Causal Inference

a summary

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1 General

Causal Roadmap (Petersen and van der Laan, 2014) systematic approach linking causality to statistical procedures

1. Specifying Knowledge. structural causal model (unifying counterfactual language, structural equations, & causal graphs): a set of possible data-generating processes, expresses background knowledge and its limits

2. Linking Data. specifying measured variables and sampling specifics (latter can be incorporated into the model)

3. Specifying Target. define hypothetical experiment: decide

1. variables to intervene on: one (point treatment), multiple (longitudinal, censoring/missing, (in)direct effects)
2. intervention scheme: static, dynamic, stochastic
3. counterfactual summary of interest: absolute or relative, marginal structural models, interaction, effect modification
4. population of interest: whole, subset, different population

4. Assessing Identifiability. are knowledge and data sufficient to derive estimand and if not, what else is needed?

5. Select Estimand. current best answer: knowledge-based assumptions + which minimal convenience-based asspumptions (transparency) gets as close as possible

6. Estimate. choose estimator by statistical properties, nothing causal here

7. Interpret. hierarchy: statistical, counterfactual, feasible intervention, randomized trial

Average Causal Effect $\mathrm{E}\left[Y^{a=1}\right] \neq \mathrm{E}\left[Y^{a=0}\right]$

$$\mathrm{E}\left[Y^{a}\right] = \sum_{y} y p_{Y^a}(y) \qquad \text{(discrete)}$$

$$= \int y f_{Y^a}(y) dy \qquad \text{(continuous)}$$

individual causal effect $Y_i^{a=1} \neq Y_i^{a=0}$ generally unidentifiable

null hypothesis: no average causal effect

sharp null hypothesis: no causal effect for any individual

notation A, Y: random variables (differ for individuals); a, y: particular values; counterfactual $Y^{a=1}$: Y under treatment $a = 1$

stable unit treatment value assumption (SUTVA) Y_i^a is well-defined: no interference between individuals, no multiple versions of treatment (weaker: treatment variation irrelevance)

causal effect measures typically based on means

risk difference: $\Pr\left[Y^{a=1}=1\right] - \Pr\left[Y^{a=0}=1\right]$

risk ratio: $\frac{\Pr\left[Y^{a=1}=1\right]}{\Pr\left[Y^{a=0}=1\right]}$

odds ratio: $\frac{\Pr\left[Y^{a=1}=1\right]/\Pr\left[Y^{a=1}=0\right]}{\Pr\left[Y^{a=0}=1\right]/\Pr\left[Y^{a=0}=0\right]}$

number needed to treat (NNT) to save 1 life: -1/risk difference

sources of random error: sampling variability (use consistent estimators), nondeterministic counterfactuals

association compares $E\left[Y|A=1\right]$ and $E\left[Y|A=0\right]$, **causation** compares $E\left[Y^{a=1}\right]$ and $E\left[Y^{a=0}\right]$ (whole population)

Target Trial emulating an ideal randomized experiment explicitly formulate target trial & show how it is emulated → less vague causal question, helps spot issues

missing data problem unknown counterfactuals

randomized experiments: missing completely at random → exchangeability (= exogeneity as treatment is exogenous)

ideal randomized experiment: no censoring, double-blind, well-defined treatment, & adherence → association is causation

pragmatic trial: no placebo/blindness, realistic monitoring

PICO (population, intervention, comparator, outcome): some components of target trial

three types of causal effects:

intention-to-treat effect (effect of treatment assignment)

per-protocol effect (usually dynamic when toxicity arises)

other intervention effect (strategy changed during follow-up)

controlled direct effects: effect of A on Y not through B

natural direct effect A on Y if $B^{a=0}$ (cross-world quantity)

principal stratum effect A on Y for subset with $B^{a=0} = B^{a=1}$

crossover experiment: sequential treatment & outcome t=0, 1 individual causal effect $Y_{it}^{a_t=1} - Y_{it}^{a_t=0}$ only identifiable if: no carryover effect, effect $\perp\!\!\!\perp$ time, outcome $\perp\!\!\!\perp$ time

time zero if eligibility at multiple t (observational data): earliest, random t, all t (adjust variance with bootstrapping)

grace periods: usually treatment starts x months after first eligible, if death before: randomly assign strategy/copy into both

Identifiability Conditions hold in ideal experiments

consistency counterfactuals correspond to data $Y = Y^A$: if $A = a$, then $Y^a = Y$ for each individual

- precise definition of Y^a via specifying a (sufficiently well-defined a maybe impossible (effect of DNA before it was discovered), relies on expert consensus)
- linkage of counterfactuals to data (a must be seen in data)

positivity $\Pr\left[A = a|L = l\right] > 0 \ \forall\, l$ with $\Pr\left[L = l\right] > 0$;

$$f_L(l) \neq 0 \Rightarrow f_{A|L}(a|l) > 0 \ \forall a, l$$

- structural violations (inference not on full population)
- random variability (smooth over with parametric models)

can sometimes be empirically verified (if all is seen in data)

exchangeability unverifiable without randomization

- *marginal:* $Y^a \perp\!\!\!\perp A \mathrel{\widehat{=}}$ randomized experiment, counterfactuals are missing completely at random (MCAR)
- *conditional:* $Y^a \perp\!\!\!\perp A|L \mathrel{\widehat{=}}$ conditionally randomized, counterfactuals are missing at random (MAR)

alternative definition: $\Pr\left[A = 1|Y^{a=0}, L\right] = \Pr\left[A = 1|L\right]$

additional conditions:

correct measurement mismeasurement of A, Y, L results in bias

correct model specification models $\overset{\text{may}}{\rightarrow}$ misspecification bias

Effect Modification A on Y varies across levels of V

null average causal effect ≠ null causal effect per subgroup

population characteristics: causal effect measure is actually "effect in a population with a particular mix of effect modifiers"

transportability: extrapolation of effect to another population (issues: effect modification, versions of treatment, interference)

effects conditional on V may be more transportable

types: additive/multiplicative scale, qualitative (effect in opposite directions)/quantitative, surrogate/causal

calculation:

- *stratify* by V then standardize/IP weight for L,
- L as *matching* factor (ensures positivity, difficult if high-dimensional L)

collapsibility: causal risk difference and ratio are weighted averages of stratum-specific risks, can not be done for odds ratio

Interaction effects of joint interventions A and E

$$\Pr\left[Y^{1,1}{=}1\right] - \Pr\left[Y^{0,1}{=}1\right] \neq \Pr\left[Y^{1,0}{=}1\right] - \Pr\left[Y^{0,0}{=}1\right]$$

A and E have equal status and could also be considered a combined treatment AE, exchangeability for both is needed
additive scale (above): "$>$" superadditive and "$<$" subadditive;
multiplicative scale: "$>$" super- and "$<$" submultiplicative
difference to effect modification: if E is randomly assigned methods coincide, but V can not be intervened on as E can
monotonicity effect is either nonnegative or nonpositive $\forall i$
sufficient component-cause framework pedagogic model
response types for binary A: helped, immune, hurt, doomed; for binary A and E: 16 types
(minimal) sufficient causes:

- (minimal) U_1 together with $A = 1$ ensure $Y = 1$
- (minimal) U_2 together with $A = 0$ ensure $Y = 1$

sufficient cause interaction: A and E appear together in a minimal sufficient cause

causal diagrams chapter 6, include swigs from 7.5 and that one technical point

more on SWIGS p 242ff

confounding chapter 7

selection bias chapter 8

measurement bias chapter 9

random variabilty chapter 10

2 Models

Modeling data are a sample from the target population

estimand:	quantity of interest,	e. g. $\mathrm{E}[Y\|A=a]$
estimator:	function to use,	e. g. $\widehat{\mathrm{E}}[Y\|A=a]$
estimate:	apply function to data,	e. g. 4.1

model: a priori restriction of joint distribution/dose-response curve; *assumption:* no model misspecification (usually wrong)

non-parametric estimator: no restriction (saturated model) = *Fisher consistent estimator* (entire population data → true value)

parsimonious model: few parameters estimate many quantities

bias-variance trade-off:
wiggliness ↑ → misspecification bias ↓, CI width ↑

Variable Selection can induce bias if L includes:

(decendant of) collider:	*selection bias under the null*
noncollider effect of A:	*selection bias under the alternative*
mediator:	*overadjustment for mediators*

temporal ordering is not enough to conclude anything

bias amplification: e.g. by adjusting for an instrument Z (can also reduce bias)

Machine Learning L is high-dimensional
use lasso or ML for IP weighting/standardization
but: ML does not guarantee elimination of confounding and has largely unknown statistical properties
→ **doubly robust estimator:** consistent if bias $< \frac{1}{\sqrt{n}}$
sample splitting: train estimators on training sample, use resulting estimators for doubly robust method on estimation sample (CIs on estimation sample are valid, but n halved)
cross-fitting: do again the other way round, average the two estimates, get CI via bootstrapping
problems: unclear choice of algorithm, is bias small enough?

Super Learning (Van der Laan et al., 2007, 2011)
oracle selector: select best estimator of set of learners Z_i
discrete super learner: select algorithm with smallest cross-validated error (converges to oracle for large sample size)
super learner: improves asymptotically on discrete version
$\mathrm{logit}(Y=1|Z) = \sum_i \alpha_i Z_i$, with $0 < \alpha_i < 1$ and $\sum \alpha_i = 1$
weights α_i are determined inside the cross-validation; for the prediction, Z_i trained on the full data set are used
can be cross-validated itself to check for overfitting (unlikely)

2.1 Traditional Methods

Stratification calculate risk for each stratum of L
only feasible if enough data per stratum

Outcome regression chapter 15

instrumental variable estimation chapter 16

causal survival analysis chapter 17 (and technical point 22.3)

2.2 G-Methods

G-Methods *g*eneralized treatment contrasts: adjust for (surrogate) confounders L

- **standardization** two types of g-formula
- **IP weighting** also g-formula
- **g-estimation:** not needed unless longitudinal

Standardization plug-in (or parametric if so) g-formula

$$\mathrm{E}[Y^a] = \overbrace{\mathrm{E}\left[\mathrm{E}[Y|A{=}a, L{=}l]\right]}^{\text{conditional expectation}} = \overbrace{\int \mathrm{E}[Y|L=l, A=a]\, f_L[l]\, dl}^{\text{joint density estimator}}$$

weighted average of stratum-specific risks; unknowns can be estimated non-parametrically or modeled

no need to estimate $f_L[l]$/integrate as empirical distribution can be used: estimate outcome model → predict counterfactuals on whole dataset → average the results (→ CI by bootstrapping)

for discrete L $\mathrm{E}[Y|A=a] = \sum_l \mathrm{E}[Y|L=l, A=a]\Pr[L=l]$

time-varying standardize over all possible $\bar{l}$-histories
simulates joint distribution of counterfactuals $\left(Y^{\bar{a}}, \bar{L}^{\bar{a}}\right)$ for $\bar{a}$
joint density estimator (jde)

discrete: $\mathrm{E}\left[Y^{\bar{a}}\right] = \sum_{\bar{l}} \mathrm{E}\left[Y|\bar{A}=\bar{a}, \bar{L}=\bar{l}\right] \prod_{k=0}^{K} f\left(l_k|\bar{a}_{k-1}, \bar{l}_{k-1}\right)$

continuous: $\int f(y|\bar{a}, \bar{l}) \prod_{k=0}^{K} f\left(l_k|\bar{a}_{k-1}, \bar{l}_{k-1}\right) dl$

for *stochastic strategies* multiply with $\prod_{k=0}^{K} f^{int}\left(a_k|\bar{a}_{k-1}, \bar{l}_k\right)$

estimation (Young et al., 2011; Schomaker et al., 2019)
1. model $f\left(l_k|\bar{a}_{k-1}, \bar{l}_{k-1}\right)$ and $\mathrm{E}\left[Y|\bar{A}=\bar{a}, \bar{L}=\bar{l}\right]$
2. simulate data forward in time:
   at $k=0$: use empirical distribution of L_0 (observed data)
   at $k>0$: set $\bar{A}=\bar{a}$, *draw* from models estimated in 1.
3. calculate mean of $\hat{Y}^{\bar{a}}_{K,i}$ (bootstrap for CI)

iterated conditional expectation (ice)

$$\mathrm{E}\left[Y^{\bar{a}}_T\right] = \mathrm{E}\left[\mathrm{E}\left[\mathrm{E}\left[\ldots\mathrm{E}\left[Y_T|\bar{A}_{T-1}{=}\bar{a}_{T-1}, \bar{L}_T\right]\ldots|\bar{A}_0{=}a_0, L_1\right]|L_0\right]\right]$$

estimation (Schomaker et al., 2019)
1. model inside out: Q_T=E$\left[Y_T|\bar{A}_{T-1},\bar{L}_T\right]$ to Q_0=E$\left[Q_1|\bar{L}_0\right]$, predict Q_t with $\bar{A}=\bar{a}$ in each step
2. calculate mean of $\hat{Q}^{\bar{a}}_{0,i}$ (bootstrap for CI)

g-null paradox even if the sharp null holds, model misspecification can lead to it being falsely rejected

Proof: for $L_0 \to A_0 \to Y_0 \to L_1 \to A_1 \to Y_1$, $\bar{a}=(a_0,a_1)$

$$\mathrm{E}\left[Y_1^{\bar{a}}\right] \overset{\text{CE}}{=} \mathrm{E}\left[\mathrm{E}\left[Y_1^{\bar{a}}|A_0{=}a_0,L_0\right]\right]$$

(ice)
$$\overset{\text{CE*}}{=} \mathrm{E}\left[\mathrm{E}\left[\mathrm{E}\left[Y_1|\bar{L},\bar{A}{=}\bar{a},Y_0\right]|A_0{=}a_0,L_0\right]\right]$$
$$\overset{\text{LTP}}{=} \mathrm{E}\left[\sum\nolimits_{l_1}\mathrm{E}\left[Y_1|A_0{=}a_0,\bar{L},Y_0\right]\Pr\left[l_1|a_0,l_0,y_0\right]\right]$$
$$\overset{\text{LTP}}{=} \sum\nolimits_{l_0}\left[\sum\nolimits_{l_1}\mathrm{E}\left[Y_1|A_0{=}a_0,\bar{L},Y_0\right]\Pr\left[l_1|a_0,l_0,y_0\right]\right]\Pr\left[l_0\right]$$

(jde)
$$\overset{\text{sum}}{=} \sum\nolimits_{\bar{l}}\mathrm{E}\left[Y_1|A_0{=}a_0,\bar{L},Y_0\right]\Pr\left[l_1|a_0,l_0\right]\Pr\left[l_0\right]$$

CE: conditional expectation; *: exchangeability;
LTP: law of total probability

Marginal Structural Models association is causation in the IP weighted pseudo-population

associational model $\mathrm{E}\left[Y|A\right]=$ causal model $\mathrm{E}\left[Y^a\right]$

step 1: estimate/model $f\left[A|L\right]$ (and $f\left[A\right]$) $\to$ get $(S)W^A$
step 2: estimate regression parameters for pseudo-population
effect modification variables V can be included (e. g. $\beta_0+\beta_1 a+\beta_2 Va+\beta_3 V$; technically not marginal anymore), $SW^A(V)=\frac{f[A|V]}{f[A|L]}$ more efficient than SW^A

Censoring measuring joint effect of A and C

$\mathrm{E}\left[Y^{a,c=0}\right]$ is of interest

standardization $\mathrm{E}\left[Y|A=a\right]=\int \mathrm{E}\left[Y|L{=}l,A{=}a,C{=}0\right]dF_L\left[l\right]$

IP weights $W^{A,C}=W^A\times W^C$ (uses n) or $SW^{A,C}=SW^A\times SW^C$ (uses $n^{c=0}$)

g-estimation can only adjust for confounding, not selection bias $\to$ use IP weights

G-Estimation (additive) structural nested models

$$\operatorname{logit}\Pr\left[A=1|H(\psi^\dagger),L\right]=\alpha_0+\alpha_1 H(\psi^\dagger)+\alpha_2 L$$
$$H(\psi^\dagger)=Y-\psi_\dagger A$$

find $\psi^\dagger$ which renders $\alpha_1=0$; 95 %-CI: all $\psi^\dagger$ for which $p>0.05$
closed-form solution for linear models
derivation: $H(\psi^\dagger)=Y^{a=0}$

$$\operatorname{logit}\Pr\left[A=1|Y^{a=0},L\right]=\alpha_0+\alpha_1 Y^{a=0}+\alpha_2 L$$

$Y^{a=0}$ unknown, but because of exchangeability α_1 should be zero

$$Y^{a=0}=Y^a-\psi_1 a$$

equivalent to $Y^{a=0}=Y^{a=1}-\psi_1$, but using no counterfactuals
structural nested mean model

additive: $\mathrm{E}\left[Y^a-Y^{a=0}|A=a,L\right]=\beta_1 a\,(+\beta_2 aL)$

multiplicative: $\log\left(\frac{\mathrm{E}\left[Y^a|A=a,L\right]}{\mathrm{E}\left[Y^{a=0}|A=a,L\right]}\right)=\beta_1 a\,(+\beta_2 aL)$

multiplicative is preferred if Y always positive, but does not extend to longitudinal case
semi-parametric: agnostic about β_0 and effect of $L\to$ robust ↑
no time-varying: no nesting; model equals marginal structural models with missing β_0,β_3 (unspecified "no treatment")

sensitivity analysis: unmeasured confounding ($\alpha_1\neq 0$) can be examined: do procedure for different values of $\alpha_1\to$ plot α_1 vs. $\psi^\dagger\to$ how sensitive is estimate to unmeasured confounding?
effect modification: add V in both g-estimation equations
doubly robust estimators exist

IP Weighting *i*nverse *p*robability of treatment (g-formula)

$$\mathrm{E}\left[Y^a\right]=\mathrm{E}\left[\frac{I(A=a)Y}{f\left[A|L\right]}\right];W^A=\frac{1}{f\left[A|L\right]};SW^A=\frac{f(A)}{f\left[A|L\right]}$$

unknowns can be estimated non-parametrically or modeled
pseudo-population: everyone is treated & untreated ($L\not\to A$)
FRCISTG *(fully randomized causally interpreted structured graph)*: probability tree for $L\to A\to Y$, can be used to calculate/visualize simulation of values for A
for discrete $\boldsymbol{A,L}$ $f\left[a|l\right]=\Pr\left[A=a,L=l\right]$
estimators: Horvitz-Thompson; Hajek (modified version)
stabilized weights $\boldsymbol{SW^A}$ should have an average of 1 (check!)
$\to$ pseudo-population same size $\to$ CI width ↓

Standardization and IP Weighting are equivalent, ***but*** if modeled, different "no misspecification" assumptions:
standardization: outcome model
IP weighting: treatment model

doubly robust estimators: reduce model misspecification bias, consistent if either model is correct; ***e. g.:***
1. fit outcome regression with variable $R=\begin{cases}+W^A & \text{if } A{=}1\\ -W^A & \text{if } A{=}0\end{cases}$
2. standardize by averaging

2.2.1 Time-varying A

IP Weighting

$$W^{\bar{A}}=\prod_{k=0}^{K}\frac{1}{f\left(A_k|\bar{A}_{k-1},\bar{L}_k\right)}$$

$$SW^{\bar{A}}=\prod_{k=0}^{K}\frac{f\left(A_k|\bar{A}_{k-1}\right)}{f\left(A_k|\bar{A}_{k-1},\bar{L}_k\right)}$$

Doubly Robust Estimator sequential estimation
1. estimate $\hat{f}\left(A_m|\bar{A}_{m-1},\bar{L}_m\right)$ (e. g. logistic model), use it to calculate at each time m: $\widehat{W}^{\bar{A}_m}=\prod_{k=0}^{m}\frac{1}{\hat{f}\left(A_k|\bar{A}_{k-1},\bar{L}_k\right)}$ and modified IP weights at m: $\widehat{W}^{\bar{A}_{m-1},a_m}=\frac{\widehat{W}^{\bar{A}_{m-1}}}{\hat{f}\left(a_m|\bar{A}_{m-1},\bar{L}_m\right)}$
2. with $\widehat{T}_{K+1}:=Y$, recursively for $m=K,K-1,...,0$:
   (a) fit outcome regression on $\widehat{T}_{m+1}$ with variable $\widehat{W}^{\bar{A}_m}$
   (b) calculate $\widehat{T}_m$ using the outcome model with $\widehat{W}^{\bar{A}_{m-1},a_m}$
3. calculate standardized mean outcome $\widehat{\mathrm{E}}\left[Y^{\bar{a}}\right]=\mathrm{E}\left[\widehat{T}_0\right]$

valid, if treatment or outcome model correct, or treatment correct until k and outcome otherwise ($k+1$ robustness)

G-Estimation nested equations: for each time k
strutural nested mean models separate effect of each a_k

$$\mathrm{E}\left[Y^{\bar{a}_{k-1},a_k,\underline{0}_{k+1}}-Y^{\bar{a}_{k-1},\underline{0}_{k+1}}|\bar{L}^{\bar{a}_{k-1}}=\bar{l}_k,\bar{A}_{k-1}=\bar{a}_{k-1}\right]=$$
$$a_k\gamma_k\left(\bar{a}_{k-1},\bar{l}_k,\beta\right)$$

calculations

$$H_k\left(\psi^\dagger\right)=Y-\sum_{j=k}^{K}A_j\gamma_j\left(\bar{A}_{j-1},\bar{L}_j,\psi^\dagger\right)$$

function γ_j can be, e. g. constant (ψ_1), time-varying only ($\psi_1+\psi_2 k$), or dependent on treatment/covariate history

$$\text{logit}\Pr\left[A_k = 1 | H_k\left(\psi^\dagger\right), \bar{L}_k, \bar{A}_{k-1}\right] =$$

$$\alpha_0 + \alpha_1 H_k\left(\psi^\dagger\right) + \alpha_2 w_k\left(\bar{L}_k, \bar{A}_{k-1}\right)$$

find α_1 that is closest to zero

a closed form estimator exists for the linear case

Censoring $\bar{C}$: monotonic type of missing data

standardization:

$\int f(y|\bar{a}, \bar{c}{=}\bar{0}, \bar{l}) \prod_{k=0}^{K} dF\left(l_k|\bar{a}_{k-1}, c_{k-1}{=}0, \bar{l}_{k-1}\right)$

IP weighting:

$$SW^{\bar{C}} = \prod_{k=1}^{K+1} \frac{1 \cdot \Pr\left(C_k = 0 | \bar{A}_{k-1}, C_{k-1} = 0\right)}{\Pr\left(C_k = 0 | \bar{A}_{k-1}, C_{k-1} = 0, \bar{L}_k\right)}$$

2.3 Advanced Methods

TMLE *t*argeted *m*inimum *l*oss-based *e*stimation

$$O = (W, A, Y) \sim P_0$$

target $\Psi(P_0) = \Psi(\bar{Q}_0, Q_{W,0}) = \psi_0$,

often: $\text{E}_{W,0}\left[\text{E}_0(Y|A{=}1, W) - \text{E}_0(Y|A{=}0, W)\right]$

first step: outcome model $\bar{Q}_n^0(A, W)$ estimating $\bar{Q}_0$ (part of P_0)

- super learning is often used here, but leads to a biased estimate
- not all of $f(Y|A, W)$ needs to be estimated, just the relevant portion, *typically average outcome* $\text{E}_0(Y|A, W) \rightarrow$ efficiency $\uparrow$

second step: update $\bar{Q}_n^0(A, W)$ to $\bar{Q}_n^1(A, W)$ using treatment model g_n estimating $g_0 = P_0(A|W)$

1. model g_n, super learning is a popular choice here, too
2. calculate n clever covariates: $H_n^*(A, W) = \begin{cases} \frac{1}{g_n(1|W)} & \text{if } A_i{=}1 \\ \frac{1}{g_n(0|W)} & \text{if } A_i{=}0 \end{cases}$
3. update $\bar{Q}_n^0$, by estimating ϵ_n with offset logistic regression: $\text{logit}\bar{Q}_n^1(A, W) = \text{logit}\bar{Q}_n^0(A, W) + \epsilon_n H_n^*(A, W)$ (converges after first update), then calculate counterfactuals

- goal: bias reduction, get optimal bias-variance trade-off
- removes all asymptotic bias, if consistent estimator is used here

third step: use empirical distribution for $Q_{W,0}$ in a substitution estimator: $\psi_n^{TMLE} = \frac{1}{n}\sum_{i=1}^{n}\left[\bar{Q}_n^1(1, W_i) - \bar{Q}_n^1(0, W_i)\right]$

advantages: doubly robust (consistent if either outcome or treatment model is correctly specified), asymptotically efficient (if both are correct), substition estimator (more robust to outliers and sparsity)

closed form inference based on the influence curve:

$$IC_n^*(O_i) = \overbrace{\left[\frac{\mathbb{1}(A_i = 1)}{g_n(1, W_i)} - \frac{\mathbb{1}(A_i = 0)}{g_n(0, W_i)}\right]\left[Y - \bar{Q}_n^1(A_i, W_i)\right]}^{a}$$

$$+ \overbrace{\bar{Q}_n^1(1, W_i) - \bar{Q}_n^1(0, W_i) - \psi_{TMLE,n}}^{b}$$

TMLE sets the mean of the IC, $\overline{IC}_n$, to zero (b has already mean zero, see third step, the first part of a is the clever covariate)

sample variance is then: $S^2(IC_n) = \frac{1}{n}\sum_{i=1}^{n}\left(IC_n(o_i) - \bar{IC}_n\right)^2$

standard error of estimator: $\sigma_n = \sqrt{\frac{S^2(IC_n)}{n}}$

95% CI: $\psi_{TMLE,n} \pm z_{0.975}\frac{\sigma_n}{\sqrt{n}}$; p-value: $2\left[1 - \Phi\left(\left|\frac{\psi_{TMLE,n}}{\sigma_n/\sqrt{n}}\right|\right)\right]$

$$\mathcal{L}(O) = \overbrace{\Pr(Y|A, W)}^{Q_Y}\overbrace{\Pr(A|W)}^{g}\overbrace{\Pr(W)}^{Q_W}$$

$H(A, W)$ depends on target parameter and loss function but is a function of the propensitiy score update initial fit $\bar{Q}_n^* = \bar{Q}_n^0 + \hat{\epsilon}H(A, W)$

valid inference, good finite sample performance,

$H(A, W)$ comes from the influence curve, targeting ensures mean of efficient influence curve $D^*(P)$ is zero

TMLE solves $P_n D^*(P_n^*) = 0$

TMLE is a substitution estimator $\psi_n^{TMLE} = \frac{1}{2}\sum_{i=1}^{n}\bar{Q}_n^*(1, W_i) - \frac{1}{2}\sum_{i=1}^{n}\bar{Q}_n^*(0, W_i)$ therefore mean of b is zero

targeting step makes sure a also has mean zero

MLE solves $\sum_{i=1}^{n} H(A_i, W_i)\left[Y_i - \bar{Q}_n^*(A_i, W_i)\right] = 0$ where $\bar{Q}_n^*(A_i, W_i) = \hat{\epsilon}H(A, W) + \bar{Q}_n^0$ therefore obvious choice: $H(A, W) = \frac{A}{g(1,W)} - \frac{1-A}{g(0,W)}$

influence curve based inference: asymptotic linearity $\sqrt{n}\left(\psi_n^{TMLE} - \psi_0\right) \xrightarrow{D} \text{N}(0, \sigma^2)$

3 Longitudinal Data

Time-Varying Treatments compare 2 treatments
treatment history up to k: $\bar{A}_k = (A_0, A_1, ..., A_k)$
shorthand: always treated $\bar{A} = \bar{1}$, never treated $\bar{A} = (\bar{0})$

static strategy: $g = [g_0(\bar{a}_{-1}), ..., g_K(\bar{a}_{K-1})]$

dynamic strategy: $g = \left[g_0(\bar{l}_0), ..., g_K(\bar{l}_K)\right]$

stochastic strategy: non-deterministic g

optimal strategy is where $\mathrm{E}[Y^g]$ is maximized (if high is good)

Sequential Identifiability sequential versions of

exchangability: $Y^g \perp\!\!\!\perp A_k | \bar{A}_{k-1} \ \forall g, k = 0, 1, ..., K$

conditional exchangeability:

$\left(Y^g, L^g_{k+1}\right) \perp\!\!\!\perp A_k | \bar{A}_{k-1} = g\left(\bar{L}_k\right), \bar{L}^k \ \forall g, k = 0, 1, ..., K$

positivity: $f_{\bar{A}_{k-1}, \bar{L}_k}(\bar{a}_{k-1}, \bar{l}_k) \neq 0 \ \Rightarrow$

$$f_{A_k | \bar{A}_{k-1}, \bar{L}_k}(a_k | \bar{a}_{k-1}, \bar{l}_k) > 0 \ \forall \left(\bar{a}_{k-1}, \bar{l}_k\right)$$

consistency:

$Y^{\bar{a}} = Y^{\bar{a}^*}$ if $\bar{a} = \bar{a}^*$; $\quad Y^{\bar{a}} = Y$ if $\bar{A} = \bar{a}$;

$$\bar{L}^{\bar{a}}_k = \bar{L}^{\bar{a}^*}_k \text{ if } \bar{a}_{k-1} = \bar{a}^*_{k-1}; \qquad \bar{L}^{\bar{a}}_k = \bar{L}_k \text{ if } \bar{A}_{k-1} = \bar{a}_{k-1}$$

generalized backdoor criterion (static strategy): all backdoors into A_k (except through future treatments) are blocked $\forall k$

static sequential exchangeability for $Y^{\bar{a}}$

$$Y^{\bar{a}} \perp\!\!\!\perp A_k | \bar{A}_{k-1}, \bar{L}_k \quad \text{for } k = 0, 1, ..., K$$

use SWIGs to visually check d-separation

time-varying confounding $\mathrm{E}[Y^{\bar{a}} | L_0] \neq \mathrm{E}[Y | A = \bar{a}, L_0]$

Treatment-Confounder Feedback $A_0 \to L_1 \to A_1$: an unmeasured U influencing L_1 and Y turns L_1 into a collider; traditional adjustment (e. g. stratification) biased: use g-methods

g-null test sequential exchangeability & sharp null true $\Rightarrow$ $Y^g = Y \ \forall g \quad \Rightarrow \quad Y \perp\!\!\!\perp A_0 | L_0$ & $Y \perp\!\!\!\perp A_1 | A_0, L_0, L_1$; therefore: if last two independences don't hold, one assumption is violated

g-null theorem: $\mathrm{E}[Y^g] = \mathrm{E}[Y]$, if the two independences hold ($\Rightarrow$ sharp null: only if strong faithfulness (no effect cancelling))

References

If no citation is given, the information is taken from the book (Hernán and Robins, 2020)

Hernán, M. A. and Robins, J. M. (2020). *Causal inference: what if*. Boca Raton: Chapman & Hall/CRC.

Petersen, M. L. and van der Laan, M. J. (2014). Causal models and learning from data: integrating causal modeling and statistical estimation. *Epidemiology (Cambridge, Mass.)*, 25(3):418–426.

Schomaker, M., Luque-Fernandez, M. A., Leroy, V., and Davies, M.-A. (2019). Using longitudinal targeted maximum likelihood estimation in complex settings with dynamic interventions. *Statistics in medicine*, 38(24):4888–4911. ISBN: 0277-6715 Publisher: Wiley Online Library.

Van der Laan, M. J., Polley, E. C., and Hubbard, A. E. (2007). Super learner. *Statistical applications in genetics and molecular biology*, 6(1). Article 24.

Van der Laan, M. J., Rose, S., et al. (2011). *Targeted learning: causal inference for observational and experimental data*, volume 4. Springer.

Young, J. G., Cain, L. E., Robins, J. M., O'Reilly, E. J., and Hernán, M. A. (2011). Comparative effectiveness of dynamic treatment regimes: an application of the parametric g-formula. *Statistics in biosciences*, 3:119–143.