Optimal Subgroup Identification via Constrained Policy Tree Search

Wenbin Lu

Department of Statistics, North Carolina State University

Sep 17th, 2021
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.
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.
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.
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.
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?
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?
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?
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?
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?
Motivating Example 2: AIDS Clinical Trials Group Protocol 175 (ACTG 175) data

- 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 $20 \pm 5$ weeks.
- Question: How to maximize the HIV-infected subjects to be treated with ZDV+ ddI such that they can recover from the AIDS?
Motivating Example 2: AIDS Clinical Trials Group Protocol 175 (ACTG 175) data

- 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 (ddl) as treatment 1.

- **Outcome of interest** $Y$: the mean CD4 count (cells/mm$^3$) at 20 ± 5 weeks.

- **Question**: How to maximize the HIV-infected subjects to be treated with ZDV+ddl such that they can recover from the AIDS?
Motivating Example 2: AIDS Clinical Trials Group Protocol 175 (ACTG 175) data

- 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 (ddl) as treatment 1.

- **Outcome of interest** $Y$: the mean CD4 count (cells/mm³) at 20 ± 5 weeks.
- **Question**: How to maximize the HIV-infected subjects to be treated with ZDV+ ddl such that they can recover from the AIDS?
Motivating Example 2: AIDS Clinical Trials Group Protocol 175 (ACTG 175) data

- 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 (ddl) as treatment 1.
- **Outcome of interest** $Y$: the mean CD4 count (cells/mm$^3$) at $20 \pm 5$ weeks.

**Question:** How to maximize the HIV-infected subjects to be treated with ZDV+ddl such that they can recover from the AIDS?
Motivating Example 2: AIDS Clinical Trials Group Protocol 175 (ACTG 175) data

- 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.
- Question: How to maximize the HIV-infected subjects to be treated with ZDV+ ddI such that they can recover from the AIDS?
Subgroup Selection Rule

- **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)?

- A subgroup learning approach that selects as many patients with evidence of a clinically meaningful benefit from treatment as possible is desired so that more patients can receive the better treatment.
Subgroup Selection Rule

- **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)?

- A subgroup learning approach that selects as many patients with evidence of a clinically meaningful benefit from treatment as possible is desired so that more patients can receive the better treatment.
Subgroup Selection Rule

- **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)?

- A subgroup learning approach that selects as many patients with evidence of a clinically meaningful benefit from treatment as possible is desired so that more patients can receive the better treatment.
• **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)?

• A subgroup learning approach that selects as many patients with evidence of a clinically meaningful benefit from treatment as possible is desired so that more patients can receive the better treatment.
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.

- **Limitation:** focus on subgroup identification but not subgroup optimization, leading to a greatly reduced number of selected patients.
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.

- Limitation: focus on subgroup identification but not subgroup optimization, leading to a greatly reduced number of selected patients.
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.

- **Limitation**: focus on subgroup identification but not subgroup optimization, leading to a greatly reduced number of selected patients.
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.

- Limitation: focus on subgroup identification but not subgroup optimization, leading to a greatly reduced number of selected patients.
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.

• **Limitation**: focus on **subgroup identification** but not **subgroup optimization**, leading to a greatly reduced number of selected patients.
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.

<table>
<thead>
<tr>
<th>Desired Effects (Days)</th>
<th>$\delta = 84$</th>
<th>$\delta = 108$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal Subgroup Proportion</td>
<td>72%</td>
<td>51%</td>
</tr>
<tr>
<td>Virtual Twins Selected Sample Proportion</td>
<td>38.1% (0.043)</td>
<td>12.9% (0.117)</td>
</tr>
<tr>
<td>Average Treatment Effect</td>
<td>113.8 (6.2)</td>
<td>151.4 (29.2)</td>
</tr>
</tbody>
</table>

Table 2: Evaluation results under the ACTG 175 data.

<table>
<thead>
<tr>
<th>Desired Effects (cells/mm3)</th>
<th>$\delta = 0.35$</th>
<th>$\delta = 0.45$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal Subgroup Proportion</td>
<td>72%</td>
<td>50%</td>
</tr>
<tr>
<td>Virtual Twins Selected Sample Proportion</td>
<td>22.1% (0.063)</td>
<td>10.5% (0.029)</td>
</tr>
<tr>
<td>Average Treatment Effect</td>
<td>0.462 (0.043)</td>
<td>0.556 (0.050)</td>
</tr>
</tbody>
</table>
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.

<table>
<thead>
<tr>
<th>Desired Effects (Days)</th>
<th>$\delta = 84$</th>
<th>$\delta = 108$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal Subgroup Proportion</td>
<td>72%</td>
<td>51%</td>
</tr>
<tr>
<td>Virtual Twins</td>
<td>Selected Sample Proportion</td>
<td>38.1% (0.043)</td>
</tr>
<tr>
<td>Average Treatment Effect</td>
<td>113.8 (6.2)</td>
<td>151.4 (29.2)</td>
</tr>
</tbody>
</table>

Table 2: Evaluation results under the ACTG 175 data.

<table>
<thead>
<tr>
<th>Desired Effects (cells/mm3)</th>
<th>$\delta = 0.35$</th>
<th>$\delta = 0.45$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal Subgroup Proportion</td>
<td>72%</td>
<td>50%</td>
</tr>
<tr>
<td>Virtual Twins</td>
<td>Selected Sample Proportion</td>
<td>22.1% (0.063)</td>
</tr>
<tr>
<td>Average Treatment Effect</td>
<td>0.462 (0.043)</td>
<td>0.556 (0.050)</td>
</tr>
</tbody>
</table>
The VT method yields a smaller and thus less satisfactory subgroup:

**Table 1:** Evaluation results under the hematological malignancies data.

<table>
<thead>
<tr>
<th>Desired Effects (Days)</th>
<th>$\delta = 84$</th>
<th>$\delta = 108$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal Subgroup Proportion</td>
<td>72%</td>
<td>51%</td>
</tr>
<tr>
<td>Virtual Twins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selected Sample Proportion</td>
<td>38.1% (0.043)</td>
<td>12.9% (0.117)</td>
</tr>
<tr>
<td>Average Treatment Effect</td>
<td>113.8 (6.2)</td>
<td>151.4 (29.2)</td>
</tr>
</tbody>
</table>

**Table 2:** Evaluation results under the ACTG 175 data.

<table>
<thead>
<tr>
<th>Desired Effects (cells/mm3)</th>
<th>$\delta = 0.35$</th>
<th>$\delta = 0.45$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal Subgroup Proportion</td>
<td>72%</td>
<td>50%</td>
</tr>
<tr>
<td>Virtual Twins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selected Sample Proportion</td>
<td>22.1% (0.063)</td>
<td>10.5% (0.029)</td>
</tr>
<tr>
<td>Average Treatment Effect</td>
<td>0.462 (0.043)</td>
<td>0.556 (0.050)</td>
</tr>
</tbody>
</table>
Subgroup Optimization

- **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.
  - Existing optimization approaches with constraints (see e.g., Wang et al. (2018), Zhou et al. (2021)) used complex decision rules and thus were hard to interpret.
  - Solution: develop tree-based optimal SSR.
Subgroup Optimization

- **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.
  - Existing optimization approaches with constraints (see e.g., Wang et al. (2018), Zhou et al. (2021)) used complex decision rules and thus were hard to interpret.
  - Solution: develop tree-based optimal SSR.
Subgroup Optimization

- **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.
  - Existing optimization approaches with constraints (see e.g., Wang et al. (2018), Zhou et al. (2021)) used complex decision rules and thus were hard to interpret.
  - Solution: develop tree-based optimal SSR.
Subgroup Optimization

- **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.
  - Existing optimization approaches with constraints (see e.g., Wang et al. (2018), Zhou et al. (2021)) used complex decision rules and thus were hard to interpret.
  - Solution: develop tree-based optimal SSR.
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.
- Existing optimization approaches with constraints (see e.g., Wang et al. (2018), Zhou et al. (2021)) used complex decision rules and thus were hard to interpret.
- Solution: develop tree-based optimal SSR.
Subgroup Optimization

- **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.
  - Existing optimization approaches with constraints (see e.g., Wang et al. (2018), Zhou et al. (2021)) used complex decision rules and thus were hard to interpret.
  - Solution: develop tree-based optimal SSR.
Summary of Our Work

- Derive two equivalent theoretical forms of the optimal SSR based on the contrast function that describes the treatment-covariates interaction in the outcome.
- Propose a ConstrAined PolIcy Tree seArch aLgorithm (CAPITAL) to optimize the subgroup size and achieve the pre-specified clinical threshold.
- Extend to multiple constraints that penalize the inclusion of patients with negative treatment effect, and to time to event data using the restricted mean survival time as the clinically interesting mean outcome.
- Extensive simulations and real data applications are conducted to demonstrate the empirical validity of our developed method.
Summary of Our Work

• Derive two equivalent theoretical forms of the optimal SSR based on the contrast function that describes the treatment-covariates interaction in the outcome.

• Propose a ConstrAined PolIcy Tree seArch aLgorithm (CAPITAL) to optimize the subgroup size and achieve the pre-specified clinical threshold.

• Extend to multiple constraints that penalize the inclusion of patients with negative treatment effect, and to time to event data using the restricted mean survival time as the clinically interesting mean outcome.

• Extensive simulations and real data applications are conducted to demonstrate the empirical validity of our developed method.
Summary of Our Work

- Derive two equivalent theoretical forms of the optimal SSR based on the contrast function that describes the treatment-covariates interaction in the outcome.

- Propose a ConstrAined PolIcy Tree seArch aLgorithm (CAPITAL) to optimize the subgroup size and achieve the pre-specified clinical threshold.

- Extend to multiple constraints that penalize the inclusion of patients with negative treatment effect, and to time to event data using the restricted mean survival time as the clinically interesting mean outcome.

- Extensive simulations and real data applications are conducted to demonstrate the empirical validity of our developed method.
Summary of Our Work

- Derive two equivalent theoretical forms of the optimal SSR based on the contrast function that describes the treatment-covariates interaction in the outcome.
- Propose a ConstrAined PolIcy Tree seArch aLgorithm (CAPITAL) to optimize the subgroup size and achieve the pre-specified clinical threshold.
- Extend to multiple constraints that penalize the inclusion of patients with negative treatment effect, and to time to event data using the restricted mean survival time as the clinically interesting mean outcome.
- Extensive simulations and real data applications are conducted to demonstrate the empirical validity of our developed method.
Problem Formulation
Settings and Assumptions

- **Data:** \((X_i, A_i, Y_i), i = 1, \ldots, n;\)
  - \(X_i = [X^{(1)}, \ldots, X^{(r)}]^{\top} \in \mathbb{X}: r\)-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: \(\pi(x) = \Pr(A = 1 | X = x).\)

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

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

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

Under [A1] and [A2], define the contrast function:
\[ C(X) \equiv \mathbb{E}\{Y^*(1)|X\} - \mathbb{E}\{Y^*(0)|X\} = \mathbb{E}(Y|A = 1, X) - \mathbb{E}(Y|A = 0, X). \]

Under [A1] to [A3], \(C(X)\) is estimable from the observed data.
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**: \(\pi(x) = \Pr(A = 1|X = x).\)

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

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

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

Under [A1] and [A2], define the contrast function:
\[ C(X) \equiv \mathbb{E}\{Y^*(1)|X\} - \mathbb{E}\{Y^*(0)|X\} = \mathbb{E}(Y|A = 1, X) - \mathbb{E}(Y|A = 0, X). \]

Under [A1] to [A3], \(C(X)\) is estimable from the observed data.
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:** \(\pi(x) = \Pr(A = 1|X = x).\)

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

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

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

Under [A1] and [A2], define the contrast function:
\[C(X) \equiv E\{Y^*(1)|X\} - E\{Y^*(0)|X\} = E(Y|A = 1, X) - E(Y|A = 0, X).\]

Under [A1] to [A3], \(C(X)\) is estimable from the observed data.
Settings and Assumptions

- Data: \((X_i, A_i, Y_i), i = 1, \cdots , n;\)
  - \(X_i = [X^{(1)}, \cdots , X^{(r)}] \in \mathbb{X}: r\)-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: \(\pi(x) = \Pr(A = 1 | X = x).\)

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

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

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

Under [A1] and [A2], define the contrast function:
\[ C(X) \equiv \mathbb{E}\{Y^*(1)|X\} - \mathbb{E}\{Y^*(0)|X\} = \mathbb{E}(Y|A = 1, X) - \mathbb{E}(Y|A = 0, X). \]

Under [A1] to [A3], \(C(X)\) is estimable from the observed data.
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 $\Pi$.
- **Goal:** find the optimal SSR that maximizes the size of the subgroup and also maintains a desired mean outcome:

$$\max_{D \in \Pi} \Pr\{D(X) = 1\},$$

s.t. $$E\{Y^*(1)|D(X) = 1\} - E\{Y^*(0)|D(X) = 1\} \geq \delta > 0,$$

where $\delta$ is a pre-specified threshold of clinically meaningful ATE.
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 $\Pi$.
- **Goal**: find the optimal SSR that maximizes the size of the subgroup and also maintains a desired mean outcome:

\[
\max_{D \in \Pi} \Pr\{D(X) = 1\},
\]

\[
\text{s.t.} \quad E\{Y^*(1) | D(X) = 1\} - E\{Y^*(0) | D(X) = 1\} \geq \delta > 0,
\]

where $\delta$ is a pre-specified threshold of clinically meaningful ATE.
Theoretical Optimal SSR
Connect Threshold $\delta$ with Contrast Function $C(X)$

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

$$E\{Y^*(1)|D(X) = 1\} - E\{Y^*(0)|D(X) = 1\}$$

$$= E\{Y|A = 1, D(X) = 1\} - E\{Y|A = 0, D(X) = 1\}$$

$$= E\{C(X)|D(X) = 1\} \geq \delta > 0.$$

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

$$E\{C(X)|C(X) \geq \eta\} = \delta. \quad (2)$$
Figure 1: Illustration of the density function of the contrast function $C(X)$ with a cut point $\eta$ for the pre-specified threshold $\delta$.

**Remark 1:** By $\eta$, 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 $> \eta$. 
Remark 1: By $\eta$, 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 $> \eta$. 

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

Illustration of the Cut Point
Theoretical Optimal SSR

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

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

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

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

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

Equivalently, the optimal subgroup selection rule is

$$D^{opt}(x) \equiv I (E_{Z \in X}[C(Z)I\{C(Z) \geq C(x)\}] \geq \delta), \forall x \in X. \quad \text{(4)}$$
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 ($\hat{C}$) 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.
  
  ▶ 2. Develop a decision tree to partition these patients into the subgroup based on the policy tree algorithm by Athey & Wager (2021).
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 ($\hat{C}$) 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.
  - 2. Develop a decision tree to partition these patients into the subgroup based on the policy tree algorithm by Athey & Wager (2021).
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 ($\hat{C}$) 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.
  - 2. Develop a decision tree to partition these patients into the subgroup based on the policy tree algorithm by Athey & Wager (2021).
For any $L \geq 1$, a depth-$L$ decision tree $DT_L$ is specified via a splitting variable $X^{(j)} \in \{X^{(1)}, \ldots, X^{(r)}\}$, 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 $\Pi_{DT}$.

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 $\mathbb{I}\{X^{(1)}X^{(2)} > 0\}$. 

Lu, W. (NCSU)
Define Individual Rewards by Theoretical Optimal SSR

- Define $\hat{r}_i = \hat{C}(X_i) - \delta$: a patient with larger $\hat{r}_i$ is more likely to be selected into the subgroup; Sort as $\hat{r}_1 \geq \hat{r}_2 \geq \cdots \geq \hat{r}_n$;
- Define the cumulative mean as $\hat{R}(i/n) = \frac{1}{i} \sum_{j=1}^{i} \hat{r}(j)$.

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

\[
\hat{R}(i/n) \xrightarrow{p} \mathbb{E}_{Z \in X} [C(Z) \mathbb{I}\{r(\alpha) \leq C(Z) - \delta\}] - \delta
\]
\[= \mathbb{E}_{Z \in X} \{C(Z) | C(Z) \geq r(\alpha) + \delta\} - \delta,
\]
where $r(\alpha) + \delta$ is the upper $i/n$ quantile of the density of $C(X)$ when $n$ goes to infinity.

**Remark:** As long as $\hat{R}(i/n) > 0$, the selected subgroup satisfies the condition in (1) by the theoretical optimal SSR in (4) from Theorem 13.
Define Individual Rewards by Theoretical Optimal SSR

• Define $\hat{r}_i = \hat{C}(X_i) - \delta$: a patient with larger $\hat{r}_i$ is more likely to be selected into the subgroup; Sort as $\hat{r}_{(1)} \geq \hat{r}_{(2)} \geq \cdots \geq \hat{r}_{(n)}$;

• Define the cumulative mean as $\hat{R}_{(i/n)} = \frac{1}{i} \sum_{j=1}^{i} \hat{r}(j)$.

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

\[
\hat{R}_{(i/n)} \xrightarrow{p} \mathbb{E}_{Z \in X}[C(Z)I\{r(\alpha) \leq C(Z) - \delta\}] - \delta \\
= \mathbb{E}_{Z \in X}\{C(Z)|C(Z) \geq r(\alpha) + \delta\} - \delta,
\]

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

Remark: As long as $\hat{R}_{(i/n)} > 0$, the selected subgroup satisfies the condition in (1) by the theoretical optimal SSR in (4) from Theorem 13.
Define Individual Rewards by Theoretical Optimal SSR

- Define $\hat{r}_i = \hat{C}(X_i) - \delta$: a patient with larger $\hat{r}_i$ is more likely to be selected into the subgroup; Sort as $\hat{r}_1 \geq \hat{r}_2 \geq \cdots \geq \hat{r}_n$;
- Define the cumulative mean as $\hat{R}_{i/n} = \frac{1}{i} \sum_{j=1}^{i} \hat{r}(j)$.

Asymptotic Results of $\hat{R}_{i/n}$

$$
\hat{R}_{i/n} \xrightarrow{p} E_{Z \in X}[C(Z)I\{r(\alpha) \leq C(Z) - \delta\}] - \delta
= E_{Z \in X}\{C(Z)|C(Z) \geq r(\alpha) + \delta\} - \delta,
$$

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

Remark: As long as $\hat{R}_{i/n} > 0$, the selected subgroup satisfies the condition in (1) by the theoretical optimal SSR in (4) from Theorem 13.
Construct Individual Rewards at Patient Level (1)

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

**Reward 1:**

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

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

- Given $\hat{R}_{(K_i)}$ is positive, the reward $\Gamma_i^{(1)}$ is 1 if the patient is selected to be part of the subgroup; and is 0 otherwise.
- Suppose $\hat{R}_{(K_i)}$ is negative, the reward $\Gamma_i^{(1)}$ is $-1$ if the patient is selected to be in the subgroup; and is 0 otherwise.
- Thus, we can select patients with $\hat{R}_{(K_i)}$ larger than zero.
To select patients with positive $\hat{R}_{(i/n)}$ and maximize the subgroup size, we define the reward of the $i$-th individual based on the sign of $\hat{R}_{(i/n)}$.

**Reward 1:**

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

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

- Given $\hat{R}_{(K_i)}$ is positive, the reward $\Gamma_i^{(1)}$ is 1 if the patient is selected to be part of the subgroup; and is 0 otherwise.
- Suppose $\hat{R}_{(K_i)}$ is negative, the reward $\Gamma_i^{(1)}$ is $-1$ if the patient is selected to be in the subgroup; and is 0 otherwise.
- Thus, we can select patients with $\hat{R}_{(K_i)}$ larger than zero.
Construct Individual Rewards at Patient Level (1)

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

**Reward 1:**

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

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

- **Given** $\hat{R}_{(K_i)}$ is positive, the reward $\Gamma_i^{(1)}$ is 1 if the patient is selected to be part of the subgroup; and is 0 otherwise.
- **Suppose** $\hat{R}_{(K_i)}$ is negative, the reward $\Gamma_i^{(1)}$ is $-1$ if the patient is selected to be in the subgroup; and is 0 otherwise.
- Thus, we can select patients with $\hat{R}_{(K_i)}$ larger than zero.
Construct Individual Rewards at Patient Level (1)

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

**Reward 1:**

\[
\Gamma_i^{(1)}(D) = \mathbb{I}\{D(X_i) = 1\} \left[ \text{sign}\{\hat{R}(K_i)\} \right],
\]

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

- Given $\hat{R}(K_i)$ is positive, the reward $\Gamma_i^{(1)}$ is 1 if the patient is selected to be part of the subgroup; and is 0 otherwise.
- Suppose $\hat{R}(K_i)$ is negative, the reward $\Gamma_i^{(1)}$ is $-1$ if the patient is selected to be in the subgroup; and is 0 otherwise.
- Thus, we can select patients with $\hat{R}(K_i)$ larger than zero.
Construct Individual Rewards at Patient Level (1)

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

**Reward 1:**

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

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

- Given $\hat{R}_{(K_i)}$ is positive, the reward $\Gamma_i^{(1)}$
  - is 1 if the patient is selected to be part of the subgroup;
  - and is 0 otherwise.
- Suppose $\hat{R}_{(K_i)}$ is negative, the reward $\Gamma_i^{(1)}$
  - is $-1$ if the patient is selected to be in the subgroup;
  - and is 0 otherwise.
- Thus, we can select patients with $\hat{R}_{(K_i)}$ larger than zero.
Construct Individual Rewards at Patient Level (2)

To include patients who have a larger treatment effect, we propose a reward based on the value of \( \hat{R}(K_i) \) directly.

**Reward 2:**

\[
\Gamma_i^{(2)}(D) = I\{D(X_i) = 1\} \left\{ \hat{R}(K_i) \right\}.
\] (6)

- The optimal SSR is searched within the decision tree class \( \Pi_{DT} \) 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.
To include patients who have a **larger treatment effect**, we propose a reward based on the **value** of $\hat{R}_{(K_i)}$ directly.

**Reward 2:**

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

- The optimal SSR is searched within the decision tree class $\Pi_{DT}$ 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.
To include patients who have a \textbf{larger treatment effect}, we propose a reward based on the \textbf{value} of $\hat{R}(K_i)$ directly.

\textbf{Reward 2:}

$$\Gamma_i^{(2)}(D) = \mathbb{I}\{D(X_i) = 1\} \left\{ \hat{R}(K_i) \right\}.$$  \hspace{1cm} (6)

- The optimal SSR is searched within the decision tree class $\Pi_{DT}$ to \textbf{maximize the sum of the individual rewards} defined in (5) or (6).
- The decision tree \textbf{allocates} each patient to the subgroup or not, and receives the corresponding rewards.
- Use \textbf{exhaustive search} to estimate SSR that optimizes the total reward by R package ‘policytree’ (Zhou et al. 2018, Athey & Wager 2021).
- The performances are \textbf{very similar} under these two reward choices.
To include patients who have a larger treatment effect, we propose a reward based on the value of $\hat{R}(K_i)$ directly.

**Reward 2:**

$$\Gamma_i^{(2)}(D) = I\{D(X_i) = 1\} \left\{ \hat{R}(K_i) \right\}. \quad (6)$$

- The optimal SSR is searched within the decision tree class $\Pi_{DT}$ 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.
To include patients who have a larger treatment effect, we propose a reward based on the value of $\hat{R}(K_i)$ directly.

**Reward 2:**

\[
\Gamma_i^{(2)}(D) = \mathbb{I}\{D(X_i) = 1\} \left\{ \hat{R}(K_i) \right\}.
\]

- The optimal SSR is searched within the decision tree class $\Pi_{DT}$ 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.
To include patients who have a **larger treatment effect**, we propose a reward based on the **value** of $\hat{R}(K_i)$ directly.

**Reward 2:**

$$\Gamma_i^{(2)}(D) = \mathbb{I}\{D(X_i) = 1\} \left\{ \hat{R}(K_i) \right\}.$$  \hspace{1cm} (6)

- The optimal SSR is searched within the decision tree class $\Pi_{DT}$ 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.
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

\[
\max_{D \in \Pi} \Pr\{D(X) = 1\}, \\
\text{s.t. } E\{Y^*(1)|D(X) = 1\} - E\{Y^*(0)|D(X) = 1\} \geq \delta > 0, \\
\text{s.t. } E\{Y^*(1)|D(X) = 1, X = x\} - E\{Y^*(0)|D(X) = 1, X = x\} \geq \gamma, \forall x \in X,
\]

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

Individual reward under multiple constraints

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

where \(\lambda\) is the nonnegative penalty parameter that represents the trade-off between the first and the second constraint.
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

\[
\max_{D \in \Pi} \Pr\{D(X) = 1\},
\]
\[
\text{s.t. } \mathbb{E}\{Y^*(1)|D(X) = 1\} - \mathbb{E}\{Y^*(0)|D(X) = 1\} \geq \delta > 0,
\]
\[
\text{s.t. } \mathbb{E}\{Y^*(1)|D(X) = 1, X = x\} - \mathbb{E}\{Y^*(0)|D(X) = 1, X = x\} \geq \gamma, \forall x \in \mathbb{X},
\]

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

Individual reward under multiple constraints

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

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

\[
\max_{D \in \Pi} \Pr\{D(X) = 1\}, \\
\text{s.t.} \quad E\{Y^*(1)|D(X) = 1\} - E\{Y^*(0)|D(X) = 1\} \geq \delta > 0, \\
\text{s.t.} \quad E\{Y^*(1)|D(X) = 1, X = x\} - E\{Y^*(0)|D(X) = 1, X = x\} \geq \gamma, \forall x \in \mathbb{X},
\]

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

Individual reward under multiple constraints

\[
\Gamma^{(3)}_i(D) = \mathbb{I}\{D(X_i) = 1\} \left[ \hat{R}_{(K_i)} + \lambda \mathbb{I}\{\hat{C}(X_i) < 0\}\hat{C}(X_i) \right],
\]

where \( \lambda \) is the nonnegative penalty parameter that represents the trade-off between the first and the second constraint.
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

$$\max_{D \in \Pi} \mathbb{E}\{D(X) = 1\}, \quad (9)$$

s.t. $\mathbb{E}\{\min(T, L)|D(X) = 1, A = 1\} - \mathbb{E}\{\min(T, L)|D(X) = 1, A = 0\} \geq \delta,$

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 $\hat{r}_i = \hat{\mu}_1(X_i) - \hat{\mu}_0(X_i) - \delta$ to capture the distance from the estimated contrast function to the desired difference in restricted mean survival time $\delta$ for the $i$-th individual.
- Define individual rewards for survival data similarly as in (5) and (6).
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

$$\max_{D \in \Pi} \mathbb{E}\{D(X) = 1\},$$

s.t. $\mathbb{E}\{\min(T, L) | D(X) = 1, A = 1\} - \mathbb{E}\{\min(T, L) | D(X) = 1, A = 0\} \geq \delta,$

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 $\hat{r}_i = \hat{\mu}_1(X_i) - \hat{\mu}_0(X_i) - \delta$ to capture the distance from the estimated contrast function to the desired difference in restricted mean survival time $\delta$ for the $i$-th individual.
- Define individual rewards for survival data similarly as in (5) and (6).
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

$$
\max_{D \in \Pi} \mathbb{E}\{D(X) = 1\},
$$

s.t. $\mathbb{E}\{\min(T, L) | D(X) = 1, A = 1\} - \mathbb{E}\{\min(T, L) | D(X) = 1, A = 0\} \geq \delta$,

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 $\hat{r}_i = \hat{\mu}_1(X_i) - \hat{\mu}_0(X_i) - \delta$ to capture the distance from the estimated contrast function to the desired difference in restricted mean survival time $\delta$ for the $i$-th individual.
- Define individual rewards for survival data similarly as in (5) and (6).
Let $T_i$ and $C_i$ denote the survival time and the censoring time.

The optimal SSR for a survival endpoint

$$\max_{D \in \Pi} \mathbb{E}\{D(X) = 1\},$$

s.t. $\mathbb{E}\{\min(T, L)|D(X) = 1, A = 1\} - \mathbb{E}\{\min(T, L)|D(X) = 1, A = 0\} \geq \delta,$

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 $\hat{r}_i = \hat{\mu}_1(X_i) - \hat{\mu}_0(X_i) - \delta$ to capture the distance from the estimated contrast function to the desired difference in restricted mean survival time $\delta$ for the $i$-th individual.
- Define individual rewards for survival data similarly as in (5) and (6).
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

\[
\max_{D \in \Pi} \mathbb{E}\{D(X) = 1\}, \quad (9)
\]

s.t. $\mathbb{E}\{\min(T, L)|D(X) = 1, A = 1\} - \mathbb{E}\{\min(T, L)|D(X) = 1, A = 0\} \geq \delta,$

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 $\hat{r}_i = \hat{\mu}_1(X_i) - \hat{\mu}_0(X_i) - \delta$ to capture the distance from the estimated contrast function to the desired difference in restricted mean survival time $\delta$ for the $i$-th individual.

- Define individual rewards for survival data similarly as in (5) and (6).
Simulations
\begin{equation}
A \overset{iid}{\sim} \text{Bernoulli}\{0.5\}, \quad X^{(1)}, \ldots, X^{(r)} \overset{iid}{\sim} \text{Uniform}[-2, 2],
\end{equation}
\[Y = U(X) + AC(X) + \epsilon,\]

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**

  \[
  \begin{aligned}
  U(X) &= X^{(1)} + 2X^{(2)}, \\
  C(X) &= X^{(1)}. 
  \end{aligned}
  \]

- **Scenario 2**

  \[
  \begin{aligned}
  U(X) &= X^{(1)} + 2X^{(2)}, \\
  C(X) &= X^{(1)} \times X^{(2)}. 
  \end{aligned}
  \]
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: $\mathbb{I}\{X^{(1)}X^{(2)} > 0\}$. 
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%).

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

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

<table>
<thead>
<tr>
<th>Method</th>
<th>$r = 10$</th>
<th>Scenario 1</th>
<th></th>
<th>Scenario 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>$n = 200$</td>
<td>$n = 500$</td>
<td>$n = 1000$</td>
</tr>
<tr>
<td>CAPITAL</td>
<td>$\delta = 0.7$</td>
<td>Proportion</td>
<td>65%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$\Pr{\hat{D}(X)}$</td>
<td>0.62(0.16)</td>
<td>0.63(0.08)</td>
<td>0.65(0.05)</td>
</tr>
<tr>
<td></td>
<td>$ATE(\hat{D})$</td>
<td>0.66(0.28)</td>
<td>0.72(0.17)</td>
<td>0.69(0.10)</td>
</tr>
<tr>
<td></td>
<td>RCD</td>
<td>0.83(0.10)</td>
<td>0.91(0.05)</td>
<td>0.93(0.03)</td>
</tr>
<tr>
<td></td>
<td>$\delta = 1.0$</td>
<td>Proportion</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$\Pr{\hat{D}(X)}$</td>
<td>0.46(0.16)</td>
<td>0.48(0.09)</td>
<td>0.50(0.06)</td>
</tr>
<tr>
<td></td>
<td>$ATE(\hat{D})$</td>
<td>0.90(0.27)</td>
<td>1.00(0.15)</td>
<td>0.99(0.11)</td>
</tr>
<tr>
<td></td>
<td>RCD</td>
<td>0.84(0.11)</td>
<td>0.91(0.05)</td>
<td>0.94(0.03)</td>
</tr>
<tr>
<td>VT</td>
<td>$\delta = 0.7$</td>
<td>Proportion</td>
<td>65%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$\Pr{\hat{D}(X)}$</td>
<td>0.31(0.12)</td>
<td>0.34(0.09)</td>
<td>0.35(0.08)</td>
</tr>
<tr>
<td></td>
<td>$ATE(\hat{D})$</td>
<td>1.11(0.20)</td>
<td>1.27(0.17)</td>
<td>1.30(0.15)</td>
</tr>
<tr>
<td></td>
<td>RCD</td>
<td>0.66(0.12)</td>
<td>0.69(0.09)</td>
<td>0.70(0.08)</td>
</tr>
<tr>
<td></td>
<td>$\delta = 1.0$</td>
<td>Proportion</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$\Pr{\hat{D}(X)}$</td>
<td>0.21(0.13)</td>
<td>0.24(0.10)</td>
<td>0.26(0.07)</td>
</tr>
<tr>
<td></td>
<td>$ATE(\hat{D})$</td>
<td>1.19(0.21)</td>
<td>1.37(0.18)</td>
<td>1.45(0.13)</td>
</tr>
<tr>
<td></td>
<td>RCD</td>
<td>0.70(0.12)</td>
<td>0.74(0.10)</td>
<td>0.76(0.07)</td>
</tr>
</tbody>
</table>
### Evaluation of Multiple Constraints

<table>
<thead>
<tr>
<th>$r = 10$</th>
<th>Scenario 1</th>
<th>Scenario 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$n = 200$</td>
<td>$n = 500$</td>
</tr>
<tr>
<td>$\delta = 0.7$</td>
<td>Proportion</td>
<td>65%</td>
</tr>
<tr>
<td>$\lambda = 0$</td>
<td>$\Pr{\hat{D}(X)}$</td>
<td>0.63(0.16)</td>
</tr>
<tr>
<td></td>
<td>$ATE(\hat{D})$</td>
<td>0.67(0.30)</td>
</tr>
<tr>
<td></td>
<td>RCD</td>
<td>0.84(0.10)</td>
</tr>
<tr>
<td></td>
<td>RPI</td>
<td>0.78(0.13)</td>
</tr>
<tr>
<td>$\lambda = 0.5$</td>
<td>$\Pr{\hat{D}(X)}$</td>
<td>0.55(0.12)</td>
</tr>
<tr>
<td></td>
<td>$ATE(\hat{D})$</td>
<td>0.83(0.23)</td>
</tr>
<tr>
<td></td>
<td>RCD</td>
<td>0.84(0.09)</td>
</tr>
<tr>
<td></td>
<td>RPI</td>
<td>0.86(0.11)</td>
</tr>
<tr>
<td>$\lambda = 1$</td>
<td>$\Pr{\hat{D}(X)}$</td>
<td>0.52(0.11)</td>
</tr>
<tr>
<td></td>
<td>$ATE(\hat{D})$</td>
<td>0.88(0.20)</td>
</tr>
<tr>
<td></td>
<td>RCD</td>
<td>0.83(0.09)</td>
</tr>
<tr>
<td></td>
<td>RPI</td>
<td>0.88(0.09)</td>
</tr>
</tbody>
</table>

- 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 $\epsilon$ for $Y$ as: (i) normal: $\epsilon \sim iid \sim N(0, 1)$; (ii) logistic: $\epsilon \sim iid \sim \text{logistic}(0, 1)$; (iii) extreme: $\epsilon \sim iid \sim \log[-\log\{\text{Uniform}(0, 1)\}]$; 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 $E\{\min(T, L)\mid A = 1\} - E\{\min(T, L)\mid A = 0\}$. 

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

<table>
<thead>
<tr>
<th></th>
<th>Censoring Level 15%</th>
<th></th>
<th>Censoring Level 25%</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 500</td>
<td>n = 1000</td>
<td>n = 500</td>
<td>n = 1000</td>
</tr>
<tr>
<td>Case 1 (normal)</td>
<td>True δ</td>
<td>1.07</td>
<td>0.86</td>
<td>Pr{(\hat{D}(X))}</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ATE{(\hat{D})}</td>
</tr>
<tr>
<td></td>
<td>RCD</td>
<td>0.84(0.11)</td>
<td>0.88(0.07)</td>
<td>0.84(0.09)</td>
</tr>
<tr>
<td>Case 2 (logistic)</td>
<td>True δ</td>
<td>1.34</td>
<td>0.87</td>
<td>Pr{(\hat{D}(X))}</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ATE{(\hat{D})}</td>
</tr>
<tr>
<td></td>
<td>RCD</td>
<td>0.72(0.13)</td>
<td>0.80(0.10)</td>
<td>0.74(0.13)</td>
</tr>
<tr>
<td>Case 3 (extreme)</td>
<td>True δ</td>
<td>0.73</td>
<td>0.54</td>
<td>Pr{(\hat{D}(X))}</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ATE{(\hat{D})}</td>
</tr>
<tr>
<td></td>
<td>RCD</td>
<td>0.84(0.11)</td>
<td>0.89(0.08)</td>
<td>0.83(0.12)</td>
</tr>
</tbody>
</table>
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/mm$^3$) at baseline, and CD8 count (cells/mm$^3$) 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/mm$^3$) 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.
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/mm\(^3\)) at baseline, and CD8 count (cells/mm\(^3\)) 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/mm\(^3\)) 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.
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.
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 $\pm$ 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.
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.
Clinically meaningful ATEs: $\delta = 0.35$ and $0.45$ (cells/mm$^3$);

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: $ATE(\hat{D}) - ATE(\hat{D}^c)$.

Figure 6: The density of the estimated contrast $\hat{C}(X)$ for the ACTG 175.
<table>
<thead>
<tr>
<th></th>
<th>Desired Effect (Optimal Proportion)</th>
<th>$\delta = 0.35(72%)$</th>
<th>$\delta = 0.45(50%)$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CAPITAL</strong></td>
<td>$Pr{\hat{D}(X)}$</td>
<td>92.8% (0.023)</td>
<td>57.4% (0.061)</td>
</tr>
<tr>
<td></td>
<td>$ATE(\hat{D})$</td>
<td>0.250 (0.015)</td>
<td>0.313 (0.023)</td>
</tr>
<tr>
<td></td>
<td>$ATE(\hat{D}) - ATE(\hat{D}^c)$</td>
<td>0.357 (0.068)</td>
<td>0.205 (0.025)</td>
</tr>
<tr>
<td></td>
<td>RPI</td>
<td>83.0% (0.021)</td>
<td>89.2% (0.028)</td>
</tr>
<tr>
<td><strong>CAPITAL</strong></td>
<td>$Pr{\hat{D}(X)}$</td>
<td>73.4% (0.094)</td>
<td>40.3% (0.046)</td>
</tr>
<tr>
<td>with $\lambda = 2$</td>
<td>$ATE(\hat{D})$</td>
<td>0.282 (0.023)</td>
<td>0.366 (0.025)</td>
</tr>
<tr>
<td></td>
<td>$ATE(\hat{D}) - ATE(\hat{D}^c)$</td>
<td>0.222 (0.038)</td>
<td>0.235 (0.028)</td>
</tr>
<tr>
<td></td>
<td>RPI</td>
<td>86.1% (0.029)</td>
<td>95.0% (0.024)</td>
</tr>
<tr>
<td><strong>CAPITAL</strong></td>
<td>$Pr{\hat{D}(X)}$</td>
<td>35.6% (0.035)</td>
<td>32.1% (0.043)</td>
</tr>
<tr>
<td>with $\lambda = 20$</td>
<td>$ATE(\hat{D})$</td>
<td>0.381 (0.021)</td>
<td>0.391 (0.023)</td>
</tr>
<tr>
<td></td>
<td>$ATE(\hat{D}) - ATE(\hat{D}^c)$</td>
<td>0.242 (0.025)</td>
<td>0.244 (0.026)</td>
</tr>
<tr>
<td></td>
<td>RPI</td>
<td>95.9% (0.017)</td>
<td>96.5% (0.017)</td>
</tr>
<tr>
<td><strong>Virtual Twins</strong></td>
<td>$Pr{\hat{D}(X)}$</td>
<td>22.1% (0.063)</td>
<td>10.5% (0.029)</td>
</tr>
<tr>
<td></td>
<td>$ATE(\hat{D})$</td>
<td>0.462 (0.043)</td>
<td>0.556 (0.050)</td>
</tr>
<tr>
<td></td>
<td>$ATE(\hat{D}) - ATE(\hat{D}^c)$</td>
<td>0.302 (0.037)</td>
<td>0.368 (0.047)</td>
</tr>
<tr>
<td></td>
<td>RPI</td>
<td>97.8% (0.019)</td>
<td>99.6% (0.010)</td>
</tr>
</tbody>
</table>
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/mm$^3$). Right Panel: for $\delta = 0.45$ (cells/mm$^3$).
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.
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.
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.
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.
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.
Clinically meaningful ATEs: $\delta = 84$ and 108 (days);
Corresponding optimal subgroup sample proportions: 72% and 51%.

Figure 8: The density of the estimated contrast $\hat{C}(X)$ for the hematological malignancies data.
## Results for Hematological Data I: CAPITAL vs VT

<table>
<thead>
<tr>
<th>Desired Effect (Optimal Proportion)</th>
<th>$\delta = 84,(72%)$</th>
<th>$\delta = 108,(51%)$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CAPITAL</strong> with $\lambda = 0$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\Pr{\hat{D}(X)}$</td>
<td>76.7% (0.030)</td>
<td>49.5% (0.061)</td>
</tr>
<tr>
<td>$ATE(\hat{D})$</td>
<td>71.6 (5.2)</td>
<td>85.2 (10.6)</td>
</tr>
<tr>
<td>$ATE(\hat{D}) - ATE(\hat{D}^c)$</td>
<td>117.9 (12.7)</td>
<td>80.8 (12.5)</td>
</tr>
<tr>
<td><strong>RPI</strong></td>
<td>88.4% (0.030)</td>
<td>92.2% (0.029)</td>
</tr>
<tr>
<td><strong>CAPITAL</strong> with $\lambda = 0.01$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\Pr{\hat{D}(X)}$</td>
<td>75.1% (0.030)</td>
<td>40.0% (0.063)</td>
</tr>
<tr>
<td>$ATE(\hat{D})$</td>
<td>72.3 (4.8)</td>
<td>102.3 (11.3)</td>
</tr>
<tr>
<td>$ATE(\hat{D}) - ATE(\hat{D}^c)$</td>
<td>113.5 (12.3)</td>
<td>96.3 (12.4)</td>
</tr>
<tr>
<td><strong>RPI</strong></td>
<td>88.8% (0.027)</td>
<td>95.4% (0.031)</td>
</tr>
<tr>
<td><strong>CAPITAL</strong> with $\lambda = 0.02$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\Pr{\hat{D}(X)}$</td>
<td>74.1% (0.031)</td>
<td>36.7% (0.063)</td>
</tr>
<tr>
<td>$ATE(\hat{D})$</td>
<td>72.9 (4.7)</td>
<td>106.7 (10.7)</td>
</tr>
<tr>
<td>$ATE(\hat{D}) - ATE(\hat{D}^c)$</td>
<td>111.2 (12.4)</td>
<td>98.5 (10.6)</td>
</tr>
<tr>
<td><strong>RPI</strong></td>
<td>88.9% (0.026)</td>
<td>96.3% (0.029)</td>
</tr>
<tr>
<td><strong>Virtual Twins</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\Pr{\hat{D}(X)}$</td>
<td>38.1% (0.043)</td>
<td>12.9% (0.117)</td>
</tr>
<tr>
<td>$ATE(\hat{D})$</td>
<td>113.8 (6.2)</td>
<td>151.4 (29.2)</td>
</tr>
<tr>
<td>$ATE(\hat{D}) - ATE(\hat{D}^c)$</td>
<td>112.4 (7.9)</td>
<td>121.7 (21.4)</td>
</tr>
<tr>
<td><strong>RPI</strong></td>
<td>99.5% (0.010)</td>
<td>99.9% (0.003)</td>
</tr>
</tbody>
</table>
Results for Hematological Data II: Visualization for the Estimated SSR

Figure 9: The estimated optimal SSR using CAPITAL under the 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!


