Using gene genealogies to localize rare variants associated with complex traits in diploid populations

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Purpose of the study

- To compare the performance of selected association methods to localize trait-influencing causal variants within a 2-Mbp candidate genomic region.
- Our work extends that of Burkett et al. 2014, which investigated the ability to detect causal variant.
- First, we present a case study of one of 200 simulated datasets for insight into the methods.
- Then, using the 200 simulated datasets, we score which method localizes best, overall.

Data simulation

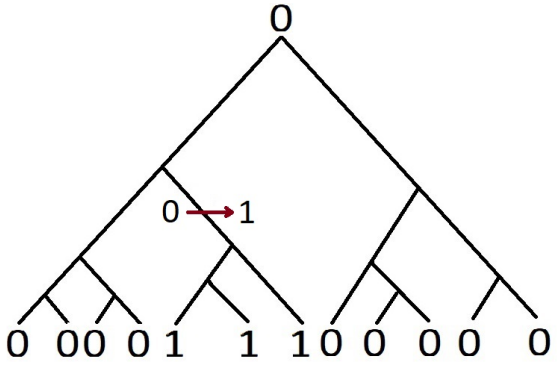
- Simulate data for 3000 haplotypes in a 2-Mbp genomic region using 'fastsimcoal2' (Excoffier et al. 2013).
  - Keep the ancestral trees connecting haplotypes.
- Randomly pair the 3000 haplotypes into 1500 diploid individuals.
- Assign disease status to the 1500 individuals based on randomly sampled risk SNVs (rSNVs) from the mid region (950kbp-1050kbp).
- Sample 50 diseased individuals (cases) and 50 non-diseased individuals (controls).

Association Methods

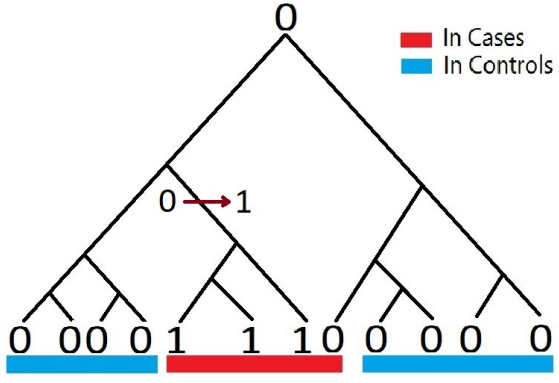
1. Single-variant method
   - Fisher's exact test
2. Pooled-variant methods
   - Variable Threshold test (VT) (Price et al. 2010)
   - C-alpha test (Neale et al. 2011)
3. Joint-modeling methods
   - CAVIARBF (Chen et al. 2015)
   - Elastic-Net (Zou & Hastie. 2005)
4. Tree-based methods
   - Blossoc (Mailund et al. 2006)
   - Naive Mantel (Burkett et al. 2014), and informed Mantel (Karunarathna & Graham. 2018)

Genealogical Trees

- Genealogical tree represents the ancestry of a genetic variant.



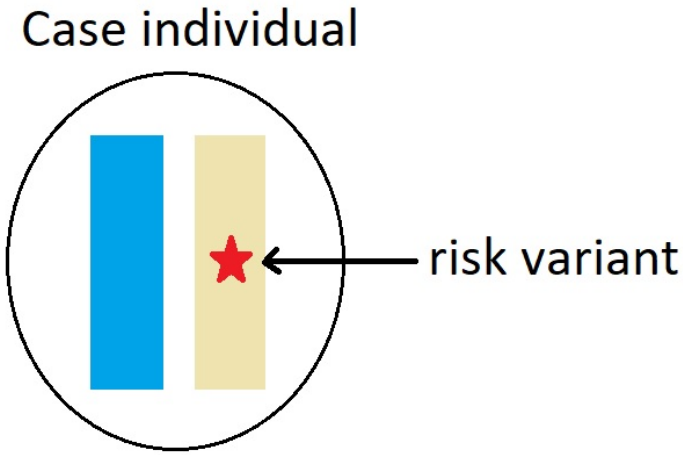
- Case alleles tend to cluster together on a tree for a variant that influences disease susceptibility.



- Tree-based methods evaluate the clustering of the disease status on the trees.

Tree-based methods

- Two methods to assess clustering of disease status in genealogical trees, Blossoc and Mantel test.
- Blossoc uses reconstructed unknown trees.
- Mantel test uses the known trees.
- Two versions of Mantel test as the bench mark for comparison: naive Mantel, and informed Mantel.



Single-variant method: Fisher's exact test

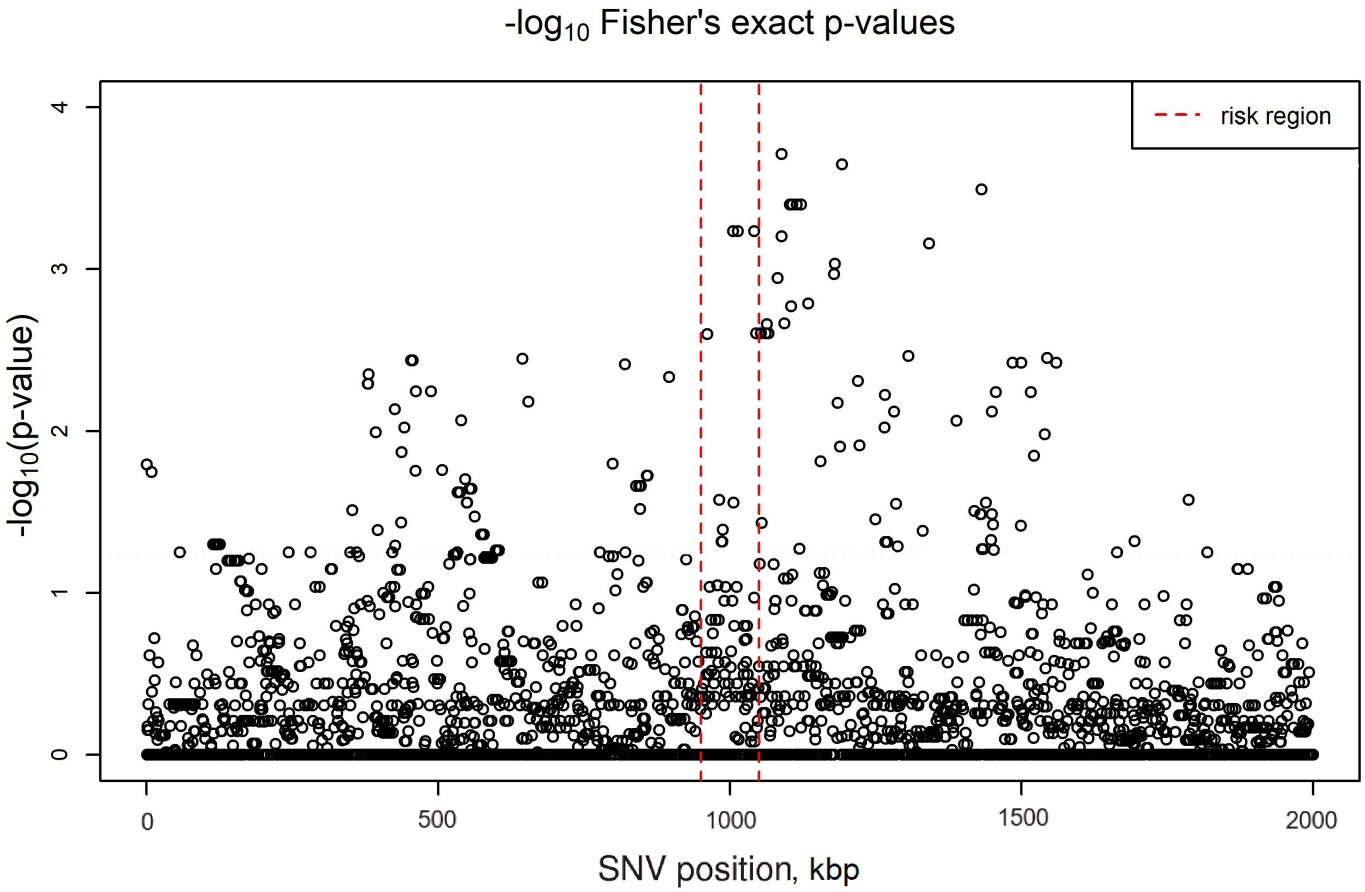


Figure 1: Manhattan plot for Fisher's exact test in the 100 case and 100 control haplotypes.

Pooled-variant methods

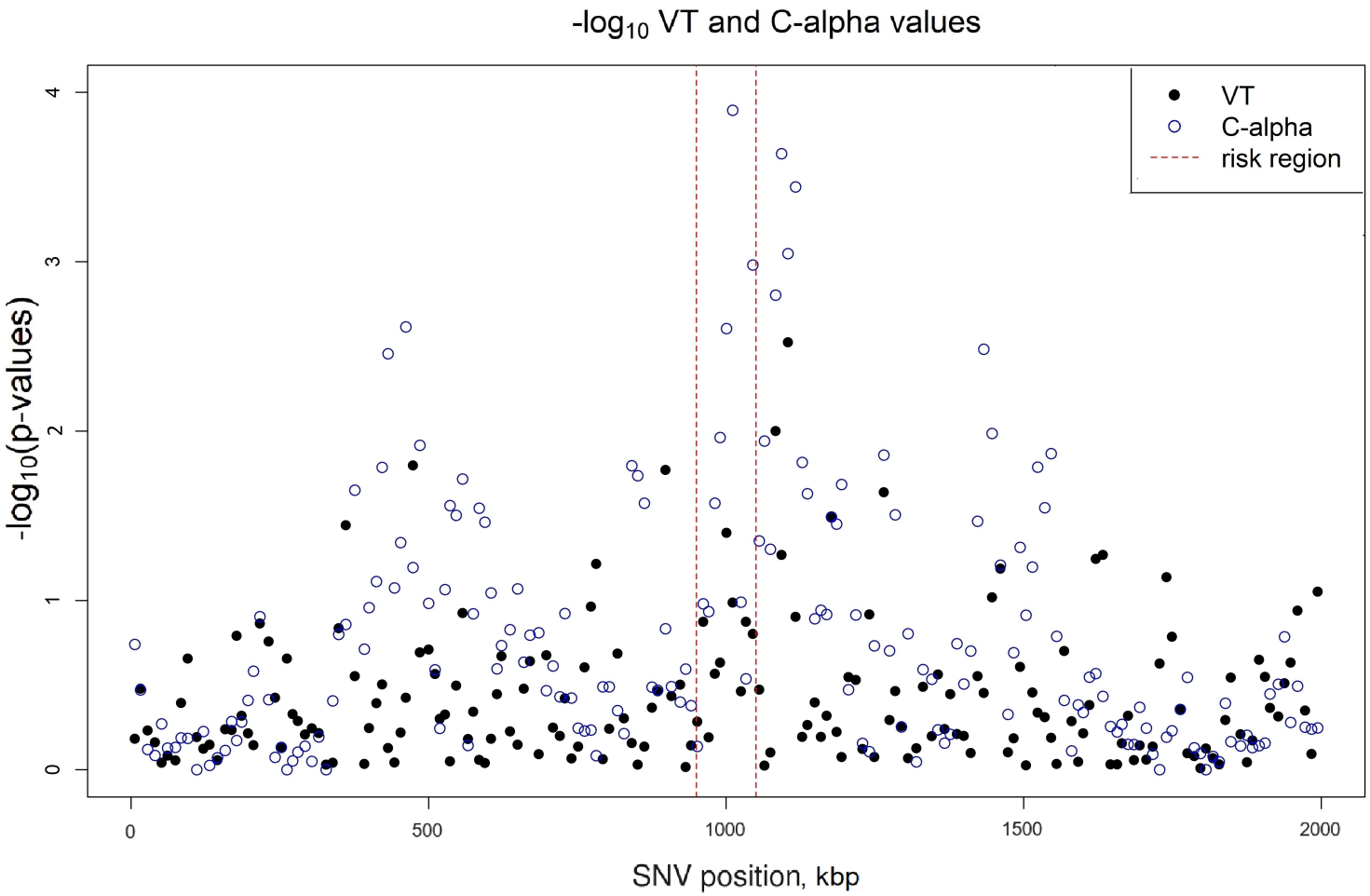


Figure 2: The negative $\log_{10}$ of p-values are shown on the vertical axes, obtained by applying VT and C-alpha tests across the simulated region using sliding windows of 20 SNVs overlapping by 5 SNVs.

Joint-modeling methods

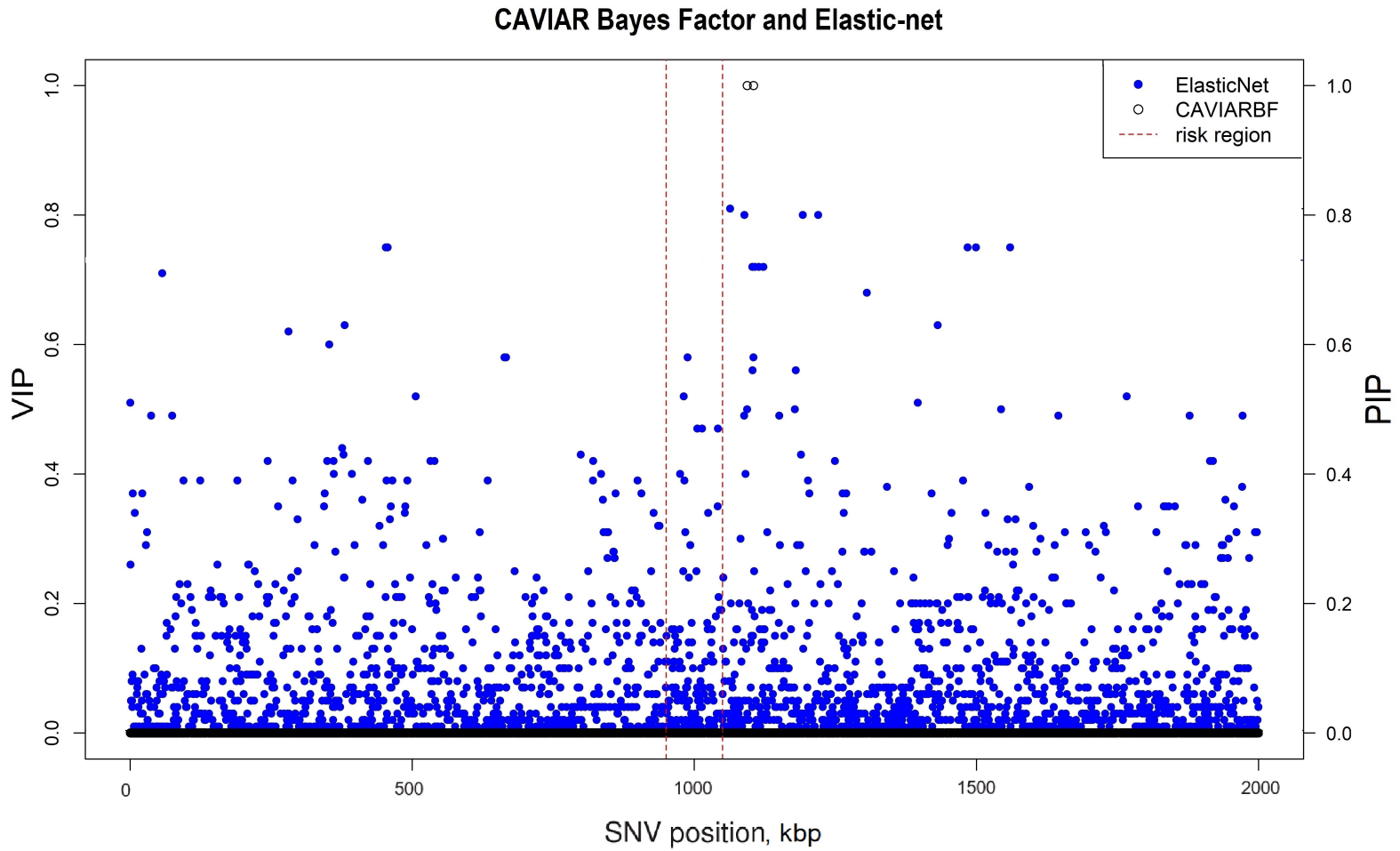


Figure 3: Variable-inclusion probabilities (VIPs) for SNVs computed from Elastic-net (left axis), and posterior inclusion probabilities (right axis), computed from CAVIARBF, across the simulated region.

Tree-based methods: Blossoc

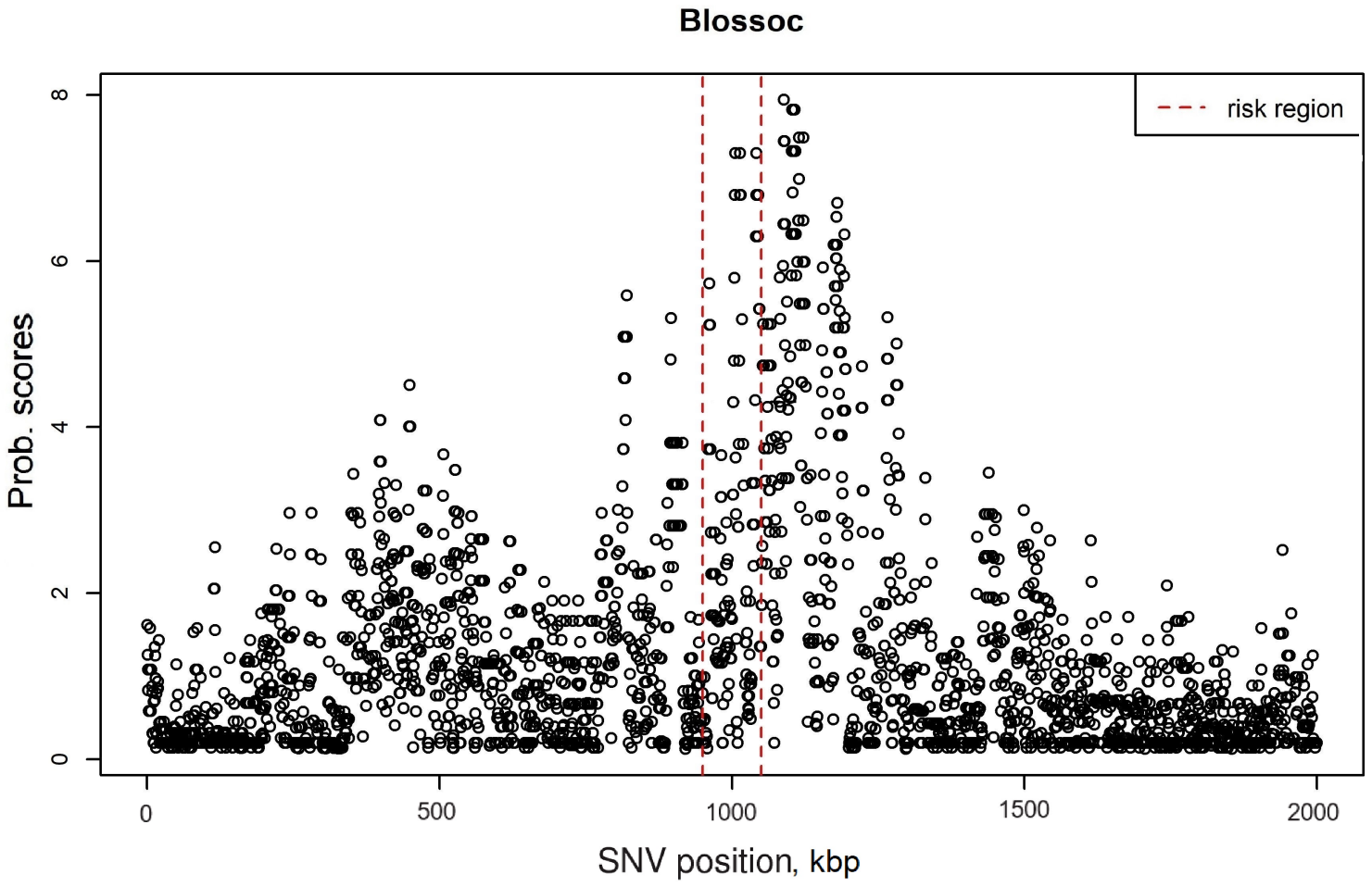


Figure 4: Plot showing the output from Blossoc.

Tree-based methods: Naive Mantel

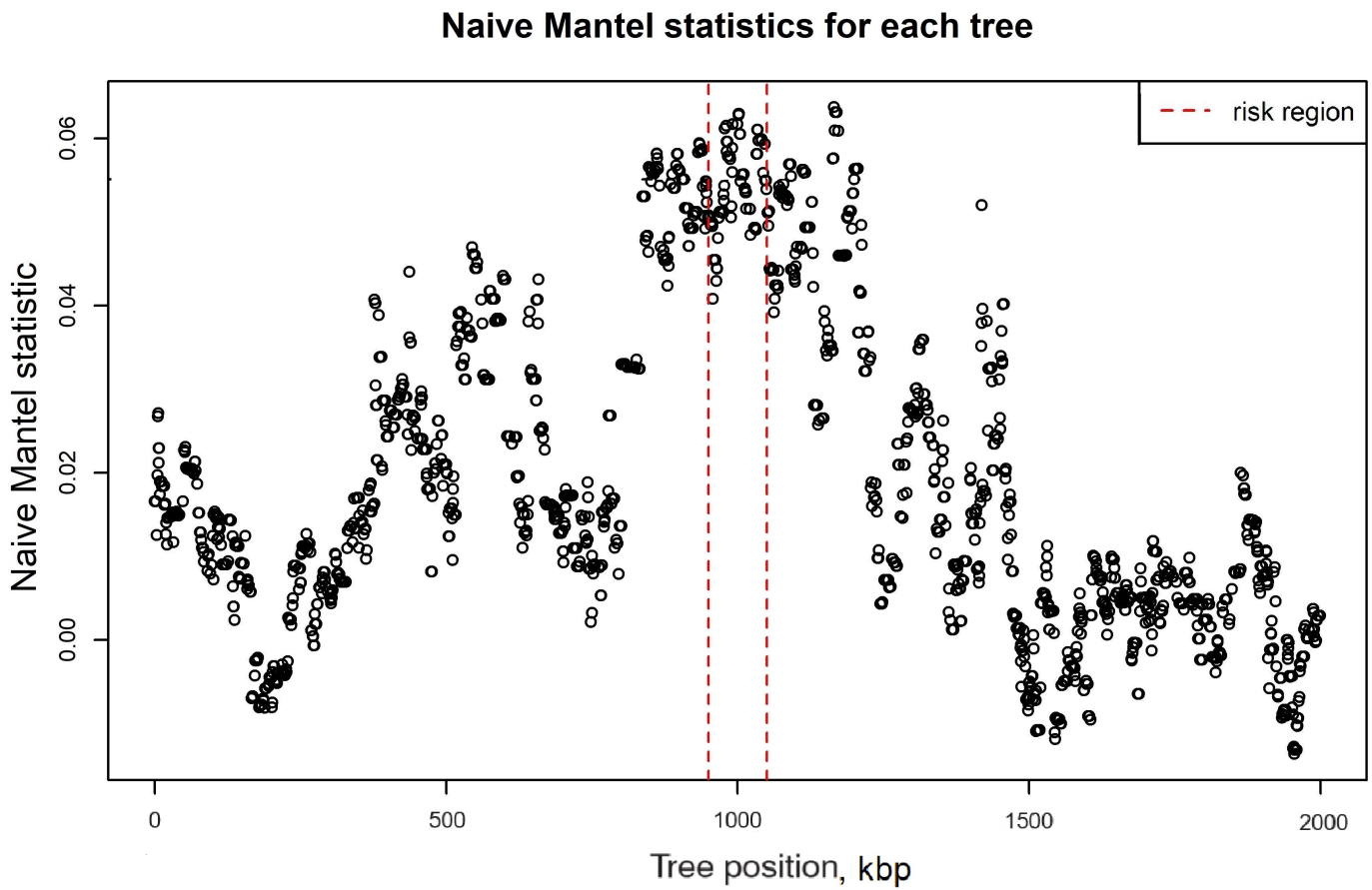


Figure 5: Naive-Mantel statistics for each tree position across the simulated region.

Tree-based methods: Informed Mantel

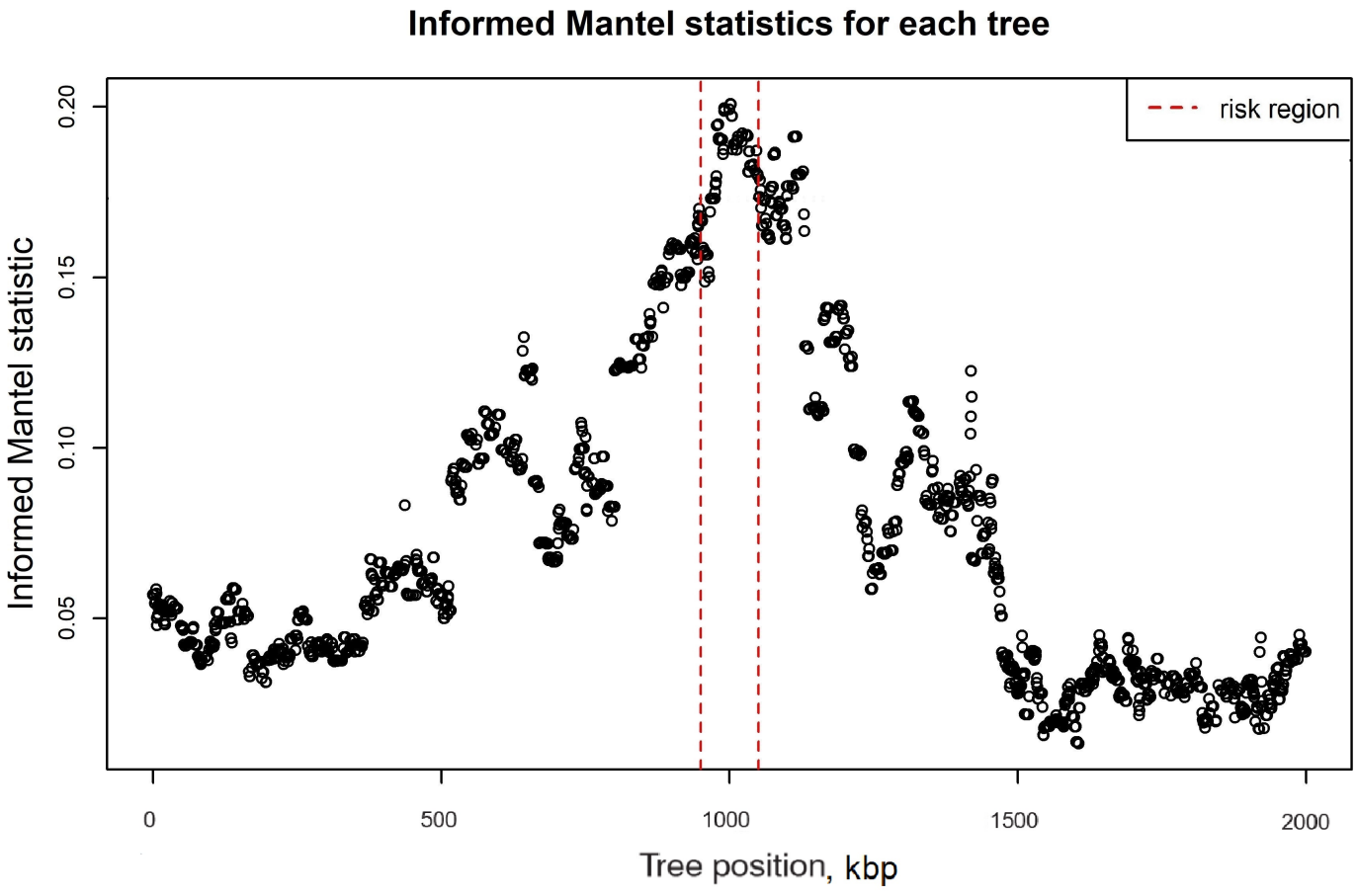


Figure 6: Informed-Mantel statistics for each tree position in the genomic region.

Signal Localization

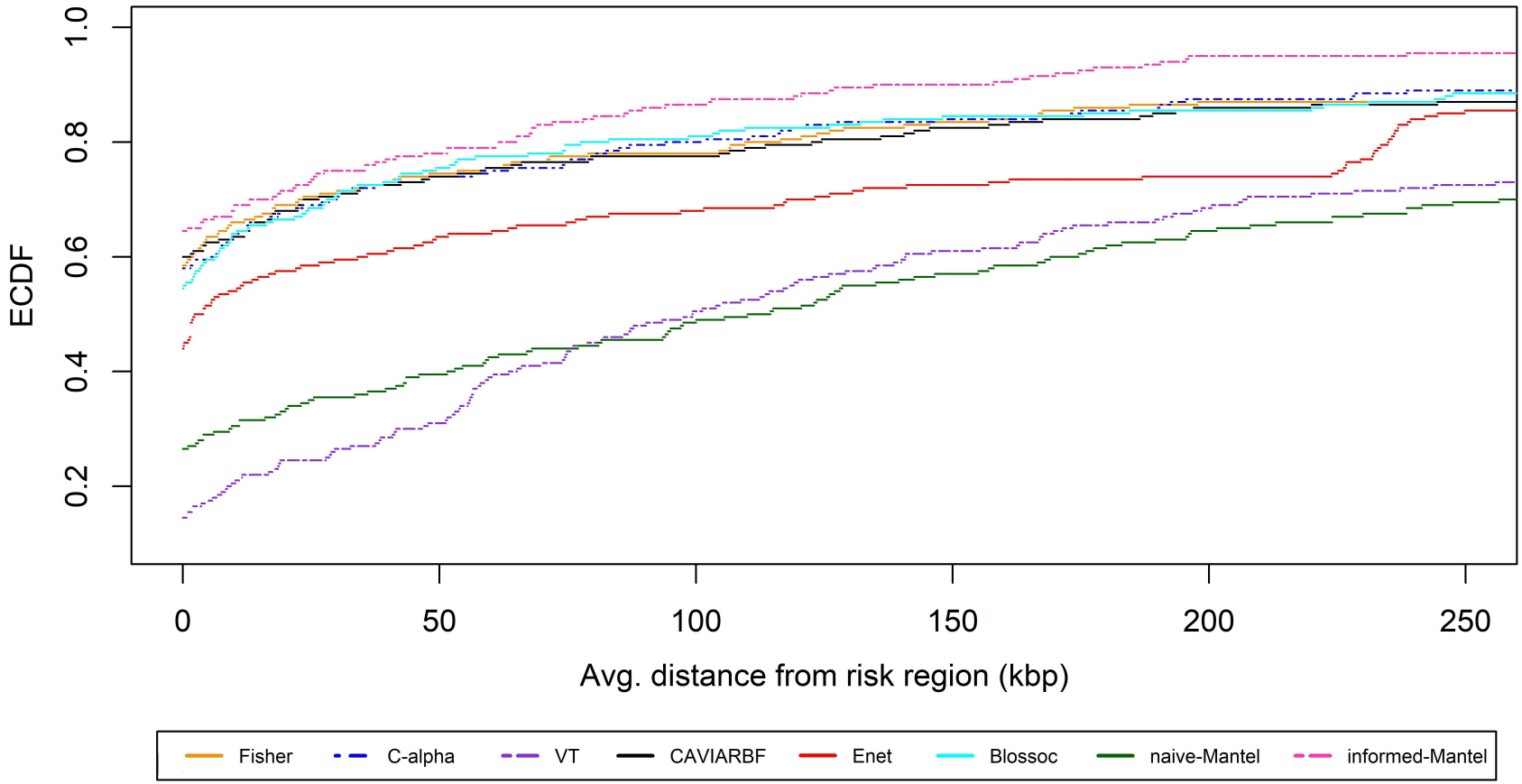


Figure 7: Empirical Cumulative Distribution Functions (ECDFs) of average distances of the peak association signals from the risk region for the 200 datasets.

Discussion

- Localization results on the example dataset.
  - C-alpha test and informed Mantel test are the only methods that successfully localize the association signal.
  - However, the peak signal from all the other methods is close to the disease risk region.
- Localization results from the simulation study.
  - Naive Mantel test performed very poorly relative to the other methods.
  - Not surprisingly, the informed Mantel test outperformed all the other methods.
  - Blossoc, CAVIARBF, C-alpha, and Fishers exact test performed better in localizing the signal.

Reference

Karunarathna, C. B., & Graham, J. (2018). Using gene genealogies to localize rare variants associated with complex traits in diploid populations. Human heredity, 83(1), 30-39.

Acknowledgements

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