



## OVERVIEW & MOTIVATIONS

- We consider the problem of efficiently estimating the effect of a stochastic shift interventions in studies with two-phase sampling of the treatment.
- We present an estimator of the average counterfactual outcome under a stochastic shift intervention with
  - consistency and efficiency guarantees,
  - a multiple double robustness property.
- The proposed estimator is asymptotically normal with estimable variance, thereby allowing for the construction of confidence intervals and hypothesis tests.
- The *txshift* R package [2] implements these estimators and leverages state-of-the-art machine learning in the procedure.

## DATA: HIV VACCINE TRIALS

- Question: How does risk of HIV infection differ under shifts of an immune response in the vaccine arm of an efficacy trial?**
- We analyze data from the HVTN 505 HIV-1 efficacy trial, as in [3]:
  - RCT  $n = 2504$ , with  $n = 189$  in the second-stage sample.
  - Background ( $W$ ): sex, age, BMI, behavioral HIV risk
  - Intervention ( $A$ ): immune markers for post-vaccination CD4 and CD8 levels.
  - Outcome ( $Y$ ): HIV-1 infection status at week 28.
- Takeaway: Variable importance measure for ranking immune responses as immunogenicity study endpoints in future HIV-1 vaccine efficacy trials.**

## METHODOLOGY II: CORRECTIONS FOR TWO-PHASE SAMPLING

- In the HVTN 505 HIV-1 trial, all infected participants and the matched subset of controls have  $A$  (immunobiomarkers) measured, thus making the observed data structure  $O = (W, \Delta A, Y) \sim P_0$ .
  - $\Delta \in \{0, 1\}$  is the missingness mechanism introduced by sampling, under which the observed immune response ( $\Delta A$ ) is arbitrarily set to 0 when unobserved.
  - We assume that, given  $V := (W, Y)$ ,  $\Delta$  is Bernoulli distributed with probability  $\Pi_0(V)$ .

- The IPCW-TMLE [5] estimates the target parameter by adding *inverse weights* to the loss function.
- Improvements in the efficiency are attainable using a TMLE based on the EIF:

$$D(P_0)(o) = \frac{\Delta}{\Pi(v)} D^F(P_0^X)(x) - \left(1 - \frac{\Delta}{\Pi(v)}\right) \mathbb{E}(D^F(P_0^X)(x) \mid \Delta = 1, V = v)$$

- This augmented estimator exhibits several desirable properties
  - efficiency*, achieving the CR bound for the class of regular asymptotically linear estimators;
  - multiple robustness*, consistency of the parameter estimate when one of  $(g, Q)$  and one of  $(\Pi, \mathbb{E}_0(D^F(P_0^X)(X) \mid \Delta = 1, V))$  is consistently estimated;
  - valid statistical inference even when  $\Pi$  is estimated nonparametrically.

## METHODOLOGY I: THE EFFECT OF A STOCHASTIC INTERVENTION

- Consider  $X = (W, A, Y) \sim P_0^X \in \mathcal{M}$ , where  $W$  is a set of baseline covariates,  $A$  a treatment, and  $Y$  an outcome of interest, with no assumptions placed on the statistical model  $\mathcal{M}$ .
- Consider a shift of the treatment (i.e.,  $d(A, W)$ ) so that  $A = A + \delta$  for a user-specified shift  $\delta$ .
- To protect against violations of the assumption of positivity, the shifting mechanism may be made a function of the observed data, where  $u(w)$  is the maximum shift with support in the data:

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

- The causal parameter is identified by the observed data parameter [4]:

$$\Psi(P_0^X) = \mathbb{E}_{P_0} \bar{Q}(d(A, W), W), \quad (1)$$

where  $\bar{Q}(d(A, W), W)$  is the conditional mean of the outcome given  $A = d(A, W)$  and  $W$ .

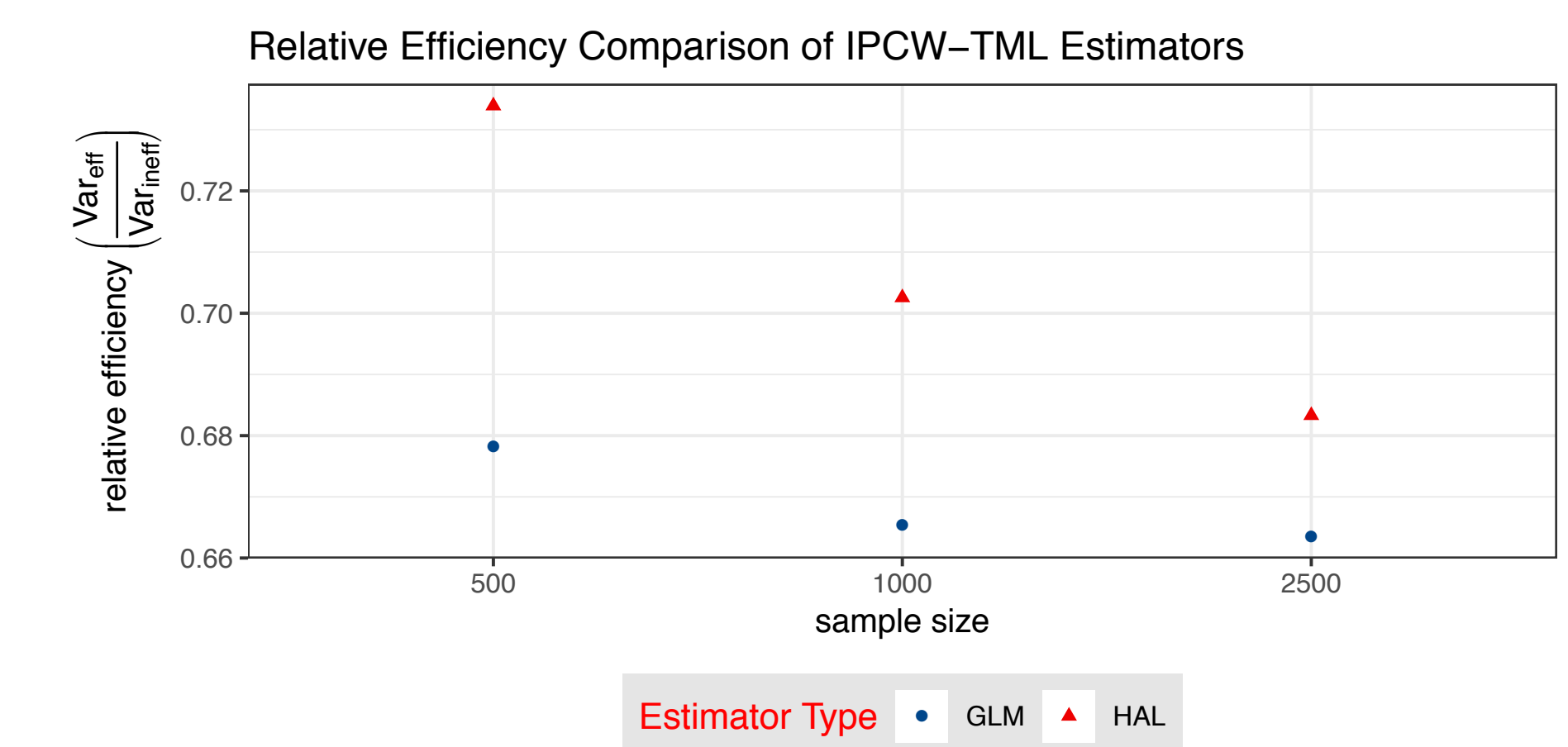
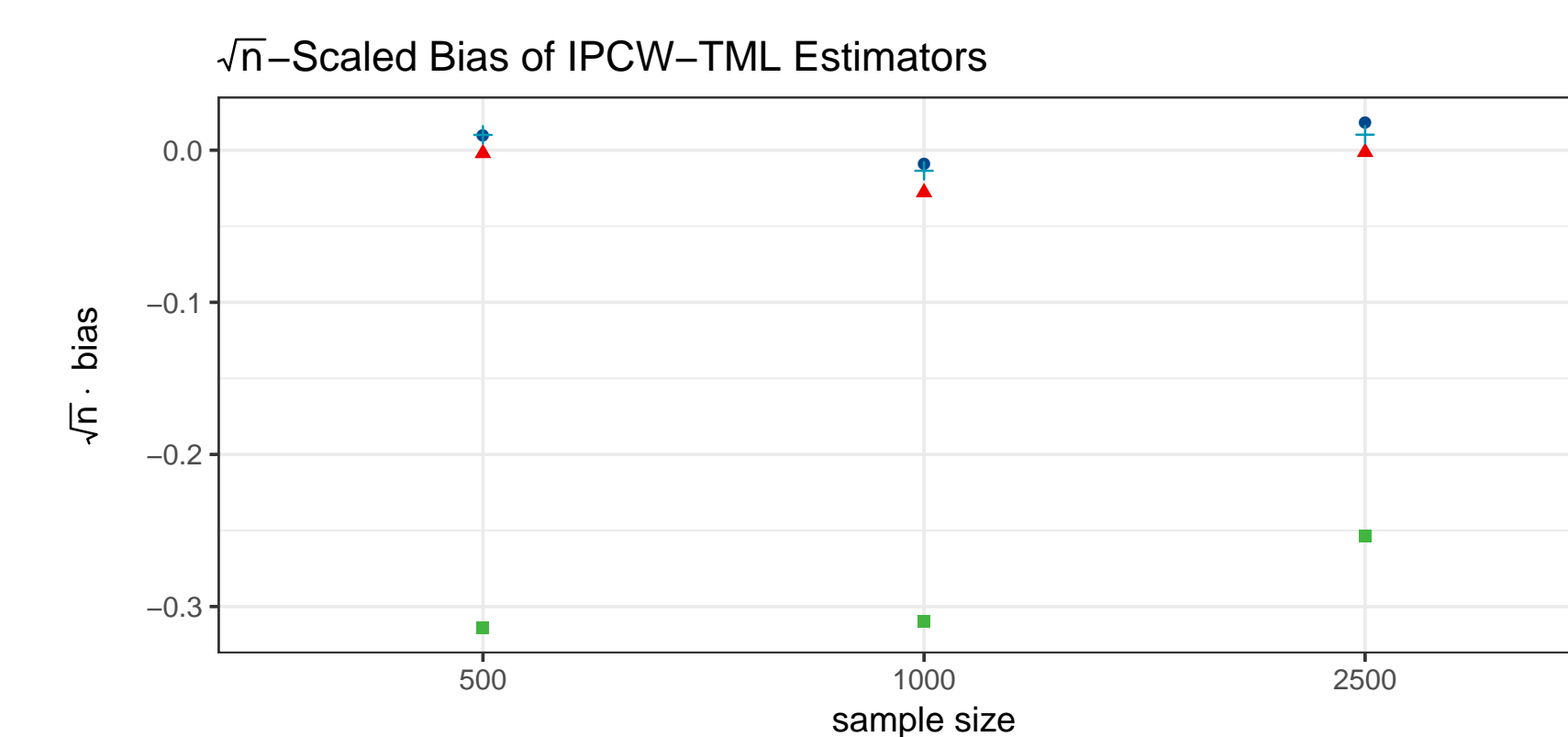
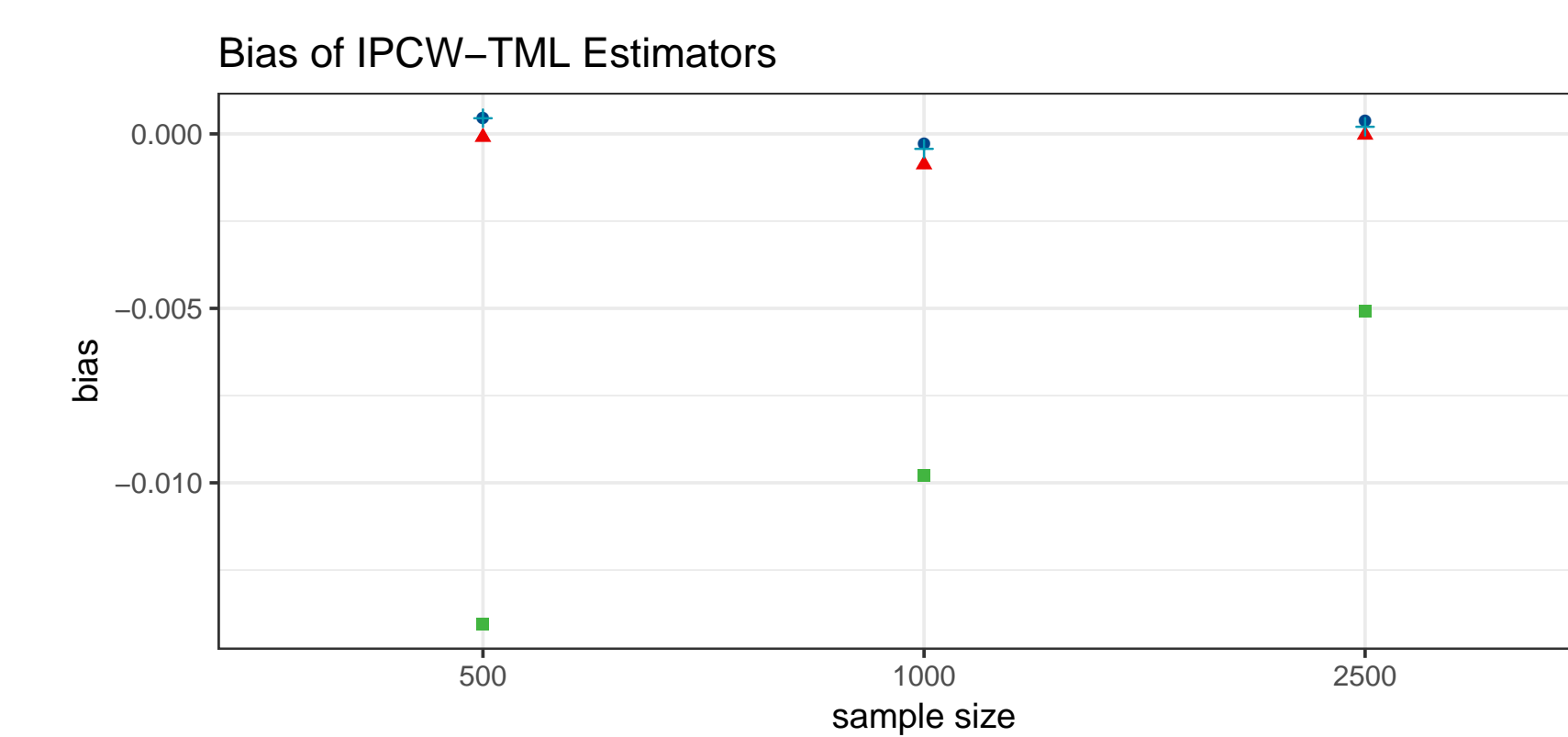
- The efficient influence function (EIF) of  $\Psi$  relative to a nonparametric model is

$$D^F(P_0^X)(x) = H(a, w)(y - \bar{Q}(a, w)) + \bar{Q}(d(a, w), w) - \Psi(P_0^X)(x), \quad (2)$$

where the auxiliary term,  $H(a, w)$ , may be expressed as

$$H(a, w) = \mathbb{I}(a < u(w)) \frac{g(a - \delta \mid w)}{g(a \mid w)} + \mathbb{I}(a \geq u(w) - \delta). \quad (3)$$

## RESULTS & DISCUSSION



- All estimators approx. unbiased in large samples; however, inefficient TMLE with HAL has bias not converging at  $n^{-\frac{1}{2}}$ .
- Fitting  $\Pi$  with HAL or GLM, efficient TMLE has lower variance than the inefficient.

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