ALTERNATIVE APPROACHES IN DEFINING TREATMENT EFFECTS

Vlad Dragalin

Quantitative Sciences, Janssen Pharmaceuticals

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Outline

Illustrative Example

Randomized, two-arm trial in patients with type 2 diabetes mellitus (T2DM)

- **Population:** patients with T2DM
- **Treatments:** experimental drug ($X = 1$) compared with control ($X = 0$)
- **Outcome variable:** HbA1c levels at 24 weeks after randomization
- **Intercurrent events**: for ethical reasons, patients are allowed to take rescue medication once their HbA1c values are above a certain threshold

Regardless of using rescue medication all patients are followed up for the whole study duration, i.e. there are no missing observations in this study

Random Experiment I

1. Sampling a subject u from a population of subjects Ω_U
2. Assigning the subject at random to one of the two treatment conditions represented by random variable $X \in \Omega_X$, where $\Omega_X = \{(X = 1, M = 1 \text{ or } 0), (X = 0, M = 1 \text{ or } 0)\}$
3. Observing the value of the outcome variable Y post-treatment, $Y \in \mathbb{R}$

All random variables refer to the random experiment represented by a probability space $(\Omega, \mathcal{F}, P)$, where

$$\Omega = \Omega_U \times \Omega_X \times \Omega_Y$$

and $\mathcal{F}$ is a σ-algebra on Ω and P is a probability measure assigning a probability to each element of Ω.

Causality Space

- All random variables have a joint distribution and a special temporal ordering.
- We use the notion of *filtration* to describe the temporal ordering: $\mathcal{F}_t, t \in T, \mathcal{F}_s \subseteq \mathcal{F}_t \subseteq \mathcal{F}, s \leq t$.
- **Causality Space:**

$$\langle(\Omega, \mathcal{F}, P), (\mathcal{F}_t, t \in T), X, Y\rangle$$

- For Random Experiment I:

$$\mathcal{F}_1 = \sigma(U), \quad \mathcal{F}_2 = \sigma(U, X), \quad \mathcal{F}_3 = \sigma(U, X, Y).$$

The population-level summary for the variable

"Treatment policy" effect

$$\Delta = E(Y \mid X = x_1) - E(Y \mid X = x_0)$$

Individual conditional expected values

$$\tau_1(u) = E(Y \mid X = x_1, U = u)$$

$$\tau_0(u) = E(Y \mid X = x_0, U = u)$$

- Notice similarity with Neyman & Rubin *potential outcome*
- Difference: the conditional expectation values are fixed not the actual ("counterfactual") values of Y, as in Neyman & Rubin approach

Average causal effect

The individual causal effect

$$\delta(u) = \tau_1(u) - \tau_0(u)$$

Causally unbiased expected value of Y given x

$$\tau_x = E(E(Y \mid X = x, U)) = \sum_u E(Y \mid X = x, U = u) \cdot P(U = u)$$

Average causal effect

$$\delta = E(\delta(U)) = \sum_u \delta(u) \cdot P(U = u) = \tau_{x_1} - \tau_{x_0}$$

Causal Bias of $E(Y \mid X = x)$

Conditional expected value of Y given x

$$E(Y \mid X = x) = \sum_u E(Y \mid X = x, U = u) \cdot P(U = u \mid X = x)$$

Causal unbiased expected value of Y given x

$$\tau_x = \sum_u E(Y \mid X = x, U = u) \cdot P(U = u)$$

Source of bias

$$P(U = u \mid X = x) = \frac{P(X = x \mid U = u)}{P(X = x)} \cdot P(U = u)$$

Causal Unbiasedness

Stochastic Independence of X and U

If X and U are stochastically independent, $X \perp\!\!\!\perp U$,

$$P(X = x \mid U = u) = P(X = x) \text{ for } \forall u,$$

then each conditional expected value $E(Y \mid X = x)$ is causally unbiased,

$$E(Y \mid X = x) = \tau_x \text{ for } \forall x,$$

and, consequently

$$\Delta = \delta$$

Causal Unbiasedness

Unit-treatment homogeneity

If Y is X-conditionally regressively independent of U, $Y \vdash U \mid X$,

$$E(Y \mid X, U) = E(Y \mid X)$$

then each conditional expected value $E(Y \mid X = x)$ is causally unbiased,

$$E(Y \mid X = x) = \tau_x \text{ for } \forall x,$$

and, consequently

$$\Delta = \delta$$

Proof

$$\sum_u E(Y \mid X = x, U = u) \cdot P(U = u) = \sum_u E(Y \mid X = x) \cdot P(U = u)$$

Example 1

U	$P(U=u)$	$P(X=x_1 \mid U=u)$	$E(Y \mid X=x_1, U=u)$	$E(Y \mid X=x_0, U=u)$	$\delta(u)$
u_1	1/2	2/3	8.5	9.1	-0.6
u_2	1/2	2/3	7.4	7.8	-0.4
τ_x			7.95	8.45	$\delta = -0.5$
$E(Y \mid X=x)$			7.95	8.45	$\Delta = -0.5$

Stochastic Independence: ✓ Unit-treatment homogeneity: ⊗

Example 2

U	$P(U = u)$	$P(X = x_1 \mid U = u)$	$E(Y \mid X = x_1, U = u)$	$E(Y \mid X = x_0, U = u)$	$\delta(u)$
u_1	1/2	1/4	8.5	9.1	-0.6
u_2	1/2	3/4	7.4	7.8	-0.4
τ_x			7.95	8.45	$\delta = -0.5$
$E(Y \mid X = x)$			7.7	8.7	$\Delta = -1.0$

Stochastic Independence: $\otimes$ Unit-treatment homogeneity: $\otimes$

Random Experiment II

1. Sampling a subject u from a population of subjects Ω_U
2. Measuring a X-covariate Z (Z may be multivariate, e.g. $Z \in \mathbb{R}^p$) and the baseline Y_0
3. Assigning the subject at random to one of the two treatment conditions represented by random variable $X \in \Omega_X$, where $\Omega_X = \{X = 1, X = 0\}$
4. Observing the value of the intercurrent event: $M = 1$ if the subject takes rescue medication; otherwise $M = 0$
5. Observing the value of the outcome variable Y post treatment, $Y \in \mathbb{R}$

All random variables refer to the random experiment represented by a probability space $(\Omega, \mathcal{F}, P)$, where

$$\Omega = \Omega_U \times \Omega_Z \times \Omega_{Y_0} \times \Omega_X \times \Omega_M \times \Omega_Y$$

and $\mathcal{F}$ is a σ-algebra on Ω.

Causality Space

For Random Experiment II

$$\langle(\Omega, \mathcal{F}, P), (\mathcal{F}_t, t \in T), X, Y\rangle$$

$$\mathcal{F}_1 = \sigma(U, Z, Y_0), \quad \mathcal{F}_2 = \sigma(U, Z, Y_0, X),$$

$$\mathcal{F}_3 = \sigma(U, Z, Y_0, X, M), \quad \mathcal{F}_4 = \sigma(U, Z, Y_0, X, M, Y).$$

Global covariates

A random variable $C_{X,t}$ satisfying:

- $\sigma(X, C_{X,t}) = \mathcal{F}_t$, for $t_X \leq t < t_Y$
- $t_X \in T$ such that $\sigma(X) \subset \mathcal{F}_{t_X}$, and $\sigma(X) \not\subseteq \mathcal{F}_s$, if $s < t_X$
- $t_Y \in T$ such that $\sigma(Y) \subset \mathcal{F}_{t_Y}$, and $\sigma(Y) \not\subseteq \mathcal{F}_s$, if $s < t_Y$

Causal Effects

$(X = x)$-Conditional Probability Measure

$$P^{X=x}(A) := P(A \mid X = x), \quad \forall A \in \mathcal{F}$$

True-outcome Variable with respect to $C_{X,t}$

$$\tau_{x,t} := E^{X=x}(Y \mid C_{X,t})$$

If $C_{X,t_X} = U$, then τ_{x,t_X} is an analog of *potential outcome*.

Average Total Effect

When $t = t_X$, we define

$$\tau_x = E(E^{X=x}(Y \mid C_{X,t_X}))$$

$$\delta = \tau_{x_1} - \tau_{x_0}$$

Causal Effects

Average Direct Effect

When $t = t_M$, $t_X < t_M < t_Y$, we define

$$\tau_{x,M} = E(E^{X=x}(Y \mid C_{X,t_M}))$$

$$\delta_M = \tau_{x_{1,M}} - \tau_{x_{0,M}}$$

In Experiment II, $C_{X,t_M} = (U, Z, Y_0, M)$

Average Indirect Effect

$$\bar{\tau}_x = \tau_x - \tau_{x,M}$$

$$\bar{\delta} = \delta - \delta_M$$

Example 3: Total Effects

Subject	M	U	$P(U=u)$	$P(X=x_1 \mid U=u)$	$E(Y \mid X=x_1, U=u)$	$E(Y \mid X=x_0, U=u)$	$\delta(u)$
S_1	0	u_1	4/10	2/3	8.5	9.1	-0.6
S_1	1	u_2	1/10	3/4	7.4	7.8	-0.4
S_2	0	u_3	4/10	2/3	10.6	11.2	-0.6
S_2	1	u_4	1/10	2/3	7.4	7.8	-0.4
τ_X					9.12	9.68	$\delta = -0.560$
$E(Y \mid X = x)$					9.099	9.728	$\Delta = -0.629$

Example 3: Direct Effects

U	M	$P(U=u \mid M=m)$	$P(X=x_1 \mid U=u)$	$E(Y \mid X=x_1, U=u)$	$E(Y \mid X=x_0, U=u)$	$\tau_{1,M}-\tau_{0,M}$	$P(U=u \mid X=x_1, M)$	$P(U=u \mid X=x_0, M)$
u_1	0	1/2	2/3	8.5	9.1	-0.6	1/2	1/2
u_3	0	1/2	2/3	10.6	11.2	-0.6	1/2	1/2
u_2	1	1/2	3/4	7.4	7.8	-0.4	9/17	3/7
u_4	1	1/2	2/3	7.4	7.8	-0.4	8/17	4/7

Stochastic Independence: ✓ Unit-treatment homogeneity: ✓

Example 3: Direct Effects

	$M = 0$		$M = 1$	
	$X = x_1$	$X = x_0$	$X = x_1$	$X = x_0$
$\tau_{x,M}$	9.55	10.15	7.4	7.8
δ_M		-0.60		-0.40
$E(Y \mid X, M)$	9.55	10.15	7.4	7.8
Δ_M		-0.60		-0.40

Identification of the Average Total Treatment Effect

Provided that both $E[E(Y \mid X = 1, M)]$ and $E[E(Y \mid X = 0, M)]$ are unbiased (i.e. equal to $\tau_{1,M}$ and $\tau_{0,M}$, respectively), the average total treatment effect can be computed (identified) as

$$\begin{aligned} E[E(Y \mid X = 1, M)] \quad - \quad & E[E(Y \mid X = 0, M)] \\ = \quad & 0.8 * (-0.6) + 0.2 * (-0.4) = -0.56 \end{aligned}$$

Causal Bias of $E(Y \mid X = x, M = m)$

Conditional expected value of Y given $X = x$ and $M = m$

$$E(Y \mid X = x, M = m) = \sum_u E(Y \mid X = x, U = u) \cdot P(U = u \mid X = x, M = m)$$

Causal unbiased value of Y given $X = x$ and $M = m$

$$\tau_{x,m} = \sum_u E(Y \mid X = x, U = u) \cdot P(U = u \mid M = m)$$

Source of bias

$$P(U = u \mid X = x, M = m) = \frac{P(X=x|M=m,U=u)}{P(X=x|M=m)} P(U = u \mid M = m)$$

Total Effects

Stochastic Independence Conditions

1. $X \perp\!\!\!\perp C_X : P(X = x \mid C_X) = P(X = x), \quad \forall x$
2. $X \perp\!\!\!\perp C_X \mid Z : P(X = x \mid C_X) = P(X = x \mid Z), \quad \forall x$
3. $X \perp\!\!\!\perp \tau : P(X = x \mid \tau) = P(X = x), \quad \forall x$ (*strong ignorability*)
4. $X \perp\!\!\!\perp \tau \mid Z : P(X = x \mid Z, \tau) = P(X = x \mid Z), \quad \forall x$

Regressively Independent Outcome Conditions

5. $Y \vdash C_X \mid X : E(Y \mid X, C_X) = E(Y \mid X), \quad \forall x$
6. $Y \vdash C_X \mid X, Z : E(Y \mid X, C_X) = E(Y \mid X, Z), \quad \forall x$

$$\{X \perp\!\!\!\perp C_X\} \vee \{Y \vdash C_X \mid X\} \Rightarrow \{X \perp\!\!\!\perp \tau\} \Rightarrow E(Y \mid X) \text{ is } C_X\text{-unbiased}$$

$$\{X \perp\!\!\!\perp C_X \mid Z\} \vee \{Y \vdash C_X \mid X, Z\} \Rightarrow \{X \perp\!\!\!\perp \tau\} \Rightarrow E(Y \mid X, Z) \text{ is } (C_X, Z)\text{-unbiased}$$

Direct Effects

Stochastic Independence Conditions

7. $X \perp\!\!\!\perp C_{X,t_M} \mid M : P(X = x \mid C_{X,t_M}) = P(X = x \mid M)$
8. $X \perp\!\!\!\perp C_{X,t_M} \mid Z_{t_M}, M : P(X = x \mid C_{X,t_M}) = P(X = x \mid M, Z_{t_M})$

Regressively Independent Outcome Conditions

9. $Y \vdash C_{X,t_M} \mid X, M : E(Y \mid X, C_{X,t_M}) = E(Y \mid X, M)$
10. $Y \vdash C_{X,t_M} \mid X, M, Z_{t_M} : E(Y \mid X, C_{X,t_M}) = E(Y \mid X, M, Z_{t_M})$

Other Definitions of Treatment Effects

Z-Conditional Causal Total Effect

$$\sum_{u} [E(Y \mid X = 1, U = u) - E(Y \mid X = 0, U = u)]\, P(U = u \mid Z = z)$$

Treatment-Conditional Average Total Effect

$$\sum_{u} [E(Y \mid X = 1, U = u) - E(Y \mid X = 0, U = u)]\, P(U = u \mid X = x^{*})$$

Average Natural Direct Effect (Pearl, 2009)

$$\sum_{u,m} [E(Y \mid X = 1, U = u) - E(Y \mid X = 0, U = u)]\, P(M = m \mid U = u) P(U = u)$$

Conclusion

- **Estimands** should be defined on the **Causality Space**: probability theory with conditional expectations and filtration
- **True outcome variable**: an alternative to potential outcome that avoids hypothetical changes in treatment variable and reference to counterfactual experiments or use of principal stratification
- **Causal treatment effects**: should be used to define the estimand
- **Causality conditions**: can be tested and used for covariate selection

Some References

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