Optimal Subgroup Identification via Constrained Policy Tree Search

Wenbin Lu

Department of Statistics, North Carolina State University

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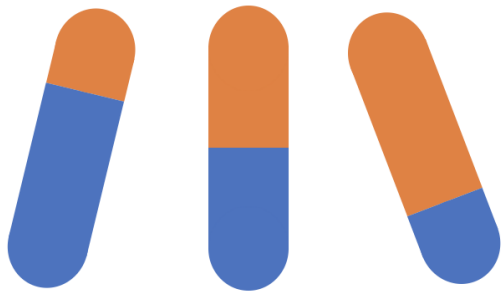
Outline

Introduction

Personalized Medicine

- A paradigm of medicine tailored to a patient's characteristics, increasingly attractive in health care.
- **Goal** is to optimize the outcome of interest by assigning the right treatment to the right patients.
- **Subgroup identification** is needed to ensure the success of personalized medicine,
- which lead to more well informed clinical decisions and improved efficiency of the treatment.



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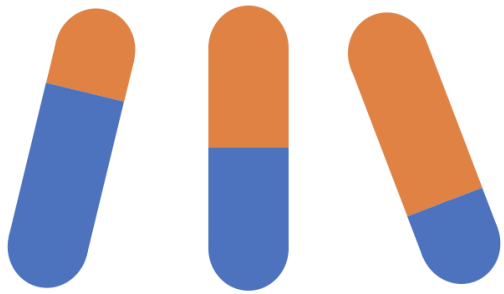

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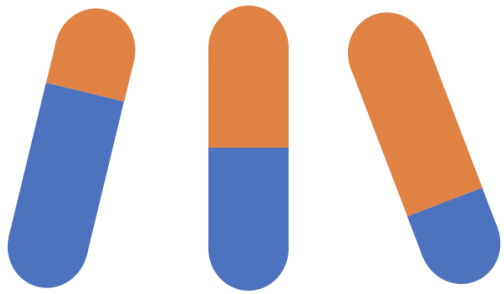

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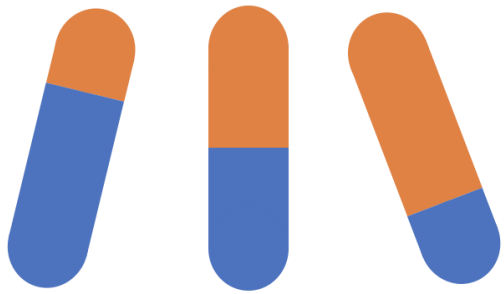

Motivating Example 1: Phase III Trial for Hematological Malignancies

- There are 599 patients with hematological malignancy enrolled.
- 14 Covariates X related to baseline disease severity and cytogenetic markers: gender, race, patient's prior therapy, prognostic score for myelodysplastic syndromes risk assessment (IPSS)...
- Two treatment A: the experimental therapy plus best supporting care as treatment 1, and the best supporting care as treatment 0.
- Outcome of interest Y: overall survival time.
- Question: How to identify a largest size of subgroup of patients with hematological malignancy, who will survive longer by taking the experimental therapy?

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- A randomized trial to examine competitive antiretroviral regimens for HIV-infected subjects.
- 12 Covariates X: age, weight, CD4 count at baseline, hemophilia, homosexual activity, history of intravenous drug use, Karnofsky score...
- Treatment A: zidovudine (ZDV) + zalcitabine (ddC) as treatment 0, and ZDV+didanosine (ddI) as treatment 1.
- Outcome of interest Y: the mean CD4 count (cells/mm3) at 20 ± 5 weeks.
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- **Subgroup selection rule (SSR)**: identify a subgroup of patients who benefits more from the targeted treatment than other treatments based on the patients' baseline covariates;
- **Desired Property 1**: How to find a SSR that maximizes the size of the selected group?
- **Desired Property 2**: Can such a SSR also achieve a pre-specified clinically desired mean outcome, such as the average treatment effect (ATE)?
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Related Works: Subgroup Identification

- Data-driven methods for subgroup identification (Lipkovich et al. 2017):
  - Song & Pepe (2004): use the selection impact curve to evaluate treatment policies based on a single baseline covariate;
  - Cai et al. (2011): use parametric scoring systems based on multiple baseline covariates to rank treatment effects and then identified subgroup using the ranked effect sizes;
  - Virtual Twins (VT) method in Foster et al. (2011): first predict the counterfactual outcome for each individual under two arms, and then infer the subgroups with an enhanced treatment effect.
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Illustration of Virtual Twins (VT) in Foster et al. (2011)

The VT method yields a smaller and thus less satisfactory subgroup:

Table 1: Evaluation results under the hematological malignancies data.

	Desired Effects (Days)	$\delta = 84$	$\delta = 108$
	Optimal Subgroup Proportion	72%	51%
Virtual Twins	Selected Sample Proportion	38.1% (0.043)	12.9% (0.117)
	Average Treatment Effect	113.8 (6.2)	151.4 (29.2)

Table 2: Evaluation results under the ACTG 175 data.

	Desired Effects (cells/mm3)	$\delta = 0.35$	$\delta = 0.45$
	Optimal Subgroup Proportion	72%	50%
Virtual Twins	Selected Sample Proportion	22.1% (0.063)	10.5% (0.029)
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- **Our Goal:** find the optimal SSR to maximize the number of the selected patients, and in the meantime, achieve the pre-specified clinically desired mean outcome.
- **Two Difficulties**:
  - A trade-off between the size of the selected subgroup and its ATE: the more patients selected, the lower ATE we can achieve.
  - Solution: constrained optimization.
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- Propose a ConstrAined PolIcy Tree seArch aLgorithm (CAPITAL) to optimize the subgroup size and achieve the pre-specified clinical threshold.
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Problem Formulation

Settings and Assumptions

- Data: (X_i, A_i, Y_i), $i = 1, \cdots, n$;
  - $X_i = [X^{(1)}, \cdots, X^{(r)}]^\top \in \mathbb{X}$: r-dimensional covariates.
  - $A_i \in \{0, 1\}$: binary treatment.
  - Y_i: outcome of interest, the larger the better.
- Potential outcomes $Y^*(a)$, $a \in \{0, 1\}$.
- Propensity score function: $\pi(x) = \mathsf{Pr}(A = 1 | X = x)$.

A1 Stable Unit Treatment Value Assumption (SUTVA): $Y = AY^*(1) + (1 - A)Y^*(0)$;

A2 Ignorability: $\{Y^*(0), Y^*(1)\} \perp\!\!\!\perp A \mid X$;

A3 Positivity: $0 < \pi(x) < 1$ for all $x \in \mathbb{X}$.

Under [A1] and [A2], define the contrast function:

$$C(X) \equiv \mathsf{E}\{Y^*(1)|X\} - \mathsf{E}\{Y^*(0)|X\} = \mathsf{E}(Y|A = 1, X) - \mathsf{E}(Y|A = 0, X).$$

Under [A1] to [A3], $C(X)$ is estimable from the observed data.

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Problem Formulation (in ATE)

- **SSR** $D(X)$: assigns the patient with baseline covariates X to the subgroup ($D(X) = 1$) or not ($D(X) = 0$).
- Denote the class of the SSR as Π.
- **Goal**: find the optimal SSR that maximizes the size of the subgroup and also maintains a desired mean outcome:

$$\begin{aligned} \max_{D \in \Pi} \quad & \Pr\{D(X) = 1\}, \\ \text{s.t.} \quad & \mathrm{E}\{Y^*(1) | D(X) = 1\} - \mathrm{E}\{Y^*(0) | D(X) = 1\} \geq \delta > 0, \end{aligned} \tag{1}$$

where δ is a pre-specified threshold of clinically meaningful ATE.

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Theoretical Optimal SSR

Connect Threshold δ with Contrast Function $C(X)$

By [A1] and [A2], the constraint in (1) can be represented by

$$\begin{aligned} & \mathsf{E}\{Y^*(1)|D(X)=1\} - \mathsf{E}\{Y^*(0)|D(X)=1\} \\ = \quad & \mathsf{E}\{Y|A=1, D(X)=1\} - \mathsf{E}\{Y|A=0, D(X)=1\} \\ = \quad & \mathsf{E}\{C(X)|D(X)=1\} \geq \delta > 0. \end{aligned}$$

Given the pre-specified threshold δ, we denote a cut point η associated with the contrast function $C(X)$ such that the expectation of the contrast function $C(X)$ larger than η achieves δ, i.e.,

$$\mathsf{E}\{C(X)|C(X) \geq \eta\} = \delta. \tag{2}$$

Illustration of the Cut Point

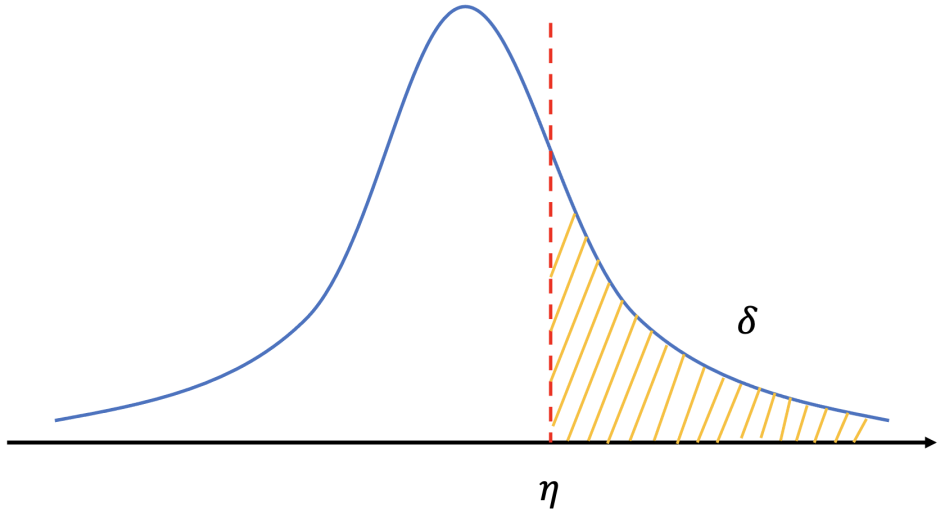

Figure 1: Illustration of the density function of the contrast function $C(X)$ with a cut point η for the pre-specified threshold δ.

Remark 1: By η, when maximizing the subgroup size, the treatment effect of each patient is ensured to meet the minimum beneficial effect size.

Remark 2: Optimal SSR should choose the patients whose contrast functions fall into the yellow area, i.e., whose treatment effects $> \eta$.

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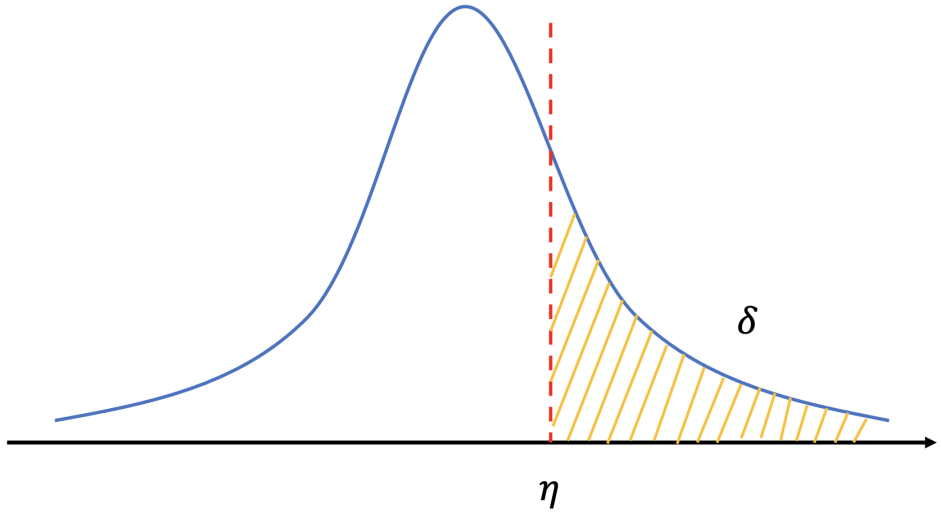

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Theoretical Optimal SSR

W.l.o.g., consider the class of the theoretical SSRs as

$$\Pi \equiv \left[\mathbb{I}\{C(X) \geq t\} : t \in \mathbb{R}\right].$$

Here, for a given t, the SSR $\mathbb{I}\{C(X) \geq t\}$ selects a patient into the subgroup if his / her contrast function is larger than t.

Theoretical Optimal SSR

Assuming (A1) and (A2), the optimal subgroup selection rule is

$$D^{opt}(x) \equiv \mathbb{I}\{C(x) \geq \eta\}, \forall x \in \mathbb{X}. \tag{3}$$

Equivalently, the optimal subgroup selection rule is

$$D^{opt}(x) \equiv \mathbb{I}\left(\mathsf{E}_{Z \in \mathbb{X}}[C(Z)\mathbb{I}\{C(Z) \geq C(x)\}] \geq \delta\right), \forall x \in \mathbb{X}. \tag{4}$$

Constrained Policy Tree Search Algorithm

Logic of CAPITAL

- By Theorem 13: the optimal SSR can be found based on the density of the contrast function.
- The density function is usually unknown: use the estimated contrast function ($\widehat{C}$) for each patient, i.e., the individual treatment effect.
- A **constrained policy tree search algorithm (CAPITAL)**: solve the optimal SSR
  - 1. Transform the constrained optimization in (1) into individual rewards defined at the patient level, to identify patients more likely to benefit from treatment.
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Class of SSR: Finite-Depth Decision Trees

For any $L \geq 1$, a depth-L decision tree DT_L is specified via a splitting variable $X^{(j)} \in \{X^{(1)}, \cdots, X^{(r)}\}$, a threshold $\Delta_L \in \mathbb{R}$, and two depth-$(L-1)$ decision trees DT_{L-1,c_1}, and DT_{L-1,c_2}, such that $DT_L(x) = DT_{L-1,c_1}(x)$ if $x^{(j)} \leq \Delta_L$, and $DT(x) = DT_{L-1,c_2}(x)$ otherwise. Denote the class of decision trees as Π_{DT}.

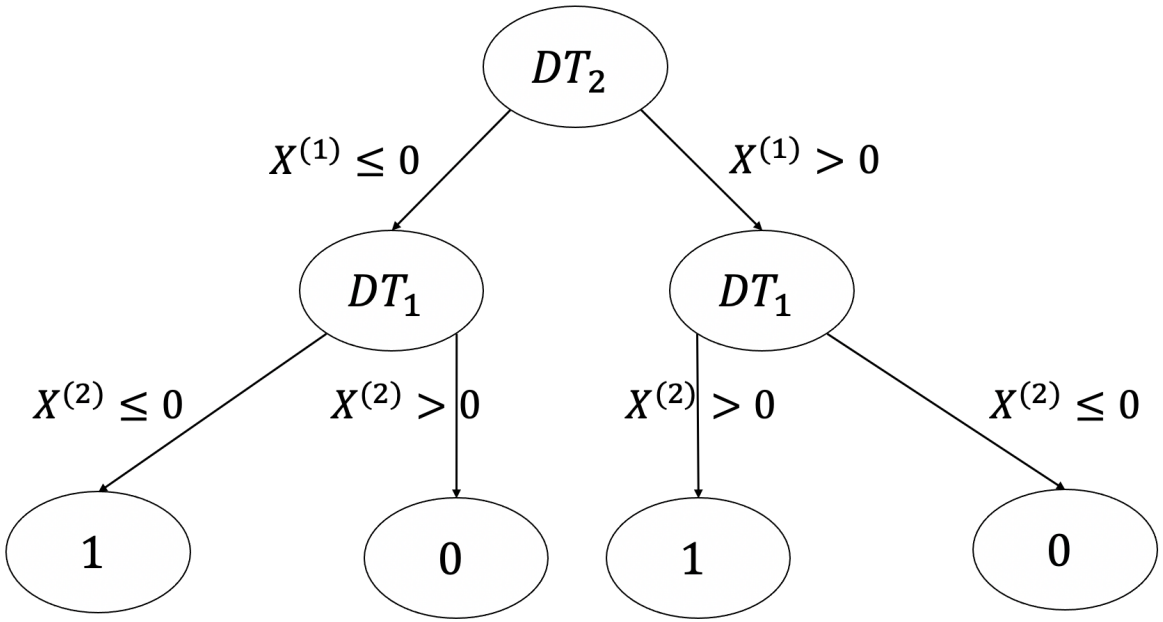

Figure 2: Illustrate of a simple $L = 2$ decision tree with splitting variables $X^{(1)}$ and $X^{(2)}$.This decision tree has a mathematical form as $\mathbb{I}\{X^{(1)}X^{(2)} > 0\}$.

Define Individual Rewards by Theoretical Optimal SSR

- Define $\widehat{r}_i = \widehat{C}(X_i) - \delta$: a patient with larger $\widehat{r}_i$ is more likely to be selected into the subgroup; Sort as $\widehat{r}_{(1)} \geq \widehat{r}_{(2)} \geq \cdots \geq \widehat{r}_{(n)}$;
- Define the cumulative mean as $\widehat{R}_{(i/n)} = \frac{1}{i}\sum_{j=1}^{i} \widehat{r}_{(j)}$.

Asymptotic Results of $\widehat{R}_{(i/n)}$

$$\begin{aligned} \widehat{R}_{(i/n)} \xrightarrow[p]{} & \quad \mathsf{E}_{Z\in\mathbb{X}}[C(Z)\mathbb{I}\{r_{(\alpha)} \leq C(Z) - \delta\}] - \delta \\ = & \quad \mathsf{E}_{Z\in\mathbb{X}}\{C(Z)|C(Z) \geq r_{(\alpha)} + \delta\} - \delta, \end{aligned}$$

where $r_{(\alpha)} + \delta$ is the upper i/n quantile of the density of $C(X)$ when n goes to infinity.

Rewark: As long as $\widehat{R}_{(i/n)} > 0$, the selected subgroup satisfies the condition in (1) by the theoretical optimal SSR in (4) from Theorem 13.

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Construct Individual Rewards at Patient Level (1)

To select patients with **positive** $\widehat{R}_{(i/n)}$ and maximize the subgroup size, we define the reward of the i-th individual based on the **sign** of $\widehat{R}_{(i/n)}$.

Reward 1:

$$\Gamma_i^{(1)}(D) = \mathbb{I}\{D(X_i) = 1\} \left[\text{sign}\{\widehat{R}_{(K_i)}\}\right], \tag{5}$$

where K_i is the rank of $\widehat{r}_i$ in the sequence $\{\widehat{r}_{(i)}\}$ or the sequence $\{\widehat{R}_{(i/n)}\}$, and 'sign' is the sign operator.

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Construct Individual Rewards at Patient Level (2)

To include patients who have a **lager treatment effect**, we propose a reward based on the **value** of $\widehat{R}_{(K_i)}$ directly.

Reward 2:

$$\Gamma_i^{(2)}(D) = \mathbb{I}\{D(X_i) = 1\} \left\{ \widehat{R}_{(K_i)} \right\}. \tag{6}$$

- The optimal SSR is searched within the decision tree class Π_{DT} to **maximize the sum of the individual rewards** defined in (5) or (6).
- The decision tree allocates each patient to the subgroup or not, and receives the corresponding rewards.
- Use exhaustive search to estimate SSR that optimizes the total reward by R package 'policytree' (Zhou et al. 2018, Athey & Wager 2021).
- The performances are very similar under these two reward choices.

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Extension to Multiple Constraints

Secondary constraints of interest: the individual treatment effect for each patient should be greater than some minimum beneficial value.

The optimal SSR under multiple constraints

$$\begin{aligned} \max_{D\in\Pi} \quad & \Pr\{D(X)=1\}, \\ \text{s.t.} \quad & \mathsf{E}\{Y^*(1)|D(X)=1\} - \mathsf{E}\{Y^*(0)|D(X)=1\} \geq \delta > 0, \\ \text{s.t.} \quad & \mathsf{E}\{Y^*(1)|D(X)=1, X=x\} - \mathsf{E}\{Y^*(0)|D(X)=1, X=x\} \geq \gamma, \forall x \in \mathbb{X}, \end{aligned} \tag{7}$$

where γ is a pre-specified minimum beneficial value, such as $\gamma = 0$.

Individual reward under multiple constraints

$$\Gamma_i^{(3)}(D) = \mathbb{I}\{D(X_i)=1\}\left[\widehat{R}_{(K_i)} + \lambda \mathbb{I}\{\widehat{C}(X_i) < 0\}\widehat{C}(X_i)\right], \tag{8}$$

where λ is the nonnegative penalty parameter that represents the trade-off between the first and the second constraint.

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Extension to Survival Data

Let T_i and C_i denote the survival time and the censoring time.

The optimal SSR for a survival endpoint

$$\max_{D \in \Pi} \quad \mathrm{E}\mathbb{I}\{D(X) = 1\}, \tag{9}$$
$$\text{s.t.} \quad \mathrm{E}\{\min(T, L) | D(X) = 1, A = 1\} - \mathrm{E}\{\min(T, L) | D(X) = 1, A = 0\} \geq \delta,$$

where L is the maximum follow up time.

- Let $\mu_0(X) = \int_0^L S(t|A = 0)dt$ and $\mu_1(X) = \int_0^L S(t|A = 1)dt$: restricted mean survival time for groups with treatment 0 and 1, where $S(t|A = 0)$ and $S(t|A = 1)$ are survival functions.
- Denote $\widehat{r}_i = \widehat{\mu}_1(X_i) - \widehat{\mu}_0(X_i) - \delta$ to capture the distance from the estimated contrast function to the desired difference in restricted mean survival time δ for the i-th individual.
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Simulations

Settings

$$
\begin{aligned}
&A \overset{iid}{\sim} \text{Bernoulli}\{0.5\}, \quad X^{(1)}, \cdots, X^{(r)} \overset{iid}{\sim} \text{Uniform}[-2, 2], \\
&Y = U(X) + AC(X) + \epsilon,
\end{aligned} \tag{10}
$$

where $U(\cdot)$ is the baseline function of the outcome and $\epsilon \overset{iid}{\sim} N(0, 1)$. Set the dimension of covariates as $r = 10$ and consider

- **Scenario 1**

$$
\begin{cases}
U(X) = X^{(1)} + 2X^{(2)}, \\
C(X) = X^{(1)}.
\end{cases}
$$

- **Scenario 2**

$$
\begin{cases}
U(X) = X^{(1)} + 2X^{(2)}, \\
C(X) = X^{(1)} \times X^{(2)}.
\end{cases}
$$

Results for Single Replicate under CAPITAL

Setting: Scenario 2 with $\delta = 1.0$ using reward in (6) for $n = 1000$.

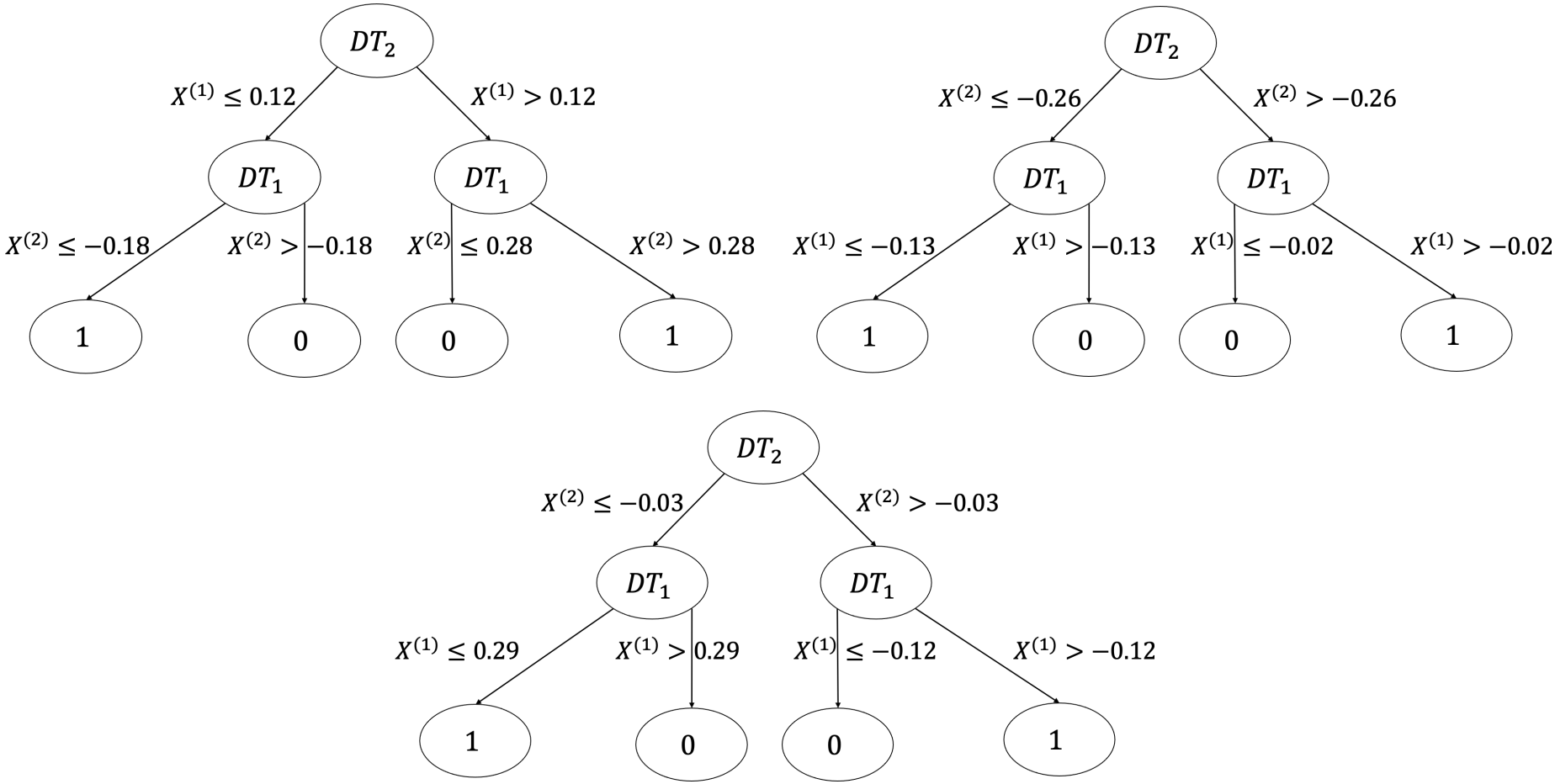

Figure 3: Upper left panel: for replicate No.1. Upper right Panel: for replicate No.2. Lower middle Panel: for replicate No.3. Optimal SSR: $\mathbb{I}\{X^{(1)}X^{(2)} > 0\}$.

Results for Single Replicate under CAPITAL

Table 3: Results for three particular replicates under Scenario 2 with $\delta = 1.0$ and $n = 1000$ (where the optimal subgroup sample proportion is 50%).

Simulation	Replicate No.1	Replicate No.2	Replicate No.3
Pr$\{\widehat{D}(X)\}$	44.5%	49.2%	55.0%
$ATE(\widehat{D})$	1.11	1.00	0.90
RCD	91.85%	92.01%	94.45%
DT_2 Split Variable (Split Value)	$X^{(1)}(0.12)$	$X^{(2)}(-0.26)$	$X^{(2)}(-0.03)$
DT_1(Left) Split Variable (Split Value)	$X^{(2)}(-0.18)$	$X^{(1)}(-0.13)$	$X^{(1)}(0.29)$
DT_1(Right) Split Variable (Split Value)	$X^{(2)}(0.28)$	$X^{(1)}(-0.02)$	$X^{(1)}(-0.12)$

- Selected sample proportion under estimated SSR: Pr$\{\widehat{D}(X)\}$;
- ATE of estimated SSR: $ATE(\widehat{D})$;
- Rate of making correct subgroup decisions by estimated SSR: RCD.

Visualization Selected Subgroup under CAPITAL

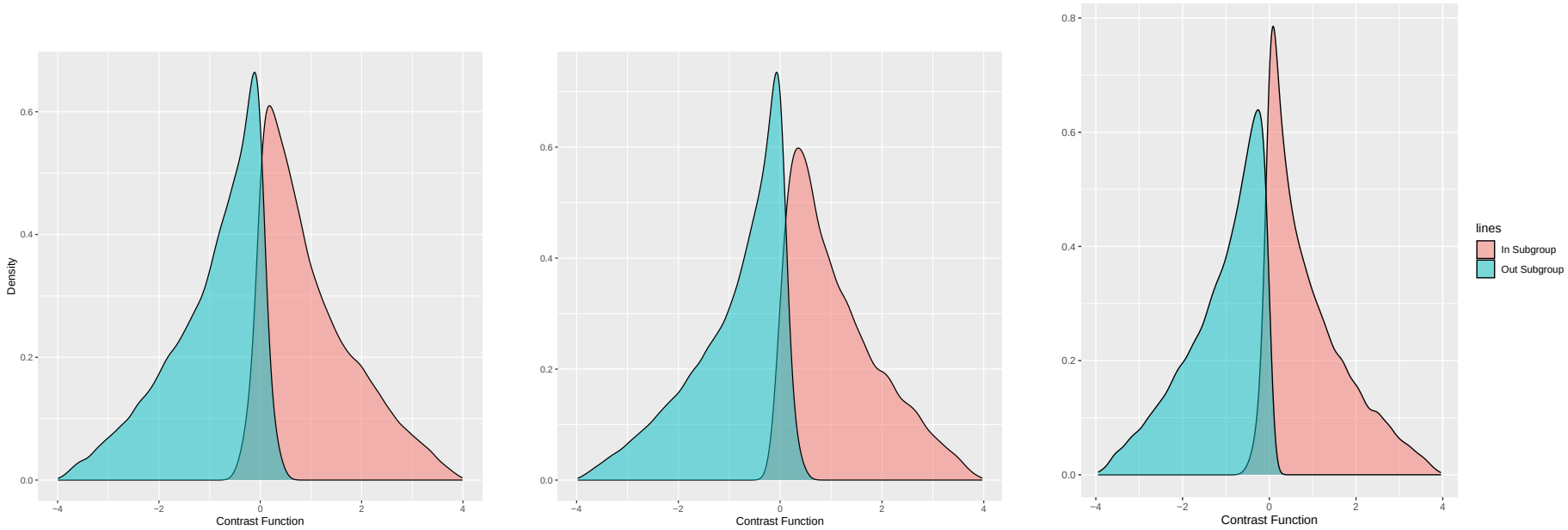

Figure 4: The density function of $C(X)$ within or outside the subgroup under Scenario 2 with $\delta = 1.0$ and $n = 1000$. Left panel: for replicate No.1. Middle Panel: for replicate No.2. Right Panel: for replicate No.3.

Comparison Studies between CAPITAL and VT

Method		$r = 10$	Scenario 1			Scenario 2		
			$n = 200$	$n = 500$	$n = 1000$	$n = 200$	$n = 500$	$n = 1000$
CAPITAL	$\delta = 0.7$	Proportion		65%			67%	
		Pr$\{\widehat{D}(X)\}$	0.62(0.16)	0.63(0.08)	0.65(0.05)	0.42(0.23)	0.51(0.11)	0.56(0.05)
		$ATE(\widehat{D})$	0.66(0.28)	0.72(0.17)	0.69(0.10)	0.72(0.47)	0.96(0.20)	0.86(0.11)
		RCD	0.83(0.10)	0.91(0.05)	0.93(0.03)	0.62(0.15)	0.81(0.08)	0.87(0.03)
	$\delta = 1.0$	Proportion		50%			50%	
		Pr$\{\widehat{D}(X)\}$	0.46(0.16)	0.48(0.09)	0.50(0.06)	0.21(0.17)	0.32(0.12)	0.40(0.06)
		$ATE(\widehat{D})$	0.90(0.27)	1.00(0.15)	0.99(0.11)	0.83(0.63)	1.31(0.27)	1.17(0.11)
		RCD	0.84(0.11)	0.91(0.05)	0.94(0.03)	0.62(0.12)	0.79(0.11)	0.88(0.05)
VT	$\delta = 0.7$	Proportion		65%			67%	
		Pr$\{\widehat{D}(X)\}$	0.31(0.12)	0.34(0.09)	0.35(0.08)	0.15(0.10)	0.19(0.09)	0.22(0.08)
		$ATE(\widehat{D})$	1.11(0.20)	1.27(0.17)	1.30(0.15)	0.85(0.61)	1.46(0.38)	1.53(0.32)
		RCD	0.66(0.12)	0.69(0.09)	0.70(0.08)	0.43(0.08)	0.51(0.09)	0.55(0.09)
	$\delta = 1.0$	Proportion		50%			50%	
		Pr$\{\widehat{D}(X)\}$	0.21(0.13)	0.24(0.10)	0.26(0.07)	0.07(0.06)	0.09(0.07)	0.14(0.07)
		$ATE(\widehat{D})$	1.19(0.21)	1.37(0.18)	1.45(0.13)	1.01(0.74)	1.67(0.49)	1.78(0.38)
		RCD	0.70(0.12)	0.74(0.10)	0.76(0.07)	0.54(0.06)	0.59(0.07)	0.64(0.07)

Evaluation of Multiple Constraints

	$r = 10$	Scenario 1			Scenario 2		
		$n = 200$	$n = 500$	$n = 1000$	$n = 200$	$n = 500$	$n = 1000$
$\delta = 0.7$	Proportion		65%			67%	
$\lambda = 0$	$\Pr\{\widehat{D}(X)\}$	0.63(0.16)	0.63(0.08)	0.65(0.05)	0.44(0.24)	0.51(0.11)	0.57(0.06)
	$ATE(\widehat{D})$	0.67(0.30)	0.72(0.17)	0.70(0.11)	0.71(0.48)	0.95(0.20)	0.85(0.11)
	RCD	0.84(0.10)	0.91(0.05)	0.93(0.03)	0.62(0.15)	0.81(0.08)	0.87(0.03)
	RPI	0.78(0.13)	0.80(0.09)	0.78(0.06)	0.74(0.16)	0.88(0.09)	0.85(0.07)
$\lambda = 0.5$	$\Pr\{\widehat{D}(X)\}$	0.55(0.12)	0.56(0.06)	0.57(0.04)	0.39(0.21)	0.48(0.10)	0.53(0.05)
	$ATE(\widehat{D})$	0.83(0.23)	0.86(0.11)	0.86(0.08)	0.77(0.48)	1.01(0.17)	0.93(0.10)
	RCD	0.84(0.09)	0.90(0.05)	0.91(0.03)	0.61(0.15)	0.79(0.08)	0.85(0.04)
	RPI	0.86(0.11)	0.88(0.07)	0.88(0.05)	0.76(0.15)	0.91(0.07)	0.90(0.05)
$\lambda = 1$	$\Pr\{\widehat{D}(X)\}$	0.52(0.11)	0.54(0.05)	0.54(0.04)	0.37(0.20)	0.46(0.09)	0.51(0.05)
	$ATE(\widehat{D})$	0.88(0.20)	0.91(0.11)	0.91(0.07)	0.79(0.48)	1.05(0.16)	0.97(0.10)
	RCD	0.83(0.09)	0.88(0.05)	0.89(0.04)	0.60(0.15)	0.78(0.08)	0.83(0.05)
	RPI	0.88(0.09)	0.90(0.06)	0.91(0.05)	0.77(0.15)	0.92(0.06)	0.92(0.05)

- Rate of positive individual treatment effect within the selected subgroup: RPI.

Settings for Survival Data

Define the survival time as $T = \exp(Y)$. Set noises ϵ for Y as: (i) normal: $\epsilon \overset{iid}{\sim} N(0,1)$; (ii) logistic: $\epsilon \overset{iid}{\sim}$ logistic$(0,1)$; (iii) extreme: $\epsilon \overset{iid}{\sim} \log[-\log\{\text{Uniform}(0,1)\}]$; and censoring levels as 15% and 25%.

Scenario 3: $U(X) = 0.1X^{(1)} + 0.2X^{(2)}, C(X) = X^{(1)}$.

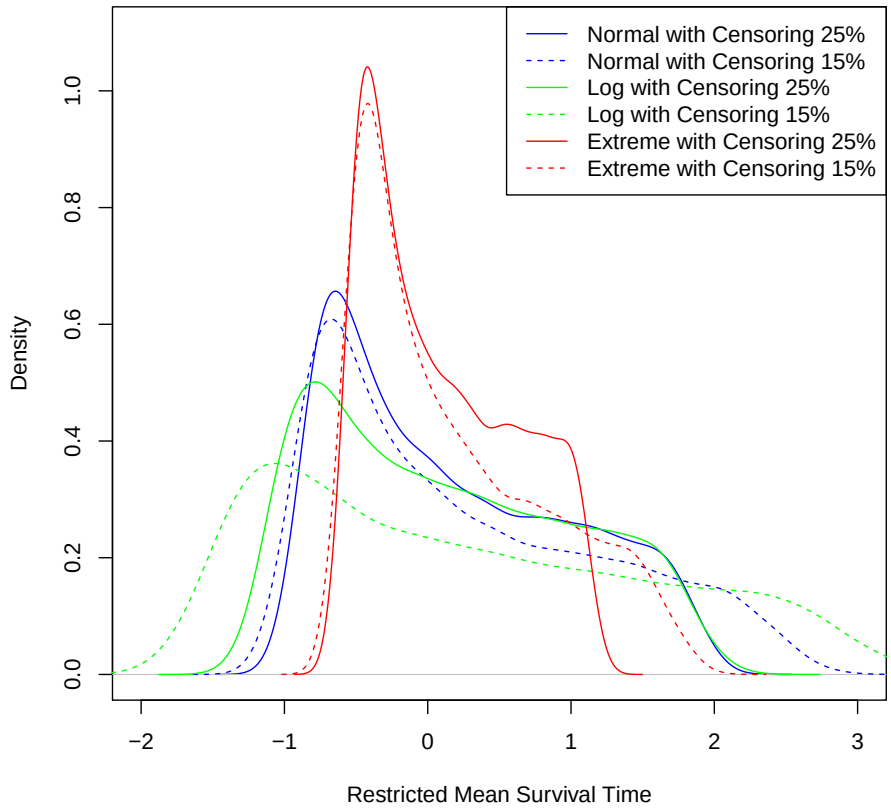

Figure 5: The density function of $\mathrm{E}\{\min(T,L)|A=1\} - \mathrm{E}\{\min(T,L)|A=0\}$.

Evaluation of Survival Data

Table 4: Empirical results of CAPITAL for the survival data under Scenario 3 (where the optimal subgroup sample proportion is 50%).

		Censoring Level 15%		Censoring Level 25%	
		$n = 500$	$n = 1000$	$n = 500$	$n = 1000$
Case 1 (normal)	True δ	1.07		0.86	
	$\Pr\{\widehat{D}(X)\}$	0.45(0.17)	0.47(0.12)	0.46(0.16)	0.48(0.11)
	$ATE(\widehat{D})$	1.07(0.31)	1.11(0.24)	0.87(0.22)	0.87(0.16)
	RCD	0.84(0.11)	0.88(0.07)	0.84(0.09)	0.90(0.06)
Case 2 (logistic)	True δ	1.34		0.87	
	$\Pr\{\widehat{D}(X)\}$	0.57(0.26)	0.56(0.18)	0.52(0.24)	0.52(0.18)
	$ATE(\widehat{D})$	0.94(0.49)	1.06(0.36)	0.63(0.31)	0.75(0.24)
	RCD	0.72(0.13)	0.80(0.10)	0.74(0.13)	0.82(0.09)
Case 3 (extreme)	True δ	0.73		0.54	
	$\Pr\{\widehat{D}(X)\}$	0.44(0.18)	0.46(0.12)	0.41(0.18)	0.44(0.12)
	$ATE(\widehat{D})$	0.76(0.21)	0.78(0.15)	0.57(0.15)	0.58(0.11)
	RCD	0.84(0.11)	0.89(0.08)	0.83(0.12)	0.88(0.08)

Application

Data Analysis I: Recall ACTG 175 data

- There are 1046 HIV-infected subjects enrolled in ACTG 175 data;
- 12 Covariates X:
  - 1) four continuous variables: age (years), weight (kg), CD4 count (cells/mm3) at baseline, and CD8 count (cells/mm3) at baseline;
  - 2) eight categorical variables: hemophilia (0=no), homosexual activity (0=no), intravenous drug use (0=no), Karnofsky score (4 levels as 70, 80, 90, and 100), race (0=white), gender (0=female), antiretroviral history (0=naive), and symptomatic status (0=asymptomatic).
- Binary Treatment A: zidovudine (ZDV) + zalcitabine (ddC) as treatment 0, and ZDV+didanosine (ddI) as treatment 1;
  - 524 patients randomized to treatment 0 and 522 patients to treatment 1, with constant propensity score $\pi(x) \equiv 0.499$.
- Outcome of interest Y: the mean CD4 count (cells/mm3) at 20 ± 5 weeks. We normalize Y by its mean and standard deviation.
- Goal: find the optimal SSR that optimizes the size of the selected subgroup and achieves the desired ATE.

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Data Analysis II: Estimated Contrast Function

- Clinically meaningful ATEs: $\delta = 0.35$ and 0.45 (cells/mm3);
- Corresponding optimal subgroup sample proportions: 72% and 50%.
- Randomly split the whole data, with 70% as a training sample to find the SSR and 30% as a testing sample to evaluate its performance.
- Difference of the ATE within the subgroup and outside the subgroup: $ATE(\widehat{D}) - ATE(\widehat{D}^c)$.

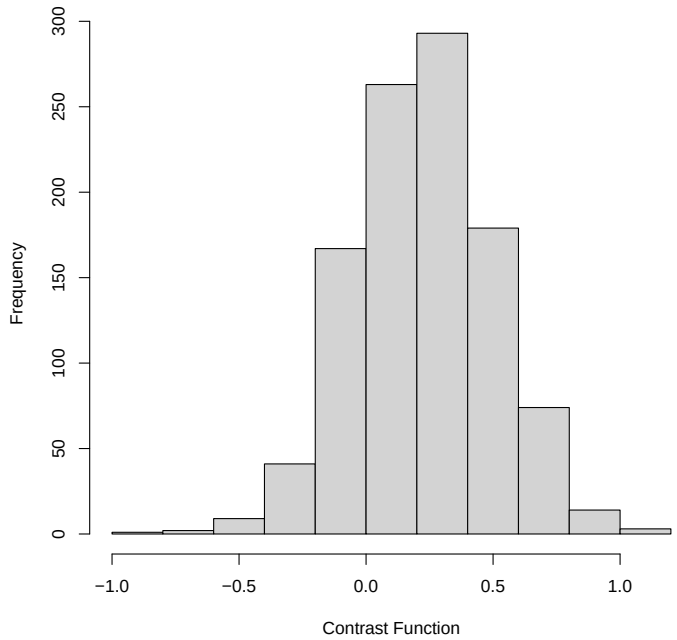

Figure 6: The density of the estimated contrast $\widehat{C}(X)$ for the ACTG 175.

Results for ACTG 175 data I: CAPITAL vs VT

	Desired Effect (Optimal Proportion)	$\delta = 0.35(72\%)$	$\delta = 0.45(50\%)$
CAPITAL with $\lambda = 0$	$\Pr\{\widehat{D}(X)\}$	92.8% (0.023)	57.4% (0.061)
	$ATE(\widehat{D})$	0.250 (0.015)	0.313 (0.023)
	$ATE(\widehat{D}) - ATE(\widehat{D}^c)$	0.357 (0.068)	0.205 (0.025)
	RPI	83.0% (0.021)	89.2% (0.028)
CAPITAL with $\lambda = 2$	$\Pr\{\widehat{D}(X)\}$	73.4% (0.094)	40.3% (0.046)
	$ATE(\widehat{D})$	0.282 (0.023)	0.366 (0.025)
	$ATE(\widehat{D}) - ATE(\widehat{D}^c)$	0.222 (0.038)	0.235 (0.028)
	RPI	86.1% (0.029)	95.0% (0.024)
CAPITAL with $\lambda = 20$	$\Pr\{\widehat{D}(X)\}$	35.6% (0.035)	32.1% (0.043)
	$ATE(\widehat{D})$	0.381 (0.021)	0.391 (0.023)
	$ATE(\widehat{D}) - ATE(\widehat{D}^c)$	0.242 (0.025)	0.244 (0.026)
	RPI	95.9% (0.017)	96.5% (0.017)
Virtual Twins	$\Pr\{\widehat{D}(X)\}$	22.1% (0.063)	10.5% (0.029)
	$ATE(\widehat{D})$	0.462 (0.043)	0.556 (0.050)
	$ATE(\widehat{D}) - ATE(\widehat{D}^c)$	0.302 (0.037)	0.368 (0.047)
	RPI	97.8% (0.019)	99.6% (0.010)

Results for ACTG 175 data II: Visualization for the Estimated SSR

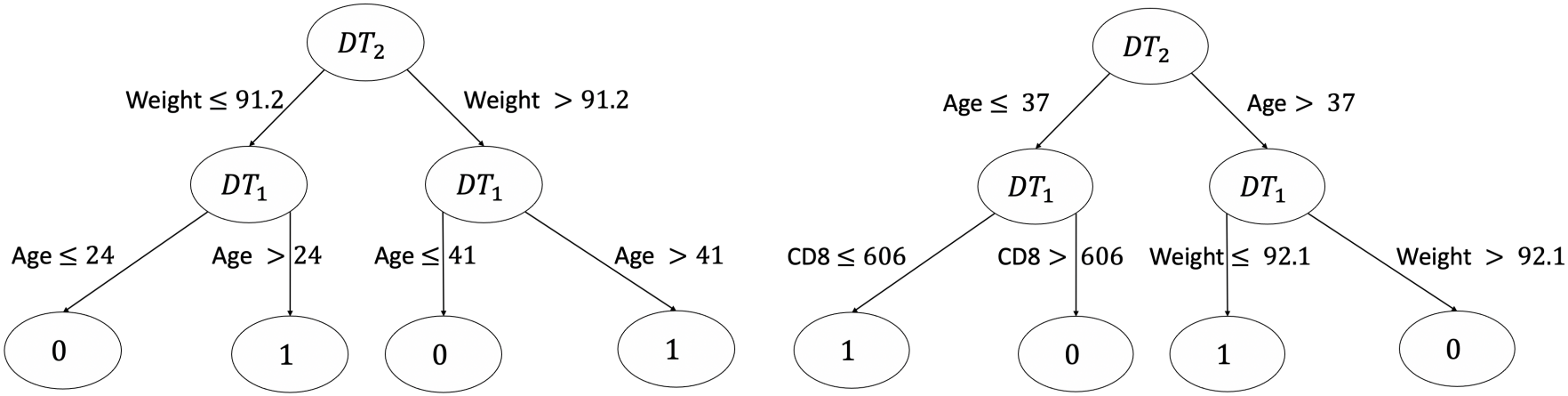

Figure 7: The estimated optimal SSR using CAPITAL under the ACTG 175 data. Left panel: for $\delta = 0.35$ (cells/mm3). Right Panel: for $\delta = 0.45$ (cells/mm3).

Data Analysis: Recall Hematological Malignancies Data

- There are 599 patients enrolled. Exclude 7 with missing records.
- 14 Covariates X:
  - 1) 12 categorical variables: gender (1=Male), race (1= Asian, 2=Black, 3=White), Cytogenetic markers 1 through 9 (0=Absent), patient's prior therapy (1=Failure, 2=Progression, 3=Relapse);
  - 2). 2 ordinal variables: Cytogenetic category (1=Very good, 2=Good, 3 =Intermediate, 4=Poor, 5=Very poor), and prognostic score for myelodysplastic syndromes risk assessment (IPSS) (1=Low, 2=Intermediate, 3=High, 4=Very high).
- Binary treatment A: the experimental therapy plus best supporting care as treatment 1, and the best supporting care as treatment 0.
  - 301 patients receiving treatment 1 and 291 receiving treatment 0.
- Outcome of interest Y: overall survival time (days).
- Goal: find the optimal SSR that maximizes the size of the selected group while achieving the desired ATE in the survival data.

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Data Analysis II: Estimated Contrast Function

- Clinically meaningful ATEs: $\delta = 84$ and 108 (days);
- Corresponding optimal subgroup sample proportions: 72% and 51%.

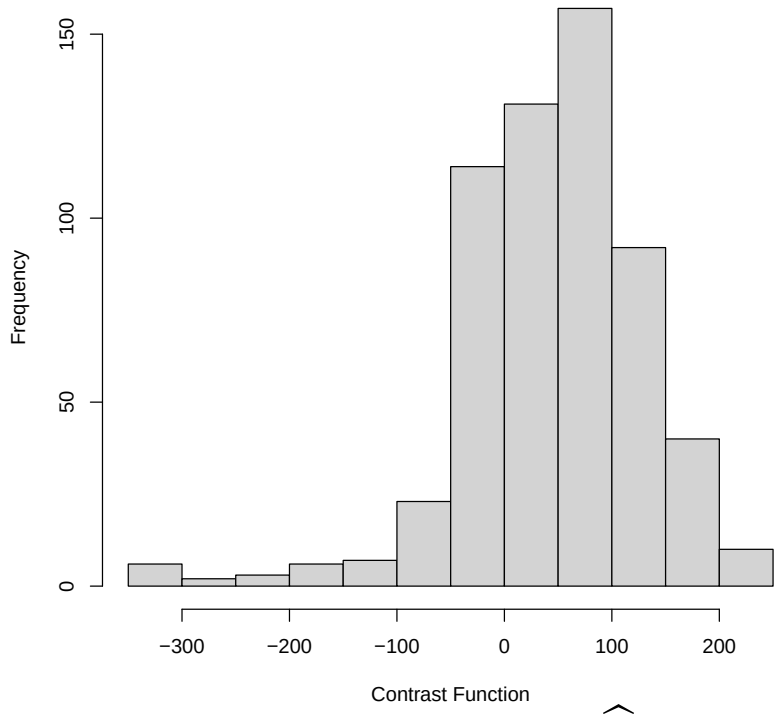

Figure 8: The density of the estimated contrast $\widehat{C}(X)$ for the hematological malignancies data.

Results for Hematological Data I: CAPITAL vs VT

	Desired Effect (Optimal Proportion)	$\delta = 84(72\%)$	$\delta = 108(51\%)$
CAPITAL	Pr$\{\widehat{D}(X)\}$	76.7% (0.030)	49.5% (0.061)
with $\lambda = 0$	$ATE(\widehat{D})$	71.6 (5.2)	85.2 (10.6)
	$ATE(\widehat{D}) - ATE(\widehat{D}^c)$	117.9 (12.7)	80.8 (12.5)
	RPI	88.4% (0.030)	92.2% (0.029)
CAPITAL	Pr$\{\widehat{D}(X)\}$	75.1% (0.030)	40.0% (0.063)
with $\lambda = 0.01$	$ATE(\widehat{D})$	72.3 (4.8)	102.3 (11.3)
	$ATE(\widehat{D}) - ATE(\widehat{D}^c)$	113.5 (12.3)	96.3 (12.4)
	RPI	88.8% (0.027)	95.4% (0.031)
CAPITAL	Pr$\{\widehat{D}(X)\}$	74.1% (0.031)	36.7% (0.063)
with $\lambda = 0.02$	$ATE(\widehat{D})$	72.9 (4.7)	106.7 (10.7)
	$ATE(\widehat{D}) - ATE(\widehat{D}^c)$	111.2 (12.4)	98.5 (10.6)
	RPI	88.9% (0.026)	96.3% (0.029)
Virtual Twins	Pr$\{\widehat{D}(X)\}$	38.1% (0.043)	12.9% (0.117)
	$ATE(\widehat{D})$	113.8 (6.2)	151.4 (29.2)
	$ATE(\widehat{D}) - ATE(\widehat{D}^c)$	112.4 (7.9)	121.7 (21.4)
	RPI	99.5% (0.010)	99.9% (0.003)

Results for Hematological Data II: Visualization for the Estimated SSR

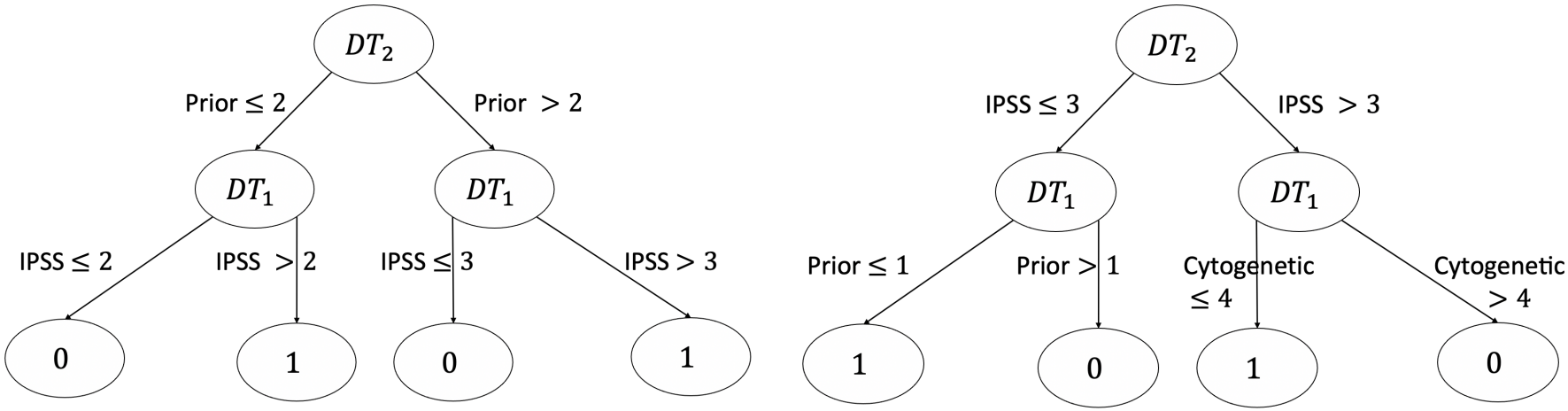

Figure 9: The estimated optimal SSR using CAPITAL under tthe hematological malignancies data. Left panel: for $\delta = 84$ (days). Right Panel: for $\delta = 108$ (days).

Coauthors:

- Hengrui Cai (student at NC State),
- Rachel Marceau (Merck),
- Devan Mehrotra (Merck),
- Lingkang Huang (Merck).

Thank You!

Athey, S. & Wager, S. (2021), 'Policy learning with observational data', *Econometrica* **89**(1), 133–161.

Cai, T., Tian, L., Wong, P. H. & Wei, L. (2011), 'Analysis of randomized comparative clinical trial data for personalized treatment selections', *Biostatistics* **12**(2), 270–282.

Foster, J. C., Taylor, J. M. & Ruberg, S. J. (2011), 'Subgroup identification from randomized clinical trial data', *Statistics in medicine* **30**(24), 2867–2880.

Lipkovich, I., Dmitrienko, A. & B D'Agostino Sr, R. (2017), 'Tutorial in biostatistics: data-driven subgroup identification and analysis in clinical trials', *Statistics in medicine* **36**(1), 136–196.

Song, X. & Pepe, M. S. (2004), 'Evaluating markers for selecting a patient's treatment', *Biometrics* **60**(4), 874–883.

Wang, Y., Fu, H. & Zeng, D. (2018), 'Learning optimal personalized treatment rules in consideration of benefit and risk: with an application to treating type 2 diabetes patients with insulin therapies', *Journal of the American Statistical Association* **113**(521), 1–13.

Zhou, J., Zhang, J., Lu, W. & Li, X. (2021), 'On restricted optimal treatment regime estimation for competing risks data', *Biostatistics* **22**(2), 217–232.

Zhou, Z., Athey, S. & Wager, S. (2018), 'Offline multi-action policy learning: Generalization and optimization', *arXiv preprint arXiv:1810.04778* .