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Longitudinal Mediation Analysis with Time-varying Mediators and Exposures, with Application to Survival Outcomes

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Abstract

In this paper, we study the effect of a time-varying exposure mediated by a time-varying intermediate variable. We consider general longitudinal settings, including survival outcomes. At a given time point, the exposure and mediator of interest are influenced by past covariates, mediators and exposures, and affect future covariates, mediators and exposures. Right censoring, if present, occurs in response to past history. To address the challenges in mediation analysis that are unique to these settings, we propose a formulation in terms of random interventions based on conditional distributions for the mediator. This formulation, in particular, allows for well-defined natural direct and indirect effects in the survival setting, and natural decomposition of the standard total effect. Upon establishing identifiability and the corresponding statistical estimands, we derive the efficient influence curves and establish their robustness properties. Applying Targeted Maximum Likelihood Estimation, we use these efficient influence curves to construct multiply robust and efficient estimators. We also present an inverse probability weighted estimator and a nested non-targeted substitution estimator for these parameters.

Keywords

Natural direct effects; natural indirect effects; mediation analysis; mediation formula; survival; time-varying; targeted maximum likelihood estimator; IPTW; G-computation

1 Introduction

An exposure often acts on an outcome of interest directly, and/or indirectly through the mediation of some intermediate variables. Identifying and quantifying these two types of effects contribute to further understanding of the underlying causal mechanism. Modern developments in formal nonparametric causal inference have produced many advances in causal mediation analysis in non-longitudinal settings. (e.g. [18], [10], [17], [14], [22], [28], [5], [8], [7], [12], [20], [21], [32], [9]). Causal mediation in a longitudinal setting, by contrast, has received relatively little attention. One option is the *controlled direct effect* (e.g. Pearl [10]), which compares the outcomes under different exposure regimens while the mediators are fixed to some common pre-specified values. Its analysis is very similar to that of a time-varying exposure in a non-mediation setting; we refer the reader to existing literature on this topic (e.g. [16], [6], [19], [13]). Controlled direct effects are of interest if

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the exposure effect at a particular mediator value constitutes a meaningful scientific question. If that is not the case, one may ask a different direct effect question: what would be the effect of exposure on the outcome if the mediator takes its value as if exposure were absent? This question is formalized using the so-called *natural direct effect* parameter by Robins and Greenland [18] and Pearl [10] in a non-longitudinal setting. The natural direct effect has a complementary *natural indirect effect*; together they provide a decomposition of the overall effect of the exposure on the outcome. The challenges in extending the above mediation formulation to the longitudinal setting have been studied in Avin et al. [1], which established that the corresponding natural direct effect and indirect effect parameters would not be identifiable in the presence of confounders of the mediator-outcome relationship that are affected by the exposure. Such confounders, however, are ubiquitous in longitudinal applications.

As an alternative, random (stochastic) interventions (RI) based formulation to causal mediation was proposed in Didelez et al. [4]. Under this formulation, a mediator is regarded as an intervention variable onto which a given distribution is enforced, as opposed to a counterfactual variable resulting from a different intervention. The corresponding natural direct effect and indirect effect parameters have different interpretation than those under the formulations in Robins and Greenland [18] and Pearl [10], but their identifiability is at hand even in the presence of exposure-induced mediator-outcome confounder (e.g. VanderWeele et al. [30]). Zheng and van der Laan [31] proposed an RI formulation to causal mediation, through *conditional* mediator distributions, in a survival setting with point exposure and time-varying mediators and confounders. VanderWeele and Tchetgen Tchetgen [29] proposed an RI formulation, through *marginal* mediator distributions, in a time-varying exposure and mediator setting. In this paper, we extend the work in [31] to formulate causal mediation through conditional mediator distributions in general time-varying exposure and mediator settings with survival or non-survival outcomes.

The challenges in longitudinal mediation analysis are exemplified in the different effects captured (and corresponding identifiability conditions) under the marginal distribution intervention in [29] and the conditional distribution intervention proposed here. We will illustrate these differences with examples and further discussions in section 2.4.

The natural direct and indirect effects proposed here can all be defined in terms of the corresponding version of the mediation functional. We develop a general semiparametric inference framework for this *conditional mediation functional*. More specifically, in section 3, we will derive the efficient influence curves under a locally saturated semiparametric model, and establish their robustness properties. In section 4, we present three estimators for the conditional mediation functional: a nested non-targeted substitution estimator, which uses a regression-based representation of the identifying expression, an Inverse Probability Weighted (IPW) estimator, and an efficient and multiply robust Targeted Maximum Likelihood Estimator (TMLE). We study the empirical performance of these estimators in a simulation study in section 5.

2 The Mediation Formula, Natural Direct and Indirect Effects

2.1 Data structure, causal model and likelihood

Consider the data structure

$$O = (L_0, A_1, R_1, Z_1, L_1, \dots, A_t, R_t, Z_t, L_t, \dots, A_\tau, R_\tau, Z_\tau, L_\tau \supset Y_\tau) \sim P_0,$$

where L_0 encodes baseline covariates, and for $t = 1, \dots, \tau$, A_t encodes the time-varying exposure (and in addition may also include a censoring indicator), Z_t denotes the time-varying mediators, R_t and L_t denote the time-varying covariates. This representation of the data structure encodes a time-ordering of the variables within each time t : A_t precedes other variables, R_t are covariates that may precede Z_t and L_t , and L_t are covariates preceded by A_t , R_t , Z_t . The variables in L_t may include the outcome process $Y_\tau \in L_\tau$ in particular, L_τ will include the final outcome of interest Y_τ . This data structure allows for confounders of the exposure-outcome relation and exposure-induced confounders of the mediator-outcome relation, both within time and across time. In a survival setting with right censoring, the outcome indicator Y_t indicates whether one has died by time t , i.e. $Y_t = \mathbb{I}(\tilde{T} \leq t, T < C)$ with survival time T , censoring time C and $\tilde{T} = \min(T, C)$. We would encode the intervention variables as $A_t = (A_t^C, A_t^E)$, A_t^C is the indicator of remaining uncensored by time t and A_t^E is the exposure of interest at time t . In the case of a survival outcome or if censoring exists, Z_t , R_t , L_t are encoded with a default value after censoring or death. After a linear transformation, one may assume that Y_t is bounded between 0 and 1. The data consists of n i.i.d. copies of O .

We consider an example from diabetic care. Suppose within a large primary healthcare network, all diabetic patients are to receive ongoing education sessions and regular nutrition counseling (meetings with counselor), in addition to their routine care with their family physician. Complications are referred to higher level specialists. Consider a pilot program that integrates simplified referral procedures, enhanced curriculum for education sessions and more streamlined operations for nutrition counseling (e.g. less wait time, easier scheduling). Each year, patients may opt in and out of this program. Suppose we wish to evaluate how much the effect of the program on long-term control of type 2 diabetes is mediated by changes in attendance of nutrition counseling. The final outcome of interest is blood glucose levels at five years after diagnosis (Y_τ). Observations are taken annually ($t = 0$ is time of diagnosis, $\tau = 5$). The exposure of interest A_t is whether patient is in the program at year t , the mediator of interests Z_t is whether the patient has utilized his/her minimum nutrition counseling meetings this year. The time-varying covariates R_t denote attendance in education sessions and patient knowledge around disease and self-care (as assessed by survey). The time-varying covariates L_t denote health-related covariates such as nutritional status, disease progression, comorbidities, glucose tests results, etc. The covariates R_t are affected by program participation, and may affect utilization of nutrition counseling (better educated patients may have higher utilization of nutrition counseling) as well as subsequent disease progression and nutritional status. The covariates L_t are affected by current and previous program participation and patient engagement (some captured in R_t and Z_t), and

will affect subsequent program participation and patient engagement. Therefore, there are time-varying confounders of the exposure-outcome relationship, as well as time-varying exposure-induced confounders of the mediator-outcome relationship.

From here on, for any $1 \leq t \leq \tau$ and a time-dependent variable V , we will use the boldface $\mathbf{V}_t$ to denote the vector $(V_1, \dots, V_D)$, use $\mathbf{V}_{s,t}$ to denote the vector $(V_s, \dots, V_D)$. When referring to the entire vector $\mathbf{V}_\tau$, we will also use the shorthand $\mathbf{V}$. Degenerate indices such as $\mathbf{V}_{-1}$ signify the empty set. We encode the time-ordering of the variables using the following Non-Parametric Structural Equations Model ([11]):

$$\begin{aligned} L_0 &= f(U_{L_0}), \\ A_t &= f_{A_t}(\mathbf{A}_{t-1}, \mathbf{R}_{t-1}, \mathbf{Z}_{t-1}, \mathbf{L}_{t-1}, U_{A_t}), \\ R_t &= f_{R_t}(\mathbf{A}_t, \mathbf{R}_{t-1}, \mathbf{Z}_{t-1}, \mathbf{L}_{t-1}, U_{R_t}), \\ Z_t &= f_{Z_t}(\mathbf{A}_t, \mathbf{R}_t, \mathbf{Z}_{t-1}, \mathbf{L}_{t-1}, U_{Z_t}), \\ L_t &= f_{L_t}(\mathbf{A}_t, \mathbf{R}_t, \mathbf{Z}_t, \mathbf{L}_{t-1}, U_{L_t}). \end{aligned}$$

In words, within each time point, we assume the temporal relation between the measured variables is exposure A_t , then covariates R_t , then mediator Z_t , then covariates L_t , then outcome. For each variable V , the model posits that V is an unknown deterministic function of all variables preceding it, and some unmeasured exogenous factors. It is important to note that our formulation, identifying expression, and proposed estimators can be adapted to other choices of temporal ordering.

The observed data structure is generated from the above structural equations model without any intervention, and the likelihood of $O \sim P_0$ can be factored into the following conditional probabilities according to that time-ordering:

$$\begin{aligned} p_0(O) &= p_{0,L_0}(L_0) \\ &\times \prod_{t=1}^{\tau} \left(p_{0,A}(A_t | \mathbf{A}_{t-1}, \mathbf{R}_{t-1}, \mathbf{Z}_{t-1}, \mathbf{L}_{t-1}) p_{0,R}(R_t | \mathbf{A}_t, \mathbf{R}_{t-1}, \mathbf{Z}_{t-1}, \mathbf{L}_{t-1}) \right. \\ &\quad \left. \times p_{0,Z}(Z_t | \mathbf{A}_t, \mathbf{R}_t, \mathbf{Z}_{t-1}, \mathbf{L}_{t-1}) p_{0,L}(L_t | \mathbf{A}_t, \mathbf{R}_t, \mathbf{Z}_t, \mathbf{L}_{t-1}) \right). \end{aligned} \quad (1)$$

In the case of a survival outcome or if censoring exists, subsequent A_t, Z_t, R_t, L_t are assigned a default value with probability 1 after censoring or death, and therefore do not contribute to the likelihood.

2.2 The Counterfactual Outcome under Conditional Mediator Distribution

Let $\mathbf{a} \equiv (a_1, \dots, a_\tau)$ and $\mathbf{a}' \equiv (a'_1, \dots, a'_\tau)$ be two possible exposure regimens. Let

$$\Gamma_t^{\mathbf{a}'}(z_t | \mathbf{r}_t, \mathbf{z}_{t-1}, \mathbf{l}_{t-1}) \equiv p(Z_t(\mathbf{a}') = z_t | \mathbf{R}_t(\mathbf{a}') = \mathbf{r}_t, \mathbf{Z}_{t-1}(\mathbf{a}') = \mathbf{z}_{t-1}, \mathbf{L}_{t-1}(\mathbf{a}') = \mathbf{l}_{t-1})$$

denote the conditional probabilities of the mediators at $t = 1$, if the exposure had been set to $\mathbf{A} = \mathbf{a}'$ in the population. At each time t , within each stratum $(\mathbf{r}_b, \mathbf{z}_{t-1}, \mathbf{l}_{t-1})$, this provides a random draw of $Z_t \sim \Gamma_t^{\mathbf{a}'}$. For convenience, we will denote $\bar{\Gamma}^{\mathbf{a}'} = (\Gamma_1^{\mathbf{a}'}, \dots, \Gamma_\tau^{\mathbf{a}'})$.

Consider an intervention on the structural equations model to statically set $A_t = a_t$ and randomly draw $Z_t \sim \Gamma_t^{\mathbf{a}'}$. For $X_t \in \{R_b, L_t\}$, $t = 1$, we will use $X_t(\mathbf{a}, \bar{\Gamma}^{\mathbf{a}'})$ to denote the corresponding covariates resulting from this intervention. In terms of an ideal experiment, the data would be generated as follows. At baseline, we measure the covariates L_0 (say $L_0 = l_0$). At $t = 1$, intervene to set $A_1 = a_1$, and measure the resulting covariates $R_1(\mathbf{a}, \bar{\Gamma}^{\mathbf{a}'})$ (say it's measured to be r_1). Then, intervene to draw Z_1 according to $\Gamma_1^{\mathbf{a}'}(\cdot | l_0, r_1)$. Suppose we have drawn value z_1 , then we measure the resulting covariates $L_1(\mathbf{a}, \bar{\Gamma}^{\mathbf{a}'})$ (say it's measured to be l_1). At time $t = 2$, intervene to set $A_2 = a_2$; measure the resulting covariates $R_2(\mathbf{a}, \bar{\Gamma}^{\mathbf{a}'})$ (say it's measured to be r_2); intervene to draw Z_2 according to $\Gamma_2^{\mathbf{a}'}(\cdot | l_0, r_1, z_1, l_1, r_2)$; measure the resulting covariates $L_2(\mathbf{a}, \bar{\Gamma}^{\mathbf{a}'})$. We continue in this manner through the time points. At the end of the experiment, we denote the final outcome as $Y_\tau(\mathbf{a}, \bar{\Gamma}^{\mathbf{a}'})$ — this is the outcome if exposures were set to fixed values $\mathbf{a}$ and the mediators were set to have conditional distribution $\Gamma_t^{\mathbf{a}'}$. In contrast to the traditional non-random intervention formulation, $\Gamma_t^{\mathbf{a}'}$ is not the would-be mediator on the same person had she been under a different exposure, but simply a random variable whose distribution is specified by a given conditional probability function $\Gamma_t^{\mathbf{a}'}$ and the person's accruing history.

Let's illustrate this ideal experiment with the motivating example. Suppose $\mathbf{a} = 1$ denotes program participation throughout the study, and $\mathbf{a}' = 0$ denotes non-participation. Under the intervention described in the above experiment, at time $t = 1$, a person with covariates $L_0 = l_0$ is assigned to the program at year 1, i.e. $A_1 = 1$. His education session attendance and knowledge attainment, $R_1(\mathbf{a}, \bar{\Gamma}^{\mathbf{a}'})$, is a consequence of this participation (say it is likely to be high as a result of program). The distribution of his nutrition counseling utilization Z_1 would be Γ_1^0 , i.e. that of a person with his same baseline characteristics l_0 and his high diabetes education, but who did not participate in the program, say we drew this value to be z_1 . His disease progress, nutritional status and comorbidities $L_1(\mathbf{a}, \bar{\Gamma}^{\mathbf{a}'})$ would be a consequence of his baseline l_0 , his program participation $A_1 = 1$, his high diabetic education r_1 , and his counseling utilization pattern $\Gamma_1^0 = z_1$. At year $t = 2$, this person remains in the program i.e. $A_2 = 1$. His education session attendance and knowledge attainment, $R_2(\mathbf{a}, \bar{\Gamma}^{\mathbf{a}'})$ is a consequence of having been in the program for two years, had high attendance r_1 and had nutrition counseling utilization z_1 at year 1. The distribution of his nutrition counseling utilization Z_2 would be Γ_2^0 , i.e. that of a person with his same baseline characteristics l_0 , who did not participate in the program so far, but had his same diabetes education history r_1 , r_2 in the two years, and nutrition counseling utilization z_1 at year 1, say we drew $\Gamma_2^0 = z_2$. His year 2 disease progression, nutritional status and comorbidities $L_2(\mathbf{a}, \bar{\Gamma}^{\mathbf{a}'})$ would be a consequence of his baseline l_0 , his program participation $\mathbf{A}_2 = 1$, his diabetic education r_1 , r_2 , and his counseling utilization patterns z_1, z_2 . We continue the ideal experiment in this

manner, the final counterfactual $Y_{\tau}(1, \bar{\Gamma}')$ is the outcome of a person participating in the program, but has the nutrition counseling utilization pattern of an individual sharing his baseline characteristics, disease progression and comorbidities development, and diabetic education, but who otherwise did not participate in the program.

2.3 Causal Parameters and Identifiability

From the above formulation, we define as the *conditional mediation formula*:

$$E \left[Y_{\tau}(\mathbf{a}, \bar{\Gamma}^{\mathbf{a}'}) \right]. \quad (2)$$

To contrast the effects of two exposure regimens on an outcome at time τ , the corresponding *natural indirect effect* is defined as

$$E \left[Y_{\tau}(1, \bar{\Gamma}^1) \right] - E \left[Y_{\tau}(1, \bar{\Gamma}^0) \right], \quad (3)$$

and the *natural direct effect* is

$$E \left[Y_{\tau}(1, \bar{\Gamma}^0) \right] - E \left[Y_{\tau}(0, \bar{\Gamma}^0) \right]. \quad (4)$$

These two effects provide a decomposition of the total effect $E[Y_{\tau}(1, \bar{\Gamma}^1)] - E[Y_{\tau}(0, \bar{\Gamma}^0)]$. As we will see in the next section, this total effect is the same mathematical quantity as the traditional total effect measure $E[Y_{\tau}(1)] - E[Y_{\tau}(0)]$, where $Y_{\tau}(\mathbf{a})$ is the would-be outcome under exposure $\mathbf{A} = \mathbf{a}$ and no intervention on $\mathbf{Z}$.

In our illustrative example, the pilot program can impact disease progression as a result of increased patient education and increased utilization of nutrition counseling; the latter can be due to more streamlined counseling operations and/or due to better educated patients.

Suppose compared to other factors, program participation has large impact on increased R_1 (better diabetic-educated patients). Then the variable $R_1(1, \bar{\Gamma}^0) = r_1$ would be relatively high,

and the nutrition counseling utilization Z_1 would have distribution $\Gamma_1^0(l_0, r_1)$ i.e. that of an individual who did not participate in the program, but shares same baseline characteristics $L_0 = l_0$ and has the same high diabetes education. Suppose the program's more streamlined nutrition counseling operations has large impact on increased utilization of this service, then

$\Gamma_1^0(l_0, r_1)$ would be heavily distributed around lower utilization and $\Gamma_1^1(l_0, r_1)$ would be distributed around higher utilization for the same individual characterized by (l_0, r_1) .

Subsequently, $L_1(1, \bar{\Gamma}^0)$ vs $L_1(1, \bar{\Gamma}^1)$ would be the nutritional status and disease progression of individuals with the same baseline l_0 , diabetes education level r_1 , but with lower vs higher nutrition counseling utilization patterns as a result of programmatic improvements. Then, the indirect effect $E[Y_{\tau}(1, \bar{\Gamma}^0)] - E[Y_{\tau}(1, \bar{\Gamma}^1)]$ would capture the indirect effect (on disease

progression) of differential nutrition counseling utilization due to program's streamlined operation of this service, but not due to program's effect on differential demand for nutrition counseling as a result of better educated patients. So this indirect effect compares only the paths from exposures (program) into mediators (nutrition counseling utilization), but not from exposures into covariates (patient education) into mediators. Dual to this, the direct effect $E[Y_\tau(1, \bar{F}^0)] - E[Y_\tau(0, \bar{F}^0)]$ capture the paths from exposure into final outcome (diabetes control), from exposure into covariates into final outcome, as well as the paths from exposure into covariates into mediator into final outcome. In our example, this last set of paths would be the differential effect on diabetes progression due to increased demand for nutrition counseling as a result of better educated patients.

To proceed with the identifiability result, let us denote $L_t(\mathbf{a}, \mathbf{z})$ the counterfactual covariate at time t under an intervention to set $\mathbf{A} = \mathbf{a}$ and $\mathbf{Z} = \mathbf{z}$. The identifiability of the corresponding causal parameters only rely on the Sequential Randomization Assumptions of [15] and positivity assumptions.

Lemma 1: Suppose the following assumptions hold

$$\mathbf{A1} \quad (\mathbf{R}_{S \leq t}(\mathbf{a}'), \mathbf{Z}_{S \leq t}(\mathbf{a}'), \mathbf{L}_{S \leq t}(\mathbf{a}')) \perp A_t \mid \mathbf{A}_{t-1}, \mathbf{R}_{t-1}, \mathbf{Z}_{t-1}, \mathbf{L}_{t-1}.$$

$$\mathbf{A2} \quad (\mathbf{R}_{S \leq t}(\mathbf{a}, \mathbf{z}), \mathbf{L}_{S \leq t}(\mathbf{a}, \mathbf{z})) \perp A_t \mid \mathbf{A}_{t-1}, \mathbf{R}_{t-1}, \mathbf{Z}_{t-1}, \mathbf{L}_{t-1}.$$

In words, A1 and A2 require that conditional on observed history, there are no unmeasured confounders of the relationship between each exposure A_t and all its subsequent covariates and mediators, i.e. A_t is randomized conditional on observed history

$$\mathbf{A3} \quad (\mathbf{R}_{S > t}(\mathbf{a}, \mathbf{z}), \mathbf{L}_{S > t}(\mathbf{a}, \mathbf{z})) \perp Z_t \mid \mathbf{A}_t, \mathbf{R}_t, \mathbf{Z}_{t-1}, \mathbf{L}_{t-1}. \text{ Conditional on observed history, there are no unmeasured confounders of the relationship between each mediator } Z_t \text{ and all its subsequent covariates, i.e. } Z_t \text{ is randomized conditional on observed past.}$$

$$\mathbf{A4} \quad \text{Positivity: for all } t \geq 1 \text{ and all } \mathbf{r}, \mathbf{l}, \mathbf{z}, (i) \text{ if}$$

$$p_0(\mathbf{a}'_{t-1} \mid \mathbf{r}_{t-1}, \mathbf{z}_{t-1}, \mathbf{l}_{t-1}) > 0, \text{ then } p_0(\mathbf{a}'_t \mid \mathbf{a}'_{t-1}, \mathbf{r}_{t-1}, \mathbf{z}_{t-1}, \mathbf{l}_{t-1}) > 0; (ii) \text{ if } p_0(\mathbf{a}_{t-1}, \mathbf{r}_{t-1}, \mathbf{z}_{t-1}, \mathbf{l}_{t-1}) > 0, \text{ then } p_0(a_t \mid \mathbf{a}_{t-1}, \mathbf{r}_{t-1}, \mathbf{z}_{t-1}, \mathbf{l}_{t-1}) > 0; (iii) \text{ If } p_0(r_t \mid \mathbf{a}_t, \mathbf{r}_{t-1}, \mathbf{z}_t, \mathbf{l}_{t-1}) > 0, \text{ then } p_0(r_t \mid \mathbf{a}'_t, \mathbf{r}_{t-1}, \mathbf{z}_{t-1}, \mathbf{l}_{t-1}) > 0; (iv) \text{ If } p_0(l_t \mid \mathbf{a}_t, \mathbf{r}_t, \mathbf{z}_t, \mathbf{l}_{t-1}) > 0, \text{ then } p_0(l_t \mid \mathbf{a}'_t, \mathbf{r}_t, \mathbf{z}_t, \mathbf{l}_{t-1}) > 0; (v) \text{ if } p_0(\mathbf{a}_t, \mathbf{r}_t, \mathbf{z}_t, \mathbf{l}_{t-1}) > 0 \text{ and } p_0(z_t \mid \mathbf{a}_t, \mathbf{r}_t, \mathbf{z}_{t-1}, \mathbf{l}_{t-1}) > 0, \text{ then } p_0(z_t \mid \mathbf{a}_t, \mathbf{r}_t, \mathbf{z}_{t-1}, \mathbf{l}_{t-1}) > 0.$$

Conditions (i) and (ii) require that the exposures of interest are observed within each supported covariate and mediator stratum; (iii) and (iv) require that covariate values supported under $\mathbf{A} = \mathbf{a}$ are also supported under $\mathbf{A} = \mathbf{a}'$, and (v) requires that the mediator values supported under $\mathbf{A} = \mathbf{a}'$ are also supported under $\mathbf{A} = \mathbf{a}$.

Then the conditional mediation formula in (2) identifies to

$$\begin{aligned}
E \left[Y_{\tau}(\mathbf{a}, \bar{\Gamma}^{\mathbf{a}'}) \right] &= \Psi^{\mathbf{a}, \mathbf{a}'}(P_0) \\
&\equiv \sum_{\mathbf{r}, \mathbf{l}, \mathbf{z}} y_{\tau} p_{0, L_0}(l_0) \\
&\times \prod_{t=1}^{\tau} p_{0, R}(r_t | \mathbf{a}_t, \mathbf{r}_{t-1}, \mathbf{z}_{t-1}, \mathbf{l}_{t-1}) p_{0, Z}(z_t | \mathbf{a}'_t, \mathbf{r}_t, \mathbf{z}_{t-1}, \mathbf{l}_{t-1}) p_{0, L}(l_t | \mathbf{a}_t, \mathbf{r}_t, \mathbf{z}_t, \mathbf{l}_{t-1}).
\end{aligned} \tag{5}$$

Consequently, the natural indirect and direct effects are respectively identified to

$$E \left[Y_{\tau}(1, \bar{\Gamma}^1) \right] - E \left[Y_{\tau}(1, \bar{\Gamma}^0) \right] = \Psi^{1,1}(P_0) - \Psi^{1,0}(P_0) \tag{6}$$

$$E \left[Y_{\tau}(1, \bar{\Gamma}^0) \right] - E \left[Y_{\tau}(0, \bar{\Gamma}^0) \right] = \Psi^{1,0}(P_0) - \Psi^{0,0}(P_0). \tag{7}$$

Proof: In appendix.

As we alluded to in our earlier discussion, when $\mathbf{a} = \mathbf{a}'$, $E[Y_{\tau}(\mathbf{a}, \bar{\Gamma}^{\mathbf{a}})] = \Psi^{\mathbf{a}, \mathbf{a}}(P_0) = E[Y_{\tau}(\mathbf{a})]$. Therefore, the proposed natural direct and indirect effects provide a decomposition of the total effect

$$E[Y_{\tau}(1)] - E[Y_{\tau}(0)] = \left(E \left[Y_{\tau}(1, \bar{\Gamma}^1) \right] - E \left[Y_{\tau}(1, \bar{\Gamma}^0) \right] \right) + \left(E \left[Y_{\tau}(1, \bar{\Gamma}^0) \right] - E \left[Y_{\tau}(0, \bar{\Gamma}^0) \right] \right).$$

The consistency assumption is typical of causal inference under a counterfactual framework. The positivity assumptions (i) and (ii) are typical in the study of total exposure effects, whereas (iii) – (v) are unique to the proposed conditional random intervention. Assumptions A1–A3 are the so-called strong sequential randomization assumptions.

In our illustrative example, at a period t , assumptions A1 and A2 requires that the history of program participation, nutrition counseling and covariates (diabetes education, disease progression, comorbidities, nutritional status, lifestyle factors, etc.) account for all the confounders of the relationship between current program participation and current and future covariates and nutrition counseling utilization. Assumption A3 requires that current program participation, and previous history of program participation, nutritional service utilization and other covariates, account for all the confounders of the relationship between current nutrition counseling utilization and current and future covariates. These assumptions would be violated if, for example, there was an unrecorded event that would affect one's current program participation as well as current and future nutrition counseling utilization and covariates.

2.4 Longitudinal Mediation Analysis with Marginal vs Conditional Random Interventions

An alternative formulation of longitudinal mediation analysis has been proposed in [29] using random interventions with marginal mediator distributions (conditioning only on baseline covariates). Specifically, let $G_t^{\mathbf{a}'}$ be the marginal distribution of Z_t (conditioning on baseline L_0) under an ideal experiment setting $\mathbf{A} = \mathbf{a}'$, i.e. $G_t^{\mathbf{a}'}(z_t|L_0) = p_{Z(\mathbf{a}')} (z_t|L_0)$. Let $\mathbf{G}^{\mathbf{a}'} \equiv (G_1^{\mathbf{a}'}, \dots, G_\tau^{\mathbf{a}'})$. In our illustrative example, to generate $Y_\tau(1, \mathbf{G}^0)$, at time $t = 1$, a person with baseline characteristic $L_0 = l_0$ is set to participate in the program, and his diabetes education level R_1 is high as a result. But his nutritional service utilization Z_1 would have distribution $\sim G_1^0$, which corresponds to that of a person with same the baseline $L_0 = l_0$ but who does not participate in the program and has a resulting low diabetes education level. His disease progression $L_1(1, \mathbf{G}^0) = l_1$ would be a consequence of his L_0 , his program participation, his resulting high diabetes education level, and his counseling service utilization pattern G_1^0 . The difference in the formulation of $Y_\tau(\mathbf{a}, \mathbf{G}^{\mathbf{a}'})$ and the proposed $Y_\tau(\mathbf{a}, \bar{\Gamma}^{\mathbf{a}'})$ lies in that at each time t , $G_t^{\mathbf{a}'}$ is drawn as that of a random person with $\mathbf{A} = \mathbf{a}'$ and sharing the same baseline (i.e. marginalizing over all time-varying covariate histories under the influence of $\mathbf{A} = \mathbf{a}'$), whereas $\Gamma_t^{\mathbf{a}'}$ is drawn as that of a random person with $\mathbf{A} = \mathbf{a}'$, and sharing the same baseline and same time-varying covariate history (which are under the influence of $\mathbf{A} = \mathbf{a}$). This difference in formulation has implications for applicability, interpretation and identifiability. We discuss each in turn.

In a survival setting, the marginal-intervention counterfactual $Y_\tau(\mathbf{a}, \mathbf{G}^{\mathbf{a}'})$ is not well-defined since a person who is still alive under $\mathbf{A} = \mathbf{a}$ would be allowed to draw the mediator value of someone who has died under $\mathbf{A} = \mathbf{a}'$. On the other hand, by conditioning on the person's own time-varying history, the conditional-intervention counterfactual $Y_\tau(\mathbf{a}, \bar{\Gamma}^{\mathbf{a}'})$ circumvents this problem and thus is well-defined in the survival setting. Beyond formal definition, such time-varying covariate histories still need to be well-supported under both exposure regimens, as is apparent in the identifiability conditions for $Y_\tau(\mathbf{a}, \bar{\Gamma}^{\mathbf{a}'})$.

Consider now a non-survival setting. In our illustrative example, suppose program participation increases patients' diabetic education through its enhanced curriculum, and increases use of nutrition counseling utilization through better patient education and more streamlined counseling services, and both education and nutrition counseling have equal direct contribution to changing disease progression. Then, at time $t = 1$, under both interventions, the patient education $R_1(1, \bar{\Gamma}^0)$ and $R_1(1, \mathbf{G}^0)$ would be high due to program participation $A_1 = 1$. But the nutritional service utilization G_1^0 would be that of a non-participant who has a low diabetic education due to his non-participation in the program (e.g. less demand for nutrition counseling due to limited patient knowledge), whereas the nutritional service utilization Γ_1^0 would be that of a non-participant who has a high diabetic education but who otherwise did not participate in the program. Therefore, the indirect effect $E[Y_\tau(1, \mathbf{G}^0)] - E[Y_\tau(1, \mathbf{G}^1)]$ would capture the effect due to differential nutritional service utilization as a result of both the program's streamlined nutrition counseling services and the increased demand for these services due to program's impact on increasing patient

education. It would capture effect due to the paths from program into nutrition service utilization as well as the paths from program into patient education into nutritional service utilization. Contrast this with the indirect effect $E[Y_\tau(1, \bar{\Gamma}^0)] - E[Y_\tau(1, \bar{\Gamma}^1)]$, which captures the effect due to differential nutritional service utilization as a result of the program's streamlined nutrition counseling services (but not of increased demand due to better education). Dual to the indirect effect, the direct effect $E[Y_\tau(1, \mathbf{G}^0)] - E[Y_\tau(0, \mathbf{G}^0)]$ capture the effects due to direct paths from program into disease progression and the paths from program into patient education into disease. Contrasting these with the definitions and motivating example in section 2.3, we see that the different mediation formulations in this longitudinal setting allows one to ask different mediation questions, as the increased complexity of the data structure also offers more options for pathway analyses of interest.

We saw in (5) that $E(Y_\tau(\mathbf{a}, \bar{\Gamma}^{\mathbf{a}})) = E(Y_\tau(\mathbf{a}))$ as mathematical quantities, though under different ideal experiment formulation. On the other hand, as derived in [29],

$$\begin{aligned} & E(Y_\tau(\mathbf{a}, \mathbf{G}^{\mathbf{a}'})) \\ &= \sum_{\mathbf{r}, \mathbf{l}, \mathbf{z}} \left\{ y_\tau p_{0,L_0}(l_0) \prod_{t=1}^{\tau} p_{0,R}(r_t | \mathbf{a}_t, \mathbf{r}_{t-1}, \mathbf{z}_{t-1}, \mathbf{l}_{t-1}) p_{0,L}(l_t | \mathbf{a}_t, \mathbf{r}_t, \mathbf{z}_t, \mathbf{l}_{t-1}) \right. \\ & \quad \times \left[\sum_{\mathbf{r}', \mathbf{l}'_{\tau-1}} \prod_{t=1}^{\tau} p_{0,R}(r'_t | \mathbf{a}'_t, \mathbf{r}'_{t-1}, \mathbf{z}'_{t-1}, \mathbf{l}'_{t-1}) p_{0,Z}(z'_t | \mathbf{a}'_t, \mathbf{r}'_t, \mathbf{z}'_{t-1}, \mathbf{l}'_{t-1}) \right. \\ & \quad \left. \left. \times \prod_{t=1}^{\tau-1} p_{0,L}(l'_t | \mathbf{a}'_t, \mathbf{r}'_t, \mathbf{z}'_t, \mathbf{l}'_{t-1}) \right] \right\}. \end{aligned}$$

Therefore, $E(Y_\tau(\mathbf{a}, \mathbf{G}^{\mathbf{a}}))$ does not equal $E(Y_\tau(\mathbf{a}))$, in the presence of time-varying confounding. Hence, the total effect measure $E(Y_\tau(1, \mathbf{G}^1)) - E(Y_\tau(0, \mathbf{G}^0))$ is an alternative quantification of the total effect than the traditional $E(Y_\tau(1)) - E(Y_\tau(0))$. Hence, the choice of formulation also depends on which total effect decomposition one wishes to study.

While the proposed conditional distribution intervention provides more flexibility by allowing application in survival setting and decomposition of the standard total effect, this, however, comes at the expense of stronger identifiability conditions. To identify the marginal intervention parameter $E(Y_\tau(\mathbf{a}, \mathbf{G}^{\mathbf{a}'}))$, one can use the weaker versions of assumptions A2–A3 which only require no unmeasured confounding with respect to the final outcome of interest (as opposed to all subsequent covariates). For instance, in our example, if there was an unrecorded short-term event (e.g. short-term unemployment) that would affect one's current program participation as well as current disease status, lifestyle, nutritional service utilization, but not the final outcome, then $E(Y_\tau(\mathbf{a}, \mathbf{G}^{\mathbf{a}'}))$ would still be identified, whereas $E(Y_\tau(\mathbf{a}, \bar{\Gamma}^{\mathbf{a}'}))$ would not. Therefore, in non-survival settings, the tradeoff of identifiability versus effect interpretation and total effect decomposition would need to be carefully weighted.

The rest of this paper is devoted to the statistical inference of $\Psi^{\mathbf{a}, \mathbf{a}'}(P_0)$ in (5) and the corresponding natural indirect and direct effects in (6) and (7).

3 Efficient Influence Curve

In this section, we establish a general semiparametric inference framework for these parameters. In particular, we derive the Efficient Influence Curves (EIC) of (5), (7) and (6) under a (locally saturated) semiparametric model, and establish their robustness properties. For a given pathwise-differentiable parameter Ψ , under certain regularity conditions, the variance of the EIC of Ψ is a generalized Cramer-Rao lower bound for the variances of the influence curves of asymptotically linear estimators of Ψ . Therefore, the variance of the EIC provides an efficiency bound for the regular and asymptotically linear (RAL) estimators of Ψ . Moreover, under a locally saturated model, the influence curve of any RAL estimator is in fact the EIC. We refer the reader to [3] for general theory of efficient semiparametric inference.

3.1 Nested Expectation Representation of the Conditional Mediation Formula

Let $\mathcal{M}$ denote a locally saturated semiparametric model containing the true data generating distribution P_0 . Following an important observation by [2], we define recursively the following functionals for $t = \tau, \dots, 1$, at $P \in \mathcal{M}$.

$$\begin{aligned} \bar{Q}_{R_{\tau+1}}^{\mathbf{a}, \mathbf{a}'} &\equiv Y_{\tau}. \quad \text{Then, for each } t = \tau, \dots, 1: \\ \bar{Q}_{L_t}^{\mathbf{a}, \mathbf{a}'}(\mathbf{R}_t, \mathbf{Z}_t, \mathbf{L}_{t-1}) &\equiv \sum_{l_t} \bar{Q}_{R_{t+1}}^{\mathbf{a}, \mathbf{a}'}(\mathbf{R}_t, \mathbf{Z}_t, \mathbf{L}_{t-1}, l_t) p(l_t | \mathbf{A}_t = \mathbf{a}_t, \mathbf{R}_t, \mathbf{Z}_t, \mathbf{L}_{t-1}) \\ \bar{Q}_{Z_t}^{\mathbf{a}, \mathbf{a}'}(\mathbf{R}_t, \mathbf{Z}_{t-1}, \mathbf{L}_{t-1}) &\equiv \sum_{z_t} \bar{Q}_{L_t}^{\mathbf{a}, \mathbf{a}'}(\mathbf{R}_t, \mathbf{Z}_{t-1}, z_t, \mathbf{L}_{t-1}) p(z_t | \mathbf{A}_t = \mathbf{a}'_t, \mathbf{R}_t, \mathbf{Z}_{t-1}, \mathbf{L}_{t-1}) \\ \bar{Q}_{R_t}^{\mathbf{a}, \mathbf{a}'}(\mathbf{R}_{t-1}, \mathbf{Z}_{t-1}, \mathbf{L}_{t-1}) &\equiv \sum_{r_t} \bar{Q}_{Z_t}^{\mathbf{a}, \mathbf{a}'}(\mathbf{R}_{t-1}, r_t, \mathbf{Z}_{t-1}, \mathbf{L}_{t-1}) p(r_t | \mathbf{A}_{t-1} = \mathbf{a}_{t-1}, \mathbf{R}_{t-1}, \mathbf{Z}_{t-1}, \mathbf{L}_{t-1}). \end{aligned} \quad (8)$$

Evaluating these functionals at the data generating P_0 , we obtain a nested expectation-based representation of the identifying expression (5):

$$\Psi^{\mathbf{a}, \mathbf{a}'}(P_0) = E_{P_0} \left[\bar{Q}_{R_1}^{\mathbf{a}, \mathbf{a}'}(P_0)(L_0) \right]. \quad (9)$$

3.2 Notations

We will use $\bar{Q}^{\mathbf{a}, \mathbf{a}'}$ to denote the nested expectations $\left(\bar{Q}_{L_t}^{\mathbf{a}, \mathbf{a}'}, \bar{Q}_{Z_t}^{\mathbf{a}, \mathbf{a}'}, \bar{Q}_{R_t}^{\mathbf{a}, \mathbf{a}'} : t \geq 1 \right)$.

We use P_n to denote the empirical distribution of n i.i.d. copies of $O \sim P_0$. Given a function

$O \mapsto f(O)$, $P_n f$ denotes the empirical mean $P_n f \equiv \frac{1}{n} \sum_{i=1}^n f(O_i)$.

3.3 Efficient Influence Curves for The Mediation Formula and Direct and Indirect Effects

The mediation formula in (5) can be considered as the value at P_0 of the map

$P \mapsto \Psi^{\mathbf{a}, \mathbf{a}'}(P) \equiv E_P \left[\bar{Q}_{R_1}^{\mathbf{a}, \mathbf{a}'}(P)(L_0) \right]$ on $\mathcal{M}$. In particular, this map depends on P through $\bar{Q}^{\mathbf{a}, \mathbf{a}'}$, i.e. $\Psi^{\mathbf{a}, \mathbf{a}'}(P) = \Psi^{\mathbf{a}, \mathbf{a}'}(\bar{Q}^{\mathbf{a}, \mathbf{a}'})$. Similarly, the natural direct effect in (7) and the natural indirect effect in (6) are, respectively, the values at P_0 of the maps $P \mapsto \Psi^{NDE}(P) = \Psi^{1,0}(P) - \Psi^{0,0}(P)$ and $P \mapsto \Psi^{NIE}(P) = \Psi^{1,1}(P) - \Psi^{1,0}(P)$.

Theorem 1 (Efficient Influence Curve): Let $\Psi^{\mathbf{a}, \mathbf{a}'}: \mathcal{M} \rightarrow \mathbb{R}$ be defined as above. Suppose at $P \in \mathcal{M}$ the conditional probabilities of A_t, R_t, Z_t, L_t under the likelihood decomposition (1), are all bounded away from 0 and 1. The efficient influence curve of $\Psi^{\mathbf{a}, \mathbf{a}'}$ at P is given by $D^{*, \mathbf{a}, \mathbf{a}'}(P) \equiv D^{*, \mathbf{a}, \mathbf{a}'}(P; \Psi^{\mathbf{a}, \mathbf{a}'}(\bar{Q}^{\mathbf{a}, \mathbf{a}'}))$, with

$$D^{*, \mathbf{a}, \mathbf{a}'}(P, \psi) \equiv \sum_{t=1}^{\tau} \left(D_{L_t}^{\mathbf{a}, \mathbf{a}'}(P) + D_{Z_t}^{\mathbf{a}, \mathbf{a}'}(P) + D_{R_t}^{\mathbf{a}, \mathbf{a}'}(P) \right) + D_{L_0}^{\mathbf{a}, \mathbf{a}'}(P, \psi), \quad (10)$$

where

$$\begin{aligned} D_{L_t}^{\mathbf{a}, \mathbf{a}'}(P) &\equiv H_{L_t}^{\mathbf{a}, \mathbf{a}'} \left\{ \bar{Q}_{R_{t+1}}^{\mathbf{a}, \mathbf{a}'}(\mathbf{R}_t, \mathbf{Z}_t, \mathbf{L}_t) - \bar{Q}_{L_t}^{\mathbf{a}, \mathbf{a}'}(\mathbf{R}_t, \mathbf{Z}_t, \mathbf{L}_{t-1}) \right\} \\ D_{Z_t}^{\mathbf{a}, \mathbf{a}'}(P) &\equiv H_{Z_t}^{\mathbf{a}, \mathbf{a}'} \left\{ \bar{Q}_{L_t}^{\mathbf{a}, \mathbf{a}'}(\mathbf{R}_t, \mathbf{Z}_t, \mathbf{L}_{t-1}) - \bar{Q}_{Z_t}^{\mathbf{a}, \mathbf{a}'}(\mathbf{R}_t, \mathbf{Z}_{t-1}, \mathbf{L}_{t-1}) \right\} \\ D_{R_t}^{\mathbf{a}, \mathbf{a}'}(P) &\equiv H_{R_t}^{\mathbf{a}, \mathbf{a}'} \left\{ \bar{Q}_{Z_t}^{\mathbf{a}, \mathbf{a}'}(\mathbf{R}_t, \mathbf{Z}_{t-1}, \mathbf{L}_{t-1}) - \bar{Q}_{R_t}^{\mathbf{a}, \mathbf{a}'}(\mathbf{B}_{t-1}, \mathbf{Z}_{t-1}, \mathbf{L}_{t-1}) \right\} \\ D_{L_0}^{\mathbf{a}, \mathbf{a}'}(P, \psi) &\equiv \bar{Q}_{t=1}^{\mathbf{R}, \mathbf{a}, \mathbf{a}'}(\mathbf{L}_0) - \psi, \end{aligned}$$

with

$$H_{L_t}^{\mathbf{a}, \mathbf{a}'} \equiv \frac{I(\mathbf{A}_t \equiv \mathbf{a}_t)}{\prod_{j=1}^t p_A(a_j | \mathbf{a}_{j-1}, \mathbf{R}_{j-1}, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})} \prod_{j=1}^t \frac{p_Z(Z_j | \mathbf{a}_j', \mathbf{R}_j, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})}{p_Z(Z_j | \mathbf{a}_j, \mathbf{R}_j, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})}, \quad (11)$$

$$\begin{aligned} H_{Z_t}^{\mathbf{a}, \mathbf{a}'} &\equiv \frac{I(\mathbf{A}_t \equiv \mathbf{a}_t')}{\prod_{j=1}^t p_A(a_j' | \mathbf{a}_{j-1}', \mathbf{R}_{j-1}, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})} \\ &\times \prod_{j=1}^{t-1} \frac{p_L(L_j | \mathbf{a}_j, \mathbf{R}_j, \mathbf{Z}_j, \mathbf{L}_{j-1})}{p_L(L_j | \mathbf{a}_j', \mathbf{R}_j, \mathbf{Z}_j, \mathbf{L}_{j-1})} \prod_{j=1}^t \frac{p_R(R_j | \mathbf{a}_j, \mathbf{R}_{j-1}, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})}{p_R(R_j | \mathbf{a}_j', \mathbf{R}_{j-1}, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})} \end{aligned} \quad (12)$$

$$H_{R_t}^{\mathbf{a}, \mathbf{a}'} \equiv \frac{I(\mathbf{A}_t \equiv \mathbf{a}_t)}{\prod_{j=1}^t p_A(a_j | \mathbf{a}_{j-1}, \mathbf{R}_{j-1}, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1}) \prod_{j=1}^{t-1} p_Z(Z_j | \mathbf{a}_j, \mathbf{R}_j, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})}, \quad (13)$$

Moreover, $D^{*, \mathbf{a}, \mathbf{a}'}(P)$ is a multiply robust estimating function of $\Psi^{\mathbf{a}, \mathbf{a}'}(P)$ in the sense that if one of the following holds:

- R1** The conditional probabilities p_R , p_L and p_Z correctly specified;
- R2** The conditional probabilities p_A , p_R and p_L are correctly specified.
- R3** The conditional probabilities p_A and p_Z are correctly specified. then $E_{P_0} D^{*, \mathbf{a}, \mathbf{a}'}(P) = 0$ implies $\Psi^{\mathbf{a}, \mathbf{a}'}(P) = \Psi^{\mathbf{a}, \mathbf{a}'}(P_0)$.

Proof: See appendix.

It is easy to note that if $\mathbf{a} = \mathbf{a}'$, then (10) equals the efficient influence curve for the overall treatment effect of a time varying exposure (see e.g. [24]). The EICs of both the NDE and NIE can be derived from (10) by a simple application of the delta method. We state them in a corollary without proof.

Corollary 1: Suppose the conditions in theorem 1 hold for $\mathbf{a}, \mathbf{a}' \in \{0, 1\}$. The efficient influence curve of the natural direct effect is given by

$$D^{*, NDE}(P)(O) = D^{*, 1, 0}(P) - D^{*, 0, 0}(P),$$

and the efficient influence curve of the natural indirect effect is given by

$$D^{*, NIE}(P)(O) = D^{*, 1, 1}(P) - D^{*, 1, 0}(P).$$

Moreover, $D^{*, NDE}$ and $D^{*, NIE}$ satisfy the same robustness condition in theorem 1 for $\mathbf{a} = 0, 1$ and $\mathbf{a}' = 0, 1$.

The variances $\text{Var}_{P_0}(D^{*, \mathbf{a}, \mathbf{a}'}(P_0))$, $\text{Var}_{P_0}(D^{*, NDE}(P_0))$, and $\text{Var}_{P_0}(D^{*, NIE}(P_0))$ are generalized Cramer-Rao lower bounds for the asymptotic variances of the RAL estimators of $\Psi^{\mathbf{a}, \mathbf{a}'}(P_0)$, $\Psi^{NDE}(P_0)$, and $\Psi^{NIE}(P_0)$, respectively.

Estimators that satisfy the EIC equations will also inherit their robustness properties. We will present three estimators in the next section, one of which is robust and locally efficient.

3.3.1 Notes on estimating components of the Efficient Influence Curve—The parameter of interest (5) and the corresponding EIC (10) are represented in terms of conditional probabilities p_R , p_L , p_Z , p_A . In applications where the covariates or the mediator are high-dimensional, estimating these conditional densities may be difficult. To proceed

with the estimation in these situations, firstly we note that due to the law of iterated expectations,

$$\begin{aligned}\overline{Q}_{L_t}^{\mathbf{a}, \mathbf{a}'}(\mathbf{R}_t, \mathbf{Z}_t, \mathbf{L}_{t-1}) &= E_P \left[\overline{Q}_{R_{t+1}}^{\mathbf{a}, \mathbf{a}'}(\mathbf{R}_t, \mathbf{Z}_t, \mathbf{L}_t) | \mathbf{R}_t, \mathbf{Z}_t, \mathbf{L}_{t-1} \right] \\ \overline{Q}_{Z_t}^{\mathbf{a}, \mathbf{a}'}(\mathbf{R}_t, \mathbf{Z}_{t-1}, \mathbf{L}_{t-1}) &= E_P \left[\overline{Q}_{L_t}^{\mathbf{a}, \mathbf{a}'}(\mathbf{R}_t, \mathbf{Z}_t, \mathbf{L}_{t-1}) | \mathbf{R}_t, \mathbf{Z}_{t-1}, \mathbf{L}_{t-1} \right] \\ \overline{Q}_{R_t}^{\mathbf{a}, \mathbf{a}'}(\mathbf{R}_{t-1}, \mathbf{Z}_{t-1}, \mathbf{L}_{t-1}) &= E_P \left[\overline{Q}_{Z_t}^{\mathbf{a}, \mathbf{a}'}(\mathbf{R}_t, \mathbf{Z}_{t-1}, \mathbf{L}_{t-1}) | \mathbf{R}_{t-1}, \mathbf{Z}_{t-1}, \mathbf{L}_{t-1} \right].\end{aligned}\quad (14)$$

Therefore, one may directly estimate the expectation $\overline{Q}_{L_t}^{\mathbf{a}, \mathbf{a}'}(\mathbf{R}_t, \mathbf{Z}_t, \mathbf{L}_{t-1})$ by regressing $\overline{Q}_{R_{t+1}}^{\mathbf{a}, \mathbf{a}'}(\mathbf{R}_t, \mathbf{Z}_t, \mathbf{L}_t)$ on the covariates $(\mathbf{R}_t, \mathbf{Z}_t, \mathbf{L}_{t-1})$ using a parametric or data-adaptive algorithm, without estimating the conditional probabilities of L_t . Similarly for the expectations corresponding to Z_t and R_t .

Secondly, to replace the estimation of densities for Z_t , L_t and R_t in (11–13) with estimation of conditional probabilities of A , we define

$$\gamma^{1,s,j}(A_s | \mathbf{A}_{s-1}, \mathbf{R}_j, \mathbf{Z}_j, \mathbf{L}_{j-1}) \equiv p(A_s | \mathbf{A}_{s-1}, \mathbf{R}_j, \mathbf{Z}_j, \mathbf{L}_{j-1})$$

and

$$\gamma^{2,s,j}(A_s | \mathbf{A}_{s-1}, \mathbf{R}_j, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1}) \equiv p(A_s | \mathbf{A}_{s-1}, \mathbf{R}_j, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1}).$$

Note that these conditional probabilities of A_s differ from the conditional probabilities encoded by p_A in that the γ 's do not condition on the time-ordered parents of A_s . However, as we shall see in the following lemma, they offer an alternative to obtain robust estimators that are more suitable to real life settings where L_t, R_t, Z_t may be high dimensional.

After a few algebraic derivations (appendix 7.3), we can rewrite the expressions in the EIC as

$$\begin{aligned}H_{L_t}^{\mathbf{a}, \mathbf{a}'} &= \frac{I(\mathbf{A}_t \equiv \mathbf{a}_t)}{\prod_{j=1}^t p_A(a_j | \mathbf{a}_{j-1}, \mathbf{R}_{j-1}, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})} \\ &\times \prod_{j=1}^t \prod_{s=1}^j \frac{\gamma^{1,s,j}(a'_s | \mathbf{a}'_{s-1}, \mathbf{R}_j, \mathbf{Z}_j, \mathbf{L}_{j-1})}{\gamma^{2,s,j}(a'_s | \mathbf{a}'_{s-1}, \mathbf{R}_j, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})} \frac{\gamma^{2,s,j}(a_s | \mathbf{a}_{s-1}, \mathbf{R}_j, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})}{\gamma^{1,s,j}(a_s | \mathbf{a}_{s-1}, \mathbf{R}_j, \mathbf{Z}_j, \mathbf{L}_{j-1})} \\ H_{R_t}^{\mathbf{a}, \mathbf{a}'} &= \frac{I(\mathbf{A}_t \equiv \mathbf{a}_t)}{\prod_{j=1}^t p_A(a_j | \mathbf{a}_{j-1}, \mathbf{R}_{j-1}, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})} \\ &\times \prod_{j=1}^{t-1} \prod_{s=1}^j \frac{\gamma^{1,s,j}(a'_s | \mathbf{a}'_{s-1}, \mathbf{R}_j, \mathbf{Z}_j, \mathbf{L}_{j-1})}{\gamma^{2,s,j}(a'_s | \mathbf{a}'_{s-1}, \mathbf{R}_j, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})} \frac{\gamma^{2,s,j}(a_s | \mathbf{a}_{s-1}, \mathbf{R}_j, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})}{\gamma^{1,s,j}(a_s | \mathbf{a}_{s-1}, \mathbf{R}_j, \mathbf{Z}_j, \mathbf{L}_{j-1})}\end{aligned}$$

and

$$H_{Z_t}^{a, a'} = \frac{I(A_t \equiv a'_t)}{\prod_{j=1}^t p_A(a'_j | a'_{j-1}, \mathbf{R}_{j-1}, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})} \times \prod_{j=1}^{t-1} \prod_{s=1}^j \frac{\gamma^{1,s,j}(a'_s | a'_{s-1}, \mathbf{R}_j, \mathbf{Z}_j, \mathbf{L}_{j-1})}{\gamma^{1,s,j}(a_s | a_{s-1}, \mathbf{R}_j, \mathbf{Z}_j, \mathbf{L}_{j-1})} \times \prod_{j=1}^t \frac{p_A(a'_j | a'_{j-1}, \mathbf{R}_{j-1}, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})}{p_A(a_j | a_{j-1}, \mathbf{R}_{j-1}, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})} \prod_{s=1}^j \frac{\gamma^{2,s,j}(a_s | a_{s-1}, \mathbf{R}_j, \mathbf{Z}_j, \mathbf{L}_{j-1})}{\gamma^{2,s,j}(a'_s | a'_{s-1}, \mathbf{R}_j, \mathbf{Z}_j, \mathbf{L}_{j-1})}$$

We write $\gamma = (\gamma^{1,s,t}, \gamma^{2,s,t} : 1 \leq t \leq \tau, s \leq \bar{t})$. Based on this representation, the robustness conditions in theorem 1 can be generalized.

Corollary 2: Let γ be defined as above. If one of the following holds,

- R1** The nested regressions $\bar{Q}^{a, a'}$, as represented in (14), are correctly specified;
- R2** $p_{A,} \bar{Q}_{R_t}^{a, a'}, \bar{Q}_{L_t}^{a, a'}$, and either (p_L, p_R) or γ are correctly specified;
- R3** $p_{A,} \bar{Q}_{Z_t}^{a, a'}$, and either p_Z or γ are correctly specified, then $E_{P_0} D^{*, a, a'}(P) = 0$ implies $\Psi^{a, a'}(P) = \Psi^{a, a'}(P_0)$.

4 Estimators

In this section, we develop a nested non-targeted substitution estimator, an IPW estimator and a TMLE for the mediation functional (5). The estimators for the natural direct and indirect effects can be obtained by taking the corresponding differences. The first two estimators are consistent if the estimates of all the relevant components of P_0 are consistent. On the other hand, the TMLE satisfies the efficient influence curve equation, and hence remains unbiased under the model mis-specifications described in theorem 1. Under appropriate regularity conditions, if all the nuisance parameters are consistently estimated, then TMLE will be asymptotically efficient (e.g. [3], [25], [26]).

Let $p_{n,A}, p_{n,L}, p_{n,R}$ and $p_{n,Z}$ denote the estimators of the conditional probabilities. We will use shorthand $\bar{p}_n$ to denote these estimators. Let

$$\bar{Q}_n^{a, a'} \equiv \left(\bar{Q}_{n, L_t}^{a, a'}, \bar{Q}_{n, Z_t}^{a, a'}, \bar{Q}_{n, R_t}^{a, a'} : t \right)$$

denote the estimators of the nested expectations. These may be density-based estimators that are obtained by plugging in the density estimates $p_{n,L}, p_{n,R}$ and $p_{n,Z}$ into the definition of the expectations in (8), or they may be regression-based estimators that are obtained using the relations in (14).

4.1 Non-Targeted Substitution Estimator

The identification formula in (5) which defines that statistical estimand is generally known as the G-computation formula ([15]). Readily, it delivers a non-targeted substitution estimator, which is generally known as the G-computation estimator. To avoid estimation of densities, one can recast it in terms of $\bar{Q}^{a,a'}$, as they are represented in (9) and (14), and

obtain a non-targeted substitution estimator $\Psi^{a,a'}(\bar{Q}_n^{a,a'})$ of $\Psi^{a,a'}(P_0)$, through non-targeted estimates of the regressions $\bar{Q}^{a,a'}$.

To estimate the series of nested conditional expectations $\bar{Q}^{a,a'}(P_0)$, we can use the following algorithm, which exploits the relations in (14) to make use of available regression techniques in the literature.

1. Initiate $\bar{Q}_{R_{\tau+1}}^{a,a'} \equiv Y_{\tau}$. In our example this is the final glucose level, one may have dummy values for those that were lost to follow up.

2. At each $t = \tau, \dots, 1$, in decreasing order, we would have obtained estimators

$\bar{Q}_{n,R_{t+1}}^{a,a'}$ from the previous step. We now obtain $\bar{Q}_{n,L_t}^{a,a'}$, $\bar{Q}_{n,Z_t}^{a,a'}$, and $\bar{Q}_{n,R_t}^{a,a'}$ in that order, as follows:

- a. Regress $\bar{Q}_{n,R_{t+1}}^{a,a'}(R_t, Z_t, L_t)$ on observed values (A_b, R_b, Z_b, L_{t-1}) among observations that remained uncensored at time t . In our example, the independent variables in this regression would be histories of program participation, diabetic education, and nutrition counseling attendance up to time t and disease progression and other health-related variables up to $t-1$. We then evaluate the fitted function at the observed mediator and covariates histories R_b, Z_b, L_{t-1} and the intervened exposure $A_t = a_t$ for these uncensored observations. This can be accomplished by creating a new dataset for these uncensored units with the observed covariates and mediators, but with A_t set to a_t . This results in the estimates

$$\bar{Q}_{n,L_t}^{a,a'}(R_t, Z_t, L_{t-1}) = E \left[\bar{Q}_{n,R_{t+1}}^{a,a'}(R_t, Z_t, L_t) | A_t = a_t, R_t, Z_t, L_{t-1} \right] \text{ for those uncensored individuals.}$$

- b. Regress the newly minted $\bar{Q}_{n,L_t}^{a,a'}(R_t, Z_t, L_{t-1})$ on A_b, R_b, Z_b, L_{t-1} among observations that remained uncensored at time t . In our example, the independent variables in this regression would be histories of program participation and diabetic education up to time t , and nutrition counseling attendance disease progression and other health-related variables up to $t-1$. We then evaluate the fitted function at the observed mediator and covariate histories R_b, Z_b, L_{t-1} and the intervened exposure levels $A_t = a_t$ for these uncensored observations. This results in the estimates $\bar{Q}_{n,Z_t}^{a,a'}(R_t, L_{t-1}, Z_{t-1})$.

- c. Regress the newly obtained $\bar{Q}_{n,Z_t}^{a,a'}(\mathbf{R}_t, \mathbf{L}_{t-1}, \mathbf{Z}_{t-1})$ on $\mathbf{A}_t, \mathbf{R}_{t-1}, \mathbf{Z}_{t-1}, \mathbf{L}_{t-1}$ among observations that remained uncensored at time t . In our example, the independent variables in this regression would be histories of program participation up to time t , and diabetic education, nutrition counseling attendance disease progression and other health-related variables up to $t-1$. We then evaluate the fitted function at the observed mediator and covariate histories $\mathbf{R}_{t-1}, \mathbf{Z}_{t-1}, \mathbf{L}_{t-1}$ and the intervened exposure levels $\mathbf{A}_t = \mathbf{a}_t$ for these uncensored observations. This results in the estimates $\bar{Q}_{n,R_t}^{a,a'}(\mathbf{R}_{t-1}, \mathbf{L}_{t-1}, \mathbf{Z}_{t-1})$.

3. After running the algorithm in step (2) sequentially from $t = \tau$ down to $t = 1$, we now have $\bar{Q}_{n,R_1}^{a,a'}(L_0)$ for each of the n observations.

The Non-Targeted Substitution Estimator is given by

$$\psi_n^{NTsub} \equiv \Psi^{a,a'}(\bar{Q}_n^{a,a'}) = \frac{1}{n} \sum_{i=1}^n \bar{Q}_{n,R_1}^{a,a'}(L_{0,i}) \quad (15)$$

Consistency of ψ_n^{NTsub} relies on consistency of $\bar{Q}_n^{a,a'}$. Correct specification of $\bar{Q}^{a,a'}(P_0)$ under a finite dimensional parametric model is possible only in limited applications. Alternatively, we may use machine learning algorithms, such as Super Learner. This option is more enticing, especially when used with the regression-based approach, since there are more data-adaptive techniques available to estimate the conditional mean of a binary variable via regression. Variance estimates of this estimator can be obtained by bootstrap. Theoretical results on the asymptotic behavior, such as a central limit theorem, of the resulting estimator $\Psi^{a,a'}(\bar{Q}_n^{a,a'})$ are not available. Moreover, a non-targeted estimator $\bar{Q}_n^{a,a'}$ of $\bar{Q}^{a,a'}(P_0)$ is obtained by minimizing a global loss function for $\bar{Q}^{a,a'}(P_0)$, not for $\Psi^{a,a'}$ (P_0). This means, in particular, that the bias-variance tradeoff in $\bar{Q}_n^{a,a'}$ is optimized for the high-dimensional nuisance parameter $\bar{Q}^{a,a'}(P_0)$, instead of a much lower-dimensional parameter of interest $\Psi^{a,a'}(P_0)$. The proposed targeted estimator in section 4.3 aims to address these two issues by providing a substitution estimator that is asymptotically linear (under appropriate regularity conditions), and optimizes the bias-variance tradeoff of $\bar{Q}_n^{a,a'}$ towards $\Psi^{a,a'}(P_0)$ via an updating step.

4.2 Inverse Probability Weighted Estimator

Instead of estimating the condition expectations $\bar{Q}^{a,a'}(P_0)$, one may wish to employ the researcher's knowledge about the treatment assignment and mediator densities. To this end, consider the following function:

$$D^{IPW, \mathbf{a}, \mathbf{a}'}(p_A, p_Z)(O) \equiv Y_\tau \frac{I(\mathbf{A}_\tau = \mathbf{a}_\tau)}{\prod_{j=1}^{\tau} p_A(a_j | \mathbf{a}_{j-1}, \mathbf{R}_{j-1}, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})} \prod_{j=1}^{\tau} \frac{p_Z(Z_j | \mathbf{a}'_j, \mathbf{R}_j, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})}{p_Z(Z_j | \mathbf{a}_j, \mathbf{R}_j, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})}. \quad (16)$$

Note that

$$\begin{aligned} & E_{P_0} D^{IPW, \mathbf{a}, \mathbf{a}'}(P_0) \\ &= \sum_{\mathbf{r}, \mathbf{z}, \mathbf{l}} \left\{ y_\tau \frac{1}{\prod_{j=1}^{\tau} p_{0,A}(a_j | \mathbf{a}_{j-1}, \mathbf{r}_{j-1}, \mathbf{z}_{j-1}, \mathbf{l}_{j-1})} \prod_{j=1}^{\tau} \frac{p_{0,Z}(z_j | \mathbf{a}'_j, \mathbf{r}_j, \mathbf{z}_{j-1}, \mathbf{l}_{j-1})}{p_{0,Z}(z_j | \mathbf{a}_j, \mathbf{r}_j, \mathbf{z}_{j-1}, \mathbf{l}_{j-1})} \right. \\ & \times p_{0,L_0}(l_0) \prod_{t=1}^{\tau} \left[p_{0,A}(a_t | \mathbf{a}_{t-1}, \mathbf{r}_{t-1}, \mathbf{z}_{t-1}, \mathbf{l}_{t-1}) p_{0,R}(r_t | \mathbf{a}_t, \mathbf{r}_{t-1}, \mathbf{z}_{t-1}, \mathbf{l}_{t-1}) \right. \\ & \quad \left. \left. \times p_{0,Z}(z_t | \mathbf{a}_t, \mathbf{r}_t, \mathbf{z}_{t-1}, \mathbf{l}_{t-1}) p_{0,L}(l_t | \mathbf{a}_t, \mathbf{r}_t, \mathbf{z}_t, \mathbf{l}_{t-1}) \right] \right\} \\ &= \Psi^{\mathbf{a}, \mathbf{a}'}(P_0) = 0. \end{aligned}$$

Therefore, given estimators $p_{n,A}$ and $p_{n,Z}$, the Inverse Probability Weighted (IPW) Estimator of $\Psi^{\mathbf{a}, \mathbf{a}'}(P_0)$ is given by

$$\psi_n^{IPW} \equiv \frac{1}{n} \sum_{i=1}^n D^{IPW, \mathbf{a}, \mathbf{a}'}(p_{n,A}, p_{n,Z})(O_i) \quad (17)$$

In our example, this estimate can be obtained by taking the weighted average of the final outcome of all those with observed exposure level $\mathbf{A}_\tau = \mathbf{a}_\tau$ using weights

$\frac{1}{\prod_{j=1}^{\tau} p_A(a_j | \mathbf{a}_{j-1}, \mathbf{R}_{j-1}, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})} \prod_{j=1}^{\tau} \frac{p_Z(Z_j | \mathbf{a}'_j, \mathbf{R}_j, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})}{p_Z(Z_j | \mathbf{a}_j, \mathbf{R}_j, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})}$. The factors p_A would be the probabilities of having program participation $A_j = a_j$ at each time, under the individual's covariate (diabetes education and health status) and mediator history, and the factors p_Z are the conditional probabilities of nutritional service utilization at each time, given the individual's observed covariates and utilization history, and under the two program exposures considered.

Consistency of ψ_n^{IPW} relies on consistency of p_A and p_Z . As noted in section 3.3.1, if Z is high dimensional, we may replace estimation of the densities p_Z with estimation of the conditional probabilities $\gamma^{s,t}$. These can be estimated by regressing A_s onto the corresponding independent variables, for every pair (s, t) . This way, using (11), we can rewrite

$$\begin{aligned}
D^{IPW, \mathbf{a}, \mathbf{a}'}(p_A, p_Z) &= D^{IPW, \mathbf{a}, \mathbf{a}'}(p_A, \gamma) \\
&= Y_\tau \frac{I(\mathbf{A}_\tau \equiv \mathbf{a}_\tau)}{\prod_{j=1}^\tau p_A(a_j | \mathbf{a}_{j-1}, \mathbf{R}_{j-1}, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})} \\
&\times \prod_{j=1}^\tau \prod_{s=1}^j \frac{\gamma^{1,s,j}(a'_s | \mathbf{a}_{s-1}, \mathbf{R}_j \mathbf{Z}_j, \mathbf{L}_{j-1})}{\gamma^{1,s,j}(a_s | \mathbf{a}_{s-1}, \mathbf{R}_j \mathbf{Z}_j, \mathbf{L}_{j-1})} \frac{\gamma^{2,s,j}(a_s | \mathbf{a}_{s-1}, \mathbf{R}_j, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})}{\gamma^{2,s,j}(a'_s | \mathbf{a}_{s-1}, \mathbf{R}_j, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})}.
\end{aligned} \tag{18}$$

This IPW estimator is an asymptotically linear estimator; its influence curve involves $D^{IPW, \mathbf{a}, \mathbf{a}'}$ plus a first-order residue due to estimation of p_Z , which is part of the parameter definition. If a parametric model is used to estimate $p_{0,Z}$ the influence curve for this residual term can be derived using Delta method; otherwise, more sophisticated techniques ([23]) must be used. The corresponding variance estimation, while important, is beyond the scope

of this paper. We will approximate $\sqrt{n} \left(\psi_n^{IPW} - \Psi^{\mathbf{a}, \mathbf{a}'}(P_0) \right)$ by the sample variance $\widehat{\text{Var}} D^{IPW, \mathbf{a}, \mathbf{a}'}(p_{n,A}, p_{n,Z})$.

Due to its inverse weighting by treatment and censoring probabilities, this estimator is particularly sensitive to near positivity violations. In particular, if the outcome of interest has a bounded range, the IPW estimator is not guaranteed to stay within this range when the inverse weights become large. Substitution estimators like the non-targeted estimator in (15) and the next estimator, TMLE, can slightly mitigate this problem by incorporating global information in the parameter map. However, the effect of near positivity violations can still take form of poor smoothing in these estimators.

4.3 Targeted Maximum Likelihood Estimator

To maximize finite sample gain and provide more stable estimates in the presence of near positivity violations, one can make use of the substitution principle. The targeted maximum likelihood estimation (TMLE, [27]) provides a substitution-based estimator which also satisfies the EIC equation, thereby remaining unbiased under specific types of model misspecifications.

In a glimpse, our strategy consists of updating in a targeted manner the initial estimators $\bar{Q}_n^{\mathbf{a}, \mathbf{a}'}$ of $Q^{\mathbf{a}, \mathbf{a}'}(P_0)$ by minimizing a pre-specified loss along a least favorable (with respect to $\Psi^{\mathbf{a}, \mathbf{a}'}(P_0)$) sub-model through $\bar{Q}_n^{\mathbf{a}, \mathbf{a}'}$, then we obtain a substitution estimator of the parameter by evaluating $\Psi^{\mathbf{a}, \mathbf{a}'}$ at the updated estimator $\bar{Q}_n^{*, \mathbf{a}, \mathbf{a}'}$. As a result of this updating procedure, $\bar{p}_n$ and $\bar{Q}_n^{*, \mathbf{a}, \mathbf{a}'}$ satisfy $P_n D^{*, \mathbf{a}, \mathbf{a}'} \left(\bar{Q}_n^{*, \mathbf{a}, \mathbf{a}'}, \bar{p}_n \right) = 0$, and hence the estimator $\Psi^{\mathbf{a}, \mathbf{a}'}(\bar{Q}_n^{*, \mathbf{a}, \mathbf{a}'})$ is multiply robust, as specified in theorem 1 and corollary 3.3.1.

From the nested relationships noted (14), to update estimators of $\bar{Q}_{L_t}^{\mathbf{a}, \mathbf{a}'}$, $\bar{Q}_{Z_t}^{\mathbf{a}, \mathbf{a}'}$ and $\bar{Q}_{R_t}^{\mathbf{a}, \mathbf{a}'}$, we will use for the loss functions

$$\begin{aligned}
L(\bar{Q}_{L_t}^{\mathbf{a}, \mathbf{a}'}) &\equiv - \left\{ \bar{Q}_{L_t}^{\mathbf{a}, \mathbf{a}'} \log \left(\bar{Q}_{L_t}^{\mathbf{a}, \mathbf{a}'} \right) + (1 - \bar{Q}_{L_t}^{\mathbf{a}, \mathbf{a}'}) \log \left(1 - \bar{Q}_{L_t}^{\mathbf{a}, \mathbf{a}'} \right) \right\}, \\
L(\bar{Q}_{Z_t}^{\mathbf{a}, \mathbf{a}'}) &\equiv - \left\{ \bar{Q}_{Z_t}^{\mathbf{a}, \mathbf{a}'} \log \left(\bar{Q}_{Z_t}^{\mathbf{a}, \mathbf{a}'} \right) + (1 - \bar{Q}_{Z_t}^{\mathbf{a}, \mathbf{a}'}) \log \left(1 - \bar{Q}_{Z_t}^{\mathbf{a}, \mathbf{a}'} \right) \right\}, \\
L(\bar{Q}_{R_t}^{\mathbf{a}, \mathbf{a}'}) &\equiv - \left\{ \bar{Q}_{R_t}^{\mathbf{a}, \mathbf{a}'} \log \left(\bar{Q}_{R_t}^{\mathbf{a}, \mathbf{a}'} \right) + (1 - \bar{Q}_{R_t}^{\mathbf{a}, \mathbf{a}'}) \log \left(1 - \bar{Q}_{R_t}^{\mathbf{a}, \mathbf{a}'} \right) \right\}.
\end{aligned} \tag{19}$$

Recall that upon linear transformation, our outcome is bounded between 0 and 1, and hence these loss functions are well-defined. We define the corresponding least favorable submodels through $\bar{Q}_{L_t}^{\mathbf{a}, \mathbf{a}'}$, $\bar{Q}_{Z_t}^{\mathbf{a}, \mathbf{a}'}$ and $\bar{Q}_{R_t}^{\mathbf{a}, \mathbf{a}'}$, respectively, to be

$$\begin{aligned}
\bar{Q}_{L_t}^{\mathbf{a}, \mathbf{a}'}(\varepsilon) &= \text{expit} \left(\text{logit} \bar{Q}_{L_t}^{\mathbf{a}, \mathbf{a}'} + \varepsilon \right), \\
\bar{Q}_{Z_t}^{\mathbf{a}, \mathbf{a}'}(\varepsilon) &= \text{expit} \left(\text{logit} \bar{Q}_{Z_t}^{\mathbf{a}, \mathbf{a}'} + \varepsilon \right), \\
\bar{Q}_{R_t}^{\mathbf{a}, \mathbf{a}'}(\varepsilon) &= \text{expit} \left(\text{logit} \bar{Q}_{R_t}^{\mathbf{a}, \mathbf{a}'} + \varepsilon \right),
\end{aligned} \tag{20}$$

and note that

$$\begin{aligned}
\frac{\partial}{\partial \varepsilon} H_{L_t}^{\mathbf{a}, \mathbf{a}'}(p_A, p_Z) L \left(\bar{Q}_{L_t}^{\mathbf{a}, \mathbf{a}'}(\varepsilon) \right) \Big|_{\varepsilon=0} &= D_{L_t}^{\mathbf{a}, \mathbf{a}'}(\bar{Q}_{L_t}^{\mathbf{a}, \mathbf{a}'}, p_A, p_Z), \\
\frac{\partial}{\partial \varepsilon} H_{Z_t}^{\mathbf{a}, \mathbf{a}'}(p_A, p_L, p_R) L \left(\bar{Q}_{Z_t}^{\mathbf{a}, \mathbf{a}'}(\varepsilon) \right) \Big|_{\varepsilon=0} &= D_{Z_t}^{\mathbf{a}, \mathbf{a}'}(\bar{Q}_{Z_t}^{\mathbf{a}, \mathbf{a}'}, p_A, p_L, p_R), \\
\frac{\partial}{\partial \varepsilon} H_{R_t}^{\mathbf{a}, \mathbf{a}'}(p_A, p_Z) L \left(\bar{Q}_{R_t}^{\mathbf{a}, \mathbf{a}'}(\varepsilon) \right) \Big|_{\varepsilon=0} &= D_{R_t}^{\mathbf{a}, \mathbf{a}'}(\bar{Q}_{R_t}^{\mathbf{a}, \mathbf{a}'}, p_A, p_Z).
\end{aligned}$$

We are now ready to describe the TMLE algorithm, which will estimate, in a targeted manner, $\bar{Q}_{L_t}^{\mathbf{a}, \mathbf{a}'}$, $\bar{Q}_{Z_t}^{\mathbf{a}, \mathbf{a}'}$ and $\bar{Q}_{R_t}^{\mathbf{a}, \mathbf{a}'}$ sequentially in order of decreasing t .

1. Obtain estimators $p_{n,A}$, $p_{n,Z}$, $p_{n,L}$, $p_{n,R}$ (if high dimensional settings, estimation of $p_{n,Z}$, $p_{n,L}$, $p_{n,R}$ can be replaced with the estimators γ_n for γ defined in section 3.3.1). These estimators will be used to obtain estimates $H_{n,L_t}^{\mathbf{a}, \mathbf{a}'}$, $H_{n,Z_t}^{\mathbf{a}, \mathbf{a}'}$ and $H_{n,R_t}^{\mathbf{a}, \mathbf{a}'}$ see (11), (12) and (13).

Initiate $\bar{Q}_{R_{\tau+1}}^{\mathbf{a}, \mathbf{a}'} \equiv Y_{\tau}$.

2. At each $t = \tau, \dots, 1$, in decreasing order, we have obtained targeted estimator $\bar{Q}_{n,R_{t+1}}^{*, \mathbf{a}, \mathbf{a}'}$ from a previous step. We now obtain targeted estimator $\bar{Q}_{n,L_t}^{*, \mathbf{a}, \mathbf{a}'}$, $\bar{Q}_{n,Z_t}^{*, \mathbf{a}, \mathbf{a}'}$ and $\bar{Q}_{n,R_t}^{*, \mathbf{a}, \mathbf{a}'}$, in that order, as follows:

- a.** Regress $\overline{Q}_{n,R_{t+1}}^{*,a,a'}(R_t, Z_t, L_t)$ on observed values (A_t, R_t, Z_t, L_{t-1}) among observations that remained uncensored at time t . We then evaluate the fitted function at the observed mediator and covariates histories R_t, Z_t, L_{t-1} and the intervened exposure $A_t = a_t$ for these uncensored observations. This results in the estimates $\overline{Q}_{n,L_t}^{a,a'}(R_t, Z_t, L_{t-1})$ for those uncensored individuals. Update this estimate using
- $$\overline{Q}_{n,L_t}^{*,a,a'} \equiv \overline{Q}_{n,L_t}^{a,a'}(\varepsilon_{n,L_t}), \text{ where}$$

$$\varepsilon_{n,L_t} \equiv \arg \min_{\varepsilon} P_n H_{L_t}^{a,a'}(\bar{p}_n) L \left(\overline{Q}_{n,L_t}^{a,a'}(\varepsilon) \right).$$

This ε_{n,L_t} is the coefficient of a weighted logistic regression of the expectant $\overline{Q}_{n,R_{t+1}}^{*,a,a'}(R_t, Z_t, L_t)$ onto the intercept model with an offset $\text{logit} \left(\overline{Q}_{n,L_t}^{a,a'}(R_t, Z_t, L_{t-1}) \right)$, and weights $H_{L_t}^{a,a'}(\bar{p}_n)(A_t, R_t, Z_t, L_{t-1})$.

- b.** Next, to obtain an initial estimator $\overline{Q}_{n,Z_t}^{a,a'}$, we regress the targeted estimate $\overline{Q}_{n,L_t}^{*,a,a'}(R_t, Z_t, L_{t-1})$ constructed above on $A_t, R_t, Z_{t-1}, L_{t-1}$ among observations that remained uncensored at time t . We then evaluate the fitted function at the observed mediator and covariate histories R_t, Z_{t-1}, L_{t-1} and the intervened exposure levels $A_t = a_t$ for these uncensored observations. This results in the initial estimates $\overline{Q}_{n,Z_t}^{a,a'}(R_t, L_{t-1}, Z_{t-1})$. Update this estimate using
- $$\overline{Q}_{n,Z_t}^{*,a,a'} \equiv \overline{Q}_{n,Z_t}^{a,a'}(\varepsilon_{n,Z_t}), \text{ where}$$

$$\varepsilon_{n,Z_t} \equiv \arg \min_{\varepsilon} P_n H_{Z_t}^{a,a'}(\bar{p}_n) L \left(\overline{Q}_{n,Z_t}^{a,a'}(\varepsilon) \right).$$

- c.** Finally, to obtain an initial estimator $\overline{Q}_{n,R_t}^{a,a'}$, we regress the targeted estimate $\overline{Q}_{n,Z_t}^{*,a,a'}(R_t, Z_{t-1}, L_{t-1})$ constructed above on $A_t, R_{t-1}, Z_{t-1}, L_{t-1}$ among observations that remained uncensored at time t . We then evaluate the fitted function at the observed mediator and covariate histories $R_{t-1}, Z_{t-1}, L_{t-1}$ and the intervened exposure levels $A_t = a_t$ for these uncensored observations. This results in the initial estimates

$\bar{Q}_{n,R_t}^{\mathbf{a},\mathbf{a}'}(\mathbf{R}_{t-1}, \mathbf{L}_{t-1}, \mathbf{Z}_{t-1})$. Update this estimate using

$\bar{Q}_{n,R_t}^{*,\mathbf{a},\mathbf{a}'} \equiv \bar{Q}_{n,R_t}^{\mathbf{a},\mathbf{a}'}(\varepsilon_{n,R_t})$, where

$$\varepsilon_{n,R_t} \equiv \arg \min_{\varepsilon} P_n H_{R_t}^{\mathbf{a},\mathbf{a}'}(\bar{p}_n) L \left(\bar{Q}_{n,R_t}^{\mathbf{a},\mathbf{a}'}(\varepsilon) \right).$$

3. After running the algorithm in step (3) sequentially from $t=\tau$ down to $t=1$, we have targeted estimates $\bar{Q}_{n,R_1}^{*,\mathbf{a},\mathbf{a}'}(L_0)$ for each of the n observations.

The TMLE for $\Psi^{\mathbf{a},\mathbf{a}'}$ is given by

$$\psi_n^{TMLE} \equiv \Psi^{\mathbf{a},\mathbf{a}'}(\bar{Q}_n^{*,\mathbf{a},\mathbf{a}'}) = \frac{1}{n} \sum_{i=1}^n \bar{Q}_{n,R_1}^{*,\mathbf{a},\mathbf{a}'}(L_{0,i}) \quad (21)$$

By construction, this estimator satisfies $P_n D^{*,\mathbf{a},\mathbf{a}'}(\bar{Q}_n^{*,\mathbf{a},\mathbf{a}'}, \bar{p}_n) = 0$. Consequently, it inherits robustness of EIC described in section 3.3. Under certain regularity conditions, it is efficient at the data-generating P_0 , with influence curve $D^{*,\mathbf{a},\mathbf{a}'}(P_0)$. We could estimate the

asymptotic variance of $\sqrt{n} \left(\psi_n^{TMLE} - \Psi^{\mathbf{a},\mathbf{a}'}(P_0) \right)$ can be estimated using the sample

variance $\widehat{\text{Var}} D^{*,\mathbf{a},\mathbf{a}'} \left(\bar{Q}_n^{*,\mathbf{a},\mathbf{a}'}, \bar{p}_n \right)$.

5 Simulation Study

In this section, we conduct a simulation study to evaluate the comparative performance of these three estimators in estimating the mediation formula (5) for survival outcome Y_τ .

5.1 Data generating distribution

Consider the data structure $O = (L_0, A_1, R_1, Z_1, L_1, \dots, A_\tau, R_\tau, Z_\tau, L_\tau)$, with $\tau = 2$. L_0 encodes two baseline covariates L_{01} and L_{02} , A_t encodes a censoring indicator A_t^C of whether patient remained in the study by time t and a binary exposure A_t^E , R_t encodes covariates at time t that are directly affected by A_t and may influence Z_t and L_t , Z_t is a binary mediator of interest, L_t includes a time varying covariate L_t^1 and a death indicator Y_t of whether patient had died by time t . These variables are distributed according to the following data generating distribution

$$\begin{aligned}
L_{01} &\sim \text{Bern}(0.4); \\
L_{02} &\sim \text{Bern}(0.6); \\
A_t^C &\sim \text{Bern} \left(\text{expit}(1.5 - 0.8L_{02} - 0.4(I(t>1) \times L_{t-1}^1 + I(t=1)L_{01}) + 0.5I(t>1)A_{t-1}^E) \right) \\
A_t^E &\sim \text{Bern} \left(\text{expit}(-0.1 + 1.2L_{02} + 0.7(I(t>1) \times L_{t-1}^1 + I(t=1)L_{01}) - 0.1I(t>1)A_{t-1}^E) \right) \\
R_t &\sim \text{Bern} \left(\text{expit}(-0.8 + A_t^E + 0.1(I(t>1) \times L_{t-1}^1 + I(t=1)L_{01}) + 0.3(I(t>1) \times R_{t-1} + I(t=1)L_{02})) \right) \\
Z_t &\sim \text{Bern} \left(\text{expit}(-0.5 + 0.8L_{02} + 0.8A_t^E + R_t) \right) \\
L_t^1 &\sim \text{Bern} \left(\text{expit}(-1 + 0.3L_{02} + A_t^E + 0.7Z_t - 0.2I(t>1)L_{t-1}^1) \right) \\
Y_t &\sim \text{Bern} \left(\text{expit}(0.2 + 1.5L_{02} + R_t + 0.2L_t^1 - 0.3A_t^E - 0.3Z_t - 0.2A_t^E \times Z_t - 0.1I(t>1)R_{t-1}) \right).
\end{aligned}$$

After either censoring or death, all subsequent variables take a default value. The target parameter of interest is $\Psi^{1,0}(P_0) \approx 0.912$. To obtain this approximate, we first generated a large sample (1,000,000 observations) using the above distributions by setting $A_t^E=0$ in the equation for Z_t and $A_t^E=1$ elsewhere, as well as assigning the indicator $A_t^C=1$ (i.e. all remain in study), and then take the sample mean outcome Y_t in this large sample.

5.2 Estimators

Correctly specified conditional probabilities $\bar{p} = (p_A, p_Z, p_R, p_L)$ are obtained using logistic regressions as specified in the data-generating distributions. We estimate $\bar{Q}_{L_t}^{a,a'}$, $\bar{Q}_{Z_t}^{a,a'}$ and $\bar{Q}_{R_t}^{a,a'}$ using the regression-based approach: the so-called correctly specified estimators are obtained using Super Learner to regress the expectant on all the parent exposure, mediator and covariate history up to point t , described in steps in sections 4.1 and 4.3. The misspecified counterparts of $\bar{p}$ and $\bar{Q}^{a,a'}$ only regress on A_b in the case of nuisance parameters related to Z_t and R_b or only regress on A_t and Z_b in the case of nuisance parameters related to L_b or uses in marginal distribution, in the case of p_A . We note here that due to the nature of nested regressions, the so-called 'correct' $\bar{Q}^{a,a'}$ do not actually specify the functional form of these expectations, they only adjust for all the relevant terms; this abuse of terminology is meant to contrast with the estimators which omit important covariates. The Super Learner will be implemented using the default library of candidate algorithms, which include glm, stepAIC, bayesglm, each coupled with a correlation-based variable screening method, as well as a version with no variable screening.

We will implement the Non-Targeted Substitution Estimator (NTsub, section 4.1), the Inverse Probability Weighted Estimator (IPW, section 4.2) and the Targeted Maximum Likelihood Estimator (TMLE, section 4.3) using these nuisance parameter specifications.

Results

We considered sample sizes $n = 400$ and $n = 4000$. Bias, variance and mean squared error (MSE) for each sample size were estimated over the 1000 datasets. In the table 1 below, legend for model specifications were as follows:

As predicted by general robustness conditions in corollary 3.3.1, when the nested regressions $\bar{Q}^{a,a'}$ are correct and the conditional probabilities are mis-specified (“ $\bar{Q}^{a,a'}$ correct”), TMLE provides bias reduction over a mis-specified IPW. Similarly, when only the covariate-related nuisance parameters (p_R , p_L and $\bar{Q}_{R_t}^{a,a'}$, $\bar{Q}_{L_t}^{a,a'}$) are mis-specified (“ L misspec.”), TMLE also provides substantial bias reduction over the mis-specified IPW or NTsub Estimators. When only the Z_t -related nuisance parameters (p_Z and $\bar{Q}_{Z_t}^{a,a'}$) (“ Z misspec.”), TMLE provides bias reduction over the mis-specified NTsub estimator across sample sizes, but its bias reduction over IPW is only apparent after large sample sizes. When $\bar{Q}^{a,a'}$ are all misspecified, but correct conditional probabilities p_A , p_Z , p_L , p_R are used in the weights $H^{a,a'}$ of the TMLE updating step, we still observe bias reduction of TMLE over NTsub in this example.

We recall that the correctly specified $\bar{Q}^{a,a'}$ in this implementation are only correct up to specification of key terms, but not functional form, as that is difficult to implement. This may have resulted in certain loss of finite sample gain for TMLE under ‘all correct’ specifications, as it was expected to be more efficient than the IPW, and this efficiency gain was not apparent until larger sample sizes. This may also have contributed to speed of convergence of the corresponding NTsub estimator.

6 Summary

In this paper, we proposed to random interventions approach to formulate parameters of interest in longitudinal mediation analysis with time varying mediator and exposures. Specifically, we defined the random interventions based on conditional distributions for the mediator. In comparison to an alternative random interventions formulation based on marginal distributions of the mediator ([29]), the proposed formulation capture different pathways of mediated effect and allows for application in survival settings, but it also trades-off stronger sequential randomization assumptions.

Under the RI formulation, the treatment of interest as well as the mediator variables are regarded as intervention variables. Under the proposed formulation, one can obtain a total effect decomposition and the subsequent definition of natural direct and indirect effects that are analogous to those in [10]. By regarding the mediator variables as intervention variables, the RI formulation requires external specification of a conditional mediator distribution. This aims to capture a, say, natural direct effect that would be measured if one could first run a trial on a random sample of the population where all receive exposure $\mathbf{A} = 0$ to ascertain the conditional distributions of mediator under null exposure Γ_t^0 , and then run a second trial on a separate sample where one would randomly assign exposures to $\mathbf{A} = 1$ vs $\mathbf{A} = 0$ and intervene on mediators to have conditional distributions Γ_t^0 . It is also important to note that causal mediation, under either RI or non-RI approaches, presupposes that the mediator of interest is amenable to external manipulation. In applications where the mediator variables are not amenable to intervention in practice, we should be cautious that causal mediation could only offer answers to purely mechanistic questions defined under hypothetical experiments.

The second contribution of this paper is a general semiparametric inference framework for the resulting effect parameters. More specifically, efficient influence curves under a locally saturated semiparametric model are derived, and their robustness properties are established. In many applications where the mediator densities are difficult to estimate, regression-based estimators of these iterated expectations are viable alternatives to substitution-based estimators that rely on consistent estimation of the mediator densities. We also developed the non-targeted substitution estimator, IPW estimator and TMLE for the mediational functional.

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7 Appendix

7.1 Proof of Lemma 1 Identifiability Result

For $X_t \in (R_t, L_t)$, we also denote $X_t \left(\mathbf{a}, \left(\bar{\Gamma}_{1,s}^{\mathbf{a}'} \right) \right)$ the counterfactual covariate generated at time t by intervening to set $\mathbf{Z}_{1,s} \sim \bar{\Gamma}_{1,s}^{\mathbf{a}'}$, $\mathbf{Z}_{s,t} = \mathbf{z}_{s,t}$

$$\begin{aligned}
E(Y_\tau(\mathbf{a}, \bar{\Gamma}^{\mathbf{a}'})) &= \sum_{\mathbf{r}, \mathbf{l}, \mathbf{z}} y_\tau p[L_0=l_0] \\
&\times \prod_t \left\{ p \left[R_t(\mathbf{a}, \bar{\Gamma}^{\mathbf{a}'}) = r_t | L_0=l_0, \mathbf{R}_{t-1}(\mathbf{a}, \bar{\Gamma}^{\mathbf{a}'}) = \mathbf{r}_{t-1}, \bar{\Gamma}_{t-1}^{\mathbf{a}'} = \mathbf{z}_{t-1}, \mathbf{L}_{t-1}(\mathbf{a}, \bar{\Gamma}^{\mathbf{a}'}) = \mathbf{l}_{t-1} \right] \right. \\
&\quad \times p \left[\Gamma_t^{\mathbf{a}'} = z_t | L_0=l_0, \mathbf{R}_t(\mathbf{a}, \bar{\Gamma}^{\mathbf{a}'}) = \mathbf{r}_t, \bar{\Gamma}_{t-1}^{\mathbf{a}'} = \mathbf{z}_{t-1}, \mathbf{L}_{t-1}(\mathbf{a}, \bar{\Gamma}^{\mathbf{a}'}) = \mathbf{l}_{t-1} \right] \\
&\quad \left. \times p \left[L_t(\mathbf{a}, \bar{\Gamma}^{\mathbf{a}'}) = l_t | L_0=l_0, \mathbf{R}_t(\mathbf{a}, \bar{\Gamma}^{\mathbf{a}'}) = \mathbf{r}_t, \bar{\Gamma}_t(\mathbf{a}') = \mathbf{z}_t, \mathbf{L}_{t-1}(\mathbf{a}, \bar{\Gamma}^{\mathbf{a}'}) = \mathbf{l}_{t-1} \right] \right\}.
\end{aligned}$$

$$\begin{aligned}
\Gamma_t^{\mathbf{a}'}, p \left[\Gamma_t^{\mathbf{a}'} = z_t | \mathbf{R}_t(\mathbf{a}, \bar{\Gamma}^{\mathbf{a}'}) = \mathbf{r}_t, \bar{\Gamma}_{t-1}^{\mathbf{a}'} = \mathbf{z}_{t-1}, \mathbf{L}_{t-1}(\mathbf{a}, \bar{\Gamma}^{\mathbf{a}'}) = \mathbf{l}_{t-1} \right] &\equiv p(Z_t(\mathbf{a}')) \\
&= z_t | \mathbf{R}_t(\mathbf{a}') = \mathbf{r}_t, \mathbf{Z}_{t-1}(\mathbf{a}') \\
&= \mathbf{z}_{t-1} | \mathbf{L}_{t-1}(\mathbf{a}') = \mathbf{l}_{t-1}.
\end{aligned}$$

By definition of $\Gamma_t^{\mathbf{a}'}$, This quantity arises in traditional longitudinal total causal effect problems where one sets $\mathbf{A} = \mathbf{a}'$, and measure $\mathbf{Z}$ and $\mathbf{L}$ (Robins [15]). Therefore, under A1, it is identifiable as the conditional probability $p_0(Z_t = z_t | \mathbf{A}_t = \mathbf{a}'_t, \mathbf{Z}_{t-1} = \mathbf{z}_{t-1}, \mathbf{L}_{t-1} = \mathbf{l}_{t-1})$ from the observed data distribution.

To identify the conditional probabilities of $R_t(\mathbf{a}, \bar{\Gamma}^{\mathbf{a}'})$ and $L_t(\mathbf{a}, \bar{\Gamma}^{\mathbf{a}'})$ we demonstrate the steps for the first two, the results for the subsequent covariates can be induced thereafter. Firstly

$$p \left[R_1(\mathbf{a}, \bar{\Gamma}^{\mathbf{a}'}) = r_1 | L_0 = l_0 \right] = p \left[R_1(a_1) = r_1 | L_0 = l_0 \right] = p \left[R_1(a_1) = l_1 | A_1 = a_1, L_0 = l_0 \right] = p_0 \left[R_1 = r_1 | A_1 = a_1, L_0 = l_0 \right].$$

The first equality is by definition of the counterfactuals $R_1(\mathbf{a}, \bar{\Gamma}^{\mathbf{a}'})$. The second equality is due to the assumption A2 that given L_0 , A_1 is independent of $R_1(\mathbf{a})$. The last equality follows from consistency. Next,

$$\begin{aligned}
&p \left[L_1(\mathbf{a}, \bar{\Gamma}^{\mathbf{a}'}) = l_1 | L_0 = l_0, R_1(\mathbf{a}, \bar{\Gamma}^{\mathbf{a}'}) = r_1, \Gamma_1^{\mathbf{a}'} = z_1 \right] \\
&= p \left[L_1(a_1, z_1) = l_1 | L_0 = l_0, R_1(\mathbf{a}, \bar{\Gamma}^{\mathbf{a}'}) = r_1, \Gamma_1^{\mathbf{a}'} = z_1 \right] \\
&= p \left[L_1(a_1, z_1) = l_1 | L_0 = l_0, R_1(\mathbf{a}, \bar{\Gamma}^{\mathbf{a}'}) = r_1 \right] \\
&= p \left[L_1(a_1, z_1) = l_1 | L_0 = l_0, R_1(a_1) = r_1 \right] \\
&= p_0 \left[L_1 = l_1 | L_0 = l_0, A_1 = a_1, R_1 = r_1, Z_1 = z_1 \right]
\end{aligned}$$

The first equality is by definition of the counterfactuals $L_1(\mathbf{a}, \bar{\Gamma}^{\mathbf{a}'})$ and $L_1(\mathbf{a}, \mathbf{z})$. The second equality is due to the fact that in our ideal experiment conditional on $L_0 = l_0$ and $R_1(\mathbf{a}, \bar{\Gamma}^{\mathbf{a}'}) = R_1(a_1) = r_1$, Z_1 is a random draw from the distribution $\Gamma_1^{\mathbf{a}'}(\cdot | l_0, r_1)$, and does not affect the covariates $L_1(a_1, z_1)$, whose value only depend on $R_1(a_1) = r_1$ and l_0 . The last equality

follows from the usual argument of sequential randomization under static interventions on (A, Z) by applying assumptions A2, A3.

The positivity assumptions in A4 assure that the conditional probabilities in the identifying expression (5) are well-defined.

7.2 Proof of Theorem 1

For any $P \in \mathcal{M}$, we recall the likelihood decomposition in (1):

$$p(O) = p(L_0) \times \prod_{t=1}^{\tau} (p(A_t | \mathbf{A}_{t-1}, \mathbf{R}_{t-1}, \mathbf{Z}_{t-1}, \mathbf{L}_{t-1}) p(R_t | \mathbf{A}_t, \mathbf{R}_{t-1}, \mathbf{Z}_{t-1}, \mathbf{L}_{t-1}) \times p(Z_t | \mathbf{A}_t, \mathbf{R}_t, \mathbf{Z}_{t-1}, \mathbf{L}_{t-1}) p(L_t | \mathbf{A}_t, \mathbf{R}_t, \mathbf{Z}_t, \mathbf{L}_{t-1})).$$

For $O_j \in \{L_0, A_t, R_t, Z_t, L_t : t = 1, \dots, \tau\}$, let P_{O_j} denote the conditional probability of $P_{O_j}(O_j | Pa(O_j))$.

Let $L^2(P)$ denote the Hilbert space of mean zero functions of O , endowed with the covariance operator. Consider a rich class of one-dimensional parametric submodels $P(\epsilon)$ that are generated by only fluctuating P_{O_j} . Under our model, no restrictions are imposed on the conditional probabilities P_{O_j} . As a result, given any function $S_{O_j} \in L^2(P)$ of $(O_j, Pa(O_j))$ with finite variance and $E_P(S_{O_j}(O_j, Pa(O_j)) | Pa(O_j)) = 0$, the fluctuation $P_{O_j}(\epsilon) = (1 + \epsilon S_{O_j}(O_j, Pa(O_j)))P_{O_j}$ is a valid one-dimensional submodel with score S_{O_j} . Therefore, the tangent subspaces corresponding to fluctuations of each P_{O_j} are given by

$$\begin{aligned} T(P_{L_0}) &= \{S_{L_0}(L_0) : E_P(S_{L_0}) = 0\} \\ T(P_{A_t}) &= \{S_{A_t}(A_t, \mathbf{A}_{t-1}, \mathbf{R}_{t-1}, \mathbf{Z}_{t-1}, \mathbf{L}_{t-1}) : E_P(S_{A_t} | \mathbf{A}_{t-1}, \mathbf{R}_{t-1}, \mathbf{Z}_{t-1}, \mathbf{L}_{t-1}) = 0\} \\ T(P_{R_t}) &= \{S_{R_t}(R_t, \mathbf{A}_t, \mathbf{R}_{t-1}, \mathbf{Z}_{t-1}, \mathbf{L}_{t-1}) : E_P(S_{R_t} | \mathbf{A}_t, \mathbf{R}_{t-1}, \mathbf{Z}_{t-1}, \mathbf{L}_{t-1}) = 0\} \\ T(P_{Z_t}) &= \{S_{Z_t}(Z_t, \mathbf{A}_t, \mathbf{R}_t, \mathbf{Z}_{t-1}, \mathbf{L}_{t-1}) : E_P(S_{Z_t} | \mathbf{A}_t, \mathbf{R}_t, \mathbf{Z}_{t-1}, \mathbf{L}_{t-1}) = 0\} \\ T(P_{L_t}) &= \{S_{L_t}(L_t, \mathbf{A}_t, \mathbf{R}_t, \mathbf{Z}_t, \mathbf{L}_{t-1}) : E_P(S_{L_t} | \mathbf{A}_t, \mathbf{Z}_t, \mathbf{R}_t, \mathbf{L}_{t-1}) = 0\}. \end{aligned}$$

Due to the factorization in (1), $T(P_{O_i})$ is orthogonal to $T(P_{O_j})$ for $O_i \neq O_j$. More-over, the tangent space $T(P)$, corresponding to fluctuations of the entire likelihood, is given by the orthogonal sum of these tangent subspaces, i.e. $T(P) = \bigoplus_j T(P_{O_j})$, and any score $S(O) \in T(P)$ can be decomposed as $\sum_j S_{O_j}(O)$.

Under this generous definition of the tangent subspaces, any function $S(O)$ that has zero mean and finite variance under P is contained in $T(P)$. This implies in particular that any gradient for the pathwise derivative of $\Psi^{\mathbf{a}, \mathbf{a}'}(\cdot)$ is contained in $T(P)$, and is thus in fact the canonical gradient. Therefore, it suffices to show that $D^{*, \mathbf{a}, \mathbf{a}'}(\cdot)$ in (10) is a gradient for the pathwise derivative of $\Psi^{\mathbf{a}, \mathbf{a}'}(\cdot)$.

Indeed, for any $S(O) = \sum_j S_{O_j}(O) \in T(P)$, let $P^S(\epsilon)$ denote the fluctuation of P with score S . Under appropriate regularity conditions, the pathwise derivative at P can be expressed as

$$\begin{aligned}
& \frac{d}{d\varepsilon} \Psi^{\mathbf{a}, \mathbf{a}'}(P^S(\varepsilon))|_{\varepsilon=0} \\
&= \frac{d}{d\varepsilon} \Big|_{\varepsilon=0} \sum_{\mathbf{r}, \mathbf{z}, \mathbf{l}} y \left\{ [(1+\varepsilon S_{L_0}) p_{L_0}] (l_0) \right. \\
&\quad \times \prod_{t=1}^{\tau} \left([(1+\varepsilon S_{R_t}) p_{R_t}] (r_t | \mathbf{a}_t, \mathbf{r}_{t-1}, \mathbf{z}_{t-1}, \mathbf{l}_{t-1}) \right. \\
&\quad \times [(1+\varepsilon S_{Z_t}) p_{Z_t}] (z_t | \mathbf{a}'_t, \mathbf{r}_t, \mathbf{z}_{t-1}, \mathbf{l}_{t-1}) [(1+\varepsilon S_{L_t}) p_{L_t}] (l_t | \mathbf{a}_t, \mathbf{r}_t, \mathbf{z}_t, \mathbf{l}_{t-1}) \Big\} \\
&= \sum_{\mathbf{r}, \mathbf{z}, \mathbf{l}} y \left(p_{L_0}(l_0) \mathbf{P}_R(\mathbf{r} | \mathbf{a}, \mathbf{z}, \mathbf{l}) \mathbf{P}_Z(\mathbf{z} | \mathbf{a}', \mathbf{r}, \mathbf{l}) \mathbf{P}_L(\mathbf{l} | \mathbf{a}, \mathbf{r}, \mathbf{z}) \sum_{t=1}^{\tau} S_{L_t} \right) \quad (22)
\end{aligned}$$

$$+ \sum_{\mathbf{r}, \mathbf{z}, \mathbf{l}} y \left(p_{L_0}(l_0) \mathbf{P}_R(\mathbf{r} | \mathbf{a}, \mathbf{z}, \mathbf{l}) \mathbf{P}_Z(\mathbf{z} | \mathbf{a}', \mathbf{r}, \mathbf{l}) \mathbf{P}_L(\mathbf{l} | \mathbf{a}, \mathbf{r}, \mathbf{z}) \sum_{t=1}^{\tau} S_{Z_t} \right) \quad (23)$$

$$+ \sum_{\mathbf{r}, \mathbf{z}, \mathbf{l}} y \left(p_{L_0}(l_0) \mathbf{P}_R(\mathbf{r} | \mathbf{a}, \mathbf{z}, \mathbf{l}) \mathbf{P}_Z(\mathbf{z} | \mathbf{a}', \mathbf{r}, \mathbf{l}) \mathbf{P}_L(\mathbf{l} | \mathbf{a}, \mathbf{r}, \mathbf{z}) \sum_{t=1}^{\tau} S_{R_t} \right) \quad (24)$$

$$+ \sum_{\mathbf{r}, \mathbf{z}, \mathbf{l}} y (p_{L_0}(l_0) \mathbf{P}_R(\mathbf{r} | \mathbf{a}, \mathbf{z}, \mathbf{l}) \mathbf{P}_Z(\mathbf{z} | \mathbf{a}', \mathbf{r}, \mathbf{l}) \mathbf{P}_L(\mathbf{l} | \mathbf{a}, \mathbf{r}, \mathbf{z}) S_{L_0}), \quad (25)$$

where $\mathbf{P}_R(\mathbf{r} | \mathbf{a}, \mathbf{z}, \mathbf{l}) \equiv \prod_{t=1}^{\tau} p_{R_t}(r_t | \mathbf{A}_t = \mathbf{a}_t, \mathbf{r}_{t-1}, \mathbf{z}_{t-1}, \mathbf{l}_{t-1})$, analogously for $\mathbf{P}_L$, and $\mathbf{P}_Z(\mathbf{z} | \mathbf{a}, \mathbf{r}, \mathbf{l}) \equiv \prod_{t=1}^{\tau} p_{Z_t}(z_t | \mathbf{A}_t = \mathbf{a}'_t, \mathbf{r}_t, \mathbf{z}_{t-1}, \mathbf{l}_{t-1})$.

Note firstly that by definition of D_t^L and S_{L_t} for every $t = 1, \dots, t_0$,

$$E_P \left(D_{L_t}^{\mathbf{a}, \mathbf{a}'}(\mathbf{R}_t, \mathbf{Z}_t, \mathbf{L}_t) S_{L_t}(\mathbf{A}_t, \mathbf{R}_t, \mathbf{Z}_t, \mathbf{L}_t) \right) = \sum_{\mathbf{r}, \mathbf{z}, \mathbf{l}} y p_{L_0}(l_0) \mathbf{P}_R(\mathbf{r} | \mathbf{a}, \mathbf{z}, \mathbf{l}) \mathbf{P}_Z(\mathbf{z} | \mathbf{a}', \mathbf{r}, \mathbf{l}) \mathbf{P}_L(\mathbf{l} | \mathbf{a}, \mathbf{r}, \mathbf{z}) S_{L_t}.$$

Moreover, $D_{L_t}^{\mathbf{a}, \mathbf{a}'}(P)(\mathbf{R}_t, \mathbf{Z}_t, \mathbf{L}_t)$ satisfies $E_P \left(D_{L_t}^{\mathbf{a}, \mathbf{a}'}(P)(\mathbf{R}_t, \mathbf{Z}_t, \mathbf{L}_t) | \mathbf{R}_t, \mathbf{Z}_t, \mathbf{L}_{t-1} \right) = 0$.

Therefore $D_{L_t}^{\mathbf{a}, \mathbf{a}'}(P) \in T(P_{L_t | Pa(L_t)})$ by the definition of these tangent subspaces. It thus follows from the orthogonal decomposition of $T(P)$ that (P)

$$E_P \left\{ D_{L_t}^{\mathbf{a}, \mathbf{a}'}(P) \times S_{L_t} \right\} = E_P \left\{ D_{L_t}^{\mathbf{a}, \mathbf{a}'}(P) \left(S_{L_0} + \sum_{t=1}^{\tau} S_{A_t} + S_{Z_t} + S_{L_t} \right) \right\}.$$

By similar arguments, (23) can be written as

$$E_P \left\{ D_{Z_t}^{\mathbf{a}, \mathbf{a}'}(P) \times S_{Z_t} \right\} = E_P \left\{ D_{Z_t}^{\mathbf{a}, \mathbf{a}'}(P) \left(S_{L_0} + \sum_{t=1}^{\tau} S_{A_t} + S_{Z_t} + S_{L_t} \right) \right\},$$

(24) can be written as

$$E_P \left\{ D_{R_t}^{\mathbf{a}, \mathbf{a}'}(P) \times S_{R_t} \right\} = E_P \left\{ D_{R_t}^{\mathbf{a}, \mathbf{a}'}(P) \left(S_{L_0} + \sum_{t=1}^{\tau} S_{A_t} + S_{Z_t} + S_{L_t} \right) \right\}.$$

and (25) can be written as

$$E_P \left\{ D_{L_0}^{\mathbf{a}, \mathbf{a}'}(P) \times S_{L_0} \right\} = E_P \left\{ D_{L_0}^{\mathbf{a}, \mathbf{a}'}(P) \left(S_{L_0} + \sum_{t=1}^{\tau} S_{A_t} + S_{Z_t} + S_{L_t} \right) \right\}.$$

Combining these results, one concludes that

$$\frac{d}{d\varepsilon} \Psi^{\mathbf{a}, \mathbf{a}'}(P^S(\varepsilon))|_{\varepsilon=0} = E_P \left\{ \left(D_{L_0}^{\mathbf{a}, \mathbf{a}'}(P) + \sum_{t=1}^{\tau} D_{R_t}^{\mathbf{a}, \mathbf{a}'}(P) + D_{Z_t}^{\mathbf{a}, \mathbf{a}'}(P) + D_{L_t}^{\mathbf{a}, \mathbf{a}'}(P) \right) S \right\}$$

Therefore, $D^{*, \mathbf{a}, \mathbf{a}'}(P) \equiv D_{L_0}^{\mathbf{a}, \mathbf{a}'}(P) + \sum_{t=1}^{\tau} D_{R_t}^{\mathbf{a}, \mathbf{a}'}(P) + D_{Z_t}^{\mathbf{a}, \mathbf{a}'}(P) + D_{L_t}^{\mathbf{a}, \mathbf{a}'}(P)$ is a gradient for the pathwise derivative of $\Psi^{\mathbf{a}, \mathbf{a}'}$ at P . As discussed above, under the nonparametric model, $D^{*, \mathbf{a}, \mathbf{a}'}(P)$ is in fact the canonical gradient.

The first case of the robustness condition is trivial. In the second case, correct p_L and p_R yield that $E_{P_0} D_{R_t}^{\mathbf{a}, \mathbf{a}'}(P) = 0$ and $E_{P_0} D_{L_t}^{\mathbf{a}, \mathbf{a}'}(P) = 0$; correct p_L , p_R and p_A produce a telescopic sum over t of $D_{Z_t}^{\mathbf{a}, \mathbf{a}'}$. Specifically

$$\begin{aligned} E_{P_0} \sum_t D_{Z_t}^{\mathbf{a}, \mathbf{a}'}(P) &= \\ \sum_{\mathbf{l}_{\tau-1}, \mathbf{r}, \mathbf{z}} \bar{Q}_{L_{\tau}}(P_0)^{\mathbf{a}, \mathbf{a}'}(\mathbf{r}, \mathbf{z}, \mathbf{l}_{\tau-1}) p_{0, L_0}(\mathbf{l}_0) \mathbf{P}_{0, R}(\mathbf{r} | \mathbf{a}, \mathbf{z}, \mathbf{l}_{\tau-1}) \mathbf{P}_{0, Z}(\mathbf{z} | \mathbf{a}', \mathbf{r}, \mathbf{l}_{\tau-1}) \mathbf{P}_{0, L}(\mathbf{l}_{\tau-1} | \mathbf{a}, \mathbf{r}, \mathbf{z}) \\ &\quad - E_{P_0} \bar{Q}_{Z_1}^{\mathbf{a}, \mathbf{a}'}(\mathbf{R}_1, L_0) \\ &= \Psi^{\mathbf{a}, \mathbf{a}'}(P_0) - E_{P_0} \bar{Q}_{Z_1}^{\mathbf{a}, \mathbf{a}'}(\mathbf{R}_1, L_0) \end{aligned}$$

On the other hand, $E_{P_0} D_{L_0}^{\mathbf{a}, \mathbf{a}'}(P) = E_{P_0} \sum_{r_1} p_{0,R}(r_1 | l_0, a_1) \bar{Q}_{Z_1}^{\mathbf{a}, \mathbf{a}'}(r_1, L_0) - \Psi^{\mathbf{a}, \mathbf{a}'}(P)$.
Therefore, $E_{P_0} D_{L_0}^{*, \mathbf{a}, \mathbf{a}'}(P) = 0$ implies that

$$\begin{aligned} 0 &= E_{P_0} D_{L_0}^{*, \mathbf{a}, \mathbf{a}'}(P) = E_{P_0} \sum_t D_{Z_t}^{\mathbf{a}, \mathbf{a}'} + E_{P_0} D_{L_0}^{\mathbf{a}, \mathbf{a}'}(P) \\ &= \Psi^{\mathbf{a}, \mathbf{a}'}(P_0) - E_{P_0} \bar{Q}_{Z_1}^{\mathbf{a}, \mathbf{a}'}(\mathbf{R}_1, L_0) + E_{P_0} \sum_{r_1} p_{0,R}(r_1 | l_0, a_1) \bar{Q}_{Z_1}^{\mathbf{a}, \mathbf{a}'}(r_1, L_0) - \Psi^{\mathbf{a}, \mathbf{a}'}(P) \\ &= \Psi^{\mathbf{a}, \mathbf{a}'}(P_0) - \Psi^{\mathbf{a}, \mathbf{a}'}(P). \end{aligned}$$

Similarly, in the third case, correct p_Z yields $P_0 D_t^{Z_t, \mathbf{a}, \mathbf{a}'}(P) = 0$; the correct p_A and correct p_Z will produce the desired telescopic sums over t of $E_{P_0} D_{L_t}^{\mathbf{a}, \mathbf{a}'}(P) + E_{P_0} D_{R_t}^{\mathbf{a}, \mathbf{a}'}(P)$, leaving

$$\begin{aligned} 0 &= E_{P_0} D^{*, \mathbf{a}, \mathbf{a}'}(P) = \sum_t \left\{ E_{P_0} D_{L_t}^{\mathbf{a}, \mathbf{a}'}(P) + E_{P_0} D_{R_t}^{\mathbf{a}, \mathbf{a}'}(P) \right\} + E_{P_0} D_{L_0}^{\mathbf{a}, \mathbf{a}'}(P) \\ &= \Psi^{\mathbf{a}, \mathbf{a}'}(P_0) - E_{P_0} \bar{Q}_{R_1}^{\mathbf{a}, \mathbf{a}'}(L_0) + E_{P_0} E_{P_0} \bar{Q}_{R_1}^{\mathbf{a}, \mathbf{a}'}(L_0) - \Psi^{\mathbf{a}, \mathbf{a}'}(P) \\ &= \Psi^{\mathbf{a}, \mathbf{a}'}(P_0) - \Psi^{\mathbf{a}, \mathbf{a}'}(P). \end{aligned}$$

7.3 Derivations of γ in section 3.3.1

Firstly for $j = 1, \dots, t$, we note that

$$\begin{aligned} p_Z(Z_j | \mathbf{a}'_j, \mathbf{R}_j, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1}) &= \frac{p(Z_j, \mathbf{a}'_j, \mathbf{R}_j, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})}{p(\mathbf{a}'_j, \mathbf{R}_j, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})} = \frac{p(\mathbf{a}'_j, \mathbf{R}_j, \mathbf{Z}_j, \mathbf{L}_{j-1})}{p(\mathbf{a}'_j, \mathbf{R}_j, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})} \\ &= \frac{\prod_{s=1}^j p(a'_s | a'_{s-1}, \mathbf{R}_j, \mathbf{Z}_j, \mathbf{L}_{j-1}) p(\mathbf{R}_j, \mathbf{Z}_j, \mathbf{L}_{j-1})}{\prod_{s=1}^j p(a'_s | a'_{s-1}, \mathbf{R}_j, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1}) p(\mathbf{R}_j, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})} \\ &\equiv \prod_{s=1}^j \frac{\gamma^{1,s,j}(a'_s | a'_{s-1}, \mathbf{R}_j, \mathbf{Z}_j, \mathbf{L}_{j-1})}{\gamma^{2,s,j}(a'_s | a'_{s-1}, \mathbf{R}_j, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})} \frac{p(\mathbf{R}_j, \mathbf{Z}_j, \mathbf{L}_{j-1})}{p(\mathbf{R}_j, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})}. \end{aligned}$$

The last equality is the definition of γ . Consequently,

$$\begin{aligned} \frac{p_Z(Z_j | \mathbf{a}'_j, \mathbf{R}_j, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})}{p_Z(Z_j | \mathbf{a}_j, \mathbf{R}_j, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})} &= \frac{p(\mathbf{a}'_j, \mathbf{R}_j, \mathbf{Z}_j, \mathbf{L}_{j-1})}{p(\mathbf{a}'_j, \mathbf{R}_j, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})} \frac{p(\mathbf{a}_j, \mathbf{R}_j, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})}{p(\mathbf{a}_j, \mathbf{R}_j, \mathbf{Z}_j, \mathbf{L}_{j-1})} \\ &= \prod_{s=1}^j \frac{\gamma^{1,s,j}(a'_s | a'_{s-1}, \mathbf{R}_j, \mathbf{Z}_j, \mathbf{L}_{j-1})}{\gamma^{2,s,j}(a'_s | a'_{s-1}, \mathbf{R}_j, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})} \frac{p(\mathbf{R}_j, \mathbf{Z}_j, \mathbf{L}_{j-1})}{p(\mathbf{R}_j, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})} \\ &\quad \times \prod_{s=1}^j \frac{\gamma^{2,s,j}(a_s | a_{s-1}, \mathbf{R}_j, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})}{\gamma^{1,s,j}(a_s | a_{s-1}, \mathbf{R}_j, \mathbf{Z}_j, \mathbf{L}_{j-1})} \frac{p(\mathbf{R}_j, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})}{p(\mathbf{R}_j, \mathbf{Z}_j, \mathbf{L}_{j-1})} \\ &= \prod_{s=1}^j \frac{\gamma^{1,s,j}(a'_s | a'_{s-1}, \mathbf{R}_j, \mathbf{Z}_j, \mathbf{L}_{j-1})}{\gamma^{2,s,j}(a'_s | a'_{s-1}, \mathbf{R}_j, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})} \frac{\gamma^{2,s,j}(a_s | a_{s-1}, \mathbf{R}_j, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})}{\gamma^{1,s,j}(a_s | a_{s-1}, \mathbf{R}_j, \mathbf{Z}_j, \mathbf{L}_{j-1})} \end{aligned}$$

This derives the alternative expression of $H_{L_t}^{\mathbf{a}, \mathbf{a}'}$ and $H_{R_t}^{\mathbf{a}, \mathbf{a}'}$ in section 3.3.1. Next, for $H_{Z_t}^{\mathbf{a}, \mathbf{a}'}$, we note that

$$\begin{aligned} & p_L(L_j | \mathbf{a}_j, \mathbf{R}_j, \mathbf{Z}_j, \mathbf{L}_{j-1}) \times p_R(R_j | \mathbf{a}_j, \mathbf{R}_{j-1}, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1}) \\ &= \frac{p(\mathbf{a}_j, \mathbf{R}_j, \mathbf{Z}_j, \mathbf{L}_j)}{p(\mathbf{a}_j, \mathbf{R}_j, \mathbf{Z}_j, \mathbf{L}_{j-1})} \times \frac{p(\mathbf{a}_j, \mathbf{R}_j, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})}{p(\mathbf{a}_j, \mathbf{R}_{j-1}, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})} \\ &= \frac{p(\mathbf{a}_j, \mathbf{R}_j, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})}{p(\mathbf{a}_j, \mathbf{R}_j, \mathbf{Z}_j, \mathbf{L}_{j-1})} \times \frac{p(\mathbf{a}_j, \mathbf{R}_j, \mathbf{Z}_j, \mathbf{L}_j)}{p(\mathbf{a}_j, \mathbf{R}_{j-1}, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})} \\ &= \frac{\prod_{s=1}^j \gamma^{2,s,j}(a_s | \mathbf{a}_{s-1}, \mathbf{R}_j, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})}{\prod_{s=1}^j \gamma^{1,s,j}(a_s | \mathbf{a}_{s-1}, \mathbf{R}_j, \mathbf{Z}_j, \mathbf{L}_{j-1})} \frac{p(\mathbf{R}_j, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})}{p(\mathbf{R}_j, \mathbf{Z}_j, \mathbf{L}_{j-1})} \\ &\quad \times \frac{p(\mathbf{a}_j, \mathbf{R}_j, \mathbf{Z}_j, \mathbf{L}_j)}{p(a_j | \mathbf{a}_{j-1}, \mathbf{R}_{j-1}, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1}) p(\mathbf{a}_{j-1}, \mathbf{R}_{j-1}, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})}. \end{aligned}$$

When we take the product for $\mathbf{a}$ in $H_{Z_t}^{\mathbf{a}, \mathbf{a}'}$, we obtain

$$\begin{aligned} & \prod_{j=1}^{t-1} p_L(L_j | \mathbf{a}_j, \mathbf{R}_j, \mathbf{Z}_j, \mathbf{L}_{j-1}) \times \prod_{j=1}^t p_R(R_j | \mathbf{a}_j, \mathbf{R}_{j-1}, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1}) \\ &= \frac{\prod_{j=1}^t p(\mathbf{a}_j, \mathbf{R}_j, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})}{\prod_{j=1}^{t-1} p(\mathbf{a}_j, \mathbf{R}_j, \mathbf{Z}_j, \mathbf{L}_{j-1})} \times \\ &\quad \frac{\prod_{j=1}^t p(a_j | \mathbf{a}_{j-1}, \mathbf{R}_{j-1}, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1}) p(\mathbf{a}_{j-1}, \mathbf{R}_{j-1}, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})}{\prod_{j=1}^t \prod_{s=1}^j \gamma^{2,s,j}(a_s | \mathbf{a}_{s-1}, \mathbf{R}_j, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1}) p(\mathbf{R}_j, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})} \\ &= \frac{\prod_{j=1}^{t-1} \prod_{s=1}^j \gamma^{1,s,j}(a_s | \mathbf{a}_{s-1}, \mathbf{R}_j, \mathbf{Z}_j, \mathbf{L}_{j-1})}{\prod_{j=1}^{t-1} \prod_{s=1}^j \gamma^{1,s,j}(a_s | \mathbf{a}_{s-1}, \mathbf{R}_j, \mathbf{Z}_j, \mathbf{L}_{j-1})} \frac{1}{\prod_{j=1}^t p(a_j | \mathbf{a}_{j-1}, \mathbf{R}_{j-1}, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1}) p(L_0)}. \end{aligned}$$

Consequently

$$\begin{aligned} & \prod_{j=1}^{t-1} \frac{p_L(L_j | \mathbf{a}_j, \mathbf{R}_j, \mathbf{Z}_j, \mathbf{L}_{j-1})}{p_L(L_j | \mathbf{a}'_j, \mathbf{R}_j, \mathbf{Z}_j, \mathbf{L}_{j-1})} \times \prod_{j=1}^t \frac{p_R(R_j | \mathbf{a}_j, \mathbf{R}_{j-1}, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})}{p_R(R_j | \mathbf{a}'_j, \mathbf{R}_{j-1}, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})} \\ &= \prod_{j=1}^{t-1} \prod_{s=1}^j \frac{\gamma^{1,s,j}(a'_s | \mathbf{a}'_{s-1}, \mathbf{R}_j, \mathbf{Z}_j, \mathbf{L}_{j-1})}{\gamma^{1,s,j}(a_s | \mathbf{a}_{s-1}, \mathbf{R}_j, \mathbf{Z}_j, \mathbf{L}_{j-1})} \prod_{j=1}^t \prod_{s=1}^j \frac{\gamma^{2,s,j}(a_s | \mathbf{a}_{s-1}, \mathbf{R}_j, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})}{\gamma^{2,s,j}(a'_s | \mathbf{a}'_{s-1}, \mathbf{R}_j, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})} \\ &\quad \times \prod_{j=1}^t \frac{p(a'_j | \mathbf{a}'_{j-1}, \mathbf{R}_{j-1}, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})}{p(a_j | \mathbf{a}_{j-1}, \mathbf{R}_{j-1}, \mathbf{Z}_{j-1}, \mathbf{L}_{j-1})}. \end{aligned}$$

This derives the alternative expression of $H_{Z_t}^{\mathbf{a}, \mathbf{a}'}$ in section 3.3.1.

Table 1

Bias, variance and MSE over 1000 simulations.

	n	Bias		Var	
		500	5000	500	5000
all correct	TMLE	6.57e-04	1.87e-05	1.32e-03	1.01e-04
	IPW	1.12e-03	4.63e-05	1.24e-03	1.05e-04
	NTsub	8.42e-04	7.53e-04	9.81e-04	7.93e-05
$Q^{a, \ast}$ correct	TMLE	1.02e-03	2.61e-04	1.35e-03	1.15e-04
	IPW	4.20e-03	6.33e-03	1.86e-03	1.78e-04
L misspec.	TMLE	4.63e-04	3.11e-05	1.22e-03	1.02e-04
	IPW	1.12e-03	4.63e-05	1.24e-03	1.05e-04
	NTsub	5.28e-03	5.85e-03	6.64e-04	6.30e-05
Z misspec.	TMLE	1.41e-02	5.61e-03	3.02e-03	2.51e-04
	IPW	1.22e-02	1.46e-02	2.37e-03	2.12e-04
	NTsub	7.66e-02	7.73e-02	3.53e-03	2.93e-04
$Q^{a, \ast}$ misspec.	TMLE	1.90e-04	7.73e-05	1.25e-03	1.02e-04
	NTsub	6.86e-03	6.95e-03	7.33e-04	7.05e-05