Guidance on Individualized Treatment Rule Estimation in High Dimensions

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Motivation

Precision medicine promises to tailor patients' treatments to optimize their outcomes. Patients' pre-treatment covariates, like age, sex-at-birth, and genetic profiles, influence therapies' efficacy, safety, and tolerability outcomes. These patient characteristics, known as **treatment effect modifiers, are used to derive individualized treatment rules (ITRs) that guide personalized treatment decisions**.

While numerous methods can successfully estimate ITRs in traditional asymptotic settings, **learning ITRs from high-dimensional data with more pre-treatment covariates than patients — a common occurrence in modern clinical data — is challenging**. ITR estimators developed for such data rely on simplifying assumptions. Recent advances in treatment effect modifier detection may help.

A comparison of available methods has not been performed. Nor has an evaluation of these methods' sensitivity to assumption violations. As such, **selecting an appropriate ITR estimation strategy for high-dimensional settings is challenging for applied biomedical researchers**. Capacity for precision medicine is diminished as a result.

Primary Objectives

- **Provide guidance based on practical operating characteristics to applied scientists for ITR estimation in high dimensions.**
- **Determine whether treatment effect modifier detection procedures improve ITR estimation in high-dimensions.**

Operating Characteristics

- **Rule Quality:** An ITR is "high-quality" when its expected outcome approaches that of the optimal rule. That is, the rule approximately optimizes mean outcome in the population.
- **Accurate Interpretability:** An ITR is accurately interpretable when it recovers treatment effect modifiers reliably in terms of the false discovery, true positive, and true negative rates.
- **Computational Efficiency:** An ITR is computationally efficient when it can be estimated quickly in serial with few computational resources.

Problem Formulation

Consider n i.i.d. observations $O = (W, A, Y)$ where W is a p-length random vector of pre-treatment covariates (and possible confounders) where $p \approx n$ or $p > n$, A is a binary treatment indicator, and Y is the continuous outcome.

We aim to estimate the ITR, defined as

$$I(\mathbb{E}[Y|W,1] - \mathbb{E}[Y|W,0] > 0) \ ,$$

where $\mathbb{E}[Y|W,1] - \mathbb{E}[Y|W,0]$ is the conditional average treatment effect (CATE) under standard identifiability conditions.

References

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Estimators

The CATE estimators in the table below were used to construct ITR estimators. Filtered versions of these CATE estimators relying on the treatment effect modifier variable importance parameter methodology of Boileau et al. [1] were used to construct ITR estimators as well.

CATE Estimator	Details
Plug-In LASSO	A plug-in estimator using the LASSO [2].
Plug-In XGBoost	A plug-in estimator using XGBoost [3].
Modified Covariates LASSO	A modified covariates estimator [4] using the LASSO. The propensity score is estimated using the logistic LASSO.
Modified Covariates XGBoost	A modified covariates estimator [4] using XGBoost. The propensity score is estimated using the logistic LASSO.
Augmented Modified Covariates LASSO	An augmented modified covariates estimator [4] using the LASSO. The propensity score is estimated using the logistic LASSO.
Augmented Modified Covariates XGBoost	An augmented modified covariates estimator [4] using XGBoost. The propensity score is estimated using the logistic LASSO.
AIPW-based LASSO	An AIPW-based estimator [5] using Super Learners [6] to estimate the expected conditional outcome and the propensity score. Differences in predicted pseudo-outcomes are modelled using the LASSO.
AIPW-based Super Learner	An AIPW-based estimator [5] using Super Learners to estimate the expected conditional outcome and the propensity score. Differences in predicted pseudo-outcomes are modelled using a Super Learner.
Causal Random Forests	A causal random forest estimator [7] using cross-validation for hyperparameter selection.

Simulated Data-Generating Processes

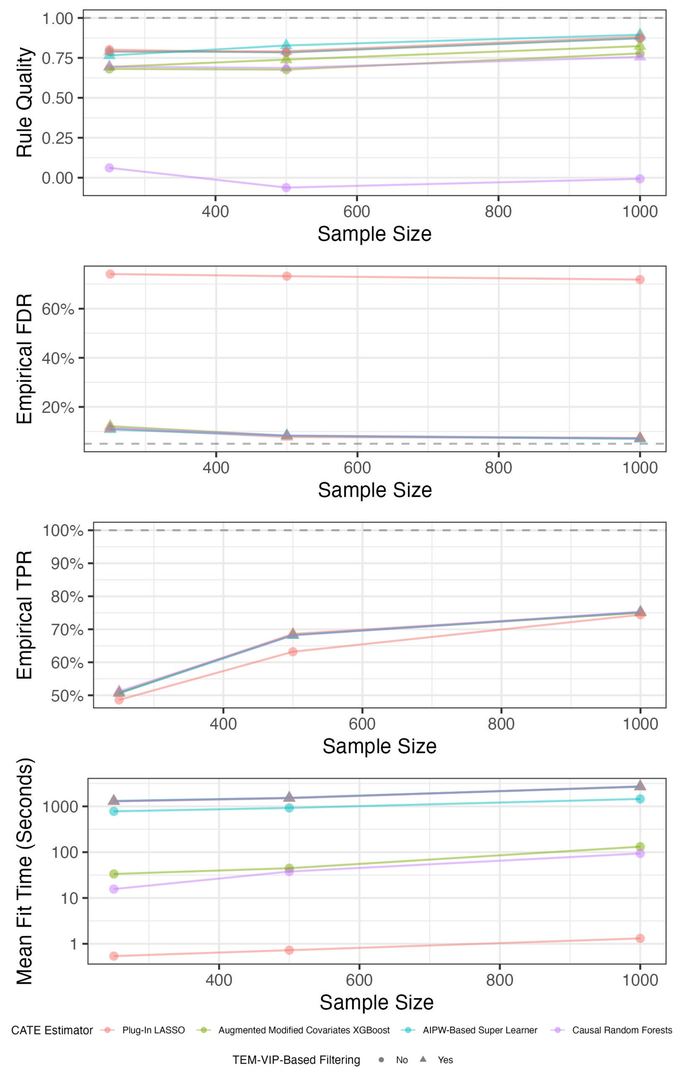
ITR estimators were benchmarked in 16 data-generating processes with continuous outcomes and binary treatment assignments **reflecting a diversity of randomized and observational studies**. Realizations of random vector O with $p = 500$ were generated according to the following data-generating process template:

$$\begin{aligned} W &\sim N(0, \Sigma) \\ A|W &\sim \text{Bernoulli}(\pi(W)) \\ Y|W, A &\sim N(\mu(W, A), 1) \ . \end{aligned}$$

Here, Σ is some 500×500 covariance matrix, $\pi(W) = \mathbb{P}[A = 1|W]$, and $\mu(W, A) = \mathbb{E}[Y|W, A]$. Data-generating processes are defined using combinations of the following factors:

$$\begin{aligned} \Sigma_1 &= I_{500\times500} \\ \Sigma_2 &= \text{Block diagonal} \\ &\times \\ \pi_1(W) &= \frac{1}{2} \\ \pi_2(W) &= \text{logit}^{-1}\left(\frac{W_1 + W_2 + W_3 + W_4}{5}\right) \\ &\times \\ \mu_1(A, W) &= A + \gamma^\top W + (\delta^{(10)})^\top WA \\ \mu_2(A, W) &= A + \gamma^\top W + (\delta^{(50)})^\top WA \\ \mu_3(A, W) &= \gamma^\top W + 2\arctan\left\{(\delta^{(10)})^\top WA\right\} \\ \mu_4(A, W) &= \gamma^\top W + 2\arctan\left\{(\delta^{(50)})^\top WA\right\} \end{aligned}$$

Results Snapshot



Practical Guidance

No estimator uniformly dominates others across all operating characteristics; tradeoffs must be made. Since rule quality is generally of primary concern, practitioners must choose between accurate interpretability and computationally efficiency. We provide the following guidance on this tradeoff when selecting an ITR estimator for high-dimensional data:

- **High-quality ITRs that are accurately interpretable:** The filtered LASSO-based plug-in and AIPW-based estimators generally produce high-quality ITR estimates while accurately recovering TEMs. These estimators are computationally intensive, however. The computational burden might be lestned by parallelizing the estimation procedure.
- **High-quality ITRs that require few computational resources:** The LASSO-based plug-in estimator produces among the most high-quality rules in our simulation studies, providing empirical evidence that it is robust to model misspecification while being exceptionally computationally efficient. This estimator's built-in feature selection capabilities should not be used for TEM discovery, however.

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Link to paper