A Flexible Approach for Predictive Biomarker Discovery

Philippe Boileau[1], Nina Ting Qi[2], Mark J. van der Laan[1] Sandrine Dudoit[1], Ning Leng[2]

[1]University of California, Berkeley; [2]Genentech Inc.

Background

- Predictive biomarkers are treatment effect modifiers.
- In high dimensions, these biomarkers are discovered using interpretable conditional average treatment effect estimators, like the modified covariates procedures of Tian et al. (2014).
- These methods make simplifying assumptions about the data-generating process, resulting in a lack of Type-I error rate control.
- High false discovery rates lead to wasted resources, negatively affecting patient outcomes.

Variable Importance Parameter

Consider n identically and independently distributed (i.i.d) full-data random vectors $X = (W, A, Y^{(0)}, Y^{(1)}) \sim P_X$.

- W: A p-length random vector of centered pretreatment biomarkers with nonzero variance.
- A: A random binary indicator of treatment assignment.
- $Y^{(0)}, Y^{(1)}$: Continuous potential outcomes under assignment to the control and treatment allocations, respectively.

Our causal variable importance parameter is $\Psi^F(P_X) = (\Psi_1^F(P_X), \ldots, \Psi_p^F(P_X))$, where

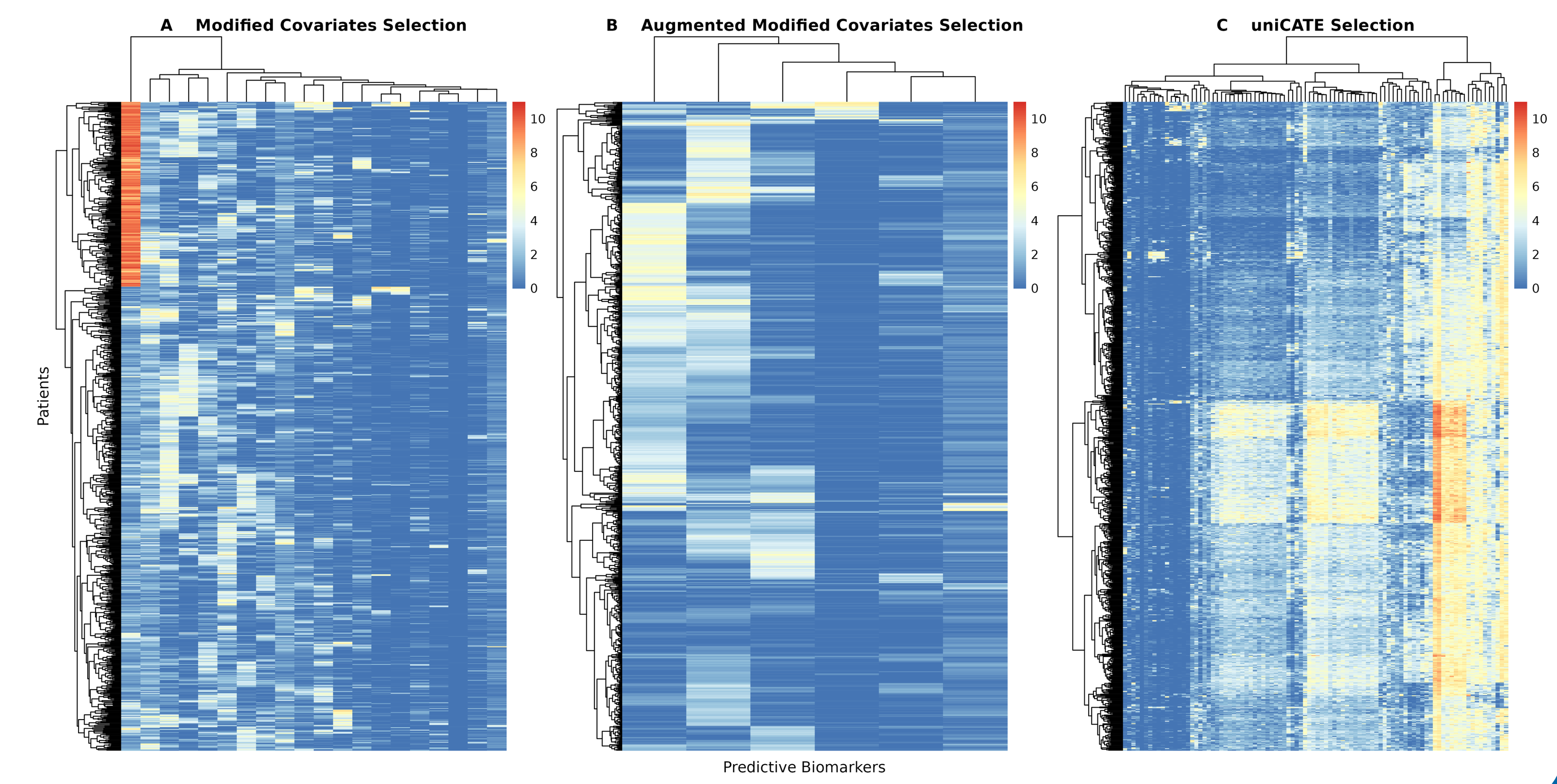
$$\Psi_j^F(P_X) \equiv \frac{\mathbb{E}_{P_X}\left[\left(Y^{(1)} - Y^{(0)}\right) W_j\right]}{\mathbb{E}_{P_X}\left[W_j^2\right]}.$$

Given access instead to n i.i.d. censored random observations $O = (W, A, Y)$ where $Y = AY^{(1)} + (1-A)Y^{(0)}$, $\Psi^F(P_X)$ is identified under the assumptions of unmeasured confounding and positivity by $\Psi(P_0) = (\Psi_1(P_0), \ldots, \Psi_p(P_0))$. Here,

$$\Psi_j(P_0) \equiv \frac{\mathbb{E}_{P_0}\left[\left(\bar{Q}_0[A=1, W] - \bar{Q}_0[A=0, W]\right) W_j\right]}{\mathbb{E}_{P_0}\left[W_j^2\right]},$$

where $\bar{Q}_0[A, W] = \mathbb{E}_{P_0}[Y|A, W]$.

Application to IMmotion 150 and 151



Inference

Let $g_0(W) = \mathbb{P}[A = 1|W]$, and let $\hat{g}$ and $\hat{\bar{Q}}$ be estimators of g_0 and $\bar{Q}_0$, respectively. Define the Augmented Inverse Probability Weighted outcome difference as

$$T(O) \equiv \left(\frac{I(A=1)}{\hat{g}(W)} - \frac{I(A=0)}{1-\hat{g}(W)}\right)\left(Y - \hat{\bar{Q}}(A, W)\right) + \hat{\bar{Q}}(1, W) - \hat{\bar{Q}}(0, W).$$

We derive from the efficient influence function of $\Psi_j(P_0)$, $D_j(O)$, the double-robust one-step estimator

$$\hat{\Psi}_j(P_n) \equiv \frac{\sum_{i=1}^n T(O_i) W_{ij}}{\sum_{i=1}^n W_{ij}^2},$$

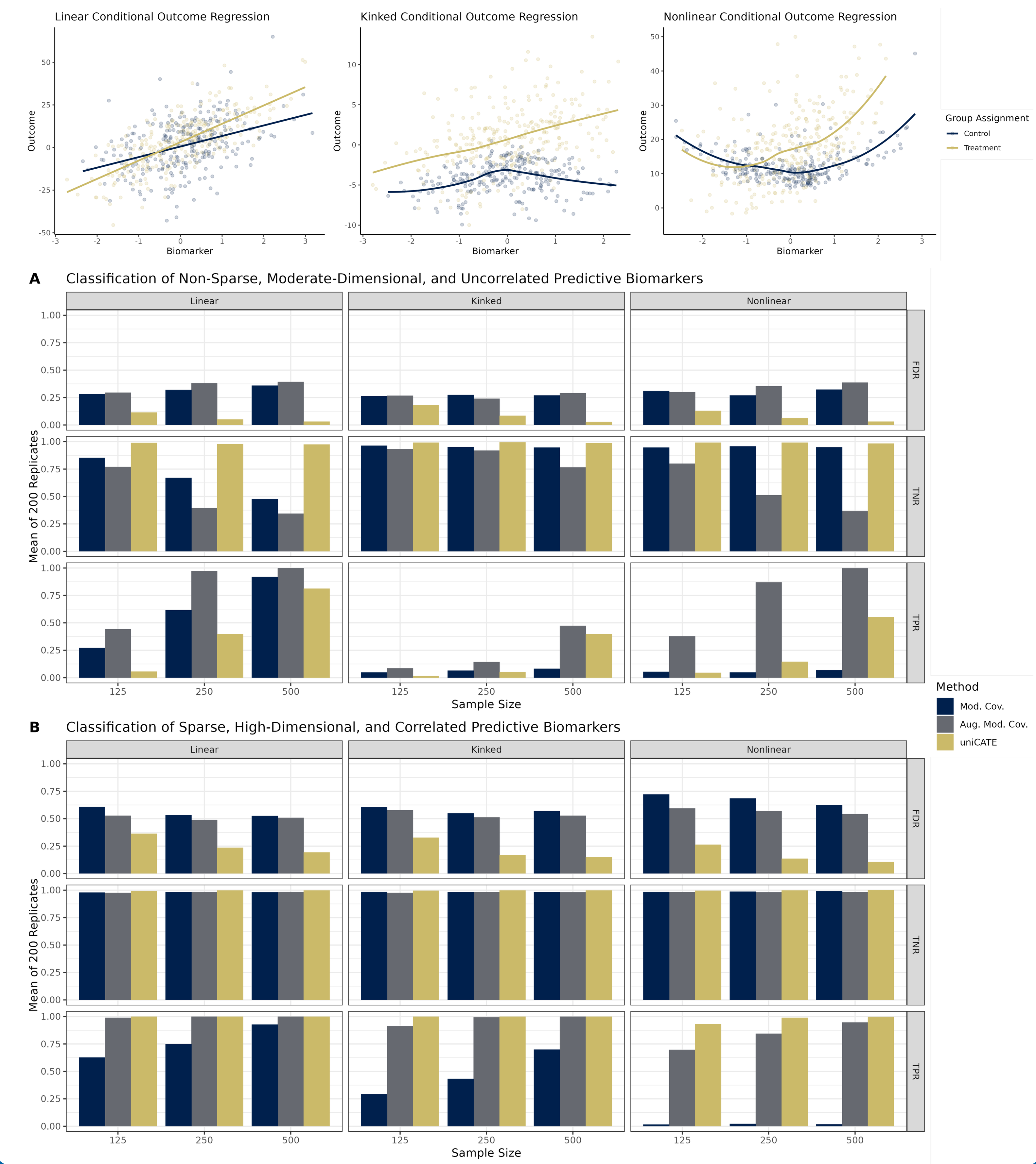
where $\sum_i W_{ij} = 0$ for all j and P_n is the empirical distribution. If $\hat{g}$ and $\hat{\bar{Q}}$ are trained using sample splitting techniques, and we assume that $\|\hat{g} - g_0\|_2 \|\hat{\bar{Q}} - \bar{Q}_0\|_2 = o_p(n^{-1/2})$, then

$$\sqrt{n}\left(\hat{\Psi}_j(P_n) - \Psi_j(P_0)\right) \xrightarrow{D} N\left(0, \mathbb{V}_{P_0}\left[D_j(O)\right]\right).$$

Funding

PB gratefully acknowledges the support of the National Science and Engineering Research Council of Canada and the Fonds de recherche du Québec – Nature et technologies.

Randomized Control Trial Simulations



Conclusion

Predictive biomarker discovery benefits from formal statistical inference procedures that control false discovery rates. This estimator is implemented in the `uniCATE` R package available at `github.com/insightsengineering/uniCATE`.

Reference

Tian et al. (2014) A Simple Method for Estimating Interactions Between a Treatment and a Large Number of Covariates, Journal of the American Statistical Association, 109:508, 1517-1532, DOI: 10.1080/01621459.2014.951443