Testing pleiotropy in multiparental populations

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April 22, 2019

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

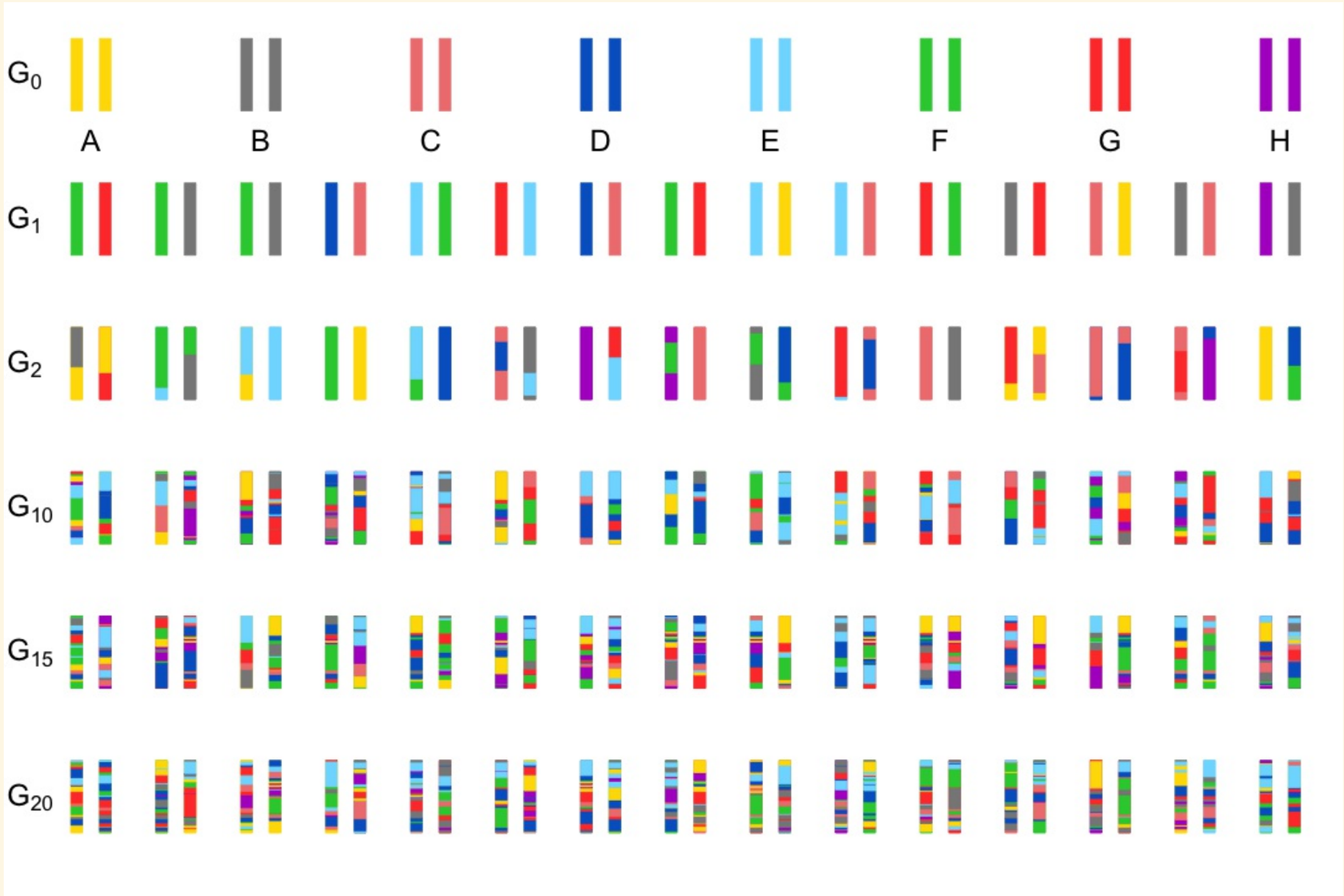
Jiang and Zeng (1995) test

- 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 two-QTL scan
  - $\mathrm{vec}(Y) = X\mathrm{vec}(B) + \mathrm{vec}(E)$
  - 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:

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

- 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

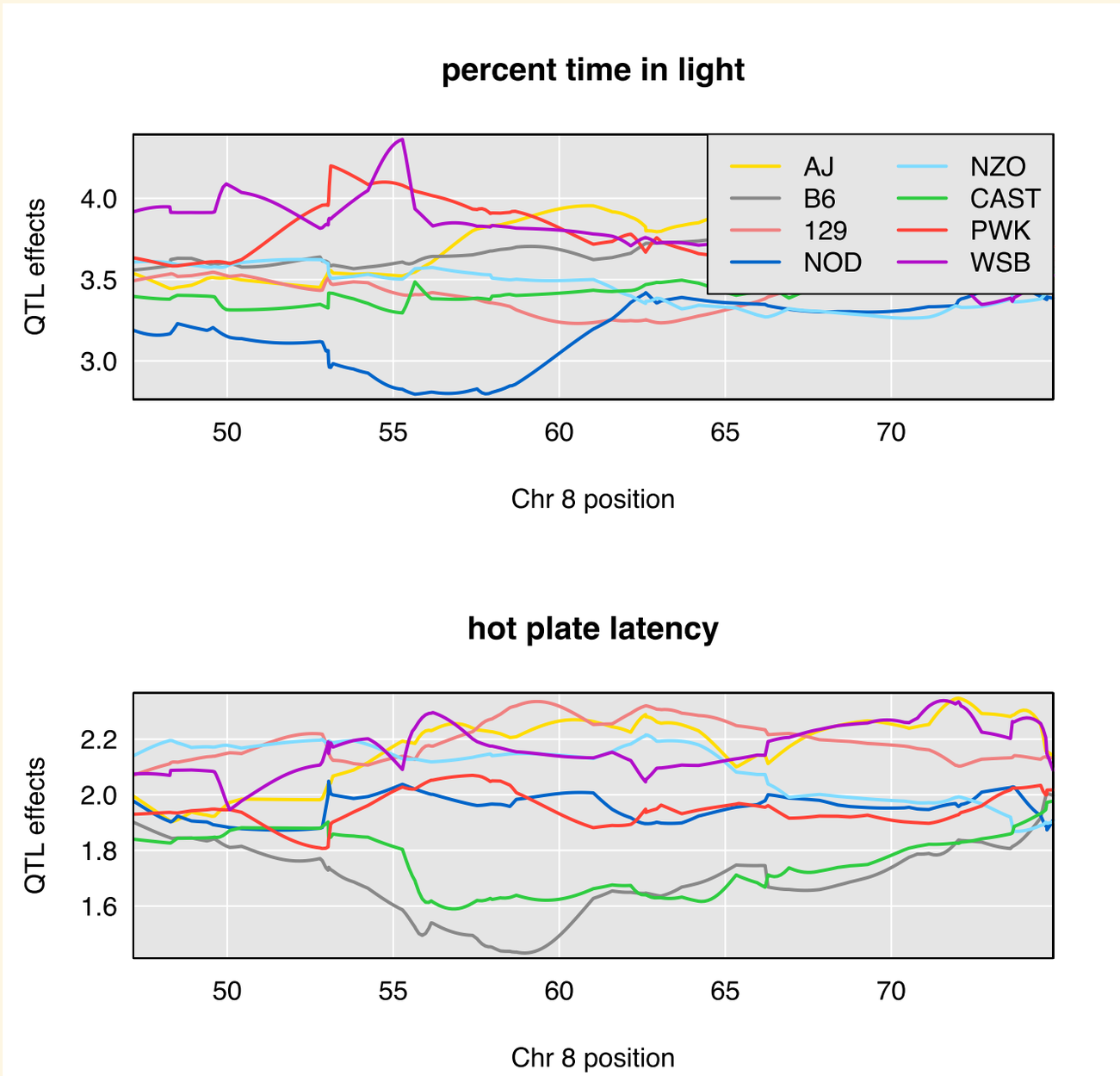
Application

- Logan, et al. (2013) and Recla, et al. (2014) studied 261 Diversity Outbred mice
- Measured about two dozen behavioral traits

Application

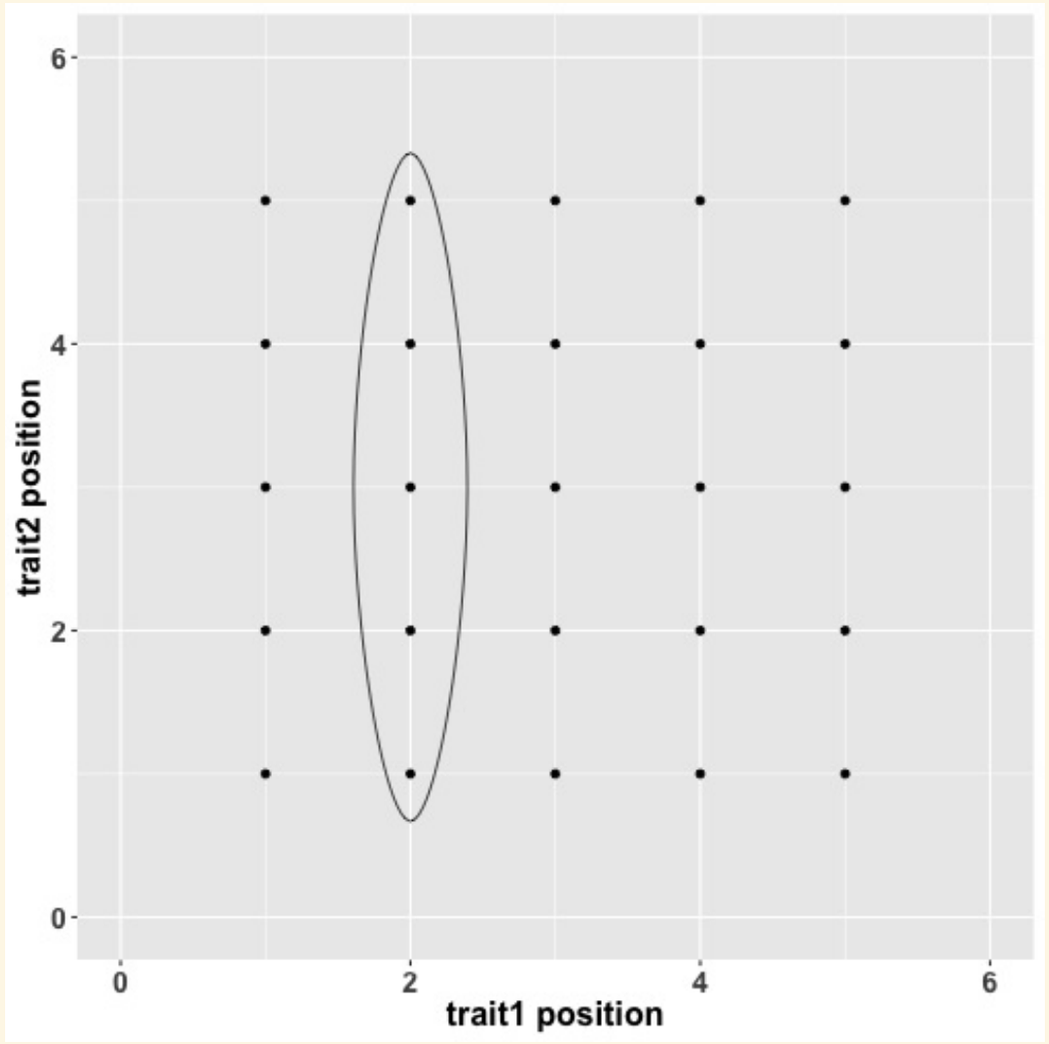
- Two traits map to Chr 8:
  - "hot plate latency" (57 cM)
  - "percent time in light" (55 cM)

Allele effects plots

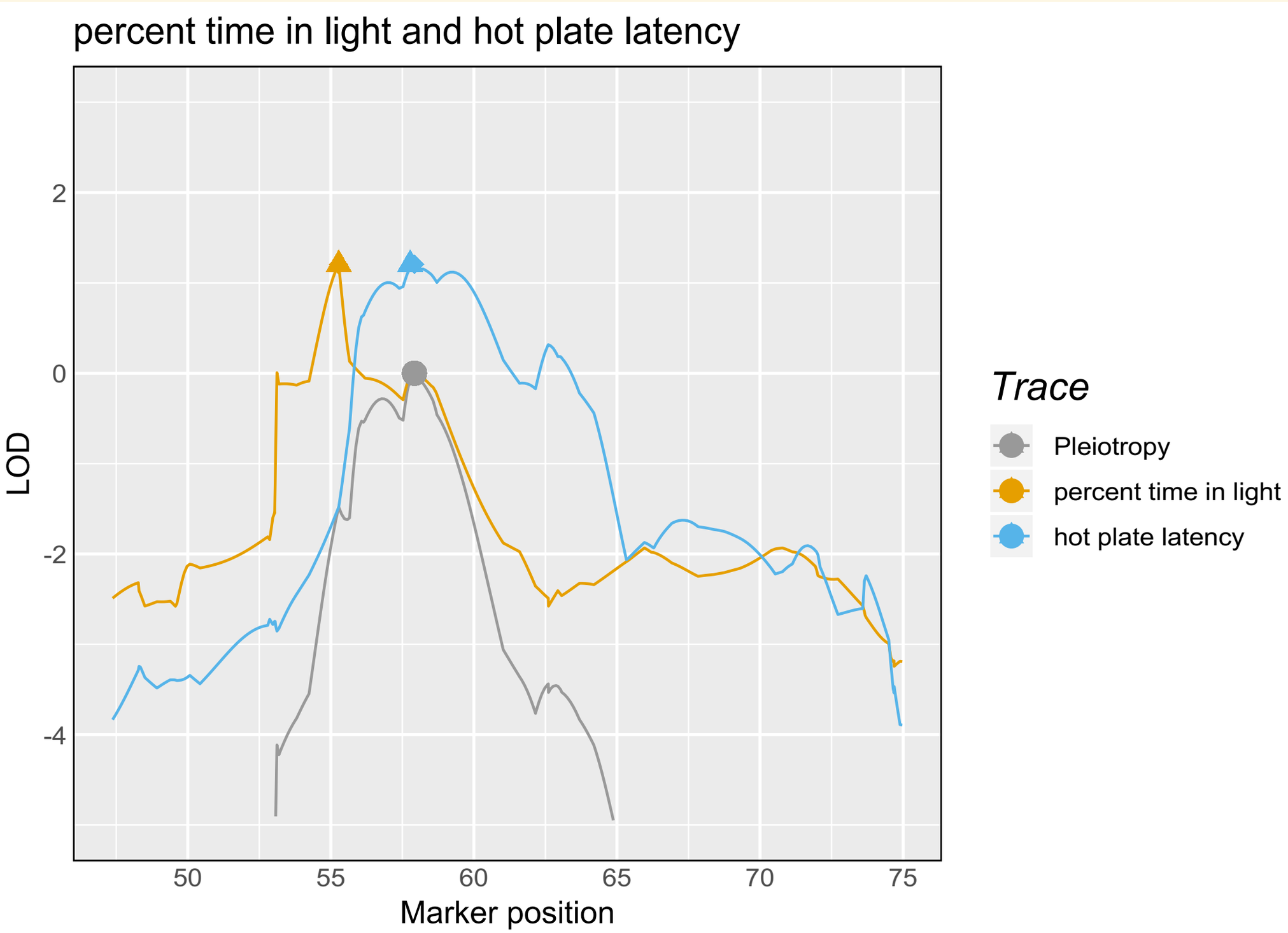


Profile LOD

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



Profile LOD


percent time in light and hot plate latency
2
0
-2
-4
LOD
50
55
60
65
70
75
Marker position
Trace
Pleiotropy
percent time in light
hot plate latency

Test results

- $\log_{10} \Lambda = 1.2$
- $p = 0.11$ (1000 bootstrap samples)

Conclusions

- Weak evidence for two separate QTL
  - One QTL affects "distance traveled in light"
  - Second QTL affects "hot plate latency"

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.

References