Non-Parametric Estimation of Optimal Individualized Treatment Rules for Survival Data

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Outline

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Preface

Aim: Introduction to Precision Medicine. Motivate non-parametric estimation approach.

Aim: Build understanding towards Bakoyannis (2023) "Estimating optimal individualized treatment rules with multistate processes", Biometrics.

Keywords: Precision Medicine , Individualised Treatment Rules, Dynamic Treatment Regimes

Individualized Treatment Rules (ITRs)

- Identify subgroups of patients that respond differently to treatment
- Extend population health outcomes
- Spare patients from aggressive treatment if unlikely to benefit

Individualized Treatment Rules (ITRs)

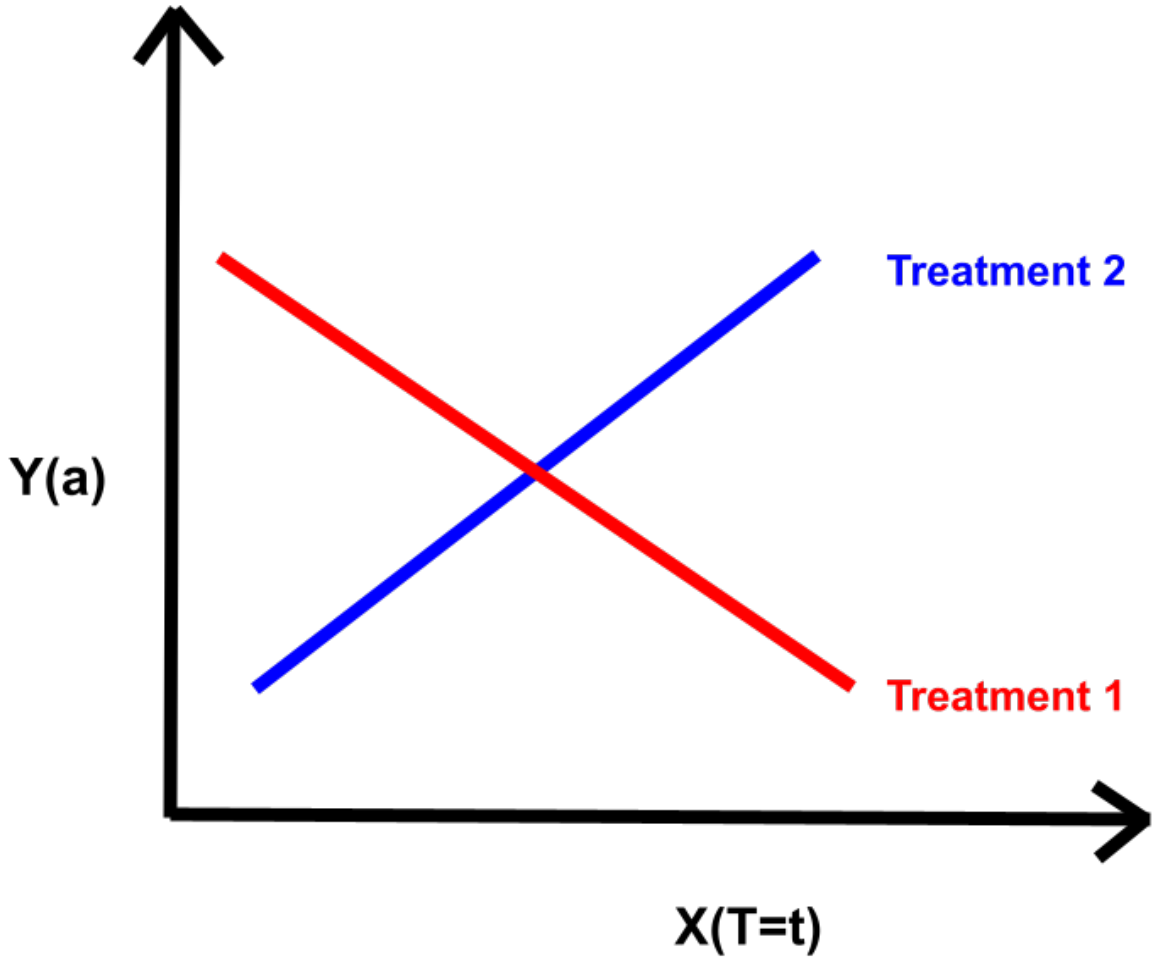


Figure: Point Exposure Prescriptive Treatment Effect

Individualized Treatment Rules (ITRs)

An Individualized Treatment Rule recommends treatment A_i to patient i given their medical characteristics X.

$$ITR := f : X \rightarrow A$$

Goal: Learn optimal ITR function that optimise expected patient outcomes $E[Y]$

Desired ITR Properties

1. Unbiased despite censored survival outcomes
2. Operate under the Causal Inference framework
3. Guarunteed Convergence in finite sample
4. Robust to model misspecification (non-parametric)

Simplest Problem Setup

- Randomized Controlled Trial (RCT) data
- Single treatment assignment stage (t=0)
- Binary treatment options: $A \in \{-1, 1\}$

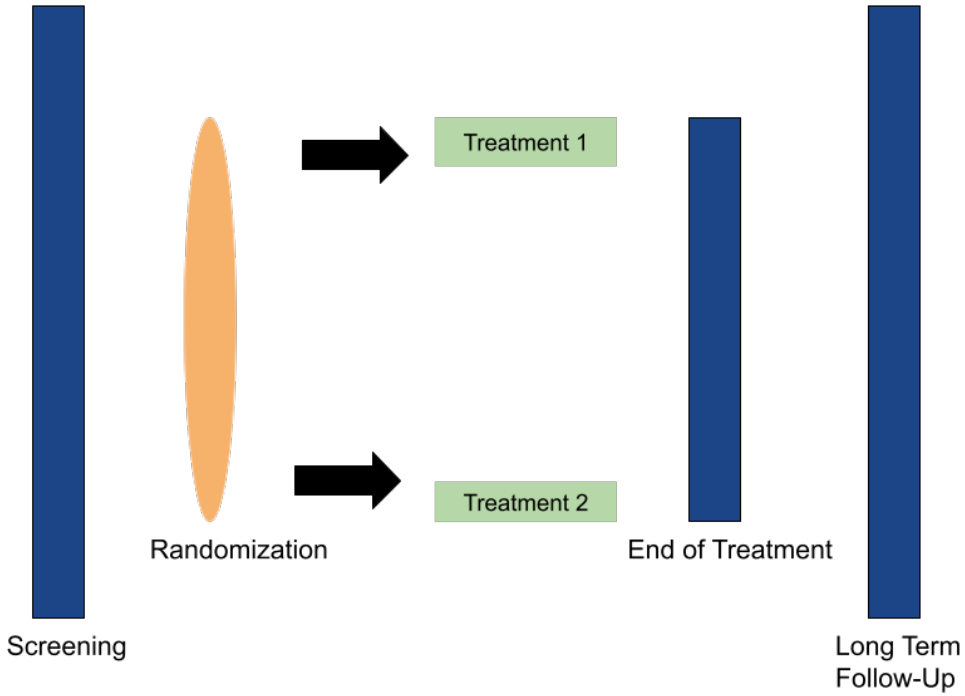


Figure: Single Stage, Two Arm

Causal Inference Framework

- Observed Outcome

$$Y_i(A = a) \tag{1}$$

- Potential Outcomes:

$$Y_i^*(A = a), Y_i^*(A \neq a) \tag{2}$$

- Individual Treatment Effect:

$$\delta_i^* = Y_i^*(1) - Y_i^*(0) \tag{3}$$

- Average Treatment Effect:

$$\begin{aligned} \delta^* &= E[Y^*(1) - Y^*(0)] \\ &= n^{-1} \sum_1^n \Big[Y_i^*(A = 1) - Y_i^*(A = 0) \Big] \end{aligned}$$

Causal Inference Framework

- **Aim:** Estimate Average Treatment Effect:

$$\delta^* = n^{-1} \sum_{1}^{n} \Big[Y_i^*(A=1) - Y_i^*(A=0) \Big]$$

- For each patient, we can only ever observe one outcome!
- Missing Data estimation methods are useful here

Causal Inference Assumptions

1. **SUTVA: Stable Unit Treatment Value Assumption.**
   i) Patients do not affect each other.
   ii) Potential Outcome is equivalent to Observed.

$$Y_i = Y_i^*(1)A_i + Y_i^*(0)(1 - A_i), i = 1, ..., n \tag{4}$$

2. **Strong Ignorability:** No unmeasured confounders

$$\{Y^*(1), Y^*(0)\} \perp\!\!\!\perp A, X \tag{5}$$

3. **Positivity:** Non-zero probabilities of each treatment being assigned to each patient

$$P(A = a|X = x) > 0, a = 0, 1 \forall x \in X \text{ s.t. } P(X = x) > 0 \tag{6}$$

Outcome Regression for Causal Inference

$$E[Y|A,X] = \beta_1 + \beta_2 a + \beta_3^T x + \beta_4^T xa + ||\lambda I|| \tag{7}$$

$$V_Q(d^*) = E\left\{\max_{a\in\mathbb{A}} Q(X,a;\beta)\right\} \tag{8}$$

Model Assumptions:

1. **Linearity:** The relationship between X and the mean of Y is linear.
2. **Homoscedasticity:** The variance of residual is the same for any value of X.
3. **Independence:** Observations are independent of each other.
4. **Normality:** For any fixed value of X, Y is normally distributed.

Inverse Probability Weighting (IPW)

Non-parametric M-estimator, $\sqrt{N}$ consistent asymptotically normal

$$E[Y] = n^{-1} \sum_{i=1}^{n} Y \frac{A_i}{\pi(A_i|X_i)^{-1}} \tag{9}$$

Bias correction:

1. Causal Inference: Propensity of Treatment

$$w_A = \frac{I(D(X) = A)}{\pi(A|X)} \tag{10}$$

2. Survival Analysis: Probability of Censoring

$$w_C = \frac{I(C > min(T, \tau))}{\pi(C|X)} \tag{11}$$

IPW toy example

Observed population: aaaaaaaa bb
Calculate Weights:

$$p(a) = .8 \Rightarrow w_{ipw}(\text{a}) = 1.25$$
$$p(\text{not a}) = 0.2 \Rightarrow w_{ipw}(\text{not a}) = 5$$

Pseudo-population: aaaaaaaaaa bbbbbbbbb
Legend:

- Black = observed units
- Blue = pseudo-units

IPW Consitency

Law of Total Expectation

$$E[X] = E[E[X|Y]]$$

- Double expectation over conditional expectation
- Can provide consistent estimates despite incomplete data

Radon-Nikodym Derivative for IPW

$$\frac{dP_d}{dP_\pi} = \frac{I(a = D(x))}{P(A = a)}$$

- Change of Probability Measure
- Relies on Positivity Assumption

Outline

Survival Data

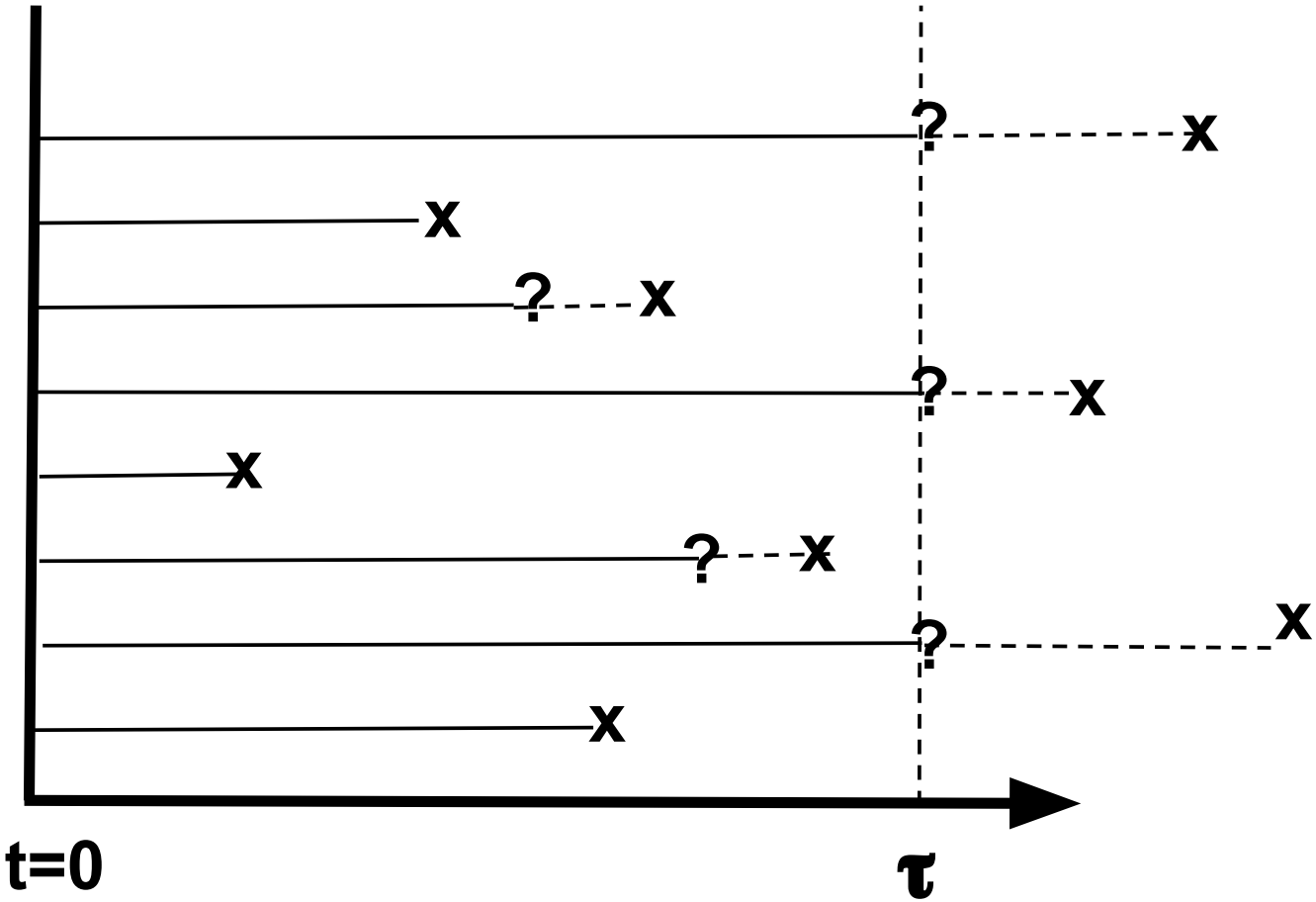


Figure: Right-Censored Survival Data

Survival Variables

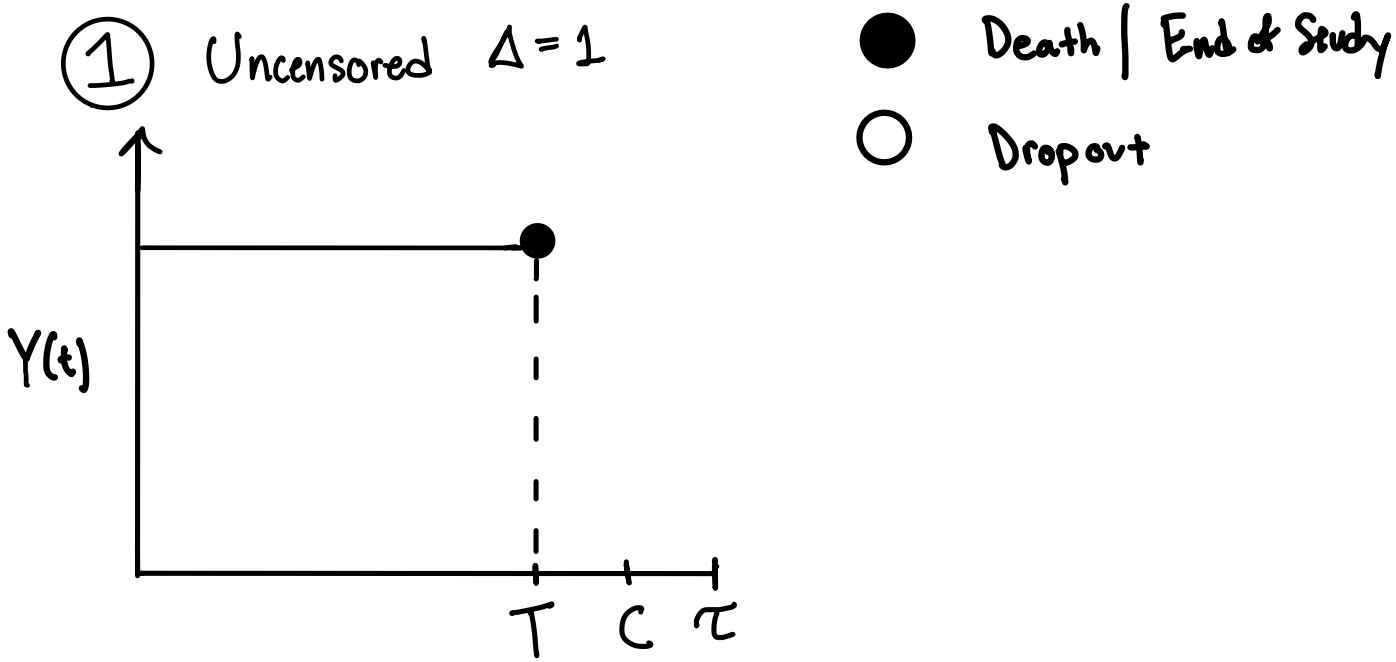
τ	End of Study
$T \in [0, +\infty]$	Survival Time
$C \in [0, +\infty]$	Censoring Time
$\tilde{T} = min(T_i, \tau)$	Restricted Survival Time
$T^* = min(\tilde{T}_i, C_i)$	Observed Restricted Survival Time
$\Delta_i = \mathbb{I}(\tilde{T}_i \leq C_i)$	Event Status

Restricted Mean Survival Time (RMST)

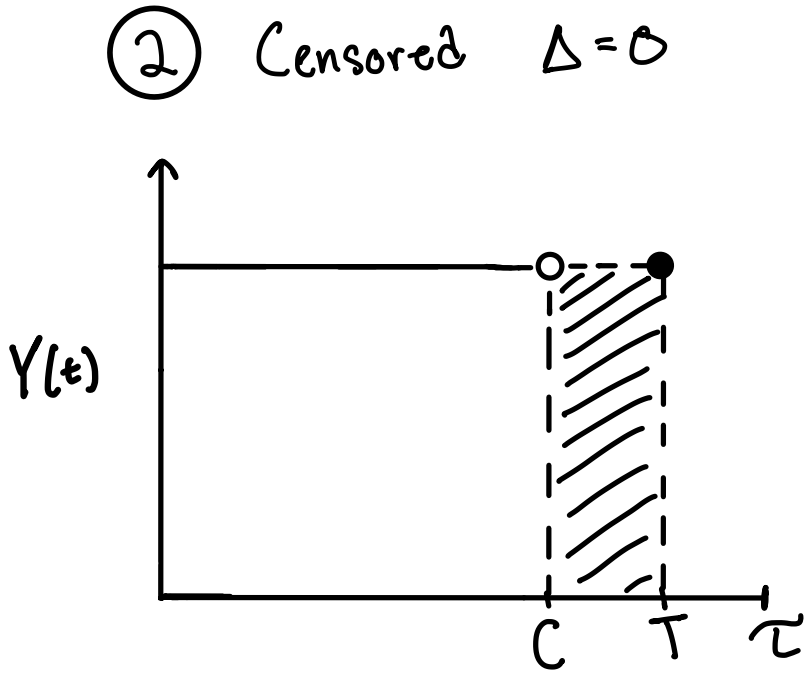
$$E_\tau[Y(t)] = \int_0^\tau Y(t)dt \tag{12}$$

- Popular estimand in biomedical applications
- Avoids difficult extrapolation beyond end-of-study
- Interpretation: Which treatment yields higher probability of surviving at least 5-years?

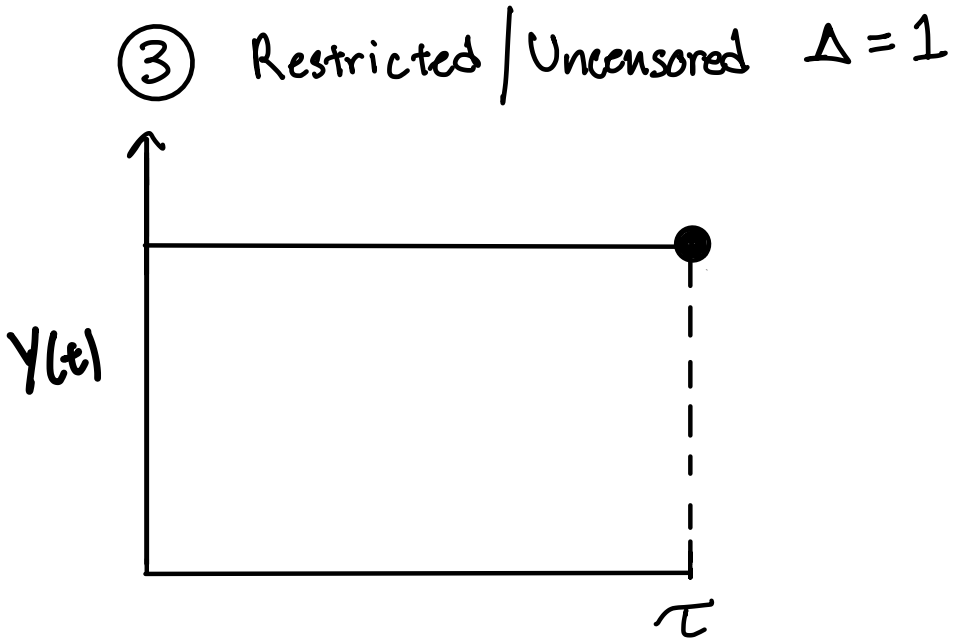
Restricted Survival - Scenario 1



Restricted Survival - Scenario 2



Restricted Survival - Scenario 3



Inverse Probability of Censoring Weighting

$$E[T] = n^{-1} \sum_{i=1}^{n} \frac{\Delta_i T_i}{P(C_i|X_i)} \tag{13}$$

- Corrects bias from right-censored observations
- Inflates observed survivals by inverse censoring probability

Survival Function

$$S(t) = P(T \geq t) = 1 - F(T \leq t) \tag{14}$$

Characterizes the probability that patient will survive up to or past time t.

Hazard Function

- Instantaneous risk of death at time t, conditioned on survival up to time t.

$$\begin{aligned} h(t) &= \lim_{\epsilon \to 0} \frac{Pr\big(t < t + \epsilon | T \geq t\big)}{\epsilon} \\ &= f(t)/S(t) \\ &= \frac{-d \log S(t)}{dt} \end{aligned} \tag{15}$$

- Mathematically transportable to Survival Function

$$S(t) = exp(-H(t)) \tag{16}$$

Kaplan-Meier Estimator

$$\hat{S}(t) \approx \prod_{i:t_i \leq t} \left(1 - \frac{d_i}{n_i}\right) \tag{17}$$

- Product-limit estimator naturally handles right-censored data
- Non-parametric estimator of survival function

Cox Proportional Hazards Regression

$$\hat{h}(t; z) = h_0(t)\psi(t) \tag{18}$$

$$\psi(t) = exp(z^T \beta),\ \beta \in \mathbb{R}^P \tag{19}$$

- Semi-parametric: Baseline hazard h_0 left unspecified
- Parameterize only proportional hazard term ψ
- Assumption: Hazard rates are proportional between groups over time

Generating Survival Times from Cox Regression

Inverse Transform Sampling

Uniformly-randomly distributed values $U \sim U[0,1]$ are plugged into the inverse CDF F^{-1} to sample from the distribution function.

$$
\begin{aligned}
S(t|x) &= 1 - F(t) && \text{Survival Function} \\
&= exp(-H(t)) && \text{by defn Eq. 16} \\
F(t) &= U \sim Unif(0,1) && \\
U &= 1 - S(t|x) && \\
&= S(t|x) && Unif(0,1) = 1 - Unif(0,1) \\
t &= S^{-1}(U) &&
\end{aligned}
$$

Outline

Value Function

- The Value $V(d)$ of a rule $D(X) = d$ is the mean health outcome $E[Y]$ on population X
- Empirically select patients from sample that coincide with treatment of proposed rule $D(X)$, i.e. $I(A = D(X))$

$$
\begin{aligned}
V(D) &= E_D(Y) \\
&= \int Y dP_D \\
&= \int Y \frac{dP_D}{dP} dP \\
&= E\Big[\frac{I(A = D(X))}{A\pi + (1 - A)/2} Y\Big]
\end{aligned} \tag{20}
$$

Direct Value Search Approach

- Treat ITR estimation as non-parametric classification problem
- Discover optimal treatment rule D^* that maximizes expected value $E_D(Y)$

$$D^* \in \arg\max_{\mathcal{D}} E^D(Y) \tag{21}$$

- Equivalent to Empirical Risk Minimization (ERM)

$$D^* \in \arg\min_{\mathcal{D}} \mathscr{R}(D) \tag{22}$$

Outline

Outcome Weighted Learning (OWL)

Zhao et al. (2012) propose using an IPW value estimator as criterion for Support Vector Machine (SVM) statistical learning algorithm
Value Function:

$$\mathcal{D}^* \in \arg\max_{\mathcal{D}} \mathbb{E}\left[\frac{\mathbb{I}(A = \mathcal{D}(X))}{A\pi + (1-A)/2} Y\right] \tag{23}$$

Specificy risk criterion to (any) classifier within the ERM framework.

$$\mathscr{R} = E\Big[\frac{I(A = D(X))}{A\pi + (1-A)/2}\phi(Af(x))\Big] \tag{24}$$

Where ϕ is a surrogate loss function (e.g., hinge loss for SVM).

Support Vector Machine (SVM)

$$\left[\frac{1}{n}\sum_{i=1}^{n}\phi\Big(y_i(w^T x - b)\Big)\right] + \lambda|w|^2 \tag{25}$$

- Statistical Learning methodology for classification
- Discriminatory hyperplane between two convex classes
- Soft-margin allows for optimisation over non-separable data
- Finite sample convergence for linear rules

Hinge Loss

- Hinge loss is surrogate for 0-1 loss
- $\phi(x) = \max(0, 1 - x)$

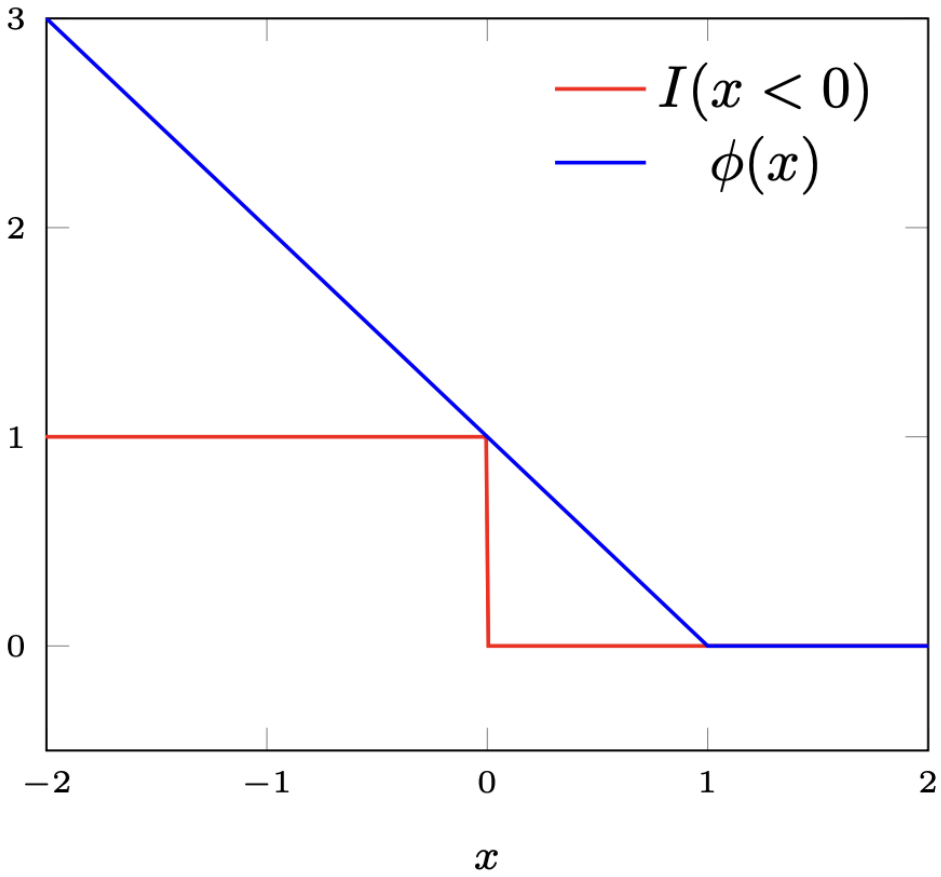


Figure: SVM Hinge Loss Function

SVM Covariance Structure

- Defined on Reproducing Hilbert Function Spaces (RHFS)
- Geometric dot-product spaces with defined covariance structure
- Focus on simple kernels:

$$\text{Euclidean:} \quad K = X^T * X$$

$$\text{Gaussian:} \quad K(x_i, x_j) = -\gamma \|x_i - x_j\|^2$$

SVM Convergence

$$\lim_{n\to\infty} \mathbb{P}\Big(d(\tilde{f}_n, f^*) > \epsilon\Big) \to 0, \forall \epsilon > 0 \tag{26}$$

- Weak convergance to tight mean gaussian limiting distribution.
- When restricted to the linear class of functions, ERM classifiers have guaranteed rate of weak convergence of $n^{-1/2}$ (Tsybakov, 2004).
- Larger the dimensionality of covariate-space the slower the convergence of the estimator, large-P *curse of dimensionality*.
- Equicontinuity assumption states that at least one continuous covariate must be involved in order to ensure
- SVM rate of convergance depends partially on separability of the given data set and the number of support points lying along the separating margin. Zhao et al. (2012)
- Reguralization Parameter λ plays role in convergence

Optimal Linear Rule

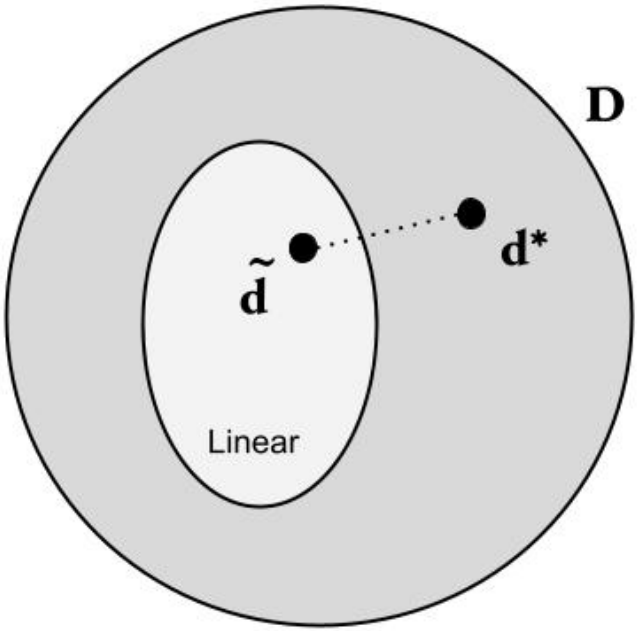


Figure: Optimal linear rule $\tilde{d}$ is a projection of true optimal rule d^* onto linear subspace.

Inverse Censoring Outcome (ICO) Method

$$V(D) = \mathbb{E}\left[\frac{\Delta_i}{\hat{S}_c(Y|A,X)} \frac{\mathbb{I}(A = \mathcal{D}(X)}{\pi(A;X)} T_i\right]$$

- Zhao et al. (2015) Extends OWL to handle right-censored data
- Compensates by Inverse Probability of Censoring weighting
- Assumes non-informative censoring
- Ignores censored outcomes $\Rightarrow$ high variance

SVM Visualisation

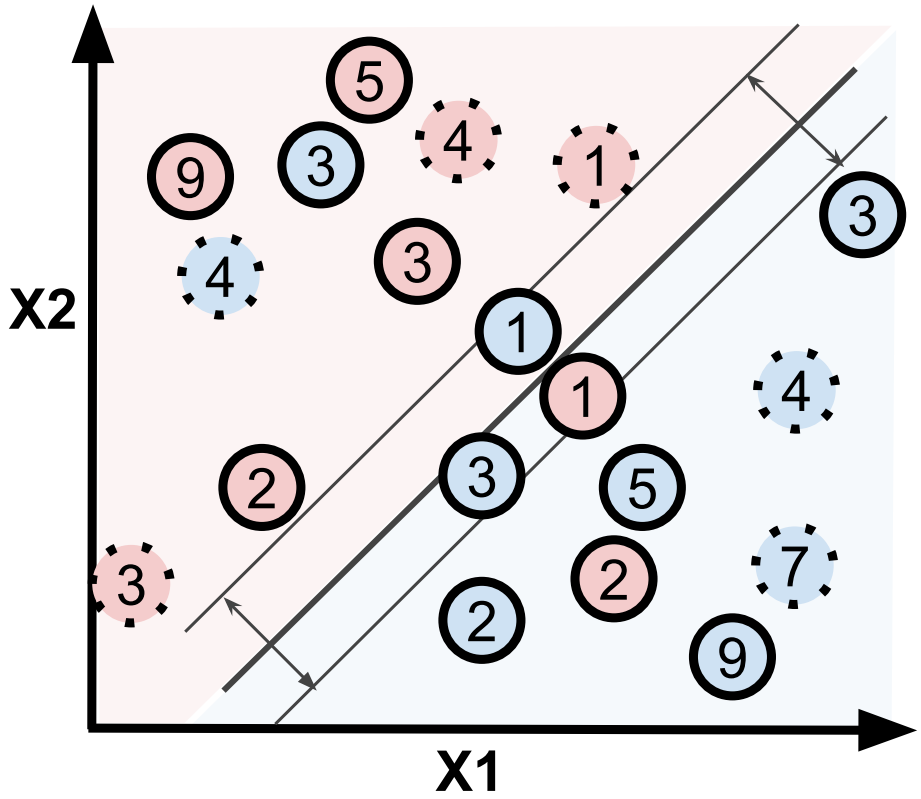


Figure: **Weighted SVM treatment classifier for right-censored data**. Number: Missclassification cost. Border: Solid=Uncensored, Dashed=Censored. Color: True Optimal Treatment

Multistate Outcome Weighted Learning (MSOWL)

$$V(D) = \mathbb{E}\left(\left[\int_0^{\tau} \frac{Y(t) I(C \geq (T_i \wedge t))}{S_c(\tilde{T} \wedge t))} dm(t) \right] \frac{\mathbb{I}(A_i = \mathcal{D}(X)}{\pi(A; X)} \right)$$

- Incorporates patient preferences of disease state & progression
- Fisher-consistent (lowest possible variance)
- Integrates each individual's multi-state stochastic process, even if censored, then take expectation
- Inverse Probability of Censoring Weighting on each Reimmanian rectangle discretized according to Kaplan-Meier event timepoints

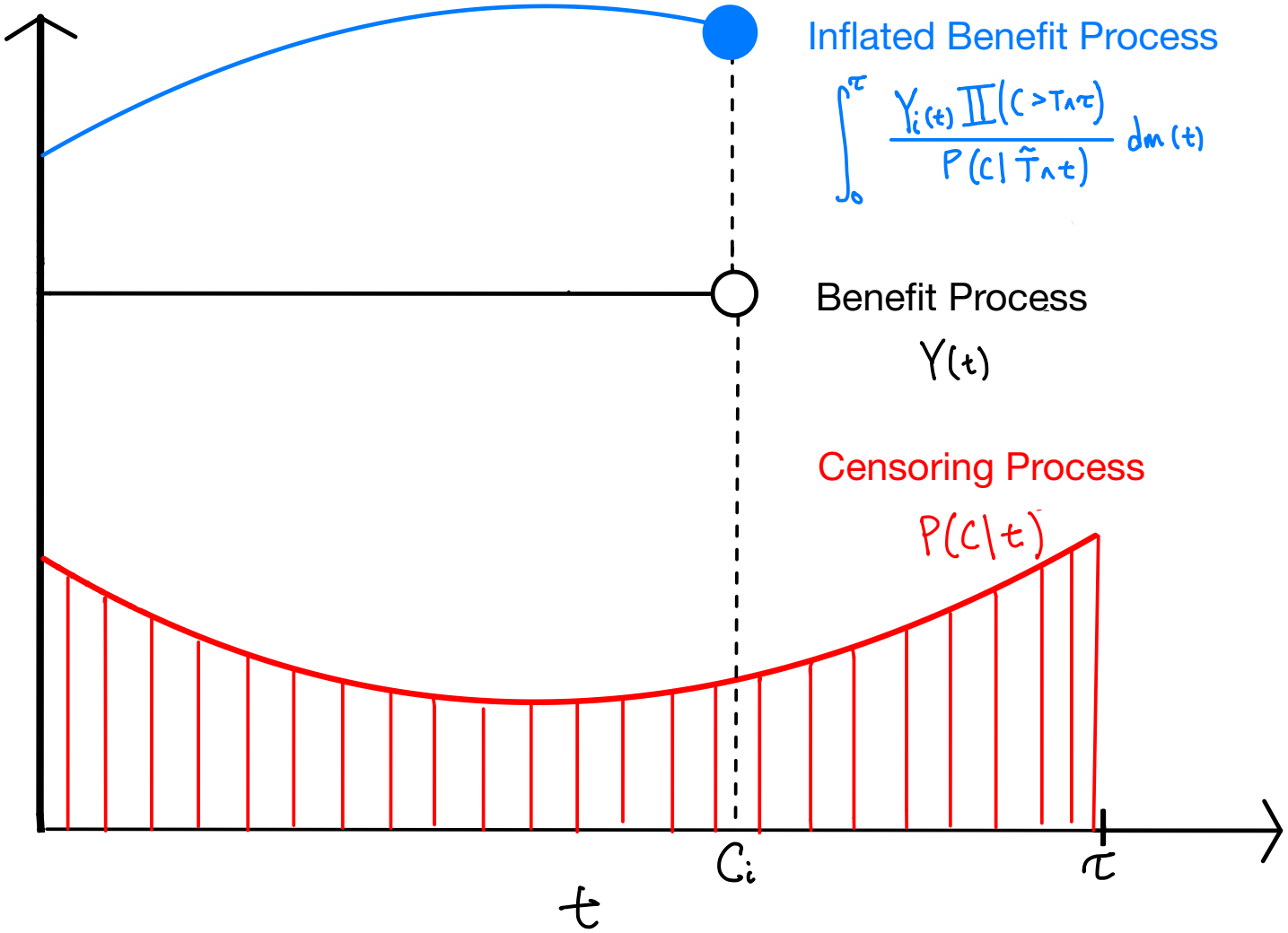


Figure: MSOWL IPCW-Inflated Stochastic Integration

Outline

Case Study with Real RCT Data

- "PRIME Trial"
- Disease: Pancreatic Cancer
- Treatments: Panitumumab (immuno) vs FOLFOX (chemo)
- Focus on Progression-Free Survival
- Clinical Markers: Age, ECOG, Sex
- Genetic Biomarker: KRAS (352 Mutant / 514 Wild-Type)
- Immunotherapy vs Chemotherapy: may reveal a delayed-response in survival curve, may invalidate Cox's proportional hazard assumption

PRIME: Survival Curves

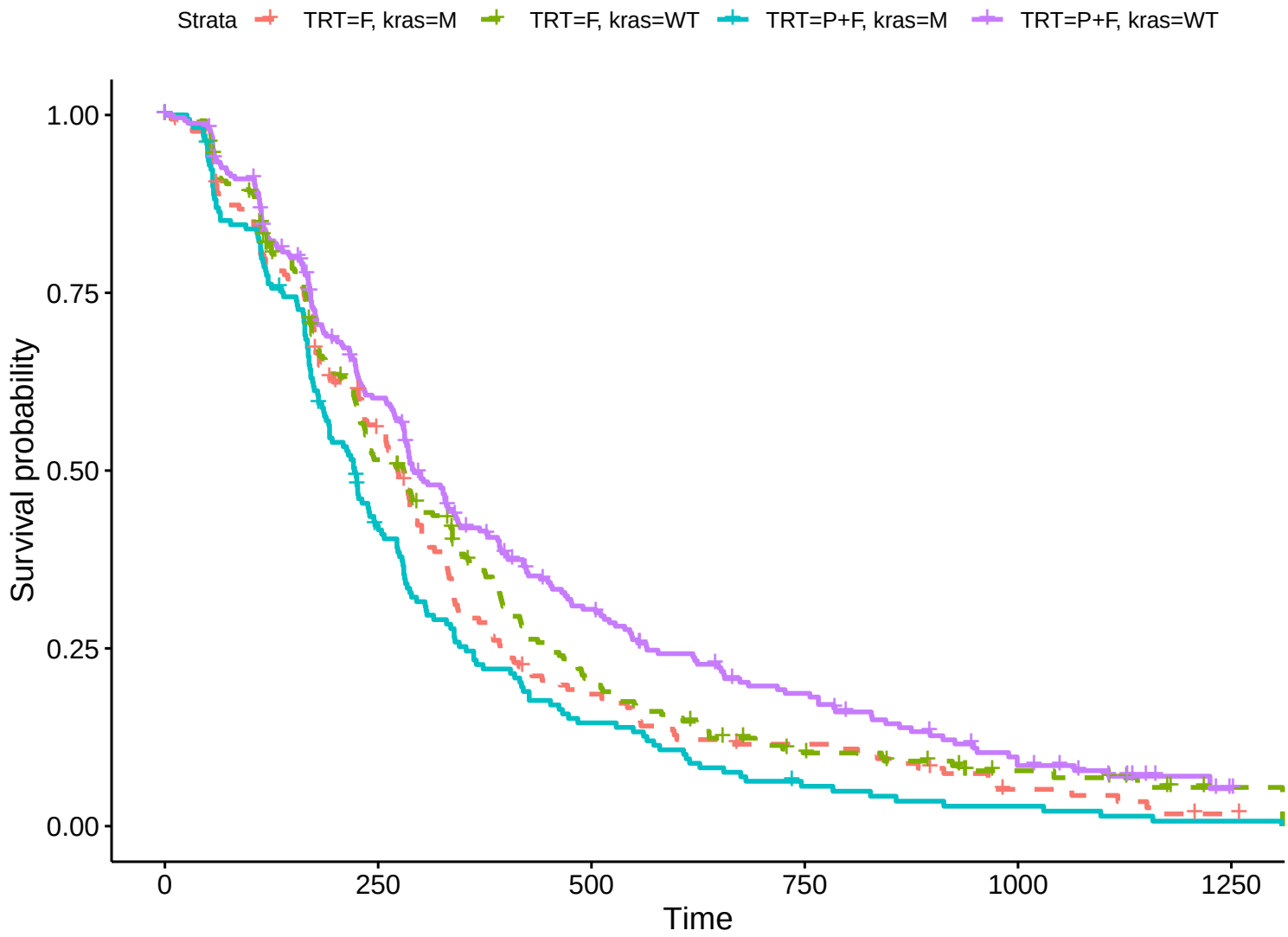


Figure: PRIME: Progression Free Survival (PFS)

ITR Comparison Results

Estimator	$\hat{V}$	SE	ll	ul
ICO	11.10	0.40	10.20	11.90
MSOWL	12.20	0.6	11.00	13.40
COX	12.40	0.50	11.40	13.40
+1	11.40	0.40	10.60	12.30
-1	11.10	0.40	10.20	11.90

Table: PRIME PFS: ITR Value Comparison (Months)

- MSOWL outperforms the One-Size-Fits-All & ICO estimators
- MSOWL & Cox yield similar values

Estimated Optimal ITRs

MSOWL Estimated Optimal Individualized Treatment Rule:

$$\hat{f}_{MSOWL} = 0.02 - 3.5e^{-8}X_{\text{AGE}} + 0.73X_{\text{SEX}} + 0.21X_{\text{ECOG}} - 1.06X_{\text{KRAS}}$$

- Sex, Ecog, and KRAS have significant effect on ITR recomendation

Outline

Summary

- OWL methods show promise for estimating ITRs with survival outcomes
- MSOWL offers improved efficiency, especially with censored data
- Tradeoffs between model flexibility and interpretability
- Importance of considering patient preferences and disease progression

Future Directions

- Find real data sets that exhibit OWL robustness w.r.t Regression
- Study effective sample size via simulation study
- Further investigation of non-linear treatment effects
- Further optimise SVM by formally explicitly minimizing aggressive treatment
- Integration of adverse event data into ITR estimation
- Extension to multiple treatment time points

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