

Leveraging the causal effects of stochastic interventions to evaluate vaccine efficacy in two-phase trials

Nima Hejazi

Division of Biostatistics, and
Center for Computational Biology,
University of California, Berkeley

 nshejazi

 nhejazi

 nimahejazi.org

with D. Benkeser, M. van der Laan, H. Janes, P. Gilbert
SER: “Methods for the thorny challenges of real studies”



The burden of HIV-1

- The HIV-1 epidemic — the facts:
 - now in its fourth decade,
 - 2.5 million new infections occurring annually worldwide,
 - new infections outpace patients starting antiretroviral therapy.
- *Most efficacious* preventive vaccine: 31% reduction rate.
- **Question:** To what extent can HIV-1 vaccines be improved by modulating immunogenic CD4⁺/CD8⁺ response profiles?

HVTN 505 trial examined new antibody boost vaccines

- HIV Vaccine Trials Network's (HVTN) 505 vaccine efficacy; randomized controlled trial, $n = 2504$ (Hammer et al. 2013).
- Immunogenic response profiles only available for two-phase sample of $n = 189$ (Janes et al. 2017) due to cost limitations.
- Two-phased sampling mechanism: 100% inclusion rate if HIV-1 positive in week 28; based on matching otherwise.
- **Question:** How would HIV-1 infection risk in week 28 have changed had immunogenic response (due to vaccine) differed?

Two-phase sampling censors the complete data structure

- Complete (unobserved) data $X = (L, A, Y) \sim P_0^X \in \mathcal{M}^X$, as per the full HVTN 505 trial cohort (Hammer et al. 2013):
 - L (baseline covariates): sex, age, BMI, behavioral HIV risk;
 - A (exposure): immunogenic response profiles (CD4+, CD8+);
 - Y (outcome of interest): HIV-1 infection status at week 28.
- Observed data $O = (C, CX) = (L, C, CA, Y)$; $C \in \{0, 1\}$ is an indicator for inclusion in the two-phase sample.
- Can we use the two-phase sample ($n = 189$) to estimate causal effects in the vaccine arm ($n \approx 1400$)? How?

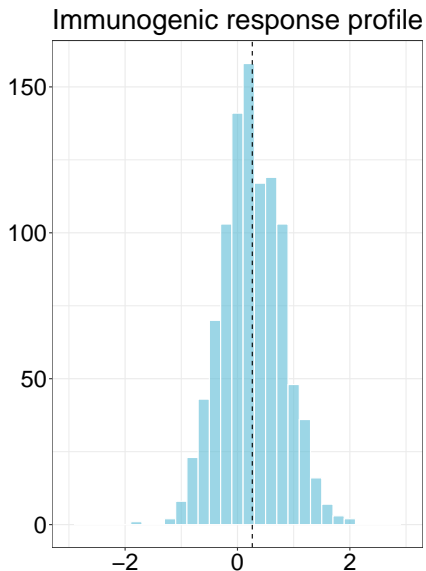
Stochastic interventions define the causal effects of shifts

- Causal estimand: counterfactual mean of HIV-1 infection under a *shifted* immunogenic response distribution.
- Díaz and van der Laan (2012; 2018): *Shift* interventions?

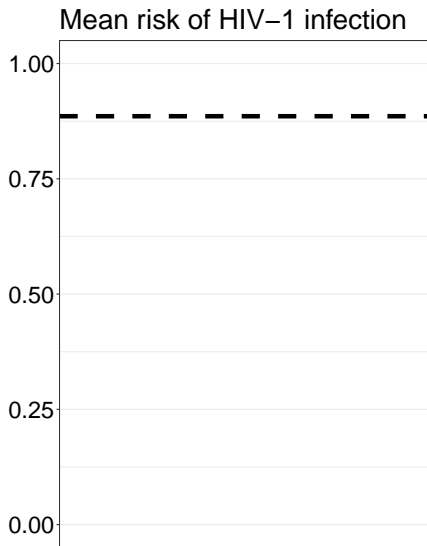
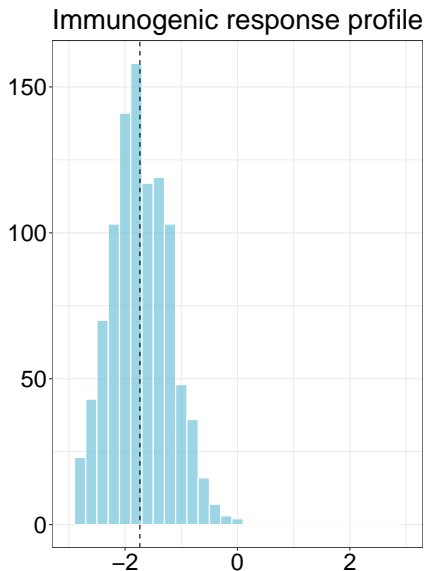
$$d(a, l) = \begin{cases} a + \delta, & \text{if plausible} \\ a, & \text{otherwise} \end{cases}$$

- Díaz and van der Laan (2012; 2018) give a statistical target parameter and influence function for the complete data case.

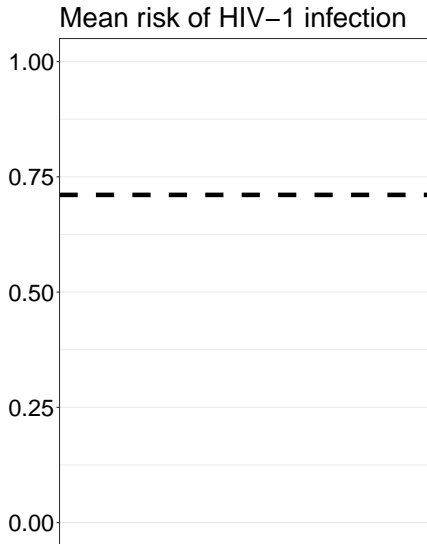
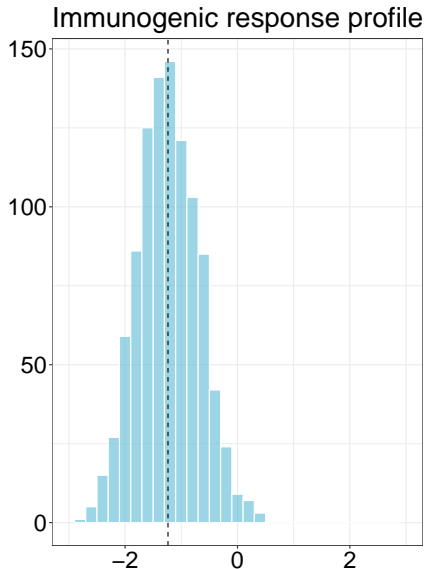
HIV-1 risk under shifted immunogenic responses



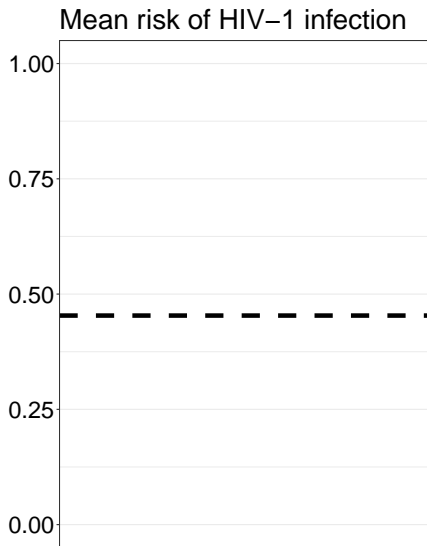
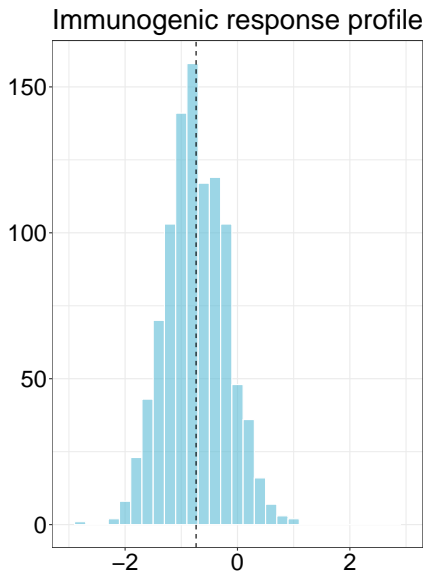
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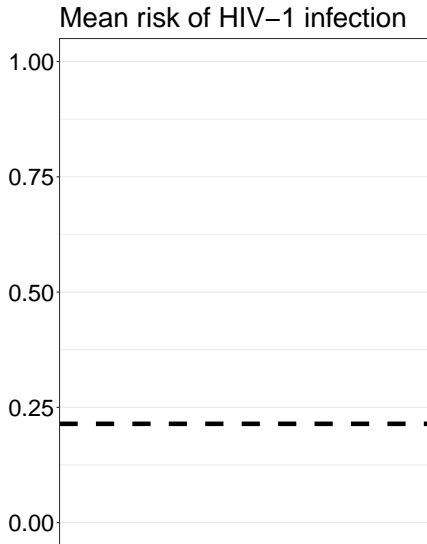
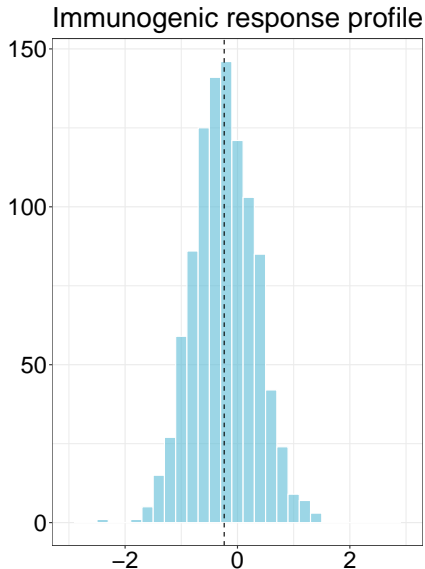
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HIV-1 risk under shifted immunogenic responses

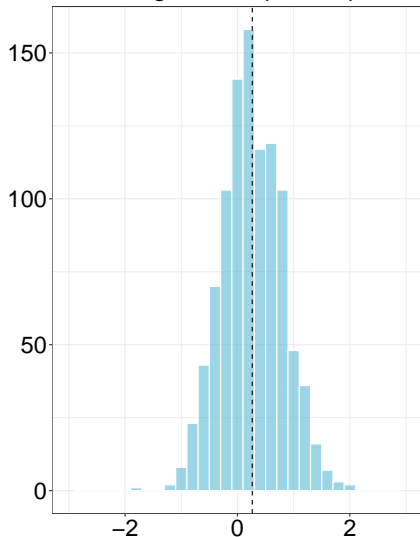


HIV-1 risk under shifted immunogenic responses

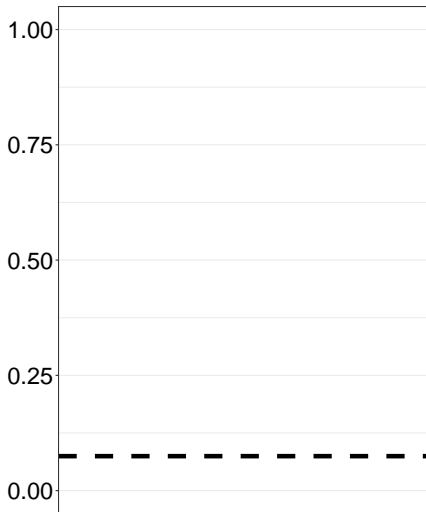


HIV-1 risk under shifted immunogenic responses

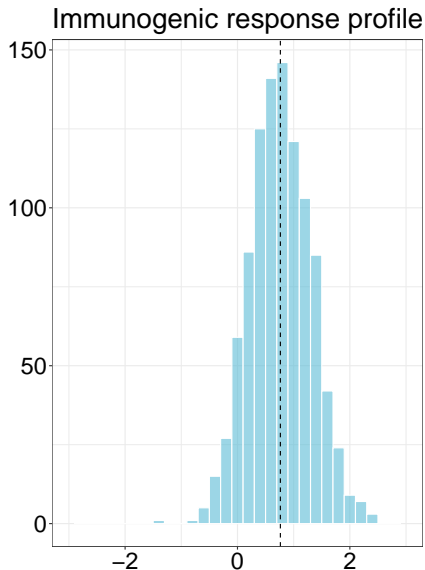
Immunogenic response profile



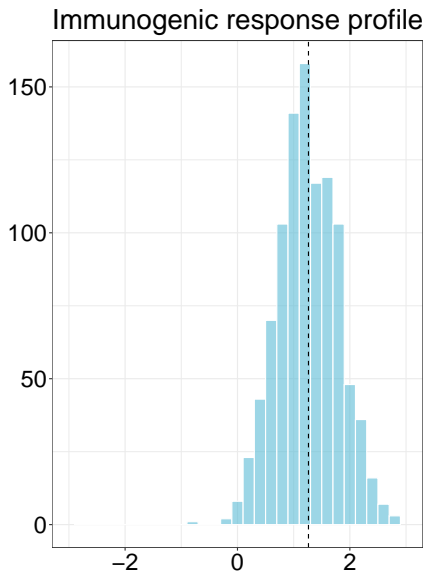
Mean risk of HIV-1 infection



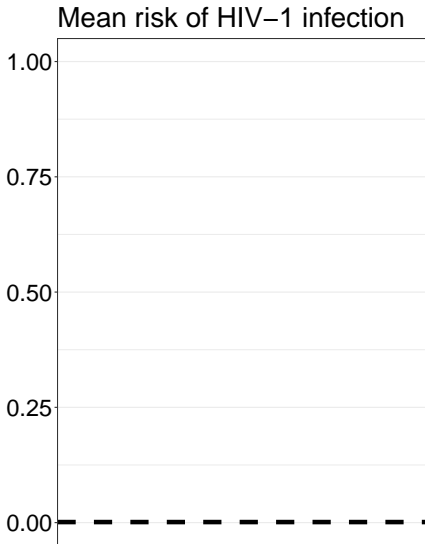
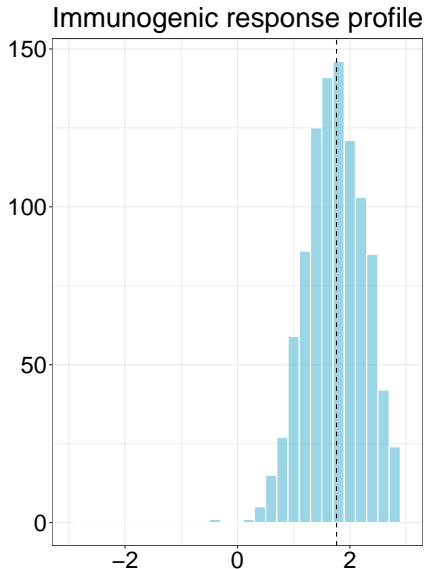
HIV-1 risk under shifted immunogenic responses



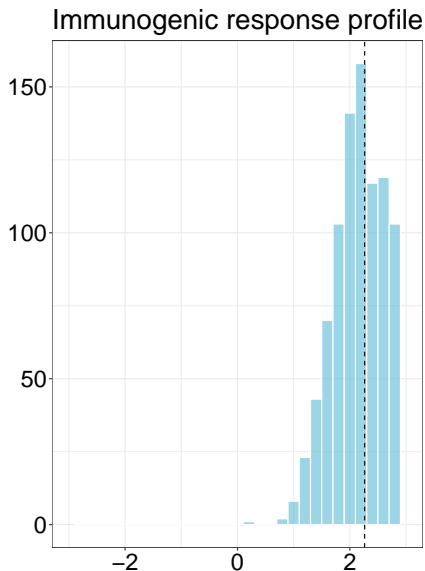
HIV-1 risk under shifted immunogenic responses



HIV-1 risk under shifted immunogenic responses



HIV-1 risk under shifted immunogenic responses



Efficient estimators in spite of two-phase sampling

- What if sampling mechanism $\pi_0(Y, L) = \mathbb{P}(C = 1 \mid Y, L)$ is not known by design? Nonparametric estimation of $\pi_0(Y, L)$?
- Building on Rose and van der Laan (2011), we provide
 - asymptotically linear and nonparametric-*efficient* estimators;
 - multiply *robust*, with two forms of double robustness;
 - Gaussian limit distributions and Wald-type confidence intervals.
- New open source software for easily using these estimators:
 - <https://github.com/nhejazi/haldensify> (densities)
 - <https://github.com/nhejazi/txshift> (one-step, TMLE)

Fighting the HIV-1 epidemic (Hejazi et al. 2020)

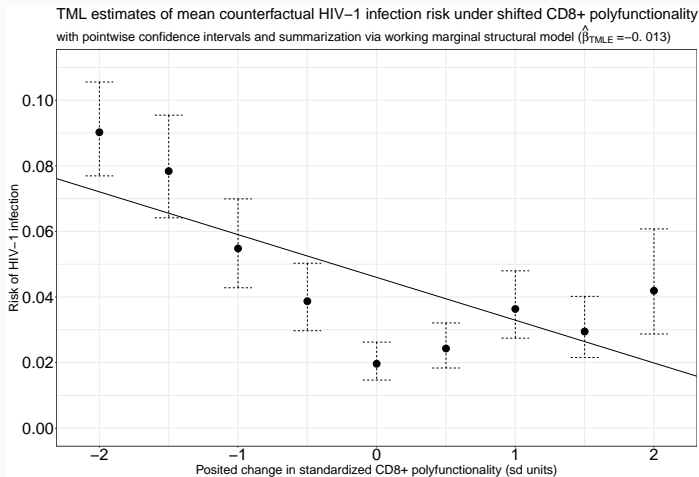


Figure 1: Analysis of HIV-1 risk as a function of CD8+ immunogenicity, using R package txshift (<https://github.com/nhejazi/txshift>.)

The big picture

- We can target immunogenic responses modulated by HIV-1 vaccines to improve future efficacy against HIV-1.
- *Stochastic* interventions constitute a flexible framework for considering **realistic** intervention policies.
- Large-scale vaccine trials often use two-phase designs — need to (carefully!) adjust for sampling complications.
- We've developed open source software for assessing the causal effects of stochastic interventions in two-phase designs.

Thank you!

 <https://nimahejazi.org>

 <https://twitter.com/nshejazi>

 <https://github.com/nhejazi>

 <https://doi.org/10.1111/biom.13375>

Appendix

From the causal to the statistical target parameter

Assumption 1: *Consistency*

$Y_i^{d(a_i, l_i)} = Y_i$ in the event $A_i = d(a_i, l_i)$, for $i = 1, \dots, n$

Assumption 2: *SUTVA*

$Y_i^{d(a_i, l_i)}$ does not depend on $d(a_j, l_j)$ for $i = 1, \dots, n$ and $j \neq i$, or lack of interference (Rubin 1978; 1980)

Assumption 3: *Strong ignorability*

$A_i \perp\!\!\!\perp Y_i^{d(a_i, l_i)} \mid L_i$, for $i = 1, \dots, n$

From the causal to the statistical target parameter

Assumption 4: *Positivity (or overlap)*

$a_i \in \mathcal{A} \implies d(a_i, l_i) \in \mathcal{A}$ for all $l \in \mathcal{L}$, where \mathcal{A} denotes the support of A conditional on $L = l_i$ for all $i = 1, \dots, n$

- This positivity assumption is not quite the same as that required for categorical interventions.
- In particular, we do not require that the intervention density place mass across all strata defined by L .
- Rather, we merely require the post-intervention quantity be seen in the observed data for given $a_i \in \mathcal{A}$ and $l_i \in \mathcal{L}$.

NPSEM with static interventions

- Use a nonparametric structural equation model (NPSEM) to describe the generation of X (Pearl 2009), specifically

$$L = f_L(U_L); A = f_A(L, U_A); Y = f_Y(A, L, U_Y)$$

- Implies a model for the distribution of counterfactual random variables generated by interventions on the process.
- A *static intervention* replaces f_A with a specific value a in its conditional support $A \mid L$.
- This requires specifying a particular value of the exposure under which to evaluate the outcome *a priori*.

NPSEM with stochastic interventions

- *Stochastic interventions* modify the value A would naturally assume by drawing from a modified exposure distribution.
- Consider the post-intervention value $A^* \sim G^*(\cdot \mid L)$; static interventions are a special case (degenerate distribution).
- Such an intervention generates a counterfactual random variable $Y_{G^*} := f_Y(A^*, L, U_Y)$, with distribution P_0^δ .
- We aim to estimate $\psi_{0,\delta} := \mathbb{E}_{P_0^\delta}\{Y_{G^*}\}$, the counterfactual mean under the post-intervention exposure distribution G^* .

Stochastic interventions for the causal effects of shifts

- Díaz and van der Laan (2012; 2018)'s *stochastic* interventions

$$d(a, l) = \begin{cases} a + \delta, & a + \delta < u(l) \quad (\text{if plausible}) \\ a, & a + \delta \geq u(l) \quad (\text{otherwise}) \end{cases}$$

- Our estimand is $\psi_{0,d} := \mathbb{E}_{P_0^d}\{Y_{d(A,L)}\}$, mean of $Y_{d(A,L)}$.
- Statistical target parameter is $\Psi(P_0^X) = \mathbb{E}_{P_0^X}\bar{Q}(d(A, L), L)$, counterfactual mean of the *shifted* outcome mechanism.
- For HVTN 505, $\psi_{0,d}$ is the counterfactual risk of HIV-1 infection, had the observed value of the immune response been altered under the rule $d(A, L)$ defining $G^*(\cdot \mid L)$.

Literature: Díaz and van der Laan (2012)

- *Proposal*: Evaluate outcome under an altered *intervention distribution* — e.g., $P_\delta(g_0)(A = a \mid L) = g_0(a - \delta(L) \mid L)$.
- Identification conditions for a statistical parameter of the counterfactual outcome $\psi_{0,d}$ under such an intervention.
- Show that the causal quantity of interest $\mathbb{E}_0\{Y_{d(A,L)}\}$ is identified by a functional of the distribution of X :

$$\psi_{0,d} = \int_{\mathcal{L}} \int_{\mathcal{A}} \mathbb{E}_{P_0^X}\{Y \mid A = d(a, l), L = l\} \cdot q_{0,A}^X(a \mid L = l) \cdot q_{0,L}^X(l) d\mu(a) d\nu(l).$$

- Provides a derivation based on the efficient influence function (EIF) with respect to the nonparametric model \mathcal{M} .

Literature: Haneuse and Rotnitzky (2013)

- *Proposal*: Characterization of stochastic interventions as *modified treatment policies* (MTPs).
- Assumption of *piecewise smooth invertibility* allows for the intervention distribution of any MTP to be recovered:

$$g_{0,\delta}(a \mid l) = \sum_{j=1}^{J(l)} I_{\delta,j} \{h_j(a, l), l\} g_0 \{h_j(a, l) \mid l\} h'_j(a, l)$$

- Such intervention policies account for the natural value of the intervention A directly yet are interpretable as the imposition of an altered intervention mechanism.
- Identification conditions for assessing the parameter of interest under such interventions appear technically complex (at first).

Literature: Young et al. (2014)

- Establishes equivalence between g-formula when proposed intervention depends on natural value and when it does not.
- This equivalence leads to a sufficient positivity condition for estimating the counterfactual mean under MTPs via the same statistical functional studied in Díaz and van der Laan (2012).
- Extends earlier identification results, providing a way to use the same statistical functional to assess $\mathbb{E}Y_{d(A,L)}$ or $\mathbb{E}Y_{d(L)}$.
- The authors also consider limits on implementing shifts $d(A, L)$, and address working in a longitudinal setting.

Literature: Díaz and van der Laan (2018)

- Builds on the original proposal, accomodating MTP-type shifts $d(A, L)$ proposed after their earlier work.
- To protect against positivity violations, considers a specific shifting mechanism:

$$d(a, l) = \begin{cases} a + \delta, & a + \delta < u(l) \\ a, & \text{otherwise} \end{cases}$$

- Proposes an improved “1-TMLE” algorithm, with a single auxiliary covariate for constructing the TML estimator.
- Our (first) contribution: implementation of this algorithm.

Flexible, efficient estimation

- The efficient influence function (EIF) is:

$$D(P_0^X)(x) = H(a, l)(y - \bar{Q}(a, l)) + \bar{Q}(d(a, l), l) - \Psi(P_0^X).$$

- The one-step estimator corrects bias by adding the empirical mean of the estimated EIF to the substitution estimator:

$$\psi_n^+ = \frac{1}{n} \sum_{i=1}^n \bar{Q}_n(d(A_i, L_i), L_i) + D_n(O_i).$$

- The TML estimator is built by updating initial estimates of \bar{Q}_n via a (logistic) tilting model, yielding

$$\psi_n^* = \frac{1}{n} \sum_{i=1}^n \bar{Q}_n^*(d(A_i, L_i), L_i).$$

- Both estimators are CAN even when nuisance parameters are estimated via flexible, machine learning techniques.

Augmented estimators for two-phase sampling designs

- Rose and van der Laan (2011) introduce the IPCW-TMLE, to be used when observed data is subject to two-phase sampling.
- *Initial proposal*: correct for two-phase sampling by using a loss function with inverse probability of censoring weights:

$$\mathcal{L}(P_0^X)(O) = \frac{C}{\pi_0(Y, L)} \mathcal{L}^F(P_0^X)(X)$$

- When the sampling mechanism $\pi_0(Y, L)$ can be estimated by a parametric form, this procedure yields an efficient estimator.
- However, when machine learning is used (e.g., when $\pi_0(Y, L)$ is not *known by design*), this is insufficient.

Efficient estimation and multiple robustness

- Then, the IPCW augmentation must be applied to the EIF:

$$D(P_0^X)(o) = \frac{c}{\pi_0(y, l)} D^F(P_0^X)(x) - \left(1 - \frac{c}{\pi_0(y, l)}\right) \cdot \mathbb{E}(D^F(P_0^X)(x) \mid C = 1, Y = y, L = l),$$

- Expresses observed data EIF $D^F(P_0^X)(o)$ in terms of full data EIF $D^F(P_0^X)(x)$; inclusion of second term ensures efficiency.
- The expectation of the full data EIF $D^F(P_0^X)(x)$, taken only over units selected by the sampling mechanism (i.e., $C = 1$).
- A unique multiple robustness property — combinations of $(g_0(L), \bar{Q}_0(A, L)) \times (\pi_0(Y, L), \mathbb{E}(D^F(P_0^X)(x) \mid C = 1, Y, L))$.

Algorithm for TML estimation

1. Construct initial estimators g_n of $g_0(A, L)$ and Q_n of $\bar{Q}_0(A, L)$, perhaps using data-adaptive regression techniques.
2. For each observation i , compute an estimate $H_n(a_i, l_i)$ of the auxiliary covariate $H(a_i, l_i)$.

3. Estimate the parameter ϵ in the logistic regression model

$$\text{logit} \bar{Q}_{\epsilon, n}(a, l) = \text{logit} \bar{Q}_n(a, l) + \epsilon H_n(a, l),$$

or an alternative regression model incorporating weights.

4. Compute TML estimator Ψ_n of the target parameter, defining update \bar{Q}_n^* of the initial estimate \bar{Q}_{n, ϵ_n} :

$$\Psi_n = \Psi(P_n^*) = \frac{1}{n} \sum_{i=1}^n \bar{Q}_n^*(d(A_i, L_i), L_i).$$

Algorithm for IPCW-TML estimation

1. Using all observed units (X), estimate sampling mechanism $\pi(Y, L)$, perhaps using data-adaptive regression methods.
2. Using only observed units in the two-phase sample $C = 1$, construct initial estimators $g_n(A, L)$ and $\bar{Q}_n(A, L)$, weighting by the sampling mechanism estimate $\pi_n(Y, L)$.
3. With the approach described for the full data case, compute $H_n(a_i, l_i)$, and fluctuate submodel via logistic regression.
4. Compute IPCW-TML estimator Ψ_n of the target parameter, by solving the IPCW-augmented EIF estimating equation.
5. Iteratively update estimated sampling weights $\pi_n(Y, L)$ and IPCW-augmented EIF, updating TML estimate in each iteration, until $\frac{1}{n} \sum_{i=1}^n \text{EIF}_i < \frac{1}{n}$.

Key properties of TML estimators

- **Asymptotic linearity:**

$$\Psi(P_n^*) - \Psi(P_0^X) = \frac{1}{n} \sum_{i=1}^n D(P_0^X)(X_i) + o_P\left(\frac{1}{\sqrt{n}}\right)$$

- **Gaussian limiting distribution:**

$$\sqrt{n}(\Psi(P_n^*) - \Psi(P_0^X)) \rightarrow N(0, \text{Var}(D(P_0^X)(X)))$$

- **Statistical inference:**

$$\text{Wald-type confidence interval : } \Psi(P_n^*) \pm z_{1-\frac{\alpha}{2}} \cdot \frac{\sigma_n}{\sqrt{n}},$$

where σ_n^2 is computed directly via $\sigma_n^2 = \frac{1}{n} \sum_{i=1}^n D^2(\cdot)(X_i)$.

Identifying the best efficient estimator

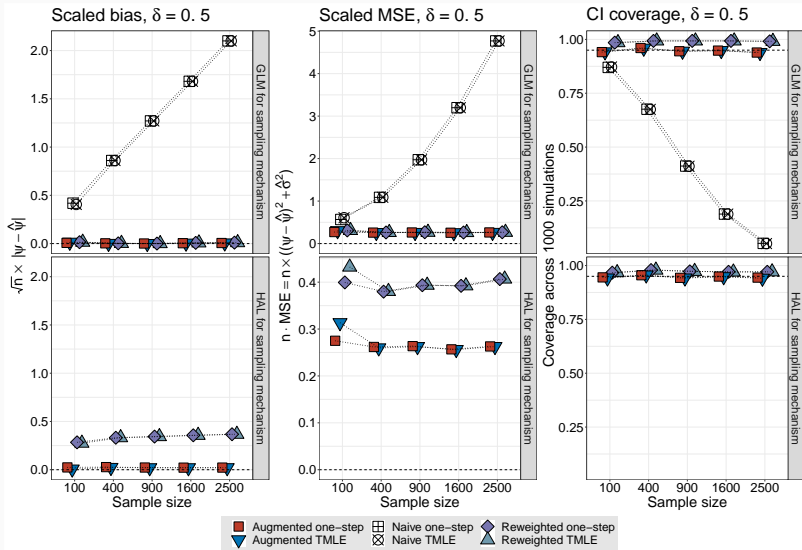


Figure 2: Relative performance of reweighted and augmented estimators.

A linear modeling perspective

- Briefly consider a simple data structure: $X = (Y, A)$; we seek to model the outcome Y as a function of A .
- To posit a linear model, consider $Y_i = \beta_0 + \beta_1 A_i + \epsilon_i$, with error $\epsilon_i \sim N(0, 1)$.
- Letting δ be a change in A , $Y_{A+\delta} - Y_A$ may be expressed

$$\begin{aligned}\mathbb{E}Y_{A+\delta} - \mathbb{E}Y_A &= [\beta_0 + \beta_1(\mathbb{E}A + \delta)] - [\beta_0 + \beta_1(\mathbb{E}A)] \\ &= \beta_0 - \beta_0 + \beta_1\mathbb{E}A - \beta_1\mathbb{E}A + \beta_1\delta \\ &= \beta_1\delta\end{aligned}$$

- Thus, a *unit shift* in A (i.e., $\delta = 1$) may be seen as inducing a change in the difference in outcomes of magnitude β_1 .

A causal inference perspective

- Consider a data structure: $(Y_a, a \in \mathcal{A})$.
- To posit a linear model, let $Y_a = \beta_0 + \beta_1 a + \epsilon_a$ for $a \in \mathcal{A}$, with error $\epsilon_a \sim N(0, \sigma_a^2) \forall a \in A$.
- For the counterfactual outcomes $(Y_{a'+\delta}, Y_{a'})$, their difference, $Y_{a'+\delta} - Y_{a'}$, for some $a' \in \mathcal{A}$, may be expressed

$$\begin{aligned}\mathbb{E}Y_{a'+\delta} - \mathbb{E}Y_{a'} &= [\beta_0 + \beta_1(a' + \delta) + \mathbb{E}\epsilon_{a'+\delta}] - [\beta_0 + \beta_1 a' + \mathbb{E}\epsilon_{a'}] \\ &= \beta_1 \delta\end{aligned}$$

- Thus, a *unit shift* for $a' \in A$ (i.e., $\delta = 1$) may be seen as inducing a change in the difference in the counterfactual outcomes of magnitude β_1 .

Slope in a semiparametric model

- Consider the stochastic intervention $g^*(\cdot | L)$:

$$\begin{aligned}\mathbb{E} Y_{g^*} &= \int_L \int_a \mathbb{E}(Y | A = a, L) g(a - \delta | L) \cdot da \cdot dP_0(L) \\ &= \int_L \int_z \mathbb{E}(Y | A = z + \delta, L) g(z | L) \cdot dz \cdot dP_0(L),\end{aligned}$$

defining the change of variable $z = a - \delta$.

- For a semiparametric model, $\mathbb{E}(Y | A = z, L) = \beta z + \theta(L)$:

$$\begin{aligned}\mathbb{E} Y_{g^*} - \mathbb{E} Y &= \int_L \int_z [\mathbb{E}(Y | A = z + \delta, L) - \mathbb{E}(Y | A = z, L)] \\ &\quad g(z | L) \cdot dz \cdot dP_0(L) \\ &= [\beta(z + \delta) + \theta(L)] - [\beta z + \theta(L)] \\ &= \beta \delta\end{aligned}$$

Nonparametric conditional density estimation

- To compute the auxiliary covariate $H(a, l)$, we need to estimate conditional densities $g(A \mid L)$ and $g(A - \delta \mid L)$.
- There is a rich literature on density estimation, we follow the approach proposed in Díaz and van der Laan (2011).

- To build a conditional density estimator, consider

$$g_{n,\alpha}(a \mid L) = \frac{\mathbb{P}(A \in [\alpha_{t-1}, \alpha_t) \mid L)}{\alpha_t - \alpha_{t-1}},$$

for $\alpha_{t-1} \leq a < \alpha_t$.

- This is a classification problem, where we estimate the probability that a value of A falls in a bin $[\alpha_{t-1}, \alpha_t)$.
- The choice of the tuning parameter t corresponds roughly to the choice of bandwidth in classical kernel density estimation.

Nonparametric conditional density estimation

- Díaz and van der Laan (2011) propose a re-formulation of this classification approach as a set of hazard regressions.
- To effectively employ this proposed re-formulation, consider

$$\mathbb{P}(A \in [\alpha_{t-1}, \alpha_t) \mid L) = \mathbb{P}(A \in [\alpha_{t-1}, \alpha_t) \mid A \geq \alpha_{t-1}, L) \times \prod_{j=1}^{t-1} \{1 - \mathbb{P}(A \in [\alpha_{j-1}, \alpha_j) \mid A \geq \alpha_{j-1}, L)\}$$

- The likelihood of this model may be expressed to correspond to the likelihood of a binary variable in a data set expressed via a long-form repeated measures structure.
- Specifically, the observation of X_i is repeated as many times as intervals $[\alpha_{t-1}, \alpha_t)$ are before the interval to which A_i belongs, and the binary variables indicating $A_i \in [\alpha_{t-1}, \alpha_t)$ are recorded.

Density estimation with the Super Learner algorithm

- To estimate $g(A | L)$ and $g(A - \delta | L)$, use a pooled hazard regression, spanning the support of A .
- We rely on the Super Learner algorithm of van der Laan et al. (2007) to build an ensemble learner that optimally weights each of the proposed regressions, using cross-validation (CV).
- The Super Learner algorithm uses V -fold CV to train each proposed regression model, weighting each by the inverse of its average risk across all V holdout sets.
- By using a library of regression estimators, we invoke the result of van der Laan et al. (2004), who prove this likelihood-based cross-validated estimator to be asymptotically optimal.

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