QUADRATIC INFERENCE FUNCTION WITH RIDGE ESTIMATOR FOR MYOPIC REGRET-REGRESSION: THE SHORT-TERM STRATEGY IN OPTIMAL DYNAMIC TREATMENT REGIMES

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QUADRATIC INFERENCE FUNCTION WITH RIDGE ESTIMATOR FOR MYOPIC REGRET-REGRESSION: THE SHORT-TERM STRATEGY IN OPTIMAL DYNAMIC TREATMENT REGIMES

ABSTRACT

A dynamic treatment regime (DTR) is a multi-stage decision rule based on treatment history. The focus in this research is on the improvement of estimation in optimal dynamic treatment regime (ODTR). This research is motivated by the regret-regression method where it is a combination of the regret function with regression modeling. A short-term strategy called the myopic regret-regression (MRr) is an alternative to regret-regression where it estimates the mean response at each time-point. This strategy has the same performance as regret-regression but MRr calculation is faster in estimation and more practical in application. However, it has a limitation on correlated data. The quadratic inference functions in myopic regret-regression (QIF-MRr) has overcome the limitation of MRr by combining the myopic regret-regression with quadratic inference functions. It is more robust and efficient regardless of any type of working correlation structure. However, singularity problem happen when estimating the parameters using QIF-MRr and more complex in computations. Hence, the ridge quadratic inference functions for myopic regret-regression (rQIF-MRr) is proposed where a ridge estimator is used to overcome the computational problem and shorten the calculation time. Comparison between methods was performed to check the efficiency and consistency in estimation using simulation with different sample sizes.

Keywords: Longitudinal data analysis, Optimal dynamic treatment regimes, Regret-regression, Ridge estimator, Quadratic inference functions.

FUNGSI PENTAKBIRAN KUADRATIK DENGAN PENGANGGAR RABUNG UNTUK REGRET-REGRESI MYOPIK: STRATEGI JANGKA PENDEK DALAM REGIM RAWATAN DINAMIK OPTIMAL

ABSTRAK

Rejim rawatan dinamik (DTR) adalah aturan keputusan pelbagai peringkat berdasarkan kepada sejarah rawatan. Fokus dalam penyelidikan ini adalah pada penambah baikkan estimasi dalam rejim rawatan dinamik optimum (ODTR). Penyelidikan ini didorong oleh kaedah regresi-kesalan di mana ia adalah gabungan fungsi kesalan dengan pemodelan regresi. Strategi jangka pendek yang diberi nama regresi-kesalan miopia (MRr), adalah alternatif kepada regresi-kesalan di mana ia menganggarkan tindak balas min pada setiap titik waktu. Strategi ini mempunyai prestasi yang sama dengan regresi-kesalan tetapi pengiraan MRr adalah lebih cepat dalam anggaran dan lebih praktikal dalam aplikasi. Namun, ia mempunyai limitasi pada data yang berkorelasi. Fungsi pentakbiran kuadratik dalam regresi-kesalan miopia (QIF-MRr) telah mengatasi limitasi MRr dengan menggabungkan regresi-kesalan miopia dengan fungsi pentakbiran kuadratik. Ia lebih mantap dan cekap tanpa mengira jenis struktur korelasi kerja. Walau bagaimanapun, masalah singulariti berlaku apabila menganggar parameter menggunakan QIF-MRr dan lebih kompleks dalam pengiraan. Oleh itu, fungsi pentakbiran kuadratik rabung dalam regresi-kesalan miopia (rQIF-MRr) dicadangkan dimana penganggar rabung digunakan untuk mengatasi masalah komputasi dan menyingkatkan masa pengiraan. Perbandingan antara kaedah dilakukan untuk memeriksa kecekapan dan konsistensi dalam anggaran menggunakan simulasi dengan ukuran sampel yang berbeza.

Kata kunci: Analisis data longitud, Rejim rawatan dinamik optimum, Regresi-kesalan, Penganggar rabung, Fungsi pentakbiran kuadratik.

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

AR(1)	:	First order autoregressive
CR	:	Convergence rate
DAG	:	Directed acyclic graphs
DRRr	:	Doubly robust regret-regression
DTR	:	Dynamic treatment regimes
GEE	:	Generalized estimating equations
GLM	:	Generalized linear model
GMM	:	Generalized methods of moments
IMOR	:	Iterative minimization of regrets
INR	:	International normalized ratio
LASSO	:	Least absolute shrinkage and selection
MRr	:	Myopic regret-regression
ODTR	:	Optimal dynamic treatment regimes
PA	:	population-avaraged
PROBIT	:	Promotion of Breastfeeding Intervention Trial
QIF	:	Quadratic inference functions
QIF-MRr	:	Quadratic inference functions for myopic regret-regression
RMSE	:	Root mean square error
rQIF-MRr	:	Ridge quadratic inference functions for myopic regret-regression
SCAD	:	Smooth clipped absolute deviation
SD	:	Standard deviation
SE	:	Standard error

SEM : Structural equation modeling

SNCFTM : Structural nested cumulative failure time model

SNDM : Structural nested distribution model

SNFTM : Structural nested failure time model

SNM : Structural nested models

SNMM : Structural nested mean models

SS : Subject-specific

LIST OF SYMBOLS

$\bar{A}_{j-1}$	:	Action given at the previous time point
A_j	:	Action given or treatment decision at time point j
A	:	Action given to the patient
$d_j(\bar{S}_j, \bar{A}_{j-1})$	:	Action to be given using all the information from the previous actions and states including the current state j
ρ	:	Correlation parameter
x_{ij}	:	Covariate
$\bar{A}_j$	:	Cumulative action given from time point 1 to time point j
$\bar{S}_j$	:	Cumulative information of the state measured from time point 1 to time point j
d	:	Decision rules
D_i	:	Diagonal matrix of marginal variances
Bias	:	Different between the estimated value with the true value
$\mathbb{P}_n$	:	Empirical average function
$E(Y)$	:	Expectation of final response
$E(Y(\underline{d}_j^{opt})\|\bar{S}_j, \bar{A}_{j-1})$	:	Expected value of the potential outcome
$E(Y(a_j, \underline{d}_{j+1}^{opt})\|\bar{S}_j, \bar{A}_{j-1})$	:	Expected value of the potential outcome if action a_j is chosen at time j, and the optimal decision rules are followed
g_N	:	Extended score function
Y	:	Final outcome Y observed at the last time point
$H(\lambda)$	:	Hat matrix of the ridge regression

n_0	:	Ideal sample size
K	:	Last time point or last number of visit
Z_j	:	Linear combination of residuals between S_j and the expected value of S_j given $(\bar{S}_{j-1}, \bar{A}_{j-1})$
e_0	:	Margin of error
υ	:	Marginal mean
h_i	:	Mean response of myopic regret-regression
$E[Y\|\bar{S}_K, \bar{A}_K]$	:	Mean response of regret-regression
k_n	:	Multiplier to scale a penalty function
b	:	Number of repetitions
$Y(a)$	:	Observed potential outcome Y under treatment a
a_j^{opt}	:	Optimal action
$\gamma_j(a_j\|\bar{S}_j, \bar{A}_{j-1})$	:	Optimal blip-to-reference function
d_j^{opt}	:	Optimal dynamic treatment regimes which optimize the expected value of outcome Y
y_{ij}	:	Outcome variable
ψ	:	Parameter estimate of the optimal blip function or the regret function
β	:	Parameter estimate of the state function
θ	:	Parameter of both state and regret function
$Q_n^{\mathcal{P}}$	:	Penalized quadratic inference function
$\mathcal{P}_\theta$	:	Penalty function
a	:	Possible actions to be given
$Y(\bar{a}_K)$	:	Potential outcome under possible action $\bar{a}_K$
$\bar{S}_j(\bar{a}_{j-1})$	:	Potential state history under the possible action $\bar{a}_{j1}$

p_0	:	Proportion of the population
Q_N	:	Quadratic inference function
d_j^{ref}	:	Reference regime
$\mu_j(a_j\|\bar{S}_j, \bar{A}_{j-1})$	:	Regret function
rQ_N	:	Ridge quadratic inference function in myopic regret-regression
n	:	Sample size
c	:	Scalar quantity
$\phi_j(S_j\|\bar{S}_{j-1}, \bar{A}_{j-1})$	:	State function
i	:	Subject of interest or patient
S	:	States of the patient
S_j	:	State of the patient at time point j
j	:	Time point or clinical visit
B	:	Total number of repetitions
$(\bar{S}_j, \bar{A}_{j-1})$	:	Treatment history
λ	:	Tuning parameter
τ	:	Unknown parameter
$Y(a')$	:	Unobserved potential outcome Y which correspond to treatment a'
$R_i(\rho)$	:	Working correlation matrix
V_i	:	Working correlation structure
Z_0	:	Z-value from standardized normal population
q_0	:	$1 - p_0$

CHAPTER 1: INTRODUCTION

1.1 Personalized Medicine

Dynamic treatment regime is a branch of personalized medicine that uses information from the patient to minimize health problems. In reality, the response of treatment for each patient is different, which inspires the development of the framework. The advantage of the personalized medicine includes the cutback in the total cost of health care, the patient received an option on intensive health care by deciding an optimal decision, and increase compliance and devotion towards treatment (Chakraborty & Moodie, 2013). Personalized medicine is a well known area of study in medicine, but less known for a statistician. It is a challenge to introduce the area in a statistical study that is often beyond the study area (scope) of traditional quantitative tools due to the evidenced-based or data-driven methodologies.

Dynamic Treatment Regimes (DTR), also known as adaptive strategies, adaptive interventions or treatment policies, is a multi-stage decision rule of personalized medicine. It defines a set of decision rules to determine the treatment individually based on their health condition and treatment history. The term 'dynamic' indicates a variation of treatment using the patient's current state and previous treatment received. The treatment varies through time, and at each visit, the clinician will consider a new set of treatments based on the treatment history. An Optimal Dynamic Treatment Regimes (ODTR) is optimal when the final mean response, $E(Y)$ is the highest. This indicates that the decision is optimal, where there is no regret in decision rules (Chakraborty & Moodie, 2013; Murphy, 2003).

Chronic diseases such as HIV infection, mental health disorder (such as depression, anxiety disorders, schizophrenia), drug and alcohol abuse, diabetes, and others need an ongoing medical intervention. Medical intervention refers to a medical treatment given to improve a medical disorder. Personalized medicine and DTR can provide the best treatment to patients who suffer from the diseases. For example, Rosthøj et al. (2006) described observational longitudinal anticoagulant data in analyzing an optimal reactive dose-changing strategy. The anticoagulant was given to patients with a history or at risk of thrombosis (an abnormal blood clotting). The goal was to ensure that the international normalized ratio (INR) value of the patient's prothrombin time stayed within the target range. The dose increased or decreased to ensure that the INR value stay within the target range for the next visit.

Another example is the study on the patient with HIV infection (Robins, Orellana, & Rotnitzky, 2008). From the study, the patient should receive highly active retroviral therapy when the CD4 cell count starts to fall below 200 cells/μl. The process of treating a patient with HIV infection is a multi-stage decision rule. The multi-stage decision rule is a sequence of decision rules where the decision made at one stage will affect the decision to be made at the another.

The Promotion of Breastfeeding Intervention Trial (PROBIT) (Kramer et al., 2001) was used by Moodie et al. (2009) to optimize the infant growth by estimating the decision rules on the duration of breastfeeding. The mother-infant was scheduled a followup visit at 6 time intervals for 12 months. Variables such as weight, length, number of hospitalizations and others were measured. At each visit, the clinician inquired whether the infant was breastfeed, or the infant had consume other liquid or solid foods. Moodie et al. (2009) estimates decision rules with the G-estimation method (Robins, 2004) which considered a long-term and short-term strategy to analyze the PROBIT data set.

The long-term strategy is a decision rule that measures the intervention outcome at the final visit. For example, to maximize the infant growth of PROBIT data set, the response is observed when the study is completed. Clinician observed the final response after the

6th interval where the 6th interval (9-12 months) is this final interval of 0-1 month, 1-2 months, 2-3 months, 3-6 months, 6-9 months and 9-12 months intervals.

Meanwhile, the short-term strategy is a decision rule that measured the outcome at each clinical visit. In short-term strategy, the response is measured at each interval where at the 1st interval (0-1 month), the clinician measured the first response. Then, followed by the second response measured at the 2nd interval (1-2 months), and so forth until it reach the measurement of the final or 6th interval (9-12 months).

Earlier works (Murphy, 2003; Robins, 2004; Moodie et al., 2007, 2009) on both the long-term and short-term strategies considered the treatment decision (measured by the regret function) and not the state function. Henderson et al. (2010) proposed the regret-regression that considered both the regret function and state function to optimize the mean outcome of the DTR. The response of the regret-regression were measured at the end of the time interval after the final time interval is reached, and considered as the long-term strategy.

The myopic regret-regression (MRr) (Mohamed, 2013) is a short-term strategy of the regret-regression, where it also considered both the regret function and state function. The mean response of the MRr was modelled at each time interval. For the short-term strategy, each time interval is treated as the only interval that we are interested in and the future measurements were ignored. The MRr provides a good estimates for longitudinal outcomes where the outcome is measured through time. However, there is no attention been given to the correlation within-subject. To solve this problem, Mohamed (2013) proposed the quadratic inference functions for myopic regret-regression (QIF-MRr), which incorporate the mean response of the MRr into the quadratic inference functions (QIF). The QIF-MRr gives consistent and efficient estimates, but often facing singularity issues during estimation.

1.2 Problem Statement

Over the years, researchers have developed optimal decision rules for providing the best possible actions to the patients based on patient treatment history. Previous methods only consider the relationships between the response across time without any consideration of the relation within-subject. Considering the relation within-subject will shows the effect of the decision been made at each time interval individually. Note that, subject in this study referring to the patient itself. The earlier works appear to have instability and computational problems that result in poor performance, as well as singularity problems that occur during parameter estimation. A new estimation strategy known as rQIF-MRr is proposed to overcome the computational problem, which will be described further in this dissertation.

1.3 Objectives

This study has three objectives to be fulfilled:

1. To propose a ridge estimator in quadratic inference functions for myopic regret-regression (QIF-MRr) to overcome the computational problem and shorten the calculation time.
2. To make comparison between QIF-MRr and the proposed method to check efficiency and consistency in estimations.
3. To illustrate the proposed method using a simulation data set with different sample sizes.

1.4 Thesis Outline

This thesis is designated as follows. Chapter 2 reviewed the previous works on the estimation strategy of ODTR. In this Chapter, we will discussed the framework of the dissertation in detail which includes notations and assumptions used throughout the dissertation. The methods used in the longitudinal analysis will be reviewed, which are the generalized estimating equations (GEE) and QIF. Then, literature for penalized method will be discussed.

The methodology of the estimation strategy used will be discussed in Chapter 3. The short-term strategy for ODTR, MRr and the QIF-MRr will be introduced and the estimation strategy called the ridge quadratic inference functions for myopic regret-regression (rQIF-MRr) will be proposed.

The performance of the proposed method will be illustrated by application to a simulated data set in Chapter 4. The estimation results which compare QIF-MRr with rQIF-MRr will be provided in this chapter. Discussion on which method gives better estimates and more efficient in estimation will be discussed in this chapter.

Finally, Chapter 5 will include the conclusions and further discussion on the future works for this research area.

CHAPTER 2: LITERATURE REVIEW

2.1 Overview

In this Chapter, we give a review of the estimation strategy for ODTR. Methods for analyzing longitudinal data will be reviewed in this chapter together with the penalized method, which will be used in the proposed method for the next chapter.

2.2 Longitudinal Data

Longitudinal data can be obtained when the outcomes or responses of each individual or subject are recorded throughout the course of treatment. Many longitudinal studies are focusing on investigating how the variability of the responses may be handled in time with covariates (Diggle et al., 1994, 2002; Qu & Song, 2004; Zeger & Liang, 1986; Asparouhov & Muthén, 2020).

The disadvantages of a longitudinal study are when the participants or subjects suddenly drop out from the studies which cause the sample size to be trimmed down. For example, Tallgren (2003) had to reduce the sample due to death, the subject moved to another area and other reasons. Reducing the sample will cause some missing data which will be problematic when the model needs a full dataset in investigating or analyzing the data. Longitudinal study also requires an enormous of time in collecting the data, and it is also expensive. Since the timeline is long for collecting the data, therefore the budget is high-cost.

The advantages of a longitudinal study is to allowed researchers to detect the effectiveness, development and changes in the characteristic of the target population for the group and individual levels. Longitudinal data also provide a series of events that can be extended to a single moment of time that can be used in the DTR studies. In DTR, researchers must observe the effectiveness, development and changes in the time-varying treatment. There are several methods available for analyzing longitudinal data and the most common one is GEE by (Liang & Zeger, 1986). The extension of GEE, the QIF (Qu & Lindsay, 2000) is used to improve the estimation of the parameter for longitudinal data.

2.3 Causal Inference

The aim of a statistical inference is to quantify the causal relationship between the action that is given with the outcome obtained from the decision that has been made. For example, we want to confidently say that the action given to the patients improves their health condition (Chakraborty & Moodie, 2013, p.9). To make certain decisions, knowledge on the data-generating process is needed which neither be computed from the data alone nor obtained from the distributions that regulate the data. It can be done by using a causal analysis, which aims to deduce the beliefs or probabilities for static conditions as well as for dynamic of beliefs given the changing conditions. For example, the changes caused by treatment or external intervention (Pearl, 2009).

The causal effect is defined to be a comparison of an individual patient's or a group of patient's potential outcomes for different possible action that can be given to the patient. Hernán (2004) has discussed the use of the causal effect in causal inference where the illustrated scenario showed how the individual effect work. In scenario 1, patient U had a heart transplant on 1st January. On the 6th January that year (after 5 days), he died. Imagine that if U had not received the transplant where all other things or factor in U life remain unchanged, he might still be alive. In this scenario, the heart transplant cause U to die. The intervention which is the interference of one's states in the affairs of another had a causal effect on U's five-day survival.

In scenario 2, patient V also had a heart transplant on 1st January. On the 6th January, V still alive. Imagine if V had not received the heart transplant where all other things and factors in V life remain unchanged, V would still be alive. The transplant did not have a causal effect on V's five-day survival.

To form causal inference which is an important aspect in modeling ODTR, some assumptions are followed throughout this work. We follows assumptions on consistency, no unmeasured confounders and positivity which will be further elaborated in Section 2.4.

In causal inference, there are three main scopes which are sequential equation modeling (SEM), graphical models and potential outcomes also known as counterfactual.

2.3.1 Structural Equation Modeling (SEM)

Structural equation modeling (SEM) is used to figure out how much the theoretical model takes to explain the sample data (Schumacker & Lomax, 2004). Generally, SEM examine the theoretical model by utilizing hypothesis testing to improve understanding on complex relationships between constructs. There are several reasons why SEM is popular. SEM is frequently used by researchers to quantitatively confirm theoretical hypotheses. Moreover, it considers measurement error when analyzing statistical data. Besides that, SEM gives alternative ways to the researchers for its capability to analyze advanced theoretical models for a complex situation. For example, Wang et al. (2018) used the SEM-path analysis approach to analyze complex relationships between psychological variables that trigger suicidal thoughts among people living with HIV/AIDS. Another example, Hui et al. (2017) determined an academic description using the SEM method in food security studies and proposed a basic structure based on family food security and children's environmental sustainability.

The history of SEM starts when Wright (1921) used a combination of equations and graph to mathematically expressed the understanding of a symptom which do not cause diseases. Given the linear system of

$$Z = \alpha_Z + \beta_{WZ} w + \beta_{XZ} x \tag{2.1}$$

$$Y = \alpha_Y + \beta_{WY}u + \beta_{XY}x + \beta_{ZY}z \tag{2.2}$$

where w, x and z are the specific values of W, X and Z. The intercept α_Y and α_Z are unmeasured random disturbances of Z and Y. Meanwhile, α_Y, α_Z, W and X are assumed to be jointly independent between each other.

2.3.2 Graphical Models

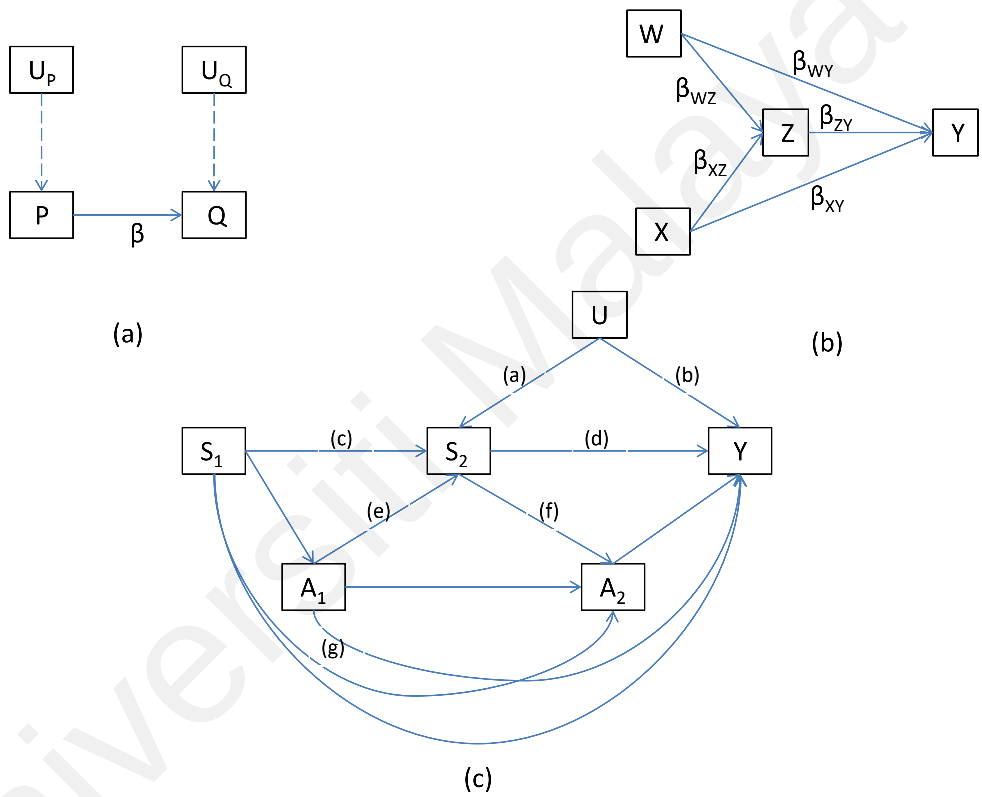

Figure 2.1: (a) Simple "path" diagram (b) Causal diagram for Equation 2.1 and Equation 2.2 (c) Two-stage DAG illustrating time-varying confounding and mediation

Figure 2.1(a) gives a simple "path diagram" to interpret causal inference using causal diagram also known as directed acyclic graphs (DAG) (Pearl & Robins, 1995; Pearl, 2009; Chakraborty & Moodie, 2013). A graph is said to be directed if all the inter-variable relationships are connected by arrows indicating that one variable causes changes in another, and acyclic if it has no closed loops (no feedback between variables). It is natural to use kinship relation in interpreting the path diagram such as parent and child.

A graph is causal if every arrow represents the presence of an effect of the causal (parent) variable on the affected (child) variable. In Figure 2.1(a), we denote P as a parent of Q and Q as a child of P. The diagram in (a) shows a presence of causal influence of P to Q (directly) while, and the absence of causal influence of Q to P. The arrows are drawn from cause (P) to the effect (Q), and the absence of an arrow (Q to P) makes the empirical claim that Nature assigns values to one variable irrespective of another. The equation can be represented in the diagram as $q = \beta p + u_Q$ and $p = u_P$, where β is a "path coefficient" which quantifies the causal effect of P to Q (directly). The variables U_P and U_Q are named "exogenous" to describe the observed or unobserved background factors that the investigator choose to keep unexplained. Figure 2.1(b) give a causal diagram or a path diagram for Equation 2.1 and Equation 2.2.

Figure 2.1(c) shows an example for two-stage DAG which illustrate the time-varying confounding and mediation (Chakraborty & Moodie, 2013). The data are collected at three time visits t_1 (sometimes called baseline), t_2 and t_3. S_1 and S_2 are the states or covariates measured at visit 1 and 2. The action A_1 was given at visit 1 in the interval of $[0, t_2)$ while, action A_2 were given at visit 2 in the interval $[t_2, t_3)$, and the outcome Y is measured at visit 3, t_3. From the diagram, A_1 acts directly on Y denoted by path (g), and it acts indirectly through S_2 by path (e) and (d) with mediator S_2. Meanwhile, state S_2 confound the relation between A_2 and Y by path (d) and (f). To obtain the unbiased estimation of the effect of A_2 and Y, S_2 needed some adjustment. However, there will be an issue when we had an unmeasured factor, V which also act as confounders.

2.3.3 Potential Outcome

In formalizing the theory of causal inference, Robins (1986) extended the work from Neyman (1923, 1990) and Rubin (1978) to determine the direct and indirect effect of time-varying treatments from experimental or observational longitudinal studies. In explaining the method for the observational data, the notion of potential outcome or counterfactual is needed. The potential outcome is defined to be a person's outcome if he had been given a certain treatment regime, probably different from the regime that he was actually been given. It is an outcome that is different from the fact, in another word, counter the fact (Rubin, 1978).

Suppose we want to investigate the causal effect of taking treatment a instead of treatment a'. A person will have an observed outcome Y of the potential outcome "Y under treatment a'" denoted as $Y(a)$, and that same person will also have an unobserved potential outcome Y denoted as $Y(a')$ which correspond to the treatment a'. At individual-level, a causal parameter can be considered as a difference in person's outcome under treatment a with outcome under treatment a' which denoted as $Y(a) - Y(a')$. The individual-level causal effect is not possible to be observed which make it impossible for the outcome of treatment a and a' to be observed without extra assumptions and further data. However, average causal effect or population-level causal parameters can be identified for observational studies with some assumptions which will be discussed in Section (2.4).

2.4 Framework for Optimal Dynamic Treatment Regime

2.4.1 Notations

Throughout the thesis, we consider a longitudinal data with sample size, n. Let K be the last number of visit for a patient. At visit $j = \{1, 2, \ldots, K\}$, the clinician will measure the current state of the patient, S_j, and the action given or treatment decision, A_j. The treatment is given based on the information of the current state and previous treatments, $(\bar{S}_j, \bar{A}_{j-1})$ also known as treatment history.

Denote that $\bar{S}_j = \{S_1, S_2, \ldots, S_j\}$, be the cumulative information of the state measured from the first visit to jth visit (i.e. history of states measured up to visit j), and $\bar{A}_j = \{A_1, A_2, \ldots, A_j\}$ be the cumulative action given from the first visit until jth visit (i.e. history of actions given up to visit j). The action given at visit j depending on the state of the patient at visit j and the action given at the previous visit, A_{j-1}. The final outcome, Y is measured at the last visit, K, which is the cumulative information of the state, $\bar{S}_K$ and action, $\bar{A}_K$. The observational order of the dynamic treatment regimes is given as $(S_1, A_1, S_2, A_2, \ldots, S_K, A_K, Y)$.

From the notion of the potential outcome or counterfactual (Rubin, 1978; Hernán, 2004) which has been discussed in Section (2.3), we denote a_j to be a set of all possible actions that can be given at visit j, where $\bar{S}_j(\bar{a}_{j-1}) = (S_1, S_2(a_1), \ldots, S_j(\bar{a}_{j-1}))$ is the potential state history under the possible action $\bar{a}_{j-1}$. We denote $Y(\bar{a}_K)$ as the potential outcome under the possible action $\bar{a}_K$.

We denote $E(Y(\underline{d}_j^{opt})|\bar{S}_j, \bar{A}_{j-1})$ as the expected value of the potential outcome or counterfactual final responses and $E(Y(a_j, \underline{d}_{j+1}^{opt})|\bar{S}_j, \bar{A}_{j-1})$ as the expected value of the potential outcome if action a_j is chosen at time j and then subsequently the optimal decision rules are followed.

We define a dynamic treatment regime, d as a set of decision rules where $d = \{d_1(S_1), \ldots, d_j(\bar{S}_j, \bar{A}_{j-1}), \ldots, d_K(\bar{S}_K, \bar{A}_{K-1})\}$. $d_1(S_1)$ is taken to be a decision rule at the first visit using the information on state at the first visit, while, $d_j(\bar{S}_j, \bar{A}_{j-1})$ is the decision made or action to be taken using all the information from the previous actions and states including the current state j. Then, we denote d_j^{opt} to be the optimal dynamic treatment regimes which optimize the expected value of outcome Y.

2.4.2 Assumptions

Three main assumptions in the potential outcome framework are consistency, no unmeasured confounders and positivity. We make a consistency assumption that the observed outcome Y is equal to the potential outcome $Y(\bar{a}_K)$ and the observed state history $\bar{S}_K$ is equal to the potential state history $\bar{S}_{\bar{a}_{K-1}}$ under the observed treatment $a_K = A_K$. The treatment is given in a way that it is possible for all the treatment options to be assigned to all patients in the population under consideration.

We also make an assumption on no unmeasured confounders where the decision for the treatment does not depend on the potential future states or the potential outcome except through the observed states and treatment history. For any regime, $\bar{a}_K$, the action given at visit j, A_j is independent of any future or potential states or outcome given the previous history,

$$A_K \perp (S_{j+1}(\bar{a}_j), \ldots, S_K(\bar{a}_{K-1}), Y(\bar{a}_K) | \bar{S}_j, \bar{A}_{j-1})$$

for $j = 1, 2, \ldots, K$. If there is no drop-out, the assumption is equivalent to the exchangeability. If the patient or subjects are censored, a further assumption that censoring is non-informative conditional on history is needed. That is, the potential outcome of a censored patients will follow the same distribution as the uncensored patients.

The third assumption is positivity where the optimal treatment regime has a nonzero or positive probability of being observed in the data. In continuous treatment, the optimal treatment regime is identifiable from the observed data. The assumption may be theoretically and practically violated. Theoretical violation happened when the design of the study prohibit a patient from taking a certain treatment. Meanwhile, practical violation happened when a part of the patients has a very low probability of receiving the treatment (Cole & Hernàn, 2008; Chakraborty & Moodie, 2013; Barrett et al., 2014).

2.5 Optimal Dynamic Treatment Regimes (ODTR)

In DTR, it is said to be optimal if the final mean outcome Y is maximized or optimized which is often called as ODTR. In other word, ODTR is a method that gives the highest value of the mean response at visit K using all the information of the previous treatment history. Hence, in this study, we will focus on the estimation of the semi-parametric method which modelled the contrasts of the conditional mean outcome. There are two strategies that the researchers put an interest to which are G-estimation (Robins, 1997, 2004) and iterative minimization of regrets (IMOR) (Murphy, 2003).

2.5.1 Structural Nested Mean Models (SNMM)

Structural nested mean models (SNMM) is an extension work from structural nested models (SNM). The SNM was used to model and estimate the joint effects of a sequence of actions. The idea of SNM is to confound the variables affected by treatment. It reparameterizes the parameter of the DAG that represent contrasts between the marginal distribution of the outcome in the manipulated graph with action, A is set to a particular value a (Robins, 1997). SNM is somewhat similar to ordinary regression models, where it parameterizes the conditional treatment effects. However, SNM does not take a condition on post-treatment variables but instead modelling the outcome at each visit conditional on the treatment and covariate history up to that visit. SNM removed the effects of future treatment to solve the unique contributions of each treatment at each visit (Vansteelandt & Joffe, 2014; Robins, 2000).

There are two kinds of SNM. The first one is the model for the effect of an action on the mean of an outcome. This includes SNMM that is related to structural nested cumulative failure time model (SNCFTM) for survival outcome. While the second one models the effect of an action on the whole distribution of an outcome. This includes structural nested distribution model (SNDM) which related to structural nested failure time model (SNFTM) for survival outcome (Vansteelandt & Joffe, 2014; Robins, 2000). Since we do not take any interest in the distribution of an outcome variable and the survival outcome, we will put our focus more on the SNMM.

SNMM is defined to be the expected difference between the potential outcome (or counterfactual responses) of a patient on a designated treatment regime from visit $j + 1$

onwards and on another designated treatment regime from visit j given the previous history. Robins's g-estimation method is derived from the optimal blip functions which is a particular class of SNMM.

Robins (2004) defined the optimal blip-to-reference function to be

$$\gamma_j(a_j|\bar{S}_j, \bar{A}_{j-1}) = E[Y(\bar{a}_j, \underline{d}_{j+1}^{opt})|\bar{S}_j, \bar{A}_{j-1})] - E[Y(\bar{a}_{j-1}, d_j^{ref}, \underline{d}_{j+1}^{opt})|\bar{S}_j, \bar{A}_{j-1})]. \quad (2.3)$$

In between $Y(\bar{a}_j, \underline{d}_{j+1}^{opt})$ and $Y(\bar{a}_{j-1}, d_j^{ref}, \underline{d}_{j+1}^{opt})$, there are at least one counterfactual outcome unless $\gamma_j(a_j|\bar{S}_j, \bar{A}_{j-1}) = 0$, where the patient are optimally treated at visit j onward. The term optimal is to indicate the treatment subsequent to visit j, while, the term blip indicate a single-stage change in treatment at visit j. Hence, the Equation (2.3) is defined to be the expected difference of the outcome when a reference regime, d_j^{ref} is used instead of the action given, a_j at visit j given the previous history $(\bar{S}_j, \bar{A}_{j-1})$ who subsequently receive the optimal regime, $\underline{d}_{j+1}^{opt}$.

There are two special cases of the SNMM which are optimal blip-to-zero and regret function. In optimal blip-to-zero, the reference regime, d_j^{ref} is taken to be a zero regime where it is defined to be a substantively meaningful treatment such as placebo (i.e. a substance that do not have any pharmacological effect but is given to satisfy a patient who supposes it to be medicine) or standard care. Hence, the optimal blip-to-zero is written as

$$\gamma_j(a_j|\bar{S}_j, \bar{A}_{j-1}) = E[Y(\bar{a}_j, \underline{d}_{j+1}^{opt})|\bar{S}_j, \bar{A}_{j-1})] - E[Y(\bar{a}_{j-1}, d_j^{ref} = 0, \underline{d}_{j+1}^{opt})|\bar{S}_j, \bar{A}_{j-1})]. \quad (2.4)$$

We will refer the optimal blip-to-zero function as optimal blip for future reference.

Another case, Moodie et al. (2007) have shown that the regret function of Murphy

(2003) at visit j

$$\mu_j(a_j|\bar{S}_j, \bar{A}_{j-1}) = E[Y(\bar{a}_{j-1}, \underline{d}_j^{opt}|\bar{S}_j, \bar{A}_{j-1})] - E[Y(\bar{a}_j, d_{j+1}^{opt}|\bar{S}_j, \bar{A}_{j-1}) \tag{2.5}$$

is actually a negative of the optimal blip, $\gamma_j(a_j|\bar{S}_j, \bar{A}_{j-1})$ which will be further discussed in Section (2.5.3.1).

Meanwhile, the standard form of the SNMM considered the difference of the expected outcome of using the reference regime, d_j^{ref} instead of action given, a_j at visit j based on the previous history, $(\bar{S}_j, \bar{A}_{j-1})$ for patients who received a zero regime instead of being treated optimally in optimal SNMM. To specify the optimal regime, the standard SNMM need an information regarding the distribution of the states and the outcomes. Furthermore, to estimate optimal decision rule, a specific parametric information of the distribution for the state variables is needed but, this is what we want to avoid when estimating the semi-parametric models as in G-estimation and IMOR.

2.5.2 G-estimation

G-estimation is a method used to estimate the parameter estimate, say ψ of the optimal blip function or the regret function. It is developed based on the knowledge of the decision or action process, A. The G-estimation method is under the same roof as the generalized methods of moments (GMM) (Hansen, 1982). One of the advantages of the GMM is that it is not computationally burdened to perform inference without a need to specified the likelihood function (Hall, 2005, p. 2). GMM is almost similar to ordinary regression methods as it realizes control for measured confounders through conditioning (Vansteelandt & Joffe, 2014).

$G_j(\psi)$ function is defined as the outcome adjusted by the expected difference of the mean outcome for patient who received treatment a_j and for another patient who was given the optimal decision at the beginning of visit j, where both of them had the same treatment and the same covariate history, $(\bar{S}_j, \bar{A}_{j-1})$ from the beginning of visit $j-1$ and were treated optimally onwards. In other word, the function $G_j(\psi)$ gives the estimate of the expected outcome in the counterfactual event where the optimal decisions are followed at visit j onwards (Barrett et al., 2014). Hence, $G_j(\psi)$ is

$$\begin{aligned} G_j(\psi) &= Y + \sum_{k=j}^{K} [\gamma_k(d_k^{opt}|\bar{S}_j, \bar{A}_{j-1}; \psi) - \gamma_k(a_k|\bar{S}_j, \bar{A}_{j-1}; \psi)] \\ &= Y + \sum_{k=j}^{K} E[\{Y(\bar{a}_{k-1}, \underline{d}_k^{opt}) - Y(\bar{a}_{k-1}, d_k^{ref} = 0, \underline{d}_{k+1}^{opt})\} \\ &\quad - \{Y(\bar{a}_k, \underline{d}_{k+1}^{opt}) - Y(\bar{a}_{k-1}, d_k^{ref} = 0, \underline{d}_{k+1}^{opt})\}|\bar{S}_j, \bar{A}_{j-1}] \\ &= Y + \sum_{k=j}^{K} E[Y(\bar{a}_{k-1}, d_k^{opt}) - Y(\bar{a}_k, \underline{d}_{k+1}^{opt})|\bar{S}_j, \bar{A}_{j-1}] \\ &= Y + \sum_{k=j}^{K} \mu_k(A_k|\bar{S}_k, \bar{A}_{k-1}; \psi). \end{aligned} \tag{2.6}$$

The probability of receiving treatment a_j was specified as $p_j(a_j|\bar{S}_j, \bar{A}_{j-1})$ and thus, the estimating equation of the G-estimation is written as

$$U(\psi) = \sum_{j=1}^{K} G_j(\psi)\{g_j(A_j|\bar{S}_j, \bar{A}_{j-1}) - E_{A_j}[g_j(A_j|\bar{S}_j, \bar{A}_{j-1})]\} \tag{2.7}$$

for some $g_j(A_j|\bar{S}_j, \bar{A}_{j-1})$ having the same dimension as ψ. The function $g_j(A_j|\bar{S}_j, \bar{A}_{j-1})$ is taken to be a vector-valued function chosen to enclose the variables thought to interact with the treatment to effect a difference in the outcome (Chakraborty & Moodie, 2013, p. 61).

The expected value of the estimating equation, $E[U(\psi)] = 0$ is an unbiased estimating equation by the assumption of no unmeasured confounder where $G_j(\psi)$ is independent of any function of past states and actions. By using a correct specification of the treatment distribution $p_j(a_j|\bar{S}_j, \bar{A}_{j-1})$, the value of $\hat{\psi}$ to $E[U(\psi)] = 0$ can be used to estimate the optimal dynamic treatment regimes.

However, $U(\psi)$ is not efficient because the estimators are not semi-parametric efficient. Semi-parametric efficiency refer to an identical approach in efficiency for simple parametric case. Thus, Robins (2004) introduced a doubly-robust version of the G-estimation also known as efficient G-estimation.

2.5.2.1 Efficient G-estimation

To tackle the inefficiency of the G-estimation method as mention above, Robins (2004) modify the estimating equation of the $U(\psi)$ making it doubly-robust by adding the term $E[G_j(\psi)|\bar{S}_j, \bar{A}_{j-1}]$ into Equation (2.7). Hence, the estimating equation of the efficient G-estimation is given as

$$U^{ef}(\psi) = \sum_{j=1}^{K} \left(G_j(\psi) - E[G_j(\psi)|\bar{S}_j, \bar{A}_{j-1}]\right) \times \left\{g_j(A_j|\bar{S}_j, \bar{A}_{j-1}) - E_{A_j}[g_j(A_j|\bar{S}_j, \bar{A}_{j-1})]\right\} \tag{2.8}$$

The Equation (2.8) will gives consistent parameter estimate, $\hat{\psi}$ given that the either the treatment allocation probability, $p_j(A_j|\bar{S}_j, \bar{A}_{j-1})$ or $E[G_j(\psi)|\bar{S}_j, \bar{A}_{j-1}]$ is modelled correctly.

There are two choices of the function $g_j(A_j|\bar{S}_j, \bar{A}_{j-1})$ that we can choose from as emphasized by Moodie et al. (2007). The first choice is simply taking

$$g_j^{simp}(A_j|\bar{S}_j, \bar{A}_{j-1}) = E\left(\frac{\partial \mu_j}{\partial \psi}\middle|\bar{S}_j, \bar{A}_j\right) \tag{2.9}$$

which can be obtained from $\mu_j(\psi)$. Another choice will be

$$g_j^{ef}(A_j|\bar{S}_j, \bar{A}_{j-1}) = E\left(\frac{\partial G_j}{\partial \psi}\middle|\bar{S}_j, \bar{A}_j\right) \tag{2.10}$$
$$= E\left(\sum_{k=j}^{K} \frac{\partial \mu_k}{\partial \psi}\middle|\bar{S}_j, \bar{A}_j\right)$$

which gives the locally efficient semi-parametric estimates for ψ. Robins (2004) has shown that the g_j^{ef} is more efficient than g_j^{simp} but more complicated to calculate as it needs the expected value of μ_k conditional on $(\bar{S}_j, \bar{A}_j)$ for $k > j$ which needed a detailed information on the states and actions development process.

2.5.2.2 Recursive G-estimation

A modification on the G-estimation method has been made to accommodate the required search algorithm when the blips are not linear and the parameters are shared across the visits. The modified G-estimation is given as

$$G_j^{mod}(\psi) = Y - \gamma_j(a_j|\bar{S}_j, \bar{A}_{j-1}; \psi) + \sum_{k=j+1}^{K} [\gamma_k(d_k^{opt}|\bar{S}_j, \bar{A}_{j-1}; \psi) - \gamma_k(a_k|\bar{S}_j, \bar{A}_{j-1}; \psi)] \tag{2.11}$$

which indicate the response of a patient modified by the expected difference between the mean outcome for someone who received a_j and someone who was given the zero regime at stage j, where both had the same previous history $(\bar{S}_j, \bar{A}_{j-1})$ and were treated optimally starting at the future visit $j + 1$.

Under the assumption of additive local rank preservation, $G_j^{mod}(\psi) = Y(\bar{a}_{j-1}, d_j^{ref} = 0, \underline{d}_j^{opt})$. Recursive estimation, $\hat{\psi}$ can be estimated using $G_j^{mod}(\psi)$, by obtaining the estimate of the $\hat{\psi}$ starting from the last stage and then going backwards until it reach the first stage. Recursive G-estimation is particularly useful when parameters are not shared across stages. In fact, it still can be used when parameters are shared. This can be done by first assuming there is no sharing across the stage, and then take the average of the inverse-covariance weighted or even the simple average of the stage-specific estimates. $G_j^{mod}(\psi)$ can also be used in Equation (2.7) or Equation (2.8) without recursion.

2.5.3 The Regret-based Method for Optimal Dynamic Treatment Regimes

Several estimation strategies used the regret function to find the parameter estimates of the mean outcome. Murphy (2003) first introduced the regret function where the parameters are estimated using IMOR. Then, Henderson et al. (2010) remodelled the mean response by implementing the regret functions into a regression model for observational responses. Barrett et al. (2014) form a doubly-robust method of the regret-regression which is shown to be equivalently the same as the reduced form of the efficient G-estimation method by Robins (2004).

2.5.3.1 Regret Function and Iterative Minimization of Regrets (IMOR)

Murphy (2003) developed a regret function

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

which satisfies

$$\inf_{a_j, p_j(a_j|\bar{S}_j, \bar{A}_{j-1})} \{\mu_j(a_j|\bar{S}_j, \bar{A}_{j-1})\} = 0.$$

The regret function measures the expected difference between the best we can expect to do given what has happened so far (i.e. $E[Y(\bar{a}_{j-1}, \underline{d}_j^{opt})|\bar{S}_j, \bar{A}_{j-1}]$), and that we select a_j at time j (i.e. $E[Y(\bar{a}_j, \underline{d}_{j+1}^{opt})|\bar{S}_j, \bar{A}_{j-1}]$). The optimal action, a_j^{opt} at visit j can be achieved if the regret function $\mu_j(a_j^{opt}|\bar{S}_j, \bar{A}_{j-1})$ is equal to zero.

In term of the regret function, the mean of Y can be written as

$$E[Y|\bar{S}_K, \bar{A}_K] = \beta_0 + \sum_{j=1}^{K} \phi_j(S_j|\bar{S}_{j-1}, \bar{A}_{j-1}) - \sum_{j=1}^{K} \mu_j(A_j|\bar{S}_j\bar{A}_{j-1}; \psi) \tag{2.13}$$

where $\phi(S_j|\bar{S}_{j-1}, \bar{A}_{j-1}) = E(Y(\underline{d}_j^{opt})|\bar{S}_{j-1}, \bar{A}_{j-1}, S_j) - E(Y(\underline{d}_{j+1}^{opt})|\bar{S}_{j-1}, \bar{A}_{j-1})$. To obtained outcome Y, it depends on the initial condition (from β_0), chance of development over time of the states, S_j (from $\phi(.)$ function in Equation (2.13)), and the chosen actions, A_j (from the regret, $\mu(.)$function in Equation (2.13)). For estimation, Murphy (2003) only parameterized the regret function, and considered the initial condition and $\phi(.)$ function as nuisance which is equivalent to zero.

To estimate the parameter, ψ in ODTR, Murphy (2003) proposed a method called IMOR by searching for $(\hat{\psi}, \hat{c})$ which satisfy

$$\begin{aligned}
&\sum_{j=1}^{K} \mathbb{P}_n[Y + \hat{c} + \sum_{k=1}^{K} \mu_k(a_k|\bar{S}_k, \bar{A}_{k-1}; \hat{\psi}) - \sum_{a} \mu_j(a|\bar{S}_j, \bar{A}_{j-1}; \hat{\psi})(p_j(a|\bar{S}_j, \bar{A}_{j-1})]^2 \\
&\quad \leq \sum_{j=1}^{K} \mathbb{P}_n[Y + c + \sum_{k\neq j}^{K} \mu_k(a_k|\bar{S}_k, \bar{A}_{k-1}; \hat{\psi}) + \mu_j(a_j|\bar{S}_j, \bar{A}_{j-1}; \psi) \\
&\qquad - \sum_{a} \mu_j(a|\bar{S}_j, \bar{A}_{j-1}; \psi) p_j(a|\bar{S}_j, \bar{A}_{j-1})]^2
\end{aligned} \tag{2.14}$$

for ψ and c. Note that, $\mathbb{P}_n$ is the empirical average function and c is a scalar quantity.

2.5.3.2 Relationship between IMOR and G-estimation

Moodie et al. (2007) has shown that the G-estimation and IMOR are actually related to each other, and the regret function is a negative of the optimal blip function with the reference regime being the optimal regime at visit j. It can be formulated as

$$\mu_j(a_j|\bar{S}_j, \bar{A}_{j-1}) = \gamma_j^{ref}(d_j^{opt}|\bar{S}_j, \bar{A}_{j-1}) - \gamma_j^{ref}(a_j|\bar{S}_j, \bar{A}_{j-1}). \tag{2.15}$$

At binary and continuous outcome, Moodie et al. (2007) has showed that,

$$\mu_j(a_j|\bar{S}_j,\bar{A}_{j-1}) = \max_j \gamma_j^{ref}(d_j^{opt}|\bar{S}_j,\bar{A}_{j-1}) - \gamma_j^{ref}(a_j|\bar{S}_j,\bar{A}_{j-1})$$
$$or \tag{2.16}$$
$$\gamma_j(a_j|\bar{S}_j,\bar{A}_{j-1}) = \mu_j(d_j^{ref}|\bar{S}_j,\bar{A}_{j-1}) - \mu_j(a_j|\bar{S}_j,\bar{A}_{j-1})$$

Robins (2004, Corollary 9.2) has showed that, for an optimal blip $\gamma_j(a_j|\bar{S}_j,\bar{A}_{j-1})$ with parameter ψ_j, the unique function $f(a_j|\bar{S}_j,\bar{A}_{j-1})$ minimizing

$$\begin{aligned} E\Bigg[\Big\{&Y - f(a_j|\bar{S}_j,\bar{A}_{j-1}) + \sum_{k=j+1}^{K}[\gamma_k(d_k^{opt}|\bar{S}_k,\bar{A}_{k-1};\psi_k) - \gamma_k(a_k|\bar{S}_k,\bar{A}_{k-1};\psi_k)] \\ &- E[Y - f(a_j|\bar{S}_j,\bar{A}_{j-1}) + \sum_{k=j+1}^{K}[\gamma_k(d_k^{opt}|\bar{S}_k,\bar{A}_{k-1},\psi_k) - \gamma_k(a_k|\bar{S}_k,\bar{A}_{k-1})]\Big\}\Bigg]^2 \end{aligned} \tag{2.17}$$

subject to $f(a_j|\bar{S}_j,\bar{A}_{j-1}) = 0$ for $a_j = d_j^{ref} = 0$ (i.e. action from the set of possible action which is not observed) is $\gamma_j(a_j|\bar{S}_j,\bar{A}_{j-1})$. It is necessary to estimate ψ_k for $k = j+1,\ldots,K$ before estimating ψ_j. In G-estimation, we can avoid simultaneous minimization by estimating the parameter recursively. For example, first we estimate ψ_K, then ψ_{K-1} and so on until we estimates all the parameters. At the minimum, $f(a_j|\bar{S}_j,\bar{A}_{j-1}) = \gamma_j(a_j|\bar{S}_j,\bar{A}_{j-1})$. Thus,

$$Y - f(a_j|\bar{S}_j,\bar{A}_{j-1}) + \sum_{k=j+1}^{K}\left[\gamma_j(d_k^{opt}|\bar{S}_k,\bar{A}_{k-1};\psi_k) - \gamma_j(a_k^{opt}|\bar{S}_k,\bar{A}_{k-1};\psi_k)\right] = G_j^{mod}(\psi_j).$$

Equation (2.17) will have the same form as Equation (2.8) using a modified version of counterfactual quantity $G_j(\psi)$, when $g_j(A_j|\bar{S}_j,\bar{A}_{j-1}) = -\frac{\partial}{\partial\psi_j}f(A_j|\bar{S}_j,\bar{A}_{j-1})$.

Another recursive minimization method is IMOR. At any visit j, taking

$$f(a_j|\bar{S}_j,\bar{A}_{j-1}) = \gamma_j(a_j|\bar{S}_j,\bar{A}_{j-1};\psi_j) = \mu_j(d_j^{ref}=0|\bar{S}_j,\bar{A}_{j-1};\psi_j) - \mu_j(a_j|\bar{S}_j,\bar{A}_{j-1};\psi_j)$$

in Equation (2.17) will results to the RHS of Equation (2.14) with

$$
\begin{aligned}
-\hat{c} &= \mu_j(d_j^{ref} = 0|\bar{S}_j, \bar{A}_{j-1}; \psi_j) + \sum_{k=1}^{j-1} \mu_k(a_k|\bar{S}_k, \bar{A}_{k-1}; \hat{\psi}_k) \\
&\quad - E[\mu_j(d_j^{ref} = 0|\bar{S}_j, \bar{A}_{j-1}; \psi_j) + \sum_{k=j+1}^{K} \mu_k(a_k|\bar{S}_k, \bar{A}_{k-1}; \hat{\psi}_k) - Y] \\
&= E[G_j^{mod}(\psi)] + \mu_j(d_j^{ref} = 0|\bar{S}_j, \bar{A}_{j-1}; \psi_j) + \sum_{k=1}^{j-1} \mu_k(a_k|\bar{S}_k, \bar{A}_{k-1}; \hat{\psi}_k) \\
&\quad - E[\mu_j(a_j|\bar{S}_j, \bar{A}_{j-1}; \psi_j)]
\end{aligned}
\tag{2.18}
$$

IMOR and G-estimation are generally not equivalent because the parameter c in Equation (2.14) changes from stage to stage. IMOR obtains the solution by using the regret function and c instead of expressing $E[G_j^{mod}(\psi)]$ explicitly. Both IMOR and G-estimation are equivalent for a single-stage case when the null hypothesis of no treatment effect, $\hat{c} = E[G_j^{mod}(\psi)] = E[Y]$ when $E[G_j^{mod}(\psi)]$ is modelled with a constant and $g_j(A_j|\bar{S}_j, \bar{A}_{j-1}) = -\frac{\partial}{\partial \psi_j} f(A_j|\bar{S}_j, \bar{A}_{j-1})$.

Robins (2004) made an argument that we can correctly specify the model easily with the blip function because we can visualize a reference regime easily compared to an unspecified optimal regime. However, it can be computationally challenging to determine the optimal regime from the blip function compared to optimal action as the optimal action is taken from the regret function straight away.

2.5.3.3 Regret-regression

In IMOR and G-estimation, the focus is only on the treatment decision without considering the importance of the covariates or the state function, where the information of the states lie in the $\phi_j(S_j|\bar{S}_{j-1}, \bar{A}_{j-1})$ function. Henderson et al. (2010) proposed a method called a regret-regression method, which take the importance on both the states and treatments into its model.

Instead of parameterizing the mean outcome semi-parametrically by avoiding the nuisance functions, $\phi_j(S_j|\bar{S}_{j-1}, \bar{A}_{j-1})$, Henderson et al. (2010) modelled the nuisance function as a linear combination of residuals between S_j and the expected value of S_j given $(\bar{S}_{j-1}, \bar{A}_{j-1})$ defined as $Z_j = S_j - E(S_j|\bar{S}_{j-1}, \bar{A}_{j-1})$. From Equation (2.13), the mean response of the regret-regression is rewritten as

$$E(Y|\bar{S}_K, \bar{A}_K) = \beta_0(S_1) + \sum_{j=2}^{K} \beta_j^T(\bar{S}_{j-1}, \bar{A}_{j-1})Z_j - \sum_{j=1}^{K} \mu_j(A_j|\bar{S}_j, \bar{A}_{j-1}; \psi), \tag{2.19}$$

where β_0 and $\beta_j(\bar{S}_{j-1}, \bar{A}_{j-1})$ are coefficients that measured the states at visit j after allowing for $(\bar{S}_{j-1}, \bar{A}_{j-1})$ while assuming that the optimal actions are given from visit j onwards. Parameters β and ψ can be estimated using the ordinary least squares by minimizing

$$SS^{Rr} = \sum_{i=1}^{n} \left(Y_i - \beta_0(S_1) - \sum_{j=2}^{K} \beta_j^T(\bar{S}_{j-1,i}, \bar{A}_{j-1,i})Z_{j,i} + \sum_{j=1}^{K} \mu_j(A_{j,i}|\bar{S}_{j,i}, \bar{A}_{j-1,i}, \psi) \right)^2. \tag{2.20}$$

The advantage of the regret-regression is it allows model checking and diagnostic assessment since it is a regression-based method.

A doubly-robust version of the regret-regression was developed by Barrett et al. (2014) to overcome the limitation of the action or state process when the model is misspecified. This method is similar to a reduced form of an efficient G-estimation method (Robins, 2004).

Doubly robust regret-regression (DRRr) is defined to be robust to misspecification of either $\phi_j(S_j|\bar{S}_{j-1}, \bar{A}_{j-1})$ or the probability density $p_j(a_j|\bar{S}_j, \bar{A}_{j-1})$ of assigning action A_j.

Barrett et al. (2014) rewrite the estimating equation for the regret-regression (denoted as EE^{Rr}) of Equation (2.20) as

$$EE^{Rr}(\psi) = \Big(Y - E(Y|\bar{S}_K, \bar{A}_K)\Big) \sum_j \frac{\partial \mu_j}{\partial \psi} \tag{2.21}$$

by focusing on estimating the parameters of the regret function, μ_j. Barrett et al. (2014) showed that the expected value of the estimating equation of Equation (2.21) is equal to zero provided that the states and the regret functions is correctly specified.

Let $\tilde{Z}_j$ and $\tilde{\mu}_j(A_j|\bar{S}_j, \bar{A}_{j-1}; \psi)$ be the postulated models of Z_j and $\mu_j(A_j|\bar{S}_j, \bar{A}_{j-1}; \psi)$ respectively. Thus, the postulated expected mean outcome is given as

$$E(Y|\bar{S}_K, \bar{A}_K) = \tilde{\beta}_0(S_1) + \sum_{k=2}^{K} \tilde{\beta}_j^T(\bar{S}_{j-1}, \bar{A}_{j-1})\tilde{Z}_j - \sum_{k=1}^{K} \tilde{\mu}_j(A_j|\bar{S}_j, \bar{A}_{j-1}; \psi).$$

The expectation of the estimating equations for the regret-regression over all random variables is then written as

$$\begin{aligned}
&E_{\bar{S}_K, \bar{A}_K, Y}\big(EE^{Rr}(\psi)\big)\\
&\quad = E_{\bar{S}_K, \bar{A}_K, Y}\left\{\left(Y - \tilde{\beta}_0 - \sum_{k=2}^{j} \tilde{\beta}_j^T(\bar{S}_{j-1}, \bar{A}_{j-1})\tilde{Z}_j + \sum_{k=1}^{K} \tilde{\mu}_j(A_j|\bar{S}_j, \bar{A}_{j-1}; \psi)\right) \sum_j \frac{\partial \tilde{\mu}_j}{\partial \psi}\right\}\\
&\qquad\qquad = E_{\bar{S}_K, \bar{A}_K}\Bigg\{\beta_0 + \sum_{k=2}^{K} \beta_j^T(\bar{S}_{j-1}, \bar{A}_{j-1})Z_j - \mu_j(A_j|\bar{S}_j, \bar{A}_{j-1}; \psi) - \tilde{\beta}_0\\
&\qquad\qquad\qquad - \sum_{k=2}^{j} \tilde{\beta}_j^T(\bar{S}_{j-1}, \bar{A}_{j-1})\tilde{Z}_j + \sum_{k=1}^{K} \tilde{\mu}_j(A_j|\bar{S}_j, \bar{A}_{j-1}; \psi)\Bigg) \sum_j \frac{\partial \tilde{\mu}_j}{\partial \psi}\Bigg\},
\end{aligned} \tag{2.22}$$

where Equation (2.22) is used to take the expectation of Y. The expression will be equal to zero provided that the regret function, μ_j and the states are correctly specified, $\tilde{\beta}_0 = \beta_0$, $\tilde{\beta}_j^T(\bar{S}_{j-1}, \bar{A}_{j-1})\tilde{Z}_j = \beta_j^T(\bar{S}_{j-1}, \bar{A}_{j-1})Z_j$ and $\tilde{\mu}_j(A_j|\bar{S}_j, \bar{A}_{j-1}; \psi) = \mu_j(A_j|\bar{S}_j, \bar{A}_{j-1}; \psi)$.

Barrett et al. (2014) extended the estimating equation of Equation (2.21) by taking the contribution of the final term to obtained doubly-robust property of the regret-regression.

Thus, the estimating equation of the DRRr is

$$EE^{DRRr}(\psi) = \left(Y - E(Y|\bar{S}_K, \bar{A}_K)\right)\left(\frac{\partial \mu_K}{\partial \psi} - E_{A_K}\left(\frac{\partial \mu_K}{\partial \psi}\right)\right), \tag{2.23}$$

where parameter $\hat{\psi}$ is consistent if the expected value of the estimating equation equal to zero.

Other literature related to the regret-regression include Clairon et al. (2017) which developed a new treatment strategy based on the regret-regression and non-minimal state-space methods which are robust to misspecification and measurement error. Meanwhile, Mohamed (2013) had introduced a short-term strategy of the regret-regression method called the myopic regret-regression (MRr). The decision rules using the MRr method are considered at each clinical visit which will explained in detail in Section 3.2.1.

2.6 Marginal Mean Models

For analyzing longitudinal data, GEE and QIF have become the focal methods used by the researchers. These two methods are very popular since there is no requirement on specifying the probability distribution when analyzing longitudinal data. The marginal mean can be modelled without knowing the correlation structure of the longitudinal data although we do usually specify a working correlation matrix and the 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.

2.6.1 Generalized Estimating Equations (GEE)

In GEE, 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 when estimating the model parameters (Diggle et al., 2002; Liang & Zeger, 1986). The GEE is an extension of the quasi-likelihood approach in analyzing longitudinal and correlated data which does not require any distributional assumptions. The correlation of outcomes within an individual can be estimated and enable to estimate the robust regression parameters with the standard errors.

Let y_{ij} be the outcome variable and x_{ij} be a $(p \times 1)$ vector of covariates. The observation is observed for subjects $i = 1, 2, \ldots, n$ at times $j = 1, 2, \ldots, K$. Assuming that the observation between subject, i is independent, the marginal mean υ_{ij} is a function of the covariates with link function $h(\upsilon_{ij}) = x_{ij}^T \theta$. Then, the variance of outcome y_{ij} is a function of the mean $\text{var}(y_{ij}) = \zeta V(\upsilon_{ij})$, where ζ is the dispersion parameter (Song et al., 2009).

The GEE solves the equation

$$\sum_{i=1}^{n} \dot{\upsilon}_i^T V_i^{-1} (Y_i - \upsilon_i) = 0 \tag{2.24}$$

where for each i, $\dot{\upsilon}_i = \partial \upsilon_i / \partial \theta$ has a dimension of $K \times p$ with p being the number of parameters θ, and $V_i = D_i^{1/2} R_i(\rho) D_i^{1/2}$ is the working correlation structure. Denote that, D_i is the diagonal matrix of marginal variances, and $R_i(\rho)$ is the working correlation matrix with parameter ρ.

Zeger et al. (1988) applied the GEE method to fit the two types of approaches which are the subject-specific (SS) and population-averaged (PA) for discrete and continuous outcomes. Ye and Pan (2006) proposed an approach for joint modelling of the mean and covariance structures of longitudinal data using GEE approach. Ye and Pan (2006) used the modified Cholesky decomposition from Pourahmadi (1999) instead of the sandwich type of working covariance structure.

Shults et al. (2009) considered the criteria for selecting an appropriate working correlation structure when dealing with binary data by choosing the nearest structure for which the model-based and the sandwich-based estimator of the covariance matrix and choose the structure that minimizes the weighted error sum of squares. Warton (2011) improvised the GEE method to analyzed high dimensional data by using a regularized sandwich estimator with general structure correlation matrix. In order to improvised its numerical suitability, Warton (2011) reduced the sample estimate toward the working correlation matrix.

Sitlani et al. (2015) illustrated the potential for increased power using GEE analyses by conducting single-study and meta-analyses for 3 large cohort studies and Nikoloulopoulos (2016) introduced the weighted scores method for generalized linear model (GLM) margins. This parametric method is a likelihood based where for model selection, the composite likelihood information criteria have been proposed as an intermediate step. Huang et al. (2016) used the GEE bias correction methods in cluster randomized trials and found that the method is suitable to deal even with a small number of clusters. Meanwhile, Kwon et al. (2017) proposed a stabilized working correlation matrix of GEE using linear shrinkage method where the minimum eigenvalue is bounded with a small positive number.

2.6.2 Quadratic Inference Functions (QIF)

The purpose of the QIF is to extend the effectiveness of GEE in analyzing longitudinal or correlated data. In QIF, the working correlation matrix is expressed as a linear combination of unknown constants and known basis matrices (Qu & Lindsay, 2000). This linear expression is substituted back to a quasi-likelihood function to obtain an extended score vector with a generalized method of moments (Hansen, 1982). To developed an adaptive estimating equations in the quasilikelihood equations, Qu and Lindsay (2003) approximate the inverse of the variance matrix without requiring any assumptions on the working correlations. A multivariate generalization of the conjugate gradient method can be used to find the estimating equations that sustained the information well at fixed low dimensions (Qu & Lindsay, 2003). It is very beneficial when the estimator of the covariance matrix is singular or close to singular, or impossible to invert owing to its large size.

Qu and Lindsay (2000) defined the inverse function of working correlation matrix, $R_i^{-1}(\rho)$ as

$$R_i^{-1}(\rho) = \sum_{l=1}^{m} \tau_l M_l \tag{2.25}$$

where $M_1, \ldots, M_m$ are known basis matrices and $\tau_1, \ldots, \tau_m$ are unknown coefficients.

Then, substituting Equation (2.25) into Equation (2.24), the estimating functions can be rewritten as

$$\sum_{i=1}^{n} \dot{\upsilon}_i^T D_i^{-\frac{1}{2}} (\tau_1 M_1 + \ldots + \tau_m M_m) D_i^{-\frac{1}{2}} (Y_i - \upsilon_i) = 0. \tag{2.26}$$

Note that, in QIF we do not require the estimation of linear coefficients τ_m which can be treated as nuisance parameters. Thus, the extended score is

$$g_N(\theta) = \frac{1}{N} \sum_{i=1}^{N} g_i(\theta) = \frac{1}{N} \begin{pmatrix} \sum_{i=1}^{N} \dot{\upsilon}_i^T D_i^{-\frac{1}{2}} M_1 D_i^{-\frac{1}{2}} (Y_i - \upsilon_i) \\ \sum_{i=1}^{N} \dot{\upsilon}_i^T D_i^{-\frac{1}{2}} M_2 D_i^{-\frac{1}{2}} (Y_i - \upsilon_i) \\ \vdots \\ \sum_{i=1}^{N} \dot{\upsilon}_i^T D_i^{-\frac{1}{2}} M_m D_i^{-\frac{1}{2}} (Y_i - \upsilon_i) \end{pmatrix} \tag{2.27}$$

is a vector with length mp where m is a number of basis matrices. Using the generalized method of moments Hansen (1982) where there are more equations than the unknown parameters, the QIF maximizes

$$Q_N(\theta) = g_N^T C_N^{-1} g_N \tag{2.28}$$

where

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

Some development in QIF method include a modification on the QIF to overcome the weakness on the non-invertible estimation of the optimal weighting matrix (Han & Song, 2011). The modification work by substituting the sample covariance matrix with a linear shrinkage estimator in order to estimate the optimal weighting matrix. The linear shrinkage estimator was proved to be consistent and asymptotically optimal under the expected quadratic loss and has a more stable numerical performance compared to the sample covariance matrix. Other modification is from Yang and Liao (2017) that modified the extended score function of the QIF method by presenting it with a robust variance estimator.

Westgate and Braun (2012) shows that the QIF can produce estimates with a large variability when there is an imbalance in the covariates and cluster size where the result is obtained from the empirical nature of weighting QIF rather than the differences in estimating equations classes. The asymptotic covariance formula is used in the QIF to obtain standard errors. Meanwhile, Westgate (2012) showed that the standard errors are biased downward in small to moderately sample size thus, inflating test size and decreasing coverage probability. To eliminate finite-sample biases which lead to substantial improvements in standard error estimates, inference and coverage, Westgate (2012) proposed adjustments to the asymptotic covariance formula. Meanwhile, Westgate and Braun (2013) proposed an alternative weighting matrix for the QIF, which asymptotically is an optimally weighted combination of the empirical covariance matrix and its model-based version, which is derived by minimizing its expected quadratic loss. The use of the weighting matrix maintains the large-sample advantages the QIF has over GEE and improves small-sample parameter estimation.

Recently, Yu, Tong, and Li (2020) solved each set of score equations by providing an alternative solution to the QIF which also combined the solutions. This solutions gives an understanding that an optimally weighted combination of estimators gained separately from the distinct sets of score equations is asymptotically equivalent to the estimator obtained via the QIF. Other recent works includes (Dumitrescu, Qian, & Rao, 2020; Lai, Liang, Wang, & Zhang, 2020).

2.7 Penalized Methods

Although the QIF method is possible to analyze longitudinal outcome, however when the dimension of the parameters is bigger than the correlation matrix, a complex computational problem such as singularity issues may occurs. To overcome this problem, the penalized term may be added to the estimating equations of the GEE and QIF.

There are several types of penalty, for example, least absolute shrinkage and selection operator (LASSO) (Tibshirani, 1996), and smoothly clipped absolute deviation (SCAD) (Fan & Li, 2001). Fu (2003) considered the bridge penalty model, $\sum_{v=1}^{p} |\theta_v|^\gamma$ for estimating equations and apply the bridge penalty to the generalized estimating equations (GEE). Note that, when $\gamma = 1$, it is defined as Lasso estimator, meanwhile, if the value of $\gamma = 2$ then it is known as a ridge. In addition, there are other method such as the elastic net method for regularization and variable selection method (Zou & Hastie, 2005). It is a convex combination of the LASSO and ridge penalty.

2.7.1 Ridge Estimator

The ridge regression model has been introduced as an alternative to the least squares estimation for poor design matrix. Hoerl and Kennard (1970) introduced a biased estimators called ridge estimators and proposed a ridge trace method to show the effects of non-orthogonality in two dimensions. The ridge estimators also known as ridge penalty can control the inflation and general instability related with the least squares estimates. In addition, the ridge penalty can also solve the multicollinearity problem in dataset. Hence, in this study, we will use the ridge penalty also known as L_2 penalty to improve the estimation in ODTR and to solve the singularity issues which gives more stability in computation.

To estimate the parameter of the ridge regression, first consider a normal linear model where Y is normally distributed with mean $X\theta$ and variance σ^2, $Y \sim N(X\theta, \sigma^2)$. The penalized residual sum of squares of the ridge regression given by Hoerl and Kennard (1970) is

$$\begin{aligned} rRSS(\theta) &= RSS(\theta) + \lambda \sum_{v=1}^{p} |\theta_v|^2 \\ &= \sum_{i=1}^{n} (Y_i - X_i\theta)^T (Y_i - X_i\theta) + \lambda \sum_{v=1}^{p} |\theta_v|^2, \end{aligned} \tag{2.29}$$

where λ is the tuning parameter.

Taking the derivative of Equation (2.29),

$$\frac{\partial rRSS(\theta)}{\partial\theta} = -2X^T(Y - X\theta) + 2\lambda\theta_v \tag{2.30}$$

and solving $U(\hat{\theta}) = X^T(Y - X\theta) - \lambda\theta$ equal to zero gives the estimate of $\hat{\theta}(\lambda)$,

$$\hat{\theta}(\lambda) = (X^T X + \lambda I_p)^{-1} X^T Y.$$

The residual of the ridge regression is

$$\begin{aligned} e(\lambda) &= Y - \hat{Y} \\ &= Y - X\hat{\theta} \\ &= Y - X(X^T X + \lambda I_p)^{-1} X^T Y \\ &= (I - X(X^T X + \lambda I_p)^{-1} X^T) Y \\ &= (I - H(\lambda))Y. \end{aligned} \tag{2.31}$$

where the $H(\lambda)$ is the hat matrix of the ridge regression

$$H(\lambda) = X(X^T X + \lambda I)^{-1} X^T. \tag{2.32}$$

Now, suppose that there is a weight associated with each observation. Then, we have Y to be normally distributed with mean $X\theta$ and covariance Σ, $Y \sim N(X\theta, \Sigma)$. The penalized weighted sum of squares using ridge regression is

$$rWSS(\theta) = \sum_{i=1}^{n} (Y_i - X_i\theta)^T \Sigma^{-1} (Y_i - X_i\theta) + \lambda \sum_{v=1}^{p} |\theta_v|^2. \tag{2.33}$$

Taking the derivative of Equation (2.33) gives

$$\frac{\partial rWSS(\theta)}{\partial\theta} = -2X^T \Sigma^{-1} (Y - X\theta) + 2\lambda\theta, \tag{2.34}$$

where the weighted score function $U(\hat{\theta}) = X^T \Sigma^{-1} (Y - X\hat{\theta}) - \lambda\hat{\theta}$ is equivalent to solving

$$X^T \Sigma^{-1} (Y - X\hat{\theta}) - \lambda\hat{\theta} = 0. \tag{2.35}$$

Thus, the parameter estimates, $\hat{\theta}(\lambda)$ for the weighted ridge regression is

$$\hat{\theta}(\lambda) = (X^T \Sigma^{-1} X + \lambda I_p)^{-1} X^T \Sigma^{-1} Y.$$

The residual of the weighted ridge regression is

$$\begin{aligned} e(\lambda) &= Y - \hat{Y} \\ &= Y - X\hat{\theta} \\ &= Y - X(X^T \Sigma^{-1} X + \lambda I_p)^{-1} X^T \Sigma^{-1} Y \\ &= (I - H(\lambda))Y, \end{aligned} \tag{2.36}$$

and the hat matrix, $H(\lambda)$ for the weighted ridge regression is

$$H(\lambda) = X(X^T \Sigma^{-1} X + \lambda I_p)^{-1} X^T \Sigma^{-1}. \tag{2.37}$$

The penalty function are widely been used in model selection for high dimensional data where the number of predictors are bigger than the sample size. For longitudinal data analysis, Mũller et al. (2017) note that the function C_N of the QIF method faced singularity problem for autogressive with order 1, AR(1) and exchangeable working correlation structures. To counter this problem, Mũller et al. (2017) defined the method called rQIF by applying the ridge penalty into the C_N function. Meanwhile, Song et al. (2009) used penalty approach to compose model selection through the QIF method where model selection is practically been employ on high dimensional data. The data is said to be high in dimension when the variables are bigger than the sample sizes.

When the errors are correlated, Akdeniz and Roozbeh (2019) proposed a generalized difference-based almost unbiased ridge estimator for the parameter in partially linear model. From the analysis, Akdeniz and Roozbeh (2019) noticed that the degree of correlation is the main factors that affecting the performance of the estimators. In the context of robust regression, a ridge rank regression estimator can be used when there is a multicollinearity. Roozbeh et al. (2020) proposed and demonstrated that a generalized cross-validation criterion allows the shrinkage ridge rank regression to perform well in the term of minimum risk function. The generalized cross-validation method strikes a balance between the estimators' precision and the bias introduced by ridge estimation (Arashi et al., 2021).

2.8 Summary

In this chapter, we have reviewed estimation strategies for ODTR which are SNMM, G-Estimation, IMOR, and regret-regression. To begin with, we start by explaining the longitudinal data and causal inference. Then, we give a framework for ODTR which includes the notation and assumptions needed. After introducing the estimation strategies for ODTR, we reviewed methods for analyzing longitudinal data which are GEE and QIF. Next, we reviewed the ridge estimator that is for the proposed method in Chapter 3.

CHAPTER 3: METHODOLOGY

3.1 Introduction

We begin with the MRr introduced by Mohamed (2013) which is a short-term strategy of the regret-regression. In MRr, the response considered is a longitudinal outcome where the response is measured at a current visit j and the model is fitted at each visit j. The myopic decision rules is defined to be a sequence of decision rules that maximizes a short-term criteria, where all future measurement are ignored, and each visit is treated to be the only visit that we are interested in. Then, we give a methodology for QIF-MRr which is a combination between the MRr with QIF to analyze ODTR. Then, we extend the work by proposing rQIF-MRr to overcome the limitations of QIF-MRr in estimating small sample sizes and handling singularity issue.

3.2 Estimating Optimal Dynamic Treatment Regimes (ODTR) for Longitudinal Outcomes

For each subject i, suppose $Y_i = (Y_{i1}, Y_{i2}, \ldots, Y_{iK})^T$ be the vector of longitudinal outcomes for $j = 1, 2, \ldots, K$, and let the mean vector $h_i = E(Y_i|\bar{S}_i, \bar{A}_i, \theta)$. Note that, $\bar{S}_i = (S_{i1}, S_{i2}, \ldots, S_{iK})^T$ and $\bar{A}_i = (A_{i1}, A_{i2}, \ldots, A_{iK})^T$ are the vector of states and action given for subject i respectively.

The states and actions, $(\bar{S}_i, \bar{A}_i)$ are assumed to be independent between the subjects and dependent within a subject. The difference between the regret-regression with the MRr is that, the MRr estimate the ODTR at each visit, while, the regret-regression estimate the ODTR at the end of visit (after the observations for the case study has fully obtained). Figure 3.1 illustrates different types of observational sequence. Figure 3.1 (a) shows the general observational order of the dynamic treatment regimes. Figure 3.1 (b) and (c) give the observational order for the regret-regression and MRr respectively.

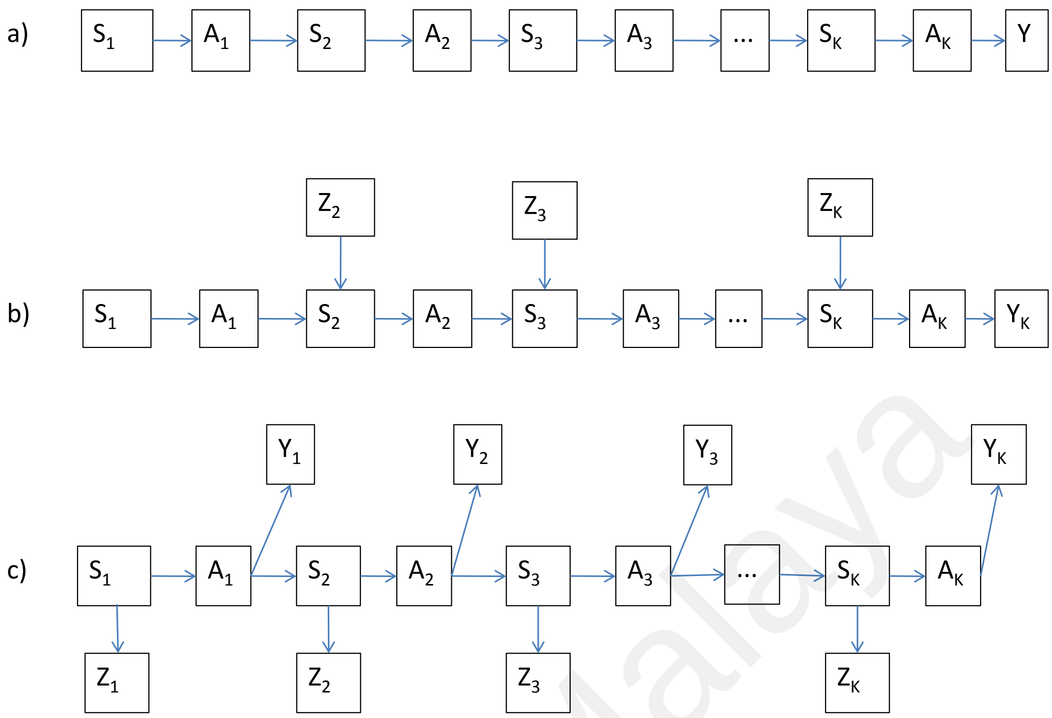

Figure 3.1: (a) General observational order (b) Observational order for regret-regression (c) Observational order for MRr

3.2.1 Myopic Regret-regression (MRr)

The mean response of MRr for $j = 1, 2, \ldots, K$ is

$$E(Y_j|\bar{S}_j, \bar{A}_j, \beta, \psi) = \beta_j^T(\bar{S}_{j-1}, \bar{A}_{j-1})Z_j - \mu_j(A_j|\bar{S}_j, \bar{A}_{j-1}, \psi), \tag{3.1}$$

where $\mu_j(A_j|\bar{S}_j, \bar{A}_{j-1}, \psi)$ is a regret function. Note that, $\beta_j(\bar{S}_{j-1}, \bar{A}_{j-1})$ are coefficients that measure the states at visit j after allowing for $(\bar{S}_{j-1}, \bar{A}_{j-1})$ while assuming that the optimal actions are given from visit j onwards, and $Z_j = S_j - E(S_j|\bar{S}_{j-1}, \bar{A}_{j-1})$ is a linear combination of residuals between S_j and the expected value of S_j given $(\bar{S}_{j-1}, \bar{A}_{j-1})$ as in Section (2.5.3.3). Similar to Equation (2.13) in Murphy (2003), Equation (3.1) can be rewritten as

$$E(Y_j|\bar{S}_j, \bar{A}_j, \beta, \psi) = \beta_0 + \phi_j(S_j|\bar{S}_{j-1}, \bar{A}_{j-1}|\beta) - \mu_j(A_j|\bar{S}_j, \bar{A}_{j-1}, \psi), \tag{3.2}$$

where $\phi_j(S_j|\bar{S}_{j-1}, \bar{A}_{j-1}|\beta)$ is a state function.

Let $\theta = (\beta, \psi)$, then for each interval j, the sum of squares of error for the MRr is

$$\begin{aligned} SS_{MRr}(\theta) &= \sum_{i=1}^{n}(Y_i - E(Y_j|\bar{S}_j, \bar{A}_j, \theta))^2 \\ &= \sum_{i=1}^{n}\left\{Y_i^2 - 2E(Y_j|\bar{S}_j, \bar{A}_j, \theta)Y_i + E(Y_j|\bar{S}_j, \bar{A}_j, \theta)^2\right\}. \end{aligned} \tag{3.3}$$

Taking the derivative of Equation (3.3) will gives

$$\frac{\partial SS_{MRr}(\theta)}{\partial\theta} = \sum_{i=1}^{n}\left\{-2\left(\frac{\partial E(Y_j|\bar{S}_j, \bar{A}_j, \theta)}{\partial\theta}\right)Y_i + 2\left(\frac{\partial E(Y_j|\bar{S}_j, \bar{A}_j, \theta)}{\partial\theta}\right)E(Y_j|\bar{S}_j, \bar{A}_j, \theta)\right\}. \tag{3.4}$$

Solving Equation (3.4) equal to zero gives

$$\sum_{i=1}^{n}\left\{\left(\frac{\partial E(Y_j|\bar{S}_j, \bar{A}_j, \theta)}{\partial\theta}\right)(Y_i - E(Y_j|\bar{S}_j, \bar{A}_j, \theta))\right\} = 0. \tag{3.5}$$

The parameter estimate, $\hat{\theta}$ can be obtained by using the ordinary least squares method by minimizing the estimating equations of the MRr method as in Equation (3.6). $\hat{\theta}$ is consistent when the expectation of the estimating equation of the MRr is zero. Following the proof on consistency by Barrett et al. (2014), we will show that $E(EE^{MRr}(\theta)) = 0$ provided that the states and regret functions are modeled correctly.

For all $i = 1, 2, \dots, n$, the estimating equation of MRr for each j is

$$EE^{MRr}(\theta) = (Y_j - E(Y_j|\bar{S}_j, \bar{A}_j))\left(\frac{\partial E(Y_j|\bar{S}_j, \bar{A}_j)}{\partial\theta}\right). \tag{3.6}$$

Let $\tilde{\beta}_0$, $\tilde{\phi}_j(S_j|\bar{S}_{j-1}, \bar{A}_{j-1}|\beta)$ and $\tilde{\mu}_j(A_j|\bar{S}_j, \bar{A}_{j-1}, \psi)$ be the postulated models for $\phi_j(S_j|\bar{S}_{j-1}, \bar{A}_{j-1}|\beta)$ and $\mu_j(A_j|\bar{S}_j, \bar{A}_{j-1}, \psi)$ respectively. Thus, the postulated model for $E(Y_j|\bar{S}_j, \bar{A}_j)$ is then

$$E(Y_j|\bar{S}_j, \bar{A}_j) = \tilde{\beta}_0 + \tilde{\phi}_j(S_j|\bar{S}_{j-1}, \bar{A}_{j-1}|\beta) - \tilde{\mu}_j(A_j|\bar{S}_j, \bar{A}_{j-1}, \psi), \tag{3.7}$$

and the expectation of the estimating equation over all random variables is

$$\begin{aligned} E_{\bar{S}_j,\bar{A}_j}(EE^{MRr}(\theta)) = E_{\bar{S}_j,\bar{A}_j}\Bigg((Y_j - \tilde{\beta} - \tilde{\phi}_j(S_j|\bar{S}_{j-1}, \bar{A}_{j-1}|\beta) \\ + \tilde{\mu}_j(A_j|\bar{S}_j, \bar{A}_{j-1}, \psi))\left(\frac{\partial E(Y_j|\bar{S}_j, \bar{A}_j, \theta)}{\partial\theta}\right)\Bigg), \end{aligned} \tag{3.8}$$

Then, substituting Equation (3.2) into Equation (3.8) gives

$$\begin{aligned} E_{\bar{S}_j,\bar{A}_j}(EE^{MRr}(\theta)) = E_{\bar{S}_j,\bar{A}_j}\Bigg((\beta_0 - \phi_j(S_j|\bar{S}_{j-1}, \bar{A}_{j-1}|\beta) + \mu_j(A_j|\bar{S}_j, \bar{A}_{j-1}, \psi) \\ - \tilde{\beta}_0 - \tilde{\phi}_j(S_j|\bar{S}_{j-1}, \bar{A}_{j-1}|\beta) + \tilde{\mu}_j(A_j|\bar{S}_j, \bar{A}_{j-1}, \psi))\left(\frac{\partial E(Y_j|\bar{S}_j, \bar{A}_j, \theta)}{\partial\theta}\right)\Bigg). \end{aligned} \tag{3.9}$$

Therefore, the expression of Equation (3.9) is equal to zero provided that the state and the regret functions are modeled correctly $\beta_0 = \tilde{\beta}_0$, $\phi_j(S_j|\bar{S}_{j-1}, \bar{A}_{j-1}|\beta) = \tilde{\phi}_j(S_j|\bar{S}_{j-1}, \bar{A}_{j-1}|\beta)$ and $\mu_j(A_j|\bar{S}_j, \bar{A}_{j-1}, \psi) = \tilde{\mu}_j(A_j|\bar{S}_j, \bar{A}_{j-1}, \psi)$.

The relation between MRr with regret-regression is that the summation of the mean response at each time j from Equation (3.1) is equivalent to the mean response of the regret-regression. Suppose, the first visit ($j = 1$),

$$\beta_j^T(\bar{S}_{j-1}, \bar{A}_{j-1})Z_j = \beta_0(S_1).$$

Then,

$$\begin{aligned}\sum_{j=1}^{K} E(Y_j|\bar{S}_j, \bar{A}_j) &= \sum_{j=1}^{K}\Big(\beta_j^T(\bar{S}_{j-1}, \bar{A}_{j-1})Z_j - \mu_j(A_j|\bar{S}_j, \bar{A}_{j-1}; \psi)\Big) \\ &= \beta_0(S_1) + \sum_{j=2}^{K}\beta_j^T(\bar{S}_{j-1}, \bar{A}_{j-1})Z_j - \sum_{j=1}^{K}\mu_j(A_j|\bar{S}_j, \bar{A}_{j-1}; \psi) \\ &= E(Y|\bar{S}_K, \bar{A}_K).\end{aligned} \tag{3.10}$$

3.2.2 Quadratic Inference Functions in Myopic Regret-regression (QIF-MRr)

Referring to Section (2.6.2), suppose $R(\rho)$ be the working correlation matrix with parameter ρ, and the inverse function of $R^{-1}(\rho)$ can be approximated by a linear combination of several basis matrices defined as

$$R^{-1}(\rho) = \sum_{l=1}^{m} \tau_l M_l. \tag{3.11}$$

There are several types of working correlation structures commonly used such as

(i) independent,

(ii) exchangeable,

(iii) first order autoregressive, AR(1),

(iv) unspecified.

For an independent working correlation structure, $R(\rho)$ is an identity matrix where

$$R^{-1}(\rho) = \tau_0 M_0 \tag{3.12}$$

and

$$M_0 = \begin{pmatrix} 1 & 0 & \dots & 0 \\ 0 & 1 & \dots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \dots & 1 \end{pmatrix}. \tag{3.13}$$

Meanwhile, for an exchangeable working correlation structure, $R(\rho)$ consists of 1's on the diagonal and ρ's everywhere off-diagonal. Then, R^{-1} is given as

$$R^{-1}(\rho) = \tau_0 M_0 + \tau_1 M_1 \tag{3.14}$$

where M_0 is an identity matrix

$$M_0 = \begin{pmatrix} 1 & 0 & \dots & 0 \\ 0 & 1 & \dots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \dots & 1 \end{pmatrix} \tag{3.15}$$

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

$$M_1 = \begin{pmatrix} 0 & 1 & \dots & 1 \\ 1 & 0 & \dots & 1 \\ \vdots & \vdots & \ddots & \vdots \\ 1 & 1 & \dots & 0 \end{pmatrix}. \tag{3.16}$$

Note that, $\tau_0 = -\{(K-2)\rho + 1\}/\{(K-1)\rho^2 - (K-2)\rho - 1\}$ and $\tau_1 = \rho/\{(K-1)\rho^2 - (K-2)\rho - 1\}$ and K is the dimension of R. For the AR(1) working correlation structure, the inverse working correlation structure can be written as

$$R^{-1}(\rho) = \tau_0 M_0 + \tau_1 M_1 + \tau_2 M_2 \tag{3.17}$$

where M_0 is an identity matrix

$$M_0 = \begin{pmatrix} 1 & 0 & \dots & 0 \\ 0 & 1 & \dots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \dots & 1 \end{pmatrix}, \tag{3.18}$$

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

$$M_1 = \begin{pmatrix} 0 & 1 & & & \dots & 0 \\ 1 & 0 & 1 & & \dots & 0 \\ 0 & 1 & 0 & 1 & \dots & 0 \\ \vdots & \vdots & \ddots & \ddots & \ddots & \vdots \\ 0 & \dots & \dots & \dots & \dots & 0 \end{pmatrix} \tag{3.19}$$

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

$$M_2 = \begin{pmatrix} 1 & 0 & \dots & 0 \\ 0 & 0 & \dots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \dots & 1 \end{pmatrix}. \tag{3.20}$$

Here $\tau_0 = (1+\rho^2)/(1-\rho^2)$, $\tau_1 = (-\rho)/(1-\rho^2)$ and $\tau_2 = (-\rho^2)/(1-\rho^2)$.

The unspecified working correlation structure can be used to determine the working correlation structure when there is some difficulty and challenges in obtaining it. For the unspecified working correlation structure, the basis matrices $M_0 = I_n$ and $M_1 = \hat{U}$, where

$$\hat{U} = \frac{1}{N}\Sigma(Y_i - h_i)(Y_i - h_i)^T, \tag{3.21}$$

and the matrix $\hat{U}$ is a consistent estimator of the variance matrix of Y (Qu & Lindsay, 2003).

Let $h_i = E(Y_j|\bar{S}_j, \bar{A}_j)$, substituting the marginal mean, υ_{ij} from Section (2.6.1) of Equation (2.24) with the mean vector of MRr, h_i, the GEE in MRr solves the equation

$$\sum_{i=1}^{n}\left(\frac{\partial h_i}{\partial \theta}\right)^T V_i^{-1}(Y_i - h_i) = 0 \tag{3.22}$$

where the partial derivative $\partial h_i/\partial(\theta)$ for each i has a dimension of $K \times p$ with p being the number of parameters θ. Then, the estimating functions can be rewritten as

$$\sum_{i=1}^{n}\left(\frac{\partial h_i}{\partial \theta}\right)^T D_i^{-\frac{1}{2}}(\tau_1 M_1 + \ldots + \tau_m M_m)D_i^{-\frac{1}{2}}(Y_i - h_i). \tag{3.23}$$

The extended score of QIF-MRr

$$g_N(\theta) = \frac{1}{N}\sum_{i=1}^{N} g_i(\theta) = \frac{1}{N}\begin{pmatrix} \sum_{i=1}^{N}\left(\frac{\partial h_i}{\partial \theta}\right)^T D_i^{-\frac{1}{2}} M_1 D_i^{-\frac{1}{2}}(Y_i - h_i) \\ \sum_{i=1}^{N}\left(\frac{\partial h_i}{\partial \theta}\right)^T D_i^{-\frac{1}{2}} M_2 D_i^{-\frac{1}{2}}(Y_i - h_i) \\ \vdots \\ \sum_{i=1}^{N}\left(\frac{\partial h_i}{\partial \theta}\right)^T D_i^{-\frac{1}{2}} M_m D_i^{-\frac{1}{2}}(Y_i - h_i) \end{pmatrix}. \tag{3.24}$$

The QIF-MRr function is then

$$Q_N(\theta) = g_N^T C_N^{-1} g_N, \tag{3.25}$$

where

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

The parameter estimates of θ can be obtained by minimizing the $Q_N(\theta)$,

$$\hat{\theta} = \arg\min_{\theta} g_N^T C_N^{-1} g_N. \tag{3.26}$$

3.3 The Proposed Method

Ridge penalty also known as the L_2 penalty was first introduced by Hoerl and Kennard (1970). In this section, the ridge QIF-MRr (rQIF-MRr) is proposed to solve singularity problem when estimating the ODTR. Although the QIF-MRr works efficiently in estimating ODTR, however, the singularity issues often arise during computation. The singularity problem can be solved by applying the ridge penalty into the estimating equations. Applying the ridge penalty into the QIF-MRr will help stabilizing the estimation.

3.3.1 Ridge Quadratic Inference Functions in Myopic Regret-regression (rQIF-MRr)

Dziak (2006) described a penalized QIF as

$$Q_n^{\mathcal{P}}(\theta) = g_N^T C_N^{-1} g_N + k_n \mathcal{P}(\theta) \tag{3.27}$$

where k_n is a multiplier to scale a penalty function and $\mathcal{P}(\theta)$ is a penalty function.

Thus, by applying the penalized QIF defined above, we propose the penalized quadratic inference functions using ridge penalty for MRr (ridge quadratic inference functions in myopic regret-regression, rQIF-MRr) as

$$rQ_N(\theta, \lambda) = g_N^T C_N^{-1} g_N + \lambda \sum_{v=1}^{p} |\theta_v|^2; \lambda \geq 0 \tag{3.28}$$

where λ is the tuning parameter, and $\sum_{v=1}^{p} |\theta_v|^2$ is a penalty function. The penalty function act as a weight during estimation, and stabilized the estimation of the parameter in computation.

Minimizing the $rQ_N(\theta, \lambda)$ function from Equation (3.28) will gives

$$\hat{\theta} = \arg\min_{\theta} g_N^T C_N^{-1} g_N + \lambda \sum_{v=1}^{p} |\theta_v|^2. \tag{3.29}$$

3.4 Conclusions

In this chapter, we begin by describing the MRr estimation strategy and proceed with describing the QIF-MRr for correlated data. The MRr, is a short-term strategy of the regret-regression where it estimate the parameters at each visit. Meanwhile, the QIF-MRr is a combination of the MRr with QIF. The QIF were majorly used in analyzing longitudinal or correlated data because it has the advantages of not requiring any distributional assumption.

We proposed the rQIF-MRr estimation strategy by applying the ridge estimator into the QIF-MRr to solve singularity problem during computation. There are several types of working correlation structures commonly used which are independent, exchangeable, AR(1) and unspecified working correlation structures. We will apply these working correlation structures into the QIF-MRr and the rQIF-MRr strategy for the application to a simulated data set in Chapter 4.

CHAPTER 4: SIMULATION STUDIES AND DISCUSSIONS

4.1 Simulation Procedure

The performance of the MRr, QIF-MRr and rQIF-MRr estimation methods were measured using simulations, that aim is to optimize the response Y_j at each time point. The simulation scenario was taken from Murphy (2003), although just one action is taken into account. Let $i = \{1, 2, \ldots, n\}$ be the subject observed and n is the sample size. Then, $j = 1, 2, \ldots, K$ be the time point where $K = 10$ is the final time point. For each subject i, the first state S_1 was generated from normal distribution with mean 0.5 and variance 0.01, i.e. $S_1 \sim N(0.5, 0.01)$. For the second state onward where $j = \{2, 3, \ldots, K\}$, states S_j were generated from normal distribution with mean, $m_j = 0.5 + 0.2S_{j-1} - 0.07A_{j-1}$, and variance 0.01, i.e. $S_j \sim N(m_j, 0.01)$. The action, A_j were generated from uniform distribution $A_j \sim U\{0, 1, 2, 3\}$. The regret function is defined as

$$\mu_j(a_j|\bar{S}_j, \bar{A}_{j-1}; \psi) = \psi_1|a_j - \psi_2 - \psi_3 S_j|$$

where $\mu_j(a_j|\bar{S}_j, \bar{A}_{j-1}; \psi) \geq 0$.

The outcomes, Y_j is generated from normal distribution with variance 0.64 and mean

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

where $Z_j = S_j - m_j$.

The true parameter value of $\theta = \{\beta, \psi\} = \{3, -5, 1.5, 0.1, 5.5\}$ and the tuning parameter $\lambda = 0.01$. We generate the data using AR(1) correlation structure with the correlation parameter $\rho = 0.1, 0.5, 0.95$. $\rho = 0.1$ indicate a low correlation in the data within subject, $\rho = 0.5$ is a medium correlation and $\rho = 0.95$ is when the data were highly correlated.

The simulation was repeated 1000 times with 3 different sample size $n = \{25, 250, 500\}$. Using the Cochran Test (Twisk, 2013),

$$n_0 = \frac{Z_0^2 p_0 q_0}{e_0^2}$$

where e_0 is a margin of error, p_0 is the proportion of the population, $q_0 = 1 - p_0$, and Z_0 is a z-value from standardized normal population, and assuming that p_0 and q_0 are 0.5, and the Z_0 is 1.96 for 95% confidence, then at least $n_0 = 385$ is an ideal sample size. Therefore, $n = 25$ and $n = 250$ are considered small sample sizes.

To estimate the parameter θ, we used the *optim* built-in function in R. The results in Section (4.2) reported the mean of the parameter estimates (Mean), standard error (SE), different between the estimated value with the true value (Bias), the root mean square error (RMSE) and the percentage of the convergence rate (CR).

A bootstrap resampling of $B = 1000$ repetitions to obtain the mean value of the estimated parameter $\hat{\theta}$ is

$$E(\hat{\theta}) = \frac{1}{B} \sum_{b=1}^{B} \hat{\theta}_b.$$

We obtained the SE by calculating the standard deviation (SD) of the parameter estimates for 1000 repetitions. Bias is calculated by taking the difference between the estimated mean of $\hat{\theta}$ with the true value, θ. Denote that, the negative value of the bias is when the mean of the $\hat{\theta}$ is bigger than the true value of θ, and the positive value of the bias is when the mean of the $\hat{\theta}$ is smaller than the true value of θ. The sign of the Bias value acts as an indicator only. Then, we calculated the RMSE as

$$\text{RMSE} = \sqrt{SE^2 + Bias^2}.$$

The number of successful converged iterations divided by the total number of repetitions multiplied by 100 percent is the convergence rate (%).

The results were given in the Section (4.2) and divided into 4 parts. First part will be the estimation results for MRr. Note that, the MRr is when the working correlation structure is independent where there is no correlation in the data set. The second to the fourth part is the comparison results in estimation between QIF-MRr with rQIF-MRr using AR(1), exchangeable and unspecified working correlation structure.

4.2 Simulation Results

4.2.1 Result on Parameter Estimates for MRr with Different Sample Sizes

Table 4.1: Parameter estimates using myopic regret-regression (MRr) with 1000 repetitions for sample size, $n = \{25, 250, 500\}$.

n	True value	Mean	SE	Bias	RMSE	CR
25	$\beta_0 = 3.0$	3.0107	0.1997	0.0107	0.2000	100%
	$\beta_1 = -5.0$	-4.9620	0.7016	0.0380	0.7026	
	$\psi_1 = 1.5$	1.4995	0.0566	-0.0005	0.0566	
	$\psi_2 = 0.1$	0.0902	0.1533	-0.0098	0.1536	
	$\psi_3 = 5.5$	5.5343	0.3680	0.0343	0.3696	
250	$\beta_0 = 3.0$	2.9987	0.0611	-0.0013	0.0611	100%
	$\beta_1 = -5.0$	-5.0023	0.2090	-0.0023	0.2090	
	$\psi_1 = 1.5$	1.5004	0.0175	0.0004	0.0175	
	$\psi_2 = 0.1$	0.0990	0.0459	-0.0010	0.0459	
	$\psi_3 = 5.5$	5.5021	0.1099	0.0021	0.1099	
500	$\beta_0 = 3.0$	3.0006	0.0441	0.0006	0.0441	100%
	$\beta_1 = -5.0$	-4.9959	0.1578	0.0041	0.1579	
	$\psi_1 = 1.5$	1.4999	0.0129	-0.0001	0.0129	
	$\psi_2 = 0.1$	0.0992	0.0328	-0.0008	0.0328	
	$\psi_3 = 5.5$	5.5038	0.0802	0.0038	0.0803	

Results in Table (4.1) give the parameter estimates for MRr method with 25, 250 and 500 sample sizes. Here, we assume that there is no correlation when generating the dataset. For $n = 25$, the estimates are slightly biased compared to the $n = 250$ and $n = 500$. The estimated mean are closer to the true value and the standard error and RMSE are smaller at n = 500 compared to n = 25 and n = 250. The parameter estimates for the MRr are consistent, since the estimates are getting closer to the true value as the sample size increases. The convergence rate of the parameter estimates for the MRr are 100% when there is no correlation in the dataset.

4.2.2 Comparison Result on Parameter Estimates Between QIF-MRr and rQIF-MRr for AR(1) Working Correlation Structures

Table 4.2: Parameter estimates of QIF-MRr and rQIF-MRr simulated using AR(1) working correlation structure for sample size, $n = 25$ with different correlation parameters, $\rho = \{0.1, 0.5, 0.95\}$.

Method	ρ	True value	Mean	SE	Bias	RMSE	CR
QIF-MRr	ρ=0.1	$\beta_0 = 3.0$	3.0442	0.3685	0.0442	0.3712	24%
		$\beta_1 = -5.0$	-4.9017	0.1962	0.0983	0.2195	
		$\psi_1 = 1.5$	1.5558	0.3601	0.0558	0.3644	
		$\psi_2 = 0.1$	0.1956	0.2691	0.0956	0.2856	
		$\psi_3 = 5.5$	5.6546	0.2147	0.1546	0.2646	
	ρ=0.5	$\beta_0 = 3.0$	3.0311	0.3521	0.0311	0.3535	20.8%
		$\beta_1 = -5.0$	-4.9223	0.1916	0.0777	0.2067	
		$\psi_1 = 1.5$	1.6086	0.3687	0.1086	0.3844	
		$\psi_2 = 0.1$	0.2245	0.3203	0.1245	0.3436	
		$\psi_3 = 5.5$	5.6301	0.2163	0.1301	0.2524	
	ρ=0.95	$\beta_0 = 3.0$	3.0824	0.3606	0.0824	0.3699	22.8 %
		$\beta_1 = -5.0$	-4.8987	0.2140	0.1013	0.2367	
		$\psi_1 = 1.5$	1.5349	0.3998	0.0349	0.4013	
		$\psi_2 = 0.1$	0.2027	0.2925	0.1027	0.3100	
		$\psi_3 = 5.5$	5.6263	0.2216	0.1263	0.2551	
rQIF-MRr	ρ=0.1	$\beta_0 = 3.0$	3.0528	0.2974	0.0528	0.3020	100%
		$\beta_1 = -5.0$	-4.9154	0.1731	0.0846	0.1926	
		$\psi_1 = 1.5$	1.5316	0.3404	0.0316	0.3419	
		$\psi_2 = 0.1$	0.2168	0.2530	0.1168	0.2786	
		$\psi_3 = 5.5$	5.6035	0.1928	0.1035	0.2188	
	ρ=0.5	$\beta_0 = 3.0$	3.0352	0.3101	0.0352	0.3121	100%
		$\beta_1 = -5.0$	-4.9165	0.1789	0.0835	0.1974	
		$\psi_1 = 1.5$	1.5513	0.3242	0.0513	0.3282	
		$\psi_2 = 0.1$	0.2155	0.2656	0.1155	0.2896	
		$\psi_3 = 5.5$	5.6063	0.2031	0.1063	0.2292	
	ρ=0.95	$\beta_0 = 3.0$	3.0503	0.2901	0.0503	0.2944	100%
		$\beta_1 = -5.0$	-4.9251	0.1698	0.0749	0.1856	
		$\psi_1 = 1.5$	1.5355	0.3352	0.0355	0.3371	
		$\psi_2 = 0.1$	0.2267	0.2618	0.1267	0.2908	
		$\psi_3 = 5.5$	5.6058	0.1846	0.1058	0.2127	

The results in Table (4.2) show that the convergence rate of the QIF-MRr is poor compared to the rQIF-MRr due to the singularity problem in computation. The result is not converge when the estimation using R gives an error code. The mean values of the parameter estimates for both methods are unbiased and close to the true value. The rQIF-MRr is more efficient than the QIF-MRr where the standard error (SE) and RMSE are smaller.

Table 4.3: Parameter estimates of QIF-MRr and rQIF-MRr simulated using AR(1) working correlation structure for sample size, n = 250 with different correlation parameters, $\rho = \{0.1, 0.5, 0.95\}$.

Method	ρ	True value	Mean	SE	Bias	RMSE	CR
QIF-MRr	ρ=0.1	$\beta_0 = 3.0$	3.0342	0.3545	0.0342	0.3561	22%
		$\beta_1 = -5.0$	-4.9183	0.2123	0.0817	0.2275	
		$\psi_1 = 1.5$	1.5646	0.3748	0.0646	0.3803	
		$\psi_2 = 0.1$	0.2417	0.3076	0.1417	0.3387	
		$\psi_3 = 5.5$	5.6450	0.2363	0.1450	0.2773	
	ρ=0.5	$\beta_0 = 3.0$	3.0896	0.3185	0.0896	0.3308	22.3%
		$\beta_1 = -5.0$	-4.9437	0.1981	0.0563	0.2060	
		$\psi_1 = 1.5$	1.5444	0.3787	0.0444	0.3813	
		$\psi_2 = 0.1$	0.2342	0.3026	0.1342	0.3311	
		$\psi_3 = 5.5$	5.6534	0.2264	0.1534	0.2735	
	ρ=0.95	$\beta_0 = 3.0$	3.0243	0.3712	0.0243	0.3720	20.4%
		$\beta_1 = -5.0$	-4.9229	0.2128	0.0771	0.2263	
		$\psi_1 = 1.5$	1.6100	0.3426	0.1100	0.3598	
		$\psi_2 = 0.1$	0.2049	0.2893	0.1049	0.3077	
		$\psi_3 = 5.5$	5.6477	0.2220	0.1477	0.2666	
rQIF-MRr	ρ=0.1	$\beta_0 = 3.0$	3.0548	0.3040	0.0548	0.3089	100%
		$\beta_1 = -5.0$	-4.9193	0.1771	0.0807	0.1946	
		$\psi_1 = 1.5$	1.5253	0.3608	0.0253	0.3617	
		$\psi_2 = 0.1$	0.2401	0.2608	0.1401	0.2961	
		$\psi_3 = 5.5$	5.5929	0.1889	0.0929	0.2105	
	ρ=0.5	$\beta_0 = 3.0$	3.0439	0.3021	0.0439	0.3052	100%
		$\beta_1 = -5.0$	-4.9328	0.1803	0.0672	0.1924	
		$\psi_1 = 1.5$	1.5293	0.3573	0.0293	0.3585	
		$\psi_2 = 0.1$	0.2535	0.2708	0.1535	0.3113	
		$\psi_3 = 5.5$	5.6064	0.1857	0.1064	0.2140	
	ρ=0.95	$\beta_0 = 3.0$	3.0584	0.2920	0.0584	0.2978	100%
		$\beta_1 = -5.0$	-4.9248	0.1784	0.0752	0.1936	
		$\psi_1 = 1.5$	1.5153	0.3729	0.0153	0.3732	
		$\psi_2 = 0.1$	0.2270	0.2671	0.1270	0.2958	
		$\psi_3 = 5.5$	5.5995	0.1937	0.0995	0.2178	

Table (4.3) show the parameter estimates of QIF-MRr and rQIF-MRr using AR(1) working correlation structure for sample size, $n = 250$. Results show that the parameter estimates using both method are unbiased with the mean of the parameter estimates is closer to the true value with small standard error and RMSE. However, the convergence rate for the rQIF-MRr is 100% compared to the QIF-MRr.

Table 4.4: Parameter estimates of QIF-MRr and rQIF-MRr simulated using AR(1) working correlation structure for sample size, $n = 500$ with different correlation parameters, $\rho = \{0.1, 0.5, 0.95\}$.

Method	ρ	True value	Mean	SE	Bias	RMSE	CR
QIF-MRr	ρ=0.1	$\beta_0 = 3.0$	3.0596	0.3803	0.0596	0.3850	22.5%
		$\beta_1 = -5.0$	-4.8988	0.2135	0.1012	0.2362	
		$\psi_1 = 1.5$	1.5561	0.3894	0.0561	0.3934	
		$\psi_2 = 0.1$	0.2037	0.2665	0.1037	0.2859	
		$\psi_3 = 5.5$	5.6269	0.2171	0.1269	0.2515	
	ρ=0.5	$\beta_0 = 3.0$	3.0292	0.3428	0.0292	0.3441	20%
		$\beta_1 = -5.0$	-4.9212	0.1961	0.0788	0.2113	
		$\psi_1 = 1.5$	1.5549	0.3340	0.0549	0.3384	
		$\psi_2 = 0.1$	0.2323	0.2759	0.1323	0.3060	
		$\psi_3 = 5.5$	5.6416	0.2295	0.1416	0.2697	
	ρ=0.95	$\beta_0 = 3.0$	3.0514	0.3118	0.0514	0.3160	22.3%
		$\beta_1 = -5.0$	-4.9067	0.2045	0.0933	0.2248	
		$\psi_1 = 1.5$	1.5637	0.3731	0.0637	0.3785	
		$\psi_2 = 0.1$	0.2107	0.2674	0.1107	0.2894	
		$\psi_3 = 5.5$	5.6302	0.2201	0.1302	0.2557	
rQIF-MRr	ρ=0.1	$\beta_0 = 3.0$	3.0324	0.3120	0.0324	0.3137	100%
		$\beta_1 = -5.0$	-4.9166	0.1656	0.0834	0.1854	
		$\psi_1 = 1.5$	1.5333	0.3342	0.0333	0.3358	
		$\psi_2 = 0.1$	0.2400	0.2625	0.1400	0.2975	
		$\psi_3 = 5.5$	5.6036	0.1999	0.1036	0.2252	
	ρ=0.5	$\beta_0 = 3.0$	3.0448	0.2970	0.0448	0.3003	100%
		$\beta_1 = -5.0$	-4.9266	0.1720	0.0734	0.1870	
		$\psi_1 = 1.5$	1.5363	0.3446	0.0363	0.3465	
		$\psi_2 = 0.1$	0.2428	0.2522	0.1428	0.2899	
		$\psi_3 = 5.5$	5.6026	0.1939	0.1026	0.2194	
	ρ=0.95	$\beta_0 = 3.0$	3.0339	0.3014	0.0339	0.3033	100%
		$\beta_1 = -5.0$	-4.9098	0.1679	0.0902	0.1907	
		$\psi_1 = 1.5$	1.5332	0.3613	0.0332	0.3628	
		$\psi_2 = 0.1$	0.2281	0.2720	0.1281	0.3007	
		$\psi_3 = 5.5$	5.6060	0.1979	0.1060	0.2245	

Results in Table (4.4) show the parameter estimates using both QIF-MRr and rQIF-MRr are unbiased and efficient. The standard error and RMSE for the rQIF-MRr are slightly better than the QIF-MRr, and the convergence rate for the rQIF-MRr is better than the QIF-MRr with 100% convergence rate.

4.2.3 Comparison Result on Parameter Estimates Between QIF-MRr and rQIF-MRr for Exchangeable Working Correlation Structures

Table 4.5: Parameter estimates of QIF-MRr and rQIF-MRr simulated using exchangeable working correlation structure for sample size, n = 25 with different correlation parameters, $\rho = \{0.1, 0.5, 0.95\}$.

Method	ρ	True value	Mean	SE	Bias	RMSE	CR
QIF-MRr	ρ=0.1	$\beta_0 = 3.0$	3.0645	0.3672	0.0645	0.3728	20.9%
		$\beta_1 = -5.0$	-4.8821	0.2071	0.1179	0.2383	
		$\psi_1 = 1.5$	1.5157	0.4074	0.0157	0.4077	
		$\psi_2 = 0.1$	0.1980	0.2941	0.0980	0.3100	
		$\psi_3 = 5.5$	5.6276	0.1952	0.1276	0.2332	
	ρ=0.5	$\beta_0 = 3.0$	3.0382	0.4092	0.0382	0.4110	20.5%
		$\beta_1 = -5.0$	-4.8863	0.1930	0.1137	0.2240	
		$\psi_1 = 1.5$	1.5769	0.3343	0.0769	0.3430	
		$\psi_2 = 0.1$	0.1984	0.2691	0.0984	0.2865	
		$\psi_3 = 5.5$	5.6305	0.2191	0.1305	0.2550	
	ρ=0.95	$\beta_0 = 3.0$	3.0917	0.3967	0.0917	0.4071	22%
		$\beta_1 = -5.0$	-4.9110	0.2219	0.0890	0.2391	
		$\psi_1 = 1.5$	1.5109	0.3888	0.0109	0.3890	
		$\psi_2 = 0.1$	0.2113	0.2789	0.1113	0.3003	
		$\psi_3 = 5.5$	5.6337	0.2271	0.1337	0.2635	
rQIF-MRr	ρ=0.1	$\beta_0 = 3.0$	3.0552	0.3411	0.0552	0.3455	100%
		$\beta_1 = -5.0$	-4.9108	0.1659	0.0892	0.1883	
		$\psi_1 = 1.5$	1.5284	0.3452	0.0284	0.3464	
		$\psi_2 = 0.1$	0.2122	0.2545	0.1122	0.2781	
		$\psi_3 = 5.5$	5.5959	0.2063	0.0959	0.2275	
	ρ=0.5	$\beta_0 = 3.0$	3.0594	0.3355	0.0594	0.3407	100%
		$\beta_1 = -5.0$	-4.9105	0.1606	0.0895	0.1838	
		$\psi_1 = 1.5$	1.5171	0.3443	0.0171	0.3447	
		$\psi_2 = 0.1$	0.2007	0.2496	0.1007	0.2691	
		$\psi_3 = 5.5$	5.6083	0.1878	0.1083	0.2168	
	ρ=0.95	$\beta_0 = 3.0$	3.0282	0.3621	0.0282	0.3632	100%
		$\beta_1 = -5.0$	-4.8960	0.1728	0.1040	0.2016	
		$\psi_1 = 1.5$	1.5156	0.3482	0.0156	0.3485	
		$\psi_2 = 0.1$	0.2070	0.2559	0.1070	0.2774	
		$\psi_3 = 5.5$	5.6102	0.2042	0.1102	0.2320	

The results in Table (4.5) show that when the data has low, medium, or high correlation, the convergence rate of the QIF-MRr using exchangeable working correlation structure is poor. Meanwhile, the rQIF-MRr with an exchangeable working correlation structure gives a 100% convergence rate. The parameter estimates for both methods are unbiased and efficient, but the rQIF-MRr is slightly more efficient than the QIF-MRr, with a smaller standard error and RMSE.

Table 4.6: Parameter estimates of QIF-MRr and rQIF-MRr simulated using exchangeable working correlation structure for sample size, n = 250 with different correlation parameters, $\rho = \{0.1, 0.5, 0.95\}$.

Method	ρ	True value	Mean	SE	Bias	RMSE	CR
QIF-MRr	ρ=0.1	$\beta_0 = 3.0$	3.0795	0.3696	0.0795	0.3780	21.1%
		$\beta_1 = -5.0$	-4.9115	0.2317	0.0885	0.2480	
		$\psi_1 = 1.5$	1.5328	0.4134	0.0328	0.4147	
		$\psi_2 = 0.1$	0.1970	0.2822	0.0970	0.2984	
		$\psi_3 = 5.5$	5.6384	0.2324	0.1384	0.2705	
	ρ=0.5	$\beta_0 = 3.0$	3.0373	0.3334	0.0373	0.3354	22%
		$\beta_1 = -5.0$	-4.8848	0.1855	0.1152	0.2184	
		$\psi_1 = 1.5$	1.5131	0.3891	0.0131	0.3893	
		$\psi_2 = 0.1$	0.2420	0.2996	0.1420	0.3315	
		$\psi_3 = 5.5$	5.6305	0.2254	0.1305	0.2604	
	ρ=0.95	$\beta_0 = 3.0$	3.0604	0.3821	0.0604	0.3868	22.2%
		$\beta_1 = -5.0$	-4.8904	0.2038	0.1096	0.2314	
		$\psi_1 = 1.5$	1.5262	0.4200	0.0262	0.4208	
		$\psi_2 = 0.1$	0.1985	0.2870	0.0985	0.3034	
		$\psi_3 = 5.5$	5.6425	0.2210	0.1425	0.2630	
rQIF-MRr	ρ=0.1	$\beta_0 = 3.0$	3.0766	0.3419	0.0766	0.3504	100%
		$\beta_1 = -5.0$	-4.9144	0.1771	0.0856	0.1968	
		$\psi_1 = 1.5$	1.4879	0.4009	-0.0121	0.4011	
		$\psi_2 = 0.1$	0.2089	0.2664	0.1089	0.2878	
		$\psi_3 = 5.5$	5.6075	0.1978	0.1075	0.2251	
	ρ=0.5	$\beta_0 = 3.0$	3.0504	0.3508	0.0504	0.3544	100%
		$\beta_1 = -5.0$	-4.9122	0.1692	0.0878	0.1906	
		$\psi_1 = 1.5$	1.5298	0.3617	0.0298	0.3629	
		$\psi_2 = 0.1$	0.2082	0.2476	0.1082	0.2702	
		$\psi_3 = 5.5$	5.6161	0.1887	0.1161	0.2215	
	ρ=0.95	$\beta_0 = 3.0$	3.0405	0.3516	0.0405	0.3540	100%
		$\beta_1 = -5.0$	-4.9118	0.1652	0.0882	0.1873	
		$\psi_1 = 1.5$	1.5146	0.3526	0.0146	0.3529	
		$\psi_2 = 0.1$	0.2040	0.2494	0.1040	0.2702	
		$\psi_3 = 5.5$	5.6124	0.1995	0.1124	0.2290	

Results in Table (4.6) show that the parameter estimates of QIF-MRr and rQIF-MRr using exchangeable working correlation structure for sample size, n = 250 are unbiased and efficient. The convergence rate for the rQIF-MRr is 100% compared with a smaller standard error and RMSE compared to the QIF-MRr.

Table 4.7: Parameter estimates of QIF-MRr and rQIF-MRr simulated using exchangeable working correlation structure for sample size, $n = 500$ with different correlation parameters, $\rho = \{0.1, 0.5, 0.95\}$.

Method	ρ	True value	Mean	SE	Bias	RMSE	CR
QIF-MRr	ρ=0.1	$\beta_0 = 3.0$	3.0790	0.3613	0.0790	0.3699	21.2%
		$\beta_1 = -5.0$	-4.8961	0.2096	0.1039	0.2340	
		$\psi_1 = 1.5$	1.5514	0.3795	0.0514	0.3830	
		$\psi_2 = 0.1$	0.1909	0.2613	0.0909	0.2767	
		$\psi_3 = 5.5$	5.6270	0.2277	0.1270	0.2607	
	ρ=0.5	$\beta_0 = 3.0$	3.0596	0.4076	0.0596	0.4119	20.7%
		$\beta_1 = -5.0$	-4.8863	0.1998	0.1137	0.2298	
		$\psi_1 = 1.5$	1.5301	0.3806	0.0301	0.3818	
		$\psi_2 = 0.1$	0.2049	0.2762	0.1049	0.2954	
		$\psi_3 = 5.5$	5.6194	0.1988	0.1194	0.2319	
	ρ=0.95	$\beta_0 = 3.0$	3.0433	0.3566	0.0433	0.3593	23.4%
		$\beta_1 = -5.0$	-4.8956	0.1836	0.1044	0.2112	
		$\psi_1 = 1.5$	1.5925	0.3413	0.0925	0.3536	
		$\psi_2 = 0.1$	0.2072	0.2833	0.1072	0.3030	
		$\psi_3 = 5.5$	5.6022	0.1977	0.1022	0.2226	
rQIF-MRr	ρ=0.1	$\beta_0 = 3.0$	3.0373	0.3554	0.0373	0.3573	100%
		$\beta_1 = -5.0$	-4.9051	0.1643	0.0949	0.1897	
		$\psi_1 = 1.5$	1.5199	0.3650	0.0199	0.3656	
		$\psi_2 = 0.1$	0.1989	0.2618	0.0989	0.2799	
		$\psi_3 = 5.5$	5.6178	0.1911	0.1178	0.2245	
	ρ=0.5	$\beta_0 = 3.0$	3.0422	0.3355	0.0422	0.3382	100%
		$\beta_1 = -5.0$	-4.9146	0.1771	0.0854	0.1966	
		$\psi_1 = 1.5$	1.5107	0.3758	0.0107	0.3759	
		$\psi_2 = 0.1$	0.2083	0.2561	0.1083	0.2781	
		$\psi_3 = 5.5$	5.6162	0.1998	0.1162	0.2311	
	ρ=0.95	$\beta_0 = 3.0$	3.0463	0.3371	0.0463	0.3402	100%
		$\beta_1 = -5.0$	-4.9026	0.1741	0.0974	0.1995	
		$\psi_1 = 1.5$	1.5032	0.3687	0.0032	0.3687	
		$\psi_2 = 0.1$	0.2198	0.2571	0.1198	0.2836	
		$\psi_3 = 5.5$	5.5970	0.1978	0.0970	0.2203	

The parameter estimates in Table (4.7) show that estimation for large sample size using rQIF-MRr with exchangeable working correlation structure are unbiased and efficient. The convergence rate for the rQIF-MRr is 100% compared to the QIF-MRr which have low convergence rate. The mean value of the parameter estimates for the rQIF-MRr is closer to the true value compared to the QIF-MRr with a smaller standard error and RMSE.

4.2.4 Comparison Result on Parameter Estimates Between QIF-MRr and rQIF-MRr for Unspecified Working Correlation Structures

Table 4.8: Parameter estimates of QIF-MRr and rQIF-MRr simulated using unspecified working correlation structure for sample size, n = 25 with different correlation parameters, $\rho = \{0.1, 0.5, 0.95\}$.

Method	ρ	True value	Mean	SE	Bias	RMSE	CR
QIF-MRr	ρ=0.1	$\beta_0 = 3.0$	2.9806	0.4761	-0.0194	0.4765	20%
		$\beta_1 = -5.0$	-4.9094	0.2694	0.0906	0.2843	
		$\psi_1 = 1.5$	1.5900	0.5022	0.0900	0.5103	
		$\psi_2 = 0.1$	0.2376	0.3304	0.1376	0.3579	
		$\psi_3 = 5.5$	5.6526	0.2461	0.1526	0.2896	
	ρ=0.5	$\beta_0 = 3.0$	3.0109	0.4180	0.0109	0.4181	20%
		$\beta_1 = -5.0$	-4.9027	0.2338	0.0973	0.2533	
		$\psi_1 = 1.5$	1.5958	0.4666	0.0958	0.4764	
		$\psi_2 = 0.1$	0.2211	0.3208	0.1211	0.3429	
		$\psi_3 = 5.5$	5.6165	0.2055	0.1165	0.2363	
	ρ=0.95	$\beta_0 = 3.0$	3.0447	0.4625	0.0447	0.4646	20.9%
		$\beta_1 = -5.0$	-4.8935	0.1912	0.1065	0.2189	
		$\psi_1 = 1.5$	1.5760	0.4772	0.0760	0.4832	
		$\psi_2 = 0.1$	0.2113	0.2811	0.1113	0.3023	
		$\psi_3 = 5.5$	5.6389	0.2353	0.1389	0.2732	
rQIF-MRr	ρ=0.1	$\beta_0 = 3.0$	3.0111	0.4069	0.0111	0.4071	100%
		$\beta_1 = -5.0$	-4.9116	0.1951	0.0884	0.2142	
		$\psi_1 = 1.5$	1.5272	0.4894	0.0272	0.4902	
		$\psi_2 = 0.1$	0.2339	0.2960	0.1339	0.3249	
		$\psi_3 = 5.5$	5.6149	0.2122	0.1149	0.2413	
	ρ=0.5	$\beta_0 = 3.0$	3.0182	0.4152	0.0182	0.4156	100%
		$\beta_1 = -5.0$	-4.9158	0.1944	0.0842	0.2118	
		$\psi_1 = 1.5$	1.5059	0.4972	0.0059	0.4972	
		$\psi_2 = 0.1$	0.2308	0.2858	0.1308	0.3143	
		$\psi_3 = 5.5$	5.6149	0.2098	0.1149	0.2392	
	ρ=0.95	$\beta_0 = 3.0$	3.0027	0.4507	0.0027	0.4507	100%
		$\beta_1 = -5.0$	-4.9160	0.2012	0.0840	0.2180	
		$\psi_1 = 1.5$	1.5389	0.4213	0.0389	0.4231	
		$\psi_2 = 0.1$	0.2321	0.2768	0.1321	0.3067	
		$\psi_3 = 5.5$	5.6229	0.2122	0.1229	0.2452	

Table (4.8) show the parameter estimates for rQIF-MRr are unbiased and efficient with 100% convergence rate. The mean of the parameter estimates for small sample size (n = 25) is closer to the true value with small standard error and RMSE compared to the

QIF-MRr.

Table 4.9: Parameter estimates of QIF-MRr and rQIF-MRr simulated using unspecified working correlation structure for sample size, $n = 250$ with different correlation parameters, $\rho = \{0.1, 0.5, 0.95\}$.

Method	ρ	True value	Mean	SE	Bias	RMSE	CR
QIF-MRr	ρ=0.1	$\beta_0 = 3.0$	3.0205	0.4501	0.0205	0.4505	21%
		$\beta_1 = -5.0$	-4.8732	0.2274	0.1268	0.2604	
		$\psi_1 = 1.5$	1.5134	0.5704	0.0134	0.5705	
		$\psi_2 = 0.1$	0.2207	0.2386	0.1207	0.2674	
		$\psi_3 = 5.5$	5.6430	0.2163	0.1430	0.2593	
	ρ=0.5	$\beta_0 = 3.0$	3.0134	0.4927	0.0134	0.4929	23.9%
		$\beta_1 = -5.0$	-4.9163	0.2173	0.0837	0.2329	
		$\psi_1 = 1.5$	1.5621	0.5429	0.0621	0.5464	
		$\psi_2 = 0.1$	0.2426	0.3007	0.1426	0.3328	
		$\psi_3 = 5.5$	5.6344	0.2296	0.1344	0.2661	
	ρ=0.95	$\beta_0 = 3.0$	3.0244	0.4812	0.0244	0.4818	22.7%
		$\beta_1 = -5.0$	-4.8983	0.2477	0.1017	0.2677	
		$\psi_1 = 1.5$	1.5518	0.4906	0.0518	0.4933	
		$\psi_2 = 0.1$	0.2234	0.3386	0.1234	0.3604	
		$\psi_3 = 5.5$	5.6366	0.2348	0.1366	0.2717	
rQIF-MRr	ρ=0.1	$\beta_0 = 3.0$	3.0147	0.4235	0.0147	0.4238	100%
		$\beta_1 = -5.0$	-4.9023	0.1808	0.0977	0.2056	
		$\psi_1 = 1.5$	1.5090	0.5238	0.0090	0.5239	
		$\psi_2 = 0.1$	0.2143	0.2458	0.1143	0.2711	
		$\psi_3 = 5.5$	5.6126	0.1896	0.1126	0.2205	
	ρ=0.5	$\beta_0 = 3.0$	3.0168	0.4375	0.0168	0.4378	100%
		$\beta_1 = -5.0$	-4.9080	0.1873	0.0920	0.2086	
		$\psi_1 = 1.5$	1.5150	0.5350	0.0150	0.5352	
		$\psi_2 = 0.1$	0.2217	0.2578	0.1217	0.2851	
		$\psi_3 = 5.5$	5.6188	0.1978	0.1188	0.2307	
	ρ=0.95	$\beta_0 = 3.0$	3.0010	0.4080	0.0010	0.4080	100%
		$\beta_1 = -5.0$	-4.9048	0.1868	0.0952	0.2096	
		$\psi_1 = 1.5$	1.4896	0.4994	-0.0104	0.4995	
		$\psi_2 = 0.1$	0.2384	0.2704	0.1384	0.3038	
		$\psi_3 = 5.5$	5.6298	0.1930	0.1298	0.2326	

The parameter estimates of the QIF-MRr and rQIF-MRr using an unspecified working correlation structure for sample size, $n = 250$, are unbiased and efficient, as shown in Table (4.9).The convergence rate for the rQIF-MRr is 100%. The standard error and RMSE for rQIF-MRr are smaller than the QIF-MRr, and the mean value of the parameter estimates for the rQIF-MRr is closer to the true value.

Table 4.10: Parameter estimates of QIF-MRr and rQIF-MRr simulated using unspecified working correlation structure for sample size, $n = 500$ with different correlation parameters, $\rho = \{0.1, 0.5, 0.95\}$.

Method	ρ	True value	Mean	SE	Bias	RMSE	CR
QIF-MRr	ρ=0.1	$\beta_0 = 3.0$	2.9593	0.4881	-0.0407	0.4898	20.5%
		$\beta_1 = -5.0$	-4.9037	0.2389	0.0963	0.2576	
		$\psi_1 = 1.5$	1.5900	0.5650	0.0900	0.5721	
		$\psi_2 = 0.1$	0.2361	0.2575	0.1361	0.2913	
		$\psi_3 = 5.5$	5.6581	0.2357	0.1581	0.2838	
	ρ=0.5	$\beta_0 = 3.0$	3.0342	0.4024	0.0342	0.4038	21.8%
		$\beta_1 = -5.0$	-4.9305	0.2197	0.0695	0.2304	
		$\psi_1 = 1.5$	1.6050	0.5100	0.1050	0.5207	
		$\psi_2 = 0.1$	0.2631	0.2868	0.1631	0.3300	
		$\psi_3 = 5.5$	5.5904	0.2032	0.0904	0.2224	
	ρ=0.95	$\beta_0 = 3.0$	3.0129	0.4968	0.0129	0.4970	19.4%
		$\beta_1 = -5.0$	-4.9421	0.2372	0.0579	0.2442	
		$\psi_1 = 1.5$	1.5813	0.4911	0.0813	0.4978	
		$\psi_2 = 0.1$	0.2701	0.3556	0.1701	0.3941	
		$\psi_3 = 5.5$	5.6423	0.2583	0.1423	0.2948	
rQIF-MRr	ρ=0.1	$\beta_0 = 3.0$	2.9980	0.3949	-0.0020	0.3949	100%
		$\beta_1 = -5.0$	-4.9123	0.1928	0.0877	0.2119	
		$\psi_1 = 1.5$	1.5415	0.5086	0.0415	0.5103	
		$\psi_2 = 0.1$	0.2326	0.2512	0.1326	0.2840	
		$\psi_3 = 5.5$	5.6203	0.1876	0.1203	0.2228	
	ρ=0.5	$\beta_0 = 3.0$	2.9904	0.4173	-0.0096	0.4174	100%
		$\beta_1 = -5.0$	-4.9178	0.1868	0.0822	0.2041	
		$\psi_1 = 1.5$	1.5257	0.5301	0.0257	0.5307	
		$\psi_2 = 0.1$	0.2471	0.2620	0.1471	0.3005	
		$\psi_3 = 5.5$	5.6232	0.1913	0.1232	0.2275	
	ρ=0.95	$\beta_0 = 3.0$	2.9941	0.3957	-0.0059	0.3957	100%
		$\beta_1 = -5.0$	-4.9011	0.1739	0.0989	0.2000	
		$\psi_1 = 1.5$	1.5199	0.4691	0.0199	0.4696	
		$\psi_2 = 0.1$	0.2415	0.2448	0.1415	0.2827	
		$\psi_3 = 5.5$	5.6142	0.1927	0.1142	0.2240	

The parameter estimates of the QIF-MRr and rQIF-MRr using unspecified working correlation structure in Table (4.10) for sample size, $n = 500$ are unbiased and efficient. The mean of the parameter estimate for rQIF-MRr is closer to the true value, and the standard error and RMSE are smaller compared to the QIf-MRr for low, medium and high correlation. The convergence rate for rQIF-MRr is high compared to the QIF-MRr.

4.3 Discussion

When there is no correlation in the dataset, we can estimate the parameter using the MRr method. Table (4.1) show that estimation using MRr is unbiased and efficient. The mean of the parameter estimates is close to the true value with small standard error and RMSE. The convergence rate using the MRr method in estimating the ODTR is 100%.

Tables (4.2) to (4.4) give simulation results of the QIF-MRr and rQIF-MRr using AR(1) working correlation structure with 25, 250 and 500 sample sizes. In these tables, we assume that there is a correlation in the dataset. The convergence rates of the QIF-MRr are lower compared to the rQIF-MRr method, which had a 100% convergence rate. The results show that the parameter estimates for the rQIF-MRr are unbiased and efficient, as the mean value of the parameter estimates is closer to the true value, and the standard error and RMSE are small compared to the QIF-MRr method for all correlation levels in the dataset.

Tables (4.5) to (4.7) give the results on the parameter estimates of the QIF-MRr and rQIF-MRr using exchangeable working correlation structures for sample size 25, 250 and 500. For small and large sample sizes, the rQIF-MRr has a 100% convergence rate, which is better than the QIF-MRr for low, medium, and high correlation. Parameter estimates using rQIF-MRr are unbiased and more efficient than those using QIF-MRr where the mean of the parameter estimates is closer to the true value with a small standard error and RMSE.

The parameter estimates of QIF-MRr and rQIF-MRr with an unspecified working correlation structure are given in Tables (4.8) to (4.10) for sample sizes 25, 250 and 500. Compared to the AR(1) and exchangeable working correlation structures, the mean of the parameter estimates using the unspecified working correlation structure is closer to the true value. However, the standard error and RMSE for the unspecified are slightly larger than the AR(1) and exchangeable working correlation structures. The convergence rate of the rQIf-MRr for low, medium, and high correlation is 100%.

Estimation using AR(1) working correlation structure gives slightly smaller standard error and RMSE compared to the exchangeable and unspecified working correlation structures for sample sizes 25, 250, and 500 at low, medium, and high correlation. The mean of the parameter estimates using AR(1), exchangeable and unspecified working correlation structures are overall close to the true value where the value for the bias are small.

Overall, although the QIF-MRr gives unbiased and efficient parameter estimates, however, the convergence rate are small due to computational and singularity issues. Applying the ridge estimator into the QIF-MRr thus helped in stabilizing the estimation by increasing the convergence rate of the rQIF-MRr to 100%. The rQIF-MRr is suitable to use for small or large sample size at any correlation level in the dataset. Different types of working correlation structures can be used in estimation using rQIF-MRr since it gives unbiased and efficient parameter estimates.

4.4 Conclusions

The MRr approach is preferable when there is no correlation in the data set since it is less complex in computation. The computation will be much easier than the QIF-MRr and rQIF-MRr because the correlation structure does not need to be specified. In ODTR, the QIF-MRr and rQIF-MRr can be used for estimation if the dataset has a correlation. The QIF-MRr and rQIF-MRr have the advantage of not requiring the probability distribution to be specified.

Estimation using rQIF-MRr for small and large sample sizes provides unbiased and efficient parameter estimates with small standard error and RMSE, and the mean of the parameter estimates is closer to the true value. The use of a ridge estimator in QIF-MRr aids in solving the singularity problem during computation, and the rQIF-MRr has a 100% convergence rate for AR(1), exchangeable, and unspecified working correlation structures.

CHAPTER 5: CONCLUSION AND FUTURE WORK

5.1 Summary of the Study

The study of ODTR is a branch of personalized medicine and it is a promising and developing field. In personalized medicine, the patient's health was optimized based on the systematic use of individual patient information. It can be observed as a fulfillment of specific decision rules where these rules prescribe an action to be given following the given state of the patient. The ODTR is a multi-stage decision rule of personalized medicine, where the state of the patient was observed at several time-point and the action was given at each time-point the patient being observed. Note that, the decision is made at that time point may affect future decision.

Several methods for estimating ODTR have been studied and explained where the main focus on the regret function. Murphy (2003) introduced the regret function and proposed IMOR method to estimate the ODTR. Chakraborty and Moodie (2013) showed that IMOR may not converge when the sample sizes are small. In addition, the researchers may not postulate good initial values for the search algorithm in a simulation study, and misspecification of the model may cause convergence issues. Note that, Murphy (2003) only estimates the parameter of the regret functions instead of fully estimates the mean response of ODTR.

The regret-regression by Henderson et al. (2010) fully estimates the mean response of ODTR by combining the regret function with regression model. It modeled both the state function and the regret function for the estimation of parameters. Since the regret-regression is a regression-based model, it is possible to apply the usual diagnostics checking, but to estimate the parameters, one needs to obtain the observation needed till the end of the time-point of the study of interest (i.e. long-term strategy). The mean response of the regret-regression was modeled using the cumulative information of the patient obtained from the first time-point to the last time-point.

The MRr introduced by Mohamed (2013) is a short-term strategy of the regret-regression. In a short-term strategy, the ODTR was estimated at each time-point. Thus, it can estimate ODTR at the current time-point. For example, for time-point $j = \{1, 2, \ldots, j, j+1, \ldots, K\}$ the observation being observed right now is at j^{th} time-point. Therefore, it is possible to estimate ODTR based on the information from time-point 1 to time-point j for the short-term strategy, but impossible for the long-term strategy. Hence, there is no requirement to wait until the final time-point, K.

Mohamed (2013) proposed the QIF-MRr where it is a combination of the MRr with QIF. The QIF-MRr can overcome the limitation of MRr on correlated data. When estimating the parameters of the ODTR using QIF-MRr, however, a singularity issue commonly appears during computation. To overcome this problems, a newly proposed method, the rQIF-MRr is discussed in this dissertation.

5.2 Significant of the Study

The rQIF-MRr was proposed to improve the parameter estimate in estimating ODTR. The ridge estimator was incorporated into the QIF-MRr to form rQIF-MRr. In estimation, the rQIF-MRr had overcome the disadvantages of the QIF-MRr. The estimated mean of rQIF-MRr was closer to the initial values with small standard errors and RMSE compared to the QIF-MRr. In addition, the rQIF-MRr had also overcome the singularity issues that often happen during the computation of QIF-MRr and had shorten the computation time.

5.3 Future Work

There is huge potential to explore rQIF-MRr in personalized medicine particularly in estimating ODTR. Since the rQIF-MRr was build to analyze correlated data, thus it can be apply on the longitudinal observational study. For example the anticoagulant data (Rosthøj et al., 2006). The objective is to find the best dosing strategy in preventing thrombotic complications by controlling the prothrombin time measured by the International Normalized Ratio (INR). For a healthy person, he or she will take about 15 seconds for the blood to clot and controlled thromboplastin will have INR equals to 1. In anticoagulant treatment, it is essential to ensure that the INR is within a target range.

It is our interest in the future to apply different types of penalty estimators in improvising the estimation for ODTR. For example, we may consider LASSO (Tibshirani, 1996), bridge (Fu, 2003), SCAD (Fan & Li, 2001) and others which may give different efficiency in estimation.

Clairon et al. (2021) had proposed a control theory method called H^{∞}-synthesis for ODTR by applying the regret function from Murphy (2003). The H^{∞}-synthesis method holds the advantages in dealing with noisy or missing data. In a real application, missing data is a very common occurrence. This will be one of our future works where we would propose a method that can be applied when there are missing data in observation for ODTR.

In addition, in the future, it is our interest to improvise the rQIF-MRr that can be used to estimate ODTR with survival outcomes. Simoneau et al. (2020) had proposed a method for estimating ODTR with survival outcomes subject to right-censoring which requires solving a series of weighted GEE. Since the QIF is an improved version of the GEE, therefore it is possible to extend Simoneau et al. (2020) work by applying the QIF method in estimation and further testing the method for the short-term strategy.

REFERENCES

Akdeniz, F., & Roozbeh, M. (2019). Generalized difference-based weighted mixed almost unbiased ridge estimator in partially linear models. *Statistical Papers*, *60*(5), 1717–1739.

Arashi, M., Roozbeh, M., Hamzah, N., & Gasparini, M. (2021). Ridge regression and its applications in genetic studies. *Plos one*, *16*(4), 1–17.

Asparouhov, T., & Muthén, B. (2020). Comparison of models for the analysis of intensive longitudinal data. *Structural Equation Modeling: A Multidisciplinary Journal*, *27*(2), 275–297.

Barrett, J. K., Henderson, R., & Rosthøj, S. (2014). Doubly robust estimation of optimal dynamic treatment regimes. *Statistics in Biosciences*, *6*(2), 244–260.

Chakraborty, B., & Moodie, E. E. (2013). *Statistical methods for dynamic treatment regimes*. Springer.

Clairon, Q., Henderson, R., Young, N., Wilson, E., & Taylor, C. J. (2021). Adaptive treatment and robust control. *Biometrics*, *77*(1), 223–236.

Clairon, Q., Wilson, E. D., Henderson, R., & Taylor, C. J. (2017). Adaptive biomedical treatment and robust control. *IFAC-PapersOnLine*, *50*(1), 12191–12196.

Cole, S. R., & Hernàn, M. A. (2008). Constructing inverse probability weights for marginal structural models. *American Journal of Epidemiology*, *168*(6), 656-664.

Diggle, P. J., Heagerty, P., Liang, K., & Zeger, S. L. (2002). *Analysis of longitudinal data* (Second ed.). Oxford University Press.

Diggle, P. J., Liang, K., & Zeger, S. L. (1994). *Analysis of longitudinal data* (First ed.). Oxford University Press.

Dumitrescu, L., Qian, W., & Rao, J. (2020). Inference for longitudinal data from complex sampling surveys: An approach based on quadratic inference functions. *Scandinavian Journal of Statistics*, *48*(1), 246–274.

Dziak, J. J. (2006). *Penalized quadratic inference functions for variable selection in longitudinal research* (PHD Thesis). The Pennsylvania State University.

Fan, J., & Li, R. (2001). Variable selection via nonconcave penalized likelihood and its oracle properties. *Journal of the American statistical Association*, *96*(456), 1348–1360.

Fu, W. J. (2003). Penalized estimating equations. *Biometrics*, *59*(1), 126–132.

Hall, A. R. (2005). *Generalized method of moments: Advanced texts in econometrics*. Oxford University Press.

Han, P., & Song, P. X. (2011). A note on improving quadratic inference functions using a linear shrinkage approach. *Statistics and Probability Letters*, *81*(3), 438-445.

Hansen, L. P. (1982). Large sample properties of generalized method of moments estimators. *Econometrica*, *50*(4), 1029-1054.

Henderson, R., Ansell, P., & Alshibani, D. (2010). Regret-regression for optimal dynamic treatment regimes. *Biometrics*, *66*(4), 1192-1201.

Hernán, M. A. (2004). A definition of causal effect for epidemiological research. *Journal of Epidemiology & Community Health*, *58*(4), 265–271.

Hoerl, A. E., & Kennard, R. W. (1970). Ridge regression: Biased estimation to nonorthogonal problems. *Technometrics*, *12*(1), 55-67.

Huang, S., Fiero, M. H., & Bell, M. L. (2016). Generalized estimating equations in cluster randomized trials with a small number of clusters: Review of practice and simulation study. *Cinical Trials*, *13*(4), 445-449.

Hui, H., Binti, N. A., Salarzadeh Jenatabadi, H., et al. (2017). Family food security and children's environment: A comprehensive analysis with structural equation modeling. *Sustainability*, *9*(7), 1220.

Kramer, M. S., Chalmers, B., Hodnett, E. D., Sevkovskaya, Z., Dzikovich, I., Shapiro, S., ... others (2001). Promotion of breastfeeding intervention trial (probit): a randomized trial in the republic of belarus. *Jama*, *285*(4), 413–420.

Kwon, Y., Choi, Y. G., Park, T., Ziegler, A., & Paik, M. C. (2017). Generalized estimating equations with stabilized working correlation structure. *Computational Statistics & Data Analysis*, *106*(*), 1-11.

Lai, P., Liang, W., Wang, F., & Zhang, Q. (2020). Feature screening of quadratic inference functions for ultrahigh dimensional longitudinal data. *Journal of Statistical Computation and Simulation*, 1–17.

Liang, K., & Zeger, S. (1986). Longitudinal data analysis using generalized linear models. *Biometrika*, *73*(1), 13-22.

Mohamed, N. A. (2013). *Optimal dynamic treatment regimes: Regret-regression method with myopic strategies* (PHD Thesis). Newcastle University.

Moodie, E. E., Platt, R. W., & Kramer, M. S. (2009). Estimating response-maximized decision rules with applications to breastfeeding. *Journal of the American Statistical Association*, *104*(485), 155–165.

Moodie, E. E., Richardson, T. S., & Stephens, D. A. (2007). Demystifying optimal dynamic treatment regimes. *Biometrics*, *63*(2), 447-455.

Mũller, S., Wang, S., & Welsh, A. (2017, July). Robustness and efficiency of quadratic inference function estimator. University of Wollongong, Australia. Retrieved on 8 April 2019, from `https://niasra.uow.edu.au/content/groups/public/@web/@inf/@math/documents/mm/uow236277.pdf`

Murphy, S. A. (2003). Optimal dynamic treatment regimes. *Journal of the Royal Statistical Society, Series B (with discussion)*, *65*(2), 331-366.

Neyman, J. (1923). On the application of probability theory to agricultural experiments. essay in principles. section 9 (translation published in 1990). *Statistical Science*, *5*, 465-480.

Neyman, J. (1990). On the application of probability theory to agricultural experiments. (engl. transl. by d. m. dabrowska and t. p. speed). *Statistical Science*, *5*, 465-480.

Nikoloulopoulos, A. K. (2016). Correlation structure and variable selection in generalized estiating equations via composite likelihood information criteria. *Statistics in Medicine*, *35*(14), 2377-2390.

Pearl, J. (2009). Causal inference in statistics: An overview. *Statistics Surveys*, *3*, 96-146.

Pearl, J., & Robins, J. (1995). Probabilistic evaluation of sequential plans from causal models with hidden variables. In *Proceedings of the eleventh conference on uncertainty in artificial intelligence* (pp. 444–453). San Francisco, CA, USA: Morgan Kaufmann Publishers Inc.

Pourahmadi, M. (1999). Joint mean-covariance models with applications to longitudinal data: unconstained parameterisation. *Biometrika*, *86*(3), 677-690.

Qu, A., & Lindsay, B. (2003). Building adaptive estimating equations when inverse of covariance estimation is difficult. *Journal of the Royal Statistical Society. Series B*, *65*(1), 127-142.

Qu, A., & Lindsay, B., B.and Li. (2000). Improving generalized estimating equations using quadratic inference function. *Biometrika*, *87*(4), 823-836.

Qu, A., & Song, P. (2004). Assessing robustness of generalized estimating equations and quadratic inference functions. *Biometrika*, *91*(2), 447-459.

Robins, J. M. (1986). A new approach to causal inference in mortality studies with sustained exposure periods-application to control of he healthy worker survivor effect. *Mathematical Modelling*, *7*(9-12), 1393-1512.

Robins, J. M. (1997). Causal inference from complex longitudinal data. *Latent Variable Modelling and Application to Causality*, *M. Berkane, Editor. NY: Springer Verlag*, 69-117.

Robins, J. M. (2000). Marginal structural models versus structural nested models as tools for causal inference. In M. E. Halloran & D. Berry (Eds.), *Statistical models in epidemiology, the environment, and clinical trials* (pp. 95–133). Springer New York.

Robins, J. M. (2004). Optimal structural nested models for optimal sequential decisions. In *Proceedings of the second seattle symposium in biostatistics* (pp. 189–326).

Robins, J. M., Orellana, L., & Rotnitzky, A. (2008). Estimation and extrapolation of optimal treatment and testing strategies. *Statistics in Medicine, Wiley InterScience*, *27*(23), 4678-4721.

Roozbeh, M., Arashi, M., & Hamzah, N. A. (2020). Generalized cross-validation for simultaneous optimization of tuning parameters in ridge regression. *Iranian Journal of Science and Technology, Transactions A: Science*, *44*(2), 473–485.

Rosthøj, S., Fullwood, C., Henderson, R., & Steward, S. (2006). Estimation of optimal dynamic anticoagulation regimes from observational data: A regret based approach. *Statistics in Medicine, Wiley InterScience*, *25*(24), 4197-4215.

Rubin, D. B. (1978). Bayesian inference for causal effects: The role of randomization. *The Annals of Statistics*, *6*, 34-58.

Schumacker, R. E., & Lomax, R. G. (2004). *A beginner's guide to structural equation modeling*. Psychology Press.

Shults, J., Sun, W., Tu, X., Kim, H., Amsterdam, J., Hilbe, J. M., & Ten-Have, T. (2009). A comparison of several approaches for choosing between working correlation structures in generalized estimating equation analysis of longitudinal binary data. *Statistics in Medicine*, *28*(18), 2338-2355.

Simoneau, G., Moodie, E. E., Nijjar, J. S., Platt, R. W., Investigators, S. E. R. A. I. C., et al. (2020). Estimating optimal dynamic treatment regimes with survival outcomes. *Journal of the American Statistical Association*, *115*(531), 1531–1539.

Sitlani, C. M., Rice, K. M., Lumley, T., McKnight, B., Cupples, L. A., Avery, C. L., . . . Psaty, B. M. (2015). Generalized estimating equations for genome-wide association studies using longitudianl phenotype data. *Statistics in Medicine*, *34*(1), 118-130.

Song, P., Jiang, Z., Park, E., & Qu, A. (2009). Quadratic inference functions in marginal models for longitudinal data. *Statistics in Medicine*, *28*(29), 3683-3696.

Tallgren, A. (2003). The continuing reduction of the residual alveolar ridges in complete denture wearers: A mixed-longitudinal study covering 25 years. *The Journal of Prosthetic Dentistry*, *89*(5), 427-435.

Tibshirani, R. (1996). Regression shrinkage and selection via the lasso. *Journal of the Royal Statistical Society: Series B (Methodological)*, *58*(1), 267–288.

Twisk, J. W. (2013). *Applied longitudinal data analysis for epidemiology: a practical guide*. cambridge university press.

Vansteelandt, S., & Joffe, M. (2014). Structural nested models and g-estimation: The partially realized promise. *Statistical Science*, *29*(4), 707-731.

Wang, W., Wang, Y., Xiao, C., Yao, X., Yang, Y., Yan, H., & Li, S. (2018). Psychological pathway to suicidal ideation among people living with hiv/aids in china: A structural equation model. *Psychiatry research*, *260*, 255–261.

Warton, D. I. (2011). Regularized sandwich estimators for analysis of high-dimensional data using generalized estimating equations. *Biometrics*, *67*(1), 116-123.

Westgate, P. M. (2012). A bias-corrected covariance estimatefor improved inference with quadratic inference function. *Statistics in Medicine*, *31*(29), 4003-4022.

Westgate, P. M., & Braun, T. M. (2012). The effect of cluster size imbalance and covariates on the estimation performance of quadratic inference functions. *Statistics in Medicine*, *31*(20), 2209-2222.

Westgate, P. M., & Braun, T. M. (2013). An improved quadratic inference function for parameter estimation in the analysis of correlated data. *Statistics in Medicine*, *32*(11), 3260-3273.

Wright, S. (1921). Correlation and causation. *Journal of Agricultural Research*, *20*, 557-585.

Yang, W., & Liao, S. (2017). A study of quadratic inference functions with alternative weighting matrices. *Communications in Statistics-Simulation and Computation*, *46*(2), 994–1007.

Ye, H., & Pan, J. (2006). Modelling of covariance structures in generalised estimating equations for longitudinal data. *Biometrika*, *93*(4), 927-941.

Yu, H., Tong, G., & Li, F. (2020). A note on the estimation and inference with quadratic inference functions for correlated outcomes. *Communications in Statistics-Simulation and Computation*, 1–12.

Zeger, S. L., & Liang, K. Y. (1986). Longitudinal data analysis for discrete and continuous outcomes. *Biometrics*, *42*(1), 121-130.

Zeger, S. L., Liang, K. Y., & Albert, P. S. (1988). Models for longitudinal data: A generalized estimating equation approach. *Biometrics*, *44*(4), 1049-1060.

Zou, H., & Hastie, T. (2005). Regularization and variable selection via the elastic net. *Journal of the royal statistical society: series B (statistical methodology)*, *67*(2), 301–320.