Robust Nonparametric Inference for Stochastic Interventions Under Multi-Stage Sampling

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Preview: Summary

- The evaluation of vaccine efficacy is a high-impact scientific problem that leads to numerous statistical challenges.
- Stochastic interventions provide a flexible framework through which these statistical problems may be viewed from the perspective of causal inference.
- Standard targeted minimum loss-based estimation may be augmented to handle multi-stage sampling designs, like those common in efficacy trials.
- Statistical software is now readily available for deploying these types of techniques in a number of settings. We apply these methods in efficacy trials.

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Motivation: Let's meet the data

- HIV Vaccine Trials Network (HVTN) 505 HIV-1 vaccine efficacy trial.
- 2504 participants, with all observed cases matched to controls after collection of endpoints of interest.
- Background quantities (W): sex, age, BMI, etc.
- Variables of interest (A): biomarkers of immune response (e.g., T-Cell response).
- Outcome of interest (Y): HIV-1 infection risk.
- **Question**: How would changes in the immune response profile impact risk of HIV-1 infection?

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Preventive Vaccines for HIV

- Substantial heterogeneity is present in the genetic characteristics of HIV.
- Preventive HIV vaccines constructed using only several antigens (out of a great many).
- **Success:** Protect well against infection caused by virus strains *similar* to the source strain.
- **Failure:** Don't protect against disease caused by strains antigenically *dissimilar* to source strain.

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Sieve Analysis: A Brief History

- The study of whether and how the efficacy of a vaccine varies with the virus' characteristics.
- Why "sieve"? Vaccine as a barrier against select strains, but dissimilar strains break through.
- Identification of sieve effects guides decisions for future development of multivalent vaccines.
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Immune Response and Vaccine Efficacy

- A 12-color intracellular cytokine staining (ICS) assay was performed.
- Cryopreserved peripheral blood mononuclear cells were stimulated with synthetic HIV-1 peptide pools.
- Immune responses of interest were
  1. Total magnitude of the $CD4^+$ T-cell response.
  2. COMPASS Env-specific $CD4^+$ T-cell polyfunctionality score.
  3. Total magnitude of the $CD8^+$ T-cell response.
  4. COMPASS Env-specific $CD8^+$ T-cell polyfunctionality score.
  5. $CD4^+$ and $CD8^+$ T-cell $\log_{10}$-transformed total magnitude variables.

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Immune Reponse and Vaccine Efficacy

- *Goal:* Evaluate the immune response variables among vaccine recipients as predictors of HIV-1 infection.
- Cox proportional hazard models that account for case-control sampling design and adjust for the baseline covariates.
- $\lambda\left(t; Z = z\right) = \lambda_0(t) \exp\left(\beta^T z\right), \quad t \geq 0.$
  - $\Rightarrow$ Semiparametric overall.
  - $\Rightarrow$ nonparametric in λ_0, parametric in β.
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- Cox model: assumption of proportional hazards.
- Such models are a matter of convenience: does $\hat{\beta}$ answer our scientific questions?
  - → Perhaps not.
- Is consideration being given to whether the data could have been generated by a process that is consistent with the assumptions of the Cox model?
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Interlude: Causal Inference

1. Motivation: “We do not have knowledge of a thing until we have grasped its why, that is to say, its cause.” –Aristotle
2. Our question of interest concerns the manner in which changes in a given immune response profile affect risk of HIV-1 infection.
   - → This is a question of causality.
   - → How does *intervening* on immune response profile cause changes in the risk of HIV-1 infection?
3. But how do we go about thinking about intervening on continuous quantities (e.g., immune response profile measures)?
4. Classical causal parameters (e.g., ATE) are not well suited for answering these sorts of questions.

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Causal Inference and Vaccine Efficacy

- Consider observing n individuals in a data structure of the form specified above.
- To formalize, consider $O = (W, A, Y) \sim P_0 \in \mathcal{M}$, where we make no assumptions on the statistical model containing P_0.
- For the treatment A, we would normally be limited to thinking about counterfactual means (i.e., $\mathbb{E}Y_a$ for $A = a$) or similar quantities.
- This requires specifying a particular value of the treatment (i.e., $A = a$) under which to evaluate the outcome.

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Stochastic Treatment Regimes

- Rather than a deterministic intervention, consider a shift of the treatment (i.e., instead of $A = a$, consider $A = a + \delta$).
- This is a far more flexible approach. We need not specify a given value of the treatment but rather a shift (δ) of the treatment.
- In this setting, the effect of the intervention appears as $\mathbb{E}Y_{a+\delta} - \mathbb{E}Y_a$, where $A = a$ is simply the observed value of treatment.
- To compare with the linear model, the shift δ may be thought of as analogous to shifts in the slope of the regression line.

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Problems with Stochastic Interventions

- Even though we employ a more flexible type of intervention, the common assumptions (and problems!) of causal inference still arise.
  - Randomization: $A \perp\!\!\!\perp Y \mid W$
  - Positivity: $0 < P(A \mid W) < 1$ everywhere. The propensity score is bounded in $(0, 1)$.
- To protect against positivity violations, a clever shifting mechanism: $d(a, w) = a + \delta$, if $a + \delta < u(w)$ and $d(a, w) = a$ otherwise.
- The shift $d(A, W)$ is now a function of the observed data, and the shift intervention $(a + \delta)$ is only applied when there is support in the observed data.

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Parameters for Treatment Shifting

- Let's consider a simple target parameter: the average treatment effect (ATE):

$$\Psi(P) = \mathbb{E}\bar{Q}(A, W)I(A \leq \delta) + \mathbb{E}\bar{Q}(A, W)I(A > \delta)$$

- Assume *piecewise smooth invertibility* of $d(a, w)$ in order to obtain a pathwise differentiability of the parameter.
- This makes semiparametric-efficient estimation in the nonparametric model possible when relying on stochastic interventions.
- The parameter now corresponds to our scientific question of interest: How does shifting immune response by an amount δ affect the risk of HIV-1 infection?

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- The parameter now corresponds to our scientific question of interest: How does shifting immune response by an amount δ affect the risk of HIV-1 infection?

Parameters for Treatment Shifting

- Let's consider a simple target parameter: the average treatment effect (ATE):

$$\Psi(P) = \mathbb{E}\bar{Q}(A, W)I(A \leq \delta) + \mathbb{E}\bar{Q}(A, W)I(A > \delta)$$

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Semiparametric-Efficient Estimation

- Our parameter of interest is

$$\Psi(P) = \mathbb{E}_P \bar{Q}(d(A, W), W)$$

- For which the efficient influence function (EIF) is

$$D(P)(o) = H(a, w)y - \bar{Q}(a, w) + \bar{Q}(d(a, w), w) - \Psi(P)$$

- The auxiliary covariate introduced (i.e., $H(a, w)$) may be expressed

$$H(a, w) = I(a < u(w)) \frac{g_0(a - \delta \mid w)}{g_0(a \mid w)} + I(a \geq u(w) - \delta)$$

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Target Minimum Loss-Based Estimation

- TMLEs provide semiparametric-efficient estimation and robust inference in nonparametric models.
- **Asymptotic linearity:**

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

- **Limiting distribution:**

$$\sqrt{n}(\Psi_n - \Psi) \to N(0, Var(D(P_0)))$$

- **Statistical inference:**

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Statistical Inference for TMLEs

- Asymptotic distribution of TML estimators has been studied thoroughly:
  $\psi_n - \psi_0 = (P_n - P_0) \cdot D(P_0) + R(\hat{P}^*, P_0)$, giving
  $\psi_n - \psi_0 = (P_n - P_0) \cdot D(P_0) + o_P\left(\frac{1}{\sqrt{n}}\right)$.
- Have a *Gaussian limiting distribution* $\sqrt{n}(\psi_n - \psi) \to N(0, V(D(P_0)))$ when ψ exhibits asymptotically linearity.
- **Statistical inference** using Wald-type confidence intervals: $\Psi_n \pm z_\alpha \cdot \frac{\sigma_n}{\sqrt{n}}$, where σ_n^2 is an estimator of $V(D(P_0))$.
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Complication: Multi-Stage Sampling

- In the 505 HIV-1 trial, all infected individuals are matched to pairs using a complex mechanism.
- Using our observed data structure $O = (W, A, Y)$, let us introduce $V = (W, Y)$, where V is the set of variables used to define the sampling mechanism.
- Thus, the observed data structure is now represented $O = (W, \Delta A, Y)$ wrt to the full data structure.
  - In the above, let $\Delta = I(V)$ be binary st $\Delta \in \{0, 1\}$.
  - Further, let $\Pi_0(V) = P(\Delta = 1 \mid V)$ and $\Pi_n(V)$ be an estimator of $\Pi_0(V)$.
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Multi-Stage Sampling with TMLEs

- Rose & van der Laan (2011) introduce an IPCW-TMLE to be used when the data structure takes the form $O = (V, \Delta, \Delta X)$, for multi-stage sampling designs.
- How? Use an IPC-weighted loss function:

$$\mathcal{L}(P_X)(O) = \frac{\Delta}{\Pi_n(V)} \mathcal{L}^F(P_X)(X)$$

- The IPCW-TMLE solves the full-data efficient influence function (EIF) equation:

$$0 = \frac{1}{n} \sum_{i=1}^{n} \frac{\Delta_i}{\Pi_n(V_i)} D^F(P^*_{X,n})(X_i).$$

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Efficiency Under Multi-Stage Sampling

- When working in a nonparametric model, it is necessary to use a nonparametric estimator of the missingness mechanism to obtain full efficiency.
- In many practical settings, this further complicates the efficient influence function estimating equation

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Putting It Together: Multiple Robustness

- We now have a semiparametric-efficient and robust procedure for assessing the effect of the intervention $d(a, w) = a + \delta$ even in the presence of multi-stage sampling.
- Due to the nature of the IPCW-TMLE, we have a form of multiple double robustness — in terms of combinations of (g, Q) and $(\Pi, \mathbb{E}_0(D^F(P^F) \mid V))$.
- This allows us to assess how simple (additive) shifts of immune response variables affect the risk of HIV-1 infection.

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Software package: R/txshift

R/ `txshift`

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> Targeted Learning of Continuous Intervention Effects with Stochastic Treatment Regimes

Authors: Nima Hejazi and David Benkeser

What's `txshift`?

The `txshift` R package is designed to provide facilities to compute targeted maximum likelihood estimates (TMLE) of the population-level causal effect of interventions based on stochastic mechanisms for treatment assignment (Muñoz and van der Laan (2012)). As opposed to the original algorithm given for computing such a TMLE, `txshift` implements and builds upon subsequent work by Díaz and van der Laan (2018), who reveal a simplified algorithm for computing the TML estimator of the shift intervention causal effect parameter.

Figure: `https://github.com/nhejazi/txshift`

- Variable importance for continuous interventions.
- Take it for a test drive! Coming soon . . .

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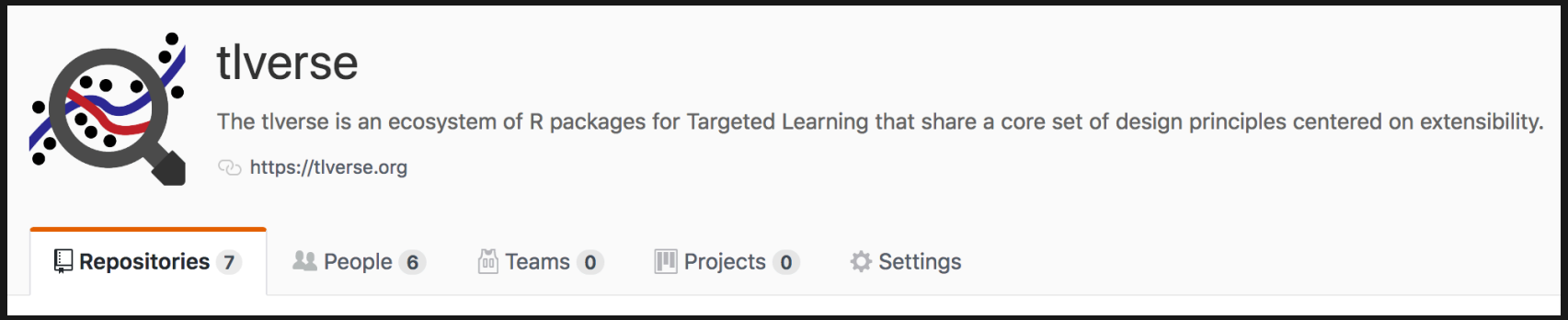
Software Ecosystem: The tlverse!



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- This is a new framework for Targeted Learning with a focus on extensibility.
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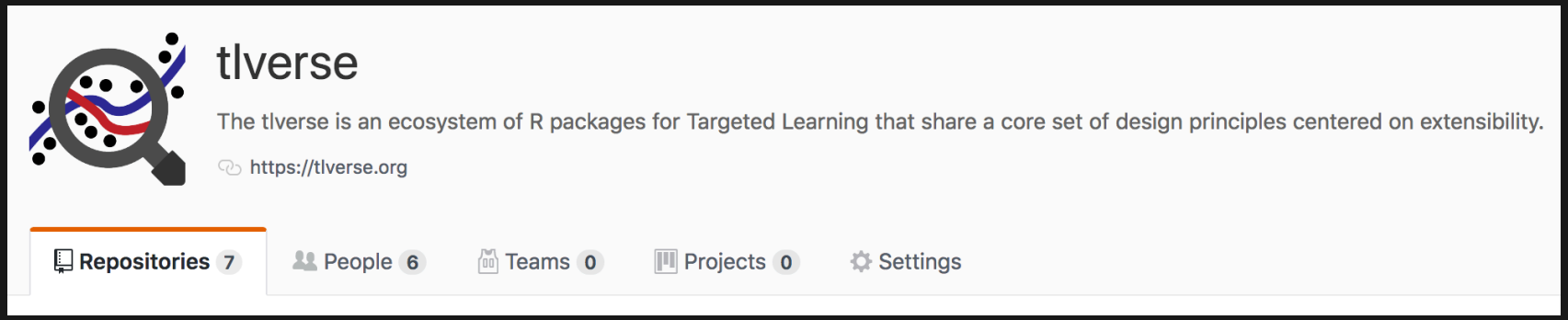

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Future Work

- Exploration of different forms of stochastic treatment shifts — EH Kennedy provides a shift in propensity score space in a recent JASA manuscript currently in press (collaboration in progress).
- Further refinement of the available software, explore how to provide a more efficient and extensible system, including stronger integration with the tlverse.
- Refinements of statistical theory so as to better work with quantities common in survival analysis: hazards? survival?
- Assessment of efficacy trials other than the HVTN 505 HIV-1 vaccine trial — perhaps further scientific findings?

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Review: Summary

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- Stochastic interventions provide a flexible framework through which these statistical problems may be viewed from the perspective of causal inference.
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Acknowledgments

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Mark J. van der Laan	University of California, Berkeley
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Holly E. Janes	Fred Hutchinson Cancer Research Center

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Thank you.

Slides: goo.gl/LAoDUJ

Notes: goo.gl/Vq6v5o

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