Generalizable Recommendation to a Target Population by Leveraging Randomized and Observational Studies

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Overview

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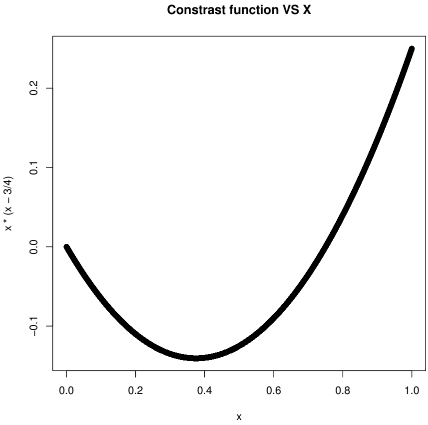
2. Proposed Method
   - Estimation of Transferring Weights
   - Construction of Decision Rules
     - Linear Rule
     - Decision Tree
3. Simulation
4. Conclusion and Discussion

Motivation

- Personalized medicine focuses on the recommendation of treatment to patients based on their individual characteristics. The golden standard is to use randomized clinical trials (RCT).
- Comparing with the complex non-linear decision rules, clinicians are interested in parsimonious decision rules (e.g., linear or decision tree rules) which are more interpretable.
- **Issue**: There is selection bias in RCT (i.e., people's characteristics distribution in RCT may be very different from the target population), can a parsimonious optimal rule derived from it really be the optimal rule to the target population?

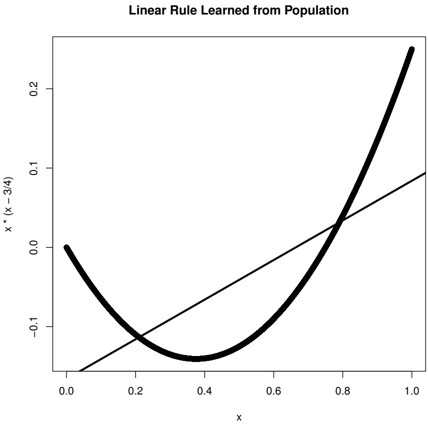
Motivation

- Population level: $E\{Y^*(a)|X\} = X(X - 3/4)a$, where $a \in \{0,1\}$ and $X \sim Unif(0,1)$, so the contrast function is $\tau(X) = X(X - 3/4)$.



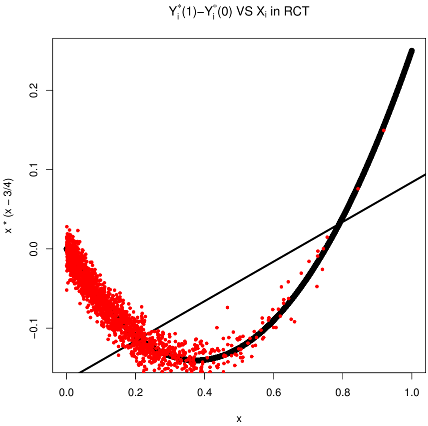
Motivation

- Population level: best approximated linear rule.



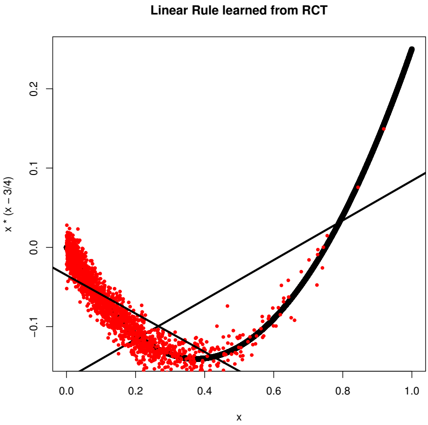
Motivation

- Sampling mechanism: Whether to participate in RCT is distributed as Bernoulli($\frac{e^{-8X}}{1+e^{-8X}}$).

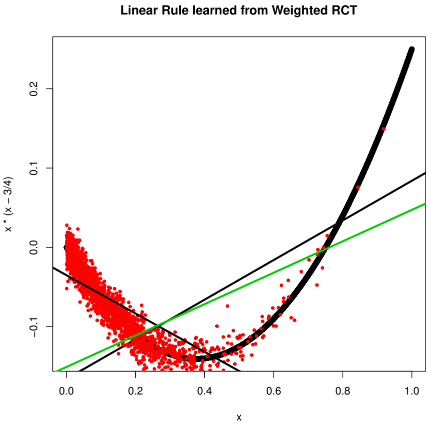


Motivation

- The approximated linear rule learned from RCT samples.



- The approximated linear rule learned from the weighted RCT samples.



Motivation

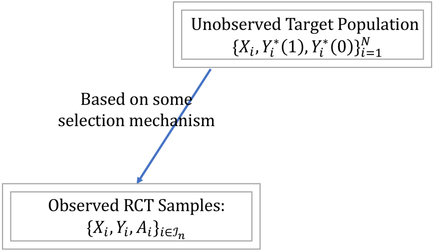
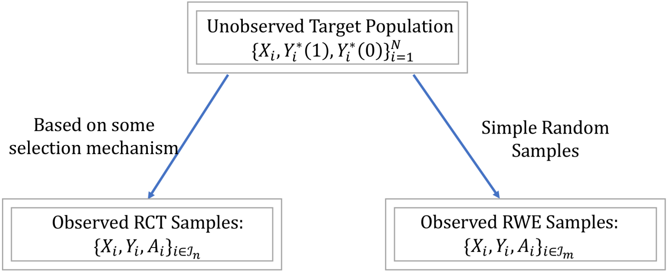


Figure: Demonstration of samples from two sources

- In the era of big data, massive real-world databases, such as electronic health records, claims databases, and disease registry, provide rich real-world patient information.

Motivation



- But there may exist unmeasured confounders affecting treatment and outcomes. It would rely on unverifiable assumptions and causal inference methods to derive a rule only from RWE.
- How can we use these information? Use the information in RWE to correct covariate distributions in RCT!

Overview

Estimation of Transferring Weights

- Notations:
  - Treatment $A \in \mathcal{A} = \{0, 1\}$
  - Covariates $X \in \mathbf{R}^p$
  - Potential outcomes $Y^*(0), Y^*(1) \in \mathbf{R}$, the larger the better
  - Target population size N
  - Index set of RCT samples $\mathcal{I}_n$ with size n
  - Index set of RWE samples $\mathcal{I}_m$ with size m
  - $\widetilde{\delta}_i = 1$ means the ith individual is in RCT.
- Assume the covariate distribution in RWE is the same as that in the target population. Thus $\frac{1}{m}\sum_{i \in \mathcal{I}_m} X_i$ would be an unbiased estimator of $E(X)$, the covariate expectation in the target population.
- Note that $E\left\{\frac{\widetilde{\delta}_i X_i}{P(\widetilde{\delta}_i=1|X_i)}\right\} = E\left\{E\left\{\frac{\widetilde{\delta}_i X_i}{P(\widetilde{\delta}_i=1|X_i)}\middle| X_i\right\}\right\} = E(X_i)$,
- Goal: to find transferring weights $\widetilde{w}_i := \frac{1}{P(\widetilde{\delta}_i=1|X_i)}$.

Estimation of Transferring Weights

- (1) Method of propensity score:
  Posit a logistic regression model for $P(\widetilde{\delta}_i = 1|X_i)$, i.e.,
  $\pi(X_i;\alpha) := P(\widetilde{\delta}_i = 1|X_i;\alpha) = \frac{\exp(\alpha^\intercal X_i)}{1+\exp(\alpha^\intercal X_i)}$, where $\alpha \in \mathbf{R}^p$, so we can get the maximum likelihood estimator

$$
\begin{aligned}
\hat{\alpha} =& \underset{\alpha}{\mathrm{argmax}} \sum_{i=1}^{N} \{\widetilde{\delta}_i \log \pi(x_i;\alpha) + (1-\widetilde{\delta}_i) \log(1-\pi(x_i;\alpha))\} \\
=& \underset{\alpha}{\mathrm{argmax}} \sum_{i=1}^{N} \{\widetilde{\delta}_i(\alpha^\intercal x_i) - \log(1+\exp(\alpha^\intercal x_i))\} \\
\approx& \underset{\alpha}{\mathrm{argmax}} \Big\{ \sum_{i=1}^{N} \widetilde{\delta}_i(\alpha^\intercal x_i) - \sum_{i\in\mathcal{I}_m} \frac{N}{m} \log(1+\exp(\alpha^\intercal x_i)) \Big\}.
\end{aligned}
$$

Estimation of Transferring Weights

- (2)Method of estimating equations:

$$\frac{1}{N}\sum_{i=1}^{N}\frac{\widetilde{\delta}_i X_i}{P(\widetilde{\delta}_i = 1|X_i;\alpha)} = \frac{1}{m}\sum_{i\in\mathcal{I}_m} X_i,$$

where $P(\widetilde{\delta}_i = 1|X_i;\alpha)$ is modeled same as in the above (1). So we can solve p equations to get $\hat{\alpha}$.

Construction of Linear Rules

- Define conditional causal effect $\tau(X) = E\{Y^*(1) - Y^*(0)|X\}$
- Use a linear model to approximate the true conditional causal effect, assuming $\tau(X;\beta^*) = X^\intercal\beta^*$. By ordinary least square, we can get the target population parameter

$$\beta_N^* = \arg\min_{\beta} \sum_{i=1}^{N}\{Y_i^* - X_i^\intercal\beta\}^2 = \{\frac{1}{N}\sum_{i=1}^{N} X_i X_i^\intercal\}^{-1}\frac{1}{N}\sum_{i=1}^{N} X_i Y_i^*,$$

  where $Y_i^* = Y_i^*(1) - Y_i^*(0)$. Note that $\beta_N^* \xrightarrow{p} \beta^*$, with $N \to \infty$.
- Question: how to estimate β_N^* using data from RCT and estimated transferring weights?

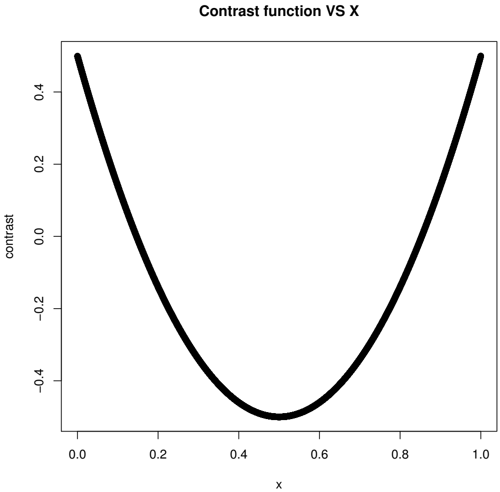
Construction of Linear Rules

- Note that $P(A=1|X)$ is known in RCT. Assume *No Unmeasured Confounders* and *Stable Unit Treatment Value*, (Rubin, 1980), we have $E\{\frac{AY}{P(A=1|X)} - \frac{(1-A)Y}{1-P(A=1|X)}|X\} = \tau(X)$.
- Denote $\widehat{Y}_i^* = \frac{A_iY_i}{P(A_i=1|X_i)} - \frac{(1-A_i)Y_i}{1-P(A_i=1|X_i)}$, so replace Y_i^* with $\widehat{Y}_i^*$.
- Add $\widetilde{w}_i$ into least square loss function:

$$\begin{aligned}\hat{\beta}^* &= \arg\min_{\beta} \sum_{i\in\mathcal{I}_n} \color{red}{\widetilde{w}_i}\{\widehat{Y}_i^* - X_i^\intercal\beta\}^2 \\ &= \{\frac{1}{N}\sum_{i=1}^{N}\widetilde{w}_i(X_i;\hat{\alpha})\widetilde{\delta}_iX_iX_i^\intercal\}^{-1}\frac{1}{N}\sum_{i=1}^{N}\widetilde{w}_i(X_i;\hat{\alpha})\widetilde{\delta}_iX_iY_i^* \\ &\xrightarrow{p} \beta^*.\end{aligned}$$

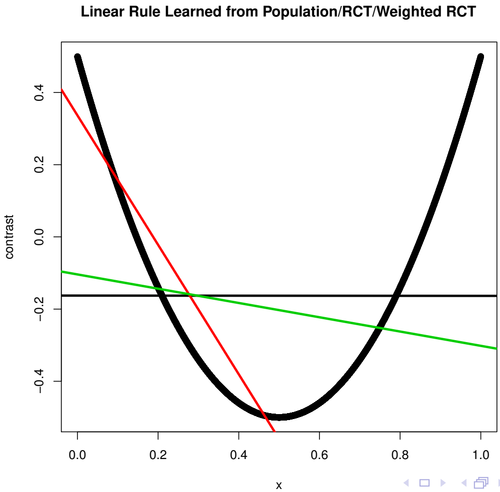
Construction of Linear Results

- But there is some problems when using linear rules...



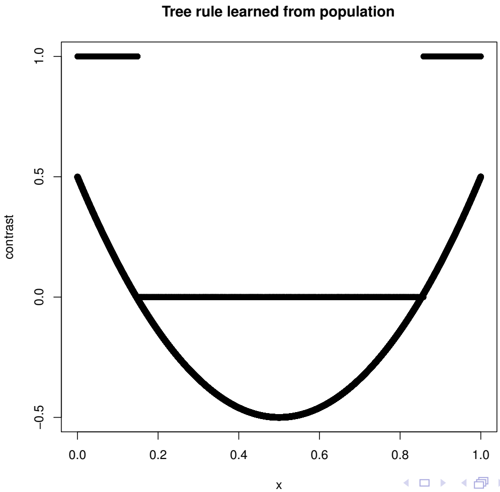
Construction of Linear Results

- Even the linear rule learned from population (black) doesn't make sense...

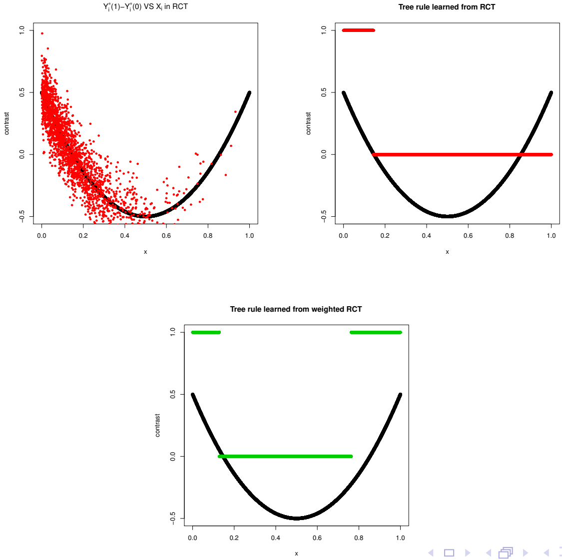


Construction of Decision Tree

- Thus we also consider some nonparametric interpretable rules: decision tree.



Construction of Decision Tree



Construction of Decision Tree

- Let the policy $D : \mathrm{dom}\ X \to \{0,1\}$ and the value of the policy D is defined as $V(D) = E_D(Y) = E[Y^*\{D(X)\}]$ over the target population.
- Following the work in Wang et al. (2016) (a variant of outcome weighted learning (Zhao et al., 2012)), to maximize $V(D)$ is equivalent to $\min_D \sum_{i \in \mathcal{I}_n} \frac{|\widetilde{R}_i|}{\pi(A_i, X_i)} I[\{(2A_i - 1)\mathrm{sign}(\widetilde{R}_i) + 1\}/2 \neq D(X_i)]$, where $\widetilde{R}_i = Y_i - \widehat{R}_i$, and the predicted $\hat{R}_i$ is fitted by outcomes Y_i only on X_i, and $\pi(A_i, X_i) = A_i P(A_i = 1 \mid X_i) + (1 - A_i)\{1 - P(A_i = 1 \mid X_i)\}$.
- Note that $E_D(Y_i) = E_{\text{population}}\{E_D(Y_i | X_i)\} = E_{\text{RCT}}\{\widetilde{w}_i E_D(Y_i | X_i)\}$.
- Thus add wegihts into the loss function as follows:

$$\min_D \sum_{i \in \mathcal{I}_n} \frac{\widetilde{w}_i |\widetilde{R}_i|}{\pi(A_i, X_i)} I[\{(2A_i - 1)\mathrm{sign}(\widetilde{R}_i) + 1\}/2 \neq D(X_i)].$$

Construction of Decision Tree

Here is the procedure of transfer-weighted O-learning:
Step 1: Use data from RCT and RWE to obtain transfer-weights with the method (1) or method (2) all units in the RCT, we denoted as $\widetilde{w}_i, i \in \mathcal{I}_n$. If unweighted, then $\widetilde{w}_i = 1$.
Step 2 (optional): Propensity score estimation $\widehat{\pi}(A_i, H_i)$. We can let all propensity score be known, since we are considering the RCT.
Step 3: Use random forest to do regression of Y_i on features X_i within the RCT data to get $\widehat{R}_i$.
Step 4: Calculate $\widetilde{R}_i = Y_i - \widehat{R}_i$, and implement O-learning, i.e., fit a weighted classification tree to estimate the decision function D, where weights are $\frac{\widetilde{w}_i|\widetilde{R}_i|}{\widehat{\pi}(A_i,X_i)}$, and the labels are $\{(2A_i - 1)\mathrm{sign}(\widetilde{R}_i) + 1\}/2$, $i \in \mathcal{I}_n$.

Overview

Simulation

We consider the setting when the true conditional causal effect is not linear:

$$Y_i = 1 + X_{i1} + A_i \beta \widetilde{X}_i + \epsilon_i,$$

where

- $N = 10^6$,
- $\widetilde{X}_i = (\cos(1) - \frac{1}{2}, \quad \cos(X_{i1}) - \frac{1}{2}, \quad \cos(X_{i2}) - \frac{1}{2}, \quad \cos(X_{i3}) - \frac{1}{2})^\intercal,$
- $X_i = (X_{i1}, X_{i2}, X_{i3})^\intercal \sim N(\mathbf{1}, I_3),$
- $A_i \sim \mathrm{Bernoulli}(0.5),$
- $\beta = (1, 2, 3, 4)$
- $\epsilon_i \sim N(0, 0.5^2), i = 1, \cdots, N$ independently .
- Let $\alpha = (\alpha_1, 1, -2, 1)$, where $\alpha_1 \in \{-11, -10, -9\}$

We consider value MSE and optimal action accuracy rate.

Simulation

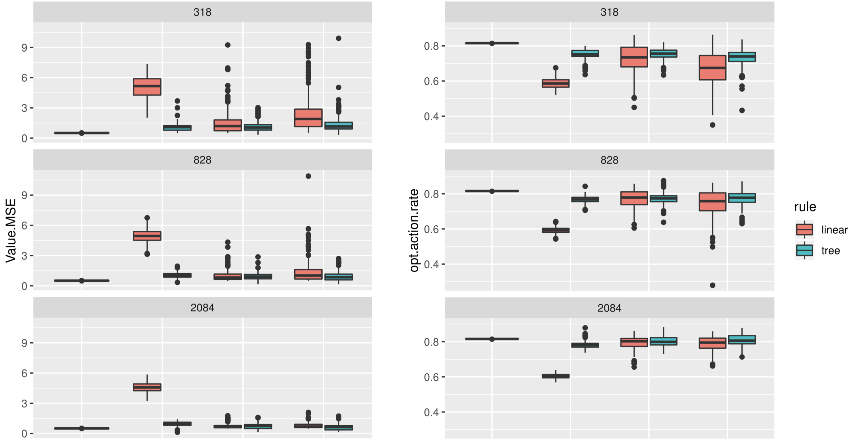


Figure: Evaluation results, subtitles are the sample size in RCT. Column 1: the approximated linear rule from the population; Column 2: Unweighted; Column 3: Weighted (1); Column 4 Weighted (2).

Overview

Conclusion and Discussion

- We propose two approaches of how to estimate the transferring weights to correct covariate distribution in randomized study so as to give generalizable recommendations to the target population.
- The transferring weights can be easily applied to any loss functions, and can have better performance for simple-structure decision rules.
  - If the decision rule is "correctly specified" (often difficult in practice), transfer weighting is not necessary.
- Ongoing work: Consider more kinds of interpretable decision rules, such as decision list (Zhang et al., 2018).
- Future work:
  - We might consider multiple actions in the future.
  - Consider more robust ways to estimate the transferring weights especially when the model $P(\tilde{\delta} = 1|X)$ is misspecified.

References

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