Combining Causal Inference and Machine Learning for Model-Agnostic Discovery in High-Dimensional Biology

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Preview

1. Modern computational biology research produces complex, heterogeneous data — innovative statistical inference still tied to simplistic and challenging-to-verify modeling assumptions.
2. *Model misspecification* seriously undermines the scientific utility of common, classical statistical modeling approaches.
3. Non/semi-parametric inference facilitates constructing robust estimators that easily bring machine learning into the fold.
4. Variance moderation strengthens hypothesis testing strategies, reducing false positives and preserving power under instability.

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A common problem

- *Question*: What factors are associated ("causally" perhaps) with a health outcome of interest (e.g., cancer, death).
- *Experiment*: Assign[?] patients to novel therapy vs. standard of care (or exposure) and then evaluate outcome's occurrence.
- *Goal*: Deepen mechanistic insights — how does the therapy or exposure biologically operate? Identify intervention points.
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Let's meet the data: Benzene exposure and miRNA

- *Question*: Which miRNA (non-coding regulators) are affected by a target occupational exposure (benzene)?
- *Why?* Attempt to decipher how patterns of miRNA disregulation may impact subsequent disease states.
- *Study*: Cohort study of occupational exposure to benzene with 125 individuals and 22K candidate miRNA assayed.
- *Goal*: Characterize biological mechanisms or signatures derived from or attributable to exposure.

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- *Why?* Attempt to understand how smoking induces regulatory and functional changes that relate to disease (e.g., cancer).
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Data structure and notation

- Consider a structural causal model (SCM) (Pearl 2000) to describe how data on a single unit O was generated:

$$L = f_L(U_L); A = f_A(L, U_A); Y = f_Y(A, L, U_Y).$$

- f_L, f_A, f_Y are unknown but deterministic functions; U_L, U_A, U_Y are exogenous (unobserved) random errors.
- $Y = (Y_b : b = 1, \ldots B)$ is a vector of biomarker outcomes (e.g., $B = 22\text{K}$ for miRNA, $B = 450\text{K}$ for CpG sites).
- Temporal ordering between variables: L (sex-at-birth, age), A (smoking, benzene), Y_b (biomarker measurement for site b).
- Data on a single study unit $O = (L, A, Y)$, with $O \sim P_0 \in \mathscr{M}$, of which we observe n i.i.d. copies, $O_1, \ldots, O_n$.

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Hypothetical interventions and causal inference

- *Static* interventions consider replacing f_A with an assigned value $a \in \mathscr{A}$ deterministically. "What if everyone smoked?"
- Generates "counterfactual" RV $Y(a) = (Y_b(a), b : 1, \ldots B)$: the expression of the B biomarkers if A had been set to a.
- Viewed as *potential outcomes* (POs) (Rubin 2005), $Y_b(1)$ when setting $A = 1$ and $Y_b(0)$ when setting $A = 0$.
- Note that $Y_b = AY_b(1) + (1 - A)Y_b(0)$ — only partially seeing the POs is the *fundamental problem of causal inference*.
- Causal inference yields interpretable, scientifically well-aligned estimands, e.g., the average treatment effect (ATE).

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A familiar workhorse: the linear model

- The linear model is *semiparametric* — linear in parameters!
- Flexible: transformations (X_j^2), interactions ($X_j X_k$).
- For biomarker Y_b, fit *working* linear model, $\mathbb{E}_0[Y_b \mid X] = X\beta$, letting (wlog) $X_1 \equiv A$ be the exposure and β_1 its "effect".
- Under this working model, the parameter β_1 is the ATE, but *only if* there are no interactions (i.e., without flexibility).
- Test the contrast of interest with a standard t-test:

$$t_b = \frac{\hat{\beta}_b - \beta_{b,H_0}}{\hat{\sigma}_b}$$

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Variance moderation to the rescue?!

- When sample size is small, σ_b^2 may be so small (by chance) that even small effects $(\hat{\beta}_b - \beta_{b,H_0})$ give large t_b.
- False positives! Many biomarkers flagged relevant despite small effect size, only since variance is even smaller still.
- Can we do better? A **moderated** t-test (Smyth 2004):

$$\tilde{t}_b = \frac{\hat{\beta}_b - \beta_{b,H_0}}{\tilde{\sigma}_b} \quad \text{where} \quad \tilde{\sigma}_b^2 = \frac{\sigma_b^2 d_b + \sigma_0^2 d_0}{d_b + d_0}$$

- Helps reduce erroneously large t_b by "averaging out" low variance across each of the many biomarkers.

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Variable importance measures as target parameters!

- If the working model is incorrect, β_b does not correspond to the ATE — results polluted by *misspecification bias*.
- The statistical functional identifying the ATE may be used as an interpretable variable importance measure (VIM):

$$\psi_{b,0} \equiv \Psi_b(P_0) = \mathbb{E}_{L,0}[\mathbb{E}_0[Y_b \mid A = 1, L] - \mathbb{E}_0[Y_b \mid A = 0, L]]$$

- $\psi_{b,0}$ is a mapping ($\Psi_b(P_0)$) that depends on the underlying true (but unknown) distribution $P_0 \in \mathscr{M}$ — model-agnostic!
- The statistical functional *identifies* the ATE under untestable assumptions (no unmeasured confounding, positivity).

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Locally efficient estimation

- An estimator $\hat{\psi}_b$ is asymptotically linear if it admits the form

$$\hat{\psi}_b - \psi_{b,0} = \frac{1}{n}\sum_{i=1}^{n} D_b(O_i; P_0) + o_P\left(\frac{1}{\sqrt{n}}\right),$$

  where $D_b(O; P_0)$ is the efficient influence function (wrt $\mathscr{M}$), whose asymptotic variance is the *efficiency bound*.

- $D_b(O; P_0)$ helps construct efficient estimators. For ATE,

$$D_b(O_i; P_0) = \left[\frac{2A_i - 1}{g_0(L_i)}\right](Y_{b,i} - \overline{Q}_{0,b}(A_i, L_i)) + \overline{Q}_{0,b}(1, L_i) - \overline{Q}_{0,b}(0, L_i) - \psi_{b,0},$$

  where $g_0(L) = \mathbb{P}_0(A = 1 \mid L)$ is the "propensity score" and $\overline{Q}_{0,b}(A, L) = \mathbb{E}_0[Y_b \mid A, L]$ is conditional outcome mean.

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Constructing locally efficient estimators

- Examining $D_b(O; P_0)$, we know we must estimate $g_0(L)$ and $\overline{Q}_{0,b}(A, L)$, but how exactly we do this is unspecified.
- No need to try to exactly specify functional forms or assume we know the underlying true data-generating distribution P_0.
- Instead, machine learning to estimate $g_0(L)$ and $\overline{Q}_{0,b}(A, L)$, e.g., by ensemble modeling (van der Laan et al. 2007).
- One-step estimator (Bickel et al. 1993) "debiased" by an additive correction: $\hat{\psi}_b^+ = \hat{\psi}_b + n^{-1} \sum_{i=1}^n \hat{D}_b(O_i)$.
- A valid variance estimator: $\hat{\mathbb{V}}(\hat{\psi}_b^+) = n^{-1} \sum_{i=1}^n \hat{D}_b^2(O_i)$, but small-sample behavior may be erratic.

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- Moderated t-statistic of Smyth (2004) naturally extends to locally efficient estimators by noticing

$$\tilde{t}_b = \frac{\hat{\psi}_b^+ - \cancel{\psi_{b,0}}\ 0}{\tilde{\sigma}_b},$$

  where the *moderated* influence function variance is

$$\tilde{\sigma}_b^2 = \frac{\hat{\sigma}_b^2 d_b + \hat{\sigma}_0^2 d_0}{d_b + d_0}$$

- Preserves robust variance estimator while adding stability by "averaging out" potentially erratic variance across biomarkers.
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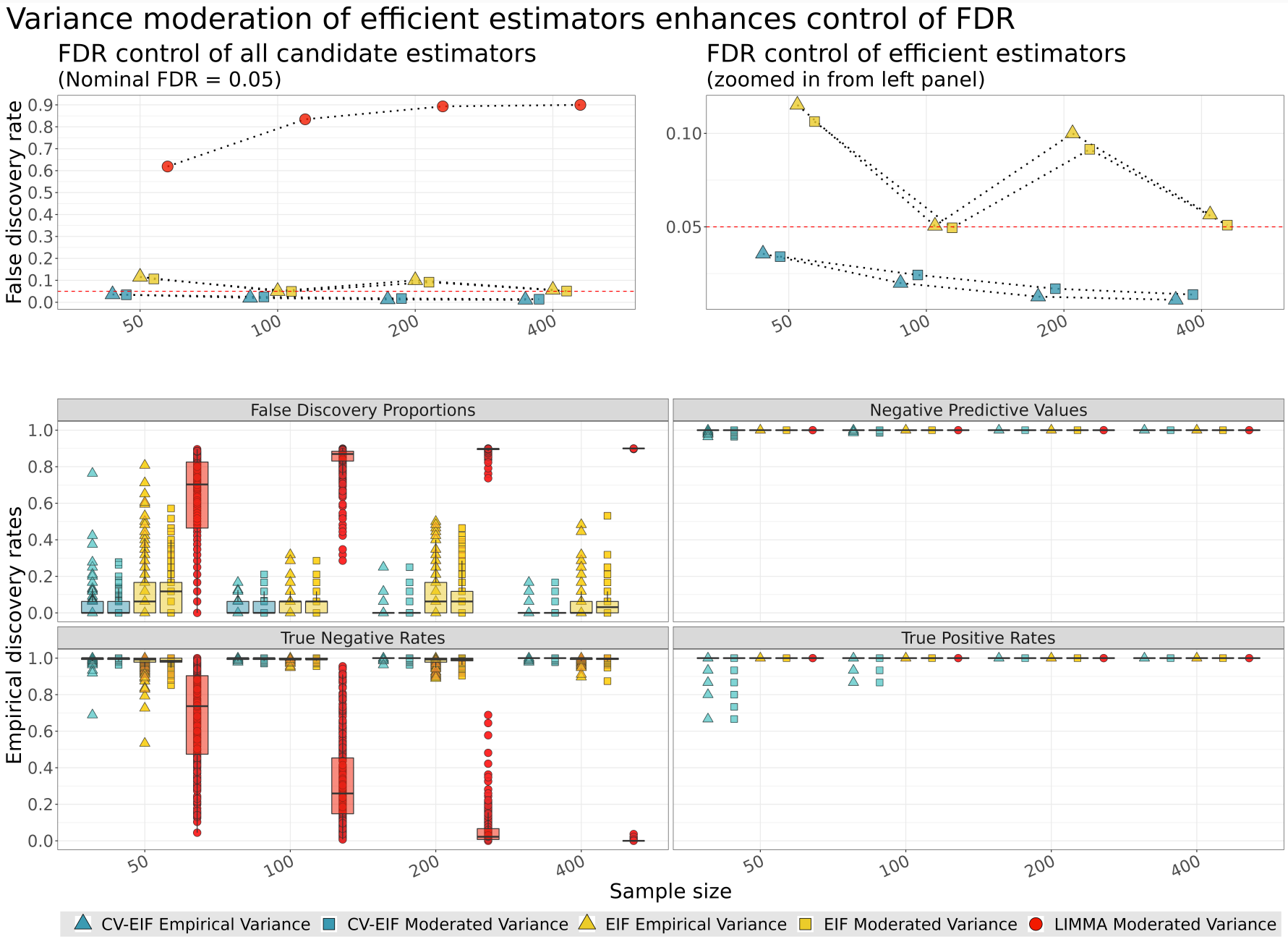
Let's take a look: Numerical study



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- Apply a filtering procedure to reduce the set of candidate biomarkers (Tuglus and van der Laan 2009) (optional).
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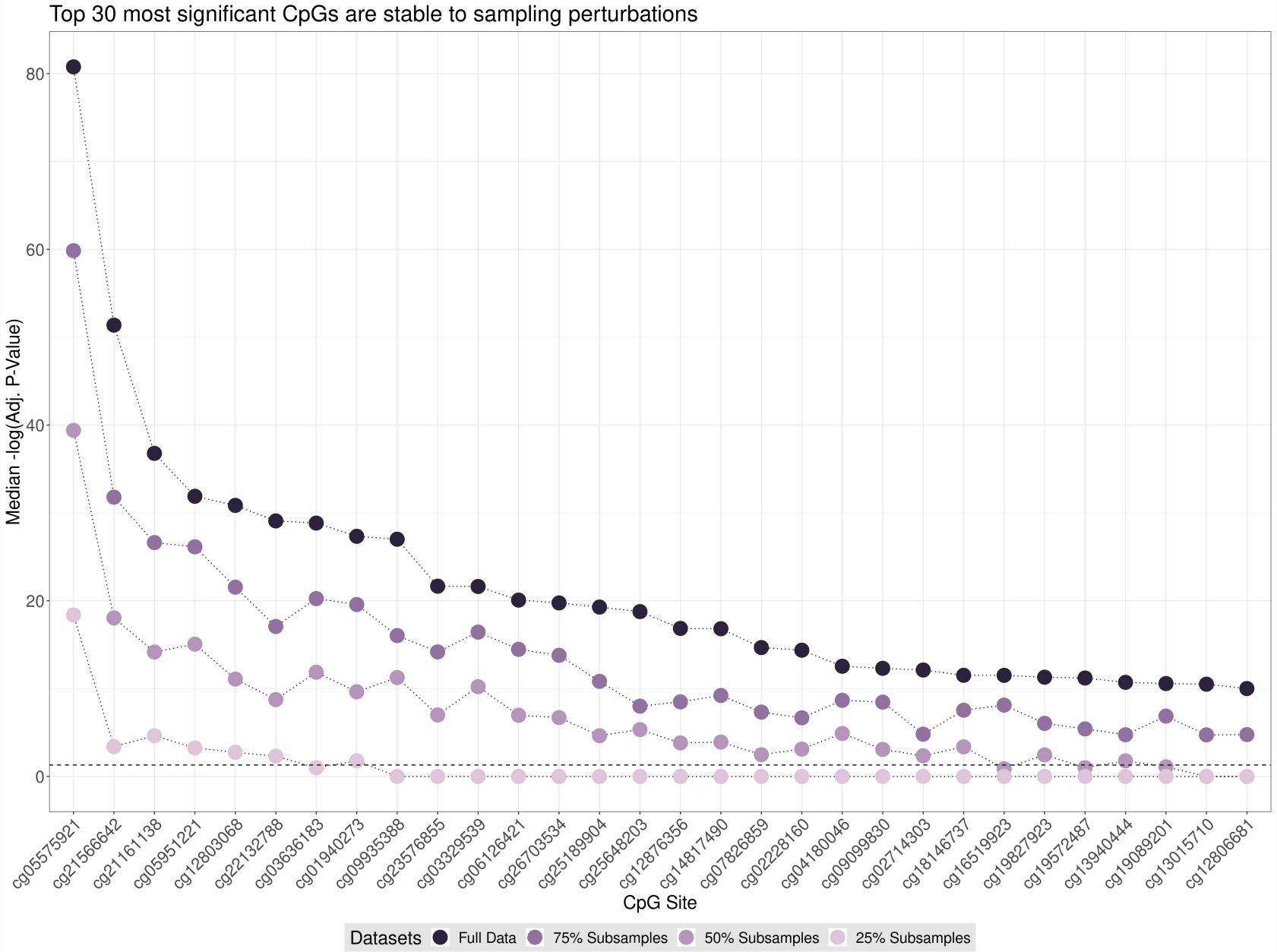
Ranking differentially methylated CpGs



Open-source software: `R/biotmle`!

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- Incorporates machine learning and allows cross-validation.
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- Where can you find it?
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Review

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Thank you

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