A Reference-Free R-Learner for Treatment Recommendation

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Outline

Causal Effects for Multiple Treatments

Task: Practice of personalized medicine requires **a causal understanding of the treatment effects of pharmacological agents in patients of specific clinical characteristics**

- Causal effect: a contrast of the values of counterfactual outcomes
- Goal: estimation of heterogeneous treatment effect (HTE) given multiple options

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Multiple treatments scenario

- Treatment assignment: $T \in \{1, 2, ..., K\}, K > 2$
- K potential outcomes: $Y^{(1)}, ..., Y^{(K)} \in \mathbb{R}$
- Factual outcome: $Y = \sum_{k=1}^{K} 1[T = k]Y^{(k)}$
- Heterogeneous Treatment Effects: $\tau_j^{(k)}(\mathbf{x}) = \mathbb{E}[Y^{(k)} - Y^{(j)} \mid \mathbf{X} = \mathbf{x}], k \neq j$ with reference treatment, j.
- Propensity scores: $\pi^{(k)}(\mathbf{x}) = \Pr(T = k \mid \mathbf{X} = \mathbf{x})$, i.e., $\pi^{(1)}(\mathbf{x}), ..., \pi^{(K-1)}(\mathbf{x}), \pi^{(K)}(\mathbf{x}) = 1 - \sum_{k=1}^{K-1} \pi^{(k)}(\mathbf{x})$

Assumptions of Causal Inference in Neyman-Rubin Framework

- Assumption 1 (Ignorability): $\{Y^{(k)}, k = 1, ..., K\} \perp T \mid \mathbf{X}$.
- Assumption 2 (Positivity): $\pi^{(k)}(\mathbf{X}) \in (0, 1)$.
- Assumption 3 (Stable Unit Treatment Value Assumption): No interference & No hidden variations of treatment

Estimation of HTE by R-learner[1]

R-learner adopts the idea of Robinson's decomposition[2]

$$\mathbb{E}[Y \mid \mathbf{X}, T] = m(\mathbf{X}) + \sum_{k \neq j} (1[T = k] - \pi^{(k)}(\mathbf{X}))\tau_j^{(k)}(\mathbf{X}), \quad (1)$$

where $m(\mathbf{X}) = E[Y \mid \mathbf{X}]$.

[1] X Nie, S Wager, Quasi-oracle estimation of heterogeneous treatment effects, Biometrika, Volume 108, Issue 2, June 2021, Pages 299–319

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Two-Step Estimation for $\boldsymbol{\tau}_j(\cdot) = \left(\tau_j^{(1)}(\cdot), ..., \tau_j^{(j-1)}(\cdot), \tau_j^{(j+1)}(\cdot)..., \tau_j^{(K)}(\cdot)\right)$

1. Obtain $\hat{m}(\cdot)$ and $\hat{\pi}(\cdot)$ using the regression spline method for GLM
2. Estimate $\boldsymbol{\tau}_j(\cdot)$ by minimizing the least square loss function

$$\hat{\boldsymbol{\tau}}_j(\cdot) = \arg\min_{\boldsymbol{\tau}_j \in \mathcal{F}} \frac{1}{n} \sum_{i=1}^{n} \left(Y_i - \hat{m}(\mathbf{X}_i) - \sum_{k \neq j} (1[T_i = k]\hat{\pi}^{(k)}(\mathbf{X}_i))\tau_j^{(k)}(\mathbf{X}_i) \right)^2 \tag{2}$$

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Causal Effects for Multiple Treatments

Treatment Recommendation:

Optimal treatment

$$k^* = \begin{cases} j & \text{if } \hat{\tau}_j^{(k)}(\mathbf{X}) < 0 \text{ for any } k \neq j, \\ \arg\max_k \{\hat{\tau}_j^{(k)}(\mathbf{X}), k \neq j\} & \text{else} \end{cases}$$

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Issue: Recommendation may be inconsistent depending on the choice of reference treatment j.

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Example:

Suppose there are 3 treatments T_1, T_2, T_3

- S1: T_1 as reference, $\tau_1^{(2)}, \tau_1^{(3)}$
- S2: T_2 as reference, $\tau_2^{(1)}, \tau_2^{(3)}$
- S3: T_3 as reference, $\tau_3^{(1)}, \tau_3^{(2)}$

Table 1: Probability of disagreement of ranking treatment effects in the standard R-learner.

	Balanced		
	BA	CA	DA
N=2000, p = 18			
S1 vs. S2	0.364	0.419	0.352
S1 vs. S3	0.351	0.327	0.329
S2 vs. S3	0.360	0.347	0.407
Average	0.358	0.364	0.363

Proposed Method: Reference-Free Treatment Recommendation

Redefine the HTE for treatment k as

$$\tau^{(k)}(\mathbf{X}) = E(Y^{(k)} - Y \mid \mathbf{X}) = E(Y \mid T = k, \mathbf{X}) - E(Y \mid \mathbf{X}), k = 1, ..., K \tag{3}$$

Reference-Invariant R-Learner:

$$E[Y \mid T, \mathbf{X}] = m(\mathbf{X}) + \sum_{k=1}^{K} 1[T = k]\tau^{(k)}(\mathbf{X}) \tag{4}$$

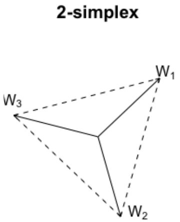
where $\sum_{k=1}^{K} \tau^{(k)}(\mathbf{X})\pi^{(k)}(\mathbf{X}) \equiv 0$ for any $\mathbf{X}$

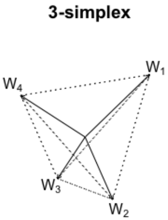
The second step of estimation procedure for $\boldsymbol{\tau}(\cdot) = (\tau^{(1)}, \tau^{(2)}, ..., \tau^{(K)}(\cdot))$

$$\hat{\boldsymbol{\tau}}(\cdot) = \arg\min_{\tau \in \mathcal{F}} \quad \frac{1}{n}\sum_{i=1}^{n}\left(Y_i - \hat{m}(\mathbf{X}_i) - \sum_{k=1}^{K} 1[T_i = k]\tau^{(k)}(\mathbf{X}_i)\right)^2$$

$$\text{s.t.} \quad \sum_{k=1}^{K} \tau^{(k)}(\mathbf{X}_i)\hat{\pi}^{(k)}(\mathbf{X}_i) = 0, \quad i = 1, 2, ..., n.$$

Simplex:A k-simplex is a k-dimensional polytope which is the convex hull of its $k+1$ vertices





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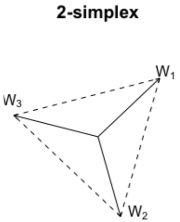

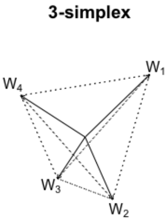

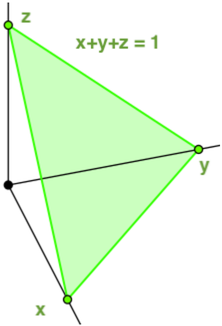

Proposed Method: Reference-Free Treatment Recommendation

Construct the $(K-1)$-simplex as[3]

$$W_k = \begin{cases} (K-1)^{-1/2}\zeta_{K-1}, & k=1 \\ -\frac{1+K^{1/2}}{(K-1)^{3/2}}\zeta_{K-1} + \left(\frac{K}{K-1}\right)^{1/2} e_{K-1}^{(k-1)}, & 2 \le k \le K \end{cases}$$

$\Rightarrow \sum_{k=1}^{K} \langle \boldsymbol{v}, W_k \rangle = 0$ for any arbitrary vector $\boldsymbol{v} \in \mathbb{R}^{K-1}$

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If we could find a mapping $f : \mathbb{R}^p \to \mathbb{R}^{K-1}$ such that

$$\langle f(\mathbf{X}), W_k \rangle = \tau^{(k)}(\mathbf{X})\pi^{(k)}(\mathbf{X}), \text{ for } k = 1, ..., K$$

the constraints are no longer needed if we work on $f(\cdot)$ instead of $\boldsymbol{\tau}(\cdot)$.

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$$\hat{f}(\cdot) = \arg\min_{f \in \mathcal{F}} \frac{1}{n} \sum_{i=1}^{n} (Y_i - \hat{m}(\mathbf{X}_i) - \sum_{k=1}^{K} 1[T_i = k] \langle f(\mathbf{X}_i), W_k / \hat{\pi}^{(k)}(\mathbf{X}_i) \rangle)^2$$

To control the complexity of the estimated function $\hat{f}(\cdot)$:

$$\hat{f}(\cdot) = \arg\min_{f} \frac{1}{n} \sum_{i=1}^{n} \left(Y_i - \hat{m}(\mathbf{X}_i) - \sum_{k=1}^{K} 1[T_i = k] \langle f(\mathbf{X}_i), W_k / \hat{\pi}^{(k)}(\mathbf{X}_i) \rangle \right)^2 + \lambda J(f)$$

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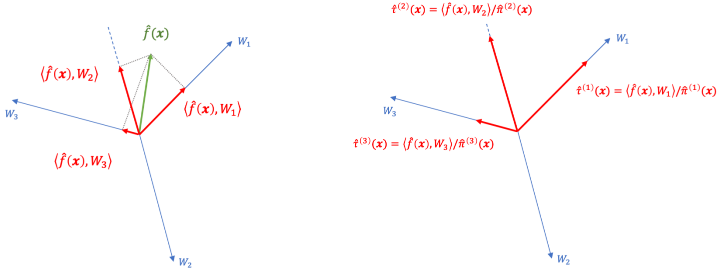
Estimated HTE given patient with covariates **X**

$$\hat{\tau}^{(k)}(\mathbf{X}) = \langle \hat{f}(\mathbf{X}), W_k/\hat{\pi}^{(k)}(\mathbf{X})\rangle, \quad k = 1, 2, ..., K.$$



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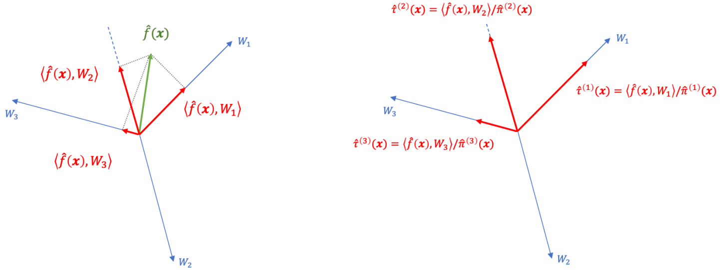

Optimal treatment

$$\text{Recommended Treatment } k^* = \arg\max_k \left\{\hat{\tau}^{(k)}(\mathbf{X}), k = 1, 2, \ldots K\right\}$$

Simulation Study: Data Generation

The outcome Y_i are generated from

$$Y_i = c(\mathbf{X}_i) + \sum_{k=1}^{K} 1[T_i = k] b^{(k)}(\mathbf{X}_i) + \varepsilon_i$$

with $K = 3$, $\mathbf{X}_i \sim N_p(0, 1), i = 1, ..., n$, $\varepsilon_i \sim N(0, 1)$

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Optimal Treatment Designs $b^{(k)}(\cdot)$

- Balanced Design
  - each treatment has the same chance to be the optimal one
- Unbalanced Design
  - treatment 1 is the optimal one for most subjects; while treatment 3 has the least treatment effect

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Treatment Assignment Mechanism $\pi^{(k)}(\cdot)$**:**

- Balanced Assignment (BA):
    - the observed treatment distribution is balanced
- Concordance Assignment (CA):
    - treatment 1 dominants the observed treatment assignments
- Discordance Assignment (DA):
    - treatment 3 dominants the observed treatment assignments

Simulation study: Data generation

- Size of training sample: $n \in \{2000, 4000\}$
- Size of testing sample 10000
- 100 repetitions

	Optimal Treatment Allocation		**Treatment Assignment**		
	Balanced	Unbalanced	BA	CA	DA
Treatment 1	3333 ± 53	8012 ± 41	3336 ± 48	6305 ± 50	1026 ± 29
Treatment 2	3330 ± 48	1565 ± 35	3331 ± 49	2669 ± 41	2668 ± 46
Treatment 3	3338 ± 46	423 ± 17	3333 ± 44	1025 ± 31	6306 ± 50

- Number of variables $p \in \{9, 18\}$ but only first 6 are influential

Simulation Study: Results

Table 2: Comparison of recommendation accuracy for the optimal treatment among the R-learners.

	Balanced			Unbalanced		
	BA	CA	DA	BA	CA	DA
N=2000, p = 9						
S	83±2.2%	67.1±5.7%	68.5±6.7%	83.4±2.9%	80±2%	79.5±4.3%
R1	84.3±2.1%	67±5.7%	61±2.3%	83.6±2.8%	81.5±3.2%	79.2±2.8%
R2	84.4±2%	66.6±6.7%	66.7±6.2%	81.8±2.4%	80.6±2.4%	78.7±3.1%
R3	84.2±2%	61±2.5%	66.7±5.8%	83.9±2.7%	82.5±2.7%	79.5±2.8%
N=2000, p = 18						
S	81.8±2%	64.2±4.9%	66.4±5.8%	82.5±2.5%	80.2±2%	79.6±2.8%
R1	83±1.9%	63.9±4.4%	60.2±1.9%	82.4±2.3%	81.4±2.5%	79.5±1.4%
R2	82.9±2%	62.9±4.9%	63.4±4.9%	81±1.7%	80.3±2%	78.6±2.6%
R3	82.8±1.8%	60.1±1.9%	64.2±4.6%	82.8±2.3%	82.2±2.5%	79.1±2.9%
N=4000, p = 9						
S	86.1±1.4%	75.1±5.3%	76.1±4%	85.2±2.5%	81.2±2.7%	83±2.6%
R1	87.3±1.5%	74.1±6.6%	62.9±2.3%	85.7±2.7%	84.8±2.9%	80.2±1%
R2	87.6±1.7%	73.8±6.6%	74.4±6.5%	83.7±2.9%	82.7±3.1%	80.7±2.8%
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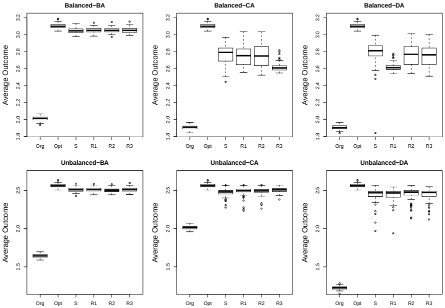

Figure 1: Comparison of the predicted average outcome based on the recommended treatment from the R-learners with n = 2000 and p = 9.

- Simplex R-learner provides consistent recommendations in constrast to standard R-learner
- Recommendation accuracy increased with the sample size
- Accuracy is not strongly affected by the number of noise variables
- Both simplex and standard R-learner significantly improve the treatment benefit
- The predicted overall benefit is close to the ideal case in most cases

Application to SPRINT Study

Objective: Make recommendations based on patient characteristics to reduce the systolic blood pressure (SBP) from the following three classes of antihypertensive agents:

- Thiazide diuretics
  - *Chlorthalidone*
- Calcium channel blockers (CCB)
  - *Amlodipine*
- Angiotensin-converting-enzyme (ACE) inhibitors
  - *Lisinopril*

Continuous Variables	
Systolic blood pressure: mm Hg	130.9±13.0
Potassium: mmol/L	4.2±0.5
Sodium: mmol/L	139.9±2.4
Estimated GFR: ml/min/1.73 m^2	77.1±20.4
Serum Creatinine: mg/dL	1.0±0.3
Total Cholesterol: mg/dL	192.0±40.6
HDL: mg/dL	52.2±17.2
Framingham Risk Score	17.2±2.4
Age: yr	67.0±9.2
Body-mass index (BMI)	29.2±5.5
Categorical Variables	
Gender: no.(%)	
Female	626(31.1)
Male	1385(68.9)
Smoke Status: no.(%)	
Not Current Smoker	1700(84.5)
Current Smoker	311(15.5)
Race: no.(%)	
Spanish	167(8.3)
White	1217(60.5)
Black	598(29.7)
Other	29(1.4)

Application to SPRINT Study

Table 3: Allocation of Amlodipine, Chlorthalidone, and Lisinopril from original assignment and algorithm recommendation

	Amlodipine		**Chlorthalidone**		**Lisinopril**		**Overall**	
	Size	Benefit(mm Hg)	Size	Benefit(mm Hg)	Size	Benefit(mm Hg)	Size	Benefit(mm Hg)
Assigned	507	0.04(13.61)	608	0.78(14.4)	896	-0.66(14.53)	2011	-0.05(14.27)
Same as Recommend	18	3.61(14.69)	356	2.06(15.59)	42	1.62(14.72)	416	2.08(15.43)
Recommend	145	1.57(5.74)	1584	1.85(8.58)	282	-0.34(4.95)	2011	1.52(8.02)

- The algorithm's recommendation is highly consistent with the current clinical guidelines for hypertension treatment (James et al. 2014)
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- A closer examine of baseline distribution of covariates is also revealing

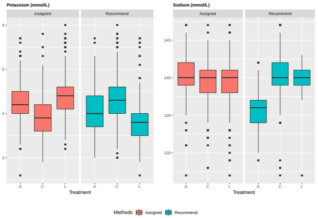

Figure 2: Comparison of SBP benefit between assigned and recommended

Conclusions:

- The proposed method broadens the use of R-learning methods from causal inference to treatment recommendation in multiple treatment scenario
- Simplex R-learner generates therapeutic recommendations that are not influenced by the selection of reference treatment
- Regression spline is adopted to simplify the numerical computation without assuming a specific parametric form
- The proposed simplex R-learner is easy to implement

Future work

- Extend the simplex R-learner to other types of outcome

THANKS!