Efficient Semi-supervised Estimation of Optimal Individualized Treatment Regime with Survival Outcome

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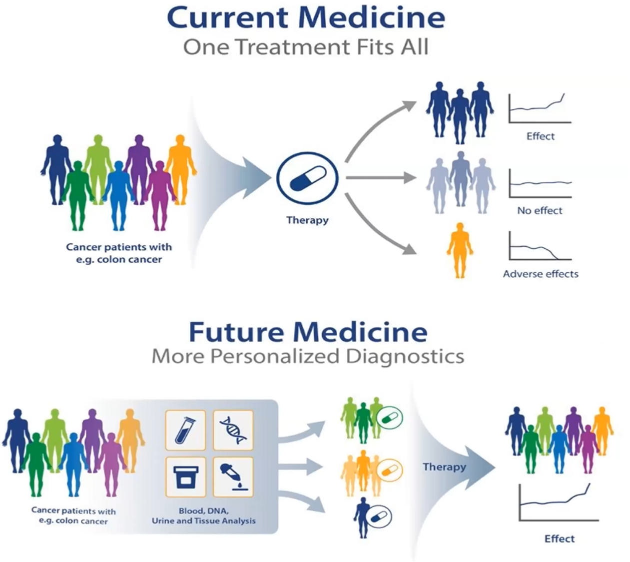
Outline

Motivations from precision medicine



Optimal ITR

- **Focus problem**: Recommend tailored individualized treatment regimes **(ITR)** to patients based on their unique **characteristics** to achieve **optimal outcomes**.
- **ITR**: A **mapping** from the support of **covariates** to the collection of **treatments**, i.e. $d(\mathbf{X}) : \mathcal{X} \to \mathcal{A}$.
- **Optimal ITR**: The treatment regime that **maximizes** some functional of the potential outcome distribution, like the **value function** (the expected potential outcome).
- Finding the optimal ITR has been studied intensively in the literature, with important applications in practice, such as disease management and public policy making.

Semi-supervised data framework

- The outcomes are often more difficult or more expensive to acquire than the covariates.
- For electronic medical records (EMR) data, a challenge arises from that a large portion of outcomes of interest and/or treatment information may not be available.
- Whether the unlabeled data with only covariates information can be utilized to improve efficiency for the estimation of the optimal ITR.

Outline

Data framework

Notation $(\mathbf{X}, A, Y, \Delta)$

- $\mathbf{X} \in \mathcal{X} \subseteq \mathbb{R}^p$: p-vector covariates with bounded support $\mathcal{X}$.
- $A \in \mathcal{A} = \{0, 1\}$: the treatment indicator;
- $Y = \min\{T, C\}$: the observed survival time with true survival time $T \in \mathbb{R}^+$ and random censoring variable $C \in [0, L] \subseteq \mathbb{R}^+$;
- $\Delta = I(T \leqslant C)$: the censoring indicator.

Observations $\mathcal{L} \cup \mathcal{U}$

- $\mathcal{L} = \{(\mathbf{X}_i, A_i, Y_i, \Delta_i) : i = 1, 2, \ldots, n\}$: iid labeled observations;
- $\mathcal{U} = \{(\mathbf{X}_i, A_i) : i = n+1, n+2, \ldots, n+N, N \geq 1\}$: iid unlabeled observations.

Data framework

Semi-supervised assumptions

- $\mathcal{L} \perp \mathcal{U}$;
- Covariates $\mathbf{X}$ follow the same distribution in $\mathcal{L}$ and $\mathcal{U}$;
- $\frac{n}{n+N} = \rho_{n,N} \to \rho \in [0, 1)$ as $n, N \to \infty$.

Potential outcome framework

Let $T^*(a)$ be the potential outcome under treatment $a \in \mathcal{A}$. Assume that

- (SUTVA) $T = T^*(1)A + T^*(0)(1 - A)$;
- (Ignorability) $A \perp \{T^*(0), T^*(1)\} \mid \mathbf{X}$.
- (Positivity) $0 < P(A = 1|X) < 1$.

Data framework

The observed outcome $Y = T^*(d_\beta(\mathbf{X}))$ when $A = d_\beta(\mathbf{X})$ and $\Delta = 1$. This leads us to define an **Induced missing data structure**.

- Decision function:
  $d_\beta(\mathbf{X}) \in \mathcal{D} = \{I(\beta'\mathbf{X} > 0) : \beta \in \mathcal{B} \subseteq \mathbb{R}^p, \|\beta\| = 1\}$;
- Missing data indicator: $R(\beta) = [Ad_\beta(\mathbf{X}) + (1 - A)\{1 - d_\beta(\mathbf{X})\}]\Delta$;
- Represent $\mathcal{L} = \{(\mathbf{X}_i, R_i(\beta)Y_i, R_i(\beta)) : i = 1, 2, \ldots, n\}$;
- IPW-based estimation for value function:

$$E[T^*(d_\beta)] = E\left[\frac{R(\beta)}{\pi_R(\beta)} Y\right]$$

  with $\pi_R(\beta) = P(R(\beta) = 1|\mathbf{X}, A)$.

Basic idea

Motivation

- $E\left[\frac{R(\boldsymbol{\beta})}{\pi_R(\boldsymbol{\beta})}Y \middle| \boldsymbol{\beta}'\mathbf{X}\right] \neq E\left[\frac{R(\boldsymbol{\beta})}{\pi_R(\boldsymbol{\beta})}Y\right]$ with a positive probability almost surely;
- Robust representation: $E\left[\frac{R(\boldsymbol{\beta})}{\pi_R(\boldsymbol{\beta})}Y\right] = E[\phi(\mathbf{X};\boldsymbol{\beta})] + E\left[\frac{R(\boldsymbol{\beta})}{\pi_R(\boldsymbol{\beta})}Y - \phi(\mathbf{X};\boldsymbol{\beta})\right]$ for an arbitrary function $\phi(\mathbf{X};\boldsymbol{\beta})$.

Value function estimation

- Supervised: $P_n\left[\frac{R(\boldsymbol{\beta})}{\pi_R(\boldsymbol{\beta})}Y\right]$;
- Semi-supervised: $P_{n+N}[\phi(\mathbf{X};\boldsymbol{\beta})] + P_n\left[\frac{R(\boldsymbol{\beta})}{\pi_R(\boldsymbol{\beta})}Y - \phi(\mathbf{X};\boldsymbol{\beta})\right]$.

Methodology

Consider the RCT with $\pi_A(X) = 0.5$, then $\pi_R(\beta) = \frac{1}{2}P(C \geqslant t|\mathbf{X}, A)$. Thus we can simplify the form

$$\beta_0 = \arg\max_{\beta \in \mathcal{B}} E[T^*(d_\beta)] = \arg\max_{\beta \in \mathcal{B}} E\left[\frac{(2A-1)\Delta Y}{S_C(Y \mid \mathbf{X}, A)} d_\beta\right]$$

by leaving out the terms that are not relevant to β, where $S_C(Y \mid \mathbf{X}, A) = P(C \geqslant t|\mathbf{X}, A)$.

Methodology

Estimators for nuisance parameter

- $\widehat{S}_C(Y|\mathbf{X}, A)$: Kaplan-Meier estimator for $S_C(Y|\mathbf{X}, A)$;
- $\widehat{\mu}(\beta'\mathbf{X})$: kernel smoothing estimator for $E\left[\frac{(2A-1)\Delta Y}{S_C(Y|\mathbf{X},A)}\middle|\beta'\mathbf{X}\right]$.

Estimators for β

- Supervised: $\widehat{\beta}_L = \underset{\beta\in\mathcal{B}}{\arg\max}\, P_n\left[\frac{(2A-1)\Delta Y}{\widehat{S}_C(Y|\mathbf{X},A)} d_\beta\right]$;
- Semi-supervised:
  $\widehat{\beta}_{SS} = \underset{\beta\in\mathcal{B}}{\arg\max}\, P_{n+N}\left[\widehat{\mu}(\beta'\mathbf{X})\right] + P_n\left[\left\{\frac{(2A-1)\Delta Y}{\widehat{S}_C(Y|\mathbf{X},A)} - \widehat{\mu}(\beta'\mathbf{X})\right\} d_\beta\right]$.

Methodology

Address the sharp-edge effect

- Replace the decision indicator function $d_{\boldsymbol{\beta}} = I(\boldsymbol{\beta}'\mathbf{X} > 0)$ with the smoothed decision function $\tilde{d}_{\boldsymbol{\beta}} = \Phi\left(\frac{\boldsymbol{\beta}'\mathbf{X}}{\tilde{h}_n}\right)$ in the value function estimations;
- Denote the corresponding kernel-smoothed supervised and semi-supervised estimators as $\tilde{\boldsymbol{\beta}}_L$ and $\tilde{\boldsymbol{\beta}}_{SS}$ respectively;
- $\Phi(\cdot)$: the cumulative distribution function of the standard normal distribution $N(0, 1)$;
- $\tilde{h}_n$: a sequence of bandwidths satisfying $\tilde{h}_n = o(n^{-\frac{1}{5}})$.

Outline

Asymptotic properties

Theorem 1 (Consistency)

Under some regularity conditions, as $n \to \infty$ and $N \to \infty$, we have

(a) $\tilde{\beta}_L \to \beta_0$ in probability.

(b) $\tilde{\beta}_{SS} \to \beta_0$ in probability.

Asymptotic properties

To simlify the technical proof, we adopt an equivalent identification condition that $|\beta_1| = 1$ w.l.o.g. Let $\mathbf{X} = (X_1, \mathbf{X}'_{-1})'$ and $\boldsymbol{\beta}_\cdot = (\beta_{\cdot,1}, \boldsymbol{\beta}'_{\cdot,-1})'$. Let $a_1 = \int \zeta \dot{\phi}(\zeta) d\zeta$, $a_2 = \int \phi^2(\zeta) d\zeta$, $Q = a_1 E[\mathbf{X}_{-1}\mathbf{X}'_{-1} G^{(1)}(0, \mathbf{X}_{-1}) f(0|\mathbf{X}_{-1})]$, $D = \frac{1}{2} a_2 E[\mathbf{X}_{-1}\mathbf{X}'_{-1} E[T^*(1)^2 + T^*(0)^2 | z = 0, \mathbf{X}_{-1}] f(0|\mathbf{X}_{-1})]$ and $D^* = a_2 E[\mu^2(0)\mathbf{X}_{-1}\mathbf{X}'_{-1} f(0|\mathbf{X}_{-1})]$.

Theorem 2 (Asymptotic normality)

Under some regularity conditions, as $n \to \infty$ and $N \to \infty$ and $\tilde{h}_n = o(n^{-\frac{1}{5}})$, we have

(a) $\sqrt{n\tilde{h}_n}\left(\tilde{\boldsymbol{\beta}}_{L,-1} - \boldsymbol{\beta}_{0,-1}\right) \to N(0, \Sigma_L)$ in distribution,

(b) $\sqrt{n\tilde{h}_n}\left(\tilde{\boldsymbol{\beta}}_{SS,-1} - \boldsymbol{\beta}_{0,-1}\right) \to N(0, \Sigma_L - (1-\rho)\Sigma_S)$ in distribution,

where $\Sigma_L = Q^{-1} D Q^{-1}$, $\Sigma_S = Q^{-1} D^* Q^{-1}$.

Asymptotic properties

To further illustrate the advantages of the smoothing technique in terms of convergence rate, we provide the following theorem.

Theorem 3

Under conditions C1-C5 and C8, we have

(a) $\left|\widehat{\beta}_L - \beta_0\right| = O_p(n^{-\frac{1}{3}})$,

(b) $\left|\widehat{\beta}_{SS} - \beta_0\right| = O_p(n^{-\frac{1}{3}})$.

Theorem 3 states that the convergence rate of the estimated parameters without smoothing is $O_p(n^{-\frac{1}{3}})$, which is slower than $O_p((n\tilde{h}_n)^{-\frac{1}{2}})$, which could be arbitrarily close to $n^{-\frac{2}{5}}$ under the assumption that $\tilde{h}_n = o(n^{-\frac{1}{5}})$.

Outline

Numerical Simulations

Data Generation: $\mathbf{X} = (X_1, X_2)$, $P(X_1 = 1) = P(X_1 = -1) = 0.5$, $X_2 \sim U(-1, 1)$; $A \sim Bernoulli(0.5)$, $\epsilon \sim N(0, 1)$, $\eta_0 = (0.25, -0.25)$; $\beta_0 = (1, 1)$.

- Case 1: $T = \exp\{\eta_0' \mathbf{X} + A\beta_0' \mathbf{X} + \epsilon\}$;
- Case 2: $T = \exp\{\sin(\eta_0' \mathbf{X}) + A\beta_0' \mathbf{X} + \epsilon\}$;
- Case 3: $T = \exp\{(\eta_0' \mathbf{X})^2 + A\beta_0' \mathbf{X} + \epsilon\}$;

The censoring time C follows an exponential distribution such that the observations have the corresponding censoring rate. The observed response $Y = \min\{T, C\}$ with censoring indicator $\Delta = I(T \leqslant C)$.

Dimension increase: $X_1 \sim Bernoulli(0.5)$, $X_i\ (i = 2, \ldots, p) \sim U(-1, 1)$. Fix $n = 500$, $N = 2000$, cr=10%. The parameters in the AFT model built in Case 1 for generating T are set as

- Case 4: $p = 4$, $\eta_0 = (0.25, -0.25, 0.25, 0.25)$, $\beta_0 = (1, 0, 1, -1)$;
- Case 5: $p = 6$, $\eta_0 = (0.25, -0.25, 0.25, 0.25, 0.25, 0.25)$, $\beta_0 = (0, 1, 1, 1, -1, 1)$.

Table: The results for Csae 1 (cr=30%)

Est	N		β_1	β_2	PCD
Sup		Bias	-0.015	-0.056	91.18%
		SD	0.192	0.162	
		MSE	0.0371	0.0294	
SS	1000	Bias	-0.020	-0.036	91.82%
		SD	0.158	0.126	
		MSE	0.0254	0.0172	
		EFF	31.6%	41.6%	
	2500	Bias	-0.024	-0.029	91.87%
		SD	0.152	0.119	
		MSE	0.0237	0.0150	
		EFF	36.2%	48.9%	
	5000	Bias	-0.026	-0.024	91.88%
		SD	0.149	0.116	
		MSE	0.0229	0.0140	
		EFF	38.3%	52.2%	

Table: The results for csae 1 (cr=40%)

Est	N		β_1	β_2	PCD
Sup		Bias	-0.029	-0.054	90.17%
		SD	0.213	0.180	
		MSE	0.0462	0.0353	
SS	1000	Bias	-0.049	-0.012	90.24%
		SD	0.171	0.125	
		MSE	0.0316	0.0158	
		EFF	31.5%	55.3%	
	2500	Bias	-0.049	-0.008	90.47%
		SD	0.165	0.119	
		MSE	0.0296	0.0142	
		EFF	35.9%	59.7%	
	5000	Bias	-0.049	-0.005	90.65%
		SD	0.160	0.115	
		MSE	0.0280	0.0133	
		EFF	39.4%	62.5%	

Table: The results for Case 4

Est		β_1	β_2	β_3	β_4	PCD
Sup	Bias	-0.031	-0.004	-0.038	0.055	87.89%
	SD	0.161	0.195	0.160	0.164	
	SE	0.157	0.188	0.158	0.156	
	MSE	0.0269	0.0380	0.0270	0.0299	
	CP	93.3%	93.4%	94.0%	93.3%	
SS	Bias	-0.023	0.002	-0.033	0.035	88.88%
	SD	0.132	0.167	0.137	0.135	
	SE	0.134	0.163	0.135	0.131	
	MSE	0.0180	0.0279	0.0199	0.0195	
	CP	95.3%	93.7%	92.2%	93.8%	
	EFF	33.2%	26.7%	26.6%	35.0%	

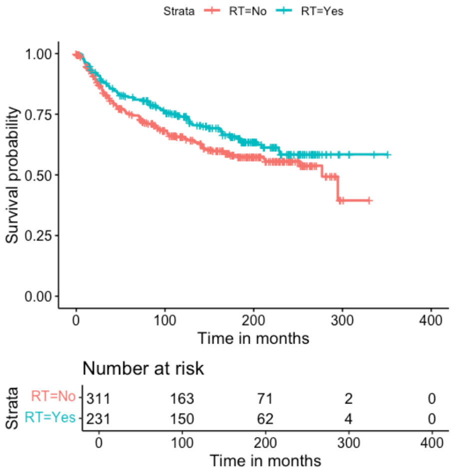
Outline

Molecular Taxonomy of Breast Cancer International Consortium (METABRIC)

- Goal: Study the effect of **radio therapy** ($A = 1$, Yes; $A = 0$, No) on **relapse free survival time** Y in breast cancer patients.
- Covariates: 3 continuous and 2 discrete.
  - **age** at diagnosis;
  - tumor **size**;
  - **TMB** (non-synonymous);
  - neoplasm histologic **grade**, coded as 1, 2, and 3;
  - the type of breast **surgery**, coded as -1 for breast-conserving surgery and 1 for mastectomy.

We use dummy variable encoding to represent the three-category variable 'grade' as two binary variables that grade1 (1, grade = 1; -1, grade $\neq$ 1) and grade2 (1, grade = 2; -1, grade $\neq$ 2).

The next figure shows the estimated Kaplan-Meier survival curves of **relapse free survival time** in months for the groups of labeled patients who received and did not receive **radio therapy**, respectively.



Real Data Analysis: METABRIC

- Labeled data: $n = 446$ patients who did not receive chemotherapy and hormone therapy, but only radio therapy (or not) with censoring rate about 40%.
- Unlabeled data: $N = 1413$ patients whose covariates were fully observed in the remaining dataset.

The next table reports the estimator (Est) of β which indexed the optimal ITR, the corresponding standard error (SE) estimated based on 200 resampling-based bootstrap samples, and P-value which is calculated by $2 - 2\Phi\left(\frac{|\text{Est}|}{\text{SE}}\right)$. Significant P-value is marked blue.

Real Data Analysis: METABRIC

Table: Estimated parameters indexing the optimal ITR for METABRIC.

Method	Sup			SS		
Predictors	Est	SE	P-value	Est	SE	P-value
intercept	-0.121	0.093	0.193	-0.110	0.063	0.079
age	-0.003	0.123	0.981	0.087	0.073	0.235
size	-0.096	0.100	0.341	-0.104	0.050	0.038
TMB	0.082	0.157	0.603	0.312	0.134	0.020
grade1	0.201	0.143	0.158	0.045	0.126	0.723
grade2	0.173	0.129	0.180	0.065	0.120	0.586
surgery	-0.948	0.074	0.000	-0.931	0.067	0.000

Real Data Analysis: METABRIC

Table: Treatment recommendation for METABRIC study

ITR	sup	SS
RT=Yes	752	762
RT=No	1107	1097

Under the optimal ITR obtained by the **supervised** method, the average recurrence-free survival time for breast cancer patients is **122.95** months. In contrast, the optimal ITR obtained by our **semi-supervised** method increases this average to **123.75** months.

Thank you for listening.