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, et al. (1995) test

- Two-parent crosses

- Applies to two traits that co-map

- H_0: Pleiotropy

- H_A: Two separate QTL

Jiang, et al. (1995) test

- Perform a two-dimensional two-QTL scan

  - $vec(Y) = Xvec(B) + vec(E)$

  - Calculate likelihood at each position

- Calculate likelihood ratio test statistic

Multiparental populations

Challenges in multiparental populations

- Complex patterns of relatedness

Multivariate random effects

- Multiple founder lines

Fixed effect for each founder allele

Test procedure

- Model:

$$vec(Y) = Xvec(B) + vec(G) + vec(E)$$

- Calculate likelihoods at every grid point
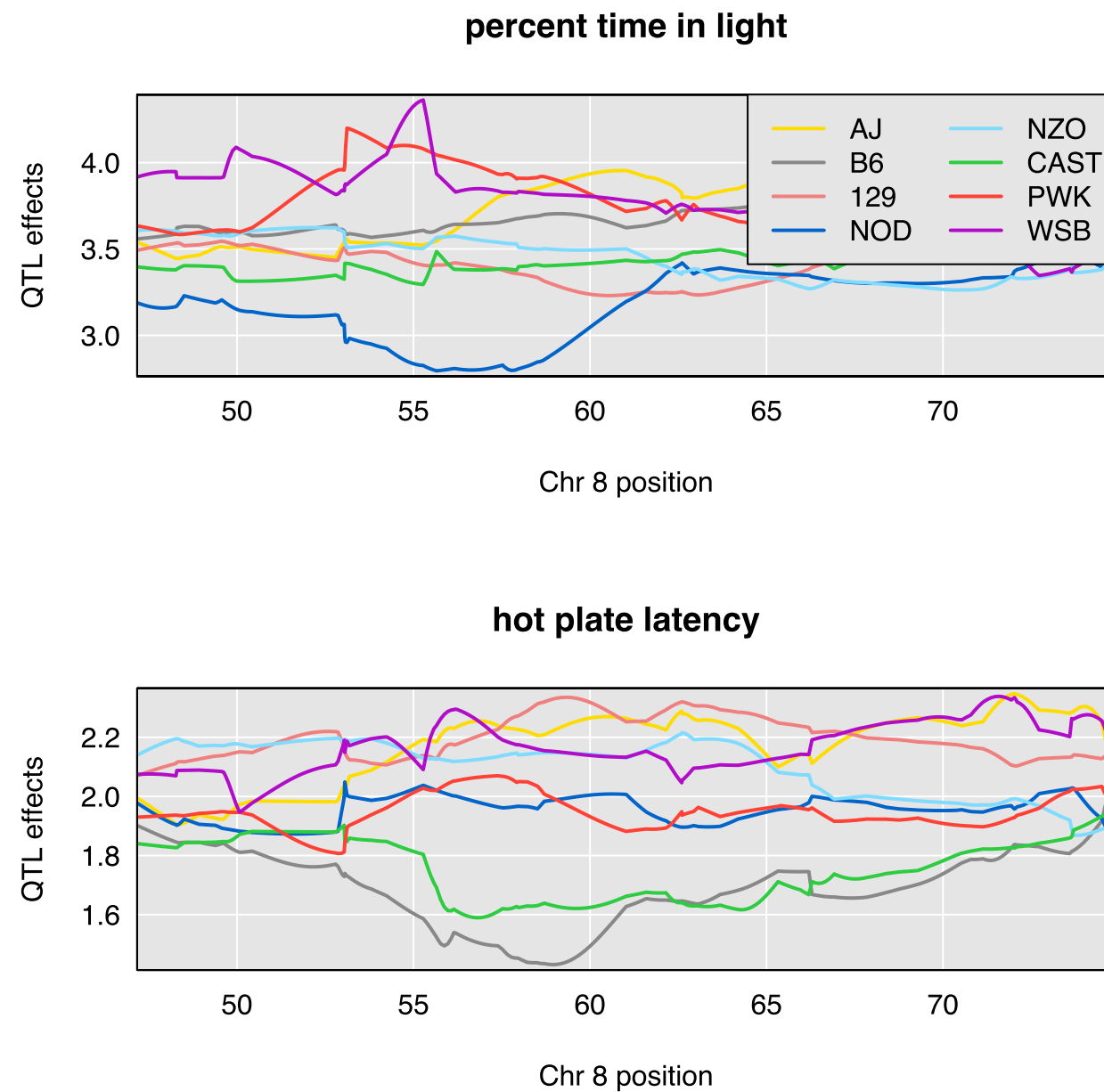
Test procedure

- Test statistic:

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

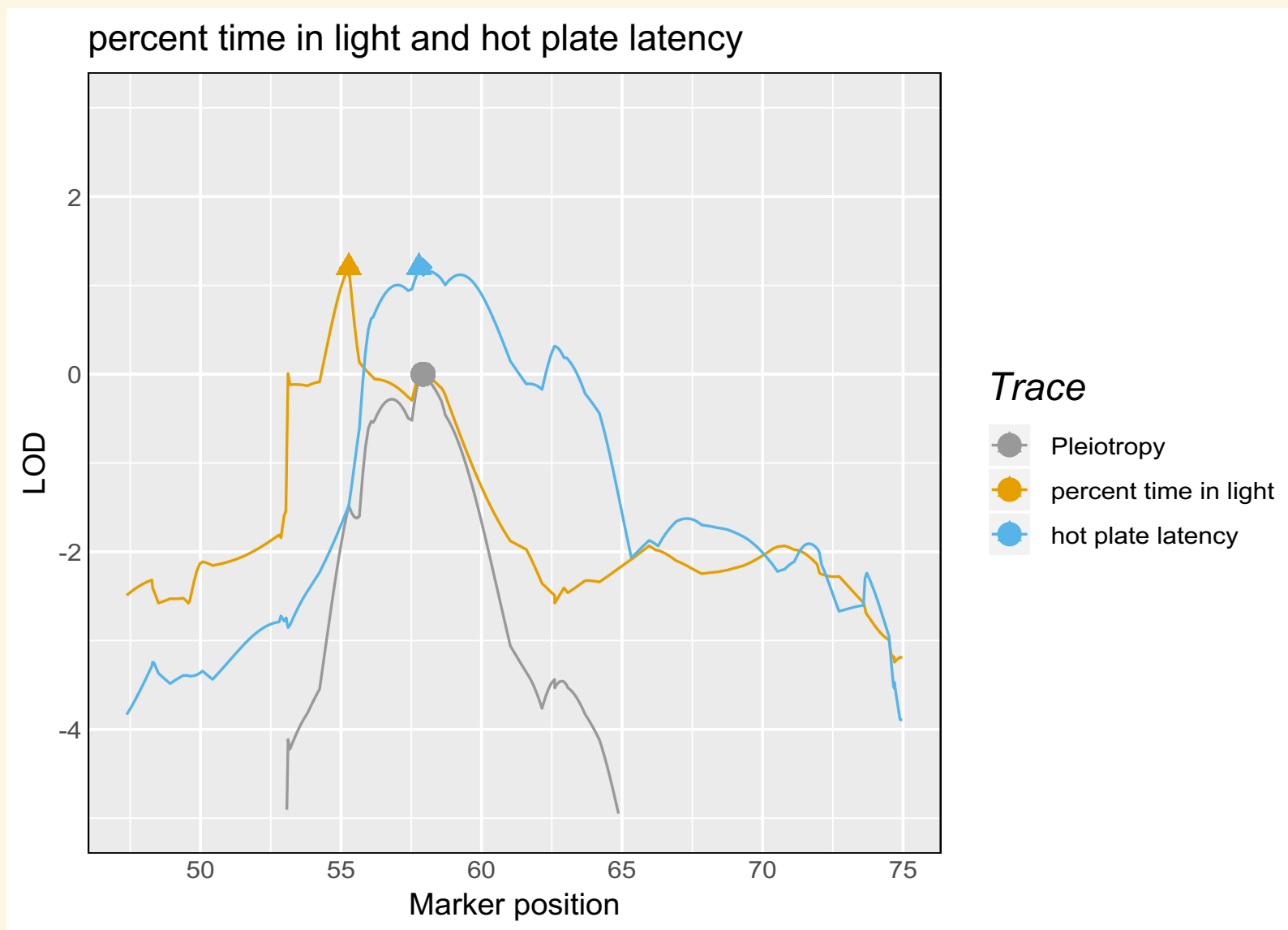- Parametric bootstrap to get a p-value

Application

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

- Measured about two dozen behavioral traits

- Two traits map to Chr 8:

  - "hot plate latency" (57 cM)

  - "percent time in light" (55 cM)

Allele effects plots

Profile LOD

$$\text{profile LOD}_{\text{trait } 1}(\lambda_1) = max_{\lambda_2} LOD(\lambda_1, \lambda_2)$$

percent time in light and hot plate latency

Test results

- $\log_{10}\Lambda = 1.2$

- $p = 0.11$ (1000 bootstrap samples)

qtl2pleio R package

- Functions for d-variate, d-QTL scan & profile LOD plots

- Uses C++ for matrix calculations (via Rcpp and RcppEigen)

- Uses `gemma2` R implementation of GEMMA EM algorithm for multivariate random effects

- Unit tests, vignettes, and version control

References

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

Logan, R. W, 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, 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.

References