



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?

- Baseline covariates(L): sex, age, BMI, behavioral HIV risk.
- Intervention(s) (A): post-vaccination T-cell activity markers.
- Outcome (Y): HIV-1 infection status at week 28 of trial.
- 12-color intracellular cytokine staining (ICS) assay.
- Cryopreserved peripheral blood mononuclear cells were stimulated with synthetic HIV-1 peptide pools.
- All immune responses are assayed *after* the endpoints of interest (HIV-1 infection status) are collected.
- **Conclusion:** Understanding which immune responses impact vaccine efficacy helps develop more efficacious vaccines.
- A vaccine effective at preventing HIV-1 acquisition would be a cost-effective and durable approach to halting the worldwide epidemic.

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?

- P_0^X — true (unknown) distribution of the full data X .
- \mathcal{M}_{NP}^X — nonparametric statistical model.
- Observed data O is a masked version of the full data X .

Stochastic interventions define the causal effects of shifts

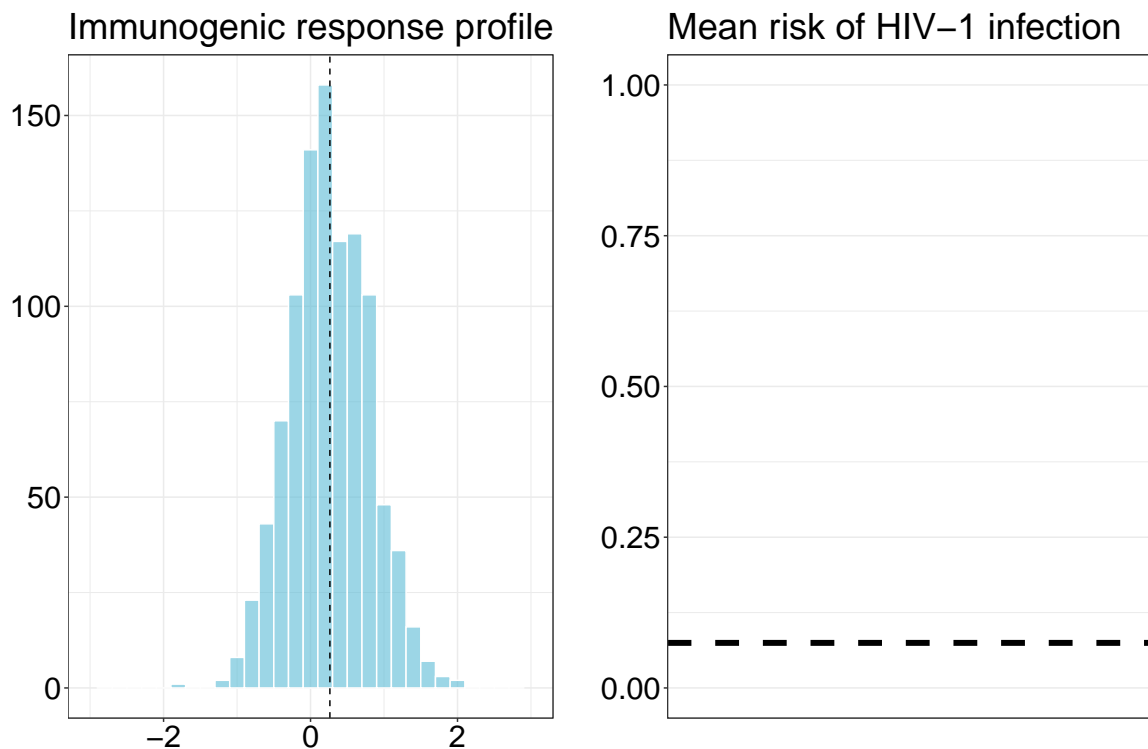
- Causal estimand: counterfactual mean of HIV-1 infection under a *shifted* immunogenic response distribution.
- Díaz and van der Laan (2012; 2018): *Shift* interventions?

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

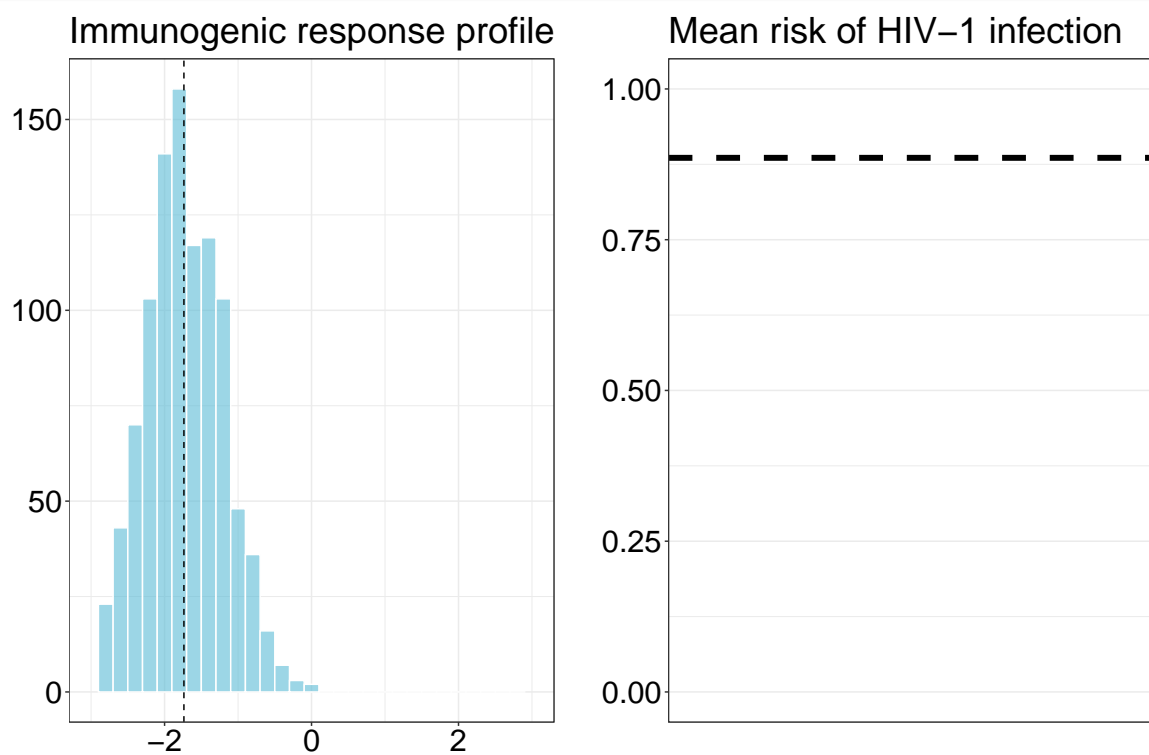
- Díaz and van der Laan (2012; 2018) give a statistical target parameter and influence function for the complete data case.

- For HVTN 505, $\psi_{0,d}$ is the counterfactual risk of HIV-1 infection, had the observed value of the immune response been modified to originate from the distribution of the rule $d(A, W)$.
- Several different ways to consider stochastic interventions.
- Starts with Mark and Ivan's simple stochastic shift.
- Extensions to modified treatment policies.
- The new value of A may be denoted $A^* \sim G^*(\cdot | W)$, where $A^* = d(W, U^*)$ for a rule d and random error U^* .

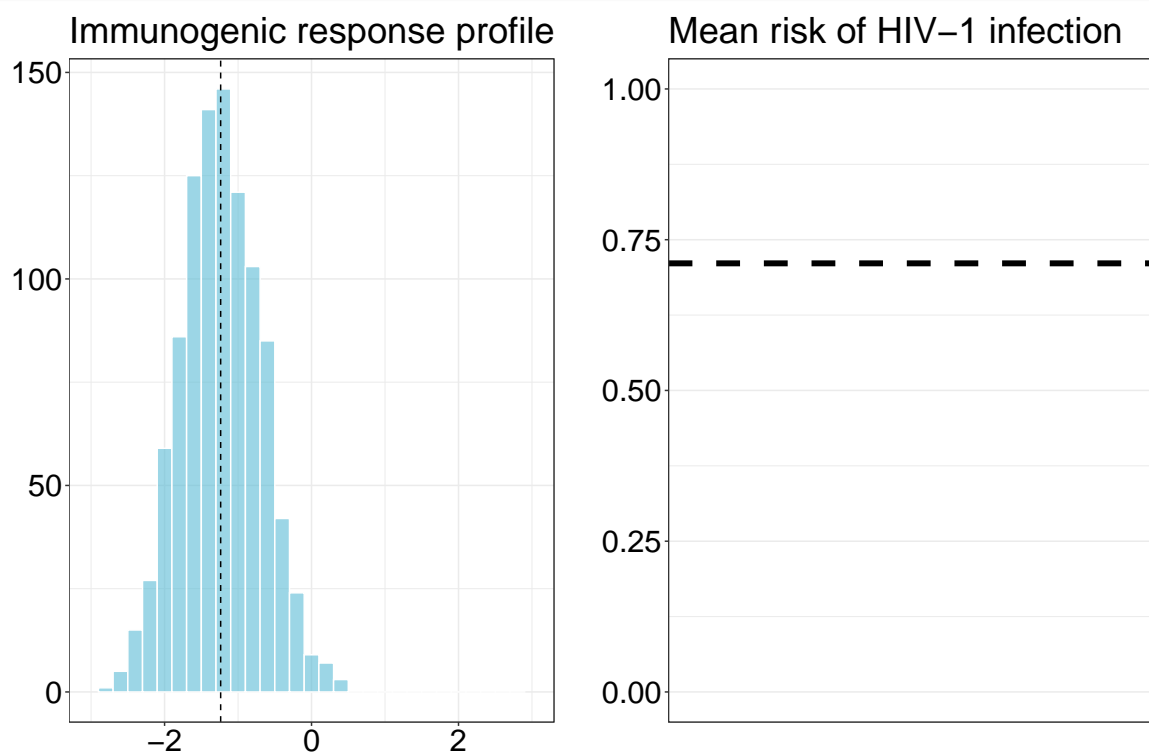
HIV-1 risk under shifted immunogenic responses



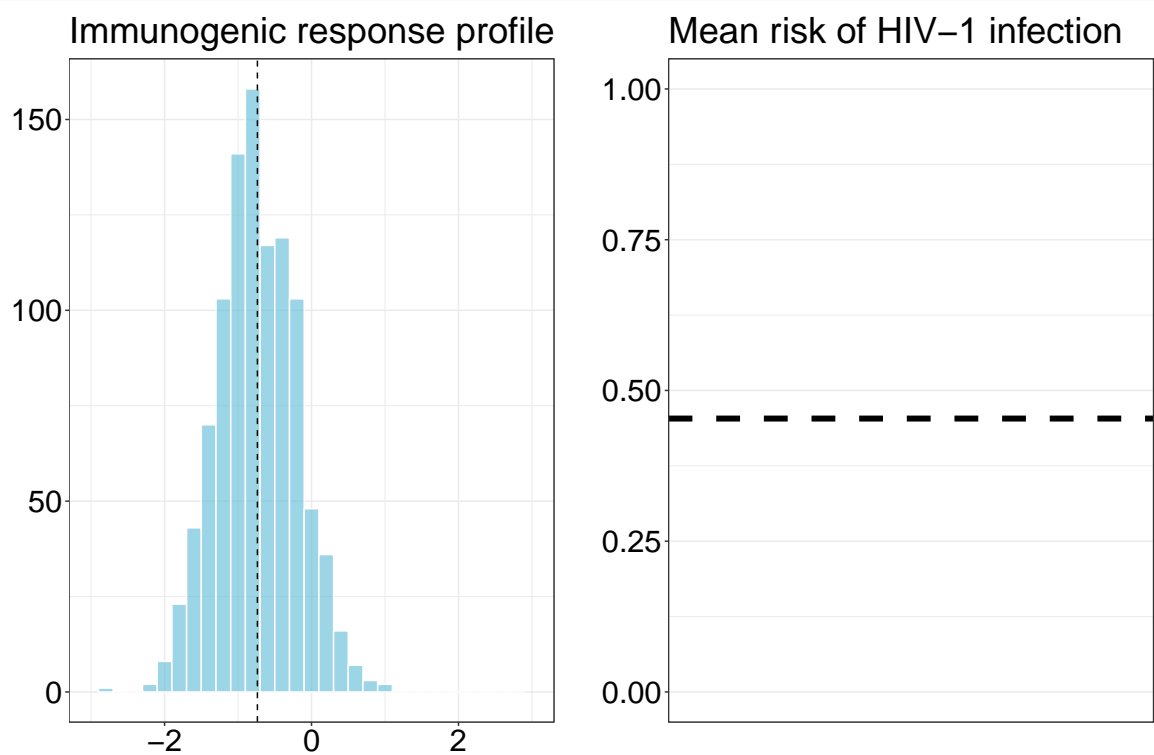
HIV-1 risk under shifted immunogenic responses



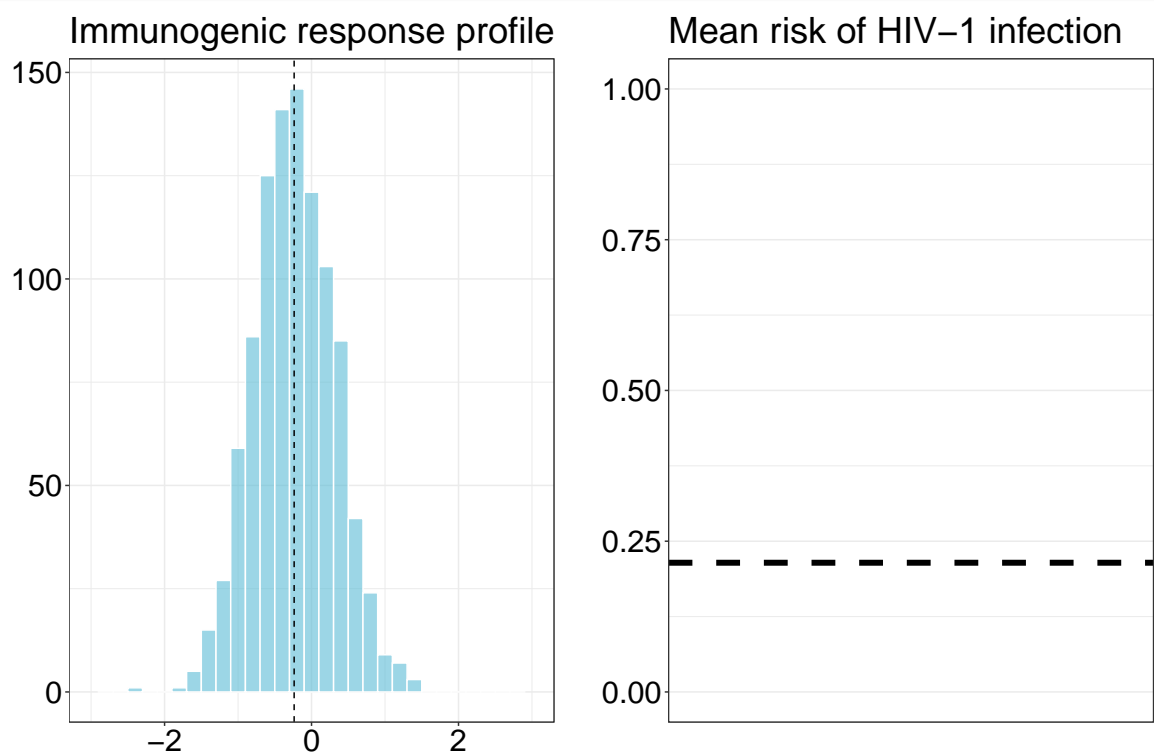
HIV-1 risk under shifted immunogenic responses



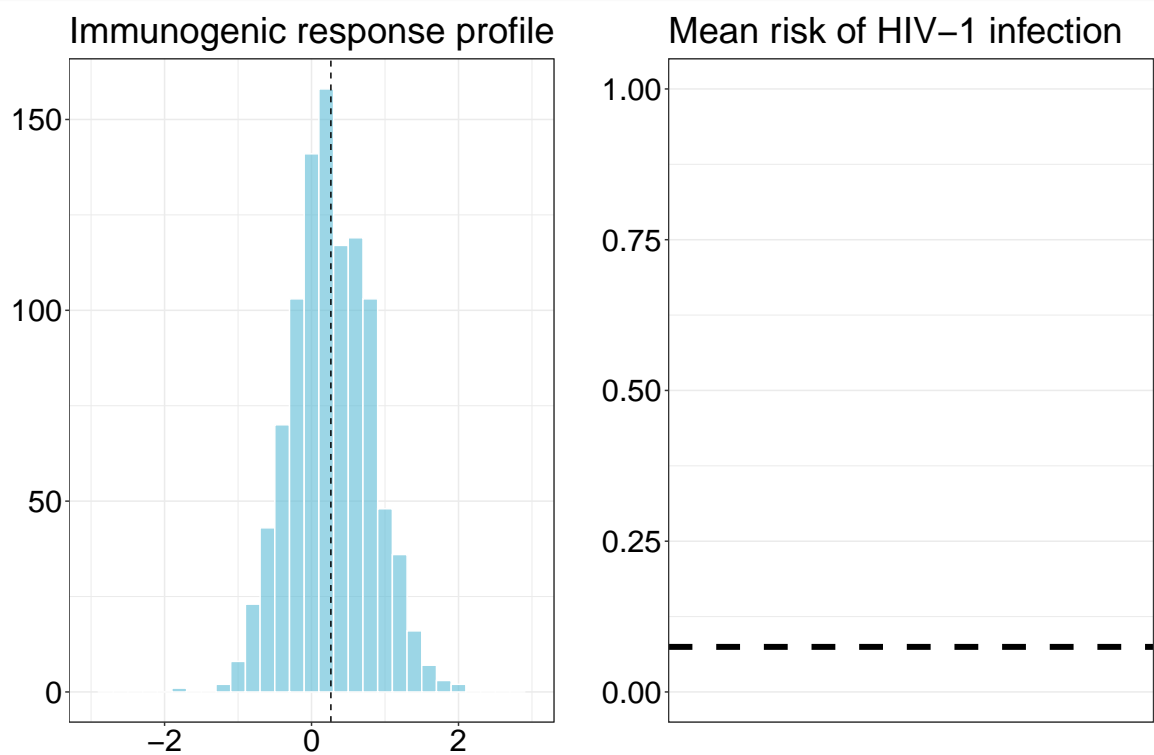
HIV-1 risk under shifted immunogenic responses



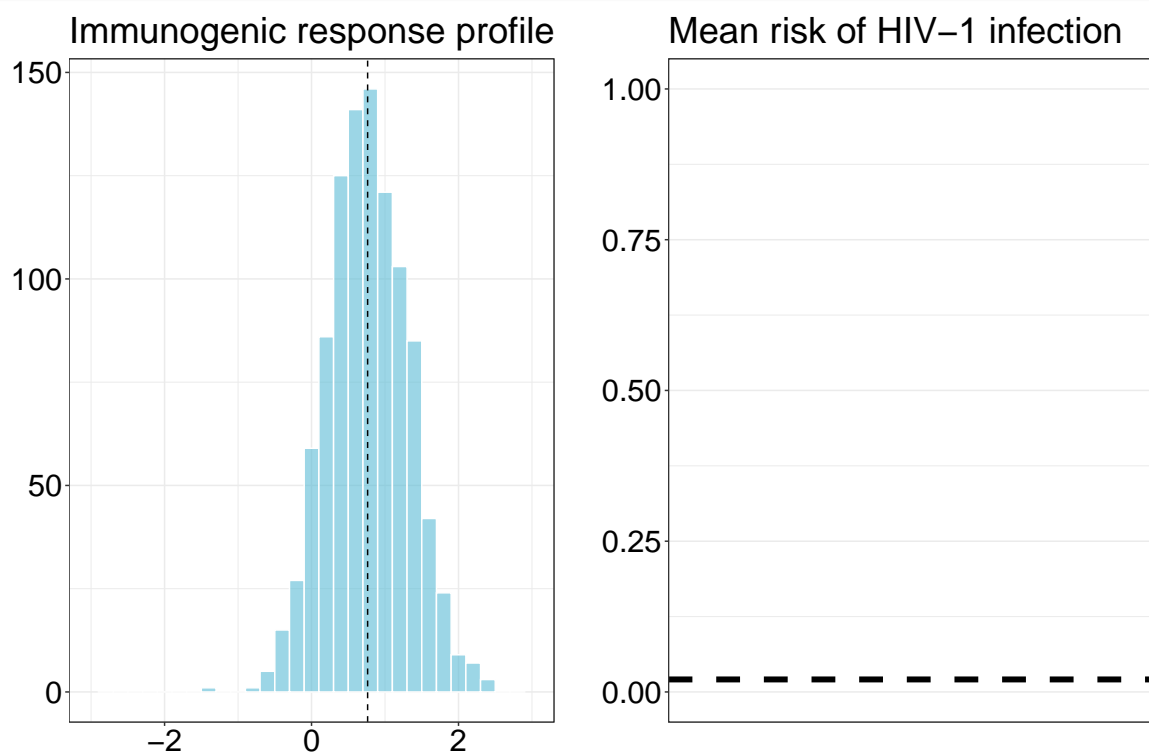
HIV-1 risk under shifted immunogenic responses



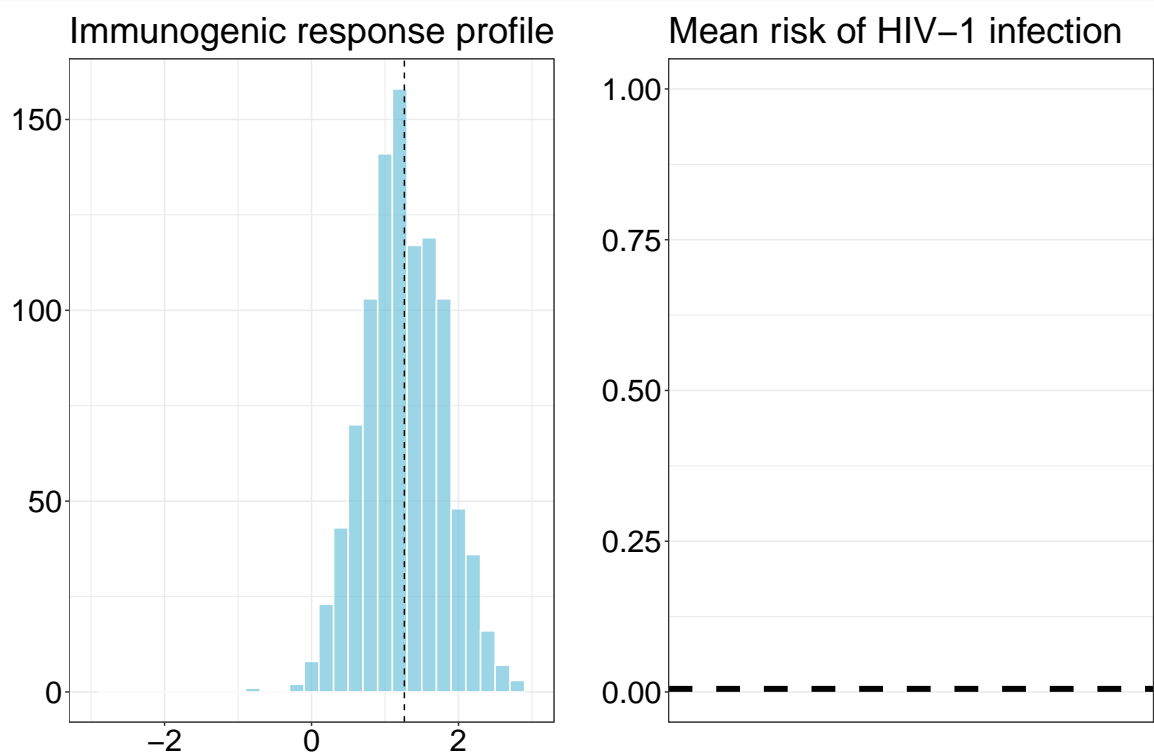
HIV-1 risk under shifted immunogenic responses



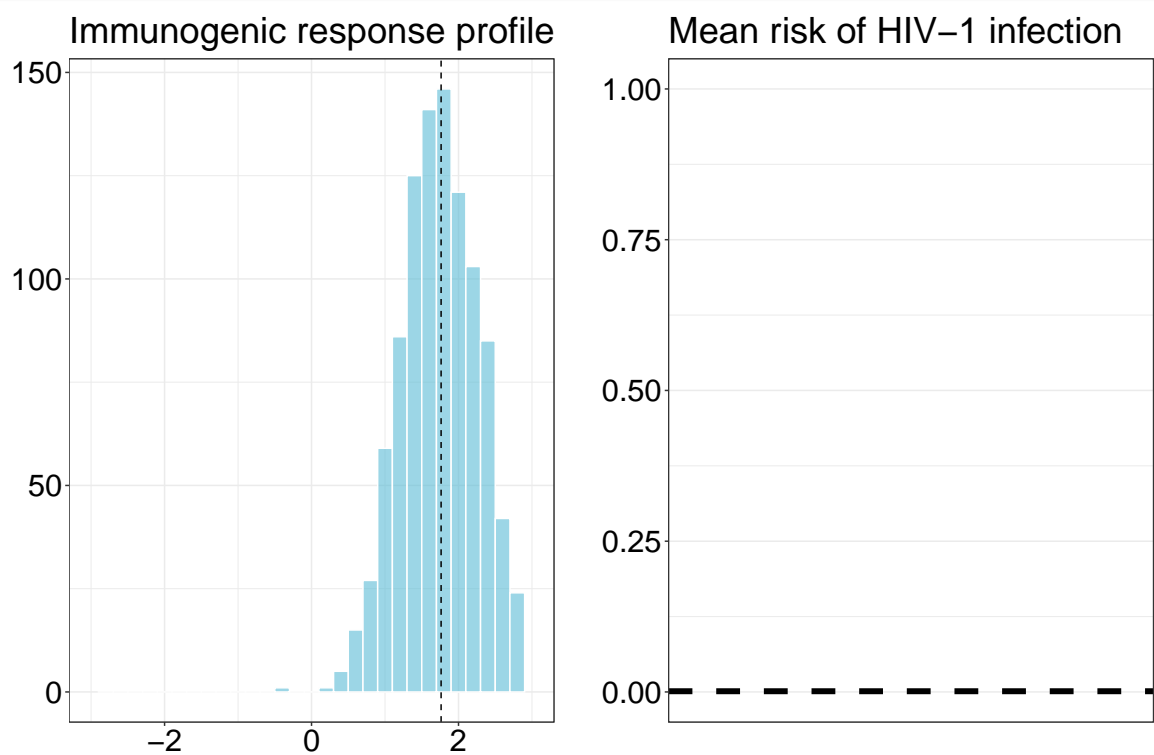
HIV-1 risk under shifted immunogenic responses



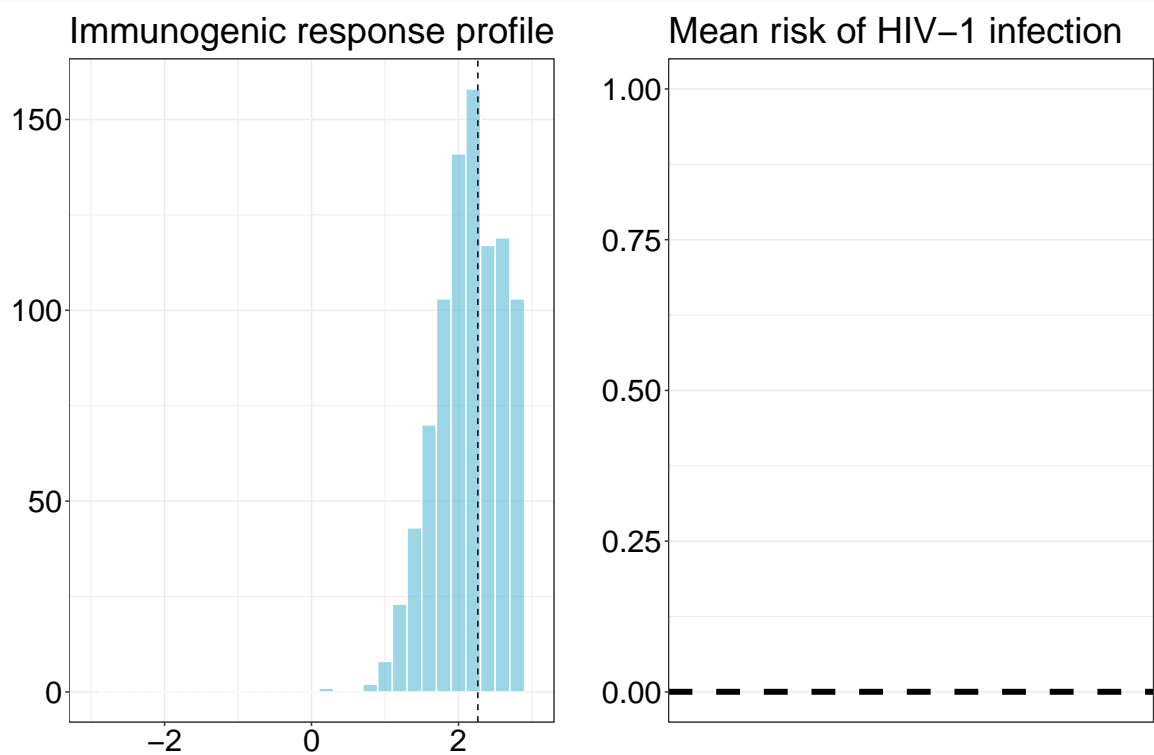
HIV-1 risk under shifted immunogenic responses



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 $\pi_0(Y, W) = \mathbb{P}(\Delta = 1 \mid Y, W)$ is not known by design? Nonparametric estimation of $\pi_0(Y, W)$?
- 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)

- **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:**

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

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

Fighting the HIV-1 epidemic

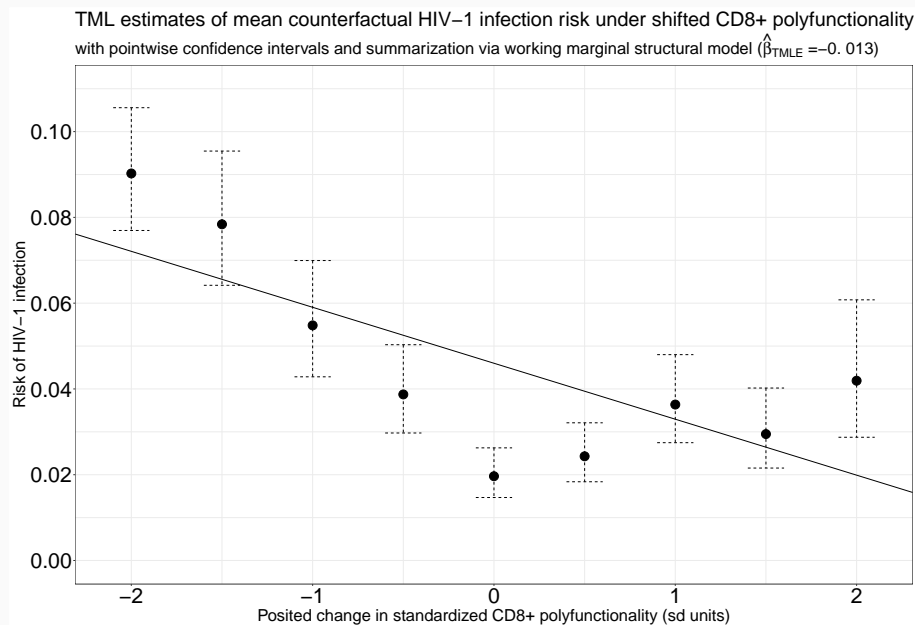


Figure 1: Analysis of HIV-1 risk as a function of CD8+ immunogenicity, using R package txshift (<https://github.com/nhejazi/txshift>.)

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 $A^* \sim G^*(\cdot | L)$; 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 $\Psi(P_0^X) = \mathbb{E}_{P_0^X}\overline{Q}(d(A, L), L)$, 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 $G^*(\cdot \mid L)$.

- Causal estimand: counterfactual mean of HIV-1 infection (risk) under a *shifted* immunogenic response distribution.

Literature: Díaz and van der Laan (2012)

- *Proposal*: Evaluate outcome under an altered *intervention distribution* — e.g., $P_\delta(g_0)(A = a | L) = g_0(a - \delta(L) | L)$.
- 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 :

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

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

- The identification result allows us to write down the causal quantity of interest in terms of a functional of the observed data.
- Key innovation: loosening standard assumptions through a change in the observed intervention mechanism.
- Problem: globally altering an intervention mechanism does not necessarily respect individual characteristics.
- The authors build IPW, A-IPW, and TML estimators, comparing the three different approaches.
- IMPORTANT: gives the g-computation formula for identification of this estimator from the observed data structure.

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:

$$g_{0,\delta}(a \mid l) = \sum_{j=1}^{J(l)} l_{\delta,j} \{h_j(a, l), l\} g_0 \{h_j(a, l) \mid l\} h_j'(a, l)$$
- 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).

- Shifts of the form $d(A, L)$ are considerably more interesting since these are realistic intervention policies.
- Example: consider an individual with an extremely high immune response but whose baseline covariates L suggest we shift the response still higher. Such a shift may not be biologically plausible (impossible, even) but we cannot account for this if the shift is only a function of L .
- The authors build IPW, outcome regression, and non-iterative doubly robust estimators, as well as an approach based on MSMs.
- Piecewise smooth invertibility: This assumption ensures that we can use the change of variable formula when computing integrals over A and it is useful to study the estimators that we propose in this paper.

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.

- Semiparametric-efficient estimation thru solving efficient influence function estimating equation wrt the model \mathcal{M} .
- The auxiliary covariate simplifies when the treatment is in the limits (conditional on W) — i.e., for $A_i \in (u(l) - \delta, u(l))$, then we have $H(a, l) = \frac{g_0(a - \delta | l)}{g_0(a | l)} + 1$.
- Need to explicitly remind the audience what $u(l)$ is again. It's only appeared once at this point, and only been mentioned in passing.

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} :

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

- We recommend using nonparametric methods for the initial estimators, as consistent estimation is necessary for efficiency of the estimator Ψ_n .
- Intuition for the submodel fluctuation?

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 $\frac{1}{n} \sum_{i=1}^n \text{EIF}_i < \frac{1}{n}$.

- We recommend using nonparametric methods for the initial estimators, as consistent estimation is necessary for efficiency of the estimator Ψ_n .
- Intuition for the submodel fluctuation?
- This process includes the use of HAL to fit the regression of the EIF contributions on the sampling node $\{Y, L\}$.

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 $\sigma_n^2 = \frac{1}{n} \sum_{i=1}^n D^2(\cdot)(X_i)$.

Under the additional condition that the remainder term $R(\hat{P}^*, P_0)$ decays as $o_P\left(\frac{1}{\sqrt{n}}\right)$, we have that $\Psi_n - \Psi_0 = (P_n - P_0) \cdot D(P_0) + o_P\left(\frac{1}{\sqrt{n}}\right)$, which, by a central limit theorem, establishes a Gaussian limiting distribution for the estimator, with variance $V(D(P_0))$, the variance of the efficient influence function when Ψ admits an asymptotically linear representation.

The above implies that Ψ_n is a \sqrt{n} -consistent estimator of Ψ , that it is asymptotically normal (as given above), and that it is locally efficient. This allows us to build Wald-type confidence intervals, where σ_n^2 is an estimator of $V(D(P_0))$. The estimator σ_n^2 may be obtained using the bootstrap or computed directly via $\sigma_n^2 = \frac{1}{n} \sum_{i=1}^n D^2(\bar{Q}_n^*, g_n)(O_i)$

We obtain semiparametric-efficient estimation and robust inference in the nonparametric model \mathcal{M} by solving the efficient influence function.

1. If $D(\bar{Q}_n^*, g_n)$ converges to $D(P_0)$ in $L_2(P_0)$ norm.
2. The size of the class of functions \bar{Q}_n^* and g_n is bounded (technically, $\exists \mathcal{F}$ st $D(\bar{Q}_n^*, g_n) \in \mathcal{F}$ whp, where \mathcal{F} is a Donsker class)

Identifying the best efficient estimator

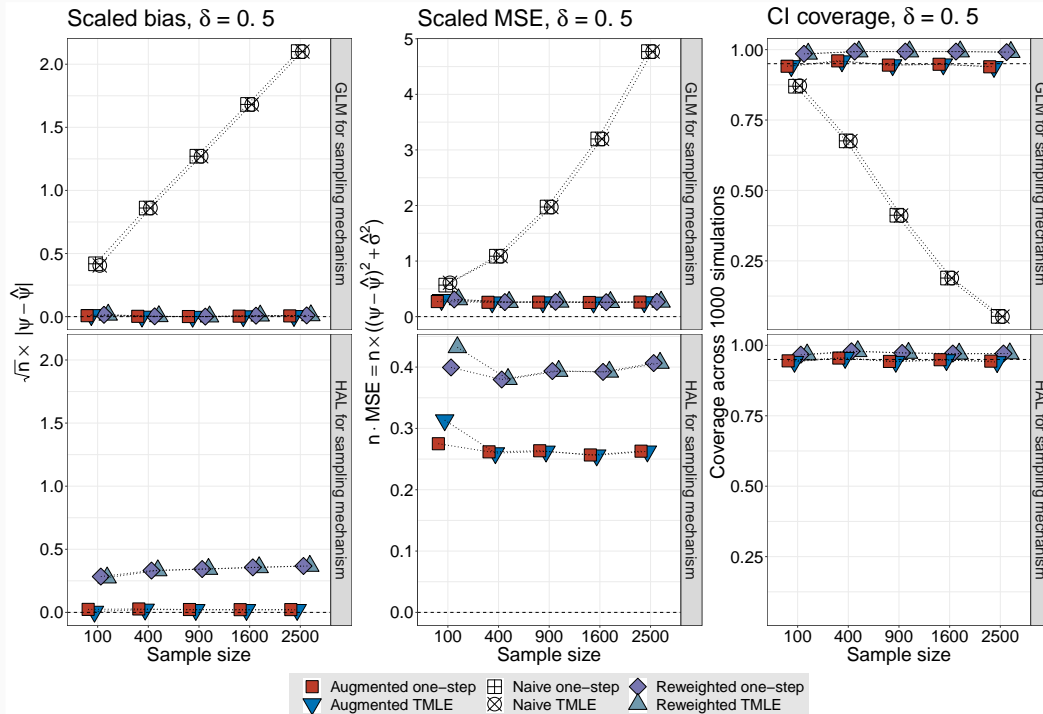


Figure 2: Relative performance of reweighted and augmented estimators.

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 .

- We extend this result to the mean counterfactual outcomes under the nonparametric model \mathcal{M} .
- Linear modeling analogy re: conversation with Alan on 22 August.

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 $\epsilon_a \sim N(0, \sigma_a^2) \forall a \in \mathcal{A}$.
- 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 $a' \in \mathcal{A}$ (i.e., $\delta = 1$) may be seen as inducing a change in the difference in the counterfactual outcomes of magnitude β_1 .

- Note that this analysis is exactly what we're told we **cannot** do in linear models 101 — that is, the slope of a regression line cannot be interpreted as *causing* a change in the outcome.
- We extend this result to the mean counterfactual outcomes under the nonparametric model \mathcal{M} .
- Linear modeling analogy re: conversation with Alan on 22 August.
- Example updated to incorporate counterfactuals re: conversation with David on 30 August

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 $g(A | L)$ and $g(A - \delta | L)$.
- 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

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

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.

- The auxiliary covariate simplifies when the treatment is in the limits (conditional on L) — i.e., for $A_i \in (u(l) - \delta, u(l))$, then we have $H(a, l) = \frac{g_0(a - \delta | l)}{g_0(a | l)} + 1$.
- Asymptotically optimal in the sense that it performs as well as the oracle selector as the sample size increases.

References

- Breiman, L. (1996). Stacked regressions. *Machine Learning*, 24(1):49–64.
- Díaz, I. and van der Laan, M. J. (2011). Super learner based conditional density estimation with application to marginal structural models. *The international journal of biostatistics*, 7(1):1–20.
- Díaz, I. and van der Laan, M. J. (2012). Population intervention causal effects based on stochastic interventions. *Biometrics*, 68(2):541–549.
- Díaz, I. and van der Laan, M. J. (2018). Stochastic treatment regimes. In *Targeted Learning in Data Science: Causal Inference for Complex Longitudinal Studies*, pages 167–180. Springer Science & Business Media.
- Dudoit, S. and van der Laan, M. J. (2005). Asymptotics of cross-validated risk estimation in estimator selection and performance assessment. *Statistical Methodology*, 2(2):131–154.

Hammer, S. M., Sobieszczyk, M. E., Janes, H., Karuna, S. T., Mulligan, M. J., Grove, D., Koblin, B. A., Buchbinder, S. P., Keefer, M. C., Tomaras, G. D., et al. (2013). Efficacy trial of a DNA/rAd5 HIV-1 preventive vaccine. *New England Journal of Medicine*, 369(22):2083–2092.

Haneuse, S. and Rotnitzky, A. (2013). Estimation of the effect of interventions that modify the received treatment. *Statistics in medicine*, 32(30):5260–5277.

Holland, P. W. (1986). Statistics and causal inference. *Journal of the American statistical Association*, 81(396):945–960.

Janes, H. E., Cohen, K. W., Frahm, N., De Rosa, S. C., Sanchez, B., Hural, J., Magaret, C. A., Karuna, S., Bentley, C., Gottardo, R., et al. (2017). Higher t-cell responses induced by dna/rad5 hiv-1 preventive vaccine are associated with lower hiv-1 infection risk in an efficacy trial. *The Journal of infectious diseases*, 215(9):1376–1385.

Kennedy, E. H. (2018). Nonparametric causal effects based on incremental propensity score interventions. *Journal of the American Statistical Association*, (just-accepted).

Kennedy, E. H., Ma, Z., McHugh, M. D., and Small, D. S. (2017). Non-parametric methods for doubly robust estimation of continuous treatment effects. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*, 79(4):1229–1245.

Pearl, J. (2009). *Causality: Models, Reasoning, and Inference*. Cambridge University Press.

Rose, S. and van der Laan, M. J. (2011). A targeted maximum likelihood estimator for two-stage designs. *The International Journal of Biostatistics*, 7(1):1–21.

Rosenbaum, P. R. and Rubin, D. B. (1983). The central role of the propensity score in observational studies for causal effects. *Biometrika*, 70(1):41–55.

- Rubin, D. B. (1978). Bayesian inference for causal effects: The role of randomization. *The Annals of statistics*, pages 34–58.
- Rubin, D. B. (1980). Randomization analysis of experimental data: The fisher randomization test comment. *Journal of the American Statistical Association*, 75(371):591–593.
- Rubin, D. B. (2005). Causal inference using potential outcomes: Design, modeling, decisions. *Journal of the American Statistical Association*, 100(469):322–331.
- van der Laan, M. J., Dudoit, S., and Keles, S. (2004). Asymptotic optimality of likelihood-based cross-validation. *Statistical Applications in Genetics and Molecular Biology*, 3(1):1–23.
- van der Laan, M. J., Polley, E. C., and Hubbard, A. E. (2007). Super Learner. *Statistical Applications in Genetics and Molecular Biology*, 6(1).
- van der Laan, M. J. and Rubin, D. (2006). Targeted maximum likelihood learning. *The International Journal of Biostatistics*, 2(1).

- Wolpert, D. H. (1992). Stacked generalization. *Neural networks*, 5(2):241–259.
- Young, J. G., Hernán, M. A., and Robins, J. M. (2014). Identification, estimation and approximation of risk under interventions that depend on the natural value of treatment using observational data. *Epidemiologic methods*, 3(1):1–19.