

Testing pleiotropy in multiparental populations

Frederick Boehm

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Introduction

- Tens of thousands of traits with RNA sequencing and mass spectrometry can be measured
- Multiparental populations offer high-resolution QTL mapping
- Together, high-dimensional traits and multiparental populations can inform complex trait genetics
- New analysis tools, such as a pleiotropy test for multiparental populations, are needed

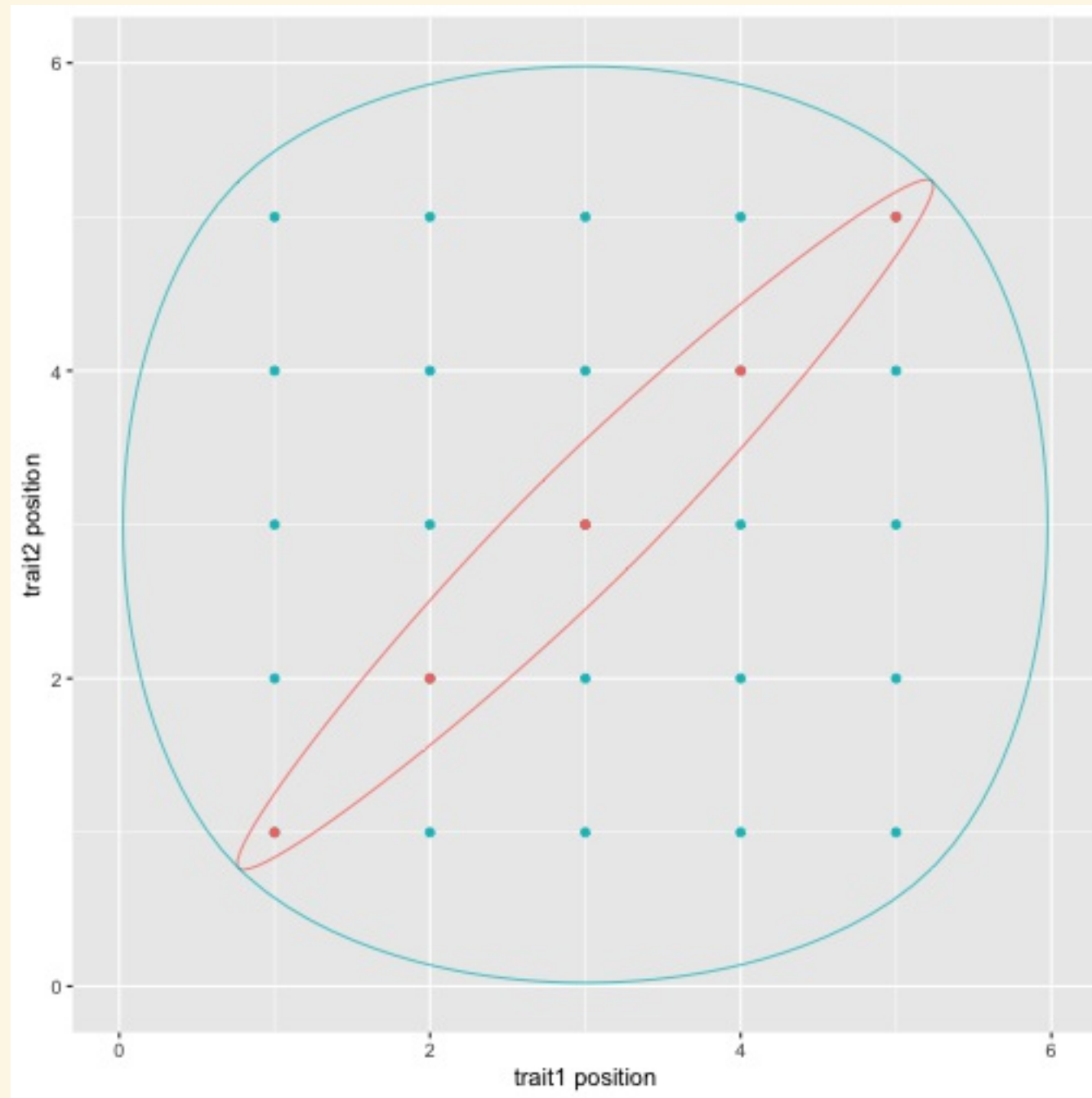
Jiang and Zeng (1995) test

- Two-parent crosses
- Applies to two traits that co-map
- H_0 : Pleiotropy
- H_A : Two separate QTL

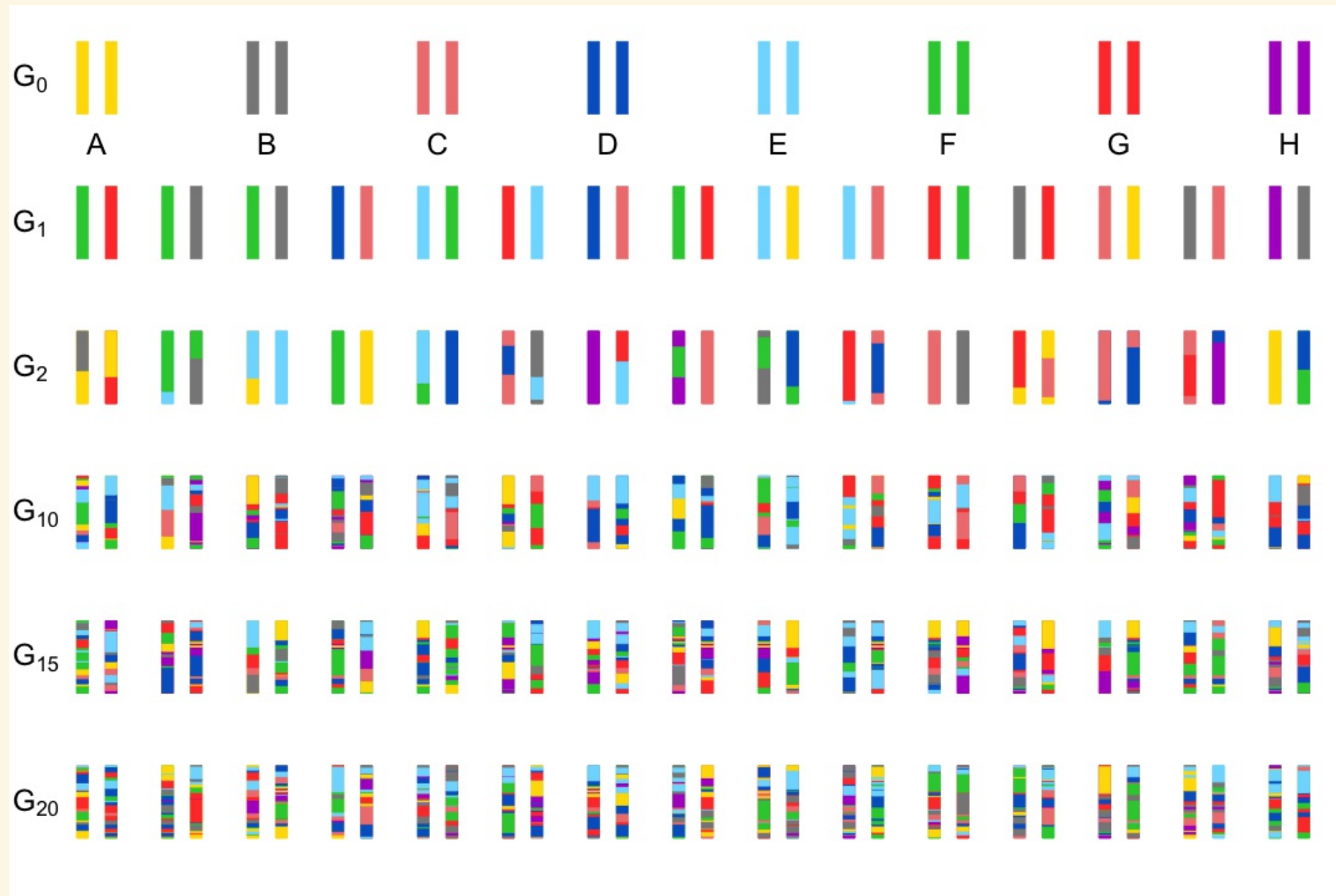
Jiang and Zeng (1995) test

- Perform a two-dimensional QTL scan
- $Y = XB + E$
- Calculate likelihood ratio test statistic

Jiang and Zeng (1995) test



Multiparental populations



Challenges in multiparental populations

- Complex patterns of relatedness
- Multiple founder lines
- Determining statistical significance

Solutions to challenges

- Complex patterns of relatedness
- Multiple founder lines
- Determining statistical significance

Test procedure

- Fit the model:

$$\text{vec}(Y) = X\text{vec}(B) + \text{vec}(G) + \text{vec}(E)$$

for each ordered pair of markers

- G: Polygenic random effects
- E: Random errors
- Calculate likelihood for each ordered pair of markers

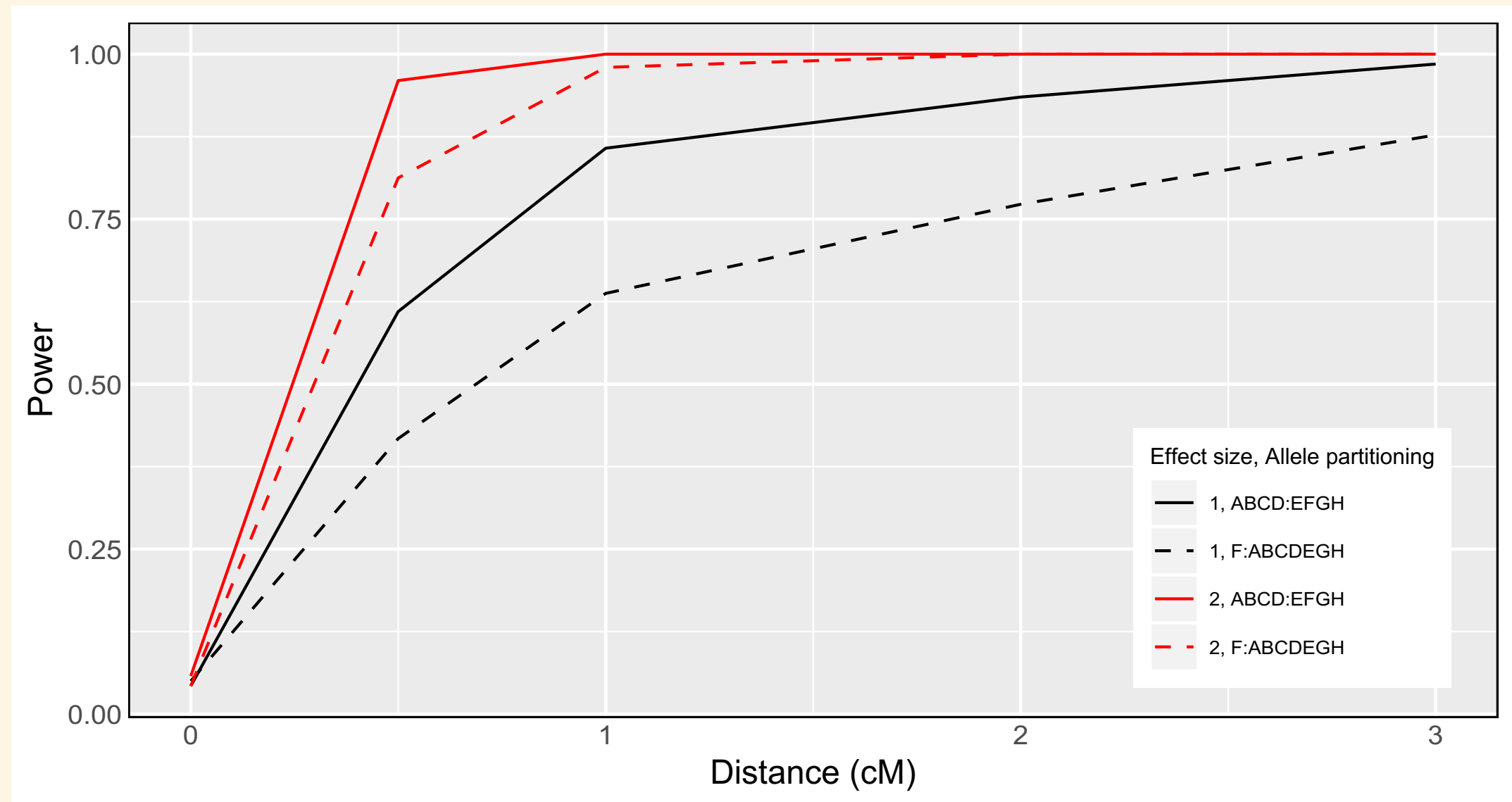
Test procedure

- Test statistic:

$$-\log_{10} \frac{\text{max likelihood under pleiotropy}}{\text{max likelihood for separate QTL}}$$

- Parametric bootstrap to get p-value

Test characteristics



Diversity Outbred Mice

- Multiparental population arising from 8 inbred lines
 - Complementary to Collaborative Cross

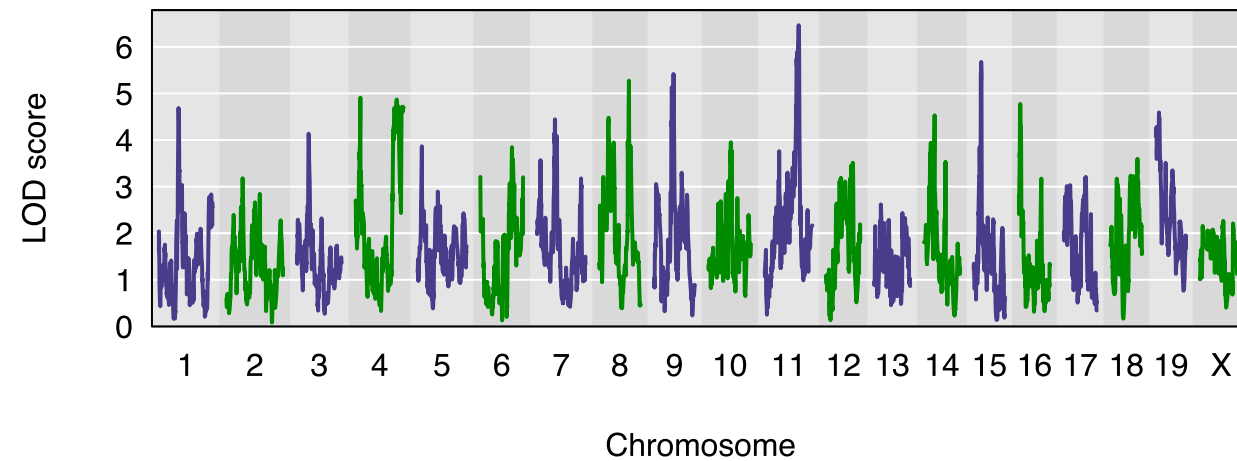


Application

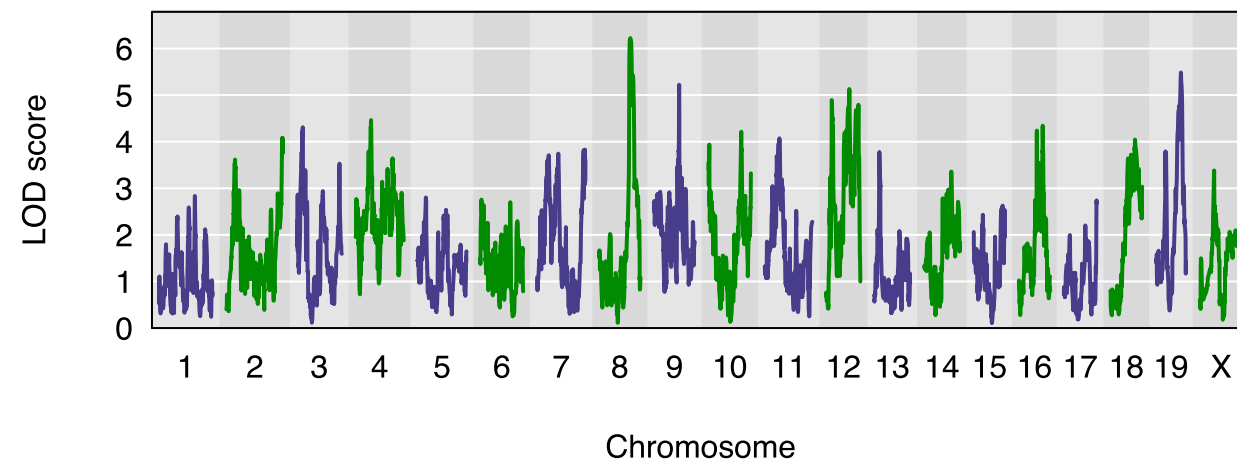
- Logan, et al. (2013) and Recla, et al. (2014) studied 261 Diversity Outbred mice
 - Chromosome 8 QTL affecting "hot plate latency" at 57 cM:
 - Chromosome 8 QTL for "percent time in light" at 55 cM
 - Does affect "percent time in light"?

QTL scan results

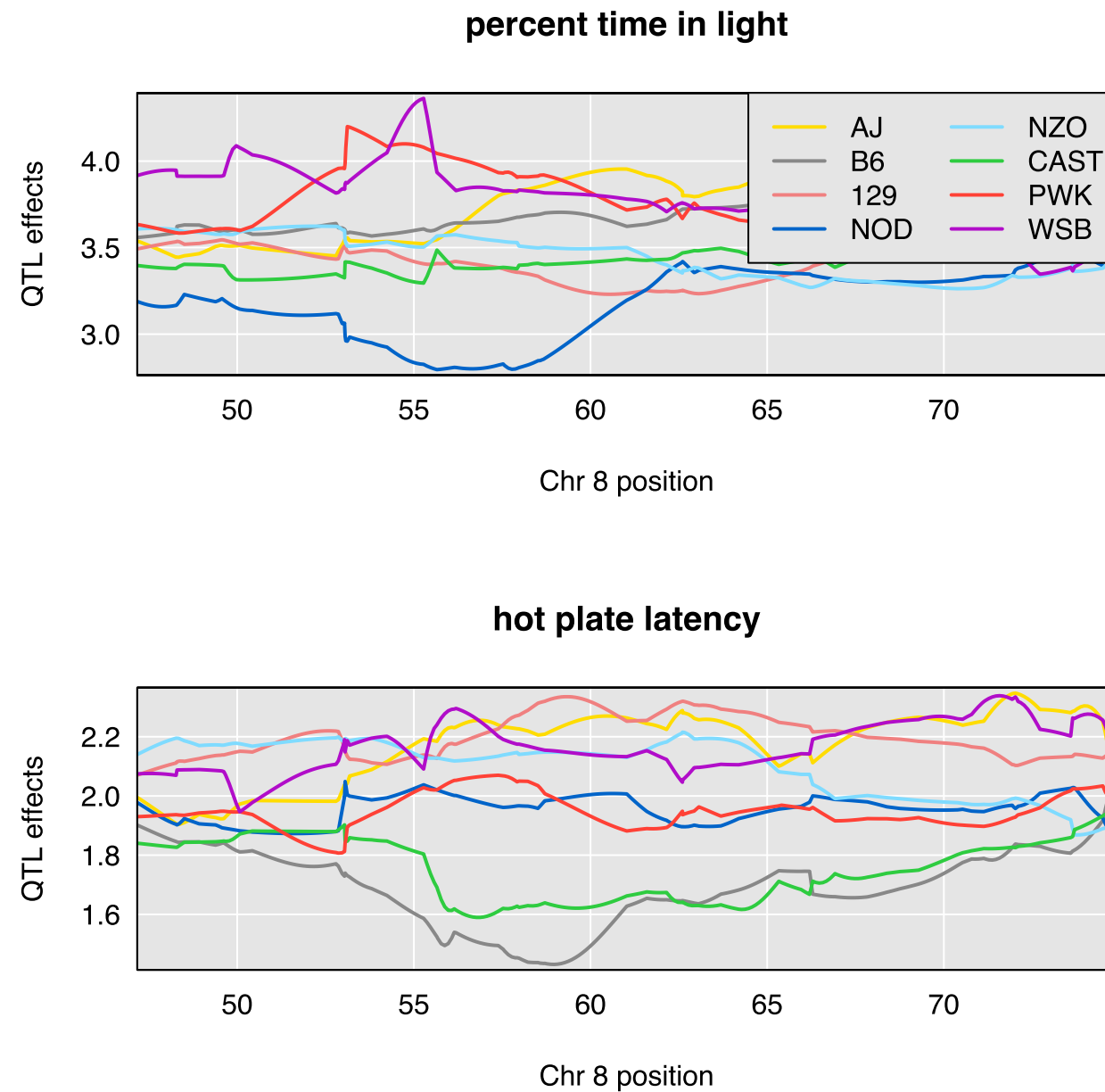
percent time in light



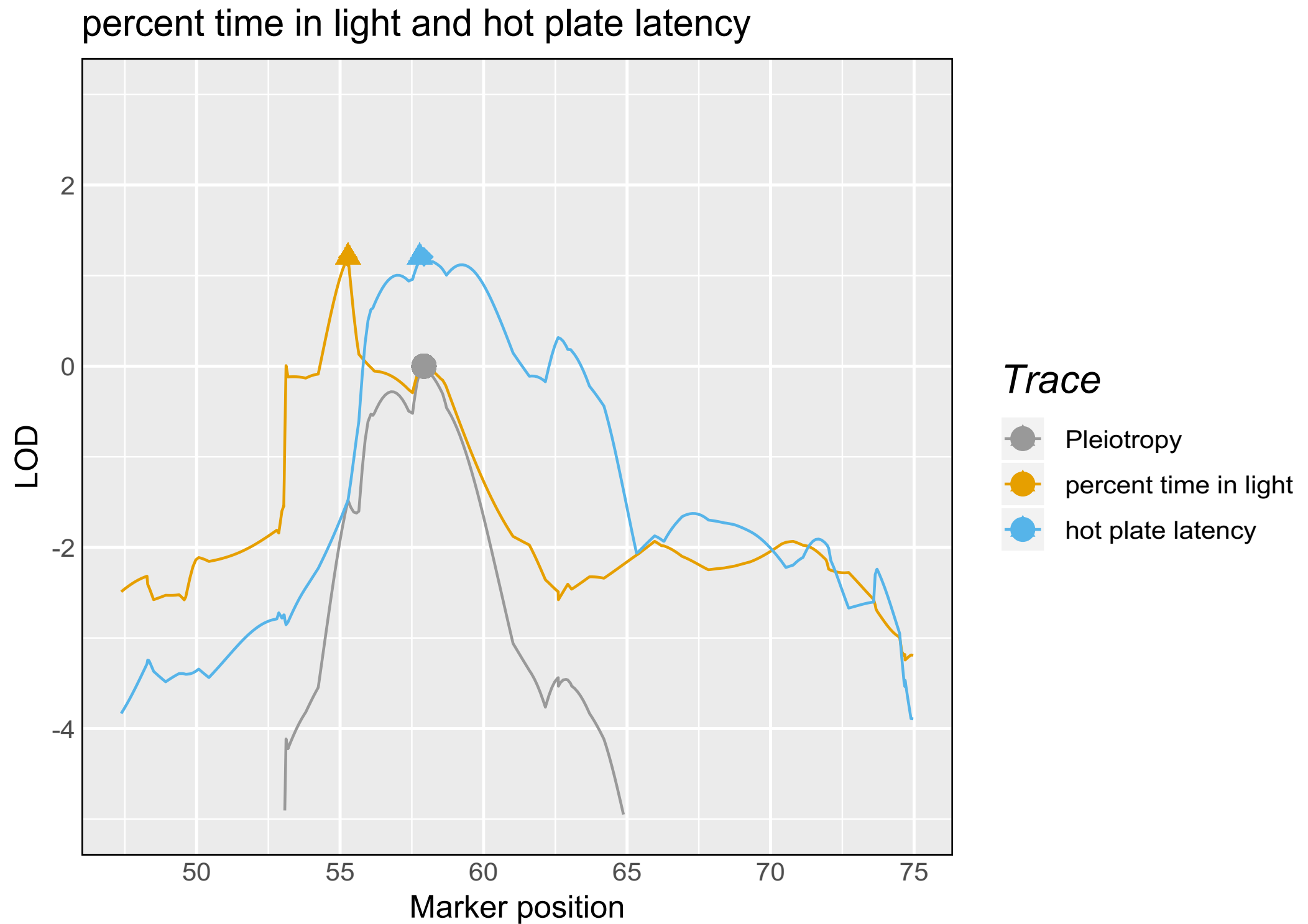
hot plate latency



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 and affects "hot plate latency"

qtl2pleio R package development

Design elements

- Written mostly in R
 - Some calculations in C++, via Rcpp package
 - C++ Eigen library and RcppEigen for matrix algebra
 - User interacts only with R functions

Design elements

- Tutorial vignettes demonstrate functionality
- Unit tests included via R package
- Documentation with R package
- Package website with R package

R packages book

- Hadley Wickham's "R packages" book as a guide



Open-source R package

- Hosted on github
- Install via `install.packages("R package")`
- `commits` publicly visible
- Travis CI for testing after every commit

Binder integration

- Enhances reproducibility
- Uses Docker images
- Downloads R packages for a specified date (or commit on Github)

Binder integration: 2 new files

- `install.R`
 - contains code to install R packages
- `runtime.txt`
 - contains one line of text to indicate date for CRAN packages

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: 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: 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: 25.5-6, pp. 211-222.