Treatment Effect Heterogeneity Trees

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Treatment effect heterogeneity

- In the era of “personalized” medicine, there is much interest in identifying subgroups where treatment is particularly beneficial/harmful.
- For continuous outcome $Y$ and covariates $X$, we seek to describe how

$$E(Y(1) - Y(0) \mid X)$$

varies with $X$, where $Y(Z)$ is the counterfactual outcome under treatment $Z$. 
Treatment effect heterogeneity

- In a randomized trial, under mild assumptions

\[ E(Y(1) - Y(0) \mid X) = E(Y \mid Z = 1, X) - E(Y \mid Z = 0, X) \]

hence we can identify the quantity of interest.

- The standard approach to looking for effect modification is to fit a regression model with interactions:

\[ E(Y \mid Z, X) = \beta_0 + \beta_1 Z + \beta_2 X + \beta_3 X \cdot Z \]
Treatment effect heterogeneity

\[ E(Y \mid Z, X) = \beta_0 + \beta_1 Z + \beta_2 X + \beta_3 X \cdot Z \]

- For continuous covariates \( X \), this does not identify subgroups
- Higher-order synergistic effects are missed unless pre-specified
- Type I error \( P(\text{reject } H_0 : \beta_3 = 0) \) is controlled when there is no treatment effect heterogeneity
Our goal

Develop a method which:

1. Discovers population subgroups experiencing differential causal treatment effects
2. Protects Type I error
Our proposal, **Treatment Effect Heterogeneity Trees (TEHTrees)**, combines *matching* and *decision trees*:

1. Match (with replacement) on the *prognostic score* estimated by *SuperLearner*
2. Calculate the within-pair differences in the outcome
3. Fit *conditional inference tree* with *linear mixed models* to identify distinct subgroups
Not typically considered in randomized trials, since by design $Z \perp X$, but...

- Consider forming a matched pair of subjects $i$ and $j$ with
  - $Z_i = 1, Z_j = 0$
  - $X_i = X_j = X$ ("perfect" matching)
- Within-pair differences $Y_i - Y_j$ have expectation

$$E(Y_i - Y_j \mid Z_i = 1, Z_j = 0, X_i = X_j = X) = E(Y(1) - Y(0) \mid X)$$

so these matched pairs can be used to understand effect heterogeneity.
Matching

- Exact matching is generally not possible
- Since treatment is randomized, *propensity score* is unhelpful

Instead, match on the *prognostic score* (Hansen, 2008)

\[ \Psi(X) = E(Y \mid X) \]
The prognostic score has the balancing property

\[ Y \perp X \mid \Psi(X) \]

This can be used to show that within-pair differences for pairs matched on \( \Psi(X) \) are independent of all components of \( X \) which do not modify the effect of \( X \)
Good behavior of the prognostic score requires that model for $\Psi$ be correctly specified.

Since we don’t know the right model, we use *SuperLearner* (Polley et al., 2007):
- Ensemble-based method
- Weights of base learners calculated to minimize prediction error

Our current implementation uses SuperLearner with 7 base learners (GLM, random forest, GAM, MARS, etc.)
**Goal:** Model within-pair differences as a function of covariates to find subgroups experiencing different treatment effects
Regression trees

The diagram illustrates a decision tree with the following structure:

- **Root Node**: Hunger < 1.8
  - **Yes**: Wanting < -0.57
    - **Rest.eat >= 1.2**
      - -1, n=15
    - **Rest.eat < 1.2**
      - -0.41, n=50
  - **No**: Wanting >= -0.57
    - **Rrvf < -1.1**
      - -0.42, n=21
      - **Rrvf >= -1.1**
        - **Rest.eat >= 0.51**
          - -0.19, n=35
        - **Rest.eat < 0.51**
          - 0.36, n=91

The tree is used to make decisions based on the values of Hunger, Wanting, and Rest.eat.
Conditional inference trees

Most popular approach (CART) does not explicitly control Type I error since:

- Splits are chosen greedily across variables and split points
- Matching with replacement induces correlation between pairs

So instead, we use **conditional inference trees** (Hothorn et al., 2006)
Key feature: Splits are determined from multiplicity-adjusted p-values from univariate regressions
To account for between-pair correlation, our adaptation of conditional inference trees calculates these p-values from **linear mixed effects models** with a random subject-specific intercept.
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To recap:

1. Match (with replacement) on the *prognostic score* estimated by *SuperLearner*
2. Calculate the within-pair differences in the outcome
3. Fit a *conditional inference tree* with *linear mixed models* to identify distinct subgroups
Simulations - Type I error

We generated data from the model

\[ Y = Z + \sum_{j=1}^{5} \beta_j X_j + \theta f(X) \]

for various choices of \( \theta \) and \( f \):

- \( \theta = 0 \) (Base model)
- \( \theta \neq 0, \ f(X) = X_1 \cdot X_2 \)
- \( \theta \neq 0, \ f(X) = \sqrt{|X_3|} \)
- \( \theta \neq 0, \ f(X) = I(X_4 > 0) \)
Simulations - Type I error

Type I error = any split in conditional inference tree

<table>
<thead>
<tr>
<th>Model</th>
<th>Type I error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base model</td>
<td>0.026</td>
</tr>
<tr>
<td>Base model + $X_1 \cdot X_2$</td>
<td>0.012</td>
</tr>
<tr>
<td>Base model + $\sqrt{</td>
<td>X_3</td>
</tr>
<tr>
<td>Base model + $I(X_4 &gt; 0)$</td>
<td>0.044</td>
</tr>
<tr>
<td>Base model + all above</td>
<td>0.048</td>
</tr>
</tbody>
</table>
Data generated from

\[ Y = Z + \sum_{j=1}^{5} \beta_j X_j + \tau Z \cdot g(X) \]

with \( \tau \neq 0 \) and

- \( g(X) = X_1 \) (continuous interaction)
- \( g(X) = I(X_1 > 0) \) (threshold)
- \( g(X) = X_1 + I(X_1 > 0) + I(X_3 > -1, X_4 < 1) \) (combined)
Simulations - Power

**Figure:** Distribution of first split for three simulation scenarios
• TEHTrees provide a general-purpose framework for detecting heterogeneous causal effects while controlling Type I error.

• Lots of flexibility to choose:
  • Matching procedure
  • Modeling method for prognostic score
  • Partitioning procedure