Chapter 6.2: Post-treatment confounding:
Principal Stratification

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Post-Treatment Confounding

- So far most of the problems discussed adjust for pre-treatment confounding, i.e. covariates.
- Confounding occurs after treatment (but before the final outcome) poses different challenges to causal inference.
- Post-treatment confounding: a post-treatment intermediate variable $D$ lies in the causal pathway between $Z$ and $Y$:

$$Z \rightarrow D \rightarrow Y.$$ 

- Known as “endogenous” selection problems in economics.
- Rosenbaum (1984) show: adjusting post-treatment variables $D$ in the same way as pre-treatment covariates $X$ leads to biased causal effects.
- Include a wide range of (seemingly different) problems.
Example: Noncompliance in Randomized Experiments

- Noncompliance in RCT is a special case of post-treatment/assignment confounding.
- (Randomly) assigned treatment $Z$; actual trt $D$; outcome $Y$.
- Noncompliance: $Z$ usually strongly affects $D$, but still $D \neq Z$ for some units.
- Post-assignment confounding: units with $Z = 1, D = d$ are usually not the same as units with $Z = 0, D = d$, and thus a direct comparison leads to biased causal estimate.
Example: Selection Bias in Cluster Randomized Trials
Li et al. (2022, Clinical Trials)

- Cluster randomized trials (CRT): treatment assigned at cluster (not individual) level
- CRT often first assigns treatment and then recruits study units, open-labeled
- Subject to post-assignment selection bias, if there is obvious or perceived advantage of one treatment over another
- Assignment: $Z$; recruitment indicator: $D$
- The problem: the recruited sample consists of units with $D = 1$, but the recruited trt group $(Z = 1, D = 1)$ is different from the recruited control group $Z = 0, D = 1$
- This is due to the post-assignment self selection of recruitment status, breaking the initial randomization.
Example: Censoring (or Truncation) by Death
(Zhang and Rubin, 2003, JEBS)

- Goal: randomized study of a drug’s effect on Quality Of Life (QOL) two years after treatment
  - Treatment $Z$: randomized to trt (0) and control (1)
  - Outcome $Y$: QOL two years post-randomization
  - Intermediate outcome $D_i$: Indicator of two-year survival

- Complication: Some subjects will die before completion of the study; QOL for these subjects is not well defined

- Such outcomes are called “censored” or “truncated” by death

- Statistical challenge: QOL is only defined on survived units ($D = 1$). If the treatment has a non-zero effect on survival, then the survived trt units $Z = 1, D = 1$ are different from survived con units $Z = 1, D = 0$
Principal Stratification

(Frangakis and Rubin, 2002, Biometrics)

- Frangakis and Rubin (2002) generalized the IV approach to noncompliance (Angrist et al. 1996) to principal stratification, applicable to all post-treatment confounding

- Assuming a binary $D$: units can be classified into four groups according to the joint potential values of $D$, $S_i = (D_i(0), D_i(1))$:

  00  =  \{i : D_i(0) = 0, D_i(1) = 0\}

  10  =  \{i : D_i(0) = 1, D_i(1) = 0\}

  01  =  \{i : D_i(0) = 0, D_i(1) = 1\}

  11  =  \{i : D_i(0) = 1, D_i(1) = 1\}

- This cross-classification of units is the principal stratification with respect to the (binary) post-treatment variable $D$. 
Properties of Principal Stratification

▶ **Key property**: Principal stratum membership \( S_i \) is not affected by treatment assignment

▶ Principal stratum membership only reflects subject’s characteristics: it can be viewed as a pre-treatment variable

▶ Therefore comparison of potential outcomes \( Y_i(0) \) and \( Y_i(1) \) is a well-defined causal effect, because it is defined on a common set of units (the same principal stratum)

▶ **Principal Causal Effect** \((PCE)\):

\[
\tau^{PCE} = \mathbb{E}[Y_i(1) - Y_i(0)|S_i = (d_0, d_1)] \quad d_0, d_1 \in \{0, 1\}
\]
PS Example 1: Treatment Noncompliance
Angrist et al., 1996

\[ D_i(z) = \text{Treatment received given assignment } z \text{ for } z = 0, 1 \]

\[ D_i(z) = \begin{cases} 
0, & \text{if subject } i \text{ received control given assignment } z; \\
1, & \text{if subject } i \text{ received active trt given assignment } z. 
\end{cases} \]

00 = \{i : D_i(0) = 0, D_i(1) = 0\} = \text{Never Takers}

10 = \{i : D_i(0) = 1, D_i(1) = 0\} = \text{Defiers}

01 = \{i : D_i(0) = 0, D_i(1) = 1\} = \text{Compliers}

11 = \{i : D_i(0) = 1, D_i(1) = 1\} = \text{Always Takers}

\[ \tau^{CACE} = E[Y_i(1) - Y_i(0) \mid D_i(0) = 0, D_i(1) = 1] \]
PS Example 2: Censoring (or Truncation) by Death

\[ D_i(z) = \text{Indicator for two-year survival given assignment } z, \quad z = 0, 1 \]

\[ D_i(z) = \begin{cases} 
0, & \text{if subject } i \text{ dies given assignment } z; \\
1, & \text{if subject } i \text{ lives given assignment } z. 
\end{cases} \]

▸ Never Survivals: Subjects who will die no matter how treated

\[ 00 = \{ i : D_i(0) = 0, D_i(1) = 0 \} \]

▸ Defiant Survivals: Subjects who will die if treated but live otherwise

\[ 10 = \{ i : D_i(0) = 1, D_i(1) = 0 \} \]

▸ Compliant Survivals: Subjects who will live if treated but die otherwise

\[ 01 = \{ i : D_i(0) = 0, D_i(1) = 1 \} \]

▸ Always Survivals: Subjects who will live no matter how treated

\[ 11 = \{ i : D_i(0) = 1, D_i(1) = 1 \} \]
Censoring (or Truncation) by Death

- A well defined causal effect of the active treatment versus the control treatment on QOL exists only for the always-survivors $11 = \{i : D_i(0) = 1, D_i(1) = 1\}$:

$$\tau^{SACE} = E\left[Y_i(1) - Y_i(0) \mid D_i(0) = 1, D_i(1) = 1\right]$$

where $SACE$ stands for Survival Average Causal Effect

- For the $10 = \{i : D_i(0) = 1, D_i(1) = 0\}$ and $01 = \{i : D_i(0) = 0, D_i(1) = 1\}$ groups, the average causal effect on QOL involves to assume we know how to trade off a particular QOL and being dead (and out of misery)

- For the $00 = \{i : D_i(0) = 0, D_i(1) = 0\}$ group there is no QOL to compare
Censoring by Death: Additional Examples

- Evaluating the causal effects of job training programs on wages (Zhang et al., 2008, 2009)
  \[ D(z) = \text{Indicator of employment given assignment } z \]

- Evaluating the causal effects of a special educational intervention on final test scores (Zhang & Rubin, 2003)
  \[ D(z) = \text{Graduation indicator given assignment } z \]

- Evaluating the causal effect of Breast Self-Examination (BSE) teaching courses on quality of execution of BSE (Mattei & Mealli, 2007)
  \[ D(z) = \text{Indicator of BSE practice given assignment } z \]

- Evaluating the effectiveness of degree programs on employment status of their graduates (Grilli & Mealli, 2008)
  \[ D(z) = \text{Graduation indicator given assignment } z \]
**PS Example 3: Selection Bias in CRT**

Li et al., 2022

- $D_i(z)$: Recruitment status given assignment $z$, $D_i(z) = 0$ un-recruited; $D_i(z) = 1$ recruited

- **Principal strata**

  - $00 = \{i : D_i(0) = 0, D_i(1) = 0\} = \text{Never recruited}$
  - $10 = \{i : D_i(0) = 1, D_i(1) = 0\} = \text{Defiers}$
  - $01 = \{i : D_i(0) = 0, D_i(1) = 1\} = \text{Compliant recruited}$
  - $11 = \{i : D_i(0) = 1, D_i(1) = 1\} = \text{Always recruited}$

- The recruited units are all with $D = 1$; we do not observe unrecruited units $D = 0$

- What are the causal estimands: (i) $\tau^{overall} = E[Y_i(1) - Y_i(0)]$ for the overall population; (ii) $\tau^{recruited} = E[Y_i(1) - Y_i(0) \mid D_i = 1]$

  \[\tau^{overall} \neq \tau^{recruited}\], unless under homogeneous treatment effects
A hypothetical example: selection bias in CRT
Li et al., 2022

Assume (i) monotonicity, i.e. no defiant-recruited, and (ii) equal proportions of each stratum in the overall population.

True causal effects: $\tau^a = 20$, $\tau^c = 15$, $\tau^n = 10$, $\tau^{overall} = 15$

A naïve ITT estimate of the recruited data: $\hat{\tau} = 27.5 - 10 = 17.5$, biased
Example: Selection bias in CRT

- Core reason of selection bias in CRT:
  - The recruited trt group $Z = 1, D = 1$ consists of always-recruited and compliant-recruited
  - The recruited control group $Z = 1, D = 1$ consists of only always-recruited
- Thus the two groups are not comparable, breaking randomization.
- “Randomization protects against confounding, but not against selection bias when the selection occurs after the randomization” (Hernan and Robins, p103)
- Also known as recruitment bias or identification bias in literature
- Consequences
  - With recruited sample alone, we can only estimate $\tau^{recruited}$
  - To estimate the overall effect $\tau^{overall}$, we need additional data on unrecruited units; standard covariate adjustment is not adequate
Principal Stratification: Central Challenge

- The above three examples differ in settings and goal, but all share the same fundamental feature: post-treatment confounding bias.

- All can be formulated via the principal stratification framework; additional examples of PS are given at the end of the slides.

- Central challenge in inference of Principal Stratification: individual principal strata memberships are not observed, because of the fundamental problem of causal inference.

- Additional assumptions are required for identifying PCE.

- Different PS settings share the same estimation and inferential procedure, but differ in estimands of interest and specific identification assumptions.
PS Estimation and Inference: Assumptions

- Assumption 1: Unconfoundedness of treatment assignment

\[ \{Y_i(0), Y_i(1), D_i(0), D_i(1)\} \perp Z_i \mid X_i \]

- Ignorability implies

- Principal stratum membership \( S_i \) has the same distribution between the treatment arms (within cells defined by \( X \))

\[ D_i(0), D_i(1) \perp Z_i \mid X_i \]

- Latent Ignorability ("latent" because conditioning on a latent variable: PS):

\[ \{Y_i(0), Y_i(1)\} \perp Z_i \mid D_i(0), D_i(1), X_i \]
Focusing on the case of binary $Z$ and $D$

The observed $(Z, D)$ cells consist of mixtures of principal strata:

<table>
<thead>
<tr>
<th>$Z$</th>
<th>$D$</th>
<th>$S$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>[C, NT]</td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>[AT, D]</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>[NT, D]</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>[C, AT]</td>
</tr>
</tbody>
</table>

Monotonicity assumptions reduce some of these mixtures to one component, but generally not enough to identify all principal causal effects.

Estimation of PS inherently involves latent mixture models: disentangle the latent mixtures (i.e. principal strata) from observed data.
PS Estimation and Inference: Moment-based

- In the simplest case of binary treatment, a single binary intermediate variable and no covariates, under monotonicity and exclusion restriction (ER), moment estimate (2SLS in Angrist et al. 2002) of CACE is available.

- Large sample variance is available.

- Without ER and/or monotonicity, one can instead find nonparametric bounds for CACE (e.g. Grilli and Mealli, 2007), but the bounds can be often too wide to be informative.

- Limitations: (i) does not utilize the mixture structure, inefficient; (ii) difficult to extend to general setting, e.g. covariates, nonbinary treatments, truncation by death...
PS: Mixture Model Approach

- Six quantities are associated with each unit: \( Y_i(1), Y_i(0), D_i(1), D_i(0), X_i, Z_i \),

- Four are observed, \( Y_{i \text{obs}} = Y_i(Z_i) \), \( D_{i \text{obs}} = D_i(Z_i) \), \( Z_i, X_i \), and the rest two are unobserved \( Y_{i \text{mis}} = Y_i(1 - Z_i) \), \( D_{i \text{mis}} = D_i(1 - Z_i) \);

- Consequently the principal strata membership \( S_i = (D_i(0), D_i(1)) \)—the label of components in mixture model—is unobserved

- Two ways to handling the latent mixture label: (i) integrate out (expectation) the label; (ii) impute the label.

- Key questions in the latent mixture model approach: (i) What models do we need to specify? (ii) What is the likelihood?
PS: Complete data likelihood

- The probability density function of all random variables as

\[
\prod_i \Pr(Y_i(0), Y_i(1), D_i(0), D_i(1), Z_i, X_i, \theta)
\]

\[
= \prod_i \Pr(Z_i | Y_i(0), Y_i(1), S_i, X_i, \theta) \Pr(Y_i(0), Y_i(1) | S_i, X_i, \theta) \Pr(S_i | X_i, \theta) \Pr(X_i | \theta)
\]

\[
\propto \prod_i \Pr(Y_i(0) | S_i, X_i; \theta)^{(1-Z_i)} \Pr(Y_i(1) | S_i, X_i; \theta)^{Z_i} \Pr(S_i | X_i; \theta)
\]

where \( \theta \) is the global parameter with prior distribution \( p(\theta) \)

- Second equality/proportional to sign is due to (1) unconfoundedness and (2) we condition on \( X \)

- So one needs to specify two models:
  - The principal strata model (S-model): \( \Pr(S_i | X_i, \theta) \)
  - The outcome model given stratum (Y-model):
    \( \Pr(Y_i(z) | S_i, X_i, \theta) \)
Complete intermediate data likelihood

- Complete intermediate data likelihood:

\[
\prod_i \Pr(Y_i(0) \mid S_i, X_i; \theta)^{(1-Z_i)} \Pr(Y_i(1) \mid S_i, X_i; \theta)^{Z_i} \Pr(S_i \mid X_i; \theta).
\]

- Without any constraints, the complete intermediate data likelihood is a product of four components, each corresponding to an observed cell of \(Z, D\) and being a mixture of two principal strata:

\[
Lik \propto \prod_{i: Z_i=0, D_i=0} (\pi_{i,c} f_{i,c0} + \pi_{i,n} f_{i,n0}) \times \prod_{i: Z_i=0, D_i=1} (\pi_{i,a} f_{i,a0} + \pi_{i,d} f_{i,d0})
\]
\[
\times \prod_{i: Z_i=1, D_i=0} (\pi_{i,n} f_{i,n1} + \pi_{i,d} f_{i,d1}) \times \prod_{i: Z_i=1, D_i=1} (\pi_{i,a} f_{i,a1} + \pi_{i,c} f_{i,c1}),
\]

where \(f_{i,sz} = \Pr(Y_i(z) \mid S_i = s, X_i; \theta)\) and \(\pi_{i,s} = \Pr(S_i = s \mid X_i; \theta)\)

- This is the latent mixture model
Parameter Estimation: Likelihood

- The complete intermediate data likelihood is not directly observable because of the missing principal strata membership $S$.

- How do assumptions simplify the computation?
  - Monotonicity: $\pi_{i,d} = 0$
  - ER: $f_{i,n0} = f_{i,n1} = f_{i,n}$; $f_{i,a0} = f_{i,a1} = f_{i,a}$

- With monotonicity and ER, the complete intermediate data likelihood reduces to:

$$Lik \propto \prod_{i:Z_i=0,D_i=0} \left( \pi_{i,c} f_{i,c0} + \pi_{i,n} f_{i,n} \right) \times \prod_{i:Z_i=0,D_i=1} \left( \pi_{i,a} f_{i,a} \right) \times \prod_{i:Z_i=1,D_i=0} \left( \pi_{i,n} f_{i,n} \right) \times \prod_{i:Z_i=1,D_i=1} \left( \pi_{i,a} f_{i,a} + \pi_{i,c} f_{i,c1} \right),$$
Parameter Estimation: EM algorithm

- Using the EM algorithm to estimate the parameters
  - E-step: the unobserved principal strata are replaced by their expectations given the data and the current estimates of the parameters
  - M-step: the likelihood conditional on the expected principal strata is maximized

- Case study: Zhang and Rubin (2003, JBES)
Parameter Estimation: Bayesian Approach

Imbens and Rubin (1997, AOS)

- Similar to the likelihood approach: adding priors, substitute EM with posterior simulation via MCMC

- Bayesian inference considers the observed values of the six quantities to be realizations of random variables, and the unobserved values to be unobserved random variables (Rubin, 1978, AOS)

- Goal: to get the posterior predictive distributions of the missing data $Y_{i}^{mis} = Y_i(1 - Z_i), D^{mis} = D_i(1 - Z_i)$
Outline of Bayesian Inference of PS

- Assuming unconfoundedness
- The *posterior predictive distribution* of the missing potential outcomes is proportional to the complete data likelihood (as before):

\[
\Pr(Y_{mis}, D_{mis}|Y_{obs}, D_{obs}, Z, X, \theta) \propto \prod_i \Pr(Y_i(0), Y_i(1)|S_i, X_i, \theta) \Pr(S_i|X_i, \theta)p(\theta).
\]

where \(\theta\) is the global parameter with prior distribution \(p(\theta)\)

- Besides the S-model and Y-model, we need specify a prior distribution for \(\theta\): \(p(\theta)\)

- The above implicitly assumes: the parameters for each component in the second row of (1) are *a priori* distinct and independent
Outline of Bayesian Inference of PS

- The posterior distribution of $\theta$ is generally not tractable
- One can use a Gibbs sampler to simulate from the joint posterior distribution $\Pr(\theta, D^{mis} | Y^{obs}, D^{obs}, Z, X)$ by iteratively drawing between
  - $\Pr(D^{mis} | Y^{obs}, D^{obs}, Z, X, \theta)$ (Parallel to the E-step)
  - $\Pr(\theta | Y^{obs}, D^{obs}, D^{mis}, Z, X)$ (Parallel to the M-step)
- $\Pr(\theta | Y^{obs}, D^{obs}, D^{mis}, Z, X)$ is proportional to the complete intermediate data likelihood:

$$
\Pr(\theta | Y^{obs}, D^{obs}, D^{mis}, Z, X) 
\propto p(\theta) \prod_i \Pr(Y_i(0) | S_i, X_i)^{(1-Z_i)} \Pr(Y_i(1) | S_i, X_i)^{Z_i} \Pr(S_i | X_i)
$$
Weak Identifiability

- From the Bayesian perspective, PCEs are always identified under ignorability because with proper prior distributions of the parameters, posterior distributions of the causal estimands are always proper (in Lindley’s sense)
- But some estimands are weakly identified, with substantial regions of flatness in their posterior distributions
- This is different from the none-or-all point identification under the frequentist paradigm
- Some weakly identifiable parameters are still informative about the causal effects
- Bayesian inference for causal estimands can be sharpened by additional assumptions such as monotonicity and ER
- Case study: Imbens and Rubin (1997, AOS)
Case study: Effect of debit card on cash holding

Mercatanti and Li, 2017, JRSSC

- Goal: study the effects of using debit cards on the cash holding behaviour of consumers
- As debit cards can be viewed as a substitute of cash in some ways, they may reduce the cash demand, which is important for central banks as cash demand is an important factor in monetary policy
- Complication: some people who possess debit cards do not use them
- The interest is in the effect of using cards rather than possessing cards
- Key: cards are issued by banks (treatment assigned) but the choice of use depends on individual (treatment received), which can be viewed a post-treatment variable
Effect of debit card on cash holding

- \( Z_i \): indicator of unit \( i \) possessing a debit card
- \( D_i \): indicator of unit \( i \) using a debit card
- \( Y_i \): average amount of cash held by unit \( i \)
- \( X_i \): pre-treatment covariates
- Potential outcomes of \( Y \) and \( D \).
- Principal strata of card usage: \( S_i = (D_i(0), D_i(1)) \)
- Causal estimands: CACE

\[
\tau^{CATE} \equiv \mathbb{E}[Y_i(1) - Y_i(0) \mid S_i = c]
\]

and CATT (average causal effect of the treated compliers)

\[
\tau^{CATT} \equiv \mathbb{E}[Y_i(1) - Y_i(0) \mid S_i = c, Z_i = 1]
\]

- In randomized experiments, CATT equals CACE.
Assumptions

- **Monotonicity (no defiers or always-takers):** \( D_i(0) = 0 \). Satisfied automatically.

- **Overlap:** \( 0 < \Pr(Z_i = 1 | X_i) < 1 \), for all \( i \).

- **Unconfoundedness:** \( \{Y_i(1), Y_i(0), D_i(1), D_i(0)\} \perp Z_i | X_i \).

- **Exclusion Restriction for never-takers:**

\[
\mathbb{E}[Y_i(1)|X_i, S_i = n] = \mathbb{E}[Y_i(0)|X_i, S_i = n].
\]

- **Exclusion Restriction for compliers:** For all units with \( S_i = (0, 1) \), the effect of card possession is only through using the card.

In observational studies, these assumptions must be conditional on covariates, and CATT and CATE are usually different.
Parametric Models

- A logistic regression model for principal stratum membership $G$:
  \[
  \text{logit}(\Pr(S_i = n|X_i = x)) = \alpha_0 + x \cdot \alpha.
  \]

- A linear regression model for continuous potential outcomes, with different intercepts and slopes for different strata:
  \[
  \Pr(Y_i(z)|S_i, X_i = x) = 1_{S_i=c} \cdot (\beta_{c0} + z \cdot \theta_c + x \cdot \beta_{c1}) + 1_{S_i=n} \cdot (\beta_{n0} + x \cdot \beta_{n1}) + \epsilon_i,
  \]
  where $\epsilon_i \sim N(0, \sigma^2)$ and $1_{S_i=s}$ is an indicator function.

- Here $\theta_c$ equals CATE, and the CATT can be subsequently estimated by averaging the differences between the observed outcomes for treated compliers and their estimated counterfactuals:
  \[
  \tilde{\tau}_{CATT} = \frac{\sum_i D_i \cdot Z_i \cdot [Y_i - (\hat{\beta}_{c0} + X_i \cdot \hat{\beta}_{c1})]}{\sum_i D_i \cdot Z_i}.
  \]
Extending Monotonicity

- Monotonicity plays a crucial role in identification and estimation of principal stratification.

- To extend PS to complex settings, e.g. multi-valued or multiple intermediate variables $D$, it is crucial to specify case-specific monotonicity assumptions to reduce no. of strata.

- One example: both treatment switching and discontinuation.

- A case study (Liu, Wruck, Li, 2024)
  - Treatment: aspirin low (81mg daily) vs. high dose (325mg daily)
  - Both treatment switching and discontinuation (patients stopped taking aspirin entirely)
  - Consider actual treatment levels $D$ are three: discontinue (*), low (0), high (1)
  - Without restrictions, nine ($3 \times 3$) possible strata $S = (D(0), D(1))$
Extending Monotonicity: Example

- Specify more elaborate monotonicity assumptions according to the real context

- Liu et al. (2024) assumes:
  
  1. If $D_i(0) = \ast$, then $D_i(1) = \ast$, namely, if a patient would discontinue under the 81 mg assignment, then he/she would also discontinue under the 325 mg assignment;

  2. if $D_i(0) = 1$, then $D_i(1) = 1$, namely, if a patient would take 325 mg under the 81 mg assignment, then he/she would also take 325 mg under the 325 mg assignment.

- Assumption ii implies the original monotonicity when there is no discontinuation

- With this monotonicity, the number of strata reduced from 9 to 5: $S \in \{(\ast, \ast), (0, \ast), (0, 0), (0, 1), (1, 1)\}$
Principal Stratification: a key strength is its flexibility in formulating a wide range of seemingly different settings.

However, different settings target at different principal strata and require different assumptions (besides unconfoundedness and monotonicity):

<table>
<thead>
<tr>
<th>setting</th>
<th>target strata</th>
<th>assumptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>noncompliance</td>
<td>compliers (01)</td>
<td>ER for noncompliers</td>
</tr>
<tr>
<td>censoring by death</td>
<td>always-survivors (11)</td>
<td>case-dependent</td>
</tr>
<tr>
<td>selection bias in CRT</td>
<td>(11) &amp; (01)</td>
<td>need additional data</td>
</tr>
</tbody>
</table>

The flexibility brings challenges in providing a generally applicable algorithm, case-dependent implementation.
Mixture models: pros and cons

- Conceptually, inference of all the PS settings can be handled by mixture models, straightforward to extend to more complex settings (e.g. clustering, covariates, non-binary IV).

- Challenges of mixture model: (i) requires substantial stat and programming expertise; (ii) often not stable.

- Difficulty in implementation prevents the wide adoption of principal stratification.

- An alternative approach is the weighting via *principal score* (Jo and Stuart, 2009).
Bypassing mixture models: Principal Score

- Principal score (Jo and Stuart, 2009): $e_s(X) = \Pr(S = s \mid X)$

- Key assumption: **principal ignorability (PI)** $Y(z) \perp S \mid X$, which implies the same conditional expectations across mixture components (strata)

- PI: a strong assumption in parallel with the standard ignorability assumption

- PI holds only when we have adequate background covariates

- Assuming unconfoundedness, monotonicity and PI, one can use weighting to estimate PCEs (Ding and, 2017; Jiang et al. 2022), bypassing mixture models

- PI assumption is the key: assuming strata membership is fully encoded in covariates
“PStrata” R Package

- Estimation and inference of PS is challenging: mixture models are hard; Bayesian inference is hard (for most practitioners)
- R package “PStrata" (Liu and Li, 2023): implement most common PS settings via Bayesian mixture model: noncompliance, truncation by death; continuous/binary outcomes, survival outcomes
  - R: interface, main function, standardized inputs (S-model, Y-model, priors, setting, assumptions (e.g. monotonicity, ER))
  - Stan: backstage posterior sampling given a likelihood
  - C++: connecting R and Stan – take in R input and output text Stan code of the data likelihood
- Also implement the principal score approach
- https://cran.r-project.org/web/packages/PStrata/index.html
- For illustration, see HW4.
Characterize and Visualize Principal Strata

- Principal strata, by definition, are latent. But it is helpful to characterize and visualize.

- With mixture model, we can:
  - calculate each unit’s probability of being in each stratum,
  - based on which randomly draw each unit’s principal stratum membership.
  - Then plot these individual probabilities or/and present a table of baseline characteristics of units in each stratum.

- Good separation in probabilities between strata is desirable, implying stronger identification of the strata.
Characterize and Visualize Principal Strata: Example

The upper left plot shows the probability of each strata, and the upper right plot shows the average treatment effect within each strata. Point mass of 0 are observed in never takers and always takers due to ER. The lower plot shows the estimated mean effect of treatment group and control group, under each stratum.
Multiple Intermediate Variables

- Often there are multiple intermediate variables in a study. Exponentially increases the number of principal strata. Additional assumptions are required to identify the causal effects.

- The Faenza Randomized Experiment on Breast Self-Examination (BSE): conducted between Jan 1988 and Dec 1990 at the Oncologic Center of the Faenza Health District in Italy.

- Two BSE teaching methods were compared:
  - a *standard treatment* of receiving mailed information only, and
  - a *new treatment* of additional attendance in a self-exam course.

- The question of interest is the effect of an enhanced training class on BSE practices and quality of self-exam execution.
Complications

- The Faenza BSE study suffers from complications due to
  - *noncompliance* with the randomly assigned treatment: only 55% of the women assigned to the new treatment complied with their assignment;
  - *missing outcomes* following treatment noncompliance: only 65% of the women responded to the post-test questionnaire;
  - “*censoring by death*”: quality of self exams is not only unobserved but also undefined on the sample space for women who do not practice BSE.

- For illustration, here we will only consider noncompliance and censoring by death.
Estimands of interest

- **Causal Estimands on BSE practice outcome**
  - Intention-To-Treat (ITT) effect;
  - Complier Average Causal Effect (CACE);
  - Never-taker Average Causal Effect (NACE).

- **Causal Estimands on BSE quality outcome**
  - ITT effect for all women who would practice BSE under both assignments;
  - average causal effect for compliers who would practice BSE who would practice BSE under both treatments.
Potential Outcomes

If woman \( i \) in the study \( (i = 1, \ldots, N) \) is to be assigned to treatment \( z \) (\( z = 1 \) or \( z = 0 \)), we denote the following:

- **Indicator of the treatment received:**
  \[
  D_i(z) = \begin{cases} 
  P, & \text{if the woman attends the training program;} \\
  p, & \text{if the woman receives only mailed information on BSE.} 
  \end{cases}
  \]

- **BSE practice indicator:**
  \[
  W_i(z) = \begin{cases} 
  B, & \text{if the woman practices BSE;} \\
  b, & \text{otherwise.} 
  \end{cases}
  \]

- **Potential quality outcome:**
  \[
  Y_i(z) = \begin{cases} 
  H, & \text{if the woman practices BSE with “High” quality;} \\
  L, & \text{if the woman practices BSE with “Low” quality;} \\
  *, & \text{if the woman does not practice BSE.} 
  \end{cases}
  \]
Principal Stratification

- The variable $D_i(1)$ defines the compliance behavior of subject $i$:
  - If $D_i(1) = P$, then woman $i$ is a “complier”;
  - if $D_i(1) = p$, then woman $i$ is a “never-taker”.

- The vector $(W_i(0), W_i(1))$ defines the BSE practice behavior of subject $i$. 
Principal Stratification

\[ P_{BB} = \{ i : D_i(1) = P, W_i(0) = B, W_i(1) = B \} \] : compliers who would practice BSE under both treatment arms;

\[ P_{bB} = \{ i : D_i(1) = P, W_i(0) = b, W_i(1) = B \} \] : compliers who would not practice BSE under control but would practice BSE under treatment;

\[ P_{Bb} = \{ i : D_i(1) = P, W_i(0) = B, W_i(1) = b \} \] : compliers who would practice BSE under control but would not practice BSE under treatment;

\[ P_{bb} = \{ i : D_i(1) = P, W_i(0) = b, W_i(1) = b \} \] : compliers who would practice BSE under neither treatment arms;

\[ p_{BB} = \{ i : D_i(1) = p, W_i(0) = B, W_i(1) = B \} \] : never-takers who would practice BSE under both treatment arms;

\[ p_{bB} = \{ i : D_i(1) = p, W_i(0) = b, W_i(1) = B \} \] : never-takers who would not practice BSE under control but would practice BSE under treatment;

\[ p_{Bb} = \{ i : D_i(1) = p, W_i(0) = B, W_i(1) = b \} \] : never-takers who would practice BSE under control but would not practice BSE under treatment;

\[ p_{bb} = \{ i : D_i(1) = p, W_i(0) = b, W_i(1) = b \} \] : never-takers who would practice BSE under neither treatment arms.
Principal stratification and associated pattern for potential outcomes

<table>
<thead>
<tr>
<th>Principal Stratum</th>
<th>$D_i(1)$</th>
<th>$W_i(0)$</th>
<th>$W_i(1)$</th>
<th>$Y_i(0)$</th>
<th>$Y_i(1)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$PBB$</td>
<td>$P$</td>
<td>$B$</td>
<td>$B$</td>
<td>$\in {L, H}$</td>
<td>$\in {L, H}$</td>
</tr>
<tr>
<td>$PbB$</td>
<td>$P$</td>
<td>$b$</td>
<td>$B$</td>
<td>$*$</td>
<td>$\in {L, H}$</td>
</tr>
<tr>
<td>$PBB$</td>
<td>$P$</td>
<td>$B$</td>
<td>$b$</td>
<td>$\in {L, H}$</td>
<td>$*$</td>
</tr>
<tr>
<td>$Pbb$</td>
<td>$P$</td>
<td>$b$</td>
<td>$b$</td>
<td>$*$</td>
<td>$*$</td>
</tr>
<tr>
<td>$pBB$</td>
<td>$p$</td>
<td>$B$</td>
<td>$B$</td>
<td>$\in {L, H}$</td>
<td>$\in {L, H}$</td>
</tr>
<tr>
<td>$pbB$</td>
<td>$p$</td>
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<td>$*$</td>
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<td>$pBB$</td>
<td>$p$</td>
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<td>$b$</td>
<td>$\in {L, H}$</td>
<td>$*$</td>
</tr>
<tr>
<td>$pbb$</td>
<td>$p$</td>
<td>$b$</td>
<td>$b$</td>
<td>$*$</td>
<td>$*$</td>
</tr>
</tbody>
</table>
Principal Stratification: More Extensions

- Continuous intermediate variables: the key is to model the intermediate variable in a parsimonious way, e.g. bivariate Gaussian (Jin and Rubin, 2008, JASA), Gaussian copula (Bartolluci and Grill, 2011, JASA), Dirichlet Process Mixture (Schwartz, Li, Mealli, 2011, JASA)

- Reduce variance using secondary outcomes and covariates (Mealli and Pacini, 2013, JASA)

- Sequential treatments (Ricardi, Mattei, Mealli, 2020, JASA)

- Sensitivity analysis (Schwartz et al. 2012, SIM)
Additional PS Example: Direct and Indirect Causal Effects
Sjöander et al., 2009; Schwartz et al., 2011

- Treatment = Physical activity (PA)
  \[ Z_i = \begin{cases} 
    0, & \text{if subject } i \text{’s PA level is low;} \\
    1, & \text{if subject } i \text{’s PA level is high.} 
  \end{cases} \]

- Intermediate Outcome: Body Mass index (BMI) after “assignment” of PA
  \[ D_i(z) = \begin{cases} 
    H, & \text{if unit } i \text{ is obese (BMI is high) given assignment } z; \\
    L, & \text{if unit } i \text{ is not obese (BMI is low) given assignment } z. 
  \end{cases} \]

- Primary Outcome: CardioVascular Disease (CVD) after “assignment” of PA
  \[ Y_i(z) = \begin{cases} 
    1, & \text{if unit } i \text{ reports at least one CVD event before end of follow-up given assignment } z; \\
    0, & \text{if unit } i \text{ remains undiagnosed through follow-up given assignment } z. 
  \end{cases} \]

- The total effect of physical activity will be a combination of the direct effect of PA on CVD and the indirect effect mediated by BMI.
Subjects who would be obese under both PA levels: BMI is unaffected by PA

\[ HH = \{ i : D_i(0) = H, D_i(1) = H \} \]

Subjects who would be obese under high PA level and would not be obese under low PA level

\[ LH = \{ i : D_i(0) = L, D_i(1) = H \} \]

Subjects who would not be obese under high PA level and would be obese under low PA level

\[ HL = \{ i : D_i(0) = H, D_i(1) = L \} \]

Subjects would not be obese under both PA levels: BMI is unaffected by PA

\[ LL = \{ i : D_i(0) = L, D_i(1) = L \} \]

A direct causal effect of PA, after controlling for BMI, exists if there is a causal effect of PA on CVD for subjects for whom the treatment does not affect BMI (i.e., basic principal strata \( HH \) and \( LL \))
Hypothetical Example (1)

<table>
<thead>
<tr>
<th>Principal Stratum</th>
<th>Post-trt Var.</th>
<th>Pot. Outcome CVD rates (%)</th>
<th>Obs Data from a Randomized Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Average of ( (D_{i}^{\text{obs}}, Y_{i}^{\text{obs}}) ) given assignment</td>
</tr>
<tr>
<td>( S_{i} )</td>
<td>( D_{i}(1) )</td>
<td>( D_{i}(0) )</td>
<td>( Z_{i}^{\text{obs}} = 1 )</td>
</tr>
<tr>
<td>Not Obese</td>
<td>( L )</td>
<td>( L )</td>
<td>( Z_{i}^{\text{obs}} = 0 )</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>10</td>
<td>(( L, 10 ))</td>
</tr>
<tr>
<td>Normal</td>
<td>( L )</td>
<td>( H )</td>
<td>(( L, 20 ))</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>50</td>
<td>( (H, 50) )</td>
</tr>
<tr>
<td>Obese</td>
<td>( H )</td>
<td>( H )</td>
<td>( (H, 50) )</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>50</td>
<td></td>
</tr>
</tbody>
</table>

Assume there are no special units: \( LH = \emptyset \)

Equal proportions for each prin stratum
Hypothetical Example (2)

Full Data

<table>
<thead>
<tr>
<th>Principal Stratum</th>
<th>Post-trt Var. BMI</th>
<th>Pot. Outcome CVD rates (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( S_i )</td>
<td>( D_i(1) )</td>
<td>( D_i(0) )</td>
</tr>
<tr>
<td>Not Obese</td>
<td>( L )</td>
<td>( L )</td>
</tr>
<tr>
<td>Normal</td>
<td>( L )</td>
<td>( H )</td>
</tr>
<tr>
<td>Obese</td>
<td>( H )</td>
<td>( H )</td>
</tr>
</tbody>
</table>

Assume there are no special units: \( LH = \emptyset \)

Equal proportions for each prin stratum

Obs Data from a Randomized Study

Average of \( (D_{i}^{obs}, Y_{i}^{obs}) \) given assignment

\[ Z_{i}^{obs} = 1 \]

\[ Z_{i}^{obs} = 0 \]

\( Z_{i}^{obs} = 1 \)

\( (L, 20) \)

\( (L, 20) \)

\( Z_{i}^{obs} = 0 \)

\( (H, 50) \)

\( (H, 50) \)
Additional Examples of Direct and Indirect Effects

▶ Evaluating to what extent the causal effects of a new drug treatment having side-effects is be mediated by the effect of taking additional medication to counter its side-effects (Pearl, 2001)

▶ The causal effects of a training program on participants’ earnings might be mediated by lock-in effects, that is, the loss of labour market experience (Flores & Flores-Lagunes, 2009)

▶ Evaluating the extent to which smoking during pregnancy affects the incidence on low birth weight through a shorter gestation time might inform policy makers on promoting drugs that lengthen gestation time (Flores & Flores-Lagunes, 2009)

▶ Evaluating to what extent the effect of military service on veterans’ earnings is channelled by subsidized higher education (Angrist & Chen, 2008)

▶ A special case of mediation (direct and indirect effects) is Surrogate Endpoints
Additional PS Example: Surrogate Endpoints

- Often in clinical trials the primary outcome may be rare, late-occurring or costly to obtain.

- Instead researchers may rely on 'surrogate" or "biomarker" endpoints: easier-to-measure variables known to have a strong association with the true endpoint to reliably extract information on the effect of the treatment.

- Example: in a randomized trial to evaluate the efficacy of a HIV vaccine, the primary outcome is HIV infection, which may take place after a considerable period of time. Count of CD4 cells in blood has long been used as a surrogate endpoint for HIV infection.

- There have been different definitions of surrogate endpoints.
Principal Surrogates

- Frangakis and Rubin (2002) defines “principal surrogates” on based principal stratification; principal surrogates have a causal interpretation.

- For a variable $D$ measured after treatment but before the true endpoint occurs, define an **associative effect** to be the causal effects for the principal strata with $d_0 \neq d_1$, and a **dissociative effect** to be the causal effects for the principal strata with $d_0 = d_1 = d$.

- $D$ is a principal surrogate if the dissociative effect is zero for all $w$.

- The quality of $D$ as a surrogate is determined by its associative effects relative to its dissociative effects - “causal effect predictiveness”.


Rosenbaum, P. R. (1984). The consequences of adjustment for a concomitant variable that has been affected by the treatment. JRSS-A, 147(5), 656-666.
