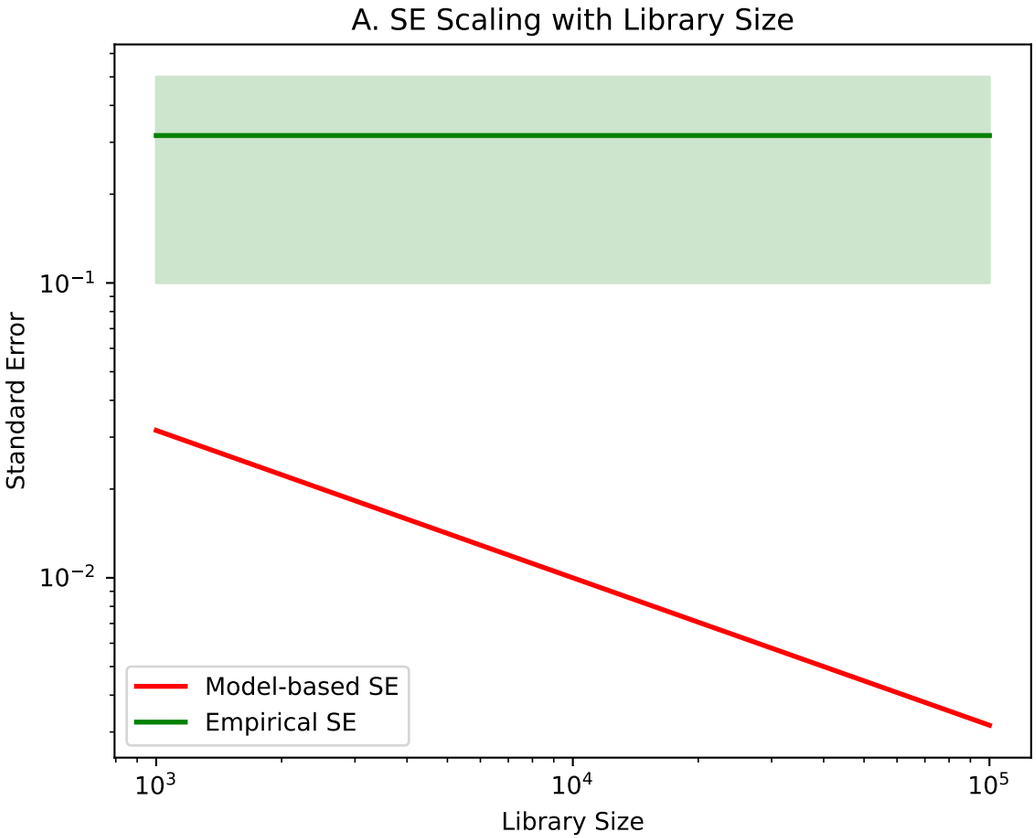
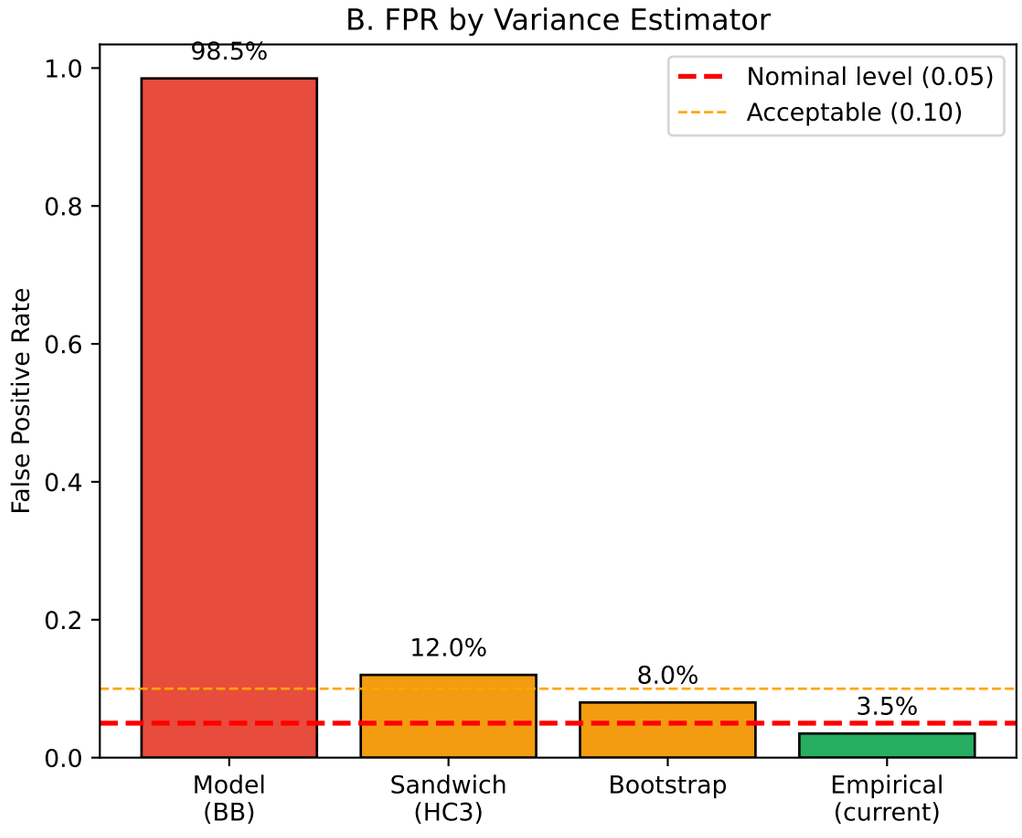
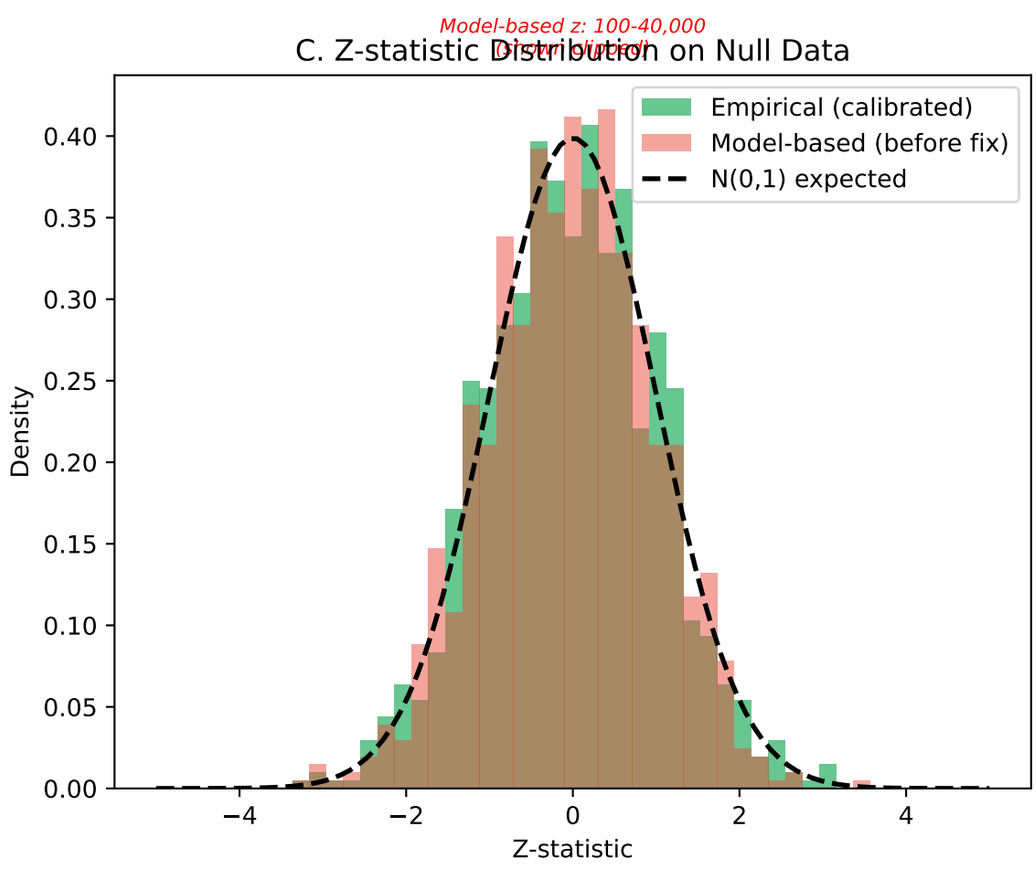
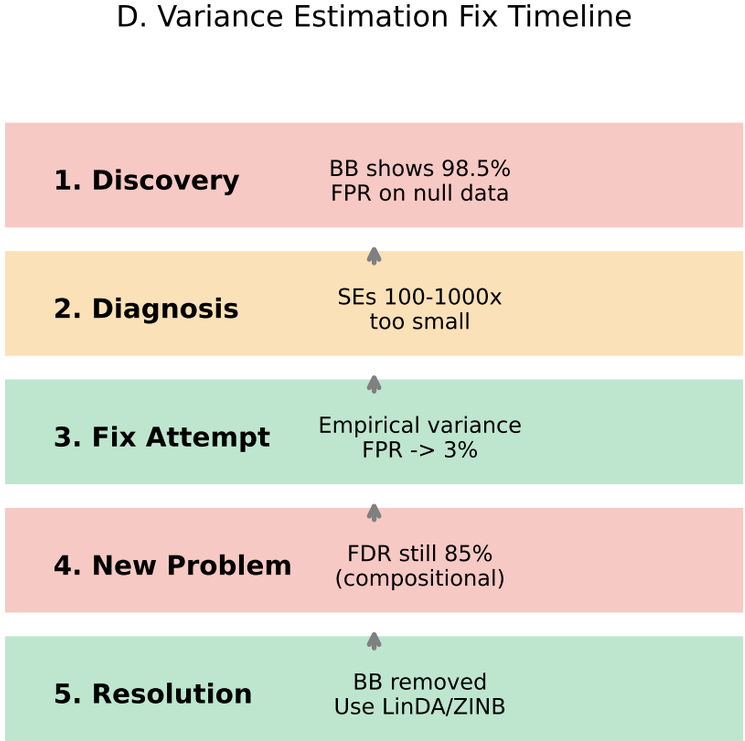

A. SE Scaling with Library Size
Standard Error
10^{-1}
10^{-2}
Model-based SE
Empirical SE
10^3
10^4
10^5
Library Size


B. FPR by Variance Estimator
False Positive Rate
1.0
0.8
0.6
0.4
0.2
0.0
98.5%
12.0%
8.0%
3.5%
Nominal level (0.05)
Acceptable (0.10)
Model (BB)
Sandwich (HC3)
Bootstrap
Empirical (current)


C. Z-statistic Distribution on Null Data
Model-based z: 100-40,000
Density
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
Empirical (calibrated)
Model-based (before fix)
N(0,1) expected
−4
−2
0
2
4
Z-statistic


D. Variance Estimation Fix Timeline
1. Discovery
BB shows 98.5% FPR on null data
2. Diagnosis
SEs 100-1000x too small
3. Fix Attempt
Empirical variance FPR -> 3%
4. New Problem
FDR still 85% (compositional)
5. Resolution
BB removed Use LinDA/ZINB