Congenial Causal Inference with Binary Structural Nested Mean Models

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Abstract

Structural nested mean models (SNMMs) are among the fundamental tools for inferring causal effects of time-dependent exposures from longitudinal studies. With binary outcomes, however, current methods for estimating multiplicative and additive SNMM parameters suffer from variation dependence between the causal SNMM parameters and the non-causal nuisance parameters. Estimating methods for logistic SNMMs do not suffer from this dependence. Unfortunately, in contrast with the multiplicative and additive models, unbiased estimation of the causal parameters of a logistic SNMM rely on additional modeling assumptions even when the treatment probabilities are known. These difficulties have hindered the uptake of SNMMs in epidemiological practice, where binary outcomes are common. We solve the variation dependence problem for the binary multiplicative SNMM by a reparametrization of the non-causal nuisance parameters. Our novel nuisance parameters are variation independent of the causal parameters, and hence allows the fitting of a multiplicative SNMM by unconstrained maximum likelihood. It also allows one to construct true (i.e. congenial) doubly robust estimators of the causal parameters. Along the way, we prove that an additive SNMM with binary outcomes does not admit a variation independent parametrization, thus explaining why we restrict ourselves to the multiplicative SNMM.

Keywords: Bivariate mapping; Likelihood inference; Longitudinal studies; Variation independence

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1 Introduction

In biomedical studies researchers are often interested in inferring causal effects of time-dependent exposures from longitudinal studies. For example, suppose one is interested in estimating the (joint) effect of maternal stress on childhood illness from longitudinal observational data. The relationships among observed variables may be represented by the causal directed acyclic graph (DAG, Pearl, 2009) in Figure 1, in which $A_0$ and $A_1$ denote maternal stress levels at baseline and the first follow-up, respectively, $L_1$ is the intermediate covariate encoding whether or not the child is ill at the first follow-up, and $Y$ is the outcome of interest encoding whether or not the child is ill at the second follow-up. The node $U$ denotes unmeasured variables such as the child’s underlying immune status that is a common cause of $L_1$ and $Y$. There may also be covariates $L_0$ measured at baseline, in which case one can add $L_0$ and a directed edge from $L_0$ to every other variable to Figure 1.

![Figure 1: A DAG illustrating time-varying treatments and confounders. The baseline covariates $L_0$ are omitted for brevity. Variables $A_0, L_1, A_1, Y$ are observed; $U$ is unobserved.](image)

As discussed below, the causal graph in Figure 1 implies that, even though $U$ is unmeasured, the joint causal effect of $A_0$ and $A_1$ on $Y$ is identified from the observed data. However, conventional regression adjustment methods cannot be used to estimate the joint effect of $A_0$ and $A_1$, regardless of whether or not one adjusts for the time-dependent confounder $L_1$ in the regression, as 1) $L_1$ mediates the effect of $A_0$ on $Y$; 2) $L_1$ is a confounder for the effect of $A_1$ on $Y$; 3) $L_1$ is a collider (Pearl, 2009) on the path $A_0 \rightarrow L_1 \leftarrow U \rightarrow Y$ (Robins, 1986). This problem can be overcome with the structural nested mean models (SNMMs) (Robins, 1994), which model the contrasts of potential outcomes $Y(a_0, a_1)$ rather than the observed outcome $Y$. In the simplest case where there is only one follow-up so that the observed data consist of $L_0, A_0$ and $Y$, the SNMM is known as the structural mean model (SMM) and takes the following form:

$$g(E[Y(1) \mid A_0 = 1, L_0 = l_0]) - g(E[Y(0) \mid A_0 = 1, L_0 = l_0]) = B(l_0; \alpha),$$

(1)
where $g$ is the link function, $Y(a_0)$ is the potential outcome that would have been observed under treatment $a_0$ and $B(l_0; \alpha)$ is a function known up to a finite-dimensional parameter $\alpha$ such that $B(l_0; 0) = 0$. A leading special is the linear specification $B(l_0; \alpha) = \alpha^T l_0$. Under the sequential ignorability assumption (Robins, 1986), the structural model (1) implies the following observed data model:

$$g(E[Y | A_0 = 1, L_0 = l_0]) - g(E[Y | A_0 = 0, L_0 = l_0]) = B(l_0; \alpha).$$

Model (2) is semiparametric as it does not specify the full regression model $g(E[Y | A_0 = a_0, L_0 = l_0])$. To enable maximum likelihood estimation, one may assume an additional baseline mean model $E[Y | A_0 = 0, L_0 = l_0; \zeta]$, resulting in a generalized linear model (GLM). Alternatively, with the log or identity link, estimation of $\alpha$ is usually based on g-estimation methods, which are doubly robust in the sense that they yield estimators which are consistent and asymptotically normal (CAN) under correct specification of either a model for the density of treatments or the baseline mean model.

However, when $Y$ is binary and the link $g$ is the log or the identity function, even for the simple point exposure case, a baseline mean model $P(Y = 1 | A_0 = 0, L_0 = l_0; \zeta)$ is not variation independent of the SMM and hence can be “uncongenial” (Meng, 1994). In this case, maximum likelihood estimation requires constrained optimization in a restricted parameter space, and with a new covariate value for $L_0$, the maximum likelihood estimator (MLE) $(\hat{\alpha}_{\text{mle}}, \hat{\zeta}_{\text{zeta}})$ may still imply a fitted risk $\hat{P}(Y = 1 | A_0 = 1, L_0 = 0)$ to be greater than one. Additionally, the g-estimators fail to be truly doubly robust because of the uncongenial baseline model. On the other hand, when the link $g$ is the logistic function, it is not possible to use g-estimation methods for estimating parameters in SNMMs (Robins, 2000). In particular, unlike the case with the additive or multiplicative SNMM, it is not possible to guarantee consistent estimation of logistic SNMM parameters even in randomized trials (Robins and Rotnitzky, 2004). Inference for logistic SNMMs is also much more complicated than that for the multiplicative or additive SNMMs; see, for example, Vansteelandt and Goetghebeur (2003); Robins and Rotnitzky (2004) and Matsouaka and Tchetgen Tchetgen (2014). Furthermore, the logistic SNMMs estimate odds ratios which are not collapsible (Rothman et al., 2008). The non-collapsibility of the odds ratio also limits the interpretability and generalizability of estimates from logistic SNMMs.

For the reasons mentioned above, over the past two decades SNMMs were regarded as inappropriate for inferring causal effects with binary outcomes (e.g. Robins, 2000; Vansteelandt and Joffe, 2014). This
also partly explains why the SNMM has not been as popular as its younger sibling, the marginal structural model (Robins, 2000). Richardson et al. (2017) offered a novel approach to overcoming these problems in the point exposure case. These authors noted that the baseline risk model included in a GLM is often not of primary interest; instead, it is a *nuisance* model to aid estimation of the SMM parameter. To resolve the variation dependence between the *conventional* nuisance model and the SMM, they introduce a novel nuisance model that is variation independent of the SMM with the log or identity link. In conjunction with the SMM, their nuisance model gives rise to a likelihood for \( P(Y = 1 \mid A_0 = a_0, L_0 = l_0) \) so that one can use unconstrained maximum likelihood for estimation. Furthermore, it permits true doubly robust \( g \)-estimation as the nuisance model is congenial with the SMM.

In this paper, we study the more challenging case of time-varying treatments. As we show later in Proposition 3.1, unlike in the point exposure case, the causal parameters of binary additive SNMMs are generally variation *dependent* of each other. We show, however, that the causal parameters of binary multiplicative SNMMs are variation *independent* of each other. For the latter, in parallel to Richardson et al. (2017)’s work, we develop novel nuisance models that are variation independent of the multiplicative SNMMs. In the point exposure case, our nuisance models reduce to that of Richardson et al. (2017). To focus on the main idea, although our nuisance models certainly also permit doubly robust \( g \)-estimation, we only discuss likelihood inference in this paper. Throughout we assume that the time varying treatments, covariates and outcome are binary, but do not place restrictions on the distributions of baseline covariates \( L_0 \).

The rest of this article is organized as follows. In Section 2 we review Richardson et al. (2017)’s work on binary SMMs, as well as Robins (1994)’s work on SNMMs. In Section 3 we present our main results on parameterizations for the binary multiplicative and additive SNMMs. Our approach is then illustrated with both simulated and real data analyses in Section 4. We further discuss implications of the current work and directions for future research in Section 5.

## 2 Framework and problem description

### 2.1 Review of binary structural mean models

Consider a biomedical study with binary treatment \( A_0 \), binary outcome \( Y \) and general baseline covariates \( L_0 \). Under the conditional ignorability condition that \( A_0 \perp\!
\!\!
\perp Y(a_0) \mid L_0 \), the SMM parameters are identified and, depending on the link, they can be interpreted as (monotone transformations of) the conditional relative
risk (RR), conditional risk difference (RD) or conditional odds ratio (OR) defined as

\[
RR(l_0) = \frac{p_1(l_0)}{p_0(l_0)}, \quad RD(l_0) = p_1(l_0) - p_0(l_0), \quad OR(l_0) = \frac{p_1(l_0)(1 - p_0(l_0))}{p_0(l_0)(1 - p_1(l_0))}
\]

respectively, where \( p_1(l_0) = P(Y = 1 \mid A_0 = 1, L_0 = l_0) \) and \( p_0(l_0) = P(Y = 1 \mid A_0 = 0, L_0 = l_0) \). In comparison with the OR, the RR and RD are arguably easier to interpret, partly because they are collapsible in the sense that in the absence of confounding, the marginal RR or RD always lies within the convex hull of the conditional RRs or RDs (Rothman et al., 2008). Moreover, it is possible to guarantee consistent estimation of the conditional RR and RD if one correctly specifies the functional form of \( RR(l_0) \) and \( RD(l_0) \) in a randomized trial while it is not possible to do so for the OR (Robins, 2000). Hence over the last three decades, many researchers argued for the use of multiplicative and additive SMMs over the logistic SMM; see Lumley et al. (2006) and references therein.

Despite these advantages, the application of multiplicative and additive SMMs in practice so far has been relatively infrequent compared to the logistic SMM. Arguably this was due to lack of a good nuisance model for estimating parameters in the multiplicative and additive SMMs. To be concrete, note that for maximum likelihood estimation, one needs to specify a model for a variation independent nuisance function \( \phi(l_0) \) such that the probabilities \((p_1(l_0), p_0(l_0))\) can be uniquely identified from \((RD(l_0), \phi(l_0))\) or \((RR(l_0), \phi(l_0))\).

The commonly used generalized linear modeling approach essentially chooses \( \phi(l_0) \) to be (a monotone transformation of) the baseline risk \( p_0(l_0) \). For example, with a log link a GLM specifies

\[
\log(RR(l_0)) = \alpha^T l_0, \quad (3)
\]

\[
\log(p_0(l_0)) = \mu^T l_0. \quad (4)
\]

However, the models (3) and (4) are variation dependent as the range of \( \alpha \) depends on the specific value of \( \mu \). To solve this problem, Richardson et al. (2017) introduce a novel nuisance function, the \( l_0 \)-specific odds product:

\[
OP(l_0) = \frac{p_0(l_0)p_1(l_0)}{(1 - p_0(l_0))(1 - p_1(l_0))}
\]

and show that it is variation independent of both the \( RD(l_0) \) and \( RR(l_0) \). Furthermore, given \( l_0 \), the map-
Figure 2: L’Abbé plots: Lines of constant: (Left) log RR ∈ (−3, −2.5, . . . , 3), OP = 0.5 (red curve); (Right) RD ∈ {−0.9, −0.8, . . . , 0.9}, OP = 0.5 (red curve).

are both smooth bijections from $\mathbb{D} \times \mathbb{R}^+$ to $(0, 1)^2$, where $\mathbb{R}^+ = (0, \infty)$, $\mathbb{D} = \mathbb{R}^+$ for $RR(l_0)$ and $\mathbb{D} = (-1, 1)$ for $RD(l_0)$. Figure 2 gives an illustration. One can see that each contour line of relative risk or risk difference intersects with the contour line of odds product at one and only one point, so that these parameters are variation independent and the maps in (5) are bijections. The latter feature is important as it allows likelihood inference and risk predictions with these models.

2.2 Structural nested mean models

In this paper we consider a more general biomedical study with longitudinal measurements at multiple time points 0, . . . , K. Let $A_k$ and $L_k$ denote the binary treatment indicator and covariate measurement at time $k$, respectively and $Y$ be the outcome measured at time $K + 1$. We also let $\bar{A}_k$ and $\bar{L}_k$ denote the treatment and covariate history up to time $k$, that is $\bar{A}_k = (A_0, \ldots, A_k)$ and $\bar{L}_k = (L_0, \ldots, L_k)$. We presume that the covariate measurement precedes treatment at the same time point. We use $Y(\bar{a}_k, 0)$ to denote the outcome.
that would have been observed had the subject been exposed to treatment \( \bar{a}_k \) until time \( k \) and treatment 0 thereafter. Implicit in this notation is the assumption of no interference between different subjects.

Following Robins (1986), we make the sequential ignorability assumption such that

\[
A_k \perp Y(\bar{a}_K), \bar{L}_K(\bar{a}_K) \mid \bar{L}_k, \bar{A}_{k-1} = \bar{a}_{k-1}
\]

for all \( \bar{a}_K \in \{0, 1\}^K \). In words, this captures the notion that there are no confounders for the effect of \( A_k \) on \( Y \) except for the history before \( A_k \), that is the covariates history \( \bar{L}_k \) and treatment history \( \bar{A}_{k-1} \). We also make the positivity assumption such that

\[
P(A_k = a_k \mid \bar{L}_k = \bar{l}_k, \bar{A}_{k-1} = \bar{a}_{k-1}) \in (0, 1), k = 0, \ldots, K
\]

as long as \( P(\bar{L}_k = \bar{l}_k, \bar{A}_{k-1} = \bar{a}_{k-1}) > 0 \).

Suppose we are interested in modeling comparisons of the mean potential outcomes

\[
g(E[Y(\bar{a}_K)]) - g(E[Y(\bar{a}_K^*)]) : \bar{a}_K, \bar{a}_K^* \in \{0, 1\}^K,
\]

where \( g \) is a link function denoting the scale on which one wishes to measure the treatment effect. The potential outcomes in (8) may be identified through the g-formula (Robins, 1986),

\[
E[Y(\bar{a}_K)] = \sum_{\bar{l}_K} E[Y \mid \bar{A}_K = \bar{a}_K, \bar{L}_K = \bar{l}_K] \times \prod_{k=0}^{K} f(l_k \mid \bar{A}_{k-1} = \bar{a}_{k-1}, \bar{L}_{k-1} = \bar{l}_{k-1}),
\]

where \( \bar{A}_{-1} \equiv \emptyset \). In practice, estimation of these causal contrasts may be based on parametric modeling assumptions on components of the g-formula:

\[
P(L_k = 1 \mid \bar{A}_{k-1} = \bar{a}_{k-1}, \bar{L}_{k-1} = \bar{l}_{k-1}) \quad \text{and} \quad E[Y \mid \bar{A}_K = \bar{a}_K, \bar{L}_K = \bar{l}_K].
\]

Similar to other parametric approaches, the aforementioned estimation approach for the contrast (8) may be biased if the models for (10) are misspecified. This bias is particularly problematic if the primary interest lies in testing the null hypothesis that \( E[Y(\bar{a}_K)] \) is the same for every \( \bar{a}_K \). Note that even under this null, in general \( E[Y \mid \bar{A}_K = \bar{a}_K, \bar{L}_K = \bar{l}_K] \) and \( P(L_k = 1 \mid \bar{A}_{k-1} = \bar{a}_{k-1}, \bar{L}_{k-1} = \bar{l}_{k-1}) \) will both depend
on $\bar{a}_K$ due to collider bias, so that with (even slight) model misspecification, the probability limit of the right hand side of (9) will falsely depend on $\bar{a}_K$. Therefore, the type I error rate based on such modeling assumptions may tend to one as the sample size goes to infinity. This is known as the ‘null paradox’ (Robins and Wasserman, 1997).

To avoid the null paradox, Robins (1994) proposed the SNMMs that directly model the conditional causal contrasts:

$$B(\bar{l}_k, \bar{a}_{k-1}; \alpha) \equiv g\{E(Y(\bar{a}_{k-1}, 1, 0) \mid \bar{L}_k = \bar{l}_k, \bar{A}_{k-1} = \bar{a}_{k-1}; \alpha)\} - g\{E(Y(\bar{a}_{k-1}, 0, 0) \mid \bar{L}_k = \bar{l}_k, \bar{A}_{k-1} = \bar{a}_{k-1}; \alpha)\}$$

for $k = 0, \ldots, K$, where $B(\bar{l}_k, \bar{a}_{k-1}; 0) = 0$. The key feature of SNMMs is that they are guaranteed to be correctly specified under the global causal nulls given in equation (13) below.

The contrasts (11) are called blip functions as they describe the effect of receiving a last ‘blip’ of treatment at time $k$ and then not receiving treatment thereafter (versus not receiving treatment at times $k, \ldots, K$).

As a concrete example, when $K = 1$, the SNMMs model the following blip functions:

$$k = 0: \quad B(l_0) = g(E[Y(1, 0) \mid L_0 = l_0]) - g(E[Y(0, 0) \mid L_0 = l_0]),$$

$$k = 1: \quad g(E[Y(1, 1) \mid L_0 = l_0, A_0 = 1, L_1 = l_1] - g(E[Y(1, 0) \mid L_0 = l_0, A_0 = 1, L_1 = l_1]),$$

$$g(E[Y(0, 1) \mid L_0 = l_0, A_0 = 0, L_1 = l_1] - g(E[Y(0, 0) \mid L_0 = l_0, A_0 = 0, L_1 = l_1]).$$

The SNMMs are often used for analysis of dynamic treatment regimes, where a dynamic regime is one in which a subject’s treatment choice $A_k$ depends on the intermediate responses up to that point $\bar{L}_k$. In fact, under sequentially ignorability (6) and the positivity assumption (7), the so-called g-null hypothesis

$$\mathcal{H}_0 : E[Y(g)] = E[Y] \quad \text{for all } g \in \mathbb{G},$$

is equivalent to all the contrasts in (11) being equal 0, where $\mathbb{G}$ denotes the set of all generalized treatment regimes consisting of all non-dynamic and dynamic treatment regimes (Robins, 1994). This statement holds
regardless of the specific modeling assumptions placed on (11), since the SNMMs are guaranteed to be correctly specified under the g-null.

**Remark 1:** An alternative way to avoid the null paradox is to place modeling assumptions on the marginal potential outcomes \( g\{E[Y(\bar{a}_K)]\} \), resulting in the marginal structural model (MSM) (Robins, 2000). Compared with the MSM, the SNMM has the following important advantages: (a) it can detect violation of the g-null while the MSM can only detect violation of the static regime null that \( H_{0,\text{static}} : E[Y(\bar{a}_K)] = E[Y] \) for all \( \bar{a}_K \); (b) it can model effect modification by time-dependent covariates and thus can be used for estimation of the optimal treatment regime (Robins, 2004).

## 3 Parameterizations of binary SNMMs

We now consider full parametric likelihood based inference of the SNMM parameters. In general, maximum likelihood fitting of \( \alpha \) involves specifying additional nuisance models, as the SNMMs alone do not give rise to the likelihood in (10). Moreover, *unconstrained* maximum likelihood estimation of SNMM parameters requires that (I) the SNMMs are variation independent of each other; (II) the nuisance models are variation independent of the SNMMs; (III) there exists a bijection between the likelihood in (10) and the combination of the SNMMs and the nuisance models. In Section 3.1, we show that (I) is true for multiplicative SNMMs but not for additive SNMMs. In other words, in general estimators for the additive SNMM parameters may not be obtained via unconstrained maximum likelihood estimation. On the other hand, to construct an unconstrained MLE for the multiplicative SNMM parameters, in Section 3.2 and 3.3, we propose novel nuisance models that satisfy criteria (II) and (III).

### 3.1 Variation independence of SNMM parameters

**Proposition 3.1:** If \( K \geq 1 \), then the additive SNMMs are *variation dependent* of each other, while the multiplicative SNMMs are variation independent of each other.

Proposition 3.1 may be surprising at first sight. To provide heuristics, we show Proposition 3.1 in the case of \( K = 1 \). A formal proof will become obvious later given Theorem 2.
When $K = 1$, the additive SNMMs model a sequence of contrasts including

$$E[Y(1, 0) - Y(0, 0)] \in (-1, 1),$$

$$E[Y(1, 1) - Y(1, 0) \mid A_0 = 1, L_1 = l_1] \in (-1, 1).$$

Marginalizing (15) over the distribution of $L_1$ conditional on $A_0 = 1$ and using the sequential ignorability assumption (6), we get

$$E[Y(1, 1) - Y(1, 0)] \in (-1, 1).$$

If (14) were variation independent of (15) (and hence (16)), then the range of the sum of (14) and (16) would be $(-2, 2)$. This contradicts the fact that the range of $E[Y(1, 1) - Y(0, 0) \mid A_0 = 1]$ is $(-1, 1)$.

The reasoning above does not constitute a contradiction for the multiplicative SNMM as it specifies a sequence of differences of the form $\log \{E[Y(\bar{a}_k, 0) \mid \bar{L}_k = \bar{l}_k, \bar{A}_k = \bar{a}_k]\} - \log \{E[Y(a_{k-1}, 0) \mid \bar{L}_k = \bar{l}_k, \bar{A}_k = \bar{a}_k]\} \in \mathbb{R}$. In simple terms, the multiplicative SNMMs are variation independent as $\mathbb{R} + \mathbb{R} = \mathbb{R}$, whereas the additive SNMMs are variation dependent as $(-1, 1) + (-1, 1) \nsubseteq (-1, 1)$; here interval additions are defined as $(x_1, x_2) + (y_1, y_2) = \{x + y \mid x \in (x_1, x_2), y \in (y_1, y_2)\} = (x_1 + y_1, x_2 + y_2)$.

We can also explain Proposition 3.1 with the graphs in Figure 3. As shown in Figure 3 (a) and (c), with additive SNMMs, the second stage blips $E[Y(a_0, 1) - Y(a_0, 0) \mid A_0 = a_0, L_1 = l_1], l_1 = 0, 1$ may impose constraints on the second stage baseline quantities $E[Y(a_0, 0) \mid A_0 = a_0, L_1 = l_1]$. Marginalizing over the distribution of $L_1$ given $A_0$, these constraints may then imply constraints on $E[Y(a_0, 0) \mid A_0 = a_0]$, which, by the sequential ignorability assumption, equals $E[Y(a_0, 0)]$. The constraints on $E[Y(a_0), 0], a_0 = 0, 1$ are shown in the red and blue rectangles in Figure 3 (b), respectively. The intersection of these rectangles, i.e. the dotted region in Figure 3 (b), defines the constraints on $(E[Y(0, 0)], E[Y(1, 0)])$ implied by the second stage blips. One may see that some contour lines of $E[Y(1, 0) - Y(0, 0)]$, such as the gray lines in Figure 3 (b), have no intersection with the dotted feasible region for $(E[Y(0, 0)], E[Y(1, 0)])$. This shows that the second stage blips may imply constraints on the possible values of the first stage blip $E[Y(1, 0) - Y(0, 0)]$, so that they are variation dependent of each other.

We can apply the same reasoning to the multiplicative SNMMs, as illustrated in Figure 4. Given any values for the second stage blips, the feasible region for $(E[Y(0, 0)], E[Y(1, 0)])$ always includes the origin. Hence, unlike the case with additive SNMMs, this feasible region will always intersect with any contour
Figure 3: Illustration of variation dependence of additive blip functions. The lines at 45 degrees in (a) give values for the second stage additive blip quantities $E[Y(0, 1) - Y(0, 0) | A_0 = 0, L_1 = l_1, l_1 = 0, 1]$. Similarly (c) shows the second stage blips with $A_0 = 1$. (b) shows the first stage blip $E[Y(1, 0) - Y(0, 0)]$. The dotted arrows from (a), (c) to (b) show restrictions placed on the first stage quantities $E[Y(a_0, 0)]$, due to restrictions on the second stage quantities $E[Y(a_0, 0) | A_0 = a_0, L_1 = l_1]$. The dotted area in (b) shows the feasible region of $(E[Y(0, 0)], E[Y(1, 0)])$ given the second stage quantities depicted in (a) and (c), and the two gray lines at 45 degrees are two contour lines for the first stage blip $E[Y(1, 0) - Y(0, 0)]$ that are not feasible, i.e. that do no intersect with the dotted region. See the text for more explanation.

3.2 Parameterization for the multiplicative SNMM

We now discuss choice of the nuisance models for the binary multiplicative SNMM. To fix ideas, we first consider the case with $K = 1$. Our nuisance models include models on the association between the intermediate covariate $L_1$ and the outcome $Y$, and a model on the so-called generalized odds product function. The former is in parallel to the SNMM parameters which characterize the effect of treatments $A_0, A_1$ on the outcome $Y$, while the latter can be seen as a generalization of Richardson et al. (2017)’s nuisance model for the point exposure case.

**Theorem 1:** Suppose that the sequential ignorability assumption (6) holds. Let $\mathcal{M}$ denote the 10-dimensional
Figure 4: Illustration of variation independence of multiplicative blip functions. The lines through the origin in (a) give values for the second stage additive blip quantities $E[Y(0, 1) | A_0 = 0, L_1 = l_1] / E[Y(0, 0) | A_0 = 0, L_1 = l_1]$, $l_1 = 0, 1$. Similarly (c) shows the second stage blips with $A_0 = 1$. In (b) the intersection of the shaded regions indicates possible values for $(E[Y(0, 0)], E[Y(1, 0)])$. Since this set contains the origin $(0, 0)$, it will intersect any contour line for the multiplicative first stage blip. Thus the first and second stage multiplicative blips are variation independent.
models consisting of the SNMMs on

\[ \theta(*) \equiv \frac{E[Y(1,0)]}{E[Y(0,0)]}, \]

\[ \theta(1,1) \equiv \frac{E[Y(1,1) | A_0 = 1, L_1 = 1]}{E[Y(1,0) | A_0 = 1, L_1 = 1]} = \frac{E[Y | A_0 = 1, L_1 = 1, A_1 = 1]}{E[Y | A_0 = 1, L_1 = 1, A_1 = 0]}, \]

\[ \theta(1,0) \equiv \frac{E[Y(1,1) | A_0 = 1, L_1 = 0]}{E[Y(1,0) | A_0 = 1, L_1 = 0]} = \frac{E[Y | A_0 = 1, L_1 = 0, A_1 = 1]}{E[Y | A_0 = 1, L_1 = 0, A_1 = 0]}, \]

\[ \theta(0,1) \equiv \frac{E[Y(0,0) | A_0 = 0, L_1 = 1]}{E[Y(0,1) | A_0 = 0, L_1 = 1]} = \frac{E[Y | A_0 = 0, L_1 = 1, A_1 = 1]}{E[Y | A_0 = 0, L_1 = 1, A_1 = 0]}, \]

\[ \theta(0,0) \equiv \frac{E[Y(0,0) | A_0 = 0, L_1 = 0]}{E[Y(0,1) | A_0 = 0, L_1 = 0]} = \frac{E[Y | A_0 = 0, L_1 = 0, A_1 = 1]}{E[Y | A_0 = 0, L_1 = 0, A_1 = 0]} \]

and models on the following nuisance functions:

\[ \phi(0) \equiv \frac{E[Y(0,0) | A_0 = 0, L_1 = 1]}{E[Y(0,0) | A_0 = 0, L_1 = 0]} = \frac{E[Y | A_0 = 0, L_1 = 1, A_1 = 0]}{E[Y | A_0 = 0, L_1 = 0, A_1 = 0]}, \]

\[ \phi(1) \equiv \frac{E[Y(1,0) | A_0 = 1, L_1 = 1]}{E[Y(1,0) | A_0 = 1, L_1 = 0]} = \frac{E[Y | A_0 = 1, L_1 = 1, A_1 = 0]}{E[Y | A_0 = 1, L_1 = 0, A_1 = 0]}, \]

\[ \text{gop} = \frac{\prod_{a_0=0,1} \prod_{l_1=0,1} \prod_{a_1=0,1} E[Y | A_0 = a_0, L_1 = l_1, A_1 = a_1]}{\prod_{a_0=0,1} \prod_{l_1=0,1} \prod_{a_1=0,1} (1 - E[Y | A_0 = a_0, L_1 = l_1, A_1 = a_1])}, \]

\[ \eta(0) \equiv E[L_1 | A_0 = 0], \]

\[ \eta(1) \equiv E[L_1 | A_0 = 1], \]

where we have suppressed the dependence on the baseline covariates $L_0$ throughout.

For any realization of $L_0$, the map given by

\[ (\theta(*), \theta(1,1), \theta(1,0), \theta(0,1), \theta(0,0), \phi(0), \phi(1), \text{gop}, \eta(0), \eta(1)) \rightarrow \]

\[ (P(Y = 1 | A_0 = a_0, L_1 = l_1, A_1 = a_1), a_0, l_1, a_1 \in \{0,1\}; \eta(0), \eta(1)) \quad (17) \]

is a bijection from $\mathbb{R}^8 \times (0,1)^2$ to $(0,1)^{10}$. Furthermore, models in $\mathcal{M}$ are variation independent of each other.

Suppose models in $\mathcal{M}$ are specified up to a finite dimensional parameter, then these parameters may
be estimated directly via unconstrained maximum likelihood based on the bijection (17). Alternatively, a two-step procedure may be employed, in which one first estimates the model parameters for $\eta(0)$ and $\eta(1)$ by maximizing the likelihood associated with $P(L_1 = 1 \mid A_0, L_0)$, and then maximize the likelihood associated with $P(Y = 1 \mid A_1, L_1, A_0, L_0)$ conditional on estimates of $\eta(0)$ and $\eta(1)$. Inference can then be performed based on the non-parametric bootstrap.

### 3.3 The general case

To describe parameterizations for the binary multiplicative SNMM in the general case, we first introduce some notation:

- $\vec{\theta}_k \equiv (0, \ldots, 0)$;
- $E[Y(\bar{a}_k, 0)] \equiv E[Y(\bar{a}_k, \vec{\theta}_{K-k})]$;
- $\theta(\bar{a}_{k-1}, \bar{l}_k) \equiv \frac{E[Y(\bar{a}_{k-1}, 1, 0) \mid \bar{A}_k = (\bar{a}_{k-1}, 1), \bar{L}_k = \bar{l}_k]}{E[Y(\bar{a}_{k-1}, 0, 0) \mid \bar{A}_k = (\bar{a}_{k-1}, 1), \bar{L}_k = \bar{l}_k]}$;
- $\phi(\bar{a}_k, \bar{l}_k) \equiv \frac{E[Y(\bar{a}_k, 0) \mid \bar{A}_k = \bar{a}_k, \bar{L}_k = \bar{l}_k, L_{k+1} = 1]}{E[Y(\bar{a}_k, 0) \mid \bar{A}_k = \bar{a}_k, \bar{L}_k = \bar{l}_k, L_{k+1} = 0]}$;
- $\eta(\bar{a}_k, \bar{l}_k) \equiv E[L_{k+1} \mid \bar{A}_k = \bar{a}_k, \bar{L}_k = \bar{l}_k]$.

We also let $\bar{a}_{-1} = \emptyset$ so that

- $\theta(\bar{a}_{-1}, \bar{l}_0) \equiv \frac{E[Y(1, 0) \mid \bar{A}_0 = 1, L_0 = l_0]}{E[Y(0, 0) \mid A_0 = 1, L_0 = l_0]}$.

The following Theorem 2 gives the general form of our nuisance parameters for binary multiplicative SNMMS.

**Theorem 2:** Let $\mathcal{M}$ denote the multidimensional models consisting of the SNMMs on

$$\theta = (\theta(\bar{a}_{k-1}, \bar{l}_k) : k = 0, \ldots, K)$$

and models on the following nuisance functions

$$\phi = (\phi(\bar{a}_k, \bar{l}_k) : k = 0, \ldots, K - 1),$$

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\[
GOP = \frac{\prod_{\bar{a}_K, \bar{l}_K} E[Y \mid \bar{A}_K = \bar{a}_K, \bar{L}_K = \bar{l}_K]}{\prod_{\bar{a}_K, \bar{l}_K} (1 - E[Y \mid A_K = \bar{a}_K, L_K = \bar{l}_K])},
\]

\[
\eta = (\eta(\bar{a}_k, \bar{l}_k) : k = 0, \ldots, K - 1),
\]

where we have suppressed the dependence on the baseline covariates \(L_0\) throughout.

For any realization of \(L_0\), the map given by

\[
(\theta, \phi, GOP, \eta) \rightarrow (E[Y \mid \bar{A}_K = \bar{a}_K, \bar{L}_K = \bar{l}_K], \eta)
\]

is a bijection from \((\mathbb{R}^+)^{d_1} \times (0, 1)^{d_2}\) to \((0, 1)^d\), where \(d_1 = 2^{2K+1}, d_2 = \sum_{k=0}^{K-1} 2^{2k+1}\), \(d = d_1 + d_2\). Furthermore, models in \(\mathcal{M}\) are variation independent of each other.

Algorithm 1 describes the procedure for computing the mapping (18). It also serves as an outline for the proof of Theorem 2, which can be found in Appendix B. One may also see that the dimension of the domain for the mapping (18) agrees with the dimension of its range, since \(\theta\) is of dimension \(\sum_{k=0}^{K} 2^{2k}\), \(\phi\) is of dimension \(\sum_{k=0}^{K-1} 2^{2k+1}\), \(GOP\) is of dimension 1 and \((E[Y \mid \bar{A}_K = \bar{a}_K, \bar{L}_K = \bar{l}_K], \bar{a}_K \in \{0, 1\}^{K+1}, \bar{l}_K \in \{0, 1\}^K)\) is of dimension \(2^{2K+1}\). Following these expressions, the dimension of model parameters \((\theta, \phi, GOP, \eta)\) grows exponentially with \(K\). To avoid possible identification problems with large number of follow-ups and moderate sample size, in practice one may make further dimension reducing assumptions on \(\mathcal{M}\), as we illustrate in Section 4.2.

4 Data illustrations

4.1 Simulation studies

We first evaluate the finite sample performance of our estimators with synthetic data. In our simulation, the baseline covariates \(L_0\) include an intercept and a binary random variable generated from a Bernoulli distribution with mean \(1/2\). Conditional on \(L_0\), the treatments \(A_0, A_1\) and intermediate covariate \(L_1\) were generated from the following models:

\[
P(A_0 = 1 \mid L_0) = \expit(\xi_1^T L_0);
\]
Algorithm 1 An algorithm for computing $E[Y \mid \bar{A}_K = \bar{\alpha}_k, \bar{L}_K = \bar{l}_K]$ from $(\theta, \phi, \text{GOP}, \eta)$

1. Compute

\[
\begin{align*}
\frac{E[Y \mid \bar{A}_K = (\bar{a}_{k-1}, 1, 0), \bar{L}_K = (\bar{l}_k, 0)]}{E[Y \mid \bar{A}_K = (\bar{a}_k, 0), \bar{L}_K = (\bar{l}_k, 0)]}
\end{align*}
\]

and

\[
\begin{align*}
\frac{E[Y \mid \bar{A}_K = (\bar{a}_{k-1}, 0, 0), \bar{L}_K = (\bar{l}_k, 0)]}{E[Y \mid \bar{A}_K = (\bar{a}_k, 0), \bar{L}_K = (\bar{l}_k, 0)]}
\end{align*}
\]

using equations (25) and (26) in Appendix B.

2. For $k = 0, \ldots, K$

compute

\[
\begin{align*}
\frac{E[Y \mid \bar{A}_K = (\bar{a}_{k-1}, 1, 0), \bar{L}_K = (\bar{l}_k, 0)]}{E[Y \mid \bar{A}_K = 0, \bar{L}_K = 0]}
\end{align*}
\]

sequentially by

\[
\begin{align*}
&\frac{E[Y \mid \bar{A}_K = (\bar{a}_{k-1}, 1, 0), \bar{L}_K = (\bar{l}_k, 0)]}{E[Y \mid \bar{A}_K = 0, \bar{L}_K = 0]} = \frac{E[Y \mid \bar{A}_K = (\bar{a}_k, 0), \bar{L}_K = (\bar{l}_k, 0)]}{E[Y \mid \bar{A}_K = 0, \bar{L}_K = 0]} \times \frac{E[Y \mid \bar{A}_K = (\bar{a}_{k-1}, 0, 0), \bar{L}_K = (\bar{l}_k, 0)]}{E[Y \mid \bar{A}_K = 0, \bar{L}_K = 0]},

&\frac{E[Y \mid \bar{A}_K = (\bar{a}_k, 0), \bar{L}_K = (\bar{l}_k, 0)]}{E[Y \mid \bar{A}_K = 0, \bar{L}_K = 0]} = \frac{E[Y \mid \bar{A}_K = (\bar{a}_k, 0), \bar{L}_K = (\bar{l}_k, 0)]}{E[Y \mid \bar{A}_K = 0, \bar{L}_K = 0]} \times \frac{E[Y \mid \bar{A}_K = (\bar{a}_{k-1}, 0, 0), \bar{L}_K = (\bar{l}_k, 0)]}{E[Y \mid \bar{A}_K = 0, \bar{L}_K = 0]},
\end{align*}
\]

3. Find

\[
r_{\max} = \max_{\bar{a}_K, \bar{l}_K} r_{\bar{a}_K, \bar{l}_K},
\]

where $r_{\bar{a}_K, \bar{l}_K} = E[Y \mid \bar{A}_K = \bar{a}_K, \bar{L}_K = \bar{l}_K] / E[Y \mid \bar{A}_K = 0, \bar{L}_K = 0]$ is computed in Step 2.

4. Compute

\[
k_{\bar{a}_K, \bar{l}_K} = \frac{r_{\bar{a}_K, \bar{l}_K}}{r_{\max}}.
\]

5. Let $p_{\bar{a}_K, \bar{l}_K} = E[Y \mid \bar{A}_K = \bar{a}_K, \bar{L}_K = \bar{l}_K]$, and

\[
g(x) = \sum_{i \in \mathcal{I}} \log(k_i) + 2^{K+1} \log(x) - \sum_{i \in \mathcal{I}} \log(1 - k_i x) - \log(\text{GOP}),
\]

where $\mathcal{I} = \{ (\bar{a}_K, \bar{l}_K) : \bar{a}_K \in \{0, 1\}^K, \bar{l}_K \in \{0, 1\}^K \}$. Find the unique root of $g(x)$ in the interval $(0, 1)$. Set $p_{\max}$ to be this root.

6. Compute

\[
E[Y \mid \bar{A}_K = \bar{a}_K, \bar{L}_K = \bar{l}_K] = k_{\bar{a}_K, \bar{l}_K} \times p_{\max}.
\]
\[ P(L_1 = 1 \mid A_0 = 0, L_0) = \expit(\gamma_0^T L_0); \]
\[ P(L_1 = 1 \mid A_0 = 1, L_0) = \expit(\gamma_1^T L_0); \]
\[ P(A_1 = 1 \mid L_1, A_0, L_0) = \expit(\epsilon_2^T L_0 + \epsilon_3 A_0 + \epsilon_4 L_1), \]

where \( \epsilon_1 = \epsilon_2 = (0.1, -0.5)^T, \epsilon_3 = 0.1, \epsilon_4 = -0.5, \gamma_0 = \gamma_1 = (-0.5, 0.1)^T. \)

The outcome \( Y \) was generated indirectly through the following models:

\[ \theta(k) = \exp(\alpha_k^T L_0), k = \cdot, (1, 1), (1, 0), (0, 1), (0, 0); \]
\[ \phi(k) = \exp(\beta_k^T L_0), k = 0, 1; \]
\[ \text{gop} = \exp(\delta^T L_0), \]

where \( \alpha_k = (0, -0.5)^T \) for all \( k \); \( \beta_0 = \beta_1 = \delta = (-0.5, 0.1)^T. \)

We compare two estimation methods: 1) MLE: direct maximization of the full likelihood \( P(Y = y \mid A_1, L_1 = l_1, A_0, L_0)P(L_1 = l_1 \mid A_0, L_0); \) 2) 2-step MLE: first estimate \( \gamma_0, \gamma_1 \) using a logistic regression of \( L_1 \) given \( L_0 \) and \( A_0 \), and then conditional on estimates of \( \gamma_0, \gamma_1 \), maximize the likelihood \( P(Y = y \mid A_1, L_1, A_0). \) Note that the remaining parts of the observed data likelihood \( P(A_1 = a_1 \mid L_1, A_0, L_0), P(A_0 = a_0 \mid L_0) \) and \( P(L_0 = l_0) \) do not appear in the g-formula (9). Thus they contain no information on our parameters of interest and need not be modeled. As a summary measure, we also estimated the causal contrast \( E[Y(1, 1)]/E[Y(0, 0)] \) using the g-formula (9), where components of the g-formula (10) were estimated using the models on \( \theta(\cdot), \theta(1, 1), \theta(1, 0), \theta(0, 1), \theta(0, 0), \phi(0), \phi(1), \text{gop}, \eta(0), \eta(1). \) All the simulation results are based on 1000 Monte-Carlo runs of \( n = 1000 \) units.

Table 1 summarizes the simulation results. Both methods yield estimators with small biases relative to their standard errors, confirming consistency of the proposed estimators. The estimates of the 2-step MLE are essentially the same to those of the MLE, which suggests that the conditional distribution of the outcome \( Y \), i.e. \( P(Y = y \mid A_1, L_1, A_0, L_0) \) contains little information on \( \gamma_0 \) and \( \gamma_1 \) relative to \( P(L_1 = l_1 \mid A_0, L_0). \)

One may also notice that estimates of the model parameters for gop are much less stable than estimates for the other parameters. This is because in our simulations, for a wide range of values of gop (holding the other parameters fixed), the fitted values for \( p_{\max} \) were close to 1, so that the likelihood contains relatively little information about \( p_{\max} \) and hence gop. On the other hand, the unstable estimates of gop do not translate
Table 1: Biases \times 1000 (Monte Carlo standard errors \times 1000) of the maximum likelihood and 2-step maximum likelihood estimators. The sample size is 1000.

| SNMM parameters | MLE | 2-step MLE |
|-----------------|-----|------------|
| \theta(\ast)    | 0.78(5.5) 2.2(6.9) | 0.79(5.5) 2.2(6.9) |
| \theta(1, 1)    | -2.4(13) -110(29) | -2.4(13) -110(29) |
| \theta(1, 0)    | 3.6(6.4) -35(14) | 3.6(6.4) -35(14) |
| \theta(0, 1)    | -12(13) 17(16) | -12(13) 17(16) |
| \theta(0, 0)    | -3.4(6.4) -12(8.4) | -3.3(6.4) -12(8.4) |

| Nuisance parameters | MLE | 2-step MLE |
|---------------------|-----|------------|
| \phi(0)             | -19(11) 5.0(12) | -19(11) 4.9(12) |
| \phi(1)             | -17(8.9) 14(13) | -17(8.9) 14(13) |
| gop                 | -54(36) -82(57) | -54(36) -82(57) |
| \eta(0)             | -2.0(5.9) 7.2(7.9) | -2.0(5.9) 7.1(7.9) |
| \eta(1)             | -2.0(5.5) 1.6(8.4) | -1.9(5.5) 1.7(8.4) |

| Marginal causal parameters | MLE | 2-step MLE |
|----------------------------|-----|------------|
| \[E[Y(0, 0)]\]            | -1.3(1.3) | -1.3(1.3)  |
| \[E[Y(1, 1)]\]            | 0.44(1.8) | 0.44(1.8)  |
| \[E[Y(1, 1)]/E[Y(0, 0)]\]| 3.1(3.0)  | 3.1(3.0)   |

Into inflated variance for estimates of the probabilities \(E[Y \mid \bar{A}_1, \bar{L}_1]\) or any marginal causal contrasts. For example, our estimates of \(E[Y(1, 1)]/E[Y(0, 0)]\) are still very stable in spite of the instability in estimating the gop parameters.

4.2 Application to the Mothers’ Stress-Children’s Morbidity study

To illustrate the proposed novel methods, we reanalyze data from the Mothers’ Stress-Children’s Morbidity (MSCM) study (Zeger and Liang, 1986), which consist of observations on 167 mothers with infants aged between 18 months and 5 years. Daily observations were taken on mothers’ stress level and whether or not their child was ill. The total length of follow-up is 30 days. Similar to Robins et al. (1999), we are interested in whether or not maternal stress has an influence on child illness. Following Zeger and Liang (1986), we use the first 9 days of records to illustrate use of the SNMM so that \(K = 7\). The treatment variables are maternal stress indicators in the first 8 days, denoted as \(A_0, \ldots, A_7\); the outcome of interest is whether or not the child is ill at the 9th day; the time-varying confounders are child illness in the first 8 days: \(L_0, \ldots, L_7\), and the
time-independent baseline confounders include household size, child’s race, employment and marital status. To distinguish the time-independent confounders from the time-varying confounder measured at baseline, we use $X$ to denote the former, and $L_0$ for the latter. Note that the outcomes, time-varying confounders and predictor are all dichotomous. In the data set made available to us, the time-independent confounders are also dichotomous. There are 147 mother-child pairs with complete observations on all these variables and for illustrative purpose, we restrict our analysis to these pairs. Figure 5 shows the observations in the first 9 days. There seems to be a strong correlation between maternal stress and children’s illness, which may be due to confounding by children’s illness at earlier time points. Our formal causal analysis assumes that all confounders are measured, and correctly adjusts for these, assuming correct parametric specification.

We assume the following causal models:

$$
\log \frac{E[Y(\bar{a}_{k-1}, 1, 0) | \bar{A}_k = \bar{a}_k, \bar{L}_k = \bar{l}_k, X]}{E[Y(\bar{a}_{k-1}, 0) | A_k = a_k, L_k = l_k, X]} = \alpha_0(1 - l_k) + \alpha_1 l_k + \alpha_2^T X, \quad k = 0, \ldots, K
$$

and the following nuisance models:

$$
\log \frac{E[Y(0) | L_0 = 1, X]}{E[Y(0) | L_0 = 0, X]} = \beta_0 + \beta_1^T X,
$$

$$
\log \frac{E[Y(\bar{a}_k, 0) | \bar{A}_k = \bar{a}_k, \bar{L}_k = \bar{l}_k, L_{k+1} = 1, X]}{E[Y(\bar{a}_k, 0) | A_k = a_k, L_k = l_k, L_{k+1} = 0, X]} = \beta_0(1 - a_k) + \beta_1 a_k + \beta_2^T X, \quad k = 0, \ldots, K - 1;
$$

Figure 5: Mothers’ stress and children’s illness evolving over time.
\[ \text{GOP}(\bar{a}_K, \bar{l}_K; X) = \delta^T X; \]
\[ \logit(E[L_{k+1} | \bar{A}_k = \bar{a}_k, \bar{L}_k = \bar{l}_k, X]) = \gamma_{001}(a_k = l_k = 0) + \gamma_{011}(a_k = 0, l_k = 1) + \gamma_{101}(a_k = 1, l_k = 0) + \gamma_{111}(a_k = l_k = 1) + \gamma_2 X, k = 0, \ldots, K - 1. \]

These models imply the Markov assumptions that \( \theta, \phi \) and \( \eta \) depend on the past history only through the most recent \( L_k, A_k \) and \((A_k, L_k)\), respectively, and that such dependences are homogeneous over time:

\[ \theta(\bar{a}_{k-1}, \bar{l}_k) = \theta(l_k), \phi(\bar{a}_k, \bar{l}_k) = \phi(a_k), \eta(\bar{a}_k, \bar{l}_k) = \eta(a_k, l_k). \] (19)

In practice, since the dimension of \( E[Y | \bar{A}_K, \bar{L}_K] \) grows exponentially with \( K \), Algorithm 1, and specifically Steps 2 – 5 may be computationally prohibitive even when \( K \) is as small as seven. To resolve this problem, instead of computing \( r_{\bar{a}_K, \bar{l}_K} \) for each \((\bar{a}_K, \bar{l}_K)\), we develop a dynamic programming method to compute the exact value of \( r_{\text{max}} \); the details are provided in Appendix C. Dynamic programming is applicable here due to our Markov assumption that \( \theta, \phi \) and \( \eta \) depend on the past history only through the most recent \( L_k \) or \( A_k \). The dynamic programming method has also been used before in the optimal structural nested models (Robins, 2004, a.k.a. A-learning) literature. Furthermore, in Step 5, we approximate \( g(x) \) by

\[ h_m(x) = \frac{d_1}{m} \sum_{i=1}^{m} \log(k_i) + d_1 \log(x) - \frac{d_1}{m} \sum_{i=1}^{m} \log(1 - k_i x) - \log(\text{GOP}), \]

where \( i = 1, \ldots, m \) are random samples drawn from a uniform distribution on the set \( \{0, 1\}^{d_1} \). To choose \( m \) in practice, one may start with a small number, say \( m = 100 \), and then increase \( m \) until \( h_m(x) \) is stable up to a threshold specified a priori. With the dynamic programming method and Monte Carlo approximation, the computational cost is reduced from \( \mathcal{O}(\exp(K)) \) to \( \mathcal{O}(K) \).

We first tested the g-null mean hypothesis (13). Note that as \( Y \) is binary, the g-null mean hypothesis coincides with the g-null hypothesis of Robins (1986, §6). A valid level-\( \alpha \) test may be obtained by testing \((\alpha_0, \alpha_1, \alpha_2^T) = 0 \). In our analysis, we used 2-step maximum likelihood for parameter estimation, non-parametric bootstrap for variance estimation and a multivariate Wald-test for testing the g-null. The p-value was 0.526, suggesting that we have failed to reject the g-null (mean) hypothesis at the 0.05 level. Note that as discussed by Robins et al. (1999, §6), the standard generalized estimating equation approach of Zeger and Liang (1986) cannot be used to test the g-null hypothesis in the presence of time-dependent confounding by
Table 2: Estimated regression coefficients with 95% Wald-type confidence intervals for the multiplicative SNMMs and nuisance models.

| Index (a_k or l_k) | \( \alpha_{l_k} \) | \( \beta_{a_k} \) | \( \delta \) | \( \gamma_{0l_k} \) | \( \gamma_{1l_k} \) |
|--------------------|------------------|-----------------|------------|-----------------|-----------------|
| 0                  | -0.15 (-0.83,0.53) | 0.71 (-0.28,1.69) | 390 (-400,1200) | -2.39 (-2.95,-1.83) | -2.09 (-2.93,-1.25) |
| 1                  | -0.28 (-0.94,0.39) | 0.45 (-0.56,1.46) | - | -0.26 (-0.75,0.23) | -0.22 (-1.00,0.57) |
| *                  | - | 0.43 (-0.80,1.66) | - | - | - |

Time-independent confounders

|                        |                  |                  |            |            |            |
|------------------------|------------------|------------------|------------|------------|------------|
| Household size > 3     | 0.30 (-0.37,0.97) | -0.36 (-1.21,0.48) | 58 (-820,940) | -0.68 (-1.04,-0.32) | - |
| Race non-white         | 0.28 (-0.38,0.94) | -0.25 (-1.18,0.69) | 200 (-500,900) | 0.47 (0.07,0.87) | - |
| Employed               | 0.08 (-0.30,0.47) | -0.01 (-0.57,0.55) | 350 (-790,1500) | 0.06 (-0.42,0.53) | - |
| Married                | -0.15 (-0.72,0.41) | 0.08 (-0.42,0.58) | -170 (-730,390) | 0.16 (-0.19,0.50) | - |

We then report estimates of the parameters \( (\alpha_0, \alpha_1, \beta_0, \beta_1, \delta, \gamma_{00}, \gamma_{01}, \gamma_{10}, \gamma_{11}) \) in Table 2. Although \( (\alpha_0, \alpha_1) \) and \( (\gamma_{10} - \gamma_{00}, \gamma_{11} - \gamma_{01}) \) both encode relationships between maternal stress and children’s illness, the former has a causal interpretation, whereas the latter does not due to time-dependent confounding. We also notice that estimates of the parameters associated with the generalized odds product are very unstable. This is expected since, similar to our observations in the simulation studies, in this data application the observed data likelihood contains very little information on GOP: for a wide range of values of GOP (holding the other parameters fixed), \( p_{\text{max}} \) is very close to 1. For the same reason, this instability in the estimates for GOP does not affect our estimation for other parameters.

We also compare the regime where all mothers are subject to substantial stress for 8 consecutive days, versus the regime where all mothers are never stressed during these 8 days, possibly due to a fully effective intervention program. Compared to the latter, the former regime is estimated to result in a 4.850 (95% CI [1.202, 8.498]) fold increase in risk of childhood illness in the 9th day, suggesting a statistically significant causal effect by comparing these extreme regimes. Note that, even though we failed to reject the overall g-null in a test with six degrees of freedom, we find statistical significance when comparing this particular pair, for which we anticipate the causal effect to be the largest.
5 Discussion

In this paper we introduce a general approach for causal inference from complex longitudinal data with binary outcomes and time-varying confounders. Our approach is based on the SNMMs developed by Robins (1994), which overcome the null paradox of the g-formula and have many important advantages over the marginal structural models as detailed in Section 2.2. Furthermore, the SNMMs provide natural non-centrality parameters to describe deviations from the causal g-null. When the outcome is unconstrained, both the multiplicative SNMMs and additive SNMMs are variation independent of the conventional nuisance models as described in Robins (1997, Appendix 2, p.36) and Robins (1994), respectively. However, the conventional multiplicative and additive SNMMs are not suitable for inferring causal effects with binary outcomes as they do not naturally respect the fact that probabilities are bounded above by one, whereas the logistic SNMMs cannot be used in combination with g-estimation methods that are guaranteed to yield a valid test of the g-null in randomized trials. We address this problem in two ways: for binary multiplicative SNMMs we introduce novel nuisance models so that the SNMM parameters can be estimated in a congenial way; for binary additive SNMMs we show that the SNMMs are variation dependent on each other (and hence uncongenial) so that additive SNMMs should probably be avoided when analyzing dichotomous outcomes.

We have mainly focused on likelihood inference in this paper. Doubly robust g-estimation methods could also be used in combination with our novel parameterizations. However, we leave this to future work as it is tangential to our goal of demonstrating the utility of our novel nuisance modeling. As noted in Richardson et al. (2017, Remark 3.1), the double robustness of g-estimators is a useful property only if the nuisance models are congenial of the SNMMs. Hence our novel nuisance models are also required for g-estimation methods.

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Appendix

A Proof of Theorem 1

Proof. Let \( p_{a_0 l_1 a_1} = E[Y \mid A_0 = a_0, L_1 = l_1, A_1 = a_1] \), We first note that due to the g-formula (Robins, 1986),

\[
\theta(*) = \frac{\eta(1)p_{110} + (1 - \eta(1))p_{100}}{\eta(0)p_{010} + (1 - \eta(0))p_{000}}
\]

\[
= \frac{\eta(1)\eta(0)p_{110} + 1 - \eta(1)}{\eta(0)\eta(0)p_{010} + 1 - \eta(0)\eta(0)p_{000}} \times \frac{p_{100}}{p_{000}}
\]

\[
= \frac{\eta(1)\phi(1) + 1 - \eta(1)}{\eta(0)\phi(0) + 1 - \eta(0)} \times \frac{p_{100}}{p_{000}},
\]

hence

\[
(\theta(*), \theta(1, 1), \ldots, \theta(0, 0), \phi(0), \phi(1), \eta(0), \eta(1)) \rightarrow \left(\frac{p_{110}}{p_{000}}, \frac{p_{111}}{p_{110}}, \frac{p_{101}}{p_{100}}, \frac{p_{011}}{p_{000}}, \frac{p_{010}}{p_{000}}, \frac{p_{011}}{p_{100}}, \eta(0), \eta(1)\right)
\]

(20)

is an automorphism on \((\mathbb{R}^+)^8 \times (0, 1)^2\); note that in simple terms, the mapping (20) simply replaces \( \theta(*) \) with \( \frac{p_{100}}{p_{000}} \). Applying simple algebra to the RHS of (20), we have that

\[
(\theta(*), \theta(1, 1), \ldots, \theta(0, 0), \phi(0), \phi(1), \eta(0), \eta(1)) \rightarrow \left(\frac{p_{111}}{p_{000}}, \frac{p_{110}}{p_{000}}, \frac{p_{101}}{p_{000}}, \frac{p_{100}}{p_{000}}, \frac{p_{011}}{p_{000}}, \frac{p_{010}}{p_{000}}, \frac{p_{011}}{p_{100}}, \eta(0), \eta(1)\right)
\]

(21)

is also an automorphism on \((\mathbb{R}^+)^8 \times (0, 1)^2\). Note that the numerators of the first seven terms on the RHS of (21) are simply consecutive terms of \( p_{a_0 l_1 a_1} \) with binary translation on the indexes. Now what is left to show is that given \( \eta(0), \eta(1) \),

\[
(p_{a_0 l_1 a_1}, a_0, l_1, a_1 \in \{0, 1\}) \rightarrow \left(\frac{p_{111}}{p_{000}}, \frac{p_{110}}{p_{000}}, \frac{p_{101}}{p_{000}}, \frac{p_{100}}{p_{000}}, \frac{p_{011}}{p_{000}}, \frac{p_{010}}{p_{000}}\right)
\]

(22)

is a bijection from \((0, 1)^8 \to (\mathbb{R}^+)^8\).

To show that (22) is a bijection, let \( c = (c_1, \ldots, c_8) \) be a vector in \((\mathbb{R}^+)^8\). We need to show that there is one and only one \( p = (p_{a_0 l_1 a_1}, a_0, l_1, a_1 \in \{0, 1\}) \in (0, 1)^8 \) such that

\[
\left(\frac{p_{111}}{p_{000}}, \frac{p_{110}}{p_{000}}, \frac{p_{101}}{p_{000}}, \frac{p_{100}}{p_{000}}, \frac{p_{011}}{p_{000}}, \frac{p_{010}}{p_{000}}, \frac{p_{011}}{p_{100}}\right) = (c_7, \ldots, c_1)
\]

(23)
and

\[ gop = c_8. \] (24)

Let \( r_{a_0,l_1,a_1} = c_{4a_0+2l_1+a_1} \) if \( 4a_0 + 2l_1 + a_1 \geq 1 \), \( r_{0,0,0} = 1 \), \( k_{a_0,l_1,a_1} = r_{a_0,l_1,a_1} / \max_{a_0,l_1,a_1} r_{a_0,l_1,a_1} \) and \( k = \{k_{a_0,l_1,a_1} : a_0, l_1, a_1 \in \{0,1\}\} \). It is easy to see that \( k_{\max} = \max_{a_0,l_1,a_1} k_{a_0,l_1,a_1} = 1 \) and

\[ \{p \in (0,1)^8 : (23) \text{ holds}\} = \{p_{\max}k : 0 < p_{\max} < 1\}. \]

Thus for any \( p \) such that (23) holds, the constraint (24) may equivalently be expressed as

\[
\log(gop) = \sum_{i=a_0,l_1,a_1} \log(k_i) + 8 \log(p_{\max}) - \sum_{i=a_0,l_1,a_1} \log(1 - k_ip_{\max}) = \log(c_8).
\]

Let \( g(p_{\max}) = \sum_{i=a_0,l_1,a_1} \log(k_i) + 8 \log(p_{\max}) - \sum_{i=a_0,l_1,a_1} \log(1 - k_ip_{\max}) - \log(c_8) \). We claim that \( g(p_{\max}) \) has one and only one solution in the interval \((0,1)\) so that there is one and only one \( p = p_{\max}k \in (0,1)^8 \) such that both (23) and (24) hold.

We now prove our claim. Note that

\[
\frac{\partial}{\partial p_{\max}} g(p_{\max}) = \frac{8}{p_{\max}} + \sum_{i=a_0,l_1,a_1} \frac{k_i}{1 - k_ip_{\max}} > 0
\]

since, by construction, \( k_ip_{\max} < 1 \) for all \( i \). Hence \( g(p_{\max}) \) is monotone on \((0,1)\). Furthermore, \( \lim_{p_{\max} \to 0} g(p_{\max}) = -\infty \), \( \lim_{p_{\max} \to 1} g(p_{\max}) = +\infty \) and \( g(p_{\max}) \) is also continuous on \((0,1)\). As a result, \( g(p_{\max}) \) has one and only one root in \((0,1)\).

Lastly, since the domain of \( M \), i.e. \((\mathbb{R}^+)^8 \times (0,1)^2\) is the Cartesian product of the marginal domains of models in \( M \), models in \( M \) are variation independent of each other.

We have hence finished the proof.

\[ \square \]

**B Proof of Theorem 2**

**Proof.** We follow the outline provided in Algorithm 1. First, note that

\[
\theta(\bar{a}_{k-1}, \bar{l}_k) = E[Y(\bar{a}_{k-1},1,0) \mid \bar{A}_k = (\bar{a}_{k-1},1), \bar{L}_k = \bar{l}_k] = E[Y(\bar{a}_{k-1},0,0) \mid \bar{A}_k = (\bar{a}_{k-1},1), \bar{L}_k = \bar{l}_k]
\]
\[
E[Y(\tilde{a}_{k-1}, 1, 0) \mid \tilde{A}_k = (\tilde{a}_{k-1}, 1), \tilde{L}_k = \tilde{l}_k] \\
E[Y(\tilde{a}_{k-1}, 0, 0) \mid \tilde{A}_k = (\tilde{a}_{k-1}, 0), L_k = l_k]
\]
(by sequential ignorability)

\[
\eta((\tilde{a}_{k-1}, 1), \tilde{l}_k)E[Y(\tilde{a}_{k-1}, 1, 0) \mid \tilde{A}_k = (\tilde{a}_{k-1}, 1), \tilde{L}_{k+1} = (\tilde{l}_k, 1)] + (1 - \eta((\tilde{a}_{k-1}, 1), \tilde{l}_k))E[Y(\tilde{a}_{k-1}, 1, 0) \mid \tilde{A}_k = (\tilde{a}_{k-1}, 1), \tilde{L}_{k+1} = (\tilde{l}_k, 0)] \\
\eta((\tilde{a}_{k-1}, 0), \tilde{l}_k)E[Y(\tilde{a}_{k-1}, 0, 0) \mid \tilde{A}_k = (\tilde{a}_{k-1}, 0), L_{k+1} = (l_k, 1)] + (1 - \eta((\tilde{a}_{k-1}, 0), \tilde{l}_k))E[Y(\tilde{a}_{k-1}, 0, 0) \mid \tilde{A}_k = (\tilde{a}_{k-1}, 0), L_{k+1} = (l_k, 0)]
\]
(by law of total expectation)

\[
\eta((\tilde{a}_{k-1}, 1), \tilde{l}_k)\phi((\tilde{a}_{k-1}, 1, \tilde{l}_k)) + 1 - \eta((\tilde{a}_{k-1}, 1), \tilde{l}_k) \times E[Y(\tilde{a}_{k-1}, 1, 0) \mid \tilde{A}_k = (\tilde{a}_{k-1}, 1), \tilde{L}_{k+1} = (\tilde{l}_k, 0)] \\
\eta((\tilde{a}_{k-1}, 0), \tilde{l}_k)\phi((\tilde{a}_{k-1}, 0, \tilde{l}_k)) + 1 - \eta((\tilde{a}_{k-1}, 0), \tilde{l}_k) \times E[Y(\tilde{a}_{k-1}, 0, 0) \mid \tilde{A}_k = (\tilde{a}_{k-1}, 0), L_{k+1} = (l_k, 0)]
\]
(by sequential ignorability)

\[
= \ldots
\]

\[
E[Y \mid \tilde{A}_K = (\tilde{a}_{k-1}, 1, 0), \tilde{L}_K = (\tilde{l}_k, 0)] \\
E[Y \mid \tilde{A}_K = (\tilde{a}_{k-1}, 0, 0), \tilde{L}_K = (\tilde{l}_k, 0)]
\]

(25)

Similarly,

\[
\phi(\tilde{a}_k, \tilde{l}_k)
\]

\[
= E[Y(\tilde{a}_k, 0) \mid \tilde{A}_{k+1} = (\tilde{a}_k, 0), \tilde{L}_{k+1} = (\tilde{l}_k, 1)] \\
E[Y(\tilde{a}_k, 0) \mid \tilde{A}_{k+1} = (\tilde{a}_k, 0), L_{k+2} = (l_k, 0)]
\]
(by sequential ignorability)

\[
\eta((\tilde{a}_k, 0), (\tilde{l}_k, 1))E[Y(\tilde{a}_k, 0) \mid \tilde{A}_{k+1} = (\tilde{a}_k, 0), \tilde{L}_{k+2} = (\tilde{l}_k, 1)] + (1 - \eta((\tilde{a}_k, 0), (\tilde{l}_k, 1)))E[Y(\tilde{a}_k, 0) \mid \tilde{A}_{k+1} = (\tilde{a}_k, 0), L_{k+2} = (l_k, 0)] \\
\eta((\tilde{a}_k, 0), (l_k, 0))E[Y(\tilde{a}_k, 0) \mid \tilde{A}_{k+1} = (\tilde{a}_k, 0), L_{k+2} = (l_k, 0)]
\]
(by law of total expectation)

\[
\eta((\tilde{a}_k, 0), (\tilde{l}_k, 1))\phi((\tilde{a}_k, 0, (\tilde{l}_k, 1))) + 1 - \eta((\tilde{a}_k, 0), (\tilde{l}_k, 1)) \times E[Y(\tilde{a}_k, 0) \mid \tilde{A}_{k+1} = (\tilde{a}_k, 0), \tilde{L}_{k+2} = (\tilde{l}_k, 1)] \\
\eta((\tilde{a}_k, 0), (l_k, 0))\phi((\tilde{a}_k, 0, (l_k, 0))) + 1 - \eta((\tilde{a}_k, 0), (l_k, 0)) \times E[Y(\tilde{a}_k, 0) \mid \tilde{A}_{k+1} = (\tilde{a}_k, 0), L_{k+2} = (l_k, 0)]
\]
(by sequential ignorability)

\[
= \ldots
\]

\[
E[Y \mid \tilde{A}_K = (\tilde{a}_k, 0), \tilde{L}_K = (\tilde{l}_k, 1)] \\
E[Y \mid \tilde{A}_K = (\tilde{a}_k, 0), L_K = (l_k, 0)]
\]

(26)
Hence by recursive arguments, it is easy to see that the mapping

\[
(\theta, \phi, GOP, \eta) \rightarrow \left( \begin{array}{l}
E[Y \mid A_K = (\bar{a}_{k-1}, 1, 0), L_K = (\bar{l}_{k}, 0)] \\
E[Y \mid A_K = (\bar{a}_{k-1}, 0, 0), L_K = (\bar{l}_{k}, 0)] \\
E[Y \mid A_K = (\bar{a}_{k}, 0), L_K = (\bar{l}_{k}, 1, 0)]
\end{array} \right),
\]

is an automorphism on \((\mathbb{R}^+)^{d_1} \times (0,1)^{d_2}\). Applying simple algebra to the RHS of (27) as in Step 2 of Algorithm 1, we have that

\[
(\theta, \phi, GOP, \eta) \rightarrow \left( \begin{array}{l}
E[Y \mid A_K = (\bar{a}_{K}, \bar{L}_K, \bar{l}_K)] \\
E[Y \mid A_K = (\bar{a}_{K}, 0, L_K = 0)]
\end{array} \right),
\]

is also an automorphism on \((\mathbb{R}^+)^{d_1} \times (0,1)^{d_2}\).

Now what is left to show is that given \(\eta\),

\[
(E[Y \mid A_K = \bar{a}_K, \bar{L}_K = \bar{l}_K], (\bar{a}_K, \bar{l}_K) \in \{0,1\}^{2K+1}) \rightarrow
\]

\[
\left( \begin{array}{l}
E[Y \mid A_K = \bar{a}_K, \bar{L}_K = \bar{l}_K] \\
E[Y \mid A_K = 0, L_K = 0]
\end{array} \right), (\bar{a}_K, \bar{l}_K) \in \{0,1\}^{2K+1} \setminus \{\bar{0}_{2K+1}\}; GOP
\]

is a bijection from \((0,1)^{d_1}\) to \((\mathbb{R}^+)^{d_1}\).

Arguing as in the proof of Theorem 1, to show that (28) is bijective, let \(c\) be a vector in \((\mathbb{R}^+)^{d_1}\). We need to show that there is one and only one \(p = (p_{\bar{a}_K, \bar{l}_K}, a_K \in \{0,1\}^{K+1}, l_K \in \{0,1\}^K) \in (0,1)^{d_1}\) such that

\[
\left( \begin{array}{l}
E[Y \mid A_K = \bar{a}_K, \bar{L}_K = \bar{l}_K] \\
E[Y \mid A_K = 0, L_K = 0]
\end{array} \right), a_K \in \{0,1\}^{K+1}, l_K \in \{0,1\}^K; GOP
\]

\(= c\).

Define \(k\) and \(p_{max}\) in a manner similar to the proof of Theorem 1. Equation (29) may equivalently be expressed as:

\[
\log(GOP) = \sum_{\bar{a}_K, \bar{l}_K} \log(k_{\bar{a}_K, \bar{l}_K}) + d_1 \log(p_{max}) - \sum_{\bar{a}_K, \bar{l}_K} \log(1 - k_{\bar{a}_K, \bar{l}_K} p_{max}) = \log(c_{d_1}).
\]

Let \(g(p_{max}) = \sum_{\bar{a}_K, \bar{l}_K} \log(k_{\bar{a}_K, \bar{l}_K}) + d_1 \log(p_{max}) - \sum_{\bar{a}_K, \bar{l}_K} \log(1 - k_{\bar{a}_K, \bar{l}_K} p_{max}) - \log(c_{d_1})\). Using the same argument as in the proof of Theorem 1, one may show that \(g(p_{max})\) has one and only one solution in the interval \((0,1)\) so that there is one and only one \(p = p_{max} k \in (0,1)^{d_1}\) such that (29) holds.

Lastly, since the domain of \(\mathcal{M}\), i.e. \((\mathbb{R}^+)^{d_1} \times (0,1)^{d_2}\) is the Cartesian product of the marginal domains of models in \(\mathcal{M}\), models in \(\mathcal{M}\) are variation independent of each other.

We have hence finished our proof. □
Computation of \( r_{\text{max}} \) in Step 3 of Algorithm 1 under the Markov assumption

Note that under assumption (19), for \( m > k \), we have

\[
\eta((\tilde{a}_{k-1}, 1, \tilde{o}_{m-k}), (\tilde{l}_{k}, \tilde{o}_{m-k})) = \eta((\tilde{a}_{k-1}, 0, \tilde{o}_{m-k}), (\tilde{l}_{k}, \tilde{o}_{m-k}))
\]
\[
\phi((\tilde{a}_{k-1}, 1, \tilde{o}_{m-k}), (\tilde{l}_{k}, \tilde{o}_{m-k})) = \phi((\tilde{a}_{k-1}, 0, \tilde{o}_{m-k}), (\tilde{l}_{k}, \tilde{o}_{m-k}))
\]

so that

\[
\frac{\eta((\tilde{a}_{k-1}, 1, \tilde{o}_{m-k}), (\tilde{l}_{k}, \tilde{o}_{m-k}))\phi((\tilde{a}_{k-1}, 1, \tilde{o}_{m-k}), (\tilde{l}_{k}, \tilde{o}_{m-k})) + 1 - \eta((\tilde{a}_{k-1}, 1, \tilde{o}_{m-k}), (\tilde{l}_{k}, \tilde{o}_{m-k}))}{\eta((\tilde{a}_{k-1}, 0, \tilde{o}_{m-k}), (\tilde{l}_{k}, \tilde{o}_{m-k}))\phi((\tilde{a}_{k-1}, 0, \tilde{o}_{m-k}), (\tilde{l}_{k}, \tilde{o}_{m-k})) + 1 - \eta((\tilde{a}_{k-1}, 0, \tilde{o}_{m-k}), (\tilde{l}_{k}, \tilde{o}_{m-k}))} = 1.
\]

Consequently, (25) implies that for \( k < K \),

\[
\theta(\tilde{a}_{k-1}, \tilde{l}_k) = \prod_{m=k}^{K-1} \frac{\eta((\tilde{a}_{k-1}, 1, \tilde{o}_{m-k}), (\tilde{l}_{k}, \tilde{o}_{m-k}))\phi((\tilde{a}_{k-1}, 1, \tilde{o}_{m-k}), (\tilde{l}_{k}, \tilde{o}_{m-k})) + 1 - \eta((\tilde{a}_{k-1}, 1, \tilde{o}_{m-k}), (\tilde{l}_{k}, \tilde{o}_{m-k}))}{\eta((\tilde{a}_{k-1}, 0, \tilde{o}_{m-k}), (\tilde{l}_{k}, \tilde{o}_{m-k}))\phi((\tilde{a}_{k-1}, 0, \tilde{o}_{m-k}), (\tilde{l}_{k}, \tilde{o}_{m-k})) + 1 - \eta((\tilde{a}_{k-1}, 0, \tilde{o}_{m-k}), (\tilde{l}_{k}, \tilde{o}_{m-k}))} \times \frac{E[Y \mid \tilde{A}_K = (\tilde{a}_{k-1}, 1, 0), \tilde{L}_K = (\tilde{l}_{k}, 0)]}{E[Y \mid \tilde{A}_K = (\tilde{a}_{k-1}, 0, 0), \tilde{L}_K = (\tilde{l}_{k}, 0)]}
\]

so that

\[
\frac{E[Y \mid \tilde{A}_K = (\tilde{a}_{k-1}, 1, 0), \tilde{L}_K = (\tilde{l}_{k}, 0)]}{E[Y \mid \tilde{A}_K = (\tilde{a}_{k-1}, 0, 0), \tilde{L}_K = (\tilde{l}_{k}, 0)]} = \theta(\tilde{a}_{k-1}, \tilde{l}_k) / \theta(\tilde{l}_k) = \frac{\eta(\tilde{a}_{k-1}, 1, \tilde{l}_k)\phi(\tilde{a}_{k-1}, 1, \tilde{l}_k) + 1 - \eta(\tilde{a}_{k-1}, 1, \tilde{l}_k)}{\eta(\tilde{a}_{k-1}, 0, \tilde{l}_k)\phi(\tilde{a}_{k-1}, 0, \tilde{l}_k) + 1 - \eta(\tilde{a}_{k-1}, 0, \tilde{l}_k)}
\]

which only depends on \( l_k \). One can also see that

\[
\frac{E[Y \mid \tilde{A}_K = (\tilde{a}_{K-1}, 1), \tilde{L}_K = \tilde{l}_K]}{E[Y \mid \tilde{A}_K = (\tilde{a}_{K-1}, 0), \tilde{L}_K = \tilde{l}_K]} \text{ only depends on } l_{K-1}.
\]

Similarly, (26) implies that for \( k < K \),

\[
\phi(\tilde{a}_k, \tilde{l}_k) = \frac{\eta(\tilde{a}_k, 0, \tilde{o}_{m-k}), (\tilde{l}_k, 0, \tilde{o}_{m-k})\phi(\tilde{a}_k, 0, \tilde{o}_{m-k}), (\tilde{l}_k, 0, \tilde{o}_{m-k}) + 1 - \eta(\tilde{a}_k, 0, \tilde{o}_{m-k}), (\tilde{l}_k, 0, \tilde{o}_{m-k}))}{\eta(\tilde{a}_k, 0, \tilde{o}_{m-k}), (\tilde{l}_k, 0, \tilde{o}_{m-k})\phi(\tilde{a}_k, 0, \tilde{o}_{m-k}), (\tilde{l}_k, 0, \tilde{o}_{m-k}) + 1 - \eta(\tilde{a}_k, 0, \tilde{o}_{m-k}), (\tilde{l}_k, 0, \tilde{o}_{m-k}))}
\]

which only depends on \( l_k \).
These are well-defined as due to (30) and (31), which only depends on 

Given the value of \( O \)

so that

\[
E[Y | \bar{A}_K = (\bar{a}_k, 0), \bar{L}_K = (\bar{l}_k, 1, 0)] = \phi(\bar{a}_k, \bar{l}_k) \frac{\eta((\bar{a}_k, 0), (\bar{l}_k, 1)) + 1 - \eta((\bar{a}_k, 0), (\bar{l}_k, 1))}{\eta((\bar{a}_k, 0), (\bar{l}_k, 0)) + 1 - \eta((\bar{a}_k, 0), (\bar{l}_k, 0))} \times \frac{E[Y | \bar{A}_K = (\bar{a}_k, 0), \bar{L}_K = (\bar{l}_k, 0, 0)]}{E[Y | \bar{A}_K = (\bar{a}_k, 0), \bar{L}_K = (\bar{l}_k, 1, 0)]}
\]

which only depends on \( a_k \). One can also see that 

\[
\frac{E[Y | \bar{A}_K = \bar{a}_K, \bar{L}_K = (\bar{l}_{K-1}, 1)]}{E[Y | \bar{A}_K = \bar{a}_K, \bar{L}_K = (\bar{l}_{K-1}, 0)]}
\]

only depends on \( a_{K-1} \).

Given (30) and (31), we can now use dynamic programming to find \( r_{\text{max}} \). Specifically, define the following functions:

\[
O(a_k) = \max_{l_{k+1}, \ldots, l_K, a_{k+1}, \ldots, a_K} \frac{E[Y | \bar{A}_K = \bar{a}_K, \bar{l}_K = \bar{l}_k]}{E[Y | \bar{A}_K = (\bar{a}_k, 0), \bar{l}_K = (\bar{l}_k, 0)]}
\]

\[
O(l_k) = \max_{l_{k+1}, \ldots, l_K, a_{k}, \ldots, a_K} \frac{E[Y | \bar{A}_K = \bar{a}_K, \bar{l}_K = \bar{l}_k]}{E[Y | \bar{A}_K = (\bar{a}_k, 0), \bar{l}_K = (\bar{l}_k, 0)]}
\]

These are well-defined as due to (30) and (31), \( O(a_k) \) and \( O(l_k) \) only depend on \( a_k \) and \( l_k \), respectively.

The algorithm proceeds by computing \( O(a_k) \) and \( O(l_k) \) sequentially. First note that

\[
O(l_K) = \max_{a_K} \frac{E[Y | \bar{A}_K = \bar{a}_K, \bar{l}_K = \bar{l}_k]}{E[Y | \bar{A}_K = (\bar{a}_k, 0), \bar{l}_K = (\bar{l}_k, 0)]}
\]

Given the value of \( O(l_{k+1}) \), we have

\[
O(a_k) = \max_{l_{k+1}, \ldots, l_K, a_{k+1}, \ldots, a_K} \frac{E[Y | \bar{A}_K = \bar{a}_K, \bar{l}_K = \bar{l}_k]}{E[Y | \bar{A}_K = (\bar{a}_k, 0), \bar{l}_K = (\bar{l}_k, 0)]} \times \frac{E[Y | \bar{A}_K = (\bar{a}_k, 0), \bar{l}_K = (\bar{l}_k, l_{k+1}, 0)]}{E[Y | \bar{A}_K = (\bar{a}_k, 0), \bar{l}_K = (\bar{l}_k, 0)]}
\]

\[
= \max_{l_{k+1}} \left\{ E[Y | \bar{A}_K = (\bar{a}_k, 0), \bar{l}_K = (\bar{l}_k, l_{k+1}, 0)] \times O(l_{k+1}) \right\}
\]

\[
= \max_{l_{k+1}} \left\{ E[Y | \bar{A}_K = (\bar{a}_k, 0), \bar{l}_K = (\bar{l}_k, l_{k+1}, 0)] \times O(l_{k+1}) \right\}
\]
and similarly

$$O(l_k) = \max_{a_k} \left\{ \frac{E[Y | \bar{A}_K = (\bar{a}_{k-1}, a_k, \bar{0}_{K-k}), \bar{l}_K = (\bar{l}_k, \bar{0}_{K-k})]}{E[Y | A_K = (\bar{a}_{k-1}, 0, \bar{0}_{K-k}), l_K = (l_k, \bar{0}_{K-k})]} \times O(a_k) \right\}.$$ 

Finally we get that

$$O(l_0) = \max_{l_1, \ldots, l_K, a_0, \ldots, a_K} \frac{E[Y | \bar{A}_K = \bar{a}_K, \bar{l}_K = \bar{l}_K]}{E[Y | A_K = \bar{0}_{K+1}, l_K = \bar{0}_K]} = r_{\text{max}}.$$
References

Lumley, T., Kronmal, R., and Ma, S. (2006). Relative risk regression in medical research: models, contrasts, estimators, and algorithms. *UW Biostatistics Working Paper Series*. Working paper 293. http://biostats.bepress.com/uwbiostat/paper293/. Last accessed on Jul 13, 2015.

Matsouaka, R. A. and Tchetgen Tchetgen, E. J. (2014). Likelihood based estimation of logistic structural nested mean models with an instrumental variable. Last accessed on Oct 10, 2016.

Meng, X.-L. (1994). Multiple-imputation inferences with uncongenial sources of input. *Statistical Science*, 9:538–558.

Pearl, J. (2009). *Causality*. Cambridge University Press.

Richardson, T. S., Robins, J. M., and Wang, L. (2017). On modeling and estimation for the relative risk and risk difference. *Journal of the American Statistical Association*, pages 1–10.

Robins, J. M. (1986). A new approach to causal inference in mortality studies with a sustained exposure period – application to control of the healthy worker survivor effect. *Mathematical Modelling*, 7(9):1393–1512.

Robins, J. M. (1994). Correcting for non-compliance in randomized trials using structural nested mean models. *Communications in Statistics-Theory and methods*, 23(8):2379–2412.

Robins, J. M. (1997). Causal inference from complex longitudinal data. In *Latent variable modeling and applications to causality*, pages 69–117. Springer.

Robins, J. M. (2000). Marginal structural models versus structural nested models as tools for causal inference. In *Statistical models in epidemiology, the environment, and clinical trials*, pages 95–133. Springer.

Robins, J. M. (2004). Optimal structural nested models for optimal sequential decisions. In *Proceedings of the second seattle Symposium in Biostatistics*, pages 189–326. Springer.

Robins, J. M., Greenland, S., and Hu, F.-C. (1999). Estimation of the causal effect of a time-varying exposure on the marginal mean of a repeated binary outcome. *Journal of the American Statistical Association*, 94(447):687–700.
Robins, J. M. and Rotnitzky, A. (2004). Estimation of treatment effects in randomised trials with non-compliance and a dichotomous outcome using structural mean models. *Biometrika*, 91(4):763–783.

Robins, J. M. and Wasserman, L. (1997). Estimation of effects of sequential treatments by reparameterizing directed acyclic graphs. In *Proceedings of the thirteenth conference on uncertainty in artificial intelligence*, pages 409–420. Morgan Kaufmann Publishers Inc.

Rothman, K. J., Greenland, S., and Lash, T. L. (2008). *Modern Epidemiology*. Lippincott Williams & Wilkins, 3rd edition.

Vansteelandt, S. and Goetghebeur, E. (2003). Causal inference with generalized structural mean models. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*, 65(4):817–835.

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

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