residuals against the states there is evidence against model M_2 and M_4 and no evidence against the other models, where the results again matched the plots with pooling.

4.4.2 Wild Bootstrap in Regret-Regression Method

Bootstrapping, introduced by Efron (1979) is a general approach in statistical inference based on building a sampling distribution. The idea is to use the sample data as a population. We assume the sample data are independent and identically distributed. The *bootstrapping* method can be implemented by constructing a number of resamples (assumed to be of equal size) obtained by random sampling with replacement from the original dataset. We can use the repeated bootstrap samples either to compute the estimated standard error of an estimator or to perform hypothesis tests.

Inference on the parameters needs some special care especially when handling error terms which are heteroskedastic (Atkinson, 1982; Eicker, 1967). For the bootstrap to be effective usually there is an assumption that the responses are identically distributed.

To overcome these problems, a modification of bootstrapping called the wild bootstrap has been proposed (Wu, 1986; Liu, 1988; Mammen, 1993; Franke & Halim, 2007; Davidson & Flachaire, 2008). Under a variety of regularity conditions, the wild bootstrap is asymptotically justified. The wild bootstrap can be used to form a test based on the residuals from the regret-regression model (Henderson et al., 2011).

Suppose $D_i = \{D_1, D_2, \ldots, D_n\}$ are independent with mean zero and finite variances, which are not required to be equal. Then suppose

$$T = \frac{1}{\sqrt{n}} \sum_{i=1}^{n} D_i$$

converges in distribution to a variable D. Let w_i for $i = 1, 2, \ldots, n$ be independent and identically distributed with mean zero and unit variance. Then the wild bootstrap is based

on the result that

$$T^* = \frac{1}{\sqrt{n}} \sum_{i=1}^{n} w_i D_i$$

for $i = 1, 2, \ldots, n$ also converges into distribution D. The wild bootstrap generates N independent copies of w_i and then N repeated values for $T_1^*, T_2^*, \ldots, T_N^*$ as an empirical estimator of the distribution of $T_1, T_2, \ldots, T_N$. Note that each D_i occurs exactly once in each T_i^* meaning that there is no duplication or exclusion which usually happens in the standard bootstrap method.

4.4.3 Wild Bootstrap Simulation

The standard bootstrap does not require an assumption of an identical distributions but we do need to assume independence for all the subjects. The independence assumption is not true when the residuals $r_i = Y_i - E[Y_i|\bar{S}_K, \bar{A}_K]$ for $i = 1, 2, \ldots, K$ from a model are used as our statistics D_i in the definition of Section 4.4.2. Our aim is to build a test based on a contrast

$$T_i = \frac{1}{\sqrt{n}} \sum_{i=1}^{n} c_i r_i$$

where $\sum_{i=1}^{n} c_i = 0$. We then obtained N resamples of

$$T_i^* = \frac{1}{\sqrt{n}} \sum_{i=1}^{n} w_i c_i r_i.$$

An estimated p-value can be obtained by comparing the observed test statistic T with the wild bootstrap replicates T^*. In this case we will use multipliers (w_i) either with random standard normal $Z \sim N(0, 1)$ or random uniform $U\{-1, 1\}$ distribution. The wild bootstrap residuals are thus moved up or down but on the same vertical line. Then, the mean residuals from the original samples will be compared with the mean residuals from the wild bootstrap samples. Five different tests have been designed to investigate the slope and trends in the plots. The first four tests are of the form $T = \frac{1}{\sqrt{n}} \sum_{i=1}^{n} c_i r_i$ where $\sum_{i=1}^{n} c_i = 0$. We now assume the data are appropriately ordered. We do $N = 200$ wild bootstrap samples of sample size $n = 1000$ and calculate the value for each of the tests. The following tests will be considered:-

1. Test 1: The mean of the first half of the residuals when ordered against say state or regret, is contrasted with the mean of the second half. This means we split the x-axis into two parts and calculate the difference between them. This test is to see if there is an overall trend in the model.In this test,

$$c_i = \begin{cases} +1 & i = 1, \ldots, [\frac{n}{2}] \\ -1 & i = [\frac{n}{2}] + 1, \ldots, n \end{cases}$$

   Note here that $[\frac{n}{2}] = 500$ for sample size $n = 1000$.

2. Test 2: The middle third is contrasted with outer third to see whether there is curvature but not a sustained trend in the models. The x-axis is split into three parts and a contrast between them is found. Here,

$$c_i = \begin{cases} -1 & i = 1, 2, \ldots, [\frac{n}{3}] \\ +2 & i = [\frac{n}{3}] + 1, \ldots, [\frac{2n}{3}] \\ -1 & i = [\frac{2n}{3}] + 1, \ldots, n \end{cases}$$

   In this case $[\frac{n}{3}]$ is equal to 333 when we round it up for sample size $n = 1000$.

3. Test 3: For this test we look for trend only in the left tail by contrasting the first sixth of the data with the second sixth.

$$c_i = \begin{cases} +1 & i = 1, 2, \ldots, [\frac{n}{6}] \\ -1 & i = [\frac{n}{6}] + 1, \ldots, [\frac{2n}{6}] \\ 0 & i > [\frac{2n}{6}] \end{cases}$$

4. Test 4: Similar to Test 3 but to see if there is a trend on the right hand side.

$$c_i = \begin{cases} +1 & i = [\frac{4n}{6}] + 1, \ldots, [\frac{5n}{6}] \\ -1 & i = [\frac{5n}{6}] + 1, \ldots, n \\ 0 & i < [\frac{4n}{6}] \end{cases}$$

5. Test 5: This test is based on the extremum of the cumulative residuals. This will no longer have a contrast like in previous tests, but is investigated for completeness.

$$c_i = \max_{\mathrm{j}} \{ \sum_{i=1}^{j} (r_i) \}$$

   We calculate the residual $r_i = Y_i - E[Y_i | \bar{S}_{iK}, \bar{A}_{iK}]$ then in all bootstrap samples and compare the difference.

4.4.4 Simulation Results

The figures in Appendix 11.3 shows that all the lines are at the horizontal level at sample size $n = 500$. This indicates that the model M_0 could be a correct model. The null hypothesis for the wild bootstrap tests is that the mean residual is zero while the alternative hypothesis is that the mean residual is not zero for all states, regrets or x. Tables 4.5, 4.6 and 4.7 show the proportion of rejections of the null hypothesis at time points $1, 5$ and 9 using either $Z \sim N(0, 1)$ or $U\{-1, 1\}$.

Table 4.5: The estimated test sizes under the null at the first time point

		Tests				
		Test 1	Test 2	Test 3	Test 4	Test 5
$\mathbf{M_0}$						
	State	0.07	0.02	0.05	0.02	0.08
U{-1,1}	Regrets	0.08	0.09	0.02	0.05	0.04
	x	0.02	0.04	0.05	0.05	0.02
	States	0.03	0.07	0.05	0.04	0.02
Z(0,1)	Regrets	0.04	0.03	0.04	0.02	0.01
	x	0.01	0.09	0.10	0.06	0.01
$\mathbf{M_1}$						
	State	0.05	0.01	0.06	0.07	0.03
U{-1,1}	Regrets	0.35	0.15	0.03	0.16	0.02
	x	0.35	0.05	0.39	0.09	0.08
	States	0.07	0.05	0.03	0.01	0.07
Z(0,1)	Regrets	0.40	0.16	0.06	0.12	0.01
	x	0.29	0.03	0.42	0.13	0.09
$\mathbf{M_2}$						
	State	0.04	0.12	0.08	0.09	0.07
U{-1,1}	Regrets	0.12	0.08	0.16	0.07	0.18
	x	0.24	0.10	0.07	0.07	0.00
	States	0.04	0.11	0.06	0.13	0.09
Z(0,1)	Regrets	0.09	0.07	0.17	0.10	0.19
	x	0.23	0.15	0.06	0.06	0.00
$\mathbf{M_3}$						
	State	0.03	0.06	0.05	0.08	0.02
U{-1,1}	Regrets	0.05	0.17	0.08	0.09	0.09
	x	0.47	0.10	0.07	0.15	0.56
	States	0.05	0.08	0.05	0.07	0.05
Z(0,1)	Regrets	0.06	0.25	0.02	0.11	0.17
	x	0.40	0.14	0.10	0.17	0.51
$\mathbf{M_4}$						
	State	0.05	0.09	0.03	0.14	0.12
U{-1,1}	Regrets	0.09	0.02	0.06	0.10	0.15
	x	0.31	0.07	0.08	0.11	0.00
	States	0.07	0.11	0.11	0.12	0.12
Z(0,1)	Regrets	0.08	0.05	0.07	0.05	0.16
	x	0.25	0.02	0.04	0.01	0.00

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		Tests				
		Test 1	Test 2	Test 3	Test 4	Test 5
$\mathbf{M_5}$						
	State	0.05	0.09	0.06	0.07	0.08
U{-1,1}	Regrets	0.02	0.02	0.06	0.13	0.13
	x	1.00	0.69	0.85	1.00	1.00
	States	0.04	0.05	0.05	0.08	0.02
Z(0,1)	Regrets	0.04	0.04	0.02	0.09	0.14
	x	1.00	0.54	0.87	1.00	1.00

Table 4.5 shows the estimated power of the five wild bootstrap tests, based on 1000 simulations of datasets of size $n = 500$ using the first time point only. In each case there are 200 wild bootstrap samples. Under M_0, all tests have approximately the correct size. Test 1,2 and to a lesser extent 4 have some power to detect misspecification for the regrets while Tests 1,2 and 3 have detect misspecification for covariates, x for model M_1. We also found that all tests have the correct size for state for model M_1. Tests 1 and 2 in model M_2 have detected misspecification for the regrets and x and it seems that Test 2 have detect misspecification for all state, regrets and x. For model M_3, Tests 1 and 2 have detected some power against the null for x and Test 2 for the regrets. Meanwhile, model M_4 only show some power when Test 1 against x and Test 5 when test against the regrets. All tests have high power for M_5 when plotted against x.

Table 4.6: The estimated test sizes under the null at the fifth time point

		Tests				
		Test 1	Test 2	Test 3	Test 4	Test 5
$\mathbf{M_0}$						
	State	0.05	0.02	0.03	0.08	0.06
U{-1,1}	Regrets	0.07	0.04	0.05	0.07	0.05
	x	0.02	0.05	0.05	0.07	0.01
	States	0.02	0.03	0.02	0.03	0.02
Z(0,1)	Regrets	0.03	0.05	0.04	0.04	0.05
	x	0.02	0.03	0.04	0.05	0.02
$\mathbf{M_1}$						
	State	0.03	0.04	0.06	0.05	0.02
U{-1,1}	Regrets	0.65	0.11	0.05	0.16	0.01
	x	0.24	0.02	0.51	0.19	0.10

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		Tests				
		Test 1	Test 2	Test 3	Test 4	Test 5
	States	0.05	0.10	0.06	0.11	0.01
Z(0,1)	Regrets	0.60	0.06	0.02	0.22	0.01
	x	0.24	0.03	0.36	0.10	0.07
$\mathbf{M_2}$						
	State	0.09	0.40	0.22	0.40	0.46
U{-1,1}	Regrets	0.07	0.06	0.23	0.06	0.12
	x	0.17	0.10	0.13	0.10	0.01
	States	0.08	0.38	0.19	0.24	0.42
Z(0,1)	Regrets	0.05	0.05	0.20	0.09	0.12
	x	0.27	0.09	0.18	0.08	0.02
$\mathbf{M_3}$						
	State	0.10	0.07	0.13	0.06	0.00
U{-1,1}	Regrets	0.02	0.17	0.03	0.11	0.08
	x	0.29	0.09	0.10	0.15	0.47
	States	0.09	0.16	0.11	0.04	0.01
Z(0,1)	Regrets	0.03	0.12	0.05	0.07	0.08
	x	0.43	0.15	0.09	0.22	0.59
$\mathbf{M_4}$						
	State	0.08	0.47	0.21	0.28	0.36
U{-1,1}	Regrets	0.09	0.02	0.06	0.10	0.15
	x	0.23	0.08	0.10	0.05	0.02
	States	0.06	0.38	0.30	0.37	0.39
Z(0,1)	Regrets	0.06	0.03	0.05	0.05	0.13
	x	0.22	0.05	0.07	0.06	0.00
$\mathbf{M_5}$						
	State	0.03	0.10	0.07	0.18	0.05
U{-1,1}	Regrets	0.01	0.05	0.03	0.08	0.03
	x	1.00	0.62	0.83	1.00	1.00
	States	0.03	0.10	0.12	0.09	0.09
Z(0,1)	Regrets	0.07	0.05	0.02	0.12	0.12
	x	1.00	0.64	0.86	1.00	1.00

Table 4.7: The estimated test sizes under the null at the ninth time point

		Tests				
		Test 1	Test 2	Test 3	Test 4	Test 5
$\mathbf{M_0}$						
	State	0.02	0.05	0.07	0.03	0.03
U{-1,1}	Regrets	0.02	0.04	0.04	0.05	0.02
	x	0.02	0.04	0.05	0.01	0.01
	States	0.04	0.05	0.07	0.04	0.04
Z(0,1)	Regrets	0.03	0.04	0.06	0.06	0.06
	x	0.01	0.07	0.04	0.02	0.02
$\mathbf{M_1}$						
	State	0.04	0.06	0.07	0.07	0.01
U{-1,1}	Regrets	0.56	0.13	0.04	0.12	0.00
	x	0.33	0.01	0.44	0.16	0.10
	States	0.04	0.03	0.05	0.07	0.04
Z(0,1)	Regrets	0.52	0.09	0.04	0.21	0.02
	x	0.31	0.02	0.45	0.13	0.09
$\mathbf{M_2}$						
	State	0.06	0.41	0.20	0.39	0.34
U{-1,1}	Regrets	0.06	0.03	0.20	0.09	0.06
	x	0.19	0.08	0.05	0.08	0.01
	States	0.15	0.42	0.21	0.26	0.43
Z(0,1)	Regrets	0.03	0.06	0.20	0.06	0.00
	x	0.24	0.06	0.09	0.06	0.00
$\mathbf{M_3}$						
	State	0.08	0.13	0.10	0.09	0.01
U{-1,1}	Regrets	0.03	0.15	0.08	0.13	0.04
	x	0.34	0.08	0.09	0.23	0.50
	States	0.10	0.10	0.09	0.06	0.03
Z(0,1)	Regrets	0.07	0.12	0.02	0.16	0.07
	x	0.38	0.05	0.14	0.16	0.49
$\mathbf{M_4}$						
	State	0.06	0.36	0.25	0.28	0.26
U{-1,1}	Regrets	0.04	0.05	0.02	0.07	0.04
	x	0.22	0.07	0.06	0.09	0.00
	States	0.09	0.33	0.19	0.33	0.35
Z(0,1)	Regrets	0.06	0.03	0.06	0.08	0.00
	x	0.24	0.05	0.06	0.09	0.00

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		Tests				
		Test 1	Test 2	Test 3	Test 4	Test 5
$\mathbf{M_5}$						
	State	0.07	0.11	0.08	0.18	0.08
U{-1,1}	Regrets	0.05	0.01	0.02	0.06	0.02
	x	1.00	0.64	0.87	1.00	1.00
	States	0.03	0.10	0.12	0.09	0.09
Z(0,1)	Regrets	0.04	0.04	0.03	0.07	0.00
	x	1.00	0.68	0.87	1.00	1.00

Tables 4.6 and 4.7 show the estimated power using the wild bootstrap tests at time points 5 and 9. Similar to results found in Table 4.5, the model M_0 again has the correct size. Tests 1 and 3 show some misspecification against x and Test 1 against the regrets for model M_1 at both time points. For model M_2, Test 5 detect misspecification against state at time point 5 and all tests except test 1 at time point 9 while Test 1 only show misspecification against x at both time points.

Misspecification for model M_3 is detected at Tests 1 and 5 when plotted against x. The results at time points 5 and 9 are found different from time point 1 for model M_4 where at time point 1, some power have shown at Test 1 when test against x and Test 5 when test against the regrets. However, at time points 5 and 9, it shown that Test 1 detect misspecification when test against x and Tests 2,3,4 and perhaps 5 when test against the states. Again, we found similar results as time point 1 for both time points 5 and 9 where all tests have high power for model M_5 when plotted against covariate x.

Overall, we found Test 1 has detected some misspecification against x for all models and only model M_5 reject the null hypothesis when test against the covariates, x for all the wild bootstrap tests.

4.5 Conclusions

The investigation of covariate effects in the regret-regression method is possible by allowing the regret function to depend on covariates. In the simulation, we consider six possible models where the true model is

$$M_0 : \mu_j = e^{\psi_1+\psi_2 x}(A_j - \psi_3 - \psi_4 S_j - \psi_5 x)^2.$$

and we considered five misspecified models. The main purpose of creating a misspecified model is to investigate the effect of the missing parameters or covariates in the model and also to test the sensitivity of the model. We assess the model adequacy for each model by

examining the residuals through the residual plots and wild bootstrap test. We found that the true model had no trend in the residual plot while the wild bootstrap test show that the model is correct either by using $U\{-1, 1\}$ or $Z(0, 1)$ multipliers.

At any level of x, the optimal response is achievable if we choose low actions with low states or medium level with medium states but this decision was not correct for model M_1 at low x where low actions with low states does not give an optimal response. We also found that the estimated regrets are almost equal to the true regret when covariates x are at a high level with a medium level of states.

The diagnostic method is used to identify any unusual characteristics that may influenced the decisions. We divided the diagnostic into two parts, i.e the residual plots and the wild bootstrap. The wild bootstrap is used to perform a test to confirm about the pattern or trends in the models.

We found that the residual plots against regret and covariates x have shown some pattern and trend in the models whereas the residuals against states have not shown any pattern or trend for all of the models.

The wild bootstrap test showed that similar results occurs either in $Z \sim N(0, 1)$ or $U\{-1, 1\}$. We also found that all the tests are good to test the residuals. Testing against covariates, x was found to be the best for model M_5.

According to the previous results we can conclude that true model, M_0 is of course the best among the rest in terms of the parameter estimates of ψ and the estimates of the optimal response, Y using the optimal decisions supported by the wildbootstrap test. This is in contrast with model M_5 where it show poor performance in estimation and also when testing against x using the wild bootstrap tests. Besides of the true model M_0, we can say that models M_1 and M_3 are performing well for this analysis and perhaps these three model can be used for future analysis.

Chapter 5

Application of Regret-Regression in Dose-Finding for Anticoagulant Data.

In this chapter we illustrate the use of regret-regression on data giving anticoagulation treatment for a group of 303 patients. The anticoagulant in use was Warfarin which is also known as Coumadin, Jantoven, Marevan, Lawarin, and Waran. Initially it was a pesticide against rats and mice and is still marketed for this purpose, although more potential poisons such as brodifacoum have been produced (Kohn & Pelz, 2000; Rost et al., 2009). Warfarin was found in the early 1950s to be effective and safe for preventing thrombosis and embolism (abnormal formation and migration of blood clots).

Warfarin works against vitamin K which is particularly found in fresh plant-based foods. Vitamin K plays an important role in our body's natural clotting process in the liver to make blood clotting proteins. Warfarin reduces the liver's ability to use vitamin K to produce normally functioning forms of the blood clotting proteins (Bell & Caldwell, 1973; Suttie, 1990).

Prothrombin time (PT) is a blood test that measures the time to blood clot and can be used to check for bleeding problems. It is commonly measured using blood plasma. A PT test is also known as INR (International Normalized Ratio) test. The INR provides a way of standardising the results of Prothrombin time tests. The INR is used to determine the blood clotting time, in the measure of Warfarin dosage, liver damage, and vitamin K status (Poller, 2004; Christensen et al., 2010; Kim et al., 2010).

The result (in seconds) for Prothrombin time (PT) performed on a normal individual will vary depending on what type of analytical system is used. The INR was devised to standardise the results. The ISI value(International Sensitivity Index) has been introduced to indicate how a particular batch of tissue factor compares to an internationally standardised sample. The ISI value is usually between 1.0 and 2.0. The INR is the ratio of a patient's Prothrombin time to a normal (control) sample, powered by the ISI value.

$$\text{INR} = \left(\frac{\text{PT}_{\text{test}}}{\text{PT}_{\text{normal}}}\right)^{\text{ISI}}.$$

The Prothrombin time is the time that takes plasma to clot after addition of tissue factor obtained from animals. This measures the quality of coagulation. The speed of coagulation is affected by levels of factor VII in the body. Factor VII has a short half-life which needs vitamin K. The Prothrombin time can be prolonged as a result of deficiencies in vitamin K, which can be caused by Warfarin, malabsorption, or lack of intestinal colonisation by bacteria (such as in newborns). Moreover, poor factor VII synthesis due to liver disease or increased consumption of vitamin K may prolong the PT.

A high INR level such as INR=5 indicates that there is a high chance of bleeding, whereas if the INR is low such as 0.5, then there is a high chance of having a clot. The normal range for a healthy person is 0.9 to 1.3, and for people on Warfarin therapy, 2.0 to 3.0.

5.1 The Warfarin Data

Rosthøj et al. (2006) analysed data on 350 patients given Warfarin from one hospital between February 1995 till August 2000. The treatment time varied from 16 days to almost five years which involved 2 to 124 clinic visits. The data also contain covariates which include age, sex and diagnosis.

The original data were unbalanced but Rosthøj et al. (2006) used a subset of complete cases where she concentrate on the first 14 clinic visits for the 303 Warfarin treated patients with at least 14 visits. The first four visits were considered as induction and the analysis concentrated on the remaining 10 visits. At each visit, j the state S_j is defined. After consultation Rosthøj et al. (2006) selected

$$S_j = \begin{cases} 0 & \text{(INR in range)} \\ \frac{D_j}{R} & \text{(otherwise)} \end{cases}$$

where D_j is the difference (positive or negative) between INR at time j and the nearest boundary of the target range, and R is the width of that target range where R typically is between 1 or 2. Half of the visits had INR in range, i.e $S_j = 0$. The INR of the patient has positive skewed distribution with range -1.53 to 5.00. The lower and upper quantiles is between -0.19 and 0.80 and the median is 0.25. The final response, Y is the overall percentage of time INR was within target range over the ten visits.

For the actions, Rosthøj et al. (2006) defined A_j to be change in prescribed dose at visit j, since usually a decision consists of two stages: first, whether or not to change dose; second, if changing to what value. There is also a third stage but this was not considered. The dose level (and change in dose) is a discrete variable, determined by the $0.5, 1, 3$ and 5mg of Warfarin tablet, but in practice, a fairly large number of combinations have been used. Rosthøj et al. (2006) found 61 per cent of visits leave the dose unchanged. The dose change distribution is fairly symmetric which is about zero, with standard deviation close to 1mg but sometimes changed to very large changes with the range between -9 to

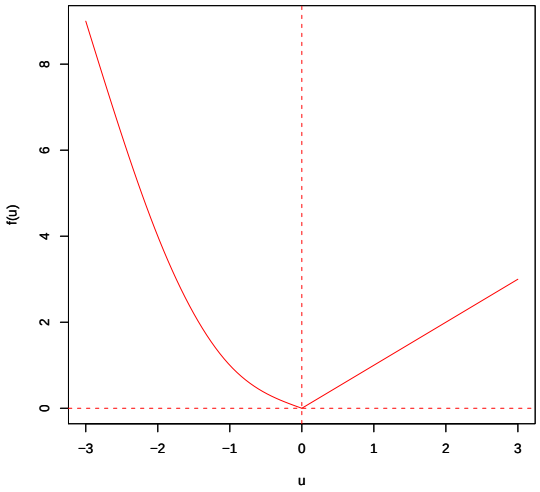

Figure 5.1: Regret function with link function $f(u) = u$ if $u \geq 0$ and $f(u) = u^2$ otherwise.

+8 units.

5.2 The Regret Model

Henderson et al. (2009) selected a model which was based on a categorisation of the current states, S_j^*. The categorised values were $S_j^* = 2, 1, 0, -1, -2$ which corresponded to very high, high, zero, low and very low INR values. The median of the positive S_j was the cut-off between very high and high level while the median of the negative S_j was the cut-off between the low and very low INR values.

The optimal actions were bounded at ± 3. Only three out of the 2727 observed actions fell outside of this range. For each category of state, a separate asymmetric regret function was fitted. Henderson et al. (2009) has fitted several regret models to the data. However, the regret function

$$\mu_j(a_j|\bar{S}_j, \bar{A}_{j-1}, S_j^* = s; \psi) = \psi_{s1} f(A_j - \psi_{s2} - \psi_{s3} S_{j-1})$$

fit the data reasonably well for category $S_j^* = s$. The link function for the regret function is $f(u) = u$ if $u \geq 0$ and $f(u) = u^2$ otherwise (see Figure 5.1) and the optimal decision rule is $\underline{d}_j^{opt} = \psi_{s2} + \psi_{s3} S_{j-1}$.

Rosthøj et al. (2006) have tried to use Murphy's method but could only fit a very simple model, Equation (3.1) and discussed some problems that occur when fitting the model into the application of the anticoagulant data. Furthermore, Henderson et al. (2009) have found that the regret-regression gave different parameter estimates when using this simple model.

Figure 5.2 shows the residuals against fitted regret and observation state for the warfarin data. The plots show an adequate fitted model with an apparent random scatter. The

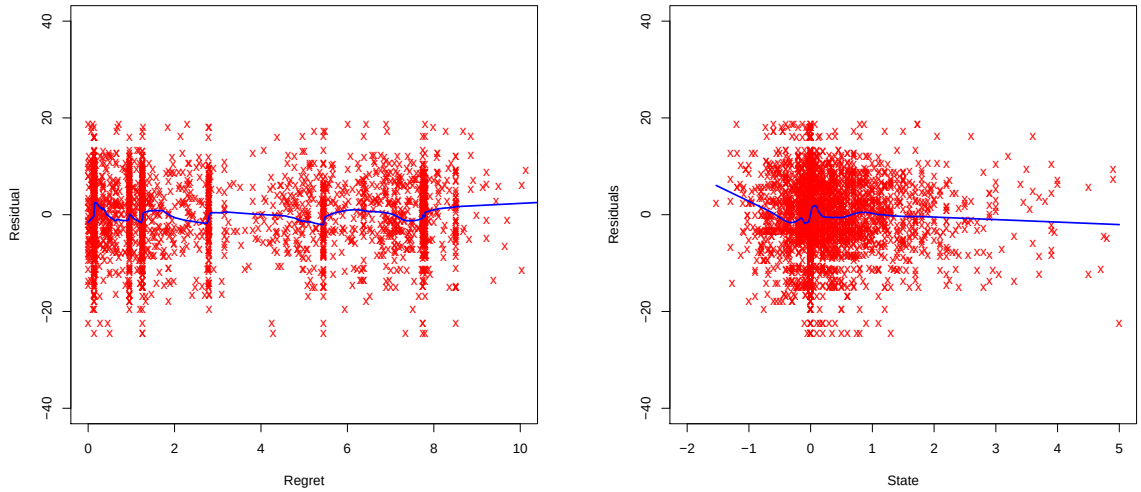

Figure 5.2: Residual plots for anticoagulant data, comparing residuals with fitted regrets and state observations

blue line show a smoother through the data. It is seen that this is almost flat, except perhaps at very low states. Table 5.1 shows the parameter estimates for ψ and the associated SE from 100 bootstrap samples. The parameter ψ_{s2} indicates that if the current state is low, there is a need to increase the dose and if the current state is high, then a decrease of dose is needed. There is no need to change the dose if the current state is in range.

Figure 5.3 of the estimated regret function is similar to that given by Henderson et al. (2009). This plot shows the estimated regret functions with categorised state, S_j^*. The three lines in each subplot indicates whether the previous state was in range (solid green line), above the range (dotted blue line) and below the range (dashed red line). The first subplot indicates that at a very low current state where the clotting time is found too short, an increase of dose is suggested to minimise the regret. A similar explanation applies to the low current state.

If the current state is in range, there is no need to increase or decrease the dose. If we choose to decrease the dose when the previous state was in the low range, the regrets tends to increase. The last two subplots show the current state at the very high or high level, where the regrets start to increase as we increase the dosage.

From the regret function $\mu_j(a_j|\bar{S}_j, \bar{A}_{j-1}, S_j^* = s; \psi)$, we know that the parameter ψ_{s3} is related to the previous state, S_{j-1}. We can describe the parameter ψ_3 if we refer to the Table 5.1 and Figure 5.3 together. We see the actions are influenced by the previous states, S_{j-1} for the first four categories of S_j^* . If the current state and the previous state are in low condition, an increase of dose is needed to reduce the regrets. If the current and previous state are in high level, the dose needs to be reduced to minimise the regrets. From these two conditions, more drastic dose changes are needed if the two states have the same signs while smaller changes of dose are recommended if they have opposite signs. In the fifth category of S_j^*, the previous state, S_j seems unimportant for an optimal

S_j^*	ψ_{s1}	SE	ψ_{s2}	SE	ψ_{s3}	SE
-2	-0.6023	0.0825	2.1333	0.0805	-1.0763	0.0427
-1	-0.3981	0.0776	2.7917	0.1432	-1.5835	0.0698
0	-0.9600	0.2079	-0.1193	0.0674	-1.1317	0.1018
1	-2.3450	0.0760	-2.3211	0.0500	-0.9170	0.1283
2	-2.8208	0.1292	-2.9614	0.0900	0.2296	0.1188

Table 5.1: Parameter estimates and bootstrap standard errors

actions.

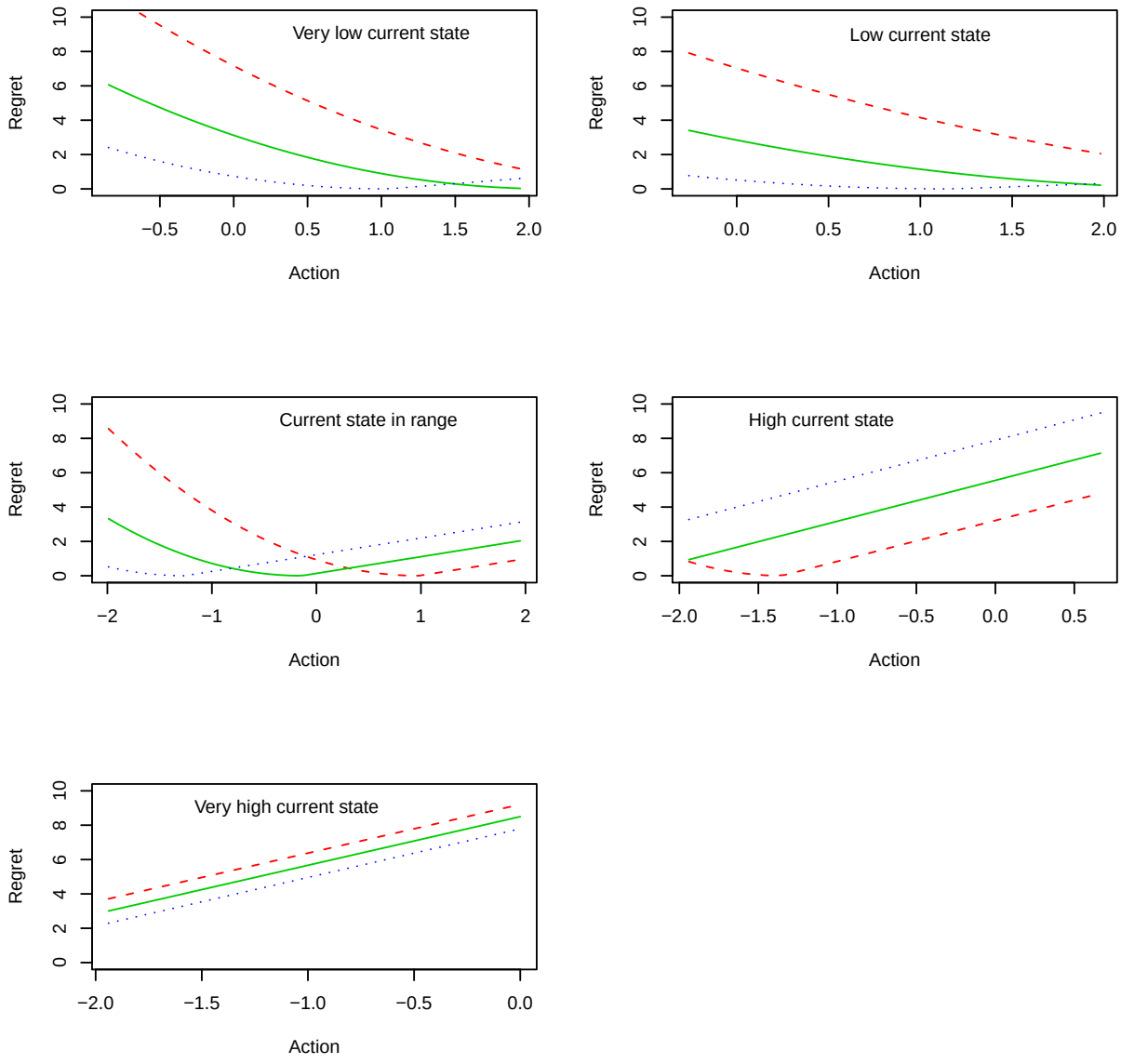

Figure 5.3: The estimated regret functions for categorised state, $S_j^* = s$. The three lines in each subplot indicate whether previous state was in range (solid green line), above the range (dotted blue line) and below the range (dashed red line).

5.3 The State Residual, Z_j

The state residuals $Z_j = S_j - E[S_j|\bar{S}_{j-1}, \bar{A}_{j-1}]$ were obtained from a mixture model for S_j. This mixture model has two components: a logistic component when $P(S_j = 0)$ (INR values are in range) and a linear component for $|S_j|$ when $(S_j \neq 0)$. When the INR of the patient is in range, Henderson et al. (2009) used the logistic function and linear function when the INR of the patient is out of range.

The covariates used in the model consisted of the previous states and previous actions as well as a variety of indicator variables for states and actions. We use indicator to indicate the INR status of the patient. The indicator of states known as $istate$ has the value zero if the states is not equal to zero (INR values are not in range) and one if the states is equal to zero (the INR values in range):

$$istate = \begin{cases} 0, S_j \neq 0 & \text{(INR not in range)} \\ 1, S_j = 0 & \text{(INR in range).} \end{cases}$$

Similarly, we use indicator if dose is changed. This indicator, $iacts$ takes the value zero if there is a change in dose and one if there is no change in dose:

$$iacts = \begin{cases} 0 & \text{(changing dose)} \\ 1 & \text{(no change in dose).} \end{cases}$$

	Coefficient	SE	Z	*p-value*
Intercept	0.238	0.192	1.237	0.216
S_{j-1}	-0.128	0.147	-0.869	0.385
$istates_{j-1}$	-0.238	0.203	-1.171	0.242
A_{j-1}	-0.105	0.131	-0.798	0.425
$iacts_{j-1}$	-0.157	0.185	-0.850	0.395
S_{j-2}	-0.104	0.075	-1.382	0.167
$istates_{j-2}$	0.008	0.149	0.056	0.956
A_{j-2}	-0.114	0.084	-1.347	0.178
$iacts_{j-2}$	0.117	0.096	1.216	0.224
S_{j-3}	-0.042	0.046	-0.898	0.369
$istates_{j-3}$	0.015	0.083	0.174	0.862
A_{j-3}	-0.025	0.050	-0.495	0.621
$iacts_{j-3}$	0.010	0.083	0.120	0.904
S_{j-4}	-0.048	0.045	-1.069	0.285
$istates_{j-4}$	0.023	0.082	0.280	0.779
A_{j-4}	-0.042	0.05	-0.837	0.402
$iacts_{j-4}$	-0.053	0.082	-0.647	0.518
S_{j-1}^2	-0.113	0.042	-2.683	0.007
$S_{j-1}S_{j-1}^2$	0.033	0.036	0.924	0.356
$S_{j-1}A_{j-1}$	-0.029	0.056	-0.511	0.609
$A_{j-1}istates_{j-1}$	-0.006	0.153	-0.042	0.967
$A_{j-1}S_{j-1}^2$	0.055	0.044	1.261	0.207
$iacts_{j-1}S_{j-1}$	-0.161	0.108	-1.494	0.135
$iacts_{j-1}istates_{j-1}$	0.481	0.202	2.376	0.018
$S_{j-2}S_{j-1}$	-0.076	0.052	-1.459	0.145
$S_{j-2}istates_{j-1}$	0.053	0.102	0.517	0.605
$S_{j-2}A_{j-1}$	-0.096	0.056	-1.708	0.088
$S_{j-2}iacts_{j-1}$	-0.062	0.101	-0.610	0.542
$istates_{j-2}istates_{j-1}$	0.046	0.179	0.255	0.799
$istates_{j-2}A_{j-1}$	-0.014	0.088	-0.162	0.872
$istates_{j-2}iacts_{j-1}$	-0.162	0.180	-0.899	0.369
$A_{j-2}S_{j-1}$	0.017	0.057	0.292	0.771
$A_{j-2}istates_{j-1}$	-0.052	0.110	-0.471	0.637
$A_{j-2}A_{j-1}$	0.024	0.059	0.416	0.678
$A_{j-2}iacts_{j-1}$	0.026	0.109	0.236	0.813
$A_{j-2}S_{j-2}$	0.042	0.045	0.934	0.350

Table 5.2: Logistic regression model for S_j when $P(S_j = 0)$

	Coefficient	SE	Z	*p-value*
Intercept	1.467	0.066	22.146	0.000
S_{j-1}	0.119	0.049	2.424	0.015
$istates_{j-1}$	0.100	0.071	1.400	0.162
A_{j-1}	0.123	0.045	2.735	0.006
$iacts_{j-1}$	0.060	0.062	0.960	0.337
S_{j-2}	-0.036	0.025	-1.433	0.152
$istates_{j-2}$	0.002	0.051	0.036	0.972
A_{j-2}	-0.044	0.029	-1.477	0.140
$iacts_{j-2}$	0.000	0.033	-0.005	0.996
S_{j-3}	0.005	0.016	0.330	0.741
$istates_{j-3}$	-0.025	0.028	-0.893	0.372
A_{j-3}	-0.014	0.017	-0.864	0.388
$iacts_{j-3}$	-0.058	0.028	-2.081	0.038
S_{j-4}	-0.017	0.015	-1.114	0.266
$istates_{j-4}$	-0.032	0.028	-1.161	0.246
A_{j-4}	0.002	0.017	0.096	0.923
$iacts_{j-4}$	0.007	0.028	0.256	0.798
S_{j-1}^2	0.050	0.014	3.539	0.000
$S_{j-1}S_{j-1}^2$	-0.036	0.012	-3.077	0.002
$S_{j-1}A_{j-1}$	0.037	0.018	2.105	0.035
$A_{j-1}istates_{j-1}$	-0.081	0.052	-1.546	0.122
$A_{j-1}S_{j-1}^2$	-0.036	0.014	-2.483	0.013
$iacts_{j-1}S_{j-1}$	0.010	0.035	0.277	0.782
$iacts_{j-1}istates_{j-1}$	-0.067	0.069	-0.967	0.334
$S_{j-2}S_{j-1}$	0.028	0.017	1.711	0.087
$S_{j-2}istates_{j-1}$	0.043	0.035	1.227	0.220
$S_{j-2}A_{j-1}$	0.008	0.018	0.459	0.646
$S_{j-2}iacts_{j-1}$	-0.012	0.034	-0.359	0.719
$istates_{j-2}istates_{j-1}$	0.004	0.062	0.062	0.951
$istates_{j-2}A_{j-1}$	-0.039	0.030	-1.289	0.198
$istates_{j-2}iacts_{j-1}$	-0.106	0.062	-1.729	0.084
$A_{j-2}S_{j-1}$	0.033	0.018	1.792	0.073
$A_{j-2}istates_{j-1}$	0.053	0.037	1.438	0.151
$A_{j-2}A_{j-1}$	-0.015	0.019	-0.772	0.440
$A_{j-2}iacts_{j-1}$	0.026	0.035	0.740	0.459
$A_{j-2}S_{j-2}$	-0.010	0.015	-0.637	0.524

Table 5.3: Linear regression model for $|S_j|$ when $S_j \neq 0$

We also included all the main effects, pairwise interaction and quadratic terms (based on the best model selection) up to lag 4. We have explained earlier that the first 4 time points are the burn in period. Henderson et al. (2009) argued that all of these terms may always not be needed but since there is no interest in the model for S_j per se, therefore there is no harm in overfitting the model.

Tables 5.2 and 5.3 show that only S_{j-1}^2 and $iacts_{j-1}istates_{j-1}$ are statistically significant at the 5% level for logistic regression while the coefficients S_{j-1}, A_{j-1}, $iacts_{j-3}$, S_{j-1}^2, $S_{j-1}S_{j-1}^2$, $S_{j-1}A_{j-1}$ and $A_{j-1}S_{j-1}^2$ are found significant for the linear model. In this work we are going to use a simplified state model where we remove the nonsignificant terms.

	Coefficient	SE	*Z*	*p-value*
Intercept	0.294	0.119	2.467	0.014
$istates_{j-1}$	-0.325	0.163	-1.991	0.047
$iacts_{j-1}$	-0.492	0.108	-4.566	0.000
S_{j-1}^2	-0.125	0.036	-3.498	0.000
$istates_{j-1}iacts_{j-1}$	0.818	0.166	4.930	0.000

Table 5.4: Logistic regression model for S_j when $P(S_j = 0)$

	Coefficient	SE	*Z*	*p-value*
Intercept	1.494	0.025	59.160	0.000
S_{j-1}	0.093	0.038	2.461	0.014
A_{j-1}	0.057	0.024	2.356	0.019
$iacts_{j-3}$	-0.063	0.028	-2.271	0.023
S_{j-1}^2	0.044	0.010	4.321	0.000
$S_{j-1}A_{j-1}$	0.036	0.014	2.600	0.009
$S_{j-1}S_{j-1}^2$	-0.024	0.011	-2.210	0.027
$A_{j-1}S_{j-1}^2$	-0.012	0.010	-1.212	0.226

Table 5.5: Linear regression model for $|S_j|$ when $S_j \neq 0$

Tables 5.4 and 5.5 present the results of fitting the simplified models, using backward selection. From Table 5.4 it seems that whether that state is likely to be in range is affected by whether the previous state was in range and whether the previous action was no change in dose. If these are both true then there is a high probability of being in range, but if only one is true there is a low probability. If the previous state was a long way from range then (from the quadratic term) there is reduced probability of being in range.

Table 5.5 show an estimates and variables included in the linear regression for the state of the patient when INR not in range. As expected, the previous state, S_{j-1} was significant. We can see that $|S_j|$ tends to be larger if $|S_{j-1}|$ is large, especially if the previous action was non-zero. We also found that the previous actions, A_{j-1} and as far as third visits earlier, $iacts_{j-3}$ were significant too. The effect of actions at lag 3 is negative, suggesting that the previous decision of changing dose need to be the opposite direction. However, we left it in the model for completeness.

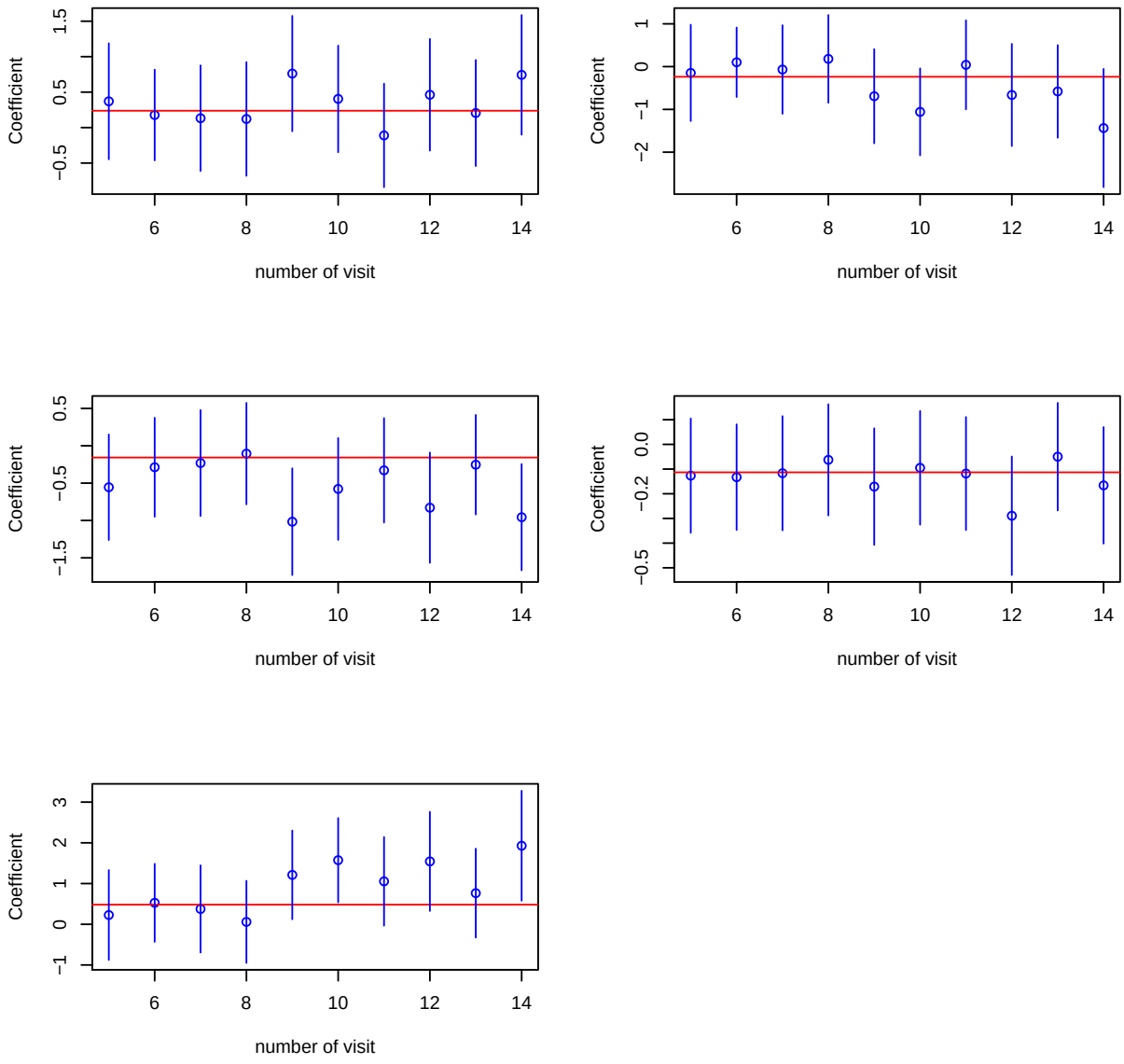

Figure 5.4: Results of fitting logistic model to each time point separately. The points mark the estimates and the vertical lines ± 2 standard errors. The red line represents the combined estimate.

In obtaining Tables 5.4 and 5.5, the pooled data over visits were used, following (Henderson et al., 2009). In Figures 5.4 and 5.5 we re-fit the model, one visit at a time, to see if there are major differences between visits. We see that overall estimates are generally within the individual confidence intervals and hence we are content with a common model.

Table 5.6 shows the new estimates and Figure 5.6 the new regret functions. The estimates and regrets are quite close to the previous state model, except for an increase in standard error. We conclude that we can choose this simplified state model for future analysis.

S_j^*	ψ_{s1}	ψ_{s2}	ψ_{s3}	SE(ψ_{s1})	SE(ψ_{s2})	SE(ψ_{s3})
-2	-0.4498	1.6734	-0.0852	0.2436	0.4142	0.5221
-1	-0.4467	2.5477	-1.0053	0.1416	0.5116	0.5046
0	-0.2621	0.1831	0.3177	0.2482	0.4579	0.5533
1	-2.5079	-1.7253	-0.6259	0.3554	0.3208	0.3705
2	-3.4457	-1.7340	0.2643	0.4802	0.3216	0.2639

Table 5.6: Parameter estimates and bootstrap standard errors for new model

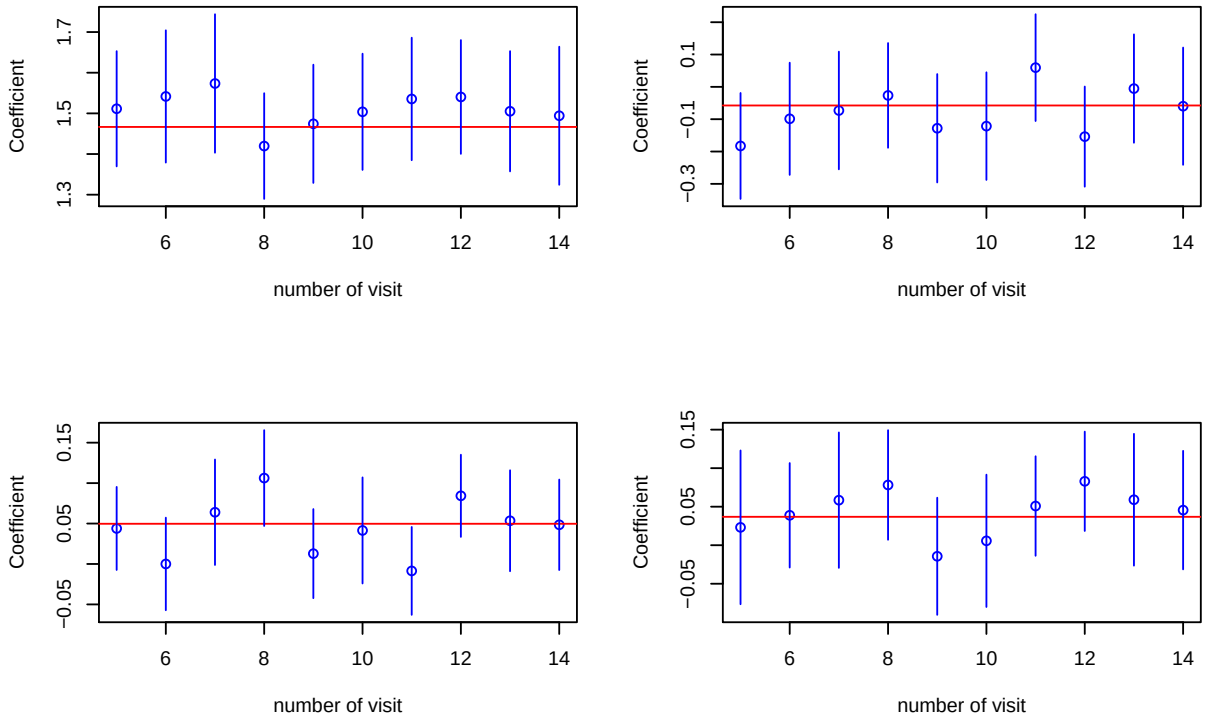

Figure 5.5: Results of fitting linear regression model to each time point separately. The points mark the estimates and the vertical lines ± 2 standard errors. The red line represents the combined estimate.

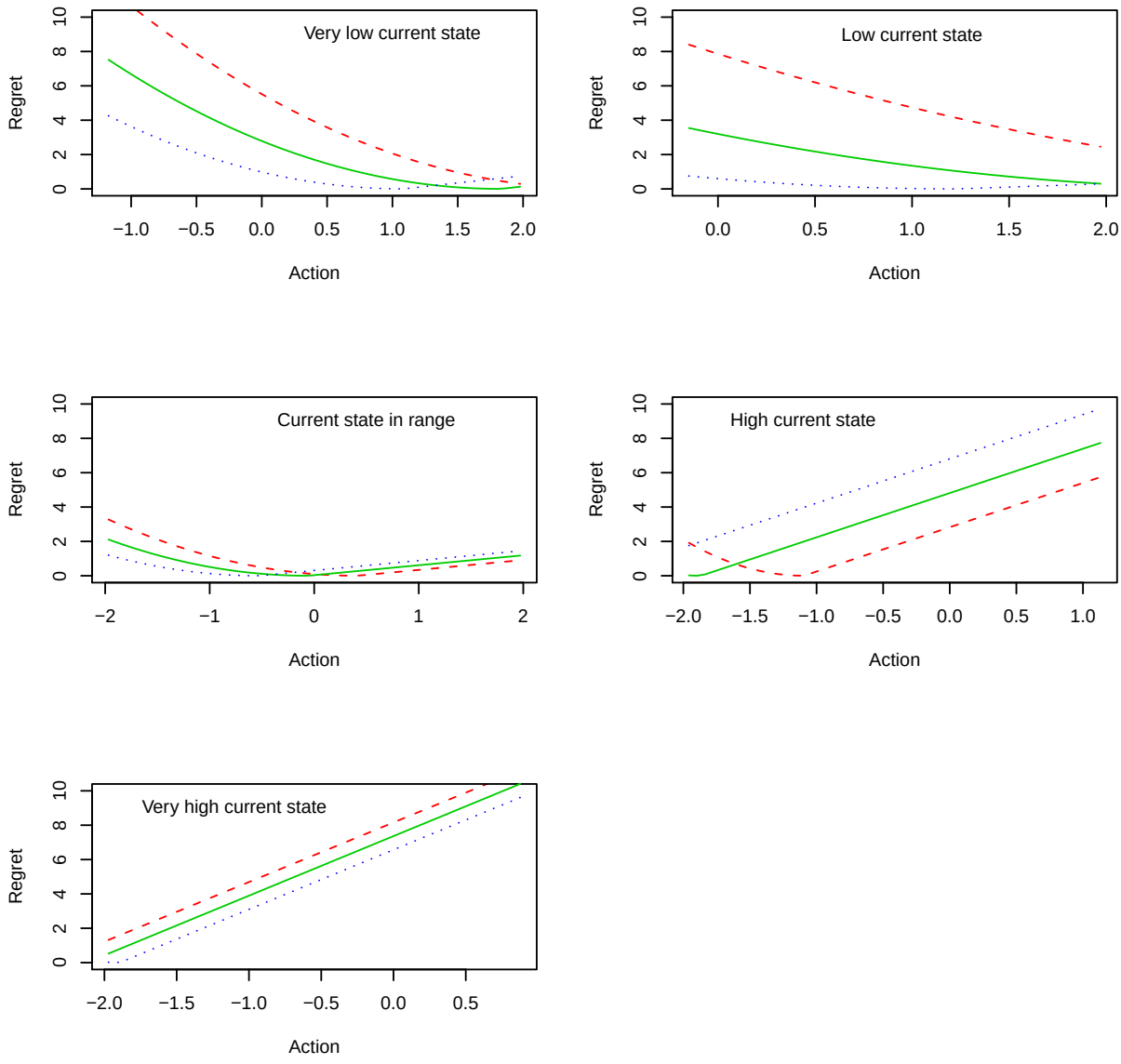

Figure 5.6: The estimated regrets function for categorised state, $S_j^* = s$. The three lines in each subplot indicate whether the previous state was in range (solid green line), above the range (dotted blue line) and below the range (dashed red line), the grey line represents the new model.

5.4 Conclusions

The regret-regression method has provided consistent estimates and is high in efficiency in the simulation and also found suitable to apply to the anticoagulant data. In this chapter we have introduced a simplified state model and we found the estimates and the regrets are quite close to the previous state model with slightly higher standard errors. Due to not much difference in performance from the previous state model, we decided to use the simplified state model for future analysis. We have not investigated the wild bootstrap diagnostic tests in this chapter but will discussed it in the following chapter.

Chapter 6

Regret-Regression with Myopic Decision Rules: Application in Anticoagulation.

Henderson et al. (2009) and Rosthøj et al. (2006) described analyses of data on the use of Warfarin for patients on long term anticoagulation. In this Warfarin data, there are 303 patients with 14 clinic visits each. At each visit, the blood clotting time using the International Normalised Ratio (INR) is taken. If the INR is too high, there is a risk of severe bleeding whilst if the INR is too low, the patients will suffer from thrombosis. Therefore, it is important to carefully adjust the dose to ensure that the INR stays within the prescribed target range.

In the analysis of Chapter 5 the state variable was either the standardised INR S_j, or a discretised version S_j^*, with five categories: very low, low, in range, high or very high. The action A_j is the change in Warfarin dose (mg), at visit j. The first four visits were considered as stabilisation period and since there is no information after the final visit, only $K = 9$ was considered. Therefore, the data for 303 patients consisted of states $S_1, S_2, \ldots, S_9$ and actions $A_1, A_2, \ldots, A_9$.

In Chapter 5 the overall percentage time in range was used as an target measure for controlling the INR. To calculate the overall PTR a linear interpolation was used between measured INR values, and the proportion of time the interpolated INR was in range was taken to be the overall PTR, which was considered to be the response Y to be maximised.

6.1 Myopic Decision Rules using the Regret-Regression Approach

A regret-regression approach can be used to estimate myopic decision rules. This can be fulfilled by taking as response a value, Y_j which is measured at the end of the jth interval, for $j = 1, 2, \ldots, K$ where $K = 9$ for our application. Each interval is then treated

individually without considering future measurements. In general, we fit the model at the end-of-interval response,Y_j not the end-of study response Y.

We will investigate this approach using regret-regression. Each S_j is regressed on history $(\bar{S}_j, \bar{A}_{j-1})$ as before and each $Z_j = S_j - E[S_j|\bar{S}_{j-1}, \bar{A}_{j-1}]$ is calculated. The state residuals Z_j were obtained from a mixture model for S_j. This mixture model was divided into two parts: logistic for $P(S_j = 0)$(INR in range) and linear when $(S_j \neq 0)$, as described in Chapter 5.

For long-term strategy, we estimated parameter vectors β and ψ for the effects of residuals and regrets respectively, by minimising the sum of squares

$$\sum_{i=1}^{n} \left\{ Y - \beta_0(S_{1,i}) - \sum_{j=2}^{K} \beta_j^T(\bar{S}_{j-1,i}, \bar{A}_{j-1,i}) Z_{j,i} - \sum_{j=1}^{K} \mu_j(A_{j,i}|\bar{S}_{j,i}, \bar{A}_{j-1,i}; \psi) \right\}^2 \quad (6.1)$$

For the myopic strategy, the proposed sum of squares is now given by

$$\sum_{i=1}^{n} \sum_{j=1}^{K} \left\{ Y_j - \beta_j^T(\bar{S}_{j,i}, \bar{A}_{j,i}) Z_{j+1,i} - \mu_j(A_{j,i}|\bar{S}_{j,i}, \bar{A}_{j-1,i}; \psi) \right\}^2. \quad (6.2)$$

Where Y_j is now the proportion of time between visit j and $j+1$ over which the interpolated INR is in range. A bootstrap standard error can be obtained from the bootstrap samples and we can examine the residuals between the observed and fitted values for diagnostic assessment, as previously.

6.2 Comparison between Long-Term and Myopic Decision Rules to Optimise the PTR Response with Application to Warfarin Data

PTR response	S_j^*	ψ_{s1}	ψ_{s2}	ψ_{s3}	SE(ψ_{s1})	SE(ψ_{s2})	SE(ψ_{s3})
Long-term, Y	-2	-0.4498	1.6734	-0.0852	0.2436	0.4142	0.5221
	-1	-0.4467	2.5477	-1.0053	0.1416	0.5116	0.5046
	0	-0.2621	0.1831	0.3177	0.2482	0.4579	0.5533
	1	-2.5079	-1.7253	-0.6259	0.3554	0.3208	0.3705
	2	-3.4457	-1.7340	0.2643	0.4802	0.3216	0.2639
Myopic-term, Y_j	-2	-0.8677	1.8034	-0.1056	0.2136	0.3631	0.3526
	-1	-0.3921	2.2565	-0.2116	0.1825	0.3835	0.2647
	0	-0.2503	-0.0123	-0.1969	0.1874	0.2930	0.3009
	1	-2.4391	-1.4150	-0.1851	0.3994	0.2287	0.2553
	2	-3.1987	-1.5248	-0.1538	0.3855	0.1545	0.1368

Table 6.1: Parameter estimates and bootstrap standard errors for long-term and myopic PTR response

Results are presented in Tables 6.1 for the overall response and the myopic response using the regret functions in Section 5.2 and 1000 bootstrap samples for standard errors. The estimates are generally very similar, except perhaps for $\hat{\psi}_{s3}$, though these are all within noise of zero.

Figure 6.1 compares the estimated regret functions between these two responses at a variety of combinations of current and previous state. This plot shows that there is little difference in regrets for both strategies except at the very high current state where the long-term strategy is slightly higher than the myopic strategy. We can conclude that the general patterns in this plot suggest that if the current state is low (clotting time is quick) then we need to increase the dose and if the current state is high or at the very high level, then a decrease is suggested for both of the strategies.

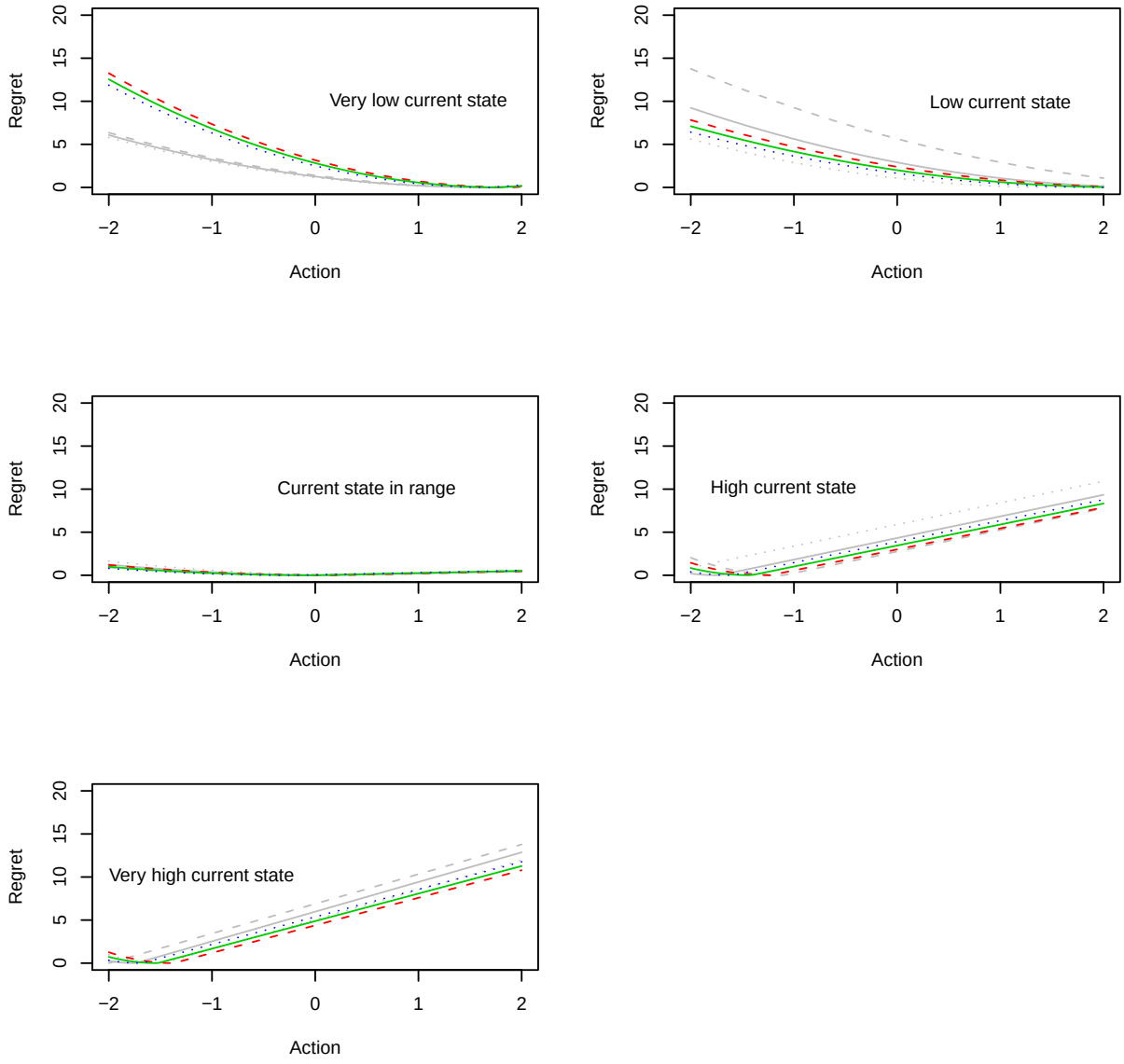

Figure 6.1: Comparison of the estimated regret functions for categorised states S_j^* between long-term response Y and myopic response Y_j. The three coloured lines in each subplot indicates whether the previous state was in range (solid green line), above the range (dotted blue line) and below the range (dashed red line) when the myopic response Y_j is used. The grey lines, with the same styles, show regrets when the overall response Y is used.

6.3 Number of Visits with INR In Range

In this section we investigate a new response Y^* which is the percentage or proportion of visits for which INR is in range. This new response Y^* has only two possible values, zero and one at each visit. The value one indicates that INR is in range ($S_j = 0$) while value zero indicates that INR is not in range ($S_j \neq 0$). The new response Y_j^* thus is given by

$$Y_j^* = \begin{cases} 0, S_j \neq 0 & (\text{INR}_j \text{not in range}) \\ 1, S_j = 0 & (\text{INR}_j \text{in range}) \end{cases}$$

For the long term strategy, the response Y^* is sum of the Y_j^*, the overall measured INR in range scaled by 100. The regret-regression method can again be applied here to estimate myopic decision rules for the new response Y_j^*. The response Y_j^* is measured at the end of the jth interval, for $j = 1, 2, \ldots, K$ where $K = 9$.

The long-term response Y^* is termed as the long-term binary response and the myopic response Y_j^* is referred to as myopic binary response, for future analysis for easier differentiation from the PTR responses.

INR response	S_j^*	ψ_{s1}	ψ_{s2}	ψ_{s3}	SE(ψ_{s1})	SE(ψ_{s2})	SE(ψ_{s3})
Long-term, Y^*	-2	-0.5470	1.5131	-0.0288	0.1951	0.3357	0.2840
	-1	-0.9401	2.5647	-0.1900	0.2572	0.3110	0.1788
	0	-0.1793	-0.1130	0.0498	0.1712	0.3236	0.4084
	1	-2.9218	-2.1704	0.1285	0.2436	0.2506	0.2146
	2	-3.3429	-1.2335	0.3744	0.3709	0.1557	0.1787
Myopic-term, Y_j^*	-2	-0.8381	1.5276	-0.2297	0.2473	0.6998	0.4547
	-1	-0.2454	1.2605	0.0397	0.2370	0.9298	0.4014
	0	-0.3197	-0.1306	-0.1255	0.2468	0.4673	0.4791
	1	-2.2790	-1.1304	0.1081	0.5395	0.2595	0.2811
	2	-2.9447	-1.4597	-0.1410	0.4998	0.2355	0.2024

Table 6.2: Parameter estimates and bootstrap standard errors for long-term and myopic INR binary response

Table 6.2 shows the parameter estimates and standard errors obtained from 1000 bootstrap samples. We see that the parameter estimates for both strategies are quite similar.

Figure 6.2 compares the estimated regrets between long-term binary response and myopic binary response at a variety of combinations of current and previous states. As expected, we found that there is almost no difference in both strategies except at the very high current state where the long term strategy has slightly higher regret than myopic strategy.

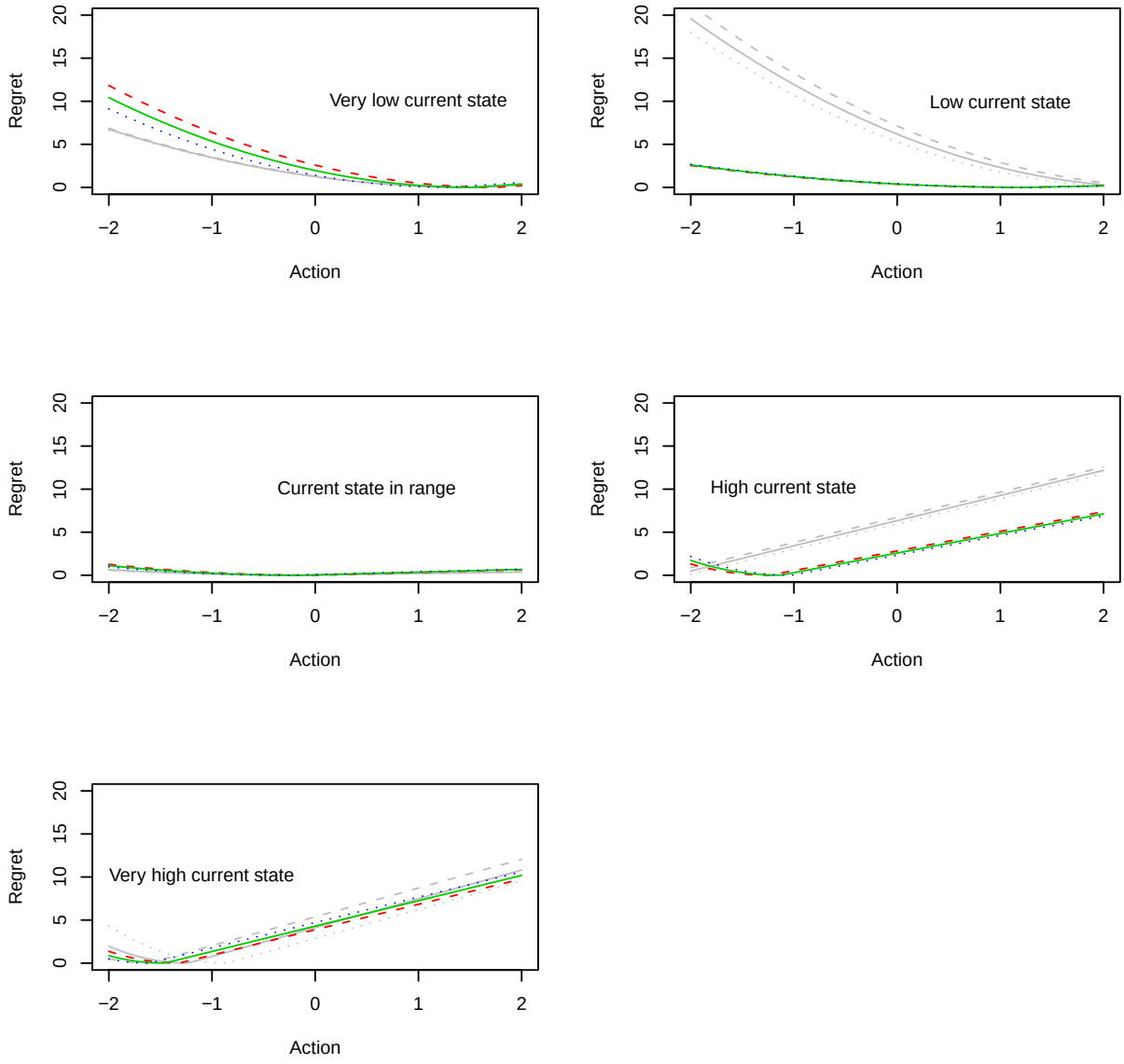

Figure 6.2: Comparison of the estimated regret functions for categorised states S_j^* between long-term response Y^* and myopic response Y_j^*. The three coloured lines in each subplot indicates whether the previous state was in range (solid green line), above the range (dotted blue line) and below the range (dashed red line) when the myopic response Y_j^* is used. The grey lines, with the same styles, show regrets when the overall response Y^* is used.

6.4 Extended Myopic Decision Rules with Two-Time Points or Two-Step Ahead

In this section we now look two steps ahead. We also make comparisons between a one-step strategy and a two steps strategy.

We estimate the the myopic decisions for two-step ahead responses using the regret-regression method of Section 6.1. The response, $Y_j^{(2)}$ is measured at the end of the jth interval, for $j = 1, 2, \ldots, K$ where $K = 8$. We will repeat the same procedures for the analysis using the PTR response $Y_j^{(2)}$ found in Section 6.2 and binary response $Y_j^{(2*)}$ which is similar to Section 6.3. These responses are defined in the obvious way, as the proportion of time INR is in range , or the proportion of visits with INR in range, between visit j and now visit $j + 2$. We define the sum of squares for the two steps method using the PTR response as

$$\sum_{i=1}^{n}\sum_{j=1}^{K}\left\{Y_j^{(2)} - \beta_j^T(\bar{S}_{j,i}, \bar{A}_{j,i})Z_{j+1,i} - \mu_j(A_{j,i}|\bar{S}_{j,i}, \bar{A}_{j-1,i}; \psi)\right\}^2 \tag{6.3}$$

and the sum of squares for the two steps method using the binary response

$$\sum_{i=1}^{n}\sum_{j=1}^{K}\left\{Y_j^{(2*)} - \beta_j^T(\bar{S}_{j,i}, \bar{A}_{j,i})Z_{j+1,i} - \mu_j(A_{j,i}|\bar{S}_{j,i}, \bar{A}_{j-1,i}; \psi)\right\}^2. \tag{6.4}$$

PTR response	S_j^*	ψ_{s1}	ψ_{s2}	ψ_{s3}	SE(ψ_{s1})	SE(ψ_{s2})	SE(ψ_{s3})
Long-term, Y	-2	-0.4498	1.6734	-0.0852	0.2436	0.4142	0.5221
	-1	-0.4467	2.5477	-1.0053	0.1416	0.5116	0.5046
	0	-0.2621	0.1831	0.3177	0.2482	0.4579	0.5533
	1	-2.5079	-1.7253	-0.6259	0.3554	0.3208	0.3705
	2	-3.4457	-1.7340	0.2643	0.4802	0.3216	0.2639
One Step, Y_j	-2	-0.8677	1.8034	-0.1056	0.2136	0.3631	0.3526
	-1	-0.3921	2.2565	-0.2116	0.1825	0.3835	0.2647
	0	-0.2503	-0.0123	-0.1969	0.1874	0.2930	0.3009
	1	-2.4391	-1.4150	-0.1851	0.3994	0.2287	0.2553
	2	-3.1987	-1.5248	-0.1538	0.3855	0.1545	0.1368
Two Steps, $Y_j^{(2)}$	-2	-1.0601	1.8507	-0.1916	0.5787	0.6350	0.3776
	-1	-0.2454	2.1413	-0.0555	0.1565	0.8653	0.6984
	0	-0.4299	-0.1358	0.0050	0.4812	0.7356	0.7813
	1	-2.3144	-1.3927	-0.2272	0.8028	0.4703	0.2518
	2	-2.5635	-1.8319	-0.3547	0.5132	0.2123	0.1723

Table 6.3: Parameter estimates and bootstrap standard errors for PTR response.

Table 6.3 gives the parameter estimates and bootstrap standard errors obtained from 1000 resamples for the Warfarin data. We see the parameter estimates are little different from the one step strategy and long term strategy but with larger bootstrap standard errors.

Figure 6.3 gives a comparison between the estimated regrets for long-term PTR response $Y^{(2)}$ and two steps method PTR response $Y_j^{(2)}$. At the very low current state and low dosage, the estimated regrets for two-steps ahead is slightly higher than the long term strategy. In general there are little differences between the regret functions.

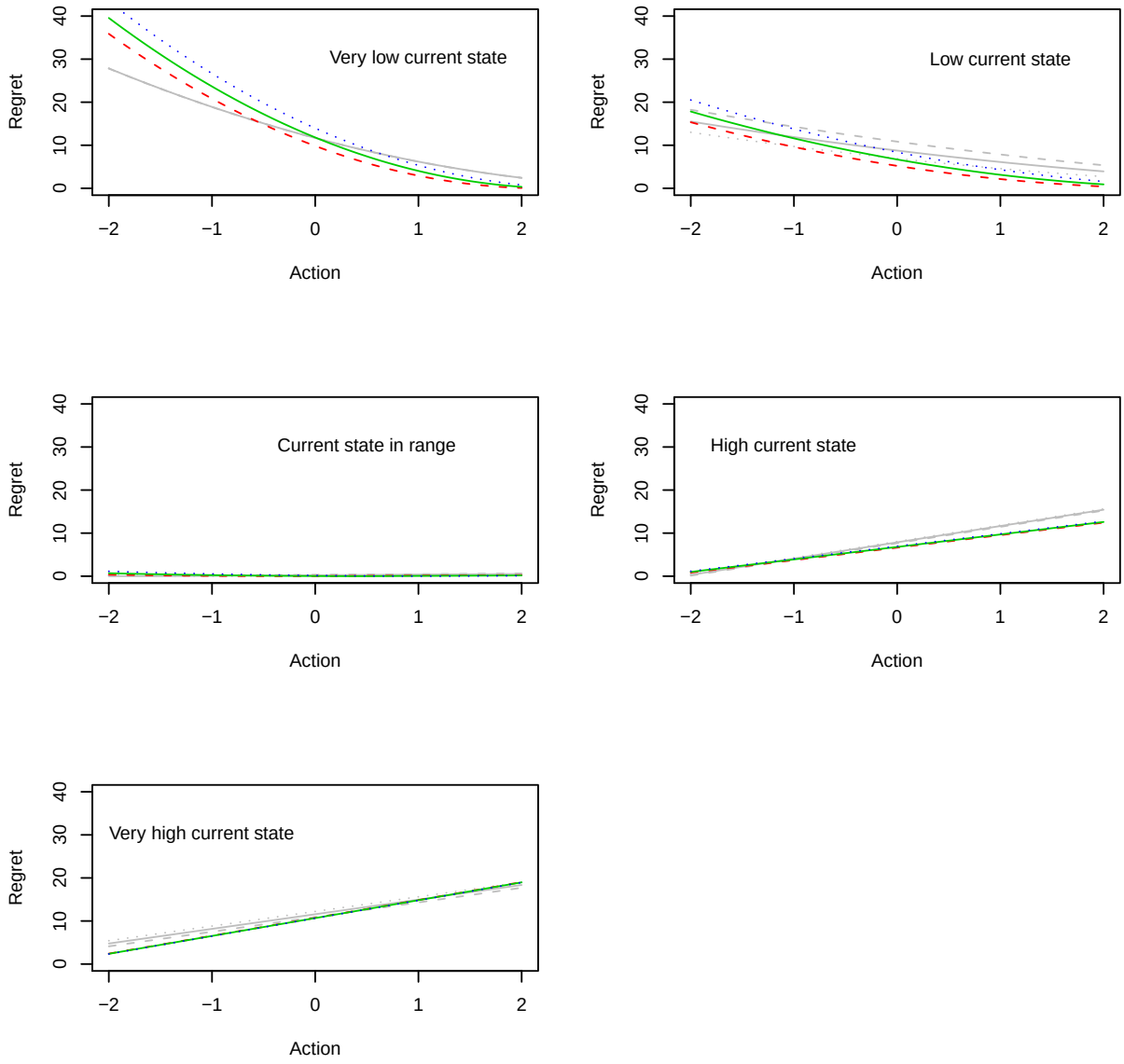

Figure 6.3: Comparison of the estimated regret functions for categorised states S_j^* between long-term response $Y^{(2)}$ and two steps method response $Y_j^{(2)}$. The three coloured lines in each subplot indicate whether the previous state was in range (solid green line), above the range (dotted blue line) and below the range (dashed red line) when the two steps method response $Y_j^{(2)}$ is used. The grey lines, with the same styles, show regrets when the overall response $Y^{(2)}$ is used.

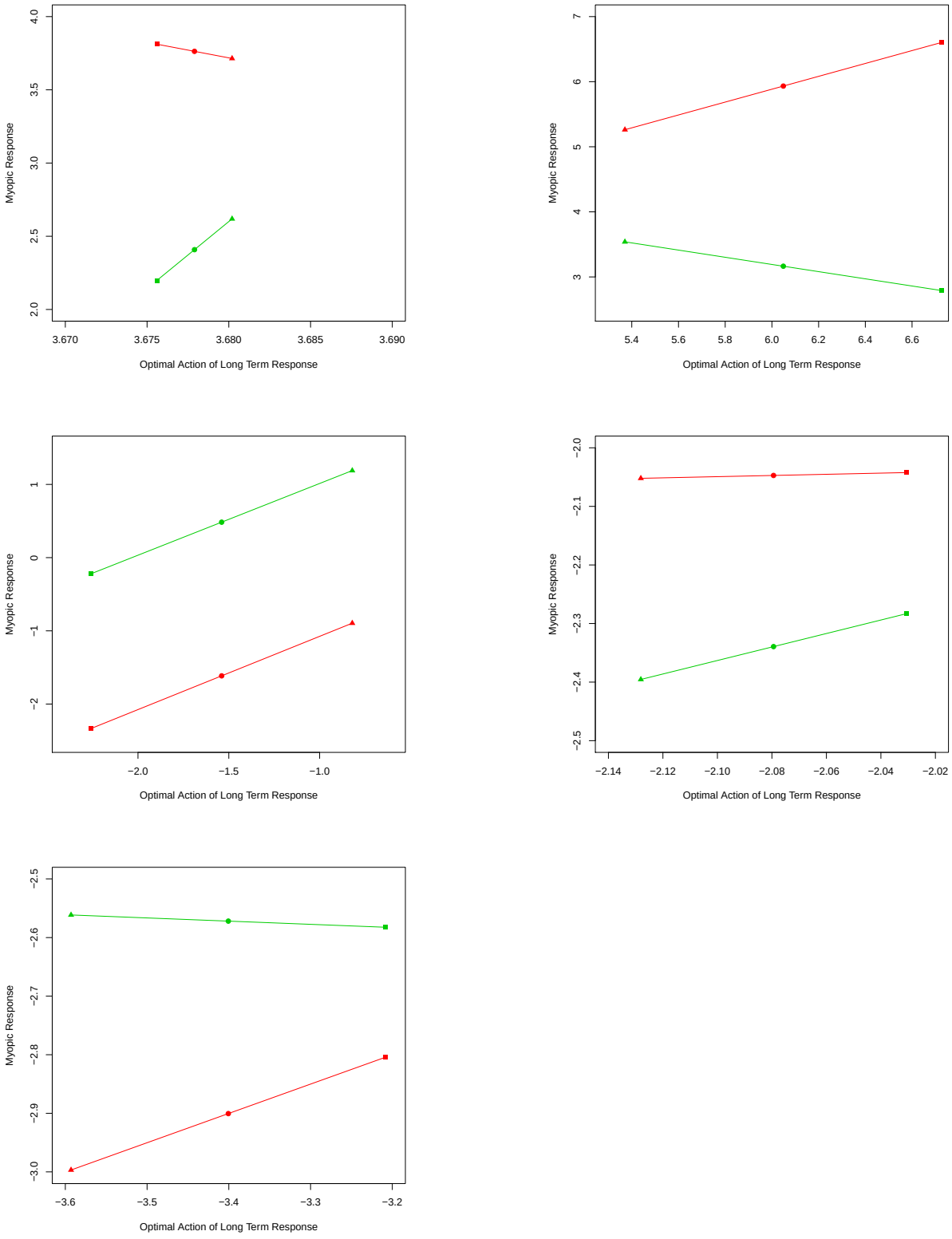

Figure 6.4: Optimal actions under long-term PTR response against optimal actions for myopic decisions.

Figure 6.4 shows the relationships between the optimal actions with long-term PTR response and the optimal actions using myopic one step strategy (red line) and two-step strategy (green line). The symbol ■ indicates low previous state, • indicates normal previous state and ▲ indicates high previous state.The first subplot represents very low previous state, then the remaining plots are low, in range, high and very high previous states.

We found that there is a positive relationship between one step and long term strategies except at the very low previous state. A positive relationship also occurs between two step and the long term strategy except for low and very high previous state, where there is a slight negative relationship among them.

INR response	S_j^*	ψ_{s1}	ψ_{s2}	ψ_{s3}	SE(ψ_{s1})	SE(ψ_{s2})	SE(ψ_{s3})
Long-term, Y^*	-2	-0.5470	1.5131	-0.0288	0.1951	0.3357	0.2840
	-1	-0.9401	2.5647	-0.1900	0.2572	0.3110	0.1788
	0	-0.1793	-0.1130	0.0498	0.1712	0.3236	0.4084
	1	-2.9218	-2.1704	0.1285	0.2436	0.2506	0.2146
	2	-3.3429	-1.2335	0.3744	0.3709	0.1557	0.1787
Myopic-term, Y_j^*	-2	-0.8381	1.5276	-0.2297	0.2473	0.6998	0.4547
	-1	-0.2454	1.2605	0.0397	0.2370	0.9298	0.4014
	0	-0.3197	-0.1306	-0.1255	0.2468	0.4673	0.4791
	1	-2.2790	-1.1304	0.1081	0.5395	0.2595	0.2811
	2	-2.9447	-1.4597	-0.1410	0.4998	0.2355	0.2024
Two steps, $Y_j^{(2*)}$	-2	-0.6894	1.2212	-0.7128	0.4821	0.9212	0.9168
	-1	0.0113	1.3439	0.1414	0.2020	1.2999	1.3355
	0	-0.5062	-0.3932	-0.2807	0.5915	0.9050	0.7686
	1	-1.7245	-1.1495	-0.0251	0.9379	0.5211	0.3293
	2	-1.4819	-1.8438	-0.5468	0.3968	0.3481	0.3617

Table 6.4: Parameter estimates and bootstrap standard errors for INR binary response.

Turning now to the binary/count response $Y_j^{(2*)}$ Table 6.4 gives the parameter estimates and bootstrap error for 1000 resamples. This is to be compared with the corresponding table for long-term and one step binary responses. Figure 6.5 shows the corresponding regret functions and Figure 6.6 compares optimal actions. Coefficients are often, not always, attenuated towards zero, and standard errors are generally high. Overall however there is little difference in the fitted regret functions whether we look at one step, two steps or to the end of the study.

This is similarity to the PTR results for the relationship of the optimal actions where we found a positive relationship between one step and long term except at the very low previous state. However there is a slight difference from the two step method as a negative relationship occurs at the very low, low and very high previous states.

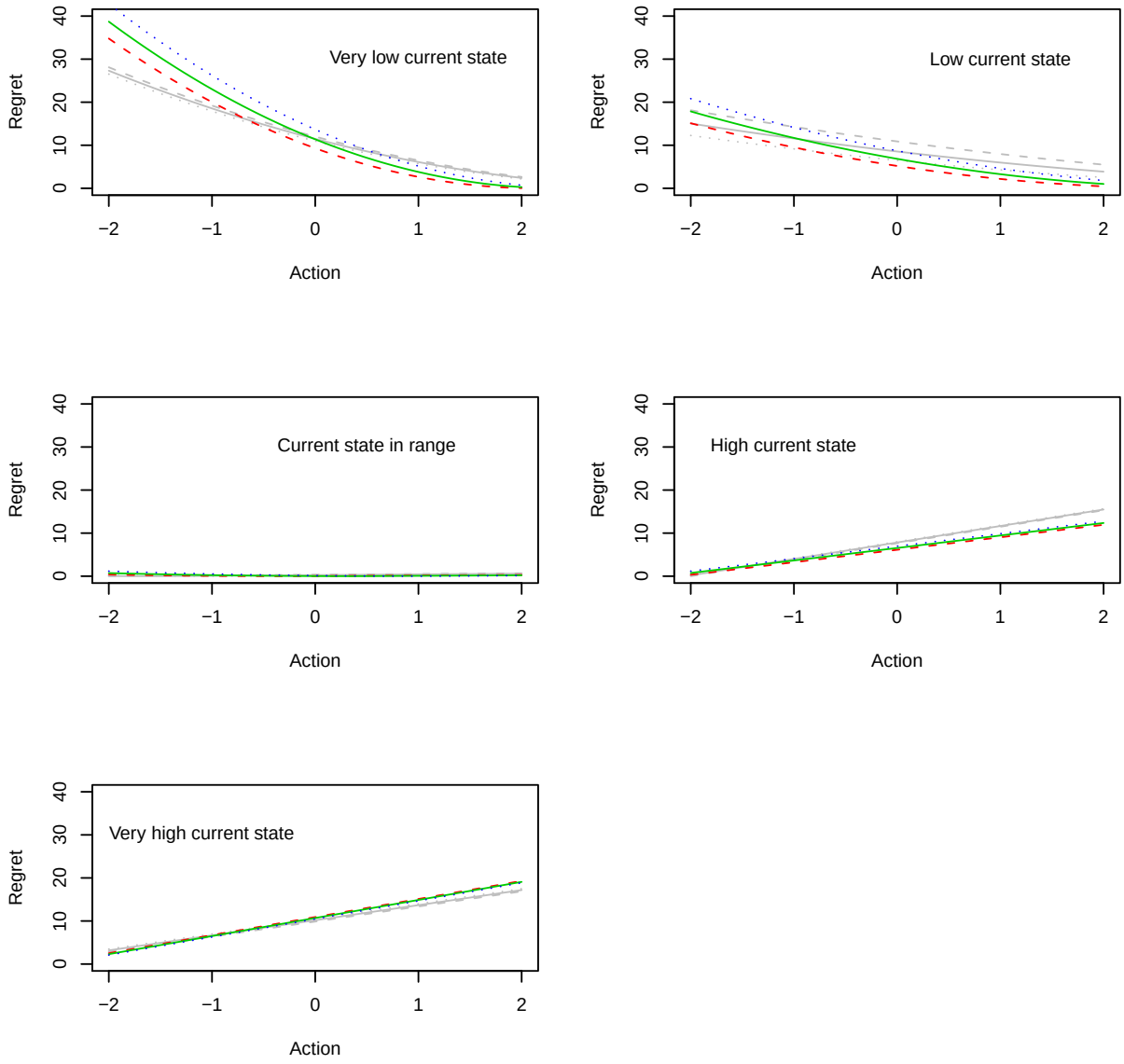

Figure 6.5: Comparison of the estimated regret functions for categorised states S_j^* between long-term response $Y^{(2*)}$ and two steps method response $Y_j^{(2*)}$. The three coloured lines in each subplot indicate whether the previous state was in range (solid green line), above the range (dotted blue line) and below the range (dashed red line) when the two steps method response $Y_j^{(2*)}$ is used. The grey lines, with the same styles, show regrets when the overall response $Y^{(2*)}$ is used.

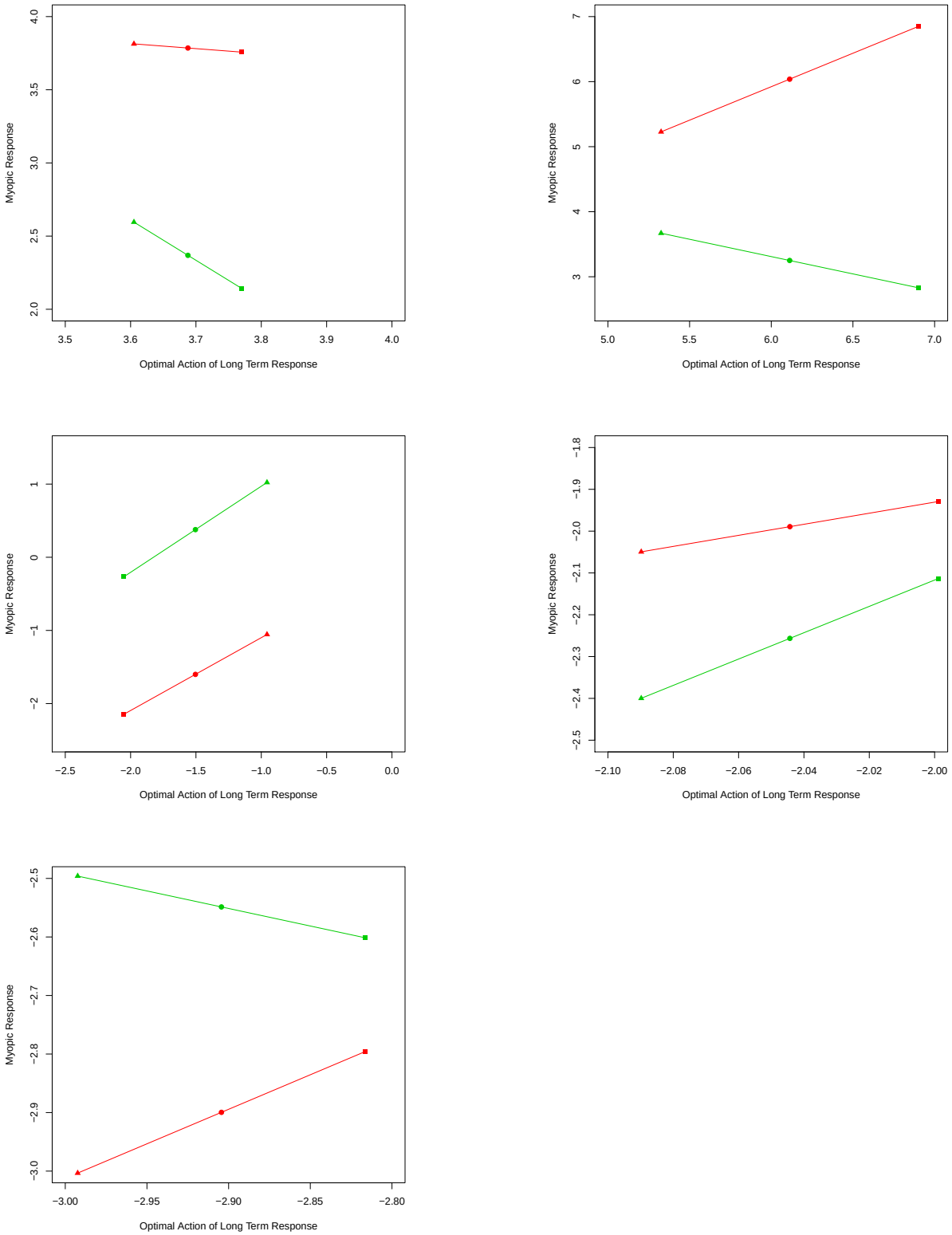

Figure 6.6: The optimal actions for the long-term percentage binary response against optimal actions for myopic decisions.

6.5 Diagnostic Test

We compare residuals between observed and fitted values using the long term strategy and both one step and two steps strategies, and also for both PTR continuous responses and binary in/out range responses.

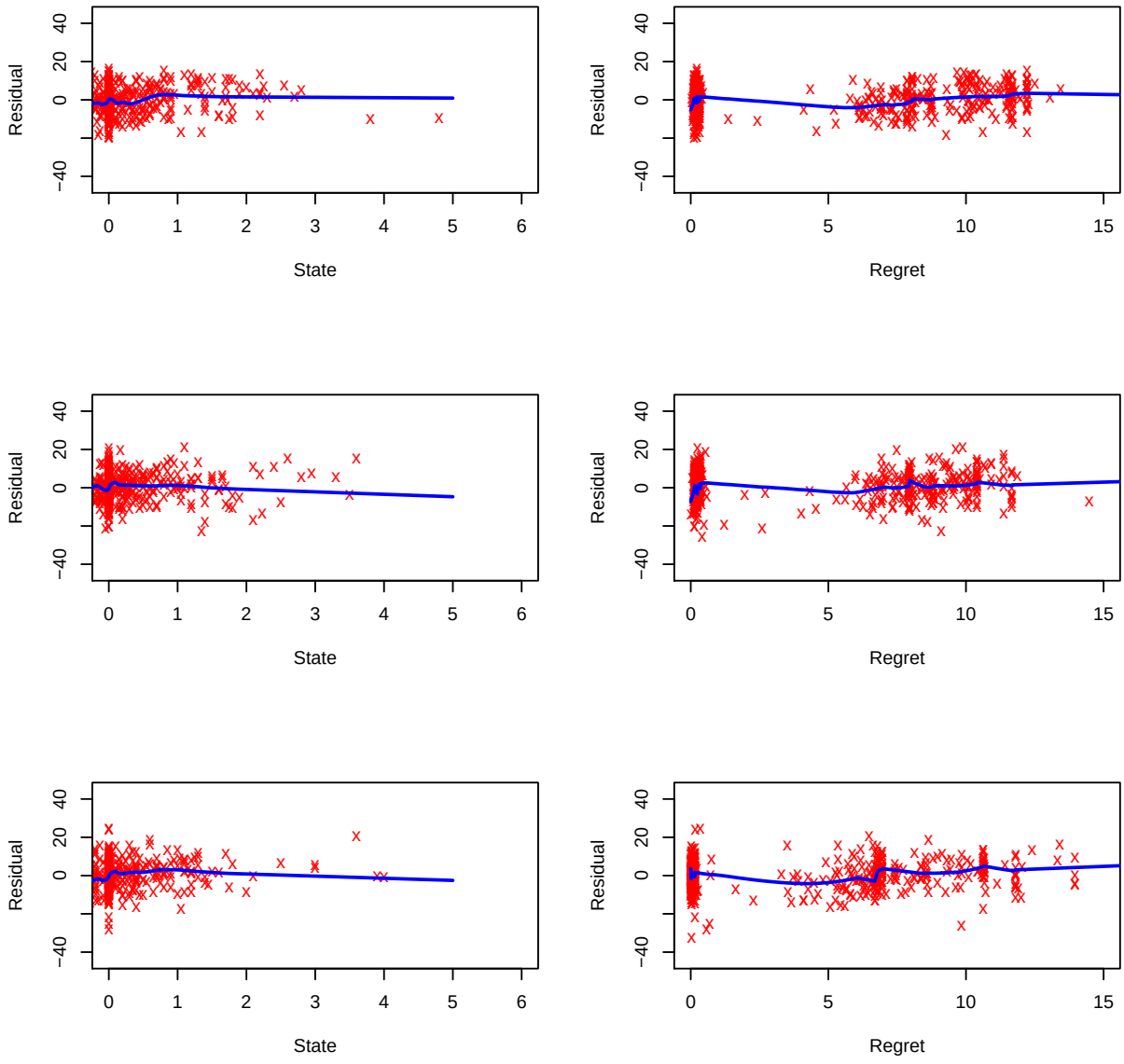

Figure 6.7: Residual plots for Warfarin data. The left plots compare residuals with the state and the right plots with the fitted regret values. The top row is based on the long-term PTR response Y, the second row is based on the one-step PTR response Y_j and the bottom row on the two-steps ahead PTR response $Y_j^{(2)}$.

Figure 6.7 shows the residuals against fitted regret and states for the Warfarin data for all three methods, with the PTR response. Generally, all the plots show an adequate fitted model with random scatter. The blue lines shows smoothers throughout the data. We use the Friedman's SuperSmoother, the nonparametric smoothing which can be obtained from the built-in function, *supsmu* in R. In all cases, there is no obvious trend in all the

plots.

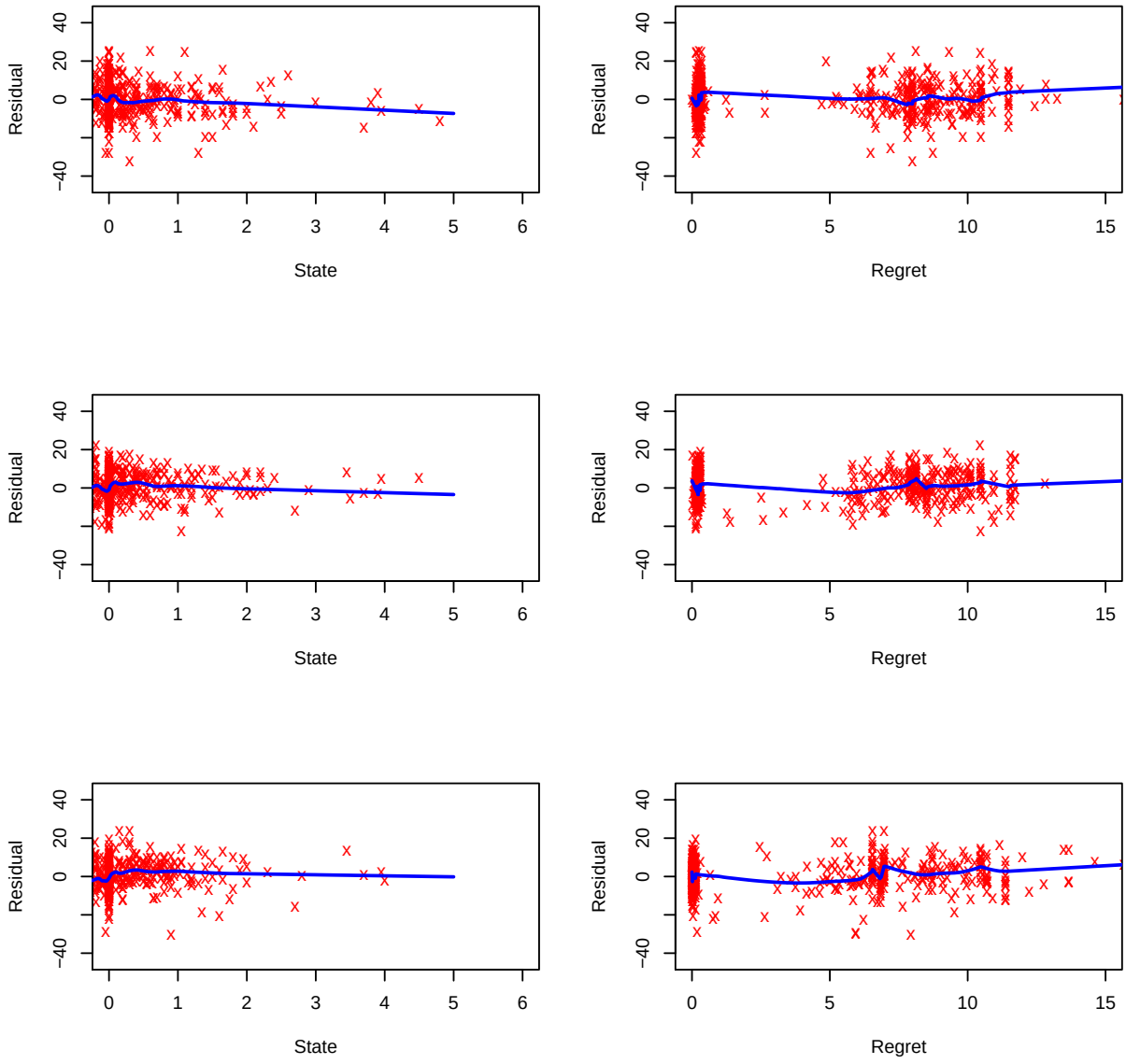

Figure 6.8: Residual plot for Warfarin data. The left plots compare residuals with the state and the right plots with the fitted regret values. The top row is based on the long-term binary response Y^*, the second row is based on the one-step binary response Y_j^* and the bottom row on the two-steps ahead binary response $Y_j^{(2*)}$.

Figure 6.8 provides similar plots for the binary response. Again the smooth trends, shown as blue lines, are almost flat, suggesting no systematic departure from assumptions and no real differences between choice of response. There is some evidence that residuals tend to be negative at very low regret values.

6.6 Wild bootstrap Tests

We follow the wild bootstrap tests procedure as described to Section 4.4.3 in Chapter 4. We will run the tests for both the PTR and the binary INR responses at time points $1, 5$ and 8 using either $Z \sim N(0, 1)$ or $U\{-1, 1\}$ as multiplier.

6.6.1 Wild bootstrap Tests for PTR Response

Table 6.5: Estimated p-value for wild bootstrap tests at first time point

		Tests				
		Test 1	Test 2	Test 3	Test 4	Test 5
Long-term, Y						
Z(0,1)	State	0.000	0.030	0.000	0.035	0.000
	Regrets	0.000	0.655	0.205	0.725	0.000
U{-1,1}	States	0.000	0.010	0.025	0.015	0.000
	Regrets	0.000	0.650	0.260	0.765	0.000
Myopic-term, Y_j						
Z(0,1)	State	0.110	0.065	0.000	0.065	0.010
	Regrets	0.030	0.155	0.195	0.560	0.005
U{-1,1}	States	0.175	0.055	0.005	0.170	0.030
	Regrets	0.030	0.175	0.230	0.555	0.000
Two steps, $Y_j^{(2)}$						
Z(0,1)	State	0.695	0.720	0.495	0.340	0.215
	Regrets	0.230	0.665	0.560	0.425	0.265
U{-1,1}	States	0.730	0.665	0.415	0.365	0.270
	Regrets	0.210	0.770	0.580	0.365	0.320

Table 6.6: Estimated p-value for wild bootstrap tests at fifth time point

		Tests				
		Test 1	Test 2	Test 3	Test 4	Test 5
Long-term, Y						
Z(0,1)	State	0.000	0.000	0.195	0.020	0.000
	Regrets	0.000	0.125	0.000	0.035	0.000
U{-1,1}	States	0.000	0.000	0.120	0.025	0.000
	Regrets	0.000	0.125	0.000	0.010	0.000

Continued on next page

		Tests				
		Test 1	Test 2	Test 3	Test 4	Test 5
Myopic-term, Y_j						
Z(0,1)	State	0.010	0.000	0.005	0.225	0.000
	Regrets	0.010	0.000	0.005	0.225	0.000
U{-1,1}	States	0.010	0.000	0.010	0.240	0.005
	Regrets	0.000	0.035	0.690	0.020	0.000
Two steps, $Y_j^{(2)}$						
Z(0,1)	State	0.015	0.000	0.005	0.000	0.000
	Regrets	0.000	0.045	0.040	0.105	0.000
U{-1,1}	States	0.010	0.000	0.000	0.000	0.000
	Regrets	0.000	0.075	0.025	0.150	0.000

Table 6.7: Estimated p-value for wild bootstrap tests at eighth time point

		Tests				
		Test 1	Test 2	Test 3	Test 4	Test 5
Long-term, Y						
Z(0,1)	State	0.000	0.000	0.065	0.000	0.000
	Regrets	0.000	0.135	0.000	0.135	0.000
U{-1,1}	States	0.000	0.000	0.060	0.000	0.000
	Regrets	0.000	0.105	0.005	0.080	0.000
Myopic-term, Y_j						
Z(0,1)	State	0.000	0.000	0.015	0.000	0.000
	Regrets	0.000	0.605	0.950	0.0950	0.000
U{-1,1}	States	0.000	0.000	0.040	0.000	0.000
	Regrets	0.000	0.555	0.970	0.110	0.000
Two steps, $Y_j^{(2)}$						
Z(0,1)	State	0.100	0.000	0.000	0.035	0.000
	Regrets	0.000	0.055	0.250	0.200	0.000
U{-1,1}	States	0.125	0.000	0.000	0.040	0.000
	Regrets	0.000	0.010	0.255	0.240	0.000

Tables 6.5, 6.6 and 6.7 show the proportion of rejections at time points $1, 5$ and 8 using either $Z \sim N(0,1)$ or $U\{-1,1\}$. For the first time point there are significant departures

from the model assumptions when considering residuals against state for long term Y, and some evidence against regrets (Tests 1 and 5). Tests 3 and 5 suggest some problems for the myopic method when residuals are plotted against states. There is no evidence of problems with the model for two step responses.

At the fifth and eighth time points most tests give significant results when residuals are plotted against either states or regrets, with occasional exceptions (notably Test 3)

6.6.2 Wild bootstrap Tests for INR Response

Table 6.8: Estimated p-value for wild bootstrap tests at first time point

		Tests				
		Test 1	Test 2	Test 3	Test 4	Test 5
Long-term, Y						
Z(0,1)	State	0.230	0.265	0.155	0.100	0.040
	Regrets	0.075	0.010	0.140	0.180	0.025
U{-1,1}	States	0.165	0.290	0.140	0.090	0.065
	Regrets	0.090	0.000	0.185	0.135	0.025
Myopic-term, Y_j						
Z(0,1)	State	0.740	0.480	0.310	0.210	0.305
	Regrets	0.350	0.850	0.730	0.105	0.195
U{-1,1}	States	0.775	0.480	0.210	0.200	0.315
	Regrets	0.320	0.850	0.625	0.070	0.240
Two steps, $Y_j^{(2)}$						
Z(0,1)	State	0.095	0.270	0.635	0.495	0.505
	Regrets	0.355	0.520	0.125	0.815	0.850
U{-1,1}	States	0.110	0.275	0.555	0.480	0.575
	Regrets	0.260	0.510	0.145	0.795	0.875

Table 6.9: Estimated p-value for wild bootstrap tests at fifth time point

		Tests				
		Test 1	Test 2	Test 3	Test 4	Test 5
Long-term, Y						
Z(0,1)	State	0.005	0.000	0.040	0.090	0.000
	Regrets	0.000	0.025	0.015	0.265	0.000
U{-1,1}	States	0.000	0.000	0.050	0.075	0.000

Continued on next page

		Tests				
		Test 1	Test 2	Test 3	Test 4	Test 5
	Regrets	0.000	0.015	0.020	0.250	0.000
Myopic-term, Y_j						
Z(0,1)	State	0.035	0.000	0.005	0.260	0.000
	Regrets	0.000	0.230	0.385	0.530	0.000
U{-1,1}	States	0.070	0.000	0.000	0.210	0.000
	Regrets	0.000	0.195	0.465	0.610	0.000
Two steps, $Y_j^{(2)}$						
Z(0,1)	State	0.095	0.000	0.000	0.170	0.000
	Regrets	0.000	0.925	0.000	0.305	0.000
U{-1,1}	States	0.040	0.000	0.005	0.130	0.000
	Regrets	0.000	0.945	0.000	0.270	0.000

Table 6.10: Estimated p-value for wild bootstrap tests at eighth time point

		Tests				
		Test 1	Test 2	Test 3	Test 4	Test 5
Long-term, Y						
Z(0,1)	State	0.000	0.000	0.015	0.000	0.000
	Regrets	0.000	0.110	0.010	0.840	0.000
U{-1,1}	States	0.000	0.000	0.035	0.000	0.000
	Regrets	0.000	0.120	0.005	0.875	0.000
Myopic-term, Y_j						
Z(0,1)	State	0.030	0.000	0.000	0.000	0.000
	Regrets	0.000	0.060	0.185	0.010	0.000
U{-1,1}	States	0.035	0.000	0.000	0.000	0.000
	Regrets	0.000	0.080	0.160	0.020	0.000
Two steps, $Y_j^{(2)}$						
Z(0,1)	State	0.065	0.000	0.000	0.545	0.000
	Regrets	0.000	0.755	0.000	0.115	0.000
U{-1,1}	States	0.045	0.000	0.000	0.645	0.000
	Regrets	0.000	0.755	0.000	0.110	0.000

Tables 6.8, 6.9 and 6.10 show p-values for the wild bootstrap tests when using the INR response. Generally at time point one the results are not significant, whereas the opposite is true for time point five and eight. Tests 2 and 4 seems to fail to detect departures more often than the others.

Overall we found that the myopic two-steps ahead shown no evidence of problem in both PTR and INR responses and there is slight evidence of problem for the long term and myopic one-step. At time point one, we can see that almost all the results are non-significant which indicates that there is no evidence of problem for all the methods either in state or regrets for both responses.

In considering all these results we bear in mind the large sample size, and the fact that a significant result is not necessary an important one. From the previous residual plots, it seems that any trends or patterns in the residuals are quite small.

6.7 Conclusions

The regret-regression approach can be applied to myopic decision rules as well as final response. The advantage of using the myopic rules is the response Y_j is measured at the end of each interval j and there is no need to wait until the end of the study to measure Y. For myopic decision rules we have choose the one step method Y_j or two steps method $Y_j^{(2)}$ to compare with the long term response Y. We considered two different cases which are the continuous (PTR) case and the discrete/binary (INR) case.

When we compare the estimated regret between the long term response with one step or the two steps method under the PTR response, we found that there is only slight difference between these methods and similar results were found under the INR response. The residual plots show that there is almost no trend or obvious pattern occur for all responses although many of the wild bootstrap tests are significant, especially at fifth and eighth time points. Although there is not much difference between the long-term and the myopic in both responses, we prefer the myopic decision rules because the decision is much quicker and more practical in application than the long-term response, Y.

Chapter 7

Generalised Estimating Equations for Myopic Regret-Regression

7.1 Introduction to Generalised Estimating Equations in Longitudinal Data Analysis

Linear regression is an approach to obtain the relationship between a dependent variable Y and explanatory variables x_i. We can collect all responses into a vector Y and all covariates in a design matrix X. If we assume $E[Y] = X\beta$ then we can use the ordinary least squares method (OLS) to estimate β by minimising

$$SS(\beta) = (Y - X\beta)^T(Y - X\beta). \tag{7.1}$$

Minimising the Equation (7.1) is equivalent to solving $U(\hat{\beta}) = 0$ where $U(\beta)$ is the score function

$$U(\beta) = X^T(Y - X\beta).$$

If the distribution of Y is normal with var$(Y) = \sigma^2 I_n$ then the OLS method is equivalent to maximum likelihood. Furthermore, if we have $Y \sim N(X\beta, \Sigma)$, maximum likelihood is equivalent to minimising the weighted sum of squares, WSS(β), to find $\hat{\beta}$ where

$$\text{WSS}(\beta) = (Y - X\beta)^T\Sigma^{-1}(Y - X\beta).$$

Equivalently, $\hat{\beta}$ solves

$$X^T\Sigma^{-1}(Y - X\hat{\beta}) = 0.$$

The Generalised Estimating Equation (GEE) method was introduced by Liang & Zeger (1986). This provides a general approach for the analysis of correlated data without requiring distributional assumptions, such as Y being multivariate Normal.

In previous chapters, we have made an assumption for the optimal dynamic treatment regimes that there is no correlation occur between subject however, if we consider a longi-

tudinal data set, there is a higher chance that the correlation is possible to happens within an individual. A GEE model allows the correlation of outcomes within an individual to be estimated and managed to generate the regression coefficients and their standard errors. Secondly, the GEE model allows the calculation of robust estimates for the standard errors of the regression coefficients. For longitudinal data which has a repeated measurements on each individual suppose that $Y_i = X_i\beta + \epsilon_i$ is a vector of length m_i and var$(Y_i) = \Sigma_i$. We solve

$$\sum_{i=1}^{n} X_i^T \Sigma_i^{-1}(Y_i - X_i\beta) = 0. \tag{7.2}$$

More generally, we might have $Y_i = h(X_i, \beta) + \epsilon_i$ still with length m_i and var$(Y_i) = \Sigma_i$. We now have the estimating equation

$$\sum_{i=1}^{n} (\frac{\partial h}{\partial \beta})^T \Sigma_i^{-1}(Y_i - h(X_i, \beta)) = 0. \tag{7.3}$$

We can show that Equation (7.3) is an unbiased estimating equation for any distribution of Y by taking expectations with respect to Y given X. This result is not affected if we change the variance matrix Σ to any other invertible matrix, V_i of the same dimension. Hence, the generalised estimating equation (GEE) is given by

$$\sum_{i=1}^{n} (\frac{\partial h}{\partial \beta})^T V_i^{-1}(Y_i - h(X_i, \beta)) = 0. \tag{7.4}$$

Solving still leads to consistent estimation. Usually V is referred to as a working correlation matrix (Liang & Zeger, 1986).

Thus the GEE approach provides consistency of estimation of parameters (and standard errors) even when the correlation structure is misspecified. Choice of V affects only the efficiency of estimation, not the large sample validity. Several specifications for V are commonly adopted:

1. *Independent*, $V_i = I_n$ where the off-diagonal elements of the working correlation matrix are zero and the diagonals are the same.

2. *Exchangeable*, $(V_i)_{jk} = \rho$ for $j \neq k$ where the off-diagonal elements of the correlation matrix are equal.

3. *Autoregressive*, $(V_i)_{jk} = \rho^{|j-k|}$ for $j \neq k$ which assumes correlations to be an exponential function of the time lag.

In this analysis we will have 3 different types of ρ to represent the correlation that occur between subject:

1. $\rho = 0$ for no correlation

2. $\rho = 0.5$ for low correlation

3. $\rho = 0.9$ for high correlation

Note here that $\rho = 0$ also can be used to obtain the identity working correlation matrix where the off-diagonal elements are zero and the diagonals elements are equal to one.

7.2 Myopic Decision Rules Using The Regret-Regression Approach

We have discussed in detail the regret-regression method proposed by Henderson et al. (2009) in previous chapters. The regret-regression method takes the regret function of Murphy (2003) into a regression model for observed responses directly. A regret-regression approach also can be used to estimate myopic decision rules. Previously we assumed that a final response, Y was available after all decisions are complete. We can also consider situations where a response Y_j is available immediately after decision j as described in Chapter 6. The method is a straightforward adaptation of the previous method: we simply treat the interval as the only interval that we are interested in and ignore all future measurements. In general, the model is fitted at the end-of-interval response, Y_j not the end-of study response Y. We refer to the general Equation (2.23) and define the model as

$$E[Y_j|\bar{S}_K, \bar{A}_K] = \beta_0(S_1) + \phi_j(S_j|\bar{S}_{j-1}, \bar{A}_{j-1}) - \mu_j(A_j|\bar{S}_j, \bar{A}_{j-1}, \psi) \tag{7.5}$$

The ϕ term is a function that compares the expected response under the optimal rule at S_j and the expected response of the optimal rule at S_{j-1} while the μ_j term is the regret, which contrasts the expected response under the optimal rule with the expected response under action a_j, given the previous history.

We can model ϕ as a linear combination of residuals between S_j and define $Z_j = S_j - E(S_j|\bar{S}_{j-1}, \bar{A}_{j-1})$ as previously. In the myopic case

$$E[Y_j|\bar{S}_K, \bar{A}_K] = \beta_0(S_1) + \beta_1(\bar{S}_{j-1}, \bar{A}_{j-1})Z_j - \mu_j(A_j|\bar{S}_j, \bar{A}_{j-1}, \psi) \tag{7.6}$$

The parameters β and ψ were estimated in the previous chapter by using ordinary least squares which is equivalent to minimising

$$\begin{aligned} SS &= \sum_{i=1}^{n}\sum_{j=1}^{K}\{Y_{ij} - E[Y_{ij}]\}^2 \\ &= \sum_{i=1}^{n}\sum_{j=1}^{K}\{Y_{ij} - \beta_0 - \beta_1 Z_{ij} + \mu_{ij}\}^2 \end{aligned} \tag{7.7}$$

In this case we took no account of correlations between responses Y_{ij} and Y_{iK} on the same person. A weighted sum of squares or GEE method might be applied to the myopic regret-regression method in an attempt to improve efficiency. In this case we minimise

$$WSS = \sum_{i=1}^{n} \{Y_i - E[Y_i]\}^T \Sigma^{-1} \{Y_i - E[Y_i]\}$$
$$= \sum_{i=1}^{n} \{Y_i - \beta_0 - \beta_1 Z_i + \mu_i\}^T V_i^{-1} \{Y_i - \beta_0 - \beta_1 Z_i + \mu_i\} \quad (7.8)$$

where now Y_i, Z_i and μ_i are vectors of responses, residuals and regrets for subject i. The generalised estimating equation (GEE) is

$$\sum_{i=1}^{n} \left(\frac{\partial(\beta_0 + \beta_1 Z_i - \mu_i)}{\partial \beta} \right)^T V_i^{-1} (Y_i - (\beta_0 + \beta_1 Z_i - \mu_i)) = 0 \quad (7.9)$$

where $h(X_i, \beta) = \beta_0 + \beta_1 Z_i - \mu_i$ and Y_i is the vector of responses for subject i and V_i is a working correlation matrix. We can consider as in Section 7.1 the independence, exchangeable or autoregressive working correlations.

7.3 Simulation Using The Myopic Regret-Regression Method

In this section we describe simulation using the myopic regret-regression method. No assumption is made for the distribution for Y_{ij}, since we only model the mean response $E[Y_{ij}|\bar{S}_j, \bar{A}_j]$.

7.3.1 Generating Data

We start our simulation with sample size $n = 1000$ with $K = 10$ time points. We generate the data similar to Section 4.2.1 in Chapter 4 where we considered one action per time point chosen randomly from $\{0, 1, 2, 3\}$. Each individual starts with first state simulated as

$$S_1 \sim N(0.5, 0.01)$$

then, for $j = 2, \ldots, 10$

$$S_j \sim N(m_j, 0.01)$$

where $m_j = 0.5 + 0.2S_{j-1} - 0.07A_{j-1}$. We will have one regret function when we have one action per time point as discussed earlier. Suppose the true regret parameter is $\psi = (1.5, 0.1, 5.5)$ and the regret function at timepoint j given the previous history is

$$\mu_j(A_j) = \psi_1(A_j - \psi_2 S_j - \psi_3)^2.$$

The simulated mean of the response $E[Y_j]$ at each time point is

$$\beta_1 + \beta_2(S_j - m_j) - \mu_j(A_j)$$

and we take Y_j to be normally distributed with mean $E[Y_j]$ and variance $\sigma_Y^2 = 0.64$. Specifically

$$Y_j = \beta_1 + \beta_2(S_j - m_j) - \mu_j(A_j) + \epsilon_j. \tag{7.10}$$

We take the vector $\boldsymbol{\epsilon} \sim N(0, \sigma_Y^2 \Sigma)$ as a matrix with dimension $K \times K$ where Σ is *autoregressive* true correlation matrix.

We can obtain simulations by taking $\Sigma = CC^T$ by using the Cholesky decomposition. By definition the Cholesky decomposition is a decomposition of a positive-definite matrix into the product of a lower triangular matrix and its conjugate transpose. We take $\boldsymbol{\epsilon} = C\boldsymbol{Z}$ where $\boldsymbol{Z} \sim N(0, I_R)$ and so

$$\begin{aligned} \text{var}(\boldsymbol{\epsilon}) &= \sigma_Y^2 C \text{var}(\boldsymbol{Z}) C^T \\ &= \sigma_Y^2 C C^T \\ &= \sigma_Y^2 \Sigma \end{aligned} \tag{7.11}$$

We then take the vector of K responses (for a generic subject) as

$$Y = E[Y|\bar{S}_{K-1}, \bar{A}_{K-1}] + \epsilon.$$

7.3.2 Fitting The Model

We can estimate the parameter $\theta = (\beta, \psi)$ by minimising the weighted least squares in Equation (7.8) or using the *OLS* method found in Equation (7.7). For both methods we estimated parameters using the *optim* and *lm* built-in routines in R.

Our estimation procedure has been divided into two parts so that the algorithms will converge much faster. Hence we adopt an iterative procedure. We fix ψ_2 and ψ_3 and estimate the parameters $(\beta_1, \beta_2, \psi_1)$ directly since closed forms are available as the expected value of response is linear in $(\beta_1, \beta_2, \psi_1)$. We can exploit the general result that

$$(Y - X\gamma)^T \Sigma^{-1} (Y - X\gamma)$$

is minimised at

$$\hat{\gamma} = (X^T \Sigma^{-1} X)^{-1} X^t \Sigma^{-1} Y,$$

i.e. there is a closed form. We then search for (ψ_2, ψ_3) using the *optim*-method to minimise the appropriate sum of squares.

Data are generated from the simulation procedure described earlier with sample size 1000 and 1000 repetitions. In each simulation, we generate using an autoregressive error structure with parameter ρ.

Then, we fit the model using the weighted least squares (WLS) method to estimate $\hat{\psi}$ and $\hat{\beta}$ at different assumed values of ρ for the working correlation matrix. We are using the true correlation matrix if we have the same ρ for generating the data and fitting

the model or a misspecified working correlation matrix for different values of ρ between generating the data and fitting the model. We also estimate the mean and SE of $\hat{\psi}$ and $\hat{\beta}$ for the model.

7.3.3 Simulation Result

		$\rho_{True} = 0.0$		$\rho_{True} = 0.5$		$\rho_{True} = 0.9$	
	True	θ_{est}	θ_{SE}	θ_{est}	θ_{SE}	θ_{est}	θ_{SE}
$\rho_{assumed} = 0.0$	$\beta_1 = 3.000$	3.0005	0.0227	3.0006	0.0255	2.9999	0.0305
	$\beta_2 = -5.000$	-4.9951	0.1617	-4.9922	0.1610	-4.9996	0.1423
	$\psi_1 = 1.500$	1.4999	0.0069	1.4998	0.0070	1.5001	0.0067
	$\psi_2 = 0.100$	0.0995	0.0108	0.0997	0.0109	0.0999	0.0104
	$\psi_3 = 5.500$	5.5012	0.0252	5.5011	0.0257	5.5001	0.0245
$\rho_{assumed} = 0.5$	$\beta_1 = 3.000$	2.9996	0.0231	3.0004	0.0249	3.0007	0.0312
	$\beta_2 = -5.000$	-5.0026	0.1687	-4.9943	0.1584	-4.9978	0.1446
	$\psi_1 = 1.500$	1.5002	0.0068	1.4998	0.0068	1.5000	0.0068
	$\psi_2 = 0.100$	0.1001	0.0107	0.0997	0.0108	0.0999	0.0105
	$\psi_3 = 5.500$	5.4996	0.0251	5.5011	0.0249	5.5004	0.0247
$\rho_{assumed} = 0.9$	$\beta_1 = 3.000$	3.0005	0.0230	2.9992	0.0249	2.9995	0.0305
	$\beta_2 = -5.000$	-4.9948	0.1635	-4.9999	0.1593	-5.0006	0.1396
	$\psi_1 = 1.500$	1.4998	0.0068	1.5003	0.0071	1.5001	0.0068
	$\psi_2 = 0.100$	0.0999	0.0108	0.0998	0.0111	0.0999	0.0105
	$\psi_3 = 5.500$	5.5006	0.0249	5.4997	0.0263	5.5000	0.0246

Table 7.1: Parameter estimates using different working correlations of ρ for one step ahead with 1000 repetitions and sample size $n = 1000$.

Table 7.1 shows the parameter estimates using different values of ρ at sample size $n = 1000$. We generate the data using ρ_{true} and use the parameter $\rho_{assumed}$ when fitting the model both with autoregressive structure. Results when estimating the parameters using the true correlation matrix can be found on the diagonal of Table 7.1. The off-diagonal give results with misspecified ρ.

Almost all estimates are unbiased with small standard error. Using the true working correlation matrix, our estimates have slightly smaller standard error when compared to misspecified working correlations at any ρ, though the differences are minor.

7.4 Myopic Two-Steps Ahead Using The Regret-Regression Method.

We further our investigation of myopic decision rules for two-steps ahead using the regret-regression method. Let our response at the first time point be

$$Y_1 = \beta_0 + \beta_1 Z_1 - \mu_1 + \epsilon_1$$

and at the second time point we take

$$Y_2 = \beta_0 + \beta_2 Z_1 - \mu_2 + \epsilon_2.$$

Then, by combining these two time points we obtain

$$Y_1^* = Y_1 + Y_2 = 2\beta_0 + \beta_1 Z_1 + \beta_2 Z_1 - \mu_1 - \mu_2 + \epsilon_1 + \epsilon_2 \tag{7.12}$$

More generally we can write a two-steps ahead response as

$$Y_j^* = Y_j + Y_{j+1} = 2\beta_0 + \beta_j Z_j + \beta_{j+1} Z_j - (\mu_j + \mu_{j+1}) + (\epsilon_j + \epsilon_{j+1}) \tag{7.13}$$

for $j = 1, 2, \ldots, K-2$. For estimation using the GEE method we need to compute the covariance or correlation matrix of these new responses. From Equation (7.13)

$$Y_j^* = f_j(\bar{S}_j, \bar{A}_j) + \epsilon_j + \epsilon_{j+1} \tag{7.14}$$

and for any u

$$Y_{j+u}^* = f_{j+u}(\bar{S}_j, \bar{A}_j) + \epsilon_{j+u} + \epsilon_{j+u+1} \tag{7.15}$$

Hence

$$\begin{aligned} cov(Y_j^*, Y_{j+u}^* | \bar{S}_K, \bar{A}_K) &= cov(\epsilon_j + \epsilon_{j+1}, \epsilon_{j+u} + \epsilon_{j+u+1}) \\ &= cov(\epsilon_j, \epsilon_{j+u}) + cov(\epsilon_j, \epsilon_{j+u+1}) \\ &\quad + cov(\epsilon_{j+1}, \epsilon_{j+u}) + cov(\epsilon_{j+1}, \epsilon_{j+u+1}) \end{aligned} \tag{7.16}$$

where

$$cov(\epsilon_j, \epsilon_k) = \sigma_Y^2 V_{jk} = \sigma_Y^2 \rho^{|j-k|} \tag{7.17}$$

where V_{jk} is the element of the working correlation matrix. Therefore

$$\begin{aligned} cov(Y_j^*, Y_{j+u}^* | \bar{S}_K, \bar{A}_K) &= \sigma^2 \{\rho^{|u|} + \rho^{|u+1|} + \rho^{|u-1|} + \rho^{|u|}\} \\ &= \sigma^2 \{2\rho^{|u|} + \rho^{|u+1|} + \rho^{|u-1|}\}. \end{aligned} \tag{7.18}$$

		$\rho_{True} = 0.0$		$\rho_{True} = 0.5$		$\rho_{True} = 0.9$	
	True Estimates	θ_{est}	θ_{SE}	θ_{est}	θ_{SE}	θ_{est}	θ_{SE}
$\rho_{assumed} = 0.0$	$\beta_1 = 3.000$	3.0000	0.0117	3.0002	0.0162	3.0005	0.0242
	$\beta_2 = -5.000$	-4.9992	0.0614	-4.997	0.0773	-5.0003	0.0827
	$\psi_1 = 1.500$	1.5000	0.0013	1.5000	0.0016	1.5001	0.0019
	$\psi_2 = 0.100$	0.1001	0.0153	0.1005	0.0190	0.1006	0.0199
	$\psi_3 = 5.500$	5.5011	0.0354	5.4990	0.0410	5.5006	0.0445
$\rho_{assumed} = 0.5$	$\beta_1 = 3.000$	3.0001	0.0122	2.9996	0.0165	3.0012	0.0235
	$\beta_2 = -5.000$	-5.0012	0.0640	-4.9990	0.0763	-4.9998	0.0874
	$\psi_1 = 1.500$	1.5000	0.0013	1.5000	0.0016	1.5001	0.0018
	$\psi_2 = 0.100$	0.1001	0.0184	0.0997	0.0157	0.0993	0.0103
	$\psi_3 = 5.500$	5.4987	0.0413	5.5002	0.0349	5.5010	0.0242
$\rho_{assumed} = 0.9$	$\beta_1 = 3.000$	2.9994	0.0117	2.9984	0.0176	3.0002	0.0247
	$\beta_2 = -5.000$	-5.0000	0.0626	-4.9992	0.0810	-5.0000	0.0839
	$\psi_1 = 1.500$	1.5000	0.0013	1.5000	0.0017	1.5000	0.0018
	$\psi_2 = 0.100$	0.0994	0.0224	0.0989	0.0169	0.0999	0.0082
	$\psi_3 = 5.500$	5.5019	0.0503	5.5025	0.0384	5.5003	0.0195

Table 7.2: Parameter estimates using true ρ and wrong covariance matrices for two steps ahead with sample size $n = 1000$ and 1000 repetitions.

Table 7.2 shows the parameter estimates under a variety of working correlation structures. For this simulation, the naive *autoregressive* working correlation matrix will be assumed in estimation. This is to test whether weighted least squares still can give good parameter estimates or otherwise. Similarly to the one-step ahead, we use the ρ_{True} to generate the data and $\rho_{assumed}$ when fitting the model.

Although we are using the wrong covariance matrix, we see that almost all estimates are unbiased with small standard error. Using the true ρ in the assumed working correlations matrix, our estimates have slightly smaller standard error compared to misspecified ρ except when $\rho_{True} = \rho_{assumed} = 0.5$ and $\rho_{True} = \rho_{assumed} = 0.9$. This may be due to random simulation noise. We found that as ρ_{True} is increased, the standard error also increased.

		$\rho_{True} = 0.0$		$\rho_{True} = 0.5$		$\rho_{True} = 0.9$	
	True Estimates	θ_{est}	θ_{SE}	θ_{est}	θ_{SE}	θ_{est}	θ_{SE}
$\rho_{assumed} = 0.0$	$\beta_1 = 3.000$	2.9996	0.0118	3.0004	0.0170	2.9990	0.0245
	$\beta_2 = -5.000$	-5.0017	0.0629	-5.0013	0.0767	-5.0071	0.0872
	$\psi_1 = 1.500$	1.5000	0.0013	1.5000	0.0017	1.4999	0.0018
	$\psi_2 = 0.100$	0.0988	0.0330	0.1005	0.0217	0.0997	0.0131
	$\psi_3 = 5.500$	5.5016	0.0706	5.4987	0.0480	5.5007	0.0298
$\rho_{assumed} = 0.5$	$\beta_1 = 3.000$	3.0002	0.0125	3.0004	0.0166	3.0006	0.0231
	$\beta_2 = -5.000$	-5.0007	0.0627	-4.9998	0.0763	-4.9962	0.0832
	$\psi_1 = 1.500$	1.5000	0.0014	1.5001	0.0016	1.5000	0.0019
	$\psi_2 = 0.100$	0.0997	0.0496	0.0971	0.0289	0.0994	0.0127
	$\psi_3 = 5.500$	5.5032	0.1112	5.5063	0.0654	5.5015	0.0282
$\rho_{assumed} = 0.9$	$\beta_1 = 3.000$	3.0002	0.0117	3.0007	0.0169	3.0000	0.0242
	$\beta_2 = -5.000$	-4.9995	0.0664	-5.0008	0.0796	-4.9933	0.0866
	$\psi_1 = 1.500$	1.5000	0.0013	1.5000	0.0016	1.5001	0.0019
	$\psi_2 = 0.100$	0.101	0.0544	0.0979	0.0332	0.1002	0.0143
	$\psi_3 = 5.500$	5.4987	0.1198	5.5059	0.0755	5.5001	0.0318

Table 7.3: Parameter estimates using different ρ with true covariance matrix for two-steps ahead method and 1000 repetitions.

Table 7.3 shows the parameter estimates using different values of ρ when we use the true covariance matrix obtained from Equation (7.18). When using the true covariance matrix the estimates are all unbiased and have slightly smaller standard error when compared to the case when misspecified working correlations are used, except when $\rho_{True} = \rho_{assumed} = 0.0$ and $\rho_{True} = \rho_{assumed} = 0.9$. The standard errors seem to increase as ρ_{True} increases. When we compare Table 7.3 and Table 7.2 we see that there are little differences in the parameter estimates when using either the true covariance matrix or naive autoregressive matrix as a weight for the sum of squares.

7.5 Conclusions

The GEE method provides a general approach for the analysis of correlated data and does not require any distributional assumptions. It is found suitable to apply to the myopic regret-regression method either with one-step ahead or the two-steps ahead which has been highlighted in this chapter.

Generally the estimates using the GEE method are good as almost all the estimates are unbiased and have small standard errors. Although we have assumed that there are differences between ρ when generating data (ρ_{True}) and fitting the model ($\rho_{assumed}$), the GEE still provides consistent estimates but slightly higher in standard errors.

The GEE method provides consistent estimates provided the true correlation structured is correctly specified. However GEE is not efficient when correlation is misspecified. It is also quite sensitive to the outliers, Diggle et al. (2002) and Qu & Lindsay (2000).

The quadratic inference function (QIF) is an extended version of GEE. It is claimed to be efficient even with a misspecified correlation structure. The characteristics of QIF will be described in detail in Chapter 8.

Chapter 8

Quadratic Inference Function (QIF) for Myopic Regret-Regression.

8.1 Overview of QIF.

The quadratic inference function (QIF) was introduced by Qu & Lindsay (2000). It is aimed at extending the effectiveness of generalised estimating equations(GEEs). Methods based on estimating equations are popular since there is no requirement to specify a probability distribution. The mean response can be modelled without knowing the correlation structure of the longitudinal data although we do usually specify a working correlation matrix and choice of that may affect the efficiency of the model. Under the QIF method, we only need to know the *type* of working correlation but not the parameter values. A further advantage is that it is claimed to be robust to outliers (Qu & Song, 2004; Song et al., 2009).

Under the GEE method, the relationship between the response and covariates is modelled separately from the correlation between repeated measurements on the same individual. A working correlation matrix between successive measurements, is needed however when estimating the model parameters (Diggle et al., 2002; Liang & Zeger, 1986). Examples of working correlation include the independent, exchangeable and autoregressive of order 1 (AR(1)) forms.

The working correlation matrix under QIF is expressed as a linear combination of unknown constants and known basis matrices (Qu & Lindsay, 2000). This linear expression is substituted back to a quasilikelihood function to obtain an extended score vector with a generalised method of moments (Hansen, 1982).

8.2 Quadratic Inference Function and Myopic Regret-Regression

The parameter estimates for myopic decision rules can be obtained by regret-regression as discussed in Chapter 7. The mean model for time j is defined as

$$h_j(\theta) = E[Y_j|\bar{S}_K, \bar{A}_K] = \beta_0 + \beta_1(S_j|\bar{S}_{j-1}, \bar{A}_{j-1})Z_j - \mu_j(A_j|\bar{S}_{j-1}, \bar{A}_{j-1}; \psi) \quad (8.1)$$

where $Z_j = S_j - E(S_j|\bar{S}_{j-1}, \bar{A}_{j-1})$ and the $\mu_j(A_j|\bar{S}_{j-1}, \bar{A}_{j-1}; \psi)$ term is the regret. The myopic rules maximise the response Y_j immediately after decision j in contrast to the long term response which maximises the final response Y after all the decisions are complete.

8.2.1 Quadratic Inference Function (QIF)

The QIF method uses $R(\alpha)$ as a working correlation structures. The inverse of the working correlation matrix, $R^{-1}(\alpha)$ can be approximated by a linear combination of several basis matrices:

$$R^{-1} = \sum_{i=1}^{m} \tau_i M_i \quad (8.2)$$

where $M_1, \ldots, M_m$ are known basis matrices and $\tau_1, \ldots, \tau_m$ are unknown coefficients. Suppose $R(\alpha)$ is an exchangeable correlation matrix with 1s on the diagonal and α's everywhere off diagonal. Then R^{-1} may be written as

$$R^{-1} = \tau_0 M_0 + \tau_1 M_1$$

where M_0 is an identity matrix

$$M_0 = \begin{pmatrix} 1 & 0 & \ldots & 0 \\ 0 & 1 & \ldots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \ldots & 1 \end{pmatrix} \quad (8.3)$$

and M_1 is a matrix with diagonal elements 0 and off diagonal elements 1,

$$M_1 = \begin{pmatrix} 0 & 1 & \ldots & 1 \\ 1 & 0 & \ldots & 1 \\ \vdots & \vdots & \ddots & \vdots \\ 1 & 1 & \ldots & 0 \end{pmatrix} \quad (8.4)$$

Here we have $\tau_0 = -\{(K-2)\alpha + 1\}/\{(K-1)\alpha^2 - (K-2)\alpha - 1\}$ and $\tau_1 = \alpha/\{(K-1)\alpha^2 - (K-2)\alpha - 1\}$ and K is the dimension of R. If we have an autoregressive AR(1)

working correlation matrix with parameter $\rho^{|i-j|}$ for $i \neq j$ then

$$R^{-1} = \tau_0 M_0 + \tau_1 M_1 + \tau_2 M_2$$

where again M_0 is an identity matrix

$$M_0 = \begin{pmatrix} 1 & 0 & \dots & 0 \\ 0 & 1 & \dots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \dots & 1 \end{pmatrix} \tag{8.5}$$

and M_1 is a matrix with 1 on the two main off-diagonals and 0 elsewhere,

$$M_1 = \begin{pmatrix} 0 & 1 & & & \dots & 0 \\ 1 & 0 & 1 & & \dots & 0 \\ 0 & 1 & 0 & 1 & \dots & 0 \\ \vdots & \vdots & \ddots & \ddots & \ddots & \vdots \\ 0 & \dots & \dots & \dots & \dots & 0 \end{pmatrix} \tag{8.6}$$

while M_2 is a matrix with 1 on the corners $(1,1)$ and (K,K) and 0 elsewhere.

$$M_2 = \begin{pmatrix} 1 & 0 & \dots & 0 \\ 0 & 0 & \dots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \dots & 1 \end{pmatrix} \tag{8.7}$$

Here $\tau_0 = (1+\rho^2)/(1-\rho^2)$, $\tau_1 = (-\rho)/(1-\rho^2)$ and $\tau_2 = (-\rho^2)/(1-\rho^2)$. The GEE solves the equation

$$\sum_{i=1}^{n} (\frac{\partial h_i}{\partial \theta})^T V_i^{-1} (Y_i - h_i) = 0 \tag{8.8}$$

Suppose for each person i, Y_i is the response vector $(Y_{i1}, \dots, Y_{iK})'$ with length K and so is $h_i = (h_{i1}, \dots, h_{iK})'$. Let $V_i = D_i^{1/2} R(\alpha) D_i^{1/2}$ where D_i is the diagonal matrix of marginal variances and $R(\alpha)$ is the working correlation matrix. The partial derivative for each person i, $\partial h_i / \partial \theta$ has dimension of $K \times p$ with p being the length of the vector $\theta = (\beta, \psi)$. Consider the following class of estimating functions obtained by substituting Equation (8.2) into Equation (8.8)

$$\sum_{i=1}^{n} (\frac{\partial h_i}{\partial \theta})^T D_i^{-\frac{1}{2}} (\tau_1 M_1 + \dots + \tau_m M_m) D_i^{-\frac{1}{2}} (Y_i - h_i) \tag{8.9}$$

The following extended score $g_N(\theta)$ is a matrix with $(mp \times 1)$ dimension defined as

$$g_N(\theta) = \frac{1}{N}\sum_{i=1}^{N} g_i(\theta) = \frac{1}{N}\begin{pmatrix} \sum_{i=1}^{n} & (\frac{\partial h_i}{\partial \theta})^T & D_i^{-\frac{1}{2}} M_1 D_i^{-\frac{1}{2}} & (Y_i - h_i) \\ \sum_{i=1}^{n} & (\frac{\partial h_i}{\partial \theta})^T & D_i^{-\frac{1}{2}} M_2 D_i^{-\frac{1}{2}} & (Y_i - h_i) \\ & \vdots & & \\ \sum_{i=1}^{n} & (\frac{\partial h_i}{\partial \theta})^T & D_i^{-\frac{1}{2}} M_m D_i^{-\frac{1}{2}} & (Y_i - h_i) \end{pmatrix} \tag{8.10}$$

Using the generalised method of moments described by Hansen (1982) where there are more equations than unknown parameters, we minimise the QIF as

$$Q_N(\theta) = g_N^T C_N^{-1} g_N \tag{8.11}$$

where

$$C_N = \frac{1}{N^2}\sum_{i=1}^{N} g_i^T(\theta) g_i(\theta).$$

8.3 Comparisons Between QIF and GEE Methods in Myopic Regret-Regression using Simulations.

In this section we illustrate the use of QIF in longitudinal data and compare the results obtained from GEE and QIF using simulations. We generate the data in a similar way to Section 7.3.1 with sample size $n = 1000$ and $K = 10$ timepoints. At each time point, the actions A_j are taken as $U(\{0, 1, 2, 3\})$ and the first state is simulated as $S_1 \sim N(0.5, 0.01)$ and then $S_j \sim N(m_j, 0.01)$ for $j = 2, \ldots, 10$. The mean of S_j for $j = 2, \ldots, 10$ is $m_j = 0.5 + 0.2S_{j-1} - 0.07A_{j-1}$. The mean model for Y_j conditional on the past at timepoint j is

$$h_j(\theta) = E[Y_j|\bar{S}_K, \bar{A}_K] = \beta_0 + \beta_1 Z_j - \mu_j(A_j|\bar{S}_{j-1}, \bar{A}_{j-1}) \tag{8.12}$$

where

$$\mu_j = \psi_1 \mid A_j - \psi_2 - \psi_3 S_j \mid . \tag{8.13}$$

This is different from the regret function found in Section 7.3.1. We chose the absolute rather than quadratic form to simplify the $\partial h_i/\partial\theta$ term required in Equation (8.9). We define

$$I_j = \begin{cases} 1 & \text{if} \quad A_j - \psi_2 - \psi_3 S_j \geq 0 \\ -1 & \text{if} \quad A_j - \psi_2 - \psi_3 S_j < 0 \end{cases} \tag{8.14}$$

So I_j is a vector of length K for each person. The response vector Y_j has Normal distribution with mean $E[Y_j]$ and variance $\sigma_Y^2 = 0.64$. The vector $\epsilon \sim N(0, \sigma_Y^2\Sigma)$ is a matrix $(K \times K)$ and Σ is the AR(1) true correlation matrix when generating the data.

To estimate the parameter θ, we begin by estimating the residuals between S_j and a fitted value to obtain Z_j as when using the regret-regression method. Then, we follow

Equation (8.12) by differentiating $h_j(\theta)$ with respect to $\theta = (\beta_0, \beta_1, \psi_1, \psi_2, \psi_3)$ to obtain $\partial h_i/\partial\theta$ as

$$h_j = \hat{Y}_j = \beta_0 + \beta_1 Z_j - \psi_1 \mid A_j - \psi_2 - \psi_3 S_j \mid .$$

For each person i, the partial derivative with respect to β_0 is

$$\frac{\partial h_i}{\partial \beta_0} = \begin{pmatrix} 1 \\ \vdots \\ 1 \end{pmatrix}$$

and the partial derivative with respect to β_1 is

$$\frac{\partial h_i}{\partial \beta_1} = Z_i$$

where Z_i is the residual vector for person i. The remaining derivatives of h_i with respect to ψ_1, ψ_2 and ψ_3 are

$$\frac{\partial h_i}{\partial \psi_1} = -I_i,$$

$$\frac{\partial h_i}{\partial \psi_2} = \psi_1 I_i,$$

$$\frac{\partial h_i}{\partial \psi_3} = \psi_1 S_j I_i.$$

where as stated I_i is a vector of indicators for the sign of the regrets for person i found in Equation (8.14). To minimise the Q_N, we first obtain $g_i(\theta)$ defined at (8.10):

$$g_i(\theta) = \begin{pmatrix} (\frac{\partial h_i}{\partial \theta})^T & D_i^{-\frac{1}{2}} M_1 D_i^{-\frac{1}{2}} & (Y_i - h_i) \\ (\frac{\partial h_i}{\partial \theta})^T & D_i^{-\frac{1}{2}} M_2 D_i^{-\frac{1}{2}} & (Y_i - h_i) \\ \vdots & & \\ (\frac{\partial h_i}{\partial \theta})^T & D_i^{-\frac{1}{2}} M_m D_i^{-\frac{1}{2}} & (Y_i - h_i) \end{pmatrix} \tag{8.15}$$

For each subject i we have Y_i and h_i with $(K \times 1)$ dimension. The D_i is a marginal variances from the diagonal covariance matrix for the ith person and $M_1, \ldots, M_m$ are the basis functions for the working correlation matrix found in Section 8.2.1, which all have dimension $(K \times K)$. The derivatives of the $h_j(\theta)$ term, $\partial h^T/\partial\theta$ have $(p \times K)$ dimension and so the vector $g_i(\theta)$. We then follow the simulation procedure by getting the extended score $g_N(\theta)$.

$$g_N(\theta) = \frac{1}{N}\sum_{i=1}^{N} g_i(\theta) = \frac{1}{N} \begin{pmatrix} \sum_{i=1}^n & (\frac{\partial h_i}{\partial \theta})^T & M_1 & (Y_i - h_i) \\ \sum_{i=1}^n & (\frac{\partial h_i}{\partial \theta})^T & M_2 & (Y_i - h_i) \\ \vdots & & & \\ \sum_{i=1}^n & (\frac{\partial h_i}{\partial \theta})^T & M_m & (Y_i - h_i) \end{pmatrix}. \tag{8.16}$$

where for the moment we have assumed D_i to be an identity matrix. By minimising Q_N found in Equation 8.11, the estimated parameter $\hat{\theta}$ is obtained

$$\hat{\theta} = \arg\min_{\theta} g_N^T C_N^{-1} g_N$$

where

$$C_N^{-1} = \frac{1}{N^2} \sum_{i=1}^{N} g_i^T(\theta) g_i(\theta).$$

The data are generated as described earlier with sample size $n = 1000$ and repeated 2000 times. At each simulation, we generate using an AR(1) error structure with parameter ρ. Then we fitted the model using the Q_N function with various extended score $g_N(\theta)$ structures. We assume the AR(1) to be the true correlation matrix and we use AR(1) for generating the data and fitting the model and assume the exchangeable or any other matrix form to be a misspecified working correlation for this simulation.

8.4 Simulation of QIF Method with Constant Covariance Structure $D_i = I_n$

In this section we demonstrate a simulation using constant variance when fitting the model. We assumed D_i to be an identity matrix with an extended score $g_N(\theta)$ as in Equation (8.16). When generating the data, the $\epsilon \sim N(0, \sigma_Y^2 \Sigma)$ where $\sigma_Y^2 = 0.64$ and Σ is an AR(1) correlation structure for all time points.

8.4.1 QIF with AR(1) Working Covariance Structure

		$\rho_{True} = 0.0$		$\rho_{True} = 0.5$		$\rho_{True} = 0.9$	
	True	θ_{est}	θ_{SE}	θ_{est}	θ_{SE}	θ_{est}	θ_{SE}
GEE$_{\rho_{assumed=0.0}}$	$\beta_1 = 3.000$	3.0010	0.0220	3.0006	0.0246	3.001	0.0261
	$\beta_2 = -5.000$	-4.9941	0.1605	-4.9996	0.1736	-4.9993	0.1863
	$\psi_1 = 1.500$	1.4996	0.0068	1.4999	0.0076	1.4997	0.0083
	$\psi_2 = 0.100$	0.0999	0.0105	0.1005	0.0121	0.1002	0.0134
	$\psi_3 = 5.500$	5.5012	0.0243	5.4995	0.0274	5.5005	0.0303
GEE$_{\rho_{assumed=0.5}}$	$\beta_1 = 3.000$	3.0004	0.0253	3.0007	0.0231	3.0002	0.0230
	$\beta_2 = -5.000$	-5.0000	0.1576	-4.9967	0.1411	-4.9930	0.1405
	$\psi_1 = 1.500$	1.4999	0.0068	1.4999	0.0056	1.4998	0.0057
	$\psi_2 = 0.100$	0.1001	0.0110	0.0998	0.0090	0.0996	0.0093
	$\psi_3 = 5.500$	5.5002	0.0257	5.5006	0.0211	5.5012	0.0218
GEE$_{\rho_{assumed=0.9}}$	$\beta_1 = 3.000$	2.9989	0.0305	3.0000	0.0261	3.0003	0.0257
	$\beta_2 = -5.000$	-4.9970	0.1444	-4.9985	0.1017	-4.9960	0.1006
	$\psi_1 = 1.500$	1.5000	0.0067	1.5001	0.0050	1.4999	0.0038
	$\psi_2 = 0.100$	0.0998	0.0105	0.1000	0.0061	0.0999	0.0048
	$\psi_3 = 5.500$	5.5004	0.0250	5.5000	0.0171	5.5005	0.0121
$QIF_{AR(1)}$	$\beta_1 = 3.000$	3.0000	0.0138	3.0000	0.0162	3.0004	0.0223
	$\beta_2 = -5.000$	-4.9992	0.1146	-4.9986	0.0984	-4.9986	0.0569
	$\psi_1 = 1.500$	1.5000	0.0063	1.4999	0.0034	1.4999	0.0028
	$\psi_2 = 0.100$	0.1002	0.0074	0.0999	0.0055	0.1001	0.0035
	$\psi_3 = 5.500$	5.4997	0.0201	5.5004	0.0138	5.5001	0.0104

Table 8.1: Comparisons of parameter estimates using QIF and GEE methods with $AR(1)$ working correlation. Sample size, $n = 1000$ and 2000 repetitions. The GEE method estimated the parameter using different values of ρ. We used $\rho = (0.0, 0.5, 0.9)$ where $\rho = 0.0$ represents low working correlation, $\rho = 0.5$ represent medium working correlation and $\rho = 0.9$ for high working correlation for GEEs.

Table 8.1 show the results using the GEE and QIF methods. Each column in the table represents a different value of ρ used when generating the data. We used GEE with three different values of ρ in an assumed autoregressive working correlation matrix. The true correlation matrix can be found on the diagonal of Table 8.1 while the off-diagonal provide the results with misspecified ρ.

The true correlation matrix should gives a better results than the misspecified ρ but this is not happen for true correlation matrix, GEE with $\rho = 0.5$ where the standard errors

for β_1 and β_2 are slightly higher compared with the others on the same row. This is due the random simulation noise but the differences is not too obvious.

For QIF we again assumed the autoregressive form, but this time there is no need to specify a parameter. In all cases the estimates are apparently unbiased but there is strong evidence that QIF is more efficient.

8.4.2 QIF with Exchangeable Working Covariance Structure

		$\rho_{True} = 0.0$		$\rho_{True} = 0.5$		$\rho_{True} = 0.9$	
	True	θ_{est}	θ_{SE}	θ_{est}	θ_{SE}	θ_{est}	θ_{SE}
GEE$_{\rho_{assumed=0.0}}$	$\beta_1 = 3.000$	3.0002	0.0223	3.0007	0.0231	3.0010	0.0235
	$\beta_2 = -5.000$	-5.0019	0.1642	-4.9965	0.1641	-4.9900	0.1637
	$\psi_1 = 1.500$	1.5000	0.0068	1.4997	0.0069	1.4996	0.0072
	$\psi_2 = 0.100$	0.1001	0.0106	0.0999	0.0111	0.0997	0.0111
	$\psi_3 = 5.500$	5.4998	0.0253	5.5008	0.0256	5.5015	0.0258
GEE$_{\rho_{assumed=0.5}}$	$\beta_1 = 3.000$	2.9996	0.0253	3.0002	0.0240	3.0009	0.0255
	$\beta_2 = -5.000$	-5.0007	0.1584	-4.9977	0.1532	-4.9906	0.1591
	$\psi_1 = 1.500$	1.5000	0.0068	1.5000	0.0066	1.4998	0.0069
	$\psi_2 = 0.100$	0.1001	0.0108	0.0998	0.0101	0.0995	0.0101
	$\psi_3 = 5.500$	5.4998	0.0253	5.5005	0.0239	5.5013	0.0247
GEE$_{\rho_{assumed=0.9}}$	$\beta_1 = 3.000$	3.0004	0.0306	3.0005	0.0264	3.0007	0.0274
	$\beta_2 = -5.000$	-5.0017	0.1421	-5.0022	0.1202	-4.9962	0.1250
	$\psi_1 = 1.500$	1.5000	0.0068	1.5000	0.0056	1.4998	0.0047
	$\psi_2 = 0.100$	0.1001	0.0103	0.1002	0.0070	0.0999	0.0070
	$\psi_3 = 5.500$	5.5000	0.0244	5.4997	0.0177	5.5006	0.0176
$QIF_{exchangeable}$	$\beta_1 = 3.000$	2.9996	0.0137	3.0002	0.0176	3.0000	0.0226
	$\beta_2 = -5.000$	-4.9981	0.1123	-5.0021	0.1065	-4.9993	0.0755
	$\psi_1 = 1.500$	1.4999	0.0061	1.5000	0.0045	1.5001	0.0037
	$\psi_2 = 0.100$	0.1000	0.0074	0.1000	0.0067	0.1000	0.0044
	$\psi_3 = 5.500$	5.5003	0.0195	5.4999	0.0169	5.4999	0.0127

Table 8.2: Comparisons of parameter estimates using QIF and GEE methods with exchangeable working correlation. Sample size, $n = 1000$ and 2000 repetitions.

Results in Table 8.2 were obtained from the GEE and QIF methods under the exchangeable correlation structure. We have found that there is a random simulation noise occur for the true correlation matrices, GEE $\rho = 0.0$ and GEE $\rho = 0.9$ which have slightly higher SE than the others on the same rows especially for the parameter estimates β_1 and β_2. Overall we see that both methods give consistent parameter estimates and it is also seen that QIF has better efficiency than GEE.

8.4.3 Misspecification of the QIF Method

In Table 8.3 we give results when the QIF method is used but the form of the assumed correlation matrix may be incorrect. The data are generated with autoregressive AR(1) structure and that form is correctly assumed for the first block of results. In the second

		$\rho_{True} = 0.0$		$\rho_{True} = 0.5$		$\rho_{True} = 0.9$	
	True	θ_{est}	θ_{SE}	θ_{est}	θ_{SE}	θ_{est}	θ_{SE}
$QIF_{AR(1)}$	$\beta_1 = 3.000$	3.0000	0.0138	3.0000	0.0162	3.0004	0.0223
	$\beta_2 = -5.000$	-4.9992	0.1146	-4.9986	0.0984	-4.9986	0.0569
	$\psi_1 = 1.500$	1.5000	0.0063	1.4999	0.0050	1.4999	0.0028
	$\psi_2 = 0.100$	0.1002	0.0074	0.0999	0.0061	0.1001	0.0035
	$\psi_3 = 5.500$	5.4997	0.0201	5.5004	0.0171	5.5001	0.0104
$QIF_{exchangeable}$	$\beta_1 = 3.000$	2.9996	0.0137	3.0002	0.0176	3.0000	0.0236
	$\beta_2 = -5.000$	-4.9981	0.1123	-5.0021	0.1065	-4.9993	0.0755
	$\psi_1 = 1.500$	1.4999	0.0061	1.5000	0.0056	1.5001	0.0037
	$\psi_2 = 0.100$	0.1000	0.0074	0.1000	0.0067	0.1000	0.0044
	$\psi_3 = 5.500$	5.5003	0.0195	5.4999	0.0177	5.4999	0.0127
$QIF_{AR(1)M12}$	$\beta_1 = 3.000$	3.0008	0.0173	2.9999	0.0227	2.9999	0.0302
	$\beta_2 = -5.000$	-5.0026	0.2595	-4.9970	0.2536	-5.0087	0.2637
	$\psi_1 = 1.500$	1.4999	0.0124	1.4995	0.0121	1.5001	0.0121
	$\psi_2 = 0.100$	0.1002	0.0160	0.0997	0.0155	0.1001	0.0157
	$\psi_3 = 5.500$	5.5002	0.0380	5.5016	0.0357	5.4997	0.0383
$QIF_{AR(1)M2}$	$\beta_1 = 3.000$	3.0002	0.0306	3.0006	0.0294	3.0007	0.0317
	$\beta_2 = -5.000$	-5.0026	0.2728	-5.0013	0.2678	-4.9948	0.2651
	$\psi_1 = 1.500$	1.4998	0.0143	1.4999	0.0145	1.4998	0.0147
	$\psi_2 = 0.100$	0.0993	0.0185	0.1003	0.0186	0.1001	0.0188
	$\psi_3 = 5.500$	5.5018	0.0490	5.4999	0.0484	5.5003	0.0487

Table 8.3: Comparisons of parameter estimates using QIF AR(1) and exchangeable working correlation matrices. The rows labelled $QIF_{AR(1)M12}$ and $QIF_{AR(1)M2}$ are the misspecified model with different types of M working correlation structures found in Section 8.2.1. The simulation uses sample size, $n = 1000$ and 2000 repetitions.

block we mistakenly assumed an exchangeable form. Meanwhile in block three we use just the matrices (8.6) and (8.7) in the expansion (8.2) and in block four we use just matrix (8.7).

In all cases the mean parameter estimates are close to the true values. The standard errors when the exchangeable structure is mistakenly assumed are only a little higher than when the true correlation structure (AR(1)) is used. If however, only part of the series expansion (8.2) is used then standard errors are increased.

8.5 Simulation of the QIF Method using Unequal Variances, $D_i \neq I_n$

We now consider the effect of constant or different variances at each time point. We consider two approaches:

1. Q_1: When generating the data, we take $Var(\epsilon_j) = \sigma_Y^2 \Sigma$ where $\sigma_Y^2 = 0.64$ and Σ is take to have AR(1) correlation structure for all j. We assume $D_i = I_n$ so there is homogeneity in variance when fitting the model. The extended score, $g_N(\theta)$ for

		$\rho_{True} = 0.0$		$\rho_{True} = 0.5$		$\rho_{True} = 0.9$	
	True	θ_{est}	θ_{SE}	θ_{est}	θ_{SE}	θ_{est}	θ_{SE}
$AR(1)_{Q1}$	$\beta_1 = 3.000$	3.0000	0.0138	3.0000	0.0162	3.0004	0.0223
	$\beta_2 = -5.000$	-4.9992	0.1146	-4.9986	0.0984	-4.9986	0.0569
	$\psi_1 = 1.500$	1.5000	0.0063	1.4999	0.0050	1.4999	0.0028
	$\psi_2 = 0.100$	0.1002	0.0074	0.0999	0.0061	0.1001	0.0035
	$\psi_3 = 5.500$	5.4997	0.0201	5.5004	0.0171	5.5001	0.0104
$AR(1)_{Q2}$	$\beta_1 = 3.000$	6.5988	0.0619	6.5891	0.0678	6.5730	0.0729
	$\beta_2 = -5.000$	-4.5793	0.5397	-4.6395	0.5689	-4.7760	0.5843
	$\psi_1 = 1.500$	6.0980	0.0429	6.0974	0.0406	6.0940	0.0376
	$\psi_2 = 0.100$	-0.4231	0.0294	-0.4229	0.0299	-0.4162	0.0299
	$\psi_3 = 5.500$	6.1767	0.0661	6.1714	0.0686	6.1525	0.0705

Table 8.4: Comparisons of parameter estimates between QIF methods using the general covariance structure and constant covariance structure for the autoregressive (AR(1)) covariance structure . Sample size, $n = 1000$ and 2000 repetitions.

constant variance is

$$g_N(\theta) = \frac{1}{N}\sum_{i=1}^{N} g_i(\theta) = \frac{1}{N}\begin{pmatrix} \sum_{i=1}^{n} & (\frac{\partial h_i}{\partial \theta})^T & M_1 & (Y_i - h_i) \\ \sum_{i=1}^{n} & (\frac{\partial h_i}{\partial \theta})^T & M_2 & (Y_i - h_i) \\ \vdots & & & \\ \sum_{i=1}^{n} & (\frac{\partial h_i}{\partial \theta})^T & M_m & (Y_i - h_i) \end{pmatrix}$$

2. Q_2: We simulate the first five time points with $Var(\epsilon_j) = \sigma_Y^2 \Sigma$ and the remaining five time points with $Var(\epsilon_j) = 2\sigma_Y^2 \Sigma$. We take $\sigma_Y^2 = 0.64$ and the correlation matrix Σ is taken to have autoregressive form. We fit the model by assuming the diagonal elements of D_i to be unequal as described above. The extended score will be

$$g_N(\theta) = \frac{1}{N}\sum_{i=1}^{N} g_i(\theta) = \frac{1}{N}\begin{pmatrix} (\frac{\partial h_i}{\partial \theta})^T & D_i^{-\frac{1}{2}} M_1 D_i^{-\frac{1}{2}} & (Y_i - h_i) \\ (\frac{\partial h_i}{\partial \theta})^T & D_i^{-\frac{1}{2}} M_2 D_i^{-\frac{1}{2}} & (Y_i - h_i) \\ \vdots & & \\ (\frac{\partial h_i}{\partial \theta})^T & D_i^{-\frac{1}{2}} M_m D_i^{-\frac{1}{2}} & (Y_i - h_i) \end{pmatrix}.$$

8.5.1 Comparison of the QIF Method using the AR(1) Working Covariance Structure

Table 8.4 shows the parameter estimates using the AR(1) true covariance structure. We found the Q_2 structure has poor performance when compared to the true covariance structure Q_1 where almost all the estimates are far away from the true values. Although Q_2 has poor estimates, the standard errors for all the parameters are small for all parameters except β_2. Recall that in Q_2 we falsely assume unequal variances, as described previously.

8.5.2 Comparison of the QIF Method using the Exchangeable Working Covariance Structure

		$\rho_{True} = 0.0$		$\rho_{True} = 0.5$		$\rho_{True} = 0.9$	
	True	θ_{est}	θ_{SE}	θ_{est}	θ_{SE}	θ_{est}	θ_{SE}
Ex_{Q1}	$\beta_1 = 3.000$	2.9996	0.0137	3.0002	0.0176	3.0000	0.0236
	$\beta_2 = -5.000$	-4.9981	0.1123	-5.0021	0.1065	-4.9993	0.0755
	$\psi_1 = 1.500$	1.4999	0.0061	1.5000	0.0056	1.5001	0.0037
	$\psi_2 = 0.100$	0.1000	0.0074	0.1000	0.0067	0.1000	0.0044
	$\psi_3 = 5.500$	5.5003	0.0195	5.4999	0.0177	5.4999	0.0127
Ex_{Q2}	$\beta_1 = 3.000$	6.5272	0.0643	6.5058	0.0646	6.4874	0.0687
	$\beta_2 = -5.000$	-6.0642	0.6019	-6.3394	0.583	-6.5974	0.5761
	$\psi_1 = 1.500$	6.1144	0.0387	6.1121	0.0395	6.1114	0.0387
	$\psi_2 = 0.100$	-0.3717	0.0331	-0.3639	0.033	-0.3548	0.0323
	$\psi_3 = 5.500$	6.0356	0.077	6.0135	0.0758	5.9874	0.0747

Table 8.5: Comparisons of parameter estimates between QIF methods using the exchangeable working covariance structure. We use sample size $n = 1000$ and 2000 repetitions.

Table 8.5 show the parameter estimates using the exchangeable covariance structure. As expected, the Q_2 exchangeable structure has similar results to the Q_2 AR(1) with poor estimates. Clearly we need to be sure that D_i is correctly specified when using QIF.

8.6 Application to Warfarin Data

We extend the investigation of estimating equations in myopic regret-regression by considering their application to the Warfarin data. The Warfarin data has been described in detail in Chapter 5.

The response Y_j is measured at each time point j for $j = 1, 2, \ldots, K$ where in this application we have $K = 9$ as described in Chapter 6. Each S_j is regressed on previous history $(\bar{S}_{j-1}, \bar{A}_{j-1})$ and each residual $Z_j = S_j - E[S_j|\bar{S}_{j-1}, \bar{A}_{j-1}]$ is defined. Such state residuals Z_j were obtained from a mixture model for S_j. As presented in detail in Chapter 5, this mixture model has a logistic part when $P(S_j = 0)$ where INR is in range so $S_j = 0$ and linear when $S_j \neq 0$. The mean model for Y_j given the previous history at time point j is

$$h_j(\theta) = \beta_0 + \beta_1 Z_j - \mu_j(A_j|\bar{S}_{j-1}, \bar{A}_{j-1}; \psi).$$

Similar to Section 8.3, the regret function at time j is

$$\mu_j(A_j|\bar{S}_{j-1}, \bar{A}_{j-1}) = \psi_1|A_j - \psi_2 - \psi_3 S_j|.$$

We define I_j to be a vector of length K for person i with

$$I_j = \begin{cases} 1 & \text{if} \quad A_j - \psi_2 - \psi_3 S_j \geq 0 \\ -1 & \text{if} \quad A_j - \psi_2 - \psi_3 S_j < 0 \end{cases}$$

which is to simplify the $\partial h_i/\partial\theta$ term in Equation (8.9). We begin by obtaining Z_j by estimating the residuals between states, S_j. We follow the method in Section 8.3 for obtaining the $g_i(\theta)$, the extended score $g_N(\theta)$ and the partial derivatives $\partial h_i/\partial\theta$ for each person. In estimation we use θ equal to $(8.00, 0.00, 2.00, 0.25, -5.00)$ as an initial value and obtain $\hat{\theta}$ by minimising

$$\hat{\theta} = \arg\min_{\theta} g_N^T C_N^{-1} g_N$$

where

$$C_N^{-1} = \frac{1}{N^2}\sum_{i=1}^{N} g_i^T(\theta) g_i(\theta).$$

We make a comparison between QIF and GEE methods using different types of covariance structure similar to Section 8.4 and 8.5. We further investigate the use of QIF method by misspecifying the method in a similar way to Section 8.4.3. This is to test the consistency and efficiency of the QIF method in an application to real data.

The QIF method is easy to apply as long as we know the basis matrices M_i. However, there is some limitation in using the *known type* of covariance structure when we have no idea which working correlation structure is the most appropriate. To overcome this problem we are going to apply an unspecified covariance structure to the QIF method by Qu & Lindsay (2003) and Qu & Song (2004). For the unspecified covariance structure, we have the basis matrices M_0, an identity matrix, and $M_1 = \hat{U}$, where

$$\hat{U} = \frac{1}{N}\sum (Y_i - h_i)(Y_i - h_i)^T.$$

We use the initial value of $\theta = (8.00, 0.00, 2.00, 0.25, -5.00)$ to calculate the h term, given that θ is unknown for this application and follow the QIF estimation procedure to estimate $\hat{\theta}$ and obtained SE from 1000 bootstrap resampling. The matrix $\hat{U}$ is a consistent estimator of the variance matrix of Y (Qu & Song, 2004). By using the unspecified covariance structure we can compare it with the *known type* of covariance structure, i.e. AR(1) and exchangeable covariance structures.

Meanwhile the GEE unstructured working correlation assumes that correlations may be different for each pair of observation (Pan & Connett, 2002). For example, if we have an unstructured 3×3 working correlation then

$$V_i^{-1} = \begin{pmatrix} 1 & \rho_{12} & \rho_{13} \\ \rho_{12} & 1 & \rho_{23} \\ \rho_{13} & \rho_{23} & 1 \end{pmatrix} \tag{8.17}$$

It is also possible to compare the QIF unspecified covariance matrix with the GEE unstructured working correlation which will be described later.

8.6.1 Comparison of Methods using AR(1) Working Covariance Structure.

Methods	Ests	$\hat{\beta}_1$	$\hat{\beta}_2$	$\hat{\psi}_1$	$\hat{\psi}_2$	$\hat{\psi}_3$
Regret-regression	$\hat{\theta}$	6.3342	-2.0293	0.5858	0.0000	-3.1949
	$SE_{\hat{\theta}}$	0.1311	0.1127	0.1470	0.0036	1.2421
$GEE_{AR(1)_{\rho=0.5}}$	$\hat{\theta}$	6.1052	-2.5687	0.8274	0.1916	-1.0278
	$SE_{\hat{\theta}}$	0.1937	0.2131	0.4269	2.3116	3.2735
$GEE_{AR(1)_{\rho=0.9}}$	$\hat{\theta}$	5.9260	-2.7432	0.1383	0.9995	-1.9310
	$SE_{\hat{\theta}}$	0.1638	0.0895	0.2025	1.9707	2.8979
$QIF_{AR(1)}$	$\hat{\theta}$	9.9736	1.4953	1.8110	0.0497	-9.8336
	$SE_{\hat{\theta}}$	0.4095	0.4263	0.2697	0.0623	0.3963

Table 8.6: Comparison of Warfarin parameter estimates between the regret-regression, GEE and QIF methods. The GEE and QIF methods use the AR(1) working correlation matrix.

Table 8.6 compares parameter estimates between regret-regression, GEE and QIF methods using the AR(1) working correlation matrix. Recall we do not use any working correlation matrix for the regret-regression method. We found the regret-regression method has more efficient estimates than the GEE and QIF using the AR(1) working correlation matrix.

The table also show that almost all methods have small standard errors except for parameters ψ_2 and ψ_3 under GEE when $\rho = 0.5$ and $\rho = 0.9$. The QIF method under the AR(1) working correlation matrix seems not to provide good estimates which indicates that the AR(1) working correlation matrix may not be appropriate for this application.

8.6.2 Comparison of Methods using Exchangeable Working Covariance Structure.

Methods	Ests	$\hat{\beta}_1$	$\hat{\beta}_2$	$\hat{\psi}_1$	$\hat{\psi}_2$	$\hat{\psi}_3$
Regret-regression	$\hat{\theta}$	6.3342	-2.0293	0.5858	0.0002	-3.1949
	$SE_{\hat{\theta}}$	0.1311	0.1127	0.1470	0.0036	1.2421
$GEE_{Exchangeable_{\rho=0.5}}$	$\hat{\theta}$	6.3299	-2.0066	0.3688	-0.0010	-5.0011
	$SE_{\hat{\theta}}$	0.1010	0.1127	0.2529	0.0443	1.3775
$GEE_{Exchangeable_{\rho=0.9}}$	$\hat{\theta}$	6.3271	-2.0040	0.3170	0.0007	-5.7704
	$SE_{\hat{\theta}}$	0.1811	0.3968	0.1171	0.5047	1.4748
$QIF_{Exchangeable}$	$\hat{\theta}$	6.5541	-2.3530	0.4898	-0.1219	-2.5758
	$SE_{\hat{\theta}}$	0.1931	0.1788	0.1832	0.4483	0.5982

Table 8.7: Comparison of Warfarin parameter estimates between the regret-regression, GEE and QIF methods. The GEE and QIF methods are using the exchangeable working correlation matrix.

We found the parameter estimates in Table 8.7 using the regret-regression method still give apparently better estimates than the GEE and the QIF methods with a exchangeable working correlation matrix. Almost all the methods have small SE except for ψ_3 in

GEE for both $\rho = 0.5$ and $\rho = 0.9$. Although the QIF method under the exchangeable working correlation matrix has slightly higher SE than the regret-regression and GEE methods, it gives more reasonable estimates than the QIF method under the AR(1) working correlation. This indicates that the exchangeable working correlation matrix may be an appropriate correlation matrix for this application.

8.6.3 Different Forms of QIF.

In this section we make comparison of various types of QIF model:

1. QIF$_{AR(1)M1}$ we use the matrix M_1 with 1 on the two main off-diagonals and 0 elsewhere,
$$M_1 = \begin{pmatrix} 0 & 1 & & & \dots & 0 \\ 1 & 0 & 1 & & \dots & 0 \\ 0 & 1 & 0 & 1 & \dots & 0 \\ \vdots & \vdots & \ddots & \ddots & \ddots & \vdots \\ 0 & \dots & \dots & \dots & \dots & 0 \end{pmatrix}$$

2. QIF$_{AR(1)M2}$ where M_2 is a matrix with 1 on the corners $(1,1)$ and $(10,10)$ and 0 elsewhere.
$$M_2 = \begin{pmatrix} 1 & 0 & \dots & 0 \\ 0 & 0 & \dots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \dots & 1 \end{pmatrix}$$

3. QIF$_{AR(1)M12}$ we use both matrices M_1 and M_2 from the AR(1) basis working correlation matrix.

4. QIF$_{ExchangeableM1}$ where we use the matrix M_1 with diagonal elements 0 and off diagonal elements 1 from exchangeable working correlation matrix,
$$M_1 = \begin{pmatrix} 0 & 1 & \dots & 1 \\ 1 & 0 & \dots & 1 \\ \vdots & \vdots & \ddots & \vdots \\ 1 & 1 & \dots & 0 \end{pmatrix}$$

Table 8.8 shows the results of fitting with the different forms of QIF. The previous results have shown that QIF under the AR(1) working correlation matrix was not appropriate while QIF$_{Exchangeable}$ is more suitable for this application. Overall we found that almost all the parameter estimates have higher standard errors when compared to QIF$_{AR(1)}$ and QIF$_{Exchangeable}$. None of these methods can be recommended.

In the next section we will make a comparison between the QIF method using the unspecified working correlation with the QIF$_{Exchangeable}$ and QIF$_{AR(1)}$.

Methods	Ests	$\hat{\beta}_1$	$\hat{\beta}_2$	$\hat{\psi}_1$	$\hat{\psi}_2$	$\hat{\psi}_3$
$\text{QIF}_{AR(1)}$	$\hat{\theta}$	9.9736	1.4953	1.8110	0.0497	-9.8336
	$\text{SE}_{\hat{\theta}}$	0.4095	0.4263	0.2697	0.0623	0.3963
$\text{QIF}_{AR(1)M1}$	$\hat{\theta}$	8.7751	1.1018	1.3711	0.1400	-9.6500
	$\text{SE}_{\hat{\theta}}$	0.9438	1.2146	0.6466	0.0975	0.9316
$\text{QIF}_{AR(1)M2}$	$\hat{\theta}$	6.1423	-1.8627	0.0262	0.0032	-3.4563
	$\text{SE}_{\hat{\theta}}$	0.9176	1.0514	0.7280	0.3305	0.6474
$\text{QIF}_{AR(1)M12}$	$\hat{\theta}$	11.6213	1.8513	4.2489	0.3373	-4.973
	$\text{SE}_{\hat{\theta}}$	0.8165	0.9462	0.6124	0.3134	0.7946
$\text{QIF}_{Exchangeable}$	$\hat{\theta}$	6.5541	-2.3530	0.4898	-0.1219	-2.5758
	$\text{SE}_{\hat{\theta}}$	0.1931	0.1788	0.1832	0.4483	0.5982
$\text{QIF}_{ExchangableM1}$	$\hat{\theta}$	17.2056	6.6621	0.5336	-18.3458	-18.1997
	$\text{SE}_{\hat{\theta}}$	1.1402	2.8030	0.4025	0.8487	2.7030

Table 8.8: Comparisons of Warfarin parameter estimates using QIF AR(1) and exchangeable covariance structures with different types of M basis matrices found in Section 8.2.1.

8.6.4 Comparison of Methods Using Unspecified Working Covariance Structure.

Methods	Ests	$\hat{\beta}_1$	$\hat{\beta}_2$	$\hat{\psi}_1$	$\hat{\psi}_2$	$\hat{\psi}_3$
Regret-regression	$\hat{\theta}$	6.3342	-2.0293	0.5858	0.0002	-3.1949
	$\text{SE}_{\hat{\theta}}$	0.1311	0.1127	0.1470	0.0036	1.2421
$\text{GEE}_{AR(1)_{\rho=0.5}}$	$\hat{\theta}$	6.1052	-2.5687	0.8274	0.1916	-1.0278
	$\text{SE}_{\hat{\theta}}$	0.1937	0.2131	0.4269	2.3116	3.2735
$\text{GEE}_{AR(1)_{\rho=0.9}}$	$\hat{\theta}$	5.9260	-2.7432	0.1383	0.9995	-1.9310
	$\text{SE}_{\hat{\theta}}$	0.1638	0.0895	0.2025	1.9707	2.8979
$\text{GEE}_{Exchangeable_{\rho=0.5}}$	$\hat{\theta}$	6.3299	-2.0066	0.3688	-0.0010	-5.0011
	$\text{SE}_{\hat{\theta}}$	0.1010	0.1127	0.2529	0.0443	1.3775
$\text{GEE}_{Exchangeable_{\rho=0.9}}$	$\hat{\theta}$	6.3271	-2.0040	0.3170	-0.0007	-5.7704
	$\text{SE}_{\hat{\theta}}$	0.1811	0.3968	0.1171	0.5047	1.4748
$\text{GEE}_{Unstructured}$	$\hat{\theta}$	6.3031	-2.0485	0.6714	0.0025	-2.8195
	$\text{SE}_{\hat{\theta}}$	0.1315	0.0984	0.1231	0.0117	0.6586
$\text{QIF}_{Unspecified}$	$\hat{\theta}$	6.2917	-2.0149	0.6271	-0.0507	-3.5008
	$\text{SE}_{\hat{\theta}}$	0.1781	0.2923	0.1791	0.1149	1.5128

Table 8.9: Comparison of parameter estimates between the regret-regression, GEE and QIF using unspecified working correlation structure for Warfarin data. We used different types of working correlation matrices for the GEE method.

In addition to investigating the QIF method using an unspecified working correlation, we also investigate the GEE method using an unstructured working correlation. Table 8.9 shows that GEE with unstructured correlation structure has better estimates and smaller standard errors than the exchangeable or AR(1) forms for the Warfarin data.

Based on the results from Table 8.9 we can conclude that the regret-regression method still gives best performance in parameter estimates and may be robust for this application.

8.7 Conclusions

The QIF method is suitable for the myopic regret-regression method. Theoretically the QIF has an advantage of producing parameter estimates with equal or greater efficiency than GEE. They are equally efficient when the correct covariance structure is assumed but QIF is more efficient than GEE when the working correlation is misspecified.

Although QIF may have some advantages over GEE, in practice QIF is not guaranteed to be superior for parameter estimation. The QIF method using the unspecified correlation structure can provide an optional choice of working correlation when we have no idea which correlation structure to choose. We also found that QIF under the known type correlation structure is quite sensitive to the choice of the basis matrices M in the linear series (8.2).

We can conclude that the QIF method is preferable to GEE due to the desirable characteristics highlighted above. We will further our investigation by assessing the robustness of GEE for myopic regret-regression method in the following chapter.

Chapter 9

Influential Observations in Myopic Regret-Regression Method: Application to Warfarin Data.

9.1 Introduction to One Case Deletion for GEE Method

The GEE method has been discussed in detail in Chapter 7. We now introduce one-case deletion diagnostics for GEE to identify the influence of observations on the estimated parameters. We will use a Cook's distance measure to assess the influence of deleting an observation and introduce a feasible one-step approximation for GEE.

Ziegler & Arminger (1996), Preisser & Qaqish (1996) and Preisser & Qaqish (1999) have developed regression diagnostics for the marginal mean model for GEE using cluster deletion and Cook's distance. Deletion diagnostics have been proposed by Haslett (1999) for a generalised linear model with correlated errors. Christensen et al. (1992), Banerjee & Frees (1997) and Haslett & Dillane (2004) used deletion diagnostics in the linear mixed model and generalised linear mixed model by Xiang & Tse (2002). Qu & Song (2004) proposed using the QIF method when dealing with outliers or contaminated data (Huber, 1981; Ronchetti & Trojani, 2001; Mills et al., 2002; Holland & Welsh, 1977; Hampel et al., 1986).

9.2 Case Deletion for Multiple Linear Regression

In a linear regression model, an observation is considered to be influential if the important features of the analysis are changed when the observation is deleted (Cook, 1986, 1979, 1977; Chatterjee & Hadi, 1986). The influence of an observation is related to the residual and residual variance. Consider a multiple linear regression model

$$Y = X\beta + \epsilon \tag{9.1}$$

where Y is $n \times 1$ vector of response variables. The explanatory variables X form a matrix which full rank with dimension $n \times p$. The coefficient β is the $p \times 1$ parameter to be estimated and ϵ is a vector of independent random variables with zero mean and unknown variance σ^2. By least squares method we get

$$\hat{\beta} = (X^T X)^{-1} X^T Y.$$

The variance of $\hat{\beta}$ is given by

$$\text{Var}(\hat{\beta}) = \sigma^2 (X^T X)^{-1}.$$

Then, the fitted Y is

$$\begin{aligned} \hat{Y} &= X\beta \\ &= X(X^T X)^{-1} X^T Y \\ &= HY \end{aligned}$$

where the hat matrix H is defined as

$$H = X(X^T X)^{-1} X^T, \tag{9.2}$$

and the variance is

$$\text{Var}(\hat{Y}) = \sigma^2 H.$$

Suppose the residual vector is

$$\begin{aligned} e &= Y - \hat{Y} \\ &= (I - H)Y \end{aligned}$$

and has variance

$$\text{Var}(e) = \sigma^2 (I - H).$$

Cook's Distance measures the influence of an observation. It can be used to assess the influence when deleting an observation on the overall model fit (Cook & Weisberg, 1982). We follow standard notation as in Velleman & Welsch (1981) where we use Y_i to denote the ith row of Y and subscript notation $[i]$ to indicate the deletion of the ith observation. Cook (1977) suggested measuring the influence of the ith data point, through the distance

$$D_i = (\hat{\beta}_{[i]} - \hat{\beta})^T (X^T X)(\hat{\beta}_{[i]} - \hat{\beta})/(ps^2) \tag{9.3}$$

where $\hat{\beta}$ denotes the estimate of β and $\hat{\beta_{[i]}}$ denotes the estimate of β without the ith data

point and s^2 is the residual variance. More generally, we can replace

$$(X^T X)/ps^2$$

by $Var^{-1}(\hat{\beta})$ and we now have

$$D_i = (\hat{\beta}_{[i]} - \hat{\beta})^T Var^{-1}(\hat{\beta})(\hat{\beta} - \hat{\beta}_{[i]}) \tag{9.4}$$

A plot of D_i against i will validate which, if any, observations have a large effect on $\hat{\beta}$.

9.2.1 Cook's Distance for GEE Methods

We begin with the mean model from the myopic regret-regression method

$$h(Z_j;\theta) = E[Y_j|\bar{S}_K, \bar{A}_K] = \beta_0 + \beta_1(S_j|\bar{S}_{j-1}, \bar{A}_{j-1})Z_j - \mu_j(A_j|\bar{S}_{j-1}, \bar{A}_{j-1};\psi)$$

where $Z_j = S_j - E(S_j|\bar{S}_{j-1}, \bar{A}_{j-1})$ and the μ_j term is the regret function given as

$$\mu_j = \psi_1 \mid A_j - \psi_2 - \psi_3 S_j \mid .$$

for simplicity. We define as previously

$$I_j = \begin{cases} 1 & \text{if} \quad A_j - \psi_2 - \psi_3 S_j \geq 0 \\ -1 & \text{if} \quad A_j - \psi_2 - \psi_3 S_j < 0 \end{cases}$$

For each person i, let $Y_i = (Y_{i1}, \ldots, Y_{iK})$ for $i = 1, \ldots, n$ and $h_i = (h_{i1}(Z_{i1}, \theta), h_{i2}(Z_{i2}, \theta), \ldots)$. The diagnostics measure the influence of a deleted observation m with the overall fitted model. The deletion diagnostics for person m using Cook's distance for GEE is given by

$$D_m = (\hat{\theta}_{[m]} - \hat{\theta})^T Var^{-1}(\hat{\theta})(\hat{\theta}_{[m]} - \hat{\theta}). \tag{9.5}$$

Recall in Section 7.2 where we applied the myopic regret-regression to the GEE method. We minimise the weighted sum of squares (WSS) from Equation 7.8 to obtain $\hat{\theta}$. We take the value of $Var(\hat{\theta})$ by resampling the data using the bootstrap method.

9.2.2 Approximate Influence for GEE Method

The regret-regression and GEE methods use numerical search procedures to get the estimates and this can be quite slow. Repeating the procedure for each case in turn can be very slow. Therefore we investigate an approximation method that can be used in GEE. We start with

$$0 = \sum_{i=1}^{n} (\frac{\partial h}{\partial \theta})^T V_i^{-1}(Y_i - h_i(\theta)) \tag{9.6}$$

where $h_i(\theta)$ is the mean model given by

$$h_j(\theta) = \beta_0 + \beta_1(S_j|\bar{S}_{j-1}, \bar{A}_{j-1})Z_j - \mu_j(A_j|\bar{S}_{j-1}, \bar{A}_{j-1}; \psi).$$

We now let

$$f_i(\hat{\theta} = (\hat{\beta}, \hat{\psi})) = \left(\frac{\partial(\beta_0 + \beta_1 Z_j - \mu_j)}{\partial\beta}\right)^T V_i^{-1}(Y_i - (\beta_0 + \beta_1 Z_j - \mu_j)) \tag{9.7}$$

Then (9.6) becomes

$$0 = \sum_{i=1}^{n} f_i(\hat{\theta}).$$

Suppose we are interested in case m. Then

$$\begin{aligned} 0 &= f_m(\hat{\theta}) + \sum_{i \neq m} f_i(\hat{\theta}) \\ &= f_m(\hat{\theta}) + F_m(\hat{\theta}). \end{aligned} \tag{9.8}$$

Now suppose we delete person m. We obtain $\hat{\theta}_{[m]}$ by solving

$$0 = F_m(\hat{\theta}_{[m]}).$$

Taking a Taylor expansion gives

$$\begin{aligned} 0 &= F_m(\hat{\theta}_{[m]}) \\ &\simeq F_m(\hat{\theta}) + \frac{\partial F_m}{\partial\theta}(\hat{\theta}_{[m]} - \hat{\theta}) \\ &= -f_m(\hat{\theta}) + \frac{\partial F_m}{\partial\theta}(\hat{\theta}_{[m]} - \hat{\theta}) \end{aligned} \tag{9.9}$$

Using where we have used (9.8) generalised inverse matrix to avoid a possible singularity problem in inverting a matrix, we multiply both sides by

$$\left(\left(\frac{\partial F_m}{\partial\theta}\right)^T \left(\frac{\partial F_m}{\partial\theta}\right)\right)^{-1} \left(\frac{\partial F_m}{\partial\theta}\right)^T$$

where the partial derivatives is a matrix with dimension $p \times p$. To obtain the partial derivative $\partial F_m/\partial\theta$ we start with the f_i function defined in the earlier section. Given that

$$\begin{aligned} \sum_{i=1}^{n} f_i(\theta) &= \sum_{i=1}^{n} \frac{\partial h_i}{\partial\theta} V_i^{-1}(Y_i - h_i) \\ &= \sum_{j=1}^{n}\sum_{k=1}^{K} \frac{\partial h_{ij}}{\partial\theta} V_{jk}^{-1}(Y_k - h_k), \end{aligned} \tag{9.10}$$

then the partial derivative for f_i is

$$\frac{\partial f_i}{\partial \theta} = \sum_{j=1}^{n}\sum_{k=1}^{K} \frac{\partial^2 h_{ij}}{\partial \theta^T \partial \theta} V_{jk}^{-1}(Y_k - h_k) - \sum_{j=1}^{n}\sum_{k=1}^{K} \frac{\partial h_{ij}}{\partial \theta} V_{jk}^{-1} \frac{\partial h_{ik}}{\partial \theta}. \tag{9.11}$$

The first derivatives, $\partial h_{ij}/\partial\theta$ can be found in Section 8.3. For the second derivatives we have

$$\frac{\partial^2 h_{ij}}{\partial \theta^T \partial \theta} = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & I_{ij} & S_{ij}I_{ij} \\ 0 & 0 & I_{ij} & 0 & 0 \\ 0 & 0 & S_{ij}I_{ij} & 0 & 0 \end{pmatrix}, \tag{9.12}$$

i.e. a matrix with dimension 5×5 which has 0 on the diagonal and all elements are zero except

$$\frac{\partial h_{ij}}{\partial \psi_1 \partial \psi_2} = \frac{\partial h_{ij}}{\partial \psi_2 \partial \psi_1} = I_{ij}$$

and

$$\frac{\partial h_{ij}}{\partial \psi_1 \partial \psi_3} = \frac{\partial h_{ij}}{\partial \psi_3 \partial \psi_1} = S_{ij}I_{ij}.$$

Hence the approximation of the distance measure $(\hat{\theta}_{[}m] - \hat{\theta})$ is found:

$$\hat{\theta}_{[m]} - \hat{\theta} \simeq \left(\left(\frac{\partial F_m}{\partial \theta} \right)^T \left(\frac{\partial F_m}{\partial \theta} \right) \right)^{-1} \left(\frac{\partial F_m}{\partial \theta} \right)^T f_m(\hat{\theta}). \tag{9.13}$$

9.2.3 Case Deletion for Warfarin Data

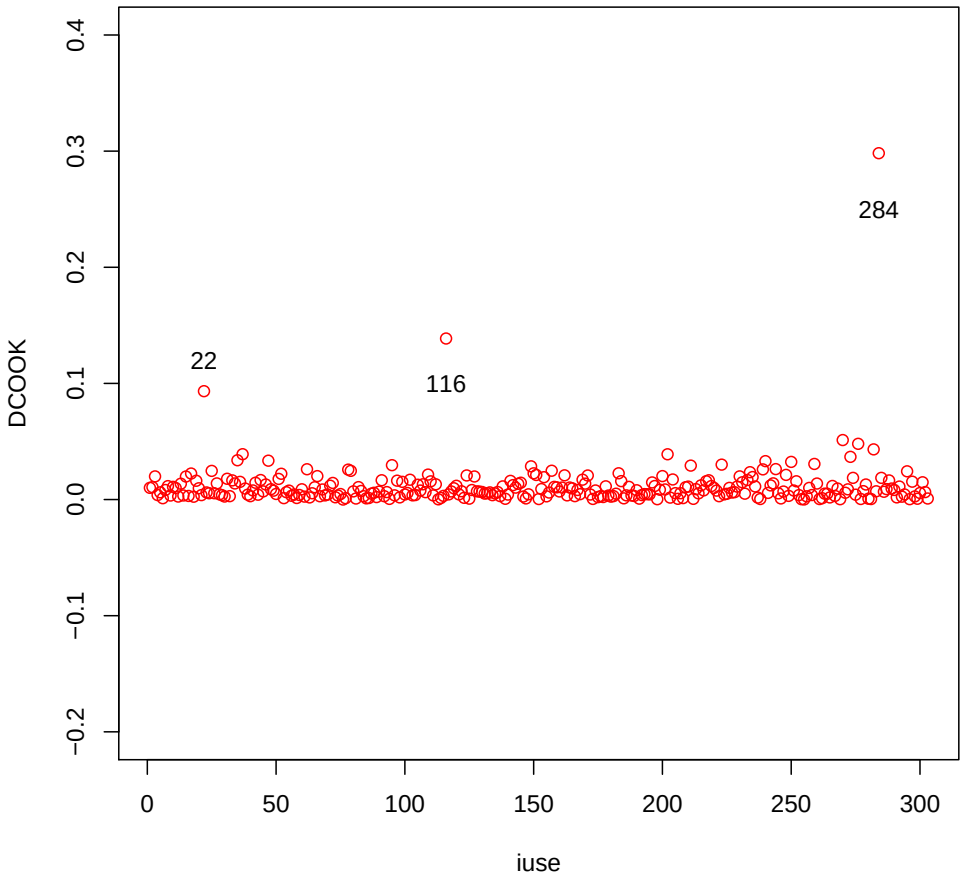

Figure 9.1: Cook's residual plot for regret-regression on Warfarin data.

Plot 9.1 shows the distance measure as in Equation (9.5)

$$D_m = (\hat{\theta}_{[m]} - \hat{\theta})^T Var^{-1}(\hat{\theta})(\hat{\theta}_{[m]} - \hat{\theta})$$

for each m when the regret-regression method is used for parameter estimation. We found there are three possible outliers: cases $22, 116$ and 284.

Rosthøj et al. (2006) defined A_j to be change in prescribed dose at visit j. The dose change distribution is quite symmetric with mean -0.01132 which is quite close to 0. There were occasional very large changes, with range between -9 to +8 units for all patients. Rosthøj et al. (2006) took the optimal actions to be bounded at ± 3. For cases 22, we found there are five times where the dose remain unchanged, with 0 units but at visit 10, the dose fell out of range with -4 units. This leads to this patient with high influence. Meanwhile case 116 has 7 visits with unchanged dose and high dose changes ($+2.5$ units) at the end of visits, 12 and 13. Case 284 has six visits with unchanged dose but have 2 extreme out of range dose changes at visit 6 with -9 units and visit 7 with $+8$ units.

The state at time j, S_j is defined as the proportion of the difference, either positive or negative between INR at time j with the width of that target range. Rosthøj et al. (2006) decided $S_j = 0$ as INR in range and $S_j \neq 0$ if INR is not in range. The state distribution is positively skewed with range -1.53 to 5.00 and the mean is 0.2133. The lower and upper quantiles are -0.19 and 0.80, and the median is 0.25.

We found there are 4 times where the INR in range for case 22. There are 4 times at the very high state found at visit 3, 5, 7 and 8, and 2 times at the very low state, at visits 2 and 10. Patient 116 had only 3 times where the INR was in range at visits 5, 6 and 13. We found at visits 1, 2, 3, 8 and 10 the patient was in very high state and visits 4, 7, 11 and 12 with very low state. Patient 284 had 6 times with INR in range over the visits and 4 times with very high state, at visits 4, 6, 7 and 10 while the very low state was found only at visit 5. Overall it seems these three cases are influential because they have occasional very high dose changes.

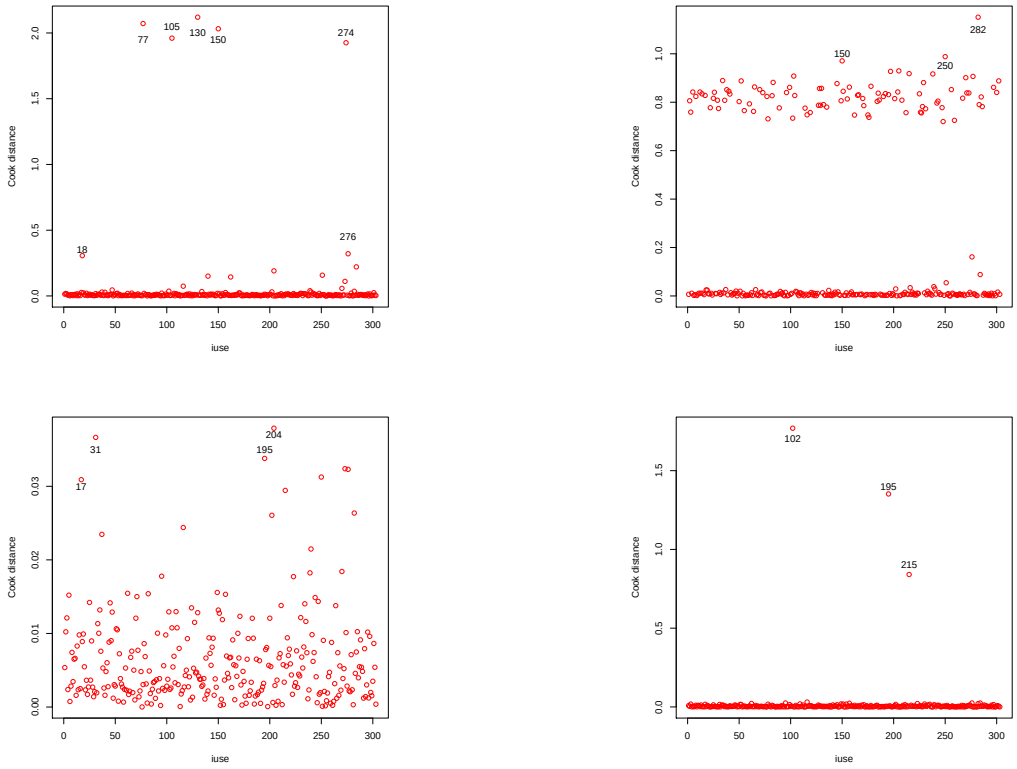

Figure 9.2: Cook's residual plots for Warfarin data under GEE-AR(1) (top row) and GEE-exchangeable (bottom row) at $\rho = 0.5$ (left column) and $\rho = 0.9$ (right column).

Figures 9.2 show the Cook's residual plots for GEE under AR(1) or exchangeable working correlation for estimation. The first row represent GEE AR(1) working correlation matrix and the second row represent GEE exchangeable matrix. The first column has GEE with $\rho = 0.5$ and second column has GEE with $\rho = 0.9$. We see that the different methods yield very different influential observations. We found a very high influential observations for cases 77, 130 and 150 under the GEE-AR(1) at $\rho = 0.5$ and case 102 under the GEE-exchangeable working correlation at $\rho = 0.9$. We also found the influential observations are scattered around Cook's distance$= 0.8$ but cases 150, 250 and 282 are obviously stand out among the other high influential observations under the GEE-AR(1) at $\rho = 0.9$.

The three previously identified cases usually no longer stand out. This is seen in Figure 9.3, which show, the Cook's distance for these cases for GEE under AR(1) or exchangeable working correlation plotted against the regret-regression Cook's distance. We can see there is a positive relationship between the GEEs and the regret-regression method. The Cook's distance for GEE-AR(1) when $\rho = 0.5$ and GEE-exchangeable when $\rho = 0.5$ and $\rho = 0.9$ are smaller than the Cook's distance for the regret-regression method. However, the result is difference under the GEE-AR(1) at $\rho = 0.9$ where the Cook's distance is much higher than the Cook's distance for the regret-regression method.

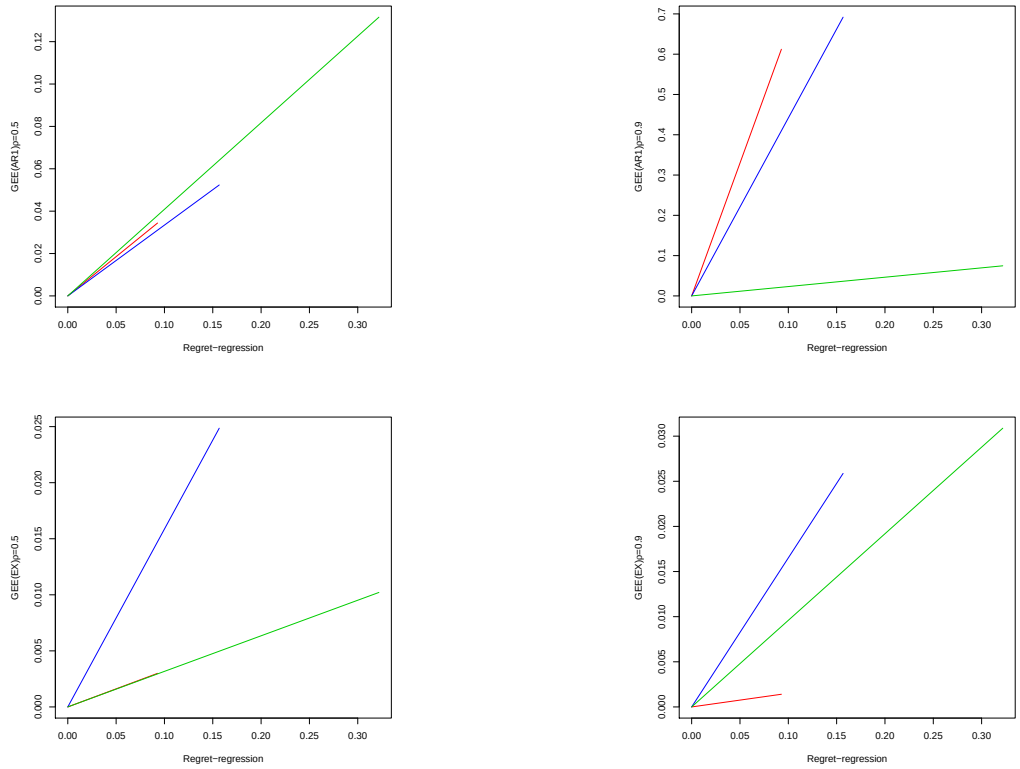

Figure 9.3: Comparison plots between Cook's distance for regret-regression and GEE using AR(1) and exchangeable working correlation for one-case deletion Warfarin data. The top row is the GEE under AR(1) and bottom row is the GEE under the exchangeable working correlation matrix at $\rho = 0.5$ (left column) and $\rho = 0.9$ (right column). The red line for deletion case 22, the blue line indicate the deletion case 116 and the green line for deletion case 284.

Table 9.1 shows how the parameter estimates change when these cases are deleted. For regret-regression method we found the distance to be small except for $\hat{\psi}_1$ and $\hat{\psi}_3$. Deleting cases 116 and 284 give greater changes than deleting case 22. The distance for GEE under AR(1) with $\rho = 0.5$ is also considered small except for $\hat{\psi}_1$ when deleting case 22. Similar to the regret-regression method, removing patients 116 and 284 gave large changes.

In contrast to the previous results, we found the GEE-AR(1) at $\rho = 0.9$ had large effects for all cases especially $\hat{\psi}_3$ for cases 22 and 116. There are small changes when deleting any cases for GEE-exchangeable method at $\rho = 0.5$. Similar results apply to the GEE-exchangeable method with $\rho = 0.9$ except for cases 116 and 284, especially $\hat{\psi}_1$ and $\hat{\psi}_3$.

Table 9.2 shows the comparison of methods using the approximation distance measures. Using the approximation method, we found the changes in parameter estimates for GEE either AR(1) or Exchangeable working correlation at $\rho = 0.5$ and $\rho = 0.9$ are much smaller and the results are quite similar as in Table 9.1 except there are no longer very large differences under GEE AR(1) with $\rho = 0.9$.

	Without Deletion	Remove 22nd patient		Remove 116th patient		Remove 284th patient	
Methods	Estimates	Est	Diff	Est	Diff	Est	Diff
Regret-regression	$\hat{\beta}_1 = 6.334$	6.340	0.006	6.352	0.018	6.345	0.011
	$\hat{\beta}_2 = -2.029$	-2.026	0.004	-2.018	0.012	-2.042	-0.012
	$\hat{\psi}_1 = 0.586$	0.628	0.043	0.633	0.048	0.660	0.074
	$\hat{\psi}_2 = 0.000$	0.000	0.000	0.000	0.000	0.000	0.000
	$\hat{\psi}_3 = -3.196$	-3.024	0.172	-3.032	0.164	-2.881	0.316
$\text{GEE}_{AR(1)\rho=0.5}$	$\hat{\beta}_1 = 6.105$	6.115	0.009	6.136	0.031	6.131	0.026
	$\hat{\beta}_2 = -2.569$	-2.565	0.004	-2.545	0.024	-2.560	0.009
	$\hat{\psi}_1 = 0.827$	0.857	0.029	0.883	0.056	0.948	0.121
	$\hat{\psi}_2 = 0.192$	0.194	0.002	0.187	-0.005	0.160	-0.032
	$\hat{\psi}_3 = -1.028$	-1.021	0.006	-1.056	-0.029	-0.969	0.058
$\text{GEE}_{AR(1)\rho=0.9}$	$\hat{\beta}_1 = 5.933$	5.930	-0.002	5.957	0.025	5.950	-0.155
	$\hat{\beta}_2 = -2.736$	-2.743	-0.006	-2.737	-0.001	-2.743	-0.175
	$\hat{\psi}_1 = 0.275$	0.142	-0.133	0.169	-0.106	0.317	-0.511
	$\hat{\psi}_2 = 0.491$	0.997	0.507	0.951	0.460	0.444	0.253
	$\hat{\psi}_3 = -1.070$	-1.922	-0.852	-1.876	-0.805	-1.025	0.003
$\text{GEE}_{Ex(\rho=0.5)}$	$\hat{\beta}_1 = 6.330$	6.335	0.005	6.346	0.016	6.337	0.008
	$\hat{\beta}_2 = -2.007$	-2.000	0.006	-1.992	0.015	-2.015	-0.009
	$\hat{\psi}_1 = 0.368$	0.373	0.005	0.377	0.009	0.372	0.004
	$\hat{\psi}_2 = 0.000$	0.000	0.000	0.000	0.000	0.000	0.000
	$\hat{\psi}_3 = -5.011$	-5.000	0.011	-5.000	0.011	-5.000	0.011
$\text{GEE}_{Ex(\rho=0.9)}$	$\hat{\beta}_1 = 6.327$	6.331	0.004	6.346	0.019	6.337	0.010
	$\hat{\beta}_2 = -2.004$	-1.998	0.006	-1.991	0.013	-2.015	-0.011
	$\hat{\psi}_1 = 0.317$	0.321	0.003	0.368	0.050	0.363	0.045
	$\hat{\psi}_2 = 0.000$	0.000	0.000	0.000	0.000	0.000	0.000
	$\hat{\psi}_3 = -5.767$	-5.770	-0.003	-5.125	0.642	-5.125	0.642

Table 9.1: The parameter estimates and the differences when cases 22, 116 and 284 are deleted in turn for Warfarin data.

	Without Deletion	Remove 22nd patient		Remove 116th patient		Remove 284th patient	
Methods	Estimates	Est	Diff	Est	Diff	Est	Diff
$\text{GEE}_{AR(1)\rho=0.5}$	$\hat{\beta}_1 = 6.105$	6.102	-0.003	6.104	-0.001	6.125	0.019
	$\hat{\beta}_2 = -2.569$	-2.564	0.004	-2.559	0.009	-2.579	-0.010
	$\hat{\psi}_1 = 0.827$	0.831	0.004	0.832	0.005	0.827	0.000
	$\hat{\psi}_2 = 0.192$	0.207	0.015	0.211	0.019	0.175	-0.017
	$\hat{\psi}_3 = -1.028$	-1.049	-0.021	-1.063	-0.035	-1.060	-0.032
$\text{GEE}_{AR(1)\rho=0.9}$	$\hat{\beta}_1 = 5.926$	5.920	-0.006	5.918	-0.008	5.957	0.031
	$\hat{\beta}_2 = -2.743$	-2.741	0.002	-2.737	0.007	-2.751	-0.007
	$\hat{\psi}_1 = 0.138$	0.142	0.004	0.143	0.005	0.140	0.002
	$\hat{\psi}_2 = 1.000$	1.013	0.013	1.016	0.016	0.985	-0.014
	$\hat{\psi}_3 = -1.931$	-1.950	-0.019	-1.964	-0.033	-1.960	-0.029
$\text{GEE}_{Ex(\rho=0.5)}$	$\hat{\beta}_1 = 6.330$	6.326	-0.004	6.334	0.004	6.351	0.021
	$\hat{\beta}_2 = -2.007$	-1.998	0.008	-1.992	0.015	-2.017	-0.011
	$\hat{\psi}_1 = 0.369$	0.370	0.001	0.370	0.002	0.362	-0.007
	$\hat{\psi}_2 = 0.000$	0.016	0.016	0.016	0.016	-0.031	-0.031
	$\hat{\psi}_3 = -5.001$	-5.024	-0.023	-5.051	-0.050	-5.062	-0.061
$\text{GEE}_{Ex(\rho=0.9)}$	$\hat{\beta}_1 = 6.327$	6.323	-0.004	6.331	0.004	6.347	0.020
	$\hat{\beta}_2 = -2.004$	-1.996	0.008	-1.989	0.015	-2.014	-0.010
	$\hat{\psi}_1 = 0.317$	0.318	0.001	0.319	0.002	0.311	-0.006
	$\hat{\psi}_2 = 0.000$	0.016	0.016	0.017	0.017	-0.029	-0.029
	$\hat{\psi}_3 = -5.770$	-5.792	-0.022	-5.819	-0.048	-5.828	-0.058

Table 9.2: The parameter estimates and the differences when cases 22, 116 and 284 are deleted in turn, using approximation method for Warfarin data.

9.3 Conclusions

To test the robustness of the GEE method, we have investigated one-case deletion using the Cook's distance and an approximation method. One case deletion is used to identify influential observations and to see the effect of the deleted observations on the model fit. We found three cases to be influential in regret-regression, namely 22, 116 and 284. These patient all had at least one very large dose change.

Usually there was little correlation between influence under regret-regression and influence under GEE. This is an area of further work.

Chapter 10

Conclusion and Future Works

This thesis explores an alternative method for finding optimal dynamic treatment regimes, the regret-regression method. In Chapter 2 we have shown that the regret-regression method provides better estimates in optimal dynamic treatment regimes with consistent estimates and high efficiency in the simulations when compared to the Murphy and Robins methods. It is also less challenging in computation than Murphy and Robins methods.

The sensitivity of the model is tested in Chapter 3, where we misspecified the initial values for the Murphy and the regret-regression methods. The Murphy method found robust for large samples in all the misspecification tests through giving a good convergence rates estimates except for the test with unequal action probabilities which depend on states at time j where a correct specifications of the action model was needed. A similar procedure was used for regret-regression method and it is also robust in estimates. However a correct state model is needed.

We extended the investigation by including the covariate effects into the regret-regression method using simulation in Chapter 4. We created six possible models which contain one true model and five misspecified models with the aim of investigating the effect of the missing parameters or covariates in the model. Diagnostic assessment was used to identify any unusual characteristics by looking at the residual plots and using a wild bootstrap test. The wild bootstrap is used to confirm there are no trends in the residuals.

The regret-regression method was applied to data on anticoagulation. In Chapter 5 we introduced a simplified state model by removing the nonsignificant covariate terms from the previous state model due to there being little difference in performance compared with the previous state model. We used the myopic decision rules for the regret-regression method with application to the anticoagulant data in Chapter 6.

Myopic decision rules have an advantage we do not have to wait until the end of the study to measure the response Y and hence these are more practical for real application. We chose to use the one step method Y_j and two steps method $Y_j^{(2)}$ to compare with the long term response Y and considered two different cases: the continuous (PTR) case and the discrete/binary (INR) case. Overall we found there is a little difference when comparing between the long term with one step or the two steps method. Diagnostic

assessment using the residual plot and wild bootstrap were used to investigate the model adequacy. The residual plots and wild bootstrap tests showed that there was no real trend for all responses, though some are statistically significant. Therefore, the myopic decision rules using the regret-regression method is valid for future investigation.

The GEE method provides a general approach for the analysis of correlated data and does not require any distributional assumptions. The GEE method was applied to the myopic regret-regression method either with one-step or the two-steps methods in Chapter 7. In simulation, we assumed an AR(1) the true working correlation structure and we found that the estimates are generally good with either the true or misspecified working correlation for one and two step methods and various ρ. We prefer to use the one step method rather than two steps methods due to its simplicity.

The extended version of GEE is known as the quadratic inference function (QIF). It is efficient even with a misspecified correlation structure. The characteristics of QIF were described in detail in Chapter 8. Both GEE and QIF were investigated using the myopic regret-regression method via simulation and application to Warfarin data. Similar to the GEE results, the QIF myopic regret-regression is also robust in estimation. The final part, Chapter 9 investigated the influential observations in Warfarin data using the GEE myopic regret-regression method.

We investigated the one-case deletion for GEE method using the Cook's distance and the approximation method. Some differences in influence were detected depending on fitting method. Overall results shown that the observation 284 is considered as most influential for the myopic regret-regression and GEE methods with AR(1) and GEE exchangeable working correlation matrices at various ρ. The approximation method suggested in this chapter has provided an alternative method to find the influence of a case much more quickly then by case deletion.

10.1 Future Works

We can extend our work on the influential observations with application to Warfarin data using the QIF method. Beside of investigating the distance measurement using Cook or the approximation method, we found it is useful to investigate the parameter estimates using both methods and then compare the methods together. However, this needs more research. It also will be useful to investigate the myopic regret-regression with covariates and then apply it to the Warfarin data.

One of the assumptions made throughout the thesis is that observations are made at the same times on all individuals. In practice this is unrealistic as visits times in observational data will vary between individuals and over time. A major research topic for the future will be to extend the regret-regression or other estimation methods to incorporate unbalanced data.

In this thesis we only considered one data set and it would be useful further work

which involve testing on more data. Other authors have worked with very simple data, i.e. binary treatments and two time points, and there are no published data sets with more realistic structures.

Chapter 11

Appendix

11.1 Chapter4: Appendix 1

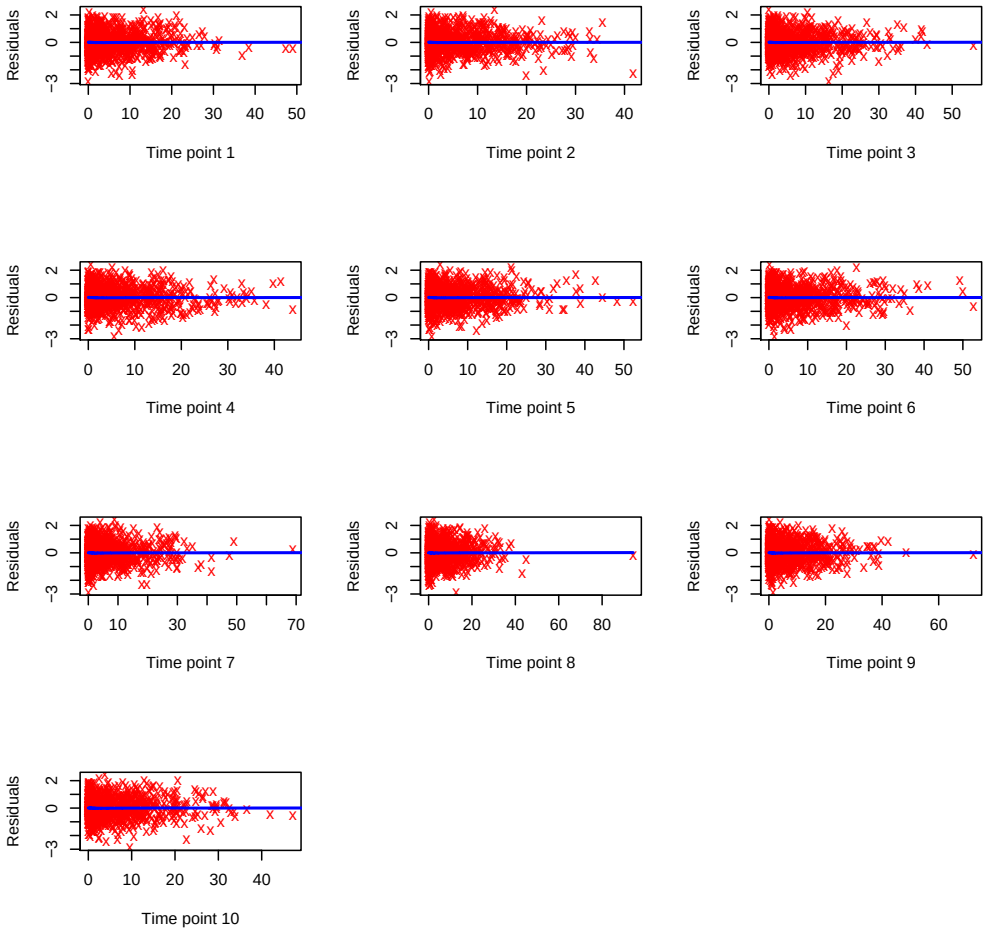

Figure 11.1: Residuals plotted against the regrets for model M_0 at different time points.

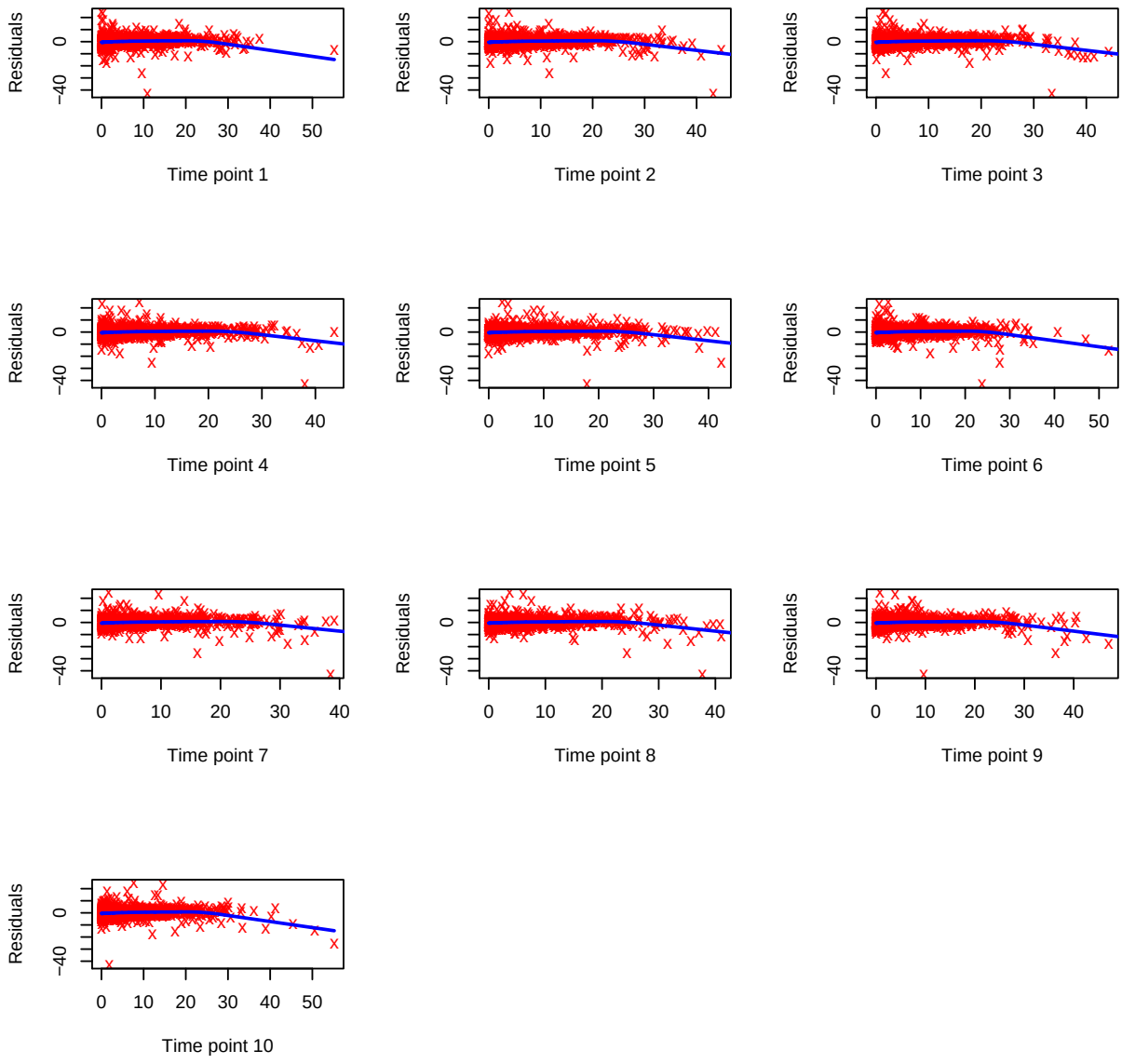

Figure 11.2: Residuals plotted against the regrets for model M_1 at different time points.

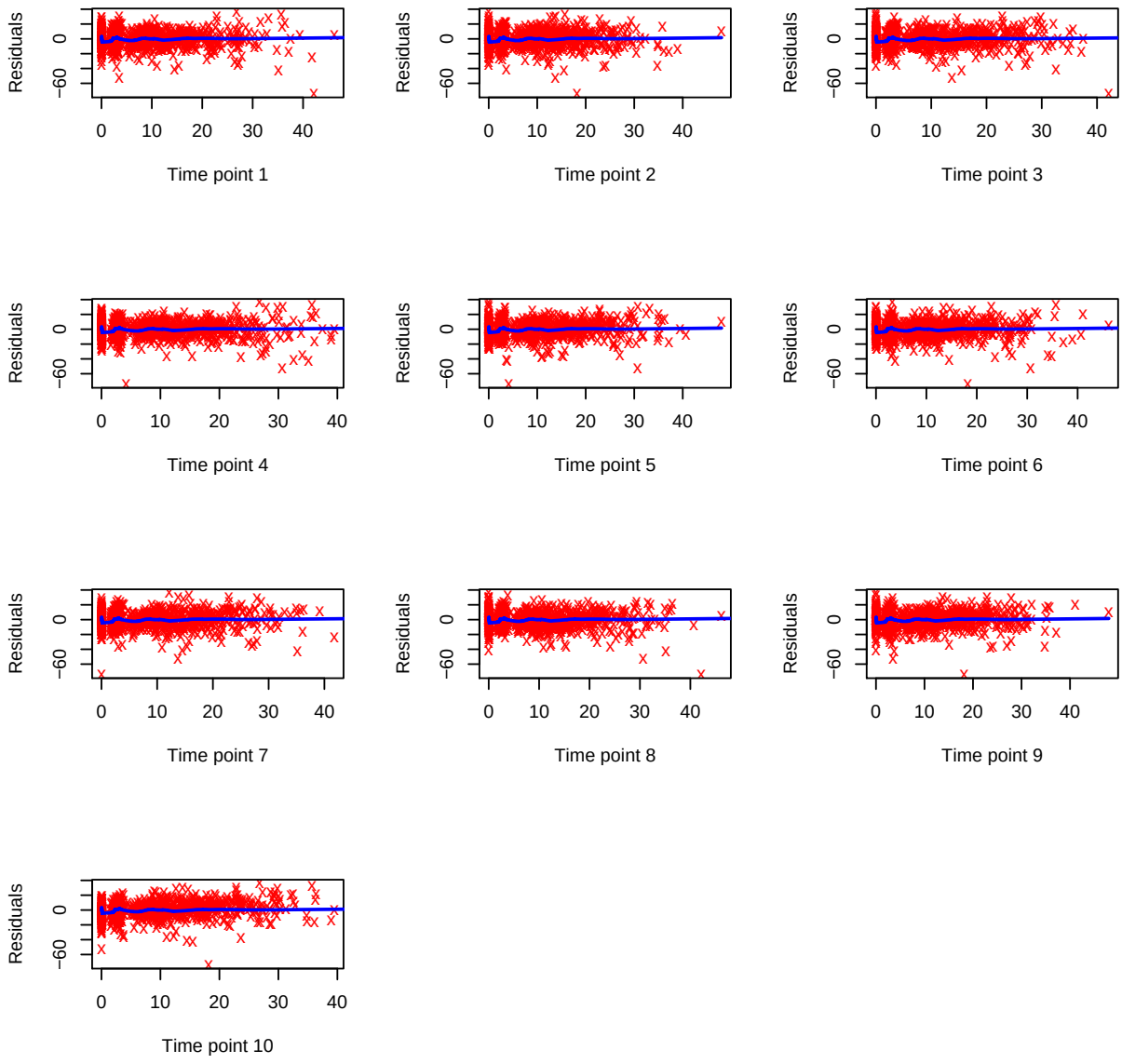

Figure 11.3: Residuals plotted against the regrets for model M_2 at different time points.

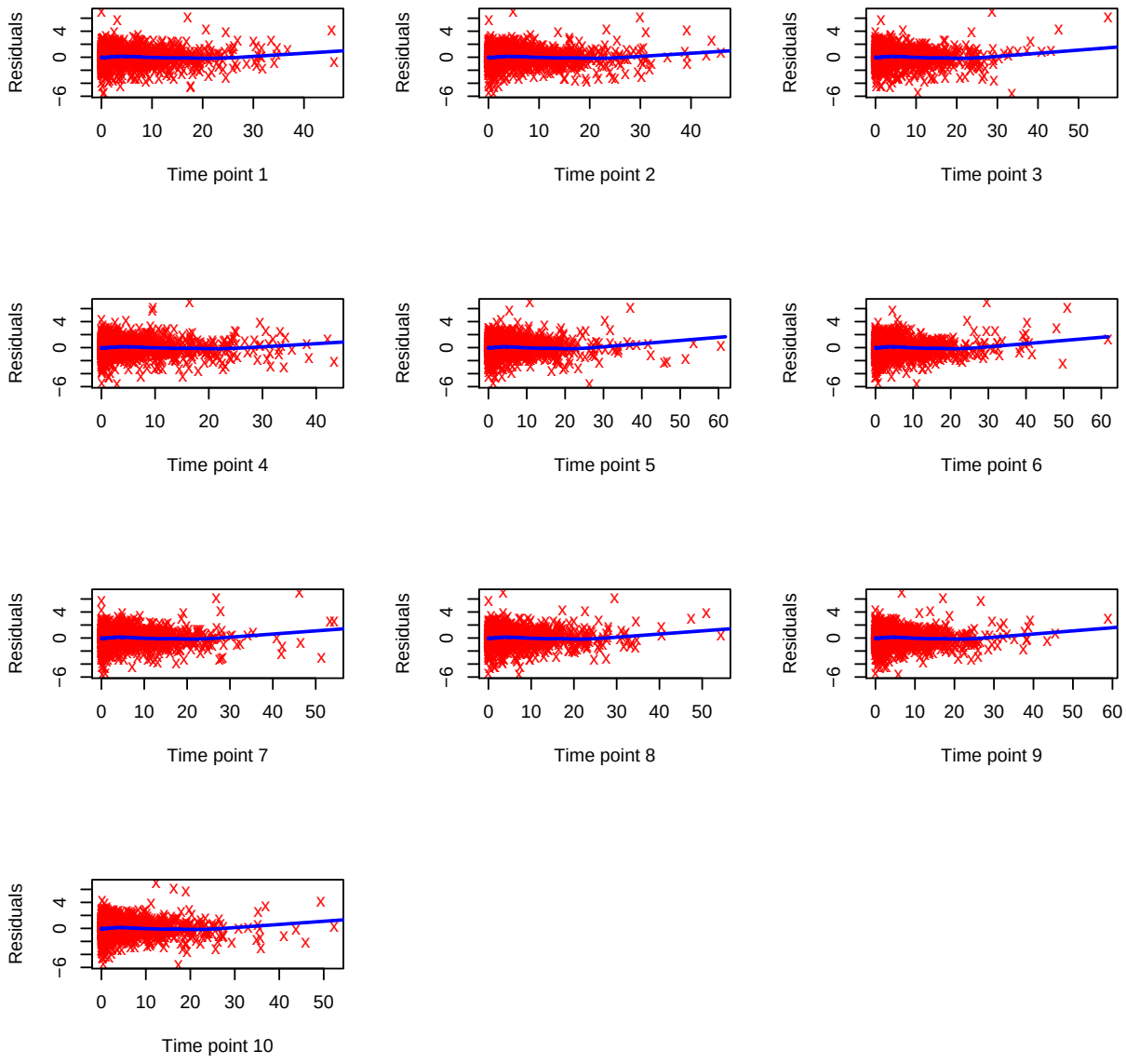

Figure 11.4: Residuals plotted against the regrets for model M_3 at different time points.

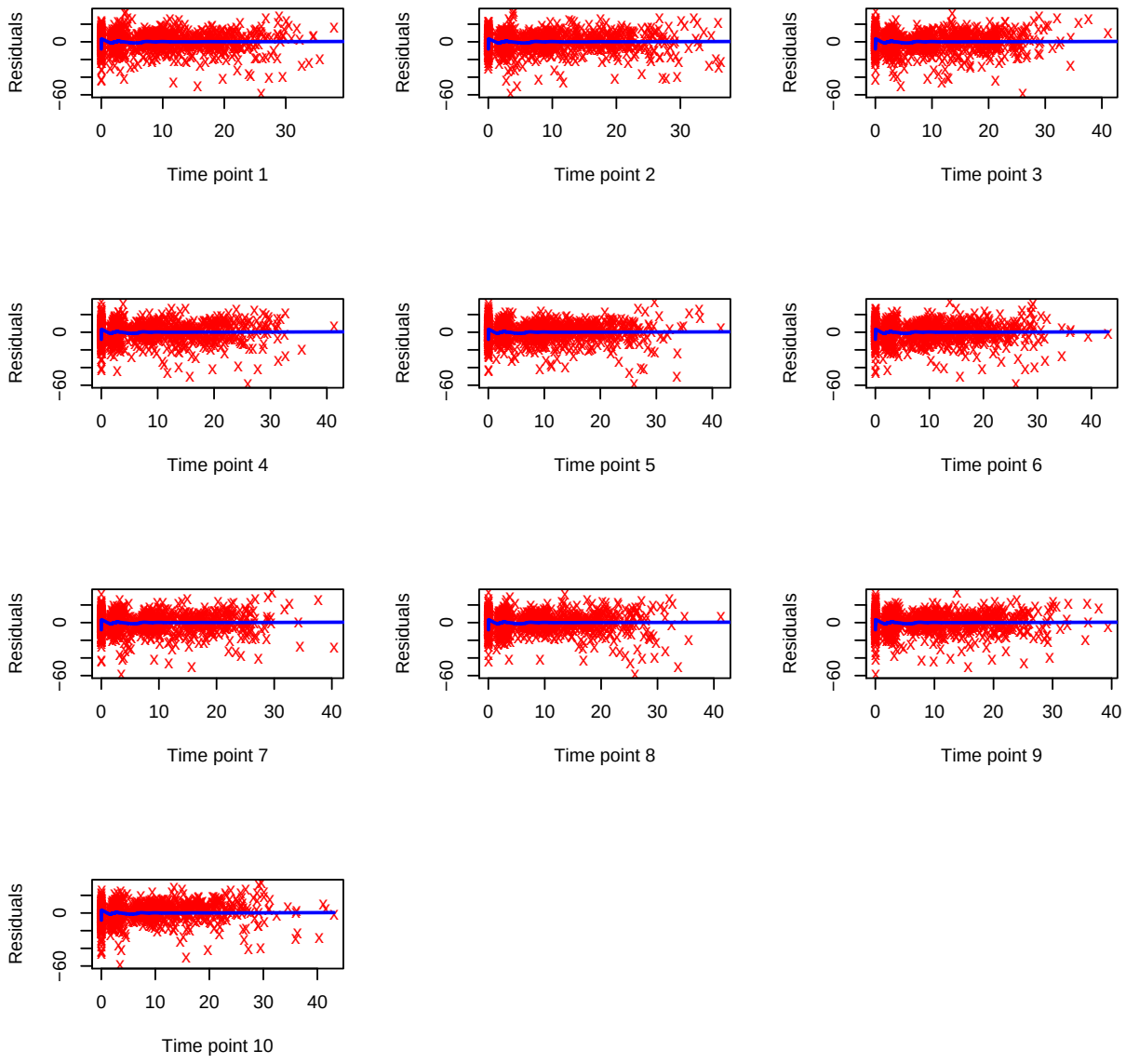

Figure 11.5: Residuals plotted against the regrets for model M_4 at different time points.

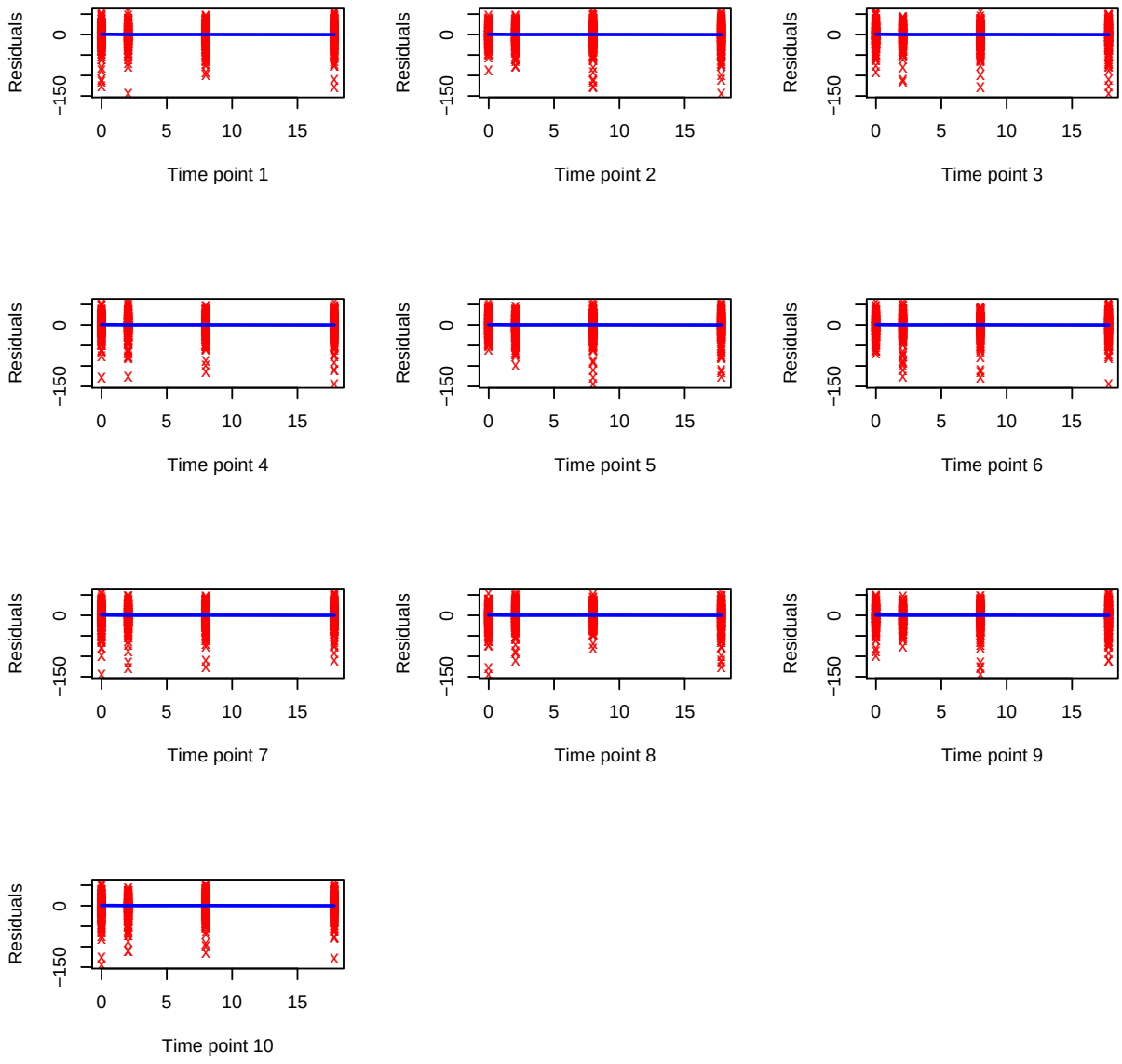

Figure 11.6: Residuals plotted against the regrets for model M_5 at different time points.

11.2 Chapter4: Appendix 2

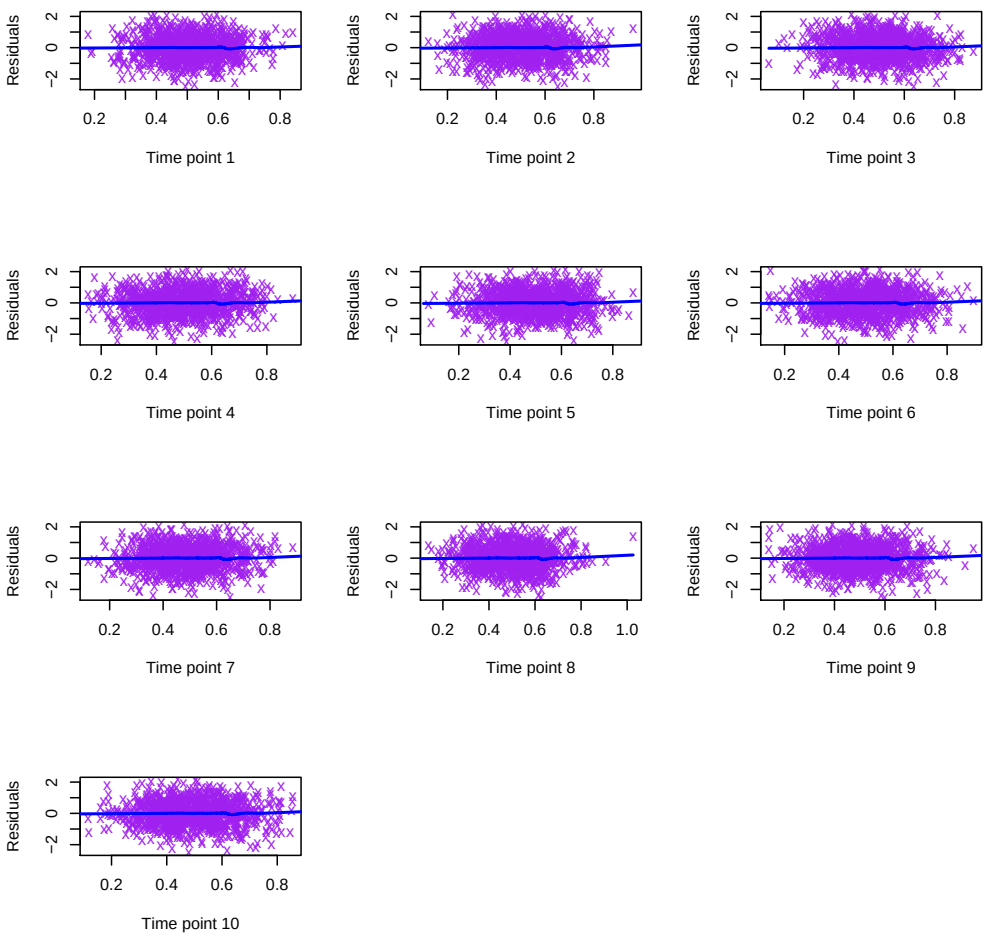

Figure 11.7: Residuals plotted against the states for model M_0 at different time points.

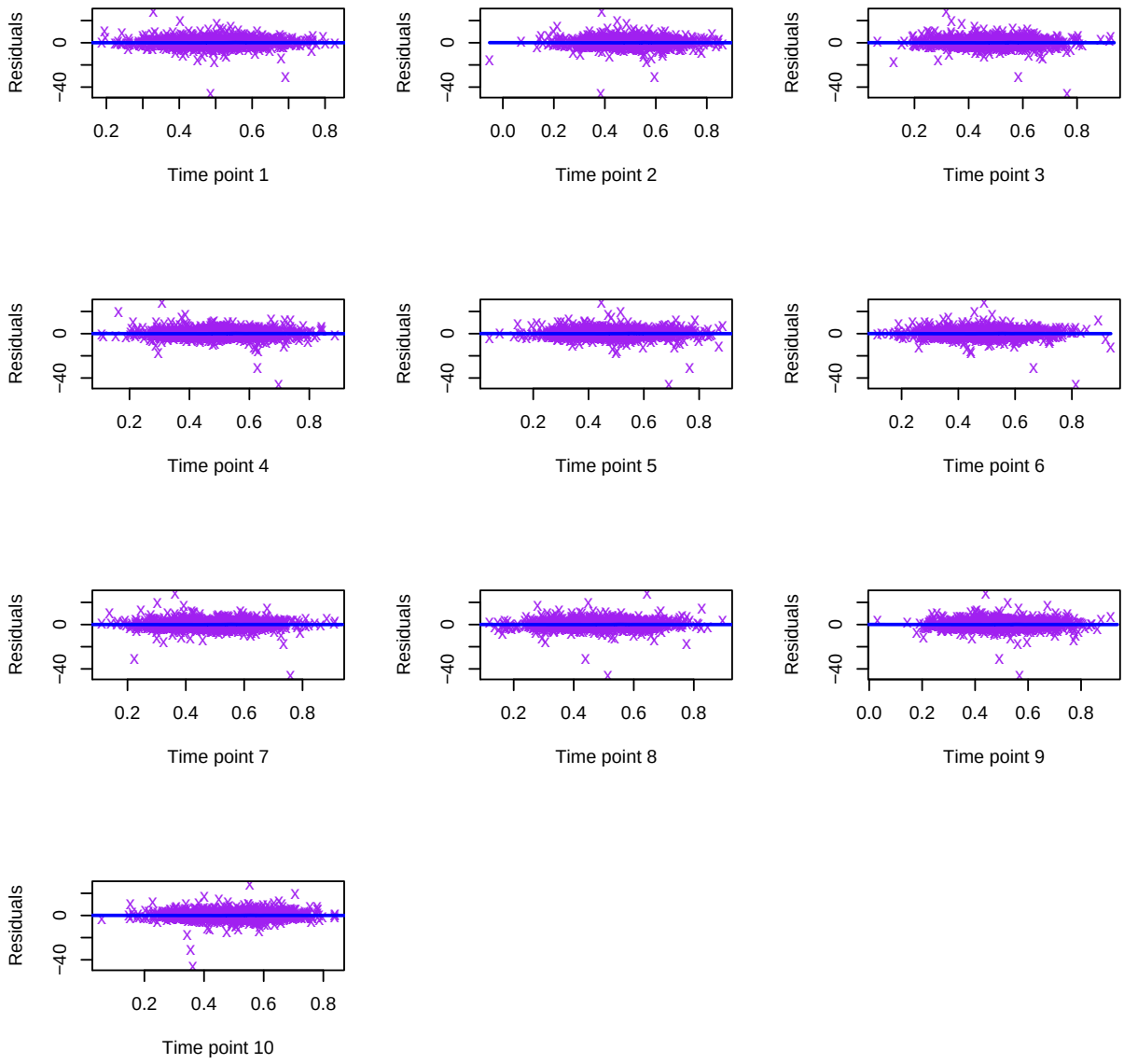

Figure 11.8: Residuals plotted against the states for model M_1 at different time points.

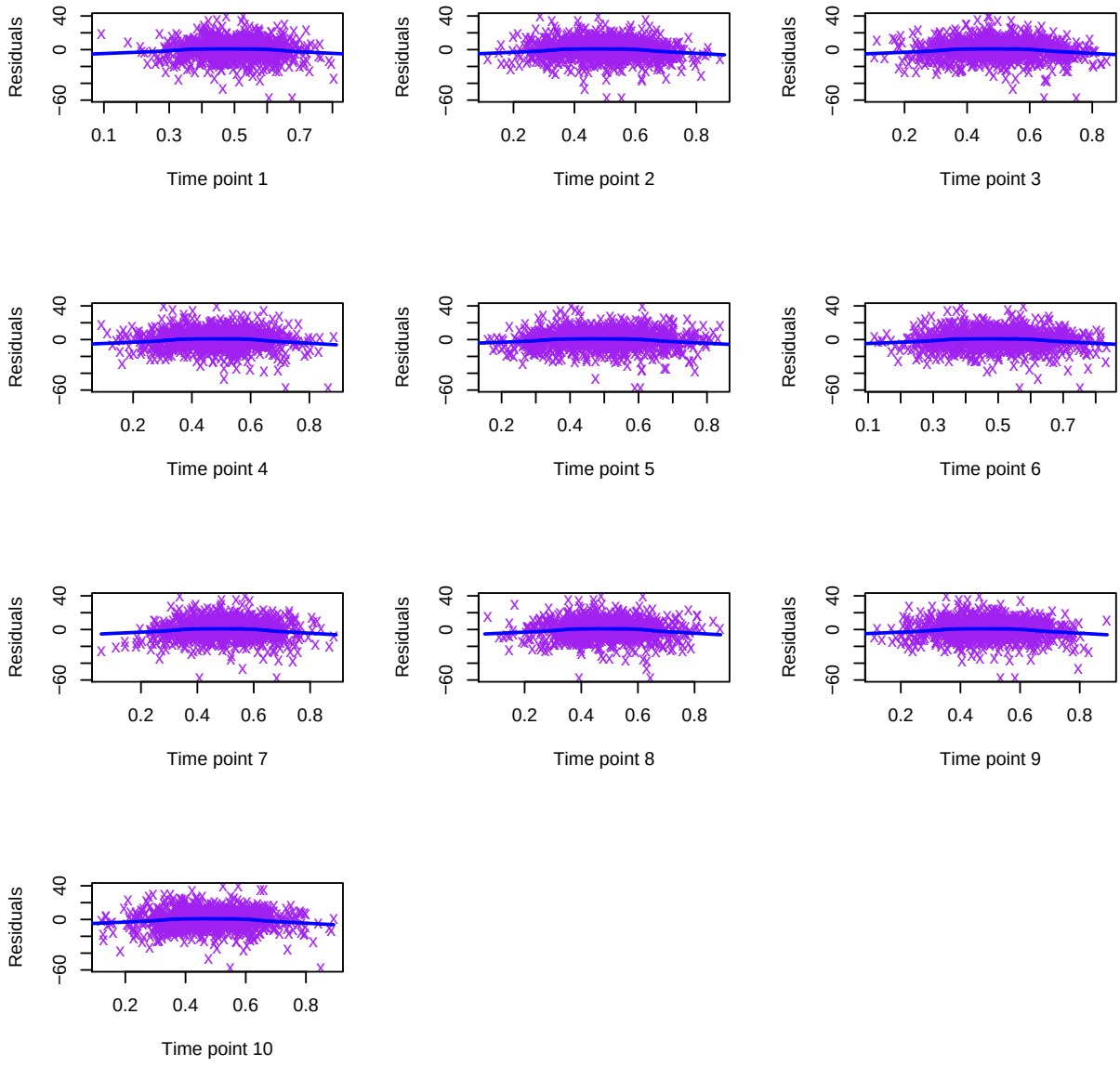

Figure 11.9: Residuals plotted against the states for model M_2 at different time points.

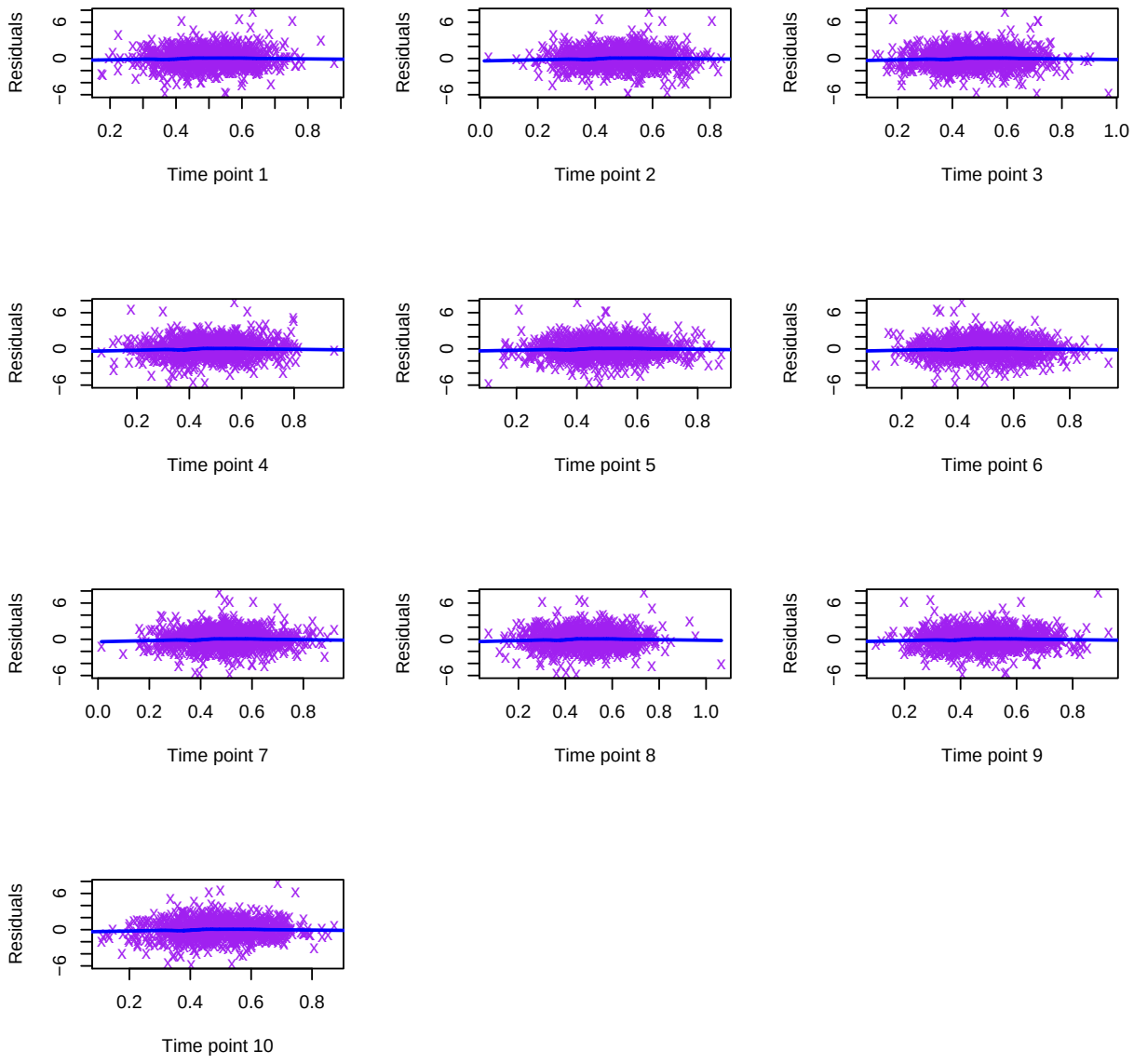

Figure 11.10: Residuals plotted against the states for model M_3 at different time points.

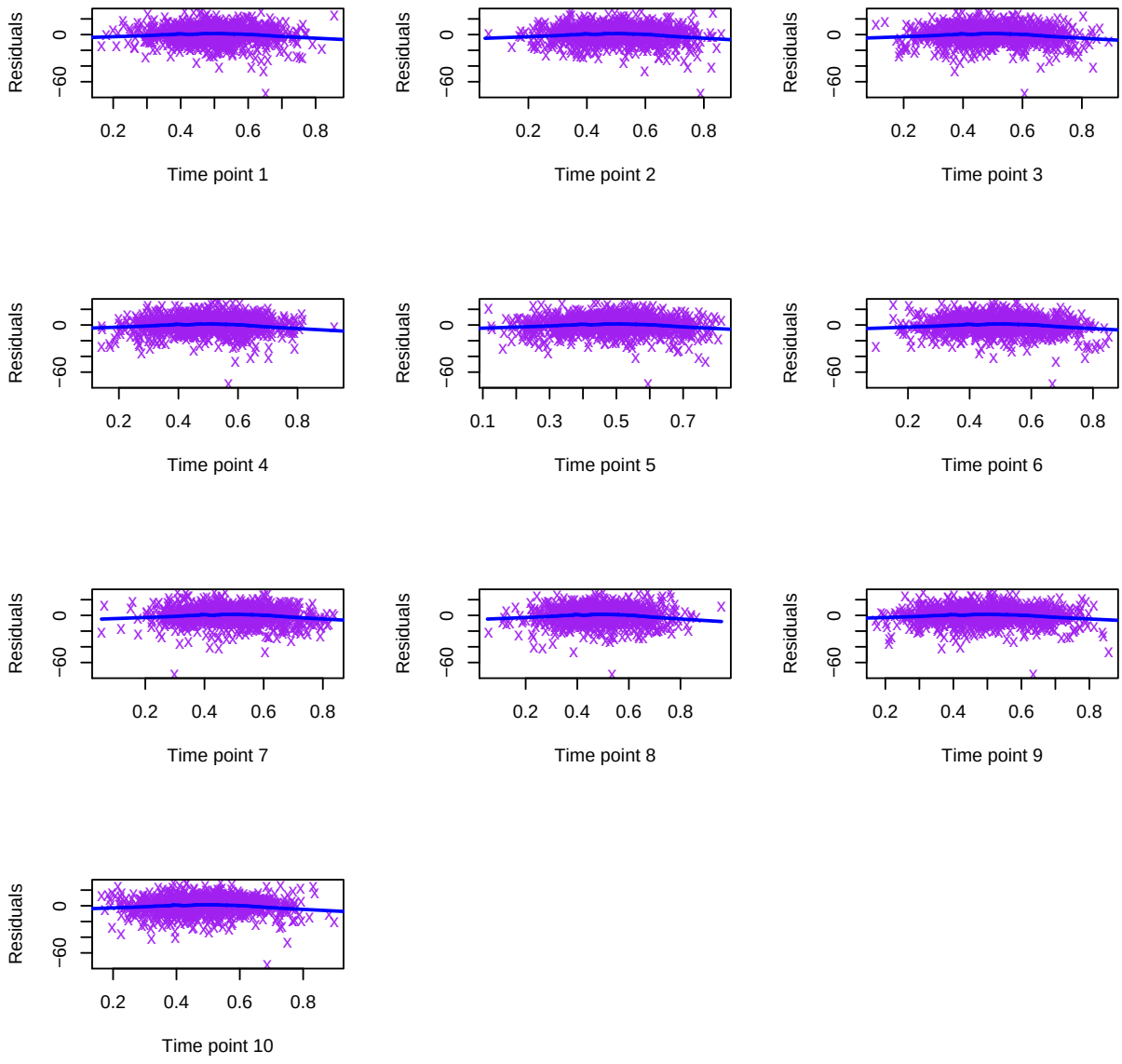

Figure 11.11: Residuals plotted against the states for model M_4 at different time points.

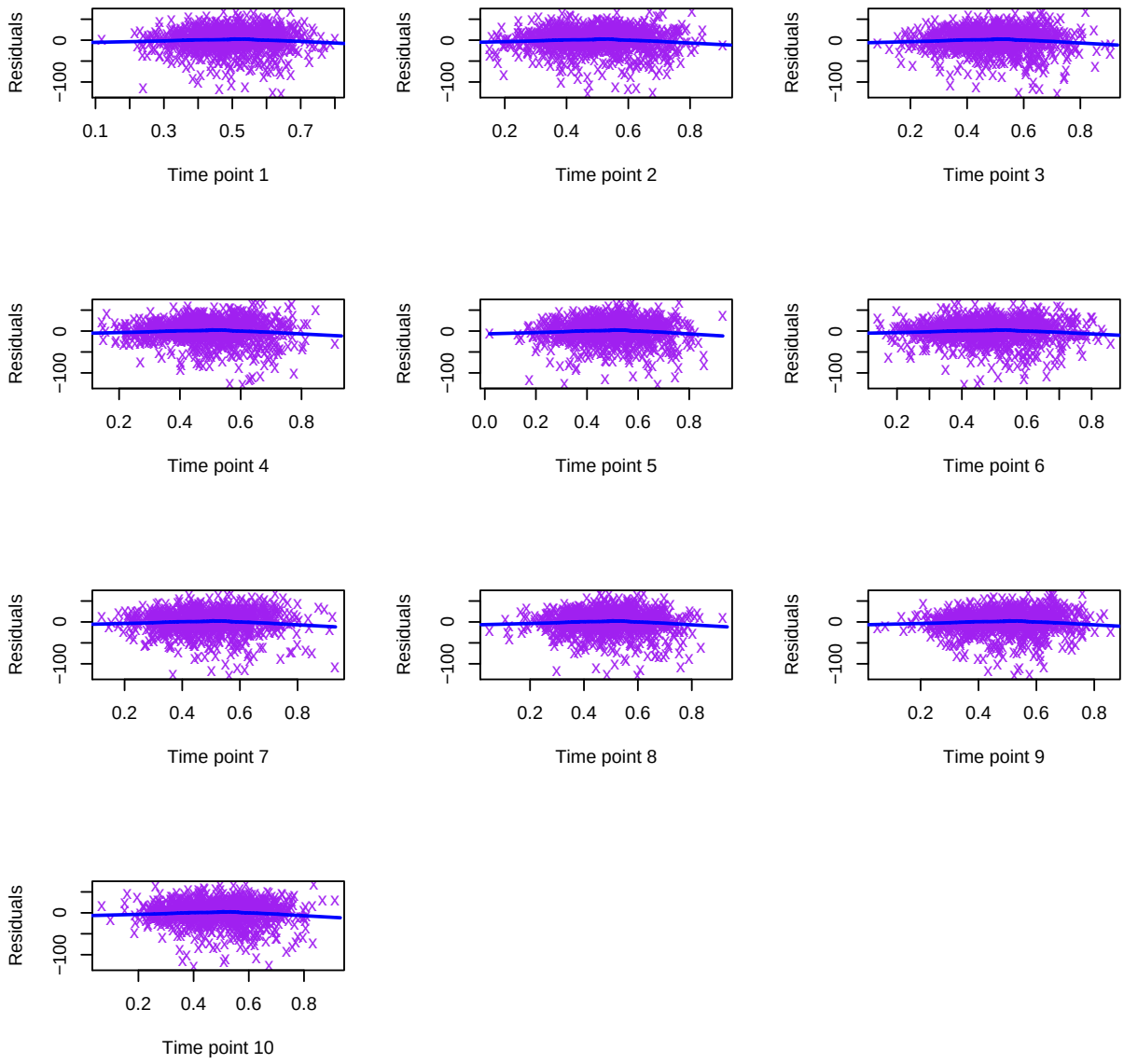

Figure 11.12: Residuals plotted against the states for model M_5 at different time points.

11.3 Chapter4: Appendix 3

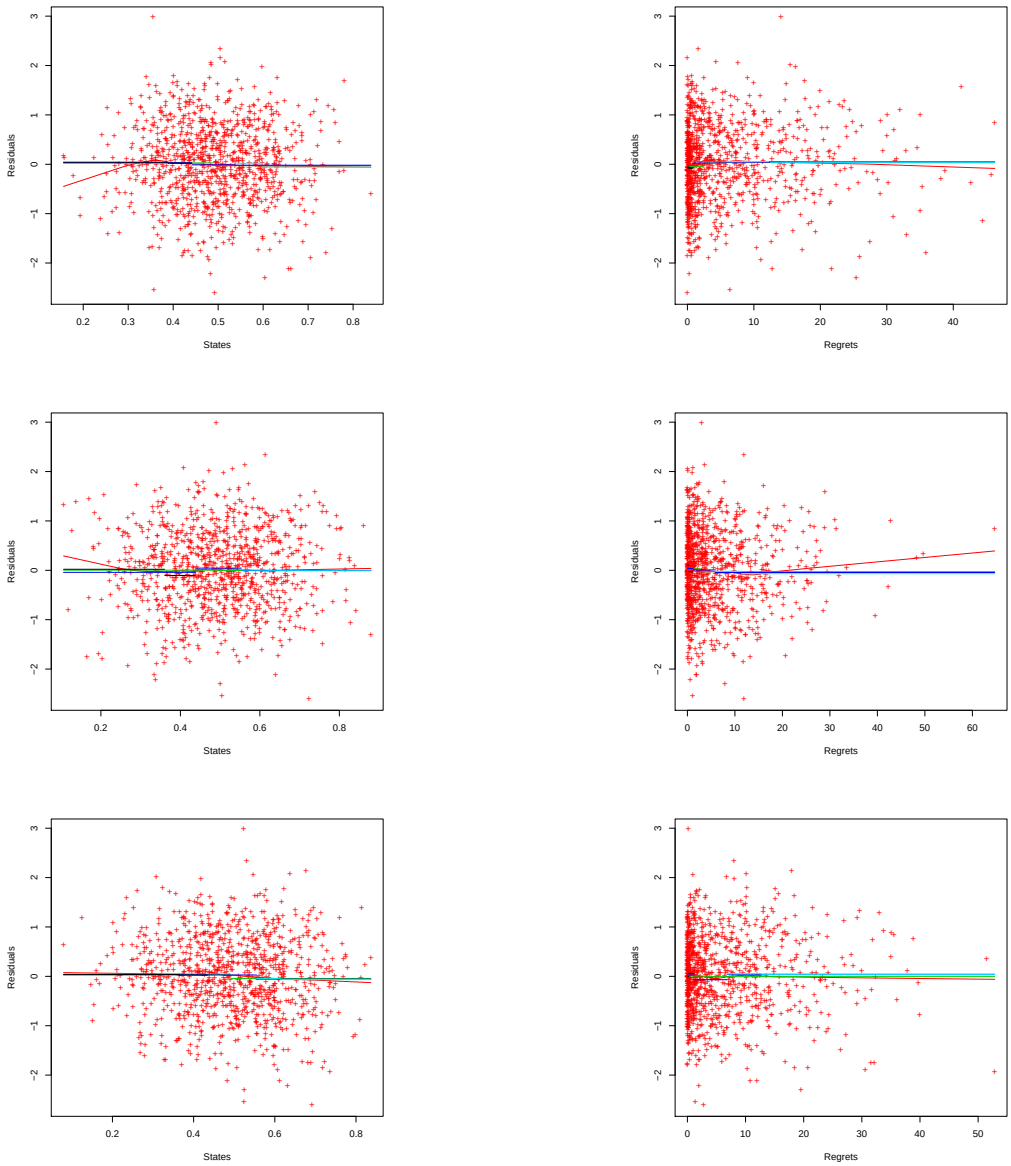

Figure 11.13: The mean residual plots at selected time points $1, 5, 9$ for model M_0. Each row represent the timepoints where the first row for time point one, second row for time point five and third row for time point nine. The first column represent the residuals against the states plots while the second column is for the residuals against the regrets at selected time points. Each colour lines correspond to the wild bootstrap test for different models on the Murphy's simulated data. The green line is for Test 1, dark blue line for Test 2, black line for Test 3, light blue line for Test 4 and red line for Test 5.

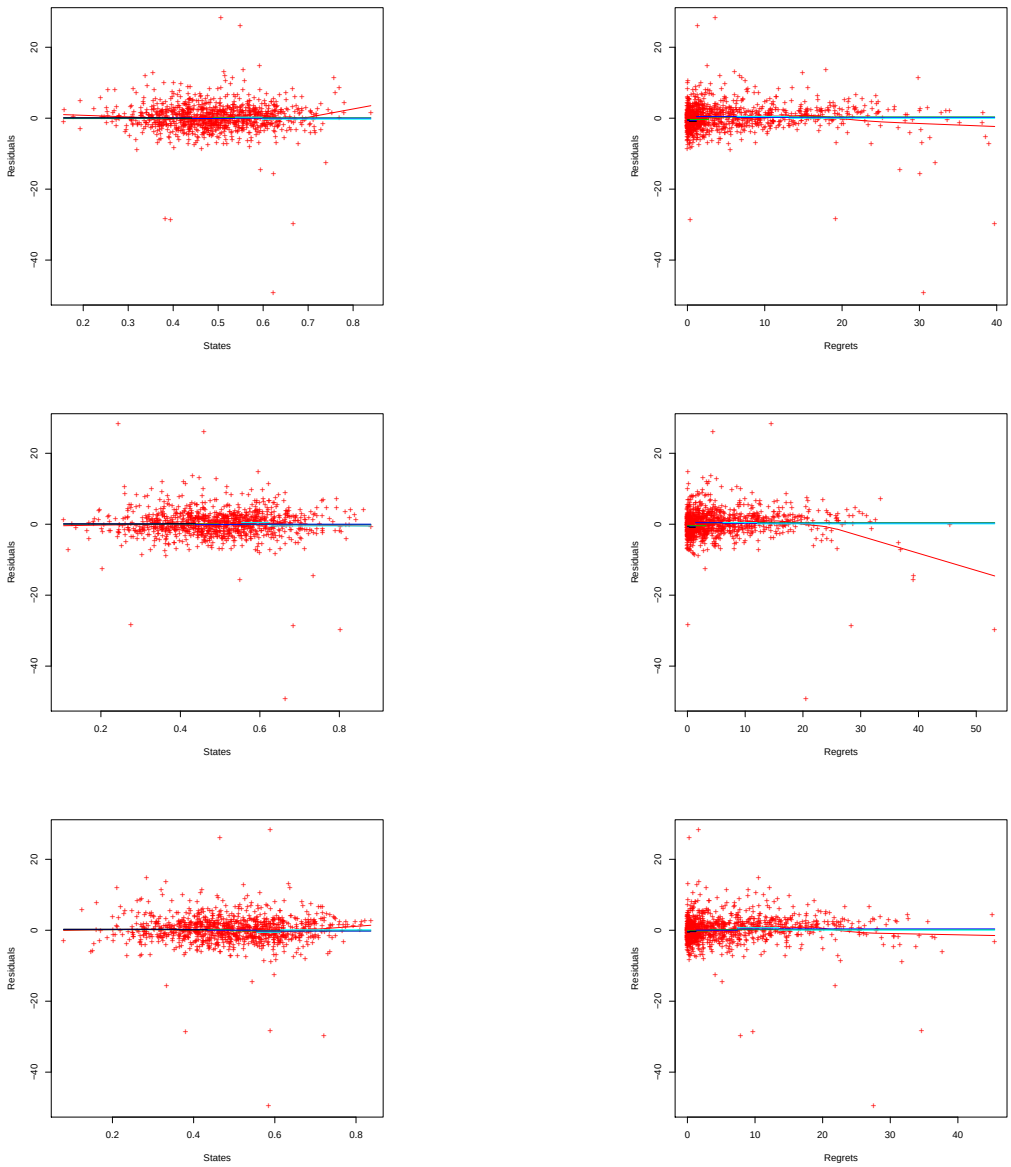

Figure 11.14: The mean residual plots at selected time points $1, 5, 9$ for model M_1. Each row represent the timepoints where the first row for time point one, second row for time point five and third row for time point nine. The first column represent the residuals against the states plots while the second column is for the residuals against the regrets at selected time points. Each colour lines correspond to the wild bootstrap test for different models on the Murphy's simulated data. The green line is for Test 1, dark blue line for Test 2, black line for Test 3, light blue line for Test 4 and red line for Test 5.

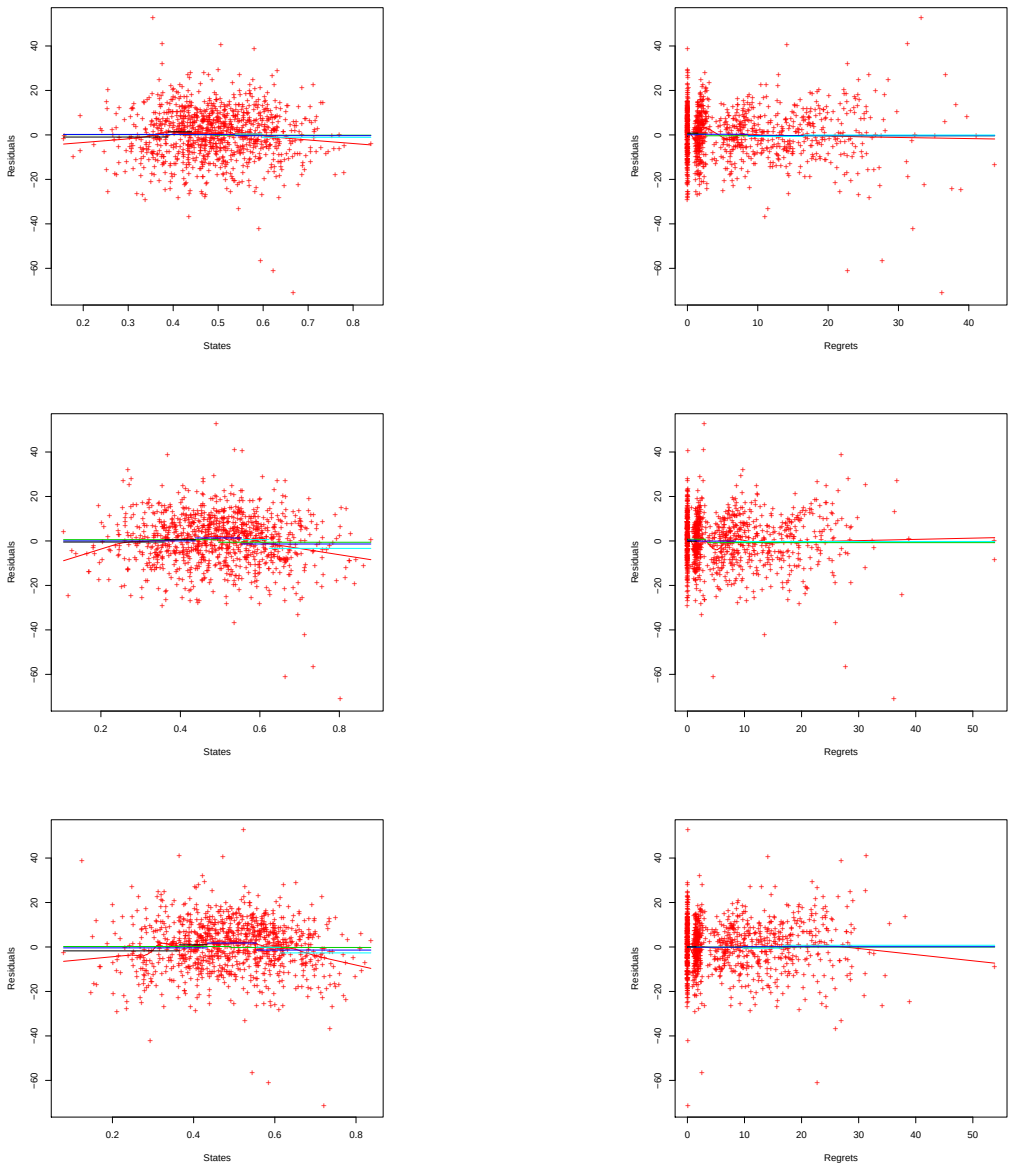

Figure 11.15: The mean residual plots at selected time points $1, 5, 9$ for model M_2. Each row represent the timepoints where the first row for time point one, second row for time point five and third row for time point nine. The first column represent the residuals against the states plots while the second column is for the residuals against the regrets at selected time points. Each colour lines correspond to the wild bootstrap test for different models on the Murphy's simulated data. The green line is for Test 1, dark blue line for Test 2, black line for Test 3, light blue line for Test 4 and red line for Test 5.

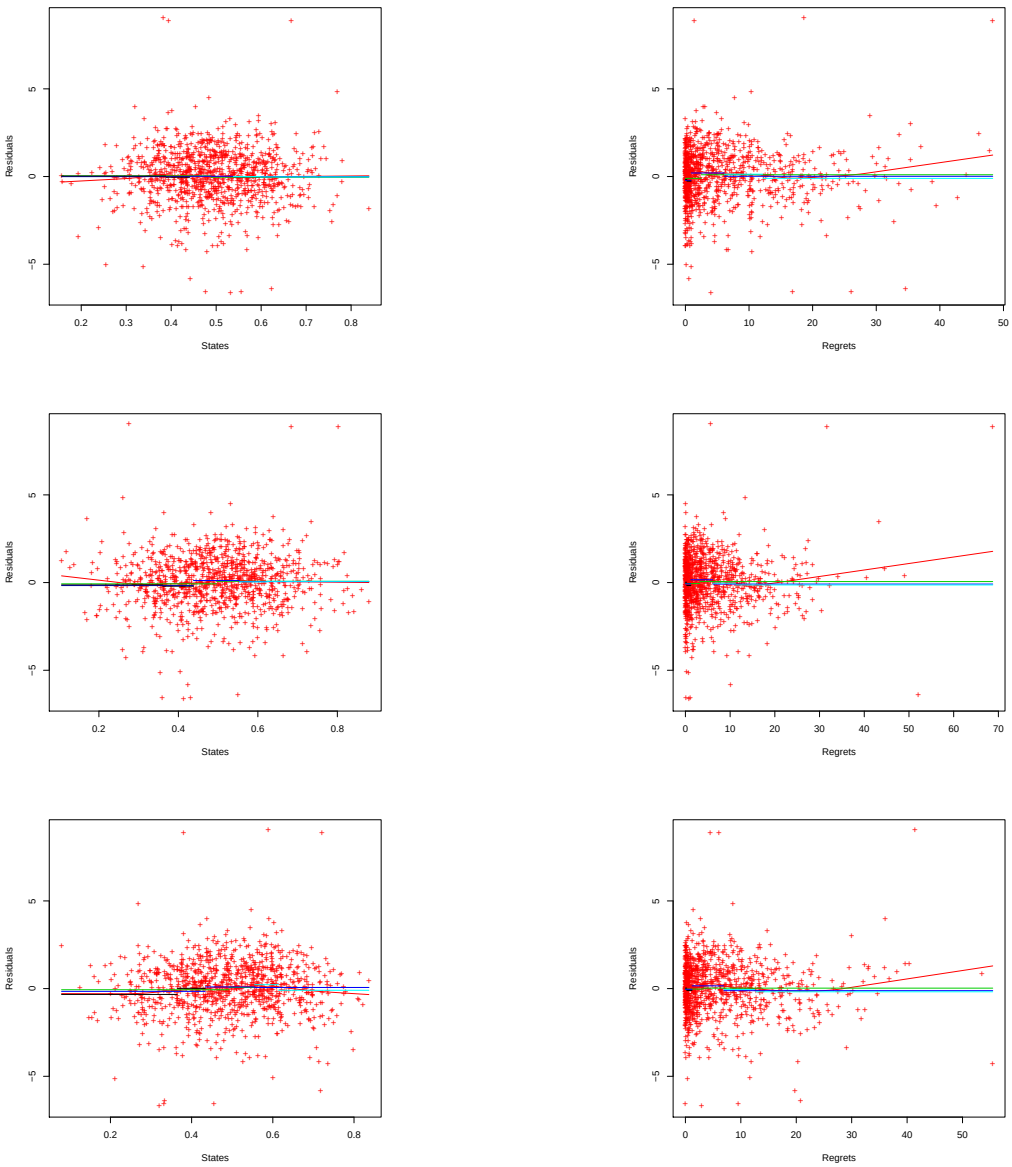

Figure 11.16: The mean residual plots at selected time points $1, 5, 9$ for model M_3. Each row represent the timepoints where the first row for time point one, second row for time point five and third row for time point nine. The first column represent the residuals against the states plots while the second column is for the residuals against the regrets at selected time points. Each colour lines correspond to the wild bootstrap test for different models on the Murphy's simulated data. The green line is for Test 1, dark blue line for Test 2, black line for Test 3, light blue line for Test 4 and red line for Test 5.

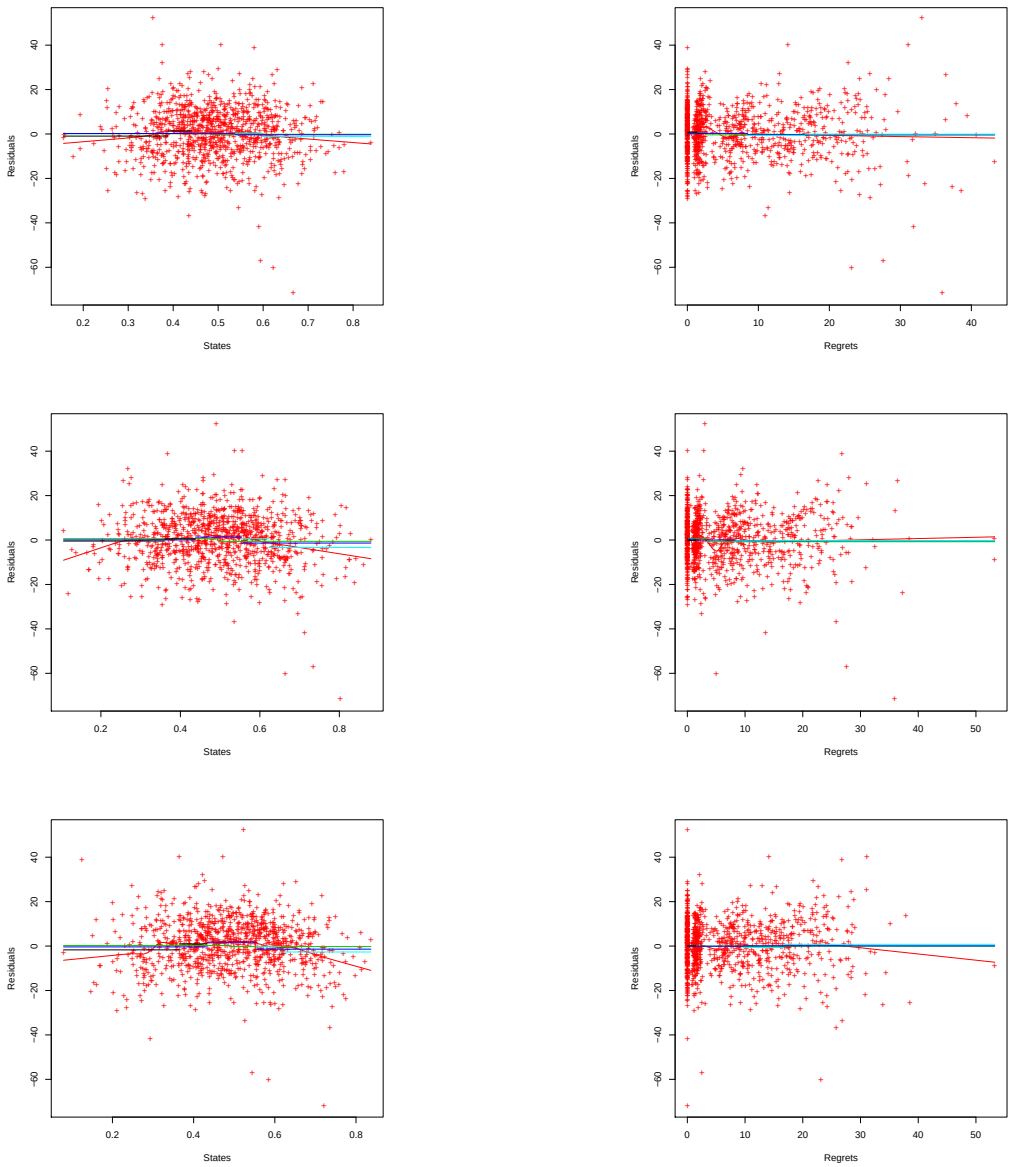

Figure 11.17: The mean residual plots at selected time points $1, 5, 9$ for model M_4. Each row represent the timepoints where the first row for time point one, second row for time point five and third row for time point nine. The first column represent the residuals against the states plots while the second column is for the residuals against the regrets at selected time points. Each colour lines correspond to the wild bootstrap test for different models on the Murphy's simulated data. The green line is for Test 1, dark blue line for Test 2, black line for Test 3, light blue line for Test 4 and red line for Test 5.

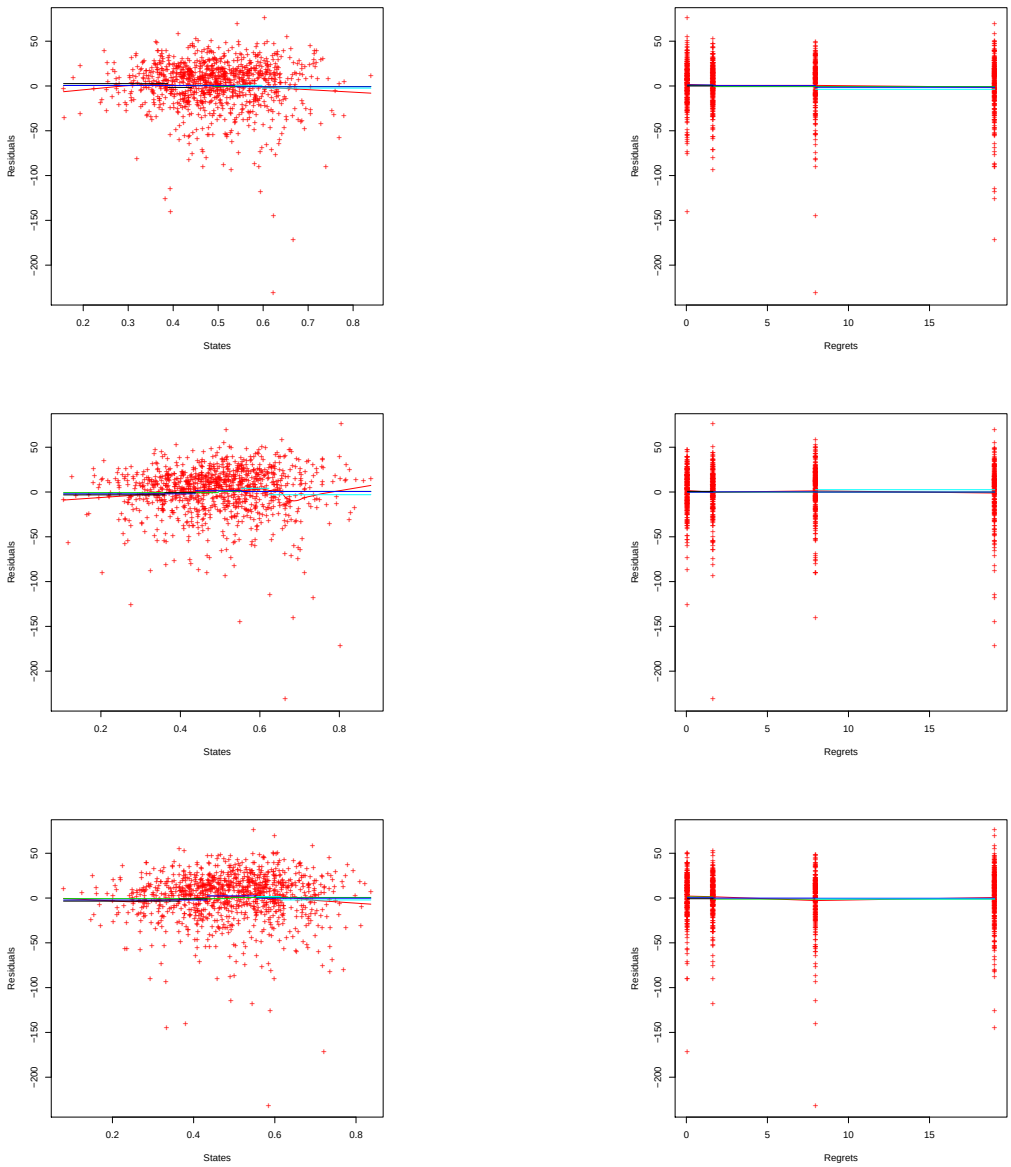

Figure 11.18: The mean residual plots at selected time points $1, 5, 9$ for model M_5. Each row represent the timepoints where the first row for time point one, second row for time point five and third row for time point nine. The first column represent the residuals against the states plots while the second column is for the residuals against the regrets at selected time points. Each colour lines correspond to the wild bootstrap test for different models on the Murphy's simulated data. The green line is for Test 1, dark blue line for Test 2, black line for Test 3, light blue line for Test 4 and red line for Test 5.

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