7. Regimes Based on Time-to-Event Outcomes

Motivation

Chronic disease research: Cancer, CVD, etc

- The outcome of interest is a *time to an event*
- Overall survival time (OS): Time to the event (death, failure)
- Disease-free survival time (DFS): Time a patient survives without recurrence/symptoms (variations: event-free survival, EFS; distant recurrence-free survival, DRFS)
- Progression-free survival time (PFS): Time a patient survives without disease getting worse (progressing)

Motivation

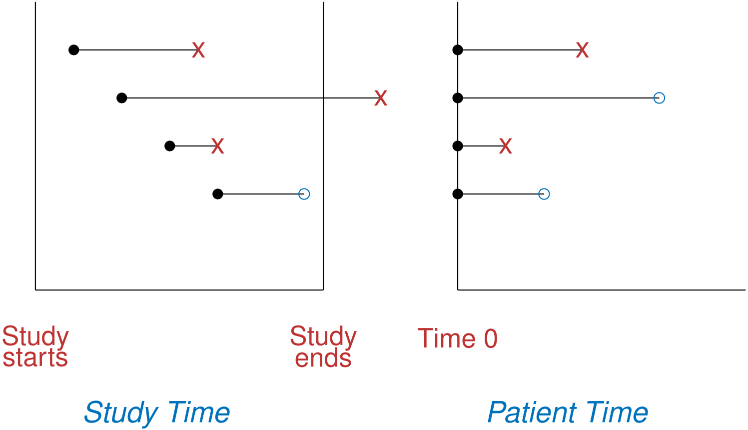
Key challenge: Censoring

- Studies are of limited duration, so the outcome may not be achieved by the end of the study for some participants (*administrative censoring*)
- Subjects may drop out of the study and are thus lost to follow up before the event is ascertained
- A competing risk prevents observation of the outcome (e.g., hit by a bus)

Result: For such individuals, only the time to censoring is observed

- Time on study (administrative censoring) or time the individual left the study

Censoring and staggered study entry



The time to event outcome of interest is usually time from study entry until occurence of the event (right-hand panel)

Motivation

Survival analysis: Body of methods for addressing questions regarding the distribution of the outcome in the presence of censoring

Treatment regimes: Specialized framework required

- Single decision: Time to event outcome may be censored for some individuals in the observed data
- Multiple decisions:
  - Timing of decisions may be different for different individuals (e.g. ascertainment of intermediate response)
  - Time to event outcome may be censored for some individuals in the observed data
  - The outcome can occur at any time following Decision 1, so that an individual may not reach all K decision points before achieving the event
  - Number of decision points reached and times at which decisions are made are *random*

7. Regimes Based on Time-to-Event Outcomes

Important quantities

Outcome: T, nonnegative (continuous) random variable with probability density $p(t)$, $t \geq 0$

- *Survival function/distribution:* For $u \geq 0$

$$\mathcal{S}(u) = P(T > u) = \int_u^\infty p(t)\,dt = 1 - F(u) \text{ so that } p(u) = -\frac{d\mathcal{S}(u)}{du}$$

- *Hazard function:* Aka hazard rate; for $u \geq 0$

$$\lambda(u) = \lim_{du \to 0} du^{-1} P(u \leq T < U + du \,|\, T \geq u)$$

where $\lambda(u) \geq 0$; can think of $\lambda(u)\,du \approx$ probability of an individual at time u experiencing the event in the next instant of time

Important quantities

Outcome: T, nonnegative (continuous) random variable with probability density $p(t)$, $t \geq 0$

- $\lambda(u) = p(u)/\mathcal{S}(u) = -d \log\{\mathcal{S}(u)\}$
- *Cumulative hazard*

$$\Lambda(u) = \int_0^u \lambda(t)\,dt = -\log\{\mathcal{S}(u)\}$$

  and thus

$$\mathcal{S}(u) = \exp\{-\Lambda(u)\} = \exp\left\{-\int_0^u \lambda(t)\,dt\right\}$$

Observed data

Standard characterization: T may not be observed

- What is observed: Time to the event or censoring, whichever comes first
- Formally: Consider T as *potential event time* and define *potential censoring time* C (more on interpretation later)
- *Observable outcome data:*

$$U = \min(T, C), \qquad \Delta = \mathrm{I}(T \leq C)$$

  so that the observed data from a study with n participants are i.i.d.

$$(U_i, \Delta_i), \quad i = 1, \ldots, n$$

- In addition: Individual covariates Z (possibly including treatment received)

$$(Z_i, U_i, \Delta_i), \quad i = 1, \ldots, n$$

Inferential objectives

Standard objectives: Based on the observed data

- Estimate survival and hazard functions
- Compare survival and hazard functions for different treatments
- Relationships between the time-to-event outcome and covariates

Parametric modeling

One approach: Adopt a fully parametric specification

- Exponential: $p(u) = \lambda \exp(-\lambda u)$

$$\lambda(u) = \lambda, \quad \mathcal{S}(u) = \exp(-\lambda u)$$

- Weibull: $p(u) = \alpha\lambda u^{\alpha-1} \exp(-\lambda u^{\alpha})$

$$\lambda(u) = \alpha\lambda u^{\alpha-1}, \quad \mathcal{S}(u) = \exp(-\lambda u^{\alpha})$$

- Lognormal, gamma, log-logistic, etc
- Fit the parametric model to the observed data (U_i, Δ_i), $i = 1, \dots, n$ by maximizing the *observed data likelihood* to estimate the survival function, hazard function, etc

Nonparametric estimation

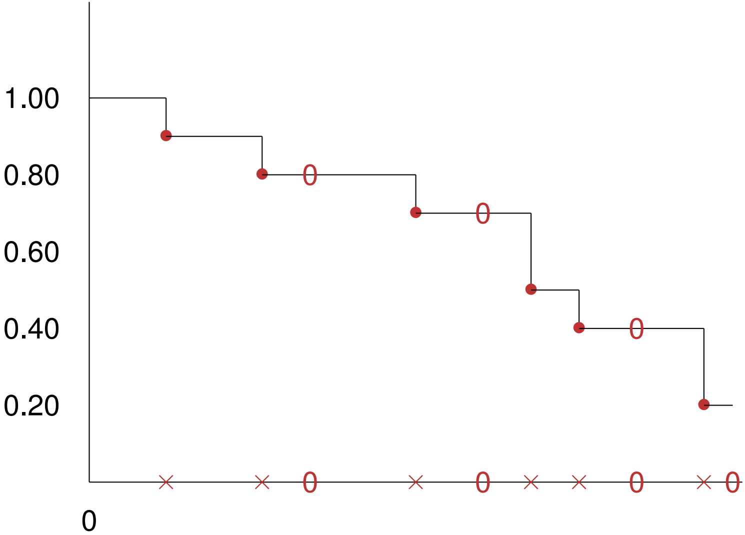
Another approach: Estimate the survival and hazard functions nonparametrically based on (U_i, Δ_i), $i = 1, \ldots, n$

- Can be shown: A nonparametric estimator for $\mathcal{S}(u)$ is the *Kaplan-Meier* or *product-limit* estimator

$$\widehat{\mathcal{S}}(u) = \prod_{j:t_j \leq u} \left(1 - \frac{1}{r_j}\right)$$

  where $0 \leq t_1 < \cdots \leq t_m$ are the distinct realized event times and r_j is the number of individuals in the sample at risk for the event at t_j (assuming no ties); i.e., $r_j = \#\{i : U_i \geq t_j\}$
- The most widely used approach for estimating a survival function

Kaplan-Meier estimator



Regression modeling

(Baseline) covariates Z: Conditional on Z

- Hazard function given Z

$$\lambda(u|z) = \lim_{du \to 0} du^{-1} P(u \leq T < U + du \,|\, T \geq u, Z = z)$$

- Survival function given Z

$$\mathcal{S}(u|z) = \exp\left\{-\int_0^u \lambda(t|z)\, dt\right\}$$

Regression modeling

Accelerated failure time model: Linear on the log scale

$$\log T = \beta_0 + \beta_1^T Z + \sigma\epsilon$$

- $\epsilon \sim$ extreme value distribution $\rightarrow$ T given Z is Weibull
- $\epsilon \sim$ normal $\rightarrow$ T given Z is normal
- Implies change of time scale

$$\mathcal{S}(u|z) = \mathcal{S}_0\{u \exp(-\beta_1^T z)\}, \quad \mathcal{S}_0(u) = \mathcal{S}(u|0)$$

$$\lambda(u|z) = \lambda_0\{u \exp(-\beta_1^T z)\} \exp(-\beta_1^T z)$$

- Frankly, this model is rarely used in practice

Regression modeling

Proportional hazards model: Most popular

$$\lambda(u|z) = \lambda_0(u)\exp\{g(z;\beta_1)\}, \qquad \mathcal{S}(u|z) = \mathcal{S}_0(u)^{\exp\{g(z;\beta_1)\}}$$

- $\lambda_0(u) \geq 0$ is a baseline hazard function , usually left unspecified (*semiparametric model*)
- Usually, $g(x;\beta_1) = \beta_1^T z$ (*Cox model*)
- Implies constant hazard ratio throughout time

$$\frac{\lambda(u|z)}{\lambda(u|z^*)} = \frac{\exp\{g(z;\beta_1)\}}{\exp\{g(z^*;\beta_1)\}}$$

- E.g., if $Z = A = 0,1$ is treatment indicator, Cox model

$$\frac{\lambda(u|1)}{\lambda(u|0)} = \frac{\lambda_0(u)\exp(\beta_1)}{\lambda_0(u)} = \exp(\beta_1)$$

is the *hazard ratio* (or *relative risk*) and β_1 is the *log hazard ratio*

Regression modeling

Hazard ratio:

$$\frac{\lambda(u|1)}{\lambda(u|0)} = \frac{\lambda_0(u)\exp(\beta_1)}{\lambda_0(u)} = \exp(\beta_1)$$

- $\beta_1 > 0$ gives hazard ratio > 1, which implies that the hazard rate of achieving the event is higher for treatment 1 than for treatment 0 (so that treatment 1 results in shorter event times on average)
- $\beta_1 = 0$ gives hazard ratio $= 1$, so same hazard rate
- $\beta_1 < 0$ gives hazard ratio < 1, which implies that hazard rate is lower for treatment 1 than treatment 0 (treatment 1 results in longer event times on average)
- Generalizes in obvious way to

$$\frac{\lambda(u|z)}{\lambda(u|z^*)} = \exp\{\beta_1(z - z^*)\}$$

Regression modeling

Important: Proportional hazards is an *assumption* and ideally should be checked (often isn't)

Partial likelihood: Cox (1972, 1975) proposed estimating β_1 by maximizing

$$PL(\beta_1) = \prod_{i=1}^{n} \left(\frac{\exp(\beta_1^T Z_i)}{\sum_{j \in \mathcal{R}_i} \exp(\beta_1^T Z_j)} \right)^{\Delta_i}, \quad \mathcal{R}_i = \mathrm{I}(j : U_j > U_i)$$

- And Breslow (1972) proposed estimating the baseline cumulative hazard function $\Lambda_0(u) = \int_0^u \lambda_0(t)\, dt$ by

$$\widehat{\Lambda}_0(u) = \sum_{i=1}^{n} \frac{\mathrm{I}(U_i \leq u)\Delta_i}{\sum_{j \in \mathcal{R}_i} \exp(\beta_1^T Z_j)}$$

Regression modeling

Remarks:

- Extends to *time-dependent covariate* $Z(u)$ = covariate history through time u

$$\lambda\{u|z(u)\} = \lim_{du\to 0} du^{-1} P\{u \leq T < u + du | T \geq u, Z(u) = z(u)\}$$

- Proportional hazards model

$$\lambda\{u|z(u)\} = \lambda_0(u)\exp[g\{z(u);\beta\}]$$

- Causal interpretations suspect when $Z(u)$ is treatment history

7. Regimes Based on Time-to-Event Outcomes

Potential outcomes

For simplicity: Two treatment options, $\mathcal{A}_1 = \{0, 1\}$

- X_1 = baseline information, history $H_1 = X_1$ at the time of the decision for a randomly chosen individual
- $T^*(a_1)$ is the potential time-to-event for a randomly chosen individual if he were to receive option $a_1 \in \mathcal{A}_1$
- Set of all potential outcomes

$$W^* = \{T^*(0), T^*(1)\}$$

Treatment regimes: $d = \{d_1(h_1)\}$ in $\mathcal{D}$

- For any $d \in \mathcal{D}$ define

$$T^*(d) = T^*(1)\mathrm{I}\{d_1(H_1) = 1\} + T^*(0)\mathrm{I}\{d_1(H_1) = 0\}$$

- $T^*(d)$ is the time-to-event a randomly chosen individual in the population would achieve if treated according to d

Functions of time-to-event outcome

Of interest: Certain functions of outcome

$$f\{T^*(d)\}$$

where $f(\cdot)$ is a known, monotone nondecreasing function

- $f(t) = t$, the outcome itself
- $f(t) = \mathrm{I}(t \geq r)$ for fixed time r; $f\{T^*(d)\}$ indicates if an individual would survive to r under regime d
- $f(t) = \min(t, L)$ for fixed time L; $f\{T^*(d)\}$ is the truncated time-to-event through time L under d, *restricted lifetime*
- Restricted lifetime is considered when survival to some prespecified time is of interest; e.g., $L = 1$ if effects of treatment are expected to manifest within one year
- Often limited to considering restricted lifetime because individuals are followed for a finite time period; L should be $<$ the maximum follow up time

Value of a regime

For given $f(\cdot)$: The value of $d \in \mathcal{D}$ is

$$\mathcal{V}(d) = E[f\{T^*(d)\}]$$

- For $f(t) = \text{I}(t \geq r)$, $E[f\{T^*(d)\}] = P\{T^*(d) \geq r\}$ = survival probability at time r if population follows d
- For $f(t) = \min(t, L)$, $E[f(T^*(d)\}]$ is the mean restricted lifetime if population follows d

Optimal regime d^{opt}: Satisfies

$$\mathcal{V}(d^{opt}) \geq \mathcal{V}(d) \quad \text{for all } d \in \mathcal{D}$$

Observed data

Point exposure study: For a given individual

- A_1 = treatment actually received, taking values $a_1 \in \mathcal{A}_1$
- Ideally, would observe time-to-event outcome T and thus observed data (H_1, A_1, T), and the single decision methods discussed previously would be straightforward using i.i.d.

$$(H_{1i}, A_{1i}, T_i), \quad i = 1, \ldots, n$$

- Censoring: C = potential censoring time, T = potential event time

$$U = \min(T, C), \qquad \Delta = \text{I}(T \leq C)$$

- Observed data (H_1, A_1, U, Δ); study data are i.i.d.

$$(H_{1i}, A_{1i}, U_i, \Delta_i), \quad i = 1, \ldots, n. \tag{7.1}$$

Objectives: Based on the observed data (7.1)

- Estimate $\mathcal{V}(d) = E[f\{T^*(d)\}]$ for fixed $d \in \mathcal{D}$
- Estimate an optimal regime $d^{opt} \in \mathcal{D}$ and its value $\mathcal{V}(d^{opt})$

Identifiability assumptions

SUTVA: Analogous to (3.4)

$$T_i = T_i^*(1)A_{1i} + T_i^*(0)(1 - A_{1i}), \quad i = 1, \ldots, n \tag{7.2}$$

- T can be viewed as potential (potentially observable) event time in the sense of (7.2)

No unmeasured confounders assumption (NUC): Analogous to (3.5)

$$\{T^*(1), T^*(0)\} \perp\!\!\!\perp A_1 | H_1, \quad \text{equivalently,} \quad W^* \perp\!\!\!\perp A_1 | H_1 \tag{7.3}$$

Identifiability assumptions

Perspective on censoring: Although C is referred to as "potential," we do not consider potential outcomes $C^*(a_1)$, say, for $a_1 \in \mathcal{A}_1$ analogous to $T^*(a_1)$

- View censoring as an *external process*, similar to treatment assignment
- E.g., Administrative censoring is purely a result of the study, unrelated to treatment received
- Censoring due to drop out is viewed as depending only on observed past history and not potential outcomes

Identifiability assumptions

Noninformative censoring: Standard assumption

$$\{T^*(1), T^*(0)\} \perp\!\!\!\perp C | H_1, A_1, \quad \text{equivalently,} \quad W^* \perp\!\!\!\perp C | H_1, A_1 \tag{7.4}$$

Under SUTVA (7.2), (7.4) implies

$$T \perp\!\!\!\perp C | H_1, A_1 \tag{7.5}$$

which is the usual statement in the conventional notation

- Hazard function for time to potential censoring given (H_1, A_1)

$$\lambda_C(u | h_1, a_1) = \lim_{du \to 0} du^{-1} P(u \leq C < u + du \,|\, C \geq u, H_1 = h_1, A_1 = a_1) \tag{7.6}$$

- Under (7.5), (7.6) is equivalent to the cause-specific hazard function

$$\lim_{du \to 0} du^{-1} P(u \leq U < u + du, \Delta = 0 \,|\, U \geq u, H_1, A_1)$$

Identifiability assumptions

Noninformative censoring:

- A weaker assumption implied by (7.4) is

$$
\begin{aligned}
&\lambda_C(u|H_1, A_1, W^*) \\
&= \lim_{du \to 0} du^{-1} P(u \leq U < u + du, \Delta = 0 \,|\, U \geq u, H_1, A_1, W^*) \\
&= \lim_{du \to 0} du^{-1} P(u \leq U < u + du, \Delta = 0 \,|\, U \geq u, H_1, A_1) \\
&= \lambda_C(u|H_1, A_1)
\end{aligned} \tag{7.7}
$$

Identifiability assumptions

Positivity assumption: More involved than (3.6)

- First require for all $h_1 \in \mathcal{H}_1$ such that $P(H_1 = h_1) > 0$

$$P(A_1 = a_1 | H_1 = h_1) > 0, \quad a_1 = 0, 1 \tag{7.8}$$

- Also require

$$\begin{aligned} &P(C \geq T \mid T = u, H_1 = h_1, A_1 = a_1) \\ &\qquad = P(C \geq u \mid T = u, H_1 = h_1, A_1 = a_1) > 0 \end{aligned} \tag{7.9}$$

  for all $u \geq 0$, h_1, and a_1 such that $P(T = u, H_1 = h_1, A_1 = a_1) > 0$

- Under noninformative censoring (7.4) and (7.5), (7.9) simplifies to

$$P(C \geq u \mid H_1 = h_1, A_1 = a_1) > 0 \tag{7.10}$$

Identifiability assumptions

Positivity assumption:

- Cannot estimate $E[f\{T^*(d)\}]$ for $f(t) = t$ unless the support of T is in [0, max follow up time]
- Cannot estimate $E[f\{T^*(d)\}]$ for $f(t) = \text{I}(t \geq r)$ unless $r \leq$ max follow up time
- Consider instead restricted lifetime, $f(t) = \min(t, L)$ for $L \leq$ max follow up time
- Under these conditions (7.9) is modified to

$$P\{C \geq \min(u, L) \mid T = u, H_1 = h_1, A_1 = a_1)\} > 0$$

and similarly for (7.10)

Conventional survival analysis: Can estimate a hazard ratio or survival function from data involving restricted time L

- But when interest is in expectation of a function of survival time, limited to functions that involve truncation at L

7. Regimes Based on Time-to-Event Outcomes

Estimation

Methods for estimation of:

- $\mathcal{V}(d)$ for fixed $d \in \mathcal{D}$
- $d^{opt} \in \mathcal{D}$ and $\mathcal{V}(d^{opt})$
- Assume SUTVA (7.2), (7.2), no unmeasured confounders (7.3), noninformative censoring as in (7.4), (7.5), and positivity assumptions (7.8) and (7.9) or (7.10)

Outcome regression

Analogous previous results: For any $d \in \mathcal{D}$

$$\mathcal{V}(d) = E[Q_1(H_1, 1)\text{I}\{d_1(H_1) = 1\} + Q_1(H_1, 0)\text{I}\{d_1(H_1) = 0\}]$$

$$Q_1(h_1, a_1) = E\{f(T)|H_1 = h_1, A_1 = a_1\}$$

- d^{opt} has rule

$$d^{opt}(h_1) = \text{I}\{Q_1(h_1, 1) > Q_1(h_1, 0)\}$$

- Suggests positing a model $Q_1(h_1, a_1; \beta_1)$ for $Q_1(h_1, a_1)$ and fitting based on the observed data (7.1)
- Such a model can be deduced from a model for the distribution of T or $f(T)$ given (H_1, A_1), such as the proportional hazards model

Outcome regression

Proportional hazards model: Hazard of event at time u

$$\lambda_{T1}(u|h_1,a_1) = \lim_{du\rightarrow 0} du^{-1} P(u \leq T < u{+}du \,|\, T \geq u, H_1 = h_1, A_1 = a_1)$$

- Proportional hazards model

$$\lambda_{T1}(u|h_1,a_1;\beta_1) = \lambda_{T10}(u)\exp\{g_{T1}(h_1,a_1;\xi_1)\} \qquad (7.11)$$

  $\lambda_{T10}(u)$ is an arbitrary baseline hazard function

- E.g., could take

$$g_{T1}(h_1,a_1;\xi_1) = \xi_{11}^T h_1 + \xi_{12} a_1 + \xi_{13}^T h_1 a_1, \quad \xi_1 = (\xi_{11}^T, \xi_{12}, \xi_{13}^T)^T$$

  $\beta_1 = \{\lambda_{T01}(\cdot), \xi_1^T\}^T$

- Under (7.4), can estimate ξ_1 by $\widehat{\xi}_1$ maximizing the usual partial likelihood and $\lambda_{T01}(\cdot)$ using the Breslow estimator $\widehat{\lambda}_{T01}(\cdot)$

Outcome regression

Survival function model: $\mathcal{S}_{T1}(u|h_1, a_1; \beta_1)$, follows from (7.11)

$$\mathcal{S}_{T1}(u|h_1, a_1) = \exp\left\{-\int_0^u \lambda_{T1}(w|h_1, a_1)\, dw\right\}$$

- Implied model for $Q_1(h_1, a_1)$

$$Q_1(h_1, a_1; \beta_1) = \int_0^\infty f(u)\, \{-d\mathcal{S}_{T1}(u|h_1, a_1; \beta_1)\} \tag{7.12}$$

- Can estimate $Q_1(h_1, a_1)$ by $Q_1(h_1, a_1; \widehat{\beta}_1)$, $\widehat{\beta}_1 = \{\widehat{\lambda}_{01}(\cdot), \widehat{\xi}_1^T\}^T$
- With restricted lifetime (7.12) becomes

$$\int_0^L u\, \{-d\mathcal{S}_{T1}(u|h_1, a_1; \beta_1)\} + L\mathcal{S}_{T1}(L|h_1, a_1; \beta_1)$$

Outcome regression

Estimator for $\mathcal{V}(d)$ for fixed, given $d \in \mathcal{D}$:

$$\widehat{\mathcal{V}}_Q(d) \tag{7.13}$$

$$= n^{-1} \sum_{i=1}^{n} \Big[Q_1(H_{1i}, 1; \widehat{\beta}_1) \text{I}\{d_1(H_{1i}) = 1\} + Q_1(H_{1i}, 0; \widehat{\beta}_1) I\{d_1(H_{1i}) = 0\} \Big]$$

Estimators for rule $d_1^{opt}(h_1)$ characterizing d^{opt} and $\mathcal{V}(d^{opt})$:

$$\widehat{d}_{Q,1}^{opt}(h_1) = \text{I}\{Q_1(h_1, 1; \widehat{\beta}_1) > Q_1(h_1, 0; \widehat{\beta}_1)\} \tag{7.14}$$

$$\widehat{\mathcal{V}}_Q(d^{opt}) = n^{-1} \sum_{i=1}^{n} \Big[Q_1(H_{1i}, 1; \widehat{\beta}_1) \text{I}\{\widehat{d}_1^{opt}(H_{1i}) = 1\} + Q_1(H_{1i}, 0; \widehat{\beta}_1) \text{I}\{\widehat{d}_1^{opt}(H_{1i}) = 0\} \Big] \tag{7.15}$$

Inverse probability of censoring regression

Previous approach: Model $Q_1(h_1, a_1) = E\{f(T) | H_1 = h_1, A_1 = a_1\}$ indirectly through a model for the hazard

- Advantage: Under noninformative censoring, can estimate the hazard function model with no assumption on the distribution of C given H_1 and A_1

Alternative approach: Model $Q_1(h_1, a_1)$ directly

- E.g., for $f(t) = \min(t, L)$, specify a model for mean restricted lifetime $Q_1(h_1, a_1) = E\{\min(T, L) | H_1 = h_1, A_1 = a_1\}$ such as

$$Q_1(h_1, a_1; \beta_1) = \exp(\beta_{11} + \beta_{12}^T h_1 + \beta_{13} a_1 + \beta_{14}^T h_1 a_1), \;\; \beta_1 = (\beta_{11}, \beta_{12}^T, \beta_{13}, \beta_{14}^T)^T$$

- With *no censoring*, estimator $\widehat{\beta}_1$ solves (OLS)

$$\sum_{i=1}^{n} \frac{\partial Q_1(H_{1i}, A_{1i}; \beta_1)}{\partial \beta_1} \{f(T_i) - Q_1(H_{1i}, A_{1i}; \beta_1)\} = 0$$

- Unbiased estimating equation if $Q_1(h_1, a_1; \beta_1)$ correctly specified

Inverse probability of censoring regression

With censoring: T_i is not observed for all $i = 1, \ldots, n$; observed when $\Delta_i = 1$; otherwise is censored and thus "missing"

- Suggests inverse weighting by the probability of being observed
- To this end, define the "survival function for censoring"

$$\mathcal{K}(u|h_1, a_1) = P(C \geq u \mid H_1 = h_1, A_1 = a_1)$$
$$= \exp\left\{ - \int_0^u \lambda_C(w|h_1, a_1)\, dw \right\} \tag{7.16}$$

- Estimating equation

$$\sum_{i=1}^{n} \frac{\Delta_i}{\mathcal{K}(U_i|H_{1i}, A_{1i})} \frac{\partial Q_1(H_{1i}, A_{1i}; \beta_1)}{\partial \beta_1} \{f(U_i) - Q_1(H_{1i}, A_{1i}; \beta_1)\} = 0 \tag{7.17}$$

Inverse probability of censoring regression

Restricted lifetime: Define $T^L = \min(T, L)$

- Can express (7.10) equivalently as

$$P(C \geq u \mid T^L = u, H_1 = h_1, A_1 = a_1) > 0$$

  for all u, h_1, and a_1 such that $P(T^L = u, H_1 = h_1, A_1 = a_1) > 0$, $u > L$

- Define

$$U^L = \min(T^L, C) = \min(T, L, C), \;\; \Delta^L = \text{I}(T^L \leq C) = \text{I}\{\min(T, L) \leq C\}$$

  $\Delta^L = 1$ if $U \geq L$, because $T^L = \min(T, L) = L$ regardless of whether the event time is ultimately censored or not

- Replace U_i and Δ_i in (7.17) by U_i^L and Δ_i^L

Inverse probability of censoring regression

Can show: The estimating function in (7.17) is unbiased

- That is, can demonstrate that

$$E_\beta \left[\frac{\Delta}{\mathcal{K}(U|H_1, A_1)} \frac{\partial Q_1(H_1, A_1; \beta_1)}{\partial \beta_1} \{ f(U) - Q_1(H_1, A_1; \beta_1) \} \right] = 0$$

- Exercise for the diligent student

$\mathcal{K}(u|h_1, a_1)$ **is unknown:** Posit and fit a model

- E.g., a proportional hazards model

$$\lambda_C(u|h_1, a_1; \beta_C) = \lambda_{0C}(u) \exp\{g_C(h_1, a_1; \xi_C)\}, \;\; \beta_C = \{\lambda_{0C}(t), \xi_C^T\}^T$$

which implies a model $\mathcal{K}(u|h_1, a_1; \beta_C)$ from (7.16)

- Fit using the "data" (reverse roles of T and C)

$$(H_{1i}, A_{1i}, U_i, 1 - \Delta_i), \;\; i = 1, \ldots, n$$

Inverse probability of censoring regression

Result: Estimate β_1 by the solution $\widehat{\beta}_1$ to

$$\sum_{i=1}^{n} \frac{\Delta_i}{\widehat{\mathcal{K}}(U_i|H_{1i}, A_{1i})} \frac{\partial Q_1(H_{1i}, A_{1i}; \beta_1)}{\partial \beta_1} \{f(U_i) - Q_1(H_{1i}, A_{1i}; \beta_1)\} = 0 \tag{7.18}$$

- Estimator for $\mathcal{K}(u|h_1, a_1)$ is substituted

$$\widehat{\mathcal{K}}(u|h_1, a_1) = \mathcal{K}(u|h_1, a_1; \widehat{\beta}_C)$$

- For restricted lifetime, U_i, Δ_i replaced by U_i^L, Δ_i^L in (7.18)
- Estimate $\mathcal{V}(d)$ for fixed $d \in \mathcal{D}$, d^{opt}, and $\mathcal{V}(d^{opt})$ by substitution of the fitted model $Q_1(h_1, a_1; \widehat{\beta}_1)$ as in (7.13), (7.14), and (7.15) to yield estimators $\widehat{\mathcal{V}}_{IPCW}(d)$, $\widehat{d}^{opt}_{IPCW}$, and $\widehat{\mathcal{V}}_{IPCW}(d^{opt})$

Inverse probability weighted estimation

Concern: Misspecification of the model (implied or direct) $Q_1(h_1, a_1; \beta_1)$

- Restrict attention to a class of regimes $\mathcal{D}_\eta \subset \mathcal{D}$ indexed by parameter $\eta = \eta_1$ with elements

$$d_\eta = \{d_1(h_1; \eta_1)\}$$

- Estimate

$$d_\eta^{opt} = \{d_1(h_1; \eta_1^{opt})\}, \quad \eta_1^{opt} = \arg\max_{\eta_1} \mathcal{V}(d_\eta)$$

- Choose $\mathcal{D}_\eta$ based on the same considerations discussed previously and consider inverse probability weighted estimators $\widehat{\mathcal{V}}(d_\eta)$
- Maximize $\widehat{\mathcal{V}}(d_\eta)$ in η to obtain

$$\widehat{d}_\eta^{opt} = \{d_1(h_1; \widehat{\eta}^{opt})\}, \quad \widehat{\eta}^{opt} = \arg\max_{\eta_1} \widehat{\mathcal{V}}(d_\eta)$$

Inverse probability weighted estimation

No censoring: AIPW estimator (IPW special case)

$$\widehat{\mathcal{V}}_{AIPW}(d) = n^{-1} \sum_{i=1}^{n} \left\{ \frac{\mathcal{C}_{d,i} f(T_i)}{\pi_{d,1}(H_{1i};\widehat{\gamma}_1)} - \frac{\mathcal{C}_{d,i} - \pi_{d,1}(H_{1i};\widehat{\gamma}_1)}{\pi_{d,1}(H_{1i};\widehat{\gamma}_1)} \mathcal{Q}_{d,1}(H_{1i};\widehat{\beta}_1) \right\} \tag{7.19}$$

$$\mathcal{C}_d = \text{I}\{A_1 = d_1(H_1)\} = A_1 \text{I}\{d_1(H_1) = 1\} + (1 - A_1)\text{I}\{d_1(H_1) = 0\}$$

$$\pi_{d,1}(H_1;\widehat{\gamma}_1) = \pi_1(H_1;\widehat{\gamma}_1)\text{I}\{d_1(H_1) = 1\} + \{1 - \pi_1(H_1;\widehat{\gamma}_1)\}\text{I}\{d_1(H_1) = 0\}$$

$$\begin{aligned} \mathcal{Q}_{d,1}(H_1;\widehat{\beta}_1) &= Q_1(H_1, 1;\widehat{\beta}_1)\text{I}\{d_1(H_1) = 1\} + Q_1(H_1, 0;\widehat{\beta}_1)\text{I}\{d_1(H_1) = 0\} \\ &= Q_1\{H_1, d_1(H_1);\widehat{\beta}_1\} \end{aligned}$$

- Propensity model $\pi_1(h_1;\gamma_1)$ for $\pi_1(h_1) = P(A_1 = 1 | H_1 = h_1)$, estimator $\widehat{\gamma}_1$ for γ_1
- $Q_1(h_1, a_1;\beta_1)$ is a model for $E\{f(T) | H_1 = h_1, A_1 = a_1\}$, estimator $\widehat{\beta}_1$ for β_1
- (7.19) is well defined if $\pi_{d,1}(H_1) > 0$ for all $d \in \mathcal{D}$; holds under positivity

Inverse probability weighted estimation

Censoring: Estimator in same spirit as (7.19)

- T is observed only when $\Delta = 1$, so $T^*(d)$ is observed when $\mathcal{C}_d = 1$ and $\Delta = 1$
- Suggests leading IPW term should depend on such individuals; thus, derive probability that $T^*(d)$ is observed conditional on $T^*(1)$, $T^*(0)$, and H_1

$$P\{\mathcal{C}_d = 1, \Delta = 1 | T^*(1), T^*(0), H_1\} \tag{7.20}$$
$$= P\{\mathcal{C}_d = 1 | T^*(1), T^*(0), H_1\} P\{\Delta = 1 | \mathcal{C}_d = 1, T^*(1), T^*(0), H_1\}$$

- By NUC (7.3), first term in (7.20)

$$P\{\mathcal{C}_d = 1 | T^*(1), T^*(0), H_1\} = P\{\mathcal{C}_d = 1 | H_1\} = \pi_{d,1}(H_1)$$

- Second term in (7.20) on next slide, using the definition of Δ

Inverse probability weighted estimation

$$
\begin{aligned}
&P\{C \geq T | \mathcal{C}_d = 1, T^*(1), T^*(0), H_1\} \\
&= P\{C \geq T^*(d) | \mathcal{C}_d = 1, T^*(1), T^*(0), H_1\} && (7.21) \\
&= P\{C \geq T^*(1) | \mathcal{C}_d = 1, T^*(1), T^*(0), H_1\} \mathrm{I}\{d_1(H_1) = 1\} \\
&\quad + P\{C \geq T^*(0) | \mathcal{C}_d = 1, T^*(1), T^*(0), H_1\} \mathrm{I}\{d_1(H_1) = 0\} && (7.22) \\
&= P\{C \geq T^*(1) | T^*(1), T^*(0), A_1 = 1, d_1(H_1) = 1, H_1\} \mathrm{I}\{d_1(H_1) = 1\} \\
&\quad + P\{C \geq T^*(0) | T^*(1), T^*(0), A_1 = 0, d_1(H_1) = 0, H_1\} \mathrm{I}\{d_1(H_1) = 0\} && (7.23) \\
&= P\{C \geq T^*(d) | T^*(1), T^*(0), A_1 = 1, H_1\} \mathrm{I}\{d_1(H_1) = 1\} \\
&\quad + P\{C \geq T^*(d) | T^*(1), T^*(0), A_1 = 0, H_1\} \mathrm{I}\{d_1(H_1) = 0\} \\
&= \mathcal{K}\{T^*(d) | H_1, 1) \mathrm{I}\{d_1(H_1) = 1\} + \mathcal{K}\{T^*(d) | H_1, 0) \mathrm{I}\{d_1(H_1) = 0\} && (7.24)
\end{aligned}
$$

- (7.21) by SUTVA, (7.22) because $\mathrm{I}\{d_1(H_1) = 1\} + \mathrm{I}\{d_1(H_1) = 0\} = 1$
- (7.23) by definition of $\mathcal{C}_d$, (7.24) by noninformative censoring (7.4)

Inverse probability weighted estimation

Thus: Combining, from (7.20)

$$P\{\mathcal{C}_d = 1, \Delta = 1 | T^*(1), T^*(0), H_1\} = \pi_{d,1}(H_1)\mathcal{K}_d\{T^*(d)|H_1\}.$$

$$\begin{aligned}\mathcal{K}_d(u|H_1) &= \mathcal{K}(u|H_1, 1)\mathrm{I}\{d_1(H_1) = 1\} + \mathcal{K}(u|H_1, 0)\mathrm{I}\{d_1(H_1) = 0\} \\ &= \mathcal{K}\{u|H_1, d_1(H_1)\},\end{aligned}$$

Can then show: Using the above

$$\begin{aligned} E\left\{\frac{\mathcal{C}_d \Delta f(U)}{\pi_{d,1}(H_1)\mathcal{K}_d(U|H_1)}\right\} &= E\left\{\frac{\mathcal{C}_d \Delta f(T)}{\pi_{d,1}(H_1)\mathcal{K}_d(T|H_1)}\right\} \\ &= E\left[\frac{\mathcal{C}_d \Delta f\{T^*(d)\}}{\pi_{d,1}(H_1)\mathcal{K}_d\{T^*(d)|H_1\}}\right] \\ &= E\left(E\left[\left.\frac{\mathcal{C}_d \Delta f\{T^*(d)\}}{\pi_{d,1}(H_1)\mathcal{K}_d\{T^*(d)|H_1\}}\right| T^*(1), T^*(0), H_1\right]\right) \\ &= E\left[\frac{f\{T^*(d)\}E\{\mathcal{C}_d \Delta | T^*(1), T^*(0), H_1\}}{\pi_{d,1}(H_1)\mathcal{K}_d\{T^*(d)|H_1\}}\right] = E[f\{T^*(d)\}] = \mathcal{V}(d) \end{aligned}$$

Inverse probability weighted estimation

IPW estimator:

$$\widehat{\mathcal{V}}_{IPW}(d) = n^{-1} \sum_{i=1}^{n} \frac{\mathcal{C}_{d,i} \Delta_i f(U_i)}{\pi_{d,1}(H_{1i}; \widehat{\gamma}_1) \widehat{\mathcal{K}}_d(U_i | H_{1i})} \qquad (7.25)$$

$$\begin{aligned} \widehat{\mathcal{K}}_d(u|H_1) &= \widehat{\mathcal{K}}(u|H_1, 1)\mathrm{I}\{d_1(H_1) = 1\} + \widehat{\mathcal{K}}(u|H_1, 0)\mathrm{I}\{d_1(H_1) = 0\} \\ &= \widehat{\mathcal{K}}\{u|H_1, d_1(H_1)\} \end{aligned}$$

- $\widehat{\mathcal{K}}(u|h_1, a_1)$ is a fitted model for $\mathcal{K}(u|h_1, a_1)$
- If $f(t) = \min(t, L)$, with $T^L = \min(T, L)$, replace U_i and Δ_i in (7.25) by $U_i^L = \min(T_i^L, C_i)$ and $\Delta_i^L = \mathrm{I}(T_i^L \leq C_i)$
- (7.25) is a consistent estimator for $\mathcal{V}(d)$ if models $\pi_1(h_1; \gamma)$ and $\mathcal{K}(u|h_1, a_1; \beta_C)$, are correctly specified

Inverse probability weighted estimation

AIPW estimator:

$$\widehat{\mathcal{V}}_{AIPW}(d) \tag{7.26}$$
$$= n^{-1} \sum_{i=1}^{n} \left\{ \frac{\mathcal{C}_{d,i} \Delta_i f(U_i)}{\pi_{d,1}(H_{1i}; \widehat{\gamma}_1) \widehat{\mathcal{K}}_d(U_i | H_{1i})} - \frac{\mathcal{C}_{d,i} - \pi_{d,1}(H_{1i}; \widehat{\gamma}_1)}{\pi_{d,1}(H_{1i}; \widehat{\gamma}_1)} \mathcal{Q}_{d,1}(H_{1i}; \widehat{\beta}_1) \right\}$$

- If $f(t) = \min(t, L)$, with $T^L = \min(T, L)$, replace U_i and Δ_i in (7.25) by $U_i^L = \min(T_i^L, C_i)$ and $\Delta_i^L = \text{I}(T_i^L \leq C_i)$
- Augmentation term "captures back" information from individuals with $\mathcal{C}_d = 0$ who received treatment inconsistent with d
- What about information from individuals for whom $\mathcal{C}_d = 1$ but for whom $\Delta = 0$ because the time-to-event outcome was censored (and thus $T^*(d)$ is "missing")?

Inverse probability weighted estimation

Semiparametric theory: Bai et al. (2017) derive the *locally efficient estimator* that recovers this information through an additional augmentation term

- Define $N_C(u) = \text{I}(U \leq u, \Delta = 0)$, $Y(u) = \text{I}(U \geq u)$, and the martingale increment for censoring at time u
  $dM_{C,1}(u|h_1, a_1) = dN_C(u) - \lambda_C(u|h_1, a_1)Y(u)\,du$
- The augmentation term is

$$\frac{\mathcal{C}_d}{\pi_{d,1}(H_1)} \int_0^\infty \frac{dM_{C,d}(u|H_1)}{\mathcal{K}_d(u|H_1)} m_{d,1}(u|H_1), \qquad (7.27)$$

$$\begin{aligned} dM_{C,d}(u|h_1) &= dM_{C,1}(u|h_1, 1)\text{I}\{d_1(h_1) = 1\} + dM_{C,1}(u|h_1, 0)\text{I}\{d_1(h_1) = 0\} \\ &= dM_{C,1}\{u|h_1, d_1(h_1)\} \end{aligned}$$

$$\begin{aligned} m_{d,1}(u|h_1) &= m_1(u|h_1, 1)\text{I}\{d_1(h_1) = 1\} + m_1(u|h_1, 0)\text{I}\{d_1(h_1) = 0\} \\ &= m_1\{u|h_1, d_1(h_1)\} \end{aligned}$$

$$m_1(u|h_1, a_1) = E\{f(T)|T \geq u, H_1 = h_1, A_1 = a_1\}$$

Inverse probability weighted estimation

Implementation: Estimate the quantities in (7.27)

- Model $\lambda_C(u|h_1, a_1; \beta_C)$ yields model $\mathcal{K}(u|h_1, a_1; \beta_C)$ and thus estimator $\widehat{\mathcal{K}}_d(u|H_1)$
- Estimator for $dM_{C,d}(u|h_1)$

$$d\widehat{M}_{C,d}(u|h_1) = d\widehat{M}_{C,1}\{u|h_1, d_1(h_1)\}$$

$$d\widehat{M}_{C,1}(u|h_1, a_1) = dN_C(u) - \lambda_C(u|h_1, a_1; \widehat{\beta}_C)Y(u)\,du;$$

- With a model $\mathcal{S}_{T1}(u|h_1, a_1; \beta_1)$ for $\mathcal{S}_{T1}(u|h_1, a_1)$

$$m_1(u|h_1, a_1; \widehat{\beta}_1) = \int_u^\infty f(w) \frac{\{-d\mathcal{S}_{T1}(w|h_1, a_1; \widehat{\beta}_1)\}}{\mathcal{S}_{T1}(u|h_1, a_1; \widehat{\beta}_1)}$$

$$m_{d,1}(u|h_1; \widehat{\beta}_1) = m_1\{u|h_1, d_1(h_1); \widehat{\beta}_1\}$$

Inverse probability weighted estimation

Locally efficient estimator:

$$\widehat{\mathcal{V}}_{LE}(d) = n^{-1} \sum_{i=1}^{n} \Bigg\{ \frac{\mathcal{C}_{d,i} \Delta_i f(U_i)}{\pi_{d,1}(H_{1i}; \widehat{\gamma}_1) \widehat{\mathcal{K}}_d(U_i | H_{1i})} - \frac{\mathcal{C}_{d,i} - \pi_{d,1}(H_{1i}; \widehat{\gamma}_1)}{\pi_{d,1}(H_{1i}; \widehat{\gamma}_1)} \mathcal{Q}_{d,1}(H_{1i}; \widehat{\beta}_1) + \frac{\mathcal{C}_{d,i}}{\pi_{d,1}(H_{1i}, \widehat{\gamma}_1)} \int_0^\infty \frac{d\widehat{M}_{C,d}(u | H_{1i})}{\widehat{\mathcal{K}}_d(u | H_{1i})} m_{d,1}(u | H_{1i}; \widehat{\beta}_1) \Bigg\} \qquad (7.28)$$

- When $f(t) = \min(t, L)$, use U_i^L and Δ_i^L and change upper limit of integration in (7.27) to L

$$m_1(u | h_1, a_1; \widehat{\beta}_1) = \int_u^L w \frac{\{-d\mathcal{S}_{T1}(w | h_1, a_1; \widehat{\beta}_1)\}}{\mathcal{S}_{T1}(u | h_1, a_1; \widehat{\beta}_1)} + L \frac{\mathcal{S}_{T1}(L | h_1, a_1)}{\mathcal{S}_{T1}(u | h_1, a_1)}$$

Inverse probability weighted estimation

- Can replace $\pi_{d,1}(H_{1i};\widehat{\gamma}_1)$ by

$$\pi_1(H_{1i};\widehat{\gamma}_1)\mathrm{I}(A_{1i}=1)+\{1-\pi_1(H_{1i};\widehat{\gamma}_1)\}\mathrm{I}(A_{1i}=0)$$
$$=\pi_1(H_{1i};\widehat{\gamma}_1)A_{1i}+\{1-\pi_1(H_{1i};\widehat{\gamma}_1)\}(1-A_{1i})$$

  and $\widehat{\mathcal{K}}_d(u|H_{1i})$ by $\widehat{\mathcal{K}}(u|H_{1i},A_{1i})$, $d\widehat{M}_{C,d}(u|H_{1i})$ by $d\widehat{M}_{C,1}(u|H_{1i},A_{1i})$, and $m_{d,1}(u|H_{1i};\widehat{\beta}_1)$ by $m_1(u|H_{1i},A_{1i};\widehat{\beta}_1)$

- $\widehat{\mathcal{V}}_{LE}(d)$ is doubly robust; consistent if either both $\pi(h_1;\gamma)$ and $\mathcal{K}(u|H_1,A_1;\beta_C)$ are correct or if $\mathcal{S}_{T1}(u|h_1,a_1;\beta_1)$ is correct
- In a randomized study, $\pi_1(H_1)$ is known, and if censoring is administrative so that $\mathcal{K}(u|H_1,A_1)=P(C\geq u|H_1,A_1)=\mathcal{K}(u)$, $\widehat{\mathcal{V}}_{IPW}(d)$, $\widehat{\mathcal{V}}_{AIPW}(d)$, and $\widehat{\mathcal{V}}_{LE}(d)$ are all consistent; can estimate $\mathcal{K}(u)$ by the Kaplan-Meier estimator

Inverse probability weighted estimation

Estimation of d_η^{opt}: Maximize any of $\widehat{\mathcal{V}}_{IPW}(d_\eta)$, $\widehat{\mathcal{V}}_{AIPW}(d_\eta)$, or $\widehat{\mathcal{V}}_{LE}(d_\eta)$ in η_1 to obtain $\widehat{\eta}_{1,IPW}^{opt}$, $\widehat{\eta}_{1,AIPW}^{opt}$, or $\widehat{\eta}_{1,LE}^{opt}$

$$\widehat{d}_{\eta,IPW}^{opt} = \{d_1(h_1, \widehat{\eta}_{1,IPW}^{opt})\}, \quad \widehat{d}_{\eta,AIPW}^{opt} = \{d_1(h_1, \widehat{\eta}_{1,AIPW}^{opt})\},$$

$$\text{or} \quad \widehat{d}_{\eta,LE}^{opt} = \{d_1(h_1, \widehat{\eta}_{1,LE}^{opt})\}$$

- Substitute $\widehat{d}_{\eta,IPW}^{opt}$, $\widehat{d}_{\eta,AIPW}^{opt}$, or $\widehat{d}_{\eta,LE}^{opt}$ in (7.25), (7.26), or (7.28) to obtain $\widehat{\mathcal{V}}_{IPW}(d_\eta^{opt})$, $\widehat{\mathcal{V}}_{AIPW}(d_\eta^{opt})$, and $\widehat{\mathcal{V}}_{LE}(d_\eta^{opt})$
- Estimation based on $\widehat{\mathcal{V}}_{LE}(d)$ is expected to be of higher quality

7. Regimes Based on Time-to-Event Outcomes

Considerations for time-to-event outcome

Situation: Maximum of K decision points (take $K \geq 2$)

- Timing of decisions can be different for different individuals
- All individuals present at Decision 1, but not all will reach all K decision points
- An individual who does not experience the event between Decisions $k-1$ and k has history h_k including $(x_1, a_1, \ldots, x_{k-1}, a_{k-1}, x_k)$ and the times of Decisions $1, \ldots, k$
- An individual who does experience the event between Decisions $k-1$ and k has history h_j, $j = k, \ldots, K$, including $(x_1, a_1, \ldots, x_{k-1}, a_{k-1}, x_k)$, the times of Decisions $1, \ldots, k$, an indicator that the event occurred, and the event time
- Once the event time is achieved, no further treatment decisions are required

Regimes

Class $\mathcal{D}$ of all possible regimes: Ψ-specific regimes in $d \in \mathcal{D}$

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

- Rule $d_k(h_k)$ maps history to a treatment option in $\mathcal{A}_k$ *as long as* h_k indicates that the event has not yet occurred
- If, for $k = 2, \dots, K$, h_k indicates that the time-to-event outcome was achieved prior to Decision k, then $d_k(h_k)$ is understood to make no selection of a treatment option from $\mathcal{A}_k$
- I.e., $\Psi_k(h_k)$ is the empty set, so that $d_k(h_k)$ can be considered as null if h_k indicates that the event occurred prior to Decision k
- So for an individual who achieves the event between Decisions $k-1$ and k, there are no decisions to be made at decision points $k, \dots, K$
- $\mathcal{D}$ comprises all regimes satisfying these conditions

Potential outcomes

For a randomly chosen individual with X_1: For a given treatment sequence $\overline{a} = (a_1, \ldots, a_K) \in \overline{\mathcal{A}}$

- Define

$$\begin{aligned} \varkappa_k^*(\overline{a}_{k-1}) &= 1 \quad \text{if the individual reaches Decision } k \\ &= 0 \quad \text{otherwise} \end{aligned}$$

- $\varkappa_1 = 1$, as all individuals reach Decision 1
- If $\varkappa_k^*(\overline{a}_{k-1}) = 1$, then $\varkappa_j^*(\overline{a}_{j-1}) = 1$ for $j = 2, \ldots, k-1$
- If $\varkappa_k^*(\overline{a}_{k-1}) = 0$, then $\varkappa_j^*(\overline{a}_{j-1}) = 0$ for $j = k+1, \ldots, K$
- Largest decision point k for which $\varkappa_k^*(\overline{a}_{k-1}) = 1$

$$\varkappa^*(\overline{a}) = \max_j \{j : \ \varkappa_j^*(\overline{a}_{j-1}) = 1\}$$

- If $\varkappa_k^*(\overline{a}_{k-1}) = 1$ and $\varkappa_{k+1}^*(\overline{a}_k) = 0$, then $\varkappa^*(\overline{a}) = k$

Potential outcomes

For a randomly chosen individual with X_1: For a given treatment sequence $\overline{a} = (a_1, \ldots, a_K) \in \overline{\mathcal{A}}$

- Define $\mathcal{T}_k^*(\overline{a}_{k-1})$, $k = 2, \ldots, \varkappa^*(\overline{a})$, to be the time of Decision k, measured from baseline; $\mathcal{T}_1 = 0$ is time of Decision 1
- Define $X_k^*(\overline{a}_{k-1})$ be the intervening information between Decisions $k-1$ and k following options $\overline{a}_{k-1}$ at Decisions $1, \ldots, k-1$
- Define potential event time $T^*(\overline{a}_{\varkappa^*(\overline{a})})$
- Potential information on an individual under $\overline{a}$

$$\Big[\varkappa_1, \varkappa_2^*(a_1), \varkappa_3^*(\overline{a}_2), \ldots, \varkappa_K^*(\overline{a}_{K-1}), \varkappa^*(\overline{a}) = \max_j\{j : \varkappa_j^*(\overline{a}_{j-1}) = 1\},$$
$$\mathcal{T}_1, X_1, \mathcal{T}_2^*(a_1), X_2^*(a_1), \mathcal{T}_3^*(\overline{a}_2), X_3^*(\overline{a}_2), \ldots,$$
$$\mathcal{T}^*_{\varkappa^*(\overline{a})}(\overline{a}_{\varkappa^*(\overline{a})-1}), X^*_{\varkappa^*(\overline{a})}(\overline{a}_{\varkappa^*(\overline{a})-1}), T^*(\overline{a}_{\varkappa^*(\overline{a})})\Big]$$

$\varkappa_1$, $\mathcal{T}_1$, and X_1 included for completeness

Potential outcomes

Set of all potential outcomes:

$$W^* = \Big[\varkappa_2^*(a_1), \varkappa_3^*(\overline{a}_2), \ldots, \varkappa_K^*(\overline{a}_{K-1}), \varkappa^*(\overline{a}) = \max_j\{j: \ \varkappa_j^*(\overline{a}_{j-1}) = 1\},$$

$$\mathcal{T}_2^*(a_1), X_2^*(a_1), \mathcal{T}_3^*(\overline{a}_2), X_3^*(\overline{a}_2), \ldots, \mathcal{T}_{\varkappa^*(\overline{a})}^*(\overline{a}_{\varkappa^*(\overline{a})-1}), X_{\varkappa^*(\overline{a})}^*(\overline{a}_{\varkappa^*(\overline{a})-1}),$$

$$T^*(\overline{a}_{\varkappa^*(\overline{a})}), \quad \text{for all } \overline{a} \in \overline{\mathcal{A}}\Big]$$

- Define

$$S_2^*(a_1) = \mathrm{I}\{\varkappa_1 = 1, \varkappa_2^*(a_1) = 0\}\, T^*(a_1) + \mathrm{I}\{\varkappa_2^*(a_1) = 1\}\mathcal{T}_2^*(a_1)$$

$$S_3^*(a_2) = \mathrm{I}\{\varkappa_2^*(a_1) = 1, \varkappa_3^*(\overline{a}_2) = 0\}\, T^*(\overline{a}_2) + \mathrm{I}\{\varkappa_3^*(\overline{a}_2) = 1\}\mathcal{T}_3^*(\overline{a}_2)$$

$$\vdots$$

$$S_k^*(a_{k-1}) = \mathrm{I}\{\varkappa_{k-1}^*(\overline{a}_{k-2}) = 1, \varkappa_k^*(\overline{a}_{k-1}) = 0\}\, T^*(\overline{a}_{k-1}) + \mathrm{I}\{\varkappa_k^*(\overline{a}_{k-1}) = 1\}\mathcal{T}_k^*(\overline{a}_{k-1})$$

$$S_{K+1}^*(\overline{a}) = \mathrm{I}\{\varkappa^*(\overline{a}) = K\}\, T^*(\overline{a})$$

Potential outcomes

Potential outcomes associated with $d \in \mathcal{D}$: With $\overline{d}_k = (d_1, \ldots, d_k)$, define in the obvious way

- $\varkappa^*_k(\overline{d}_{k-1})$, $\varkappa^*(d) = \max_j\{j : \varkappa^*_j(\overline{d}_{j-1}) = 1\}$
- $k = 2, \ldots, \varkappa^*(d)$, $\mathcal{T}^*_k(\overline{d}_{k-1})$, $X^*_k(\overline{d}_{k-1})$
- Event time under d: $T^*(d) = T^*(\overline{d}_{\varkappa^*(d)})$
- Then the potential outcomes under d are

$$\Big[\varkappa_1, \varkappa^*_2(d_1), \varkappa^*_3(\overline{d}_2), \ldots, \varkappa^*_K(\overline{d}_{K-1}), \varkappa^*(d) = \max_j\{j : \varkappa^*_j(\overline{d}_{j-1}) = 1\},$$
$$\mathcal{T}_1, X_1, \mathcal{T}^*_2(d_1), X^*_2(d_1), \mathcal{T}^*_3(\overline{d}_2), X^*_3(\overline{d}_2), \ldots,$$
$$\mathcal{T}^*_{\varkappa^*(d)}(\overline{d}_{\varkappa^*(d)-1}), X^*_{\varkappa^*(d)}(\overline{d}_{\varkappa^*(d)-1}), T^*(d) = T^*(\overline{d}_{\varkappa^*(d)})\Big] \tag{7.29}$$

- Potential outcome of interest $f\{T^*(d)\}$, with value $\mathcal{V}(d) = E[f\{T^*(d)\}]$
- $d^{opt} \in \mathcal{D}$ satisfies $\mathcal{V}(d^{opt}) \geq \mathcal{V}(d)$ for all $d \in \mathcal{D}$

Data, no censoring

Observed data: With no censoring

- All individuals receive an option in $\mathcal{A}_1$ at Decision 1, $\mathcal{T}_1 = 0$
- $\varkappa$ = observed number of decisions reached, $1 \leq \varkappa \leq K$
- Observed times of decision points reached, $\mathcal{T}_1, \ldots, \mathcal{T}_\varkappa$
- $\mathcal{T}_k$ precedes X_k, $\overline{\mathcal{T}}_k = (\mathcal{T}_1, \ldots, \mathcal{T}_k)$, $k = 1, \ldots, \varkappa$
- Observed data are

$$(\varkappa, \mathcal{T}_1, X_1, A_1, \mathcal{T}_2, X_2, A_2, \ldots, \mathcal{T}_\varkappa, X_\varkappa, A_\varkappa, T) \tag{7.30}$$

Data, no censoring

History: $H_1 = \{\mathcal{T}_1, X_1\}$

$$\begin{aligned} H_2 &= (\mathcal{T}_1, X_1, A_1, \mathcal{T}_2, X_2) = (\overline{\mathcal{T}}_2, \overline{X}_2, A_1), \quad && \varkappa \geq 2 \\ &= (\mathcal{T}_1, X_1, A_1, T), && \varkappa < 2 \end{aligned}$$

For $k = 3, \ldots, K$

$$\begin{aligned} H_k &= (\mathcal{T}_1, X_1, A_1, \mathcal{T}_2, X_2, A_2, \ldots, \mathcal{T}_k, X_k) \\ &= (\overline{\mathcal{T}}_k, \overline{X}_k, \overline{A}_{k-1}), && \varkappa \geq k \\ &= (\mathcal{T}_1, X_1, A_1, \mathcal{T}_2, X_2, A_2 \ldots, \mathcal{T}_\varkappa, X_\varkappa, A_\varkappa, T) \\ &= (\overline{\mathcal{T}}_\varkappa, \overline{X}_\varkappa, \overline{A}_\varkappa, T), && \varkappa < k \end{aligned}$$

Succinctly written as

$$\begin{gathered} H_k = \{(\mathcal{T}_j, X_j, A_j)\mathrm{I}(\varkappa \geq j), j = 1, \ldots, k-1, (\mathcal{T}_k, X_k)\mathrm{I}(\varkappa \geq k), \\ \mathrm{I}(\varkappa < k), T\,\mathrm{I}(\varkappa < k)\}, \quad k = 1, \ldots, K \end{gathered}$$

Data, censoring

Observed data: With censoring

- κ = number of decision points observed to be reached, determined by occurrence of *the event or censoring, whichever comes first*
- Observed data are

$$(\kappa, \mathcal{T}_1, X_1, A_1, \mathcal{T}_2, X_2, A_2, \ldots, \mathcal{T}_\kappa, X_\kappa, A_\kappa, U, \Delta) \tag{7.31}$$

- Note that it must be that $\kappa \leq \varkappa$

Data, censoring

History:

$$\begin{aligned} H_k &= (\mathcal{T}_1, X_1, A_1, \mathcal{T}_2, X_2, A_2, \dots, \mathcal{T}_k, X_k) \\ &= (\overline{\mathcal{T}}_k, \overline{X}_k, \overline{A}_{k-1}), & \kappa \geq k \\ &= (\mathcal{T}_1, X_1, A_1, \mathcal{T}_2, X_2, A_2, \dots, \mathcal{T}_\kappa, X_\kappa, A_\kappa, U, \Delta) \\ &= (\overline{\mathcal{T}}_\kappa, \overline{X}_\kappa, \overline{A}_\kappa, U, \Delta), & \kappa < k \end{aligned}$$

Succinctly written as

$$\begin{aligned} H_k = \{ & (\mathcal{T}_j, X_j, A_j) \mathrm{I}(\varkappa \geq j), j = 1, \dots, k-1, (\mathcal{T}_k, X_k) \mathrm{I}(\kappa \geq k), \\ & \mathrm{I}(\kappa < k),\ (U, \Delta) \mathrm{I}(\kappa < k) \}, \quad k = 1, \dots, K \end{aligned}$$

History to time u:

$$\begin{aligned} H(u) = \{ & (\mathcal{T}_1, X_1, A_1), \mathrm{I}(\kappa \geq 2, \mathcal{T}_2 \leq u), \mathrm{I}(\kappa \geq 2, \mathcal{T}_2 \leq u)(\mathcal{T}_2, X_2, A_2), \dots, \\ & \mathrm{I}(\kappa \geq k, \mathcal{T}_k \leq u), \mathrm{I}(\kappa \geq k, \mathcal{T}_k \leq u)(\mathcal{T}_k, X_k, A_k), k = 3, \dots, K, \\ & \mathrm{I}(U < u), (U, \Delta)\, \mathrm{I}(U < u) \} \end{aligned}$$

Identifiability assumptions

No censoring:

- SUTVA: $\varkappa = \max_j \{j : \varkappa_j^*(\overline{A}_{j-1}) = 1\}$

$$X_k = X_k^*(\overline{A}_{k-1}), \quad \mathcal{T}_k = \mathcal{T}_k^*(\overline{A}_{k-1}), \quad k = 1, \ldots, \varkappa, \quad T = T^*(\overline{A}_\varkappa) \tag{7.32}$$

- SRA:

$$W^* \perp\!\!\!\perp A_k | H_k, \varkappa \geq k, \quad k = 1, \ldots, K \tag{7.33}$$

- Positivity: Informally (should be in terms of feasible sets as before)

$$P(A_k = a_k \mid H_k = h_k, \varkappa \geq k) > 0, \quad k = 1, \ldots, K \tag{7.34}$$

for all $a_k \in \mathcal{A}_k$ feasible for history h_k and all h_k satisfying $P(H_k = h_k, \varkappa \geq k) > 0$

Identifiability assumptions

Censoring: As before, an external process

- $\Delta = 0$: U is time to censoring, result of an external process taking place when individuals are observed
- $\Delta = 1$: U is event time, dictated by potential outcomes under treatments already received
- SUTVA: Reflects these considerations

$$\kappa = \max_j \{j: \varkappa_j^*(\overline{A}_{j-1}) = 1\} \text{ and } U = T^*(\overline{A}_\kappa) \text{ when } \Delta = 1$$

$$\kappa = \max_j \{j: \varkappa_j^*(\overline{A}_{j-1}) = 1 \text{ and } U > \mathcal{T}_j^*(\overline{A}_{j-1})\} \text{ when } \Delta = 0$$

$$X_k = X_k^*(\overline{A}_{k-1}), \quad \mathcal{T}_k = \mathcal{T}_k^*(\overline{A}_{k-1}), \quad k = 1, \ldots, \kappa \qquad (7.35)$$

- When $\Delta = 1$, $\kappa = \varkappa$, $U = T$, as expected
- Compare to (7.32)

Identifiability assumptions

Additional assumptions:

- SRA: Modifying (7.33)

$$W^* \perp\!\!\!\perp A_k | H_k, \kappa \geq k, \quad k = 1, \ldots, K \tag{7.36}$$

- Noninformative censoring: Analogous to (7.7)

$$\begin{aligned} &\lambda_C\{u|H(u), W^*\} \qquad (7.37)\\ &= \lim_{du \to 0} du^{-1} P\{u \leq U < u + du, \Delta = 0 \,|\, U \geq u, H(u), W^*\} \\ &= \lim_{du \to 0} du^{-1} P\{u \leq U < u + du, \Delta = 0 \,|\, U \geq u, H(u)\} \\ &= \lambda_C\{u|H(u)\} \end{aligned}$$

- Can express in terms of components of $H(u)$ relevant to u

$$\lambda_C\{u|H(u)\} = \lambda_C(u|H_k, A_k) \quad \text{for all } \{u : H(u) = (H_k, A_k)\}$$

taken to be continuous in u

Identifiability assumptions

Positivity assumption (informal): More involved than (7.34); built up sequentially

- Decision 1 : $P(A_1 = a_1 \mid H_1 = h_1, \kappa \geq 1) > 0$ for all $a_1 \in \mathcal{A}_1$ feasible for h_1 and all h_1 satisfying

$$P(H_1 = h_1, \kappa \geq 1) = P(H_1 = h_1) > 0$$

- Need positive probability of no censoring before Decision 2 or event

$$P\{U \geq u \mid S_2^*(a_1) = u, H_1 = h_1, A_1 = a_1, \kappa \geq 1\} > 0$$

  for all feasible a_1, h_1, u with

$$P\{S_2^*(a_1) = u, H_1 = h_1, A_1 = a_1, \kappa \geq 1\} > 0$$

Identifiability assumptions

Positivity assumption:

- Can be shown: Under (7.37)

$$P\{U \geq u \mid S_2^*(a_1) = u, H_1 = h_1, A_1 = a_1, \kappa \geq 1\} = \exp\left\{-\int_0^u \lambda_C(w|h_1, a_1)\, dw\right\}$$

- Decision 2: $P(A_2 = a_2 \mid H_2 = h_2, \kappa \geq 2) > 0$ for all $a_2 \in \mathcal{A}_2$ feasible for h_2, given Decision 2 is reached, and all h_2 satisfying

$$P(H_2 = h_2, \kappa \geq 2) > 0$$

- Need positive probability of no censoring before Decision 2 or event

$$P\{U \geq u \mid S_3^*(\overline{a}_2) = u, H_2 = h_2, A_2 = a_2, \kappa \geq 2\} > 0$$

  for all feasible a_2, h_2, and u with

$$P\{S_3^*(\overline{a}_2) = u, H_2 = h_2, A_2 = a_2, \kappa \geq 2\} > 0$$

Identifiability assumptions

Positivity assumption: $k = 3, \dots, K-1$

- Decision k: $P(A_k = a_k \mid H_k = h_k, \kappa \geq k) > 0$ for all $a_k \in \mathcal{A}_k$ feasible for h_k, given Decision k is reached, and all h_k satisfying

$$P(H_k = h_k, \kappa \geq k) > 0$$

- And

$$P\{U \geq u \mid S^*_{k+1}(\overline{a}_k) = u, H_k = h_k, A_k = a_k, \kappa \geq k\}$$
$$= \exp\left\{-\int_{\tau_k}^{u} \lambda_C(w|h_k, a_k)\, dw\right\} > 0$$

for all feasible a_k, associated h_k, and u with

$$P\{S^*_{k+1}(\overline{a}_k) = u, H_k = h_k, A_k = a_k, \kappa \geq k\} > 0$$

Identifiability assumptions

Positivity assumption:

- Decision K: $P(A_K = a_K \mid H_K = h_K, \kappa = K) > 0$ for all $a_K \in \mathcal{A}_K$ feasible for h_K and for all possible h_K satisfying

$$P(H_K = h_K, \kappa = K) > 0$$

- And

$$P\{U \geq u \mid S^*_{K+1}(\overline{a}) = u, H_K = h_K, A_K = a_K, \kappa = K\}$$
$$= \exp\left\{-\int_{\tau_K}^{u} \lambda_C(w|h_K, a_K)\, dw\right\} > 0$$

for all feasible a_K, associated h_K, and u with

$$P\{S^*_{K+1}(\overline{a}) = u, H_K = h_K, A_K = a_K, \kappa = K\} > 0$$

Identifiability assumptions

Restricted lifetime: With $f(t) = \min(t, L)$, can modify

- Define
$$\kappa^L = \max_k \{k = 1, \ldots, \kappa : \mathcal{T}_k \leq L\}$$
the largest decision point reached before event, censoring, or L
- Replace $\kappa \geq k$ by $\kappa^L \geq k$, $U \geq u$ by $U \geq \min(u, L)$, and upper limit of integration by $\min(u, L)$, $k = 1, \ldots, K - 1$
- Replace $\kappa = K$ by $\kappa^L = K$, $U \geq u$ by $U \geq \min(u, L)$, and upper limit of integration by $\min(u, L)$
- No need to redefine H_k

Recursive representation of $d \in \mathcal{D}$

Censoring:

- Decision 1: $h_1 = (\tau_1, x_1)$, $\tau_1 = 0$, option selected $d_1(h_1) = d_1(\tau_1, x_1)$
- If Decision 2 is reached (no event or censoring), $\kappa \geq 2$, $h_2 = (\tau_1, x_1, a_1, \tau_2, x_2) = (\overline{\tau}_2, \overline{x}_2, a_1)$, option selected

$$d_2\{\overline{\tau}_2, \overline{x}_2, d_1(\tau_1, x_1)\}$$

- If event or censoring between Decisions 1 and 2, $\kappa < 2$, and all subsequent rules are null
- In general, for $k \leq \kappa$

$$\overline{d}_2(\overline{\tau}_2, \overline{x}_2) = [d_1(\tau_1, x_1), d_2\{\overline{\tau}_2, \overline{x}_2, d_1(\tau_1, x_1)\}]$$

$$\overline{d}_3(\overline{\tau}_3, \overline{x}_3) = [d_1(\tau_1, x_1), d_2\{\overline{\tau}_2, \overline{x}_2, d_1(\tau_1, x_1)\}, d_3\{\overline{\tau}_3, \overline{x}_3, \overline{d}_2(\overline{\tau}_2, \overline{x}_2)\}]$$

$$\vdots$$

$$\overline{d}_k(\overline{\tau}_k, \overline{x}_k) = [d_1(\tau_1 x_1), d_2\{\overline{\tau}_2, \overline{x}_2, d_1(\tau_1, x_1)\}, \ldots, d_k\{\overline{\tau}_k, \overline{x}_k, \overline{d}_{k-1}(\overline{\tau}_{k-1}, \overline{x}_{k-1})\}]$$

Recursive representation of $d \in \mathcal{D}$

Censoring:

- If $\kappa = K$

$$\overline{d}_K(\overline{\tau}_K, \overline{x}_K) = [d_1(\tau_1, x_1), d_2\{\overline{\tau}_2, \overline{x}_2, d_1(\tau_1, x_1)\}, \ldots, \\ d_K\{\overline{\tau}_K, \overline{x}_K, \overline{d}_{K-1}(\overline{\tau}_{K-1}, \overline{x}_{K-1})\}]$$

- If an individual does not reach all K decisions, $\kappa < K$, a recursive definition for $k > \kappa$ is not required, but we can write

$$\overline{d}_k(\overline{\tau}_\kappa, \overline{x}_\kappa) = [d_1(\tau_1, x_1), d_2\{\overline{\tau}_2, \overline{x}_2, d_1(\tau_1, x_1)\}, \ldots, \\ d_\kappa\{\overline{\tau}_\kappa, \overline{x}_\kappa, \overline{d}_{\kappa-1}(\overline{\tau}_{\kappa-1}, \overline{x}_{\kappa-1})\}]$$

  so depends only on decision times and information through Decision κ

7. Regimes Based on Time-to-Event Outcomes

Identifiability result

Under SUTVA, SRA, noninformative censoring, positivity: The joint distribution of the potential outcomes

$$W_d^* = \Big[\varkappa^*(d), \mathcal{T}_1, X_1, \mathcal{T}_2^*(d_1), X_2^*(d_1), \mathcal{T}_3^*(\overline{d}_2), X_3^*(\overline{d}_2), \ldots, \\ \mathcal{T}^*_{\varkappa^*(d)}(\overline{d}_{\varkappa^*(d)-1}), X^*_{\varkappa^*(d)}(\overline{d}_{\varkappa^*(d)-1}), T^*(d) = T^*(\overline{d}_{\varkappa^*(d)})\Big]$$

in (7.29) can be expressed in terms of that of the observed data (7.30) or (7.31)

- Analogous to previous g-computation argument
- Leads to g-computation algorithm and other methods for estimation of $\mathcal{V}(d)$ for fixed $d \in \mathcal{D}$ and for an optimal unrestricted or restricted regime

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