

5. Time-Dependent Treatment Assignments

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Thus far we have focused attention on point exposure studies where we evaluate the effect that treatment, given at a single point in time, will have on future response. In many cases, treatment decisions are more complex where several treatment decisions have to be made over time possibly depending on intervening information. This is certainly the case for the treatment of chronic diseases such as cancer, HIV disease, cardiovascular disease, diabetes, etc. We shall now study causality with time-dependent treatments in longitudinal studies (i.e., studies where data are collected over time).

For simplicity we will assume that treatment decisions will be made at a finite number of times which we will denote by t_0, \dots, t_M . These decision points may be fixed times or random times. We denote by t_0 the baseline time where treatment is first initiated. As an illustrative example, a patient with cancer may receive an initial first line induction chemotherapy to try to destroy or at least lessen the tumor load. If this induction therapy has an effect and the patient has a "response," then they may receive additional chemotherapy as "maintenance" therapy; whereas, if they don't respond, then the patient may receive some "new salvage therapy."

In this example there are two decision points; the first is when the person is first treated and the second is at the point that their response status is established. Note that the second treatment is not at a fixed time and is affected by the response or non-response of the individual.

The data that are observed from such longitudinal studies can be summarized as the time-ordered variables

$$(L_0, A_0, L_1, A_1, \dots, L_M, A_M, Y), \quad (5.2.1)$$

where L_0 denotes all the covariate information obtained prior to any treatment at decision time t_0 . L_0 is also referred to as a vector of baseline covariates. A_0 (action) refers to the first treatment given at time t_0 among a possible set of treatments A_0 . L_1 denotes any additional (time-dependent) covariates that are obtained on the patient between decision points t_0 and t_1 ; whereas, A_1 is the treatment given at decision point t_1 among a possible set of treatments A_1 (no treatment may be one of the options).

Continuing in this fashion, L_j denotes any additional covariates obtained on the patient between decision points t_{j-1} and t_j and A_j

is the treatment given at decision point t_j ,
 (the $(j+1)$ st decision point) among the set
 of treatments A_j . 5.3

Finally, the outcome (response) of interest
 is denoted by Y . The value of Y is determined
 after the final treatment t_M .

Remark: What may be considered time-dependent
 treatments versus time-dependent covariates
 is not necessarily obvious. For our purposes,
 we will consider time-dependent treatments to
 be those variables that we are interested
 in manipulating to affect outcome. \ddagger

We will use the "overbar" notation to denote the
 history of time-dependent variables. That is,

$$\bar{L}_j = (L_0, \dots, L_j) \text{ and } \bar{A}_j = (A_0, \dots, A_j),$$

$$\bar{L} = (L_0, \dots, L_M) \text{ and } \bar{A} = (A_0, \dots, A_M).$$

The longitudinal data described above are assumed to
 be collected from a relevant population we
 wish to study. Thus the observed data
 can be summarized as

$$O_i = (L_{0i}, A_{0i}, \dots, L_{Mi}, A_{Mi}, Y_i), i=1, \dots, n \quad (5.3.1)$$

$$\text{or } (L_i, A_i, Y_i), i=1, \dots, n.$$

The treatment A_{0i}, \dots, A_{Mi} , chosen respectively from the set of treatments A_0, \dots, A_M , can be assigned at random in a sequentially randomized intervention study, or may be given to patients according to the desires of the patient and physicians in an observational study.

In order to establish causal relationships, we will introduce the idea of potential outcomes similar to (albeit more complex) point exposure studies.

Let $\bar{A}_j = A_0 \times \dots \times A_j$

denote the set of all possible combinations of treatments that can be given at decision points t_0, \dots, t_j ; (i.e., the set of all $(j+1)$ -dimensional vectors (a_0, \dots, a_j) where $a_0 \in A_0, \dots, a_j \in A_j$). We also denote $\bar{A} = \bar{A}_M$.

We now introduce the set of all potential outcomes

$$\mathcal{W} = \left\{ L_0^*, L_1^*(a_0), L_2^*(\bar{a}_1), \dots, L_M^*(\bar{a}_{M-1}), V^*(\bar{a}) \right\}, \quad (5.4.1)$$

for $a_0 \in A_0, \bar{a}_1 \in \bar{A}_1, \dots, \bar{a}_{M-1} \in \bar{A}_{M-1}, \bar{a} \in \bar{A}$.

to denote the potential time-dependent covariates from decision point t_0 through decision point t_M .

and the potential response of a randomly chosen individual from our population if, possibly contrary to fact, this individual were given treatment (a_0, \dots, a_M) at decision points (t_0, \dots, t_M) .

Remark: We are implicitly assuming that

$$L_j^*(\bar{a}) = L_j^*(\bar{a}_{j-1}).$$

That is, the potential outcomes for the time-dependent covariates measured between times t_{j-1} and t_j only depend on treatments assigned through t_{j-1} and are not affected by future treatments.

Potential outcomes allow us to compare different combinations of treatments and their effect on outcome. For example if we wanted to compare two different combinations of treatments say $\bar{a}^{(1)} = (a_0^{(1)}, \dots, a_M^{(1)})$ versus $\bar{a}^{(2)} = (a_0^{(2)}, \dots, a_M^{(2)})$ then we could consider $E\{Y^*(\bar{a}^{(1)})\}$ versus $E\{Y^*(\bar{a}^{(2)})\}$. That is, $E\{Y^*(\bar{a}^{(1)})\}$ would denote the mean response of a population of patients had everyone received $a_0^{(1)}$ at time t_0 , $a_1^{(1)}$ at time $t_1, \dots, a_M^{(1)}$ at time t_M , and $E\{Y^*(\bar{a}^{(2)})\}$ would denote the mean response of a population of patients had everyone received $a_0^{(2)}$ at time t_0 , $a_1^{(2)}, \dots, a_M^{(2)}$ at time t_M .

The better combinations of treatments between $\bar{a}^{(1)}$ and $\bar{a}^{(2)}$ would be the one which gave the larger mean response.

Treatments $\bar{a}^{(1)}$ and $\bar{a}^{(2)}$ are examples of static treatment strategies or non-dynamic treatment regimes in that everyone in the population would receive $a_0^{(1)}$ at time t_0 , ..., $a_{T_1}^{(1)}$ at time t_{T_1} with treatment strategy $\bar{a}^{(1)}$, regardless of any intervening information on that patient.

Such treatment strategies may be too limiting. We may indeed want to let treatment assignments depend on intervening information on the patient. Indeed, this is usually the way a patient is treated in practice. For example, if a patient is receiving a chemotherapeutic drug for treatment of their cancer and has a toxic reaction, then the physician may lower the dose or discontinue the drug entirely. Decisions on whether to continue the drug may also depend on other factors that are observed on the patient. These more realistic treatment strategies are referred to as dynamic treatment regimes.

More formally, a dynamic treatment regime, denoted by g is a vector of functions $g = (g_0, \dots, g_M)$, where for every $j=0, \dots, M$

g_j is a function which, at decision point t_j , assigns a treatment $a_j \in A_j$ for each realization

\bar{l}_j of \bar{L}_j ; i.e., for every $\bar{l}_j \in \bar{L}_j$,

$$g_j(\bar{l}_j) = a_j \in A_j, j=0, \dots, M.$$

Thus the dynamic treatment regime "g" allows the treatment assignment at the t_j to be influenced by the history of time-dependent covariates observed up to decision time t_j . Therefore,

$$g = (g_0, \dots, g_M)$$

where $g_j : \bar{L}_j \rightarrow A_j$,

~~as~~ \bar{L}_j consists of all possible combinations of (l_0, \dots, l_j) , and A_j is the set of possible treatments that could be assigned at decision time t_j .

Consider the simple example where $M=1$, L_0, L_1 are binary variables $\star_0 = (a_{00}, a_{01})$ and $\star_1 = (a_{10}, a_{11})$.

Let $g = (g_0, g_1)$, where

$$g_0(0) = a_{00}$$

$$g_0(1) = a_{01}$$

$$g_1(0, 0) = a_{10}$$

$$g_1(0, 1) = a_{11}$$

$$g_1(1, 0) = a_{11}$$

$$g_1(1, 1) = a_{10}.$$

That is, according to treatment regime g , if a patient enters the study and, at baseline (t_0), has $L_0=0$, they are assigned treatment a_{00} at baseline. If between the first and second decision points we measure $L_1=1$; i.e., $(L_0, L_1) = (0, 1)$, then he/she is assigned treatment a_{11} at decision time t_1 .

Similarly if $L_0=1$ they receive treatment a_{01} at time t_0 , if then $L_1=1$, then they receive a_{10} at time t_1 .

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Note that even for this simple scenario there are $2^6 = 64$ different combinations of treatment regimes of which $2^2 = 4$ are non-dynamic treatment regimes.

In some cases not all treatment options at decision point t_j may be suitable for all patients. Therefore, we will denote by

$$\underline{\Phi}_j(\underline{l}_j, \underline{a}_{j-}) \subset \underline{A}_j; \quad (5.9.1)$$

the set of treatments that can be given to patients at decision point t_j ; if $\underline{l}_j = \underline{l}_j$ and $\underline{A}_{j-} = \underline{a}_{j-}$. We shall also denote the entire set of treatment regimes by \mathcal{Y} .

Let us denote by $\tilde{Y}(g)$ the potential outcome (response) of a randomly selected individual from our population had they (contrary to fact) received treatment in accordance to treatment regime g . Ideally we would like to find the optimal such regime; that is among all $g \in \mathcal{Y}$, the one which maximizes $E\{\tilde{Y}(g)\}$.

We can also define the potential outcomes

$$\tilde{L}_1(g), \dots, \tilde{L}_M(g) \text{ as well as } \tilde{Y}(g)$$

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to denote the potential outcomes of the time-dependent covariates $L_j, j=1, \dots, M$ had the patient received treatment according to treatment regime g .

Recall that in (5.4.1) we defined the entire set of potential outcomes as

$$W = \left[\{L_0, L_1^*(\alpha_0), \dots, L_M^*(\bar{\alpha}_M), Y(\bar{\alpha})\} \text{ for all } \bar{\alpha} \in \mathbb{A} \right].$$

Now, for any treatment regime $g \in \mathcal{G}$ we can define

$$\{L_0, \tilde{L}_1(g), \dots, \tilde{L}_M(g), \tilde{Y}(g)\}$$

recursively as follows:

$$\begin{aligned}\tilde{L}_1(g) &= L_1^* \{g_0(L_0)\} \\ \tilde{L}_2(g) &= L_2^* [g_0(L_0), g_1 \{ \tilde{L}_1(g) \}] \\ &\vdots\end{aligned}\tag{5.10.1}$$

$$\tilde{Y}(g) = Y^* [g_0(L_0), \dots, g_M \{ \tilde{L}_M(g) \}].$$

Thus for any $g \in \mathcal{G}$, the potential outcomes

$\{L_0, \tilde{L}_1(g), \dots, \tilde{L}_M(g), \tilde{Y}(g)\}$ is a function of W .

We will also use the shorthand notation that

$$\bar{g}_j(\bar{l}_j) = \{g_0(l_0), g_1(\bar{l}_1), \dots, g_j(\bar{l}_j)\}.$$

If we were able to observe the potential outcomes \mathcal{W} , then we would be able to evaluate

$E\{\tilde{Y}(g)\}$ directly for different $g \in \mathcal{G}$ which would be useful in defining good treatment strategies; i.e., strategies g where $E\{\tilde{Y}(g)\}$ were large, with the ultimate goal of finding the optimal dynamic treatment regime

$$g^{opt} = \arg \max_{g \in \mathcal{G}} E\{\tilde{Y}(g)\}.$$

Of course this is not the case. What we get to observe are the data given by
 (5.3.1) $O_i, i=1, \dots, n,$

$$\text{where } O_i = (L_{0i}, A_{0i}, \dots, L_{Mi}, A_{Mi}, Y_i)$$

are the observed data for the i -th individual in a clinical trial (sequentially randomized treatment intervention study) or an observational study.

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Therefore the question that needs to be addressed is when can we deduce the distribution of $\tilde{Y}(g)$ or even $\{\tilde{L}_0, \tilde{L}_1(g), \dots, \tilde{L}_M(g), \tilde{Y}(g)\}$

from the distribution of the observed data

$O = (L_0, A_0, \dots, L_n, A_n, Y)$ for different

treatment regimes g ?

If we resolve this question of identifiability, then this will imply that we have the ability to estimate different parameters

regarding the distribution of $\{\tilde{L}_0, \tilde{L}_1(g), \dots, \tilde{L}_M(g), \tilde{Y}(g)\}$ using a sample of observed data

$O_{ij}, i=1, \dots, n$. Then, of course, we will need to derive useful models and methods to estimate the parameters in these models.

Identifiability

As with point exposure studies, there will be two key sets of assumptions necessary for identification. There will be a generalization of SUTVA (the stable unit treatment value assumption) and the no unmeasured confounders assumption.

SUTVA: Analogous to the point exposure study, we will assume that

$$L_j = \sum_{\bar{a}_{j-1} \in \bar{\mathcal{A}}_{j-1}} L_j^*(\bar{a}_{j-1}) I(\bar{A}_{j-1} = \bar{a}_{j-1}), j=0, \dots, M$$

and

$$Y = \sum_{\bar{a} \in \bar{\mathcal{A}}} Y^*(\bar{a}) I(\bar{A} = \bar{a}). \quad (5.13.1)$$

In other words, the time-dependent covariates that are observed and the response that is observed in an experimental condition where a patient receives the combinations of treatments $\bar{A} = \bar{a}$, will be the same regardless of experimental condition and equal to the corresponding potential outcomes for that set of treatments.

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We can also write this as

$$L_j = L_j^*(\bar{A}_{j-1}), j=1, \dots, M \text{ and } Y = Y^*(\bar{A}).$$

No unmeasured confounders. Sometimes this assumption is also referred to as the sequential randomization assumption (SRA).

This is a generalization of the strong ignorability assumption that Rubin made for point exposure studies.

The strongest version of this assumption is that

$$(W \perp\!\!\!\perp A_j \mid \bar{A}_{j-1}, \bar{L}_j), j=0, \dots, M, (5.14.1)$$

where W is the set of all potential outcomes defined by (5.4.1).

In words, SRA assumes that, conditional on the observed time-dependent covariate history and time-dependent treatment history up to decision point t_j , the treatment assignment A_j is made independently of the potential outcomes.

Remarks

1. This assumption can be weakened. For example, if we define "underbar" notation to be the set of future observations; i.e., $\underline{a}_j = (a_j, a_{j+1}, \dots, a_M)$ then it suffices for our purposes to assume

$$\left[\left\{ L_{j+1}^*(\bar{A}_{j-1}, \underline{a}_j), \dots, L_M^*(\bar{A}_{j-1}, \underline{a}_j), V^*(\bar{A}_{j-1}, \underline{a}_j) \right\} \perp\!\!\!\perp A_j \mid \bar{A}_{j-1}, \bar{L}_j \right]. \quad (5.15.1)$$

Keep in mind that

$$\bar{L}_k(\bar{A}_{j-1}, \underline{a}_j) = \bar{L}_k(\bar{A}_{j-1}, a_j, \dots, a_{k-1}) \quad \text{for } j+1 \leq k \leq M.$$

2. In a clinical trial where we would randomize patients, at time t_j , to different treatments among A_j with prespecified probabilities that may depend on \bar{A}_{j-1} and \bar{L}_j , then assumption (5.14.1) would have to be true. This is why we refer to this assumption as the sequential randomization assumption.

However, in an observational study, if we identify a critical decision point t_j where ~~some~~ patients receive different treatments, then presumably the decision on which treatment a patient should be given can only depend on characteristics of that patient and not additionally on potential or future outcomes.

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Consequently, at some level, we can expect that the SRA assumption (5.14.1) or (5.15.1) must hold. The difficulty is that some characteristics that were used in the treatment decision process may have not been captured in the observed data "L's" and if, in addition, these characteristics also affect future outcomes, then the SRA assumption may be violated.

This is the major difficulty with observational studies. Whether or not the SRA assumption is tenable must be based on subjective judgment. If one were to design an observational study then all efforts should be made to capture all relevant information that affects treatment decisions. Collaboration between clinicians and statisticians would be crucial. #

We will now show that with the SUTVA and SRA assumptions we can identify the joint distribution of $\{L_0, \tilde{L}_1(g), \dots, L_M(g), Y(g)\}$ from the joint distribution of the observed data $(L_0, A_0, \dots, L_M, A_M, Y)$ using Robin's g-computation algorithm.

g-computation algorithm

We begin by first introducing some notation. Let us denote the joint density of the observed data as

$$p(y, a_M, l_M, \dots, l_1, a_0, l_0) \quad (5.17.1)$$

$y, a_M, l_M, \dots, l_1, a_0, l_0$

For simplicity, I will consider discrete distributions; that is (5.17.1) could then be written as

$$P(y=y, A_M=a_M, \dots, A_0=a_0, L_0=l_0).$$

However, all the calculations can be generalized to continuous distributions in a straightforward fashion. Keeping in mind that whenever we consider transformations of the random variables then we must keep track of the appropriate Jacobians.

By the law of conditional expectations, the joint density (5.17.1) is

$$\begin{aligned} & p(y | \bar{a}_M, \bar{l}_M) \times p(a_M | \bar{l}_M, \bar{a}_{M-1}) \\ & \quad y | \bar{A}_M, \bar{L}_M \qquad \qquad \qquad A_M | \bar{L}_M, \bar{A}_{M-1} \\ & \times p(l_M | \bar{a}_{M-1}, \bar{l}_{M-1}) \times p(a_{M-1} | \bar{l}_{M-1}, \bar{a}_{M-2}) \\ & \quad \bar{l}_M | \bar{A}_{M-1}, \bar{L}_{M-1} \qquad \qquad \qquad A_{M-1} | \bar{L}_{M-1}, \bar{A}_{M-2} \quad (5.17.2) \\ & \vdots \\ & \times p(l_1 | a_0, l_0) \qquad \qquad \qquad p(a_0 | l_0) \\ & \quad \bar{l}_1 | A_0, L_0 \qquad \qquad \qquad A_0 | L_0 \\ & \times p(l_0). \end{aligned}$$

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The g -computation algorithm states that the joint distribution of the potential outcomes $\{l_0, \tilde{l}_1(g), \dots, \tilde{l}_M(g), \tilde{y}(g)\}$ for a fixed treatment regime $g \in \mathcal{Y}$ can be obtained as

$$\begin{aligned}
 & p_{l_0, \tilde{l}_1(g), \dots, \tilde{l}_M(g), \tilde{y}(g)}(l_0, l_1, \dots, l_M, y) \\
 & = p_{l_0} (l_0) \times p_{l_1 | l_0, A_0} \{l_1 | l_0, g(l_0)\} \times \dots \times p_{l_M | l_{M-1}, A_{M-1}} \{l_M | l_{M-1}, g_{M-1}(l_{M-1})\} \\
 & \quad \times p_{y | l_M, A_M} \{y | l_M, g_M(l_M)\}. \tag{5.18.1}
 \end{aligned}$$

Remarks:

1. Note that the right-hand side of (5.18.1) only involves the joint distribution of the observed data and, moreover, uses every other conditional density in (5.17.2).
2. In order that (5.18.1) hold we will need the SUTVA and SRA assumptions to hold as well as an additional positivity assumption. The positivity assumption states that

$$p_{A_j | \tilde{l}_j, A_{j-1}} \{g_j(\tilde{l}_j) | \tilde{l}_j, g_{j-1}(\tilde{l}_{j-1})\} > 0 \tag{5.18.2}$$

whenever $p_{\tilde{l}_j | A_j, A_{j-1}} \{\tilde{l}_j, g_{j-1}(\tilde{l}_{j-1})\} > 0$ for $j=0, \dots, M$.

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The positivity assumption formalizes the idea that in order for us to evaluate the joint density of a dynamic treatment regime g , then for patients in our study who have been given treatment through decision points $(j-1)$ in accordance to treatment regime " g "; i.e., for any realizations

$$\left\{ \bar{L}_j = \bar{l}_j, \bar{A}_{j-1} = \bar{g}_{j-1}(\bar{l}_{j-1}), \dots \right\},$$

there must be a positive probability that they will receive treatment at decision point j that is also consistent with the treatment regime g ; i.e.,

$$A_j = g_j(\bar{l}_j).$$

If that were not the case then the experimental study that generated the observed data would not have sufficient information for us to evaluate treatment regime g . #

We are now in position to prove the g -computation algorithm given by (5.18.1)

Before giving the proof of the g-computation algorithm 5.20 we first present a simple but useful lemma.

Lemma: Assume $A \perp\!\!\!\perp W|Z$ and consider two functions $f_1(W)$ and $f_2(W)$. If the event $\{A=a, f_2(W)=f_2, Z=z\}$ has positive probability then

$$P\{f_1(W)=f_1, A=a, f_2(W)=f_2, Z=z\} = P\{f_1(W)=f_1, f_2(W)=f_2, Z=z\}. \quad (5.20.1)$$

Proof: $A \perp\!\!\!\perp W|Z \Rightarrow A \perp\!\!\!\perp \{f_1(W), f_2(W)\}|Z$. The left hand side of (5.20.1) can be written as

$$\frac{P\{f_1(W)=f_1, f_2(W)=f_2 | A=a, Z=z\}}{P\{f_2(W)=f_2 | A=a, Z=z\}}. \quad (5.20.2)$$

Because the event $\{A=a, Z=z\}$ has positive probability and by the conditional independence assumption, we obtain that (5.20.2) is equal to

$$\frac{P\{f_1(W)=f_1, f_2(W)=f_2 | Z=z\}}{P\{f_2(W)=f_2 | Z=z\}} = P\{f_1(W)=f_1, f_2(W)=f_2, Z=z\}. \quad \text{H}$$

Proof of the g-computation algorithm.

Consider realizations (l_0, \dots, l_M, y) such that

$$P\{\tilde{l}_0=l_0, \tilde{l}_1(g)=l_1, \dots, \tilde{l}_M(g)=l_M, \tilde{Y}(g)=y\} > 0.$$

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Let us examine a typical term on the right-hand side of (5.18.1)_j say. $P\{L_j = l_j \mid \bar{L}_{j-1} = \bar{l}_{j-1}, \bar{A}_{j-1} = \bar{g}_{j-1}(\bar{l}_{j-1})\}$.

We will prove two things: For all $j=0, \dots, M$,

$$(i) P\{\bar{L}_{j-1} = \bar{l}_{j-1}, \bar{A}_{j-1} = \bar{g}_{j-1}(\bar{l}_{j-1})\} > 0 \quad (5.21.1)$$

and

$$(ii) P\{L_j = l_j \mid \bar{L}_{j-1} = \bar{l}_{j-1}, \bar{A}_{j-1} = \bar{g}_{j-1}(\bar{l}_{j-1})\} = P\{\tilde{L}_j(g) = l_j \mid \tilde{L}_{j-1}(g) = \bar{l}_{j-1}\}. \quad (5.21.2)$$

Assuming we proved (i) consider the proof of (ii).

By SUTVA, the left-hand side of (5.21.2) is equal to

$$P\{\tilde{L}_j(g) = l_j \mid \bar{L}_{j-1} = \bar{l}_{j-1}, \bar{A}_{j-2} = \bar{g}_{j-2}(\bar{l}_{j-2}), A_{j-1} = g_{j-1}(\bar{l}_{j-1})\}. \quad (5.21.3)$$

$\underbrace{\qquad\qquad\qquad}_{\{\bar{A}_{j-1} = \bar{g}_{j-1}(\bar{l}_{j-1})\}}$

We already noted in (5.10.1) that $\tilde{L}_j(g)$ is a function of W (the set of potential outcomes). Therefore by SRA (5.14.1)

$\tilde{L}_j(g) \perp\!\!\!\perp A_{j-1} \mid \bar{A}_{j-2}, \bar{L}_{j-1}$, which implies that (5.21.3) is equal to

$$P\{\tilde{L}_j(g) = l_j \mid \bar{A}_{j-2} = \bar{g}_{j-2}(\bar{l}_{j-2}), \bar{L}_{j-1} = \bar{l}_{j-1}\},$$

$$\therefore P\{\tilde{L}_j(g) = l_j \mid \bar{A}_{j-2} = \bar{g}_{j-2}(\bar{l}_{j-2}), \bar{L}_{j-2} = \bar{l}_{j-2}, \tilde{L}_{j-1}(g) = l_{j-1}\} \text{ by SUTVA.}$$

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$$= P \{ \tilde{L}_j(g) = l_j \mid \bar{A}_{j-3} = \bar{g}_{j-3}(\bar{l}_{j-3}), \bar{L}_{j-2} = \bar{l}_{j-2}, \tilde{L}_{j-1}(g) = l_{j-1}, A_{j-2} = g_{j-2}(\bar{l}_{j-2}) \} \quad (5.22.1)$$

Using the lemma and letting $\tilde{L}_j(g) = f_1(w)$, $\tilde{L}_{j-1}(g) = f_2(w)$,
 $A = A_{j-2}$, $Z = (\bar{A}_{j-3}, \bar{L}_{j-2})$, we obtain that

$A \perp\!\!\!\perp Z$ by SRA, and consequently (5.22.1)
is equal to

$$P \{ \tilde{L}_j(g) = l_j \mid \bar{A}_{j-3} = \bar{g}_{j-3}(\bar{l}_{j-3}), \bar{L}_{j-2} = \bar{l}_{j-2}, \tilde{L}_{j-1}(g) = l_{j-1} \}$$

$$= P \{ \tilde{L}_j(g) = l_j \mid \bar{A}_{j-3} = \bar{g}_{j-3}(\bar{l}_{j-3}), \bar{L}_{j-3} = \bar{l}_{j-3}, \tilde{L}_{j-2}(g) = l_{j-2}, \tilde{L}_{j-1}(g) = l_{j-1} \}, \quad (5.22.2)$$

Next letting $A = A_{j-3}$, $Z = (\bar{A}_{j-4}, \bar{L}_{j-3})$, $f_1(w) = \tilde{L}_j(g)$,
 $f_2(w) = \{ \tilde{L}_{j-2}(g), \tilde{L}_{j-1}(g) \}$ we obtain that (5.22.2) equals

$$P \{ \tilde{L}_j(g) = l_j \mid \bar{A}_{j-4} = \bar{g}_{j-4}(\bar{l}_{j-4}), \bar{L}_{j-3} = \bar{l}_{j-3}, \tilde{L}_{j-2}(g) = l_{j-2}, \tilde{L}_{j-1}(g) = l_{j-1} \}$$

⋮

Continuing in this fashion we obtain

$$P \{ \tilde{L}_j(g) = l_j \mid \tilde{L}_{j-1}(g) = l_{j-1} \} > 0 \quad (\text{By assumption on the realizations } l_0, \dots, l_m, y).$$

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We will prove (ii) by induction. Assume we showed that

$$P\{\bar{L}_{j-2} = \bar{l}_{j-2}, \bar{A}_{j-2} = \bar{g}_{j-2}(\bar{l}_{j-2})\} > 0, \text{ then}$$

$$P\{\bar{L}_{j-1} = \bar{l}_{j-1}, \bar{A}_{j-2} = \bar{g}_{j-2}(\bar{l}_{j-2})\} =$$

$$P\{\bar{L}_{j-1} = \bar{l}_{j-1} \mid \bar{L}_{j-2} = \bar{l}_{j-2}, \bar{A}_{j-2} = \bar{g}_{j-2}(\bar{l}_{j-2})\} \times P\{\bar{L}_{j-2} = \bar{l}_{j-2}, \bar{A}_{j-2} = \bar{g}_{j-2}(\bar{l}_{j-2})\}$$

$$= P\{\bar{L}_{j-1}^{(q)} = \bar{l}_{j-1} \mid \bar{L}_{j-2}^{(q)} = \bar{l}_{j-2}\} \times P\{\bar{L}_{j-2} = \bar{l}_{j-2}, \bar{A}_{j-2} = \bar{g}_{j-2}(\bar{l}_{j-2})\} > 0.$$

follows from proof
of ii

$$\text{If } P\{\bar{L}_{j-1} = \bar{l}_{j-1}, \bar{A}_{j-2} = \bar{g}_{j-2}(\bar{l}_{j-2})\} > 0, \text{ then}$$

$$P\{\bar{L}_{j-1} = \bar{l}_{j-1}, \bar{A}_{j-1} = \bar{g}_{j-1}(\bar{l}_{j-1})\} =$$

$$P\{\bar{A}_{j-1} = \bar{g}_{j-1}(\bar{l}_{j-1}) \mid \bar{L}_{j-1} = \bar{l}_{j-1}, \bar{A}_{j-2} = \bar{g}_{j-2}(\bar{l}_{j-2})\} \times P\{\bar{L}_{j-1} = \bar{l}_{j-1}, \bar{A}_{j-2} = \bar{g}_{j-2}(\bar{l}_{j-2})\} > 0.$$

> 0 by positivity
assumption

Thus we have shown that if

$$P\{\bar{L}_{j-2} = \bar{l}_{j-2}, \bar{A}_{j-2} = \bar{g}_{j-2}(\bar{l}_{j-2})\} > 0$$

$$\Rightarrow P\{\bar{L}_{j-1} = \bar{l}_{j-1}, \bar{A}_{j-1} = \bar{g}_{j-1}(\bar{l}_{j-1})\} > 0.$$

The proof is complete by noting that

$$P\{L_0 = l_0, A_0 = g_0(l_0)\} = P(L_0 = l_0) \times P\{A_0 = g_0(l_0) | L_0 = l_0\}$$

by assumption
 on realizations ≥ 0
 by positivity
 assumption

Summarizing, we have shown that for realizations l_0, \dots, l_M, y such that

$P\{L_0 = l_0, \tilde{L}_1(g) = l_1, \dots, \tilde{L}_M(g) = l_M, \tilde{Y}(g) = y\} \geq 0$
 that the right hand side of (5.18-1) is
 equal to

$$\begin{aligned}
 & P(L_0 = l_0) \times P\{\tilde{L}_1(g) = l_1 | L_0 = l_0\} \times \dots \times P\{\tilde{L}_M(g) = l_M | \tilde{L}_{M-1}(g) = \bar{l}_{M-1}\} \\
 & \quad \times P\{\tilde{Y}(g) = y | \tilde{L}_M(g) = \bar{l}_M\} \\
 & = P\{L_0 = l_0, \tilde{L}_1(g) = l_1, \dots, \tilde{L}_M(g) = l_M, \tilde{Y}(g) = y\},
 \end{aligned}$$

thus proving the validity of the g -computation algorithm.

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It is convenient to write the right-hand side of (5.18.1) as

$$\frac{p\{y|\bar{l}_M, \bar{g}_M(\bar{l}_M)\} \times \prod_{j=1}^M p\{l_j|\bar{l}_{j-1}, \bar{g}_{j-1}(l_{j-1})\}}{Y|\bar{l}_M, \bar{A}_M} \times \prod_{j=1}^M p_{L_j}(l_j).$$

If we were interested in deducing the marginal density of $\bar{Y}(y)$, then we would need to integrate out all the l 's; i.e.,

$$p_{\bar{Y}(y)}^{(y)} = \int_{Y|\bar{l}_M, \bar{A}_M} \prod_{j=1}^M p\{l_j|\bar{l}_{j-1}, \bar{g}_{j-1}(l_{j-1})\} \times p_{L_j}(l_j) dV_M(l_M) \cdots dV_0(l_0), \quad (5.25.1)$$

$$dM \times dM \times \cdots \times d_0$$

where $L_M \times \cdots \times L_0$ is the sample space consisting of all realizations of (l_M, \dots, l_0) , and $dV_M(l_M) \cdots dV_0(l_0)$ refers to a dominating measure $V_M \times \cdots \times V_0$. For our purposes, we will be using Lebesgue measure for continuous L 's and counting measure for discrete L 's.

5.2B

Therefore, in theory, we have shown that under appropriate assumptions (SUTVA, SRA, positivity) we can deduce the distribution of $\tilde{Y}(g)$; i.e., the distribution of the response had everyone in the population received treatment in accordance to treatment-regime g (dynamic or non-dynamic). from the distribution of the observable data

$$(\bar{L}, \bar{A}, Y).$$

If we wanted to use the g -computation algorithm to estimate the distribution of $\tilde{Y}(g)$, or the expectation of $\tilde{Y}(g)$, for a given treatment regime g using a sample of observed data $O_i; i=1, \dots, n$ where $O_i = (\bar{L}_i, \bar{A}_i, Y_i)$, we could proceed as follows:

We would posit models for the conditional density

$$p_{\bar{L}_j}(\bar{l}_j | \bar{L}_{j-1}, \bar{A}_{j-1}; \psi_j), \quad j=1, \dots, M \quad (5.2B.1)$$

$$P_{\bar{L}_0}(l_0; \psi_0),$$

and

$$p_{Y|\bar{L}, \bar{A}}(y | \bar{L}, \bar{A}; \psi_{M+1}),$$

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in terms of parameters $(\psi_0^T, \dots, \psi_{M+1}^T)^T$
 where ψ_j are themselves vector of parameters.

The parameters $(\psi_0^T, \dots, \psi_{M+1}^T)^T$ can be obtained
 by maximizing the following partial likelihood

$$\prod_{i=1}^n \left\{ \frac{p(Y_i | \bar{L}_i; \bar{A}_i; \psi_{M+1})}{y_i | \bar{L}_i, \bar{A}_i} \prod_{j=1}^M p(L_{ji} | \bar{L}_{j-1}, \bar{A}_{j-1}; \psi_j) p(l_0; \psi_0) \right\}$$

to obtain estimators $(\hat{\psi}_{0,n}^T, \dots, \hat{\psi}_{M+1,n}^T)^T$.

Integrating out the l 's as in (5.25.1) would be prohibitive. Therefore a suggestion given by Robins is to approximate the distribution of y_{ig} for any $g \in \mathcal{G}$ using Monte-Carlo integration.

Specifically, we would proceed as follows:

For $r = 1, \dots, K$ (number of simulations) and a fixed treatment regime $g \in \mathcal{G}$,

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(i) generate random l_{0r} from $p_{L_0}(l_0; \hat{\psi}_{0n})$ (ii) generate random l_{1r} from $p_{L_1|L_0, A_0} \{ l_1 | l_{0r}, g(l_{0r}); \hat{\psi}_{1n} \}$ \vdots (iii) generate random l_{jr} from $p_{L_j|L_{j-1}, A_{j-1}} \{ l_j | \bar{l}_{j-1,r}, \bar{g}_{j-1}(\bar{l}_{j-1,r}); \hat{\psi}_{jn} \}, j=2, \dots, M$ (iv) generate $\tilde{y}_r(g)$ from $p_{Y|\bar{L}, \bar{A}} \{ y | \bar{l}_r, \bar{g}_M(\bar{l}_r) \}.$

The value $\tilde{y}_1(g), \dots, \tilde{y}_k(g)$ represent a random sample from the estimated distribution of $\tilde{Y}(g)$. So, for example, we could estimate

 $E\{\tilde{Y}(g)\}$ by

$$K^{-1} \sum_{r=1}^k \tilde{y}_r(g).$$

Remarks:

1. We can imagine that the modeling exercise for (5.28.1) can be a daunting task especially when M (the number of decision points) becomes large and the covariates L_0, \dots, L_M are high-dimensional.
2. Even if we were able to obtain reasonable models in (5.28.1) and therefore were able to obtain reasonable estimators for $E\tilde{Y}(g)$, the number of possible treatment regimes that we may want to consider can be enormous. It is not obvious how we would go about to find good treatment regimes or the optimal treatment regime g^{opt} .
3. Notice that the g -computation algorithm used every other conditional density of the likelihood of the observed data (5.17.2). We did not use or need to specify models for

$$P_{A_j | \bar{L}_j, \bar{A}_{j-1}}^{(a_j | \bar{l}_j, \bar{a}_{j-1})}, j = 0, \dots, M \quad (5.29.1)$$

in order to carry out the g -computation algorithm. There are another class of estimators for the distribution of $\tilde{Y}(g)$ which actually use (5.29.1). These are inverse propensity score weighted estimator which we now describe.

Inverse propensity score weighted estimator 5.3.0
for the distribution of response of treatment regimes

Consider a specific dynamic treatment regime $g \in \mathcal{G}$ and assume the data that are collected from a longitudinal study satisfy

(i) SUTVA

(ii) SRA

(iii) positivity assumption.

We define the propensity score as

$$P\{\bar{A} = \bar{g}(\bar{L}) | W\} \quad (5.30.1)$$

$$P\{A_0 = g_0(L_0), A_1 = g_1(L_1), \dots, A_M = g_M(L_M) | W\}.$$

Under the above assumptions, the propensity score can be written as

$$P\{A_0 = g_0(L_0) | W\} \times P\{A_1 = g_1(L_1) | A_0 = g_0(L_0), W\} \times \dots \times (5.30.2)$$

$$P\{A_j = g_j(\bar{L}_j) | \bar{A}_{j+1} = \bar{g}_{j+1}(\bar{L}_{j+1}), W\} \times \dots \times P\{A_M = g_M(\bar{L}_M) | \bar{A}_{M-1} = \bar{g}_{M-1}(\bar{L}_{M-1}), W\}.$$

Consider the j -th term in (5.30.2); namely

$$P\{A_j = g_j(\bar{L}_j) | \bar{A}_{j+1} = \bar{g}_{j+1}(\bar{L}_{j+1}), W\}. \quad (5.30.3)$$

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We have already argued that $\bar{L}_j(g)$ is a function of W (the set of potential outcomes). Therefore, there is no loss of generality in writing the j th term (5.30.3) as

$$P\{A_j = g_j(\bar{L}_j) \mid \bar{A}_{j-1} = \bar{g}_{j-1}(\bar{L}_{j-1}), \bar{L}_j(g), W\}. \quad (5.31.1)$$

By SUTVA, (5.31.1) is equal to

$$P\{A_j = g_j(\bar{L}_j) \mid \bar{A}_{j-1} = \bar{g}_{j-1}(\bar{L}_{j-1}), \bar{L}_j, W\},$$

and by SRA is equal to

$$P\{A_j = g_j(\bar{L}_j) \mid \bar{A}_{j-1} = \bar{g}_{j-1}(\bar{L}_{j-1}), L_j\}, \quad (5.31.2)$$

which is a function of the distribution of the observables

$$\frac{p_{A_j \mid \bar{A}_{j-1}, L_j}(a_j \mid \bar{a}_{j-1}, \bar{l}_j)}{p_{A_j \mid \bar{A}_{j-1}}(a_j)}.$$

Consequently the propensity score (5.30.1) is equal to

$$\prod_{j=0}^m \frac{p_{A_j \mid \bar{A}_{j-1}, L_j}(g_j(\bar{L}_j) \mid \bar{g}_{j-1}(\bar{L}_{j-1}), \bar{L}_j)}{p_{A_j \mid \bar{A}_{j-1}}(g_j)}. \quad (5.31.3)$$

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We also note that by SOTVA

the event $\{\bar{A}_{j-1} = \bar{g}_{j-1}(\bar{L}_{j-1}), L_j\}$ for all $j=1, \dots, M$

is equivalent to

$\{\bar{A}_{j-1} = \bar{g}_{j-1}(\bar{L}_{j-1}^{(q)}), \bar{L}_j^{(q)}\}$ for all $j=1, \dots, M$

Therefore the propensity score (5.31.3) can also be written as

$$\prod_{j=0}^M p\left[\bar{g}_{j-1}(\bar{L}_{j-1}^{(q)}) \mid \bar{g}_{j-1}(\bar{L}_{j-1}^{(q)}), \bar{L}_j^{(q)}\right] \quad (5.32.1)$$

making it clear that this is a function of W .

Using the propensity score, we now show that an unbiased estimator for

$$p(l_0, l_1, \dots, l_M, y) \\ L_0, \bar{L}_1^{(q)}, \dots, \bar{L}_M^{(q)}, \bar{Y}^{(q)}$$

$$= P\{l_0 = l_0, \bar{L}_1^{(q)} = l_1, \dots, \bar{L}_M^{(q)} = l_M, \bar{Y}^{(q)} = y\}$$

can be obtained by the inverse propensity score weighted statistic

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$$\mathbb{P}\{\bar{A}_0 = g_0(l_0), \dots, \bar{A}_M = g_M(\bar{l}_M) \mid \bar{I} \}, \quad \bar{I} \mid \bar{l}_0 = l_0, \dots, \bar{l}_M = l_M, Y = y \}$$

(5.33.1)

$$\prod_{j=0}^M \frac{\mathbb{P}\{\bar{g}_j(\bar{l}_j) \mid \bar{g}_{j-1}(\bar{l}_{j-1}), \bar{l}_j\}}{\mathbb{P}\{\bar{A}_j \mid \bar{A}_{j-1}, \bar{l}_j\}}.$$

Proof: We have already argued that the denominator of (5.33.1) is equal to

$$\mathbb{P}\{\bar{A} = \bar{g}(\bar{l}) \mid W\}.$$

Because of this and by SUTVA, we now write (5.33.1) as

$$\mathbb{P}\{\bar{A} = \bar{g}(\bar{l}) \mid \bar{l}_0 = l_0, \tilde{l}_1(g) = l_1, \dots, \tilde{l}_M(g) = l_M, \tilde{Y}(g) = y\}$$

(5.33.2)

$$\mathbb{P}\{\bar{A} = \bar{g}(\bar{l}) \mid W\}$$

We compute the expectation of (5.33.2) by using iterated conditional expectations where we first condition on W to obtain

$$\mathbb{E}\left(E[\mathbb{P}\{\bar{A} = \bar{g}(\bar{l}) \mid W\} \mid \bar{l}_0 = l_0, \dots, \tilde{l}_M(g) = l_M, \tilde{Y}(g) = y]\right)$$

$$\mathbb{P}\{\bar{A} = \bar{g}(\bar{l}) \mid W\}$$

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$$= E \left[\frac{P\{\bar{A} = \bar{g}(\bar{L})/W\}}{P\{\bar{A} = \bar{g}(\bar{L})/W\}} \right] \underbrace{I\{L_0 = l_0, \dots, L_M = l_M, \tilde{Y}(g) = y\}}_{(5.34)}.$$

The positivity assumption implies that

$$P\{\bar{A} = \bar{g}(\bar{L})/W\} > 0 \text{ almost surely}$$

which implies that $\frac{P\{\bar{A} = \bar{g}(\bar{L})/W\}}{P\{\bar{A} = \bar{g}(\bar{L})/W\}} = 1$ almost surely,

in which case (5.34.1) is equal to

$$E \left[I\{L_0 = l_0, \dots, L_M = l_M, \tilde{Y}(g) = y\} \right]$$

$$= p(l_0, \dots, l_M, y),$$

$$L_0, \tilde{L}_1(g), \dots, \tilde{L}_M(g), \tilde{Y}(g)$$

giving us the desired result. #

Similarly, we can show that an unbiased estimator for $E\{\tilde{Y}(g)\}$ is

$$\overline{I\{\bar{A} = \bar{g}(\bar{L})\}} Y$$

$$\frac{1}{n} \sum_{j=0}^n p\left\{ g_j(\bar{L}_j) \mid \bar{g}_{j+1}(\bar{L}_{j+1}), \bar{L}_j \right\}$$

$$A_j / A_{j+1}, \bar{L}_j$$

$$\textcircled{2} \quad \left[\prod_{j=0}^m I\{A_j = g_j(\bar{L}_j)\} \right] Y$$

$$\cdot \prod_{j=0}^m P\{g_j(\bar{L}_j) | \bar{g}_{j-1}(\bar{L}_{j-1}), \bar{L}_j\}.$$

If we knew the elements of the propensity score

$$p(a_j | \bar{a}_{j-1}, \bar{l}_j)$$

$$A_j | \bar{A}_{j-1}, \bar{L}_j$$

as might be the case in a sequentially randomized intervention study, then we can obtain an estimator for $E[Y|g]\}$ using

$$\frac{n^{-1} \sum_i I\{A_i = g(\bar{L}_i)\} Y_i}{\sum_{j=0}^m P\{g_j(\bar{L}_j) | \bar{g}_{j-1}(\bar{L}_{j-1}), \bar{L}_j\}} \quad (5.35.1)$$

$$\frac{\sum_{j=0}^m P\{g_j(\bar{L}_j) | \bar{g}_{j-1}(\bar{L}_{j-1}), \bar{L}_j\}}{\sum_{j=0}^m P\{g_j(\bar{L}_j) | \bar{g}_{j-1}(\bar{L}_{j-1}), \bar{L}_j\}}$$

In observational studies, the propensity score is not known and must be estimated using the observed data. To do so we posit models for

$$p(a_j | \bar{a}_{j-1}, \bar{l}_j; \gamma_j), j=0, \dots, M$$

using parameters $(\gamma_0^T, \dots, \gamma_M^T)^T$.

5.36

The parameters γ can be estimated by maximizing the partial likelihood

$$\prod_{i=1}^n \left\{ \prod_{j=0}^M p(A_{ji} | A_{j-1}, L_{ji}; \gamma_j) \right\} \cdot \frac{1}{\prod_{j=0}^M A_j | A_{j-1}, L_j} \quad (5.36.1)$$

The inverse propensity score weighted estimator for $E\{\bar{Y}(g)\}$ is then

$$\hat{Y} = \frac{1}{n} \sum_{i=1}^n \left[\prod_{j=0}^M \frac{A_j | A_{j-1}, L_j}{p(\bar{A}_{ji} | \bar{L}_{ji})} \right] Y_i \quad (5.36.2)$$

For example, if the treatment $A_{ji}, j=0, \dots, M$ were all binary, then we could posit models for

$$P(A_{ji}=1 | A_{j-1}, L_j) = \bar{\pi}_j(\bar{A}_{j-1}, \bar{L}_{ji}; \gamma_j),$$

then (5.36.1) would equal

$$\prod_{i=1}^n \left[\prod_{j=0}^M \frac{\bar{\pi}_j(\bar{A}_{j-1}, \bar{L}_{ji}; \gamma_j)}{1 - \bar{\pi}_j(\bar{A}_{j-1}, \bar{L}_{ji}; \gamma_j)} \right].$$

For example, logistic regression models could be used for $\bar{\pi}_j(\bar{A}_{j-1}, \bar{L}_{ji}; \gamma_j)$ which would allow standard software to be used to estimate the parameters γ .

The asymptotic properties of $\hat{\mu}_n(g)$, the estimator for $E\tilde{g}(g)$, could then be obtained by using the stacked m-estimator

$$\sum_{i=1}^n \left\{ \frac{1}{m} \sum_{j=0}^M \underbrace{\mathbb{P}\{g_j(\bar{L}_{ji}) \mid g_{j-1}(\bar{L}_{j-1,i}), L_{ji}; j \leq j\}}_{A_j | \bar{A}_{j-1}, \bar{L}_i} - \mu(g) \right\} = 0$$

together with the estimating equations
for $\gamma_j, j=0, \dots, M$.

Remarks

- To compute the inverse propensity score weighted estimator we proceed as follows. Let $D = (\bar{L}, \bar{A})$ denote the observed covariates and treatments, in which case the observed data can be summarized as (D, Y) . For any treatment regime g , we define the consistency function

$$C_g(D_i) = I\{A_{0i} = g_0(L_{0i}), A_{1i} = g_1(L_{1i}), \dots, A_{Mi} = g_M(L_{Mi})\};$$

that is, for any combination of covariates and treatments D , $C_g(D)$ is equal to one if these are consistent with treatment regime g , and

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is equal to zero if they are not.

Also defined

$$\pi(D_i) = \prod_{j=0}^M p_{A_j | \bar{A}_{j-i}, L_j} (A_{ji}, \bar{A}_{j-i}, L_j). \quad (5.38.1)$$

In that case, the inverse weighted propensity score estimator of $\mu_g = E\{\tilde{Y}(g)\}$ can be expressed as

$$\frac{n}{\pi(D_i)} \sum_{j=1}^n C_g(D_i) Y_j. \quad (5.38.2)$$

2. Although, in theory, inverse propensity score weighted estimators give consistent, asymptotically normal estimators, in practice, these are feasible only if the number of decision points M and the number of treatment options is not too large. Otherwise, the number of individuals

$\{i : \text{such that } I\{\bar{A}_i = \bar{g}(L_i)\}\}$ becomes so small as to give unstable estimators. Therefore, other modeling strategies need to be considered as we will discuss later.

The key assumption that allows us to make causal comparisons is the sequential randomization assumption. One way to guarantee that this assumption holds is to conduct a sequentially randomized study. Such studies have also been called SMART (Sequential Multiple Assignment Randomized Trial) Studies. Specifically, at the j th decision point we assign one of the potential treatments $a_j \in \underline{\Phi}_j(l_j; \bar{a}_{j-1}) \subset A_j$ at random with probability

$$P(A_j=a_j | l_j; \bar{a}_{j-1}), \quad a_j \in \underline{\Phi}_j(l_j; \bar{a}_{j-1}),$$

which is predetermined by the investigator, where

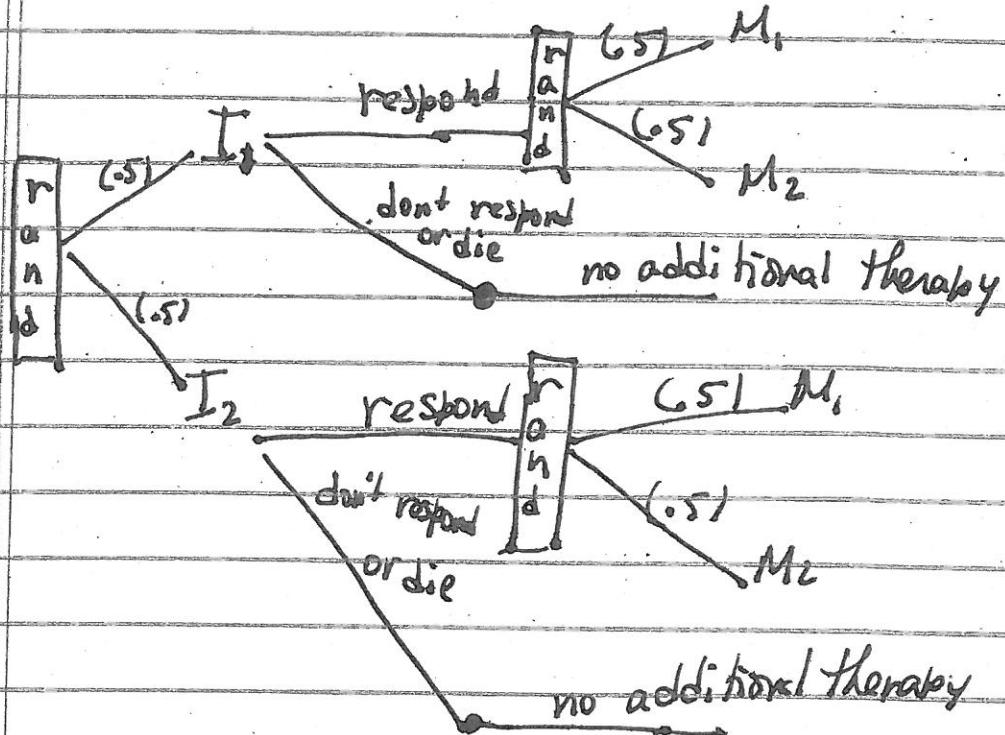
$$\sum_{a_j \in \underline{\Phi}_j(l_j; \bar{a}_{j-1})} P(A_j=a_j | l_j; \bar{a}_{j-1}) = 1.$$

Because the sequential randomization assumption holds, we are able to use the methods discussed previously to derive estimators for the mean response of treatment regimes. We can compare the mean response for different regimes or, if there are a relatively small number of such regimes that we want to focus on, then we can look for the best such regime; i.e., the one that gives the largest mean response.

5.40

Let me illustrate using two examples of two-stage designs in cancer clinical trials. The first was a design used in Cancer and Leukemia Group B (CALGB) protocol 8923. This was a double-blind placebo controlled two-stage trial examining the effects of infusion of granulocyte-macrophage colony-stimulating factor (GM-CSF) after initial chemotherapy with acute myelogenous leukemia (AML) patients. GM-CSF administered after chemotherapy might assist patient recovery by allowing more rapid reconstitution of bone marrow-derived lineages, thus reducing the number of deaths due to such complications. Patients were randomized to GM-CSF or placebo following standard chemotherapy. Later, patients achieving complete remission were randomized to one of two intensification therapies.

Let us denote the two induction therapies by I_1, I_2 , where $I_1 = \text{GM-CSF}$ and $I_2 = \text{placebo}$. If patients responded then they could receive additional maintenance therapy where the options are denoted by M_1 and M_2 . Thus the design of the study can be depicted as



The primary outcome of this study was time to death and the goal was to find the best combination of induction and maintenance therapy which leads to the largest expected lifetime.

We summarize the data that are observed as (for a single individual)

$$(L_0, A_0, L_1, A_1, Y),$$

where L_0 denotes baseline covariates,

L_1 denotes covariates measured between baseline and the first decision point, and

$Y = \text{time to death}$.

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We will also define $V_0 CL_0$ and $V_1 CL_1$ to be a subset of the variables which actually were used to determine the randomization probabilities.

A_0 and A_1 are the interventions at baseline and at the second stage respectively.

For our problem $A_0 = \{I_1, I_2\}$

$A_1 = \{M_1, M_2, \text{no additional intervention}\}$

$V_0 = \emptyset$

$V_1 = R = \begin{cases} 1 & \text{if patient responds} \\ 0 & \text{if no response or death before response} \end{cases}$

$\overline{\Phi}_{l_0}(l_0) = \{I_1, I_2\}$ for all l_0

randomization probabilities at baseline:

$$P(A_0 = I_1 | l_0 = l_0) = .5, \quad P(A_0 = I_2 | l_0 = l_0) = .5,$$

$\overline{\Phi}_{l_0}(l_1, a_0) = \{M_1, M_2\}$ if $r=1$

$\overline{\Phi}_{l_0}(l_1, a_0) = \{\text{no additional intervention}\}$ if $r=0$.

5.43

randomization probabilities at second stage

$$P(A_1 = M_1 | R=1) = P(A_1 = M_2 | R=1) = .5;$$

$$P(A_1 = N | R=0) = 1.0.$$

Let us consider a specific treatment regime

$g = (I_1, M_1, N)$, where we use this shorthand notation to denote the treatment regime

"give treatment I_1 as induction therapy, if the patient responds give maintenance therapy M_1 ; otherwise, no additional therapy".

Specifically, $g_0(l_0) = I_1$ for all l_0 ,

$$g_1(l_1) = M_1 \text{ if } R=1,$$

$$g_1(l_1) = N \text{ if } R=0.$$

Note: that this is an example of a simple dynamic treatment regime because the treatment at the second stage depends on whether the patient responds or not after the initial treatment.

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There are four such simple treatment regimes that can be examined from the design of such a study; namely, $\{I_1, M_1, N\}$, $\{I_1, M_2, N\}$, $\{I_2, M_1, N\}$ and $\{I_2, M_2, N\}$.

However, we have the ability to examine any treatment regime of where

$$g_0: L_0 \rightarrow \{I_1, I_2\}$$

$$g_1: (L_0 \times L_1)_{R=1} \rightarrow \{M_1, M_2\} \text{ as long as } R=1$$

$$: (L_0 \times L_1)_{R=0} \rightarrow N \text{ as long as } R=0,$$

and L_0 denotes the sample space for L_0
and

$(L_0 \times L_1)_{R=1}$ denotes all the possible values
of (l_0, l_1) such that $R=1$, $(L_0 \times L_1)_{R=0}$ when $R=0$.

Clearly with such a design if $R=0$ then a patient will receive no additional therapy regardless of any additional information about L_0 or L_1 .

Assuming that the survival times are not right-censored, then the observed data from such a clinical trial can be summarized as

$$(L_0, A_0, L_1, A_1, Y_i), i=1, \dots, n.$$

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If we want to estimate $E\{Y(g)\}$, we can use the inverse propensity score weighted estimator (5.38.2); namely,

$$n^{-1} \sum_{i=1}^n \frac{C_g(D_i)}{\pi(D_i)} Y_i$$

For example, if we consider the treatment regime $g = \{I_1, M_1, N\}$, then the estimator for $E\{Y(g)\}$ can be written as

$$n^{-1} \sum_{i=1}^n I(A_{0i}=I_1) \{ I(A_{1i}=M_1, R_i=1) + I(A_{1i}=N, R_i=0) \} Y_i$$

$$(0.5) \{ 0.5 I(R_i=1) + I(R_i=0) \}$$

Improved estimators for $E\{Y(g)\}$ could be obtained by estimating the randomization probabilities using sample proportions.

That is, we can estimate

$$\hat{p}_1 = \hat{P}(A_i = I_1) \text{ by } \hat{p}_{1n} = \bar{n}^{-1} \sum_{i=1}^n I(A_{0i}=I_1)$$

$$\text{and } \hat{p}_2 = P(A_i=M_1 | R_i=1, A_{0i}=I_1) \text{ by}$$

$$\hat{p}_{2n} = \frac{\sum_{i=1}^n I(A_{1i}=M_1, R_i=1, A_{0i}=I_1)}{\sum_{i=1}^n I(R_i=1, A_{0i}=I_1)}$$

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in which case the estimator for $E\{\tilde{Y}(q)\}$ would be

$$\frac{1}{n} \sum_{i=1}^n I(A_{0i}=I_1) \{ I(A_{1i}=M_1, R_i=1) + I(R_i=0) \} / \hat{P}_{1n} \{ \hat{P}_{2n} I(R_i=1) + I(R_i=0) \} \quad (5.46.1)$$

A straightforward way to derive the large sample properties of (5.46.1) is to use the stacked m-estimator

$$\sum_{i=1}^n \left\{ \frac{C_g(I_i)}{P_i} Y_i - E\{\tilde{Y}(q)\} \right\} = 0$$

$$\sum_{i=1}^n \left\{ I(A_{0i}=I_1) - b_1 \right\} = 0$$

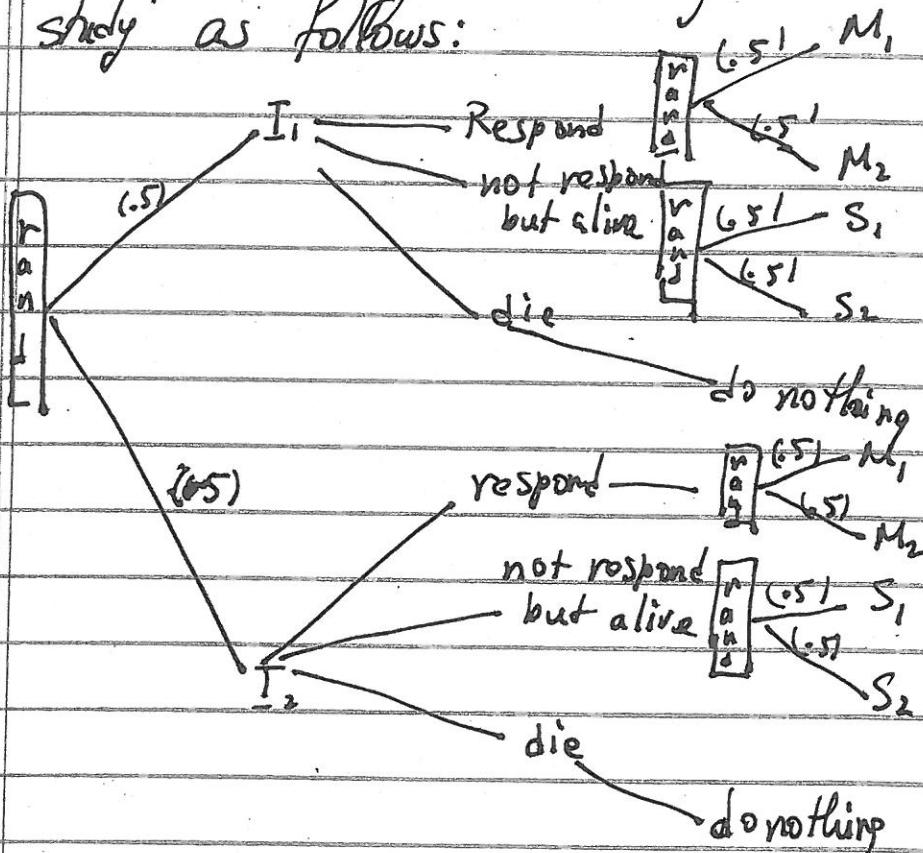
$$\sum_{i=1}^n I\{A_{0i}=I_1, R_i=1\} \{ I(A_{1i}=M_1) - b_2 \} = 0$$

and derive the asymptotic joint distribution

$$\text{of } (\hat{E}_n \{ \tilde{Y}(q) \}, \hat{P}_{1n}, \hat{P}_{2n}),$$

where $C_g(I_i) = I(A_{0i}=I_1) \{ I(A_{1i}=M_1, R_i=1) + I(R_i=0) \}$.

In the previous example, patients that didn't respond were assigned to usual care (no additional treatment). In some cases we may also want to give such patients salvage therapy, or, at least, be able to evaluate the effect that different salvage therapies (if there are more than one) may have on survival. Say, for example, we have two competing salvage therapies, S_1, S_2 . In that case, we may have designed a SMART study as follows:



We can summarize the main dynamic treatment regimes in such a SMART study as:

$$g = (I_j, M_{j'}, S_{j''}, N), j, j', j'' = 1, 2,$$

to denote "give treatment I_j as induction therapy, if the patient responds give maintenance therapy $M_{j'}$; if the patient doesn't respond and is still alive give salvage therapy $S_{j''}$ ", and, of course, if the patient dies before response status is ascertained do nothing".

To handle this setting we define the variable R to take on values 0, 1, 2 where

$R=0$ denotes death prior to response status,
 $R=1$ if patient responds to initial therapy,
and $R=2$ if patient doesn't respond to initial therapy and is still alive.

In that case, $E^N Y(g = (I_j, M_{j'}, S_{j''}, N))$ can be estimated by

$$\frac{1}{n} \sum_{i=1}^n I(A_{0i}=I_j) \{ I(A_{1i}=M_{j'}, R_i=1) + I(A_{2i}=S_{j''}, R_i=2) + I(R_i=0) \} Y_i$$

$$\cdot .5 \{ .5 I(R_i=1) + .5 I(R_i=2) + I(R_i=0) \}$$

As before, the randomization probabilities can be estimated by the appropriate sample proportion to obtain more efficient estimators.

Remarks:

- 1. In a SMART study, the same individual may contribute to more than one dynamic treatment regime. For example, if an individual receives I_1 at induction, responds, and then receives M_1 as maintenance therapy, then such an individual is consistent with either treatment regime

I_1, M_1, S_1, N

or I_1, M_1, S_2, N .

If a patient receives treatment I_1 at induction and then dies before their response status is determined, then such a patient is consistent with treatment regimes

I_1, M_1, S_1, N

I_1, M_1, S_2, N

I_1, M_2, S_1, N

I_1, M_2, S_2, N .

2. SMART studies are a good way to evaluate the effect of combinations of treatments given over time. Unfortunately, they are hardly ever used in practice except for studies in substance abuse and behavioral studies. This is unfortunate, in my opinion, because a great deal can be learned from such designs. The general current practice is to conduct point-of-exposure randomized clinical trials on different subsets of patients and then to recommend combinations of treatments over time by cobbling together the results of such individual studies.

Because of this, there has been little research devoted to the design and sample size considerations for such studies. I.e., how many decision points should be considered?, how many treatments at each decision point? How large a sample size is necessary? I believe this will be a fertile research area for statisticians in the future.

Notes to myself regarding some technical issues for the inverse propensity score weighted estimator for the distribution of a treatment regime.

For (5.30.1) we defined the propensity score as $P\{\bar{A} = \bar{g}(\bar{L})/N\}$. Let us consider only a subset of N that involves the treatment regime g ; i.e., $IN_g = \{\bar{l}_0, \tilde{L}_1(g), \dots, \tilde{L}_M(g), \tilde{Y}(g)\}$.

We have already argued $W_g \subset W$. Let us also denote by \mathcal{Y}_g as the set of realization $(l_0, l_1, \dots, l_M, y)$ of IN_g that have positive mass; i.e., where

$$P\{\bar{l}_0 = l_0, \tilde{L}_1(g) = l_1, \dots, \tilde{L}_M(g) = l_M, \tilde{Y}(g) = y\} > 0.$$

In order to prove results for the "IPSWE" it suffices to define the propensity score as

$$P\{\bar{A} = \bar{g}(\bar{L})/IN_g\}.$$

Identical arguments as those given on pages 530-532 lead us to conclude that

55.2

$$P\{\bar{A} = \bar{g}(\bar{l}) / W_g\} =$$

$$\prod_{j=0}^m P_{A_j | \bar{A}_{j+1}, \bar{L}_j} \{ g_j(\bar{l}_j) | \bar{g}_{j+1}(\bar{l}_{j+1}), \bar{L}_j \} \quad (55.2.1)$$

$$= \prod_{j=0}^m \frac{P_{A_j | \bar{A}_{j+1}, \bar{L}_j} \{ \bar{g}_j \bar{g}_{j+1} \bar{L}_j(g) \}}{P_{A_j | \bar{A}_{j+1}, \bar{L}_j} \{ \bar{g}_j \bar{g}_{j+1} \bar{L}_j(g) \}} \cdot (55.2.2)$$

However, we need the technical argument that (55.2.1) and (55.2.2) were strictly positive for any any element $(l_0, l_1, \dots, l_m, y) \in W_g$.

This certainly would be true if we could show that for any $(l_0, \dots, y) \in W$ that

$$P\{\bar{A}_j = \bar{g}_{j+1}(\bar{l}_{j+1}), \bar{l}_j = \bar{l}_j\} > 0 \quad (55.2.3)$$

$$\text{and } P\{\bar{A}_j = \bar{g}_j(\bar{l}_j) | \bar{A}_{j+1} = \bar{g}_{j+1}(\bar{l}_{j+1}), \bar{L}_j = \bar{l}_j\} > 0 \quad (55.2.4)$$

for all $j=0, \dots, M$.

Under the positivity assumption we showed that (55.2.3) was true by an induction proof of page (5.2.3) and (55.2.4) is true follows directly from the positivity assumption.