



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, $< 1\text{ppm}$, $> 5\text{ppm}$).
- Outcome ($Y = (Y_b : b = 1, \dots, B)$): vector of gene expression measures, after full quantile normalization.

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 .
- $\tilde{T}(Z)$, the resultant $B \times B$ empirical distance matrix, encodes the dissimilarity between pairs of biomarker association profiles.
- When $\tilde{T}(b, b')$ is small, the biomarkers b and b' have similar contributions to the target parameter Ψ , across the n subjects.
- Supervised clustering* may be performed by applying standard unsupervised clustering algorithms to the matrix \tilde{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 \tilde{T} of biomarkers is a group whose causal differential expression profiles varies similarly with the treatment $A \in \{0, 1\}$.

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 $Y = (Y_b, b = 1, \dots, B)$ 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:

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

where $Q_0^b(A, W) \equiv \mathbb{E}_{P_0}(Y_b | A, W)$ and may be estimated via *ensemble machine learning* [4, 5, 6].

- Like the estimator $\hat{\beta}$ in a linear model $m(A, W | \beta)$, $\Psi_b(P_n)$ is **asymptotically linear** (for Ψ_b) [7]:

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

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

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

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

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

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

RESULTS

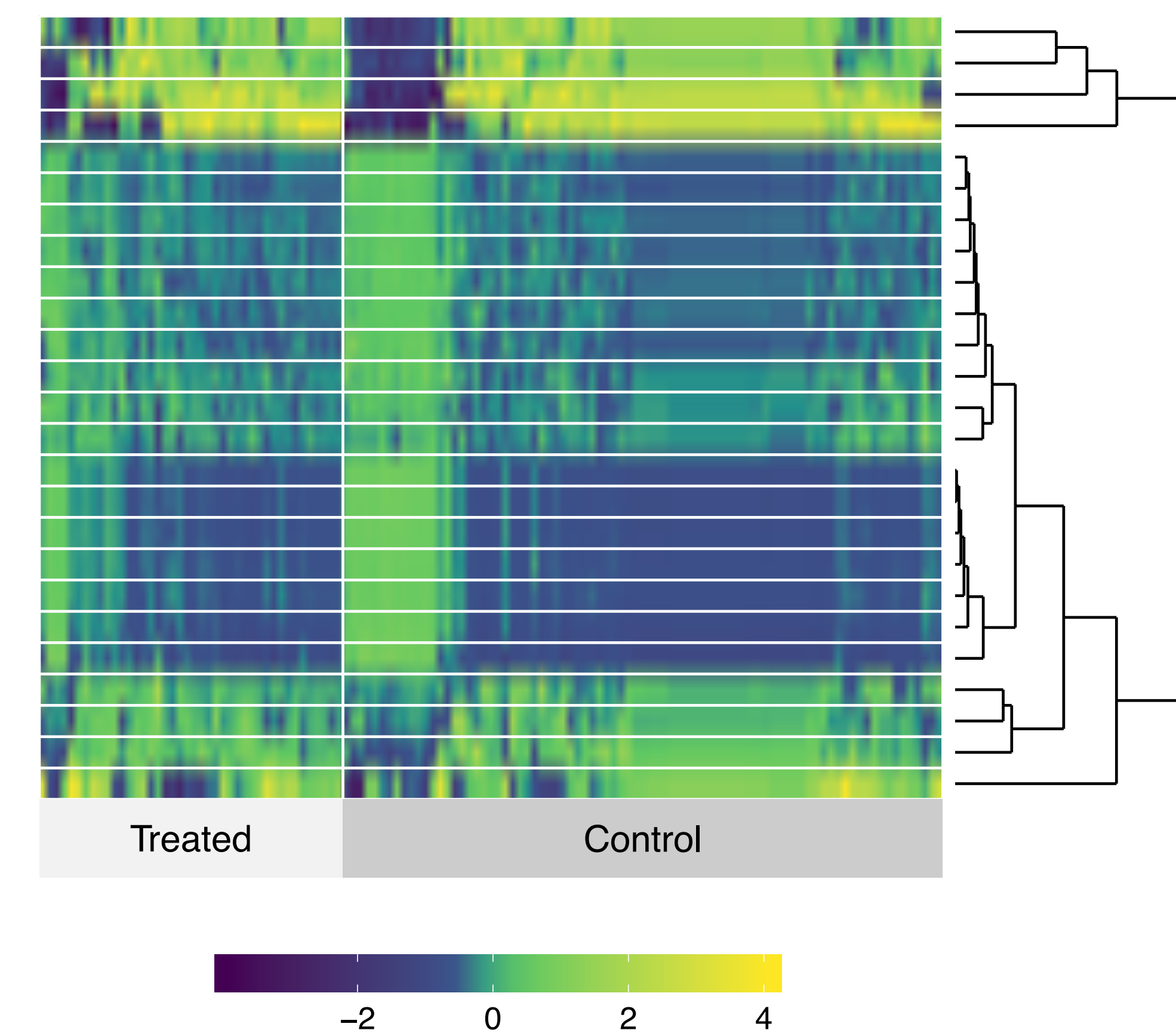


Figure 1: Supervised heatmap of top 25 biomarkers.

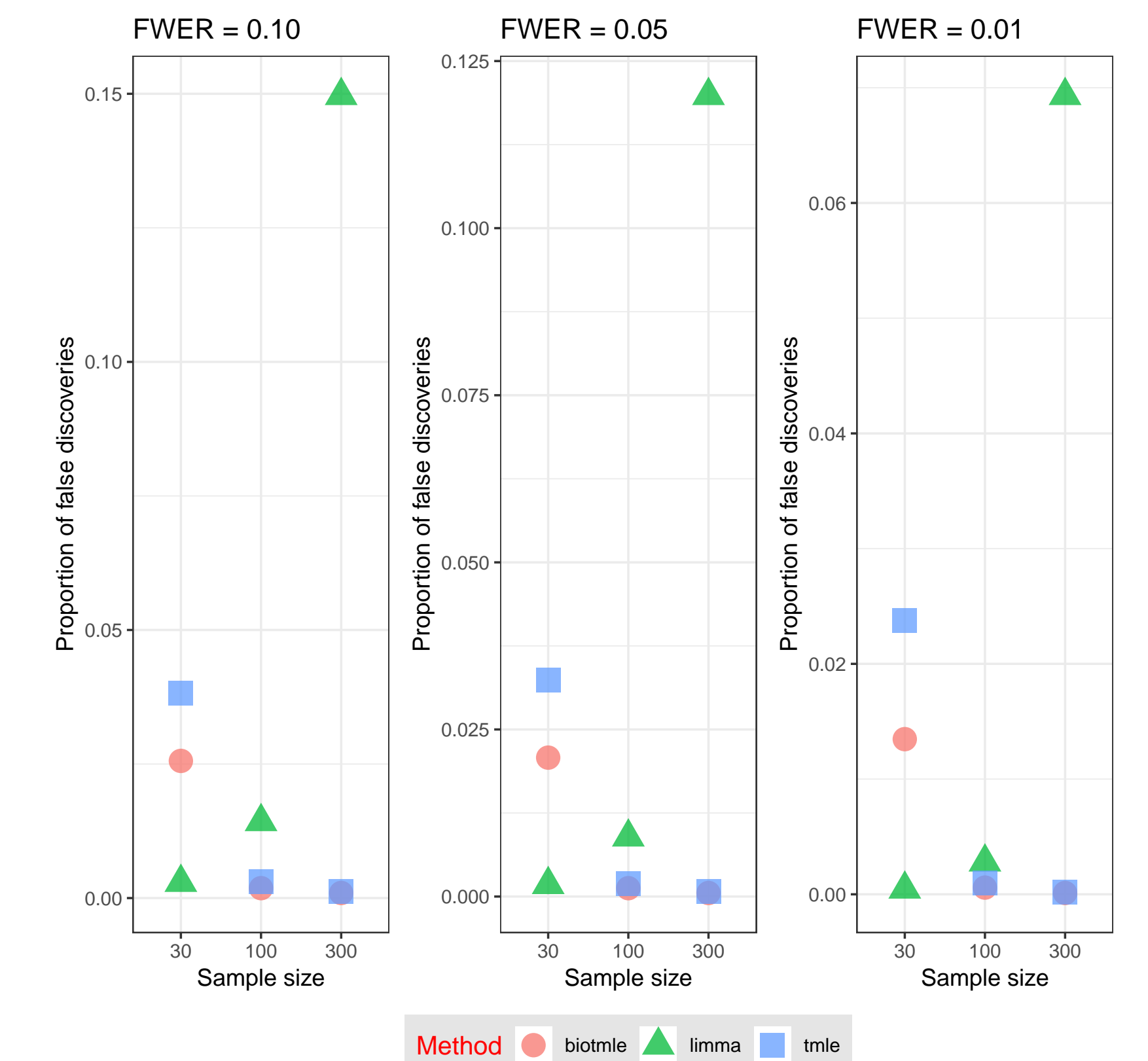


Figure 2: Enhanced error rate control with variance-moderated efficient estimator (*n.b.*, y-axis scales differ).

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