Leveraging allelic series to enhance QTL detection

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Introduction

- In CC and DO, we typically work with 8 founder allele probabilities

$$Trait = p_A b_A + p_B b_B + p_C b_C + p_D b_D + p_E b_E + p_F b_F + p_G b_G + p_H b_H + \epsilon$$

- Standard QTL methods allow every founder to have its own allele
- However, founders often share alleles
- Thus, in DO and CC, some QTL have fewer than 8 alleles
- Using this fact in our QTL scans may enhance QTL detection **(Jansen, Jannink, and Beavis 2003)**

Objectives

1. Infer QTL allelic series in CC mice
2. Use CC QTL allelic series to map QTL in DO mice

Methods

- We measured *M. tuberculosis* burden in lungs and spleen in a DO cohort (763 mice) and a CC cohort (53 lines)
    - We also measured cytokine levels in the CC cohort

Allelic series informs QTL mapping in a second cohort

- We mapped QTL in CC cohort with standard methods **(Broman et al. 2019)**
- We used Tree-based Inference of Multi-allelism with Bayesian Regression (TIMBR) **(Crouse 2018)** to infer allelic series at CC QTL
- For each CC QTL, we scanned the DO cohort with reduced models that reflected the CC QTL allelic series
    - Example of reducing a model with inferred allelic series For the allelic series: 0,1,1,0,2,1,0,0:

1. Set $p_0 = p_A + p_D + p_G + p_H, p_1 = p_B + p_C + p_F$ $p_2 = p_E$
2. Use model

$$Y = \beta_0 p_0 + \beta_1 p_1 + \beta_2 p_2 + \epsilon$$

in QTL scan

Results

1. Traditional QTL mapping in CC identified 40 QTL peaks for 11 traits
2. For each CC QTL, we:
    1. inferred allelic series
    2. fitted reduced linear models (informed by allelic series) for QTL detection in DO
    3. identified any proximal DO QTL with LOD greater than 2

QTL peaks on Chr 3

trait	cohort	chr	pos	lod
VEGF in CC	CC	3	130.95	6.86
Peak weight in DO	DO	3	137.27	4.27
Euthanasia weight in DO	DO	3	137.27	4.77

Future research

1. Determine DO QTL p-values with approximate permutation tests **(Churchill and Doerge 1994)**
2. Use multiple allelic series per CC QTL

References

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