


Evaluating the causal impacts of vaccine-induced immune responses in two-phase vaccine efficacy trials


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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).
- **Question:** How would HIV-1 infection risk in week 28 have changed had immunogenic response (due to vaccine) differed?
- Immunogenic response profiles only available for second-stage 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.

- 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): immune response profile for CD4+ and 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 second-stage sample.

- P_0^X — true (unknown) distribution of the full data X ,
- \mathcal{M}_{NP}^X — nonparametric statistical model.

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

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

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 $l_i \in \mathcal{L}$.

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.

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 $(g_0(L), \bar{Q}_0(A, L)) \times (\pi_0(Y, L), \mathbb{E}(D^F(P_0^X)(x) \mid C = 1, Y, L))$.

Fighting the HIV-1 epidemic with preventive vaccines

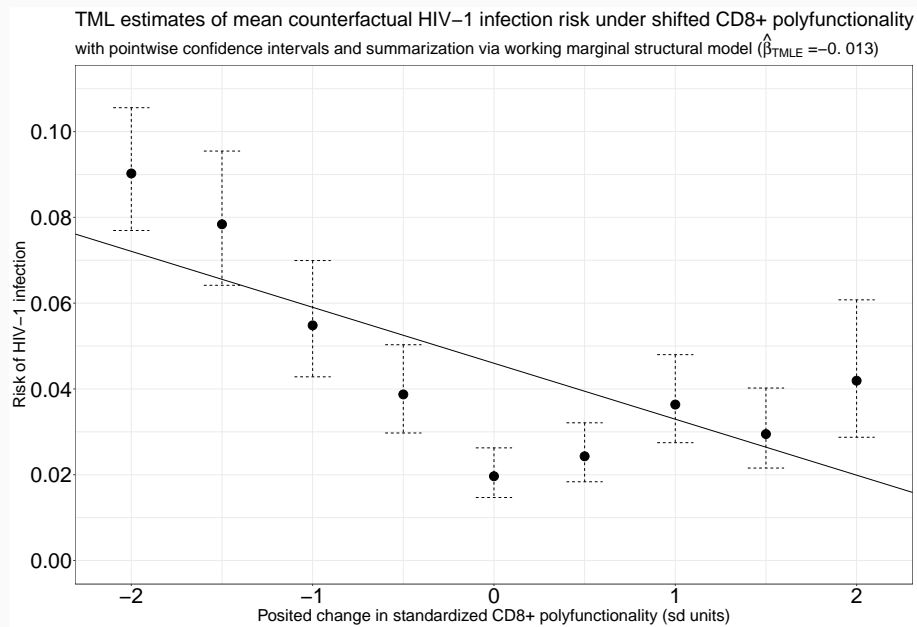


Figure 1: Analysis of HIV-1 risk as a function of CD8+ immunogenicity, using R package txshift (<https://github.com/nhejazi/txshift>.)

Big picture takeaways

- Vaccine efficacy evaluation helps to develop enhanced vaccines better informed by biological properties of the target disease.
- HIV-1 vaccines modulate immunogenic response profiles as part of their mechanism for lowering HIV-1 infection risk.
- *Stochastic* interventions constitute a flexible framework for considering **realistic** treatment/intervention policies.
- Large-scale (vaccine) trials often use two-phase designs — need to (carefully!) accommodate for sampling complications.
- We've developed robust, open source statistical software for assessing stochastic interventions in observational studies.

Thank you!

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

At “Warp Speed” – COVID-19 Vaccine Trials

COVID-19 Vaccine Development

- *Nucleic acid vaccines*: Moderna (mRNA), Pfizer (mRNA)
- *Viral-vectored vaccines*: AstraZeneca (chimpanzee adenovirus), Janssen (human adenovirus)
- *Subunit vaccines*: NovaVax, Sanofi / GlaxoSmithKline
- *Weakened/inactivated vaccines*: Sinopharm, Sinovac

- Nucleic acid vaccines have never been approved before, but are quick to manufacture.
- Viral-vectored vaccines are also quick to manufacture but can develop immunity against vector.
- Subunit vaccines are a construct of several effective vaccines, but are slower to manufacture and often require an adjuvant.

“Operation Warp Speed” (OWS)

- Do we have the time? Polio (7 years), Measles (9 years), Chickenpox (34 years), Mumps (4 years), HPV (15 years).
- OWS: “300M doses of safe, effective vaccine by 01 Jan. 2021”.
- How? Typical process timeline (73 months) replaced by an *accelerated* process of 14 months.
- COVID-19 Prevention Network (CoVPN):
 - formed by NIAID to establish a unified clinical trial network for evaluating vaccines and monoclonal antibodies.
 - Statisticians: primary trial design/analysis, sequential efficacy monitoring, safety monitoring, immune correlates.

Immune Correlates of Protection (Plotkin and Gilbert 2012)

- Correlate of Protection (CoP): immune marker statistically predictive of vaccine efficacy, not necessarily mechanistic.
- Mechanistic CoP (mCoP): immune marker that is mechanistically and causally responsible for protection.
- Nonmechanistic CoP (nCoP): immune marker that is predictive but not a causal agent of protection.
- A CoP is a *candidate surrogate* endpoint (Prentice 1989) — primary endpoint in future trials if reliably predictive.

Measuring Correlates: Two-Phase Designs

- Running assays on $> 30,000$ blood draws is timely, expensive, and, as it turns out, statistically unnecessary.
- Instead we measure immune responses via a case-cohort design (Prentice 1986):
 - a stratified random subcohort (≈ 1600 individuals)
 - all SARS-CoV-2 and COVID endpoints
- Case-cohort designs are a special case of two-phase sampling (Breslow et al. 2003; 2009):
 - Phase 1: measure baseline, vaccine, endpoint on everyone
 - Phase 2: given baseline, vaccine, endpoint, select members of immune response subcohort with (possibly known) probability

Estimation in Two-Phase Designs

- Observed data structure: $O = (L, A, Z, CM, Y, C)$
 - $A \in \{0, 1\}$: randomized vaccination assignment
 - Z : post-vaccination confounder (e.g., unblinded risky behavior)
 - M : candidate mCoPs (causal mediators)
 - Y : symptomatic SARS-CoV-2 infection
 - $C := f(Y, L)$: selection into second-phase sample
- But what about $O = (L, A, Z, CM, \Delta, \tilde{T}, C)$?
 - $\tilde{T} = \min(T_F, T_C)$: possibly right-censored time to symptomatic SARS-CoV-2 infection
 - $\Delta = \mathbb{I}(T_F < T_C)$: observed symptomatic SARS-CoV-2 infection
 - Can C still be a function of \tilde{T} ?

- Goal: assess *indirect* effect of vaccination through mCoPs.
- Define/identify new mCoPs to be used as surrogate endpoints.
- Could also have missing outcome in the binary endpoint case.

Causal Mediation Analysis: Explanation and Mechanism

- Identification assumptions:
 - A1: No unmeasured confounding of $\{A, Y\}$ relationship.
 - A2: No unmeasured confounding of $\{M, Y\}$ relationship.
 - A3: No unmeasured confounding of $\{A, M\}$ relationship.
 - A4: No $\{M, Y\}$ confounder affected by A , i.e., no Z .
- *Indirect* effects: thru pathways involving candidate mCoPs.
 - Natural (in)direct effects (Robins and Greenland 1992, Pearl 2013): binary A and M , no Z , “cross-world” independence.
 - Stochastic (in)direct effects (Díaz and Hejazi 2020): continuous A and M , no Z ; no “cross-world” exclusion.
 - Interventional (in)direct effects (Díaz et al. 2020): binary A , continuous M , Z ok, no “cross-world” exclusion.
 - Stochastic interventional (in)direct effects (Hejazi et al. 2020): continuous A and M , Z ok, no “cross-world” exclusion.

- A1, A3 hold in randomized trials.
- A2 may not hold: include all mutual $\{M, Y\}$ predictors, then perform sensitivity analysis.
- A4 usually doesn't hold: either measure M right after A or develop more flexible effect definitions.
- "Cross-world" independence: $Y(a, m) \perp M(a') \quad \forall m$; un-testable in RCTs
- Extensions for two-phase sampling???

Appendix

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:

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

- 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, accommodating 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.

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.

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)

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 second-stage 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 $\{Y, L\}$.

Identifying the best efficient estimator

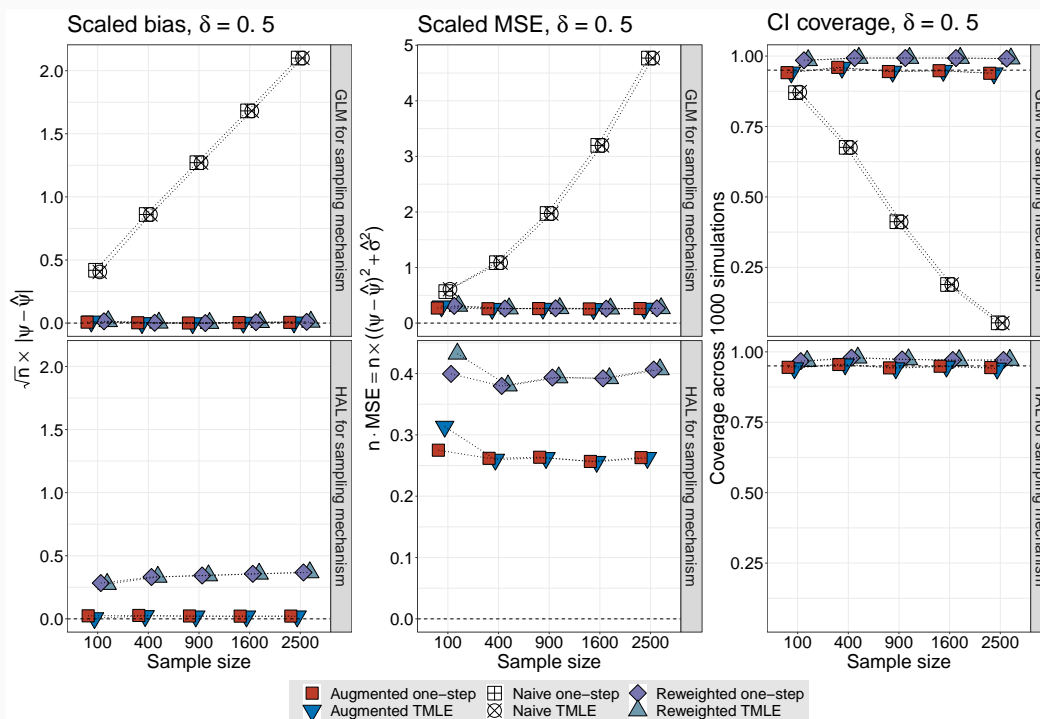


Figure 2: Relative performance of reweighted and augmented estimators.

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, $\mathbb{E}(Y | A = z, L) = \beta z + \theta(L)$:

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

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