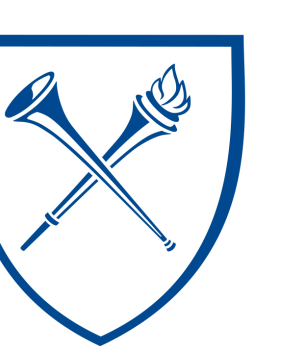




# Robust Nonparametric Inference for Stochastic Interventions Under Multi-Stage Sampling

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## 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

- Our approach is motivated by application to investigations of the effects of immune responses on HIV vaccine efficacy.
- Question: How does risk of HIV infection differ under shifts of an immune response in the vaccine arm of an efficacy trial?**
- We simulate a data structure based on the HVTN 505 HIV-1 efficacy trial, as in [3]:
  - 2504 participants, with all observed cases matched to controls.
  - Background ( $W$ ): sex, age, BMI, etc.
  - Intervention ( $A$ ): immunobiomarkers (i.e., T-Cell profiles from ICS assays on preserved HIV-1-stimulated PBMCs).
  - Outcome ( $Y$ ): HIV-1 infection status.
- Takeaway: Variable importance measure for ranking immune responses by utility as immunogenicity study endpoints in all future HIV-1 vaccine efficacy trials.**

## METHODOLOGY II: CORRECTIONS FOR TWO-PHASE SAMPLING

- In the HVTN 505 HIV-1 trial, all infected individuals are matched to controls using a complex matching mechanism, which makes the observed data structure  $O = (W, \Delta A, Y)$ .
  - $\Delta \in \{0, 1\}$  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] provides an avenue to estimate the target parameter by inverse weighting.
- Improvements in the efficiency of the IPCW-TMLE may be attained through a more complex EIF:

$$0 = P_n \frac{\Delta}{\Pi_n^*(V)} D^F(P_{X,n}^*) - \left\{ \frac{\Delta}{\Pi_n^*(V)} - 1 \right\} \mathbb{E}_n(D^F(P_{X,n}^0) \mid \Delta = 1, V) \quad (1)$$

- 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  $(\Pi, \mathbb{E}_0(D^F(P^F) \mid V))$  is consistently estimated;
  - valid statistical inference even when  $\Pi_0$  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  $\mathcal{M}$ .
- Rather than a deterministic intervention, consider a shift of the treatment 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, introduced in [4]:

$$\Psi(P_0) = \mathbb{E}_{P_0} \bar{Q}(d(A, W), W). \quad (2)$$

- The efficient influence function (EIF), given in [1], is

$$D^F(P_0^X)(x) = H(a, w)y - \bar{Q}(a, w) + \bar{Q}(d(a, w), w) - \Psi(P_0^X)(x), \quad (3)$$

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

$$H(a, w) = \mathbb{I}(a < u(w)) \frac{g_0(a - \delta \mid w)}{g_0(a \mid w)} + \mathbb{I}(a \geq u(w) - \delta). \quad (4)$$

## RESULTS & DISCUSSION

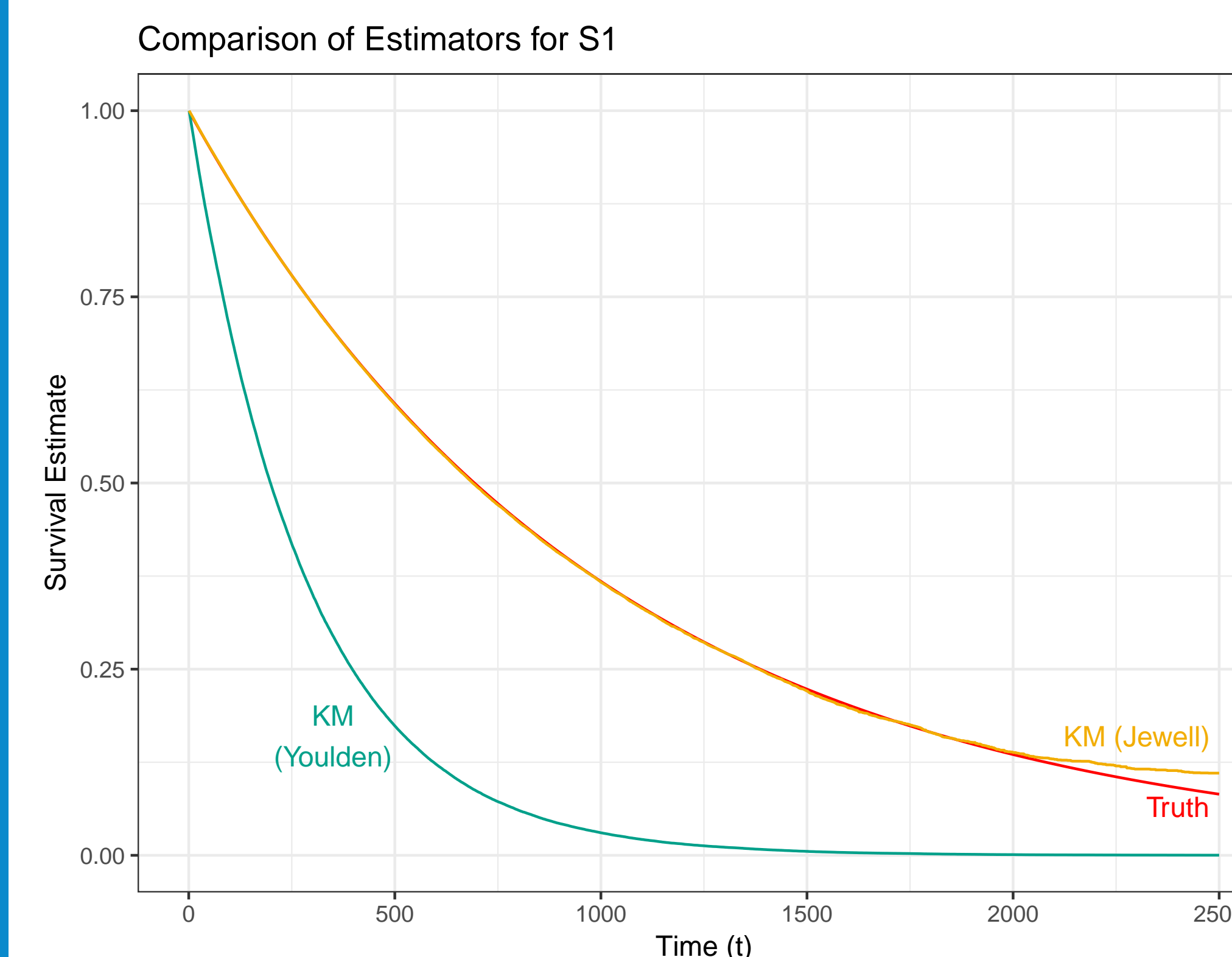


Figure 1: This figure demonstrates...

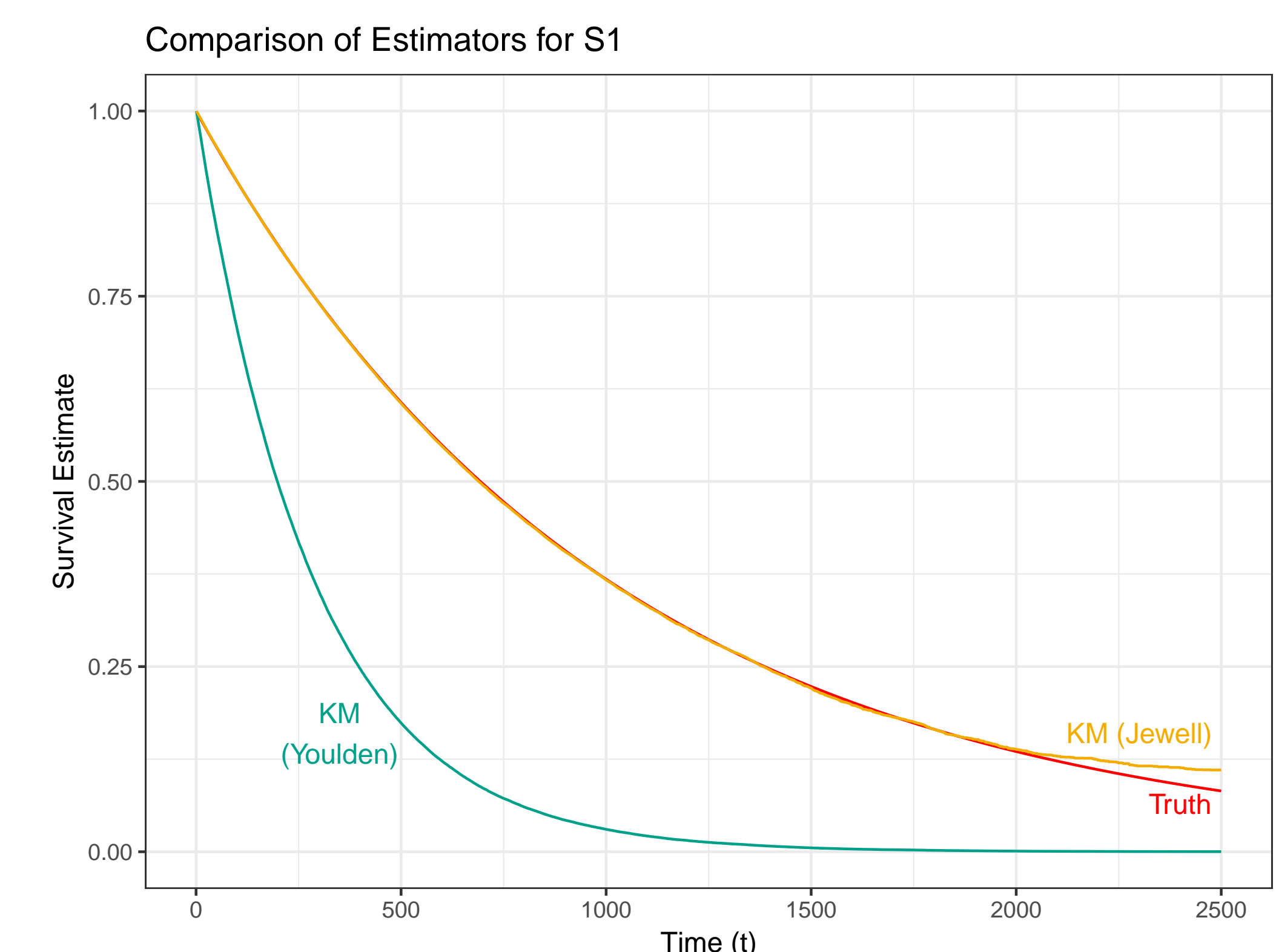


Figure 2: This figure demonstrates...

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