CHAPTER 1

Estimation of the causal effects of time-varying exposures

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1.1 Introduction

In this chapter we describe methods for the estimation of the causal effect of a time-varying exposure on an outcome of interest from longitudinal data collected in an observational study. The terms exposure and treatment will be used synonymously and interchangeably. We assume a fixed study population, i.e., a closed cohort with a well-defined, known start of follow-up date for each subject. Time will refer to time since start of follow-up, which we also refer to as time since baseline. We only consider estimation of the effect of exposures occurring at or after the start of follow-up because the estimation of the effects of pre-baseline exposures is not possible without making strong untestable assumptions. We refer to the exposure received at start of follow-up as the baseline exposure. Baseline covariates refer to covariates, including pre-baseline exposure, that occur prior to the baseline exposure. We classify exposures as either fixed or time-varying.

We define an exposure to be fixed if every subject's baseline exposure level determines the subject's exposure level at all later times. Exposures can be fixed because they only occur at the start of follow-up (e.g., a bomb explosion, a one-dose vaccine, a surgical intervention), because they do not change over time (e.g., genotype), or because they evolve over time in a deterministic way (e.g., time since baseline exposure).

Any exposure that is not fixed is said to be time-varying. Some examples of time-varying exposures are a subject's smoking status, a drug whose dose is readjusted according to the patient's clinical response, a surgical intervention that is administered to different study patients at different times from start of follow-up, and the phenotypic expression (say, mRNA level) of a genotype that responds to changing environmental factors.

We shall need to consider time-dependent confounders as well as time-varying exposures. For present purposes, one may consider a time-varying covariate to be a time-dependent confounder if a post-baseline value of the covariate is both an independent predictor of (i.e., a risk factor for) both subsequent exposure and the outcome within strata jointly determined by baseline covariates and prior exposure. A more precise definition is given in Section 1.3. For a fixed exposure, time dependent confounding is absent because baseline exposure fully determines later exposure. As a consequence, in the absence of confounding by unmeasured baseline covariates or model misspecification, conventional methods to adjust for confounding by baseline covariates such as stratification, matching and/or regression deliver consistent estimates of a causal effect of a fixed exposure. In contrast, when interest focuses on the causal effect of a time-varying exposure on an outcome, even when confounding by unmeasured factors and model misspecification are both absent, conventional analytic methods may be biased and result in estimates of effect that may fail to have a causal interpretation, regardless of whether or not one adjusts for the time-dependent confounders in the analysis (Robins 1986, Hernán et al, 2004). In fact, if (i) time-dependent confounding is present and (ii) within strata of the baseline covariates, baseline exposure

predicts the subsequent evolution of the time-dependent confounders, then conventional analytic methods can be biased and falsely find an exposure effect even under the sharp null hypothesis of no net, direct, or indirect effect of exposure on the outcome of any subject (see Section 1.4).

Nearly all exposures of epidemiologic interest are time-varying. However, because of the greater complexity of analytic methods that appropriately control for time-dependent confounding, introductory treatments of causal inference often consider only the case of fixed exposures.

This chapter provides an introduction to causal inference for time-varying exposures in the presence of time-dependent confounding. We will discuss three different methods to estimate the effect of a time-varying exposures: the g-computation algorithm formula (the "g-formula"), inverse probability of treatment weighting (IPTW) of marginal structural models (MSMs), and g-estimation of structural nested models. We refer to the collection of these methods as g-methods. If we used only completely saturated (i.e., non-parametric) models, all three methods would give identical estimates of the effect of treatment. However, in realistic longitudinal studies, the data are sparse and high dimensional. Therefore possibly misspecified non-saturated models must be used. As a consequence, the three methods can provide different estimates. The method of choice will then depend both on the causal contrast of primary substantive interest and on the method's robustness to model misspecification (see Section 1.5)

The chapter is organized as follows. First, we review causal inference with fixed exposures. Second, we generalize to time-varying exposures. Third, we analyze a simple hypothetical study of a time-varying exposure using saturated models to illustrate both the bias of conventional analytic methods and the validity of and agreement between the three g-methods. Fourth, we introduce general MSMs and structural nested models in order to estimate optimal dynamic treatment regimes. Finally, we examine the strengths and weaknesses of each of our three methods in the analysis of realistic study data. In the interest of brevity, we limit ourselves to the case where (i) covariate and exposure data are collected at fixed equal-spaced intervals, e.g., at weekly clinic visits, (ii) censoring, missed visits, and measurement error are absent, (iii) the outcome is a univariate continuous random variable Y measured at end of follow-up, and (iv) there is no unmeasured confounding. Extensions to settings in which (i)-(iv) are violated can be found in prior work by Robins and collaborators. Violations of (i) are discussed in Robins (1997a) and Robins (1998); of (ii) in Robins. Rotnitzky, and Zhao (1995), van der Laan and Robins (2003), and Robins (2003); of (iii) in Robins (1994, 1997a), and Hernán, Brumback, and Robins (2001, 2002); of (iv) in Robins, Rotnitzky, and Scharfstein (1999) and Brumback et al (2004).

1.2 Fixed exposures

We observe on each of N study subjects a fixed dichotomous exposure A that can take values 0 (unexposed) or 1 (exposed), an outcome Y measured at the end of follow-up, and a vector L of baseline covariates. Capital letters such as Y or A will refer to random variables, i.e., a variable which can take on different values for different study subjects. Small letters such as y and a refer to the possible values of Y and A. Thus the random variable A can take on the two values $a = 1$ or $a = 0$. Let Y_a denote the counterfactual or potential outcome for a given subject under exposure level a. For a dichotomous A we have two counterfactual variables $Y_{a=1}$ and $Y_{a=0}$. For example, for a subject whose outcome would be three under exposure and would be one under non exposure, we would write $Y_{a=1} = 3$ and $Y_{a=0} = 1$ and $Y_{a=1} - Y_{a=0} = 2$. If in the actual study this subject were exposed, then his observed Y would be 3. That is, Y_a is the random variable representing the outcome Y that would be observed for a given subject were he or she to experience exposure level a. Furthermore,

a subject's observed outcome Y is the counterfactual outcome Y_a corresponding to the treatment $A = a$ that the subject actually received. Implicit in our definition of a potential outcome is the assumption that a given subject's response is not affected by other subjects' treatment. This assumption cannot always be taken for granted. For example, it often fails in vaccine efficacy trials conducted within a single city, because the vaccine exposure of other subjects can affect the outcome (infection status) of an unvaccinated subject through the mechanism of herd immunity. Standard statistical summaries of uncertainty due to sampling variability, such as a confidence interval for a proportion, only have meaning if we assume the N study subjects have been randomly sampled from a large source population of size M, such that N/M is very small. Because we plan to discuss sampling variability, we make this assumption, although we recognize that the assumed source population is ill-defined, even hypothetical. Probability statements and expected values will refer to proportions and averages in the source population.

The contrast $Y_{a=1} - Y_{a=0}$ is said to be the individual causal effect of exposure on a subject. The average or mean causal effect in the population is then $\mathrm{E}[Y_{a=1} - Y_{a=0}] = \mathrm{E}[Y_{a=1}] - \mathrm{E}[Y_{a=0}]$. We say that the exposure A has a causal effect (protective or harmful) on the mean of the outcome Y if $\mathrm{E}[Y_{a=1}] - \mathrm{E}[Y_{a=0}] \neq 0$. When Y is a dichotomous outcome variable, then the mean of Y_a equals the risk of Y_a, i.e., $\mathrm{E}[Y_a] = \Pr[Y_a = 1]$, and we refer to $\mathrm{E}[Y_{a=1}] - \mathrm{E}[Y_{a=0}]$, $\mathrm{E}[Y_{a=1}] / \mathrm{E}[Y_{a=0}]$, and $\mathrm{E}[Y_{a=1}] / \{1 - \mathrm{E}[Y_{a=1}]\} / (\mathrm{E}[Y_{a=0}] / \{1 - \mathrm{E}[Y_{a=0}]\})$ as the causal risk difference, causal risk ratio, and causal odds ratio, respectively. Some equivalent statements that denote an average causal effect are: the causal risk difference differs from 0, the causal risk ratio differs from 1, and the causal odds ratio differs from 1.

We now provide conditions, which we refer to as identifiability conditions, under which it is possible to obtain, from observational data, consistent estimates of counterfactual quantities such as $\mathrm{E}[Y_a]$ and thus the causal risk difference and the causal risk and odds ratio for binary Y. First some notation. For any random variables, $B \amalg C|L = l$ means B and C are statistically independent within the stratum of subjects in the source population with $L = l$. Thus, if B and C are dichotomous, $B \amalg C|L = l$ says the B-C odds ratio is 1 in the l-stratum-specific 2×2 table of B versus C. $B \amalg C|L$ means B and C are statistically independent in every stratum of L. Thus if L takes on 4 possible values, $B \amalg C|L$ implies that the 4 l-stratum-specific odds ratios are all 1. The three identifiability conditions are (Rosenbaum and Rubin, 1983):

1. Consistency: If $A = a$ for a given subject, then $Y_a = Y$ for that subject.
2. Conditional exchangeability or, equivalently, no unmeasured confounding given data on baseline covariates L:

$$Y_a \amalg A|L = l \text{ for each possible value } a \text{ of } A \text{ and } l \text{ of } L$$

3. Positivity: If $f_L[l] \neq 0$, then $f_{A|L}[a|l] > 0$ for all a , where $f_L[l] = \Pr[L = l]$ is the population marginal probability that L takes the value l and $f_{A|L}[a|l] = \Pr[A = a|L = l]$ is the conditional probability that A takes the value a among subjects in the population with L equal to l. [The above assumed L and A were discrete variables. If L and/or A were continuous variables, we would interpret $f_L[l]$ and/or $f_{A|L}[a|l]$ as the marginal density of L and/or the conditional density of A given L, and drop $\Pr[L = l]$ and/or $\Pr[A = a|L = l]$ from the definition of positivity.]

These three conditions generally hold in an ideal two-armed randomized experiment with full compliance. Consistency states that, for a subject who was exposed, i.e., $A = 1$, her potential outcome $Y_{a=1}$ is equal to her observed outcome Y and thus is known (although her outcome $Y_{a=0}$ remains unknown). Analogously, for an unexposed subject, i.e., $A = 0$, her potential outcome $Y_{a=0}$ would equal her observed outcome Y, but $Y_{a=1}$ would remain unknown. Positivity means that the exposure was not deterministically allocated within any

level l of the covariates L. That is, not all source population subjects with a given value l of L were assigned to be exposed or unexposed (Hernán and Robins, 2006a). Note that, even under positivity, all study subjects with $L = l$ could, by chance, be exposed because the study population is a small sample of the source population.

Before explaining conditional exchangeability, we discuss unconditional exchangeability. Unconditional or marginal exchangeability of the exposed and unexposed subgroups of the source population, written as $Y_{a=1} \amalg A$ and $Y_{a=0} \amalg A$, implies that the exposed, had they been unexposed, would have experienced the same distribution of outcomes as the unexposed did. Exchangeability also implies that the previous sentence holds true if one swaps the words "exposed" and "unexposed." Unconditional randomization ensures unconditional exchangeability because the distributions of risk factors in the exposed and unexposed groups are guaranteed to be the same. Conditional exchangeability only requires that exchangeability is achieved within levels of the measured variables in L. For example, conditional—but not unconditional—exchangeability would hold in a randomized experiment in which exposure was randomly assigned (i) within levels l of a baseline covariate L that is an independent risk factor for Y, and (ii) the randomization probabilities $\Pr(A = 1|L = l)$ vary with l.

Unconditional exchangeability and conditional exchangeability can be translated into the language of causal directed acyclic graphs or DAGs (Pearl, 1995; Spirtes, Glymour and Scheines, 1993). The Appendix contains the requisite background material on the representation of counterfactual causal models by causal DAGs. Consider the three causal DAGs of Figure 1 (Robins et al, 2000) in which L and U represent vectors of measured and unmeasured baseline causes of Y, respectively. The causal DAG in Figure 1a can represent a randomized experiment in which each subject is randomized to exposure with the same probability $\Pr(A = 1)$. Therefore the conditional probability of exposure does not depend on L or U, i.e., $\Pr(A = 1|L = l, U = u) = \Pr(A = 1)$. We then say that there is "no confounding by measured variables L or unmeasured variables U". Equivalently, the exposed and the unexposed are unconditionally exchangeable (i.e., $Y_a \amalg A$) because the exposure A and the outcome Y do not share any common causes. When unconditional exchangeability holds, association is causation. That is, the mean outcome had, contrary to fact, all study subjects been exposed to level a, i.e., $\mathrm{E}[Y_a]$, equals the mean $\mathrm{E}[Y|A = a]$ among the subset of the study population actually treated with a. Hence, for binary Y, the crude risk difference $\mathrm{E}[Y|A = 1] - \mathrm{E}[Y|A = 0]$ is the causal risk difference $\mathrm{E}[Y_{a=1}] - \mathrm{E}[Y_{a=0}]$, so consistent estimation of the average causal effect is possible, even without data on L.

The causal DAG in Figure 1b can represent a randomized experiment in which each subject is randomized to exposure with probability $\Pr(A = 1|L = l)$ that depends on the subject's value of L but not on U, i.e., $\Pr(A = 1|L = l, U = u) = \Pr(A = 1|L = l)$. We then say that there is confounding but the measured covariates are sufficient to adjust for it, so there is no unmeasured confounding. Equivalently, the exposed and the unexposed are conditionally exchangeable given L because, even though the exposure A and the outcome Y share some common causes U, the non causal association between exposure and outcome can be blocked by conditioning on the measured covariates L. In this setting, marginal association is not causation i.e., $\mathrm{E}[Y_a] \neq \mathrm{E}[Y|A = a]$. However, within a stratum l of L, association is causation, i.e., $\mathrm{E}[Y_a|L = l] = \mathrm{E}[Y|A = a, L = l]$. Furthermore, by using data on L, $\mathrm{E}[Y_a]$ can still be consistently estimated.

The causal DAG in Figure 1c represents a study in which the conditional probability of exposure $\Pr(A = 1|L = l, U = u)$ depends on the unmeasured variables U as well as the measured variables L and thus cannot possibly represent a randomized experiment. We say that there is unmeasured confounding. Equivalently, the exposed and the unexposed are not conditionally exchangeable given L because we cannot block all non causal associations between exposure and outcome by conditioning on the measured covariates L. In this setting

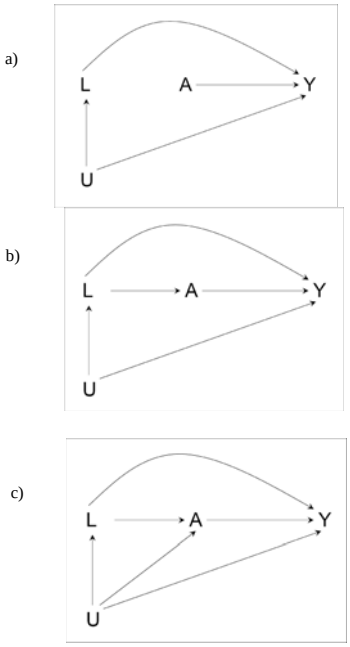


Figure 1.1 *Fixed exposure*

neither $\mathrm{E}[Y_a|L=l]$ nor $\mathrm{E}[Y_a]$ can be consistently estimated, at least without further strong assumptions.

When the (three) identifiability conditions hold, one can use any of the three analytic methods discussed below—g-formula, inverse probability weighting (IPTW; see Chapter 20), or g-estimation—to consistently estimate $\mathrm{E}[Y_a]$. We first describe the g-formula and IPTW to estimate the counterfactual mean $\mathrm{E}[Y_a]$. A description of structural nested models will be deferred to Section 1.4.

For a given value a of a fixed exposure A and vector L of baseline covariates, the g-formula (based on covariates L) for $\mathrm{E}[Y_a]$ is defined to be the weighted sum of the l-stratum-specific means of Y among those exposed to level a in the population with weights equal to the frequency of the L strata. That is,

$$\sum_l \mathrm{E}[Y|A=a, L=l]\ \Pr[L=l]$$

where the sum is over all values l of L in the population. Epidemiologists refer to the g-formula for $\mathrm{E}[Y_{a=1}]$ as the standardized mean of Y in the exposed ($A=1$). Note the g-formula depends on the distribution in the population of the observed variables (A, L, Y). In practice, this distribution will be estimated from the study data.

When L takes values on a continuous scale, then the sum $\sum$ is replaced by an integral, and the g-formula becomes

$$\int \mathrm{E}[Y|A=a, L=l]\ dF_L[l]$$

The IPTW formulas for $\mathrm{E}[Y_{a=1}]$ and $\mathrm{E}[Y_{a=0}]$ based on L is the mean of Y among the exposed ($A=1$) and unexposed respectively in a pseudo-population constructed by weighting each subject in the population by their subject-specific inverse probability of treatment

weight (IPTW)

$$SW = \frac{f[A]}{f[A|L]}$$

where $f[A]$ and $f[A|L]$ are the probability densities $f_A[a]$ and $f_{A|L}[a|l]$ evaluated at the subject's data A, and A and L, respectively. In a randomized experiment, $f[A|L]$ is known by design. In an observational study it must be estimated from the study data. Consider a subject with $A = 0$ and L equal to a particular value, say l^*. Suppose that 2/3 of the population with $L = l^*$ but 1/3 of the total population is exposed. Then, although in the true population each subject counts equally, in the pseudo-population, our subject has weight 2 and thus counts as two subjects since $f[A] = \Pr(A = 0) = 1 - 1/3 = 2/3$, $f[A|L] = 1 - 2/3 = 1/3$, and $SW = 2$. In contrast, a second subject with $A = 1$ and $L = l^*$ has $SW = (1/3)/(2/3) = 1/2$ and so only counts as 1/2 a person.

We refer to the subject-specific SW as stabilized weights and to the pseudo-population created by these weights as a stabilized pseudo-population. In fact, as shown in the next paragraph, the IPTW formula for $\mathrm{E}[Y_a]$ does not actually depend on the numerator of SW. Thus, we could alternatively create an unstabilized pseudo-population by weighting each subject by their unstabilized weight

$$W = \frac{1}{f[A|L]}$$

However, as discussed in later sections, there are other settings in which stabilized or unstabilized weights cannot be used interchangeably.

Mathematically, the respective IPTW formulas for $\mathrm{E}[Y_a]$ in the stabilized and unstabilized populations are $\mathrm{E}\left[\frac{I(A=a)f[A]}{f[A|L]}Y\right] / \mathrm{E}\left[\frac{I(A=a)f[A]}{f[A|L]}\right]$ and $\mathrm{E}\left[\frac{I(A=a)}{f[A|L]}Y\right] / \mathrm{E}\left[\frac{I(A=a)}{f[A|L]}\right]$, since (i) $\mathrm{E}\left[N\frac{I(A=a)f[A]}{f[A|L]}\right]$ and $\mathrm{E}\left[N\frac{I(A=a)}{f[A|L]}\right]$ are the number of subjects in the stabilized and unstabilized pseudo-populations with $A = a$, and (ii) $\mathrm{E}\left[N\frac{I(A=a)f[A]}{f[A|L]}Y\right]$ and $\mathrm{E}\left[N\frac{I(A=a)}{f[A|L]}\right]$ are the sum of their Y values. Here $I(\cdot)$ is the indicator function defined by $I(B) = 1$ if B is true, 0 otherwise. Hernán and Robins (2006a) discuss the mathematical equivalence between the g-formula/standardization and IPTW (based on either stabilized or unstabilized weights) for fixed exposures under positivity. This equivalence extends to time-varying exposures as discussed in Section 1.3. The equivalence for fixed exposures is based on the mathematical identities $\mathrm{E}\left[\frac{I(A=a)f[A]}{f[A|L]}Y\right] / \mathrm{E}\left[\frac{I(A=a)f[A]}{f[A|L]}\right] = \mathrm{E}\left[\frac{I(A=a)}{f[A|L]}Y\right] / \mathrm{E}\left[\frac{I(A=a)}{f[A|L]}\right] = \int \mathrm{E}[Y|A=a, L=l]\, dF_L[l]$.

When exposure is unconditionally randomized (Figure 1a) both the g-formula and the IPTW estimate for $\mathrm{E}[Y_a]$ are equal to the unadjusted (i.e., crude) mean $\mathrm{E}[Y|A=a]$ of Y among those with exposure level a in the population because the exposure A and the covariate L are independent, which implies $F[l] = F[l|a]$ in the g-formula, and $f[A|L] = f[A]$ for IPTW.

On the other hand, when the randomization is conditional on L (Figure 1b), then the average causal effect differs from the crude risk difference $\mathrm{E}[Y|A=1] - \mathrm{E}[Y|A=0]$ and data on L are needed to consistently estimate $\mathrm{E}[Y_a]$. The g-formula estimates $\mathrm{E}[Y_a]$ by effectively simulating the joint distribution of the variables L, A, and Y that would have been observed in a hypothetical study in which every subject received exposure a. The IPTW method effectively simulates the data that would have been observed had, contrary to fact, exposure been unconditionally randomized. Specifically, both stabilized and unstabilized

IPTW creates a pseudo-population in which (i) the mean of Y_a is identical to that in the actual study population but (ii) the exposure A is independent of L so that, if the causal graph in Figure 1b holds in the actual population, the causal graph in Figure 1a with no arrow from L to A will hold in the pseudo-population. The only difference between stabilized and unstabilized IPTW is that in the unstabilized pseudo-population $\Pr(A=1) = 1/2$ while in the stabilized pseudo-population $\Pr(A=1)$ is as in the actual population. Thus $\mathrm{E}[Y_a]$ in the actual population is $\mathrm{E}_{ps}[Y|A=a]$ where the subscript ps is to remind us that we are taking the average of Y among subjects with $A=a$ in either pseudo-population. For example, suppose in the actual population there are three exposed subjects with SW equal to 1/3, 2, 1/2 and Y equal to 3, 6, 4, respectively. Then $\mathrm{E}[Y_a] = \mathrm{E}_{ps}[Y|A=1] = \frac{3\times 1/3+6\times 2+4\times 1/2}{1/3+2+1/2} = 5.3$ while $\mathrm{E}[Y|A=1] = \frac{3\times 1+6\times 1+4\times 1}{3} = 4$. In summary, when the three identifiability conditions hold, the average causal effect $\mathrm{E}[Y_{a=1}] - \mathrm{E}[Y_{a=0}]$ in the population is the crude risk difference $\mathrm{E}_{ps}[Y|A=1] - \mathrm{E}_{ps}[Y|A=0]$ in the pseudo-population.

What about observational studies? Imagine for a second that the three identifiability conditions—consistency, conditional exchangeability, positivity—are met in a particular observational study. Then there is no conceptual difference between such an observational study and a randomized experiment. Taken together, the three conditions imply that the observational study can be conceptualized as a randomized experiment and hence that the g-formula, IPTW, or g-estimation can also be used to estimate counterfactual quantities like $\mathrm{E}[Y_a]$ from the observational data. A difference between randomized experiments and observational studies is that the conditional probability of exposure is not known in the latter and thus needs to be estimated from the data. We discuss this issue in detail in the next section.

The major weakness of observational studies is that, unlike in randomized experiments with full compliance, the three identifiability conditions are not guaranteed by design. Positivity may not hold if subjects with certain baseline characteristics are always exposed (or unexposed) because of prevailing treatment practices in the community. In that case, subjects with those baseline characteristics are often excluded from the study population for purposes of causal inference. Conditional exchangeability will not hold if the exposed and the unexposed differ with respect to unmeasured risk factors as in Figure 1c, i.e., if there is unmeasured confounding. Unfortunately, the presence of conditional exchangeability cannot be empirically tested. Even consistency cannot always be taken for granted in observational studies because the counterfactual outcomes themselves are sometimes not well defined, which renders causal inferences ambiguous (Robins and Greenland, 2000; Hernán, 2005). Thus, in observational studies, an investigator who assumes these conditions hold may be mistaken; hence, causal inference from observational data is a risky business. When the consistency and conditional exchangeability conditions fail to hold, the IPTW and g-formula for $\mathrm{E}[Y_a]$ based on L are still well defined and can be estimated from the observed data; however the formulas no longer equal $\mathrm{E}[Y_a]$ and thus do not have the causal interpretation as the mean of Y had all subjects received treatment a. When positivity fails to hold for treatment level a, the IPTW formula remains well defined but fails to equal $\mathrm{E}[Y_a]$, while the g-formula is undefined (Hernán and Robins, 2006a).

In summary, causal inference from observational data relies on the strong assumption that the observational study can be likened to a randomized experiment with randomization probabilities that depend on the measured covariates. Often this assumption is not explicit. Although investigators cannot prove that the observational-randomized analogy is 100% correct for any particular study, they can use their subject-matter knowledge to collect data on many relevant covariates and hope to increase the likelihood that the analogy is approximately correct. We next describe how to conceptualize observational studies as randomized experiments when the exposure changes over time.

1.3 Time-varying exposures

To develop methods for the estimation of the causal effects of time-varying exposures, we need to generalize the definition of causal effect and the three identifiability conditions of the previous section. For simplicity, we consider a study of the effect of a time-dependent dichotomous exposure $A(t)$ on a continuous outcome Y measured at end of follow-up at time $K+1$ from study entry. [$A(t)$ is identical to A_t used in Chapters 20 and 22.]) Subjects change exposure only at weekly clinic visits so $A(t)$ is recorded at fixed times $t = 0, 1, ..., K$ in weeks from baseline. We use overbars to denote history, i.e., the exposure history through time (i.e. week) t is $\bar{A}(t) = \{A(0), A(1), ..., A(t)\}$. The possible change in exposure at week t occurs after data are available on the history $\overline{L}(t) = \{L(0), L(1), ..., L(t)\}$ of a vector of possibly time dependent covariates. We denote a subject's total exposure and covariate history by $\bar{A} = \bar{A}(K)$ and $\overline{L} = \overline{L}(K)$.

1.3.1 Nondynamic regimes

To describe causal contrasts for time-varying exposures, we first need to define exposure regimes or plans. For simplicity, we temporarily restrict our description to static (nondynamic) treatment regimes $\bar{a} = \{a(0), a(1), ..., a(K)\}$ where $a(t)$ is 1 if the regime specifies that the subject is to be exposed at time t, 0 otherwise, and $\bar{a}(t)$ represents exposure history under regime $\bar{a}$ through week t. Note $\bar{a}(K) = \bar{a}$. Associated with each of the 2^K regimes $\bar{a}$ is the subject's counterfactual outcome $Y_{\bar{a}}$ under exposure regime $\bar{a}$. Some examples of regimes $\bar{a}$ are 'continuous exposure' $\{1, 1, ..., 1\}$, 'no exposure' $\{0, 0, ..., 0\}$, 'exposure during the first two periods only' $\{1, 1, 0, 0..., 0\}$, and 'exposure every other period' $\{1, 0, 1, 0, ...\}$.

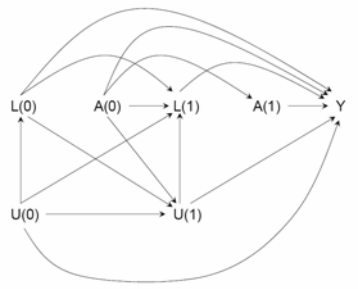
We say that the time-varying exposure $A(t)$ has a causal effect on the average value of Y if $\mathrm{E}[Y_{\bar{a}}] - \mathrm{E}[Y_{\bar{a}'}] \neq 0$ for at least two regimes $\bar{a}$ and $\bar{a}'$. The g-formula, IPTW, and g-estimation can provide consistent estimates of counterfactual quantities like $\mathrm{E}[Y_{\bar{a}}]$ under generalizations of our previous definitions of consistency, conditional exchangeability, and positivity. Specifically, the generalized identifiability conditions are

1. Consistency: If $\bar{A} = \bar{a}$ for a given subject, then $Y_{\bar{a}} = Y$ for that subject.
2. Conditional exchangeability: $Y_{\bar{a}} \amalg A(t) | \bar{A}(t-1) = \bar{a}(t-1), \bar{L}(t) = \bar{l}(t)$ for all regimes $\bar{a}$
3. Positivity: If $f_{\bar{A}(t-1),\bar{L}(t)}\left[\bar{a}(t-1), \bar{l}(t)\right] \neq 0$, then $f_{A(t)|\bar{A}(t-1),\bar{L}(t)}\left[a(t)|\bar{a}(t-1), \bar{l}(t)\right] > 0$ for all $a(t)$.

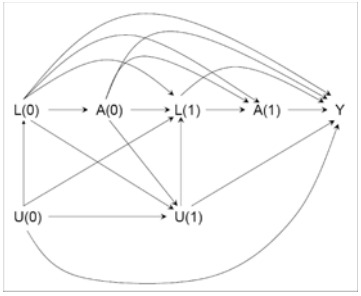
The three conditions generally hold in ideal sequentially randomized experiments with full compliance. A sequentially randomized experiment is a randomized experiment in which the exposure value at each successive visit t is randomly assigned with known randomization probabilities (bounded away from 0 and 1) that, by design, may depend on a subject's past exposure $\bar{A}(t-1)$ and covariate history $\bar{L}(t)$ through t. In the setting of time-varying exposures, the assumption of conditional exchangeability is sometimes referred to as the assumption of sequential randomization or the assumption of no unmeasured confounders.

As for fixed exposures, exchangeability and conditional exchangeability can be represented by causal DAGs. The DAGs in Figures 2a to 2c are the time-varying analogs of those in Figures 1a to 1c (Robins et al 2000). Figure 2a represents a sequentially randomized experiment in which the randomization probabilities at each time t depend at most on a subject's past exposure history, which is the proper generalization of "no confounding by measured or unmeasured variables" to a sequentially randomized experiment. In particular, the causal DAG in Figure 2a implies unconditional or marginal exchangeability, which we write in two different but mathematically equivalent ways: For all t and $\bar{a}$, $Y_{\bar{a}} \amalg A(t) | \bar{A}(t-1) = \bar{a}(t-1)$ or $Y_{\bar{a}} \amalg \overline{A}$. As with fixed exposures, unconditional exchangeability means that association is causation; that is, $\mathrm{E}[Y_{\bar{a}}] = \mathrm{E}\left[Y | \bar{A} = \bar{a}\right]$ and $\mathrm{E}[Y_{\bar{a}}] - \mathrm{E}[Y_{\bar{a}'}] = \mathrm{E}\left[Y | \overline{A} = \bar{a}\right] -$

a)



b)



c)

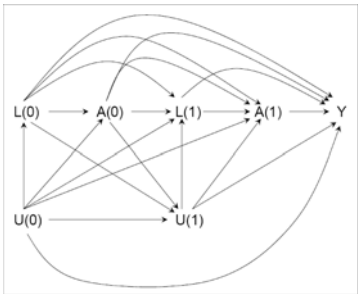


Figure 1.2 *Time-varying exposure*

$\mathrm{E}\left[Y|\overline{A}=\bar{a}'\right]$, so data on the measured covariates $\bar{L}$ need not be used to estimate average causal effects.

Figure 2b represents a sequentially randomized experiment in which the randomization probabilities at each time t depend on past exposure and measured covariate history but not further on unmeasured covariates, i.e., there is confounding by measured covariates but no unmeasured confounding. Thus the three identifiability conditions hold. In this setting, there is time-dependent confounding by $\overline{L}$, and association is not causation; however, by using data on $\bar{L}$, $\mathrm{E}\left[Y_{\bar{a}}\right]$ can still be consistently estimated by using g-methods as described below.

Figure 2b also motivates the following precise definition of time-dependent confounding due to measured covariates. We say there is confounding for $\mathrm{E}\left[Y_{\bar{a}}\right]$ if (i) the mean outcome $\mathrm{E}\left[Y_{\bar{a}}\right]$ had, contrary to fact, all study subjects followed regime $\bar{a}$ differs from the mean $\mathrm{E}\left[Y|\overline{A}=\bar{a}\right]$ of Y (equivalently, $Y_{\bar{a}}$) among the subset of subjects who followed regime $\bar{a}$ in the actual study. We say the confounding is solely time-independent (i.e., wholly attributable to baseline covariates) if $\mathrm{E}\left[Y_{\bar{a}}|L\left(0\right)\right] = \mathrm{E}\left[Y|\overline{A}=\bar{a},L\left(0\right)\right]$, as would be the case if the only arrows pointing into $A\left(1\right)$ on Figure 2b were from $A\left(0\right)$ and $L\left(0\right)$. In contrast, if

the identifiability conditions hold, but $\mathrm{E}\left[Y_{\bar{a}}|L\left(0\right)\right] \neq \mathrm{E}\left[Y|\overline{A}=\bar{a},L\left(0\right)\right]$, we say that time-dependent confounding is present.

Figure 2c represents a study in which the probability of exposure depends on variables U that cause Y and are unmeasured and thus cannot possibly represent a sequentially randomized experiment. In Figure 2c there is unmeasured confounding, and thus causal effects cannot be consistently estimated.

The expressions for the g-formula and IPTW presented above for fixed exposures need to be generalized for time-varying exposures. For example, with $L\left(t\right)$ discrete, the g-formula based on $\bar{L}$ for the counterfactual mean $\mathrm{E}\left[Y_{\bar{a}^*}\right]$ is

$$\sum_{\bar{l}} \mathrm{E}\left[Y|\bar{A}=\bar{a}^*,\bar{L}=\bar{l}\right] \prod_{k=0}^{K} f\left[l(k)|\overline{A}(k-1)=\bar{a}^*(k-1),\overline{L}\left(k-1\right)=\bar{l}(k-1)\right], \qquad (1.1)$$

where the sum is over all possible $\bar{l}$-histories and $\bar{l}(k-1)$ is the history $\bar{l}=\bar{l}\left(K\right)$ through time $k-1$. Experience with this formula will be developed in Section 1.4 by working through an example.

Note the g-formula for $\mathrm{E}\left[Y_{\bar{a}^*}\right]$ is simply the mean of Y under a joint density $f_g\left(o\right)$ that differs from the observed density

$$f_{obs}\left(o\right) = f\left[y|\overline{A}(k)=\bar{a}(k),\overline{L}\left(k\right)=\bar{l}(k)\right] \prod_{k=0}^{K} f\left[l(k)|\overline{A}(k-1)=\bar{a}(k-1),\overline{L}\left(k-1\right)=\bar{l}(k-1)\right]$$
$$\times \prod_{k=0}^{K} f\left[a(k)|\overline{A}(k-1)=\bar{a}(k-1),\overline{L}\left(k\right)=\bar{l}(k)\right]$$

for $O=\left(\bar{A},\overline{L},Y\right)$ only in that each $f\left[a(k)|\overline{A}(k-1)=\bar{a}(k-1),\overline{L}\left(k\right)=\bar{l}(k)\right]$ is replaced by a degenerate distribution that takes value $a^*(k)$ specified by the regime $\bar{a}^*$ with probability one.

When applied to data from a sequential randomized experiment like the one represented in the causal DAG of Figure 2b, the g-formula estimates $\mathrm{E}\left[Y_{\overline{a}}\right]$ by effectively simulating the joint distribution of the variables $\overline{L}$, $\overline{A}$, and Y that would have been observed in a hypothetical study where every subject received exposure $\overline{a}$. However even in a sequentially randomized experiment, $\mathrm{E}\left[Y|\bar{A}=\bar{a},\bar{L}=\bar{l}\right]$ and $f\left[l(k)|\bar{a}(k-1),\bar{l}(k-1)\right]$ will not be known, so estimates $\widehat{\mathrm{E}}\left[Y|\bar{A}=\bar{a},\bar{L}=\bar{l}\right]$ and $\widehat{f}\left[l(k)|\bar{a}(k-1),\bar{l}(k-1)\right]$ have to used in the g-formula (1.1). In realistic experiments, these estimates must come from fitting parsimonious non-saturated models. Model misspecification will result in biased estimates of $\mathrm{E}\left[Y_{\bar{a}}\right]$, even though the identifiability conditions hold. Robins and Wasserman (1997) showed that if the sharp null hypothesis of no effect of exposure on Y is true, that is,

$$Y_{\bar{a}} - Y_{\bar{a}'} = 0 \text{ with probability 1 for all } \bar{a}' \text{ and } \bar{a},$$

then standard non-saturated models $\mathrm{E}\left[Y|\bar{A}=\bar{a},\bar{L}=\bar{l};\upsilon\right]$ and $f\left[l(k)|\bar{a}(k-1),\bar{l}(k-1);\omega\right]$ based on distinct (i.e., variation-independent) parameters υ and ω cannot all be correct whenever $L(k)$ has any discrete components. As a consequence, in large studies, inference based on the estimated g-formula will result in the sharp null hypothesis being falsely rejected, whenever it is true, even in a sequentially randomized experiment. This phenomenon is referred to as the null paradox of the estimated g-formula. Fortunately, neither IPTW estimation or g-estimation suffer from the null paradox and thus are more robust methodologies. Furthermore, even in a fixed exposure randomized trial, $\mathrm{E}\left[Y|A=a,L=l\right]$ is unknown and must be estimated by fitting a non-saturated model when L is high dimensional. The estimated g-formula will generally be biased when the model for $\mathrm{E}\left[Y|A=a,L=l\right]$ is misspecified and the known randomization probabilities depend on L. However the null paradox exists only with time-varying exposures.

The IPTW formula based on $\bar{L}$ for the counterfactual mean $\mathrm{E}\left[Y_{\bar{a}}\right]$ is the average of Y among subjects with $\overline{A} = \bar{a}$ in a stabilized or unstabilized pseudo-population constructed by weighting each subject by their subject-specific stabilized IPTW

$$SW = \prod_{k=0}^{K} \frac{f\left[A(k)|\bar{A}(k-1)\right]}{f\left[A(k)|\bar{A}(k-1), \bar{L}(k)\right]},$$

or their unstabilized IPTW

$$W = \prod_{k=0}^{K} \frac{1}{f\left[A(k)|\bar{A}(k-1), \bar{L}(k)\right]}$$

each a product over time-specific weights. When the three identifiability conditions hold, either IPTW creates a pseudo-population in which (i) the mean of $Y_{\overline{a}}$ is identical to that in the actual population but (ii) like on DAG 2a, the randomization probabilities at each time t depend at most on past exposure history. The only difference is that in the unstabilized pseudo-population $\Pr_{ps}\left[A\left(k\right) = 1|\bar{A}(k-1), \bar{L}(k)\right] = 1/2$ while in the stabilized pseudo-population $\Pr_{ps}\left[A\left(k\right) = 1|\bar{A}(k-1), \bar{L}(k)\right]$ is $\Pr\left[A\left(k\right) = 1|\bar{A}(k-1)\right]$ from the actual population. Thus $\mathrm{E}\left[Y_{\overline{a}}\right]$ in the actual population is $\mathrm{E}_{ps}\left[Y|\overline{A} = \overline{a}\right]$, where the subscript ps refers to either pseudo-population. Hence the average causal effect $\mathrm{E}\left[Y_{\bar{a}}\right] - \mathrm{E}\left[Y_{\bar{a}'}\right]$ is $\mathrm{E}_{ps}\left[Y|\overline{A} = \bar{a}\right] - \mathrm{E}_{ps}\left[Y|\overline{A} = \bar{a}'\right]$.

One can estimate $\mathrm{E}_{ps}\left[Y|\overline{A} = \bar{a}\right]$ from the observed study data by the average of Y among subjects with $\overline{A} = \bar{a}$ in a stabilized or unstabilized pseudo-study population constructed by weighting each study subject by SW or W.

If one replaces $f\left[A(k)|\bar{A}(k-1), \bar{L}(k)\right]$ in SW or W with an estimate $\widehat{f}\left[A(k)|\bar{A}(k-1), \bar{L}(k)\right]$ based on a misspecified logistic model for the $\Pr\left[A\left(k\right) = 1|\bar{A}(k-1), \bar{L}(k\right]$, the resulting estimates of $\mathrm{E}\left[Y_{\bar{a}}\right]$ and $\mathrm{E}\left[Y_{\bar{a}}\right] - \mathrm{E}\left[Y_{\bar{a}'}\right]$ will be biased. In contrast, replacing the numerator of SW with an estimate $\widehat{f}\left[A(k)|\bar{A}(k-1)\right]$ based on a misspecified model does not result in bias. These remarks apply also to the IPTW estimation of marginal structural models considered in the following subsection. Now, in a sequentially randomized experiment, the denominators of the weights are known by design and so need not be estimated. As a consequence, in contrast to the estimated g-formula, in a sequentially randomized experiment, IPTW estimation unbiasedly estimates $\mathrm{E}_{ps}\left[Y|\overline{A} = \bar{a}\right] - \mathrm{E}_{ps}\left[Y|\overline{A} = \bar{a}'\right]$ and so is never misleading.

When the three identifiability conditions hold in an observational study with a time-varying exposure, the observational study can be conceptualized as a sequentially randomized experiment, except that the probabilities $f\left[A(k)|\bar{A}(k-1), \bar{L}(k)\right]$ are unknown and must be estimated. However, the validity of these conditions is not guaranteed by design and is not subject to empirical verification. The best one can do is to use subject-matter knowledge to collect data on many potential time-dependent confounders. Furthermore, even if the identifiability conditions hold, bias in estimation of $\mathrm{E}\left[Y_{\bar{a}}\right]$ and $\mathrm{E}\left[Y_{\bar{a}}\right] - \mathrm{E}\left[Y_{\bar{a}'}\right]$ can occur (i) when using IPTW estimation due to misspecification of logistic models for $\Pr\left[A(k) = 1|\bar{A}(k-1), \bar{L}(k)\right]$ and (ii) when using the estimated g-formula due to misspecification of models for $\mathrm{E}\left[Y|\bar{A} = \bar{a}, \bar{L} = \bar{l}\right]$ and $f\left[l(k)|\bar{a}(k-1), \bar{l}(k-1)\right]$. However, the robustness of IPTW methods to model mispecification can be increased by using doubly robust estimators as described in Bang and Robins (2005) (see Chapter 20 for a discussion of doubly robust estimators).

1.3.2 Marginal structural models

If, as is not infrequent in practice, K is of the order of 100 and the number of study subjects is of order 1000, then the 2^{100} unknown quantities $\mathrm{E}\left[Y_{\bar{a}}\right]$ far exceeds the sample size. Thus

very few subjects in the observed study population follow any given regime, so we need to specify a non-saturated model for the $\mathrm{E}\left[Y_{\bar{a}}\right]$ that combines information from many regimes to help estimate a given $\mathrm{E}\left[Y_{\bar{a}}\right]$. The price paid for modelling $\mathrm{E}\left[Y_{\bar{a}}\right]$ is yet another threat to the validity of our estimates due to possible model misspecification.

Suppose for a continuous response Y it is hypothesized that the effect of treatment history $\bar{a}$ on the mean outcome increases linearly as a function of the cumulative exposure $cum\left(\bar{a}\right) = \sum_{t=0}^{K} a(t)$ under regime $\bar{a}$. This hypothesis is encoded in the marginal structural mean model

$$\mathrm{E}\left[Y_{\overline{a}}\right] = \eta_0 + \eta_1 cum\left(\bar{a}\right) \tag{1.2}$$

for all $\overline{a}$. The model is referred to as a marginal structural model (MSM) because it models the marginal mean of the counterfactuals $Y_{\overline{a}}$ and models for counterfactuals are often referred to as structural models. There are 2^K different unknown quantities on the left hand side of model (1.2), one for each of the 2^K different regimes $\bar{a}$, but only 2 unknown parameters η_0 and η_1 on the right hand side. It follows that the MSM (1.2) is not a saturated (i.e., nonparametric) model, because saturated models must have an equal number of unknowns on both sides of their defining equation. Any unsaturated model may be misspecified. For example, MSM (1.2) would be misspecified if $\mathrm{E}\left[Y_{\overline{a}}\right]$ either depended on some function of the regime $\bar{a}$ other than cumulative exposure (say, cumulative exposure only in the final 5 weeks $cum_{-5}\left(\bar{a}\right) = \sum_{K-5=0}^{K} a(t)$) or depended nonlinearly (say, quadratically) on cumulative exposure. It follows that we need methods both to test whether MSM (1.2) is correctly specified and to estimate the parameters η_0 and η_1. It is important to note that under the null hypothesis, the MSM is correctly specified with $\eta_1 = 0$. Thus MSMs are not subject to the null paradox.

MSMs are fit by IPTW as described, for example, by Robins, Hernán, and Brumback (2000). Specifically, Robins (1998) has shown that if we fit the ordinary linear regression model

$$\mathrm{E}\left[Y|\overline{A}\right] = \gamma_0 + \gamma_1 cum\left(\overline{A}\right) \tag{1.3}$$

to the observed data by weighted least squares with weights SW or W, then, under the three identifiability conditions the weighted least squares estimates of γ_0 and γ_1 are consistent for the causal parameters η_0 and η_1 of the MSM (1.2) (but are inconsistent for the association parameters γ_0 and γ_1 of model (1.3)) because weighted least squares with weights SW or W is simply ordinary least squares (OLS) in the stabilized or unstabilized unconfounded pseudo-population, respectively. In these populations the association being estimated with OLS is causation.

A robust variance estimator (as used, for example, for GEE models, see Chapter 3) can be used to set confidence intervals for η_0 and η_1 and thus for any $\mathrm{E}\left[Y_{\overline{a}}\right]$ of interest. These intervals remain valid, even when estimates are substituted for the numerator and/or denominator weights, provided the model for the denominator weights is correctly specified. For a non-saturated model like MSM (1.2) the length of the intervals will typically be much narrower when the model is fit with the weights SW than with the weights W, so the SW weights are preferred.

Further, if we fit the model

$$\mathrm{E}\left[Y|\overline{A}\right] = \gamma_0 + \gamma_1 cum\left(\overline{A}\right) + \gamma_2 cum_{-5}\left(\overline{A}\right) + \gamma_3 cum\left(\overline{A}\right)^2$$

by weighted least squares with weights SW or W, a Wald test on two degrees of freedom of the joint hypothesis $\gamma_2 = \gamma_3 = 0$ is a test of the null hypothesis that MSM (1.2) is correctly specified with high power against the particular directions of misspecification mentioned above, especially if the weights SW are used.

Suppose it was further hypothesized that, for a particular dichotomous component V of the vector of baseline covariates $L(0)$, there might exist a qualitative V-exposure effect modification with the result that exposure might be harmful to subjects with $V = 0$ and beneficial to those with $V = 1$, or vice versa. To examine this hypothesis, we would elaborate MSM (1.2) as

$$\mathrm{E}\left[Y_{\overline{a}}|V\right] = \eta_0 + \eta_1 cum\left(\bar{a}\right) + \eta_2 V + \eta_3 cum\left(\bar{a}\right) V,$$

an MSM conditional on the baseline covariate V. Qualitative effect modification is present if η_1 and $\eta_1 + \eta_3$ are of opposite signs. We can estimate the model parameters by fitting the ordinary linear regression model $\mathrm{E}\left[Y|\overline{A}, V\right] = \gamma_0 + \gamma_1 cum\left(\overline{A}\right) + \gamma_2 V + \gamma_3 V cum\left(\overline{A}\right)$ by weighted least squares with model weights SW or W. However, Robins (1998) showed that for an MSM defined conditional on a baseline covariate V, confidence intervals will still be valid but narrower if, rather than using weights SW or W, we use the weights $SW(V) = \prod_{k=0}^{K} \frac{f\left[A(k)|\bar{A}(k-1), V\right]}{f\left[A(k)|\bar{A}(k-1), \bar{L}(k)\right]}$ that differs from SW by adding V to the conditioning event in the numerator.

1.3.3 Dynamic regimes

So far we have only considered estimation of the mean outcome $\mathrm{E}\left[Y_{\bar{a}}\right]$ under the 2^K static or nondynamic regimes $\bar{a}$. However to characterize the optimal treatment strategy, it is usually necessary to consider dynamic regimes as well.

A non-random dynamic regime is a treatment strategy or rule in which the treatment $a(t)$ at time t depends in a deterministic manner on the evolution of a subject's measured time dependent covariates $\bar{L}(t)$ and, possibly, treatments $\overline{A}(t-1)$ up to t. An example would be the dynamic regime "take the treatment methotrexate at week t if and only if the neutrophil count has been greater than 1000 for 3 consecutive weeks and the patient was not on treatment at week $t-1$." Mathematically, when $A(t)$ is a binary treatment , a non-random dynamic regime g is a collection of functions $\left\{g_k\left[\bar{a}(k-1), \bar{l}(k)\right]; k = 0, ..., K\right\}$ each with range the two point set $\{0, 1\}$, where $g_k\left[\bar{a}(k-1), \bar{l}(k)\right]$ specifies the treatment to be taken at k for a subject with past history $\left[\bar{a}(k-1), \bar{l}(k)\right]$. In our methotrexate example, $g_k\left[\bar{a}(k-1), \bar{l}(k)\right]$ is 1 if a subject's $a(k-1)$ is zero and his $\bar{l}(k)$ implies that his neutrophil count has been greater than 1000 at weeks $k, k-1, k-2$ (so k must be at least 2); otherwise $g_k\left[\bar{a}(k-1), \bar{l}(k)\right]$ is 0.

A random dynamic regime is a treatment strategy where the treatment $a(t)$ at time t depends in a probabilistic way on $\bar{l}(t)$ and possibly $\overline{a}(t-1)$. An example would be "if the neutrophil count has been greater than 1000 for 3 consecutive weeks, randomize the subject to take methotrexate at week t with randomization probability 0.80, otherwise use randomization probability 0.10." Thus, a random dynamic regime is precisely a sequentially randomized experiment.

Now let g represent a regime—dynamic or nondynamic, deterministic or random—and let Y_g denote the counterfactual outcome had regime g been followed. If high values of the outcome are considered beneficial, then the optimal regime g_{opt} maximizes the average outcome $\mathrm{E}\left[Y_g\right]$ over all regimes. In fact we need only try to find the optimal regime among the deterministic regimes as no random strategy can ever be preferred to the optimal deterministic strategy. Furthermore the above example indicates that this optimal deterministic treatment strategy must be a dynamic regime whenever the treatment is a potentially toxic prescription drug such as methotrexate, as it is essential to temporarily discontinue the drug when a severe toxicity such as neutropenia develops. Random regimes (i.e., ordinary randomized trials and sequentially randomized trials) remain scientifically necessary because, before the trial, it is unknown which deterministic regime is optimal.

Under a slight strengthening of the identifiability conditions, $\mathrm{E}[Y_g]$ for a deterministic dynamic regime g can be estimated from the data collected in a sequentially randomized trial by the average of Y among subjects in the unstabilized (but not in the stabilized) pseudo-study population who followed the regime g, i.e., subjects whose observed covariate and treatment history is consistent with following regime g. Note this is our first example of a result that is true for the unstabilized but not the stabilized IPTW estimation. The required strengthening is that we need the "strengthened" identifiability conditions:

1. "Strengthened" consistency: For any regime g, if, for a given subject, $A_k = g_k\left[\overline{A}(k-1), \overline{L}(k)\right]$ at each time k, then $Y_g = Y$ and $\bar{L}_g(K) = \bar{L}(K)$ for that subject, where $\bar{L}_g(k)$ is the counterfactual L-history through time k under regime g.

   Remark: For any regime g for which the treatment at each k does not depend on past treatment history so $g_k\left[\bar{a}(k-1), \bar{l}(k)\right] = g_k\left[\bar{l}(k)\right]$, we can write the "strengthened" consistency condition as follows: if $\overline{A} = \overline{g}_K\left[\overline{L}(K)\right]$ for a given subject, then $Y_g = Y$ and $\bar{L}_g(K) = \bar{L}(K)$ for that subject, where $\overline{g}_k\left[\overline{L}(k)\right]$ is the treatment through time k of a subject following regime g with covariate history $\overline{L}(k)$
2. "Strengthened" conditional exchangeability: For any t, $\bar{l}(t)$ and regime g

$$Y_g \amalg A(t) | \bar{L}(t) = \bar{l}(t), A(k) = g_k\left[\overline{A}(k-1), \overline{L}(k)\right] \text{ for } k = 0, ..., t-1$$

   Remark: For any regime g for which the treatment at each k does not depend on past treatment history so $g_k\left[\bar{a}(k-1), \bar{l}(k)\right] = g_k\left[\bar{l}(k)\right]$, we can write "strengthened" conditional exchangeability as follows: For all t, $\bar{l}(t)$, and regimes g

$$Y_g \amalg A(t) |, \bar{L}(t) = \bar{l}(t), \bar{A}(t-1) = \overline{g}_{t-1}\left[\bar{l}(t-1)\right]$$

3. Positivity assumption remains unchanged.

Strengthened conditions 1 and 2 will hold on any causal DAG, such as that corresponding to a sequentially randomized trial, in which all parents of treatment variables $A(m)$ are measured variables. This implication follows from two facts. First, any such causal DAG satisfies both of the following conditions

1. "Full" consistency: $Y_{\bar{a}} = Y_{\bar{a}^*}$ if $\overline{a}^* = \overline{a}$, $Y = Y_{\bar{a}}$ if $\overline{A} = \bar{a}$, $\bar{L}_{\overline{a}}(m) = \bar{L}_{\overline{a}^*}(m)$ if $\overline{a}^*(m-1) = \overline{a}(m-1)$, $\bar{L}_{\overline{a}}(m) = \bar{L}(m)$ if $\overline{A}(m-1) = \overline{a}(m-1)$, where $\bar{L}_{\overline{a}}(m)$ is the counterfactual L-history through time m under regime $\overline{a}$.
2. "Full" conditional exchangeability

$$\left(Y_{\overline{\mathcal{A}}}, \bar{L}_{\overline{\mathcal{A}}}\right) \amalg A(t) | \bar{A}(t-1), \bar{L}(t)$$

   where $\overline{\mathcal{A}}$ denotes the set of all 2^K regimes $\bar{a}$, $Y_{\overline{\mathcal{A}}}$ denotes the set of all 2^K counterfactuals $Y_{\bar{a}}$, and $\bar{L}_{\overline{\mathcal{A}}}$ denotes the set of all 2^K counterfactual covariate histories $\bar{L}_{\overline{a}}$ through the end of the study.

Second, the "full" consistency and "full" conditional exchangeability conditions imply both the strengthened conditions, even though the "full" conditions only refer to nondynamic regimes (Robins, 1986).

Remark: Associated with each regime g with treatment $g_k\left[\bar{a}(k-1), \bar{l}(k)\right]$ depending on past treatment and covariate history is another regime $g^{\triangle}$ with treatment $g_k^{\triangle}\left[\bar{l}(k)\right]$ depending only on past covariate history such that, if "full" consistency holds, any subject following regime g from time zero will have the same treatment, covariate, and outcome history as when following regime $g^{\triangle}$ from time zero. In particular, $Y_g = Y_{g^{\triangle}}$ and $\bar{L}_g(K) = \bar{L}_{g^{\triangle}}(K)$. Specifically $g^{\triangle}$ is defined in terms of g recursively by $g_0^{\triangle}[l(0)] = g_0[\bar{a}(-1) = 0, l(0)]$ (by convention, $\bar{a}(-1)$ can only take the value zero) and $g_k^{\triangle}\left[\bar{l}(k)\right] = g_k\left[g_{k-1}^{\triangle}\left[\bar{l}(k-1)\right], \bar{l}(k)\right]$.

For the dynamic methotrexate regime g described earlier, $g^{\triangle}$ is the regime take methotrexate at k if and only if your $\bar{l}(k)$ implies your neutrophil count has been greater than 1000 for m consecutive weeks and m is an odd number greater than or equal to three. Requiring m to be odd guarantees that no subject will ever take methotrexate for two consecutive weeks, as specified by regime g. For any regime g for which treatment at each k already does not depend on past treatment history, g and $g^{\triangle}$ are the identical set of functions. The above definition of $g^{\triangle}$ in terms of g guarantees that a subject has followed regime g through time t in the observed data, (i.e., $A(k) = g_k\left[\overline{A}(k-1), \overline{L}(k)\right]$ for $k \leq t$) if and only if the subject has followed regime $g^{\triangle}$ through t (i.e., $A(k) = g_k^{\triangle}\left[\overline{L}(k)\right]$ for $k \leq t$).

"Full" consistency is a natural assumption that we will always assume. Therefore, in view of the last remark, unless stated otherwise, we will henceforth use the term 'dynamic regime' to refer to dynamic regimes for which the treatment at each k depends on past covariate but not on past treatment history.

The above discussion raises the question whether it is substantively plausible that $\mathrm{E}[Y_g]$ is identifiable by the g-formula for nondynamic g but not for dynamic g, because conditional exchangeability, but neither "full" nor "strengthened" conditional exchangeability, holds. Robins (1986) showed that this state of affairs is indeed substantively plausible. For example, it can occur when there exist unmeasured common causes U of treatment $A(k)$ and a risk factor $L(t)$, $k < t$, but there do not exist unmeasured common causes of the $A(k)$ and Y. In the appendix, we provide a general graphical criterion due to Robins (1997b) that can be used to determine the set of regimes g for which conditional exchangeability holds.

Of course, very few subjects in the observed study population follow any given regime, so, in practice, we need to combine information from many different regimes to estimate a given $\mathrm{E}[Y_g]$. We show in Sections 1.4 and 1.5 that this combination can be accomplished through g-estimation of nested structural models or IPTW estimation of dynamic MSMs (as defined in Section 1.5). Finally, we note we can also estimate $\mathrm{E}[Y_g]$ under the strengthened identifiability conditions using the g-formula (1.1) modified by replacing $\bar{a}(k-1)$ by $\overline{g}\left\{\bar{l}(k-1)\right\}$ and $\bar{a}$ by $\overline{g}\left\{\bar{l}(K)\right\}$. However, as discussed above, the estimated g-formula, in contrast to g-estimation of nested structural models, suffers from the null paradox, and thus is not robust.

Under the strengthened identifiability conditions, we will see in Section 1.5 below that g-methods can be used to estimate not only $\mathrm{E}[Y_g]$ but also the optimal (deterministic) treatment regime from observational data, even though, in most observational studies, subjects are either not following any particular deterministic regime. The reason this strategy succeeds is that we may conceptualize the subjects in such an observational study as following a random dynamic regime, with unknown randomization probabilities that must be estimated from the data.

1.4 Analysis of a hypothetical study

1.4.1 The study

Table 1.1 contains data from a hypothetical study of the effect of antiretroviral therapy on a global health score Y measured at the end of follow-up in 32,000 HIV-infected subjects. Y is a function of CD4 cell count, serum HIV RNA, and certain biochemical measures of possible drug toxicity with higher values of Y signifying better health. The variables $A(0)$ and $A(1)$ are 1 if a subject received antiretroviral therapy at times $t = 0$ and $t = 1$, respectively, and 0 otherwise. The binary variable $L(1)$ is temporally prior to $A(1)$ and is 1 if the subject's CD4 cell count was greater than 200 cells/μL at time $t = 1$. To save space, the table displays one row per combination of values of $A(0)$, $L(1)$, and $A(1)$, rather than one row per subject. For each of the 8 combinations, the table provides the number

Table 1.1 *The study data*

Row	$A(0)$	$L(1)$	$A(1)$	N	$\mathrm{E}[Y\|A(0), L(1), A(1)]$
1	0	1	0	2000	200
2	0	1	1	6000	220
3	0	0	0	6000	50
4	0	0	1	2000	70
5	1	1	0	3000	130
6	1	1	1	9000	110
7	1	0	0	3000	230
8	1	0	1	1000	250

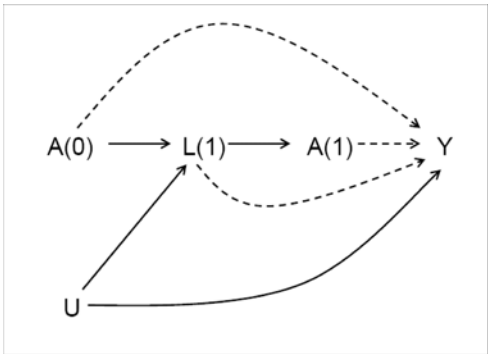


Figure 1.3 *Causal DAG in the study population*

of subjects and the average value of the outcome $\mathrm{E}[Y|A(0), L(1), A(1)]$. Thus, in row 1 of Table 1.1 $\mathrm{E}[Y|A(0), L(1), A(1)] = 200$ means $\mathrm{E}[Y|A(0) = 0, L(1) = 1, A(1) = 0] = 200$. We suppose sampling variability is absent and we assume consistency. Further, by inspection of Table 1.1, we can conclude that the positivity condition is satisfied, because otherwise one or more of the eight rows would have had zero subjects.

For the present, we suppose the data arose from a sequentially randomized trial in which treatment at time 1 is randomly assigned with probability that depends on prior exposure and covariate history. Because our interest is in the implications of time-dependent confounding by $L(1)$, we did not bother to include a measured baseline covariate $L(0)$. Alternatively, one can assume that a measured baseline covariate $L(0)$ exists but that the data in Table 1.1 are from a single stratum $l(0)$ of $L(0)$.

1.4.2 A priori causal assumptions

We assume Figure 3 is the causal DAG corresponding to this study. In Figure 3, U denotes a subject's baseline immunological function, an unmeasured variable that therefore does not appear in Table 1.1. The dotted arrows from $A(0)$ to Y, L to Y, and $A(1)$ to Y emphasize that we do not know based on prior subject matter knowledge, whether these causal arrows are present; in fact our goal will be to use the data in Table 1.1 to determine, as far as possible, which of these arrows are present. We will later see that the data from Table 1.1 imply that (i) the arrow from $A(1)$ to Y is present and that (ii) the arrow from $A(0)$ to Y, or the arrow from L to Y, or both are present.

We now describe how, before observing the data, we used our subject matter knowledge

to decide that Figure 3 was an appropriate causal DAG. First note the causal DAG in Figure 3, like that in Figure 2b, is not a complete DAG because there do not exist direct arrows from U into either treatment. This is justified by our assumption that the study was a sequentially randomized trial. The absence of these arrows implies strengthened conditional exchangeability, i.e., $Y_g \amalg A(0)$ and $Y_g \amalg A(1)|A(0) = a(0), L(1) = l(1)$ for all regimes g, whether static or dynamic. The arrows from U to Y and from U to CD4 cell count $L(1)$ are justified on subject-matter grounds by the well known effects of immunosuppression on viral load and CD4 cell count. The arrow from $A(0)$ to $L(1)$ is justified by prior knowledge of the effect of antiretroviral therapy on CD4 cell count. The arrows into $A(1)$ are justified by our knowledge that treatment at time 1 was randomly assigned with probability that depends on prior exposure and covariate history.

1.4.3 Testing our causal assumptions

Now assumptions concerning causal relations based on subject matter knowledge can sometimes be mistaken. However, under the sole assumption that the study satisfies conditional exchangeability (implied by the assumption of no arrows from U into either treatment), we can use the data in Table 1.1 to empirically confirm or refute whether the arrows argued for on subject-matter grounds are actually present. To carry this out, we assume that the dashed arrows are actually present until we can prove otherwise. If the causal arrow from $A(0)$ to $L(1)$ were not present in Figure 3, $A(0)$ and $L(1)$ would be d-separated and thus independent by the causal Markov assumption (see definitions in Appendix). But the data refutes independence because $\Pr[L(1) = 1|A(0) = 1] = 0.75$ differs from $\Pr[L(1) = 1|A(0) = 0] = 0.50$.

Here is an alternative but closely related argument that results in the same conclusion. A causal arrow from $A(0)$ to $L(1)$ exists if the average causal effect $\mathrm{E}\left[L_{a(0)=1}(1)\right] - \mathrm{E}\left[L_{a(0)=0}(1)\right]$ of the fixed exposure $A(0)$ on the outcome $L(1)$ is non-zero. Because there is no confounding for the effect of $A(0)$ on $L(1)$, association is causation and thus $\mathrm{E}\left[L_{a(0)=1}(1)\right] - \mathrm{E}\left[L_{a(0)=0}(1)\right] = \mathrm{E}[L(1)|A(0) = 1] - \mathrm{E}[L(1)|A(0) = 0]$, which is non-zero.

Next if the causal arrow from $A(0)$ to $A(1)$ was not present in Figure 3, $A(1)$ and $A(0)$ would be d-separated, and thus independent, given $L(1)$, which is refuted by the data in Table 1.1. Similarly if the causal arrow from $L(1)$ to $A(1)$ was not present in Figure 3, $A(1)$ and $L(1)$ would be d-separated, and thus independent, given $A(0)$, which is refuted by the data in Table 1.1

1.4.4 Determining which dotted arrows are present

A fixed exposure analysis of $A(1)$

We can use the data in Table 1.1 to try to determine which of the dotted arrows in Figure 3 are present. In Figure 3, if the causal arrow from $A(1)$ to Y was not present, $A(1)$ and Y would be d-separated, and thus independent, given $L(1)$ and $A(0)$, which is refuted by the data in Table 1.1 because, for example, $\mathrm{E}[Y|A(0) = 0, L(1) = 0, A(1) = 1] = 70$ and $\mathrm{E}[Y|A(0) = 0, L(1) = 0, A(1) = 0] = 50$. Thus we conclude that $A(1)$ has a causal effect on Y.

Here is another way to think about this. View the effect of $A(1)$ as that of a fixed baseline exposure in a study beginning at time 1 with baseline covariates $(A(0), L(1))$. Then a causal arrow from $A(1)$ to Y exists if the average causal effect $\mathrm{E}\left[Y_{a(1)=1}|A(0), L(1)\right] - \mathrm{E}\left[Y_{a(1)=0}|A(0), L(1)\right]$ is non-zero in any of the 4 strata determined by joint levels of $(A(0), L(1))$. But since, by sequential randomization, there is no confounding for the effect of $A(1)$ on Y within levels of $(A(0), L(1))$ (equivalently, all non causal paths from $A(1)$ to Y are blocked when we condition on $(A(0), L(1))$, conditional association is cau-

sation and $\mathrm{E}\left[Y_{a(1)=1}|A(0),L(1)\right] - \mathrm{E}\left[Y_{a(1)=0}|A(0),L(1)\right] = \mathrm{E}\left[Y|A(1)=1,A(0),L(1)\right] - \mathrm{E}\left[Y(1)|A(1)=0,A(0),L(1)\right]$ which, for example, is non-zero in the stratum $A(0)=0, L(1)=0$.

We were able to use standard analytic methods (e.g., stratification) to prove the existence of the arrows from $A(1)$ to Y or from $A(0)$ to $L(1)$, because these causal questions were reducible to questions about the effects of fixed treatments.

Our analysis of the effect of $A(1)$ on Y raises alternative interesting points about confounding. Suppose the arrow from $L(1)$ to Y does not exist. Then $L(1)$ would not be a direct cause of Y and thus the source of confounding for the effect of $A(1)$ on Y (i.e., the causal confounder) would be the unmeasured common cause U; nonetheless data on $L(1)$ still suffices to block backdoor (i.e., non causal) paths from $A(1)$ to Y and thus to control confounding. Further, even were the data in Table 1.1 not available, we would expect (i) $L(1)$ to be associated with exposure $A\left(1\right)$ within strata of $A\left(0\right)$ (i.e., $L(1)\amalg A\left(1\right)|A\left(0\right)$ is false) since the path $L(1) \rightarrow A\left(1\right)$ is not blocked by conditioning on $A\left(0\right)$ and (ii) $L(1)$ to be an independent risk factor for Y within one or more of the 4 joint strata of $(A(1), A(0))$ (i.e., $L(1)\amalg Y|A\left(1\right), A\left(0\right)$ is false or, equivalently, $\mathrm{E}\left[Y|L(1)=1,A(1),A(0)\right] \neq \mathrm{E}\left[Y|L(1)=0,A(1),A(0)\right]$) because the path $L(1) \longleftarrow U \rightarrow Y$ is not blocked by conditioning on $A(1)$ and $A(0)$. In this setting, we follow common practice and refer to $L(1)$ as a confounder for the effect of $A(1)$ on Y (although not as a causal confounder) given data on $A(0)$, because, within levels of $A(0)$, $L(1)$ is the measured risk factor that is used to control confounding. Note we can empirically confirm that $L(1) \amalg Y|A\left(1\right), A\left(0\right)$ and $L(1) \amalg A\left(1\right)|A\left(0\right)$ are false using the data in Table 1.1. We find that such is the case.

Joint effects, direct effects, and g-methods

Conventional methods, however, may fail to identify the presence (or absence) of causal arrows that correspond to a joint effect of the time-varying exposure $[A(0), A(1)]$. A class of joint effects that are often of interest in epidemiology are the (controlled) direct effects of $A(0)$ on Y not mediated through $A(1)$. With dichotomous exposures, there exist two such direct effects. First, the direct effect of the baseline exposure $A(0)$ when the later exposure $A(1)$ is set (i.e., forced) to be 0 is, by definition, the counterfactual contrast $\mathrm{E}\left[Y_{\bar{a}=\{1,0\}}\right] - \mathrm{E}\left[Y_{\bar{a}=\{0,0\}}\right] = \mathrm{E}\left[Y_{\bar{a}=\{1,0\}} - Y_{\bar{a}=\{0,0\}}\right]$, which is the average of the individual causal effects $Y_{\bar{a}=\{1,0\}} - Y_{\bar{a}=\{0,0\}}$ that quantify the effect of baseline exposure when later exposure is withheld. Note this formal definition for the direct effect of $A(0)$ with $A(1)$ set to zero makes clear that the question of whether $A(0)$ directly affects Y not through $A(1)$ is a question about the effect of joint interventions on $A(0)$ and $A(1)$. The second direct effect is the direct effect of $A(0)$ when the exposure $A(1)$ is set to 1 which, by definition, is the counterfactual contrast $\mathrm{E}\left[Y_{\bar{a}=\{1,1\}}\right] - \mathrm{E}\left[Y_{\bar{a}=\{0,1\}}\right] = \mathrm{E}\left[Y_{\bar{a}=\{1,1\}} - Y_{\bar{a}=\{0,1\}}\right]$ that quantifies the effect of the baseline exposure when exposure at time 1 is always given.

When, on the causal DAG in Figure 3, the dotted arrows from $A(0)$ to Y and $L(1)$ to Y are both absent, the direct effects $\mathrm{E}\left[Y_{\bar{a}=\{1,0\}}\right] - \mathrm{E}\left[Y_{\bar{a}=\{0,0\}}\right]$ and $\mathrm{E}\left[Y_{\bar{a}=\{1,1\}}\right] - \mathrm{E}\left[Y_{\bar{a}=\{0,1\}}\right]$ will both be zero, as then the only sequence of directed arrows from $A(0)$ to Y would go through $A(1)$. If one or both of the direct effects are non-zero, then a sequence of directed arrows from $A(0)$ to Y that avoids $A(1)$ must exist and thus one or both of the dotted arrows from $A(0)$ to Y and $L(1)$ to Y must be present. However, in order to determine from the data in Table 1.1 whether either or both direct effects are non-zero requires appropriate use of methods for causal inference with time-varying exposures like the g-formula, IPTW, or g-estimation, because, as we demonstrate below, conventional methods fail, even when the three identifiability conditions hold.

G-formula

If we can estimate the counterfactual means $\mathrm{E}\left[Y_{\bar{a}=\{0,0\}}\right], \mathrm{E}\left[Y_{\bar{a}=\{1,0\}}\right], \mathrm{E}\left[Y_{\bar{a}=\{0,1\}}\right]$, and $\mathrm{E}\left[Y_{\bar{a}=\{1,1\}}\right]$ under the 4 possible static regimes, we can estimate both direct effects. All four means can be consistently estimated by the g-formula, because the three identifiability conditions hold in a sequentially randomized trial. Because the confounder $L(1)$ is a binary variable the g-formula can be explicitly written as

$$\begin{aligned}\mathrm{E}\left[Y_{\bar{a}}\right] = &\mathrm{E}\left[Y|A(0)=a(0),A(1)=a(1),L(1)=0\right]\Pr\left[L(1)=0|A(0)=a(0)\right]\\ &+\mathrm{E}\left[Y|A(0)=a(0),A(1)=a(1),L(1)=1\right]\Pr\left[L(1)=1|A(0)=a(0)\right]\end{aligned}$$

for $\bar{a}=\{a(0),a(1)\}$. Using this formula, the four means under each of the regimes are $\mathrm{E}\left[Y_{\bar{a}=\{0,0\}}\right] = 200\times\frac{8000}{16000}+50\times\frac{8000}{16000} = 125$, $\mathrm{E}\left[Y_{\bar{a}=\{0,1\}}\right] = 145$, $\mathrm{E}\left[Y_{\bar{a}=\{1,0\}}\right] = 155$, $\mathrm{E}\left[Y_{\bar{a}=\{1,1\}}\right] = 145$.

We conclude that there is a direct effect of $A(0)$ on the mean of Y when $A(1)$ is set to 0 but not when $A(1)$ is set to 1. As a consequence we know that one or both of the $A(0)$ to Y and $L(1)$ to Y arrows must be present. However, we cannot determine whether the causal arrow from $L(1)$ to Y is present as the causal effect of $L(1)$ on Y cannot be consistently estimated because of the unblockable backdoor path $L(1)\leftarrow U\rightarrow Y$. As a consequence of our inability to determine the causal effect of $L(1)$ on Y, we also cannot determine in general, whether none (corresponding to no arrow from $A(0)$ to Y), some, or all of the nonzero direct effect of $A(0)$ on Y when $A(1)$ is withheld is due to a direct causal effect of $A(0)$ on Y not through $L(1)$.

1.4.5 Why standard methods fail

We will show that when there exists, as in our study, a post baseline covariate $L\left(1\right)$ that (i) is caused by (or shares a common cause with) baseline exposure $A(0)$ and (ii) is a confounder for the effect of a subsequent exposure $A\left(1\right)$ on a response Y, standard analytic methods that use stratification, regression, or matching for covariate adjustment cannot be used to estimate causal contrasts that depend on the joint effects of both the baseline and subsequent exposures. We will see that the difficulty with standard methods is that to estimate the joint effects of $A(0)$ and $A\left(1\right)$, we must adjust for the confounding effect of $L\left(1\right)$ to consistently estimate the effect of $A\left(1\right)$ on Y; but if we adjust for the confounding by stratification, regression or matching on $L\left(1\right)$, we cannot consistently estimate the effect of $A\left(0\right)$, because the association of $L\left(1\right)$ with $A\left(0\right)$ results in selection bias, even under the null hypothesis of no causal effect (direct, indirect or net) of $A\left(0\right)$ on Y.

As a specific example, we consider the causal contrast $\mathrm{E}\left[Y_{\bar{a}=\{1,1\}}\right]-\mathrm{E}\left[Y_{\bar{a}=\{0,1\}}\right]$ representing the direct effect of $A(0)$ on Y when treated with $A(1)$, which we have shown to take the value 0 in our study. If one did not know about g-methods, a natural, but naive, attempt to estimate $\mathrm{E}\left[Y_{\bar{a}=\{1,1\}}\right]-\mathrm{E}\left[Y_{\bar{a}=\{0,1\}}\right]$ from the data in Table 1.1 would be to calculate the associational contrast $\mathrm{E}\left[Y|A(0)=1,A(1)=1\right]-\mathrm{E}\left[Y|A(0)=0,A(1)=1\right]$. From Table 1.1 we obtain

$$\mathrm{E}\left[Y|A(0)=1,A(1)=1\right] = \tfrac{1}{10000}\left(110\times 9000+250\times 1000\right) = 124$$
$$\mathrm{E}\left[Y|A(0)=0,A(1)=1\right] = \tfrac{1}{8000}\left(220\times 6000+70\times 2000\right) = 182.5$$

Because this analysis fails to adjust for the confounder $L(1)$ of $A(1)$'s effect on Y, the associational contrast $\mathrm{E}\left[Y|A(0)=1,A(1)=1\right]-\mathrm{E}\left[Y|A(0)=0,A(1)=1\right] = -58.5$ is non-causal and biased as an estimate of the causal contrast $\mathrm{E}\left[Y_{\bar{a}=\{1,1\}}\right]-\mathrm{E}\left[Y_{\bar{a}=\{0,1\}}\right] = 0$. Had the causal DAG in Figure 3 not had the arrow from $L(1)$ to $A(1)$, there would have then been no confounding by either the measured factors $L(1)$ or the unmeasured factors U for either of the exposures, and we would have found that association was causation, i.e. that $\mathrm{E}\left[Y|A(0)=1,A(1)=1\right]-\mathrm{E}\left[Y|A(0)=0,A(1)=1\right]$ was equal to $\mathrm{E}\left[Y_{\bar{a}=\{1,1\}}\right]-\mathrm{E}\left[Y_{\bar{a}=\{0,1\}}\right]$.

Table 1.2 *The study population collapsed over* $L(1)$

$A(0)$	$A(1)$	N	$\mathrm{E}[Y\|A(0),A(1)]$	
0	0	8000	87.5	$=\gamma_0$
0	1	8000	182.5	$=\gamma_0+\gamma_2$
1	0	6000	180	$=\gamma_0+\gamma_1$
1	1	10000	124	$=\gamma_0+\gamma_1+\gamma_2+\gamma_3$

It will prove later useful for us to consider the saturated conditional association model

$$\mathrm{E}[Y|A(0)=a(0),A(1)=a(1)]=\gamma_0+\gamma_1 a(0)+\gamma_2 a(1)+\gamma_3 a(0)a(1) \tag{1.4}$$

We can estimate the model parameters by collapsing the population data over $L(1)$ as shown in Table 1.2. We can then calculate the parameters values from the equations

$\mathrm{E}[Y|A(0)=0,A(1)=0]=\gamma_0$
$\mathrm{E}[Y|A(0)=0,A(1)=1]=\gamma_0+\gamma_2$
$\mathrm{E}[Y|A(0)=1,A(1)=0]=\gamma_0+\gamma_1$
$\mathrm{E}[Y|A(0)=1,A(1)=1]=\gamma_0+\gamma_1+\gamma_2+\gamma_3$

and the values of $\mathrm{E}[Y|A(0)=a(0),A(1)=a(1)]$ in Table 1.2.

We find $\gamma_0=87.5,\gamma_1=92.5,\gamma_2=95$ and $\gamma_3=-151$. These parameter estimates are precisely those that result from fitting, by ordinary least squares, a linear model for the outcome Y that contains, as regressors, an intercept, $A(0)$, $A(1)$, and the product $A(0)\times A(1)$. Note that if we were given the values of the γ-parameters, we could use the above equations in the other direction to calculate the conditional means $\mathrm{E}[Y|A(0)=a(0),A(1)=a(1)]$.

Upon recognizing that the above associational contrast was biased for $\mathrm{E}\left[Y_{\bar{a}=\{1,1\}}\right]-\mathrm{E}\left[Y_{\bar{a}=\{0,1\}}\right]$ due to uncontrolled confounding by $L(1)$, it is natural to try to adjust for confounding by computing the two l-stratum-specific associations $\mathrm{E}[Y|A(0)=1,L(1)=0,A(1)=1]-\mathrm{E}[Y|A(0)=0,L(1)=0,A(1)=1]=250-70=180$, and $\mathrm{E}[Y|A(0)=1,L(1)=1,A(1)=1]-\mathrm{E}[Y|A(0)=0,L(1)=1,A(1)=1]=110-220=-110$ or their weighted average $-110\frac{20}{32}+180\frac{12}{32}=69.75$, with weights determined by the distribution of L in the study population of 32000. Note $\Pr(L=1)=\frac{20}{32}$. Neither of the l-stratum-specific associations nor their population weighted average is a valid unbiased estimate of the actual causal contrast $\mathrm{E}\left[Y_{\bar{a}=\{1,1\}}\right]-\mathrm{E}\left[Y_{\bar{a}=\{0,1\}}\right]=0$. The bias in the l-stratum specific associations reflect the selection bias that is induced when one conditions on a covariate $L(1)$, that is both a predictor of Y given $A(0)$ and $A(1)$ and is caused by treatment $A(0)$ (Rosenbaum, 1984; Robins 1986).

This selection bias can be understood with the help of causal graphs (Hernán et al, 2004). To do so consider another study whose causal graph is also given by Figure 3, but modified so that all three dotted arrows are absent. The modified graph implies that neither $A(0)$ nor $A(1)$ has a direct, indirect, or net effect on Y. Yet, even in this setting, we would expect that the two l-stratum-specific associations would still remain non-zero and therefore biased for $\mathrm{E}\left[Y_{\bar{a}=\{1,1\}}\right]-\mathrm{E}\left[Y_{\bar{a}=\{0,1\}}\right]=0$. To see why, note the associational l-stratum-specific associations are zero only when Y and $A(0)$ are conditionally independent given $A(1)=1$ and L. But we would not expect such conditional independence because, on the modified graph, the path $A(0)\rightarrow L(1)\longleftarrow U\rightarrow Y$ connecting Y and $A(0)$ is opened when we condition (i.e., stratify) on the collider $L(1)$ and/or $L(1)$'s descendant $A(1)$ (see definitions in Appendix). In our study, conditioning on $A(1)=1$ and $L(1)$ similarly results in selection bias; however, the presence of the arrow from $A(1)$ to Y and of one or both of the arrows from $A(0)$ to Y and $L(1)$ to Y makes a purely graphical demonstration of the bias less clear.

Table 1.3 *The stabilized pseudo-population*

$A(0)$	$L(1)$	$A(1)$	N	$\mathrm{E}[Y\|A(0),L(1),A(1)]$	$f[A(1)\|A(0)]$	$f[A(1)\|L(1),A(0)]$	SW	N pseudo-pop.
0	1	0	2000	200	0.50	0.25	2	4000
0	1	1	6000	220	0.50	0.75	$\frac{2}{3}$	4000
0	0	0	6000	50	0.50	0.75	$\frac{2}{3}$	4000
0	0	1	2000	70	0.50	0.25	2	4000
1	1	0	3000	130	0.375	0.25	1.5	4500
1	1	1	9000	110	0.625	0.75	$\frac{5}{6}$	7500
1	0	0	3000	230	0.375	0.75	0.5	1500
1	0	1	1000	250	0.625	0.25	2.5	2500

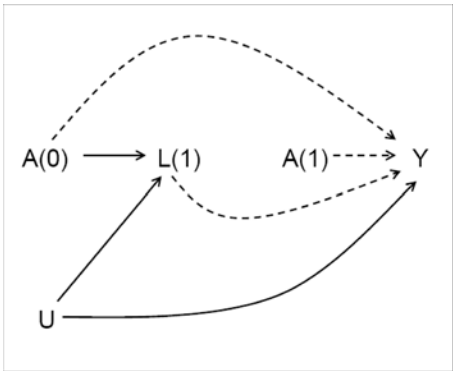


Figure 1.4 *Causal DAG in the pseudo-population simulated by IPTW*

1.4.6 IPTW and marginal structural models

We now describe how to use IPTW for estimating the counterfactual means $\mathrm{E}[Y_{\bar{a}}]$ under the four static regimes $\bar{a} = \{a(0), a(1)\}$. The first step is to create a stabilized pseudo-population by weighting the subjects in each row in Table 1.1 by the stabilized weights $SW = \dfrac{f[A(0)]\, f[A(1)|A(0)]}{f[A(0)]\, f[A(1)|A(0), L(1)]} = \dfrac{f[A(1)|A(0)]}{f[A(1)|A(0), L(1)]}$. Note that the factor $f[A(0)]$ cancels, because in our study the potential confounder $L(0)$ is absent. Table 1.3 records the values of $f[A(1)|A(0)]$, $f[A(1)|A(0), L(1)]$, SW, and the number of subjects in the pseudo-population.

For example, for the first row:

$$f[A(1)|A(0)] = \Pr[A(1) = 0|A(0) = 0] = 8000/16000 = 0.5 \text{ and}$$
$$f[A(1)|A(0), L(1)] = \Pr[A(1) = 0|A(0) = 0, L(1) = 1] = 2000/8000 = 0.25$$

Each of the 2000 subjects in the first row therefore receives the weight $SW = 0.5/0.25 = 2$. Hence, the row contributes $4000 = 2 \times 2000$ subjects to the pseudo-population. The IPTW weights eliminate the arrow between $L(1)$ and $A(1)$ in the pseudo-population as shown in Figure 4. The absence of the arrow can be easily confirmed by checking whether $A(1) \amalg_{ps} L(1)|A(0)$, where $\amalg_{ps}$ represents independence in the pseudo-population. This conditional independence holds in the pseudo-population of our example because

$$\Pr_{ps}[A(1) = 1|A(0) = 1, L(1) = 0] = \Pr_{ps}[A(1) = 1|A(0) = 1, L(1) = 1] = 3/8, \text{ and}$$
$$\Pr_{ps}[A(1) = 1|A(0) = 0, L(1) = 0] = \Pr_{ps}[A(1) = 1|A(0) = 0, L(1) = 1] = 1/2$$

Therefore the causal DAG corresponding to the pseudo-population lacks the arrow $L(1)$

Table 1.4 *The stabilized pseudo-population collapsed over* $L(1)$

$A(0)$	$A(1)$	N	$\mathrm{E}[Y\|A(0),A(1)]$	
0	0	8000	125	$=\theta_0$
0	1	8000	145	$=\theta_0+\theta_2$
1	0	6000	155	$=\theta_0+\theta_1$
1	1	10000	145	$=\theta_0+\theta_1+\theta_2+\theta_3$

to $A(1)$. The absence of this arrow signifies that there is no confounding by $L(1)$ in the pseudo-population and hence that adjustment by stratification is not necessary. That is, $\mathrm{E}_{ps}[Y|A(0)=a(0),A(1)=a(1)] = \mathrm{E}_{ps}\left[Y_{\bar{a}=\{a(0),a(1)\}}\right]$ in the pseudo-population. Thus, as shown in Table 1.4, we can collapse the pseudo-population data over $L(1)$, obtain $\mathrm{E}_{ps}[Y|A(0),A(1)]$ for each of the four combinations of values of $A(0)$ and $A(1)$, and conduct an unadjusted analysis.

For example, the direct effect of $A(0)$ on the mean of Y when $A(1)$ is set to 0 is $\mathrm{E}_{ps}[Y|A(0)=1,A(1)=0] - \mathrm{E}[Y|A(0)=0,A(1)=0] = 155-125 = 30$. As expected, the values of $\mathrm{E}[Y_{\bar{a}}]$ obtained by IPTW, i.e., the values of $\mathrm{E}_{ps}[Y|A(0),A(1)]$ in the pseudo-population, are equal to those obtained by the g-formula.

In this oversimplified example, we do not need to use models to estimate the inverse probability weights because they can be easily calculated by hand from the data. Also, we do not need models for the counterfactual means $\mathrm{E}[Y_{\bar{a}}]$ because these means can be calculated by hand. However, for pedagogic purposes, let us consider the saturated marginal structural mean model

$$\mathrm{E}[Y_{\bar{a}}] = \eta_0 + \eta_1 a(0) + \eta_2 a(1) + \eta_3 a(0)a(1)$$

We can use the pseudo-population data to calculate the parameters η_0, η_1, η_2 and η_3 because

$$\mathrm{E}\left[Y_{\bar{a}=\{0,0\}}\right] = \eta_0$$
$$\mathrm{E}\left[Y_{\bar{a}=\{0,1\}}\right] = \eta_0 + \eta_2$$
$$\mathrm{E}\left[Y_{\bar{a}=\{1,0\}}\right] = \eta_0 + \eta_1$$
$$\mathrm{E}\left[Y_{\bar{a}=\{1,1\}}\right] = \eta_0 + \eta_1 + \eta_2 + \eta_3$$

and therefore, using the estimates for $\mathrm{E}\left[Y_{\bar{a}=\{a(0),a(1)\}}\right]$ in Table 1.4, $\eta_0 = 125$, $\eta_1 = 30$, $\eta_2 = 20$, and $\eta_3 = -30$. This estimation procedure is equivalent to fitting linear model (1.4) by weighted least squares with each subject weighted by SW (e.g., `PROC REG` with a `weight` statement in SAS). Because of confounding, the parameters η of the marginal structural mean model differ from the parameters γ of the associational mean model (1.4).

The parameters η can be used to test hypotheses about the joint effect of exposures $A(0), A(1)$. For example, the hypothesis that $A(0)$ has no direct effect on the mean of Y when $A(1)$ is set to 1, i.e., $\mathrm{E}\left[Y_{\bar{a}=\{1,1\}}\right] = \mathrm{E}\left[Y_{\bar{a}=\{0,1\}}\right]$, implies $\eta_0+\eta_1+\eta_2+\eta_3 = \eta_0+\eta_2$. This would be true only if $\eta_1+\eta_3 = 0$, which is the case. Similarly, the hypothesis that $A(0)$ has no direct effect on the mean of Y when $A(1)$ is set to 0, i.e., $\mathrm{E}\left[Y_{\bar{a}=\{1,0\}}\right] = \mathrm{E}\left[Y_{\bar{a}=\{0,0\}}\right]$, implies $\eta_0+\eta_1 = \eta_0$. This would be true only if $\eta_1 = 0$, which is not the case. Suppose we had fit the non-saturated misspecified marginal structural model

$$\mathrm{E}[Y_{\bar{a}}] = \eta_0 + \eta_1 a(0) + \eta_2 a(1)$$

by weighted least squares with weights SW and then used the parameter estimates to estimate the counterfactual means $\mathrm{E}[Y_{\bar{a}}]$. Because of misspecification bias, these estimated means would have differed from those obtained from the saturated model and from the g-formula.

Table 1.5 *The unstabilized pseudo-population*

$A(0)$	$L(1)$	$A(1)$	N	$\mathrm{E}[Y\|A(0),L(1),A(1)]$	$f[A(0)]$	$f[A(1)\|L(1),A(0)]$	SW	N pseudo-pop.
0	1	0	2000	200	0.50	0.25	8	16000
0	1	1	6000	220	0.50	0.75	8/3	16000
0	0	0	6000	50	0.50	0.75	8/3	16000
0	0	1	2000	70	0.50	0.25	8	16000
1	1	0	3000	130	0.50	0.25	8	24000
1	1	1	9000	110	0.50	0.75	8/3	24000
1	0	0	3000	230	0.50	0.75	8/3	8000
1	0	1	1000	250	0.50	0.25	8/3	8000

1.4.7 Methods for dynamic regimes

G-formula

The four regimes $g = \{a(0), a(1)\}$ that we have compared constitute all possible combinations of fixed values of $a(0)$ and $a(1)$ and thus all possible static regimes in our example. We next consider dynamic regimes such as $g = \{1, L(1)\}$, which is the regime "always treat at time 0, treat at time 1 only if $L(1) = 1$." Note the same dynamic regime applied to different people may result in different exposure values. For example, the regime $g = \{1, L(1)\}$ will be the regime $\{1, 1\}$ for those subjects with $L(1) = 1$ under $a(0) = 1$, and $g = \{1, 0\}$ for those with $L(1) = 0$ under $a(0) = 1$. The g-formula for the dynamic regime $g = \{1, L(1)\}$ is the generalization of the g-formula for static regimes in which the exposure $A(1)$ is set to 1 when $L(1) = 1$ and $A(1)$ is set to 0 when $L(1) = 0$. In our example

$$\begin{aligned}\mathrm{E}\left[Y_{g=(\{1,L(1)\})}\right] &= \mathrm{E}[Y|A(0)=1,A(1)=1,L(1)=1]\ \Pr[L(1)=1|A(0)=1] \\ &+ \mathrm{E}[Y|A(0)=1,A(1)=0,L(1)=0]\ \Pr[L(1)=0|A(0)=1] \\ &= 110 \times \frac{12}{16} + 230\frac{4}{16} = 140.\end{aligned}$$

The above formula can be written more succinctly as

$$\mathrm{E}\left[Y_{g=(\{1,L(1)\})}\right] = \sum_{l(1)} \mathrm{E}[Y|A(0)=1,A(1)=l(1),L(1)=l(1)]\ \Pr[L(1)=l(1)|A(0)=1].$$

IPTW

We now describe how to use IPTW for estimating the counterfactual means $\mathrm{E}\left[Y_{g=(\{1,L(1)\})}\right]$. The first step is to create a unstabilized pseudo-population by weighting the subjects in each row in Table 1.1 by the unstabilized weights $W = 1/\{f[A(0)]\, f[A(1)|A(0),L(1)]\}$. Note we use $f[A(0)]$ rather than $f[A(0)|L(0)]$, because in our study no potential confounder $L(0)$ is present. Table 1.5 records the values of $f[A(0)]$, $f[A(1)|A(0),L(1)]$, W, and the number of subjects in the unstabilized pseudo-population.

The IPTW estimate of $\mathrm{E}\left[Y_{g=(\{1,L(1)\})}\right]$ is the average of Y among the subjects in the unstabilized pseudo-population who followed regime $g = \{1, L(1)\}$. Only the subjects with $A(0) = 1, L(1) = 1, A(1) = 1$ and $A(0) = 1, L(1) = 0, A(1) = 0$ followed $g = \{1, L(1)\}$. Thus $\mathrm{E}\left[Y_{g=(\{1,L(1)\})}\right] = \frac{24000\times110+8000\times230}{32000} = 140$, as was also obtained with the g-formula.

G-estimation

G-estimation of structural nested models is a third method for estimation of counterfactual means. The "g-" indicates that g-estimation, like the g-formula is a general method that can be further used to estimate counterfactual means $\mathrm{E}\left[Y_g\right]$ under any static or dynamic regime g. We begin with a saturated locally rank preserving structural nested model (SNM) for our example. The model has one equation for each treatment time with one unknown parameter β_0^* in the time 0 equation and a vector β_1^* of 4 unknown parameters in the time 1 equation:

$$Y_{g=\{a(0),0\}} = Y_{g=\{0,0\}} + \beta_0^* a(0) \tag{1.5}$$

$$Y_{g=\{a(0),a(1)\}} = Y_{g=\{a(0),0\}} + \beta_{1,1}^* a(1) + \beta_{1,2}^* a(1) L_{g=\{a(0)\}}(1) + \beta_{1,3}^* a(1)a(0) + \beta_{1,4}^* a(1)a(0) L_{g=\{a(0)\}}(1) \tag{1.6}$$

By evaluating equation (1.5) at $a(0) = 1$, we see the parameter $\beta_0^* = Y_{g=\{1,0\}} - Y_{g=\{0,0\}}$ represents the subject-specific direct effect of treatment $a(0)$ on the outcome when treatment $a(1)$ is withheld, i.e., set to zero. Under our model, this direct effect β_0^* is exactly the same for every subject. Thus if $Y_{g=\{0,0\}}$ for subject i exceeds $Y_{g=\{0,0\}}$for subject j, the same ranking of i and j will hold for $Y_{g=\{1,0\}}$; the model preserves ranks across regimes and we therefore refer to equation (1.5) as a rank preserving model.

The 4 parameters β_1^* in equation (1.6) parameterize the effect of a $a(1)$ on Y within the 4 possible levels of past treatment and covariate history. For example $\beta_{1,1}^*$ and $\beta_{1,1}^* + \beta_{1,2}^*$ are, respectively, the effect of $a(1)$ on Y when $a(0)$ is withheld among the subset of subjects with $L_{g=\{0\}}(1) = 0$ and the subset with $L_{g=\{0\}}(1) = 1$. Here $L_{g=\{0\}}(1)$ is the counterfactual value of $L(1)$ when $a(0)$ is withheld. If $\beta_{1,1}^*$ and $\beta_{1,1}^* + \beta_{1,2}^*$ are of opposite sign, then there is a qualitative modification by $L(1)$ of the effect $a(1)$ on Y when $a(0)$ is withheld. Similarly $\beta_{1,1}^* + \beta_{1,3}^*$ and $\beta_{1,1}^* + \beta_{1,3}^* + \beta_{1,5}^*$ are the effect of $a(1)$ when $a(0)$ is taken among the subset of subjects with $L_{g=\{1\}}(1) = 0$ and the subset with $L_{g=\{1\}}(1) = 1$, respectively. If they are of different sign, there is a qualitative modification by $L(1)$ of the effect of $a(1)$ on Y when $a(0)$ is taken. Thus a SNM models the degree to which the effect of current treatment is modified by past treatment and past time-dependent covariate history. In contrast, nondynamic marginal structural models can only model effect modification by baseline covariates V, a subset of $L(0)$.

Finally we note that if $Y_{g=\{1,0\}}$ for subject i exceeds $Y_{g=\{1,0\}}$ for subject j, we can only be certain that $Y_{g=\{1,1\}}$ for subject i also exceeds $Y_{g=\{1,1\}}$ for subject j, if both have the same values of $L_{g=(1)}$. Because the preservation of the ranking on the counterfactual Y depends on local factors (i.e., the value $L_{g=(1)}$), we refer to equation (1.6) as a locally rank preserving model.

We next describe how we can estimate the parameters under the assumption of conditional exchangeability. We then show how to use our parameter estimates to estimate $\mathrm{E}\left[Y_{g=(\{1,L(1)\})}\right]$.

G-estimation of the parameters under conditional exchangeability: We begin by estimating the parameter vector β_1^*. To do so, in Table 1.6 we first use the SNM to calculate the mean of $Y_{\{A(0),0\}}$ in terms of the unknown parameter vector β_1^*. To help understand these calculations, consider the expression $220 - \beta_{1,1}^* - \beta_{1,2}^*$ for the mean of $Y_{\{A(0),0\}} = Y_{\{0,0\}}$ among subjects with $A(0) = 0, L(1) = 1, A(1) = 1$ in the second data row of Table 1.6. By consistency, the observed $L(1)$ of 1 equals $L_{g=\{0\}}(1)$ and the observed mean 220 of Y is the mean of $Y_{g=\{0,1\}}$. By solving eq. (1.6) for $Y_{g=\{0,0\}}$ after substituting $\{0,1\}$ for $\{a(0), a(1)\}$ and 1 for $L_{g=\{a(0)\}}(1)$, we obtain $220 - \beta_{1,1}^* - \beta_{1,2}^*$ upon taking means.

We now estimate β_1^* under the assumption of conditional exchangeability. Conditional exchangeability implies that (i) $Y_{g=\{0,0\}} \amalg A(0)$ and (ii) $Y_{\{a(0),0\}} \amalg A(1) | A(0) = a(0), L(1) =$

Table 1.6 *The g-estimation procedure*

$A(0)$	$L(1)$	$A(1)$	N	Y	$Y_{\{A(0),0\}}$	$Y_{\{0,0\}}$
0	1	0	2000	200	200	200
0	1	1	6000	220	$220-\beta^*_{1,1}-\beta^*_{1,2}$	$220-\beta^*_{1,1}-\beta^*_{1,2}$
0	0	0	6000	50	50	50
0	0	1	2000	70	$70-\beta^*_{1,1}$	$70-\beta^*_{1,1}$
1	1	0	3000	130	130	$130-\beta^*_0$
1	1	1	9000	110	$110-\beta^*_0-\beta^*_{1,1}-\beta^*_{1,2}-\beta^*_{1,3}-\beta^*_{1,4}$	$110-\beta^*_0-\beta^*_{1,1}-\beta^*_{1,2}-\beta^*_{1,3}-\beta^*_{1,4}$
1	0	0	3000	230	230	$230-\beta^*_0$
1	0	1	1000	250	$250-\beta^*_{1,1}-\beta^*_{1,3}$	$250-\beta^*_0-\beta^*_{1,1}-\beta^*_{1,3}$

$l(1)$. Now condition (ii) implies that, within any of the four joint strata of. $(A(0), L(1))$, the mean of $Y_{\{A(0),0\}}$ among subjects with $A(1) = 1$ is equal to the mean among subjects with $A(1) = 0$. Consider first the stratum $(A(0), L(1)) = (0, 0)$. From data rows 3 and 4 in Table 1.6, we find that the mean when $A(1) = 0$ is 50 and is $70-\beta^*_{1,1}$ when $A(1) = 1$. Hence $\beta^*_{1,1} = 20$. Next we equate the means of $Y_{\{A(0),0\}}$ in data rows 1 and 2 corresponding to stratum $(A(0), L(1)) = (0, 1)$ to obtain $200 = 220-\beta^*_{1,1}-\beta^*_{1,2}$. Since $\beta^*_{1,1} = 20$, we conclude $\beta^*_{1,2} = 0$.

Continuing we equate the means of $Y_{\{A(0),0\}}$ in data rows 7 and 8 to obtain $230 = 250 - \beta^*_{1,1} - \beta^*_{1,3}$. Since $\beta^*_{1,1} = 20$, we conclude $\beta^*_{1,3} = 0$. Finally, equating the means of $Y_{\{A(0),0\}}$ in data rows 5 and 6, we obtain $130 = 110 - \beta^*_{1,1} - \beta^*_{1,2} - \beta^*_{1,3} - \beta^*_{1.4}$ so $130 = 110 - 20 - \beta^*_{1,4}$. Thus $\beta^*_{1,4} = -40$.

To estimate β^*_0, we first substitute $\beta^*_{1,1} = 20, \beta^*_{1,2} = \beta^*_{1,3} = 0, \beta^*_{1,4} = -40$ into the expressions for the mean of $Y_{\{A(0),0\}}$ in Table 1.6. We then use eq. (1.5) to obtain the mean of $Y_{\{0,0\}}$ for each data row in Table 1.6 by subtracting $\beta^*_0 A(0)$ from the mean of $Y_{\{A(0),0\}}$. Now our assumption $Y_{\{0,0\}} \amalg A(0)$ implies that the means of $Y_{\{0,0\}}$ among the 16000 subjects with $A(0) = 1$ and the 16000 subjects with $A(0) = 0$ are identical. The mean among subjects with $A(0) = 0$ is $200\frac{8000}{16000} + 50\frac{8000}{16000} = 125$. The mean among subjects with $A(0) = 1$ is $130\frac{12000}{16000} + 230\frac{4000}{16000} - \beta^*_0 = 155 - \beta^*_0$. Hence $\beta^*_0 = 30$.

This method of estimation is referred to as g-estimation.

Estimation of $\mathrm{E}[Y_g]$ *using locally rank preserving nested structural models* We now use the above results to estimate various counterfactual population means.

Since 125 is the mean of $Y_{g=\{0,0\}}$ both in subjects with $A(0) = 0$ and $A(0) = 1$, we conclude that the population mean $\mathrm{E}\left[Y_{g=\{0,0\}}\right]$ is 125.

Further by eq. (1.5), $\mathrm{E}\left[Y_{g=\{1,0\}} - Y_{g=\{0,0\}}\right] = \beta^*_0 = 30$. Thus $\mathrm{E}\left[Y_{g=\{1,0\}}\right] = \mathrm{E}\left[Y_{g=\{0,0\}}\right] + \beta^*_0 = 125 + 30 = 155$.

Next, by eq. (1.6), $\mathrm{E}\left[Y_{g=\{0,1\}} - Y_{g=\{0,0\}}\right] = \mathrm{E}\left[\beta^*_{1,1} + \beta^*_{1,2} L_{g=\{0\}}(1)\right] = \beta^*_{1,1} + \beta^*_{1,2}\, \mathrm{E}\left[L_{g=\{0\}}(1)\right] = \beta^*_{1,1} = 20$ since $\beta^*_{1,2} = 0$. Hence $\mathrm{E}\left[Y_{g=\{0,1\}}\right] = 145$.

Next, by eq. (1.6), $\mathrm{E}\left[Y_{g=\{1,1\}} - Y_{g=\{0,0\}}\right] = \mathrm{E}\left[\beta^*_0 + \beta^*_{1,1} + \beta^*_{1,3} + \left(\beta^*_{1,2} + \beta^*_{1,4}\right) L_{g=(1)}(1)\right] = 30 + 20 + (-40)\, \mathrm{E}\left[L_{g=(1)}(1)\right]$. We conclude that knowledge of the parameters of our SNM is not sufficient to estimate $\mathrm{E}\left[Y_{g=\{1,1\}} - Y_{g=\{0,0\}}\right]$. We also need to know $\mathrm{E}\left[L_{g=\{1\}}(1)\right]$. But, as noted previously, $\mathrm{E}\left[L_{g=\{1\}}(1)\right] = \mathrm{E}[L(1) \,|\, A(0) = 1] = 3/4$, as association is causation for the effect of $A(0)$ on $L(1)$. Thus $\mathrm{E}\left[Y_{g=\{1,1\}} - Y_{g=\{0,0\}}\right] = 30 + 20 - 40\,(3/4)) = 20$ so $\mathrm{E}\left[Y_{g=\{1,1\}}\right] = 145$.

Finally to obtain $\mathrm{E}\left[Y_{g=\{1,L(1)\}}\right]$, we note that $Y_{g=\{1,L(1)\}} = Y_{g=\{1,1\}}$ if $L_{g=\{1\}}(1) = 1$ and $Y_{g=\{1,L(1)\}} = Y_{g=\{1,0\}}$ if $L_{g=\{1\}}(1) = 0$. Thus in the 3/4 of subjects with $L_{g=\{1\}}(1) =$

$1, Y_{g=\{1,L(1)\}} - Y_{g=\{0,0\}} = Y_{g=\{1,1\}} - Y_{g=\{0,0\}} = \beta_0^* + \beta_{1,1}^* + \beta_{1,3}^* + \beta_{1,2}^* + \beta_{1,4}^* = 30 + 20 - 40 = 10$. In the 1/4 of subjects with $L_{g=\{1\}}(1) = 0$, $Y_{g=\{1,L(1)\}} - Y_{g=\{0,0\}} = Y_{g=\{1,0\}} - Y_{g=\{0,0\}} = \beta_0^* = 30$. Thus the mean of $Y_{g=\{1,L(1)\}} - Y_{g=\{0,0\}}$ is

$10\,(3/4) + 30\,(1/4) = 15$. Hence, $\mathrm{E}\left[Y_{g=\{1,1\}}\right] = 125 + 15 = 140$.

All of these results agree with those obtained by the g-formula and by IPTW.

Estimation of $\mathrm{E}[Y_g]$ *without local rank preservation* We noted above that local rank preservation implies that the direct effect of treatment $A(0)$ on the outcome when treatment $A(1)$ is withheld is the same for each subject. This assumption is clearly biologically implausible in view of between-subject heterogeneity in unmeasured genetic and environmental background risks. To overcome this limitation we consider a saturated structural nested mean model (SNMM) that assumes

$$\mathrm{E}\left[Y_{g=\{a_0,0\}}\right] = \mathrm{E}\left[Y_{g=\{0,0\}}\right] + \beta_0^* a(0) \text{ and}$$

$$\begin{aligned}\mathrm{E}\left[Y_{g=\{a_0,a_1\}} | L(1) = l(1), A(0) = a(0)\right] &= \mathrm{E}\left[Y_{g=\{a_0,0\}} | L(1) = l(1), A(0) = a(0)\right] \\ &\quad + \beta_{1,1}^* a(1) + \beta_{1,2}^* a(1) l(1) + \beta_{1,3}^* a(1) a(0) + \beta_{1,4}^* a(1) a(0) l(1)\end{aligned}$$

This model is a model for unconditional and conditional average treatment effects and thus is totally agnostic as to the question of whether or not there is between subject heterogeneity in the effect of treatment. Nonetheless, Robins (1994, 1997b) has proved the previous estimates of the parameters β_0^* and β_1^* and the means $\mathrm{E}[Y_g]$ obtained with g-estimation remain valid under the structural nested mean model, provided the strengthened identifiability conditions hold.

1.5 G-estimation in practice and the choice among g-methods

1.5.1 G-estimation of unsaturated structural nested mean models

In practice, we need to combine information from many different regimes to estimate a given $\mathrm{E}[Y_g]$. To accomplish this goal we shall fit an unsaturated structural nested mean model by g-estimation.

The general form of an additive structural nested mean model is as follows. For each treatment time $m = 0, ..., K$,

$$\begin{aligned}&\mathrm{E}\left[Y_{g=\{\overline{a}(m-1),a(m),\underline{0}(m+1)\}} | \overline{L}_{\overline{a}(m-1)}(m) = \overline{l}(m), \overline{A}(m-1) = \overline{a}(m-1)\right] \\ &= \mathrm{E}\left[Y_{g=\{\overline{a}(m-1),\underline{0}(m)\}} | \overline{L}_{\overline{a}(m-1)}(m) = \overline{l}(m), \overline{A}(m-1) = \overline{a}(m-1)\right] + a(m)\gamma_m\left[\overline{a}(m-1), \overline{l}(m), \beta^*\right]\end{aligned} \tag{1.7}$$

where (i) $g = \{\overline{a}(m-1), a(m), \underline{0}(m+1)\}$ and $g = \{\overline{a}(m-1), \underline{0}(m)\}$ are nondynamic regimes that differ only in that the former has treatment $a(m)$ at m while the latter has treatment 0 at time m, while both have treatment $\overline{a}(m-1)$ through $m-1$ and treatment 0 from $m+1$ to the end of follow-up K, (ii) β^* is an unknown parameter vector, and (iii) $\gamma_m\left[\overline{a}(m-1), \overline{l}(m), \beta\right]$ is a known function satisfying $\gamma_m\left[\overline{a}(m-1), \overline{l}(m), 0\right] = 0$ so $\beta^* = 0$ under the null hypothesis of no effect of treatment.

Thus the SNMM $\gamma_m\left[\overline{a}(m-1), \overline{l}(m), \beta^*\right]$ models the effect on the mean of Y of a last blip of treatment of magnitude $a(m)$ at m, as a function of (i.e., as modified by) past treatment and covariate history $\left[\overline{a}(m-1), \overline{l}(m)\right]$. Further it follows from the consistency condition that we could have replaced $\overline{L}_{g=\{\overline{a}(m-1)\}}(m) = \overline{l}(m)$ by $L(m) = \overline{l}(m)$ in the conditioning event.

In the example of the previous section, we have $K = 1$, $\gamma_1\left[\overline{a}(0), \overline{l}(1), \beta^*\right] = \beta_{1,1}^* + \beta_{1,2}^* l(1) + \beta_{1,3}^* a(0) + \beta_{1,4}^* a(0) l(1)$ and $\gamma_0\left[\overline{a}(-1), \overline{l}(0), \beta^*\right] = \beta_0^*$ since $\overline{l}(0)$ and $\overline{a}(-1)$ can both be taken to be identically 0. Other possible choices of $\gamma_m\left[\overline{a}(m-1), \overline{l}(m), \beta\right]$ include (i) β, (ii) $\beta_0 + \beta_1 m$, (iii) $\beta_0 + \beta_1 m + \beta_2 a(m-1) + \beta_3^T l(m) + \beta_4^T l(m) a(m-1)$.

In model (i) the effect of a last blip of treatment $a(m)$ is the same for all m. Under model (ii) the effect varies linearly with the time m of treatment. Under model (iii), the effect of a last blip of treatment at m is modified by past treatment and covariate history.

We next describe the g-estimation algorithm for estimating the unknown parameter β^* in an observational study under the assumptions of conditional exchangeability and consistency. We note that to fit an unsaturated SNMM by g-estimation we do not require positivity to hold.

Fit a pooled logistic regression model

$$\text{logit}\Pr\left[A(m)=1|\overline{L}(m),\overline{A}(m-1)\right]=\alpha^T W(m) \tag{1.8}$$

for the probability of treatment at time (i.e., week) m for $m=0,...,K$. Here $W(m)=w_m\left[\overline{L}(m),\overline{A}(m-1)\right]$ is a vector of covariates calculated from a subject's covariate and treatment data $\left[\overline{L}(m),\overline{A}(m-1)\right]$, α^T is a row vector of unknown parameters, and each person-week is treated as an independent observation so each person contributes $K+1$ observations. Examples of $W(m)=w_m\left[\overline{L}(m),\overline{A}(m-1)\right]$ would be the transpose of the row vector $m, A(m-1), L^T(m), A(m-1)L^T(m), A(m-2), L^T(m-1), L^T(m)A(m-1)A(m-2)$, where $L(m)$ is the vector of covariates measured at time m. Let $\widehat{\alpha}$ be the MLE of α. (In a sequentially randomized experiment the preceding step is not required because $\Pr\left[A(m)=1|\overline{L}(m),\overline{A}(m-1)\right]$ is known and would not need to be estimated).

Next define

$$Y_m(\beta)=Y-\sum_{j=m}^{K}A(j)\gamma_j\left[\overline{A}(j-1),\overline{L}(j),\beta\right]$$

Note that, for each β, $Y_m(\beta)$ can be computed from the observed data. For the moment assume, as in model (i) above, β is one dimensional. Let β_{low} and β_{up} be much smaller and larger, respectively, than any substantively plausible value of β^*.

Then, separately, for each β on a grid from β_{low} to β_{up}, say $\beta_{low}, \beta_{low}+0.1, \beta_{low}+0.2, ..., \beta_{up}$, perform the score test of the hypothesis $\eta=0$ in the extended logistic model

$$\text{logit}\Pr\left[A(m)=1|\overline{L}(m),\overline{A}(m-1),Y_m(\beta)\right]=\alpha^T W(m)+\theta Y_m(\beta) \tag{1.9}$$

that adds the covariate $Y_m(\beta)$ at each time m to the above pooled logistic model. A 95% confidence interval for β^* is the set of β for which a $\alpha=0.05$ two-sided score test of the hypothesis $\theta=0$ does not reject. The g-estimate of β^* is the value of β for which the score test takes the value zero (i.e., the p-value is one.)

A heuristic argument for the validity of the g-estimation algorithm is as follows. Under a locally rank preserving model if β was equal to β^*, $Y_m(\beta)$ would equal the counterfactual $Y_{g=\left\{\overline{A}(m-1),\underline{0}(m)\right\}}$ in which a subject takes his actual treatment prior to m but no treatment from time m onwards, as shown in the previous section. But, under conditional exchangeability, $Y_{g=\left\{\overline{A}(m-1),\underline{0}(m)\right\}}$ and $A(m)$ are conditionally independent given past covariate and treatment history $\overline{L}(m),\overline{A}(m-1)$. That is, $Y_{g=\left\{\overline{A}(m-1),\underline{0}(m)\right\}}$ is not a predictor of $A(m)$ given $\left(\overline{L}(m),\overline{A}(m-1)\right)$, which implies that the coefficient θ of $Y_m(\beta)$ must be zero in the model (1.9) when $\beta=\beta^*$, provided the model $\text{logit}\Pr\left[A(m)=1|\overline{L}(m),\overline{A}(m-1)\right]=\alpha^T W(m)$ is correctly specified.

Now, we do not know the true value of β. Therefore, any value β for which the data are consistent with the parameter θ of the term $\theta Y_m(\beta)$ being zero might be the true β^*, and thus belongs in our confidence interval. If consistency with the data is defined at the 0.05 level, then our confidence interval will have coverage of 95%. Furthermore, the g-estimate $\widehat{\beta}$ of β^* is that β for which adding the term $\theta Y_m(\beta)$ does not help to predict $A(m)$ whatsoever, which is the β for which the score test of $\theta=0$ is precisely zero. The g-estimate $\widehat{\beta}$ is also the value of β for which the MLE of θ in model (1.9) is precisely zero.

It may appear peculiar that a function $Y_m(\beta)$ of the response Y measured at end of follow-up is being used to predict treatment $A(m)$ at earlier times. However, this peculiarity evaporates when one recalls that, for each β on our grid, we are testing the null hypothesis that $\beta = \beta^*$, and, under this null and a rank preserving model, $Y_m(\beta)$ is the counterfactual $Y_{g=\left\{\overline{A}(m-1),\underline{0}(m)\right\}}$, which we can view as already existing at time m (although we cannot observe its value until time K and then only if treatment in the actual study is withheld from m onwards).

These above arguments are heuristic in the sense that their validity relied on the assumption of local rank preservation and that assumption is biologically implausible. Nevertheless, Robins (1994, 1997b) proves the g-estimation algorithm is valid even in the absence of local rank preservation, provided conditional exchangeability and consistency hold.

Suppose now that the parameter β is a vector. To be concrete suppose we consider the model with $\gamma_m\left[\overline{a}(m-1), \overline{l}(m), \beta\right] = \beta_0 + \beta_1 m + \beta_2 a(m-1) + \beta_3 l(m) + \beta_4 l(m) a(m-1)$ so β is 5 dimensional, $l(m)$ is 1 dimensional and we would use a 5 dimensional grid, one dimension for each component of β. So if we had 20 grid points for each component we would have 20^5 different values of β on our 5 dimensional grid. Now to estimate 5 parameters one requires 5 additional covariates. Specifically, let $Q_m = q_m\left[\bar{L}(m), \bar{A}(m-1)\right]$ be a 5 dimensional vector of functions of $\overline{L}(m), \overline{A}(m-1)$, such as $q_m^T\left[\bar{L}(m), \bar{A}(m-1)\right] = [1, m, A(m-1), L(m), L(m) A(m-1)]$. We use an extended model that includes five linear functions $Q_m Y_m(\beta)$ of $Y_m(\beta)$ as covariates such as

$$\text{logit}\Pr\left[A(m) = 1 | \overline{L}(m), \overline{A}(m-1), Y_m(\beta)\right] = \alpha^T W(m) + \theta^T Q_m Y_m(\beta),$$

The particular choice of the functions $Q_m = q_m\left[\bar{L}(m), \bar{A}(m-1)\right]$ does not affect the consistency of the point estimate, but it determines the width of its confidence interval. See Robins (1994) for the optimal choice of Q_m.

Our g-estimate $\widehat{\beta}$ is the β for which the 5 degree of freedom score test that all 5 components of θ equal zero are precisely zero. A 95% joint confidence interval for β are the set of β on our 5 dimensional grid for which the 5 degree of freedom score test does not reject at the 5% level. Such an interval is computationally demanding. A less demanding approach is to use a Wald interval $\widehat{\beta}_j \pm 1.96$ s.e.$\left(\widehat{\beta}_j\right)$ for each component β_j of β centered at its g-estimate $\widehat{\beta}_j$.This gives a univariate 95% large sample confidence interval for each β_j. [A simultaneous (i.e., joint) 95% large sample confidence interval for all β_j requires a constant greater than 1.96 in the Wald interval.]

When the dimension of β is greater than 2, finding $\widehat{\beta}$ by search over a grid is generally computationally prohibitive. However when, as in all the examples we have discussed, $\gamma_m\left[\overline{a}(m-1), \overline{l}(m), \beta\right] = \beta^T R_m$ is linear in β with $R_m = r_m\left(\bar{L}(m), \bar{A}(m-1)\right)$ being a vector of known functions, then, given the estimator expit$\left\{\widehat{\alpha}^T W(m)\right\}$ of $\Pr\left[A(m) = 1 | \overline{L}(m), \overline{A}(m-1)\right]$, there is an explicit closed form expression for $\widehat{\beta}$ given by

$$\widehat{\beta} = \left\{\sum_{i=1,m=0}^{i=N,m=K} A_i(m) X_{im}(\widehat{\alpha}) Q_{im} S_{im}^T\right\}^{-1} \left\{\sum_{i=1,m=0}^{i=N,m=K} Y_i X_{im}(\widehat{\alpha}) Q_{im}\right\} \tag{1.10}$$

with $X_{im}(\widehat{\alpha}) = \left[A(m)_i - \text{expit}\left\{\widehat{\alpha}^T W_i(m)\right\}\right]$, $S_{im} = \sum_{i=1,j=m}^{i=N,j=K} R_{im}$, and the choice of $Q_{im} = q_m\left[\bar{L}_i(m), \bar{A}_i(m-1)\right]$ affects efficiency but not consistency. In fact, when $\gamma_m\left[\overline{a}(m-1), \overline{l}(m), \beta\right] = \beta^T R_m$ is linear in β, we can obtain a closed-form doubly robust estimator $\widetilde{\beta}$ of β^* by specifying a working model $\varsigma^T D_m = \varsigma^T d_m\left[\bar{L}(m), \bar{A}(m-1)\right]$ for $E\left[Y_m(\beta^*) | \bar{L}(m), \bar{A}(m-1)\right] =$

$E\left[Y_{g=\left\{\overline{A}(m-1),\underline{0}(m)\right\}}|\bar{L}(m),\bar{A}(m-1)\right]$ and defining

$$\begin{pmatrix} \widetilde{\beta} \\ \widetilde{\varsigma} \end{pmatrix} = \left\{ \sum_{i=1,m=0}^{i=N,m=K} \begin{pmatrix} A_i(m) X_{im}(\widehat{\alpha}) Q_{im} \\ D_{im} \end{pmatrix} (S_{im}^T, D_{im}^T) \right\}^{-1} \left\{ \sum_{i=1,m=0}^{i=N,m=K} Y_i \begin{pmatrix} X_{im}(\widehat{\alpha}) Q_{im} \\ D_{im} \end{pmatrix} \right\} \tag{1.11}$$

Specifically $\widetilde{\beta}$ will be a CAN estimator of β^* if either the model $\varsigma^T D_m$ for $E\left[Y_{g=\left\{\overline{A}(m-1),\underline{0}(m)\right\}}|\bar{L}(m),\bar{A}(m-1)\right]$ is correct or the model $\alpha^T W(m)$ for $\text{logit}\left\{\Pr\left[A(m)=1|\overline{L}(m),\overline{A}(m-1)\right]\right\}$ is correct.

1.5.2 Monte Carlo estimation of $\mathrm{E}[Y_g]$ *after g-estimation of a SNMM*

Suppose the strengthened identifiability assumptions hold, one has obtained a doubly robust g-estimate $\widetilde{\beta}$ of a SNMM $\gamma_m\left[\overline{a}(m-1),\overline{l}(m),\beta\right]$ and one wishes to estimate $\mathrm{E}[Y_g]$ for a given static or dynamic regime g. To do so, one can use the following steps of a Monte Carlo algorithm.

1. Estimate the mean response $\mathrm{E}\left[Y_{g=\overline{0}_K}\right]$ had treatment always been withheld by the sample average of $Y_0\left(\widetilde{\beta}\right)$ over the N study subjects. Call the estimate $\widehat{\mathrm{E}}\left[Y_{g=\overline{0}_K}\right]$.
2. First fit a parametric model for $f\left[l(k)|\bar{a}(k-1),\bar{l}(k-1)\right]$ to the data, pooled over persons and times, and let $\widehat{f}\left[l(k)|\bar{a}(k-1),\bar{l}(k-1)\right]$ denote the estimate of $f\left[l(k)|\bar{a}(k-1),\bar{l}(k-1)\right]$ under the model.
3. Do for $v=1,...,V$,
   (a) Draw $l_v(0)$ from $\widehat{f}[l(0)]$.
   (b) Recursively for $k=1,...,K$ draw $l_v(k)$ from $\widehat{f}\left[l(k)|\bar{a}_v(k-1),\bar{l}_v(k-1)\right]$ with $\bar{a}_v(k-1)=\overline{g}_{k-1}\left\{\bar{l}_v(k-1)\right\}$, the treatment history corresponding to the regime g.
   (c) Let $\widehat{\Delta}_{g,v}=\sum_{j=0}^{j=K} a_v(j)\gamma_j\left[\overline{a}_v(j-1),\overline{l}_v(j),\widetilde{\beta}\right]$ be the vth Monte Carlo estimate of $Y_g-Y_{g=\overline{0}_K}$, where $a_v(j)=g_j\left\{\bar{l}_v(j-1)\right\}$.
4. Let $\widehat{\mathrm{E}}[Y_g]=\widehat{\mathrm{E}}\left[Y_{g=\overline{0}_K}\right]+\sum_{v=1}^{v=V}\widehat{\Delta}_{g,v}/V$ be the estimate of $\widehat{\mathrm{E}}[Y_g]$.

If the model for $f\left[l(k)|\bar{a}(k-1),\bar{l}(k-1)\right]$, the SNMM $\gamma_m\left[\overline{a}(m-1),\overline{l}(m),\beta\right]$, and either the treatment model $\text{logit}\Pr\left[A(m)=1|\overline{L}(m),\overline{A}(m-1)\right]=\alpha^{*,T}W_m$ or the model $E\left[Y_{g=\left\{\overline{A}(m-1),\underline{0}(m)\right\}}|\bar{L}(m),\bar{A}(m-1)\right]=\varsigma^{*,T}D_m$ are correctly specified, then $\widehat{\mathrm{E}}[Y_g]$ is consistent for $\mathrm{E}[Y_g]$. Confidence intervals can be obtained using the nonparametric bootstrap.

Our approach based on g-estimation does not suffer from the null paradox. In fact under the null hypothesis of no treatment effect, mispecification of the model for $f\left[l(k)|\bar{a}(k-1),\bar{l}(k-1)\right]$ does not result in bias. To understand why, note that under the null, any SNMM $\gamma_m\left[\overline{a}(m-1),\overline{l}(m),\beta\right]$ is correctly specified with $\beta^*=0$ being the true parameter and $\gamma_m\left[\overline{a}(m-1),\overline{l}(m),\beta^*\right]=0$. Thus $\gamma_m\left[\overline{a}(m-1),\overline{l}(m),\widetilde{\beta}\right]$ will converge to 0 if $\widetilde{\beta}$ is consistent for $\beta^*=0$ (i.e., if either the treatment model or the model for $E\left[Y_{g=\left\{\overline{A}(m-1),\underline{0}(m)\right\}}|\bar{L}(m),\bar{A}(m-1)\right]$ is correct). Thus $\widehat{\Delta}_{g,v}$ will converge to zero and $\widehat{\mathrm{E}}[Y_g]$ to $\widehat{\mathrm{E}}\left[Y_{g=\overline{0}_K}\right]$ even if the model for $f\left[l(k)|\bar{a}(k-1),\bar{l}(k-1)\right]$ is incorrect. We conclude that under the null, all we require for

valid inference is that the conditional exchangeability and consistency assumptions hold and we either know (as in a sequentially randomized experiment) $\Pr\left[A(m)=1|\overline{L}(m),\overline{A}(m-1)\right]$ or have a correct model for either $\Pr\left[A(m)=1|\overline{L}(m),\overline{A}(m-1)\right]$ or $E\left[Y_{g=\left\{\overline{A}(m-1),\underline{0}(m)\right\}}|\bar{L}(m),\bar{A}(m-1)\right]$.

Suppose that there is no effect modification by past covariate history, as with the SNMM

$$\gamma_m\left[\overline{a}\left(m-1\right),\overline{l}\left(m\right),\beta\right]=\beta_0+\beta_1 m+\beta_2 a\left(m-1\right)+\beta_3 a\left(m-2\right)+\beta_4 a\left(m-1\right)a\left(m-2\right) \tag{1.12}$$

Then we can write $\gamma_m\left[\overline{a}\left(m-1\right),\overline{l}\left(m\right),\beta\right]$ as $\gamma_m\left[\overline{a}\left(m-1\right),\beta\right]$. In that case to estimate $\mathrm{E}\left[Y_{g=(\overline{a})}\right]$ for any nondynamic regime $\overline{a}$, we do not need to use the above Monte Carlo algorithm to simulate the $L(k)$. Rather

$$\widehat{\mathrm{E}}\left[Y_{g=\overline{a}}\right]=\widehat{\mathrm{E}}\left[Y_{g=\overline{0}_K}\right]+\sum_{k=0}^{K}a(k)\gamma_k\left[\overline{a}\left(k-1\right),\widetilde{\beta}\right]$$

However, if one wants to estimate $\mathrm{E}\left[Y_g\right]$ for a dynamic regime, the previous Monte Carlo algorithm is required.

In fact, a SNMM is an MSM if and only if for all $\overline{a}\left(m-1\right),\overline{l}\left(m\right),\beta$

$$\gamma_m\left[\overline{a}\left(m-1\right),\overline{l}\left(m\right),\beta\right]=\gamma_m\left[\overline{a}\left(m-1\right),\beta\right] \tag{1.13}$$

Specifically it is a nondynamic MSM with the functional form

$$\mathrm{E}\left[Y_{g=\overline{a}}\right]=\eta_0^*+\sum_{k=0}^{K}a(k)\gamma_k\left[\overline{a}\left(k-1\right),\beta^*\right], \tag{1.14}$$

where $\mathrm{E}\left[Y_{g=\overline{0}_K}\right]=\eta_0^*$. However, such an SNMM model is not simply an MSM, because, in addition to (1.14), it also imposes the additional strong assumption (1.13) that effect modification by past covariate history is absent. In contrast, an MSM such as (1.14) is agnostic as to whether there is effect modification by time-varying covariates.

If we specify an SNMM that assumes (1.13), then we can estimate β^* either by g-estimation or IPTW. However the most efficient g-estimator will be more efficient than the most efficient IPTW estimator when the SNMM (and thus the MSM) is correctly specified, because g-estimation uses the additional assumption of no effect modification by past covariates to increase efficiency.

In contrast, suppose the MSM (1.14) is correct but the SNMM (1.12) is incorrect because assumption (1.13) does not hold. Then the g-estimates of β^* and $\mathrm{E}\left[Y_{g=(\overline{a})}\right]$ will be biased, while the IPTW estimates remain unbiased. Thus we have a classic variance-bias trade off. Given the MSM (1.14), g-estimation can increase efficiency if (1.13) is correct, but introduces bias if (1.13) is incorrect.

1.5.3 Time-varying instrumental variables and g-estimation.

Suppose at each week m we obtain data both on whether a drug treatment of interest was prescribed by a subject's physician as well as data on whether the subject actually took the drug, say based on a blood test. We assume both variables are binary and let $A_p\left(m\right)$ and $A_d\left(m\right)$ respectively denote the treatment prescribed and taken in week m. We define $A\left(m\right)=\left[A_p\left(m\right),A_d\left(m\right)\right]$. Now in many settings it might be reasonable to assume that we had conditional exchangeability with respect to the prescribed treatment but not with respect to the actual treatment, because the covariates influencing a physician's prescriptions have been recorded in the medical record, while the reasons a given patient does or does not comply with his his physician's advice may depend on unmeasured patient characteristics that also directly affect the outcome Y. Thus we only assume for all $\bar{a}$

$$Y_{\bar{a}}\amalg A_p(t)|\bar{A}(t-1)=\bar{a}(t-1),\bar{L}(t)=\bar{l}(t) \tag{1.15}$$

If we had (joint) conditional exchangeability for both $A_p(m)$ and $A_d(m)$, the SNMM (1.7) would be precisely equivalent to the SNMM

$$\begin{aligned}&\mathrm{E}\left[Y_{g=\{\overline{a}(m-1),a(m),\underline{0}(m+1)\}}|\overline{L}_{g=\{\overline{a}(m-1)\}}\left(m\right)=\overline{l}\left(m\right),\overline{A}(m\ )=\overline{a}\left(m\ \right)\right] \qquad (1.16)\\ &=\mathrm{E}\left[Y_{g=\{\overline{a}(m-1),\underline{0}(m)\}}|\overline{L}_{g=\{\overline{a}(m-1)\}}\left(m\right)=\overline{l}\left(m\right),\overline{A}(m\ )=\overline{a}\left(m\right)\right]+a(m)\gamma_m\left[\overline{a}\left(m-1\right),\overline{l}\left(m\right),\beta^*\right]\end{aligned}$$

that adds $A(m)=a(m)$ to the conditioning event on both sides of equation (1.7). However, when only conditional exchangeability (1.15) for $A_p(m)$ holds, the two models differ. It is only model (1.16) whose parameters can remain identified under the sole restriction (1.15). Specifically, given SNMM (1.16), we can estimate the parameter β^* by g-estimation as described above except now we replace the models for $\text{logit}\Pr\left[A(m)=1|\overline{L}(m),\overline{A}(m-1)\right]$ and $\text{logit}\Pr\left[A(m)=1|\overline{L}(m),\overline{A}(m-1),Y_m\left(\beta\right)\right]$ with models for $\text{logit}\Pr\left[A_p(m)=1|\overline{L}(m),\overline{A}(m-1)\right]$ and $\text{logit}\Pr\left[A_p(m)=1|\overline{L}(m),\overline{A}(m-1),Y_m\left(\beta\right)\right]$. This choice reflects the fact that it is only $A_p(m)$ that is conditionally independent of the counterfactuals given $\left[\overline{L}(m),\overline{A}(m-1)\right]$, and thus only $A_p(m)$ that can be used as the outcome variable in g-estimation.

We might also wish to assume that the prescribed dose has no direct effect on the response Y except through the actual dose, i.e., the counterfactual outcome $Y_{\bar{a}}=Y_{\bar{a}_p,\overline{a}_d}$ only depends on $\overline{a}_d$. In that case we can simply write $Y_{\bar{a}}$ as $Y_{\overline{a}_d}$. This assumption is referred to as the exclusion restriction for $\bar{a}_p$ relative to the effect of $\overline{a}_d$ on Y. A variable such as $\bar{a}_p$ that satisfies (1.15) and the exclusion restriction relative to the effect of $\overline{a}_d$ on Y is said to be a time-dependent instrumental variable for the effect of treatment $\overline{a}_d$ on Y. In that case we can replace $a(m)\gamma_m\left[\overline{a}\left(m-1\right),\overline{l}\left(m\right),\beta^*\right]$ by $a_d(m)\gamma_m\left[\overline{a}\left(m-1\right),\overline{l}\left(m\right),\beta^*\right]$. However, when conditional exchangeability with respect to the actual treatment $A_d\left(m\right)$ does not hold, $A_p\left(m\right)$ can still be a non-causal effect modifier;; as a consequence, we cannot replace $a(m)\gamma_m\left[\overline{a}\left(m-1\right),\overline{l}\left(m\right),\beta^*\right]$ by $a_d(m)\gamma_m\left[\overline{a}_d\left(m-1\right),\overline{l}\left(m\right),\beta^*\right]$. In fact $A_p\left(m\right)$ can still be a non-causal effect modifier even if $\bar{a}_p$ satisfies the stronger exclusion restriction of no direct effect of $\bar{a}_p$ on either Y or $\overline{L}$ (except through actual dose $\overline{a}_d$) so both $Y_{\bar{a}}$ and $\overline{L}_{\overline{a}}$ only depend on $\overline{a}_d$. For example, in the SNMM

$$a(m)\gamma_m\left[\overline{a}\left(m-1\right),\overline{l}\left(m\right),\beta^*\right]=a_d(m)\left[\beta_0^*+\beta_1^*a_p\left(m-1\right)+\beta_2^{*T}a_p\left(m-1\right)l\left(m\right)\right]$$

it may still be the case that neither β_1^* nor β_2^{*T} are zero (Hernán and Robins, 2006b).

Furthermore when conditional exchangeability with respect to the actual treatment $A_d\left(m\right)$ does not hold, although the sample average of $Y_0\left(\widetilde{\beta}\right)$ still is consistent for $\mathrm{E}\left[Y_{g=\overline{0}_K}\right]$, it is not possible to consistently estimate $\mathrm{E}\left[Y_g\right]$ for any other regime g, static or dynamic, without further untestable assumptions such as those in theorems 8.8 and 8.10 of Robins, Rotnitzky, and Scharfstein (1999) and in Section 7 of Robins (2004).

1.5.4 Dynamic and general SNMMs and MSMs

Both MSMs and SNMMs are models for nondynamic regimes. Henceforth we shall refer to them as nondynamic MSMs and SNMMs. With the aid of a model for $f\left[l(k)|\bar{a}(k-1),\bar{l}(k-1)\right]$ and Monte Carlo simulation, we have seen that nondynamic SNMMs can be used to estimate $\mathrm{E}\left[Y_g\right]$ for any regime, static or dynamic. Analogously, Robins (1999) shows that with the aid of a model for particular aspects of $f\left[y|\bar{a}(K),\bar{l}(K)\right]\prod_{l=0}^{K}f\left[l(k)|\bar{a}(k-1),\bar{l}(k-1)\right]$ and simulation, nondynamic MSMs can also be used to estimate the mean $\mathrm{E}\left[Y_g\right]$ of any dynamic regime. However, for nondynamic MSMs, this calculation is exceedingly difficult, requiring, as an intermediate step, that one solve many integral equations.

Modified versions of both SNMMs and MSMs, which we shall refer to as dynamic-regime SNMMs and MSMs, can be used to directly estimate the means $\mathrm{E}\left[Y_g\right]$ of dynamic regimes

without requiring the aid of alternative models or simulation. A special case of a dynamic SNMM was considered by Murphy (2003). Robins (2004) built upon her work and introduced a comprehensive class of dynamic SNMM. A simple dynamic MSM comparing two regimes was considered by Hernán et al (2006). Dynamic MSMs in full generality were first introduced by Orellana et al (2006) and, shortly thereafter, independently by van der Laan et al (2006). Both built on earlier work by Robins (1993) and Murphy, van der Laan, and Robins (2001).

For pedagogic purposes, we shall be ahistorical and first discuss dynamic MSMs.

Dynamic and general MSMs

We begin with a simplified version of an example considered by Orellana et al (2006). We consider an observational study of treatment-naive subjects recently infected with HIV. Subjects return to clinic weekly to have various clinical and laboratory measurements made. Let $L(t)$ be the vector of measurements made at week t including CD4 cell count. We let $A(t)$ denote the indicator of whether antiretroviral therapy is taken during week t. For simplicity we assume that once antiretroviral therapy is begun, it is never stopped. Let Y be a composite health outcome measured at the end of the study at time $K+1$, higher values of which are preferable. Let $g = x$ denote the dynamic regime "begin antiretroviral therapy the first time t the measured CD4 count falls below x," where x is measured in whole numbers less than 1000. Let $\mathcal{X} = \{0, 1, ..., 999\}$. Then $\{g = x; x \in \mathcal{X}\}$ denotes the set of all such regimes. Consider the dynamic regime MSM

$$\mathrm{E}\left[Y_{g=x}|V\right] = h\left(x, V, \beta^*\right) \tag{1.17}$$

for the conditional mean of the counterfactual $Y_{g=x}$ given a subset V of the baseline covariates $L(0)$ where

$$h\left(x, V, \beta\right) = h_1\left(x, V, \beta_1\right) + h_2\left(V, \beta_2\right), \tag{1.18}$$

$$h_1\left(x, V, 0\right) = 0 \tag{1.19}$$

so $\beta_1^* = 0$ is the null hypothesis that all regimes in $\{g = x; x \in \mathcal{X}\}$ have the same mean given V.

As an example, for V binary, we might choose $h_1\left(x, V, \beta_1\right) = \beta_1^T r\left(x, v\right)$ where $\beta_1^T r\left(x, v\right) = \beta_{1,1}\left(x - 350\right) + \beta_{1,2}\left(x - 350\right)^2 + \beta_{1,3}\left(x - 350\right)^3 + \beta_{1,4}\left(x - 350\right) V$

and $h_2\left(V, \beta_2\right) = \beta_{2,1} + \beta_{2,2} V$. Before describing how β^* can be estimated using standard weighted least squares software, we require the following observations.

Consider a subject who started antiretroviral therapy at a CD4 cell count of 250 in week t whose lowest prior CD4 count was 300. Then this subject's observed data was consistent with having followed regime $g = x$ for $x = 251, 252, ..., 300$. In fact the subject followed all of these regimes. Consider a subject who never started therapy and whose lowest CD4 count was 225. Then this subject followed regimes $g = x$ for $x = 0, 1, \ ..., 225$. Finally consider a subject who started antiretroviral therapy at a CD4 cell count of 250 in week t whose lowest previous CD4 counts was less than 250. Then this subject failed to follow any regime in the set $\{g = x; x \in \mathcal{X}\}$. In contrast, for the nondynamic MSM $\mathrm{E}\left[Y_{\overline{a}}|V\right] = h\left(\overline{a}, V, \beta^*\right)$, each subject follows one and only one of the regimes whose means are being modelled—the regime $\overline{a}$ corresponding to the subject's actual treatment history $\overline{A}$. It is this difference that makes estimation of a dynamic MSM a bit more involved than estimation of a nondynamic MSM.

We are now ready to describe our fitting procedure. Let Γ_i be the number of regimes followed by subject i. We create an artificial data set of size $\Gamma = \sum_{i=1}^{N} \Gamma_i$, with each subject i, for $i = 1, ..., N$, contributing Γ_i artificial observations $\left(Y_i, V_i, x_{i1}\right), \left(Y_i, V_i, x_{i2}\right), ..., \left(Y_i, V_i, x_{i\Gamma_i}\right)$, where the x_{ik} denote the regimes followed by subject i. We then fit by weighted least squares

with an independence working covariance matrix the regression model

$$\mathrm{E}\left[Y|x,V\right]=h\left(x,V,\gamma\right)$$

to the artificial data set using estimates of the weights

$$SW\left(x,V\right)=\prod_{k=0}^{K}\frac{f^{*}\left[x|V\right]}{f\left[A(k)|\bar{A}(k-1),\bar{L}(k)\right]}$$

where $f^{*}\left[x|V\right]$ is any density for x given V. For example, it could be an estimate of the density of x given V based on the artificial data set. Orellana et al (2006) show that this IPTW estimator, say, $\widehat{\beta}$, of γ based on the artificial data set converges to the parameter β^{*} of our dynamic MSM under the strengthened identifiability conditions. Orellana et al (2006) also discuss how to construct more efficient estimators and doubly robust estimators. The optimal treatment regime in the class $\{g=x;x\in\mathcal{X}\}$ for a subject with $V=v$ is estimated as the value of x that maximizes $h\left(x,v,\widehat{\beta}\right)$ or, equivalently, $h_{1}\left(x,v,\widehat{\beta}_{1}\right)$ over $x\in\mathcal{X}$.

The general case can be treated using the same notation. Specifically, given any set of regimes $\{g=x;x\in\mathcal{X}\}$ (whether static, dynamic, or both) indexed by x taking values in a (possibly infinite) set X and an MSM (1.17) satisfying (1.18) and (1.19), we can proceed as above except now the index x need not be a real number and a different calculation will be required to determine which regimes in $\{g=x;x\in\mathcal{X}\}$ each study subject followed. For example, consider another HIV study, where now subjects may repeatedly start and stop therapy and we consider the regimes "take therapy at t if and only if the current white blood count exceeds w and a certain liver function test has value less than b." Here b and w are nonnegative integers in the range 0-10,000. Then $x=(w,b)$. An example of a choice for $h_{1}\left(x,V,\beta_{1}\right)$ is $\beta_{1,1}\left(b-100\right)+\beta_{1,2}\left(b-100\right)^{2}+\beta_{1,4}\left(w-1000\right)+\beta_{1,5}\left(w-1000\right)^{2}+\beta_{1,6}\left(b-100\right)V$

$+\beta_{1,7}\left(w-1000\right)V+\beta_{1,8}\left(w-1000\right)\left(b-100\right)$. Note that from the perspective presented in this paragraph, the general case includes nondynamic MSMs as a special case. Thus we henceforth refer to model (1.17) as a general MSM, subsuming all previous MSM categories. However, we have only discussed examples where the number of regimes followed by any subject is finite. Orellana et al (2006) extend these dynamic MSM methods to the case where that number is uncountable rather than finite.

MSMs and the positivity condition: Specifying a general MSM can also allow us to weaken positivity requirements. We say the positivity assumption holds for a regime g if, for all t,
$f_{\bar{A}(t-1),\bar{L}(t)}\left[\overline{g}_{t}(\bar{l}(t-1)),\bar{l}(t)\right]\neq0$ implies $f_{A(t)|\bar{A}(t-1),\bar{L}(t)}\left[g_{t}(\bar{l}(t))|\bar{a}(t-1),\overline{l}(t)\right]>0$. Then for any regime $g=x^{*}$ for which the positivity assumption fails, we simply remove any observation (Y,V,x^{*}) from the artificial data. We can then either interpret our MSM model as a model for $\mathrm{E}\left[Y_{g=x}|V\right],x\in\mathcal{X}_{pos}\subset\mathcal{X}$, where $x\in\mathcal{X}_{pos}$ if $g=x$ satisfies positivity, or as a model for $\mathrm{E}\left[Y_{g=x}|V\right],x\in\mathcal{X}$. In the latter case, one is identifying $\mathrm{E}\left[Y_{g=x^{*}}|V\right]$ for non-positive regimes $g=x^{*}$ by model-based extrapolation.

Semilinear MSMs: Recall that a SNMM was guaranteed to be correctly specified under the sharp null hypothesis of no treatment effect with true parameter value $\beta^{*}=0$; as a consequence, g-estimation of a SNMM always provides valid inferences in a sequentially randomized experiment when the sharp null holds. In contrast, the MSM (1.17) satisfying (1.18) and (1.19) is not guaranteed to be correctly specified under the sharp null, whenever V is not binary; under the sharp null, $Y_{g=x}=Y$, $\beta_{1}^{*}=0$ so $h_{1}\left(x,V,\beta_{1}^{*}\right)=0$, and thus the MSM reduces to $\mathrm{E}\left[Y|V\right]=h_{2}\left(V,\beta_{2}\right)$. But the assumed functional form $h_{2}\left(V,\beta_{2}\right)$ may be incorrect. Furthermore, the IPTW estimates of β_{2} and β_{1} are generally correlated. Thus mispecification of the functional form $h_{2}\left(V,\beta_{2}\right)$ can result in invalid inferences in a sequentially randomized experiment, even under the sharp null. To overcome this difficulty, we

follow Robins (1999) and consider the semilinear general MSM

$$\mathrm{E}\left[Y_{g=x}|V\right] = h_1\left(x, V, \beta_1^*\right) + h_2^*\left(V\right)$$

with $h_2^*\left(V\right)$ allowed to be an arbitrary unknown function, so as to prevent bias in the estimation of $h_1\left(x, V, \beta_1^*\right)$ from misspecification of a parametric model for $h_2^*\left(V\right)$. The estimator $\widetilde{\beta}_1$that sets to zero the sample average of $SW\left(x, V\right)\left\{Y - h_1\left(x, V, \beta_1^*\right)\right\}\left\{q\left(x, V\right) - \int q\left(x, V\right) dF^*\left[x|V\right]\right\}$ over the Γ artificial data vectors $\left(Y, V, x\right)$ can be shown to be a consistent asymptotically normal estimator of β_1^* when the model $h_1\left(x, V, \beta_1^*\right)$ is correct, guaranteeing valid inferences in a sequentially randomized experiment. Robins (1998, 1999) proved this result for nondynamic MSMs and Orellana et al (2006)show it for general MSMs. Orellana et al (2006) also construct locally efficient doubly robust estimators of β_1^* in semilinear general MSMs.

In fact when $h_1\left(x, V, \beta_1\right) = \beta_1^T r\left(x, V\right)$ is linear in β_1, it is simple to trick standard weighted least squares software into computing a CAN estimator of β_1^*. Specifically, we consider the model $h\left(x, V; \beta\right) = \beta_1^T r\left(x, V\right) + h_2\left(V; \beta_2\right)$ with $h_2\left(V; \beta_2\right) = \beta_2^T R$, where $R = \sum_x r\left(x, V\right) f^*\left(x|V\right)$. Then first component $\widehat{\beta}_1$ of the aforementioned weighted least squares estimator $\widehat{\beta} = \left(\widehat{\beta}_1, \widehat{\beta}_2\right)$ with estimated weights $\widehat{SW}\left(x, V\right) = \prod_{k=0}^{K} \frac{f^*\left[x|V\right]}{f\left[A(k)|\bar{A}(k-1), \bar{L}(k); \widehat{\alpha}\right]}$ applied to the artificial data is a CAN estimator of β_1^* when the model $\alpha^T W\left(k\right)$ for $logit\left\{pr\left[A(k) = 1|\bar{A}(k-1), \bar{L}(k)\right]\right\}$ is correct even when the model $h_2\left(V; \beta_2\right) = \beta_2^T R$ for $h_2^*\left(V\right)$ is incorrect.

In summary, following Robins (1999), we suggest, when possible, semilinear general MSMs be substituted for general MSMs.

General SNMMs and optimal regime SNMMs

In this section, for reasons discussed below, we need to explicitly consider regimes g in which the treatment $g_m\left[\overline{a}\left(m-1\right), \overline{l}\left(m\right)\right]$ specified by the regime g at time m is allowed to depend on both past treatment history and past covariate history. Suppose we are interested in a particular such regime g^*. Then we define a g^*-SNMM to be a model for the effect of treatment $a(m)$ versus treatment 0 at each time m (as a function of treatment and covariate history up to m) when treatment g^* is followed beginning at time $m+1$. Let $Y_{g=\left\{\overline{a}(m-1), a(m), \underline{g}^*(m+1)\right\}}$ be the outcome Y under the regime that follows the nondynamic regime $\left(\overline{a}\left(m-1\right), a\left(m\right)\right)$ through week (time) m and then the regime g^* from $m+1$. Then a g^*-SNMM is defined exactly like the SNMM (1.7), except that $Y_{g=\left\{\overline{a}(m-1), a(m), \underline{g}^*(m+1)\right\}}$ replaces $Y_{g=\{\overline{a}(m-1), a(m), \underline{0}(m+1)\}}$ and $Y_{g=\left\{\overline{a}(m-1), \underline{g}^*(m)\right\}}$ replaces $Y_{g=\{\overline{a}(m-1), \underline{0}(m)\}}$. Also we write the known function $\gamma_m\left[\overline{a}\left(m-1\right), \overline{l}\left(m\right), \beta\right]$ as $\gamma_m^{g^*}\left[\overline{a}\left(m-1\right), \overline{l}\left(m\right), \beta\right]$ to remind us we are now estimating a g^*-SNMM for a given regime g^*. Note that a g^*-SNMM with g^* the regime where treatment is always withheld is precisely the SNMM (1.7).

To estimate the parameter β^* of $\gamma_m^{g^*}\left[\overline{a}\left(m-1\right), \overline{l}\left(m\right), \beta^*\right]$, we use g-estimation as described previously except we redefine $Y_m\left(\beta\right)$ to be

$$Y_m\left(\beta\right) = Y + \sum_{j=m}^{K}\left\{g_j^*\left[\overline{A}\left(j-1\right), \overline{L}\left(j\right)\right] - A(j)\right\}\gamma_j^{g^*}\left[\overline{A}\left(j-1\right), \overline{L}\left(j\right), \beta\right] \tag{1.20}$$

Again we can motivate this modification by considering a locally rank preserving version of the model. We say a g^*-SNMM model is locally rank preserving if $Y_{g=\left\{\overline{a}(m-1), \underline{g}^*(m)\right\}} = Y_{g=\left\{\overline{a}(m), \underline{g}^*(m+1)\right\}} - a\left(m\right)\gamma_m^{g^*}\left[\overline{a}\left(m-1\right), \overline{l}\left(m\right), \beta\right]$ with probability one for each m. In that case $Y_m\left(\beta^*\right) = Y_{g=\left\{\overline{A}(m-1), \underline{g}^*(m)\right\}}$ and in particular $Y_0\left(\beta^*\right) = Y_{g*}$. This reflects the fact that at each time $j \geq m$, $Y_m\left(\beta^*\right)$ subtracts from the subject's observed Y the effect

$A(j)\gamma_j^{g^*}\left[\overline{A}(j-1),\overline{L}(j),\beta^*\right]$ of the subject's observed treatment $A(j)$ and replaces it with the effect $g_j^*\left[\overline{A}(j-1),\overline{L}(j)\right]\gamma_j^{g^*}\left[\overline{A}(j-1),\overline{L}(j),\beta^*\right]$ of the treatment $g_j^*\left[\overline{A}(j-1),\overline{L}(j)\right]$ that the subject would have had at j had, possibly contrary to fact, she began to follow regime g^* at time j.

Now, even in the absence of local rank preservation, it can be proved that, in the absence of model mispecification, under the strengthened identifiability conditions, (i) the g-estimate $\widehat{\beta}$, now based on (1.20), is consistent for the parameter β^* of $\gamma_m^{g^*}\left[\overline{a}(m-1),\overline{l}(m),\beta^*\right]$, (ii) the sample average $\widehat{\mathrm{E}}[Y_{g^*}]=N^{-1}\sum_{i=1}^{N}Y_{0,i}\left(\widehat{\beta}\right)$ of $Y_0\left(\widehat{\beta}\right)$ is consistent for $\mathrm{E}[Y_{g*}]$, and (iii), for any other regime g, $\widehat{\mathrm{E}}[Y_g]=\widehat{\mathrm{E}}[Y_{g^*}]+\sum_{v=1}^{v=V}\widehat{\Delta}_{g,v}^{g^*}/V$ is consistent for $\widehat{\mathrm{E}}[Y_g]$ as $V\to\infty$, where $\widehat{\Delta}_{g,v}^{g^*}$ is defined exactly like $\widehat{\Delta}_{g,v}$ above except that $a_v(j)\gamma_j\left[\overline{a}_v(j-1),\overline{l}_v(j),\widehat{\beta}\right]$ $a_v(j)\gamma_j\left[\overline{a}_v(j-1),\overline{l}_v(j),\widehat{\beta}\right]$ is replaced by $\left[a_v(j)-g_j^*\left(\overline{a}_v(j-1),\overline{l}_v(j)\right)\right]\gamma_j^{g^*}\left[\overline{a}_v(j-1),\overline{l}_v(j),\widehat{\beta}\right]$ with $\widehat{\beta}$ based on (1.20). When $\gamma_j^{g^*}\left[\overline{A}(j-1),\overline{L}(j),\beta\right]=\beta^T R_m$, we have the closed form expression

$$\widehat{\beta}=\left\{\sum_{i=1,m=0}^{i=N,m=K}\left\{A_i(m)-g_m^*\left(\overline{A}_i(m-1),\overline{L}_i(m)\right)\right\}X_{im}(\widehat{\alpha})Q_{im}S_{im}^T\right\}^{-1}\left\{\sum_{i=1,m=0}^{i=N,m=K}Y_iX_{im}(\widehat{\alpha})Q_{im}\right\} \tag{1.21}$$

Optimal regime SNMMs: A primary use of g^*-SNMMs is in attempting to estimate the optimal treatment strategy g^{opt} that maximizes $\mathrm{E}[Y_g]$ over all treatment regimes g, including nondynamic and dynamic regimes in which treatment depends on past covariate history alone, and dynamic regimes in which treatment depends on past covariate and treatment history. To do so we specify an optimal treatment SNMM, g_{opt}-SNMM, based on a function $\gamma_m^{g_{opt}}\left[\overline{a}(m-1),\overline{l}(m),\beta\right]$. As an example we might specify that

$$\begin{aligned}&\gamma_m^{g_{opt}}\left[\overline{a}(m-1),\overline{l}(m),\beta\right] \\ &=\beta_0+\beta_1 m+\beta_2 a(m-1)+\beta_3^T l(m)+\beta_4^T l(m)a(m-1)+\beta_5^T l(m-1)+\beta_6^T l(m-1)a(m-1)\end{aligned} \tag{1.22}$$

If the g_{opt}-SNMM were correctly specified and we knew the true β^*, then we would know the optimal treatment regime. Specifically, the optimal treatment $g_{opt,m}\left[\overline{a}(m-1),\overline{l}(m)\right]$ at time m given past treatment and covariate history $\left[\overline{a}(m-1),\overline{l}(m)\right]$ is to take treatment if and only if $\gamma_m^{g_{opt}}\left[\overline{a}(m-1),\overline{l}(m),\beta^*\right]$ exceeds zero. That is $g_{opt,m}\left[\overline{a}(m-1),\overline{l}(m)\right]=I\left(\gamma_m^{g_{opt}}\left[\overline{a}(m-1),\overline{l}(m),\beta\right]>0\right)$ where $I(B)=1$ if B holds and is zero otherwise.

To understand heuristically why this is the case, assume a locally rank preserving model and suppose at the very last treatment time K, a subject has past history $\overline{a}(K-1),\overline{l}(K)$. If the subject does not take treatment at K, her outcome will be $Y_{g=\{\overline{a}(K-1),0_K\}}$ while if she takes treatment it will be $Y_{g=\{\overline{a}(K-1),1_K\}}$. Now, according to a locally rank preserving g_{opt}-SNMM, $Y_{g=\{\overline{a}(K-1),0_K\}}=Y_{g=\{\overline{a}(K-1),1_K\}}-\gamma_K^{g_{opt}}\left[\overline{a}(K-1),\overline{l}(K),\beta^*\right]$. Since high values of Y are desirable the optimal treatment choice is to take treatment if and only if $\gamma_K^{g_{opt}}\left[\overline{a}(K-1),\overline{l}(K),\beta^*\right]$ exceeds zero. (If $\gamma_K^{g_{opt}}\left[\overline{a}(K-1),\overline{l}(K),\beta^*\right]$ is precisely zero, it does not matter whether treatment is taken; in such cases, we choose not to treat simply to break the "tie.") Now we continue by backward induction. Specifically, suppose we know the optimal regime from $m+1$ onwards. Consider a subject at time m with past history $\overline{a}(m-1),\overline{l}(m)$. Such a subject will follow the known optimal regime from $m+1$ onwards. But she must decide what treatment to take at m. If she does not take treatment at m, her outcome will be $Y_{g=\left\{\overline{a}(m-1),0,\underline{g}_{opt}(m+1)\right\}}$ while if she takes treatment at m, her outcome

will be $Y_{g=\left\{\overline{a}(m-1),1,\underline{g}_{opt}(m+1)\right\}}$. But according to the model, $Y_{g=\left\{\overline{a}(m-1),0,\underline{g}_{opt}(m+1)\right\}} = Y_{g=\left\{\overline{a}(m-1),1,\underline{g}_{opt}(m+1)\right\}} - \gamma_m^{g_{opt}}\left[\overline{a}\left(m-1\right),\overline{l}\left(m\right),\beta^*\right]$ so she should take treatment if and only if $\gamma_m^{g_{opt}}\left[\overline{a}\left(m-1\right),\overline{l}\left(m\right),\beta^*\right]$ exceeds zero. Even in the absence of local rank preservation, it can be proved that under the strengthened exchangeability conditions, the optimal decision is to treat if and only if $\gamma_m^{g_{opt}}\left[\overline{a}\left(m-1\right),\overline{l}\left(m\right),\beta^*\right]$ exceeds zero.

Now if we knew $\gamma_m^{g_{opt}}\left[\overline{a}\left(m-1\right),\overline{l}\left(m\right),\beta^*\right]$ and thus we knew the optimal regime, we would simply have each subject in the population follow the optimal regime beginning at time 0, where at each time m the covariates $L(m)$ must be measured and recorded, so the evolving covariate data necessary to follow the optimal regime will be available.

Thus it only remains to estimate β^* by g-estimation based on eq. (1.20) in order to obtain an estimate $\widehat{g}_{opt,m}\left[\overline{a}\left(m-1\right),\overline{l}\left(m\right)\right] = I\left(\gamma_m^{g_{opt}}\left[\overline{a}\left(m-1\right),\overline{l}\left(m\right),\widehat{\beta}\right]>0\right)$ of the optimal regime and an estimate $\widehat{\mathrm{E}}\left[Y_{g_{opt}}\right] = N^{-1}\sum_{i=1}^{N} Y_{0,i}\left(\widehat{\beta}\right)$ of the mean $\mathrm{E}\left[Y_{g_{opt}}\right]$ of Y when the population is treated optimally. When specialized to the regime g_{opt}, eq. (1.20) becomes

$$
\begin{aligned}
Y_m\left(\beta\right) &= Y + \sum_{j=m}^{K}\left\{g_{opt,j}\left(\overline{A}\left(j-1\right),\overline{L}\left(j\right)\right) - A(j)\right\}\gamma_j^{g_{opt}}\left[\overline{A}\left(j-1\right),\overline{L}\left(j\right),\beta\right] \qquad (1.23)\\
&= Y + \sum_{j=m}^{K}\left[I\left\{\gamma_j^{g_{opt}}\left[\overline{A}\left(j-1\right),\overline{L}\left(j\right),\beta\right]>0\right\} - A(j)\right]\gamma_j^{g_{opt}}\left[\overline{A}\left(j-1\right),\overline{L}\left(j\right),\beta\right]
\end{aligned}
$$

that differs from earlier in that the regime g_{opt} itself is a function of the parameter β and thus unknown. Nonetheless one can use g-estimation based on $Y_m\left(\beta\right)$ to estimate β and set confidence intervals by searching over a grid of β values. However when the dimension of β is moderate so that finding $\widehat{\beta}$ by search is computationally prohibitive, there is no longer an explicit closed form expression for the g-estimate $\widehat{\beta}$ based on (1.23), even when $\gamma_m^{g_{opt}}\left[\overline{a}\left(m-1\right),\overline{l}\left(m\right),\beta\ \right]$ is linear in β, because β now occurs within an indicator function. In fact the g-estimate $\widehat{\beta}$ is exceedingly difficult to compute. However, the following different, computationally tractable, approach can be used when $\gamma_m^{g_{opt}}\left[\overline{A}\left(m-1\right),\overline{L}\left(m\right),\beta\right]$ is linear in β, i.e., $\gamma_m^{g_{opt}}\left[\overline{A}\left(m-1\right),\overline{L}\left(m\right),\beta\right] = R_m^T\beta$, where R_m is a known vector function of $\left\{\overline{A}\left(m-1\right),\overline{L}\left(m\right)\right\}$.

A closed form estimator of the optimal regime: Suppose for the moment that $\gamma_m^{g_{opt}}\left[\overline{a}\left(m-1\right),\overline{l}\left(m\right),\beta\right] = R_m^T\beta_m$ is linear in β and has a separate variation independent parameter vector at each time m, so $\beta^T = \left(\beta_0^T,...,\beta_K^T\right)$. Define $P_m\left(\widehat{\alpha}\right) = \mathrm{expit}\left(\widehat{\alpha}^T W\left(k\right)\right)$ to be the estimate of $\Pr\left[A(m)=1|\overline{L}(m),\overline{A}(m-1)\right]$ based on the fit of the model (1.8). Specify a working model $\varsigma_m^T D_m = \varsigma_m^T d_m\left[\bar{L}(m),\bar{A}(m-1)\right]$ for $\mathrm{E}\left[Y_m\left(\beta^*\right)|\bar{L}(m),\bar{A}(m-1)\right]$. Now, beginning with β_K, we recursively obtain the closed form doubly robust estimates $\widetilde{\beta}_m$ of the β_m, with $\left(\widetilde{\beta}_m,\widetilde{\eta}_m,\widetilde{\varsigma}_m\right)$ the OLS estimator of $(\beta_m,\eta_m,\varsigma_m)$ in the regression model $Y_{m+1}\left(\underline{\widetilde{\beta}}_{m+1}\right) = A\left(m\right)R_m^T\beta_m + P_m\left(\widehat{\alpha}\right)R_m^T\eta_m + D_m^T\varsigma_m + \epsilon$. Here $Y_{K+1}\left(\underline{\widetilde{\beta}}_{K+1}\right) = Y$ and $Y_{m+1}\left(\underline{\widetilde{\beta}}_{m+1}\right) = Y + \sum_{j=m+1}^{K}\left[I\left\{R_j^T\widetilde{\beta}_j>0\right\} - A(j)\right]R_j^T\widetilde{\beta}_j$. The $\widetilde{\beta}_m$ are CAN for the β_m^* if either all the models $\varsigma_m^T D_m$ are correct or the model (1.8) is correct

Remark: The $\widetilde{\beta}_m$ are possibly inefficient members of the following general class of estimators: beginning with $m=K$, we recursively obtain consistent closed form estimates

$\widetilde{\beta}_m(\mathbf{s},\mathbf{q})$ of the β_m, indexed by vectors of functions

$$\widetilde{\beta}_m(\mathbf{s},\mathbf{q}) = \left[\sum_{i=1}^{i=N} A_i(m)\, X_{im}(\widehat{\alpha})\, Q_{im} R_{im}^T\right]^{-1} \left[\sum_{i=1}^{i=N} \left\{Y_{m+1}\left(\underline{\widetilde{\beta}}_{m+1}\right)_j - S_{im}\right\} X_{im}(\widehat{\alpha})\, Q_{im}\right] \tag{1.24}$$

where, $\sum_{j=K+1}^{K}$ is defined to be 0, $X_m(\widehat{\alpha}) = \left\{A(m) - \widehat{P}_m(\widehat{\alpha})\right\} W_m$, and the choice of the $S_m = s_m\left(\bar{L}(m), \bar{A}(m-1)\right)$ and $Q_m = q_m\left[\bar{L}(m), \bar{A}(m-1)\right]$ affect efficiency but not consistency when the model (1.8) is correct.

Now suppose in our g_{opt}-SNMM the same parameter vector β applies to each time m. To be concrete, consider the g_{opt}-SNMM (1.22). In that case, we first estimate a bigger model that has a separate variation-independent parameter vector β_m at each time m; model (1.22) is then the submodel that imposes $\beta_m = \beta$ for all m. Let $\widetilde{\Omega}^{-1}$ be a nonparametric bootstrap estimate of the covariance matrix of $\left(\widetilde{\beta}_0, ..., \widetilde{\beta}_K\right)$. We then estimate β by an inverse covariance weighted average $\widehat{\beta} = 1_{K+1}^T \widetilde{\Omega}^{-1} \left(\widetilde{\beta}_0, ..., \widetilde{\beta}_K\right)^T / \left(1_{K+1}^T \widetilde{\Omega}^{-1} 1_{K+1}\right)$ of the $\widetilde{\beta}_m$, where 1_{K+1} is a $K+1$ vector with all components equal to 1.

Note that the g_{opt}-SNMM (1.22) is a non-saturated model. For example, it assumes the optimal regime does not depend on covariate values two weeks in the past or treatment values three weeks in the past, which may be incorrect. If the g_{opt}-SNMM is badly misspecified, then the estimated optimal regime $\widehat{g}_{opt,m}\left[\overline{a}(m-1), \overline{l}(m)\right]$ may be a poor estimate of the actual optimal regime. Because in realistic studies highly non-saturated g_{opt}-SNMM must be employed, misspecification can be a serious problem.

We note that in using a g_{opt}-SNMM to find the optimal regime, it was necessary for us to estimate the treatment strategy $g_{opt} = \left\{g_{opt,0}\left[\overline{l}(0)\right], g_{opt,0}\left[a(0), \overline{l}(1)\right], ..., g_{opt,K}\left[\overline{a}(K-1), \overline{l}(K)\right]\right\}$ that maximized $\mathrm{E}[Y_g]$ over all treatment regimes g, including regimes in which treatment depends on past treatment as well as covariate history. However, as discussed earlier, one can always construct a regime $g_{opt}^{\Delta} = \left\{g_{opt,0}^{\Delta}\left[\overline{l}(0)\right], g_{opt,0}^{\Delta}\left[\overline{l}(1)\right], ..., g_{opt,K}^{\Delta}\left[\overline{l}(K)\right]\right\}$ in which treatment depends only on past covariate history such that following regime g_{opt}^{Δ} from time 0 onwards is precisely equivalent to following g_{opt} from time 0. Nonetheless, it can be important to know g_{opt} rather than only g_{opt}^{Δ} as the following example shows. Suppose a (random) member of the source population has observed history $\left(\overline{A}(m-1), \overline{L}(m)\right) = \left(\overline{a}(m-1), \overline{l}(m)\right)$ (under standard care) that is not consistent with following the optimal regime g_{opt} and comes to our attention only at time m. We wish to intervene beginning at m and give the subject the optimal treatment strategy from time m onwards. Under the strengthened exchangeability conditions, the optimal treatment strategy for such a subject is $\left\{g_{opt,0}\left[a(m-1), \overline{l}(m)\right], ..., g_{opt,K}\left[\overline{a}(K-1), \overline{l}(K)\right]\right\}$. This strategy can be implemented only if we know (or have a good estimate of) g_{opt}; knowledge of g_{opt}^{Δ} does not suffice.

Finally we return to our hypothetical study of Section 1.4 in order to provide a worked example of optimal regime estimation.

Estimation of the optimal regime in our hypothetical study: We estimate the optimal regime twice. First we use a very intuitive approach that unfortunately does not generalize beyond our simple toy example. Second we use our closed form optimal regime estimator to estimate a saturated optimal regime SNMM.

An intuitive approach: By Eq. (1.23), $Y_1(\beta_1^*)$ is the value of Y had subjects followed their observed $A(0)$ and then followed the optimal regime at time 1. Since the subjects in rows 1 and 2 of Table 1.7 are exchangeable and their treatments only differ at time 1, it is immediate that the mean of $Y_1(\beta_1^*)$ for the subjects in rows 1 and 2 is the greater of 200 and 220. Arguing similarly for rows 3 and 4, 5 and 6, 7 and 8, we can immediately fill in

Table 1.7 *An intuitive approach to estimate the optimal regime*

$A(0)$	$L(1)$	$A(1)$	N	Y	$Y_1(\beta_1^*)$	$Y_0(\beta_1^*)$
0	1	0	2000	200	220	235
0	1	1	6000	220	220	235
0	0	0	6000	50	70	85
0	0	1	2000	70	70	85
1	1	0	3000	130	130	130
1	1	1	9000	110	130	130
1	0	0	3000	230	250	250
1	0	1	1000	250	250	250

the $Y_1(\beta_1^*)$ column in Table 1.7 without even explicitly estimating β_1^*. By comparing the $Y_1(\beta_1^*)$ column to the Y column in rows 5-8, we discover that if treatment was taken at time 0, it is optimal to take treatment at time 1 if and only if $L(1) = 0$. Comparing the $Y_1(\beta_1^*)$ and the Y columns in rows 1-4, we discover if treatment was not taken at time 0, it should be taken at time 1, regardless of $L(1)$. We conclude that the only remaining possibilities for g_{opt} are g_1 = "take treatment at time 0 and then take treatment at time 1 only if $L(1)$ is 0" and g_2 ="do not take treatment at time 0 but take treatment at time 1." Since subjects in rows 1-4 are exchangeable with those in rows 5-8 and $Y_1(\beta_1^*)$ equals Y_{g_2} for subjects in rows 1-4 and equals Y_{g_1} for subjects in rows 5-8, we can determine the optimal regime by comparing the mean of $Y_1(\beta_1^*)$ in rows 1-4 to that in rows 5-8. Now the mean in rows 1-4 is $220 \times \frac{8000}{16000} + 70 \times \frac{8000}{16000} = 145$ while that in rows 5-8 is $130 \times \frac{12000}{16000} + 250 \times \frac{4000}{16000} = 160$. We conclude that the regime g_1 is optimal and $\mathrm{E}\left[Y_{g_1}\right] = 160$. That 160 is the mean of Y_{g_1} can be confirmed using the g-computation algorithm, unstabilized IPTW or by using calculations based on the ordinary SNMM as in Section 1.4.

Closed form optimal regime estimator: We now repeat the analysis but this time using the closed form optimal regime estimator of a saturated optimal regime SNMM. By the model saturated and no baseline $L(0)$ in our example, we have with $K = 1$ $\gamma_1^{g_{opt}}\left[\overline{a}(0), \overline{l}(1), \beta^*\right] = \beta_{1,1}^* + \beta_{1,2}^* l(1) + \beta_{1,3}^* a(0) + \beta_{1,4}^* a(0) l(1)$ and $\gamma_0^{g_{opt}}\left[\overline{a}(-1), \overline{l}(0), \beta^*\right] = \beta_0^*$. We note that at the last time K, $\gamma_K^{g^*}\left[\overline{a}(0), \overline{l}(1), \beta^*\right]$ is the same for all g^*-SNMM so, with $K = 1$, $\beta_{1,1}^* = 20$, $\beta_{1,2}^* = \beta_{1,3}^* = 0$, $\beta_{1,4}^* = -40$ as in Section 1.4. [The reader can also verify that the OLS estimator of β_1^* described above also returns these values.] Thus $\gamma_1^{g_{opt}}\left[\overline{a}(0), \overline{l}(1), \beta^*\right]$ takes the 4 values $\gamma_1^{g_{opt}}(0,0) = \beta_{1,1}^* = 20$, $\gamma_1^{g_{opt}}(1,0) = \beta_{1,1}^* = 20$, $\gamma_1^{g_{opt}}(0,1) = \beta_{1,1}^* + \beta_{1,3}^* = 20$, $\gamma_1^{g_{opt}}(1,1) = \beta_{1,1}^* + \beta_{1,2}^* + \beta_{1,3}^* + \beta_{1,4}^* = -20$. Thus $g_{opt,1}\left[\overline{a}(0), \overline{l}(1)\right] = I\left(\gamma_1^{g_{opt}}\left[\overline{a}(0), \overline{l}(1), \beta^*\right] > 0\right)$ takes the 4 values

$$g_{opt,1}(0,0) = g_{opt,1}(0,1) = g_{opt,1}(1,0) = 1, g_{opt,1}(1,1) = 0 \tag{1.25}$$

Now $Y_1(\beta_1^*) = Y + \sum_{j=1}^{1}\left\{g_{opt,j}\left[\overline{A}(j-1), \overline{L}(j)\right] - A(j)\right\}\gamma_j^{g_{opt}}\left[\overline{A}(j-1), \overline{L}(j), \beta\right]$ so $Y_1(\beta_1^*) = Y$ if $g_{opt,1}\left[\overline{A}(0), \overline{L}(1)\right] = A(1)$.

Hence $Y_1(\beta_1^*) = Y$ if $\left[A(1) = 1 \text{ and } \left(\overline{A}(0), \overline{L}(1)\right) \neq (1,1)\right]$ or if $\left[A(1) = 0 \text{ and } \left(\overline{A}(0), \overline{L}(1)\right) = (1,1)\right]$.

If $\left(\overline{A}(0), \overline{L}(1)\right) = (1,1)$ and $A(1) = 1$, $Y_1(\beta_1^*) = Y - (-20) = Y + 20$.

If $\left(\overline{A}(0), \overline{L}(1)\right) \neq (1,1), A(1) = 0, Y_1(\beta_1^*) = Y + 20$.

Using the row-specific means of Y given in the table, we obtain again the same results for $Y_1(\beta_1^*)$ column as above. Next in order to estimate the parameter β_0^* of $\gamma_0^{g_{opt}}\left[\overline{a}(-1), \overline{l}(0), \beta_0^*\right]$ we fit by OLS the regression model $Y_1(\beta_1^*) = \beta_0 A(0) R_0 + \eta_0 P_0 R_0 + \epsilon$. with $R_0 = 1$ and $P_0 = pr\left[A(0) = 1\right] = 1/2$. That is we fit the model $Y_1(\beta_1^*) = \beta_0 A(0) + \nu_0 + \epsilon$ by OLS

where $\nu_0 = \eta_0/2$. The OLS estimate of β_0 is just the contrast $E\left[Y_1\left(\beta_1^*\right)|A\left(0\right)=1\right] - E\left[Y_1\left(\beta_1^*\right)|A\left(0\right)=0\right]$. Above we calculated the mean of $Y_1\left(\beta_1^*\right)$ to be 145 among subjects with $A\left(0\right) = 1$ (rows 1-4 of Table 1.7) and 160 among subjects with $A\left(0\right) = 0$ (rows 5-8). So $\beta_0^* = 15$. Hence, $g_{opt,0} = I\left(\gamma_0^{g_{opt}}\left[\overline{a}\left(-1\right), \overline{l}\left(0\right), \beta_0^*\right] > 0\right) = I\left(\beta_0^* > 0\right) = 1$. We conclude the optimal treatment $g_{opt,0} = 1$ at time 0 is to "take treatment." The optimal treatment at time 1 given that one followed the optimal treatment at time 0 is, by eq. (1.25), $g_{opt,1}\left(1,0\right) = 1$ if $l(1) = 0$ and $g_{opt,1}\left(1,1\right) = 0$ if $l(1) = 1$. Thus we again conclude the optimal regime is $g_1 =$"take treatment at time 0 and then take treatment at time 1 only if $L(1)$ is 0." Finally we compute $Y_0\left(\beta^*\right)$ for each subject by adding $\left[g_{opt,0} - A(0)\right]\gamma_0^{g_{opt}}\left[\overline{a}\left(-1\right), \overline{l}\left(0\right), \beta_0^*\right] = \left[1 - A(0)\right]15$ to $Y_1\left(\beta_1^*\right)$. As expected the mean of $Y_0\left(\beta^*\right)$ is the mean of $\mathrm{E}\left[Y_{g_1}\right] = 160$ in both rows 1-4 and rows 5-8.

1.6 Strengths and weaknesses

As mentioned previously, owing to the null paradox, methods based on the estimated g-formula should be avoided whenever the null hypothesis of no treatment effect has not yet been excluded.

MSMs have the advantage that they are easy to understand and easy to fit with standard off-the-shelf software that allows for weights. These two points explain their rapid adoption compared to SNMs. The usefulness of MSMs has been extended by the introduction of dynamic MSMs.

However IPTW estimation of MSMs have four drawbacks not shared by g-estimation of SNMs. First if the number of time periods is great the product in the denominator of the weights can become very small for some subjects who then receive inordinately large weights, leading both to bias when the weights must be estimated [and to so-called pseudo bias (Scharfstein et al, 1999) even when they are known] and to imprecision. Problems with large or even truly infinite weights (when positivity does not hold) can be somewhat ameliorated but not cured, by using bounded doubly robust estimators (Robins, Rotnitzky, and Sued, 2007), adjusting for baseline covariates and then using the covariates in the numerator of the weights, downweighting regimes $g = x$ associated with very small weights, using locally semiparametric efficient estimators or bounded influence estimators for non-saturated MSMs (as these estimators downweight regimes $g = x$ that result in excessively large weights in a near optimal fashion), and using diagnostics for the undue influence of large weights and for the consequences of truncating large weights (Wang et al, 2006). Second, MSMs cannot be used to estimate causal effects when treatment is confounded but an instrumental variable is available. Third, although not discussed in this chapter, sensitivity analysis models for MSMs are much more restrictive and less useful than those for SNMs. Fourth, SNMs, in contrast to MSMs, allow one to directly model interactions between treatment and evolving time dependent covariates and so to directly look for qualitative effect modification.

Disadvantages of SNMs compared with MSMs include:

(i) SNMs cannot be easily used to compare nondynamic regimes when there is effect modification by a time dependent covariate.

(ii) although SNMMs with a log link can be fit by g-estimation, logistic SNMMs cannot, making SNMMs difficult to use for non-rare dichotomous responses.

(iii) SNM models for failure time data have had to be based on accelerated failure time-like models that are difficult to fit in the presence of censoring because the objective function is non-smooth.

Problems (ii) and (iii) may soon be resolved. Richardson and Robins (2007) have recently developed methods for fitting risk ratio models to non-rare binary responses that can resolve problem (ii). An alternative approach is given in van der Laan, Hubbard, and Jewell (2007).

Page, Hernán, and Robins (2005) have developed cumulative incidence structural nested failure time models to solve problem (iii).

In terms of estimation of optimal regimes both MSMs and SNMs have their distinct place. General MSMs are excellent for estimating the optimal regime in any rather small prespecified classes of regimes (such as the optimal CD4 cell count at which to start therapy) that still may include all logistically feasible regimes, particularly in settings with resource constraints that preclude implementing complex regimes.

In contrast, the method of backward induction on which g-estimation of optimal regime SNMs is based, requires that the set of potential regimes from which the optimal is to be selected include all functions of an increasing (in time) amount of information (i.e., of an increasing sigma field). Thus, optimal regime SNMs are useful for estimating the optimal regime in the huge class of dynamic regimes in which treatment at each m can depend on any function of the entire measured past $\overline{l}(m), \overline{a}(m-1)$ (the case considered above) or, as described in Section 7 of Robins (2004) in the smaller, but still large, class in which treatment at each m can depend on any function of $\overline{w}(m), \overline{a}(m-1)$ where $W(m)$ is a subvector of the covariates in $L(m)$. Even if $W(m)$ is just CD4 cell count at m, it is possible that the optimal treatment decision at time m may be a complex function of CD4 cell counts at all past times. Such a regime, though optimal, may be logistically impossible to implement, in which case it may be necessary to choose among a smaller class of logistically feasible regimes by fitting a general MSM.

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1.7 Appendix: Causal directed acyclic graphs

We define a directed acyclic graph (DAG) G to be a graph whose nodes (vertices) are random variables $V = (V_1, \ldots, V_M)$ with directed edges (arrows) and no directed cycles. We use PA_m to denote the parents of V_m, i.e., the set of nodes from which there is a direct arrow into V_m. The variable V_j is a descendant of V_m if there is a sequence of nodes connected by edges between V_m and V_j such that, following the direction indicated by the arrows, one can reach V_j by starting at V_m. For example, consider the causal DAG in Figure 1b that represents the causal structure of an observational study with no unmeasured confounding or the effect of A on Y. In this DAG, $M = 4$ and we can choose $V_1 = U$, $V_2 = L$, $V_3 = A$, $V_4 = Y$; the parents PA_m of $V_4 = Y$ are (U, L, A) and the non-descendants of A are (U, L).

A causal DAG is a DAG in which 1) the lack of an arrow from node V_j to V_m can be interpreted as the absence of a direct causal effect of V_j on V_m (relative to the other variables on the graph), 2) all common causes, even if unmeasured, of any pair of variables on the graph are themselves on the graph. In Figure 1b, the lack of a direct arrow between U and A indicates that unmeasured factors U do not have a direct causal effect (causative or preventive) on the patient's treatment. Also, the inclusion of the measured variables (L, A, Y) implies that the causal DAG must also include the unmeasured common causes U. Note a causal DAG model makes no reference to and is agnostic as to the existence of counterfactuals.

Our causal DAGs are of no practical use unless we make some assumption linking the causal structure represented by the DAG to the statistical data obtained in an epidemiologic study, which we do through the causal Markov assumption. First some definitions that apply to any DAG, causal or not.

We say the data a DAG G represents the joint density of its node variables V if and only

if $f(v)$ satisfies the Markov factorization

$$f(v) = \prod_{j=1}^{M} f(v_j \mid pa_j) \ . \tag{1.26}$$

That is, the density $f(v)$ can be factorized as the product of the probability of each variable given its parents. This factorization is equivalent to the statement that the non-descendants of a given variable V_j are independent of V_j conditional on the parents of V_j.

The causal Markov assumption (CMA) states that the joint distribution of the variables on a causal graph satisfy the Markov factorization (1.26). Because of the causal meaning of parents and descendants on a causal DAG, the CMA is equivalent to the statement that, conditional on its direct causes (i.e., parents), a variable V is independent of any variable it does not cause (i.e., any non-descendant of V). The Markov factorization (1.26) logically implies additional statistical independencies and, specifically, it implies that a set of variables A is conditionally independent of another set of variables B given a third set of variables Z if A is d-separated from B given Z on the graph G, written $\left(A \coprod_{\text{d-sep}} B|Z\right)_G$, where d-separation, described below, is a statement about the topology of the graph. To check for unconditional (i.e., marginal) independence we make Z the empty set. In the following a path between A and B is any sequence of nodes and edges (where the direction of the arrows are ignored) that connects A to B. A variable C is a collider on a path between variables A and B if the edges on the path that meet at C both have arrows pointing at C.

Unconditional d-separation $\left(A \coprod_{\text{d-sep}} B\right)_G$: A variable A is d-separated from variable B on a DAG G if and only if all paths between them are blocked. The path is blocked if there is a collider on the path. If a path is not blocked, we say it is unblocked, active, or open, all of which are synonymous. We say a set of variables A is d-separated from a set of variables B if and only if each variable in A is d-separated from every variable in B. Thus $\left(A \coprod_{d-sep} B\right)_G$ if and only if every path from A to B is blocked. If even one path is unblocked, we write $(A \not\coprod_{d-sep} B)_G$.

Conditional d-separation $\left(A \coprod_{\text{d-sep}} B|Z\right)_G$: We say two variables A and B are d-separated given (or by) a set of variables $Z = (Z_1, \ldots, Z_k)$ if all paths between A and B are blocked where, when we condition on Z, a path between A and B is blocked if *(i)* there is any variable $Z_m \in Z$ on the path that is not a collider or *(ii)* there is a collider on the path such that neither the collider itself nor any of its descendants are in Z. A set of variables A is d-separated from a set of variables B given Z if and only if each variable in A is d-separated from every variable in B given Z.

The CMA allows one to deduce that d-separation implies statistical independence, but does not allow one to deduce that d-connection (i.e. the absence of d-separation) implies statistical dependence. However, d-connected variables will generally be independent only if there is an exact balancing of positive and negative causal effects. Because such precise fortuitous balancing of effects is highly unlikely to occur, we shall henceforth assume that d-connected variables are dependent. This is often referred to as the assumption of faithfulness or stability.

A causal DAG model that includes counterfactuals is a nonparametric structural equation model (NPSEM). First some notation. For any random variable W, let $\mathcal{W}$ denote the support (i.e., the set of possible values w) of W. For any $w_1, \ldots, w_m$, define $\overline{w}_m = (w_1, \ldots, w_m)$. Let R denote any subset of variables in V and let r be a value of R. Then $V_m(r)$ denotes the counterfactual value of V_m when R is set to r.

An NPSEM represented by a DAG G with vertex set V assumes the existence of mutually

independent unobserved random variables (errors) ϵ_m and deterministic unknown functions $f_m(pa_m, \epsilon_m)$ such that $V_1 = f_1(\epsilon_1)$ and the one-step ahead counterfactual $V_m(\overline{v}_{m-1}) \equiv V_m(pa_m)$ is given by $f_m(pa_m, \epsilon_m)$, and both V_m and the counterfactuals $V_m(r)$ for any $R \subset V$ are obtained recursively from V_1 and the $V_m(\overline{v}_{m-1})$, $m > 1$. For example, $V_3(v_1) = V_3\{v_1, V_2(v_1)\}$ and $V_3 = V_3\{V_1, V_2(V_1)\}$.

In Figure 1b, $Y(a) = V_4(v_3) = f_4(V_1, V_2, v_3, \epsilon_4) = f_Y(U, L, a, \epsilon_Y)$ where, we define, $f_Y = f_4, \epsilon_Y = \epsilon_4$ since $Y = V_4$. A DAG G representing an NPSEM is a causal DAG for which the CMA holds because the independence of the error terms ϵ_m both implies the CMA holds and is essentially equivalent to the requirement that all common causes of any variables on the graph are themselves on the causal DAG. Although an NPSEM is a causal DAG, not all causal DAG models are NPSEMs. Indeed as mentioned above, a causal DAG model makes no reference to and is agnostic about the existence of counterfactuals. In the main body of the paper, we use the term causal DAG to mean a causal DAG representing an NPSEM. All the results for NPSEMs described in this paper actually hold under the slightly weaker assumptions encoded in a fully randomized causally interpreted structured tree graph (FRCISTG) models of Robins (1986). All NPSEMs are FRCISTGs but not all FRCISTGs are NPSEMs.

A graphical condition for g-identifiability:

Theorem (Robins, 1997b): Given a DAG G whose vertex set consists of the random variables that are elements of the random vectors $Y, X_m, A_m, m = 0, ..., K$, whose edges are consistent with the (partial) ordering $X_0 A_0 X_1 A_1 .... X_K A_K Y$, in the sense that the earlier variables in the ordering are nondescendants of later variables. Suppose $X_m = (L_m, U_m)$. We observe Y and , for each m, (A_m, L_m). The U_m are unobserved. Let L_m^* denote an arbitrary element (vertex) in the set of vertices L_m. Consider a set of functions $g = \{g_m; m = 0, ..., K\}$ where g_m has domain the support $\overline{\mathcal{L}}_m$ of $\overline{L}_m$ and range the support $\mathcal{A}_m$ of A_m. We say A_m is g-unconnected to a node $L_k^*, k \leq m$, if $g_m\left(\overline{l}_m^{(1)}\right) = g_m\left(\overline{l}_m^{(2)}\right)$ whenever $\overline{l}_m^{(1)}$ and $\overline{l}_m^{(2)}$ differ only in l_k^*. Otherwise A_m is g-connected to $L_k^*, k \leq m$. Define the g-formula $b_{g,l}$ and $b_{g,x}$ for g based on l and x respectively to be

$$b_{g,l} = \sum_{\overline{l}} \mathrm{E}\left[Y|\bar{A} = \overline{g}(\overline{l}), \bar{L} = \overline{l}\right] \prod_{k=0}^{K} f\left[l_k|\overline{A}_{k-1} = \overline{g}_{k-1}\left(\overline{l}_{k-1}\right), \overline{L}_{k-1} = \overline{l}_{k-1}\right]$$

$$b_{g,x} = \sum_{\overline{x}=(\overline{l},\overline{u})} \mathrm{E}\left[Y|\bar{A} = \overline{g}(\overline{l}), \overline{X} = \overline{x}\right] \prod_{k=0}^{K} f\left[l_k|\overline{A}_{k-1} = \overline{g}_{k-1}\left(\overline{l}_{k-1}\right), \overline{X}_{k-1} = \overline{x}_{k-1}\right].$$

and note $b_{g,l}$ is a function of the joint distribution of the observables and thus always identified.

(i) A sufficient condition for $b_{g,x} = b_{g,l}$ is that for $m = 0, ..., K$, A_m and Y are d-separated given $\left(\overline{L}_m, \overline{A}_{m-1}\right)$ on the DAG G_m^g given built from DAG G from the following three rules:

1. Remove all arrows out of A_m on DAG G.
2. Remove all arrows into $A_{m+1}, ..., A_K$ on DAG G.
3. For $s = m+1, ..., K$ add arrows from L_j^* to A_s if A_s is $g-$connected to $L_j^*, j \leq s$.

(ii): If for $m = 0, ..., K$, A_m and Y are d-separated given $\left(\overline{L}_m, \overline{A}_{m-1}\right)$ on the DAG G_m^g and $Y_g \amalg A_m|\overline{X}_m, \overline{A}_{m-1}$, then $Y_g \amalg A_m|\overline{L}_m, \overline{A}_{m-1}$.

Corollary (Robins, 1997b): If the DAG G in the above theorem is a causal DAG representing an NPSEM or FRCISTG and A_m and Y are d-separated given $\left(\overline{L}_m, \overline{A}_{m-1}\right)$ on the DAG G_m^g for all m, then $Y_g \amalg A_m|\overline{L}_m, \overline{A}_{m-1}$ and $\mathrm{E}[Y_g] = b_{g,l}$ and so is identified by the g-formula based on the observed data.

Proof: Robins (1986) proved that $\mathrm{E}[Y_g] = b_{g,x}$ and $Y_g \amalg A_m|\overline{X}_m, \overline{A}_{m-1}$ if G represents

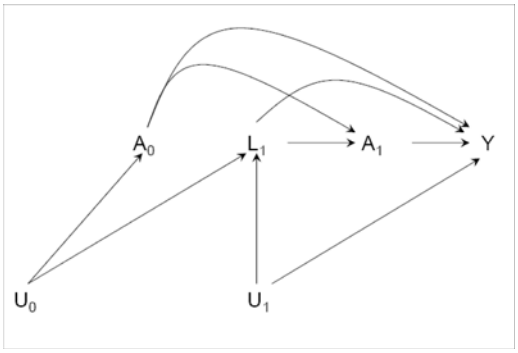

Figure 1.5 *Example of causal DAG*

an FRCISTG. Further Robins (1995) proved an NPSEM is an FRCISTG. The corollary now follows from the preceding theorem.

Example: Consider the DAG G in Figure 5. We shall consider the nondynamic regime $g = \overline{a} = (a_0, a_1)$ and the dynamic regimes $g = (a_0, g_1(l_1) = l_1)$ and $g = (a_0, g_1(l_1) = 1 - l_1)$.

Note for the regime $g = \overline{a}$, we have $g_1(l_1) = a_1$. Hence A_1 is g-unconnected to a node L_1 for $g = \overline{a}$, but A_1 is g-connected to node L_1 for the two dynamic g.

Now the graph G_1^g is G with the arrow out of A_1 removed for all three g. Further A_1 and Y are d-separated given (A_0, L_1) on G_1^g. For g nondynamic, G_0^g is G with all arrows out of A_0 removed and all arrows into A_1 removed; furthermore A_0 and Y are d-separated on G_1^g. For g dynamic, G_0^g is G with all arrows out of A_0 removed and a single arrow into A_1 originating at L_1; therefore A_0 and Y are not d-separated on G_1^g because of the unblocked path $A_0 \leftarrow U_0 \rightarrow L_1 \rightarrow A_1 \rightarrow Y$. We conclude that if DAG G in Figure 5 represents an NPSEM, then, in the absence of data on U_0 and U_1, $\mathrm{E}[Y_{g=\overline{a}}]$ is identified and equals $b_{g=\overline{a},l}$. However, for g dynamic, $\mathrm{E}[Y_g]$ does not equal $b_{g\ ,l}$ and in fact $\mathrm{E}[Y_g]$ is not identified.

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