The winner's curse under dependence: repairing empirical Bayes using convoluted densities

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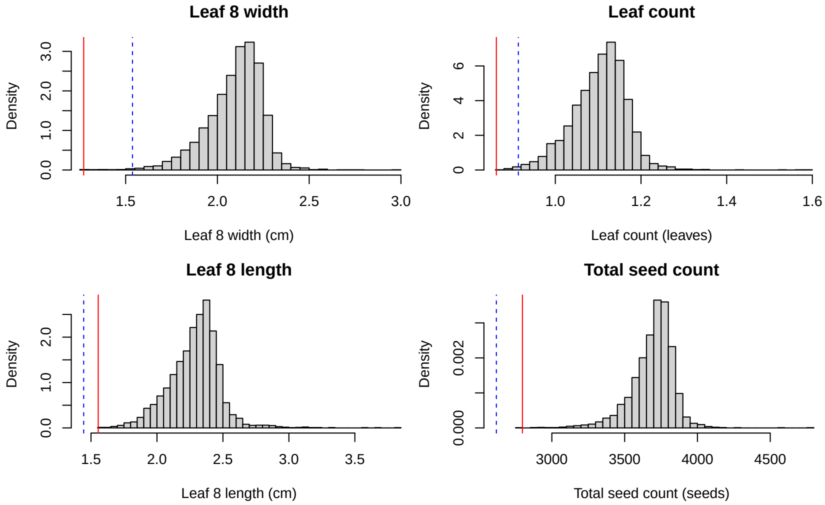
VIB-UGENT CENTER FOR PLANT SYSTEMS BIOLOGY

Motivating example: Brassica napus field trial

- Leaf **gene expression** measured in autumn 2016, **phenotypes** in spring 2017 [3]
- Scientific aim: predict phenotypes from gene expression, estimate RMSE (γ) [2]
  - Single gene models (GLS): $\hat{y}_i = \hat{\beta}_0 + \hat{\beta} x_i$
  - Multigene model (elastic net): $\hat{y}_i = \hat{\beta}_0 + \mathbf{x}_i \hat{\boldsymbol{\beta}}$

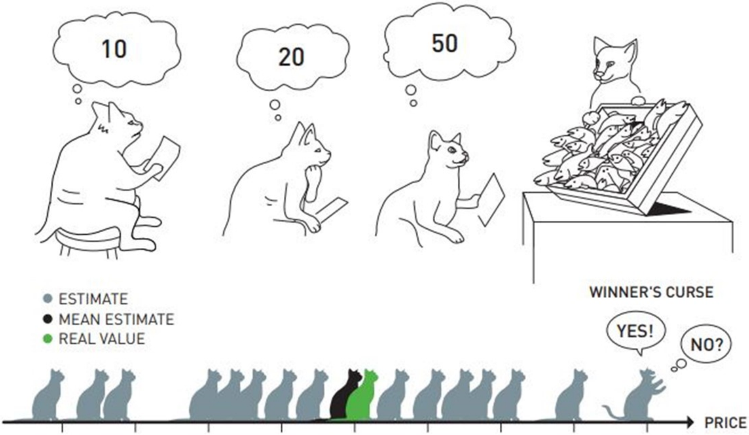
RMSE estimates



Winner's curse

- Only the **most extreme estimates** are of interest
- Estimates $\hat{\gamma}$ are small because
  1) True value γ is small
  2) Estimation error $\hat{\gamma} - \gamma$ is small
- Subset of smallest estimates is **biased**
- $E(\hat{\gamma} - \gamma \mid \hat{\gamma} < c) > 0$ despite $E(\hat{\gamma} - \gamma) = 0$

The auction winner's curse

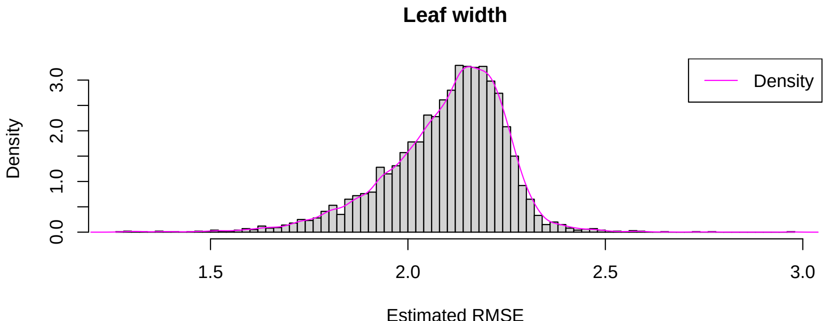


Empirical Bayes: Tweedie's formula [4, 5]

- Bayesian statistics = **immune** to selection bias

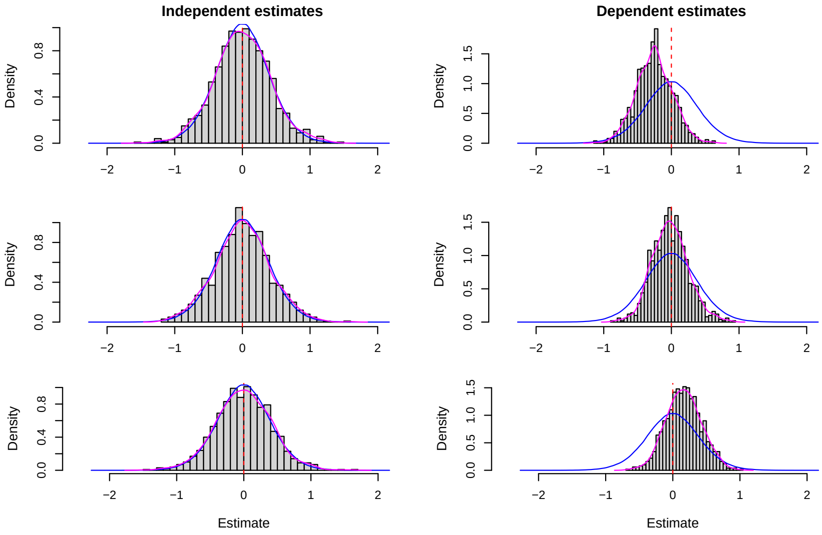
$$E(\gamma_j \mid \hat{\gamma}_j) = \hat{\gamma}_j + \hat{\sigma}^2_{\hat{\gamma}_j} \frac{d\log\left(\hat{f}(\hat{\gamma})\right)}{d\hat{\gamma}}$$

- raw estimate $\hat{\gamma}_j$ and its variance $\hat{\sigma}^2_{\hat{\gamma}_j}$
- $\frac{d\log\left(\hat{f}(\hat{\gamma})\right)}{d\hat{\gamma}}$: derivative of log-density
- No need for **prior density**!



A complication: dependence

- All γ_j's are estimated on the same outcome vector $\mathbf{y}$
  - **Correlated estimates** $=>$ $log(\hat{f}(\gamma))$ is too steep



A theoretical analysis: Hermite polynomials

- Under strong dependence, $\hat{f}(z)$ behaves as a **random function** even as $p \to \infty$ [1, 6]

$$\hat{f}(z) = \phi(z) \sum_{v=0}^{\infty} W_v h_v(z), \tag{1}$$

- $h_v(z)$ the v-th Hermite polynomial, $W_0 = 1$

$$\begin{aligned} E(W_v) &= 0 \text{ if v>1} \\ \text{Var}(W_v) &= \frac{\alpha_v}{v!} = \frac{\int_{-1}^{1} \rho^v dG(\rho)}{v!} \end{aligned} \tag{2}$$

- Dependence introduces **bias** in Tweedie's formula

Our solution: convolution

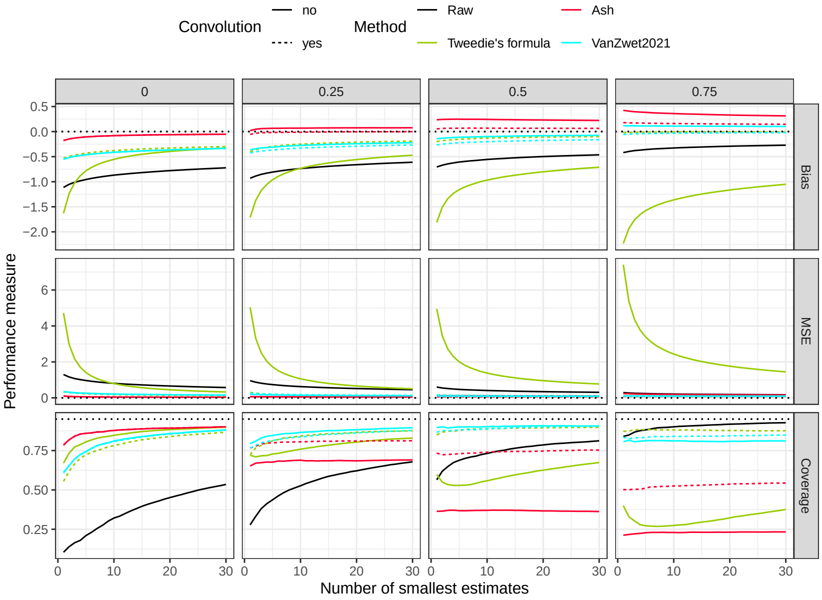
- $\hat{f}(z)$ is too narrow on average

$$E_W\left(\text{Var}_z(z|\mathbf{W})\right) = 1 - \alpha_1 \tag{3}$$

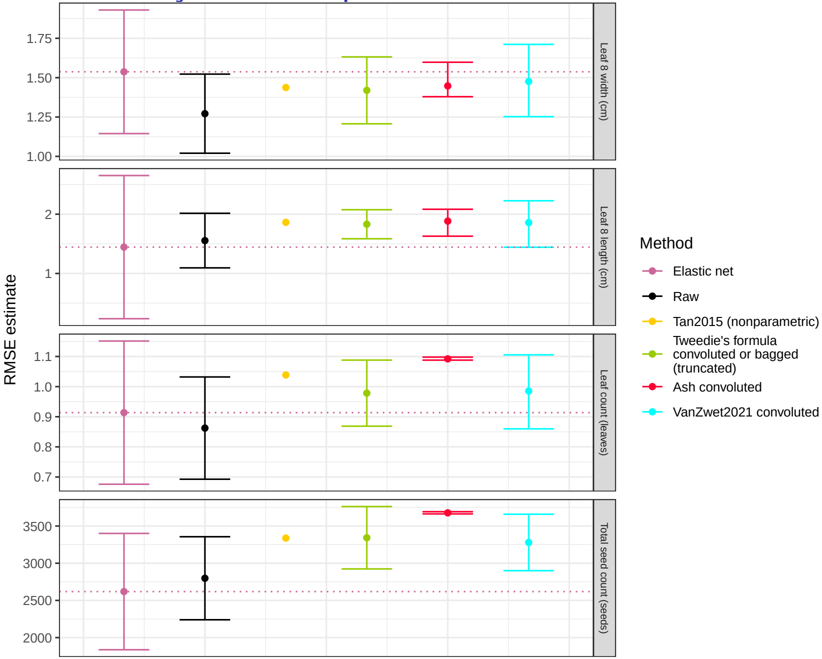
- α_1: average pairwise correlation between the z_j's
- Solution: **convolute** $\hat{f}(z)$ with $N(0, \alpha_1)$

$$\tilde{f}(z) = p^{-1} \sum_{j=1}^{p} r_j(z|z_j, \alpha_1). \tag{4}$$

Simulation study



Real data analysis: B. napus revisited



Conclusions

- Formal proof that **Tweedie's formula** is biased under strong dependence
- Solution: **convolution** with a single parameter normal distribution
- Superiority of single marker gene predictions may be **illusory**

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Abstract

The winner's curse is a form of selection bias that arises when estimates are obtained for a large number of features, but only a subset of most extreme estimates is reported. It occurs in large scale significance testing as well as in rank-based selection, and imperils reproducibility of findings and follow-up study design. Several methods correcting for this selection bias have been proposed, but questions remain on their susceptibility to dependence between features since theoretical analyses and comparative studies are few. We prove that estimation through Tweedie's formula is biased in presence of strong dependence, and propose a convolution of its density estimator to restore its competitive performance, which also aids other empirical Bayes methods. Furthermore, we perform a comprehensive simulation study comparing different classes of winner's curse correction methods for point estimates as well as confidence intervals under dependence. We find a bootstrap method by Tan et al. (2015) and empirical Bayes methods with density convolution to perform best at correcting the selection bias, although this correction generally does not improve the feature ranking. Finally, we apply the methods to a comparison of single-feature versus multi-feature prediction models in predicting *Brassica napus* phenotypes from gene expression data, demonstrating that the superiority of the best single-feature model may be illusory.

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