Testing pleiotropy in multiparental populations

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Introduction

- 10,000+ traits with RNA sequencing and mass spectrometry

- Multiparental populations offer high-resolution QTL mapping

- New analysis tools, such as a pleiotropy test for multiparental populations, are needed
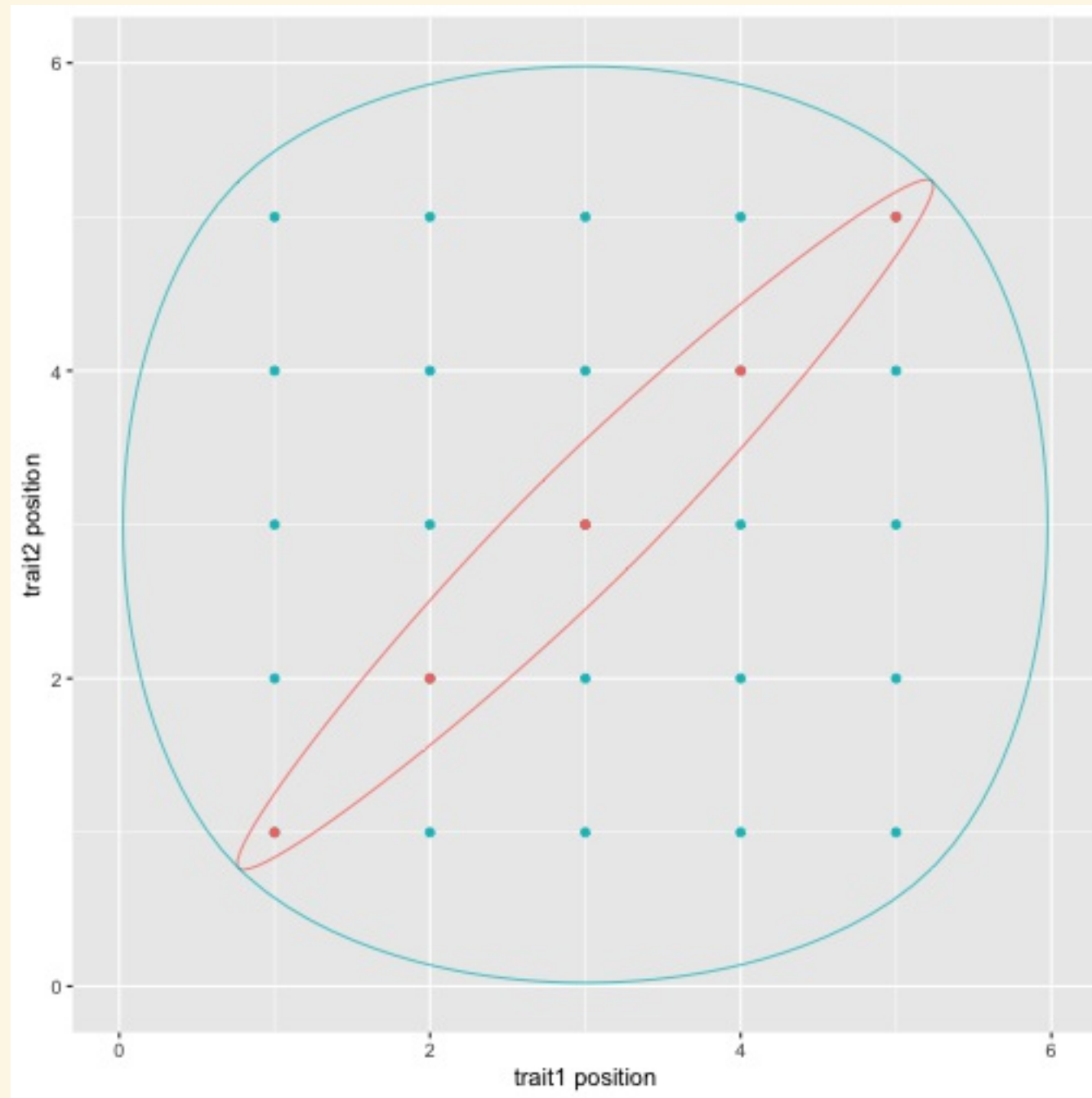
Jiang and Zeng (1995) test

- Two-parent crosses

- Applies to two traits that co-map

- H_0 : Pleiotropy
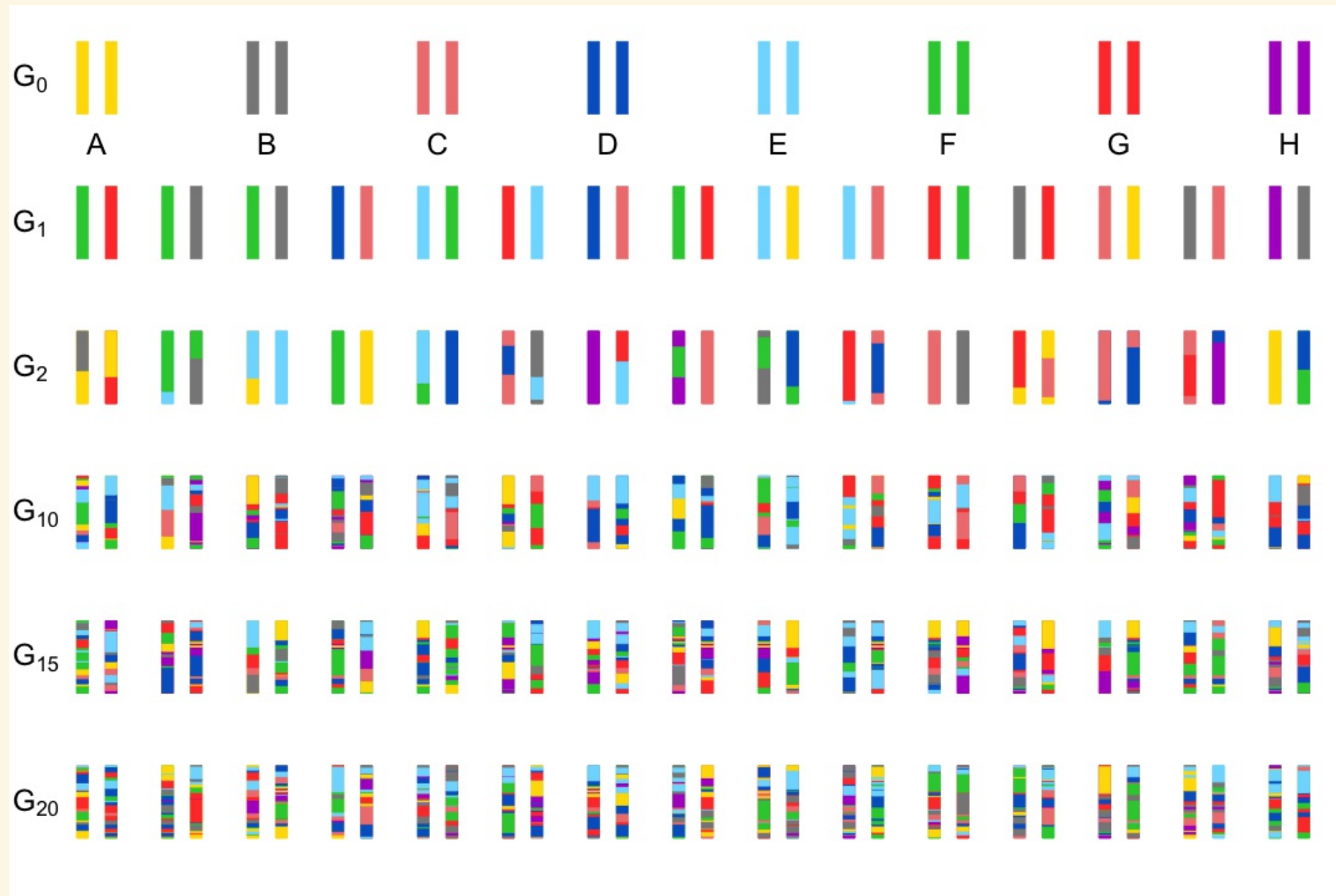
- H_A : Two separate QTL

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

Challenges in multiparental populations

- Complex patterns of relatedness

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- Determining statistical significance

Test procedure

- Model:

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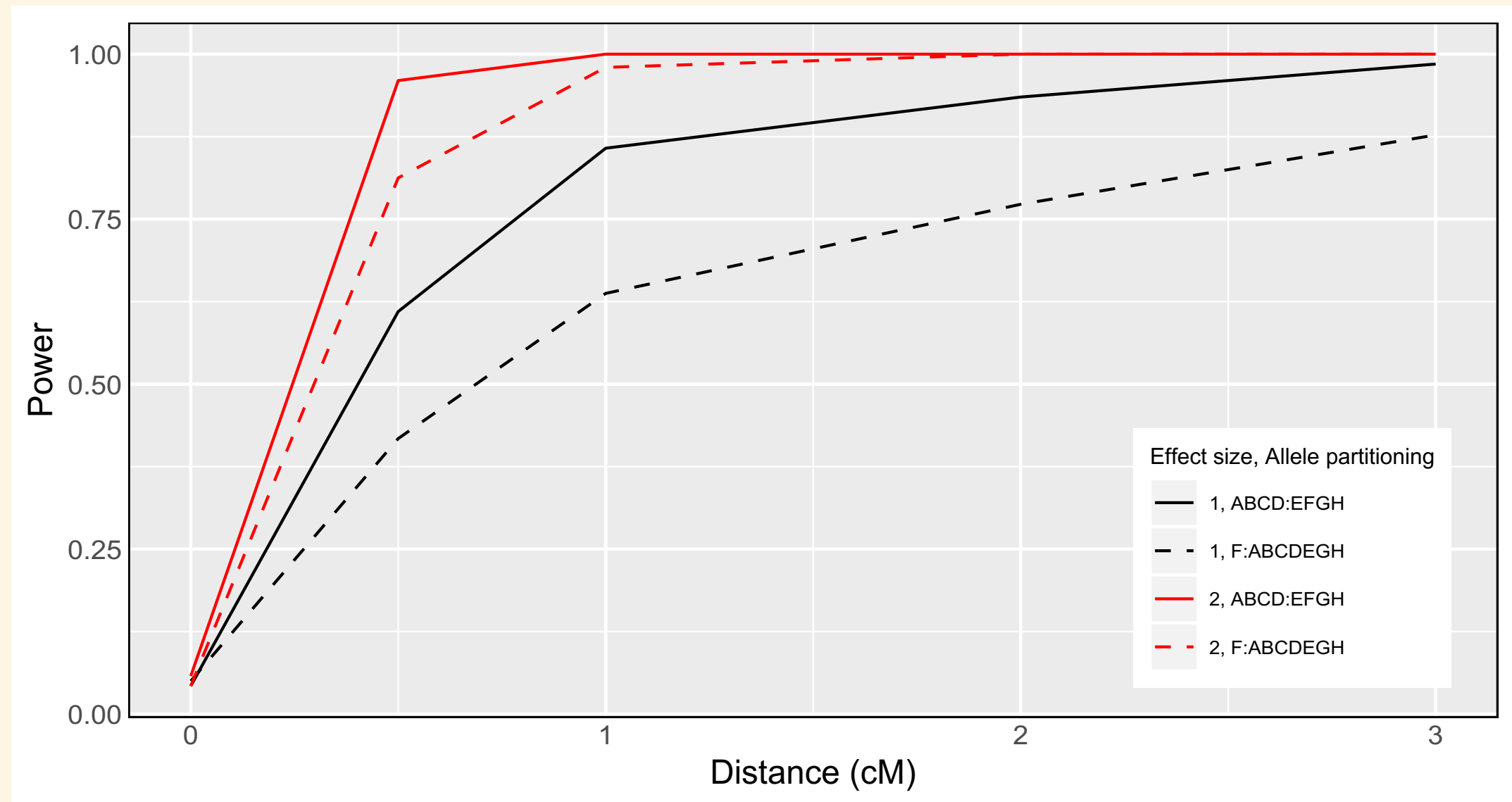
- Calculate likelihoods

Test procedure

- Test statistic:

$$-\log \frac{\text{max(likelihood under pleiotropy)}}{\text{max(likelihood for separate QTL)}}$$

- Parametric bootstrap to get p-value

Test characteristics

Diversity Outbred Mice

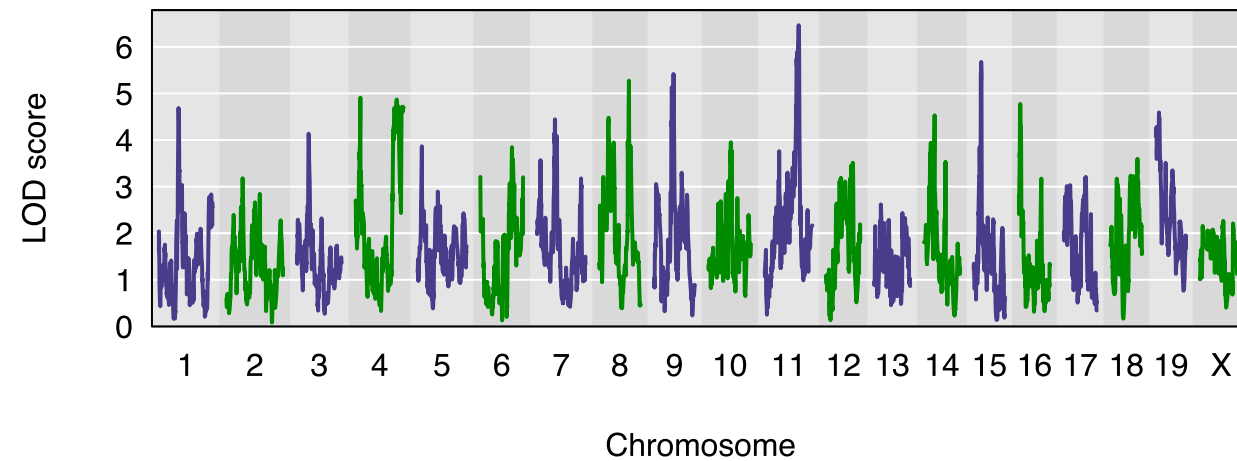- Multiparental population arising from 8 inbred lines
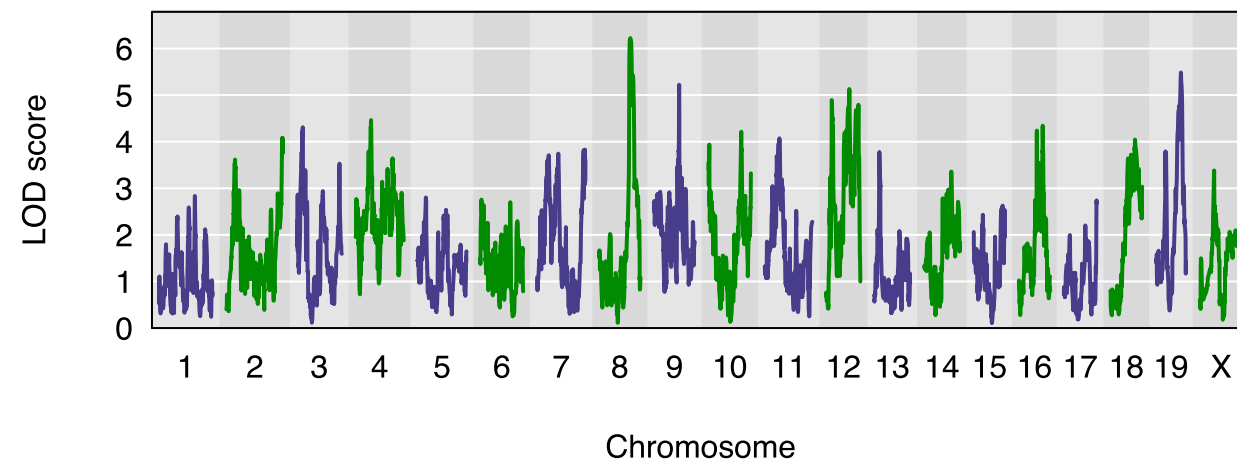
Application

- Logan, et al. (2013) and Recla, et al. (2014) studied 261 Diversity Outbred mice

- Two traits map to Chr 8:

  - "hot plate latency" (57 cM)

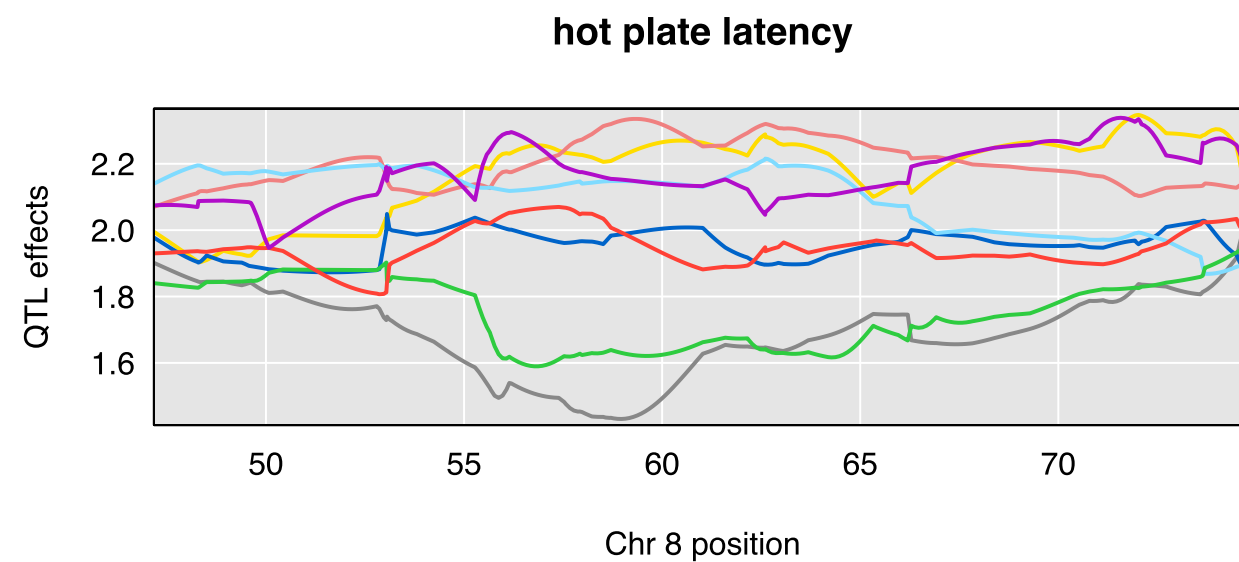 - "percent time in light" (55 cM)

QTL scan results

percent time in light

hot plate latency

14

Allele effects plots

Profile LOD plot

percent time in light and hot plate latency
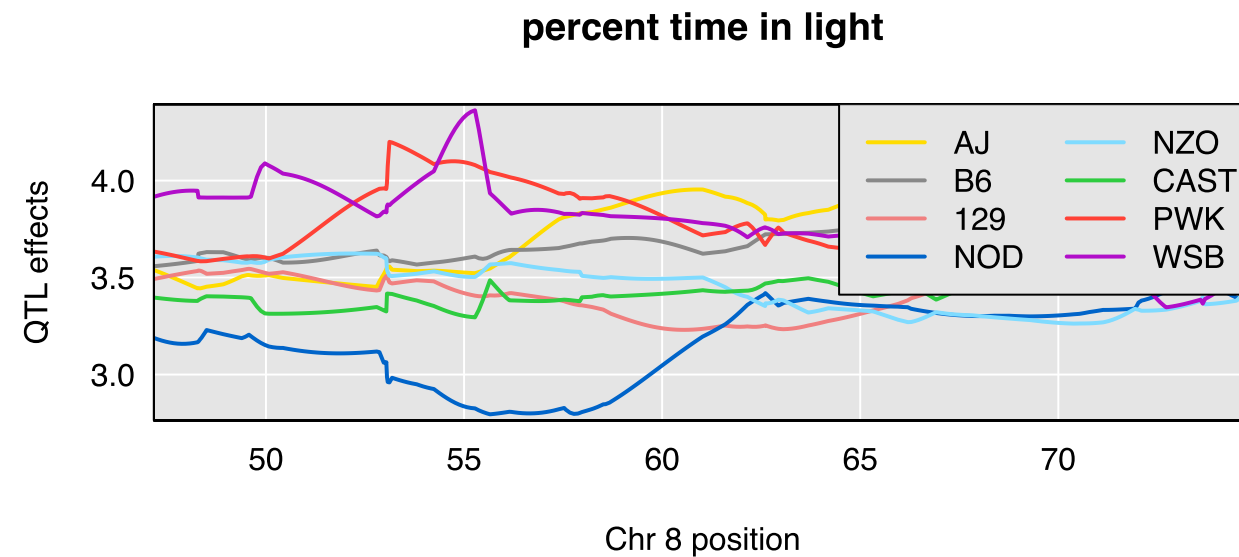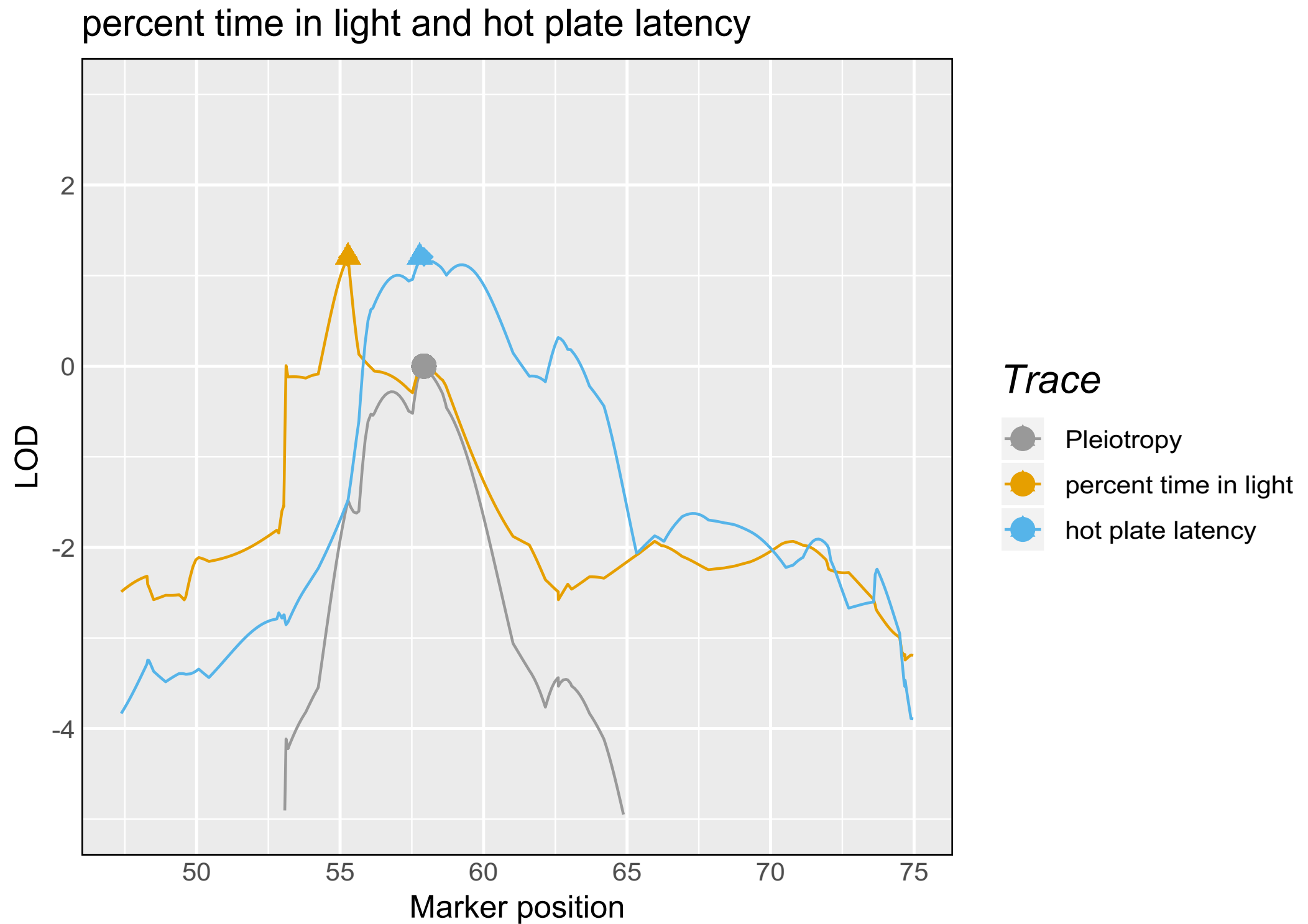
Test results

- p = 0.11 (1000 bootstrap samples)

Conclusions

- Weak evidence for two separate QTL

    - One QTL affects "distance traveled in light"

    - Second QTL affects "hot plate latency"

Mediation analysis and pleiotropy testing

Mediation analysis

Chick, et al. (2016)

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   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

- Biorxiv pre-print: http://bit.ly/boehm-biorxiv

References

Chick, J. M, S. C. Munger, et al. (2016). "Defining the consequences of genetic variation on a proteome-wide scale". In: 534.7608, p. 500.

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.

References

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.