Testing pleiotropy vs. separate QTL in multiparental populations

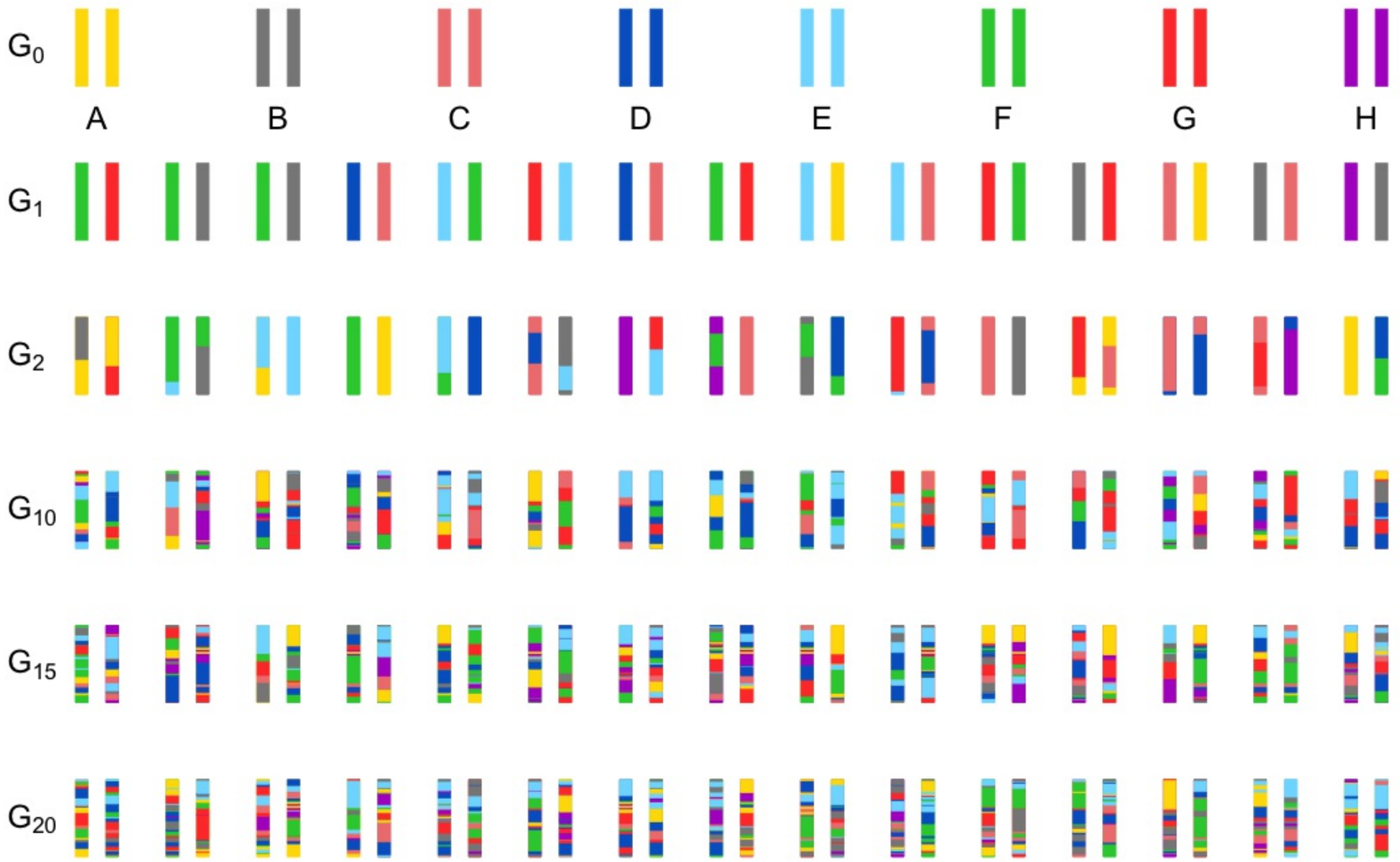
Frederick Boehm

March 6, 2019

Introduction

- Experimentalists can now measure tens of thousands of phenotypes with RNA sequencing and mass spectrometry
- Multiparental populations enable high-resolution QTL mapping
- Together, high-dimensional phenotypes and multiparental populations can inform complex trait genetics
- New analysis tools, such as our test of pleiotropy vs. separate QTL for multiparental populations, are needed

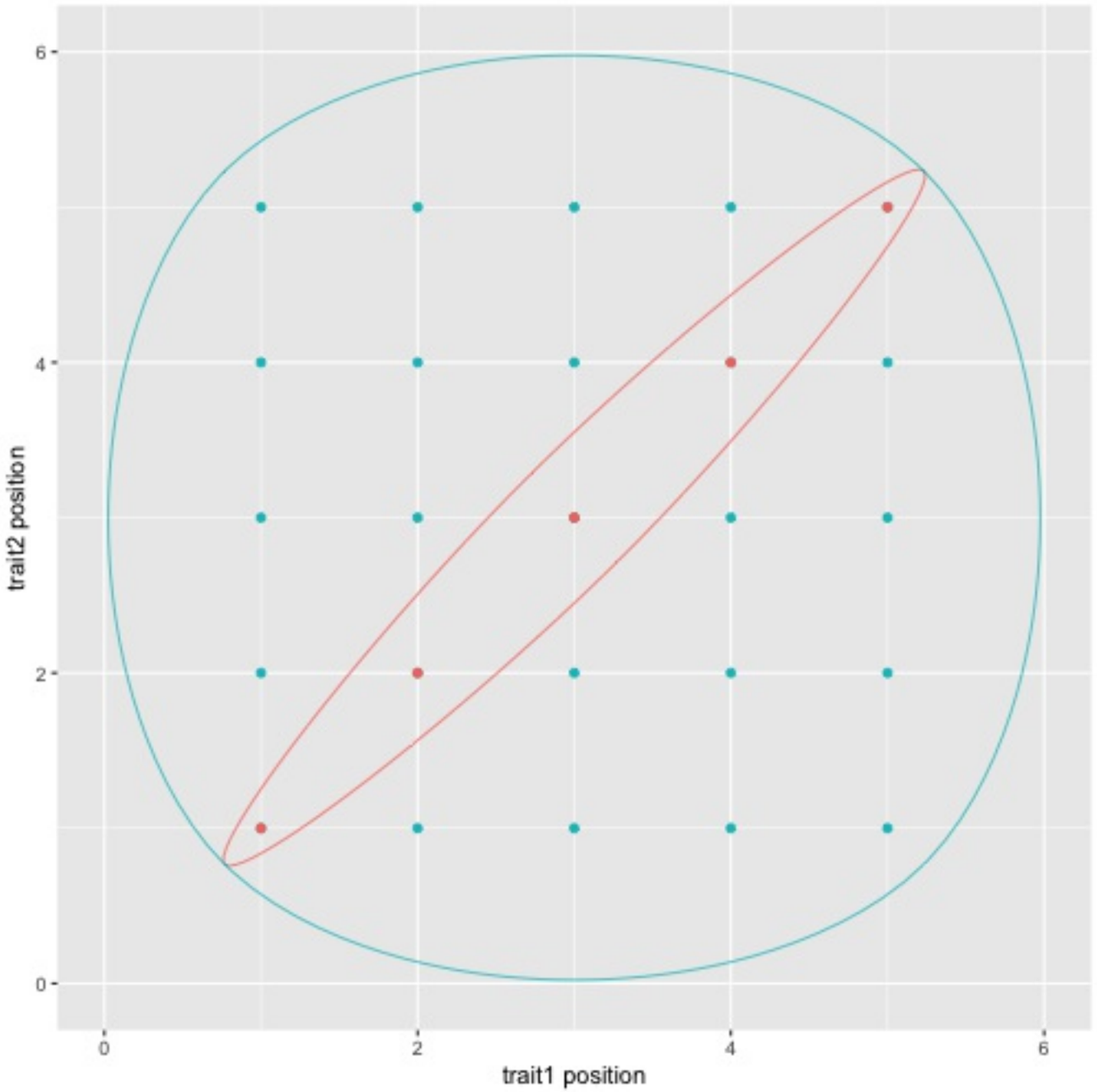
Multiparental populations



Jiang and Zeng (1995) test

- Pleiotropy test for two-parent crosses
  - Applies to two traits that map to a single genomic region
  - Pleiotropy is the null hypothesis
  - Two separate QTL is the alternative hypothesis
  - Perform a two-dimensional QTL scan
  - Calculate likelihood ratio test statistic

Jiang and Zeng (1995) test



Challenges in multiparental populations

1. Complex patterns of relatedness
2. Multiple founder lines (vs. exactly two founder lines in Jiang and Zeng (1995))
3. Determining statistical significance

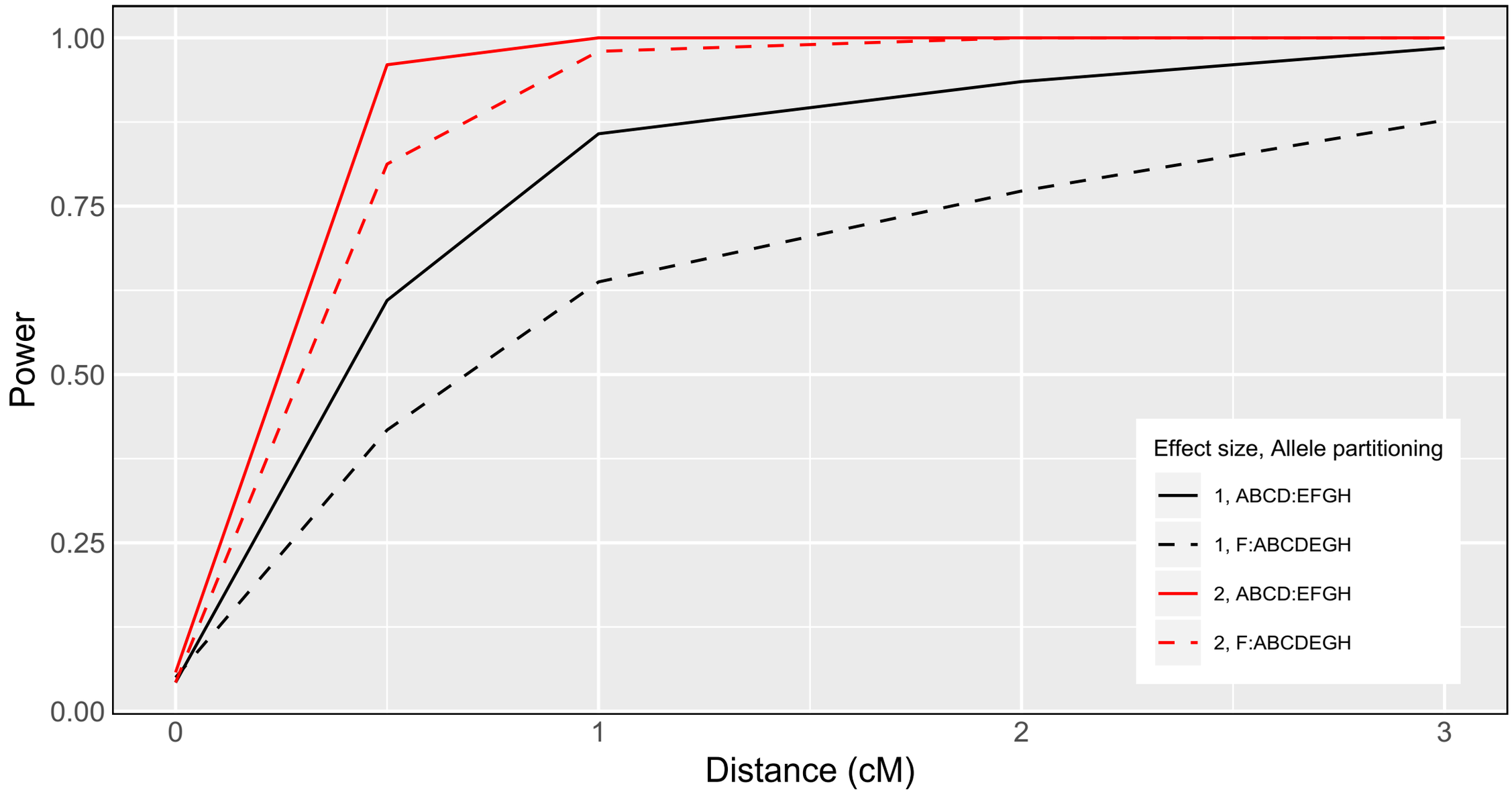
Solutions to challenges

1. Multivariate random effects to account for relatedness
2. Fixed effect for each founder allele
3. Parametric bootstrap to assess statistical significance

Test procedure

- Fit the model: $$Y = XB + G + E$$ for each ordered pair of markers
  - \(G \sim MN(0, K, V_g)\)
  - \(E \sim MN(0, I, V_e)\)
  - \(X\) contains allele probabilities
  - \(B\) contains allele effects
- Calculate likelihood for each ordered pair of markers
- Test statistic: $$- \log_{10} \frac{\max \text{likelihood under pleiotropy}}{\max \text{likelihood for separate QTL}}$$
- Parametric bootstrap to get p-value

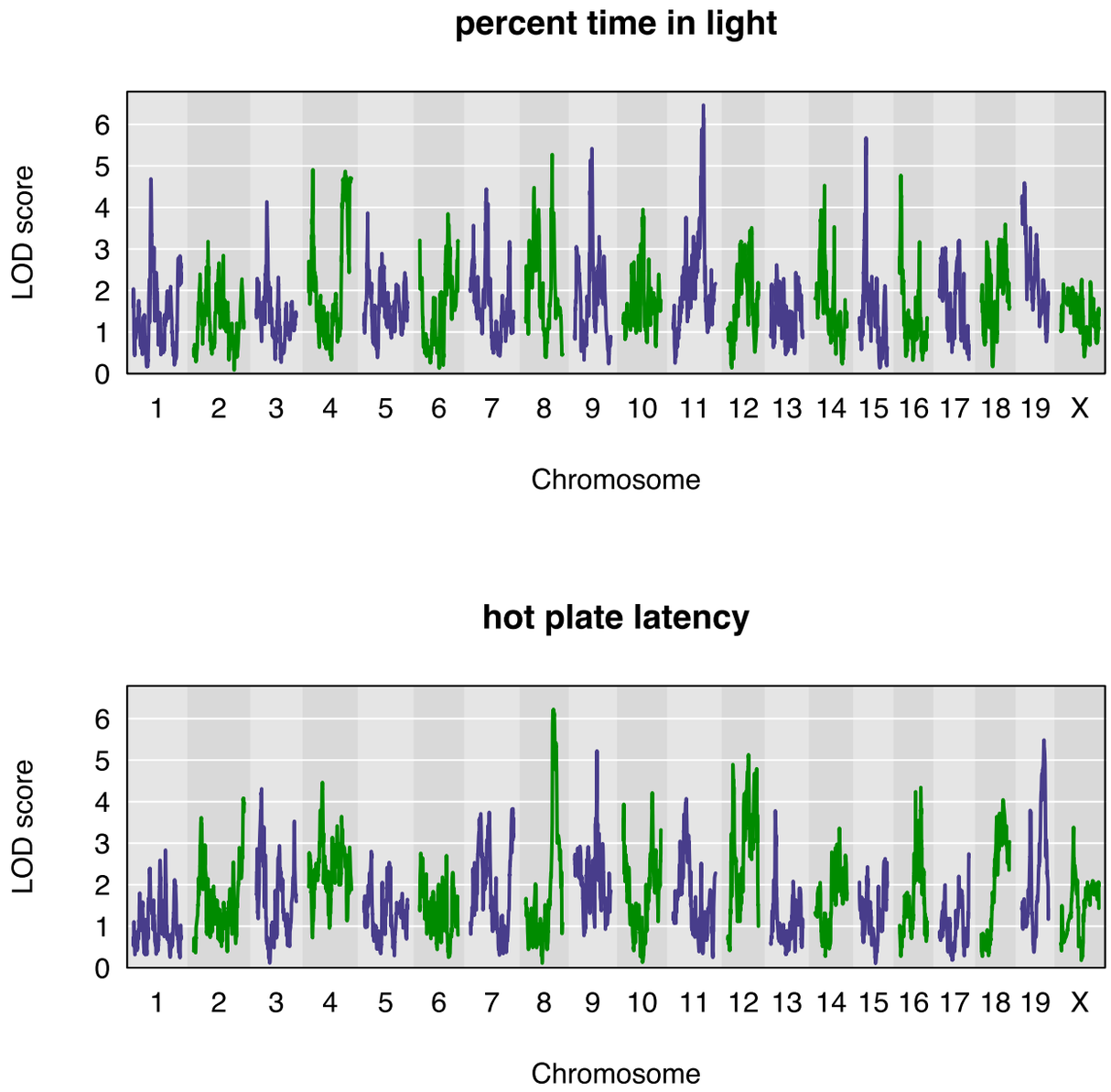
Test characteristics



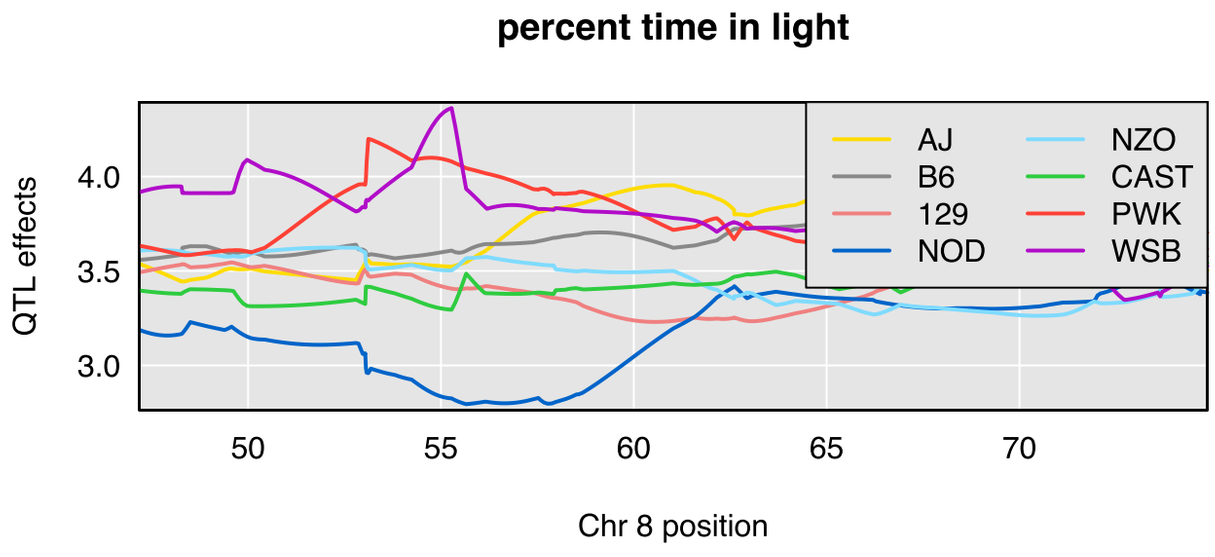
Application

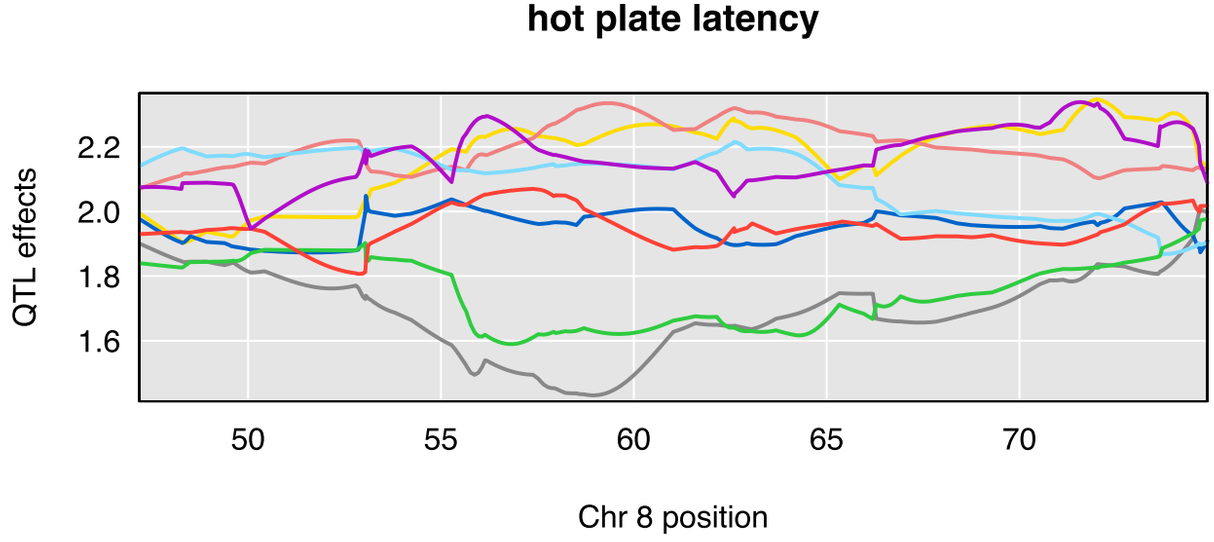
- Logan, et al. (2013) and Recla, et al. (2014) genotyped and phenotyped 261 Diversity Outbred mice
    - Identified *Hydin* as the Chromosome 8 gene affecting "hot plate latency" at 57 cM
    - Identified Chromosome 8 QTL for "percent time in light" at 55 cM
    - Motivated us to ask if *Hydin* also affects "percent time in light"

QTL scan results

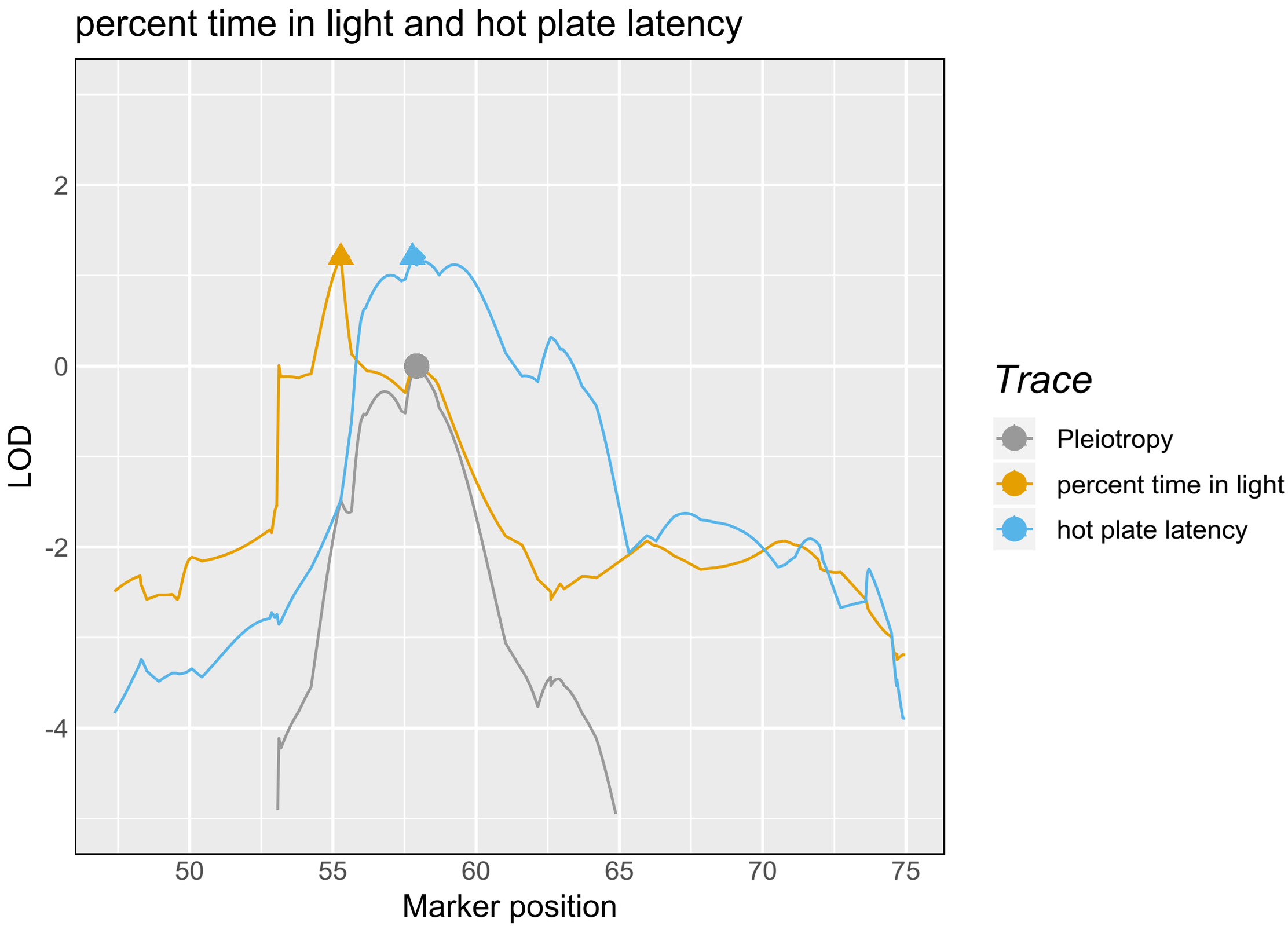


Allele effects plots





Profile LOD plot



Test results

- p = 0.11 (1000 bootstrap samples)

Conclusions

- Weak evidence for two separate QTL affecting the two phenotypes
  - One QTL affects "distance traveled in light"
  - Second QTL contains *Hydin* and affects "hot plate latency"

Future directions

Contact information

- frederick.boehm@gmail.com
- https://fboehm.us/
- qtl2pleio R package: https://github.com/fboehm/qtl2pleio
- Manuscript pre-print: https://www.biorxiv.org/content/10.1101/550939v1

References

Jiang, C. and Z. Zeng (1995). "Multiple trait analysis of genetic mapping for quantitative trait loci." In: *Genetics* 140.3, pp. 1111-1127.

Logan, R. W, R. F. Robledo, et al. (2013). "High-precision genetic mapping of behavioral traits in the diversity outbred mouse population". In: *Genes, Brain and Behavior* 12.4, pp. 424-437.

Recla, J. M, R. F. Robledo, et al. (2014). "Precise genetic mapping and integrative bioinformatics in Diversity Outbred mice reveals Hydin as a novel pain gene". In: *Mammalian genome* 25.5-6, pp. 211-222.