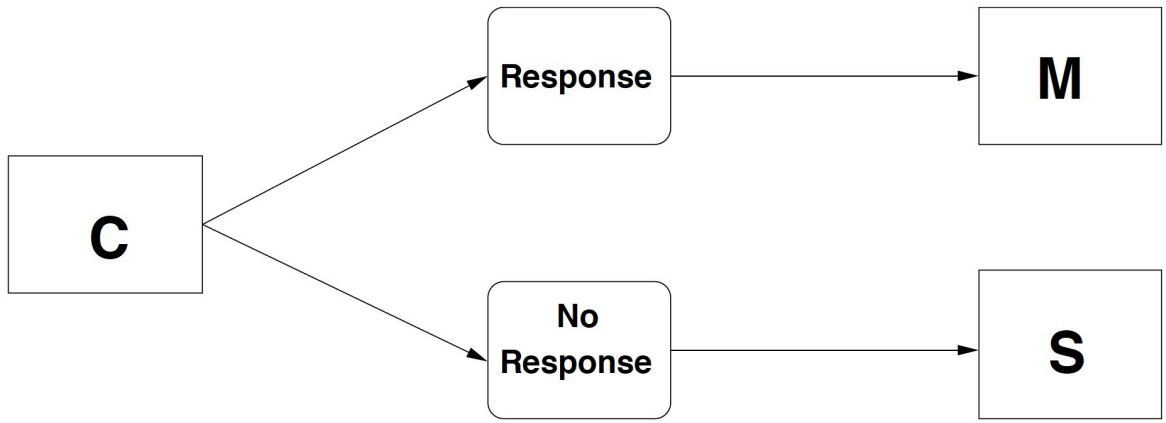
5. Multiple Decision Treatment Regimes: Framework and Fundamentals

Recall: Acute Leukemia



- *At baseline:* Information x_1, history $h_1 = x_1 \in \mathcal{H}_1$
- *Decision 1:* Set of options $\mathcal{A}_1 = \{C_1, C_2\}$; rule 1: $d_1(h_1)$: $\mathcal{H}_1 \to \mathcal{A}_1$
- *Between Decisions 1 and 2:* Collect additional information x_2, including responder status
- *Accrued information/history* $h_2 = (x_1$, therapy at decision 1, $x_2) \in \mathcal{H}_2$
- *Decision 2:* Set of options $\mathcal{A}_2 = \{M_1, M_2, S_1, S_2\}$; rule 2:

$d_2(h_2)$: $\mathcal{H}_2 \to \{M_1, M_2\}$ (responder), $d_2(h_2)$: $\mathcal{H}_2 \to \{S_1, S_2\}$ (nonresponder)

- *Treatment regime*: $d = \{d_1(h_1), d_2(h_2)\} = (d_1, d_2)$

K decision treatment regime

In general: K decision points/stages

- *Baseline information* $x_1 \in \mathcal{X}_1$, *intermediate information* $x_k \in \mathcal{X}_k$ between Decisions $k-1$ and k, $k = 2, \ldots, K$
- *Treatment options* $\mathcal{A}_k$ at Decision k, elements $a_k \in \mathcal{A}_k$, $k = 1, \ldots, K$
- *Accrued information* or *history*

$$h_1 = x_1 \in \mathcal{H}_1$$
$$h_k = (x_1, a_1, \ldots, x_{k-1}, a_{k-1}, x_k) \in \mathcal{H}_k, \quad k = 2, \ldots, K,$$

- *Decision rules* $d_1(h_1), d_2(h_2), \ldots, d_K(h_K)$, $d_k : \mathcal{H}_k \to \mathcal{A}_k$
- *Treatment regime*

$$d = \{d_1(h_1), \ldots, d_K(h_K)\} = (d_1, d_2, \ldots, d_K)$$

Notation

Overbar notation: With

$$x_k \in \mathcal{X}_k, \quad a_k \in \mathcal{A}_k, \quad k = 1, \ldots, K$$

it is convenient to define for $k = 1, \ldots, K$

$$\overline{x}_k = (x_1, \ldots, x_k), \quad \overline{a}_k = (a_1, \ldots, a_k)$$

$$\overline{\mathcal{X}}_k = \mathcal{X}_1 \times \cdots \times \mathcal{X}_k, \quad \overline{\mathcal{A}}_k = \mathcal{A}_1 \times \cdots \times \mathcal{A}_k$$

- Conventions: $\overline{a} = \overline{a}_K, \quad \overline{x} = \overline{x}_K, \quad a_0$ is null
- $h_1 = x_1, \quad h_k = (\overline{x}_k, \overline{a}_{k-1}), \quad k = 2, \ldots, K$
- $\mathcal{H}_1 = \mathcal{X}_1, \quad \mathcal{H}_k = \overline{\mathcal{X}}_k \times \overline{\mathcal{A}}_{k-1}, \quad k = 2, \ldots, K$
- $\overline{d}_k = (d_1, \ldots, d_k), \ k = 1, \ldots, K, \quad d = \overline{d}_K = (d_1, \ldots, d_K)$

Decision points

Decision points depend on the context: For example

- Acute leukemia: Decisions are at milestones in the disease progression (diagnosis, evaluation of response)
- HIV infection: Decisions are according to a schedule (at monthly clinic visits)
- Cardiovascular disease (CVD): Decisions are made upon occurrence of an event (myocardial infarction)

Perspective:

- *Timing* of decisions can be fixed (HIV) or random (leukemia)
- If any individual would reach all K decision points, the distinction is not important; *we assume this going forward*
- If different individuals can experience different numbers of decisions (CVD), the number of decisions reached is random, and a more specialized framework is required
- The latter also is the case if the outcome is a *time to an event*

Example: $K = 2$, acute leukemia

Decision 1: $\mathcal{A}_1 = \{\mathrm{C}_1, \mathrm{C}_2\}$, $x_1 = h_1$ includes age (years), baseline white blood cell count WBC_1 ($\times 10^3/\mu l$)

- Example rule:

$$d_1(h_1) = \mathrm{C}_2\, \mathrm{I}(\mathcal{C}) + \mathrm{C}_1\, \mathrm{I}(\mathcal{C}^c), \quad \mathcal{C} = \{\text{age} < 50,\ \mathrm{WBC}_1 < 10\}$$

Decision 2: $\mathcal{A}_2 = \{\mathrm{M}_1, \mathrm{M}_2, \mathrm{S}_1, \mathrm{S}_2\}$

- x_2 and thus h_2 includes Decision 2 WBC_2; ECOG, EVENT ($\geq$ grade 3 adverse event from induction therapy), RESP
- Example rule:

$$\begin{aligned} d_2(h_2) = {} & \mathrm{I}(\mathrm{RESP} = 1)\{\mathrm{M}_1\, \mathrm{I}(\mathcal{M}) + \mathrm{M}_2\, \mathrm{I}(\mathcal{M}^c)\} \\ & + \mathrm{I}(\mathrm{RESP} = 0)\{\mathrm{S}_1\, \mathrm{I}(\mathcal{S}) + \mathrm{S}_2\, \mathrm{I}(\mathcal{S}^c)\} \end{aligned} \tag{5.1}$$

$$\mathcal{M} = \{\mathrm{WBC}_1 < 11.2, \mathrm{WBC}_2 < 10.5, \mathrm{EVENT} = 0, \mathrm{ECOG} \leq 2\}$$

$$\mathcal{S} = \{\text{age} > 60, \mathrm{WBC}_2 < 11.0, \mathrm{ECOG} \geq 2\}$$

Recursive representation of rules

Fact: If the K rules in $d \in \mathcal{D}$ are *followed* by an individual, the options selected at each decision depend only on the evolving $x_1, \ldots, x_K$

- Decision 1: Option selected is $d_1(h_1) = d_1(x_1)$
- Between Decisions 1 and 2: x_2
- Decision 2: Rule $d_2(h_2) = d_2(\overline{x}_2, a_1)$, option selected depends on the option selected at Decision 1

$$d_2\{\overline{x}_2, d_1(x_1)\}$$

- Between Decisions 2 and 3: x_3
- Decision 3: Rule $d_3(h_3) = d_3(\overline{x}_3, \overline{a}_2) = d_3(\overline{x}_3, a_1, a_2)$, option selected depends on those at Decisions 1 and 2

$$d_3[\overline{x}_3, d_1(x_1), d_2\{\overline{x}_2, d_1(x_1)\}]$$

- And so on...

Recursive representation of rules

Concise representation: For $k = 2, \ldots, K$

$$
\begin{aligned}
\overline{d}_2(\overline{x}_2) &= [d_1(x_1), d_2\{\overline{x}_2, d_1(x_1)\}] \\
\overline{d}_3(\overline{x}_3) &= [d_1(x_1), d_2\{\overline{x}_2, d_1(x_1)\}, d_3\{\overline{x}_3, \overline{d}_2(\overline{x}_2)\}] \\
&\vdots \\
\overline{d}_K(\overline{x}_K) &= [d_1(x_1), d_2\{\overline{x}_2, d_1(x_1)\}, \ldots, d_K\{\overline{x}_K, \overline{d}_{K-1}(\overline{x}_{K-1})\}]
\end{aligned}
\tag{5.2}
$$

- $\overline{d}_k(\overline{x}_k)$ comprises the options selected through Decision k
- $\overline{d}(\overline{x}) = \overline{d}_K(\overline{x}_K)$
- This representation will be useful later

Redundancy

From the perspective of an individual following the K rules in d:

- The definition of rules $d_k(h_k) = d_k(\overline{x}_k, \overline{a}_{k-1})$ is redundant
- a_1 is determined by x_1, a_2 is determined by $\overline{x}_2 = (x_1, x_2)$, ...
- But definition of d_k as a function of $h_k = (\overline{x}_k, \overline{a}_{k-1})$ is useful for characterizing and estimating an optimal regime later

Illustration of redundancy: $K = 2$, $\mathcal{A}_1 = \{0, 1\}$, $\mathcal{A}_2 = \{0, 1\}$, $\mathcal{X}_1 = \{0, 1\}$, $\mathcal{X}_2 = \{0, 1\}$ (x_1 and x_2 are binary)

- $d = (d_1, d_2) \in \mathcal{D}$, $d_1 : \mathcal{H}_1 = \mathcal{X}_1 \to \mathcal{A}_1$, $d_2 : \mathcal{H}_2 = \overline{\mathcal{X}}_2 \times \mathcal{A}_1 \to \mathcal{A}_2$
- For each value of $h_1 = x_1$, d_1 must return a value in $\mathcal{A}_1$, e.g.,

$$d_1(x_1 = 0) = 0, \quad d_1(x_1 = 1) = 1$$

Redundancy

Illustration of redundancy, continued:

- For each of the $2^3 = 8$ possible values of $h_2 = (x_1, x_2, a_1)$, d_2 must return a value in $\mathcal{A}_2$, e.g.,

$$
\begin{aligned}
d_2(x_1 = 0, x_2 = 0, a_1 = 0) &= 0 \\
d_2(x_1 = 0, x_2 = 0, a_1 = 1) &= 1* \\
d_2(x_1 = 0, x_2 = 1, a_1 = 0) &= 1 \\
d_2(x_1 = 0, x_2 = 1, a_1 = 1) &= 1* \\
d_2(x_1 = 1, x_2 = 0, a_1 = 0) &= 0* \\
d_2(x_1 = 1, x_2 = 0, a_1 = 1) &= 1 \\
d_2(x_1 = 1, x_2 = 1, a_1 = 0) &= 0* \\
d_2(x_1 = 1, x_2 = 1, a_1 = 1) &= 0
\end{aligned}
$$

- Configurations with $*$ could never occur if an individual followed regime d

5. Multiple Decision Treatment Regimes: Framework and Fundamentals

Outcome of interest

Determination of outcome:

- Can be ascertained after Decision K, e.g., for HIV infected patients, outcome = viral load (viral RNA copies/mL) measured at a final clinic visit after Decision K
- Can be defined using intervening information, e.g., for HIV infected patients with CD4 count (cells/mm^3) measured at each clinic visit (Decisions $k = 2, \ldots, K$) and at a final clinic visit after Decision K

$$\text{outcome} = \text{total \# CD4 counts} > 200 \text{ cells/mm}^3$$

Convention: As for single decision case, assume larger outcomes are preferred

- E.g., because smaller viral load is better, take

$$\text{outcome} = -\text{viral load}$$

Potential outcomes for K decisions

Intuitively: For a randomly chosen individual with history X_1

- If he/she *were to receive* $a_1 \in \mathcal{A}_1$ at Decision 1, the evolution of his/her disease/disorder process after Decision 1 would be be influenced by a_1
- Suggests: $X_2^*(a_1)$ = intervening information *that would arise* between Decisions 1 and 2 after receiving $a_1 \in \mathcal{A}_1$ at Decision 1
- If he/she then *were to receive* $a_2 \in \mathcal{A}_2$ at Decision 2, the evolution of his/her disease/disorder process after Decision 2 would be influenced by a_1 followed by a_2
- Suggests: $X_3^*(\overline{a}_2)$ = intervening information *that would arise* between Decisions 2 and 3 after receiving $a_1 \in \mathcal{A}_1$ at Decision 1 and a_2 at Decision 2
- And so on...

Potential outcomes for K decisions

Ultimately: If he/she *were to receive* options $\overline{a} = \overline{a}_K = (a_1, \ldots, a_K)$ at Decisions 1,. . . ,K

$$Y^*(\overline{a}_K) = Y^*(\overline{a}) = \text{ outcome that } \textit{would be achieved}$$

Summarizing: Potential information at each decision and potential outcome if an individual *were to receive* $\overline{a} = (a_1, \ldots, a_K)$

$$\{X_1, X_2^*(a_1), X_3^*(\overline{a}_2), \ldots, X_K^*(\overline{a}_{K-1}), Y^*(\overline{a})\}$$

- X_1 may or may not be included
- Set of all possible potential outcomes for all $\overline{a} \in \overline{\mathcal{A}}$

$$W^* = \Big\{ X_2^*(a_1), X_3^*(\overline{a}_2), \ldots, X_K^*(\overline{a}_{K-1}), Y^*(\overline{a}), \\ \text{for } a_1 \in \mathcal{A}_1, \overline{a}_2 \in \overline{\mathcal{A}}_2, \ldots, \overline{a}_{K-1} \in \overline{\mathcal{A}}_{K-1}, \overline{a} \in \overline{\mathcal{A}} \Big\} \qquad (5.3)$$

Feasible sets and classes of treatment regimes

Example: Acute leukemia, $K = 2$

$$\mathcal{A}_1 = \{\mathrm{C}_1, \mathrm{C}_2\}, \quad \mathcal{A}_2 = \{\mathrm{M}_1, \mathrm{M}_2, \mathrm{S}_1, \mathrm{S}_2\}$$

- At Decision 1, both options are feasible for all patients
- At Decision 2, *only maintenance options* are feasible for patients who respond, and *only salvage options* are feasible for patients who do not respond
- Is the case *almost always* in multiple decision problems at decision points other than Decision 1
- Of course is also possible at Decision 1

Feasible sets and classes of treatment regimes

Formal specification: For any history $h_k = (\overline{x}_k, \overline{a}_{k-1}) \in \mathcal{H}_k$ at Decision k, $k = 1, \ldots, K$

- The set of feasible treatment options at Decision k is

$$\Psi_k(h_k) = \Psi_k(\overline{x}_k, \overline{a}_{k-1}) \subseteq \mathcal{A}_k, \quad k = 1, \ldots, K \tag{5.4}$$

$$\Psi_1(h_1) = \Psi_1(x_1) \subseteq \mathcal{A}_1 \quad (a_0 \text{ null})$$

- Ψ_k is a function mapping $\mathcal{H}_k$ to the set of all possible subsets of $\mathcal{A}_k$
- $\Psi_k(h_k)$ can be a strict subset of $\mathcal{A}_k$ or all of $\mathcal{A}_k$, depending on h_k
- Collectively: $\Psi = (\Psi_1, \ldots, \Psi_K)$

Feasible sets and classes of treatment regimes

Example, revisited: Acute leukemia, $K = 2$

$$\mathcal{A}_1 = \{\mathrm{C}_1, \mathrm{C}_2\}, \quad \mathcal{A}_2 = \{\mathrm{M}_1, \mathrm{M}_2, \mathrm{S}_1, \mathrm{S}_2\}$$

- Suppose C_1 and C_2 are feasible for all individuals regardless of h_1

$$\Psi_1(h_1) = \mathcal{A}_1 \quad \text{for all } h_1$$

- If h_2 indicates response

$$\Psi_2(h_2) = \{\mathrm{M}_1, \mathrm{M}_2\} \subset \mathcal{A}_2 \quad \text{for all such } h_2$$

- If h_2 indicates nonresponse

$$\Psi_2(h_2) = \{\mathrm{S}_1, \mathrm{S}_2\} \subset \mathcal{A}_2 \quad \text{for all such } h_2$$

- More complex specifications of feasible sets that take account of additional information are of course possible

Feasible sets and classes of treatment regimes

Fancier example: Acute leukemia, $K = 2$

$$\mathcal{A}_1 = \{C_1, C_2\}, \quad \mathcal{A}_2 = \{M_1, M_2, S_1, S_2\}$$

- If C_1 is contraindicated for patients with renal impairment

$$\begin{aligned} \Psi_1(h_1) &= \{C_2\} \quad \text{if } h_1 \text{ indicates renal impairment} \\ &= \{C_1, C_2\} = \mathcal{A}_1 \quad \text{if } h_1 \text{ does not} \end{aligned}$$

- If S_1 increases risk of adverse events in nonresponders with low WBC_2

$$\begin{aligned} \Psi_2(h_2) &= \{S_2\} \quad \text{if } h_2 \text{ indicates nonresponse, } WBC_2 \leq w \\ &= \{S_1, S_2\} \quad \text{if } h_2 \text{ indicates nonresponse, } WBC_2 > w \end{aligned}$$

for some threshold w ($\times 10^3/\mu l$)

Feasible sets and classes of treatment regimes

Ideally:

- Specification of the feasible sets is dictated by scientific considerations
- Disease/disorder context, available treatment options, patient population, etc
- Specification of $\Psi_k(h_k)$, $k = 1, \ldots, K$, should incorporate only information in h_k that is critical to treatment selection

Regimes and feasible sets: Given specified feasible sets Ψ

- A regime $d = (d_1, \ldots, d_K)$ whose rules select treatment options for history h_k from those in $\Psi_k(h_k)$ is defined in terms of Ψ
- Thus, *regimes are Ψ-specific*, and the relevant class of all possible regimes $\mathcal{D}$ depends on Ψ (suppressed in the notation)

Feasible sets and classes of treatment regimes

In practice: At Decision k, there is a small number ℓ_k of subsets $\mathcal{A}_{k,l} \subseteq \mathcal{A}_k$, $l = 1, \ldots, \ell_k$ that are feasible sets for all h_k

- E.g, for acute leukemia, $\ell_2 = 2$

$$\mathcal{A}_{2,1} = \{\mathrm{M}_1, \mathrm{M}_2\}, \qquad \mathcal{A}_{2,2} = \{\mathrm{S}_1, \mathrm{S}_2\}$$

- If r_2 is the component of h_2 indicating response

$$\begin{aligned} \Psi_1(h_2) &= \mathcal{A}_{2,1} \quad \text{for } h_2 \quad \text{with } r_2 = 1 \\ &= \mathcal{A}_{2,2} \quad \text{for } h_2 \quad \text{with } r_2 = 0 \end{aligned}$$

Decision rules: Different rule for each subset

- E.g., for acute leukemia, as in (5.1)

$$d_2(h_2) = \mathrm{I}(r_2 = 1)\, d_{2,1}(h_2) + \mathrm{I}(r_2 = 0)\, d_{2,2}(h_2)$$

$d_{2,1}(h_2)$ is a rule selecting maintenance therapy for responders
$d_{2,2}(h_2)$ is a rule selecting salvage therapy for nonresponders

Feasible sets and classes of treatment regimes

In general: With ℓ_k distinct subsets $\mathcal{A}_{k,l} \subseteq \mathcal{A}_k$, $l = 1, \ldots, \ell_k$, as feasible sets

- Define $s_k(h_k) = 1, \ldots, \ell_k$ according to which of these subsets $\Psi_k(h_k)$ corresponds for given h_k
- $d_{k,l}(h_k)$ is the rule corresponding to the lth subset $\mathcal{A}_{k,l}$
- Decision rule at Decision k has form

$$d_k(h_k) = \sum_{l=1}^{\ell_k} \mathrm{I}\{s_k(h_k) = l\}\, d_{k,l}(h_k) \tag{5.5}$$

- Henceforth, it is understood that $d_k(h_k)$ may be expressed as in (5.5) where appropriate

Feasible sets and classes of treatment regimes

Note: For any Ψ-specific regime $d = (d_1, \ldots, d_K)$

- At Decision k, $d_k(h_k) = d_k(\overline{x}_k, \overline{a}_{k-1})$ returns only options in $\Psi_k(h_k) = \Psi_k(\overline{x}_k, \overline{a}_{k-1})$, i.e.,

$$d_k(h_k) = d_k(\overline{x}_k, \overline{a}_{k-1}) \in \Psi_k(h_k) \subseteq \mathcal{A}_k$$

- Thus, d_k need map only a subset of $\mathcal{H}_k = \overline{\mathcal{X}}_k \times \overline{\mathcal{A}}_{k-1}$ to $\mathcal{A}_k$
- We discuss this more shortly

Potential outcomes for a fixed regime $d \in \mathcal{D}$

Intuitively: If a randomly chosen individual with history X_1 *were to receive* treatment options by following the rules in d

- Decision 1: Treatment determined by d_1
- $X_2^*(d_1)$ = intervening information *that would arise* between Decisions 1 and 2
- Decision 2: Treatment determined by d_2
- $X_3^*(\overline{d}_2)$ = intervening information *that would arise* between Decisions 2 and 3

$\vdots$

- $X_k^*(\overline{d}_{k-1})$ = intervening information *that would arise* between Decisions $k-1$ and k, $k = 2, \ldots, K$
- $Y^*(d) = Y^*(\overline{d}_K)$ = outcome *that would be achieved* if all rules in d were followed

Potential outcomes under regime d:

$$\{X_1, X_2^*(d_1), X_3^*(\overline{d}_2), \ldots, X_K^*(\overline{d}_{K-1}), Y^*(d)\} \tag{5.6}$$

Potential outcomes for a fixed regime $d \in \mathcal{D}$

Formally: These potential outcomes are functions of W^* in (5.3)

- Define

$$\overline{X}_k^*(\overline{a}_{k-1}) = \{X_1, X_2^*(a_1), X_3^*(\overline{a}_2), \ldots, X_k^*(\overline{a}_{k-1})\}, \quad k = 2, \ldots, K$$

- Then

$$X_2^*(d_1) = \sum_{a_1 \in \mathcal{A}_1} X_2^*(a_1) \mathsf{I}\{d_1(X_1) = a_1\}$$

$$X_k^*(\overline{d}_{k-1}) = \sum_{\overline{a}_{k-1} \in \overline{\mathcal{A}}_{k-1}} X_k^*(\overline{a}_{k-1}) \prod_{j=1}^{k-1} \mathsf{I}\left[d_j\{\overline{X}_j^*(\overline{a}_{j-1}), \overline{a}_{j-1}\} = a_j\right] \qquad (5.7)$$

$$k = 3, \ldots, K$$

$$Y^*(d) = \sum_{\overline{a} \in \overline{\mathcal{A}}} Y^*(\overline{a}) \prod_{j=1}^{K} \mathsf{I}\left[d_j\{\overline{X}_j^*(\overline{a}_{j-1}), \overline{a}_{j-1}\} = a_j\right]$$

- Also define

$$\overline{X}_k^*(\overline{d}_{k-1}) = \{X_1, X_2^*(d_1), X_3^*(\overline{d}_2), \ldots, X_k^*(\overline{d}_{k-1})\}, \quad k = 2, \ldots, K$$

Value of a K-decision regime

With these definitions: The *value* of $d \in \mathcal{D}$ is

$$\mathcal{V}(d) = E\{Y^*(d)\}$$

- And an optimal regime $d^{opt} \in \mathcal{D}$ satisfies

$$E\{Y^*(d^{opt})\} \geq E\{Y^*(d)\} \text{ for all } d \in \mathcal{D} \tag{5.8}$$

equivalently

$$d^{opt} = \arg\max_{d \in \mathcal{D}} E\{Y^*(d)\} = \arg\max_{d \in \mathcal{D}} \mathcal{V}(d)$$

Optimal treatment options vs. optimal decisions

For a randomly chosen individual with history H_1:

- The *optimal sequence of treatment options* for this individual is

$$\arg\max_{\overline{a}\in\overline{\mathcal{A}}} Y^*(\overline{a})$$

  which of course is not knowable in practice
- All that is known at baseline is H_1, and $d_1^{opt}, \ldots, d_K^{opt}$ select the (feasible) options corresponding to the largest expected outcome
- From the definition of $Y^*(d)$ in (5.7),

$$Y^*(d) \leq \max_{\overline{a}\in\overline{\mathcal{A}}} Y^*(\overline{a}) \text{ for all } d \in \mathcal{D} \implies Y^*(d^{opt}) \leq \max_{\overline{a}\in\overline{\mathcal{A}}} Y^*(\overline{a})$$

  so an optimal regime might not select optimal options for this individual at each decision
- Rather, d^{opt} leads to the *optimal sequence of decisions* that can be made based on the available information on this individual

Data

Ideally: For $i = 1, \ldots, n$, i.i.d.

$$(X_{1i}, A_{1i}, X_{2i}, A_{2i}, \ldots, X_{Ki}, A_{Ki}, Y_i) = (\overline{X}_{Ki}, \overline{A}_{Ki}, Y_i) = (\overline{X}_i, \overline{A}_i, Y_i) \quad (5.9)$$

- X_1 = *baseline information* at Decision 1, taking values in $\mathcal{X}_1$
- A_k = treatment option *actually received* at Decision k, $k = 1, \ldots, K$, taking values in $\mathcal{A}_k$
- X_k = *intervening information* between Decisions $k-1$ and k, $k = 2, \ldots, K$, taking values in $\mathcal{X}_k$
- $\overline{X}_k = (X_1, \ldots, X_k)$, $\overline{X} = \overline{X}_K = (X_1, \ldots, X_K)$, and $\overline{A}_k = (A_1, \ldots, A_k)$, $\overline{A} = \overline{A}_K = (A_1, \ldots, A_K)$
- History $H_1 = X_1$, $H_k = (X_1, A_1, \ldots, X_{k-1}, A_{k-1}, X_k) = (\overline{X}_k, \overline{A}_{k-1})$, $k = 2, \ldots, K$
- Y = *observed outcome* (after Decision K or function of H_K)

Data

Data sources:

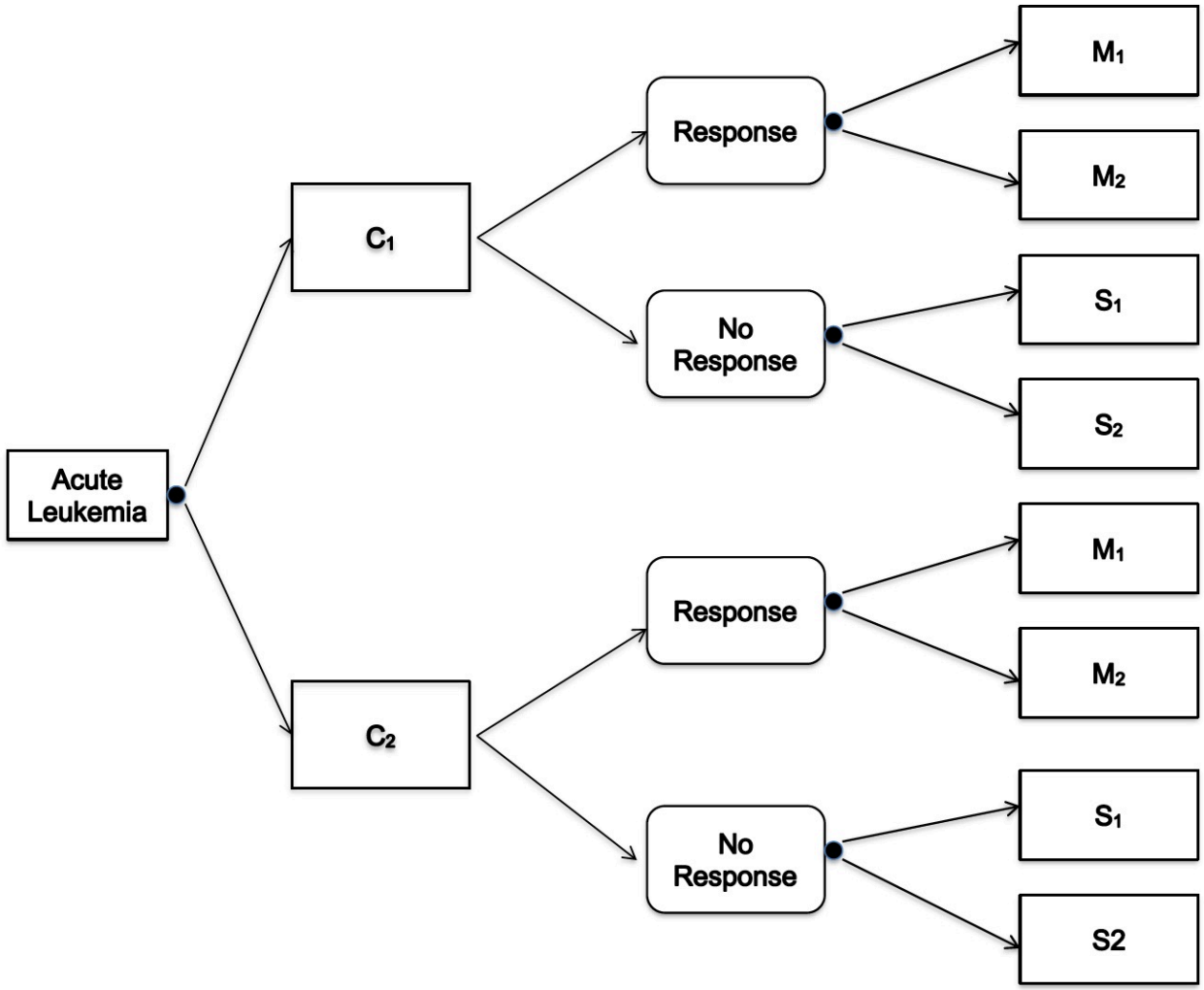
- *Longitudinal observational study:* Retrospective from an existing database, completed conventional clinical trial with followup, prospective cohort study
- *Randomized study:* Prospective clinical trial conducted specifically for this purpose (SMART)

Longitudinal observational study: Challenges

- *Time-dependent confounding:* A subject's history at each decision point is both determined by past treatments and used to select future treatments
- Characteristics associated with both treatment selection and future characteristics/ultimate outcome may not be captured in the data

Data

SMART: Randomization at ●s



Data

Do we really need data like these? Can't we just "*piece together*" an optimal regime using single decision methods on data from separate studies (with different subjects in each)?

- E.g., acute leukemia: Estimate d_1^{opt} from a study comparing $\{C_1, C_2\}$ and d_2^{opt} from separate studies comparing $\{M_1, M_2\}$ and $\{S_1, S_2\}$
- *Delayed effects:* The induction therapy with the highest proportion of responders might have other effects that render subsequent treatments less effective in regard to survival
- Require data from a study involving the same subjects over the *entire sequence* of decisions

Statistical problem

Ultimate goal: Based on the data (5.9), estimate $d^{opt} \in \mathcal{D}$ satisfying (5.8), i.e.,

$$E\{Y^*(d^{opt})\} \geq E\{Y^*(d)\} \text{ for all } d \in \mathcal{D}$$

Challenge: d^{opt} is defined in terms of the potential outcomes (5.6)

- Must be able to express this definition in terms of the observed data (5.9)
- In particular, for any $d \in \mathcal{D}$, must be able to *identify* the distribution of

$$\{X_1, X_2^*(d_1), X_3^*(\overline{d}_2), \ldots, X_K^*(\overline{d}_{K-1}), Y^*(d)\}$$

which depends on that of (X_1, W^*), from the distribution of

$$(X_1, A_1, X_2, A_2, \ldots, X_K, A_K, Y)$$

- Possible under the following assumptions generalizing those in (3.4), (3.5), and (3.6)

Identifiability assumptions

SUTVA (consistency):

$$X_k = X_k^*(\overline{A}_{k-1}) = \sum_{\overline{a}_{k-1} \in \overline{\mathcal{A}}_{k-1}} X_k^*(\overline{a}_{k-1}) \mathrm{I}(\overline{A}_{k-1} = \overline{a}_{k-1}), \quad k = 2, \ldots, K$$

$$Y = Y^*(\overline{A}) = \sum_{\overline{a} \in \overline{\mathcal{A}}} Y^*(\overline{a}) \mathrm{I}(\overline{A} = \overline{a}) \tag{5.10}$$

- Observed intervening information and the final observed outcome are those that would potentially be seen under the treatments actually received at each decision point
- Are the same (consistent) regardless of how the treatments are administered at each decision point

Identifiability assumptions

Sequential randomization assumption (SRA): Robins (1986)

$$W^* \perp\!\!\!\perp A_k | \overline{X}_k, \overline{A}_{k-1}, \quad k = 1, \ldots, K, \quad \text{where } A_0 \text{ is null} \qquad (5.11)$$

equivalently

$$W^* \perp\!\!\!\perp A_k | H_k, \quad k = 1, \ldots, K$$

- (5.11) is the strongest version; weaker versions require treatment selection $\perp\!\!\!\perp$ only of future potential outcomes
- *Unverifiable* from the observed data
- Unlikely to hold for data from a longitudinal observational study not carried out with estimation of treatment regimes in mind
- But (5.11) holds by design in a SMART

Identifiability assumptions

Positivity assumption: With feasible sets of treatment options at each decision point, more complicated

- *Intuitively:* To identify the distribution of the potential outcomes (5.6) from that of the observed data (5.9), all treatment options in the feasible sets $\Psi_k(h_k) = \Psi_k(\overline{x}_k, \overline{a}_{k-1})$ must be *represented* in the observed data, $k = 1, \ldots, K$
- That is, there must be individuals in the data who received each of the options in $\Psi_k(h_k)$, $k = 1, \ldots, K$
- E.g, acute leukemia: Decision 2: there must be responders who received each of M_1 and M_2 and nonresponders who received each of S_1 and S_2

Built up recursively. . .

Identifiability assumptions

Decision 1: Set of all possible baseline info $h_1 = x_1$

$$\Gamma_1 = \{x_1 \in \mathcal{X}_1 \text{ satisfying } P(X_1 = x_1) > 0\} \subseteq \mathcal{X}_1 = \mathcal{H}_1$$

Set of all possible histories and associated options in $\Psi_1(h_1)$

$$\Lambda_1 = \{(x_1, a_1) \text{ such that } x_1 = h_1 \in \Gamma_1, \ a_1 \in \Psi_1(h_1)\}$$

All options in Λ_1 must be represented in the data

$$P(A_1 = a_1 | H_1 = h_1) > 0 \quad \text{for all} \quad (h_1, a_1) \in \Lambda_1 \tag{5.12}$$

First component of the positivity assumption

Identifiability assumptions

Decision 2: All possible histories h_2 consistent with following a Ψ-specific regime at Decision 1

$$\Gamma_2 = \Big[(\overline{x}_2, a_1) \in \overline{\mathcal{X}}_2 \times \mathcal{A}_1 \text{ satisfying } (x_1, a_1) \in \Lambda_1 \text{ and } P\{X_2^*(a_1) = x_2 \mid X_1 = x_1\} > 0\Big] \subseteq \mathcal{H}_2$$

Under SUTVA (5.10) and SRA (5.11), equivalently

$$\Gamma_2 = \Big[(\overline{x}_2, a_1) \in \overline{\mathcal{X}}_2 \times \mathcal{A}_1 \text{ satisfying } (x_1, a_1) \in \Lambda_1 \text{ and } P(X_2 = x_2 \mid X_1 = x_1, A_1 = a_1) > 0\Big]$$

Set of all possible histories h_2 and associated options in $\Psi_2(h_2)$

$$\Lambda_2 = \{(\overline{x}_2, \overline{a}_2) \text{ such that } (\overline{x}_2, a_1) = h_2 \in \Gamma_2,\ a_2 \in \Psi_2(h_2)\}$$

Identifiability assumptions

Decision 2, continued: All options in Λ_2 must be represented in the data

$$P(A_2 = a_2 \mid H_2 = h_2) > 0 \quad \text{for all} \quad (h_2, a_2) \in \Lambda_2$$

Second component of the positivity assumption

$$\vdots$$

Decision k: All histories h_k consistent with a Ψ-specific regime through Decision $k-1$

$$\Gamma_k = \Big[(\overline{x}_k, \overline{a}_{k-1}) \in \overline{\mathcal{X}}_k \times \overline{\mathcal{A}}_{k-1} \text{ satisfying } (\overline{x}_{k-1}, \overline{a}_{k-1}) \in \Lambda_{k-1} \text{ and}$$

$$P\{X_k^*(\overline{a}_{k-1}) = x_k \mid \overline{X}_{k-1}^*(\overline{a}_{k-2}) = \overline{x}_{k-1}\} > 0\Big] \subseteq \mathcal{H}_k \quad (5.13)$$

$$= \Big[(\overline{x}_k, \overline{a}_{k-1}) \in \overline{\mathcal{X}}_k \times \overline{\mathcal{A}}_{k-1} \text{ satisfying } (\overline{x}_{k-1}, \overline{a}_{k-1}) \in \Lambda_{k-1} \text{ and}$$

$$P(X_k = x_k \mid \overline{X}_{k-1} = \overline{x}_{k-1}, \overline{A}_{k-1} = \overline{a}_{k-1}) > 0\Big] \quad (5.14)$$

Identifiability assumptions

Decision k, continued: Set of all possible histories h_k and associated options in $\Psi_k(h_k)$

$$\Lambda_k = \{(\overline{x}_k, \overline{a}_k) \text{ such that } (\overline{x}_k, \overline{a}_{k-1}) = h_k \in \Gamma_k, \ a_k \in \Psi_k(h_k)\}$$

All options in $\Psi_k(h_k)$ must be represented in the data

$$P(A_k = a_k \mid H_k = h_k) > 0 \quad \text{for all} \quad (h_k, a_k) \in \Lambda_k$$

kth component of the positivity assumption

$$\vdots$$

Identifiability assumptions

Positivity assumption: Summarizing

$$P(A_k = a_k | H_k = h_k) = P(A_k = a_k | \overline{X}_k = \overline{x}_k, \overline{A}_{k-1} = \overline{a}_{k-1}) > 0$$
$$\text{for } h_k = (\overline{x}_k, \overline{a}_{k-1}) \in \Gamma_k \text{ and } a_k \in \Psi_k(h_k) = \Psi_k(\overline{x}_k, \overline{a}_{k-1}),$$
$$k = 1, \ldots, K \tag{5.15}$$

- The positivity assumption (5.15) holds in a SMART by design if there are subjects with history h_k randomized to all options in $\Psi_k(h_k)$ at each Decision $k = 1, \ldots, K$
- No guarantee that for a given Ψ (5.15) holds for data from a longitudinal observational study (more shortly)

Identifiability assumptions

Equivalence of (5.13) and (5.14): Assuming SUTVA, SRA, need to show for any $h_k = (\overline{x}_k, \overline{a}_{k-1}) \in \Gamma_k$ in (5.13)

$$P(X_k = x_k \mid \overline{X}_{k-1} = \overline{x}_{k-1}, \overline{A}_{k-1} = \overline{a}_{k-1})$$
$$= P\{X_k^*(\overline{a}_{k-1}) = x_k \mid \overline{X}_{k-1}^*(\overline{a}_{k-2}) = \overline{x}_{k-1}\} \qquad (5.16)$$

- Proof is by induction ($k = 1, 2$ are immediate)
- Repeated use of the following lemma

  Lemma. *Let A and H be random variables, assume $W^* \perp\!\!\!\perp A|H$, and consider two functions $\mathfrak{f}_1(W^*)$ and $\mathfrak{f}_2(W^*)$ of W^*. If the event $\{\mathfrak{f}_2(W^*) = f_2, H = h, A = a\}$ has positive probability, then*

$$P\{\mathfrak{f}_1(W^*) = f_1 | \mathfrak{f}_2(W^*) = f_2, H = h, A = a\}$$
$$= P\{\mathfrak{f}_1(W^*) = f_1 | \mathfrak{f}_2(W^*) = f_2, H = h\}$$

Identifiability assumptions

Sketch of induction proof:

- We need to show for any $h_k = (\overline{x}_k, \overline{a}_{k-1}) \in \Gamma_k$ in (5.13), $k = 1, \ldots, K$

$$P(X_k = x_k \mid \overline{X}_{k-1} = \overline{x}_{k-1}, \overline{A}_{k-1} = \overline{a}_{k-1}) \\ = P\{X_k^*(\overline{a}_{k-1}) = x_k \mid \overline{X}_{k-1}^*(\overline{a}_{k-2}) = \overline{x}_{k-1}\} \qquad (5.16)$$

- (5.16) is trivial for $k = 1$
- $k = 2$: (5.12) implies $P(X_1 = x_1, A_1 = a_1) > 0$ for $(x_1, a_1) \in \Lambda_1$, so $P(X_2 = x_2 \mid X_1 = x_1, A_1 = a_1)$ is well defined. Then by SUTVA and SRA, (5.16) holds

$$P(X_2 = x_2 \mid X_1 = x_1, A_1 = a_1) = P\{X_2^*(a_1) = x_2 \mid X_1 = x_1, A_1 = a_1\} \\ = P\{X_2^*(a_1) = x_2 \mid X_1 = x_1\}$$

- For general k: Need to show $P(\overline{X}_{k-1} = \overline{x}_{k-1}, \overline{A}_{k-1} = \overline{a}_{k-1}) > 0$, so that $P(X_k = x_k \mid \overline{X}_{k-1} = \overline{x}_{k-1}, \overline{A}_{k-1} = \overline{a}_{k-1})$ is well defined, and then show (5.16)

Identifiability assumptions

- Assume this holds for $k-1$ and then show it holds for k. Thus, for $h_{k-1} = (\overline{x}_{k-1}, \overline{a}_{k-2}) \in \Gamma_{k-1}$, $P(\overline{X}_{k-2} = \overline{x}_{k-2}, \overline{A}_{k-2} = \overline{a}_{k-2}) > 0$ and

$$\begin{aligned} &P(X_{k-1} = x_{k-1} \mid \overline{X}_{k-2} = \overline{x}_{k-2}, \overline{A}_{k-2} = \overline{a}_{k-2}) \\ &\quad = P\{X^*_{k-1}(\overline{a}_{k-2}) = x_{k-1} \mid \overline{X}^*_{k-2}(\overline{a}_{k-3}) = \overline{x}_{k-2}\} > 0 \end{aligned}$$

- It follows that $P(\overline{X}_{k-1} = \overline{x}_{k-1}, \overline{A}_{k-2} = \overline{a}_{k-2}) > 0$
- Because $h_{k-1} = (\overline{x}_{k-1}, \overline{a}_{k-2}) \in \Gamma_{k-1}$ and $a_{k-1} \in \Psi_{k-1}(\overline{x}_{k-1}, \overline{a}_{k-2})$,

$$P(A_{k-1} = a_{k-1} \mid \overline{X}_{k-1} = \overline{x}_{k-1}, \overline{A}_{k-2} = \overline{a}_{k-2}) > 0$$

- It then follows that $P(\overline{X}_{k-1} = \overline{x}_{k-1}, \overline{A}_{k-1} = \overline{a}_{k-1}) > 0$ as required
- Now show (5.16) using SUTVA, SRA, and the Lemma

Identifiability assumptions

- By repeated use of SUTVA and SRA

$$P(X_k = x_k \mid \overline{X}_{k-1} = \overline{x}_{k-1}, \overline{A}_{k-1} = \overline{a}_{k-1})$$
$$= P\{X_k^*(\overline{a}_{k-1}) = x_k | \overline{X}_{k-2} = \overline{x}_{k-2}, X_{k-1}^*(\overline{a}_{k-2}) = x_{k-1}$$
$$\overline{A}_{k-3} = \overline{a}_{k-3}, A_{k-2} = a_{k-2}\}, \qquad (5.17)$$

- By the Lemma with $\mathfrak{f}_1(W^*) = X_k^*(\overline{a}_{k-1})$, $A = A_{k-2}$, $H = (\overline{X}_{k-2}, \overline{A}_{k-3})$, and $\mathfrak{f}_2(W^*) = X_{k-1}^*(\overline{a}_{k-2})$, (5.17) =

$$P\{X_k^*(\overline{a}_{k-1}) = x_k | \overline{X}_{k-2} = \overline{x}_{k-2}, X_{k-1}^*(\overline{a}_{k-2}) = x_{k-1}, \overline{A}_{k-3} = \overline{a}_{k-3}\}$$
$$= P\{X_k^*(\overline{a}_{k-1}) = x_k | \overline{X}_{k-3} = \overline{x}_{k-3}, X_{k-2}^*(\overline{a}_{k-3}) = x_{k-2}$$
$$X_{k-1}^*(\overline{a}_{k-2}) = x_{k-1}, \overline{A}_{k-4} = \overline{a}_{k-4}, A_{k-3} = a_{k-3}\} \qquad (5.18)$$

- By the Lemma with $\mathfrak{f}_1(W^*) = X_k^*(\overline{a}_{k-1})$, $A = A_{k-3}$, $H = (\overline{X}_{k-3}, \overline{A}_{k-4})$, (5.18) =

$$P\{X_k^*(\overline{a}_{k-1}) = x_k | \overline{X}_{k-3} = \overline{x}_{k-3}, X_{k-2}^*(\overline{a}_{k-3}) = x_{k-2},$$
$$X_{k-1}^*(\overline{a}_{k-2}) = x_{k-1}, \overline{A}_{k-4} = \overline{a}_{k-4}\}$$

Identifiability assumptions

- Continuing to apply the Lemma and SUTVA leads to (5.16),

$$P(X_k = x_k \mid \overline{X}_{k-1} = \overline{x}_{k-1}, \overline{A}_{k-1} = \overline{a}_{k-1})$$
$$= P\{X_k^*(\overline{a}_{k-1}) = x_k \mid \overline{X}_{k-1}^*(\overline{a}_{k-2}) = \overline{x}_{k-1}\}$$

- Because $h_k = (\overline{x}_k, \overline{a}_{k-1}) \in \Gamma_k$, the RHS is > 0
- Thus, we have shown that (5.16) holds for k and

$$P(X_k = x_k \mid \overline{X}_{k-1} = \overline{x}_{k-1}, \overline{A}_{k-1} = \overline{a}_{k-1}) > 0$$

  for $h_k = (\overline{x}_k, \overline{a}_{k-1}) \in \Gamma_k$
- Because this holds for $k = 1, 2$, the result follows by induction

Identifiability assumptions

More precise definition of a regime: A Ψ-specific regime $d = (d_1, \ldots, d_K)$ satisfies

- Each rule d_k, $k = 1, \ldots, K$, is a mapping from $\Gamma_k \subseteq \mathcal{H}_k$ into $\mathcal{A}_k$ for which $d_k(h_k) \in \Psi_k(h_k)$ for every $h_k \in \Gamma_k$
- The class $\mathcal{D}$ of Ψ-specific regimes is the set of all such d

Identifiability assumptions

Observational data: For given Ψ, no guarantee that all options in $\Psi_k(h_k)$, $k = 1, \ldots, K$, are represented in the data

- Define for $k = 1, \ldots, K$

$$\Gamma_k^{max} = \Big[(\overline{x}_k, \overline{a}_{k-1}) \in \overline{\mathcal{X}}_k \times \overline{\mathcal{A}}_{k-1} \text{ satisfying } (\overline{x}_{k-1}, \overline{a}_{k-1}) \in \Lambda_{k-1}^{max}$$
$$\text{and } P(X_k = x_k \mid \overline{X}_{k-1} = \overline{x}_{k-1}, \overline{A}_{k-1} = \overline{a}_{k-1}) > 0\Big]$$

$$\Psi_k^{max}(h_k) = \{a_k \in \mathcal{A}_k \text{ satisfying } P(A_k = a_k | H_k = h_k) > 0$$
$$\text{for all } h_k = (\overline{x}_k, \overline{a}_{k-1}) \in \Gamma_k^{max}\}$$

$$\Lambda_k^{max} = \{(\overline{x}_k, \overline{a}_k) \text{ such that } (\overline{x}_k, \overline{a}_{k-1}) = h_k \in \Gamma_k^{max},\ a_k \in \Psi_k^{max}(h_k)\}$$

- The class of regimes based on $\Psi^{max} = (\Psi_1^{max}, \ldots, \Psi_k^{max})$ is the largest that can be considered
- So must have $\Psi_k(h_k) \subseteq \Psi_k^{max}(h_k)$, $k = 1, \ldots, K$ for all $h_k \in \Gamma_k \subseteq \Gamma_k^{max}$

5. Multiple Decision Treatment Regimes: Framework and Fundamentals

Identifiability result

Goal, again: For any Ψ-specific regime $d \in \mathcal{D}$, demonstrate that we can identify the distribution of

$$\{X_1, X_2^*(d_1), X_3^*(\overline{d}_2), \ldots, X_K^*(\overline{d}_{K-1}), Y^*(d)\}$$

which depends on that of (X_1, W^*), from the distribution of

$$(X_1, A_1, X_2, A_2, \ldots, X_K, A_K, Y)$$

Recall: Recursive representation $\overline{d}_k(\overline{x}_k)$ of the treatment options selected by d through Decision k in (5.2) if an individual follows d, $k = 2, \ldots, K$

$$\overline{d}_k(\overline{x}_k) = [d_1(x_1), d_2\{\overline{x}_2, d_1(x_1)\}, \ldots, d_k\{\overline{x}_k, \overline{d}_{k-1}(\overline{x}_{k-1})\}]$$

g-Computation algorithm

Main result: Under SUTVA (5.10), SRA (5.11), and positivity assumption (5.15), the joint density of the potential outcomes $\{X_1, X_2^*(d_1), X_3^*(\overline{d}_2), \ldots, X_K^*(\overline{d}_{K-1}), Y^*(d)\}$ can be obtained as

$$p_{X_1, X_2^*(d_1), X_3^*(\overline{d}_2), \ldots, X_K^*(\overline{d}_{K-1}), Y^*(d)}(x_1, \ldots, x_K, y) \tag{5.19}$$

$$\begin{aligned} &= p_{Y|\overline{X},\overline{A}}\{y|\overline{x}, \overline{d}(\overline{x})\} \\ &\quad \times p_{X_K|\overline{X}_{K-1},\overline{A}_{K-1}}\{x_K|\overline{x}_{K-1}, \overline{d}_{K-1}(\overline{x}_{K-1})\} \\ &\quad \vdots \qquad\qquad (5.20) \\ &\quad \times p_{X_2|X_1,A_1}\{x_2|x_1, d_1(x_1)\} \\ &\quad \times p_{X_1}(x_1) \end{aligned}$$

for any realization $(x_1, x_2, \ldots, x_K, y)$ for which (5.19) is positive

- Due to Robins (1986, 1987, 2004)

g-Computation algorithm

Additional definition: Relevant realizations $(x_1, x_2, \ldots, x_K, y)$ are determined by feasible sets

- Assume $Y^*(\bar{a})$ and Y take values $y \in \mathcal{Y}$
- Define

$$\Gamma_{K+1} = \Big[(\bar{x}, \bar{a}, y) \in \bar{\mathcal{X}} \times \bar{\mathcal{A}} \times \mathcal{Y} \text{ satisfying } (\bar{x}, \bar{a}) \in \Lambda_K \text{ and } P\{Y^*(\bar{a}) = y \mid \bar{X}_K^*(\bar{a}_{K-1}) = \bar{x}_K\} > 0\Big]$$

$$= \Big[(\bar{x}, \bar{a}, y) \in \bar{\mathcal{X}} \times \bar{\mathcal{A}} \times \mathcal{Y} \text{ satisfying } (\bar{x}, \bar{a}) \in \Lambda_K \text{ and } P(Y = y \mid \bar{X} = \bar{x}, \bar{A}_{K-1} = \bar{a}_{K-1}) > 0\Big]$$

- This equality can be shown similarly to that of (5.13) and (5.14)

g-Computation algorithm

Simplification: Take all random variables discrete, so that (5.19) and (5.20) become

$$P\{X_1 = x_1, X_2^*(d_1) = x_2, \ldots, X_K^*(\overline{d}_{K-1}) = x_K, Y^*(d) = y\} \tag{5.21}$$

$$= P\{Y = y \mid \overline{X}_K = \overline{x}_K, \overline{A}_K = \overline{d}_K(\overline{x}_{K-1})\}$$
$$\times P(X_K = x_K \mid \overline{X}_{K-1} = \overline{x}_{K-1}, \overline{A}_{K-1} = \overline{d}_{K-1}(\overline{x}_{K-2})\}$$
$$\vdots \tag{5.22}$$
$$\times P\{X_2 = x_2 \mid X_1 = x_1, A_1 = d_1(x_1)\}$$
$$\times P(X_1 = x_1)$$

for any realization $(x_1, x_2, \ldots, x_K, y)$ such that

$$P\{X_1 = x_1, X_2^*(d_1) = x_2, \ldots, X_K^*(\overline{d}_{K-1}) = x_K, Y^*(d) = y\} > 0$$

- Need to show (5.21) = (5.22)

g-Computation algorithm

Demonstration: Factorize (5.21) as

$$
\begin{aligned}
&P\{X_1 = x_1, X_2^*(d_1) = x_2, \ldots, X_K^*(\overline{d}_{K-1}) = x_K, Y^*(d) = y\} \\
&\quad = P\{Y^*(d) = y \mid \overline{X}_K^*(\overline{d}_{K-1}) = \overline{x}_K\} \\
&\qquad \times P\{X_K^*(\overline{d}_{K-1}) = x_K \mid \overline{X}_{K-1}^*(\overline{d}_{K-2}) = \overline{x}_{K-1}\} \\
&\qquad \quad \vdots \\
&\qquad \times P\{X_2^*(d_1) = x_2 \mid X_1 = x_1\} \\
&\qquad \times P(X_1 = x_1)
\end{aligned}
$$

- All components on RHS are positive because (5.21) > 0

g-Computation algorithm

- From (5.22), it suffices to show

$$P\{Y^*(d) = y \mid \overline{X}_K^*(\overline{d}_{K-1}) = \overline{x}_K\}$$
$$= P\{Y = y \mid \overline{X}_K = \overline{x}_K, \overline{A}_K = \overline{d}_K(\overline{x}_{K-1})\}$$
$$\text{where } P\{Y = y \mid \overline{X}_K = \overline{x}_K, \overline{A}_K = \overline{d}_K(\overline{x}_{K-1})\} > 0$$

  and for $k = 2, \ldots, K$

$$P\{X_k^*(\overline{d}_{k-1}) = x_k \mid \overline{X}_{k-1}^*(\overline{d}_{k-2}) = \overline{x}_{K-1}\}$$
$$= P(X_k = x_k \mid \overline{X}_{k-1} = \overline{x}_{k-1}, \overline{A}_{k-1} = \overline{d}_{k-1}(\overline{x}_{k-2})\}$$
$$\text{where } P(X_k = x_k \mid \overline{X}_{k-1} = \overline{x}_{k-1}, \overline{A}_{k-1} = \overline{d}_{k-1}(\overline{x}_{k-2})\} > 0$$

- These follow immediately if, for $\overline{X}_{K+1}^*(d) = Y^*(d)$

$$\{\overline{x}_k, \overline{d}_{k-1}(\overline{x}_{k-1})\} \in \Gamma_k, \qquad k = 2, \ldots, K+1 \tag{5.23}$$

  which can be shown by induction (first show for $k = 2$)

g-Computation algorithm

Sketch of induction proof: First take $k = 2$

- Because $P(X_1 = x_1) > 0$, $x_1 \in \Gamma_1$ and d is a Ψ-specific regime, $d_1(x_1) \in \Psi_1(h_1)$, so that $\{x_1, d_1(x_1)\} \in \Lambda_1$
- Because (5.21) > 0,

$$P\{X_2^*(d_1) = x_2 \mid X_1 = x_1\} > 0 \implies \{\overline{x}_2, d_1(x_1)\} \in \Gamma_2$$

  which is (5.23) for $k = 2$
- Now assume $\{\overline{x}_{k-1}, \overline{d}_{k-2}(\overline{x}_{k-2})\} \in \Gamma_{k-1}$ is true
- Because d is a Ψ-specific regime, $d_{k-1}(\overline{x}_{k-1}) \in \Psi_{k-1}(h_k)$ and thus $\{\overline{x}_{k-1}, \overline{d}_{k-1}(\overline{x}_{k-1})\} \in \Lambda_{k-1}$
- Because (5.21) > 0,

$$P\{X_k^*(\overline{d}_{k-1}) = x_k \mid \overline{X}_{k-1}^*(\overline{d}_{k-2}) = \overline{x}_{k-1}\} > 0 \implies \{\overline{x}_k, \overline{d}_{k-1}(\overline{x}_{k-1})\} \in \Gamma_k$$

  completing the induction proof

g-Computation algorithm

General result: Compactly stated

$$p_{X_1,X_2^*(d_1),X_3^*(\overline{d}_2),\ldots,X_K^*(\overline{d}_{K-1}),Y^*(d)}(x_1,\ldots,x_K,y) \tag{5.24}$$
$$= p_{Y|\overline{X},\overline{A}}\{y|\overline{x},\overline{d}_K(\overline{x})\}\left[\prod_{k=2}^{K} p_{X_k|\overline{X}_{k-1},\overline{A}_{k-1}}\{x_k|\overline{x}_{k-1},\overline{d}_{k-1}(\overline{x}_{k-1})\}\right] p_{X_1}(x_1)$$

which implies, for example,

$$p_{Y^*(d)}(y) = \int_{\overline{\mathcal{X}}} \Bigg(p_{Y|\overline{X},\overline{A}}\{y|\overline{x},\overline{d}(\overline{x})\} \tag{5.25}$$
$$\times \left[\prod_{k=2}^{K} p_{X_k|\overline{X}_{k-1},\overline{A}_{k-1}}\{x_k|\overline{x}_{k-1},\overline{d}_{k-1}(\overline{x}_{k-1})\}\right] p_{X_1}(x_1)\Bigg) d\nu_K(x_K)\cdots d\nu_1(x_1)$$

- $d\nu_K(x_K)\cdots d\nu_1(x_1)$ is the dominating measure

g-Computation algorithm

Or the value

$$E\{Y^*(d)\} = \int_{\overline{\mathcal{X}}} \Bigg(\quad E\{Y|\overline{X} = \overline{x}, \overline{A} = \overline{d}(\overline{x})\} \tag{5.26}$$

$$\times \left[\prod_{k=2}^{K} p_{X_k|\overline{X}_{k-1},\overline{A}_{k-1}}\{x_k|\overline{x}_{k-1}, \overline{d}_{k-1}(\overline{x}_{k-1})\} \right] p_{X_1}(x_1) \Bigg) \, d\nu_K(x_K) \cdots d\nu_1(x_1)$$

- Thus, the value $\mathcal{V}(d) = E\{Y^*(d)\}$ of a regime $d \in \mathcal{D}$ can be expressed in terms of the observed data
- So it should be possible to estimate $\mathcal{V}(d)$ from these data
- As well as to estimate $\mathcal{V}(d^{opt})$ (later)...

5. Multiple Decision Treatment Regimes: Framework and Fundamentals

Fixed regime $d \in \mathcal{D}$

Of interest: Estimation of the value $\mathcal{V}(d) = E\{Y^*(d)\}$ of a *given*, or *fixed*, Ψ-specific regime $d \in \mathcal{D}$

- In its own right
- As a stepping stone to estimation of an optimal regime d^{opt}
- We consider several methods
- Throughout, take SUTVA (5.10), SRA (5.11), and positivity assumption (5.15) to hold

Estimation via g-computation

In principle: From (5.25) and (5.26), can estimate $p_{Y^*(d)}(y)$ or $E\{Y^*(d)\}$ for fixed $d \in \mathcal{D}$

- Posit parametric models, e.g., for (5.25)

$$p_{Y|\overline{X},\overline{A}}(y|\overline{x},\overline{a};\zeta_{K+1})$$
$$p_{X_k|\overline{X}_{k-1},\overline{A}_{k-1}}(x_k|\overline{x}_{k-1},\overline{a}_{k-1};\zeta_k), \quad k = 2,\ldots,K$$
$$p_{X_1}(x_1;\zeta_1)$$

  depending on $\zeta = (\zeta_1^T,\ldots,\zeta_{K+1}^T)^T$ (or for (5.26) a model for $E(Y|\overline{X} = \overline{x},\overline{A} = \overline{a})$ instead)
- Estimate ζ by maximizing the partial likelihood

$$\prod_{i=1}^{n}\left\{p_{Y|\overline{X},\overline{A}}(Y_i|\overline{X}_i,\overline{A}_i;\zeta_{K+1})\prod_{k=2}^{K}p_{X_k|\overline{X}_{k-1},\overline{A}_{k-1}}(X_{ki}|\overline{X}_{k-1,i},\overline{A}_{k-1,i};\zeta_k)\,p_{X_1}(X_{1i};\zeta_1)\right\}$$

  in ζ to obtain $\widehat{\zeta} = (\widehat{\zeta}_1^T,\ldots,\widehat{\zeta}_{K+1}^T)^T$

Estimation via g-computation

In principle:

- Substitute the fitted models in (5.25) or (5.26)

Major obstacle: (5.25) and (5.26) involve integration over the sample space $\overline{\mathcal{X}} = \mathcal{X}_1 \times \cdots \times \mathcal{X}_K$

- Except in the simplest situations, e.g., all $x_1, \ldots, x_K$ discrete and low-dimensional, the required integration is almost certainly analytically *intractable* and *computationally insurmountable*

Estimation via g-computation

Monte Carlo integration: Robins (1986) proposed approximating the distribution of $Y^*(d)$ for $d \in \mathcal{D}$; for $r = 1, \ldots, M$, simulate a realization from the distribution of $Y^*(d)$ as follows

1. Generate random x_{1r} from $p_{X_1}(x_1; \widehat{\zeta}_1)$
2. Generate random x_{2r} from $p_{X_2|X_1,A_1}\{x_2|x_{1r}, d_1(x_{1r}); \widehat{\zeta}_2\}$
3. Continue in this fashion, generating random x_{kr} from

$$p_{X_k|\overline{X}_{k-1},\overline{A}_{k-1}}\{x_k|\overline{x}_{k-1,r}, \overline{d}_{k-1}(\overline{x}_{k-1,r}); \widehat{\zeta}_k\}, \quad k = 3, \ldots, K$$

4. Generate random y_r from $p_{Y|\overline{X},\overline{A}}\{y|\overline{x}_r, \overline{d}_K(\overline{x}_r); \widehat{\zeta}_{K+1}\}$

$y_1, \ldots, y_M$ are a sample from the fitted distribution of $Y^*(d)$

Estimator for $\mathcal{V}(d) = E\{Y^*(d)\}$: $\quad \widehat{\mathcal{V}}_{GC}(d) = M^{-1} \sum_{r=1}^{M} y_r$

Estimation via g-computation

Practical challenges:

- Development of models can be daunting due to high dimension/complexity of $x_1, \ldots, x_K$
- Although specifying $p_{Y|\overline{X},\overline{A}}(y|\overline{x},\overline{a};\zeta_{K+1})$ may be feasible for univariate Y, models

$$p_{X_k|\overline{X}_{k-1},\overline{A}_{k-1}}(x_k|\overline{x}_{k-1},\overline{a}_{k-1};\zeta_k),\ k=2,\ldots,K, \quad p_{X_1}(x_1;\zeta_1)$$

  for multivariate X_k are more challenging to specify
- E.g., $X_k = (X_{k1}^T, X_{k2}^T)^T$ continuous/discrete, can factor as

$$p_{X_{k1}|X_{k2},\overline{X}_{k-1},\overline{A}_{k-1}}(x_{k1}|x_{k2},\overline{x}_{k-1},\overline{a}_{k-1};\zeta_{k1}) \times p_{X_{k2}|\overline{X}_{k-1},\overline{A}_{k-1}}(x_{k2}|\overline{x}_{k-1},\overline{a}_{k-1};\zeta_{k2})$$

$$\text{or} \quad p_{X_{k2}|X_{k1},\overline{X}_{k-1},\overline{A}_{k-1}}(x_{k2}|x_{k1},\overline{x}_{k-1},\overline{a}_{k-1};\zeta_{k2}) \times p_{X_{k1}|\overline{X}_{k-1},\overline{A}_{k-1}}(x_{k2}|\overline{x}_{k-1},\overline{a}_{k-1};\zeta_{k1})$$

Estimation via g-computation

Practical challenges, continued:

- Moreover, simulation from such models can be demanding
- Analytical derivation of approximate standard errors is not straightforward (frankly daunting!); use of a nonparametric bootstrap has been advocated, which is clearly highly computationally intensive

Bottom line: Estimation of $\mathcal{V}(d)$ via the g-computation is not commonplace in practice

- The main usefulness of g-computation is as a demonstration that it is possible to identify and estimate $\mathcal{V}(d)$ from observed data under SUTVA, SRA, and positivity
- In principle, a possible approach to estimating $d^{opt} \in \mathcal{D}$ is to maximize $\widehat{\mathcal{V}}_{GC}(d)$ over all $d \in \mathcal{D}$; clearly, this would be a formidable computational challenge (and is never done in practice)

Inverse probability weighted estimator

Motivation: Alternative representation of $E\{Y^*(d)\}$ in terms of the observed data

$$(X_1, A_1, X_2, A_2, \ldots, X_K, A_K, Y)$$

depending on

$$p_{A_1|H_1}(a_1|h_1) = P(A_1 = a_1|H_1 = h_1) = p_{A_1|X_1}(a_1|x_1)$$
$$p_{A_k|H_k}(a_k|h_k) = P(A_k = a_k|H_k = h_k) = p_{A_k|\overline{X}_k,\overline{A}_{k-1}}(a_k|\overline{x}_k, \overline{a}_{k-1})$$
$$k = 2, \ldots, K$$

Define: Evaluate at $d_1(X_1)$, $d_k\{\overline{X}_k, \overline{d}_{k-1}(\overline{X}_{k-1})\}$

$$\pi_{d,1}(X_1) = p_{A_1|X_1}\{d_1(X_1)|X_1\}$$
$$\pi_{d,k}(\overline{X}_k) = p_{A_k|\overline{X}_k,\overline{A}_{k-1}}[d_k\{\overline{X}_k, \overline{d}_{k-1}(\overline{X}_{k-1})\}|\overline{X}_k, \overline{d}_{k-1}(\overline{X}_{k-1})]$$
$$k = 2, \ldots, K$$

Inverse probability weighted estimator

Define: Indicator of consistency of options actually received with those selected by d at all K decisions

$$\mathcal{C}_d = \mathcal{C}_{\overline{d}_K} = \mathrm{I}\{A_1 = d_1(X_1), \ldots, A_K = \overline{d}_K(\overline{X}_K)\} = \mathrm{I}\{\overline{A} = \overline{d}(\overline{X})\}$$

Inverse probability weighted estimator for $\mathcal{V}(d) = E\{Y^*(d)\}$:

$$\widehat{\mathcal{V}}_{IPW}(d) = n^{-1} \sum_{i=1}^{n} \frac{\mathcal{C}_{d,i} Y_i}{\left\{\prod_{k=2}^{K} \pi_{d,k}(\overline{X}_{ki})\right\} \pi_{d,1}(X_{1i})} \tag{5.27}$$

- (5.27) is an unbiased estimator for $\mathcal{V}(d)$ because

$$E\left[\frac{\mathcal{C}_d Y}{\left\{\prod_{k=2}^{K} \pi_{d,k}(\overline{X}_k)\right\} \pi_{d,1}(X_1)}\right] = E\{Y^*(d)\} \tag{5.28}$$

  under SUTVA (5.10), SRA (5.11) and positivity assumption (5.15)

Inverse probability weighted estimator

Sketch of proof of (5.28): We show a more general result

$$E\left[\frac{\mathcal{C}_d f(\overline{X}, Y)}{\left\{\prod_{k=2}^{K} \pi_{d,k}(\overline{X}_k)\right\} \pi_{d,1}(X_1)}\right] = E[f\{\overline{X}_K^*(\overline{d}_{K-1}), Y^*(d)\}] \quad (5.29)$$

so that (5.28) follows by taking $f(\overline{x}, y) = y$

- Using SUTVA and (5.7)

$$E\left[\frac{\mathcal{C}_d f(\overline{X}, Y)}{\left\{\prod_{k=2}^{K} \pi_{d,k}(\overline{X}_k)\right\} \pi_{d,1}(X_1)}\right] = E\left(\frac{\mathcal{C}_d f\{\overline{X}_K^*(\overline{d}_{K-1}), Y^*(d)\}}{\left\{\prod_{k=2}^{K} \pi_{d,k}\{\overline{X}_k^*(\overline{d}_{k-1})\}\right] \pi_{d,1}(X_1)}\right)$$

$$= E\left\{E\left(\frac{\mathrm{I}\{\overline{A} = \overline{d}(\overline{X})\} f\{\overline{X}_K^*(\overline{d}_{K-1}), Y^*(d)\}}{\left[\prod_{k=2}^{K} \pi_{d,k}\{\overline{X}_k^*(\overline{d}_{k-1})\}\right] \pi_{d,1}(X_1)} \middle| X_1, W^*\right)\right\}$$

$$= E\left(\frac{P\{\overline{A} = \overline{d}(\overline{X}) | X_1, W^*\} f\{\overline{X}_K^*(\overline{d}_{K-1}), Y^*(d)\}}{\left[\prod_{k=2}^{K} \pi_{d,k}\{\overline{X}_k^*(\overline{d}_{k-1})\}\right] \pi_{d,1}(X_1)}\right) \quad (5.30)$$

Inverse probability weighted estimator

From (5.30): Must show

$$\left[\prod_{k=2}^{K} \pi_{d,k}\{\overline{X}_k^*(\overline{d}_{k-1})\}\right] \pi_{d,1}(X_1) = P\{\overline{A} = \overline{d}(\overline{X})|X_1, W^*\} > 0 \qquad (5.31)$$

- For (x_1, w) such that $P(X_1 = x_1, W^* = w) > 0$, show
$$P\{\overline{A} = \overline{d}(\overline{X})|X_1 = x_1, W^* = w\} > 0$$
- There exist $x_2, \ldots, x_K$ such that $P\{\overline{X}_k^*(\overline{d}_{k-1}) = \overline{x}_k\} > 0$, $k = 2, \ldots, K$, because $\overline{X}_K^*(\overline{d}_{K-1})$ is a function of W^*
- Using SUTVA

$$\begin{aligned} &P\{\overline{A} = \overline{d}(\overline{X})|X_1 = x_1, W^* = w\} \\ &\quad = P\{A_1 = d_1(x_1)|X_1 = x_1, W^* = w\} \\ &\quad \times \prod_{k=2}^{K} P[A_k = d_k\{\overline{x}_k, \overline{d}_{k-1}(\overline{x}_{k-1})\}|\overline{A}_{k-1} = \overline{d}_{k-1}(\overline{x}_{k-1}), X_1 = x_1, W^* = w] \end{aligned}$$

Inverse probability weighted estimator

- Must show each term in this factorization is well defined; true if

$$P\{\overline{A}_k = \overline{d}_k(\overline{x}_k), X_1 = x_1, W^* = w\} > 0, \quad k = 1, \ldots, K$$

- By induction; when $k = 1$

$$\begin{aligned} &P\{A_1 = d_1(x_1), X_1 = x_1, W^* = w\} \\ &\quad = P\{A_1 = d_1(x_1) \mid X_1 = x_1, W^* = w\} P(X_1 = x_1, W^* = w) \end{aligned}$$

  is positive if $P\{A_1 = d_1(x_1) \mid X_1 = x_1, W^* = w\} > 0$

- This holds because $P(X_1 = x_1) > 0$ so $x_1 \in \Gamma_1$ and $d_1(x_1) \in \Psi_1(x_1)$ so by positivity assumption

$$P\{A_1 = d_1(x_1) \mid X_1 = x_1, W^* = w\} = P\{A_1 = d_1(x_1) \mid X_1 = x_1\} > 0$$

- Now assume $P\{\overline{A}_k = \overline{d}_k(\overline{x}_k), X_1 = x_1, W^* = w\} > 0$ and show

$$P\{\overline{A}_{k+1} = \overline{d}_{k+1}(\overline{x}_{k+1}), X_1 = x_1, W^* = w\} > 0$$

Inverse probability weighted estimator

- $\overline{X}_k^*(\overline{d}_{k-1})$ includes X_1, so $(X_1 = x_1, W^* = w)$ and $\{\overline{X}_{k+1}^*(d) = \overline{x}_{k+1}, W^* = w\}$ are equivalent, and thus

$$
\begin{aligned}
&P\{\overline{A}_{k+1} = \overline{d}_{k+1}(\overline{x}_{k+1}), X_1 = x_1, W^* = w\} \\
&= P[A_{k+1} = d_{k+1}\{\overline{x}_{k+1}, \overline{d}_k(\overline{x}_k)\} | \overline{A}_k = \overline{d}_k(\overline{x}_k), \overline{X}_{k+1}^*(\overline{d}_k) = \overline{x}_{k+1}, W^* = w] \\
&\quad \times P\{\overline{A}_k = \overline{d}_k(\overline{x}_k), X_1 = x_1, W^* = w\}
\end{aligned}
$$

- Must show first RHS term is > 0; by SUTVA and SRA, this term =

$$
\begin{aligned}
&= P[A_{k+1} = d_{k+1}\{\overline{x}_{k+1}, \overline{d}_k(\overline{x}_k)\} | \overline{X}_{k+1} = \overline{x}_{k+1}, \overline{A}_k = \overline{d}_k(\overline{x}_k), W^* = w] \\
&= P[A_{k+1} = d_{k+1}\{\overline{x}_{k+1}, \overline{d}_k(\overline{x}_k)\} | \overline{X}_{k+1} = \overline{x}_{k+1}, \overline{A}_k = \overline{d}_k(\overline{x}_k)]
\end{aligned}
$$

- Because $\{x_1, d_1(x_1)\} \in \Lambda_1$ and $P\{\overline{X}_k^*(\overline{d}_{k-1}) = \overline{x}_k\} > 0$, the argument leading to (5.23) yields $\{\overline{x}_{k+1}, \overline{d}_k(\overline{x}_k)\} \in \Gamma_{k+1}$, $d_{k+1}\{\overline{x}_{k+1}, \overline{d}_k(\overline{x}_k)\} \in \Psi_{k+1}(h_{k+1})$, so this term is > 0

Inverse probability weighted estimator

- Applying these results yields

$$
\begin{aligned}
P\{\overline{A} = \overline{d}(\overline{X}) | X_1, W^*\} &= p_{A_1|X_1}\{d_1(X_1)|X_1\} \\
&\times \left(\prod_{k=2}^{K} p_{A_k|\overline{X}_k, \overline{A}_{k-1}}[d_k\{\overline{X}_k, \overline{d}_{k-1}(\overline{X}_{k-1})\}|\overline{X}_k, \overline{d}_{k-1}(\overline{X}_{k-1})] \right) \\
&= \pi_{d,1}(X_1) \left[\prod_{k=2}^{K} \pi_{d,k}\{\overline{X}_k^*(\overline{d}_{k-1})\} \right]
\end{aligned}
$$

which is the desired equality

Inverse probability weighted estimator

Result: (5.28) holds

$$E\left[\frac{\mathcal{C}_d Y}{\left\{\prod_{k=2}^{K}\pi_{d,k}(\overline{X}_k)\right\}\pi_{d,1}(X_1)}\right] = E\{Y^*(d)\}$$

- $\widehat{\mathcal{V}}_{IPW}(d)$ is an unbiased estimator for $\mathcal{V}(d)$
- Alternative representation of $E\{Y^*(d)\}$ in terms of observed data
- Taking instead for fixed y

$$f\{\overline{X}_K^*(\overline{d}_{K-1}), Y^*(d)\} = \mathrm{I}\{Y^*(d) = y\}$$

yields an alternative representation of the marginal density of $Y^*(d)$

Inverse probability weighted estimator

More generally: For fixed $(x_1, \overline{x}_2, \ldots, \overline{x}_K, y)$, treating all variables as discrete, taking

$$f\{\overline{X}^*_K(\overline{d}_{K-1}), Y^*(d)\}$$
$$= \mathrm{I}\{X_1 = x_1, X^*_2(d_1) = x_2, \ldots, X^*_K(\overline{d}_{K-1}) = x_K, Y^*(d) = y\}$$

yields an alternative representation of the joint density

$$P\{X_1 = x_1, X^*_2(d_1) = x_2, \ldots, X^*_K(\overline{d}_{K-1}) = x_K, Y^*(d) = y\}$$
$$= p_{X_1, X^*_2(d_1), X^*_3(\overline{d}_2), \ldots, X^*_K(\overline{d}_{K-1}), Y^*(d)}(x_1, \ldots, x_K, y)$$
$$= E\left[\frac{C_d \, \mathrm{I}(X_1 = x_1, X_2 = x_2, \ldots, X_K = x_K, Y = y)}{\left\{\prod_{k=2}^{K} \pi_{d,k}(\overline{X}_k)\right\} \pi_{d,1}(X_1)}\right]$$

Inverse probability weighted estimator

Denominator:

$$\left\{ \prod_{k=2}^{K} \pi_{d,k}(\overline{X}_k) \right\} \pi_{d,1}(X_1)$$

- Can be interpreted as the propensity for receiving treatment consistent with regime d through all K decisions given observed history
- Depends on the propensities of treatment given observed history

$$p_{A_k|H_k}(a_k|h_k) = P(A_k = a_k \mid H_k = h_k), \quad k = 1, \ldots, K$$

- *In practice:* Posit and fit models for the propensities depending on parameters γ_k and estimators $\widehat{\gamma}_k$, $k = 1, \ldots, K$; considerations for this momentarily
- These models induce models $\pi_{d,1}(X_1; \gamma_1)$ and $\pi_{d,k}(\overline{X}_k; \gamma_k)$

Inverse probability weighted estimator

In practice: IPW estimator

$$\widehat{\mathcal{V}}_{IPW}(d) = n^{-1} \sum_{i=1}^{n} \frac{C_{d,i} Y_i}{\left\{ \prod_{k=2}^{K} \pi_{d,k}(\overline{X}_{ki}; \widehat{\gamma}_k) \right\} \pi_{d,1}(X_{1i}; \widehat{\gamma}_1)} \tag{5.32}$$

- Consistent estimator for $\mathcal{V}(d)$ as long as the propensity models are correctly specified

Inverse probability weighted estimator

Alternative estimator:

$$\widehat{\mathcal{V}}_{IPW*}(d) = \left[\sum_{i=1}^{n} \frac{\mathcal{C}_{d,i}}{\left\{\prod_{k=2}^{K} \pi_{d,k}(\overline{X}_{ki}; \widehat{\gamma}_k)\right\} \pi_{d,1}(X_{1i}; \widehat{\gamma}_1)}\right]^{-1} \times \sum_{i=1}^{n} \frac{\mathcal{C}_{d,i} Y_i}{\left\{\prod_{k=2}^{K} \pi_{d,k}(\overline{X}_{ki}; \widehat{\gamma}_k)\right\} \pi_{d,1}(X_{1i}; \widehat{\gamma}_1)} \tag{5.33}$$

- Weighted average, also a consistent estimator
- Can be considerably more precise than $\widehat{\mathcal{V}}_{IPW}(d)$

Considerations for propensity modeling

Simplest case: Two options at each decision point, feasible for all individuals, $\mathcal{A}_k = \{0, 1\}$, $k = 1, \ldots, K$

- Can work with propensity scores

$$\pi_k(h_k) = P(A_k = 1 | H_k = h_k) = \pi_k(\overline{x}_k, \overline{a}_{k-1}), \quad k = 1, \ldots, K$$

$$p_{A_1|X_1}(a_1|x_1) = p_{A_1|H_1}(a_1|h_1) = \pi_1(h_1)^{a_1}\{1 - \pi_1(h_1)\}^{1-a_1}$$

$$p_{A_k|\overline{X}_k,\overline{A}_{k-1}}(a_k|\overline{x}_k, \overline{a}_{k-1}) = p_{A_k|H_k}(a_k|h_k) = \pi_k(h_k)^{a_k}\{1 - \pi_k(h_k)\}^{1-a_k}$$

$$k = 2, \ldots, K$$

- Using (5.2)

$$\pi_{d,1}(X_1) = \pi_1(X_1)^{d_1(X_1)}\{1 - \pi_1(X_1)\}^{1-d_1(X_1)}$$

$$\pi_{d,k}(\overline{X}_k) = \pi_k\{\overline{X}_k, \overline{d}_{k-1}(\overline{X}_{k-1})\}^{d_k\{\overline{X}_k, \overline{d}_{k-1}(\overline{X}_{k-1})\}} \times [1 - \pi_k\{\overline{X}_k, \overline{d}_{k-1}(\overline{X}_{k-1})\}]^{1-d_k\{\overline{X}_k, \overline{d}_{k-1}(\overline{X}_{k-1})\}},$$

$$k = 2, \ldots, K$$

Considerations for propensity modeling

- Can posit a parametric model $\pi_k(h_k;\gamma_k)$ for each k; e.g., logistic regression models as in (3.12)

$$\pi_k(h_k;\gamma_k) = \frac{\exp(\gamma_{k1} + \gamma_{k2}^T \widetilde{h}_k)}{1 + \exp(\gamma_{k1} + \gamma_{k2}^T \widetilde{h}_k)}, \quad \gamma_k = (\gamma_{k1}, \gamma_{k2}^T)^T, \quad k = 1, \ldots, K$$

  $\widetilde{h}_k = (1, h_k^T)^T$, $k = 1, \ldots, K$, and fit via maximum likelihood to obtain $\widehat{\gamma}_k$, $k = 1, \ldots, K$

Considerations for propensity modeling

More than 2 options: Feasible for all individuals, $\mathcal{A}_k = \{1, \ldots, m_k\}$

- As on Slide 170, with

$$\omega_k(h_k, a_k) = P(A_k = a_k | H_k = h_k), \quad k = 1, \ldots, K$$

or $\omega_k(\overline{x}_k, \overline{a}_{k-1}, a_k) = P(A_k = a_k | \overline{X}_k = \overline{x}_k, \overline{A}_{k-1} = \overline{a}_{k-1})$

where

$$\omega_k(h_k, m_k) = 1 - \sum_{a_k=1}^{m_k-1} \omega_k(h_k, a_k)$$

- Then

$$\pi_{d,1}(X_1) = \prod_{a_1=1}^{m_1} \omega_1(X_1, a_1)^{\mathrm{I}\{d_1(X_1)=a_1\}} = \sum_{a_1=1}^{m_1} \mathrm{I}\{d_1(X_1) = a_1\}\omega_1(X_1, a_1)$$

$$\pi_{d,k}(\overline{X}_k) = \prod_{a_k=1}^{m_k} \omega_k\{\overline{X}_k \overline{d}_{k-1}(\overline{X}_{k-1}), a_k\}^{\mathrm{I}[d_k\{\overline{X}_k, \overline{d}_{k-1}(\overline{X}_{k-1})\}=a_k]},$$

$$= \sum_{a_k=1}^{m_k} \mathrm{I}[d_k\{\overline{X}_k, \overline{d}_{k-1}(\overline{X}_{k-1})\} = a_k]\omega_k\{\overline{X}_k, \overline{d}_{k-1}(\overline{X}_{k-1}), a_k\}$$

Considerations for propensity modeling

- Can posit parametric models $\omega_k(h_k, a_k; \gamma_k)$ for each k e.g., multinomial (polytomous) logistic regression models

$$\omega_k(h_k, a_k; \gamma_k) = \frac{\exp(\widetilde{h}_k^T \gamma_{k,a_k})}{1 + \sum_{j=1}^{m_k - 1} \exp(\widetilde{h}_k^T \gamma_{kj})}, \quad a_k = 1, \ldots, m_k - 1$$

  $\widetilde{h}_k = (1, h_k^T)^T$, $\gamma_k = (\gamma_{k1}^T, \ldots, \gamma_{k,m_k-1}^T)^T$ and fit via maximum likelihood to obtain $\widehat{\gamma}_k$, $k = 1, \ldots, K$

Considerations for propensity modeling

Feasible sets: ℓ_k distinct subsets, each with ≥ 2 options in $\mathcal{A}_k$

$$\mathcal{A}_{k,l} = \{1, \ldots, m_{kl}\}, \quad , l = 1, \ldots, \ell_k, \quad k = 1, \ldots, K$$

- For $k = 1, \ldots, K$, $a_k \in \{1, \ldots, m_{kl}\} = \mathcal{A}_{k,l}$

$$\omega_{k,l}(h_k, a_k) = P(A_k = a_k | H_k = h_k)$$

$$\omega_{k,l}(h_k, m_{kl}) = 1 - \sum_{a_k=1}^{m_{kl}-1} \omega_{k,l}(h_k, a_k)$$

- For $k = 1, \ldots, K$, can posit ℓ_k separate logistic or multinomial (polytomous) logistic regression models

$$\omega_{k,l}(h_k, a_k; \gamma_{kl}), \quad l = 1, \ldots, \ell_k$$

Considerations for propensity modeling

- For each $k = 1, \ldots, K$, implies an overall model

$$\omega_k(h_k, a_k; \gamma_k) = \sum_{l=1}^{\ell_k} \mathrm{I}\{s_k(h_k) = l\}\, \omega_{k,l}(h_k, a_k; \gamma_{kl}), \quad \gamma_k = (\gamma_{k1}^T, \ldots, \gamma_{k\ell_k}^T)^T$$

  understood that a_k takes values in the relevant distinct subset
- For subsets with a single option, $P(A_k = a_k \mid H_k = h_k) = 1$, and no model is needed
- Induced models

$$\pi_{d,1}(X_1; \gamma_1) = \sum_{l=1}^{\ell_1} \mathrm{I}\{s_1(h_1) = l\} \prod_{a_1=1}^{m_{1l}} \omega_{1,l}(X_1, a_1; \gamma_{1l})^{\mathrm{I}\{d_1(X_1)=a_1\}}$$

$$\pi_{d,k}(\overline{X}_k; \gamma_k) = \sum_{l=1}^{\ell_k} \mathrm{I}\{s_k(h_k) = l\}$$

$$\times \prod_{a_k=1}^{m_{kl}} \omega_{k,l}\{\overline{X}_k, \overline{d}_{k-1}(\overline{X}_{k-1}), a_k; \gamma_{kl}\}^{\mathrm{I}[d_k\{\overline{X}_k, \overline{d}_{k-1}(\overline{X}_{k-1})\}=a_k)]}$$

Considerations for propensity modeling

In a SMART: Propensities are known

- As on Slide 90, preferable to estimate the propensities
- Estimate $P(A_k = a_k \mid H_k = h_k)$ by sample proportions corresponding to each distinct subset $\mathcal{A}_{k,l}$
- Example: Acute leukemia, $\ell_2 = 2$, r_2 component of h_2 indicating response

$$\begin{aligned}\Psi_2(h_2) &= \{\mathrm{M}_1, \mathrm{M}_2\} = \mathcal{A}_{2,1}, \quad r_2 = 1 \\ &= \{\mathrm{S}_1, \mathrm{S}_2\} = \mathcal{A}_{2,2}, \quad r_2 = 0\end{aligned}$$

- Estimate $P(A_2 = a_2 \mid H_2 = h_2)$ for $a_2 \in \mathcal{A}_{2,1}$ by

$$\left(\sum_{i=1}^{n} \mathrm{I}(R_{2i} = 1)\right)^{-1} \sum_{i=1}^{n} \mathrm{I}(R_{2i} = 1)\mathrm{I}(A_{2i} = a_2)$$

- Estimate $P(A_2 = a_2 \mid H_2 = h_2)$ for $a_2 \in \mathcal{A}_{2,2}$ by

$$\left(\sum_{i=1}^{n} \mathrm{I}(R_{2i} = 0)\right)^{-1} \sum_{i=1}^{n} \mathrm{I}(R_{2i} = 0)\mathrm{I}(A_{2i} = a_2)$$

Inverse probability weighted estimator

Equivalent representation: For both $\widehat{\mathcal{V}}_{IPW}(d)$ and $\widehat{\mathcal{V}}_{IPW*}(d)$

- When $\mathcal{C}_d = 1$, $A_1 = d_1(X_1)$, and $A_k = d_k\{\overline{X}_k, \overline{d}_{k-1}(\overline{X}_{k-1})\}$, $k = 2, \ldots, K$, and it is straightforward that the denominator

$$\left\{ \prod_{k=2}^{K} \pi_{d,k}(\overline{X}_{ki}; \widehat{\gamma}_k) \right\} \pi_{d,1}(X_{1i}; \widehat{\gamma}_1)$$

can be replaced by the fitted model for

$$\prod_{k=1}^{K} p_{A_k|H_k}(A_{ki}|H_{ki})$$

without altering the value of either estimator

Inverse probability weighted estimator

- E.g., with 2 feasible options at each decision point, replace the denominator by

$$\prod_{k=1}^{K} \pi_k(H_{ki}; \widehat{\gamma}_k)^{A_{ki}} \{1 - \pi_k(H_{ki}; \widehat{\gamma}_k)\}^{1-A_{ki}}$$

- With more than 2 options, by

$$\prod_{k=1}^{K} \omega_k(H_{ki}, A_{ki}; \widehat{\gamma}_k)$$

- In some literature accounts, the estimators are defined with these quantities in the denominators
- This will be important later

Inverse probability weighted estimator

Remarks:

- $\widehat{\mathcal{V}}_{IPW}(d)$ and $\widehat{\mathcal{V}}_{IPW*}(d)$ are consistent estimators as long as the propensity models are correctly specified; can be inconsistent otherwise
- Except for estimation of propensities, these estimators use data only from subjects for whom $\overline{A} = \overline{d}(\overline{X})$
- For larger K, there are likely very few such subjects
- These estimators can be unstable in finite samples due to division by propensity of treatment consistent with d small and can exhibit large sampling variation
- As in the single decision case, even if the propensities are known, it is preferable to estimate them via maximum likelihood
- Large sample approximations to the sampling distributions of $\widehat{\mathcal{V}}_{IPW}(d)$ and $\widehat{\mathcal{V}}_{IPW*}(d)$ follow from M-estimation theory

Augmented inverse probability weighted estimator

Drop out analogy: For individuals for whom $\overline{A} \neq \overline{d}(\overline{X})$

- Analogy to a *monotone coarsening* problem; i.e., "drop out"
- Under SUTVA, an individual with

$$A_1 = d_1(X_1), \ldots, A_{k-1} = d_{k-1}\{\overline{X}_{k-1}, \overline{d}_{k-2}(\overline{X}_{k-2})\}$$

but for whom

$$A_k \neq d_k\{\overline{X}_k, \overline{d}_{k-1}(\overline{X}_{k-1})\}$$

has $X_2 = X_2^*(d_1), \ldots, X_k = X_k^*(\overline{d}_{k-1})$, i.e., $\overline{X}_k = \overline{X}_k^*(\overline{d}_{k-1})$

- But his $X_{k+1}, \ldots, X_K$ and Y *do not reflect* the potential outcomes he would have if he had continued to follow rules $d_k, \ldots, d_K$
- Effectively, in terms of receiving treatment options consistent with d, the individual has "dropped out" at Decision k

Augmented inverse probability weighted estimator

Improvement: From the perspective of information on $\{X_1, \overline{X}_K^*(\overline{d}_{K-1}), Y^*(d)\}$ and especially $Y^*(d)$

- $\overline{X}_k^*(\overline{d}_{k-1})$ is observed, but $X_{k+1}^*(\overline{d}_k), \ldots, X_K^*(\overline{d}_{K-1}), Y^*(d)$ are "missing"
- Can we exploit the partial information from such individuals to gain efficiency?

Dropout analogy: Under SUTVA, SRA, and positivity, this "drop out" is according to a *missing (coarsening) at random* mechanism (shown by Zhang et al., 2013), allowing semiparametric theory for monotone coarsening at random to be used (Robins et al., 1994; Tsiatis, 2006)

Augmented inverse probability weighted estimator

Define:

- Indicator of treatment options consistent with d through Decision k

$$C_{\overline{d}_k} = \mathrm{I}\{\overline{A}_k = \overline{d}_k(\overline{X}_k)\}, \quad k = 1, \ldots, K$$

  with $C_{d_0} \equiv 1$
- For brevity, write $\overline{\pi}_{d,1}(X_1) = \pi_{d,1}(X_1)$ and

$$\overline{\pi}_{d,k}(\overline{X}_k) = \left\{ \prod_{j=2}^{k} \pi_{d,j}(\overline{X}_j) \right\} \pi_{d,1}(X_1), \quad k = 2, \ldots, K$$

  with $\overline{\pi}_{d,0} \equiv 1$
- Substitution of propensity models leads to models

$$\overline{\pi}_{d,k}(\overline{X}_k; \overline{\gamma}_k), \quad k = 1, \ldots, K$$

$\overline{\gamma}_k = (\gamma_1^T, \ldots, \gamma_k^T)^T$, $k = 1, \ldots, K$

Augmented inverse probability weighted estimator

Analogous to AIPW estimator for single decision: Under these conditions, if the models for the propensities

$$p_{A_k|H_k}(a_k|h_k), \quad k = 1, \ldots, K$$

are *correctly specified*, from semiparametric theory, all consistent and asymptotically normal estimators for $\mathcal{V}(d)$ for fixed $d \in \mathcal{D}$ are asymptotically equivalent to an estimator of the form

$$\widehat{\mathcal{V}}_{AIPW}(d) = n^{-1} \sum_{i=1}^{n} \left[\frac{C_{d,i} Y_i}{\left\{ \prod_{k=2}^{K} \pi_{d,k}(\overline{X}_{ki}; \widehat{\gamma}_k) \right\} \pi_{d,1}(X_{1i}; \widehat{\gamma}_1)} \right. \tag{5.34}$$

$$\left. + \sum_{k=1}^{K} \left\{ \frac{C_{\overline{d}_{k-1},i}}{\overline{\pi}_{d,k-1}(\overline{X}_{k-1,i}; \widehat{\overline{\gamma}}_{k-1})} - \frac{C_{\overline{d}_k,i}}{\overline{\pi}_{d,k}(\overline{X}_{ki}, \widehat{\overline{\gamma}}_k)} \right\} L_k(\overline{X}_{ki}) \right]$$

- $L_k(\overline{x}_k)$ are arbitrary functions of $\overline{x}_k$, $k = 1, \ldots, K$
- $\widehat{\overline{\gamma}}_k = (\widehat{\gamma}_1^T, \ldots, \widehat{\gamma}_k^T)^T$, $k = 1, \ldots, K$

Augmented inverse probability weighted estimator

Features of $\widehat{\mathcal{V}}_{AIPW}(d)$:

- Taking $L_k(\overline{x}_k) \equiv 0$, $k = 1, \ldots, K$, yields $\widehat{\mathcal{V}}_{IPW}(d)$ in (5.32)
- When $K = 1$, because $\mathcal{C}_{d_0} \equiv 1$, $\overline{\pi}_{d,0} \equiv 1$, and $X_1 = H_1$, (5.34) reduces to the AIPW estimator (3.16) for the single decision case
- If all K propensity models are correctly specified, so there are true values $\gamma_{k,0}$ of γ_k, $k = 1, \ldots, K$, the "augmentation term" in (5.34) evaluated at $\gamma_{k,0}$, $k = 1, \ldots, K$, converges in probability to zero for arbitrary $L_k(\overline{x}_k)$, $k = 1, \ldots, K$
- Thus, (5.34) is a consistent estimator for $\mathcal{V}(d)$ with asymptotic variance depending on the choice of $L_k(\overline{x}_k)$

Augmented inverse probability weighted estimator

Efficient estimator: From semiparametric theory, the estimator with smallest asymptotic variance among those in the class (5.34) takes

$$L_k(\overline{x}_k) = E\{Y^*(d) \mid \overline{X}_k^*(\overline{d}_{k-1}) = \overline{x}_k\}, \quad k = 1, \ldots, K \tag{5.35}$$

- The conditional expectations in (5.35) are functionals of the distribution of the potential outcomes $\{X_1, X_2^*(d_1), \ldots, X_k^*(\overline{d}_{k-1}), Y^*(d)\}$ and are *unknown* in practice
- As in the single decision case, posit and fit models

$$\mathcal{Q}_{d,k}(\overline{x}_k; \beta_k), \quad k = 1, \ldots, K, \tag{5.36}$$

  for $E\{Y^*(d) \mid \overline{X}_k^*(\overline{d}_{k-1}) = \overline{x}_k\}$, $k = 1, \ldots, K$, and substitute in (5.34)
- We present approaches to developing and fitting models (5.36) when we discuss optimal regimes later

Augmented inverse probability weighted estimator

Result: Given estimators $\widehat{\beta}_k$, $k = 1, \ldots, K$, obtained as we discuss later, the AIPW estimator is

$$\widehat{\mathcal{V}}_{AIPW}(d) = n^{-1} \sum_{i=1}^{n} \left[\frac{C_{d,i} Y_i}{\left\{ \prod_{k=2}^{K} \pi_{d,k}(\overline{X}_{ki}; \widehat{\gamma}_k) \right\} \pi_{d,1}(X_{1i}; \widehat{\gamma}_1)} \right. \tag{5.37}$$

$$\left. + \sum_{k=1}^{K} \left\{ \frac{C_{\overline{d}_{k-1},i}}{\overline{\pi}_{d,k-1}(\overline{X}_{k-1,i}; \widehat{\overline{\gamma}}_{k-1})} - \frac{C_{\overline{d}_k,i}}{\overline{\pi}_{d,k}(\overline{X}_{k,i}, \widehat{\overline{\gamma}}_k)} \right\} \mathcal{Q}_{d,k}(\overline{X}_{ki}; \widehat{\beta}_k) \right]$$

- $\widehat{\mathcal{V}}_{AIPW}(d)$ in (5.37) is doubly robust; i.e., is consistent if either (1) the models for the propensities and thus for $\pi_{d,1}(x_1)$ and $\pi_{d,k}(\overline{x}_k)$, $k = 2, \ldots, K$, *or* (2) the models for for $E\{Y^*(d) \mid \overline{X}^*_k(\overline{d}_k) = \overline{x}_k\}$ in (5.36) are correctly specified
- If the observed data are from a SMART, the propensities are known, and $\widehat{\mathcal{V}}_{AIPW}(d)$ is guaranteed to be consistent regardless of the models (5.36)

Augmented inverse probability weighted estimator

Efficient estimator: If all models are correct, $\widehat{\mathcal{V}}_{AIPW}(d)$ is efficient among estimators in class (5.37), achieving the smallest asymptotic variance

Remarks:

- $\widehat{\mathcal{V}}_{AIPW}(d)$ can exhibit considerably less sampling variation than the simple IPW estimators (5.32) and (5.33)
- As for $\widehat{\mathcal{V}}_{IPW}(d)$ and $\widehat{\mathcal{V}}_{IPW*}(d)$, large sample approximate sampling distribution can be obtained via M-estimation theory (although pretty involved)
- Zhang et al. (2013) propose (5.37) in a different but equivalent form following directly from that in Tsiatis (2006)

Estimation via marginal structural models

Alternative approach: When scientific interest focuses on regimes with simple rules that can be represented in terms of a low-dimensional parameter η

- Formally, restrict to a subset $\mathcal{D}_\eta \subset \mathcal{D}$ with elements

$$d_\eta = \{d_1(h_1; \eta_1), \ldots, d_K(h_K; \eta_K)\}, \quad \eta = (\eta_1^T, \ldots, \eta_K^T)^T$$

- *Goal:* Estimate the value of a fixed regime $d_{\eta^*} \in \mathcal{D}_\eta$ corresponding to a particular η^*, $\mathcal{V}(d_{\eta^*}) = E\{Y^*(d_{\eta^*})\}$
- As in the example coming next, $\mathcal{D}_\eta$ may be even simpler, with

$$\eta = \eta_1 = \cdots = \eta_K$$

Estimation via marginal structural models

Example: Treatment of HIV-infected patients

- K monthly clinic visits, decision on whether or not to administer antiretrovial (ARV) therapy for the next month based on CD4 T-cell count (cells/mm^3) (larger is better)
- Two feasible options: 1 = ARV therapy for the next month or 0 = no ARV therapy for the next month
- Focus on rules involving a common CD4 threshold η below which ARV therapy is administered and above which it is not

$$d_k(h_k; \eta) = \mathrm{I}(\mathrm{CD4}_k \leq \eta), \quad k = 1, \ldots, K$$

  $\mathrm{CD4}_k$= CD4 T cell count (cells/mm^3) immediately prior to Decision k
- $\mathcal{D}_\eta$ comprises regimes d_η with rules of this form
- Final outcome: $Y^*(d_\eta)$ = negative viral load (viral RNA copies/mL) measured 1 month after Decision K if administered ARV therapy using rules in d_η

Estimation via marginal structural models

Focus: Estimation of $\mathcal{V}(d_{\eta^*})$ for particular threshold η^*

- Ideal: Data from a study where HIV patients were given ARV therapy according to d_{η^*} and viral load was ascertained after Decision K
- More likely: Available data are observational, with information X_k, $k = 1, \ldots, K$, including CD4_k, options A_k actually received, and $-$final viral load Y recorded
- In these data, there are likely very few if any individuals who received ARV therapy according to the rules in d_{η^*}
- An approach to using these data to estimate $\mathcal{V}(d_{\eta^*})$ is suggested by work of Orellana et al. (2010ab)

Estimation via marginal structural models

Marginal structural model: A model for $\mathcal{V}(d_\eta)$ as a function of η

- I.e., $\mathcal{V}(d_\eta) = \mu(\eta)$ for some function $\mu(\cdot)$, posit a parametric model

$$\mathcal{V}(d_\eta) = E\{Y^*(d_\eta)\} = \mu(\eta; \alpha) \tag{5.38}$$

  referred to as a *marginal structural model* (MSM)

- For example, a quadratic model

$$\mu(\eta; \alpha) = \alpha_1 + \alpha_2\eta + \alpha_3\eta^2, \quad \alpha = (\alpha_1, \alpha_2, \alpha_3)^T$$

- Estimate α based on the data by an appopriate method to obtain $\widehat{\alpha}$, and estimate $\mathcal{V}(d_{\eta^*})$ by

$$\widehat{\mathcal{V}}_{MSM}(d_{\eta^*}) = \mu(\eta^*; \widehat{\alpha})$$

- η plays the role of "covariate" and $\mu(\eta^*; \widehat{\alpha})$ is the "predicted value" at the particular value η^* of interest

Estimation via marginal structural models

Hope: The MSM is a correct specification of the true relationship $\mu(\eta)$ across a plausible range of thresholds of interest

Estimation of α: Ideally, data from a prospective randomized study

- Each subject $i = 1, \ldots, n$ is randomized to one of m predetermined thresholds $\eta_{(j)}$, $j = 1, \ldots, m$, in the range of interest and receives ARV according to $d_{\eta_{(j)}}$
- Natural estimator $\widehat{\alpha}$ solves in α the estimating equation

$$\sum_{i=1}^{n} \sum_{j=1}^{m} C_{d_{\eta_{(j)}},i} \frac{\partial \mu(\eta_{(j)}; \alpha)}{\partial \alpha} w(\eta_{(j)}) \{ Y_i - \mu(\eta_{(j)}; \alpha) \} = 0 \qquad (5.39)$$

  where $w(\eta)$ is a weight function, $C_{d_\eta} = \mathrm{I}\{\overline{A} = \overline{d}_\eta(\overline{X})\}$
- $w(\eta) \equiv 1$ yields OLS estimation
- Each subject i has treatment experience consistent exactly one of the $\eta_{(j)}$, $j = 1, \ldots, m$
- (5.39) is an unbiased estimating equation if $\mu(\eta; \alpha)$ is correct

Estimation via marginal structural models

Observtional data: Approach is motivated by (5.39)

- Some individuals have treatment experience consistent with ≥ 1 values of η, e.g., with $K = 2$

Experience	Consistent with
CD4$_1$=300, $A_1 = 1$, CD4$_2$=400, $A_2 = 0$	$\eta \in (300, 400)$
CD4$_1$=300, $A_1 = 1$, CD4$_2$=400, $A_2 = 1$	$\eta > 400$
CD4$_1$=300, $A_1 = 0$, CD4$_2$=400, $A_2 = 0$	$\eta < 300$

- Others have treatment experience consistent with no value of η

Experience	Consistent with
CD4$_1$=300, $A_1 = 0$, CD4$_2$=400, $A_2 = 1$	no η

Estimation via marginal structural models

Observational data: Estimator $\widehat{\alpha}$ is solution to

$$\sum_{i=1}^{n} \int_{\mathcal{D}_\eta} \left[\frac{C_{d_\eta,i}}{\left\{ \prod_{k=2}^{K} \pi_{d_\eta,k}(\overline{X}_{ki}; \widehat{\gamma}_k) \right\} \pi_{d_\eta,1}(X_{1i}; \widehat{\gamma}_1)} \times \frac{\partial \mu(\eta;\alpha)}{\partial \alpha} w(\eta)\{Y_i - \mu(\eta;\alpha)\} \right] d\nu(d_\eta) = 0$$

- $d\nu(d_\eta)$ is an appropriate dominating measure on $d_\eta \in \mathcal{D}_\eta$
- $w(\eta)$ is a weight function
- A given individual i can contribute information on multiple thresholds or none at all
- As in the IPW estimators, each of her contributions is weighted by the reciprocal of an estimator for the propensity of receiving treatment consistent with d_η given observed history

Estimation via marginal structural models

For example: Interest in $\eta \in [100, 500]$, for $j = 1, \ldots, m$, partition $\eta_{(j)} = 100 + 400(j-1)/(m-1)$, $d\nu(d_\eta)$ places point mass on $\eta_{(j)}$

$$\sum_{i=1}^{n}\sum_{j=1}^{m}\left[\frac{C_{d_{\eta_{(j)}},i}}{\left\{\prod_{k=2}^{K}\pi_{\eta_{(j)},k}(\overline{X}_{ki};\widehat{\gamma}_k)\right\}\pi_{\eta_{(j)},1}(X_{1i};\widehat{\gamma}_1)} \times \frac{\partial\mu(\eta_{(j)};\alpha)}{\partial\alpha}w(\eta_{(j)})\{Y_i - \mu(\eta_{(j)};\alpha)\}\right] = 0$$

- Under SUTVA, SRA, and positivity, if $\mu(\eta;\alpha)$ and the propensity models are correctly specified, these estimating equations can be shown to be unbiased, and $\widehat{\alpha}$ is an M-estimator
- Here, if there is a sufficient # of individuals who received treatment consistent with at least one $\eta_{(j)}$, $j = 1, \ldots, m$, $\widehat{\alpha}$ should be a reasonable estimator in practice
- An augmented version of the estimating equation is possible

5. Multiple Decision Treatment Regimes: Framework and Fundamentals

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