Assessing Causal Effects in the Presence of Treatment Switching through Principal Stratification

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Randomized Clinical Trials with Treatment Switching

- Treatment switching is an intercurrent event commonly occurring in clinical trials designed to assess the effect of a treatment on the incidence of a disease
- Often switching is a prognosis-related choice
- ICH E9(R1) addendum provides guidelines on estimands and sensitivity analyses in clinical trials with treatment switching *(ICH, 2019)*
- There are various types of switching possibilities:
  - ✓ Control subjects may be allowed to start taking the active treatment
  - ✓ Treated subjects may be allowed to stop taking the active treatment
  - ✓ Subjects are allowed to start a non-trial treatment
- Focus on clinical trials with one-sided switching behavior

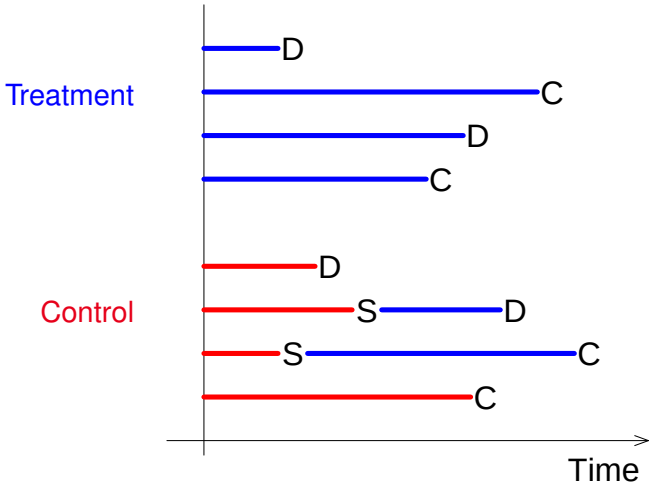
Motivating Study: Concorde Clinical Trial

(Concorde Coordinating Committee, 1994)

- Randomized controlled clinical trial involving patients with asymptomatic HIV infection
- Treatment variable: Immediate versus deferred treatment with zidovudine
  - ✓ In the control arm, treatment with zidovudine was deferred until the onset of symptoms of HIV/AIDS
- Outcome: Time-to-disease progression (time to ARC or AIDS) or death
- Some patients in the deferred arm switched to the active treatment starting zidovudine before the onset of symptoms of HIV/AIDS on the basis of low CD4 cell counts and other evidences of disease progression
- Synthetic data-set closely mimicking the Concorde trial *(White et al., 2002)*
  - ✓ The synthetic Concorde data do not include any pre-treatment variable
  - ✓ $N = 1\,000$ patients: $N/2 = 500$ patients are randomly assigned to immediate treatment with zidovudine; and $N/2 = 500$ patients are randomly assigned to deferred treatment with zidovudine

Data Structure

Randomized to:



Observed Synthetic Concorde Data

- Treatment actually assigned

  $Z_i = 1$ (Immediate zidovudine) and $Z_i = 0$ (Deferred zidovudine)

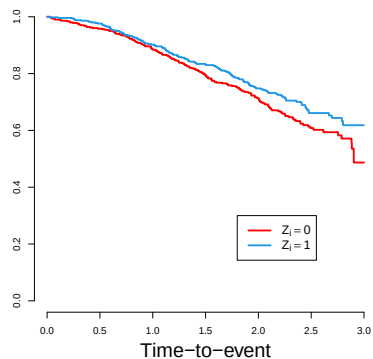
- Let Y_i^{obs} and S_i^{obs} denote the survival time and the switching time under the actual treatment assigned without censoring
- The survival time and the switching time are subject to censoring
  - ✓ The trial lasted 3 years, with staggered entry over the first 1.5 years
- Censoring time: $C_i \in [1.5, 3]$
- Observed survival time: $\tilde{Y}_i^{\text{obs}} = \min\{Y_i^{\text{obs}}, C_i\}$
- Observed switching status
  - ✓ For a patient i with $Z_i = 1$, $\tilde{S}_i^{\text{obs}} = S_i^{\text{obs}} = \overline{\mathbb{S}}$, where $\overline{\mathbb{S}}$ is a non-real value
  - ✓ For a patient i with $Z_i = 0$:

$$\tilde{S}_i^{\text{obs}} = \begin{cases} S_i^{\text{obs}} & \text{if } S_i^{\text{obs}} \in \mathbb{R}_+ \text{ and } S_i^{\text{obs}} \leq C_i \\ C_i & \text{if } (S_i^{\text{obs}} \in \mathbb{R}_+ \text{ and } S_i^{\text{obs}} > C_i) \text{ or } S_i^{\text{obs}} = \overline{\mathbb{S}} \end{cases}$$

Synthetic Concorde Data: Descriptive Statistics

Variable	Mean		
	All	$Z_i = 0$	$Z_i = 1$
Sample size	(1000)	(500)	(500)
Treatment assignment (Z_i)	0.5	0	1
$\mathbb{I}\{\tilde{S}_i^{\text{obs}} = C_i^{\text{obs}}\}$	–	0.62	–
Switching time $(\tilde{S}_i^{\text{obs}})$	–	1.55	–
$\mathbb{I}\{\tilde{Y}_i^{\text{obs}} = C_i^{\text{obs}}\}$	0.69	0.66	0.71
Survival time $(\tilde{Y}_i^{\text{obs}})$	1.93	1.89	1.97

Survival functions by assignment Z_i:
kaplan-Meier estimates



Existing Approaches to Treatment Switching

- Intention-to-Treat analysis
- Hypothetical strategy: Reconstructing the outcome a unit would have had if s/he had not switched *(ICH, 2019)*
  - ✓ Naive approaches: Censoring at switch (as-treated analysis); Excluding switchers (per-protocol analysis); Treatment as a time-varying covariate *(See Morden et al., 2011 for a review)*
  - ✓ More sophisticated approaches: Rank-preserving structural failure time model *(Robins and Tsiatis 1991; Robins 1994; White et al. 1997, 1999; White 2006)*; Inverse-probability of censoring weighting *(Robins and Finkelstein, 2000)* and Marginal structural models *(Hernán et al., 2000)*
- Time-varying treatment approach: Clinical trials with treatment switching as longitudinal causal studies with a time-varying treatment *(Petersen et al., 2014)*

Our Contribution

- We propose to re-define the problem of treatment switching using principal stratification *(Frangakis and Rubin 2002)*
  - ✓ The principal stratification approach is recognized in the ICH E9(R1) addendum as a strategy to deal with intercurrent events
- Causal estimands: principal causal effects for patients belonging to subpopulations defined by the switching behavior under the control treatment
  - ✓ Allow switching time to be nonignorable and to characterize treatment effect heterogeneity w.r.t. switching time
- Treatment switching can be viewed as a general form of noncompliance
  - ✓ Non-switchers are a specific type of compliers, because they will be exposed to treatment and control according to the protocol
- We use a Bayesian approach for inference, which allows us to properly take into account that
  - ✓ switching happens in continuous time generating a continuum of principal strata;
  - ✓ switching time is not defined for units who never switch in a particular study; and
  - ✓ both survival time and switching time are subject to censoring

Treatment Switching with Censoring: Potential Outcomes

- Patients: $i = 1, \ldots, N$
- Binary treatment: $z \in \{0, 1\} = \{\text{Control Treatment}, \text{Active Treatment}\}$
- The Stable Unit Treatment Value Assumption (SUTVA) is assumed
- $Y_i(z)$ = Survival time given assignment to treatment z, $z = 0, 1$
  - ✓ $Y_i(z)$ is a positive real number and may be right censored
- $C_i(z)$ = Censoring time given assignment to treatment z, $z = 0, 1$
  - ✓ Assumption: For $i = 1, \ldots, N$, $C_i(0) = C_i(1) = C_i$
- $S_i(z) =$ Switching status given assignment to treatment z, $z = 0, 1$
  - ✓ $S_i(1) = \overline{\mathbb{S}}$ and $S_i(0) \in \mathbb{R}_+ \cup \{\overline{\mathbb{S}}\}$
  - ✓ $S_i(0)$ might be right censored with censoring time C_i
- Natural constraint: $S_i(0) \leq Y_i(0)$, the switching time is censored by death with censoring event defined by $Y_i(0)$

Principal Stratification w.r.t. Switching Behavior

- The switching behavior is defined by $S_i(0) \in \mathbb{R}_+ \cup \{\overline{\mathbb{S}}\}$
- Basic principal strata
  - ✓ Non-switchers = $\{i : S_i(0) = \overline{\mathbb{S}}\}$: Units who would not switch to the active treatment if assigned to control no matter how long the follow-up is
  - ✓ Switchers = $\{i : S_i(0) = s, s \in \mathbb{R}_+\}$: Units who would switch to the active treatment if assigned to control at a given time point $s \in \mathbb{R}_+$
- All switchers = $\cup_{s \in \mathbb{R}_+} \{i : S_i(0) = s\}$

Treatment Switching with Censoring: Principal Causal Effects

- Average principal causal effects

$$ACE(s) = \mathbb{E}\left[Y_i(1) \mid S_i(0) = s\right] - \mathbb{E}\left[Y_i(0) \mid S_i(0) = s\right], \quad (s \in \{\overline{\mathbb{S}}\} \cup \mathbb{R}_+)$$

- Distributional principal causal effects for non-switchers

$$DCE(y \mid \overline{\mathbb{S}}) = P\left\{Y_i(1) > y \mid S_i(0) = \overline{\mathbb{S}}\right\} - P\left\{Y_i(0) > y \mid S_i(0) = \overline{\mathbb{S}}\right\}, \qquad (y \in \mathbb{R}_+)$$

- Conditional distributional principal causal effects for switchers

$$\begin{aligned} cDCE(y \mid s) &= P\left\{Y_i(1) > y \mid Y_i(1) \geq S_i(0), S_i(0) = s\right\} - P\left\{Y_i(0) > y \mid Y_i(1) \geq S_i(0), S_i(0) = s\right\} \\ &= P\left\{Y_i(1) > y \mid Y_i(1) \geq s, S_i(0) = s\right\} - P\left\{Y_i(0) > y \mid Y_i(1) \geq s, S_i(0) = s\right\}, \end{aligned}$$

$(y, s \in \mathbb{R}_+)$

- If $Y_i(1) \geq Y_i(0)$, then $Y_i(1) \geq S_i(0)$ and

$$cDCE(y \mid s) = DCE(y \mid s) \equiv P\left\{Y_i(1) > y \mid S_i(0) = s\right\} - P\left\{Y_i(0) > y \mid S_i(0) = s\right\} \quad (y, s \in \mathbb{R}_+)$$

with $cDCE(y \mid s) = DCE(y \mid s) = 0$ for $y \leq s$

Observed Data Pattern and Possible Latent Principal Strata

Z_i	$\tilde{S}_i^{\text{obs}}$	$\tilde{Y}_i^{\text{obs}}$	Principal strata	Principal stratum label
0	C_i	$Y_i^{\text{obs}} \in [0, C_i)$	$\{i : S_i(0) = \overline{\mathbb{S}}\}$	Non-switchers
0	$S_i^{\text{obs}} \leq C_i$	$Y_i^{\text{obs}} \in [S_i^{\text{obs}}, C_i]$	$\{i : S_i(0) = S_i^{\text{obs}}\}$	Switchers at time S_i^{obs}
0	$S_i^{\text{obs}} \leq C_i$	C_i	$\{i : S_i(0) = S_i^{\text{obs}}\}$	Switchers at time S_i^{obs}
0	C_i	C_i	$\{i : S_i(0) = \overline{\mathbb{S}}\}$ or $\{i : S_i(0) = s \in (C_i, +\infty)\}$	Non-switchers or Switchers at some time $s > C_i$
1	$\overline{\mathbb{S}}$	$Y_i^{\text{obs}} \in [0, C_i]$	$\{i : S_i(0) = \overline{\mathbb{S}}$ or $S_i(0) \in \mathbb{R}_+\}$	Non-switchers or Switchers
1	$\overline{\mathbb{S}}$	C_i	$\{i : S_i(0) = \overline{\mathbb{S}}$ or $S_i(0) \in \mathbb{R}_+\}$	Non-switchers or Switchers

Identification Issues under Randomization

- X_i: Vector of pre-treatment covariates
- Completely Randomized Experiment

$$P\{Z_i \mid S_i(0), Y_i(0), Y_i(1), C_i, X_i\} = P\{Z_i\}$$

- Ignorability of the Censoring Mechanism

$$P\{C_i \mid S_i(0), Y_i(0), Y_i(1), X_i\} = P\{C_i\}$$

- Randomization and ignorability of the censoring mechanism help inference, but the identification of average and distributional principal causal effects requires further structural and/or distributional assumptions

Bayesian Approach to Inference

- The Bayesian approach does not require full identification
  - ✓ “Weak identifiability” of partially identified parameters
- The Bayesian approach allows us to deal with all complications – missing data, truncation by death, censoring – simultaneously in a natural way
- In Bayesian analysis inferences are directly interpretable in probabilistic terms

Bayesian Principal Stratification

Under exchangeability, randomization, and ignorability of censoring:

$$
\begin{aligned}
& P\{\mathbf{C}, \boldsymbol{S}(0), \boldsymbol{Y}(0), \boldsymbol{Y}(1), \boldsymbol{X}\} \\
&= \int \prod_{i=1}^{n} P\{C_i, S_i(0), Y_i(0), Y_i(1), X_i \mid \boldsymbol{\theta}\}\, P(\boldsymbol{\theta}) \mathrm{d}\boldsymbol{\theta} \\
&= \int \prod_{i=1}^{n} P\{X_i \mid \boldsymbol{\theta}\}\, P\{C_i \mid X_i; \boldsymbol{\theta}\}\, P\{S_i(0) \mid C_i, X_i; \boldsymbol{\theta}\} \times \\
&\qquad P\{Y_i(0) \mid S_i(0), C_i, X_i; \boldsymbol{\theta}\}\, P\{Y_i(1) \mid Y_i(0), S_i(0), C_i, X_i; \boldsymbol{\theta}\}\, P(\boldsymbol{\theta}) \mathrm{d}\boldsymbol{\theta} \\
&\propto \int \prod_{i=1}^{n} P\{S_i(0) \mid X_i; \boldsymbol{\theta}\}\, P\{Y_i(0) \mid S_i(0), X_i; \boldsymbol{\theta}\}\, P\{Y_i(1) \mid Y_i(0), S_i(0), X_i; \boldsymbol{\theta}\}\, P(\boldsymbol{\theta}) \mathrm{d}\boldsymbol{\theta}
\end{aligned}
$$

Bayesian Approach to Inference: Parametric Assumptions

- Sub-model for the Switching Behavior: A two-part model

$$\pi(X_i) = \mathbb{E}[\mathbb{I}\{S_i(0) = \overline{\mathbb{S}} \mid X_i\}] = P\left\{S_i(0) = \overline{\mathbb{S}} \mid X_i\right\} = \frac{\exp(\eta_0 + X_i'\boldsymbol{\eta})}{1 + \exp(\eta_0 + X_i'\boldsymbol{\eta})} \qquad \eta_0 \in \mathbb{R}, \boldsymbol{\eta} \in \mathbb{R}^K,$$

and

$$(S_i(0) \mid S_i(0) \in \mathbb{R}_+, X_i) \sim \text{Weibull}\left(\alpha_S, \beta_S + X_i'\boldsymbol{\eta}_S\right), \quad \alpha_S > 0, \beta_S \in \mathbb{R}, \boldsymbol{\eta}_S \in \mathbb{R}^K$$

- Sub-models for $Y_i(0)|S_i(0), X_i$,

$$\left(Y_i(0) \mid S_i(0) = \overline{\mathbb{S}}, X_i\right) \sim \text{Weibull}\left(\bar{\alpha}_Y, \bar{\beta}_Y + X_i'\bar{\boldsymbol{\eta}}_Y\right),$$
$$(Y_i(0) \mid S_i(0) \in \mathbb{R}_+, X_i) \sim S_i(0) + \text{Weibull}\left(\alpha_Y, \beta_Y + \lambda_0 \log(S_i(0)) + X_i'\boldsymbol{\eta}_Y\right),$$

with $\bar{\alpha}_Y > 0, \bar{\beta}_Y \in \mathbb{R}, \bar{\boldsymbol{\eta}}_Y \in \mathbb{R}^K$ and $\alpha_Y > 0, \beta_Y, \lambda_0 \in \mathbb{R}, \boldsymbol{\eta}_Y \in \mathbb{R}^K$

- Sub-models for $Y_i(1)|S_i(0), Y_i(0), X_i$,

$$\left(Y_i(1) \mid S_i(0) = \overline{\mathbb{S}}, Y_i(0), X_i\right) \sim \kappa Y_i(0) + \text{Weibull}\left(\bar{\nu}_Y, \bar{\gamma}_Y + X_i'\bar{\boldsymbol{\zeta}}\right),$$
$$(Y_i(1) \mid S_i(0) \in \mathbb{R}_+, Y_i(0), X_i) \sim \kappa Y_i(0) + \text{Weibull}\left(\nu_Y, \gamma_Y + \lambda_1 \log(S_i(0)) + X_i'\boldsymbol{\zeta}\right),$$

with $\kappa \in [0, 1]$, $\bar{\nu}_Y > 0, \bar{\gamma}_Y \in \mathbb{R}, \bar{\boldsymbol{\zeta}} \in \mathbb{R}^K$ and $\nu_Y > 0, \gamma_Y, \lambda_1 \in \mathbb{R}, \boldsymbol{\zeta} \in \mathbb{R}^K$

Identification of Some Model Parameters

Dependence between $Y_i(1)$ and $Y_i(0)$

- The parameter κ characterizes the dependence between $Y_i(1)$ and $Y_i(0)$ given $S_i(0)$ and X_i
  - ✓ If $\kappa = 0$ then $Y_i(1) \perp Y_i(0) \mid S_i(0), X_i$ and If $\kappa = 1$ then $Y_i(1) \geq Y_i(0)$
- The parameter κ can be viewed as a sensitivity parameter

Association between $Y_i(1)$ and $S_i(0)$

- The parameter λ_1 describes the association between $Y_i(1)$ and $S_i(0)$ given $Y_i(0)$ and X_i for switchers
  - ✓ Because $S_i(0)$ is never observed for treated units, the observed data provide no information about the association between $Y_i(1)$ and $S_i(0)$ given $Y_i(0)$ and X_i
- Parametric assumption: $\lambda_0 = \lambda_1 \equiv \lambda$
  - ✓ Because $S_i(0)$ and $Y_i(0)$ are jointly observed for some control patients, we have some information on λ

Sensitivity Checks

- The parameters λ and κ are not identifiable nonparametrically
- Under our parametric assumptions, λ and κ enter the observed data likelihood, and thus enter the Bayesian posterior inference
- Sensitivity analysis with respect to the prior specification for λ
- Sensitivity analysis by varying κ within the range $[0, 1]$

Prior Distribution and Posterior Distribution

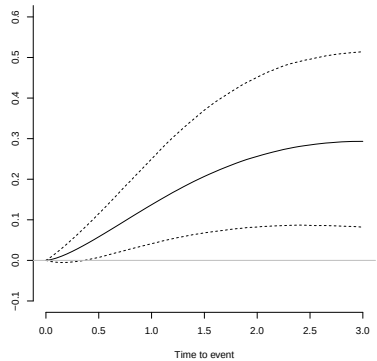
- We assume that the parameters are a priori independent
- Prior distribution
  - ✓ Normal prior distributions (mean $= 0$ and SD $= 100$) for the parameters of the logistic regression model for the probability of being a non-switcher, and for the intercept and the slope parameters of the Weibull distributions
  - ✓ Gamma prior distributions with parameters 1 and $10\,000$ for the shape parameters of the Weibull distributions
  - ✓ Normal and uniform prior distributions for the parameter λ
  - ✓ Dirac delta priors for κ concentrated at a pre-fixed value $\kappa_0 \in [0, 1]$
- Posterior distribution: MCMC Algorithm with Data Augmentation

Synthetic Concorde Clinical Data: Bayesian Principal Stratification Analysis ($\kappa = 0$)

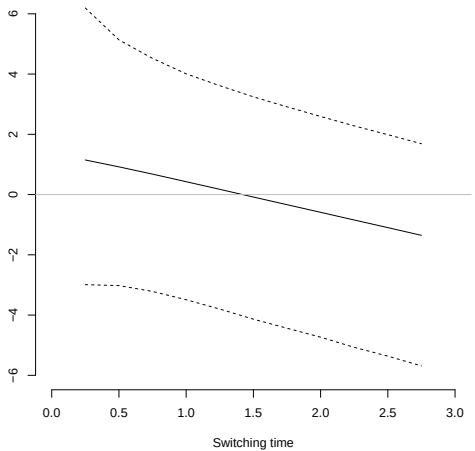
Posterior medians and 95% posterior credible intervals for principal causal effects for non-switchers

Estimand	Median	95% PCI 0.025	0.975
$\mathbb{E}[Y_i(0) \mid S_i(0) = \overline{\mathbb{S}}]$	2.02	1.44	2.97
$\mathbb{E}[Y_i(1) \mid S_i(0) = \overline{\mathbb{S}}]$	3.85	2.41	6.94
$ACE(\overline{\mathbb{S}})$	1.78	0.39	4.78

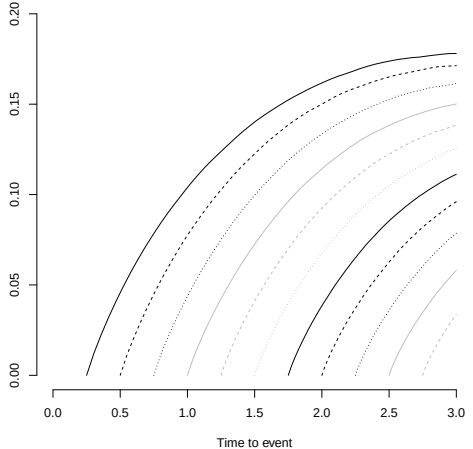
$DCE(y \mid \overline{\mathbb{S}})$



Posterior medians and 95% PCI of $ACE(s)$, $s \in \mathbb{R}_+$



Posterior medians of $cDCE(y \mid s)$ for $s = 0.25, 0.50, \ldots, 2.50, 2.75$



Sensitivity Analyses and Bayesian Posterior Predictive P-Values

- Sensitivity Analyses: Inference appears to be robust w.r.t. the prior specification for λ; some sensitivity w.r.t. the value of κ

- Bayesian PPPVs

Variable	Deviance	Signal	Noise	Signal to noise
Survival time	0.810			
Non-Switchers		0.333	0.542	0.329
Switchers		0.429	0.725	0.372
Switching time	0.478	0.398	0.336	0.568

$PPPV$ for BIC : 0.553

Discussion

- Clinical trials with treatment discontinuation
- The Role of the Pre-treatment Covariates
  - ✓ Conditioning on covariates makes structural and parametric assumptions more credible
  - ✓ Covariates usually lead to more precise inferences
  - ✓ In the principal stratification analysis, relevant information could also be obtained looking at the distribution of baseline characteristics within each principal stratum
- Extention: Treatment switching with non-ignorable censoring

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