Applications of the Kalman Filter to the Estimation of Structural Nested Mean Models

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DEDICATION

To my parents, Maryam and Javad,

for their everlasting and unconditional love and support.

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ABSTRACT

In longitudinal observational studies, standard regression methods fail to consistently estimate the causal effect of time-varying treatment due to the presence of time-varying confounders. Causal models such as structural nested mean models (SNMM) and marginal structural models (MSM) and methods of estimation such as two-stage parametric regression and propensity score approaches (g-estimation, inverse probability weighted estimators) have been developed to address inconsistency of standard methods. This thesis considers an alternate approach, specifically for estimating the causal effect of time-varying treatment in longitudinal observational studies with continuous outcomes. I relax the assumptions of two-stage parametric regression methods by placing a Markov assumption on the time-varying counterfactual outcomes. Then, by expressing the SNMM as a state space model, I estimate its causal parameters with a modified Kalman estimating equation approach (keeSNMM). I establish the theoretical properties of the method and then conduct extensive simulation studies to evaluate its performance, comparing it to other approaches in a variety of settings. I also develop diagnostics to assess the validity of the critical Markov assumption. I then propose a new estimator which replaces the working models for the doubly robust g-estimator with the Kalman smoother under the same Markov assumption (dr-keeSNMM). The new estimator will be consistent if either the propensity score or the Markov assumption is correctly specified. By using the sequential ignorability/exchangeability assumption given the longitudinal propensity score, I next develop SNMM using the longitudinal propensity score

(SNMM-LPS) and estimate its causal parameters via KEE (keeSNMM-LPS). In the last chapter I study the behaviour of my proposed methods.

ABRÉGÉ

Dans les études longitudinales, les methodes de la régression standard ne sont pas bien-adaptées à éstimer l'effet causal de la traitement/exposition dépendante du temps à cause de la présence des facteurs du confusion. Des modèles causals, par exemple les modèles moyens structurels emboîtés (Structural nested mean model: SNMM) et les modéles structurels marginaux (marginal structural model: MSM), et les méthodes d'estimation comme la régression paramétrique à deux étapes et le score de propension (g-estimation, les estimateurs ponderés à la probabilité inverse) ont été dévelopées pour répondre à l'incohérence des méthodes standard. Je me détends les hypothèses des méthodes de régression paramétrique à deux étapes en plaçant une hypothèse de Markov pour les résultats contrafactuels dépendants en temps. Ensuite, par un expression de SNMM comme une représentation d'état, j'estime ses paramètres causals en adaptant l'approche d'estimation de l'équation Kalman (Kalman estimating equation approach of SNMM: keeSNMM). J'établis les propriétés théoriques de la méthode et puis j'effectue des études de simulation vastes pour évaluer la performance du modèle en comparant à MSM et la régression standard dans une variété de paramètres de la spécification. Je dévelope aussi les diagnostiques pour évaluer la validité de l'hypothèse Markov essentielle. Je propose ensuite un nouvel estimateur qui remplace les modèles pratiques pour le g-estimateur double-robuste avec un lisseur Kalman avec la même hypothèse (dr-keeSNMM) et qui est cohérente si le score de propension ou l'hypothèse Markov est correctement spécifié. En utilisant l'hypothèse de l'ignorabilité/l'échangeabilité compte tenu du

score de propension longitudinal, je dévelope ensuite le SNMM en utilisant le score de propension longitudinal et je l'appelle le SNMM-LPS (SNMM with Longitudinal propensity score: SNMM-LPS) et j'estime ses paramètres causals selon le KEE (keeSNMM-LPS). Au chapitre final, je fais un étude des traits de nos méthodes proposées en estimant l'effet de l'allaitement maternel dans l'ensemble des données PROBIT.

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List of Abbreviation

AIDS: Acquired Immune Defficiency Syndrome.

ATEWI: The average treatment effect within interval.

ATTE: The average total treatment effect.

AZT: Zidovudine or azidothymidine is a type of antiretroviral drug used for the treatment of HIV/AIDS infection.

DAG: Directed Acyclic Graph

dr-gSNMM: Doubly Robust G-estimation of an SNMM.

dr-gSNMM-LPS: Doubly Robust G-estimation of an SNMM with Longitudinal Propensity Score.

dr-keeSNMM: Doubly Robust G-estimation of an SNMM via KEE.

DTR: Dynamic Treatment Regime.

GEE: Generalized Estimating Equation.

gSNMM: G-estimation of an SNMM.

gSNMM-LPS: G-estimation of an SNMM with Longitudinal Propensity Score.

HIV: Human Immunodefficiency Virus.

IPTW: Inverse Probability of Treatment Weighted.

KEE: Kalman Estimating Equation.

keeSNMM: Kalman Estimating Equation of an SNMM.

keeSNMM-LPS: KEE of an SNMM with Longitudinal Propensity Score.

MSM: Marginal Structural Model.

ODTR-dr-gSNMM: Doubly Robust G-estimation of an Optimal Dynamic Treatment Regime SNMM.

ODTR-dr-keeSNMM: Doubly Robust G-estimation via KEE of an Optimal Dynamic Treatment Regime SNMM.

ODTR-gSNMM: G-estimation of an Optimal Dynamic Treatment Regime SNMM.

ODTR-keeSNMM: KEE of an Optimal Dynamic Treatment Regime SNMM.

ODTR-SNMM: Optimal Dynamic Treatment Regime SNMM.

OLS: Ordinary Least Square.

PROBIT: Promotion of Breastfeeding Intervention Trial.

r-keeSNMM-LPS: Robust G-estimation to the Markov Assumption via KEE of an SNMM with Longitudinal Propensity Score.

SE: Root Mean Square Error

SE: Standard Error

SNMM: Structural Nested Mean Model.

SNMM-LPS: SNMM with Longitudinal Propensity Score.

SUTV: The Stable Unit Treatment Value Assumption.

WHO: World Health Organization.

CHAPTER 1
Introduction

In general, approaches for estimating effectiveness or efficacy can be classified as either (a) controlled experiments where one uses randomization to form comparable groups, or (b) observational studies, where group assignments are merely observed. In a controlled experiment, random assignment ensures that observed differences in outcomes after treatment reflect the causal effects of the treatment on the outcome under perfect compliance and blinding. However there are some situations where controlled experiments are impractical. For instance, many studies have reported a possible link between abortions and an increased risk of breast cancer (Russo et al. [2, 3, 4]). To conduct a controlled experiment, one would need to divide the study group into a treatment group which receive induced abortion and a control group which did not and then do cancer screening for each group after a prescribed follow-up period. Such an experiment would obviously be unethical and practically impossible to conduct, so an observational study would be the only option. In a typical observational study, treatment assignment is beyond the control of the investigator. In observational studies, one typically observes subjects in the treatment group and retrospectively draw inference about the postulated link between treatment and the outcome of interest. In recent years, such studies have become increasingly common in medicine, public health, education, sociology and psychology and their objective is to elucidate cause-and-effect relationships. A common mistake in such studies is

interpreting the correlation between treatment and outcome as causation due to the presence of confounding variables. Confounders are variables that cause both the outcome and exposure, leading to a non-causal association between exposure and outcome. Failure to account for confounding can result in biased estimation of the causal association between the outcome and the independent variables. In controlled experimentation, this problem can be diminished to a tolerable level by using randomization and blocking and adjustment. In a cross-sectional observational study, the critical assumption needed to adjust for confounding using standard methods is that there are no unmeasured confounders (Cochran [5]). In a longitudinal study, the assumption of no unmeasured confounding is that at the time of adminstration, given past pre-treatment covariates, treatment is independent of all unmeasured confounders. This assumption is called sequential randomization. In a longitudinal setting, contrary to cross sectional observational studies, even when sequential randomization holds, standard methods fail to account for confounding which induces bias in estimating the causal effect of treatment (Robins [6]).

1.1 Thesis organization and contributions

Elucidating cause-and-effect relation using standard regression methods in longitudinal observational studies requires some additional assumptions: (i) correche specification of the parametric regression model, (ii) satisfaction of the assumption of no unmeasured confounders, and (iii) past treatment history doesn't cause future time varying confounders. However the latter assumption is impractical in many applications. Thus causal methodologies have been developed to address the inconsistency of standard methods when the latter assumption doesn't hold. Structural

nested models (SNMM) have been used to adjust for the confounding effect of time varying covariates when standard methods fail. The main advantage of these models is that one can estimate treatment modification by other time varying confounders at all time intervals. In this thesis, I adopt the causal frame work of SNMM and implement the Kalman filtering algorithm (Kalman [7]) to develop new estimation methods for estimating the causal parameters of the SNMM. My thesis is organized as follows.

I start with a broad review of SNMM and other approaches in causal inference in Chapter 2. The purpose of Chapter 3 is to provide methods to estimate the causal effect of a time-varying dichotomous treatment on a time-varying outcome in the presence of measured time-varying confounding in observational data. I develop a new semi-parametric approach which doesn't require the usual restriction on the treatment model. Instead, I assume a Markov model for the counterfactual when treatment is completely withheld over time and write the SNMM in the framework of a state space model. The parameters of the counterfactual model are considered nuisance parameters. I adapt the Kalman estimating equation estimator (Jørgensen & Song [8]) so that it can be used to estimate the parameters of the SNMM (keeSNMM). I demonstrate by simulation that when the counterfactual model assumptions hold, the proposed method of estimating causal parameters by modeling the counterfactual directly is more efficient than the standard G-estimation approach. I discuss insensitivity of our methodology to the estimation of our nuisance parameters.

The keeSNMM method places restrictions on the counterfactual when treatment withheld. Drawing inference from keeSNMM requires satisfaction of these assumptions. Additional model checking criteria would then be desirable, in order to ensure that the conclusion is reliable. Despite its importance, there has been relatively little work published on how to build and check the basic assumptions of the causal models. Some work has been done on model checking for DTRs. See Chakraborty and Moodie's book (chapter 9) [9], Rich et al. [1], Henderson et al. [10] and Ertefaie et al. [11]. Estimating parameters of SNMM by modeling the counterfactual when treatment is withheld by keeSNMM not only is computationally efficient, but it also readily provides us with basic diagnostic tools, which are the focus of Chapter 4.

Residual diagnostic plots provide valuable insight into whether the model assumptions are reasonable or not. These plots can be used to check model assumptions for standard methods, for example as in multiple linear regression. In section 4.2, I discuss how to adapt these tools for checking the model assumptions of keeSNMM. In section 4.3, using simple examples, I illustrate a way to compare the performance of keeSNMM, gSNMM and MSM via IPTW and linear standard regression models via OLS. I also show the influence of different model assumptions on the estimation of the causal parameters. In section 4.4, using extensive simulation studies under different settings, I demonstrate the application of the residual diagnostic plots for evaluation of the relative performance of these four methods and in detecting deviation from the necessary causal model assumptions.

The SNMM require two different models, a model for the blip function and a model for either the propensity score when using gSNMM, or a Markov model for the

counterfactual when using keeSNMM. Both gSNMM and keeSNMM are consistent when their respective assumptions are correctly specified. Thus, the next step is to develop a solution for when the residuals demonstrate deviation from model assumptions. Doubly robust g-estimation of SNMM (dr-gSNMM) combines both modeling of the propensity score and modeling of the mean of the counterfactual and it provides consistent causal estimation if either the mean model or the propensity score model is correctly specified. Building models for the mean of counterfactual is generally problematic with a large number of observation time points. In section 5.3 of Chapter 5, I introduce an approach using g-estimation in conjunction with the Kalman filtering algorithm (dr-keeSNMM). I consider a Markov model for the counterfactual when treatment is withheld to systematically model the mean of the counterfactuals at all time points instead of using intermediate working models. Thus the additional assumption that needs to be checked is the Markov assumption. The dr-keeSNMM consistently estimates the parameters of the model if either the propensity score model or the Markov assumption is correct.

In causal inference using SNMM, it is essential to adjust for the important modifiers of the treatment effect with other pre-treatment covariates. However, adjusting for all covariates may the inflate variance of the estimated parameters and can also induce bias. As a result, dimension reduction can be beneficial when using SNMM to model modification of the treatment effect. In section 5.4 of Chapter 5, under the sequential ignorability assumption given history of observed treatment and the longitudinal propensity score, I derive SNMM using the longitudinal propensity score as a time-varying covariate (SNMM-LPS) to reduce the large dimension of covariates,

particularly with a large number of time points. I also discuss estimating the parameters of the model using keeSNMM-LPS and r-keeSNMM-LPS where r-keeSNMM-LPS is formalized in the same way as dr-keeSNMM. However, r-keeSNMM-LPS is only robust to violation of the Markov assumption when the propensity score model is correctly specified. The application of this method is suggested in two types of studies, namely (i) studies requiring adjustment for large numbers of pretreatment covariates, and (ii) when the propensity scores are known and only the propensity scores are kept as summaries of the covariates.

A dynamic treatment regime is a sequence of decision rules where the treatment decision at each time interval is tailored to the particular patient's characteristics and history for the purpose of optimizing long-term effectiveness of the program. I have found that there is no work in the literature on optimal dynamic treatment regime when the outcome is time-varying except when considering the reward function for outcomes at the end of the study period. In Chapter 6, I extend the optimal dynamic treatment regime SNMM (ODTR-SNMM) by modeling portion of the value of treatment regime on outcome at different time points. However, ODTR is still determined using the outcome at the end of the study. I place a Markov assumption on the optimal counterfactual and, by writing the problem as state space model, use ODTR-keeSNMM and ODTR-dr-keeSNMM to estimate the parameters of the model.

In the Promotion of Breastfeeding Intervention Trial (PROBIT), a program for the promotion of breastfeeding to mothers was randomized in a group of hospitals in Belarus. Maternal and infant characteristics were recorded over time. The decision to

continue to breastfeed is correlated with several maternal characteristics, suggesting that observational results may be confounded. In Chapter 7, I illustrate my proposed statistical approaches by using the PROBIT dataset. The first substantive question addressed in Chapter 7 is how estimates of the effect of breastfeeding differ as a result of changes in mothers' and infants' characteristics in the course of the study. The question is addressed first by dr-keeSNMM and keeSNMM and then by keeSNMM-LPS and r-keeSNMM-LPS. The second question of interest is the optimal time to stop breastfeeding that achieves the optimal growth, which is answered by the new ODTR-dr-keeSNMM and OdTR-keeSNMM approaches.

The final chapter contains some directions for future results and a short conclusion.

CHAPTER 2
Literature review

2.1 Setting, notation, and definitions

Assume the longitudinal study records measurements at T time points $\{j_1, \ldots, j_T\}$ for N subjects. As a result the study has $T-1$ time intervals, $\{(j_{t-1}, j_t], j = (2, \ldots, T)\}$. For each time interval, $\{(j_{t-1}, j_t], t = (2, \ldots, T)\}$, the outcome is denoted by Y_t. The vector of all other measured potential observed covariates at the end of the interval is denoted by L_t. I assume a binary treatment A_t at each time point which remains constant till the end of next interval and is assigned after observing Y_t and L_t. I also use "overbar" to denote current and past observations and "underbar" for current and future observations, as is common in the causal inference literature. For instance $\overline{A}_t = (A_1, A_2, \ldots, A_t)$, $\overline{L}_t = (L_1, L_2, \ldots, L_t)$, $\underline{Y}_t = (Y_t, Y_{t+1}, \ldots, Y_T)$ and $\underline{A}_t = (A_t, A_{t+1}, \ldots, A_{T-1})$. The pretreatment history before A_t is denoted by $H_t = (\overline{A}_{t-1}, \overline{Y}_t, \overline{L}_t)$. The entire observed data record for each subject is denoted by $O = (Y_1, L_1, A_1, \ldots, A_{T-1}, Y_T, L_T)$.

2.1.1 Dynamic and non-dynamic treatment regime

In managing chronic diseases, tailoring treatment initiation to a patient's characteristics is essential for optimizing effectiveness of the program. A dynamic treatment regime (DTR) is a sequence of decision rules that specify how treatment administration should be adjusted, changed, added or discontinued through time in response

to progress, side effects and patient burden, Lei et al. [12]. For an example of DTR on the treatment of schizophrenia see Stroup et al. [13] and Cain et al. [14].

Mathematically, a treatment regime is a function $\mathbf{g} = \{g_1, \ldots, g_T\}$ where each element maps the past history of confounders and treatment into a decision $a_t \in \mathcal{A}_t$, $g_t : \{h_t \in \mathcal{H}_t \rightarrow a_t \in \mathcal{A}_t\}$. When $\mathbf{g} = \overline{a}^*$ for all $\{h_t \in \mathcal{H}_t\}$ the treatment regime is non-dynamic in that it does not depend on past treatment, outcome or covariates history. Any treatment regime that depends on $\{h_t \in \mathcal{H}_t\}$ will be called *dynamic*. Robins [6, 15, 16] pioneered the field of dynamic treatment regime and for more information on drawing causal inference in multi-interval trials see, Murphy [17], Robins [18], Moodie et al. [19] and Chakraborty et al. [20].

2.1.2 Potential/Counterfactual outcome

One framework that has proven useful in the analysis of confounding is the counterfactual or potential outcomes approach. For example, MacMahon & Pugh [21] state that "... an association may be classed as presumptively causal when it is believed that, had the cause been altered, the effect would have been changed, that is, they are counterfactual". For simplicity, first assume a univariate setting, and also assume outcome and binary treatment are denoted by Y and A respectively. Let the outcome that would be observed for a specific subject receiving treatment be denoted by $Y^{a=1}$ and when treatment is withheld by $Y^{a=0}$. The causal contrast, $Y^{a=1} - Y^{a=0}$ is thus defined to be the causal effect of receiving treatment on the subject's outcome. However only one of these outcomes can be observed in practice, and so the other one is considered to be counterfactual. The counterfactual/potential outcome idea was introduced in the statistical literature by Neyman [22] to analyze the causal effect

of time-independent treatments in randomized experiments and Rubin [23] extended this idea to analyzing the causal effects of time-independent treatments in observational studies. Robins [6] applied this concept for developing the counterfactual theory of causal inference that extended Neyman's theory to longitudinal studies with sequential time-varying treatments and confounders. Some people prefer the term *potential outcomes* to emphasize that, depending on the treatment that is received, only one of these two outcomes can be actually observed although, prior to treatment, either one could potentially be observed. Other authors prefer the term *counterfactual outcomes* to emphasize that these outcomes represent situations that may not actually occur.

2.2 Total, direct and joint causal effect

In this section we introduce the total, direct and joint causal effect and highlight the difference between these effects using an example from Daniel et al. [24]. In order to define the total effect of a treatment, assume that the treatment is just measured at baseline, A_1 and later values are not measured and outcome Y is only measured at the end of the study. A change in A_1 leads to a change in A_2 and so on. So the total effect of A_1 on Y is equal to the direct effect of A_1 on Y and the effect of A_1 on Y through subsequent, but unmeasured, treatments. In this simple case, a change in A_1 may lead to serious changes in the distribution of $Y^{a_1}, a_1 \in \mathcal{A}_1$. Thus the distribution of Y^{a_1} for different values of $a_1 \in \mathcal{A}_1$ determine total effect of treatment A_1 for a particular subject. Now assume that treatment is measured over time, as is more common in practice. Then the distribution of $Y^{\overline{a}_{T-1}}$ could still be the same for changes in a_1 when the effect of A_1 is mediated through later treatment. The direct

causal effect of A_1 is then defined to be the effect of A_1 on Y after removing the effect of later levels of treatment. The joint effect of $\overline{A}_{T-1}$ on Y is a collection of all direct effects that includes the direct effect of A_1 on Y unmediated by $\{A_2, \ldots, A_{T-1}\}$, the direct effect of A_2 on Y unmediated by $\{A_3, \ldots, A_{T-1}\}$ and so on.

2.3 Causal DAG

An alternative causal structure for defining causal effects is given by Pearl [25]. The causal structure can be denoted by a directed acyclic graph (DAG) G in which nodes are random variables $V = (V_1, ..., V_M)$ linked by directed edges (arrows). Links are acyclic because there are no arrows from descendents (effects) to ancestors (causes). According to Pearl's terminology, a connected path is any sequence of nodes and edges that connects A to B ignoring the direction of the arrows and any path that is not a connected path is considered to be blocked. A node C is a collider on a path between nodes A and B if the edges on the path that meet at C both have arrows pointing into C. Assume that a node C lies on a path from A to B. If C is not a collider, then it does not block the path from A to B unless it is conditioned on (in which case, it then does block the path from A to B). If C is a collider, then it blocks the path from A to B unless it is conditioned on (in which case, it then does not block the path from A to B). For more details on causal diagrams see Pearl [25, 26] and Greenland et al. [27].

2.4 The impact of unmeasured confounding via DAGs

I start with an example which is adopted from Robins & Wasserman [16]. The data is collected on (A_1, L, A_2, Y) where A_1 and A_2 are the dose of zidovudine treatment received by AIDS patients. Let L be the indicator of whether a patient is

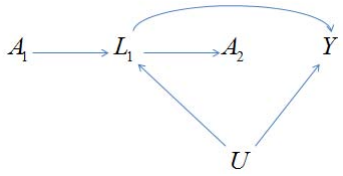


Figure 2–1: Causal diagram showing no causal arrow from treatment to outcome.

anemic or not. Let Y be the HIV viral load at the end of study and U be a hidden variable such as patient's underlying health status. The unmeasured covariate U is a risk factor for Y and L, and is independent of treatment. The null hypothesis is that there is no causal effect of treatment on the response, i.e. that (A_1, A_2) is independent of Y given L and U. The naive approach would test for the absence of arrows from A_1 to Y and from A_2 to Y. The problem with the naive test is that, if I assume the true DAG is 2–1, since U is not measured, blocking L is required to make A_2 independent of Y. However blocking L opens a path from A_1 to Y and causes association. As a consequence, the null hypothesis will be naively rejected. For technical details, see Robins & Wasserman [16]. As a result, in a longitudinal setting, standard methods are inconsistent for estimating causal effects when the following two conditions hold, (a) a time varying confounder is a predictor of subsequent value of outcome and it also predicts subsequent value of treatment, and (b) past treatment history is an independent predictor for the time varying confounder.

2.4.1 Examples of studies with time-varying confounding

Example 1: AIDS cohort study

Consider again the study of estimating the impact of zidovudine (AZT) therapy on CD4 counts in patients with AIDS. In the Multicenter AIDS Cohort Study

(MACS, Kaslow et al. [28]) patients were monitored by their doctors semi-annually. In each visit, doctors recorded a list of health indicators for each patient and used the information to determine patient AZT treatment. Past CD4 counts were naturally assumed to have a causal effect on future CD4 counts. It was also an important determinant of future therapy decisions. Similarly, past AZT therapy was an independent predictor for CD4 counts. The effect of AZT on future CD4 counts is then confounded by past CD4 counts and would result in the failure of standard estimation methods in estimating the causal effect of treatment.

Example 2: The promotion of breastfeeding intervention trial (PROBIT)

Breast milk is widely acknowledged as the most complete form of nutrition for infants, with a range of benefits for infants' health, growth, immunity and development [World Health Organization (WHO) [29, 30]]. In the Promotion of Breastfeeding Intervention Trial (PROBIT), the promotion of breastfeeding was randomized to hospitals in Belarus (Kramer et. al [31]). A total of 17,046 mother-infant pairs in 31 hospitals were studied, all of whom were initially breastfed. The dataset includes both maternal and infant characteristics. Some women in the intervention group stopped breastfeeding in the first month, while other women in the control group continued to breastfeed for many months. The decision to continue to breastfeed was correlated with several maternal characteristics, suggesting that observational results on breastfeeding effect on infant growth may be confounded.

2.5 Estimation of effects of time-varying outcome by reparameterization

Continuing with the example from Robins and Wasserman discussed in section 2.4, the question is "can one characterize the null hypothesis of no treatment effect

independent of U or not?" Robins [6] and Pearl & Robins [26] indicate that the answer is yes. The authors showed that the null hypothesis, $(A_1, A_2) \coprod Y|L, U$ holds if and only if two conditions hold: (a) $Y \coprod A_2|A_1, L$, i.e. $f(y|l, a_1, a_2) = f(y|l, a_1)$, and (b) $\sum_{l=1}^{2} f(y|a_1, l)f(l|a_1)$ doesn't depend on a_1 where, $\sum_{l=1}^{2} f(y|a_1, l)f(l|a_1)$ is the density function of y restricted to (a_1, a_2). Thus, even though U is not measured, by checking (a) and (b) which are only based on observed variables, one can say if the null hypothesis holds or not. The naive solution is to test (a) and (b) directly by using association models, for example using multiple linear regression. However, standard methods here can falsely reject the null hypothesis (Robins & Wasserman [16]). The main problem with standard methods like linear regression is that there is not a parameter ψ that takes the value zero if and only if there is a non-zero treatment effect. Addressing this problem requires reparametrization of the model. Assume that the vertices (random variables) of the causal DAG are $O = \{V_1, V_2, \ldots, V_M\}$, where under a Markov assumption on the DAG, $f(v) = \prod_{i=1}^{M} f(v_i|P_{v_i})$ where P_{v_i} is ancestor of v_i. For $O = (L_1, A_1, L_{T-1}, A_{T-1}, \ldots, L_T)$, the standard parametrization under the Markov assumption is,

$$f(O) = f(l_1)f(a_1|l_1)\ldots f(l_T|\bar{l}_{T-1}, \overline{a}_{T-1}).$$

In the reparametrization it is assumed that $f(a_t|\bar{l}_t, \overline{a}_{t-1})$ is replaced by the degenerate function so that

$$f_g(O) = f(l_1)\ldots f(l_T|\bar{l}_{T-1}, \overline{a}_{T-1})$$

and so as a consequence,

$$f_g(y) = \int f_g(y|\bar{l}_T, \bar{a}_{T-1}) \prod_{j=1}^{T} f(l_j|\bar{l}_{j-1}, \bar{a}_{j-1}) d\mu(l_j),$$

where $f_g(y)$ is the density function of Y restricted to treatment regime g. Similarly the marginal distribution of Y under g, $F_g(y)$ is

$$F_g(y) = \int P(Y < y|\bar{l}_T, \bar{a}_{T-1}) \prod_{j=1}^{T} f(l_j|\bar{l}_{j-1}, \bar{a}_{j-1}) d\mu(l_j) \tag{2.1}$$

and is referred to as the G-computation formula (Robins [6]). Robins [6] and Pearl & Robins [26] proved that under certain conditions eq. 2.1 is the distribution of Y^g that would have been observed if the entire population had been treated according to g. These conditions will be discussed in next section. In terms of this new reparametrization, the null hypothesis $(A_1, A_2) \coprod Y|L, U$ holds if and only if,

$$F_g(y) = F_{g'}(y), \text{for all } y \text{ \& all } g \text{ and } g' \text{ in } \mathcal{G}. \tag{2.2}$$

They also showed that the "g"-null hypothesis 2.2 is true if and only if

$$F_{g=\bar{a}}(y|\bar{l}_k) = F_{g'=\bar{a}'}(y|\bar{l}_k), \tag{2.3}$$

for all $y, \bar{l}_k, \bar{a}$ and $\bar{a}'$ where $\bar{a}$ and $\bar{a}'$ agree through time $j_k - 1$.

2.6 Identifiability of the causal effect of treatment

Identifying the causal effect of treatment using the counterfactuals requires a number of assumptions which will be discussed in this section. Continuing with the univariate example in section 2.1.2, evaluating the treatment effect at the individual

subject level is generally impossible. Instead one can try to evaluate the average population treatment effect by $E_g(Y^{a=1} - Y^{a=0})$, where the expectation is taken with respect to $f_g(\cdot)$ and where $f_g(\cdot)$ is the density function of Y restricted to regime g. In the longitudinal setting, the causal effect of treatment is then defined in terms of a contrast of counterfactuals where deriving the causal effect from these contrasts requires number of identifiability assumptions.

The validity of the causal model requires that the counterfactual outcome of one subject be unaffected by another subject's assigned or received treatment regime. This assumption is called the stable unit treatment value assumption (SUTVA) (Cox [32], Rubin [33]). In order to draw inference from causal adjustment methodologies using the counterfactual, one needs to link the counterfactual with the observed outcome. The consistency assumption states that the observed outcome is equal to the counterfactual outcome when actual treatment is assigned. Consistency has a key role for the counterfactual in causal adjustment methodologies. Since the focus of this thesis is on dynamic, rather than static regimes, I need a strengthened version of the sequential ignorability/exchangeability assumption. Assume that under treatment regime $g \in \mathcal{G}$, for a given subject, $A_t = g_t(H_t)$, $t = \{1, 2, \ldots, T-1\}$ then $Y_t^{\overline{g}_{t-1}} = Y_t$ and $\overline{L}_t^{\overline{g}_{t-1}} = \overline{L}_t$ for all $t = \{1, \ldots, T\}$, where $\overline{L}_t^{\overline{g}_{t-1}}$ is the history of the counterfactual through time t under regime g. Next, for any $t = (1, \ldots, T)$, $\bar{l}_t$ and regimen g, one must have that,

$$Y_m^{\overline{g}_{m-1}} \coprod A_t | \overline{L}_t, A_k = g_k(\overline{A}_{k-1}, \overline{L}_k) \text{ for all } k = \{1, \ldots, t-1\} \text{ and } m > t. \qquad (2.4)$$

That is, at a specific strata $H_t = h_t$ where $h_t = (\overline{a}_{t-1}, \overline{l}_t, \overline{y}_t)$, $\overline{a}_{T-1} = \overline{g}_{T-1}(H_{T-1})$, and $\overline{g}_{T-1}(H_{T-1}) = \{g_1(H_1), g_2(H_2), \ldots, g_{T-1}(H_{T-1})\}$, one must have that treatment is randomly assigned according to $Pr(A_t = 1|H_t = h_t)$. This assumption implies exchangeability of $Y_T^{\overline{a}_{t-1}, \underline{0}_t}$ and $Y_T^{\overline{a}_t, \underline{0}_{t+1}}$ given H_t. Under this conditional exchangeability/ignorability assumption for each stratum, H_t, causation is equivalent to association. Finally, I must make the standard positivity assumptions, that is one must assume if $f_{\overline{L}_t, \overline{Y}_t, \overline{A}_{t-1}}(\overline{l}_t, \overline{y}_t, \overline{a}_{t-1}) \neq 0$ then $f_{A_t|H_t}(a_t|h_t) > 0$. In other word, under the positivity assumption, treatment is not deterministically assigned at each time point $t = \{1, \ldots, T-1\}$. Under these assumptions, one can consistently estimate the causal effect of treatment using the causal adjustment methodologies discussed in this thesis.

2.7 Additive structural nested mean model

In longitudinal settings, the more practical question of interest is often "How to estimate the modification of treatment effects by time varying covariates at each time interval?". Under an assumption of conditional exchangeability, for a specific stratum $(\overline{A}_{t-1} = \overline{a}_{t-1}, \overline{L}_t = \overline{L}_t, \overline{Y}_t = \overline{y}_t)$, treatment is randomly assigned according to $Pr(A_t = 1|\overline{A}_{t-1} = \overline{a}_{t-1}, \overline{L}_t = \overline{L}_t, \overline{Y}_t = \overline{y}_t)$ and the counterfactuals $Y_m^{\overline{a}_{t-1}}$ and $Y_m^{\overline{a}_{t-2}, 0}$, under non-dynamic regimes $g = \{\overline{a}_t, \underline{0}_{t+1}\}$ and $g' = \{\overline{a}_{t-1}, \underline{0}_t\}$ are exchangeable. Thus, under the sequential ignorability and consistency assumption one can create comparable groups at each time interval where the difference in group means corresponds to the effect of treatment and answer the question. The effect of treatment

at interval $(j_t, j_{t+1}]$ on outcome at time m, $m = \{1, \ldots, T\}$, is defined by the counterfactual contrast and is formalized as

$$E(Y_m^{\overline{a}_t, \underline{0}_{t+1}} - Y_m^{\overline{a}_{t-1}, \underline{0}_t} | \overline{Y}_t, \overline{L}_t, \overline{A}_{t-1}; \psi) = A_t \gamma_{t,m}(\overline{A}_{t-1}, \overline{L}_t, \overline{Y}_t; \psi) \tag{2.5}$$

where $A_t\gamma_{t,m}(\overline{A}_{t-1}, \overline{L}_t, \overline{Y}_t, \psi)$ is a known function of past history through time t that is parameterized by ψ and takes the value zero if and only if $\psi = 0$. This function is called a blip function and estimates the modification of treatment effects by time varying covariates at interval $(j_t, j_{t+1}]$ on outcome at time m. In what is referred to as a blip down process, one remove the effect of A_{m-1} from Y_m to get $Y_m^{\overline{a}_{m-2}, \underline{0}_{m-1}}$, then remove the effect of A_{m-2} from $Y_m^{\overline{a}_{m-2}, \underline{0}_{m-1}}$ to get $Y_m^{\overline{a}_{m-3}, \underline{0}_{m-2}}$ and continues until removing the effect of A_{t+1} to get $Y_m^{\overline{a}_t, \underline{0}_{t+1}}$. Using the blip down process and assuming a deterministic relation known as rank preservation, one can link the observed values with the counterfactual outcome,

$$Y_m = Y_m^{(t)}(\psi) + \sum_{k=t+1}^{m-1} A_k \gamma(H_k; \psi_{k,m}).$$

where $Y_m^{(t)}(\psi)$ is the counterfactual outcome that would have been observed if the subject received treatment $\overline{a}_t$ through time t and zero onward which is linked to the observed value through blip down process. It is worth to note that, in the additive SNMM, one chooses to model one aspect of $F_g(\overline{y}_T)$ and express the null hypothesis of 2.3 based on the expected value. The additive structural nested model is a particular form of structural nested model, developed by Robins [6] and is the focus of our thesis. For more information see, Robins [34, 35, 15]. The SNM is inappropriate for estimating the direct effect of the treatment at specified time. These models are

more useful for testing the total effect of a treatment regime $\overline{A}_T$ given the sequentially ignorable assumption. For appropriate models for the estimation of direct effects, refer to Robins [36, 37].

2.7.1 G-estimation: semiparametric inference in SNMMs

The sequential ignorability assumption, eq. 2.4, is a fundamental assumption in causal inference which identifies comparable groups when treatment is not randomized. This assumption has an essential role in estimating causal parameters. A semiparametric method driven by the utility of this assumption is g-estimation. In the blip down process introduced by Robins [18], the counterfactual can be expressed by

$$Y_m = Y_m^{(t)}(\psi) + \sum_{k>t} A_k \gamma(H_k; \psi_{k,m}). \tag{2.6}$$

For binary treatment regimes, a pooled logistic model is often fitted to estimate the parameter η,

$$\text{logit}\left[Pr\{A_t = 1|H_t\}\right] = \eta^T H_t,$$

where for $t = \{1, \ldots, T-1\}$, $H_t = (\overline{Y}_t, \overline{L}_t, \overline{A}_{t-1})$ is a vector of pretreatment covariates. After estimating η under an assumption of no unmeasured confounding (sequential ignorability assumption), the propensity score model is extended to

$$\text{logit}\left[Pr(A_t = 1|H_t, Y_m^{(t)}(\psi), \{m > t\})\right] = \eta^T H_t + \theta^T Q_t \sum_{m>t} Y_m^{\overline{a}_t}(\psi),$$

where $Q_t = q_t(H_t)$ is an arbitrary vector of pretreatment covariates that has the same dimension as ψ and is chosen such that for the true value of η and ψ, $\theta = 0$. One also defines $e_t = Pr(A_t = 1|H_t)$ as the probability of receiving treatment given

past pretreatment covariates which is modeled by $pr_t(\eta) = Pr(A_t = 1|H_t;\eta)$. Note that the choice of Q_t doesn't affect the consistency of the point estimators, but it does influence the efficiency of the estimators. Let $S_\theta(\widetilde{\eta}, 0, \psi) = \frac{\partial}{\partial\theta} logL(\psi^*, \theta, \eta)$ and set $U(\psi;\eta) = S_\theta(\widetilde{\eta}, 0, \psi)$, so that

$$U(\psi;\eta) \quad = \quad P_n \left[\sum_{t=1}^{t=K} \{A_t - pr_t(\widehat{\eta})\} Q_t \sum_{m>t} Y_m^{(t)}(\psi) \right] \tag{2.7}$$

where Q_t is chosen by the analyst as a function of $H_t = (\overline{A}_{t-1}, \overline{L}_t, \overline{Y}_t)$ and has the same dimension as ψ and $P_n(Z) = \frac{1}{n}\sum_{i=1}^{n}(Z_i)$ is the expectation operation with respect to empirical distribution. $U(\psi;\eta)$ is an unbiased estimating equation, that is $E\{U(\psi;\eta)\} = 0$. I assume for the remainder of the thesis that this condition holds. Assume that $\frac{\partial}{\partial\psi}U(\psi;\eta)$ exists and is invertible. Thus, under standard regularity conditions, there is a consistent asymptotically normal (CAN) root $\widehat{\psi}$ of the estimating function $P_n\{U(\psi;\eta)\}$. Thus $\sqrt{n}(\widehat{\psi} - \psi^\dagger)$ is asymptotically normal distribution with mean zero and variance $\Sigma(\psi) = P_n\left\{\frac{\partial}{\partial\psi}U(\psi;\eta)\right\}^{-T} P_n\left\{U(\psi;\eta)^{\otimes 2}\right\} P_n\left\{\frac{\partial}{\partial\psi}U(\psi;\eta)\right\}^{-1}$ where $\psi^\dagger$ is the limiting value of $\widehat{\psi}$. I denote g-estimation of a structural nested mean model by gSNMM. Chakraborty et al. [20] have shown that g-estimation is equivalent to Q-learning, a model-free reinforcement learning technique, in some settings. The Q-Learning algorithm was proposed by Watkins [38] as a way to optimize solutions in Markov decision process problems. Thus it would be more accurate to say that Q-learning is the most popular method of estimating parameters of an SNMM. However during the course of this thesis I use g-estimation instead of Q-learning which is introduced in the field of causal inference by Robins [6].

2.7.2 Doubly robust g-estimating equations

Robins [18] improved the efficiency of g-estimation by modeling the mean of the counterfactual outcome, $E(Y_m^{(t)}(\psi)|H_t)$. By including $E(Y_m^{(t)}(\psi)|H_t;\zeta_{t,m}) = D_{t,m}(H_t;\zeta_{t,m})$ in g-estimation, Robins developed a more efficient estimating equation,

$$U(\psi;\eta,\zeta) = P_n\left[\{A_t - pr_t(\widehat{\eta})\}\, Q_t \sum_{m>t}[Y_m^{(t)}(\psi) - D_{t,m}(H_t;\zeta_{t,m})]\right].$$

Robins [18] also showed that the method, which is referred to as doubly robust g-estimation (dr-gSNMM) can consistently estimate the causal parameters if either the propensity score or the model for $E(Y_m^{(t)}(\psi)|H_t)$ is correctly specified (the double robustness property). Finding the correct model for the mean of counterfactual requires knowing the functional relationship between outcome and past history and is likely to be misspecified. However Robins showed that even when it is misspecified, it is still more efficient than gSNMM (Robins [18]). After specifying a working model for $E(Y_m^{(t)}(\psi)|H_t)$ for all $m = \{1,\ldots,T\}$ and $t = \{1,\ldots,T-1\}$, one can estimate ζ from

$$P_n\left[\frac{\partial D_{t,m}}{\partial \zeta}\left\{Y_m^{(t)}(\psi) - D_{t,m}(H_t;\zeta_{t,m})\right\}\right] = 0.$$

2.7.3 Two-Stage parametric regression estimators

Almirall et al. [39] introduced the two-stage parametric regression estimator (2SPRE) for estimating the causal parameters of SNMM. By considering a simple example I clarify the method. In our longitudinal setting assume that one observes just 2 intervals, $(1,2]$ and $(2,3]$. For each subject, $O = (L_1, Y_1, A_1, L_2, Y_2, A_2, L_3, Y_3)$

is observed where A_t is constant during interval $(t, t+1]$, $t = \{1, 2\}$. For the outcome at the end of study, the treatment effect at time interval one is $A_1\gamma_{1,3}(H_1, \psi_{1,2})$ and the treatment effect at time interval two is $A_2\gamma_{2,3}(H_2, \psi_{2,3})$ where both $\gamma_{1,2}(\cdot)$ and $\gamma_{2,2}(\cdot)$ are known linear functions of the interaction terms at their corresponding intervals, that is

$$\begin{aligned} E(Y_3^{\bar{a}_2}|H_2 = h_2) = &\{E(Y_3^{a_1,a_2}|H_2 = h_2) - E(Y_3^{a_1,0}|H_2 = h_2)\} \\ &+ \{E(Y_3^{a_1,0}|H_2 = h_2) - E(Y_3^{a_1,0}|H_1 = h_1)\} \\ &+ \{E(Y_3^{a_1}|H_1 = h_1) - E(Y_3^{0,0}|H_1 = h_1)\} \\ &+ \{E(Y_3^{0,0}|H_1 = h_1) - E(Y_3^{0,0})\} + E(Y_3^{0,0}), \end{aligned}$$

where

$$\begin{aligned} &E(Y_3^{\bar{a}_2}|H_2 = h_2) = A_2\gamma_{2,3}(H_2, \psi_{2,3}) \\ &+ A_1\gamma_{1,2}(H_1, \psi_{1,3}) + \epsilon_2(H_2, a_1) + \epsilon_1(H_1) + \mu_0. \end{aligned}$$

Almirall et al. [39] developed a two-stage regression estimator using additional model assumptions. They consider the following constraints for the nuisance functions

$$\begin{aligned} &\epsilon_2(H_2, a_1) = E(Y_3^{a_1,a_2}|H_2 = h_2) - E(Y_3^{a_1,0}|H_1 = h_1), \\ &\epsilon_1(H_1) = E(Y_3^{\bar{a}_1}|H_1 = h_1) - E(Y_3^{0,0}), \\ &E_{H_2|H_1}(\epsilon_2(H_2, a_1)) = 0, \text{ and } E_{H_1}(\epsilon_{i,1}(H_1)) = 0, \text{ and} \\ &\mu^0 = E(Y_3^{0,0}). \end{aligned}$$

They parameterize nuisance functions and estimate the parameters by using OLS in two stages. For more details see Almirall et al. [39, 40, 41] and Griffin et al. [42].

2.8 Optimal structural nested mean model

Dynamic treatment regimes are common in the management of many diseases, such as obesity, diabetes, or depression. The regimes attempt to provide more effective treatment for individual patients than what can be achieved with a static regime (Lei et al. [12]). At the beginning of these studies, the medication of interest is initiated and patients are monitored during the course of study and medication is adjusted according to a list of their important health indicators. In this sequential decision-making process, the goal is optimizing the patient's long-term clinical outcome. Thus, the question of interest is "Can one use the observational data, where treatment is received over time and results are recorded, to find the optimal regimes which optimize the patient's long-term clinical outcome?". Most of the algorithms for finding the optimal regime are derived in the field of computer science which are referred to reinforcement methods (Sutton& Barto [43]). Murphy [17] pioneered the field of finding optimal regime using a semiparametric approach which is equivalent to g-estimation in some cases and Robins [18, 44] introduced semiparametric method of optimal dynamic treatment regime SNMM (ODTR-SNMM) to estimate the optimal regime by g-estimation. For application of optimal DTR in the field of causal inference see Shepherd et al. [45] on HIV, Shortreed & Moodie [46] on schizophrenia, Moodie et al [47] and Rich et al. [1] on breastfeeding. Details regarding these approaches are contained in Chapter 5.

2.9 Single time propensity score regression

The propensity score is the probability of receiving treatment conditional on the subject's past history. One particular advantage of a randomized experiment is the exchangeability of covariates under different treatment groups that is essential in elucidating cause-and-effect. Rosenbaum & Rubin [48] defined the propensity score as a balancing score and demonstrated that one can use to create comparable groups in causal inference. Different methods based on the propensity score appear in the literature, including propensity score matching, stratification on the propensity score, inverse probability of treatment weighting using the propensity score, and covariate adjustment using the propensity score.

In a univariate setting, assume that treatment only takes on two possible values $\{0, 1\}$. For a specific patient, two counterfactual values exist under the two levels of treatment and is denoted by Y^a, $a = \{0, 1\}$. The causal effect of treatment on the patient is $Y^{a=1} - Y^{a=0}$ but the problem is that only one counterfactual is observed per subject so estimation of the effects requires certain assumptions. Let L be the vector of pretreatment covariates for the patient. The propensity score, the conditional probability of receiving treatment given past treatment history, is denoted by $e(l) = Pr(A = 1|L = l)$. To be able to consistently estimate $E(Y^{a=1} - Y^{a=0})$, three assumptions are required; (a) SUTVA, (b) the assumption of no unmeasured confounders, that is, $Y^{a=1}, Y^{a=0} \coprod A|L$, and (c) positivity, i.e. that each patient has a positive probability of being exposed to either treatment option, $0 < e(l) < 1$. When these three assumptions hold, one can estimate the causal effect of $E(Y^{a=1} - Y^{a=0})$ by using subclassification on the covariate X, (Rubin [23]),

$$E(Y^{z=1} - Y^{z=0}) = E_X\{E(Y|Z=1,X)\} - E_X\{E(Y|Z=0,X)\}. \qquad (2.8)$$

In situations where one encounters high dimensional covariates, correct model specification of $E_X\{E(Y|Z=z,X)\}$ will not be easy and one needs to reduce the dimension of the covariate set X. Rosenbaum & Rubin [48] proved that the assumption of no unmeasured confounders holds given the propensity score where $Y^{z=1}, Y^{z=0} \coprod Z|e(X)$. As a result, estimating causal effects only requires building a parametric model for $E_e\{E(Y|Z=z,e(X))$ instead of $E_X\{E(Y|Z=z,X)$.

2.10 Marginal structural models

Marginal structural models (MSM) place restrictions on the marginal distribution of the counterfactual, or on one aspect of the distribution such as its mean, see Robins [49, 35]. In MSM, only baseline covariates and treatment are adjusted for in the marginal model and adjustments for time varying confounders and covariates are reflected in the propensity score. In order to estimate the causal parameter ψ, the Horvitz-Thompson estimator is generally used where the sampling weight is the inverse of the probability of a subject receiving his observed treatment, see Horvitz and Thompson [50]. Assume that $E(Y^{\overline{a}_{T-1}}|V;\psi) = g(\overline{a}_{T-1},V,\psi)$ and one estimates the causal parameter ψ by the IPTW method. IPTW corrects for confounding by creating a pseudo-population including w^{-1} copies of a specific subject. In the pseudo-population, assuming a correct propensity score, the weighting ensures that there is no confounding. By creating a population where treatment is exogenous where treatment at each time point only depends on past treatment history. Despite

removing confounding in the pseudo-population, the causal structure in the actual population will still hold in the pseudo-population. Thus ordinary regression estimators for the pseudo-population will estimate the causal effect of treatment. Under the sequential ignorability assumption eq. 2.4, $E(Y^{\overline{a}_{T-1}})$ is the unique function of $\overline{a}_{T-1}$, $C(\overline{a}_{T-1})$ such that $E(q(\overline{a}_{T-1})(Y - C(\overline{a}_{T-1}))/W) = 0$ for all functions $q(\overline{a}_{T-1})$ where the expectation exists (Robins [49]). The inverse of the probability of observed treatment through time t for each subject is often referred to as the non-stabilized weight, $W_t = \prod_{m=1}^{t-1} \frac{1}{f(A_m|H_m)}$, whereas the stabilized weight is $SW_t = \prod_{m=1}^{t-1} \frac{f(A_m|\overline{A}_{m-1})}{f(A_m|H_m)}$.

A GEE estimator provides only the association between observed treatment and observed outcome while MSM estimators target the *causal* relationship between the possible treatment regime with its corresponding potential outcome. So the parameters of a GEE model and MSM have different interpretations. For example, consider a cohort study on HIV-infected patients. Assume that analyst wants to measure the effect of zidovudine therapy on mean CD4 count. Let the CD4 count for a specific subject at time m be denoted by Y_m, and let A_{m-1} be a binary treatment variable that indicates whether the subject received zidovudine at time interval $(m-1, m]$ or not. For instance, in the GEE model, one has $E(Y_m|\overline{A}_{m-1}) = \gamma_0 + \gamma_1 Cum[\overline{A}_{m-1}] + \gamma_2 m$ and for the MSM one has that $E(Y_m|\overline{A}_{m-1}) = \beta_0 + \beta_1 Cum[\overline{A}_{m-1}] + \beta_2 m$ where $\beta_1 Cum[\overline{A}_{m-1}] = E(Y_m^{\overline{a}_{m-1}}) - E(Y_m^{\overline{0}})$. Thus β_1 represents the causal change in the mean of CD4 count for a one unit increase in the number of treatment received. Assume that treatment administration to a new subject is based on this model in which the optimal treatment regime is the one that maximizes the benefit of treatment the expected value of CD4 count at each time point t. In this case, zidovudine therapy

should be withheld only when β_1 is negative. In contrast to β_1, γ_1 has a different interpretation. Assume that there is no treatment effect i.e., $\beta_1 = 0$. Assume that the physician only gives zidovudine therapy to patients in poor conditions who have a low CD4 count. Because the low CD4 count causes subsequent future low CD4 counts, fitting the usual GEE model would likely estimate a negative value for γ_1 because it is confounded by the association between the previous CD4 count and outcome. For other applications of MSMs, see Hernán et al. [51, 52] and Brumback et al. [53].

Although MSMs are powerful statistical models for causal inference that address the confounding due to time varying covariates, their application is limited. MSMs via IPTW can be as inefficient as standard methods for estimating parameters since information on time-varying covariates is only adjusted for in the propensity score. The problem with this innovative method is that it is restricted to the estimation of effect modification by baseline covariates. Van der Laan et al. [54], Petersen et al. [55] have developed generalized MSMs called history-adjusted marginal structural models (HA-MSM). These variations on MSMs can be used to estimate the modification of treatment effects by time-varying covariates.

2.11 Kalman estimating equation

State space models have been widely used for analyzing time series for non-normal data. The Kalman smoother is a useful tool for prediction and for estimation of latent state processes, see for example, Durbin [56], Fahmier et al. [57, 58]. The Kalman Estimating Equation is an efficient regression method for estimating the parameters of a state space model using the Kalman smoothing algorithm (Jørgensen et

al. [59, 60] and Jørgensen & Song [8]). For non-normal longitudinal data, Jørgensen & Song [8] define a class of state space models for stationary AR(1) state space processes with exponential dispersion model margins. Using the Kalman smoother algorithm, they introduced the Kalman estimating equation (KEE) approach. However, KEE by Jørgensen & Song [8] requires some assumptions that are not compatible for estimation of causal effects. In my thesis I will tailor the KEE introduced in Jørgensen & Song [59] for causal inference in longitudinal observational studies.

2.11.1 Review of the Kalman smoother algorithm

The Kalman smoother algorithm has been used for a vast array of theoretical and practical problems in communication and control theory, including prediction of random signals, separation of random signals from random noise, and detection of signals of known form in the presence of random noise. Wiener [61] showed these problems can be addressed via the Wiener-Hopf integral equation. In the Wiener-Hopf problem, a random signal $f(m)$ is observed containing a message, $g(m)$, and random noise which is often written as,

$$f(m) = g(m) + [f(m) - g(m)].$$

Wiener in 1949 showed that the best linear predictor of $g(m)$ is minimizer of the Wiener-Hopf integral equation. One of the limitations of the Wiener-Hopf equation is that this method is computationally difficult to solve directly. Kalman [7] approached the Wiener problem by using conditional expectation. First consider a simple state space model,

$$\begin{aligned} &\text{(Measurement equation)} \quad y_m = \phi x_m + d_m + \xi_m \text{ and} \\ &\text{(Transition Equation)} \qquad x_m = \theta x_{m-1} + c_m + \epsilon_m, \end{aligned} \tag{2.9}$$

where

$$\begin{pmatrix} \xi_m \\ \epsilon_m \end{pmatrix} \sim N\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} Q_m & 0 \\ 0 & W_m \end{pmatrix} \right).$$

Assume that $\{\epsilon_m : m \in T\}$ is a sequence of uncorrelated disturbances with mean zero and covariance matrix W_m, $\{x_m : m \in T\}$ is a latent vector generated by a first-order Markov process, and $\{\xi_m : t \in T\}$ is a sequence of uncorrelated disturbances with mean zero and covariance matrix Q_m. The Kalman filtering algorithm is based on the well known best linear unbiased predictor (BLUP). Let X and Y be two random variables with $\mu_X = E(X)$, $\mu_Y = E(Y)$, $\Sigma_X = Var(X)$, $\Sigma_Y = Var(Y)$ and $\Sigma_{XY} = Cov(X, Y)$. The BLUP of X given Y is written as, $\mu_{X|Y}$. Under the above assumption, I have that

$$\mu_{X|Y} = \mu_X + \Sigma_{XY}\Sigma_Y^{-1}(Y - \mu_Y). \tag{2.10}$$

An important property of the linear predictor is that the prediction error $X - \mu_{X|Y}$ is uncorrelated with Y and $Cov(X - \mu_{X|Y}, Y) = 0$. The theorem listed below is taken from Jørgensen et al. [59, 60].

Theorem 2.11.1. *Let X, Y, Z be random vectors with finite second moments. The joint predictor of X, Y given Z is given by*

$$\begin{pmatrix} X \\ Y \end{pmatrix} |Z \sim \left[\begin{pmatrix} \mu_{X|Z} \\ \mu_{Y|Z} \end{pmatrix}; \begin{matrix} C_{X|Z} & C_{XY|Z} \\ C_{YX|Z} & C_{Y|Z} \end{matrix} \right]$$

where $C_{XY|Z} = \Sigma_{XY} - \Sigma_{XZ}\Sigma_Z^{-1}\Sigma_{ZY}$.

Using eq. 2.10 and theorem 2.11.1, the linear predictor of X given Y and Z is given by

$$X| \begin{pmatrix} Y \\ Z \end{pmatrix} \sim [\mu_{X|Z} + C_{XY|Z}C_{Y|Z}^{-1}(Y - \mu_{Y|Z}); C_{X|Z} - C_{XY|Z}C_{Y|Z}^{-1}C_{YX|Z}]. \quad (2.11)$$

Eq. 2.11 provides the foundation for the Kalman filtering algorithm. By using the above results, the Kalman Filtering Algorithm can be implemented in closed form as follows:

$$\begin{aligned} a_{m|m-1} &= \theta a_{m-1|m-1} + c_m, \\ \Sigma_{m|-1} &= \theta^2 \Sigma_{m-1|m-1} + Q_m, \\ \mu_{m|m-1} &= \phi a_{m|m-1} + d_m, \\ R_{m|m-1} &= \phi^2 \Sigma_{m|m-1} + W_m, \\ K_m &= \phi \Sigma_{m|m-1} R_{m|m-1}^{-1}, \\ \Sigma_{m|m} &= \Sigma_{m|m-1} - K_m^2 F_{m|m-1}, \text{ and} \\ a_{m|m} &= a_{m|m-1} + K_m(y_m - y_{m|m-1}), \end{aligned}$$

where $a_{m|t} = E(x_m|\overline{y}_t)$, $\mu_{m|t} = E(y_m|\overline{y}_t)$, $R_{m|t} = Var(y_m|\overline{y}_t)$ and $\Sigma_{m|t} = Var(x_m|\overline{y}_t)$.

CHAPTER 3
Causal inference via Kalman filtering

3.1 Introduction

In this chapter, I will address the problem of estimating the total causal effect of a time-varying dichotomous treatment on time-varying outcome in the presence of measured confounding in non-randomized data. In longitudinal observational studies when variables are (i) risk factors of subsequent value of outcome and treatment, and also (ii) causally affected by treatment history, the issue of confounding will invariably arise. One modern causal approach to estimating causal effects from non-randomized data is using the structural nested mean model and estimating its parameters via g-estimation (gSNMM). Basic g-estimators are derived using the likelihood of the observed treatment process and are biased when this likelihood is misspecified. I introduce a semiparametric estimator which doesn't place any restriction on the treatment process. Instead, the method requires a Markov model for the counterfactual when treatment is completely is withheld over time. The parameters of this Markov model are treated as nuisance parameters. I adapt the Kalman estimating equation method introduced by Jørgensen & Song [8] for estimating the causal parameters of SNMM. I demonstrate that when the Markov model assumptions hold, the method of estimating causal parameters by modeling the counterfactual when treatment is withheld is more efficient than g-estimation. I discuss insensitivity of

my estimator to estimation of the nuisance parameters. At the end of the chapter, I highlight the utility of this method via a four-interval simulation study.

3.2 Additive SNMM as state space models

As discussed in Chapter 2, methods commonly used for estimating the parameters of SNMM are Robins' g-estimation [6, 62, 16, 18] and the two-stage regression estimators of Almirall et al. [39, 40, 41]. In a deterministic way, counterfactuals can be connected to observed values where for $m \leq T$,

$$Y_m^{\bar{a}_t,\underline{0}_{t+1}} = Y_m - \sum_{j=t+1}^{m-1} A_j \gamma_{j,m}(H_j, \psi_{j,m})$$

where $a_j\gamma_{j,m}(H_j, \psi_{j,m}) = E(Y_m^{\bar{a}_j}|H_j = h_j) - E(Y_m^{\bar{a}_{j-1},0}|H_m = h_j)$ is the blip function which measures the effect of receiving treatment for interval $(i_j, i_{j+1}]$ on the outcome at time m and no treatment there after and $\gamma_{j,m}(H_j, \psi_{j,m})$ takes the value zero if and only if $\psi_{j,m} = 0$, see section 2.7. The deterministic relationship is not required by g-estimation. In fact the described relationship need only hold in expectation. In the general form of the two-stage regression estimator, the SNMM for the conditional

mean of $Y_T^{\bar{a}_{T-1}}$ is expressed as

$$
\begin{aligned}
&E(Y_T^{\bar{a}_{T-1}}|H_{T-1}=h_{T-1}) \qquad (3.1)\\
&\quad=\{E(Y_T^{\bar{a}_{T-1}}|H_{T-1}=h_{T-1})-E(Y_T^{\bar{a}_{T-2},0}|H_{T-1}=h_{T-1})\}\\
&\quad+\{E(Y_T^{\bar{a}_{T-2},0}|H_{T-1}=h_{T-1})-E(Y_T^{\bar{a}_{T-2},0}|H_{T-2}=h_{i,T-2})\}\\
&\quad+\{E(Y_T^{\bar{a}_{T-2},0}|H_{T-2}=h_{T-2})-E(Y_T^{\bar{a}_{T-3},\underline{0}}|H_{T-2}=h_{T-2})\}\\
&\quad+\{E(Y_T^{\bar{a}_{T-3},0,0}|H_{T-2}=h_{T-2})-E(Y_T^{\bar{a}_{T-3},0,0}|H_{T-3}=h_{T-3})\}\\
&\quad\vdots\\
&\quad+\{E(Y_T^{a_1,\underline{0}_2}|H_1=h_1)-E(Y_T^{\bar{0}}|H_1=h_1)\}\\
&\quad+\{E(Y_T^{\bar{0}}|H_1=h_1)-E(Y_T^{\bar{0}})\}+E(Y_T^{\bar{0}}),
\end{aligned}
$$

which requires building many nuisance functions and restrictions, particularly when the outcome is time-varying, see section 2.7.3. I formulate the SNMM for the conditional mean of $Y_T^{\bar{a}_{T-1}}-Y_T^{\bar{0}}$. My approach doesn't depend on the nuisance functions

used by Almirall et al. [39] [eqs. 3.1], I instead define the causal contrast as

$$
\begin{aligned}
&E(Y_T^{\bar{a}_{T-1}} - Y_T^{\bar{0}} | H_{T-1} = h_{T-1}) \\
&= \{E(Y_T^{\bar{a}_{T-1}} - Y_T^{\bar{0}} | H_{T-1} = h_{T-1}) - E(Y_T^{\bar{a}_{T-2},0} - Y_T^{\bar{0}} | H_{T-1} = h_{T-1})\} \\
&+ \{E(Y_T^{\bar{a}_{T-2},0} - Y_T^{\bar{0}} | H_{T-1} = h_{T-1}) - E(Y_T^{\bar{a}_{T-2},0} - Y_T^{\bar{0}} | H_{T-2} = h_{T-2})\} \\
&+ \{E(Y_T^{\bar{a}_{T-2},0} - Y_T^{\bar{0}} | H_{T-2} = h_{T-2}) - E(Y_T^{\bar{a}_{T-3},0,0} - Y_T^{\bar{0}} | H_{T-2} = h_{T-2})\} \\
&+ \{E(Y_T^{\bar{a}_{T-3},0,0} - Y_T^{\bar{0}} | H_{T-2} = h_{T-2}) - E(Y_T^{\bar{a}_{T-3},0,0} - Y_T^{\bar{0}} | H_{T-3} = h_{T-3})\} \\
&\vdots \\
&+ \{E(Y_T^{a_1,\underline{0}_2} - Y_T^{\bar{0}} | H_1 = h_1)\}.
\end{aligned}
$$

In the next step, I assume that $E(Y_T^{\bar{a}_t} - Y_T^{\bar{0}} | H_t = h_t)$ depends on pretreatment covariates in the interval $(t, t+1]$ through their interaction with A_t, $t < T$. As a result, using the sequential ignorability assumption, for all $t < T$,

$$
\begin{aligned}
E(Y_T^{\bar{a}_{t-1}} - Y_T^0 | H_t = h_t) &= E(Y_T^{\bar{a}_t} - Y_T^0 | H_t = h_t, A_t = 0) \\
&= E(Y_T^{\bar{a}_{t-1}} - Y_T^0 | H_{t-1} = h_{t-1}),
\end{aligned}
$$

and thus,

$$
E(Y_m^{\bar{a}_{m-1}} - Y_m^{\bar{0}} | H_{m-1} = h_{m-1}) = \sum_{j=1}^{m-1} \gamma_{j,m}(H_j, \psi_{j,m}). \tag{3.2}
$$

From eq. 3.2, I define the error terms ϵ_m

$$
\epsilon_m = Y_m^{\bar{a}_{m-1}} - Y_m^{\bar{0}} - E(Y_m^{\bar{a}_{m-1}} - Y_m^{\bar{0}} | H_{m-1} = h_{m-1}).
$$

In the next step, by placing a Markov assumption on the counterfactual, I can express the SNMM for time-varying outcome in the framework of a state space model,

$$Y_m^{\overline{0}} = \beta_{0,m}^T V + \alpha_m Y_{m-1}^{\overline{0}} + \xi_m, \text{ and} \tag{3.3}$$

$$Y_m^{\overline{a}_{m-1}} = Y_m^{\overline{0}} + \sum_{j=1}^{m-1} \gamma_{j,m}(H_j, \psi_{j,m}) + \epsilon_m, \tag{3.4}$$

where ξ_m and ϵ_m for $m \in \{1, \ldots, T\}$ are two independent i.i.d series of error terms with mean zero and variances $\sigma^2 = (\sigma_1^2, \ldots, \sigma_T^2)$ and $\nu^2 = (\nu_1^2, \ldots, \nu_T^2)$ respectively. Note that $\alpha = (\alpha_1, \ldots, \alpha_T)$ is the correlation parameter vector for the Markov counterfactual process. $\gamma_{j,m}(H_j, \psi_{j,m})$ is the blip function which defines the treatment effect for time interval $(i_j, i_{j+1}]$ on outcome at time m.

3.2.1 Estimating causal parameters by the Kalman estimating equation

The Kalman estimating equation model which is introduced by Jørgensen & Song [8], estimates the parameters of a stationary non-linear state space model. In this section, I will show how to appropriately modify the Kalman estimating equation model for my causal problem by relaxing some model assumptions which are not applicable in our setting. In a general state space model there exist two sets of parameters: nuisance parameters (including parameters for the latent process and parameters in the covariance matrix) and the parameters of interest in the measurement model. First assume that the blip functions are linear and parameters are not shared between intervals i.e., that the parameters are stationary. Under known values of the nuisance parameters, one can use the following estimating equation to

estimate the causal parameters of the blip functions for outcome at time m,

$$U\left[\psi;\tau(\psi)\right]=\Gamma_m\left\{Y_m-Y_m^{\overline{0}}-\sum_{j=1}^{m-1}a_j\gamma_{j,m}(H_j,\psi_{j,m})\right\}, \tag{3.5}$$

where Γ_m is a function of $H_{m-1}=(\overline{A}_{m-1},\overline{Y}_{m-1},\overline{L}_{m-1})$ and

$$\tau(\psi)=\left\{\beta_0(\psi),\alpha(\psi),\sigma^2(\psi),\nu^2(\psi)\right\}$$

. τ is the vector of nuisance parameters for modeling the counterfactual process. The most common choice of Γ_m is $\frac{\partial}{\partial\psi}\sum_{j=1}^{m-1}a_j\gamma_{j,m}(H_j,\psi_{j,m})$. The challenge then becomes the estimation of ψ when the estimating equation depends on the unobserved counterfactual, $Y_m^{\overline{0}}$. Jørgensen & Song suggests approximating the counterfactual by its conditional expectation given all observed values. Such approximation requires independence between Y_m and $\overline{Y}_{m-1}$ given $Y_m^{\overline{0}}$ which doesn't hold in my setting and so instead of conditioning on all observed values, I propose to use $E(Y_m^{\overline{0}}|H_{m-1})$. Given the Markov assumption, it suffices to implement recursive Kalman filtering algorithm to find a closed form for $E(Y_m^{\overline{0}}|H_{m-1})$. Using theorem 2.11.1 of section 2.11.1 it is easy to show that:

$$\mu_{m|m-1} = \beta_{0,m}^T V + \alpha_m \mu_{m-1|m-1}^0 + \sum_{j=1}^{m-1} a_j \gamma_{j,m}(H_j, \psi_{j,m}), \tag{3.6}$$

$$\mu_{m|m}^0 = \alpha_m \mu_{m-1|m-1}^0 + K_m(Y_m - \mu_{m|m-1}), \tag{3.7}$$

$$R_{m|m-1} = \alpha_m^2 \Sigma_{m-1|m-1} + \nu^2 + \sigma^2, \tag{3.8}$$

$$\Sigma_{m|m} = \alpha_m^2 \Sigma_{m-1|m-1} + \nu_m^2 - K_m R_{m|m-1} K_m, \text{ and} \tag{3.9}$$

$$K_m = (\alpha_m^2 \Sigma_{m-1|m-1} + \nu_m^2)(\alpha_m^2 \Sigma_{m-1|m-1} + \nu_m^2 + \nu_m^2)^{-1}, \tag{3.10}$$

where $\mu_{m|k}^0 = E(Y_m^{\overline{0}}|H_k)$, $\mu_{m|k} = E(Y_m|H_k)$, $R_{m|k} = Var(Y_m|H_k)$ and $\Sigma_{m|k} = Var(Y_m^{\overline{0}}|\overline{H}_k)$. Since

$$E\left[\Gamma_m \left\{ Y_m - E(Y_m^{\overline{0}}|H_{m-1}) - \sum_{j=1}^{m-1} a_j \gamma_{j,m}(H_j, \psi_{m,m}) \right\}\right] = 0,$$

estimating equation 3.5 consistently estimates ψ for known values of the nuisance parameters.

3.2.2 Estimating nuisance parameters

In section 3.2.1, I showed how to estimate the causal parameter ψ when the nuisance parameters are known. Note that the KEE depends on nuisance parameters through $E(Y_m^{\overline{0}}|H_{m-1})$. Following Jørgensen & Song [8], I show how to estimate the nuisance parameters via moment estimators. I start by defining an estimator for $\beta_0 = (\beta_{0,1}, \ldots, \beta_{0,T})$. From eq. 3.7, we have that $\mu_{m|m}^0 = \alpha_m \mu_{m-1|m-1}^0 + \beta_{0,m}^T V + K_m(Y_m - \mu_{m|m-1})$ and since $cov(Y_m - \mu_{m|m-1}, \mu_{m-1|m-1}^0) = 0$ and $cov(Y_m - \mu_{m|m-1}, Y_{m+1} - \mu_{m+1|m}) = 0$, β_0 and α are estimable from modeling $\mu_{m|m}^0$ on V and $\mu_{m|m-1}^0$. For the

correlation parameter α_m,

$$\begin{aligned} Cov(\mu^0_{m|m}, \mu^0_{m-1|m-1}) &= Cov(\alpha\mu^0_{m-1|m-1} + K_m(Y_m - \mu_{m|m-1}), \mu^0_{m-1|m-1}) \\ &= \alpha_m Var(\mu^0_{i,m-1|m-1}) \end{aligned}$$

where $Cov(Y_m - \mu_{m|m-1}, \mu^0_{m-1|m-1}) = 0$. Thus

$$\alpha_m = \frac{cov(\mu^0_{m|m}, \mu^0_{m|m-1})}{var(\mu^0_{m-1|m-1})} \tag{3.11}$$

and at any specific time m, $\widehat{\alpha}_m$ can be used to estimate α_m where

$$\widehat{\alpha}_m = \frac{P_n\left\{\left(\widehat{\mu}^0_{m|m} - \widehat{\beta}^T_0 V\right)\left(\widehat{\mu}^0_{m-1|m-1} - \widehat{\beta}^T_0 V\right)\right\}}{P_n\left\{\sum_{m=1}^{T}(\widehat{\mu}^0_{m-1|m-1} - \widehat{\beta}^T_0 V)^2\right\}}. \tag{3.12}$$

α_m may be either estimated in practice by eq. 3.12 or by regressing $\mu^0_{m|m}$ on V and $\mu^0_{m|m-1}$. At this point, I have established estimators of β_0 and α and it remains to find estimators of the variances. Jørgensen estimated (ν^2, σ^2) under two assumptions: (i) a stationary model for latent process and (ii) conditional independence of Y_m and $\overline{Y}_{m-1}$ given $Y^{\overline{0}}_m$. When these assumptions hold, one can estimate (ν^2, σ^2) by moment estimators based on the marginal means of the latent and observed series. Because these two assumptions are not compatible the targeted setting, I instead momentarily set $\sigma^2 = \nu^2$, simply for mathematical convenience. Under this restriction, σ^2_m and

ν_m^2 are estimated via

$$R_{m|m-1} = var(Y_m - \mu_{m|m-1}) = \alpha_m^2 \Sigma_{m-1|m-1} + \sigma_m^2 + \nu_m^2, \text{ and so} \tag{3.13}$$

$$\nu_m^2 = \{var(Y_m - \mu_{m|m-1}) - \alpha_m^2 \Sigma_{m-1|m-1} - \sigma_m^2\}, \text{and so}$$

$$\widehat{\nu}_m^2 = \widehat{\sigma}_m^2 = \frac{1}{2} P_n \left[\left\{ Y_m - \widehat{E}(Y_m^{\overline{0}} | \overline{Y}_{m-1}) - \sum_{j=1}^{m-1} a_m \gamma_{j,m}(H_j, \psi_{j,m}) \right\}^2 \right] - \widehat{\alpha}_m^2 \widehat{\Sigma}_{m-1|m-1}. \tag{3.14}$$

If one instead assumes that $\sigma^2 = \delta\nu^2$, then the result holds, only replacing 2 by $\delta + 1$ in the denominator and the rest of algorithm is the same. Henceforth, I refer to an analysis which assumes a SNMM and estimates parameters by KEE as keeSNMM.

3.3 Nuisance insensitivity of keeSNMM

Nuisance parameter insensitivity is an important feature of an estimating equation approach, which means that there is no loss of efficiency when estimating parameters if the nuisance parameters are unknown. Under some regularity conditions, I show that the Kalman estimating equation is nuisance insensitive if $E\left\{\partial U\left[\psi, \beta_0(\psi), \tau(\psi)\right]/\partial\tau_i\right\} = 0$ which is equivalent to showing that $E(\Gamma_m \partial\mu_{m|m-1}^0/\partial\tau_i) = 0$ for all $i = 1, 2, 3$ where $\tau = (\sigma^2, \alpha, \nu^2)$. For the technical motivation, see Jorgensen & Knudsen [63] and Tsiatis [64]. The best linear unbiased estimator, $E(Y_m^{\overline{0}} | \overline{Y}_{m-1})$ is equal to $E(Y_m^{\overline{0}}) + cov(Y_m^{\overline{0}}, \overline{Y}_m) Var(\overline{Y}_m)^{-1} \left\{\overline{Y}_m - E(\overline{Y}_m)\right\}$ and the vector of nuisance parameters (τ) appear only in $cov(Y_m^{\overline{0}}, \overline{Y}_m) Var(\overline{Y}_m)^{-1}$ so the expectation of the first order derivative of $\mu_{m|m}^0$ is zero since $E[\overline{Y}_m - E(\overline{Y}_m)] = 0$. As a result, when Γ_m does not depend on $\overline{Y}_{m-1}$ our estimating equation is nuisance insensitive to nuisance

parameters in the covariance matrix. Assume that $U\left[\psi;\beta_0(\psi),\tau(\psi)\right]$ is differentiable with respect to ψ and is invertible. Thus under regularity conditions there is a consistent and asymptotically normal (CAN) root $\widehat{\psi}$ of the estimating function $P_n\left\{U\left[\psi;\beta_0(\psi),\tau(\psi)\right]\right\}$ and $\sqrt{n}(\widehat{\psi}-\psi^{\dagger})$ is asymptotically normally distributed with mean zero and variance $\Sigma(\psi)=Pn\left\{U\left[\psi;\beta_0(\psi),\tau\right]^{\otimes 2}\right\}$ where $P_n(Z)=\frac{1}{n}\sum_{i=1}^{n}Z_i$. If $U\left[\psi;\beta_0(\psi),\tau(\psi)\right]$ is not nuisance insensitive, the variance of the causal parameter $\widehat{\psi}$ must be adjusted to account for estimating the nuisance parameters in the estimating equation, which is discussed in Appendix A.

3.3.1 Average total treatment effect

Recall that the primary goal of this chapter was estimating $E(Y_m^{\overline{g}_{m-1}})$ where $\overline{g}_{m-1}=\{g_0,\ldots,g_{m-1}\}$ is a dynamic treatment regime through time $m-1$ that maps a past history of potential confounders into a decision $a_j\in\mathcal{A}_j$, $g_j:\{h_j\in\mathcal{H}_j\rightarrow a_j\in\mathcal{A}_j\}$. I propose to use the following algorithm to estimate the average total treatment effect in the population.

1. First, compute the sample average of $\widehat{E}(Y_m^0|H_{m-1})$ over all N subjects.
2. After specifying a parametric model for $f(l_m|\bar{l}_{m-1},\overline{y}_{m-1},\overline{a}_{m-1})$ and $f(y_m|\bar{l}_{m-1},\overline{y}_{m-1},\overline{a}_{m-1})$ and estimating their parameters and by considering the specified regime, g, recursively generate K samples of $(y_0,l_0,a_0,y_1,l_1,a_1,\ldots,y_T)$. Let $\delta_{\kappa,m,g}=\sum_{j=1}^{m-1}a_{\kappa,j}\gamma_{\kappa,j,m}(H_{\kappa,j},\psi_{j,m})$ be the κth Mont Carlo estimate of $Y_m^{\overline{g}_{m-1}}-Y_m^{\overline{0}}$.
3. Then $\widehat{E}(Y_m^{\overline{g}_{m-1}})=\widehat{E}(Y_m^{\overline{0}})+\frac{1}{\kappa}\sum_{j=1}^{\kappa}\delta_{j,m,g}$.

As a result, the average total treatment effect (ATTE) for an observed static treatment regime on outcome at time m is $P_j\left(\delta_{m,\overline{a}_{m-1}}\right)$.

3.4 Simulation study

In order to assess the performance of the keeSNMM approach, I implemented the following simulation study. For this purpose, 500 datasets of N subjects are generated from $M_{3,1}$,

$$Y^0_{i,m} = 0.2 + 0.3V_i + 0.4Y^0_{i,m-1} + \sqrt{5}\xi_{i,m}; \xi_{i,m} \sim N(0,1), \text{ and}$$
$$Y_{i,m} = Y^0_{i,m} + \sum_{j=1}^{m-1} A_{i,j}\{\psi_{0,j,m} + \psi_{1,j,m}A_{i,j-1} + \psi_{2,j,m}Y_{i,m}\} + \sqrt{5}\epsilon_{i,m}; \epsilon_{i,m} \sim N(0,1),$$

where $A_{i,m}$ is a binary treatment, generated from a logistic model

$$\text{logit } [Pr(A_{i,t}|A_{i,t-1}, Y_{i,t})] = 0.55 + 0.015A_{i,t-1} + 0.02Y_{i,t}.$$

and the counterfactual model is generated from a Markov model. For simplicity, the only time-varying confounder is the outcome process itself. In this model Y_1 is not affected by A_1, so that $Y_1 = Y^0_1$. Table 3–1 contains the values of the parameters for the simulation scenario. Causal parameters are estimated by both keeSNMM and gSNMM for three different sample sizes: $N = 200$, $N = 1000$ and $N = 5000$. True standard errors (SE) are estimated by the Monte Carlo simulation standard deviation. Tables 3–2 to 3–4 summarize the results of the simulation study, including average point estimates, observed standard errors and observed root mean squared root errors (RMSE). The first panel of table 3–2 summarizes the estimated parameters used in modeling the untreated counterfactual process, the second panel reports the estimated causal parameters by keeSNMM and gSNMM and the third panel shows the results for estimating the nuisance parameters. When there are no

Table 3–1: Blip functions parameters of $M_{3,1}$.

Outcome at the end of interval one
$(\psi_{0,1,2}, \psi_{1,1,2}) = (-0.4, -0.2)$
Outcome at the end of interval two
$(\psi_{0,1,3}, \psi_{1,1,3}) = (-0.2, -0.4)$
$(\psi_{0,2,3}, \psi_{1,2,3}, \psi_{2,2,3}) = (-0.1, -0.2, 0.3)$
Outcome at the end of interval three
$(\psi_{0,1,4}, \psi_{1,1,4}) = (0.1, 0.7)$
$(\psi_{0,2,4}, \psi_{1,2,4}, \psi_{2,2,4}) = (0.3, 0.5, 0.6)$
$(\psi_{0,3,4}, \psi_{1,3,4}, \psi_{2,3,4}) = (0.6, 0.3, 0.4)$
Outcome at the end of interval four
$(\psi_{0,1,5}) = (0.8)$
$(\psi_{0,2,5}, \psi_{1,2,5}, \psi_{2,2,5}) = (0.1, 0.6, 0.8)$
$(\psi_{0,3,5}, \psi_{1,3,5}, \psi_{2,3,5}) = (0.6, 0.3, 0.4)$
$(\psi_{0,4,5}, \psi_{1,4,5}, \psi_{2,4,5}) = (0.7, 0.4, 0.5)$

violations from model assumptions, that is when (i) sequential ignorability assumption holds, (ii) the blip function is correctly specified, (iii) the Markovian assumption holds, and (iv) the propensity score is correctly specified, keeSNMM performs better than gSNMM for all sample sizes, both in terms of variance and RMSE. The behavior of SEs according to sample sizes is not clear, but for all sample sizes, the SEs from keeSNMM are half the size as those from gSNMM. Figure 3–1 displays the histograms of the 500 estimates by keeSNMM, with $N = 5000$ for the causal parameters. It appears that the asymptotic normality for the causal estimators by keeSNMM holds. Figure 3–2 displays the histograms for the nuisance parameters which confirms the asymptotic normality for the nuisance parameters.

3.5 Discussion

In this chapter, by placing (i) a Markov assumption on the counterfactual process, and (ii) assuming the independence of the average total effect of the regime

$g = (\overline{a}_t, \underline{0}_{t+1})$ from the pretreatment covariates in interval $(t+1, t+2]$ given pretreatment history through time $t+1$, I express the SNMM with time-varying outcome as a state space model. Then I adapt KEE for my causal problem by relaxing its assumptions which are not compatible with our setting. The SNMM via KEE (keeSNMM) is based on modeling (a) the blip function, and (b) the Markov model for counterfactual process. The parameters of the Markov model are considered as nuisance parameters and are estimated from moment estimating equations. Through a simulation study I showed that keeSNMM is at least twice as efficient as gSNMM, i.e. to get the same efficiency from gSNMM, the sample size need to be doubled.

I discussed the nuisance parameter insensitivity of the keeSNMM which holds when the treatment effect at each specific time interval doesn't depend on past history of outcome. In Chapter 7, I will show that, in estimating the breastfeeding effect on infant's weight by keeSNMM with non-stationary causal parameters, this assumption holds and the breastfeeding effect at each interval only depends on infant's weight at baseline. When nuisance parameter insensitivity doesn't hold, the asymptotic variances of the causal parameters must be adjusted for the variation in plug in estimators of our nuisance parameters as discussed by Robins [18]. Moodie [65] developed a recursive algorithm for calculating the variances of the dr-gSNMM when the causal parameters are non-stationary. In Appendix A, I discuss finding asymptotic variances by adjusting for plug in estimator variability and by Moodie's algorithm.

The keeSNMM is computationally more efficient than 2SPR and it also provides us with graphical methofds for checking the model assumptions. In the next chapter

we introduce residual diagnostic plots for keeSNMM method. By using extensive simulation studies it is shown how useful these diagnostic methods are in (i) detecting violation from model assumptions, and (ii) evaluating the performance of SNMM via KEE and g-estimation, MSM via IPTW and standard linear regression relative to each other.

Figure 3–1: Histograms of 500 estimates in the simulation study of $M_{3,1}$ for the causal parameters.

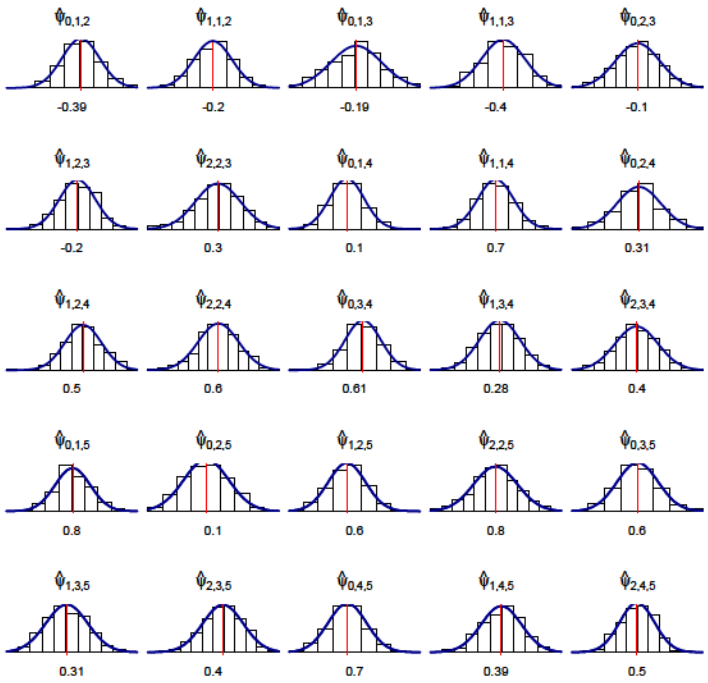


Table 3–2: Estimated causal parameters from $M_{3,1}$, N =5000. $\psi_{j,t,m}$ is the j-th causal parameter for estimating treatment effect at time interval $(t, t+1]$ on outcome at the end of interval $(m-1, m]$.

	KEE			G-estimation		
par	RMean	S.D	RMSE	Mean	S.D	RMSE
α	0.198	0.045	0.002			
$\beta 0$	0.300	0.030	0.001			
β_{01}	0.400	0.016	0.000			
σ^2	5.002	0.102	0.010			
Outcome at the end of interval $(1, 2]$						
$\psi_{0,1,2}$	-0.394	0.065	0.004	-0.396	0.103	0.011
$\psi_{1,1,2}$	-0.201	0.029	0.001	-0.200	0.048	0.002
Outcome at the end of interval $(2, 3]$						
$\psi_{0,1,3}$	-0.193	0.098	0.010	-0.200	0.169	0.029
$\psi_{1,1,3}$	-0.400	0.030	0.001	-0.398	0.047	0.002
$\psi_{0,2,3}$	-0.099	0.102	0.010	-0.104	0.177	0.031
$\psi_{1,2,3}$	-0.204	0.151	0.023	-0.199	0.215	0.046
$\psi_{2,2,3}$	0.299	0.019	0.000	0.298	0.032	0.001
Outcome at the end of interval $(3, 4]$						
$\psi_{0,1,4}$	0.097	0.119	0.014	0.093	0.165	0.027
$\psi_{1,1,4}$	0.700	0.027	0.001	0.701	0.045	0.002
$\psi_{0,2,4}$	0.310	0.134	0.018	0.310	0.217	0.047
$\psi_{1,2,4}$	0.504	0.168	0.028	0.506	0.207	0.043
$\psi_{2,2,4}$	0.600	0.020	0.000	0.599	0.032	0.001
$\psi_{0,3,4}$	0.608	0.123	0.015	0.608	0.156	0.024
$\psi_{1,3,4}$	0.282	0.170	0.029	0.281	0.198	0.040
$\psi_{2,3,4}$	0.399	0.020	0.000	0.400	0.029	0.001
Outcome at the end of interval $(4, 5]$						
$\psi_{0,1,5}$	0.801	0.027	0.001	0.802	0.048	0.002
$\psi_{0,2,5}$	0.101	0.155	0.024	0.099	0.226	0.051
$\psi_{1,2,5}$	0.597	0.128	0.016	0.604	0.223	0.050
$\psi_{2,2,5}$	0.800	0.020	0.000	0.801	0.034	0.001
$\psi_{0,3,5}$	0.602	0.125	0.016	0.601	0.213	0.045
$\psi_{1,3,5}$	0.307	0.176	0.031	0.305	0.210	0.044
$\psi_{2,3,5}$	0.399	0.019	0.000	0.399	0.029	0.001
$\psi_{0,4,5}$	0.700	0.131	0.017	0.697	0.174	0.030
$\psi_{1,4,5}$	0.395	0.169	0.029	0.401	0.208	0.043
$\psi_{2,4,5}$	0.500	0.016	0.000	0.499	0.024	0.001

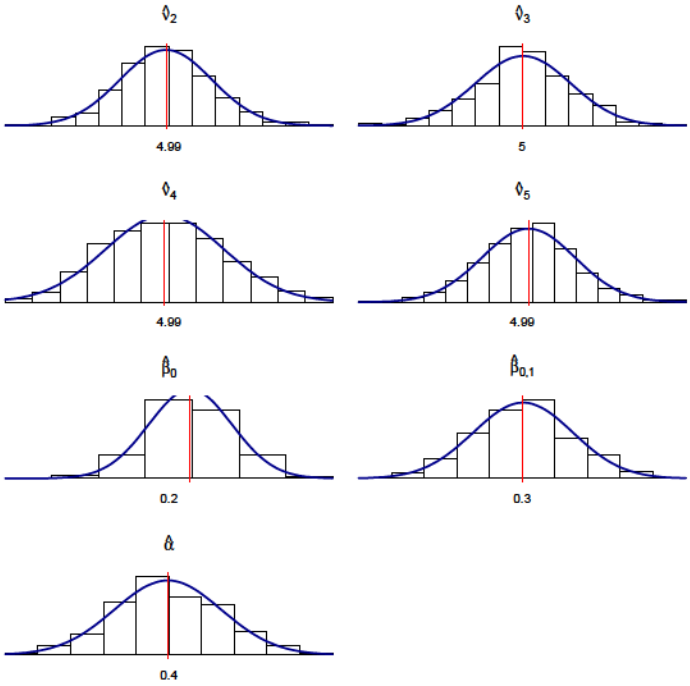
Table 3–3: Estimated causal parameters from $M_{3,1}$, for N=1000. $\psi_{j,t,m}$ is the j-th causal parameter for estimating treatment effect at time interval $(i_t, i_{t+1}]$ on outcome at the end of interval $(i_{m-1}, i_m]$.

	KEE			G-estimation		
par	Mean	S.D	RMSE	Mean	S.D	RMSE
α	0.206	0.091	0.008			
$\beta 0$	0.295	0.063	0.004			
β_{01}	0.399	0.040	0.002			
σ^2	4.967	0.235	0.056			
Outcome at the end of interval $(1, 2]$						
$\psi_{0,1,2}$	-0.398	0.143	0.020	-0.398	0.212	0.045
$\psi_{1,1,2}$	-0.198	0.069	0.005	-0.202	0.106	0.011
Outcome at the end of interval $(2, 3]$						
$\psi_{0,1,3}$	-0.203	0.219	0.048	-0.210	0.384	0.148
$\psi_{1,1,3}$	-0.397	0.064	0.004	-0.396	0.103	0.011
$\psi_{0,2,3}$	-0.077	0.214	0.046	-0.088	0.373	0.139
$\psi_{1,2,3}$	-0.217	0.338	0.115	-0.209	0.470	0.221
$\psi_{2,2,3}$	0.300	0.044	0.002	0.301	0.073	0.005
Outcome at the end of interval $(3, 4]$						
$\psi_{0,1,4}$	0.099	0.272	0.074	0.089	0.366	0.134
$\psi_{1,1,4}$	0.702	0.062	0.004	0.704	0.100	0.010
$\psi_{0,2,4}$	0.299	0.287	0.082	0.269	0.472	0.224
$\psi_{1,2,4}$	0.490	0.376	0.141	0.500	0.462	0.213
$\psi_{2,2,4}$	0.600	0.042	0.002	0.598	0.074	0.005
$\psi_{0,3,4}$	0.614	0.301	0.091	0.588	0.401	0.161
$\psi_{1,3,4}$	0.295	0.391	0.153	0.327	0.481	0.232
$\psi_{2,3,4}$	0.400	0.043	0.002	0.399	0.069	0.005
Outcome at the end of interval $(4, 5]$						
$\psi_{0,1,5}$	0.801	0.065	0.004	0.802	0.115	0.013
$\psi_{0,2,5}$	0.101	0.326	0.106	0.086	0.466	0.217
$\psi_{1,2,5}$	0.597	0.277	0.077	0.587	0.485	0.235
$\psi_{2,2,5}$	0.801	0.045	0.002	0.801	0.075	0.006
$\psi_{0,3,5}$	0.598	0.291	0.085	0.577	0.505	0.256
$\psi_{1,3,5}$	0.298	0.394	0.155	0.324	0.482	0.233
$\psi_{2,3,5}$	0.399	0.043	0.002	0.404	0.067	0.005
$\psi_{0,4,5}$	0.709	0.283	0.080	0.712	0.385	0.148
$\psi_{1,4,5}$	0.413	0.407	0.166	0.413	0.518	0.268
$\psi_{2,4,5}$	0.500	0.038	0.001	0.499	0.056	0.003

Table 3–4: Estimated causal parameters from $M_{3,1}$, for N=500. $\psi_{j,t,m}$ is the j-th causal parameter for estimating treatment effect at time interval $(t, t+1]$ on outcome at the end of interval $(m-1, m]$.

	KEE			G-estimation		
par	Mean	S.D	RMSE	Mean	S.D	RMSE
α	0.185	0.147	0.022			
$\beta 0$	0.308	0.096	0.009			
β_{01}	0.398	0.054	0.003			
σ^2	4.933	0.324	0.109			
Outcome at the end of interval $(1, 2]$						
$\psi_{0,1,2}$	-0.384	0.207	0.043	-0.387	0.298	0.089
$\psi_{1,1,2}$	-0.200	0.094	0.009	-0.196	0.152	0.023
Outcome at the end of interval $(2, 3]$						
$\psi_{0,1,3}$	-0.190	0.342	0.117	-0.215	0.551	0.304
$\psi_{1,1,3}$	-0.404	0.094	0.009	-0.395	0.155	0.024
$\psi_{0,2,3}$	-0.094	0.314	0.099	-0.100	0.527	0.278
$\psi_{1,2,3}$	-0.204	0.511	0.261	-0.186	0.669	0.448
$\psi_{2,2,3}$	0.303	0.062	0.004	0.297	0.102	0.010
Outcome at the end of interval $(3, 4]$						
$\psi_{0,1,4}$	0.095	0.388	0.151	0.057	0.545	0.299
$\psi_{1,1,4}$	0.701	0.084	0.007	0.701	0.151	0.023
$\psi_{0,2,4}$	0.329	0.410	0.169	0.287	0.705	0.497
$\psi_{1,2,4}$	0.480	0.529	0.280	0.516	0.681	0.464
$\psi_{2,2,4}$	0.602	0.060	0.004	0.600	0.110	0.012
$\psi_{0,3,4}$	0.631	0.406	0.166	0.611	0.532	0.283
$\psi_{1,3,4}$	0.286	0.573	0.329	0.321	0.708	0.502
$\psi_{2,3,4}$	0.396	0.063	0.004	0.398	0.092	0.008
Outcome at the end of interval $(4, 5]$						
$\psi_{0,1,5}$	0.798	0.090	0.008	0.804	0.164	0.027
$\psi_{0,2,5}$	0.109	0.471	0.222	0.105	0.688	0.473
$\psi_{1,2,5}$	0.595	0.398	0.158	0.611	0.703	0.494
$\psi_{2,2,5}$	0.800	0.069	0.005	0.798	0.113	0.013
$\psi_{0,3,5}$	0.637	0.422	0.179	0.643	0.700	0.492
$\psi_{1,3,5}$	0.264	0.556	0.310	0.261	0.677	0.460
$\psi_{2,3,5}$	0.392	0.061	0.004	0.393	0.099	0.010
$\psi_{0,4,5}$	0.708	0.386	0.149	0.730	0.539	0.291
$\psi_{1,4,5}$	0.397	0.553	0.306	0.401	0.679	0.461
$\psi_{2,4,5}$	0.504	0.050	0.003	0.496	0.074	0.005

Figure 3–2: Histograms of 500 estimates in the simulation study of $M_{3,1}$ for the nuisance parameters.



CHAPTER 4
Graphical model checking methods for keeSNMM

4.1 Introduction

After fitting any model, it is always important to check whether the model assumptions are reasonable before making statistical inference. Potential violations can make inferential procedures unreliable and can result in false conclusions. The keeSNMM method relies on placing restrictions on (a) the blip function, and (b) the counterfactual when treatment is withheld. So deriving inference from the keeSNMM requires satisfaction of these assumptions and additional model checking plots are needed to be sure our inference is reliable. Henderson et al. [10] and Rich et al. [1] developed the first model diagnostic methods in the field of causal inference.

In the first part of the chapter, I show that using the state space framework and Markov assumption in the keeSNMM provides us with graphical methods for checking model assumptions. In the second part of the chapter, by linking the parameters of keeSNMM, gSNMM and MSM via IPTW with the parameters of standard linear regression via OLS, I demonstrate how various model assumptions can cause differences in the estimation results. Since each of the models employ different assumptions, the validity of the comparison procedure requires satisfaction of their model assumptions, which demonstrates the usefulness of residual diagnostic plots. In the first part of my simulation studies, I show application of these models in a simple simulation example. In the second part of the simulation, I set up models

that satisfy the sequential ignorability assumption and highlight the performance of the proposed graphical methods in detecting a potentially misspecified blip function and violations of the Markov assumption.

4.2 Model diagnostics

Even if the state space model doesn't fit our causal setting correctly, then my proposed keeSNMM approach shares the advantage of standard methods like linear regression in that potential misspecification can be checked through diagnostic plots. Using eq. 3.7, $\mu^0_{m|m} = \alpha_m \mu^0_{m-1|m-1} + \beta^T_{0,m} V + K_m(Y_m - \mu_{m|m-1})$ where $cov(Y_m - \mu_{m|m-1}, \mu^0_{m-1|m-1}) = 0$, define the residual $r_m = \mu^0_{m|m} - \alpha_m \mu^0_{m-1|t-1} - \beta^T_0 V$. Note that $r_m \propto (Y_m - \mu_{m|m-1})$ so their standardized forms are identical. As a result for diagnostic purposes it is enough to apply standardized version of r_m. The standardized version of r_m is $\overline{r}_m = \frac{r_m}{\sqrt{Var(r_m)}}$ where $Var(r_m) = K^2_m R_{m|m-1}$. In both the simulation section and the real data analysis, I will use this residual to test plausibility of the modeling assumptions.

4.3 keeSNMM, gSNMM and MSM via IPTW versus linear regression via OLS

In this section I demonstrate the inherent problem of using standard regression in the presence of a time-varying confounder using a simple example. It has been seen that gSNMM and MSM via IPTW, developed by Robins and keeSNMM, avoid this problem if their specific model assumptions are satisfied. I first consider a simple example to clarify the purpose of this chapter and discuss the formulation of the SNMM and MSM. Assume a study is conducted to measure the effect of a time-varying binary treatment on an outcome measured over time for each subject. Let the only time-varying confounder be the outcome process itself and the only baseline

covariate be outcome at baseline. A_m denotes a binary time-varying treatment that is assigned after measuring Y_m and Y_1 is the measured outcome at baseline which is not affected by A_1. For clarity, I avoid allowing for interaction of A_{m-1} with Y_{m-1} in the first model $M_{4,1}$,

$$\begin{aligned} &Y_m = \beta_0 + \beta_1 A_{m-1} + \beta_2 Y_{m-1} + \epsilon_m \text{ and} \\ &\text{logit } \left[Pr\left(A_m = 1 | \overline{A}_{m-1}, \overline{Y}_m; \eta\right)\right] = \eta_0 + \eta_1 A_{m-1} + \eta_2 Y_m, \end{aligned}$$

where ϵ_m represents an i.i.d error term. To derive the correct form of the SNMM for this model, I express the blip function in terms of the contrast of the counterfactual,

$$\begin{aligned} E\left(Y_m^{\overline{a}_{m-1}} - Y_m^{\overline{a}_{m-2},0} | H_{m-1}\right) &= \beta_1 A_{m-1}, \\ E\left(Y_m^{\overline{a}_{m-2},0} - Y_m^{\overline{a}_{m-3},0,0} | H_{m-2}\right) &= \beta_1 \beta_2 A_{m-2}, \\ &\vdots \\ \text{and } E\left(Y_m^{\overline{a}_1,\underline{0}_2} - Y_m^{\underline{0}} | H_1\right) &= \beta_1 \beta_2^{m-2} A_1. \end{aligned}$$

Since there is no interaction between baseline and confounders with treatment in the main model, I don't need to modify the treatment effect at each time interval with other pretreatment covariates. For example, the effect of treatment at time interval $(t, t+1]$ on outcome Y_m is $\beta_1 \beta_2^{m-t-1}$. As a result,

$$\begin{aligned} E\left(Y_m^{\overline{a}_{m-1}} - Y_m^{\overline{0}} | H_{m-1}\right) &= \beta_1 A_{m-1} + \beta_2 \beta_1 A_{m-2} + \beta_2^2 \beta_1 A_{m-3} + ... + \beta_2^{m-2} \beta_1 A_1 \\ &= \sum_{j=1}^{m-1} \psi_j A(m-j), \end{aligned}$$

where $A(m-j)$ is equal to A_{m-j} for $m > j$ and zero otherwise. The causal effect for time interval $(t, t+1]$ on Y_m only depends on $|m-t|$, in the other words, $\psi_j = \beta_1 \beta_2^{j-1}$. In this example blip functions are linear and parameters are shared between intervals, i.e. parameters are stationary. One common suggestion for the g-estimating equation is,

$$U(\psi;\eta) = P_n \left[\sum_{t=1}^{T-1} \{A_t - pr_t(\widehat{\eta})\} Q_t \sum_{j>t} \left\{ Y_j - \sum_{k>t-1} \psi_j A(j-k) \right\} \right].$$

where the first term of this estimating equation is:

$$\begin{aligned}
&\{A_1 - pr_1(\widehat{\eta})\} Q_1 \sum_{j>1} \left\{ Y_j - \sum_{k=1}^{j-1} \psi_j A(j-k) \right\} \\
&= \{A_1 - pr_1(\widehat{\eta})\} Q_1 \sum_{j>1} \left\{ Y_j - \sum_{k=1}^{j-1} \psi_j A(j-k) \right\} \\
&= \{A_1 - pr_1(\widehat{\eta})\} Q_1 \left\{ \sum_{j>1} Y_j - \sum_{k=1}^{T-1} \psi_j \sum_{j>1} A(j-k) \right\}.
\end{aligned}$$

Even for this very simple example choosing Q_1 can be problematic because the dimension of the linear span of all possible pretreatment covariates for A_1 can be smaller than the dimension of causal parameters in the first term. I will show in section 4.4 that this problem can influence the efficiency of gSNMM. To avoid this problem, I consider the blip function with non-stationary parameters, $\gamma_{t,m}(H_t, \psi_{t,m}) = \psi_{t,m} A_t$ where $\psi_{t,m}$ is the effect of treatment at time interval $(t, t+1]$ on outcome at time m and estimate the causal parameters separately for outcome at each time point

$\{m; m \leq T\}$, by,

$$U(\psi;\eta) = P_n \left[\sum_{t=1}^{m-1} \{A_t - pr_t(\eta)\} Q_{i,t} \left\{ Y_m - \sum_{j=1}^{m-1} \psi_{j,m} A_j \right\} \right].$$

The marginal structural model for this case, i.e when there is no interaction between treatment with other covariates, is quite similar to the SNMM with two slight differences. In MSM, there exist an intercept and the main effect of baseline covariate Y_1 which varies by time. The MSM is formulated as follows,

$$\begin{aligned} Y_m^{\bar{a}_{m-1}} &= \beta_0(1 + \beta_2 + \beta_2^2 + \ldots + \beta_2^{m-1}) + \beta_1 A_{m-1} \\ &\quad + \beta_2\beta_1 A_{m-2} + \beta_2^2\beta_1 A_{m-3} + \ldots + \beta_1\beta_2^{m-1} A_1 + \beta_1\beta_2^{m-1} Y_1 \\ Y_m^{\bar{a}_{m-1}} &= \beta_0(\frac{1 - {\beta_2}^m}{1 - \beta_2}) + \omega_m Y_1 + \sum_{j=1}^{T} \psi_j A(j-t), \end{aligned}$$

where $\omega_m = \psi_m = \beta_1\beta_2^{m-1}$. Finding the links between the parameters of the SNMM and the MSM will be useful in comparing these models to demonstrate how these causal models work. These relationships help us to understand the differences in parameter interpretation of the three methods. An important and useful criteria for identifying the role of various model assumptions in the differences between parameters estimation methods is the estimated average total treatment effect (ATTE) from each method. When a subject doesn't receive any treatment over time, the $E(Y_T^{\bar{0}}) = \beta_0 \frac{1-\beta_2^T}{1-\beta_2} + \beta_1\beta_2^{T-1} Y_1$ so the averaged total treatment effect for outcome at the end of study can be defined as $E(Y_T^{\bar{a}_{T-1}} - Y_T^{\bar{0}})$ which for $M_{4,1}$ is

$$ATTE = P_n \left[\left\{ \widehat{\beta}_0 + \widehat{\beta}_1 A_{T-1} + \widehat{\beta}_2 Y_{T-1} \right\} - \beta_0 \frac{1-\beta_2^T}{1-\beta_2} - \beta_1\beta_2^{T-1} Y_1 \right]. \qquad (4.1)$$

When $\beta_0 = 0$, the ATTE for the observed treatment regime on the outcome at the end of study based on the model $M_{4,1}$, the SNMM and the MSM are

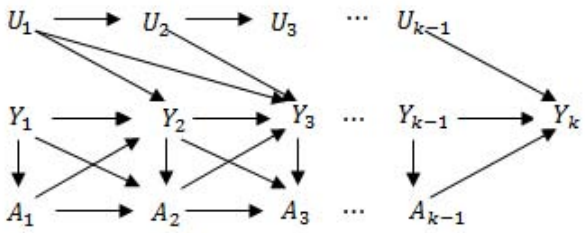
$$ATTE_{M_{4,1}} = P_n\left[\widehat{\beta}_1 A_{T-1} + \widehat{\beta}_2 Y_{T-1} - \widehat{\beta}_1\widehat{\beta}_2^{T-1} Y_1\right], \tag{4.2}$$

$$ATTE_{snmm} = P_n\left[\sum_{j=1}^{T-1}\widehat{\psi}_{j,T} A_j\right], \text{ and} \tag{4.3}$$

$$ATTE_{msm} = P_n\left[\sum_{j=1}^{T-1}\widehat{\psi}_{j,T} A_j\right]. \tag{4.4}$$

The next model, $M_{4,2}$ illustrates the potential problem associated with using stan-

Figure 4–1: Causal diagrams showing time-varying confounders affected by a time-varying unmeasured U.



dard linear regression in the presence of an unmeasured, time-varying confounder, U, which corresponds to the DAG in figure 4–1. For $M_{4,2}$, one has

$$Y_m = \beta_0 + \beta_2 Y_{m-1} + \beta_1 A_{m-1} + \beta_1^u U_{m-1} + \beta_2^u U_{m-2} + \epsilon_m,$$

$$\text{logit}\,\{(\,Pr(A_m|A_{m-1}, Y_{m-1}, L_m, Y_m\,\}) = \eta_0 + \eta_1 A_{m-1} + \eta_2 Y_{m-1} + \eta_3 Y_m, \text{ and}$$

$$U_m = \beta_0^u U_{m-1} + \nu_m,$$

The third model adds an interaction term to $M_{4,1}$,

$$Y_m = \beta_0 + \beta_1 A_{m-1} + \beta_2 Y_{m-1} + \beta_3 Y_{m-1} A_{m-1} + \epsilon_m \text{ and}$$
$$\text{logit } \left[Pr(A_m = 1 | \overline{A}_{m-1}, \overline{Y}_m)\right] = \eta_0 + \eta_1 A_{m-1} + \eta_2 Y_m,$$

and is called $M_{4,3}$. By the same approach, the SNMM is derived as

$$E(Y_m^{\overline{a}_{m-1}} - Y_t^{\overline{a}_{m-2}} | H_{m-1}) = \beta_1 A_{m-1} + \beta_3 A_{m-1} Y_{m-1},$$
$$E(Y_m^{\overline{a}_{m-2}} - Y_t^{\overline{a}_{m-3}} | H_{m-2}) = \beta_1 \beta_2 A_{m-2} + \beta_3 \beta_2 A_{m-2} Y_{m-2},$$
$$\vdots$$
$$\text{and } E(Y_m^{\overline{a}_1} - Y_m^{\overline{0}} | H_1) = \beta_1 \beta_2^{m-2} A_1 + \beta_3 \beta_2^{m-2} A_1 Y_1,$$

where

$$\begin{aligned} E\left(Y_m^{\overline{a}_{m-1}} - Y_m^0 | H_{m-1}\right) &= A_{m-1}(\beta_1 + \beta_3 Y_{m-1}) \\ &\quad + \beta_2 A_{m-2}(\beta_1 + \beta_3 Y_{m-2}) \\ &\quad + ... + \beta_2^m A_1(\beta_1 + \beta_3 Y_1) \\ &= \sum_{j=1}^{m-1} A_{m-1-j}(\psi_{0,j} + \psi_{1,j} Y_{m-1-j}). \end{aligned}$$

However, the MSM will not be the same as the SNMM because of the interaction term and is formulated as:

$$
\begin{aligned}
Y_2 &= \beta_1 A_1 + \beta_2 Y_1 + \beta_3 A_1 Y_1, \\
Y_3 &= \beta_1 A_2 + \beta_1\beta_2 A_1 + \beta_1\beta_3 A_1 A_2 \\
&\quad + \beta_2\beta_3 Y_1 A_2 + \beta_2^2 Y_1 + \beta_2\beta_3 A_1 Y_1 + \beta_3^2 A_1 A_2 Y_1, \\
Y_4 &= \beta_1 A_3 + \beta_2\beta_1 A_2 + \beta_2^2\beta_1 A_1 + \beta_2\beta_3\beta_1 A_1 A_2 \\
&\quad + \beta_1\beta_3 A_2 A_3 + \beta_3\beta_2\beta_1 A_1 A_3 + \beta_3^2\beta_1 A_1 A_2 A_3 \\
&\quad + \beta_2^3 Y_1 + \beta_2^2\beta_3 A_1 Y_1 + \beta_2^2\beta_3 Y_1 A_2 + \beta_3^2\beta_2 A_1 A_2 Y_1 \\
&\quad + \beta_3\beta_2^2 A_3 Y_1 + \beta_3^2\beta_2 A_3 A_1 Y_1 + \beta_2\beta_3^2 Y_1 A_2 A_3 + \beta_3^3 A_1 A_2 A_3 Y_1, \\
Y_5 &= \beta_2^4 Y_1 + \sum_{i=1}^{T-1} \beta_1\beta_2^{T-1-i} A_i + \sum_{i=2}^{T-1} \beta_2^2\beta_3\beta_1 A_1 A_i + \sum_{i=3}^{T-1} \beta_2\beta_3\beta_1 A_2 A_i \\
&\quad + \sum_{k\neq j\in\{3,4,2\}} \beta_1\beta_2\beta_3^2 A_1 A_k A_j + \beta_2^3\beta_3 Y_1 \sum_{i=1}^{T-1} A_i + \beta_2^2\beta_3^2 Y_1 \sum_{i\neq j} A_i A_j Y_1 \\
&\quad + \sum_{i\neq j\neq k} \beta_3^3\beta_2 A_i A_j A_k Y_1 + \beta_1\beta_3 A_3 A_4 + \beta_1\beta_3^2 A_2 A_3 A_4 + \beta_1\beta_3^3 \prod_{=1}^{4} A_k + \beta_3^4 Y_1 \prod_{=1}^{4} A_k.
\end{aligned}
$$

Both the SNMM and the MSM for $M_{4,3}$ have non-stationary parameters which need to be estimated separately at each time point.

4.4 Simulation study

4.4.1 Part one: association models

Simulation results under $M_{4,1}$

Two hundred datasets including 10,000 subjects at five time points are generated from model $M_{4,1}$ where ϵ_m is generated from normal distribution with mean zero and

variance 0.5. The sample size and the number of iterations are chosen to be large in order to minimize the Monte Carlo variation. The true values of model parameters are in table 4–1, where, $\psi_m = \omega_m = \beta_1\beta_2^{m-1}$. Firstly, I assume that $Y_m^{m-1}(\psi) =$

Table 4–1: True parameters values for the model, $M_{4,1}$.

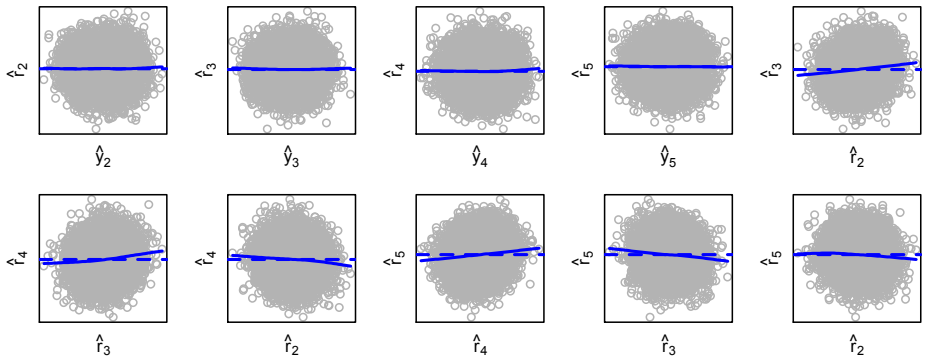
$(\beta_0, \beta_1, \beta_2)$=(0,0.5,0.5)
(η_0, η_1, η_2)=(0.5,0.15,0.1)
$(\psi_1, \psi_2, \psi_3, \psi_4)$=(0.5,0.25,0.125,0.625)
$(\omega_1, \omega_2, \omega_3, \omega_4)$=(0.5,0.25,0.125,0.0625)

$Y_m^0 + \sum_{j=1}^{m-1} \gamma_{j,m}(\overline{A}_{j-1}, \psi)$ where $\gamma_{j,m}(\overline{A}_{j-1}, \psi_{j,m}) = A_j\psi_{j,m}$ and has non-stationary parameters. I estimate the causal parameters of the SNMM for outcome at each time point separately by gSNMM and keeSNMM. The nuisance parameters are estimated separately at each time interval. The simulation results are summarized in tables 4–3 and 4–2. Table 4–3 shows a summary of the estimated causal parameters by keeSNMM, gSNMM and MSM via IPTW where $\psi_{j,m}$ is the causal effect of treatment at time interval $(j, j+1]$ on outcome at time m and the the last row summarizes the ATTE from all the methods where its true value is calculated from the main model. Table 4–2 displays the estimated nuisance parameters from keeSNMM and the estimated parameter ω for MSM. All three methods give unbiased estimation of the causal parameters. keeSNMM performs slightly better than the two others based on their root mean square errors while MSM via IPTW and gSNMM are more efficient in estimating ATTE, which is likely due to larger correlation amongst parameter estimates from keeSNMM. Residual plots, shown in figure 4–2, for keeSNMM display mild violation of the Markov assumption. Despite this modest violation, keeSNMM still performs quite well in estimating the causal parameters.

Table 4–2: Estimation of nuisance parameters from keeSNMM of the model $M_{4,1}$ and coefficients of outcome at baseline for MSM via IPTW. Observed Standard errors appear in parentheses.

$\widehat{\alpha} = \{0.500(0.009), 0.753(0.014), 0.706(0.013), 0.701(0.013)\}$
$\widehat{\sigma}^2 = \{0.125(0.002), 0.111(0.002), 0.112(0.002), 0.113(0.002)\}$
$\widehat{\beta}_0 = \{0.001(0.007), -0.002(0.009), 0.005(0.011), 0.006(0.014)\}$
$\widehat{\omega} = \{0.500(0.009), 0.252(0.011), 0.126(0.012), 0.063(0.011)\}$

Figure 4–2: Residual plots for keeSNMM on $M_{4,1}$ for 200 datasets including 10000 subjects. The causal parameters are assumed to be non-stationary. It includes plots of residuals versus fitted values at corresponding interval and residuals versus residuals at previous time intervals. Residuals have mean zero and are roughly between $(-3, 3)$.



Secondly, I fit the causal model, $Y_{i,m} = Y^{\bar{0}}_{i,m} + \sum_{j=1}^{4} \{\psi_j A_i(t-j)\}$ which has stationary parameters and use all time points to estimate ψ. The estimated causal parameters by the three methods are summarized in table 4–4. The three methods consistently estimate causal parameters while gSNMM is less efficient than the two others and keeSNMM is the most efficient one. Note that MSM via IPTW and gSNMM would likely require twice the sample size needed by keeSNMM to achieve the same level of efficiency. The residual diagnostic plots (not shown) again show slight violation of the Markov assumption, but keeSNMM still performs well. As a consequence, based on these simulation examples, keeSNMM is performing much

Table 4–3: Parameter estimation by keeSNMM and gSNMM for $M_{4,1}$ for 200 datasets including 10,000 subjects each. The causal parameters are assumed to be non-stationary and are estimated separately at each time point. This table has 5 panels. The blip function at each interval only includes the causal effect of treatment at that interval, i.e. $\psi_{j,m}$ is the causal effect of treatment at time interval $(j, j+1]$ on outcome at time m. The first panel includes the estimation of the causal parameters for outcome at the end of interval $(1, 2]$, successively, the fourth panel includes the estimation for outcome at the end of interval $(4, 5]$. Last panel shows average total treatment effect.

	keeSNMM			gSNMM			MSM via IPTW		
	Mean	SD	RMSE	Mean	SD	RMSE	Mean	SD	RMSE
Outcome at the end of interval $(1, 2]$									
$\psi_{1,2}$	0.500	0.010	0.010	0.490	0.012	0.015	0.490	0.012	0.015
Outcome at the end of interval $(2, 3]$									
$\psi_{1,3}$	0.247	0.012	0.013	0.246	0.014	0.015	0.246	0.014	0.015
$\psi_{2,3}$	0.503	0.011	0.012	0.502	0.012	0.013	0.502	0.012	0.013
Outcome at the end of interval $(2, 4]$									
$\psi_{1,4}$	0.122	0.012	0.012	0.124	0.015	0.127	0.124	0.015	0.127
$\psi_{2,4}$	0.246	0.012	0.013	0.251	0.014	0.014	0.251	0.014	0.014
$\psi_{3,4}$	0.502	0.011	0.011	0.503	0.012	0.013	0.503	0.012	0.013
Outcome at the end of interval $(4, 5]$									
$\psi_{1,5}$	0.060	0.011	0.011	0.062	0.018	0.018	0.062	0.018	0.018
$\psi_{2,5}$	0.119	0.013	0.014	0.126	0.018	0.018	0.126	0.018	0.018
$\psi_{3,5}$	0.245	0.012	0.013	0.252	0.013	0.013	0.252	0.013	0.013
$\psi_{4,5}$	0.501	0.010	0.010	0.491	0.027	0.029	0.491	0.027	0.029
Average total treatment effect (ATTE)									
$ATE = 0.623(0.0061)$	0.615	0.015	0.017	0.618	0.007	0.008	0.623	0.0006	0.005

more efficiently than gSNMM and MSM via IPTW when the causal parameters are stationary. For the rest of the simulation I consider models with non-stationary parameters.

Table 4–4: Parameter estimation by keeSNMM and gSNMM for $M_{4,1}$ for 200 dataset including 10000 subjects. The causal parameters are assumed stationary. Last row shows average total treatment effect.

	keeSNMM			gSNMM			MSM		
	Mean	SD	RMSE	Mean	SD	RMSE	Mean	SD	RMSE
ψ_4	0.058	0.010	0.011	0.041	0.094	0.096	0.063	0.011	0.011
ψ_3	0.120	0.007	0.009	0.125	0.071	0.071	0.126	0.011	0.011
ψ_2	0.245	0.006	0.008	0.251	0.043	0.043	0.252	0.011	0.011
ψ_1	0.501	0.005	0.005	0.502	0.017	0.017	0.500	0.009	0.009
Average total treatment effect (ATTE)									
$ATTE = 0.623(0.0061)$	0.628	0.008	0.009	0.600	0.027	0.018	0.61	0.006	0.016

Simulation Results Under $M_{4,2}$

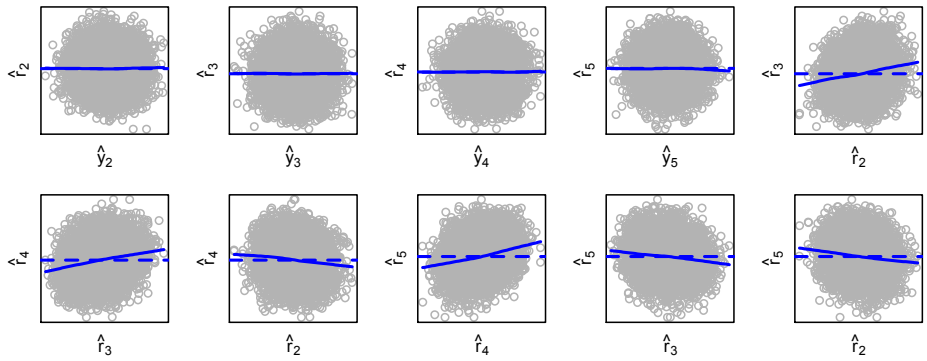
Two hundred samples including 10,000 subjects each are generated from model, $M_{4,2}$, which corresponds to DAG 4–1. True values of parameters are set to be the same as true values for model, $M_{4,2}$, table 4–1. Additional parameters $(u\beta_1, u\beta_2)$ take values $(0.4, 0.6)$. U is assumed to be unmeasured and OLS methods fail to consistently estimate the model's parameters (see table 4–5). Estimation of the causal parameters from fitting keeSNMM, gSNMM and MSM via IPTW are summarized in table 4–6. The table demonstrates that gSNMM and MSM via IPTW can consistently estimate the direct and indirect effect of the treatment on the outcome where the indirect effect is defined as the effect of the treatment through other time-varying covariates. keeSNMM can consistently estimate the direct effect of the treatment, however violation of the Markov assumption because of the unmeasured U (see figure

Table 4–5: The parameters estimation for $M_{4,2}$ for outcome at time 5 with and without adjusting for the unmeasured variable U.

	Adjusting for U		Not Adjusting for U	
	Mean	SD	Mean	SD
A_4	0.503	0.006	0.432	0.008
Y_4	0.500	0.004	0.639	0.004
$ATTE$	0.623	0.006	0.67	0.006

4–3) induces bias in estimating the indirect effect of the treatment which results in biased estimation of the ATTE.

Figure 4–3: Residual plots for keeSNMM on $M_{4,2}$ for 200 dataset including 10000 subjects. Parameters are assumed to be non- stationary. It includes plots of residuals versus fitted values at corresponding interval and residuals versus residuals at previous time intervals. Residuals have mean zero and are roughly between $(-3, 3)$.



Simulation Results Under $M_{4,3}$

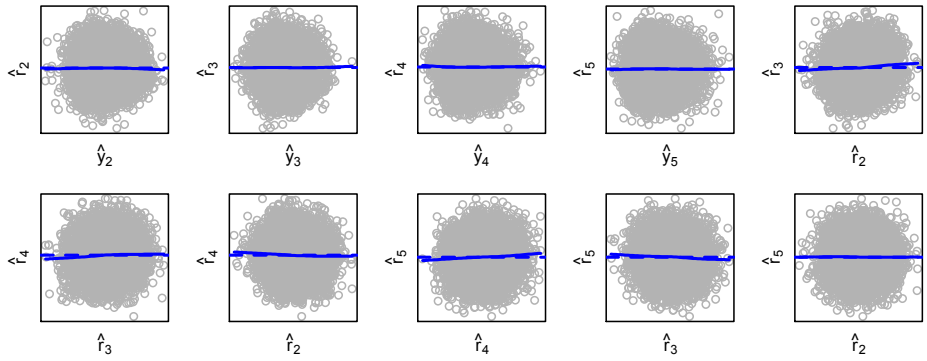
In section 4.4.1, results are reported for the standard regression models where the outcome at each time point only depends on the main effect of treatment and the outcome at the previous time point. Here, adding an interaction effect gives a more complex form of MSM. So for this more complex model, I only implement keeSNMM and gSNMM for 200 samples including 10000 subjects from $M_{4,3}$. The

Table 4–6: Parameter estimation by keeSNMM and gSNMM for $M_{4,2}$ for 200 datasets including 10000 subjects each. The causal parameters are assumed non-stationary and are estimated separately at each time point. This table has 5 panels. The blip function at each interval only includes the causal effect of treatment at that interval, i.e. $\psi_{j,m}$ is the causal effect of treatment at time interval $(j+1, j]$ on outcome at time m. The first panel includes the estimation of the causal parameters for outcome at the end of interval $(1, 2]$, successively, the fourth panel includes the estimation for outcome at the end of time interval $(4, 5]$. Last panel shows average total treatment effect.

	keeSNMM			gSNMM			MSM		
	Mean	SD	RMSE	Mean	SD	RMSE	Mean	SD	RMSE
Outcome at the end of interval $(1, 2]$									
$\psi_{1,2}$	0.50	0.02	0.02	0.50	0.03	0.03	0.50	0.02	0.02
Outcome at the end of interval $(2, 3]$									
$\psi_{1,3}$	0.22	0.03	0.04	0.25	0.03	0.03	0.29	0.02	0.05
$\psi_{2,3}$	0.46	0.03	0.05	0.50	0.03	0.03	0.45	0.02	0.06
Outcome at the end of interval $(3, 4]$									
$\psi_{1,4}$	0.10	0.03	0.04	0.12	0.04	0.04	0.14	0.03	0.04
$\psi_{2,4}$	0.16	0.04	0.09	0.25	0.04	0.04	0.23	0.03	0.04
$\psi_{3,4}$	0.46	0.03	0.05	0.50	0.03	0.03	0.50	0.03	0.03
Outcome at the end of interval $(4, 5]$									
$\psi_{1,5}$	0.04	0.03	0.04	0.06	0.06	0.06	0.06	0.03	0.03
$\psi_{2,5}$	0.04	0.04	0.09	0.13	0.05	0.05	0.11	0.04	0.04
$\psi_{3,5}$	0.15	0.03	0.11	0.26	0.03	0.03	0.25	0.03	0.03
$\psi_{4,5}$	0.45	0.03	0.06	0.42	0.08	0.11	0.51	0.03	0.04
Average total treatment effect (ATTE)									
$ATTE = 0.623(0.061)$	0.447	0.038	0.180	0.577	0.019	0.050	0.620	0.017	0.046

true values of the common parameters are set to be the same as the true values for model (see table 4–1) $M_{4,1}$ additionally setting $\beta_3 = 0.5$. By considering the blip function with non-stationary parameters, $\gamma_{j,m}(\overline{A}_{j-1}, \psi_{j,m}) = A_j(\psi_{0,j,m} + \psi_{1,j,m}Y_j)$, parameter estimates are in table 4–7 which shows that both models can consistently estimate the average total treatment effect and the direct effect of the treatment. However keeSNMM provieds biased estimation of the indirect effect of the treatment and the residual diagnostics show no violation of the Markov assumption, figure 4–4.

Figure 4–4: Residual plots for keeSNMM on $M_{4,3}$ for 200 datasets including 10000 subjects. The causal parameters are assumed to be non-stationary. It includes plots of residuals versus fitted values at corresponding interval and residuals versus residuals at previous time intervals. Residuals have mean zero and are roughly between $(-3, 3)$.



4.4.2 Part two: causal models

$M_{3,1}$ introduced in section 3.4 generates data under the sequential ignorability assumption. A dataset including 5000 subjects is generated from this model. I fit keeSNMM with a misspecified blip function which has stationary parameters, $A_{i,t}\gamma_{i,t,m}(H_{i,t}, \psi_{t,m}) = A_{i,t}(\psi_0 + \psi_1 Y_{i,t})$ and compare its residual plots with keeSNMM for the correctly specified model. I compare these results to a dataset with the same

Table 4–7: Parameter estimation by keeSNMM and gSNMM for $M_{4,3}$ for 200 datasets including 10000 subjects each. The causal parameters are assumed non-stationary and are estimated separately at each time point. This table has 5 panels. The blip function at each interval only includes the causal effect of treatment at that interval, i.e. $\psi_{k,j,m}$ is the k-th causal parameter at time interval $(j, j+1]$ on outcome at time m. The first panel includes the estimation of the causal parameters for outcome at the end of interval $(1, 2]$, successively, the fourth panel includes the estimation for outcome at the end of interval $(4, 5]$. Last panel shows average total treatment effect.

	keeSNMM			gSNMM		
	Mean	SD	RMSE	Mean	SD	RMSE
Outcome at the end of interval $(1, 2]$						
$\psi_{0,1,2}$	0.5000	0.0170	0.0003	0.5000	0.0200	0.0004
$\psi_{1,1,2}$	0.5000	0.0220	0.0005	0.5010	0.0290	0.0008
Outcome at the end of interval $(2, 3]$						
$\psi_{0,1,3}$	0.2180	0.0200	0.0014	0.2510	0.0210	0.0004
$\psi_{1,1,3}$	0.0620	0.0200	0.0357	0.2500	0.0250	0.0006
$\psi_{0,2,3}$	0.4900	0.0180	0.0004	0.5000	0.0200	0.0004
$\psi_{1,2,3}$	0.5540	0.0150	0.0031	0.4980	0.0210	0.0004
Outcome at the end of interval $(3, 4]$						
$\psi_{0,1,4}$	0.1330	0.0190	0.0004	0.1270	0.0190	0.0004
$\psi_{1,1,4}$	-0.0120	0.0200	0.0192	0.1240	0.0270	0.0007
$\psi_{0,2,4}$	0.2490	0.0210	0.0004	0.2490	0.0220	0.0005
$\psi_{1,2,4}$	0.1710	0.0150	0.0065	0.2480	0.0210	0.0004
$\psi_{0,3,4}$	0.4880	0.0190	0.0005	0.5010	0.0220	0.0005
$\psi_{1,3,4}$	0.5300	0.0130	0.0011	0.5010	0.0190	0.0004
Outcome at the end of interval $(4, 5]$						
$\psi_{0,1,5}$	0.0900	0.0180	0.0011	0.0640	0.0190	0.0004
$\psi_{1,1,5}$	-0.0250	0.0190	0.0080	0.0590	0.0260	0.0007
$\psi_{0,2,5}$	0.1550	0.0220	0.0014	0.1240	0.0230	0.0005
$\psi_{1,2,5}$	0.0690	0.0140	0.0033	0.1240	0.0180	0.0003
$\psi_{0,3,5}$	0.2660	0.0210	0.0007	0.2500	0.0220	0.0005
$\psi_{1,3,5}$	0.1660	0.0130	0.0072	0.2490	0.0180	0.0003
$\psi_{0,4,5}$	0.4760	0.0190	0.0009	0.4970	0.0220	0.0005
$\psi_{1,4,5}$	0.5340	0.0110	0.0013	0.5020	0.0160	0.0003
Average total treatment effect (ATTE)						
$ATTE = 1.141$	1.137	0.026	0.261	1.14	0.027	0.271

number of subjects from a model with the same blip function as $M_{3,1}$ but with non-Markovian counterfactual $Y^{\bar{0}}_{i,m} = \beta_0 + \beta_{01}V_i + 0.4Y^{\bar{0}}_{i,m-1} + 1.2Y^{\bar{0}}_{i,m-1} + \xi_{i,m}$ where $\xi_{i,m}$ is coming from standard normal with variance 5. Parameters are estimated using keeSNMM. Residual diagnostic plots are shown in figure 4–5. The figure illustrates that the plots perform well in detecting deviation from a misspecified blip function and the Markov assumption.

4.5 Discussion

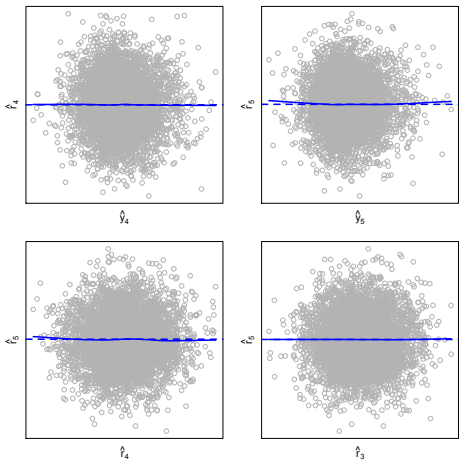
An important feature of the keeSNMM is that it provides graphical methods for checking model assumptions which is the focus of this chapter. The keeSNMM relies on placing restriction on (i) the blip function, and (ii) the counterfactual process. So methods for checking these restrictions are useful for assessing the validity of the inference. In this chapter, I adapt residual diagnostic plots used to check the model assumptions of standard methods for checking the model assumptions of keeSNMM. In the second part of the chapter, by linking the parameters of SNMM and MSM with the parameters of standard linear regression models and conducting extensive simulation studies under variety of settings, I evaluated the performance of the four methods relative to each other. I demonstrated how various model assumptions can cause differences in estimation of direct and inderect effect of the time-varying treatment. Then I showed the importance of the residual diagnostic plots for evaluation since each of the models employ different assumptions and the validity of the comparison procedure requires satisfaction of their model assumptions.

In the simulation section, I first started by generating datasets from a simple linear regression, in which the outcome is the only time-varying confounder and at

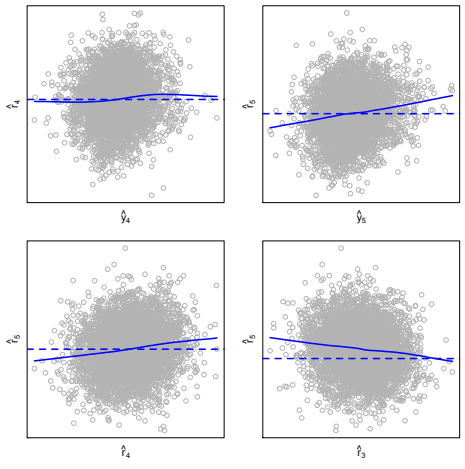
a given time point, the outcome is only affected by linear effect of the outcome and treatment at previous time point. All the methods can consistently estimate the direct effect of the treatment which goes directly to the outcome and indirect effect which is the effect of treatment through other time varying covariates on the outcome. In the second example I added an unmeasured U to the model and evaluated the performance of MSM via IPTW, gSNMM and keeSNMM in removing the effect of U in estimating the direct effect. While using OLS fails without adjusting for U, gSNMM and MSM via IPTW consistently estimate the direct and indirect effect of treatment on the outcome. Despite violation of the Markov assumption, keeSNMM can still consistently estimate the direct effect but violation from the assumption induces bias in the indirect effect estimators. In the third example, adding an interaction term gives a more complex form for the MSM, while the SNMM has still a very simple form. I avoid fitting an MSM to the more complex datasets and only apply keeSNMM and gSNMM. The result is that both methods can consistently estimate the direct effects and average total treatment effect. In the second part of our simulation studies, examples are under causal settings which illustrated the power of our residual plots in detecting model misspecification. The key point in this chapter is that, under mild violation from the Markov assumption, keeSNMM still performs well in adjusting for confounding effects in estimating the direct effect of the treatment. However, serious violation results in failure of the method. In the next chapter, I will incorporate KEE for estimating the parameters of the mean model of counterfactual in dr-gSNMM and name the method dr-keeSNMM which is

double robust if either of the Markov assumption or the propensity score is correct. I also introduce SNMM with longitudinal propensity score.

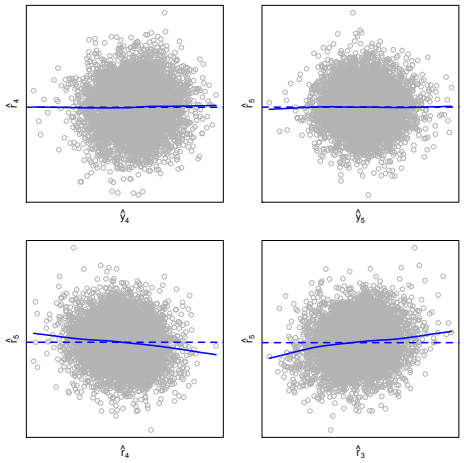
Figure 4–5: Residual diagnostic plots for $M_{3,1}$, for 50 datsets each including 5000 subjects. It has three panels each including 2 rows. Panel (a) is residual plots for keeSNMM with the correctly specified blip function. Panel (b) is residual plots for keeSNMM with the misspecified blip function. Panel (c) is residuals for keeSNMM under non-Markovian model for the counterfactual process. The first row of each panel includes plots of residuals versus fitted values at corresponding interval for intervals $(3, 4]$ and $(4, 5]$. The second row of each panel includes plots of residuals at interval $(4, 5]$ versus residuals two previous time intervals when blip function is correctly specified. For panel (a), residuals have mean zero and are roughly between $(-3, 3)$.



(a) keeSNMM of $M_{3,1}$



(b) keeSNMM on $M_{3,1}$ with the misspecified blip function



(c) keeSNMM on $M_{3,1}$, under non-Markovian model for the counterfactual process

CHAPTER 5
Doubly robust g-estimation via the Kalman filtering algorithm

5.1 Introduction

Time-varying treatment in presence of confounding variables can induce bias in deriving causal inference from observational studies and traditional parametric approaches often fail to consistently estimate causal parameters. The MSM is a powerful method in estimating causal parameters in longitudinal observational studies. However, it can only address questions such as, "How does the effect of treatment change between subjects with respect to variation in subjects' characteristics at baseline? "it cannot address questions such as "How does the effect of treatment change between subjects according to variation in subjects' characteristics over time?". As discussed in previous chapters, the SNMM can be useful for estimating the modification of treatment effect by time-varying covariates.

I have discussed two ways of estimating the causal parameters: gSNMM, which requires correct modelling of the propensity score, and keeSNMM, which requires correct modelling of the counterfactual. Both methods consistently estimate the causal parameters when their respective model assumptions are satisfied. A natural extension of the previous chapters would be to combine these two methods and develop a new method that is consistent when either of these sets of assumptions holds. Doubly robust g-estimation is a semi-parametric method, introduced by Robins [18], which combines a model for the counterfactual process with a model for

the propensity score in order to gain efficiency. Applying doubly robust g-estimation for SNMM (dr-gSNMM), requires building models for the mean of the counterfactual when the outcome is time varying. I show that, by using the Markov assumption of keeSNMM, one can model the counterfactual using keeSNMM rather than building arbitrary working models. The method is called dr-keeSNMM.

In section 5.4, I will introduce SNMM for the longitudinal propensity score which helps mitigate the growing dimension of variables that predict treatment assignment over time. This methodology is applicable in two types of studies: (i) studies which contain high dimensional vectors of pretreatment covariates, and (ii) studies whose propensity scores are known, and only those scores are kept as summaries of the covariates. One advantage of these models is that the distance of the model from the truth is easier to detect by model checking methods than models where one is adjusting for the full set of covariates.

5.2 Doubly robust g-estimation for time-varying outcome

First, I start by clarifying the application of doubly robust g-estimating equation for time-varying outcome. Assume that the parameters are stationary in our model, so a general form of dr-gSNMM can be written as

$$U\left[\psi;\eta,\zeta(\psi)\right]=\sum_{t=1}^{t=T}\left\{A_t-E(S_t(A_t)|H_t;\eta)\right\}\times \tag{5.1}$$
$$\sum_{m>t}\left\{\left(Y_m^{(t)}(\psi)-E\left[Y_m^{(t)}(\psi)|H_t;\zeta\right]\right)\right\},$$

where $Y_m^{(t)}(\psi)$ is the counterfactual outcome that would have been observed if the subject received treatment $\overline{a}_t$ through time t and received no treatment at future

time points, which is linked to the observed value of the treatment history through the blip down process. Let H_t be past history which interacts with A_t and let $S_t(A_t)$ be a well defined function of past history which interacts with A_t. Robins [18] showed that the efficient way of defining $S_t(A_t)$ is $S_t(A_t) = \{A_t - Pr(A_t|H_t;\eta)\}\, Q_t$, where Q_t is a vector of H_t with dimension equal to that of ψ is then estimated as a solution to $P_n\left[U(\psi;\eta,\zeta)\right] = 0$. Commonly, at early time intervals, there is not enough history to define Q_t, which reduces the efficiency of the estimating equation which I discussed previously in section 4.4. For the rest of the chapter, I focus on situations where the causal parameters are non-stationary and separate specification of the doubly robust g-estimating equation is required at each time point m, which can be written as

$$U\left[\psi;\eta,\zeta(\psi)\right] = \sum_{t=1}^{t=T} \left\{S_t(a_t) - E\left[S_t(a_t)|H_t;\eta\right]\right\} \times$$
$$\left\{Y_m - \sum_{j>t-1} A_j\gamma_{j,m}(H_j,\psi_{j,m}) - E\left[Y_m^{(t)}(\psi)|H_t;\zeta\right]\right\}.$$

Here ψ is estimated using a backwards substitution procedure as a solution to $P_n\left\{U(\psi;\eta,\zeta)\right\}$. As I discussed before, under correct specification of either $E\left[Y_m^{(t)}(\psi)|H_t\right]$ or the propensity score, dr-gSNMM can consistently estimate parameters. Correct specification of $E\left[Y_m^{(t)}(\psi)|H_t\right]$ requires knowing functional relation of outcome on history, which can be problematic in this method, particularly in terms of specification. However, even under a misspecified model for $E\left[Y_m^{(t)}(\psi)|H_t\right]$ and just by using a naive working model, dr-gSNMM will generally be more efficient than the gSNMM.

5.3 Doubly robust g-estimating equation via Kalman filtering algorithm

In this section, I show the advantages of using the framework of the Kalman state space model. First, it makes modeling $E\left[Y_m^{(t)}(\psi)|H_t\right]$ more straightforward than building working models for all possible values of (t, m) where $m \in (1, \ldots, T)$ and $t \in (1, \ldots, m-1)\}$. Recall the previous setting of other chapters and express the model as the following state space model,

$$\begin{aligned} Y_m^{\overline{0}} &= \alpha_m Y_{m-1}^{\overline{0}} + \beta_{0,m}^T V + \xi_m \text{ and} \\ Y_m &= Y_m^{\overline{0}} + \sum_{j=1}^{m-1} a_j \gamma_{j,m}(H_j, \psi_{j,m}) + \epsilon_m. \end{aligned} \tag{5.2}$$

dr-keeSNMM at specific time m can be formulated as

$$\begin{aligned} U\left[\psi; \eta, \zeta(\psi), \tau(\psi)\right] = \sum_{t=1}^{T} \left\{S_t(A_t) - Pr(S_t(A_t)|H_t; \eta)\right\} \times \\ \left(Y_m - \sum_{j>t} A_j \gamma_{j,m,}(H_j, \psi_{j,m}) - E\left\{Y_m^{(t)}(\psi)|H_t; \zeta\right\}\right) \end{aligned} \tag{5.3}$$

where $\tau(\psi) = \{\alpha(\psi), \beta_0(\psi), \sigma^2(\psi)\}$ is the vector of nuisance parameters used in modeling the counterfactual process, and

$$E\left[Y_m^{(t)}(\psi) - Y_m^{\overline{0}}|H_t; \zeta\right] = \sum_{j=1}^{t} A_j \gamma_{j,m}(H_j, \zeta_{j,m}).$$

By using the Kalman filtering algorithm for $m < t$, one can write

$$E(Y_m^{\overline{0}}|H_t) = \beta_{0,m}^T V + \sum_{j=t+1}^{m} \prod_{k=j+1}^{m} \alpha_k \beta_{0,j}^T V + \prod_{j=t+1}^{m} \alpha_j E(Y_{i,t}^{\overline{0}}|H_t) \tag{5.4}$$

where ζ, β_0, α and σ^2 are nuisance parameters which are estimated using KEE and, as will be discussed later, ψ is estimated in a backward procedure as a solution to

$$P_n \left[U \left\{ \psi; \eta, \zeta(\psi), \alpha(\psi), \beta_0(\psi), \sigma^2(\psi) \right\} \right] = 0.$$

dr-keeSNMM can consistently estimate the causal parameters if either the Markov assumption or the propensity score is correctly specified. It is because under sequential ignorability assumption $E\left[U\left\{\psi; \eta, \zeta(\psi), \alpha(\psi), \beta_0(\psi), \sigma^2(\psi)\right\}\right] = 0$ if either the Markov assumption or the propensity score is correctly specified.

In order to illustrate dr-keeSNMM algorithm, consider the following example. Assume that in a three-interval study, $(1,2], (2,3], (3,4]$, the observed outcomes (Y) and treatment history (A) for a specific subject is denoted by $O = (Y_1, A_1, Y_2, A_2, Y_3, A_3, Y_4)$. Assume also that treatment at time interval $(t, t+1]$ for the subject is initiated at the beginning of the interval and after observing Y_t and does not change till the end of interval. Assume that each observation is generated according to model 5.2, where the blip function for treatment at time interval $(t, t+1]$ on outcome at time m is $\gamma_{t,m}(H_t; \psi_{t,m}) = A_t(\psi_{0,t,m} + \psi_{1,t,m} Y_t)$. Let $U_{j,m}(\psi_{j,m}, \underline{\psi}_{j+1,m})$ denote the component of $U\left[\psi; \eta, \zeta(\psi), \tau(\psi)\right]$ used for specific time interval $(j, j+1]$ for the outcome at time m where $\underline{\psi}_{j+1,m} = (\psi_{j+1,m} \ldots, \psi_{m-1,m})$. The following algorithm provides a procedure for estimating causal parameters by dr-keeSNMM.

1. Set initial values for all nuisance and causal parameters.

2. Find the conditional mean and variance of the counterfactual when treatment is withheld given past and current history from equations (3.6,3.7,3.9,3.10) where

$$E\left[Y_4^{\overline{0}}\left(\psi^{\{j-1\}}\right)|H_3\right] = \alpha_4^{\{j-1\}} E\left[Y_3^{\overline{0}}\left(\psi^{j-1}\right)|H_3\right] + \beta_{0,4}^{\{j-1\}}, \tag{5.5}$$

$$\begin{aligned} E\left[Y_4^{\overline{0}}\left(\psi^{\{j-1\}}\right)|H_2\right] &= \alpha_4^{\{j-1\}}\alpha_5^{\{j-1\}} E\left[Y_2^{\overline{0}}\left(\psi^{\{j-1\}}\right)|H_2\right] + \beta_{0,4}^{\{j-1\}} \\ &\quad + \alpha_3^{\{j-1\}}\beta_{0,3}^{\{j-1\}}, \text{ and} \end{aligned} \tag{5.6}$$

$$\begin{aligned} E\left[Y_4^{\overline{0}}\left(\psi^{\{j-1\}}\right)|H_1\right] &= \alpha_4^{\{j-1\}}\alpha_3^{\{j-1\}}\alpha_2^{\{j-1\}} E\left[Y_1\left(\psi^{i-1}\right)|H_1\right] + \beta_{0,4}^{\{j-1\}} \\ &\quad + \alpha_3^{\{j-1\}}\beta_{0,3}^{\{j-1\}} + \alpha_4^{\{j-1\}}\alpha_3^{\{j-1\}}\beta_{0,2}^{\{j-1\}}. \end{aligned} \tag{5.7}$$

3. Estimate $\{\zeta_{0,k,4}, \zeta_{1,k,4} : k = (1,2,3)\}$ by regressing $Y_4^{(2)}\left(\psi^{\{j-1\}}\right) - E\left[Y_4^{\overline{0}}\left(\psi^{\{j-1\}}\right)|H_3\right]$ where

$$Y_4^{(2)}(\psi^{\{j-1\}}) = Y_4 - \psi_{0,3,4}^{\{j-1\}} A_3 - \psi_{1,3,4}^{\{j-1\}} Y_3 A_3,$$

on X_3 where $X_3 = (A_1, Y_1A_1, A_2, Y_2A_2)$,

4. Plug $\{\widehat{\zeta}_{0,k,4}, \widehat{\zeta}_{1,k,4} : k = (1,2,3)\}$ from step 3 and $E\left[Y_4^{\overline{0}}\left(\psi^{\{j-1\}}\right)|H_3\right]$ from eq. 5.5 in eq. 5.8 to update $E\left[Y_4^{(2)}\left(\psi^{\{j-1\}}\right)|H_3;\zeta\right]$,

$$E\left[Y_4^{(2)}\left(\psi^{\{j-1\}}\right)|H_3;\zeta\right] = E\left[Y_4^{\overline{0}}\left(\psi^{\{j-1\}}\right)|H_3\right] + \sum_{k=1}^{2}\left(\zeta_{0,k,4} + \zeta_{1,k,4}Y_k\right)A_k. \tag{5.8}$$

5. Set $Q_{3,4} = (1, Y_3)$ and plug in the updated value $E\left[Y_4^{(2)}\left(\psi^{\{j-1\}}\right)|H_3;\widehat{\zeta}\right]$ from step 4 in

$$\begin{aligned} &U_{3,4}(\psi_{3,4}) = (A_3 - Pr_3)\, Q_{3,4}\times \\ &\left(Y_4 - \psi_{0,3,4}A_3 - \psi_{1,3,4}Y_3A_3 - E\left[Y_4^{(2)}\left(\psi^{\{j-1\}}\right)|H_3;\widehat{\zeta}\right]\right), \end{aligned} \tag{5.9}$$

where $U_{3,4}(\psi_{3,4}, \zeta)$ is the part of the estimating equation used for estimating $\psi_{3,4} = (\psi_{0,3,4}, \psi_{1,3,4})$.

6. Update $(\psi^{\{j\}}_{0,3,4}, \psi^{\{j\}}_{1,3,4})$ as the solution to $P_n \left\{ U_{3,4} \left(\psi_{3,4} \right) \right\} = 0$.
7. Estimate $(\zeta_{0,1,4}, \zeta_{1,1,4})$ by regressing $Y_4^{(1)}(\psi^{\{j\}}) - E\left[Y_4^{\overline{0}} \left(\psi^{\{j-1\}} \right) | H_2 \right]$ on X_2 where $X_2 = (A_1, Y_1 A_1)$ and

$$Y_4^{(1)} \left(\psi^{\{j\}} \right) = Y_4 - \psi^{\{j\}}_{0,3,4} A_3 - \psi^{\{j\}}_{1,3,4} Y_3 A_3 - \psi^{\{j-1\}}_{0,2,4} A_2 + \psi^{\{j-1\}}_{1,2,4} Y_2 A_2.$$

8. Plug in the estimated parameters from 7 and $E\left[Y_4^{\overline{0}} \left(\psi^{\{j-1\}} \right) | H_2 \right]$ from eq. 5.6 to update $E(Y_4^{(1)}(\psi^{\{j\}}) | H_2; \zeta)$ according to

$$E\left[Y_4^{(1)} \left(\psi^{\{j\}} \right) | H_2; \zeta \right] = E\left[Y_4^{\overline{0}} \left(\psi^{\{j-1\}} \right) | H_2 \right] + \zeta_{0,1,4} A_1 + \zeta_{1,1,4} Y_1 A_1. \quad (5.10)$$

9. Update $(\psi^{\{j\}}_{0,2,4}, \psi^{\{j\}}_{1,2,4})$ from the solution to $P_n \left\{ U_{2,4} \left[\psi_{2,4}, \psi^{\{j\}}_{3,4}; \zeta \right] \right\} = 0$, where $Q_{2,4} = (1, Y_2)$ and

$$U_{2,4}(\psi_{2,4}; \widehat{\zeta}) = (A_2 - Pr_2)\, Q_{2,4} \times \quad (5.11)$$
$$\left(Y_4 - \psi_{0,2,4} A_2 - \psi_{1,2,4} Y_2 A_2 - \psi^{\{j\}}_{0,3,4} A_3 - \psi^{\{j\}}_{1,3,4} Y_3 A_3 - E\left[Y_4^{(1)} \left(\psi^{\{j\}} \right) | H_2 \right] \right).$$

10. Plug in $E\left[Y_4^{\overline{0}} \left(\psi^{\{j\}} \right) | H_1 \right]$ from eq. 5.7 and update $(\psi^{\{j\}}_{0,1,4}, \psi^{\{j\}}_{1,1,4})$ from the solution to $P_n \left\{ U_{1,4} \left[\psi_{1,4}, \underline{\psi}^{(j)}_{2,4} \right] \right\} = 0$, where

$$U_{1,4}(\psi_{1,4}, \underline{\psi}_{2,4}) = (A_1 - Pr_1)\, Q_{1,4} \times \quad (5.12)$$
$$\left(Y_4 - \psi_{0,1,4} A_1 - \psi_{1,1,1} Y_1 A_1 - \sum_{k=2}^{3} (\psi^{\{j\}}_{0,k,4} A_k + \psi^{\{j\}}_{1,k,4} Y_k A_k) - E\left[Y_4^0 \left(\psi^{\{j\}} \right) | H_1; \zeta \right] \right).$$

11. Estimate the causal parameters of the blip functions $\gamma_{m,3}(.)$ for $m = \{1, 2\}$ and $\gamma_{1,2}(.)$ through the same procedure as for the outcome at the end of the study.

12. Update $\alpha_m^{\{j\}}$ and $\beta_{0,m}^{\{j\}}$ from regressing $E\left[Y_m^{\overline{0}}\left(\psi^{\{j\}}\right)|H_m\right]$ on $E\left[Y_{m-1}^{\overline{0}}\left(\psi^{\{j\}}\right)|H_{t-1}\right]$ for all values of $m = \{2, 3, 4\}$.
13. Update $\sigma_m^{2\{j\}}$ according to eq. 3.14 for all values of $m = \{2, 3, 4\}$.
14. Repeat the algorithm until it converges.

5.4 Estimating treatment effects of longitudinal studies by structural nested mean model via the longitudinal propensity score

So far, I have approached the SNMM as a state space model by assuming a Markov structure for the counterfactuals when treatment is withheld and I applied the Kalman estimating equation algorithm to estimate causal parameters. I showed that it is a propensity score independent method which is straightforward to implement and provides us with graphical evidence for checking the key model assumptions. However, adjusting for differences in confounders in the blip function can be problematic for high dimensional pretreatment covariates and makes the approach subject to model misspecification that is difficult to fix.

The inverse propensity score weighting approach (Horvitz and Thompson [50]) for marginal structural models (Robins et al. [66]) is the most widely used methodology for modelling of data from observational studies. Although under correct specification of the propensity score this model consistently estimates causal parameters, it can be inefficient, since it doesn't use information from the time varying covariates except by adjusting for them in the weights. Achy-Breou et al. [67] first derived regression estimators which use longitudinal propensity scores as covariates. They express the distribution of counterfactual by replacing the covariate history in the model with the longitudinal propensity score history in G-computation according to

the G-computation formula (Robins [62]). In this section, I will introduce SNMM with longitudinal propensity score and replace the pretreatment covariates history in blip function by the longitudinal propensity score.

5.4.1 Assumptions and goals

Assume that treatment is assigned to patients at multiple time points, $t = \{1, 2, \ldots, T\}$ and let the propensity score at time t be denoted by

$$e_t = Pr(A_t = 1|H_t).$$

Assume that the propensity scores are known and that they are the only summaries of the covariates recorded. The identifiability assumptions analogous to the assumptions for single time propensity score regression are (a) the SUTVA assumption, i.e. that the outcome of patient i under treatment regime g is not affected by the treatment regime assigned to patient j, (b) the sequential ignorability assumption, i.e. that at each time point t, given the entire history on pretreatment covariates H_t, treatment A_t is randomly assigned and is independent of the counterfactual process, and (c) the positivity assumption, which states that at each time point t each patient has positive probability ($e_t > 0$) of being assigned to treatment. To estimate the treatment effect by adjusting for the effect of confounding through the longitudinal propensity score, these assumptions are essential. Achy-Brou et al. [67] showed that the sequential ignorability assumption holds if the whole history of pretreatment covariates is replaced by the history of propensity score values. For all values of $m > t$, they showed that

$$Y_m^{\bar{a}_t,0} \prod A_t | e_1, A_1 = a_1, \ldots, e_t. \tag{5.13}$$

Theorem 5.4.1. (Strong un-confoundedness given repeated measure propensity score) *Suppose that treatment at interval* $(t, t+1]$ *is randomly assigned given past history of treatment predictors. Then,*

$$A_t \perp Y_m^{\bar{a}_t,0} | e_1, A_1 = a_1, \ldots, A_{t-1} = a_{t-1}, e_t. \tag{5.14}$$

Proof: *To prove this result it suffices to show that, for* $m > t$,

A:

$$f(A_t | Y_m^{\bar{a}_t,0}, e_1, A_1 = a_1, \ldots, A_{t-1} = a_{t-1}, e_t) = e_t$$

and

B:

$$f(A_t | e_1, A_1 = a_1, \ldots, A_{t-1} = a_{t-1}, e_t) = e_t$$

For part (A), note that

$$\begin{aligned}
&f(A_t | Y_m^{\bar{a}_t,0}, e_1, A_1 = a_1, \ldots, A_{t-1} = a_{t-1}, e_t) \\
&= \int dF(A_t, H_t | Y_m^{\bar{a}_t,0}, e_1, A_1 = a_1, \ldots, A_{t-1} = a_{t-1}, e_t) \\
&= \int f(A_t | Y_m^{\bar{a}_t,0}, H_t, e_1, A_1 = a_1, \ldots, A_{t-1} = a_{t-1}, e_t) \\
&\times dF(H_t | Y_m^{\bar{a}_t,0}, e_1, A_1 = a_1, \ldots, A_{t-1} = a_{t-1}, e_t),
\end{aligned}$$

where by using sequential ignorability assumption and the fact that e_t is a function of H_t,

$$f(A_t|Y_m^{\overline{a}_t,0}, e_1, A_1 = a_1, \ldots, A_{t-1} = a_{t-1}, e_t)$$
$$= e_t \int dF(H_t|Y_m^{\overline{a}_t,0}, e_1, A_1 = a_1, \ldots, A_{t-1} = a_{t-1}, e_t) = e_t$$

The proof of B is the same as proof of A.

So, replacing the pretreatment covariates history with the propensity score history is followed by adjusting the SNMM in the following way for $m > t$,

$$E(Y_m^{\overline{a}_t} - Y_m^{\overline{a}_{t-1}}|e_1, A_1 = a_1, \ldots, A_{t-1} = a_{t-1}, e_t) = A_t\gamma_{t,m}(\overline{e}_t, \overline{a}_{t-1}, \psi_{t,m}),$$

where $\gamma_{t,k}(\overline{e}_t, \overline{a}_{t-1}, \psi_{t,k})$ is a blip function specific to time interval $(t, t+1]$ which depends on past treatment history and past and current propensity history. So in the same way as Chapter 3, I assume that $E(Y_m^{\overline{a}_t} - Y_m^0|e_1, A_1 = a_1, \ldots, A_{t-1} = a_{t-1}, e_t)$ depends on the propensity score in interval $[t, t+1)$ only through its interaction effect with a_t for all $m > t$, which implies that

$$E(Y_m^{\overline{a}_{t-1}} - Y_m^0|e_1, A_1 = a_1, \ldots, A_{t-1} = a_{t-1}, e_{t-1})$$
$$- E(Y_m^{\overline{a}_{t-1}} - Y_m^0|e_1, A_1 = a_1, \ldots, A_{t-2} = a_{t-1}, e_t) = 0$$

As a result, in a state space framework, the SNMM using the longitudinal propensity score (SNMM-LPS) model can be written as,

$$Y_k^0 = \beta_0^T V + \alpha Y_{k-1}^0 + \xi_t \text{ and} \tag{5.15}$$

$$Y_k = Y_k^0 + \sum_{t=1}^{k-1} A_t \gamma_{t,k}(e_1, A_1 = a_1, \ldots, e_{t-1}, \psi_k) + \epsilon_t, \tag{5.16}$$

where $\gamma_{t,m}(\overline{e}_t, \overline{a}_{t-1}, \psi_{t,m})$ is the blip function dependent on the longitudinal propensity score specific to interval $(t, t+1]$ for outcome at time m. Although there exist more assumptions here than in Chapter 3 and Chapter 4, reducing the dimension makes it easier to identify model misspecification using the model diagnostics discussed in Chapter 4. For a specific static regime, the joint average total treatment effect on outcome at time m is estimated by

$$ATTE = P_n \left[\sum_{t=1}^{m-1} A_t \gamma_{t,m}(\overline{e}_t, \overline{a}_{t-1}, \psi_{t,m}) \right]. \tag{5.17}$$

The SNMM-LPS approach provides a useful way to predict and compare patient outcomes under different static treatment levels by modeling only $Pr(e_{t,}|\overline{e}_{t-1}, \overline{a}_{t-1})$ for $t \in \{1, \ldots, T-1\}$. The SNMM approach discussed in Chapter 3 and 4 requires modeling $f(l_t|\bar{l}_{t-1}, \overline{y}_{t-1}, \overline{a}_{t-1})$ and $f(y_t|\bar{l}_{t-1}, \overline{y}_{t-1}, \overline{a}_{t-1})$ for $t \in \{1, \ldots, T-1\}$, which can be challenging for high dimensional data. So, the algorithm for estimating $E(Y_T^{\overline{a}_{T-1}})$ for any particular treatment regime $\overline{a}_{T-1} = \{a_1, \ldots, a_{T-1}\}$ and specific models for $Pr(e_t|\overline{e}_{t-1}, \overline{a}_{t-1})$ for all values of $t = \{1, \ldots, T\}$ is as follows.

1. Take a sample average of $\widehat{E}(Y_T^0|H_{T-1})$ over N subjects.

2. After specifying a parametric model for $Pr(e_t|\overline{e}_{t-1}, \overline{a}_{t-1})$ and estimating its parameters, the analyst recursively generates K samples where

$$\delta_{\kappa,T} = \sum_{j=1}^{T-1} a_{\kappa,j}\gamma_{\kappa,j,k}(\overline{e}_j, \overline{a}_{j-1}, \psi_{j,T}).$$

   $\delta_{\kappa,T}$ is the κ-th Mont Carlo estimate of $E(Y_T^{\overline{a}_{T-1}} - Y_T^0)$.

3. Finally, let $\widehat{E}(Y_T^{\overline{a}_{T-1}}) = \widehat{E}(Y_T^0) + P_K[\delta_T]$.

The keeSNMM-LPS can consistently estimate the causal parameters when both the propensity score and the Markov assumption are correctly specified while dr-keeSNMM-LPS is consistent even under violation of the Markov assumption when the propensity score is not misspecified. Since dr-keeSNMM-LPS will not be doubly robust in this setting and from now on I will denote it by r-keeSNMM-LPS. Achy-Breou et al. [67] introduced G-computation via the longitudinal propensity score in order to replace the modelling of pretreatment covariates, which when estimating $E\left(Y_T^{\overline{a}_{T-1}}\right)$ requires specifying models for $Pr(Y_T|e_{a_1}, a_1, \ldots, e_{a_T})$ and $Pr(e_t|e_1, a_1, \ldots, e_{t-1})$ for all values of $t = \{1, \ldots, T\}$. The SNMM-LPS approach, in contrast, requires only modeling the blip functions as a function of the longitudinal propensity score and the treatment history. This particular application of SNMM-LPS will be illustrated in Chapter 7.

5.5 Simulation study

Fifty datasets, each including 5000 subjects are generated from the three-interval example discussed in section 5.3 is simulated from the following model:

$$
\begin{aligned}
Y_1^{\overline{0}} &= 450 + \xi_1, \\
Y_2^{\overline{0}} &= 400 + 0.7Y_1^0 + \xi_2, \\
Y_3^{\overline{0}} &= 300 + 0.5Y_2^0 + \xi_3, \\
Y_4^{\overline{0}} &= 200 + 0.3Y_3^0 + \xi_4, \\
Y_2 &= Y_2^{\overline{0}} + (250 - Y_1)A_1 + \epsilon_2, \\
Y_3 &= Y_3^{\overline{0}} + (250 - Y_1)A_1 + (720 - 2Y_2)A_2 + \epsilon_3, \\
Y_4 &= Y_4^{\overline{0}} + (150 - Y_1)A_1 + (450 - 2Y_2)A_2 + (900 - 3Y_3)A_3 + \epsilon_4, \\
A_1 &\sim \text{Bernoulli}(\text{expit}\{2 - 0.002Y_1\}), \\
A_2 &\sim \text{Bernoulli}(\text{expit}\{1 - 0.001Y_2 - 0.003Y_1\}), \text{ and} \\
A_3 &\sim \text{Bernoulli}(\text{expit}\{0.2 - 0.005Y_3 - 0.004Y_2\}).
\end{aligned}
$$

In the first model, $M_{5,1}$, the counterfactuals are generated under a Markov assumption where $20 \times \epsilon_m \sim N(0,1)$ and the treatment process is generated under a logistic model. The causal parameters of the model are estimated by both keeSNMM and dr-keeSNMM under a misspecified propensity score $A_t \sim \text{Bernoulli}(\text{expit}\{\eta_0 + \eta_1 Y_t\})$. The results for the causal parameters are in table 5–1 where $(\psi_{0,t,m}, \psi_{1,t,m})$ is the causal parameters at interval $(t, t+1]$ on outcome at interval m and the last panel of the table summarizes the nuisance parameters. As expected both keeSNMM and

dr-keeSNMM consistently estimate the causal parameters of interest while keeSNMM is slightly more efficient when the propensity score is misspecified and the Markov assumption holds.

Table 5–1: Causal Parameter Estimation By keeSNMM and dr-keeSNMM From $M_{5,1}$ with Misspecified Propensity Score.

	keeSNMM			dr-keeSNMM		
parameter	Mean	S.D	RMSE	Mean	S.D	RMSE
Outcome at the end of interval $(1, 2]$						
$\psi_{0,1,2} = 250$	253.180	18.311	18.585	253.187	18.319	18.594
$\psi_{1,1,2} = -1$	-1.007	0.041	0.042	-1.007	0.041	0.042
Outcome at the end of interval $(2, 3]$						
$\psi_{0,1,3} = 250$	250.395	15.222	15.227	249.791	15.792	15.794
$\psi_{1,1,3} = -1$	-1.002	0.034	0.034	-1.0003	0.035	0.035
$\psi_{0,2,3} = 720$	720.674	6.191	6.227	720.745	6.255	6.299
$\psi_{1,2,3} = -2$	-2.001	0.011	0.011	-2.001	0.011	0.011
Outcome at the end of interval $(3, 4]$						
$\psi_{0,1,4} = 150$	146.279	11.498	12.085	145.983	11.327	12.018
$\psi_{1,1,4} = -1$	-0.992	0.025	0.027	-0.991	0.025	0.026
$\psi_{0,2,4} = 450$	450.182	5.438	5.441	450.162	5.464	5.466
$\psi_{1,2,4} = -2$	-2.0001	0.0096	0.01	-2.0001	0.0096	0.01
$\psi_{0,3,4} = 900$	899.651	2.979	3.0009	899.658	3.158	3.176
$\psi_{1,3,4} = -3$	-2.998	0.012	0.012	-2.998	0.013	0.013
Nuisance Parameters						
$\beta_0 = 400$	397.746	16.425	16.579	397.741	16.429	16.584
$\beta_{01} = 300$	301.041	18.582	18.611	301.538	19.402	19.463
$\beta_{02} = 200$	204.919	14.639	15.444	204.964	14.807	15.617
$\alpha = 0.7$	0.705	0.036	0.037	0.705	0.036	0.037
$\alpha_1 = 0.5$	0.499	0.026	0.026	0.498	0.027	0.027
$\alpha_2 = 0.3$	0.293	0.022	0.023	0.293	0.022	0.024

In the second model, $M_{5,2}$, I consider a non-Markovian model for the counterfactual where $\xi_m = 0.7\xi_{m-1} + 0.5\xi_{m-2} + 20 \times N(0, 1)$ and the treatment process is generated from the same logistic model as in $M_{5,1}$. The estimated parameters by both keeSNMM and dr-keeSNMM using a correctly specified propensity score and a misspecified propensity score $A_t \sim \text{Bernoulli}(\text{expit}\{\eta_0 + \eta_1 Y_t\})$ is summarized in table 5–2. Because the Markov assumption doesn't hold, both methods using the

misspecified propensity score fail to provide consistent estimates while dr-keeSnMM with the correctly specified propensity score performs consistently.

Table 5–2: Causal Parameter Estimation By keeSNMM and dr-keeSNMM From $M_{5,2}$

	keeSNMM			dr-keeSNMM with misspecified prop			dr-keeSNMM with correctly specified prop		
parameter	Mean	S.D	RMSE	Mean	S.D	RMSE	Mean	S.D	RMSE
Outcome at the end of interval $(1, 2]$									
$\psi_{0,1,2} = 250$	249.149	22.422	22.438	243.556	20.298	7.863	249.101	22.416	22.434
$\psi_{1,1,2} = -1$	-0.998	0.049	0.050	-0.986	0.045	0.047	-0.998	0.049	0.050
Outcome at the end of interval $(2, 3]$									
$\psi_{0,1,3} = 250$	68.473	23.061	182.986	156.419	19.0003	95.490	249.467	24.129	24.135
$\psi_{1,1,3} = -1$	-0.599	0.051	0.405	-0.794	0.042	0.210	-0.9990	0.054	0.054
$\psi_{0,2,3} = 720$	722.017	2.471	3.190	721.186	2.263	2.555	719.907	2.476	2.477
$\psi_{1,2,3} = -2$	-2.009	0.009	0.013	-2.003	0.009	0.009	-2.0004	0.0096	0.010
Outcome at the end of interval $(3, 4]$									
$\psi_{0,1,4} = 150$	-58.536	25.147	210.047	-28.327	32.925	181.341	143.606	30.647	31.307
$\psi_{1,1,4} = -1$	-0.536	0.056	0.468	-0.686	0.076	0.324	-0.986	0.069	0.070
$\psi_{0,2,4} = 450$	446.609	3.962	5.214	418.506	4.120	31.762	449.976	3.919	3.919
$\psi_{1,2,4} = -2$	-1.987	0.016	0.020	-1.853	0.018	0.148	-2.0001	0.015	0.015
$\psi_{0,3,4} = 900$	900.230	2.785	2.794	888.608	2.770	11.724	900.125	2.826	2.829
$\psi_{1,3,4} = -3$	-3.003	0.012	0.013	-2.843	0.0212	0.158	-3.0003	0.013	0.013
Nuisance parameters									
$\beta_0 = 400$	86.914	18.136	313.611	90.156	17.557	310.341	86.950	18.096	313.573
$\beta_{01} = 300$	-37.388	12.007	337.601	-78.994	11.774	379.177	-121.588	13.594	421.807
$\beta_{02} = 200$	-98.011	7.405	298.102	-54.093	8.926	254.250	-98.347	6.803	298.425
$\alpha = 0.7$	0.6958	0.0404	0.041	0.689	0.039	0.040	0.696	0.0403	0.041
$\alpha_1 = 0.5$	0.847	0.030	0.348	0.949	0.029	0.450	1.056	0.034	0.557
$\alpha_2 = 0.3$	0.988	0.025	0.689	0.927	0.032	0.627	0.993	0.023	0.709

The first panel of figure 5–1 demonstrates residuals plots for keeSNMM on simulated data from the Markovian $M_{5,1}$, with parameters estimated using the misspecified propensity score. The second panel demonstrates residuals plots for simulated data from $M_{5,2}$ with the non-Markovian counterfactual. For model, $M_{5,1}$, the residual plots do not show any deviation, confirming that dr-keeSNMM can consistently estimate the causal parameters when the propensity score is misspecified and that there is evidence that the Markov assumption holds. For model $M_{5,2}$, the residual

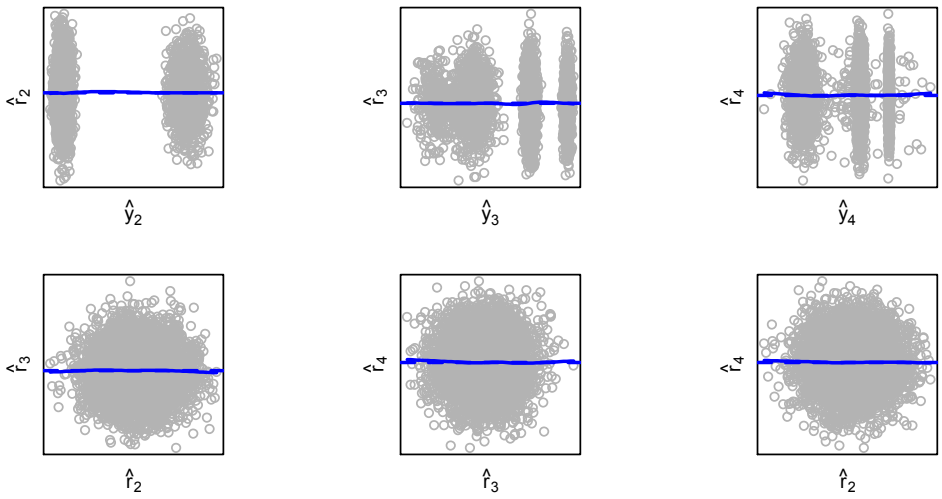
plots show clear violation of the Markov assumption while the residuals vs fitted values at the corresponding intervals do not show any meaningful pattern.

5.6 Discussion

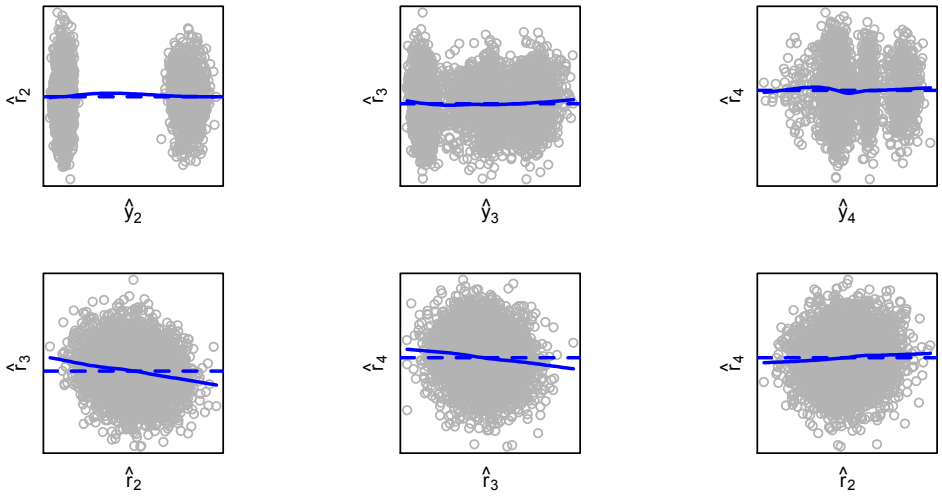
The standard dr-gSNMM method places restirictions on (i) blip function, (ii) the mean of the counterfactual, and (iii) the propensity score. The method is consistent if at least one of (ii) or (iii) is correctly specified and it is more efficient than gSNMM. Having a correct model for the mean of the counterfactual outcome process requires knowing the relationship between the outcome process and other covariates, which is not plausible. However, even when using working models, dr-gSNMM performs more efficiently than gSNMM. The problem in applying dr-gSNMM is that it requires using a working model for modeling the mean counterfactural at each time point, which can be problematic. In this chapter, I showed how using SNMM in a state space model framework and a Markov assumption can help to systematically model the mean of the counterfactual. In this method, KEE is used to estimate the parameters of the mean of the counterfactual and the additional nuisance parameters are estimated by the moment estimators discussed in Chapter 3. The method (dr-keeSNMM) is consistent if either of the propensity score or the Markov assumption is correctly specified. Similar to keeSNMM, the validity of this approach can be assessed with residual diagnostic plots. In the simulation section, I showed that when propensity score is misspecified keeSNMM is more efficient than dr-keeSNMM while under correct specification of model assumptions both methods have approximately the same efficiency.

Validity of causal inference from the SNMM depends on adjusting for the important modifiers of treatment effect with other pre-treatment covariates which makes one tend to adjust for all the covariates. However adjusting for all the covariates inflate variances of the estimated parameters and can also induce bias. As a result, dimension reduction can be beneficial in using SNMM on modification of treatment effect. In the second part of chapter 4, I developed estimators for the SNMM via the longitudinal propensity score (SNMM-LPS). Under the sequential ignorability assumption, given history of the observed treatment process and the longitudinal propensity score, I modeled blip functions on the observed history of treatment and longitudinal propensity score and estimated the parameters of the model by kee (keeSNMM-LPS). I also showed that one can estimate the parameters using r-keeSNMM-LPS which, under correct specification of the propensity score, is robust to violations of the Markov assumption.

Figure 5–1: Panel (a) includes the residual plots for drkeeSNMM on $M_{5,1}$. Panel (b) includes the residual plots on $M_{5,2}$. Each panel has two rows. First row shows residual plots versus fitted values at the corresponding interval. Second row shows residual plots vs residual at previous time interval



(a) dr-keeSNMM of $M_{5,1}$ with misspecified propensity score



(b) dr-keeSNMM of $M_{5,2}$ with non-Markovian counterfactual process

CHAPTER 6
Optimal dynamics treatment regime estimation via Kalman estimating equations

6.1 Introduction

Providing meaningfully improved health outcomes for patients by assigning the right drug at the right dose at the right time is an important research goal of clinical medicine and epidemiology. In these kinds of studies, patients are monitored by physicians over the course of their disease. A series of treatment decisions is made by using all available information on a patient up to the point that the decision is made to determine treatment level for the next interval. Estimation of the modification of treatment effects by the time-varying outcome process is essential for identifying an individual patient's optimal treatment option (Murphy [17]).

Examining various treatment regimes to come up with the optimal one requires conceptualizing a hypothetical population since information is available only under a specific treatment regime for each subject. The hypothetical population under treatment regime g belonging to class $\mathcal{G}$ is the population that would be observed if everyone received treatment regime g. And for each of these hypothetical populations the counterfactual outcome that would be observed at specific time t is denoted by Y_t^g where $g = (g_1, \ldots, g_{t-1})$. Murphy [17] introduced the class of regret modeling methods and developed estimators for optimal treatment regime estimation. Robins [18] proposed the use of dr-gSNMM with some differences from Murphy's method

([17]). In this chapter, I extend the optimal dynamic treatment regime SNMM (ODTR-SNMM) to the case of time varying outcome and use the keeSNMM and dr-keeSNMM methods to estimate the causal parameters of the model and highlight our results in a simulated context.

6.2 Optimal dynamic treatment regime for time varying outcome

I first start by the mathematical clarification of the optimal dynamic regime in the framework of causal inference (Murphy [17]) and define the optimal rules recursively. Consider a 3-interval study with the same setting as the example in chapter 5 where the set of observed measurements for each subject is denoted by $O = (Y_1, A_1, Y_2, A_2, Y_3, A_3, Y_4)$. The optimal dynamic treatment regime is defined recursively as

$$
\begin{aligned}
J_0(h_3) &= \max_{a_3} E\left[Y_4^{\overline{a}_3} | H_3 = h_3\right], \\
d_3^{opt}(h_3) &= \arg\max_{a_3} E\left[Y_4^{\overline{a}_3} | H_3\right], \\
J_1(h_2) &= \max_{a_2} E\left[J_0(H_3) | H_2 = h_2\right], \\
d_2^{opt}(h_2) &= \arg\max_{a_2} E\left[J_0(H_3) | H_2 = h_2\right], \\
J_2(h_1) &= \max_{a_1} E\left[J_1(h_2) | H_1 = h_1\right], \text{ and} \\
d_1^{opt}(h_1) &= \arg\max_{a_1} E\left[J_1(H_2) | H_1 = h_1\right],
\end{aligned}
$$

where these conditional expectations are taken with respect to the multivariate distribution of (H_t, Y_t) indexed by decision $\overline{a}_t$ and $d_t^{opt}(h_t)$ is the optimal dynamic regime

under restriction $\overline{a}_{t-1}$. The optimal rules are then,

$$\overline{d}_3^{opt} = \arg\max_{\overline{d}_3} E\left[E\left\{E\left[Y_4^{\overline{a}_3}|h_3, a_3 = d_3(h_3)\right]|h_2, a_2 = d_2(h_2)\right\}|h_1, a_1 = d_1(h_1)\right].$$

Under the assumption of no-unmeasured confounders, which always holds under the sequential ignorability assumption

$$E\left[E\left\{E\left[Y_4^{\overline{a}_3}|h_3, a_3 = d_3(h_3)\right]|h_2, a_2 = d_2(h_2)\right\}|h_1, a_1 = d_1(h_1)\right],$$

is the G-computation formula from Robins [6] and is equal to $E\left(Y_4^{\overline{a}_3}\right)$. When the multivariate distribution of (H_t, Y_t) indexed by decision $\overline{a}_t$ is unknown and only longitudinal observations are available, one can build a semi-parametric model for the optimal rule; that is, one can place restrictions on one aspect of the multivariate distribution of (H_t, Y_t), see Murphy [17]. Robin [18] used a blip function to model the optimal rule and estimated the parameters of the model by dr-gSNMM which is the focus of this chapter. So, under the sequential ignorability assumption, in the subclass of patients with history $H_t = (\overline{l}_t, \overline{y}_t, \overline{a}_{t-1})$ and who received optimal treatment from time $t+1$ onward, the difference in outcome between the treated and untreated patients at the end of interval interval $(t, t+1]$ is the effect of treatment for that time interval,

$$\gamma_{t,4}^{opt}(H_t, \psi_{t,4}) = E\left(Y_4^{\overline{a}_t, \underline{d}_{t+1}^{opt}} - Y_4^{\overline{a}_{t-1}, 0_t, \underline{d}_{t+1}^{opt}}|H_t = h_t\right). \tag{6.1}$$

Note that in eq. 6.1 $\underline{d}_{t+1}^{opt} = \left\{d_{t+1}^{opt}(h_{t+1}), \ldots, d_{4-1}^{opt}(h_{4-1})\right\}$ and $\gamma_{t,4}^{opt}(H_t, \psi_{t,4})$ is the blip function for the effect of treatment in time interval $(t, t+1]$ on outcome at time 4. It is also called blip-to-reference function which takes the reference regime to be

untreated at interval $(t, t+1]$. In contrast, the regret function (Murphy [17]) is the negative value of the blip-to-reference function when the reference is the optimal treatment at interval $(t, t+1]$,

$$\begin{aligned}\mu_{t,4}(h_t, d_t^{opt}(h_t)) &= E(Y_4^{\bar{a}_{t-1},0,\underline{d}_{t+1}^{opt}} - Y_4^{\bar{a}_{t-1},\underline{d}_t^{opt}} | H_t = h_t) \\ &= -\max_{a_t} a_t \gamma_{t,4}(h_t, \psi_{t,4}). \end{aligned} \tag{6.2}$$

The regret function is mathematically equivalent to the blip function. For the outcome at the end of study, I then defined blip functions and regret functions

$$\begin{aligned}
&E\left[Y_4^{\bar{a}_3} - Y_4^{\bar{a}_2,0} | H_3 = h_3\right] = a_3 \gamma_{3,4}^{opt}(H_3, \psi_{3,4}), \\
&E\left[Y_4^{\bar{a}_2,0} - Y_4^{\bar{a}_2,d_3^{opt}(h_2)} | H_2 = h_2\right] = -\max_{a_3} a_3 \gamma_{3,4}^{opt}(h_3, \psi_{3,4}), \\
&E\left[Y_4^{\bar{a}_2,d_3^{opt}(h_2)} - Y_T^{\bar{a}_1,0,d_3^{opt}(h_2)} | H_2 = h = 2\right] = a_2 \gamma_{2,4}^{opt}(h_2, \psi_{2,4}), \\
&E\left[Y_4^{\bar{a}_1,0,d_3^{opt}(h_2)} - Y_4^{\bar{a}_1,d_2^{opt}(h_2),d_3^{opt}(h_2)} | H_2 = h_2\right] = -\max_{a_2} a_2 \gamma_{2,4}^{opt}(h_2, \psi_{2,4}), \\
&E\left[Y_4^{a_1,d_2^{opt}(h_2),d_3^{opt}(h_3)} - Y_4^{0,d_2^{opt}(h_2),d_3^{opt}(h_3)} | H_1 = h_1\right] = \gamma_{1,4}^{opt} a_1(h_1, \psi_{1,4}), \text{ and} \\
&E\left[Y_4^{0,d_2^{opt}(h_2),d_3^{opt}(h_3)} - Y_4^{d_1^{opt}(h_1),d_2^{opt}(h_2),d_3^{opt}(h_3)} | H_1 = h_1\right] = -\max_{a_1} a_1 \gamma_{1,4}^{opt}(h_1, \psi_{1,4}).
\end{aligned}$$

With a parametric blip function, it is easy to identify the optimal regime such that, $d_t^{opt}(h_t, \psi) = \arg\max_{a_t} a_t \gamma_{t,4}^{opt}(h_t, \psi_{t,4})$ for all subjects. Equivalently, $d_t^{opt}(h_t, \psi)$ is the value where $\mu_{t,T}(h_t, a_t) = 0$. Thereby, the optimal dynamic treatment regime is a set of restricted decisions such that the first component maximizes the blip function at interval one, the second component maximizes the blip function at interval two and so fourth, such that $(T-1)$-th component maximizes the final blip function, which

is a function of the entire past history. Up to this point, I have defined blip functions for the outcome at the end of study and identified an optimal dynamic regime which maximizes the mean outcome at the end of study. Lavori [68] notes that an action which is a component of the optimal dynamic regime is not necessarily optimal for outcome at earlier time intervals. Consequently blip functions and regret functions for the effect of treatment at time interval $(t, t+1]$, on outcome at time $m < 4$ are,

$$E\left[Y_3^{\overline{a}_2} - Y_3^{a_1,0} | H_2 = h_2\right] = a_2 \gamma_{2,3}^{opt}(H_2, \psi_{2,3}), \tag{6.3}$$

$$E\left[Y_3^{a_1,0} - Y_3^{a_1,d_2^{opt}(h_2)} | H_2 = h_2\right] = -d_2^{opt}(h_2)\gamma_{2,3}^{opt}(H_2, \psi_{2,3}), \tag{6.4}$$

$$E\left[Y_3^{a_1,d_2^{opt}(h_2)} - Y_3^{0,d_2^{opt}(h_2)} | H_1 = h_1\right] = a_1 \gamma_{1,3}^{opt}(H_1, \psi_{1,3}), \tag{6.5}$$

$$E\left[Y_3^{0,d_2^{opt}(h_2)} - Y_3^{d_1^{opt}(h_1),d_2^{opt}(h_2)} | H_1 = h_1\right] = -d_1^{opt}(h_1)\gamma_{2,3}^{opt}(H_2, \psi_{2,3}), \text{ and }, \tag{6.6}$$

where $d_t^{opt}(h_t)$ for $t = \{1, 2\}$ is an optimal action restricted to $\overline{a}_{t-1}$ and is a component of the optimal dynamic regime. Y_m^{opt} is the counterfactual outcome process that would have been observed under the optimal dynamic treatment regime. By placing a Markov model on Y_m^{opt}, I can write the problem in the framework of the state space model,

$$Y_m^{opt} = \beta_{0,m} V_m + \alpha_m Y_{m-1}^{opt} + \xi_m, \tag{6.7}$$

$$Y_T = Y_T^{opt} - \sum_{k=1}^{T-1} \left\{\mu_{k,T}\left[h_k, d_k^{opt}(h_k); \psi_{k,T}\right] - a_k \gamma_{k,T}(h_k, \psi_{k,T})\right\} + \epsilon_T, \text{ and} \tag{6.8}$$

$$Y_m = Y_m^{opt} - \sum_{k=1}^{t-1} \left\{d_k^{opt}(h_k)\gamma_{k,T}(h_k, \psi_{k,m}) - a_k \gamma_{k,m}(h_k, \psi_{k,m})\right\} + \epsilon_m, \tag{6.9}$$

where ξ_m and ϵ_m are independent and homoscedastic error terms. So,

$$E\left[Y_T^m(\psi)|H_m\right] = E\left[Y_T^{opt}|H_m\right] - \sum_{k=1}^{m}\left\{\mu_{k,T}\left[h_k, d_k^{opt}(h_k); \psi_{k,T}\right] - a_k\gamma_{k,T}(h_k;\psi_{k,T})\right\},$$

which removes the optimal effect of treatment from t-th interval onward and adds the effect of observed treatment at the corresponding interval.

6.3 Steps to finding optimal dynamic treatment regime by KEE

A new way for estimating the causal parameters of ODTR-SNMM is to use keeSNMM or dr-keeSNMM. Assume that the causal parameters are non-stationary. For instance, in this example I set $\gamma_{t,m}(H_t, \psi_{t,m}) = \psi_{0,t,m} + \psi_{1,t,m}Y_t$ where $m = \{1, 2, 3, 4\}$. The backward algorithm for estimating the optimal treatment regime by keeSNMM is as follows:

1. Set the initial values for all nuisance and causal parameters.
2. Find the conditional mean and variance of the counterfactual process when treatment is withheld given past and current history from equations (3.6,3.7,3.9,3.10).
3. Regress $Y_4 - \beta_{0,4}^{\{j-1\}}V - \alpha_4^{\{j-1\}}E(Y_3^{opt}|H_3)$ on X_3, where,

$$\begin{aligned} X_3 = (A_1 - I\left[\widehat{\psi}_{0,1,4}^{\{j-1\}} - \widehat{\psi}_{1,1,4}^{\{j-1\}}Y_1 > 0\right](1, Y_1), \\ A_2 - I\left[\widehat{\psi}_{0,2,4}^{\{j-1\}} - \widehat{\psi}_{1,2,4}^{\{j-1\}}Y_2 > 0\right](1, Y_2), \\ A_3 - I\left[\widehat{\psi}_{0,3,4}^{\{j-1\}} - \widehat{\psi}_{1,3,4}^{\{j-1\}}Y_3 > 0\right](1, Y_3)) \end{aligned} \tag{6.10}$$

and update $\left(\widehat{\psi}_{0,k,4}^{\{j\}}, \widehat{\psi}_{1,k,4}^{\{j\}} : k = (1, 2, 3)\right)$.

4. Regress $Y_3 - \beta_{0,3}^{\{j-1\}} - \alpha_3^{\{j-1\}} E(Y_2^{opt}|H_2)$ on X_2, where

$$X_2 = (A_1 - I\left[\widehat{\psi}_{0,1,4}^{\{j\}} - \widehat{\psi}_{1,1,4}^{\{j\}} Y_1 > 0\right](1, Y_1)$$
$$A_2 - I\left[\widehat{\psi}_{0,2,4}^{\{j\}} - \widehat{\psi}_{1,2,4}^{\{j\}} Y_2 > 0\right](1, Y_2)) \tag{6.11}$$

   and update $\left(\widehat{\psi}_{0,k,3}^{\{j\}}, \widehat{\psi}_{1,k,j}^{\{j\}} : k = (1,2)\right)$.

5. Regress $Y_2 - \beta_{0,2}^{\{j-1\}} - \alpha_2^{\{j-1\}} E(Y_2^{opt}|H_2))$ on X_1, where

$$X_1 = (A_1 - I\left[\widehat{\psi}_{0,1,4}^{\{j\}} - \widehat{\psi}_{1,1,4}^{\{j\}} Y_1 > 0\right](1, Y_1)) \tag{6.12}$$

   and update $\left(\widehat{\psi}_{0,1,2}^{\{j\}}, \widehat{\psi}_{1,1,2}^{\{j\}}\right)$.

6. Update $\alpha_m^{\{j\}}$ and $\beta_{0,m}^{\{j\}}$ by regressing $E\left[Y_m^{opt}(\psi^{\{j\}})|H_m\right]$ on $E\left[Y_{m-1}^{opt}(\psi^{\{j\}})|H_{m-1}\right]$ for all values of $m = \{2, 3, 4\}$.

7. Update ${\sigma^2}_m^{\{j\}}$ from eq. 3.14 for all values of $m = \{2, 3, 4\}$.

8. Repeat the algorithm until it converges.

6.4 Steps to findings optimal dynamic treatment regime by dr-keeSNMM

In the following algorithm, I show how to apply the dr-keeSNMM algorithm to estimate the causal parameters of ODTR-SNMM:

1. Set initial values for all nuisance and causal parameters.

2. Find the conditional mean and variance of the counterfactual process when treatment withheld given past and current history from equations (3.6,3.7,3.9,3.10),

$$E\left[Y_4^{opt}(\psi^{\{j-1\}})|H_3\right] = \alpha_4^{\{j-1\}} E\left[Y_3^{opt}(\psi^{j-1})|H_3\right] + \beta_{0,4}^{\{j-1\}}, \tag{6.13}$$

$$\begin{aligned} E\left[Y_4^{opt}(\psi^{\{j-1\}})|H_2\right] &= \alpha_4^{\{j-1\}}\alpha_3^{\{j-1\}} E\left[Y_2^{opt}(\psi^{i-1})|H_2\right] + \beta_{0,4}^{\{j-1\}} \\ &\quad + \alpha_3^{\{j-1\}}\beta_{0,3}^{\{j-1\}}, \text{ and} \end{aligned} \tag{6.14}$$

$$\begin{aligned} E\left[Y_4^{opt}(\psi^{\{j-1\}})|H_1\right] &= \alpha_4^{\{j-1\}}\alpha_3^{\{j-1\}}\alpha_2^{\{j-1\}} E\left[Y_1^{opt}(\psi^{i-1})|H_1\right] + \beta_{0,4}^{\{j-1\}} \\ &\quad + \alpha_3^{\{j-1\}}\beta_{0,3}^{\{j-1\}} + \alpha_4^{\{j-1\}}\alpha_3^{\{j-1\}}\beta_{0,2}^{\{j-1\}}. \end{aligned} \tag{6.15}$$

3. Estimate $(\zeta_{0,k,4}, \zeta_{1,k,4}; k = \{1,2\})$ by regressing $Y_4^{(2)}\left[\psi^{\{j-1\}}\right] - E\left[Y_4^{opt}(\psi^{\{j-1\}})|H_3\right]$ on the first 4 columns of X_3 (eq. 6.10) where

$$Y_4^{(2)}(\psi^{\{j-1\}}) = Y_4 - \left(\psi_{0,3,4}^{\{j-1\}} + \psi_{1,3,4}^{\{j-1\}} Y_3\right)\left\{A_3 - I(\psi_{0,3,4}^{\{j-1\}} + \psi_{1,3,4}^{\{j-1\}} Y_3 > 0)\right\}.$$

4. Plug in $(\widehat{\zeta}_{0,k,4}, \widehat{\zeta}_{1,k,4}; K = \{1,2\})$ from step (3) and $E\left[Y_4^{opt}(\psi^{\{j-1\}})|H_3\right]$ from eq. 6.13 to update $E\left[Y_4^{(2)}(\psi^{\{j\}})|H_3\right]$ according to

$$\begin{aligned} E\left[Y_4^{(2)}(\psi^{\{j\}}|H_3;\zeta)\right] &= E\left[Y_4^{opt}(\psi^{\{j-1\}})|H_3\right] + \sum_{k=1}^{2}(\zeta_{0,k,4} + \zeta_{1,k,4}Y_k) \\ &\quad \times \left\{A_k - I(\psi_{0,k,4}^{\{j-1\}} + \psi_{1,k,4}^{\{j-1\}} Y_k > 0)\right\}. \end{aligned} \tag{6.16}$$

5. Set $Q_{3,4} = (1, Y_3)$ and plug in the updated value $E\left[Y_4^{(2)}(\psi^{\{j-1\}})|H_3;\widehat{\zeta}\right]$ from step (4) in

$$\begin{aligned} &U_{3,4}(\psi_{3,4}) = \{A_3 - pr_3(\widehat{\eta})\}\, Q_{3,4}\times \\ &\left\{Y_4 - (\psi_{0,3,4} + \psi_{1,3,4}Y_3)\left(A_3 - I\left[\psi_{0,3,4}^{\{j-1\}} + \psi_{1,3,4}^{\{j-1\}} Y_3 > 0\right]\right) - E\left[Y_4^{(2)}\left(\psi^{\{j-1\}}\right)|H_3;\widehat{\zeta}\right]\right\}. \end{aligned} \tag{6.17}$$

6. Update $\left(\psi_{0,3,4}^{\{j\}}, \psi_{1,3,4}^{\{j\}}\right)$ as the solution to $P_n\left[U_{3,4}(\psi_{3,4})\right] = 0$ in eq. 6.17.
7. Estimate $(\zeta_{0,1,4}, \zeta_{1,1,4})$ by regressing $Y_4^{(1)}(\psi_{3,4}^{\{j\}}, \psi_{2,4}^{\{j-1\}}) - E\left[Y_4^{opt}(\psi^{\{j\}})|H_2;\zeta\right]$ on the first two columns of X_3 (eq. 6.11),

$$Y_4^{(1)}(\psi_{3,4}^{\{j\}}, \psi_{2,4}^{\{j-1\}}) = Y_4 - \left\{\psi_{0,3,4}^{\{j\}} + \psi_{1,3,4}^{\{j\}} Y_3\right\}\left\{A_3 - I\left(\psi_{0,3,4}^{\{j\}} + \psi_{1,3,4}^{\{j\}} Y_3 > 0\right)\right\} - \left\{\psi_{0,2,4}^{\{j-1\}} + \psi_{1,2,4}^{\{j-1\}} Y_2\right\}\left\{A_2 - I(\psi_{0,2,4}^{\{j-1\}} + \psi_{1,2,4}^{\{j-1\}} Y_2 > 0)\right\}.$$

8. Plug in $(\widehat{\zeta}_{0,1,4}, \widehat{\zeta}_{1,1,4})$ from step (7) and $E\left[Y_4^{opt}(\psi^{\{j-1\}})|H_2\right]$ from eq. 6.14 in eq. 6.18 to update $E\left[Y_4^{(1)}(\psi^{\{j\}})|H_2;\zeta\right]$,

$$E\left[Y_4^{(1)}(\psi^{\{j\}})|H_2\right] = E\left[Y_4^{opt}(\psi^{\{j-1\}})|H_2\right] + (\zeta_{0,1,4} + \zeta_{1,1,4} Y_k) \times \left\{A_k - I(\widehat{\psi}_{0,1,4}^{\{j-1\}} + \widehat{\psi}_{1,1,4}^{\{j-1\}} Y_k > 0)\right\}. \tag{6.18}$$

9. Update $(\psi_{0,2,4}^{\{j\}}, \psi_{1,2,4}^{\{j\}})$ from $P_n\left[U_{2,4}\left(\psi_{2,4}, \psi_{3,4}^{\{j\}}\right)\right] = 0$ where and $Q_{2,4} = (1, Y_2)$ and

$$U_{2,4}(\psi_{2,4}, \psi_{3,4}^{\{j\}}) = \{A_2 - pr_2(\widehat{\eta})\}\, Q_{2,4} \times (Y_4 - \{\psi_{0,2,4} - \psi_{1,2,4} Y_2\}\left\{A_2 - I\left[\psi_{0,2,4}^{\{j-1\}} + \psi_{1,2,4}^{\{j-1\}} Y_2 > 0\right]\right\} - \left\{\psi_{0,3,4}^{\{j\}} - \psi_{1,3,4}^{\{j\}} Y_3\right\}\left\{A_3 - I\left[\psi_{0,3,4}^{\{j\}} + \psi_{1,3,4}^{\{j\}} Y_3 > 0\right]\right\} - E\left[Y_4^{(1)}\left(\psi^{\{j\}}\right)|H_2\right]. \tag{6.19}$$

10. Plug in $E\left[Y_4^{opt}\left(\psi^{\{j-1\}}\right)|H_1\right]$ from eq. 6.15 and update $(\psi_{0,1,4}^{\{j\}}, \psi_{1,1,4}^{\{j\}})$ as a solution to $P_n\left[U_{1,4}\left(\psi_{1,4}, \underline{\psi}_{2,4}^{\{j\}}\right)\right] = 0$, where

$$U_{1,4}\left(\psi_{1,4}, \underline{\psi}_{2,4}^{\{j\}}\right) = \{A_1 - pr_1(\widehat{\eta})\}\, Q_{1,4}\times$$
$$(Y_4 - \{\psi_{0,1,4} - \psi_{1,1,4}Y_2\}\left\{A_1 - I\left[\psi_{0,1,4}^{\{j-1\}} + \psi_{1,1,4}^{\{j-1\}}Y_1 > 0\right]\right\}$$
$$- \sum_{k=2}^{3}\left\{\psi_{0,k,4}^{\{j\}} - \psi_{1,k,4}^{\{j\}}Y_k\right\}\left\{A_k - I\left[\psi_{0,k,4}^{\{j\}} + \psi_{1,k,4}^{\{j\}}Y_k > 0\right]\right\} - E\left[Y_4^{opt}\left(\psi^{\{j\}}\right)|H_1\right]). \tag{6.20}$$

11. Update X_1 [eq. 6.12], X_2 [eq. 6.11] and X_3 [eq. 6.10] by $(\psi_{0,k,4}^{\{j\}}, \psi_{1,k,4}^{\{j\}})$ where $k = \{1, 2, 3\}$.
12. Estimate the causal parameters of the blip functions $\gamma_{t,3}(.)$ for $t = \{1, 2\}$ and $\gamma_{1,2}(.)$ through the same procedure as for the outcome at the end of thestudy.
13. Update $\alpha_t^{\{j\}}$ and $\beta_{0,t}^{\{j\}}$ by regressing $E\left[Y_m^{opt}(\psi^{\{j\}})|H_m\right]$ on $E\left[Y_{m-1}^{opt}(\psi^{\{j\}})|H_{m-1}\right]$ for all values of $m = \{2, 3, 4\}$.
14. Update $\sigma_m^{2\{j\}}$ from eq. 3.14 for all values of $m = \{2, 3, 4\}$.
15. Repeat the algorithm until it converges.

6.5 Simulation study

50 datasets including 5000 subjects each are simulated for the three interval example, discussed in previous sections:

$$
\begin{aligned}
Y_t^{opt} &= 400 + 0.7Y_{t-1}^{opt} + 30\xi_t, \xi_t \sim N(0,1), \\
Y_4 &= Y_4^{opt} + (A_1 - I\left[150 - Y_1 > 0\right])(150 - Y_1) \\
&\quad + (A_2 - I\left[450 - 2Y_2 > 0\right])(450 - 2Y_2) \\
&\quad + (A_3 - I\left[900 - 3Y_3 > 0\right])(900 - 3Y_3) + 30\epsilon_4, \epsilon_4 \sim N(0,1), \\
Y_3 &= Y_3^{opt} + (A_1 - I\left[150 - Y_1 > 0\right])(250 - Y_1), \\
&\quad + (A_2 - I\left[450 - 2Y_2 > 0\right])(720 - 2Y_2) + 30\epsilon_3, \epsilon_3 \sim N(0,1), \text{ and} \\
Y_2 &= Y_2^{opt} + (A_1 - I\left[150 - Y_1 > 0\right])(250 - Y_1) + 30\epsilon_2, \epsilon_2 \sim N(0,1).
\end{aligned}
$$

The structure of this simulation study is similar to simulation study by Moodie et al. [19]. I will refer to this model as model $M_{6,1}$. The estimation of causal parameters by both keeSNMM and dr-keeSNMM are summarized in table 6–1. Both models consistently estimate parameters while dr-keeSNMM is less efficient when the Markov assumption holds.

6.6 Discussion

In clinical research, the patients are monitored over time and treatment is tailored based on accruing observations on the patient for the purpose of optimizing long-term effectiveness of the program. By considering the potential effect of the current treatment on the reward at later time, the optimal treatment regime is a

Table 6–1: Estimation of causal parameters of model, $M_{6,1}$ based on 50 datasets including 5000 subjects. The causal parameters are estimated by ODTR-dr-keeSNMM and ODTR-keeSNMM.

	ODTR-keeSNMM			ODTR-dr-keeSNMM		
parameter	Mean	S.D	RMSE	Mean	S.D	RMSE
Outcome at the end of interval $(1, 2]$						
$\psi_{0,1,2} = 250$	249.474	13.564	13.574	251.755	17.866	17.952
$\psi_{1,1,2} = -1$	-0.9997	0.031	0.031	-1.004	0.040	0.040
Outcome at the end of interval $(2, 3]$						
$\psi_{0,1,3} = 250$	248.153	14.392	14.510	251.023	20.924	20.949
$\psi_{1,1,3} = -1$	-0.998	0.032	0.032	-1.003	0.046	0.046
$\psi_{0,2,3} = 720$	732.215	11.507	16.781	719.292	11.505	11.526
$\psi_{1,2,3} = -2$	-2.019	0.0180	0.026	-1.999	0.018	0.018
Outcome at the end of interval $(3, 4]$						
$\psi_{0,1,4} = 150$	145.921	14.518	15.080	155.174	57.379	57.612
$\psi_{1,1,4} = -1$	-0.991	0.032	0.034	-1.010	0.128	0.128
$\psi_{0,2,4} = 450$	455.574	9.926	11.384	446.663	10.746	11.252
$\psi_{1,2,4} = -2$	-2.007	0.016	0.018	-1.994	0.018	0.019
$\psi_{0,3,4} = 900$	900.581	2.897	2.955	900.817	3.082	3.188
$\psi_{1,3,4} = -3$	-3.0002	0.004	0.004	-3.001	0.004	0.004

regime which maximizes the reward at the end of study. In ODTR-SNMM, it is common to only consider outcome at the end of study. In this chapter, by utility of the framework of state space model, I extended the optimal dynamic treatment regime SNMM (ODTR-SNMM) for time-varying outcome. The advantage of using ODTR-dr-keeSNMM for finding the optimal treatment regime beside having diagnostic plots and a systematic method of modeling the counterfactual is that modeling the blip function for outcome at other time points provides also the immediate effect of treatment additional to its long term effect.

CHAPTER 7
Application

7.1 Introduction

The Promotion of Breastfeeding Intervention Trial (PROBIT) was a cluster randomized trial conducted in hospitals in Belarus from June 1996 to December 1997 with a one-year follow up. A total of 17,046 mother-infant pairs in 31 hospitals were studied and all of the infants were initially breastfed. Intervention sites were randomly assigned. Sixteen hospitals received an experimental intervention based on the Baby-Friendly Hospital Initiative of the World Health Organization and United Nations Children's Fund which encourage prolonged exclusive breastfeeding. Fifteen hospitals received a control intervention based on usual infant feeding practices and policies. The healthy infants were followed up at 1, 2, 3, 6, 9 and 12 months. The dataset includes both maternal and infant characteristics: the randomization arm, geographic region and rurality, mother's age, education, history of atopic pregnancy, number of previous children, previous history of breastfeeding, smoking history and current smoking status, current alcohol consumption, infant sex, gestational age, infant weight at start of interval, hospitalizations, rashes and illness in previous interval other than gastrointestinal and respiratory.

Observational studies have suggested that prolonged and exclusive breastfeeding might reduce infant's growth while the intent-to-treat (ITT) analysis showed a

statistically significant, but slight positive effect of breastfeeding through 9 months (Kramer et al. [69]). Some women in the intervention group stopped breastfeeding during the first month, while some women in the control group continued to breastfeed for many months after randomization. The decision to continue to breastfeed correlates with several maternal characteristics, suggesting that observational results on effect breastfeeding on infant growth may be confounded (Kramer et al. [31, 69, 70]).

Moodie et al. [47] analyzed the two randomized groups as if an observational study were conducted and used optimal dynamic treatment regimes to find the optimal duration of exclusive breastfeeding. As I discussed before, ODTR-SNMM requires modeling both the blip functions and the counterfactual outcome. Having tools to help us to fix or detect misspecification of these two models can be useful in the area. Rich et al.[1] reanalyzed the PROBIT data and introduced model diagnostic tools for checking the model assumptions.

Two challenges arise in applying SNMM to adjust for modifiers of the treatment effect with other pretreatment covariates: (a) building blip functions that incorporate pretreatment covariate history, and (b) testing model assumptions. I reanalyze the PROBIT data as an observational study and use three different approaches in order to estimate the effect of breastfeeding. First, I apply keeSNMM and dr-keeSNMM to adjust for modifiers of the treatment effect with other pretreatment covariates to estimate the total causal effect of breastfeeding. Next I employ keeSNMM-ODTR and drkeeSNMM-ODTR to find the optimal duration of exclusive breastfeeding. Finally, I use keeSNMM-LPS and r-keeSNMM-LPS to adjust for confounding through

the longitudinal propensity score. The ultimate goal of this chapter is to use the PROBIT dataset to highlight the applications of the methods introduced in this thesis for estimating the causal effect of treatment in a longitudinal study design.

7.2 Data structure

I begin by introducing some standard notation. I consider four intervals in our analysis, $(0,3],(3,6],(6,9]$ and $(9,12]$ months. Let A_m denotes breastfeeding status at time interval $(m-3,m]$ for a specific subject which takes the value zero when breastfeeding is stopped and the value one when breastfeeding is continued. A_m is measured at the end of interval $(m-3,m]$ and only depends on whether the mother is breastfeeding at that time or not. If the mother stops breastfeeding in the middle of the interval, $A_m = 0$ for the entire interval. Breastfeeding is not re-initiated after it has been stopped. L_m is a vector of both fixed and time-varying covariates including weight measured at the end of time interval $(m-3,m]$ for $m = \{3,6,9,12\}$. The observation vector for each subject is

$$O_i = (L_{i,0}, A_{i,3}, L_{i,3}, A_{i,6}, L_{i,6}, A_{i,9}, L_{i,9}, A_{i,12}, L_{i,12}).$$

7.3 Longitudinal propensity score model

The propensity score is estimated by using logistic models with large numbers of covariates for the probability of continuing breastfeeding based on hospital, maternal and infant characteristics: randomization arm, geographic region and rurality, mother's age, education, history of atopic pregnancy, number of previous children,

history of breastfeeding, smoking history and current smoking, current alcohol consumption, infant sex, gestational age, infant weight at start of interval, hospitalizations, rashes and illness in the previous interval other than gastrointestinal and respiratory.

7.4 drkeeSNMM and keeSNMM on modifiers of breastfeeding effect with other covariates

I started by fitting a cumulative treatment model for the effect of all fixed and time varying confounders. In a cumulative SNMM, $\gamma_{t,m} = A_t(\psi_{0,m} + \psi_{1,m}^T L_t)$ is the blip function, where its parameters are stationary and determine the effect of treatment during time interval $(t-3, t]$ on the outcome at time m. It is the simplest form of blip function, but it does not perform well according to residual diagnostic plots (not shown) which demonestrate misspecified blip functions and Markov assumption. I also tried $\gamma_{t,m} = A_t(\psi_{0,m} + \psi_{1,t,m}^T L_t)$, but it didn't perform well either. At the end, the blip functions with non-stationary parameters performed the best of all blip functions considered. In the model with non-stationary causal parameters, not only the parameters in blip function but also the subset of treatment effect modifiers were allowed to vary between intervals. The model diagnostics using the non-stationary form of the blip function indicated a much more reasonable fit.

Therefore, the final blip function, $\gamma_{t,m} = A_t(\psi_{0,t,m} + \psi_{1,t,m} L_t)$, models the modification of the effect of breastfeeding by other time varying confounders at interval $(t-3, t]$ on the outcome at time m, where L_t is a vector of baseline covariates and time varying confounders at previous time intervals, $t = \{3, 6, 9, 12\}$ and $m = \{3, 6, 9, 12\}$. I started with a simple model including only the intercept and infant weights at the previous interval. Examination of the residual diagnostic plots versus covariates

Table 7–1: Modifiers of treatment effect for SNMM on PROBIT dataset

Modifiers at $(0,3]$ on outcome at month {3,6,9,12}		
infant's baseline weight	gender	# previous children
mother's education	gastrointestinal infection	mother's smoking history
breastfeeding history		
Modifiers at $(3,6]$ on outcome at month {6,9,12}		
infant's baseline weight	gender	gastrointestinal infection at month 6
Modifiers at $(6,9]$ on outcome at month {9,12}		
infant's baseline weight	gender	
Modifiers at $(9,12]$ on outcome at month 12		
infant's baseline weight		

suggested adjusting for gastrointestinal infectious and gender for some of the blip functions. Modifiers of the treatment effect at interval one on outcome at month $\{3,6,9,12\}$ are the infant's weight at baseline, gender, number of previous children, mother's eduction, gastrointestinal infection within interval, mother's smoking history and breastfeeding history. Modifiers of the treatment effect at interval two on outcome at month $\{6,9,12\}$ are the infant's weight at baseline, gender, gastrointestinal infection at month 6. Modifiers of the treatment effect at interval three on outcome at month $\{9,12\}$ are, infant's weight at baseline and gender and modifiers of treatment effect at interval three on outcome at month 12 are the infant's weight at baseline, see table 7–1.

The expected counterfactual model is assumed to be a linear first order Markov model. Under the Markovian model for $Y_m^{\overline{0}}$ the causal parameters are estimated by dr-keeSNMM and keeSNMM and the SEs are estimated via the nonparametric bootstrap method with 2500 replications (Efron & Tibshirani [71], Canty & Riplay [72] and Davison & Hinkley [73]). Results are summarized in tables 7–3, 7–4, 7–5, and 7–2. The tables 7–3 and 7–2 summarize estimation of the causal parameters via drkeeSNMM and keeSNMM, respectively. From the residual plots in figures 7–1 one can clearly see violations of the Markov assumption, however plots of the residuals

versus corresponding fitted values show no serious misspecification for the blip functions. It should be noted that because of the diagnosed violation from the Markov assumption, inference from the keeSNMM model should be viewed with caution. From tables 7–3 and 7–2, it is clear that from dr-keeSNMM most of the parameters are not statistically significantly different from zero, even the infant weight at the start of the interval, or the occurrence of gastrointestinal and respiratory infections within the interval, which concurs with the result from Rich et al. [1]. However, most of these non-significant estimators are statistically significantly different from zero according to keeSNMM, so I decided to keep them in the model. Adjusting for modifiers of the breastfeeding effect in blip functions make the comparison between parameter estimates from keeSNMM and dr-keeSNMM difficult. Another way to compare the estimators is to use the average total treatment effect (ATTE) and the average treatment effect within interval (ATEWI), tables 7–4 and 7–5. In these two tables, $ATTE_{t,m}$ is the average total breastfeeding effect during iterval $(0, t]$ and stopping afterward on infant's weight at the end of month m. $ATEWI_{t,m}$ is the average breastfeeding effect within interval $(t-3, t]$ on the infant's weight at the end of month m, assuming that the subject then stops breastfeeding after time t. Breastfeeding within intervals $(3, 6]$ and $(6, 9]$ seemingly has a continuously negative effect on infant's weight. The immediate effect of breastfeeding within interval $(0, 3]$ is positive, however past month 3, there is not a significant difference between infants who are breastfed through month 3 and those who are not. Within intervals $(3, 6]$ and $(6, 9]$ the immediate effect and later effect are statistically significantly negative. In contrast, continuing breastfeeding after month 9 has no significant effect, either

positive or negative. As a result, based on this one-year follow up study breastfeeding after month 3 through month 9 decreases the infants' weights.

7.5 Optimal SNMM on modifiers of breastfeeding effect with other covariates

The World Health Organization (WHO) currently recommends that infants should be exclusively breastfed for the first six months of life in order to achieve optimal growth, development and health. Thereafter, infants should receive nutritionally adequate and safe complementary foods, while continuing to breastfeed for up to two years or more. Moodie et al. [47] and Rich et al. [1] using ODTR-SNMM showed that the optimal time to stop breastfeeding is month 3. There has been no work on ODTR-SNMM when outcome is time varying, but consider only the outcome at the end of study. In this section, I use ODTR-dr-keeSNMM as was discussed in chapter 6. The estimation of causal parameters for ODTR-dr-keeSNMM is summarized in table 7–6. These results are very similar to the results in table 7–2 and confirm that the optimal time to stop breastfeeding is month 3. The identical results from SNMM and optimal SNMM are because once breastfeeding is stopped it cannot be re-initiated again. Although there seem to be violations of the Markov assumption but my results from different methodologies are not inconsistent with the results obtained by Rich et al. [1] as can be seen from table 7–7. The previous authors assumed a constant effect at each time interval. The table 7–7 displays the estimated $ATTE_{t,12}$ for $t = \{3, 6, 9, 12\}$ for each interval from Rich et al. [1], and the $ATEWI$ from dr-keeSNMM and ODTR-dr-keeSNMM. So based on the one year follow up from the PROBIT data, the optimal time to stop breastfeeding is month 3 and our analysis confirms that breastfeeding has a small, but statistically

significant and negative effect, particularly between months 3 and 9, and continuing breastfeeding after month 9 has no apparent effect.

7.6 dr-keeSNMM and keeSNMM with longitudinal propensity score

Despite modelling only four time intervals and a small number of time varying confounders, constructing blip functions and interpreting causal parameters remains a challenge. In order to overcome the problem, I can instead construct the blip functions by using the propensity score as dicuss in Chapter 5. Blip functions using the longitudinal propensity score are parameterized as $\gamma_{t,m}(H_t, \psi_{t,m}) = A_t(\psi_{0,t,m} + \psi_{t,m}^T X_t)$ where X_t is a subset of $\overline{A}_{t-1}$ and $\overline{e}_t$ which adjusts for confounding by conditioning on the propensity score. In the data analysis, I set $X_t = e_t$, which assumes that the current propensity for treatment contains all the inormation about the past confounding history. The causal parameters are estimated by r-keeSNMM-LPS and keeSNMM-LPS and results are summarized in tables 7–8, 7–10, and 7–10. The results from dr-keeSNMM-LPS and keeSNMM-LPS are consistent with our results in section 7.4 where breastfeeding past month 3 through month 9 continuously decrease infants's weights and has no positive effect at later timepoints. Plots of residuals vs residuals at previous time intervals (figure 7–2) shows mild violation of the Markov assumption, however plots of residuals versus fitted values at the corresponding intervals don't show any significant pattern.

7.7 Discussion

In this chapter, I re-analysed the promotion of breastfeeding intervention trial (PROBIT) in Belarus to illustrate the application of the methods introduced in this thesis. The contradiction amongst various studies on evaluating the prolonged and

exclusive breastfeeding effect on infant's growth can be a strong evidence of the presence of confounding which is not adjusted for appropriately (Kramer et al. [69]). It is a cluster-randomized trial study, however some women in the groups of studies didn't follow the policies after randomization. As a result, continuing breastfeeding can be considered as an sequential decision-making process (made by mothers) which depends on both the mother's and the infant's characteristics. So, the analysis of the long-term effect of breastfeeding requires appropriate causal methods. By combining the two randomized groups as was done by past authors (Moodie et al.[47], Rich et al. [1]), I re-analysed the dataset as if an observational study was conducted. I applied both keeSNMM and dr-keeSNMM to adjust for modifiers of the effect of breastfeeding. I then used ODTR-keeSNMM and ODTR-drkeeSNMM to find the optimal duration of exclusive breastfeeding. Finally, I implemented keeSNMM-LPS and r-keeSNMM-LPS to adjust for confounding through the longitudinal propensity score. Although there appears to be violation of the Markov assumption, according to the residual plots, all the methods consistently confirm that breastfeeding has a statistically significant positive immediate effect in interval $(0, 3]$ and a statistically significant negative immediate and long term effect during months three to nine. As a result, based on this one-year follow up study, my methods confirmed the results of past authors that breastfeeding after month 3 through month 9 negatively affect infants's weights. It is worth to note that, the 95% confidence intervals for ATEWIs from keeSNMM and drkeeSNMM cover the ATEWIs from Rich's results. And since the differences are in terms of grams of weight, it means that the differences are

not only mostly not statistically significant, but they are not practically meaningful either.

Table 7–2: The causal parameter estimation by dr-keeSNMM: $\psi_{k,t,m}$ is the coefficient of the k-th modifiers in blip function $\gamma_{k,t,m}(H_t, \psi_{t,m})$ for time interval $(t-3, t]$ on outcome at month m. The table has 4 panels. First panel includes the modification of the causal parameters of the first interval on outcome at month 3. Second panel includes the modification of the causal parameters within each interval on outcome at month 6. Third panel includes the modification of the causal parameters within each interval on outcome at month 9. Fourth panel includes the modification of the causal parameters within each interval on month 12.

Outcome at the end of interval $(0,3]$											
	$\psi_{0,3,3}$	$\psi_{1,3,3}$	$\psi_{2,3,3}$	$\psi_{3,3,3}$	$\psi_{4,3,3}$	$\psi_{5,3,3}$	$\psi_{6,3,3}$	$\psi_{7,3,3}$	$\psi_{8,3,3}$	$\psi_{9,3,3}$	$ATEWI_{3,3}$
ES	148.704	-0.015	-18.876	-58.501	-77.209	-62.832	-12.101	21.812	-152.265	106.454	36.959
SD	135.833	0.040	32.828	44.366	64.024	34.517	51.511	122.432	131.573	50.932	11.216
LB	-117.529	-0.095	-83.220	-145.458	-202.696	-130.485	-113.062	-218.155	-410.149	6.627	14.975
UB	414.937	0.064	45.468	28.456	48.278	4.822	88.860	261.778	105.619	206.281	58.943
Outcome at the end of interval $(3,6]$											
	$\psi_{0,3,6}$	$\psi_{1,3,6}$	$\psi_{2,3,6}$	$\psi_{3,3,6}$	$\psi_{4,3,6}$	$\psi_{5,3,6}$	$\psi_{6,3,6}$	$\psi_{7,3,6}$	$\psi_{8,3,6}$	$\psi_{9,3,6}$	$ATEWI_{3,6}$
ES	137.687	-0.032	41.997	-74.999	-12.031	-46.126	-2.590	185.288	-132.418	99.248	19.157
SD	211.389	0.063	48.272	60.474	88.831	48.043	69.269	180.185	182.318	71.816	17.045
LB	-276.635	-0.155	-52.617	-193.529	-186.140	-140.290	-138.357	-167.875	-489.761	-41.513	-14.251
UB	552.009	0.092	136.610	43.531	162.078	48.038	133.177	538.452	224.926	240.008	52.565
	$\psi_{0,6,6}$	$\psi_{1,6,6}$	$\psi_{2,6,6}$	$\psi_{3,6,6}$	$ATEWI_{6,6}$						
ES	31.919	-0.025	-53.206	6.446	-36.245						
SD	124.820	0.037	29.388	79.041	6.372						
LB	-212.729	-0.097	-110.806	-148.476	-48.735						
UB	276.567	0.047	4.394	161.367	-23.756						
Outcome at the end of interval $(6,9]$											
	$\psi_{0,3,9}$	$\psi_{1,3,9}$	$\psi_{2,3,9}$	$\psi_{3,3,9}$	$\psi_{4,3,9}$	$\psi_{5,3,9}$	$\psi_{6,3,9}$	$\psi_{7,3,9}$	$\psi_{8,3,9}$	$ATEWI_{3,9}$	
ES	77.587	-0.028	39.624	17.895	78.045	-72.009	17.251	283.062	-258.230	-14.681	
SD	241.788	0.072	55.448	56.191	85.443	54.646	73.765	204.534	231.909	19.065	
LB	-396.318	-0.170	-69.053	-92.239	-89.423	-179.115	-127.327	-117.825	-712.771	-52.047	
UB	551.492	0.113	148.302	128.029	245.513	35.097	161.830	683.949	196.311	22.686	
	$\psi_{0,6,9}$	$\psi_{1,6,9}$	$\psi_{2,6,9}$	$\psi_{3,6,9}$	$ATEWI_{6,9}$						
ES	-176.243	0.025	47.541	109.668	-27.543						
SD	177.904	0.052	44.134	90.119	9.535						
LB	-524.935	-0.078	-38.961	-66.966	-46.232						
UB	172.448	0.128	134.044	286.302	-8.855						
	$\psi_{0,9,9}$	$\psi_{1,9,9}$	$\psi_{2,9,9}$	$ATEWI_{9,9}$							
ES	74.311	-0.033	-70.093	-23.527							
SD	143.613	0.042	33.575	5.288							
LB	-207.171	-0.115	-135.900	-33.892							
UB	355.793	0.049	-4.286	-13.162							
Outcome at the end of interval $(9,12]$											
	$\psi_{0,3,12}$	$\psi_{1,3,12}$	$\psi_{2,3,12}$	$\psi_{3,3,12}$	$\psi_{4,3,12}$	$\psi_{5,3,12}$	$\psi_{6,3,12}$	$\psi_{7,3,12}$	$\psi_{8,3,12}$	$ATEWI_{3,12}$	
ES	25.205	-0.004	16.729	0.796	9.189	-44.846	17.691	169.533	-363.368	-3.121	
SD	247.494	0.074	59.917	59.038	94.076	58.366	83.089	255.189	250.699	20.568	
LB	-459.882	-0.149	-100.709	-114.919	-175.200	-159.243	-145.163	-330.637	-854.739	-43.434	
UB	510.293	0.140	134.167	116.511	193.578	69.550	180.545	669.704	128.003	37.193	
	$\psi_{0,6,12}$	$\psi_{1,6,12}$	$\psi_{2,6,12}$	$\psi_{3,6,12}$	$ATEWI_{6,12}$						
ES	-2.502	-0.023	29.551	25.210	-28.971						
SD	213.028	0.062	50.672	117.823	10.979						
LB	-420.036	-0.145	-69.765	-205.723	-50.490						
UB	415.033	0.099	128.867	256.143	-7.451						
	$\psi_{0,9,12}$	$\psi_{1,9,12}$	$\psi_{2,9,12}$	$ATEWI_{9,12}$							
ES	23.974	-0.031	-24.831	-29.410							
SD	205.379	0.060	44.041	7.325							
LB	-378.569	-0.148	-111.152	-43.767							
UB	426.517	0.086	61.490	-15.053							
	$\psi_{0,12,12}$	$\psi_{1,12,12}$	$ATEWI_{12,12}$								
ES	-243.110	0.061	-4.500								
SD	164.029	0.047	2.615								
LB	-564.606	-0.032	-9.625								
UB	78.386	0.153	0.625								

Table 7–3: The causal parameter estimation by keeSNMM: $\psi_{k,t,m}$ is the coefficient of the k-th modifiers in blip function $\gamma_{k,t,m}(H_t, \psi_{t,m})$ for time interval $(t-3, t]$ on outcome at month m. The table has 4 panels. First panel includes the modification of the causal parameters of the first interval on outcome at month 3. Second panel includes the modification of the causal parameters within each interval on outcome at month 6. Third panel includes the modification of the causal parameters within each interval on outcome at month 9. Fourth panel includes the modification of the causal parameters within each interval on month 12.

Outcome at the end of interval $(0,3]$											
	$\psi_{0,3,3}$	$\psi_{1,3,3}$	$\psi_{2,3,3}$	$\psi_{3,3,3}$	$\psi_{4,3,3}$	$\psi_{5,3,3}$	$\psi_{6,3,3}$	$\psi_{7,3,3}$	$\psi_{8,3,3}$	$\psi_{9,3,3}$	$ATEWI_{3,3}$
ES	70.630	-0.047	292.201	-35.960	-143.427	41.074	33.198	19.514	-15.912	34.958	48.046
SD	95.075	0.028	12.138	18.008	27.132	13.053	18.717	49.783	51.163	18.987	7.694
LB	-115.718	-0.101	268.411	-71.256	-196.606	15.489	-3.488	-78.060	-116.190	-2.257	32.965
UB	256.978	0.007	315.991	-0.665	-90.247	66.658	69.884	117.089	84.367	72.173	63.126
Outcome at the end of interval $(3,6]$											
	$\psi_{0,3,6}$	$\psi_{1,3,6}$	$\psi_{2,3,6}$	$\psi_{3,3,6}$	$\psi_{4,3,6}$	$\psi_{5,3,6}$	$\psi_{6,3,6}$	$\psi_{7,3,6}$	$\psi_{8,3,6}$	$\psi_{9,3,6}$	$ATEWI_{3,6}$
ES	935.345	-0.336	415.939	-65.455	-171.007	83.536	61.011	118.334	-76.883	-17.008	1.504
SD	149.346	0.044	25.639	24.795	39.194	17.786	25.503	75.249	79.169	26.998	12.779
LB	642.628	-0.422	365.688	-114.052	-247.826	48.674	11.026	-29.154	-232.055	-69.924	-23.544
UB	1228.063	-0.250	466.191	-16.858	-94.187	118.397	110.996	265.821	78.288	35.909	26.551
	$\psi_{0,6,6}$	$\psi_{1,6,6}$	$\psi_{2,6,6}$	$\psi_{3,6,6}$	$ATEWI_{6,6}$						
ES	31.930	-0.024	-57.433	-20.146	-35.809						
SD	121.306	0.036	28.713	49.834	6.297						
LB	-205.829	-0.094	-113.710	-117.820	-48.151						
UB	269.689	0.046	-1.155	77.529	-23.467						
Outcome at the end of interval $(6,9]$											
	$\psi_{0,3,9}$	$\psi_{1,3,9}$	$\psi_{2,3,9}$	$\psi_{3,3,9}$	$\psi_{4,3,9}$	$\psi_{5,3,9}$	$\psi_{6,3,9}$	$\psi_{7,3,9}$	$\psi_{8,3,9}$	$ATEWI_{3,9}$	
ES	1262.439	-0.434	405.667	-77.961	-180.492	75.750	84.703	106.686	-125.256	-11.600	
SD	166.453	0.049	30.527	19.626	36.311	20.480	28.784	87.799	97.434	14.526	
LB	936.192	-0.529	345.833	-116.427	-251.662	35.609	28.286	-65.400	-316.226	-40.071	
UB	1588.686	-0.339	465.501	-39.494	-109.323	115.891	141.121	278.772	65.715	16.870	
	$\psi_{0,6,9}$	$\psi_{1,6,9}$	$\psi_{2,6,9}$	$\psi_{3,6,9}$	$ATEWI_{6,9}$						
ES	-193.507	0.031	43.695	33.364	-27.960						
SD	174.831	0.051	43.458	72.056	9.497						
LB	-536.177	-0.070	-41.483	-107.865	-46.574						
UB	149.163	0.132	128.873	174.593	-9.346						
	$\psi_{0,9,9}$	$\psi_{1,9,9}$	$\psi_{2,9,9}$	$ATEWI_{9,9}$							
ES	35.100	-0.021	-75.034	-24.022							
SD	141.599	0.041	32.943	5.314							
LB	-242.435	-0.102	-139.602	-34.438							
UB	312.635	0.059	-10.466	-13.606							
Outcome at the end of interval $(9,12]$											
	$\psi_{0,3,12}$	$\psi_{1,3,12}$	$\psi_{2,3,12}$	$\psi_{3,3,12}$	$\psi_{4,3,12}$	$\psi_{5,3,12}$	$\psi_{6,3,12}$	$\psi_{7,3,12}$	$\psi_{8,3,12}$	$ATEWI_{3,12}$	
ES	1189.362	-0.399	392.363	-78.645	-141.310	46.975	84.407	23.101	-180.773	7.918	
SD	179.228	0.052	34.295	21.669	39.310	22.328	32.221	97.443	106.566	15.648	
LB	838.075	-0.501	325.145	-121.115	-218.357	3.213	21.255	-167.887	-389.642	-22.751	
UB	1540.649	-0.296	459.580	-36.175	-64.263	90.737	147.559	214.089	28.096	38.587	
	$\psi_{0,6,12}$	$\psi_{1,6,12}$	$\psi_{2,6,12}$	$\psi_{3,6,12}$	$ATEWI_{6,12}$						
ES	-44.046	-0.010	24.019	-60.919	-29.072						
SD	210.844	0.062	50.323	84.135	10.919						
LB	-457.299	-0.130	-74.614	-225.824	-50.473						
UB	369.208	0.111	122.652	103.987	-7.671						
	$\psi_{0,9,12}$	$\psi_{1,9,12}$	$\psi_{2,9,12}$	$ATEWI_{9,12}$							
ES	12.975	-0.028	-29.802	-30.959							
SD	206.079	0.060	43.774	7.316							
LB	-390.940	-0.146	-115.600	-45.299							
UB	416.889	0.089	55.996	-16.619							
	$\psi_{0,12,12}$	$\psi_{1,12,12}$	$ATEWI_{12,12}$								
ES	-192.030	0.044	-5.276								
SD	163.584	0.047	2.620								
LB	-512.653	-0.048	-10.411								
UB	128.594	0.137	-0.141								

Table 7–4: Average treatment effect within intervals for keeSNMM and dr-keeSNMM. $ATEWI_{t,m}$ is the average effect of breastfeeding within interval $(t-3,t]$ and stopping onward, on the mean of outcome at the end of month m.

	keeSNMM	dr-keeSNMM						
	$ATEWI_{3,3}$	$ATEWI_{3,3}$						
ES	48.046	36.959						
SD	7.694	11.216						
LB	32.965	14.975						
UB	63.126	58.943						
	keeSNMM		dr-keeSNMM					
	$ATEWI_{3,6}$	$ATEWI_{6,6}$	$ATEWI_{3,6}$	$ATEWI_{6,6}$				
ES	1.504	-35.809	19.157	-36.245				
SD	12.779	6.297	17.045	6.372				
LB	-23.544	-48.151	-14.251	-48.735				
UB	26.551	-23.467	52.565	-23.756				
		keeSNMM			dr-keeSNMM			
	$ATEWI_{3,9}$	$ATEWI_{6,9}$	$ATEWI_{9,9}$	$ATEWI_{3,9}$	$ATEWI_{6,9}$	$ATEWI_{9,9}$		
ES	-11.600	-27.960	-24.022	-14.681	-27.543	-23.527		
SD	14.526	9.497	5.314	19.065	9.535	5.288		
LB	-40.071	-46.574	-34.438	-52.047	-46.232	-33.892		
UB	16.870	-9.346	-13.606	22.686	-8.855	-13.162		
			keeSNMM				dr-keeSNMM	
	$ATEWI_{3,12}$	$ATEWI_{6,12}$	$ATEWI_{9,12}$	$ATEWI_{12,12}$	$ATEWI_{3,12}$	$ATEWI_{6,12}$	$ATEWI_{9,12}$	$ATEWI_{12,12}$
ES	7.918	-29.072	-30.959	-5.276	-3.121	-28.971	-29.410	-4.500
SD	15.648	10.919	7.316	2.620	20.568	10.979	7.325	2.615
LB	-22.751	-50.473	-45.299	-10.411	-43.434	-50.490	-43.767	-9.625
UB	38.587	-7.671	-16.619	-0.141	37.193	-7.451	-15.053	0.625

Table 7–5: Average total treatment effect for keeSNMM and dr-keeSNMM. $ATTE_{t,m}$ is the average total effect of breastfeeding through month t and stopping onward, on the mean of outcome at the end of month m.

	keeSNMM	dr-keeSNMM						
	$ATTE_{3,3}$	$ATTE_{3,3}$						
ES	48.046	36.959						
SD	7.694	11.216						
LB	32.965	14.975						
UB	63.126	58.943						
	keeSNMM		dr-keeSNMM					
	$ATTE_{3,6}$	$ATTE_{6,6}$	$ATTE_{3,6}$	$ATTE_{6,6}$				
ES	1.504	-34.305	19.157	-17.088				
SD	12.779	10.633	17.045	15.535				
LB	-23.544	-55.146	-14.251	-47.537				
UB	26.551	-13.465	52.565	13.361				
		keeSNMM			dr-keeSNMM			
	$ATTE_{3,9}$	$ATTE_{6,9}$	$ATTE_{9,9}$	$ATTE_{3,9}$	$ATTE_{6,9}$	$ATTE_{9,9}$		
ES	-11.600	-39.560	-63.582	-14.681	-42.224	-65.751		
SD	14.526	13.064	11.968	19.065	18.241	17.387		
LB	-40.071	-65.166	-87.040	-52.047	-77.977	-99.830		
UB	16.870	-13.954	-40.124	22.686	-6.471	-31.671		
			keeSNMM				dr-keeSNMM	
	$ATTE_{3,12}$	$ATTE_{6,12}$	$ATTE_{9,12}$		$ATTE_{12,12}ATTE_{3,12}$	$ATTE_{6,12}$	$ATTE_{9,12}$	$ATTE_{12,12}$
ES	7.918	-21.153	-52.113	-57.388	-3.121	-32.092	-61.502	-66.001
SD	15.648	14.436	13.024	12.744	20.568	19.789	18.838	18.684
LB	-22.751	-49.447	-77.640	-82.367	-43.434	-70.877	-98.424	-102.621
UB	38.587	7.140	-26.585	-32.410	37.193	6.694	-24.579	-29.382

Table 7–6: The causal parameter estimation by ODTR-dr-keeSNMM: $\psi_{k,t,m}$ is the coefficient of the k-th modifiers in blip function $\gamma_{k,t,m}(H_t, \psi_{t,m})$ for time interval $(t-3, t]$ on outcome at month m. The table has 4 panels. First panel includes the modification of the causal parameters of the first interval on outcome at month 3. Second panel includes the modification of the causal parameters within each interval on outcome at month 6. Third panel includes the modification of the causal parameters within each interval on outcome at month 9. Fourth panel includes the modification of the causal parameters within each interval on month 12.

Outcome at the end of interval $(0,3]$											
	$\psi_{0,3,3}$	$\psi_{1,3,3}$	$\psi_{2,3,3}$	$\psi_{3,3,3}$	$\psi_{4,3,3}$	$\psi_{5,3,3}$	$\psi_{6,3,3}$	$\psi_{7,3,3}$	$\psi_{8,3,3}$	$\psi_{9,3,3}$	$ATEW_{3,3}$
ES	158.280	-0.016	-21.889	-60.643	-87.956	-67.005	-13.848	12.108	-149.971	105.863	37.521
SD	136.877	0.041	33.704	44.298	66.385	36.144	52.569	124.240	129.252	51.889	11.380
LB	-110.000	-0.096	-87.947	-147.467	-218.071	-137.848	-116.883	-231.403	-403.305	4.160	15.217
UB	426.560	0.064	44.170	26.181	42.159	3.838	89.187	255.619	103.362	207.565	59.826
Outcome at the end of interval $(3,6]$											
	$\psi_{0,3,6}$	$\psi_{1,3,6}$	$\psi_{2,3,6}$	$\psi_{3,3,6}$	$\psi_{4,3,6}$	$\psi_{5,3,6}$	$\psi_{6,3,6}$	$\psi_{7,3,6}$	$\psi_{8,3,6}$	$\psi_{9,3,6}$	$ATEW_{3,6}$
ES	144.211	-0.033	38.780	-72.888	-19.735	-46.144	3.625	177.754	-130.053	94.561	19.917
SD	216.609	0.064	50.515	60.701	92.723	49.754	71.495	183.786	179.663	73.281	17.296
LB	-280.344	-0.159	-60.230	-191.862	-201.472	-143.663	-136.505	-182.467	-482.194	-49.070	-13.983
UB	568.765	0.094	137.789	46.086	162.002	51.374	143.756	537.975	222.087	238.191	53.817
	$\psi_{0,6,6}$	$\psi_{1,6,6}$	$\psi_{2,6,6}$	$\psi_{3,6,6}$	$ATEW_{6,6}$						
ES	20.748	-0.023	-47.018	-7.491	-37.004						
SD	129.884	0.038	30.333	82.242	6.578						
LB	-233.825	-0.098	-106.471	-168.686	-49.897						
UB	275.322	0.052	12.435	153.704	-24.110						
Outcome at the end of interval $(6,9]$											
	$\psi_{0,3,9}$	$\psi_{1,3,9}$	$\psi_{2,3,9}$	$\psi_{3,3,9}$	$\psi_{4,3,9}$	$\psi_{5,3,9}$	$\psi_{6,3,9}$	$\psi_{7,3,9}$	$\psi_{8,3,9}$	$ATEW_{3,9}$	
ES	70.399	-0.026	38.400	19.710	71.655	-71.033	19.507	287.758	-255.962	-13.374	
SD	245.973	0.074	57.568	56.941	86.840	55.714	75.352	204.126	230.857	19.298	
LB	-411.708	-0.170	-74.434	-91.894	-98.551	-180.233	-128.183	-112.330	-708.441	-51.197	
UB	552.506	0.119	151.233	131.313	241.861	38.167	167.197	687.845	196.517	24.450	
	$\psi_{0,6,9}$	$\psi_{1,6,9}$	$\psi_{2,6,9}$	$\psi_{3,6,9}$	$ATEW_{6,9}$						
ES	-182.202	0.025	55.760	89.452	-29.176						
SD	186.444	0.055	45.007	93.216	9.901						
LB	-547.633	-0.084	-32.454	-93.252	-48.582						
UB	183.228	0.133	143.974	272.155	-9.769						
	$\psi_{0,9,9}$	$\psi_{1,9,9}$	$\psi_{2,9,9}$	$ATEW_{9,9}$							
ES	75.532	-0.033	-71.778	-23.441							
SD	145.676	0.042	33.830	5.300							
LB	-209.993	-0.116	-138.084	-33.830							
UB	361.057	0.050	-5.471	-13.053							
Outcome at the end of interval $(9,12]$											
	$\psi_{0,3,12}$	$\psi_{1,3,12}$	$\psi_{2,3,12}$	$\psi_{3,3,12}$	$\psi_{4,3,12}$	$\psi_{5,3,12}$	$\psi_{6,3,12}$	$\psi_{7,3,12}$	$\psi_{8,3,12}$	$ATEW_{3,12}$	
ES	16.692	-0.001	15.976	1.401	3.529	-45.177	20.639	175.756	-362.105	-1.949	
SD	250.350	0.075	62.056	59.802	96.962	59.877	85.207	257.619	249.794	20.633	
LB	-473.994	-0.148	-105.654	-115.812	-186.516	-162.536	-146.367	-329.176	-851.701	-42.390	
UB	507.377	0.145	137.607	118.614	193.573	72.182	187.644	680.689	127.491	38.491	
	$\psi_{0,6,12}$	$\psi_{1,6,12}$	$\psi_{2,6,12}$	$\psi_{3,6,12}$	$ATEW_{6,12}$						
ES	-3.451	-0.024	34.780	7.960	-29.890						
SD	219.182	0.064	51.260	118.099	11.312						
LB	-433.049	-0.150	-65.689	-223.514	-52.061						
UB	426.146	0.102	135.249	239.434	-7.719						
	$\psi_{0,9,12}$	$\psi_{1,9,12}$	$\psi_{2,9,12}$	$ATEW_{9,12}$							
ES	29.140	-0.032	-25.979	-29.542							
SD	210.251	0.061	44.297	7.368							
LB	-382.952	-0.152	-112.801	-43.983							
UB	441.232	0.087	60.844	-15.100							
	$\psi_{0,12,12}$	$\psi_{1,12,12}$	$ATEW_{12,12}$								
ES	-232.815	0.058	-4.442								
SD	164.891	0.047	2.620								
LB	-556.001	-0.035	-9.578								
UB	90.372	0.151	0.694								

Table 7–7: Comparing ODTR-dr-keeSNMM and dr-keeSNMM applied on PROBIT dataset, with results derived by Rich et al. [1]

	Rich's Results				ODTR-dr-keeSNMM			dr-keeSNMM		
Interval	Effect	SE	95% CI	ATEWI	ATEWI	SE	95% CI	ATEWI	SE	95% CI
3-6	-79.49	27.30	(-133.00, -25.99)	-34.9207	-29.890	11.312	(-52.061, -7.719)	-28.971	10.979	(-50.490, -7.451)
6-9	-87.74	23.18	(-133.18, -42.31)	-26.87745	-29.410	7.368	(-43.983,-15.10)	-29.410	7.325	(-43.767,-15.053)
9-12	-25.94	18.17	(-61.56, 9.68)	-3.678	-4.442	2.620	(-9.578 ,0.694)	-4.500	2.615	(-9.625,0.625)

Table 7–8: The causal parameter estimation by keeSNMM-LPS and dr-keeSNMM-LPS: $\psi_{k,t,m}$ is the coefficient of the k-th modifiers in blip function $\gamma_{k,t,m}(H_t, \psi_{t,m})$ for time interval $(t-3, t]$ on outcome at month m. The table has 4 panels. First panel includes the modification of the causal parameters of the first interval on outcome at month 3. Second panel includes the modification of the causal parameters within each interval on outcome at month 6. Third panel includes the modification of the causal parameters within each interval on outcome at month 9. Fourth panel includes the modification of the causal parameters within each interval on month 12.

Outcome at the end of interval $(0,3]$						
	keeSNMM-LPS			dr-keeSNMM-LPS		
	$\psi_{0,3,3}$	$\psi_{1,3,3}$	$ATEWI_{3,3}$	$\psi_{0,3,3}$	$\psi_{1,3,3}$	$ATEWI_{3,3}$
ES	-173.782	141.385	48.533	-113.240	99.777	40.553
SD	30.579	16.546	7.677	69.510	41.590	11.296
LB	-233.717	108.955	33.485	-249.481	18.261	18.413
UB	-113.848	173.816	63.580	23.000	181.293	62.692
Outcome at the end of interval $(3,6]$						
	keeSNMM-LPS			dr-keeSNMM-LPS		
	$\psi_{0,3,6}$	$\psi_{1,3,6}$	$ATEWI_{3,6}$	$\psi_{0,3,6}$	$\psi_{1,3,6}$	$ATEWI_{3,6}$
ES	-136.210	84.734	7.588	-13.829	24.317	19.117
SD	55.985	31.578	12.879	105.408	63.118	17.372
LB	-245.940	22.841	-17.654	-220.428	-99.394	-14.933
UB	-26.480	146.628	32.830	192.770	148.029	53.167
	$\psi_{0,6,6}$	$\psi_{1,6,6}$	$ATEWI_{6,6}$	$\psi_{0,6,6}$	$\psi_{1,6,6}$	$ATEWI_{6,6}$
ES	-53.204	-55.546	-39.491	-96.948	22.734	-35.993
SD	26.433	36.864	6.619	31.149	47.095	6.761
LB	-105.012	-127.800	-52.465	-157.999	-69.572	-49.244
UB	-1.396	16.708	-26.517	-35.897	115.041	-22.742
Outcome at the end of interval $(6,9]$						
	keeSNMM-LPS			dr-keeSNMM-LPS		
	$\psi_{0,3,9}$	$\psi_{1,3,9}$	$ATEWI_{3,9}$	$\psi_{0,3,9}$	$\psi_{1,3,9}$	$ATEWI_{3,9}$
ES	-179.979	99.020	-5.083	-67.469	29.069	-11.305
SD	62.116	35.687	14.681	113.928	69.263	20.120
LB	-301.727	29.074	-33.857	-290.768	-106.688	-50.739
UB	-58.231	168.967	23.691	155.830	164.825	28.130
	$\psi_{0,6,9}$	$\psi_{1,6,9}$	$ATEWI_{6,9}$	$\psi_{0,6,9}$	$\psi_{1,6,9}$	$ATEWI_{6,9}$
ES	-28.368	-67.283	-31.986	-65.681	1.104	-28.534
SD	35.674	48.157	9.764	41.742	62.899	10.057
LB	-98.289	-161.672	-51.123	-147.496	-122.178	-48.245
UB	41.553	27.105	-12.849	16.134	124.386	-8.823
	$\psi_{0,9,9}$	$\psi_{1,9,9}$	$ATEWI_{9,9}$	$\psi_{0,9,9}$	$\psi_{1,9,9}$	$ATEWI_{9,9}$
ES	12.195	-105.214	-24.483	36.269	-137.573	-25.787
SD	37.213	39.565	5.253	48.602	57.072	5.459
LB	-60.742	-182.761	-34.778	-58.990	-249.434	-36.487
UB	85.132	-27.667	-14.188	131.529	-25.713	-15.087
Outcome at the end of interval $(9,12]$						
	keeSNMM-LPS			dr-keeSNMM-LPS		
	$\psi_{0,3,12}$	$\psi_{1,3,12}$	$ATEWI_{3,12}$	$\psi_{0,3,12}$	$\psi_{1,3,12}$	$ATEWI_{3,12}$
ES	-128.838	85.030	12.877	-103.904	60.913	1.441
SD	69.552	39.682	15.714	120.768	73.354	21.549
LB	-265.160	7.254	-17.921	-340.609	-82.861	-40.795
UB	7.485	162.806	43.676	132.802	204.687	43.676
	$\psi_{0,6,12}$	$\psi_{1,6,12}$	$ATEWI_{6,12}$	$\psi_{0,6,12}$	$\psi_{1,6,12}$	$ATEWI_{6,12}$
ES	-28.704	-69.387	-32.744	-39.340	-48.340	-31.309
SD	41.224	55.896	11.205	47.976	70.932	11.379
LB	-109.504	-178.944	-54.706	-133.373	-187.367	-53.613
UB	52.096	40.170	-10.783	54.693	90.688	-9.006
	$\psi_{0,9,12}$	$\psi_{1,9,12}$	$ATEWI_{9,12}$	$\psi_{0,9,12}$	$\psi_{1,9,12}$	$ATEWI_{9,12}$
ES	15.846	-133.004	-30.818	34.181	-159.087	-32.196
SD	51.805	54.469	7.340	66.914	76.769	7.514
LB	-85.692	-239.764	-45.204	-96.970	-309.554	-46.924
UB	117.383	-26.244	-16.431	165.333	-8.620	-17.469
	$\psi_{0,12,12}$	$\psi_{1,12,12}$	$ATEWI_{12,12}$	$\psi_{0,12,12}$	$\psi_{1,12,12}$	$ATEWI_{12,12}$
ES	-38.612	-41.515	-4.867	-23.581	73.330	-4.417
SD	19.657	66.470	2.605	21.645	93.778	2.628
LB	-77.139	-171.796	-9.973	-66.004	-110.474	-9.568
UB	-0.085	88.766	0.240	18.843	257.134	0.734

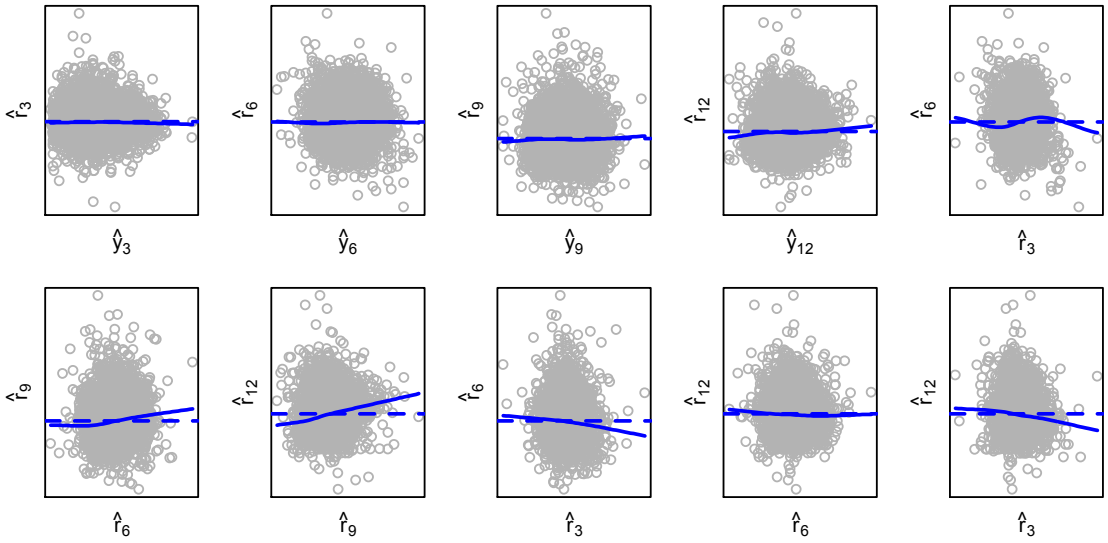
Table 7–9: Average treatment effect within intervals for keeSNMM-LPS and dr-keeSNMM-LPS. $ATEWI_{t,m}$ is the average effect of breastfeeding within interval $(t-3,t]$ and stopping onward, on the mean of outcome at the end of month m.

	keeSNMM-LPS	dr-keeSNMM-LPS						
	$ATEWI_{3,3}$	$ATEWI_{3,3}$						
ES	48.533	40.553						
SD	7.677	11.296						
LB	33.485	18.413						
UB	63.580	62.692						
	keeSNMM-LPS		dr-keeSNMM-LPS					
	$ATEWI_{3,6}$	$ATEWI_{6,6}$	$ATEWI_{3,6}$	$ATEWI_{6,6}$				
ES	7.588	-39.491	19.117	-35.993				
SD	12.879	6.619	17.372	6.761				
LB	-17.654	-52.465	-14.933	-49.244				
UB	32.830	-26.517	53.167	-22.742				
	keeSNMM-LPS			dr-keeSNMM-LPS				
	$ATEWI_{3,9}$	$ATEWI_{6,9}$	$ATEWI_{9,9}$	$ATEWI_{3,9}$	$ATEWI_{6,9}$	$ATEWI_{9,9}$		
ES	-5.083	-31.986	-24.483	-11.305	-28.534	-25.787		
SD	14.681	9.764	5.253	20.120	10.057	5.459		
LB	-33.857	-51.123	-34.778	-50.739	-48.245	-36.487		
UB	23.691	-12.849	-14.188	28.130	-8.823	-15.087		
	keeSNMM-LPS				dr-keeSNMM-LPS			
	$ATEWI_{3,12}$	$ATEWI_{6,12}$	$ATEWI_{9,12}$	$ATEWI_{12,12}$	$ATEWI_{3,12}$	$ATEWI_{6,12}$	$ATEWI_{9,12}$	$ATEWI_{12,12}$
ES	12.877	-32.744	-30.818	-4.867	1.441	-31.309	-32.196	-4.417
SD	15.714	11.205	7.340	2.605	21.549	11.379	7.514	2.628
LB	-17.921	-54.706	-45.204	-9.973	-40.795	-53.613	-46.924	-9.568
UB	43.676	-10.783	-16.431	0.240	43.676	-9.006	-17.469	0.734

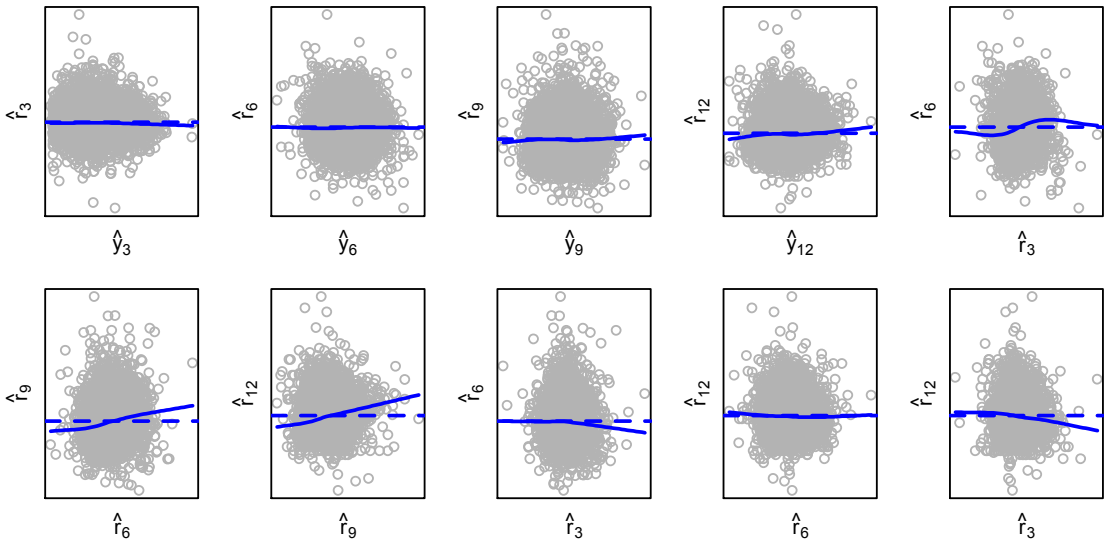
Table 7–10: Average total treatment effect for keeSNMM-LPS and dr-keeSNMM-LPS. $ATTE_{t,m}$ is the average total effect of breastfeeding through month t and stopping onward, on the mean of outcome at the end of month m.

	keeSNMM-LPS	dr-keeSNMM-LPS						
	$ATTE_{3,3}$	$ATTE_{3,3}$						
ES	48.533	40.553						
SD	7.677	11.296						
LB	33.485	18.413						
UB	63.580	62.692						
	keeSNMM-LPS		dr-keeSNMM-LPS					
	$ATTE_{3,6}$	$ATTE_{6,6}$	$ATTE_{3,6}$	$ATTE_{6,6}$				
ES	7.360	-32.027	18.944	-16.940				
SD	12.879	10.513	17.372	15.752				
LB	-17.882	-52.634	-15.106	-47.814				
UB	32.602	-11.421	52.994	13.934				
	keeSNMM-LPS			dr-keeSNMM-LPS				
	$ATTE_{3,9}$	$ATTE_{6,9}$	$ATTE_{9,9}$	$ATTE_{3,9}$	$ATTE_{6,9}$	$ATTE_{9,9}$		
ES	-5.592	-37.262	-61.779	-12.009	-40.248	-66.063		
SD	14.681	12.924	11.809	20.120	19.117	18.211		
LB	-34.366	-62.592	-84.925	-51.444	-77.717	-101.757		
UB	23.182	-11.931	-38.634	27.425	-2.778	-30.370		
	keeSNMM-LPS				dr-keeSNMM-LPS			
	$ATTE_{3,12}$	$ATTE_{6,12}$	$ATTE_{9,12}$	$ATTE_{12,12}$	$ATTE_{3,12}$	$ATTE_{6,12}$	$ATTE_{9,12}$	$ATTE_{12,12}$
ES	12.436	-19.866	-50.836	-55.653	0.752	-30.123	-62.452	-66.843
SD	15.714	14.276	12.875	12.596	21.549	20.710	19.722	19.569
LB	-18.362	-47.847	-76.072	-80.340	-41.484	-70.714	-101.106	-105.198
UB	43.235	8.114	-25.600	-30.966	42.987	10.468	-23.798	-28.488

Figure 7–1: Panel (a) includes residual plots for keeSNMM on the PROBIT dataset. Panel (b) includes the residual plots for dr-keeSNMM on the PROBIT datset. Each panel shows residual plots versus fitted values at the corresponding interval and residual plots versus residuals at previous time intervals. $\widehat{Y}_m$ are fitted values for the weight at the end of month m and $\widehat{r}_m$ is corresponding residual.

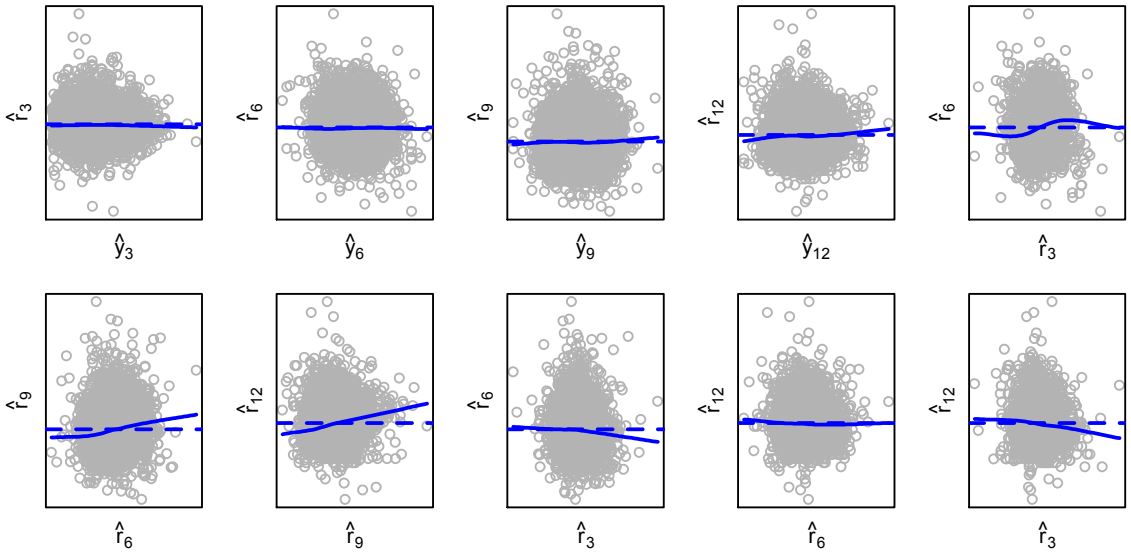


(a) keeSNMM on PROBIT dataset

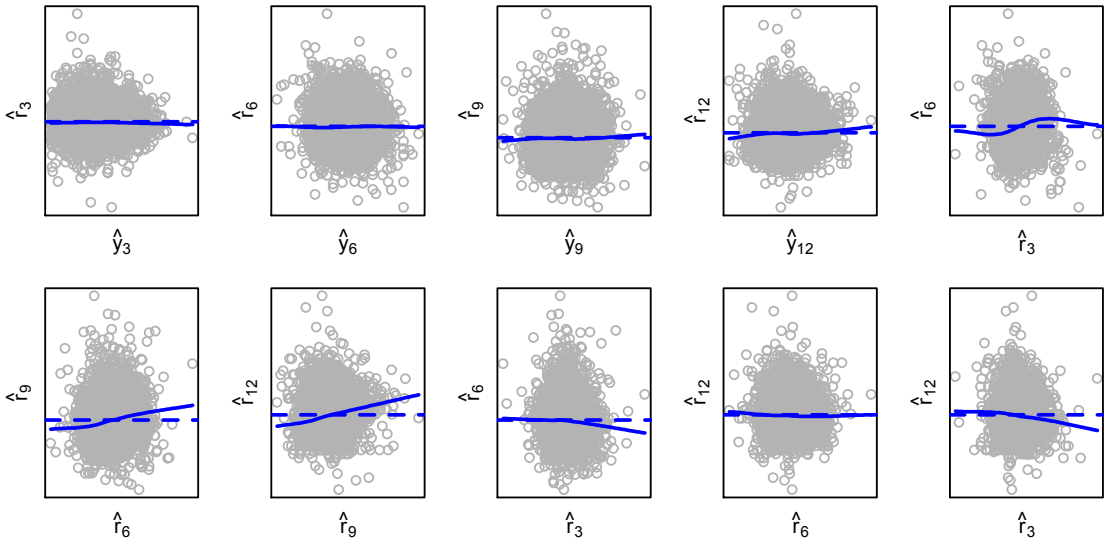


(b) drkeeSNMM on PROBIT dataset

Figure 7–2: Panel (a) includes residual plots for keeSNMM-LPS on the PROBIT dataset. Panel (b) includes the residual plots for r-keeSNMM-LPS on the PROBIT datset. Each panel shows residual plots versus fitted values at the corresponding interval and residual plots versus residuals at previous time interval. $\widehat{Y}_m$ are fitted values for the weight at the end of month m and $\widehat{r}_m$ is corresponding residual.



(a) keeSNMM-LPS on PROBIT dataset



(b) r-keeSNMM-LPS on PROBIT dataset

CHAPTER 8
Concluding remarks

Elucidating cause-and-effect relationships in longitudinal observational studies where treatment is received over time requires re-parameterization of the standard regression model. Causal models such as the structural nested mean model (SNMM) and marginal structural model (MSM), and methods like two-stage parametric regression methods (2SPR) and propensity score regression (PSR) were developed to address inconsistency of the traditional standard methods by adjusting for the confounding effect of time varying covariates. MSM is a powerful method for estimating causal parameters in longitudinal observational studies. However, these models cannot address questions like "How does the effect of treatment changes between subjects variation amongst subjects?". Consequently in situations where one is interested in estimating the modification of the treatment effect by other pre-treatment covariates, the class of MSM is impractical. In contrast, SNMM perform very well for this purpose. SNMM are semi-parametric models which characterize only portions of the value of treatment regime. G-estimation is the most popular method for estimating the causal parameters of SNMM (gSNMM). In this thesis I focus on the use of SNMM to adjust for the confounding effect of pre-treatment covariates in longitudinal studies with time-varying outcome.

After a broad review of causal methods in chapter 2, in chapter 3, by placing a Markov assumption on the counterfactual I write SNMM as an state space model

and estimate the parameters of the model by using the Kalman estimating equation (KEE) and without modeling propensity score. By a simulation study I showed that, keeSNMM is at least twice as efficient as gSNMM, i.e. to get the same efficiency from gSNMM, the sample size would need to be doubled.

The keeSNMM method proposed in Chapter 3 places restrictions on the blip function and the counterfactual process. So correct inference from the keeSNMM approach requires satisfaction of these assumptions and additional model checking plots are needed to be sure our inference is reliable. In chapter 4, I showed that estimating the causal parameters by keeSNMM not only is computationally efficient, but it also provides us with important and useful graphical diagnostic methods. The distinctive feature of these residual plots is that they can distinguish mis-specification of the blip from mis-specification in the Markov model.

The key point is that, under mild violations of the Markov assumption, keeSNMM still performs well in adjusting for confounding in estimating the direct effect of the treatment. However, serious violations results in poor performance.

Doubly robust g-estimation is a semi-parametric method for estimating the causal parameters of SNMM (dr-gSNMM) which combines a model for the mean of counterfactual outcome with a model for the propensity score to gain efficiency. Having a correct model for the mean of counterfactual outcome requires knowing the relationship between the outcome and other covariates. This is not plausible in most contexts; nonetheless using working models, dr-gSNMM generally has lower variance than gSNMM. The issue which arises in applying dr-gSNMM is building models for the mean of counterfactual when outcome is time varying. In chapter

5, I showed how one can systematically model the counterfactual via the Kalman estimating equation approach. By combining doubly robust g-estimation with KEE, I developed dr-keeSNMM, which will be consistent if either the Markov assumption holds or the propensity score is correctly specified. Through simulation studies, I showed that dr-keeSNMM can be as efficient as keeSNMM and more efficient than gSNMM in certain cases.

Dimension reduction can be beneficial when using SNMM. In many situations, it will not be easy or possible to use SNMM by adjusting for all possible confounding histories. In the second part of chapter 4, I developed the SNMM with longitudinal propensity score (SNMM-LPS) approaches. Under the sequential ignorability assumption given history of observed treatment and the longitudinal propensity score, I modeled blip functions on the observed history of treatment and longitudinal propensity score and estimated the parameters of the model by kee (keeSNMM-LPS). I also showed that one can estimate the parameters using r-keeSNMM-LPS where, under correct specification of the propensity score socre, estimation will be robust to violation of the Markov assumption.

In the management of many diseases, clinicians monitor the patient over time and sequentially adjust treatment based on multiple observations for the purpose of optimizing the long-term effectiveness of the program, typically called a dynamic treatment regime (DTR). In DTR studies, the goal is to find the optimal regime which optimizes the patient's long-term clinical outcome. In this chapter I extended the optimal dynamic treatment regime SNMM (ODTR-SNMM) by modeling the treatment regime on the outcome at different time points. However, ODTR is still

determined using the outcome at the end of the study. I place a Markov assumption on the optimal counterfactual and, by writing the problem as a state space model, ODTR-keeSNMM and ODTR-dr-keeSNMM to estimate the causal parameters of interest.

Chapter 7 is motivated by the promotion of breastfeeding intervention trial (PROBIT) in Belarus. I reanalyzed the PROBIT data in the framework of an observational study and used (a) keeSNMM and dr-keeSNMM to adjust for modifiers of the treatment effect with other pretreatment covariates to estimate breastfeeding effect; (b) ODTR-keeSNMM and ODTR-drkeeSNMM to find the optimal duration of exclusive breastfeeding; and (c) keeSNMM-LPS and dr-keeSNMM-LPS to adjust for confounding through the longitudinal propensity score. All the methods consistently confirm that breastfeeding has significant positive immediate effect in interval $(0, 3]$ and significant negative immediate and long term effect during months $(3, 9]$. As a result, based on this one-year follow up study, breastfeeding from month 3 through month 9 negatively affects the weight of the infants.

8.1 Future direction

My future research will focus on the non-linear SNMM when the outcome is time varying. The non-linear SNMM has been discussed for log-linear and logistic SNMMs by Vansteelandt & Goetghebeur [74], Ten Have et al. [75] and Comte et al. [76]. In keeSNMM, it is assumed that $\epsilon_m = Y_m^{\bar{a}_{m-1}} - Y_m^{\bar{0}} - \sum_{j=1}^{m-1} A_j \gamma_{j,m}(H_j, \psi_{j,m})$ is independent of $H_{i,m-1}$ and its variance is independent of $Y_m^{\bar{0}}$ and H_{m-1}. In the non-linear keeSNMM for time-varying outcome, in addition to considering a non-linear blip function, I could also model the variance of the error terms as a function

of the counterfactual and the past history, which to date has not been examined in the literature. I discuss the outline of the method in Appendix B for the log linear SNMM, although it is generalizable to any kind of non-linear SNMM. The plausibility of the model's assumptions, evaluation of its performance and its clinical application will be analyzed in future work.

Appendix A

Asymptotic Standard Errors

As it is discussed by Robins [18], the variances of the estimating equations used for keeSNMM, dr-keeSNMM, ODTR-dr-keeSNMM and keeSNMM-LPS need to be adjusted for the variability due to plug in estimators of the nuisance parameters. I use $p_t(a_t|H_t;\eta)$ for modeling $p_t(a_t|H_t)$, $E\left[Y_m^{(t)}(\psi)|H_t;\zeta\right]$ for modeling $E\left[Y_m^{(t)}(\psi)|H_t\right]$ where $Y_m^{(t)}(\psi) = Y_m - \sum_{j=1}^{t} A_j\gamma_{j,m}(H_j,\psi_{j,m})$, $E\left[Y_m^{\overline{0}}|Y_{m-1}^{\overline{0}};\alpha,\beta_0\right]$ for modeling $E\left[Y_m^{\overline{0}}|Y_{m-1}^{\overline{0}}\right]$ and $A_t\gamma_{t,m}(H_t,\psi_{t,m})$ for modeling $E(Y_m^{\overline{a}_t,\underline{0}_{t+1}} - Y_m^{\overline{a}_{m-1},\underline{0}_m}|H_t = h_t)$. The variances of our estimating equations can be adjusted by performing first order Taylor expansion about the limiting values of $\widehat{\eta}$, $\widehat{\zeta}(\psi)$, $\widehat{\beta}_0(\psi)$, $\widehat{\alpha}(\psi)$ which are $\eta^*, \zeta^*, \beta_0^*, \alpha^*$,

$$
\begin{aligned}
&U_{adj}(\psi,\eta^*,\zeta^*,\beta_0^*,\alpha^*)\\
&= U(\psi,\eta^*,\zeta^*,\beta_0^*,\alpha^*)\\
&+ E\left[\frac{\partial}{\partial\eta^T}U\left\{\psi,\eta^*,\zeta^*,\beta_0^*,\alpha^*\right\}\right] E\left[\frac{\partial}{\partial\eta^*}S_\eta\left\{\eta^*\right\}\right]\\
&+ E\left[\frac{\partial}{\partial(\beta^0,\alpha)^T}U\left\{\psi,\eta^*,\zeta^*,\beta_0^*,\alpha^*\right\}\right] E\left[\frac{\partial}{\partial\beta_0^*,\alpha^*}S_{\beta^0,\alpha}\left\{\beta_0^*(\psi),\alpha^*(\psi)\right\}\right]\\
&+ E\left[\frac{\partial}{\partial\zeta^T}U\left\{\psi,\eta^*,\zeta^*,\beta_0^*,\alpha^*\right\}\right] E\left[\frac{\partial}{\partial\zeta}S_\zeta\left\{\zeta^*(\psi)\right\}\right]
\end{aligned}
$$

where

$$S_{\eta}(\eta) = \frac{\partial}{\partial \eta} \log \prod_{t=0}^{T-1} p_t \left[A_t | H_t; \eta \right],$$

$$S_{\beta_0,\alpha}(\beta_0, \alpha) = \sum_{t=0}^{T} \begin{pmatrix} V \\ \mu^0_{t-1|t-1} \end{pmatrix} (\mu^0_{t|t} - \alpha \mu^0_{t-1|t-1} - \beta_0^T V) Z_t, \text{ and}$$

$$S_{\zeta}(\zeta) = \sum_{m=1}^{T} \sum_{t=0}^{T} \left[Y_m^{(t)}(\psi) - \alpha(\psi) \mu^0_{m-1|m-1} - \beta_0^T(\psi) V - \sum_{j=1}^{t} \gamma_{j,m} \left\{ H_j, \zeta_{j,t} \right\} \right].$$

By Slutsky's theorem $\sqrt{n}^{-1} P_n \left[U \left\{ \psi, \eta^*, \zeta^*, \beta_0^*, \alpha^* \right\} \right]$ is asymptotically normal with mean zero and covariance $E \left[U_{adj} \left\{ \psi, \eta^*, \zeta^*, \beta_0^*, \alpha^* \right\}^{\otimes 2} \right]$. Thus, the causal parameters $\sqrt{n}(\widehat{\psi} - \psi^{\dagger})$, where $\psi^{\dagger}$ is the limiting value of $\hat{\psi}$, has an asymptotically normal distribution with mean zero and variance

$$\Sigma^{\psi} = E \left[\left\{ \left(\frac{\partial}{\partial \psi} E \left[U_{adj} \left\{ \psi, \eta^*, \zeta^*, \beta_0^*, \alpha^* \right\} \right] \right)^{-1} U_{adj} \left(\psi, \eta^*, \zeta^*, \beta_0^*, \alpha^* \right) \right\}^{\otimes 2} \right]$$

Moodie [65] developed a recursive algorithm for calculating the variances of dr-gSNMM when the causal parameters are not shared between intervals. For calculating the variance of $\widehat{\psi}$ recursively I require additional notation, similar to what appears in Moodie [65]. Let $\psi_j = (\psi_{0,j}, \ldots, \psi_{p_j,j})$ be the causal parameters for interval $(j, j+1]$ and $p_j + 1$ be the number of parameters. $U_{adj,j}(\psi_j, \underline{\psi}^{\dagger}_{j+1}, \eta^*, \zeta^*, \beta_0^*, \alpha^*)$ is the part of $U_{adj} \left[(\psi, \eta^*, \zeta^*, \beta_0^*, \alpha^*) \right]$ used for estimating the causal parameters at interval $(j, j+1]$. One needs to find a Taylor expansion of $U_j \left[\psi_j, \widehat{\psi}_{j+1}, \widehat{\eta}, \widehat{\beta}_0(\psi_j), \widehat{\zeta}(\psi_j), \widehat{\alpha}(\psi_j) \right]$ about

the limiting values of $\left\{\widehat{\psi}_{j+1}, \widehat{\eta}, \widehat{\beta}_0(\psi_j), \widehat{\zeta}(\psi_j), \widehat{\alpha}(\psi_j)\right\}$, $(\underline{\psi}_{j+1}, \eta^*, \zeta^*, \beta_0^*, \alpha^*)$, which yields

$$
\begin{aligned}
&U^{\epsilon}_{adj}(\psi_j, \underline{\psi}^{\dagger}_{j+1}, \eta^*, \beta_0^*, \zeta^*, \alpha^*) \\
&= U_{adj,j}(\psi_j, \underline{\psi}_{j+1}, \eta^*, \zeta^*, \beta_0^*, \alpha^*) \\
&- \sum_{k>j} E\left[\frac{\partial}{\partial \psi_k} U_j\left\{\psi_k, \underline{\psi}_{k+1}, \eta^*, \zeta^*(\psi_k^{\dagger}), \beta_0^*(\psi_k^{\dagger}), \alpha^*(\psi_k^{\dagger})\right\}\right] \\
&\times \left[E\left\{\frac{\partial}{\partial \psi_k} U_{adj,k}(\psi_k, \underline{\psi}_{k+1}, \eta^*, \zeta^*, \beta_0^*, \alpha^*)\right\}\right]^{-1} \\
&\times U_{adj,k}\left\{\psi_k, \underline{\psi}_{k+1}, \eta^*, \zeta^*(\psi_k^{\dagger}), \beta_0^*(\psi_k^{\dagger}), \alpha^*(\psi_k^{\dagger})\right\} + o_p(1).
\end{aligned}
$$

Then $\sqrt{n}(\widehat{\psi}_j - \psi_j^{\dagger})$ has asymptotically normal distribution with mean zero and variance

$$
\Sigma^{\psi} = E\left[\left\{\left(\frac{\partial}{\partial \psi} E\left[U^{\epsilon}_{adj}\left\{\psi_j, \underline{\psi}^{\dagger}_{j+1}, \eta^*, \zeta^*, \beta_0^*, \alpha^*\right\}\right]\right)^{-1} U^{\epsilon}_{adj}(\psi_j, \underline{\psi}^{\dagger}_{j+1}, \eta^*, \zeta^*, \beta_0^*, \alpha^*)\right\}^{\otimes 2}\right].
$$

This procedure can also be adapted to find the asymptotic standard errors of ODTR-SNMM.

Appendix B

Non-Linear SNMM By Modeling the Variance Of The Counterfactuals

Identifying the causal effects in terms of the counterfactual outcomes under the non-linear SNMM requires additional assumptions in order to make reliable inference. Assumptions discussed previously, are (a) the SUTVA assumption, which says the outcome of patient i under treatment regime g is not affected by the treatment regime assigned to patient j, (b) the sequential ignorability assumption, which states that at each time point m, given the entire history of pretreatment covariates H_m, treatment A_m is randomly assigned and is independent of the counterfactual, and (c) the positivity assumption, which states that at each time point m each patient has positive probability ($e_m > 0$) of being assigned to treatment.

Log Linear SNMM As A State Space Model

The log linear blip function is defined as

$$\frac{E\left(Y_m^{\bar{a}_t,\underline{0}_{t^+}}|H_t, Y_m^{\bar{0}}\right)}{E\left(Y_m^{\bar{a}_{t-1},\underline{0}_t}|H_{i,t}, Y_{i,m}^{\bar{0}}\right)} = e^{a_t\gamma_{t,m}(H_t,\psi_{t,m})} \tag{8.1}$$

where the assumptions above imply

$$\frac{E\left(Y_m^{\bar{a}_t,\underline{0}_{t^+}}|H_t\right)}{E\left(Y_m^{\bar{a}_{t-1},\underline{0}_t}|H_t\right)} = e^{a_t\gamma_{m,t}(H_t,\psi_{t,m})}. \tag{8.2}$$

Similar to keeSNMM, I will formulate the SNMM for the conditional mean of $\frac{Y_T^{\bar{a}_{T-1}}}{Y_T^{\bar{0}}}$

$$
\begin{aligned}
&E\left(\frac{Y_T^{\bar{a}_{T-1}}}{Y_T^{\bar{0}}}|H_{T-1}=h_{T-1},Y_T^{\bar{0}}\right)\\
&=\left\{\frac{E\left(\frac{Y_T^{\bar{a}_{T-1}}}{Y_T^{\bar{0}}}|H_{T-1}=h_{T-1},Y_T^{\bar{0}}\right)}{E\left(\frac{Y_T^{\bar{a}_{T-2},0}}{Y_T^{\bar{0}}}|H_{T-1}=h_{T-1},Y_T^{\bar{0}}\right)}\right\}+\left\{\frac{E\left(\frac{Y_T^{\bar{a}_{T-2},0}}{Y_T^{\bar{0}}}|H_{T-1}=h_{T-1},Y_T^{\bar{0}}\right)}{E\left(\frac{Y_T^{\bar{a}_{T-2},0}}{Y_T^{\bar{0}}}|H_{T-2}=h_{T-2},Y_T^{\bar{0}}\right)}\right\}\\
&+\left\{\frac{E\left(\frac{Y_T^{\bar{a}_{T-2},0}}{Y_T^{\bar{0}}}|H_{T-2}=h_{T-2},Y_T^{\bar{0}}\right)}{E\left(\frac{Y_T^{\bar{a}_{T-3},0,0}}{Y_T^{\bar{0}}}|H_{T-2}=h_{T-2},Y_T^{\bar{0}}\right)}\right\}+\left\{\frac{E\left(\frac{Y_T^{\bar{a}_{T-3},0,0}}{Y_T^{\bar{0}}}|H_{T-2}=h_{T-2},Y_T^{\bar{0}}\right)}{E\left(\frac{Y_T^{\bar{a}_{T-3},0,0}}{Y_T^{\bar{0}}}|H_{T-3}=h_{T-3},Y_T^{\bar{0}}\right)}\right\}\\
&\vdots\\
&+\left\{E\left(\frac{Y_T^{a_1,\underline{0}_2}}{Y_T^{\bar{0}}}|H_1=h_1,Y_T^{\bar{0}}\right)\right\}.
\end{aligned}
$$

Assume that $E\left(\frac{Y_T^{\bar{a}_t,\underline{0}_{t^+}}}{Y_T^{\bar{0}}}|H_t=h_t,Y_T^{\bar{0}}\right)$ doesn't depend for pretreatment covariates on the interval $(t-1,t]$ when $A_t=0$ which implies,

$$
E\left(\frac{Y_T^{\bar{a}_{t-1},\underline{0}_t}}{Y_T^{\bar{0}}}|H_t=h_t,Y_T^{\bar{0}}\right)=E\left(\frac{Y_T^{\bar{a}_{t-1},\underline{0}_t}}{Y_T^{\bar{0}}}|H_{t-1}=h_{t-1},Y_T^{\bar{0}}\right).
$$

Consequently,

$$
E\left(\frac{Y_m^{\bar{a}_{m-1}}}{Y_m^{\bar{0}}}|H_{m-1}=h_{m-1},Y_m^{\bar{0}}\right)=e^{\sum_{j=1}^{m-1}A_{mj}\gamma_{j,m}(H_j,\psi_{j,t})}. \tag{8.3}
$$

From eq. 8.3, I define the error terms ϵ_m,

$$
\epsilon_m=Y_m^{\bar{a}_{m-1}}-E\left(\frac{Y_m^{\bar{a}_{m-1}}}{Y_m^{\bar{0}}}|H_{m-1}=h_{m-1},Y_m^{\bar{0}}\right)Y_m^{\bar{0}}.
$$

so by placing a Markov assumption on the counterfactual, the log linear SNMM in the framework of a state space model can be written as,

$$Y_m^{\overline{0}} = e^{\beta_0^T V} + \alpha Y_{m-1}^0 + \xi_m \text{ and} \tag{8.4}$$

$$Y_m^{\overline{a}_{m-1}} = Y_m^{\overline{0}} e^{\sum_{j=1}^{m-1} A_j \gamma_{j,m}(H_j, \psi_{j,m})} + \epsilon_m, \tag{8.5}$$

where $Var\left(\xi_m\right) = \sigma_m^2 \{e^{\beta_m^T V_i}\}^p$, $Var\left(\epsilon_m | H_{m-1}, Y_m^{\overline{0}}\right) = \nu_m^2 \left\{e^{\sum_{j=1}^{m-1} A_j \gamma_{j,m}(H_j, \psi_{j,m})}\right\}^p Y_m^{\overline{0}}$ and from eq. 8.1 and eq. 8.2, $e^{\gamma_{j,m}(H_j, \psi_{j,m})}$ is the blip function for the effect of a_j and takes the value one if and only if $\psi_{j,m} = 0$ for all $m \leq T$ and $j < T$.

Estimating the Parameters of Log-Linear keeSNMM

Similar to additive keeSNMM, by replacing $Y_m^{\overline{0}}$ with $E\left(Y_m^{\overline{0}} | \overline{Y}_{m-1}\right)$, the causal parameters are estimated from

$$U\left[\psi; \tau(\psi)\right] = \sum_{m=1}^{T} b_m^{-p} \frac{\partial b_m}{\partial \psi} \left(Y_m - b_m Y_m^{\overline{0}}\right). \tag{8.6}$$

where $\tau = (\beta^0, \alpha, \nu^2, \sigma^2)$. The solution of $P_n \left\{U\left[\psi; \tau(\psi)\right]\right\} = 0$ is obtained using the iterative Newton scoring algorithm,

$$\psi^{(j+1)} = \psi^{(j)} - E\left[\frac{\partial U(\psi)}{\partial \psi^T}\right]^{-1} U\left[\psi^{(j)}\right] \tag{8.7}$$

where the iterative estimation procedure proceeds by updating $E(Y_m^{\overline{0}} | \overline{Y}_{m-1})$ and ψ each in turn. $E(Y_m^{\overline{0}} | \overline{Y}_{m-1})$ is updated using the Kalman filtering algorithm, according

to

$$\begin{aligned}
\mu_{m|m-1} &= b_m \left\{ \alpha_m \mu^0_{m-1|t-1} + b^0_m \right\}, \\
R_{m|m-1} &= b^2_m u_{m-1} + b^p_m \nu^2_m b^0_m, \\
u_{m-1} &= \alpha^2_m \Sigma_{m-1|m-1} + \sigma^2_m \left\{ b^0_m \right\}^p, \\
\mu^0_{m|m} &= \alpha_m \mu^0_{m-1|m-1} + b^0_m + \frac{u_{m-1} \left\{ b_m \right\}^{1-p}}{\nu^2_m b^0_m} \left(Y_m - \mu_{m|m-1} \right), \\
\Sigma_{m|m} &= \frac{\nu^2_m b^p_m b^0_m u_{m-1}}{\nu^2_m b^p_m b^0_m + b^2_m u_{k-1}},
\end{aligned}$$

where $b_m = e^{\sum_{j=1}^m A_j \gamma_{j,m}(H_j, \psi_{j,m})}$ and $b^0_m = e^{\beta^T_0 V}$, $\mu^0_{m|k} = E\left(Y^{\bar{0}}_m | H_k\right)$, $\mu_{m|k} = E\left(Y_m | H_k\right)$, $R_{m|k} = Var(Y_m | H_k)$ and $\Sigma_{m|k} = Var\left(Y^{\bar{0}}_m | H_k\right)$. The nuisance parameters $\beta_{0,m}$ and α_m are estimated from

$$P_n \left[\sum_{m=1}^{T} V e^{\beta^T_{0,m} V} \left\{ \mu^0_{m|m} - \alpha_m \mu^0_{m-1|m-1} - \alpha_m e^{\beta^T_{0,m} V} \right\} \right]. \tag{8.8}$$

For mathematical convenience, I assume $\nu^2_m = \sigma_m$ for all $m \leq T$, so that

$$\begin{aligned}
R_{m|m-1} &= b^2_m \left[\alpha^2_m \Sigma_{m-1|m-1} + \sigma^2_m \{ b^0_m \}^p \right] + b^p_m \nu^2_m b^0_m \text{ and} \\
\nu^2_m &= \left\{ R_{m|m-1} - \alpha^2_m b^2_m \Sigma_{m-1|m-1} \right\} \left\{ b^2_m b^0_m + b^p_m b^0_m \right\}^{-1},
\end{aligned}$$

where $R_{m|m-1}$ is estimated by $P_n \left(Y_m - b_m \mu^0_{m|m-1} \right)$.

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