Variance Moderation of Locally Efficient Estimators and Supervised Clustering with Applications in High-Dimensional Biology

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OVERVIEW & MOTIVATIONS

- A general approach for applying variance moderation to locally efficient estimators in nonparametric models is introduced.
- Variance moderation stabilizes small-sample properties of semiparametric-efficient estimators,
  - curbing the error rate of tests relative to classical approaches
  - and facilitating *supervised clustering* from derived association profiles.
- Focusing on a targeted maximum likelihood estimator (TMLE), we illustrate how the proposed approach generalizes readily to any asymptotically linear estimator.
- The `biotmle` R package [1] implements the inference and clustering methods, and leverages state-of-the-art machine learning.

DATA: BENZENE BIOMARKERS

- There is a pressing need for model-free, technology-agnostic statistical methods for analyzing multiple kinds of exposome data.
- We consider a data from an occupational exposure study, generated by the *Illumina Human Ref-8 BeadChips* platform.
- Baseline (phenotypic) confounders and exposure status were collected for $n = 125$ participants, alongside expression measures for $\sim 22,000$ genes.
- Baseline covariates (W): age, sex, and smoking status.
- Exposure (A): degree of Benzene exposure (none, $<$ 1ppm, $>$ 5ppm).
- Outcome ($Y = (Y_b : b = 1, \ldots, B)$): vector of gene expression measures, after full qunatile normalization.

METHODOLOGY I: VARIANCE MODERATION & LOCAL EFFICIENCY

- Let observed data $O = (W, A, Y) \sim P_0 \in \mathcal{M}$, where W represents potential baseline confounders, A the exposure of interest, and $Y = (Y_b, b = 1, \ldots, B)$ a vector of potential biomarkers.
- We consider, as an example, the *average treatment effect* (ATE), as the causal parameter of interest, which is identified by the observed data parameter:

$$\Psi_b(P_0) = \mathbb{E}_W[Q_0^b(A = 1, W) - Q_0^b(A = 0, W)], \tag{1}$$

  where $Q_0^b(A, W) \equiv \mathbb{E}_{P_0}(Y_b \mid A, W)$ and may be estimated via *ensemble machine learning* [4, 5, 6].
- Like the estimator $\hat{\beta}$ in a linear model $m(A, W \mid \beta)$, $\Psi_b(P_n)$ is **asymptotically linear** (for Ψ_b) [7]:

$$\sqrt{n}(\Psi_b(P_n) - \Psi_b(P_0)) = \frac{1}{\sqrt{n}} \sum_{i=1}^{n} D_b(O_i) + o_p(1). \tag{2}$$

- Ψ_b has efficient influence function (EIF), relative to the nonparametric model $\mathcal{M}$:

$$D_b(P_0)(o) = \left(\frac{I(a = 1)}{g(1 \mid w)} - \frac{I(a = 0)}{g(0 \mid w)} \right) \cdot \left[y_b - Q_0^b(a, w) \right] + \left(Q_0^b(1, w) - Q_0^b(0, w) - \Psi_b(P_0)(o) \right). \tag{3}$$

- A moderated test statistic [8, 2] may be constructed for use wiht asymptotically linear estimators:

$$\widetilde{t}_b = \frac{\sqrt{n}(\Psi_b(P_n) - \psi_{\text{null}})}{\widetilde{S}_{b,n}^2} \quad \text{where} \quad \widetilde{S}_{b,n}^2 = \frac{d_0 S_0^2 + d_b S_b^2(D_{b,n})}{d_0 + d_b}, \tag{4}$$

  $\{S_b^2, d_b\}$: var. EIF and df for b^{th} biomarker; $\{S_0^2, d_0\}$: var. EIF and df for other $(B - 1)$ biomarkers.

METHODOLOGY II: SUPERVISED DISTANCE MATRICES

- Let $\phi : (W, A, Y) \mapsto D_b(P_0)(O)$ be the EIF transformation, where $D_b(P_0)(O_i)$ is the contribution of subject i to the estimate of the biomarker-specific target parameter $\Psi_{b,n}$.
- $Z = \phi(W, A, Y)$ is then a $B \times N$ matrix, where each entry (b, i) may be interpreted as the degree to which subject i deviates from the target parameter $\Psi_{b,n}$ [2], and is thus an *association profile*.
- A *supervised distance matrix* [3] may be constructed by applying an appropriate distance metric of choice (e.g., Euclidean, correlation) to the transformed values Z.
- $\widetilde{T}(Z)$, the resultant $B \times B$ empirical distance matrix, encodes the dissimilarity between pairs of biomarker association profiles.
- When $\widetilde{T}(b, b')$ is small, the biomarkers b and b' have similar contriubtions to the target parameter Ψ, across the n subjects.
- *Supervised clustering* may be performed by applying standard unsupervised clustering algorithms to the matrix $\widetilde{T}$, thereby finding groups of biomarkers that share an association profile w.r.t. Ψ.
- In the case of the average treatment effect, a supervised cluster in $\widetilde{T}$ of biomarkers is a group whose causal differential expression profiles varies similarly with the treatment $A \in \{0, 1\}$.

RESULTS

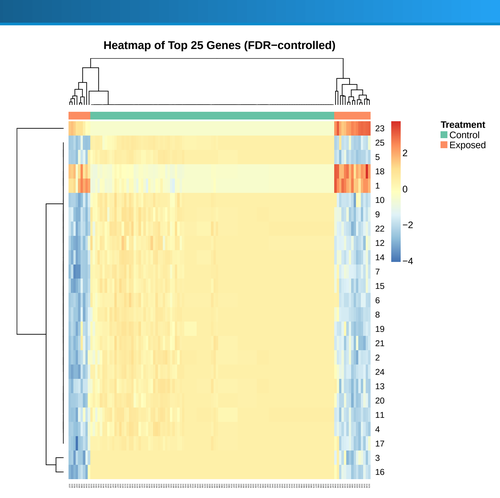

Figure 1: *Supervised heatmap* of biomarker contributions to the ATE.

Figure 2: Enhanced error rate control of the variance-moderated TMLE of the ATE.

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