Nonparametric Analysis of Delayed Treatment Effects using Single-Crossing Constraints

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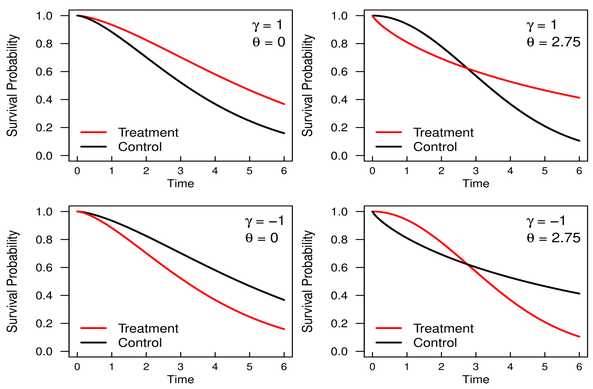
Motivation

Clinical trials involving novel immuno-oncology (I/O) therapies often exhibit survival profiles which violate the proportional hazards assumption. In such settings, the treatment of interest often shows a delayed effect where the survival curves in the two treatment arms largely overlap or cross before the two curves separate. To flexibly model these scenarios, we describe a constrained nonparametric approach which allows the survival functions to have at most one crossing point without making any additional assumptions about how the survival curves in the two treatment arms are related.

Survival Curves with a Single-Crossing Constraint

Let $S_a(t)$ be the survival curve for group a ($a = 0$ control arm, $a = 1$ active treatment arm). We assume the survival curves $S_1(t)$, $S_0(t)$ can cross **at most once**.



- With a single-crossing constraint, there are four possible survival profiles:
  (1) $S_1(t) \geq S_0(t)$ for all $t \geq 0$.
  (2) $S_0(t) \geq S_1(t)$ up to some crossing time θ, but $S_1(t) \geq S_0(t)$ for $t > \theta$.
  (3) $S_1(t) \geq S_0(t)$ up to some crossing time θ, but $S_0(t) \geq S_1(t)$ for $t > \theta$.
  (4) $S_0(t) \geq S_1(t)$ for all t.
- The parameter γ indicates which treatment has better long-term survival.
  - $\gamma = 1$: active treatment arm has better long-term survival
  - $\gamma = -1$: control arm has better long-term survival.

Two-Stage Estimation Approach

Using a **two-stage estimation procedure**, nonparametric estimates of the survival curves with a single-crossing constraint can be obtained.

Stage 1: Estimate Survival Curves for known values of the crossing parameters (θ, γ).
- Compute nonparametric estimates of the jumps $\hat{u}_{ja}(\theta, \gamma)$ in the log-survival functions $\log S_a(t)$.
- For fixed (θ, γ), this is done by maximizing the nonparametric log-likelihood subject to linear inequality constraints which ensure the single-crossing constraint holds.
- Compute the jumps $\hat{u}_{ja}(\theta_k, \gamma_k)$ over a grid of parameter values: $(\theta_1, \gamma_1), \ldots, (\theta_K, \gamma_K)$.

Stage 2: Find the best value of the crossing parameters (θ, γ) by maximizing the profile log-likelihood.
- The profile log-likelihood $\ell^P(\theta, \gamma)$ is found by plugging the jump parameters $\hat{u}_{ja}(\theta_k, \gamma_k)$ into the nonparametric log-likelihood.
- Estimates of the crossing parameters $(\hat{\theta}_{sc}, \hat{\gamma}_{sc})$ are found by finding the maximum value of $\ell^P(\theta_k, \gamma_k)$, $k = 1, \ldots, K$.

- The **single-crossing constrained** estimate of the survival function in treatment arm a is defined as:

$$\hat{S}_a^{sc}(t) = \exp\left\{ \sum_{j=1}^{m} \hat{u}_{ja}(\hat{\theta}_{sc}, \hat{\gamma}_{sc}) I(t_j \leq t) \right\},$$

where $0 < t_1 < t_2 < \ldots < t_m$ are the unique, ordered event times from both treatment arms.

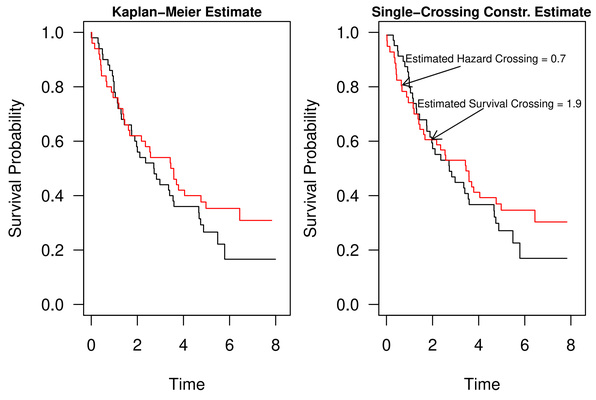


Figure: Kaplan-Meier estimates and single-crossing constrained estimates of survival curves using simulated data. The estimates of the crossing parameters are $\hat{\theta}_{sc} = 1.9$ and $\hat{\gamma}_{sc} = 1$.

Quantities of Interest using Single-Crossing Constrained Estimates

Constrained estimates of the crossing parameters and survival curves can be used to estimate **novel, interpretable measures of treatment efficacy.**

- The **proportion of patients surviving up to crossing** is defined as the parameter $\psi = S_1(\theta)$.
- Estimating this parameter can address concerns about a large percentage of patients dying before the crossing occurs.
- Using our approach, this can be estimated with

$$\hat{\psi} = \hat{S}_1^{sc}(\hat{\theta}_{sc}).$$

- The **restricted residual mean life** (RRML) can compare treatment efficacy among longer survivors.
- Our estimate of RRML with a lower truncation point at the estimated crossing time $\hat{\theta}_{sc}$ is

$$\widehat{\text{RRML}}_a(\hat{\theta}_{sc}, \tau) = \int_{\hat{\theta}_{sc}}^{\tau} \frac{\hat{S}_a^{sc}(u)}{\hat{S}_a^{sc}(t)} du.$$

- $\widehat{\text{RRML}}_a(\hat{\theta}_{sc}, \tau)$ is an estimate of the expected remaining time on study up to time τ, conditional on surviving up to the crossing time θ.

- **Crossing-time conditional survival curves** give survival probabilities conditional on the fact that one survives up to the crossing time θ.
- The estimated crossing-time conditional survival curves are defined as

$$\hat{S}_{a,cond}(t) = \hat{S}_a^{sc}(t) / \hat{S}_a^{sc}(\hat{\theta}_{sc}).$$

A Combination I/O Trial

We applied our method to a recent phase 3 trial studying the use of a combination of the immune checkpoint inhibitors nivolumab and ipilimumab in the treatment of non-small-cell lung cancer (NSCLC). The main interest in this trial was comparing overall survival in the chemotherapy arm and the nivolumab + ipilimumab arm. 583 patients were in each of the nivolumab + ipilimumab and chemotherapy arms. Median overall survival was 17.1 and 13.1 months in the combination and chemotherapy arms respectively.

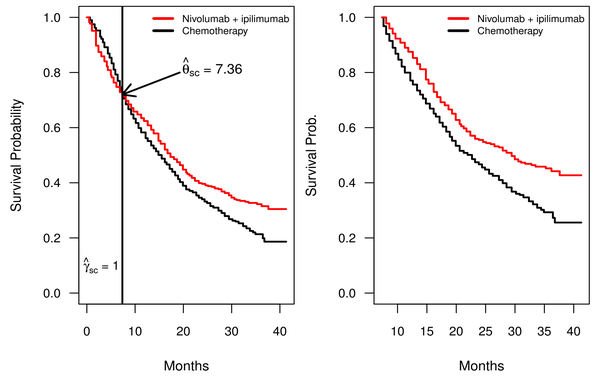


Figure: Survival estimates from the nivolumab+iplimumab vs. chemotherapy trial. The left-hand panel shows the single-crossing constrained survival curve estimates $\hat{S}_1^{sc}(t)$ and $\hat{S}_0^{sc}(t)$. The right-hand panel shows estimates $\hat{S}_{1,cond}^{sc}(t)$ and $\hat{S}_{0,cond}^{sc}(t)$ of the crossing-time conditional survival curves.

Parameter	Estimate	95% CI
θ	7.36	(4.2, 23.8)
ψ	0.73	(0.4, 0.9)
$\text{RRML}_1(\theta, 36) - \text{RRML}_0(\theta, 36)$	2.43	(1.1, 5.0)
$S_1(6) - S_0(6)$	-0.03	(-0.09, 0.02)
$S_1(12) - S_0(12)$	0.04	(-0.03, 0.12)
$S_1(24) - S_0(24)$	0.06	(-0.01, 0.13)
$S_{1,cond}(12) - S_{0,cond}(12)$	0.06	(0.0, 0.15)
$S_{1,cond}(24) - S_{0,cond}(24)$	0.08	(0.0, 0.16)

Table: Single-crossing constrained estimates of different efficacy measures for the combination I/O vs. chemotherapy trial. 95% confidence intervals were found using the bootstrap.

Conclusion

Our method provides nonparametric estimates of the survival curves in two treatment arms when these two curves are constrained to cross at most once. This method can be useful in I/O trials where it is expected that delays in treatment effect will occur. Our approach can improve estimation performance in cases where the true survival curves conform to the single crossing constraint and can be used to help estimate interpretable measures of treatment efficacy that are designed for cases of delayed treatment effect.

Selected References

[1] Chen, T-T. (2013). "Statistical issues and challenges in immuno-oncology." *Journal for immunotherapy of cancer* **1**, 18.

[2] Henderson, N.C., Nam, K., Feng, D. (2021). "Nonparametric Analysis of Delayed Treatment Effects using Single-Crossing Constraints." arXiv:2102.00409.