QTL mapping in MAGIC populations with R/qtl2

Karl Broman

Biostatistics & Medical Informatics, UW–Madison

kbroman.org
github.com/kbroman
@kwbroman
Slides: bit.ly/msu2019-12
Intercross

P₁

×

P₂

F₁

×

F₁

F₂
QTL mapping

![Diagram showing LOD scores across different chromosomes.](image)
Congenic line/NIL
Improving precision

- more recombinations
- more individuals
- more precise phenotype
- lower-level phenotypes
  - transcripts, proteins, metabolites
Genome-scale phenotypes
Advanced intercross lines

P
A
B
F₂
F₃
F₄
F₇
F₁₀
Recombinant inbred lines

P₁
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F₁
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F₂
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F₃
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F₄
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F∞

P₂
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F₁
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F₃
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F₄
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F∞
Recombinant inbred lines
Collaborative Cross

$G_0$

$G_1$

$G_2$

$G_3$

$G_4$

$\vdots$

$G_\infty$
Heterogeneous stock
MAGIC is magic

- Genetic diversity
- High-precision mapping
- Predictable linkage disequilibrium
- Phenotype replicates to reduce individual variation
- Pool phenotypes from multiple labs, environments, treatments
- Genotype once
MAGIC is magic

- Genetic diversity
- High-precision mapping
- Predictable linkage disequilibrium
- Phenotype replicates to reduce individual variation
- Pool phenotypes from multiple labs, environments, treatments
- Genotype once
- Cool name
MAGIC lines

Valdar et al., Genetics 172:1783, 2006
MAGIC lines

Valdar et al., Genetics 172:1783, 2006
MAGIC lines

Valdar et al., Genetics 172:1783, 2006
MAGIC lines

- How many?
- Which?

Valdar et al., Genetics 172:1783, 2006
MAGIC lines

Valdar et al., Genetics 172:1783, 2006
MAGIC lines

Valdar et al., Genetics 172:1783, 2006

How many?
Which?
How long?
How?

Valdar et al., Genetics 172:1783, 2006
The goal

Identify QTL

▶ Power
▶ Mapping precision
The goal

Identify QTG

- Power
- Mapping precision
The goal

Identify QTG

- Power
- Mapping precision
- Estimate QTL allele frequencies
Principles

▶ Avoid population structure
▶ Tradeoff between power for *de novo* discovery and mapping precision
▶ More QTL to find $\Rightarrow$ more QTL getting in the way?
▶ More QTL alleles $\Rightarrow$ less information about each
▶ Are QTL alleles common or rare?
How many founders?

**More**
- More general use
- More QTL
- Greater precision
- Estimate allele frequencies
- Haplotype analysis in founders

**Fewer**
- Lower residual variance
- Greater power for a particular QTL?
- Better power for epistasis
- Rare alleles are less rare
Which founders?

- Diverse
- Interesting
- No breeding problems
- Balanced: star phylogeny
How much mixing?

- More mixing ⇒ Greater mapping precision
- ...but lower power for de novo mapping
- Potential for population structure, missing alleles
- Random mating or curated mating?
- Start with many random cross directions?
Selfing or DH?

- Inbreeding gives added recombination
- But not so much as at the mixing stage
- If doubled haploids are feasible, use them
Sharing is also key

- The greatest power of MAGIC comes from sharing
  - Pooling data, exploring multiple environments/treatments
- Common software needs
  - Analysis software, database infrastructure
- Many students need to learn the same stuff
  - Joint training opportunities
19 years of R/qtl

Year

Lines of code


idea svn git

R
C
doc
R/qtl cross types

- backcross, doubled haploids, haploid
- intercross
- 2-way RIL by selfing or sibling mating
- phase-known 4-way cross
R/9t12
Now in 3D
R/qtl2 cross types

- backcross, doubled haploids, haploid
- intercross
- 2-, 4-, 8-, 16-way RIL by selfing
- 2-, 4-, 8-way RIL by sibling mating
- 2-, 3-, 8-way advanced intercross
- 6- and 19-way MAGIC
- Diversity Outbred (DO) mice
- $F_1$ of DO $\times$ inbred
- general RIL or AIL
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  "crosstype": "magic19",
  "sep": ",",
  "na.strings": ["-", "NA"],
  "comment.char": "#",
  "geno": "arabmagic_geno.csv",
  "founder_geno": "arabmagic_foundergeno.csv",
  "gmap": "arabmagic_pmap_tair9.csv",
  "pmap": "arabmagic_pmap_tair9.csv",
  "pheno": "arabmagic_pheno.csv",
  "genotypes":
    "A": 1
    "H": 2
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Control file (json or yaml)

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},
  "geno_transposed": true,
  "founder_genotype_transposed": true
}```
Reading data into R

```
library(qtl2)
arab <- read_cross2("arab_magic.json")
```
library(qtl2)
arab <- read_cross2("arab_magic.json")

19-way Arabidopsis MAGIC
Kover et al. (2009) PLoS Genet
Gnan et al. (2014) Genetics
github.com/rqtl/qtl2data
Data diagnostics


doi: 10.1534/g3.119.400165
Genotype reconstruction
Genotype reconstruction

Chr 3 position (Mbp)

Bur
Can
Col
Ct
Edi
Hi
Kn
Ler
Mt
No
Oy
Po
Rsch
Sf
Tsu
Wil
Ws
Wu
Zu

MAGIC.244

Edi

Wu
Genotype reconstruction

```r
# Import necessary packages

# Genotype reconstruction

gmap <- insert_pseudomarkers(arab$gmap, step=0.2, stepwidth="max")
pmap <- interp_map(gmap, arab$gmap, arab$pmap)
pr <- calc_genoprob(arab, gmap, error_prob=0.002, cores=24)
```
Genome scan

![Genome Scan Diagram]

- Chromosome
- LOD score
- Fruit length

The diagram shows a genome scan with LOD scores plotted against chromosome numbers. There is a notable peak around chromosome 2, indicating a region of interest for fruit length.
Genome scan

Chromosome

LOD score

fruit length

haley−knott

Imm

0 10 20 30 40

1 2 3 4 5

Chromosome
Genome scan

Chromosome
LOD score
fruit length

haley−knott
Imm
Imm w/loco
Genome scan

Chromosome
LOD score
seed weight

- haley-knott
- lmm
- lmm w/loco
out_hk <- scan1(pr, arab$pheno, cores=24)

operm_hk <- scan1perm(pr, arab$pheno, n_perm=1000, cores=24)

k <- calc_kinship(pr, cores=24)
out_lmm <- scan1(pr, arab$pheno, k, cores=24)

k_loco <- calc_kinship(pr, "loco", cores=24)
out_loco <- scan1(pr, arab$pheno, k_loco, cores=24)
SNP association scan

[Graph showing LOD scores against chromosome numbers with fruit length at the top right corner]
SNP association scan

Chromosome

LOD score

fruit length
SNP association scan

-\log_{10} \text{ p-value}

Chromosome

fruit length
SNP association scan
SNP association scan
SNP association scan

```r
snp_pr <- genoprob_to_snpprob(pr, arab)
out_snps <- scan1(snp_pr, arab$fruit, cores=24)
```
QTL effects

Fruit length (chr 2 @ 11.4 Mbp)
QTL effects

Fruit length (chr 2 @ 11.4 Mbp)

QTL effects

least squares
BLUP

Fruit length (chr 2 @ 11.4 Mbp)
QTL effects

Seed weight (chr 1 @ 21.4 Mbp)

- QTL effects
- BLUP
- least squares
QTL effects

```r
fl_peak <- max(out_hk, pmap, lodcolumn="fruit_length")
fl_pr <- pull_genoprobpos(pr, pmap, fl_peak$chr, fl_peak$pos)
fl_fit1 <- fit1(fl_pr, arab$pheno[, "fruit_length"])
fl_blup <- fit1(fl_pr, arab$pheno[, "fruit_length"], blup=TRUE)
```
Goals

- Genotype reconstructions from external software
- General models for RIL and AIL
- Sequencing-based genotype data
- Multiple-QTL models
- QTL $\times$ environment interactions
- Interactive data visualization
Slides: bit.ly/msu2019-12

kbroman.org

kbroman.org/qtl2

github.com/kbroman

@kwgbroman