QTL Mapping II:

Hidden Markov model technology

and

The pseudomarker algorithm

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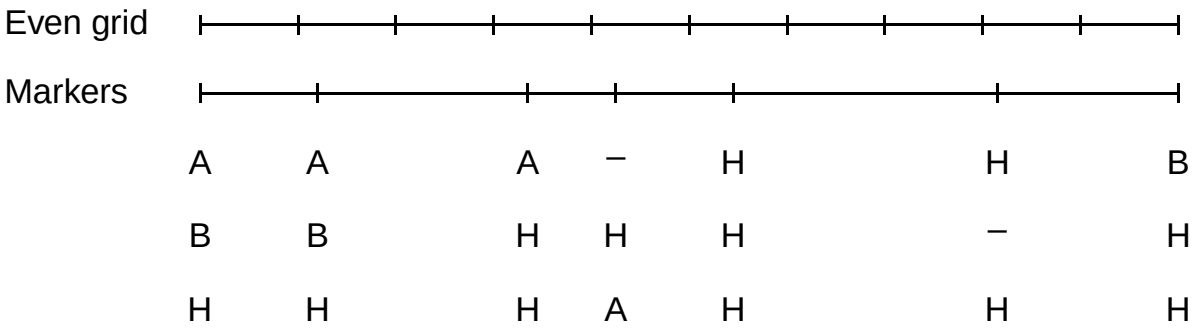
HMM technology: Outline

- The problems
- A simple solution
- Why a complex solution?
- The hidden Markov model
- Backcross, intercross
- QTL genotype probabilities
- Simulation of QTL genotypes

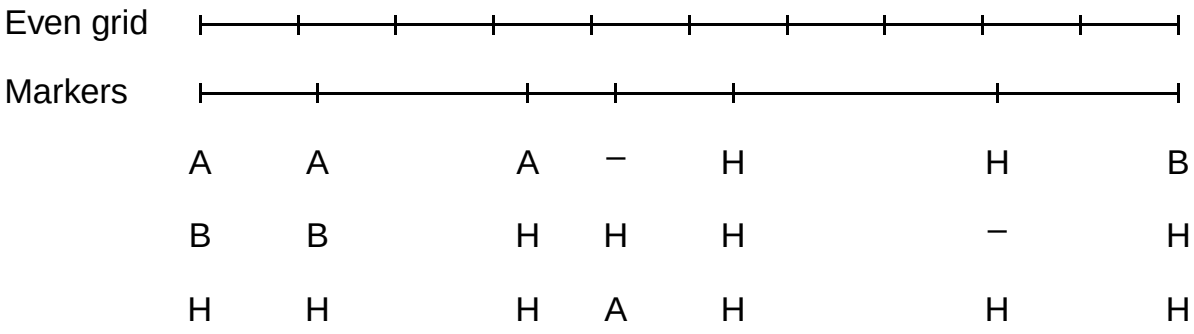
The problems

- Calculate genotype probability at an arbitrary location, conditional on multipoint marker data.
- Simulate from the joint genotype distribution on a grid, given multipoint marker data.



A simple solution

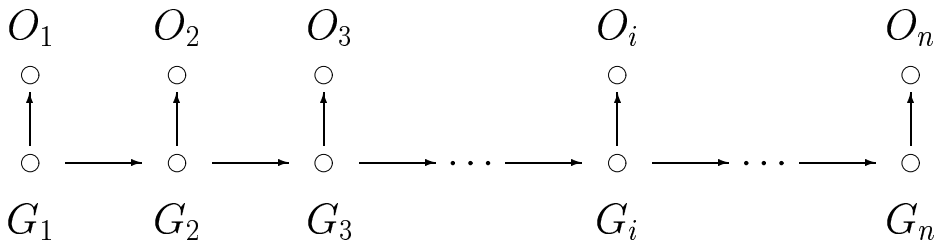
- Under the no interference (NI) model, the genotypes follow a Markov chain.
- Thus, the genotype probability depends only on the nearest flanking typed markers



Why a complex solution?

- Allow for the presence of genotyping errors
- Simply deal with partially informative genotypes (e.g., C = H or B)
- Simplify bookkeeping tasks in the implementation
- Easily extend algorithms to more complex experimental crosses (such as the four-way cross)

The hidden Markov model



- The $\{G_i\}$ (hidden states) form a Markov chain, with values in some finite set, $\mathcal{G}$.

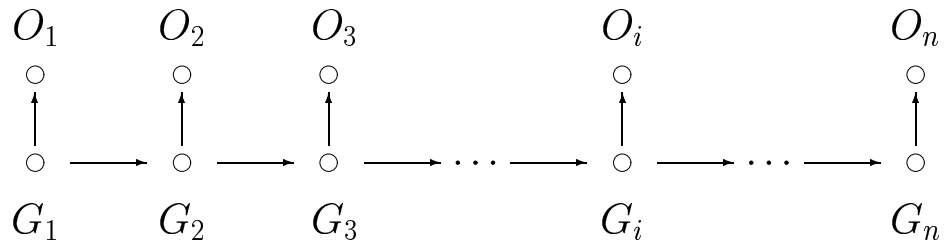
$$\Pr(G_{i+1} \mid G_i, \ldots, G_1) = \Pr(G_{i+1} \mid G_i)$$

- The observeable random variables, $\{O_i\}$, take values in another finite set, $\mathcal{O}$.

O_i depends only on G_i

- G_i = "true" genotype at marker i
- O_i = "observed genotype" (marker phenotype) at i

Model parameters



- Initiation probabilities: $\pi(g) = \Pr(G_1 = g)$

  for $g \in \mathcal{G}$

- Transition probabilities: $t_i(g, g') = \Pr(G_{i+1} = g' \mid G_i = g)$

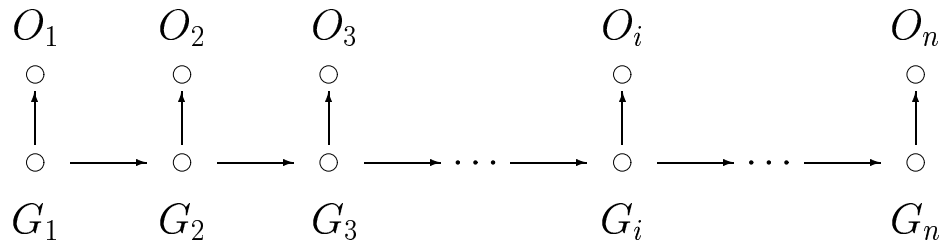
  for $i = 1, \ldots, n-1$ and $g, g' \in \mathcal{G}$

- Emission probabilities: $e_i(g, o) = \Pr(O_i = o \mid G_i = g)$

  for $i = 1, \ldots, n$, $g \in \mathcal{G}$, and $o \in \mathcal{O}$

  (We assume $e_i(g, o) \equiv e(g, o)$ for all i.)

Joint probability



$$\begin{aligned}
\Pr(\boldsymbol{G} = \boldsymbol{g}, \boldsymbol{O} = \boldsymbol{o}) &= \Pr(G_1 = g_1, \ldots, G_n = g_n, O_1 = o_1, \ldots, O_n = o_n) \\
&= \Pr(G_1 = g_1) \Pr(G_2 = g_2 \mid G_1 = g_1) \cdots \\
&\quad \cdots \Pr(G_n = g_n \mid G_{n-1} = g_{n-1}) \cdot \Pr(O_1 = o_1 \mid G_1 = g_1) \cdots \\
&\quad \cdots \Pr(O_n = o_n \mid G_n = g_n) \\
&= \pi(g_1) \prod_{i=1}^{n-1} t_i(g_i, g_{i+1}) \prod_{i=1}^{n} e(g_i, o_i)
\end{aligned}$$

The backcross

$\mathcal{G} = \{AA, AB\}$ $\mathcal{O} = \{A, H, -\}$ (– = missing)

Initiation probabilities:

$\pi(AA) = \pi(AB) = 1/2$

Transition probabilities:

r_i = recombination fraction for interval i.

$t_i(AA, AB) = t_i(AB, AA) = r_i$

$t_i(AA, AA) = t_i(AB, AB) = 1 - r_i$

Emission probabilities:

ϵ = genotyping error rate

$e(AA, A) = e(AB, H) = 1 - \epsilon$, $e(AA, -) = e(AB, -) = 1$

$e(AA, H) = e(AB, A) = \epsilon$

The intercross

We'll consider phase-unknown genotypes.

$\mathcal{G} = \{AA, AB, BB\}$

Initiation probabilities:

$\pi(AA) = \pi(BB) = 1/4$, $\pi(AB) = 1/2$

Transition probabilities, $t_i(g, g') = \Pr(G_{i+1} = g' \mid G_i = g)$:

	g'		
g	AA	AB	BB
AA	$(1 - r_i)^2$	$2r_i(1 - r_i)$	r_i^2
AB	$r_i(1 - r_i)$	$(1 - r_i)^2 + r_i^2$	$r_i(1 - r_i)$
BB	r_i^2	$2r_i(1 - r_i)$	$(1 - r_i)^2$

The intercross (cont.)

$\mathcal{O} = \{A, H, B, C, D, -\}$

– = missing = $\{A$ or H or $B\}$

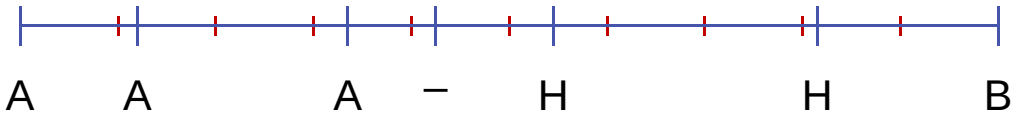
C = not A = $\{H$ or $B\}$

D = not B = $\{A$ or $H\}$

Emission probabilities, $e(g, o) = \Pr(O_i = o \mid G_i = g)$:

	o					
g	A	H	B	C	D	$-$
AA	$1-\epsilon$	$\epsilon/2$	$\epsilon/2$	ϵ	$1-\epsilon/2$	1
AB	$\epsilon/2$	$1-\epsilon$	$\epsilon/2$	$1-\epsilon/2$	$1-\epsilon/2$	1
BB	$\epsilon/2$	$\epsilon/2$	$1-\epsilon$	$1-\epsilon/2$	ϵ	1

QTL genotype probabilities



We seek to calculate $\Pr(G_i = g \mid \boldsymbol{O})$. where $\boldsymbol{O} = (O_1, O_2, \ldots, O_n)$ is the observed multipoint marker data.

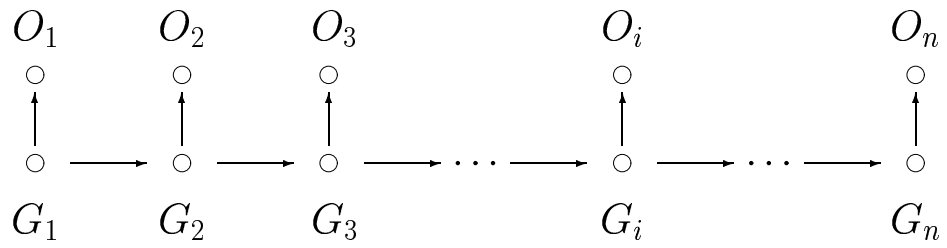
Brute force:

$$\Pr(G_i = g_i|\boldsymbol{O}) = \sum_{g_1} \cdots \sum_{g_{i-1}} \sum_{g_{i+1}} \cdots \sum_{g_n} \Pr(G_1 = g_1, \ldots, G_n = g_n|\boldsymbol{O})$$

$$\propto \sum_{g_1} \cdots \sum_{g_{i-1}} \sum_{g_{i+1}} \cdots \sum_{g_n} \pi(g_1) \prod_{j=1}^{n-1} t_j(g_j, g_{j+1}) \prod_{j=1}^{n} e(g_j, O_j)$$

For the phase-unknown intercross, this is a sum with 3^{n-1} terms; clearly this is unwieldy and unnecessary. But, of course, there is a simpler way!

The forward and backward equations



Our approach makes use of the following two sets of probabilities:

$$\begin{aligned}\alpha_i(g) &= \Pr(O_1, \ldots, O_i, G_i = g) \\ \beta_i(g) &= \Pr(O_{i+1}, \ldots, O_n | G_i = g)\end{aligned}$$

Note that once the α's and β's have been calculated, the probability that is our focus follows directly:

$$\begin{aligned}\Pr(G_i = g|\boldsymbol{O}) &= \Pr(G_i = g, \boldsymbol{O}) \;/\; \Pr(\boldsymbol{O}) \\ &= \alpha_i(g)\beta_i(g) \;/\; \textstyle\sum_{g'} \alpha_i(g')\beta_i(g')\end{aligned}$$

The forward equations

The α's are calculated inductively.

First, note that

$$\alpha_1(g) = \Pr(O_1, G_1 = g) = \pi(g)\; e(g, O_1)$$

Now, assume that we've calculated $\alpha_i(g)$ for each $g \in \mathcal{G}$. Then

$$\begin{aligned}\alpha_{i+1}(g) &= \Pr(O_1, \ldots, O_i, O_{i+1}, G_{i+1} = g) \\ &= \textstyle\sum_{g'} \Pr(O_1, \ldots, O_i, O_{i+1}, G_i = g', G_{i+1} = g) \\ &= \textstyle\sum_{g'} \Pr(O_1, \ldots, O_i, G_i = g') \Pr(G_{i+1} = g | G_i = g') \Pr(O_{i+1} | G_{i+1} = g) \\ &= e(g, O_{i+1}) \textstyle\sum_{g'} \alpha_i(g')\; t_i(g', g)\end{aligned}$$

The backward equations

The β's are calculated similarly, but moving backward.

First, we define $\beta_n(g) \equiv 1$ for all $g \in \mathcal{G}$.

Now, assume that we've calculated $\beta_i(g)$ for each $g \in \mathcal{G}$. Then

$$\begin{aligned}
\beta_{i-1}(g) &= \Pr(O_i, \ldots, O_n | G_{i-1} = g) \\
&= \textstyle\sum_{g'} \Pr(O_i, \ldots, O_n, G_i = g' | G_{i-1} = g) \\
&= \textstyle\sum_{g'} \Pr(O_{i+1}, \ldots O_n | G_i = g') \Pr(G_i = g' | G_{i-1} = g) \Pr(O_i | G_i = g') \\
&= \textstyle\sum_{g'} \beta_i(g')\ t_{i-1}(g, g')\ e(g', O_i)
\end{aligned}$$

QTL genotype probabilities

1. Calculate the α's and β's, simultaneously, via the forward and backward equations.
2. Calculate, for each i and g,

$$\begin{aligned}
\Pr(G_i = g | \boldsymbol{O}) &= \Pr(G_i = g, \boldsymbol{O}) \ / \ \Pr(\boldsymbol{O}) \\
&= \alpha_i(g)\beta_i(g) \ / \ \textstyle\sum_{g'} \alpha_i(g')\beta_i(g')
\end{aligned}$$

Simulation of QTL genotypes

We seek to simulate from the joint distribution, $\Pr(G_1, \ldots, G_n \mid \boldsymbol{O})$

[Why? We'll explain shortly.]

First draw $g_1^\star$ from the distribution

$$\Pr(G_1 = g \mid \boldsymbol{O}) = \frac{\alpha_1(g)\beta_1(g)}{\sum_{g'} \alpha_1(g')\beta_1(g')}$$

Genotypes for further loci are drawn iteratively:

having drawn $g_1^\star, \ldots, g_i^\star$, draw $g_{i+1}^\star$ from

$$\begin{aligned}
\Pr(G_{i+1} = g | \boldsymbol{O}, G_i = g_i^\star) &= \frac{\Pr(G_{i+1} = g, G_i = g_i^\star | \boldsymbol{O})}{\Pr(G_i = g_i^\star | \boldsymbol{O})} \\
&= \frac{\alpha_i(g_i^\star)\ t_i(g_i^\star, g)\ e(g, O_{i+1})\ \beta_{i+1}(g)}{\alpha_i(g_i^\star)\beta_i(g_i^\star)} \\
&= t_i(g_i^\star, g)\ e(g, O_{i+1})\ \beta_{i+1}(g)\ /\ \beta_i(g_i^\star)
\end{aligned}$$

Note that we need to fi rst calculate the β's (via the backward equations).

A practical issue

In the case of many genetic markers (or pseudomarkers), the direct calculation of α and β, as described above, will result in underflow.

$\alpha_n(g) = \Pr(O_1, O_2, \ldots, O_n, G_n = g)$ can be extremely small!

One method to deal with this is to work with $\alpha' = \log \alpha$ and $\beta' = \log \beta$.

But in the forward equations, we need

$$\alpha'_{i+1}(g) = \log e(g, O_{i+1}) + \log\{\textstyle\sum'_g \alpha_i(g')\ t_i(g', g)\}$$

This leads to the problem of calculating $\log(f_1 + f_2)$ on the basis of $g_i = \log f_i$, which may be facilitated with the following trick:

$$\begin{aligned}
\log(f_1 + f_2) &= \log(e^{g_1} + e^{g_2}) \\
&= \log\{e^{g_1}(1 + e^{g_2 - g_1})\} \\
&= g_1 + \log(1 + e^{g_2 - g_1})
\end{aligned}$$

A problem occurs when $g_2 \gg g_1$: the above formula will result in an overflow. In such a case one simply notes that $\log(f_1 + f_2) \approx g_2$.

The pseudomarker algorithm: Outline

Sen & Churchill (2001) Genetics 159:371–387

- Data structure and notation
- Basic idea
- Advantages and cautions
- An example

Data structure and notation

y = phenotypes

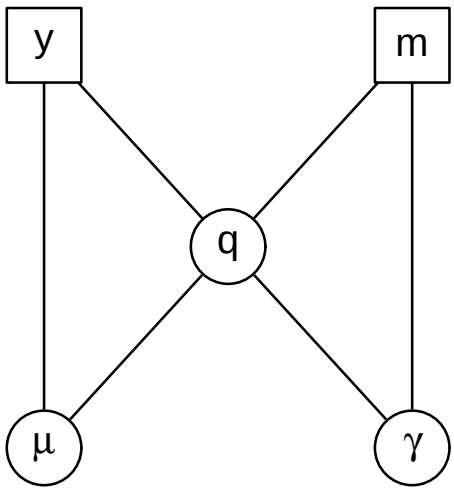
m = observed marker genotypes

q = unobserved QTL genotypes

μ = model parameters

γ = QTL locations

H = QTL model



The factorization

$$\Pr(y, m, q, \mu, \gamma) = \{\Pr(y \mid q, \mu)\ \Pr(\mu)\}\ \{\Pr(q \mid m, \gamma)\ \Pr(m)\ \Pr(\gamma)\}$$

$\Pr(y \mid q, \mu)\ \Pr(\mu)$ = genetic model part

$\Pr(q \mid m, \gamma)\ \Pr(m)\ \Pr(\gamma)$ = linkage part

The unobserved QTL genotypes play a central role.

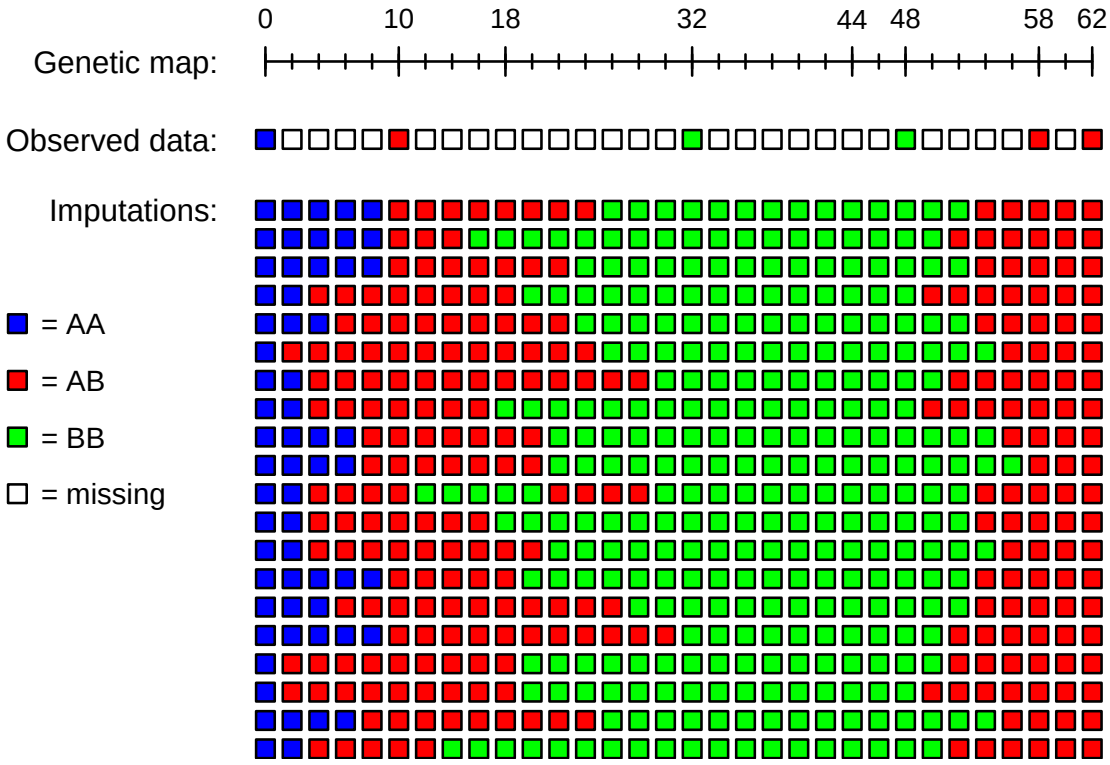
If the QTL genotypes were known, the problem reduces to

linear regression

The basic idea

- Simulate multiple realizations of the joint genotypes on a uniform grid, conditional on the observed multipoint marker data.
- Fit a QTL model with each realization, one at a time.
- Combine the realizations to get an estimate of the posterior probability of the QTL model.

Imputation illustration



Advantages

- Simple computation (just regression)
- Handle missing genotype data
- Covariates
- Any phenotype distribution
- Multi-dimensional genome scans
- Linked QTL; interacting QTL
- Modular algorithm
- No MCMC worries

Cautions

- Monte carlo error (number of imputations)
- Numerical integration error (density of pseudomarker grid)
- Model selection (as usual)
- Relatively large up-front cost for the imputations
  (biggest advantage in case of many phenotypes or many alternative models)

An example

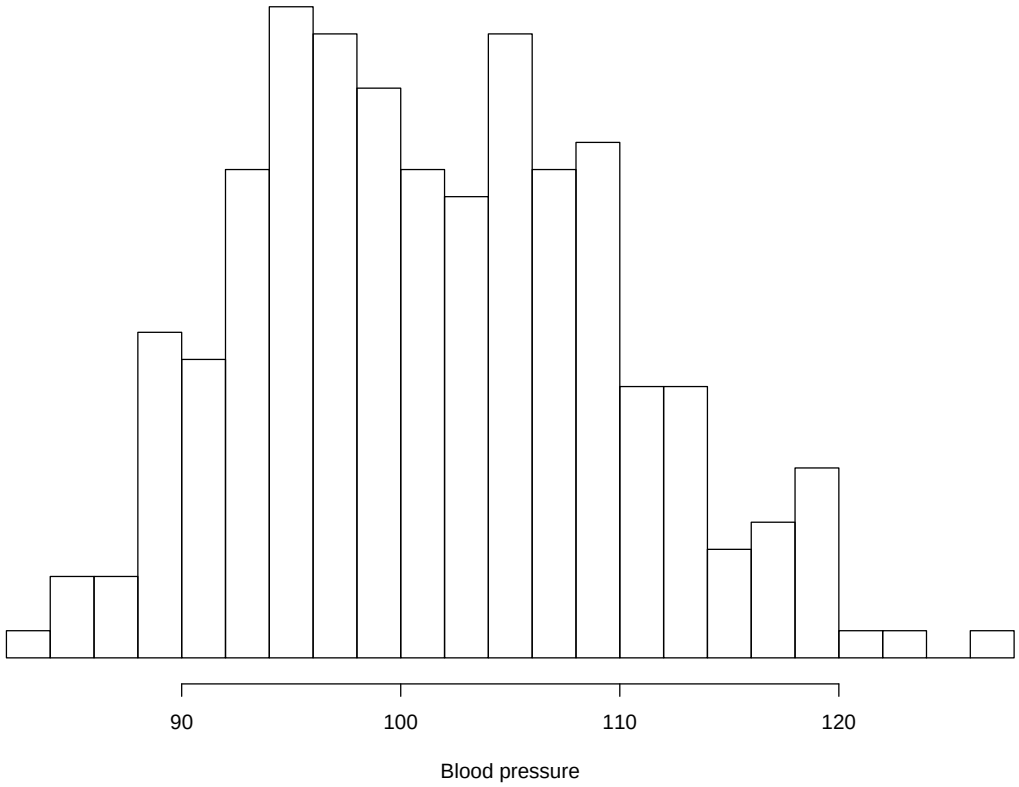
Sugiyama et al. (2001) Genomics 71:70–77

Salt-induced hypertension in the mouse.

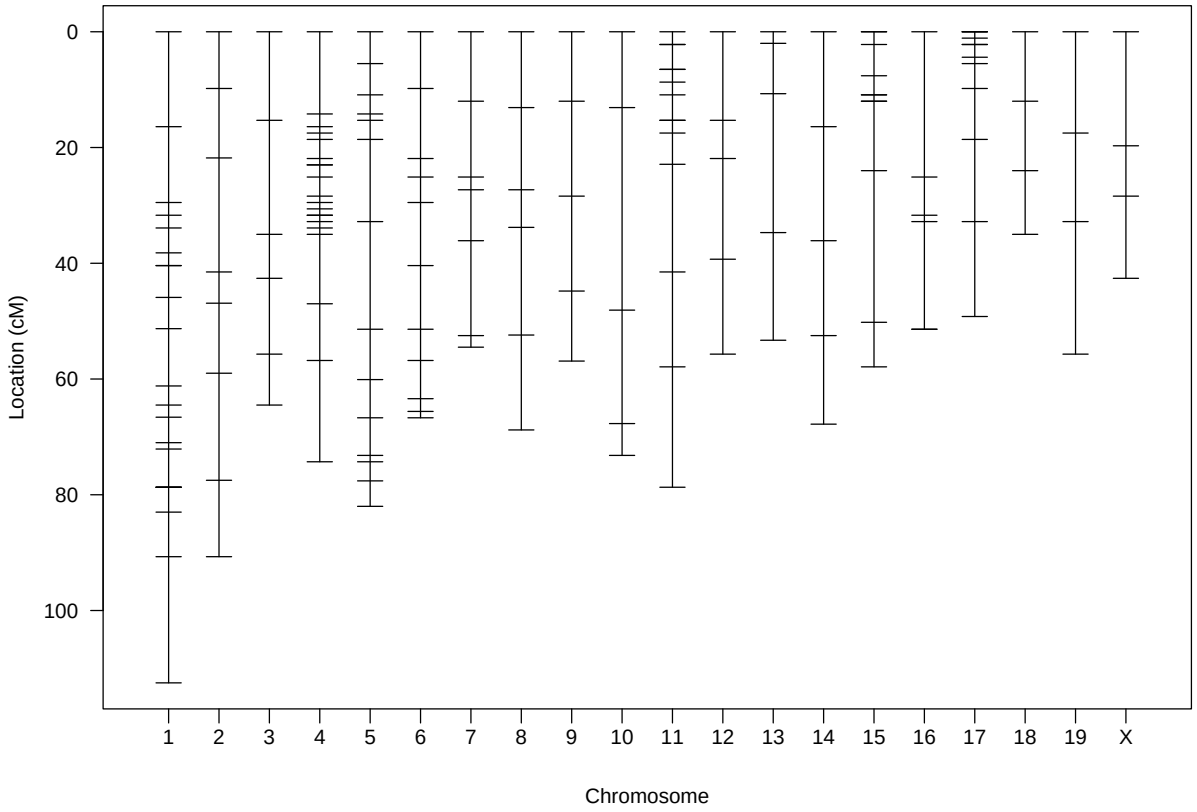
Backcross with 250 individuals.

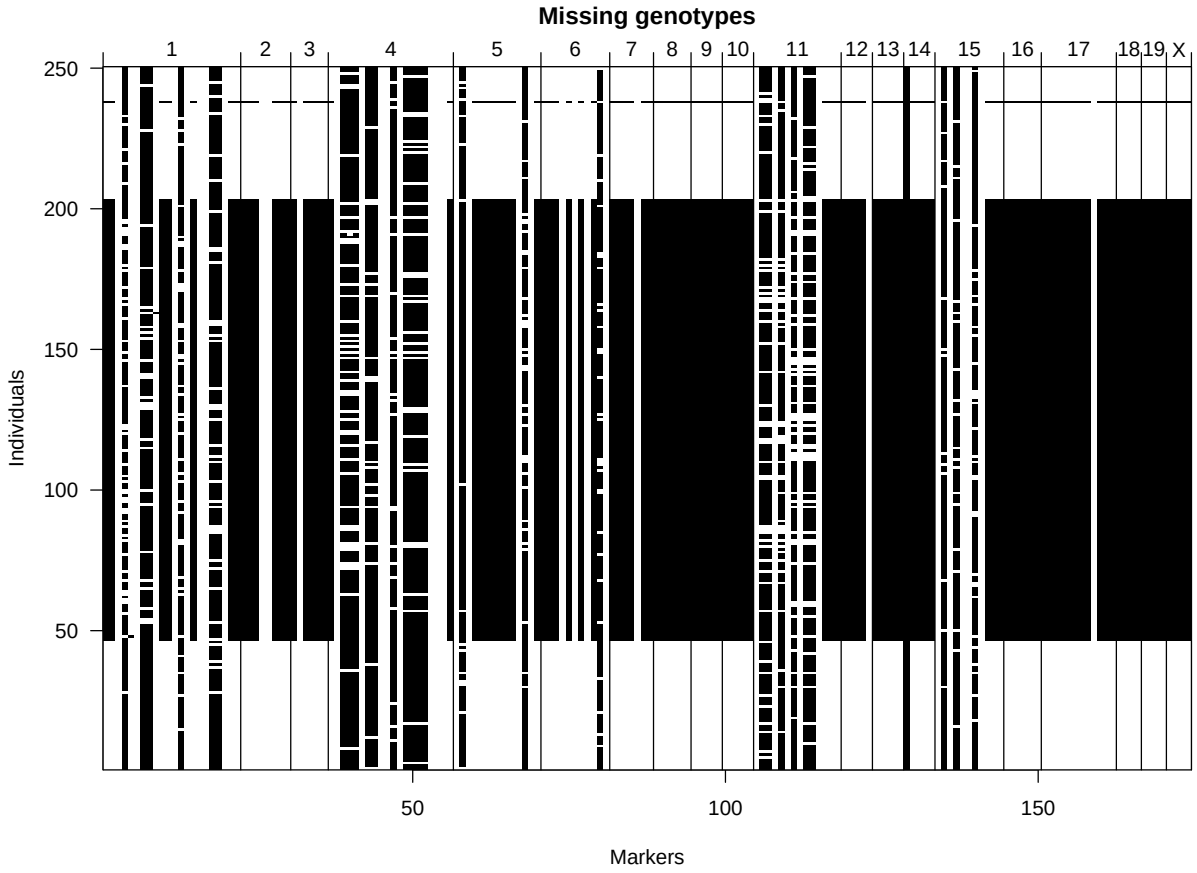
174 markers (for most, only genotyped the extremes).

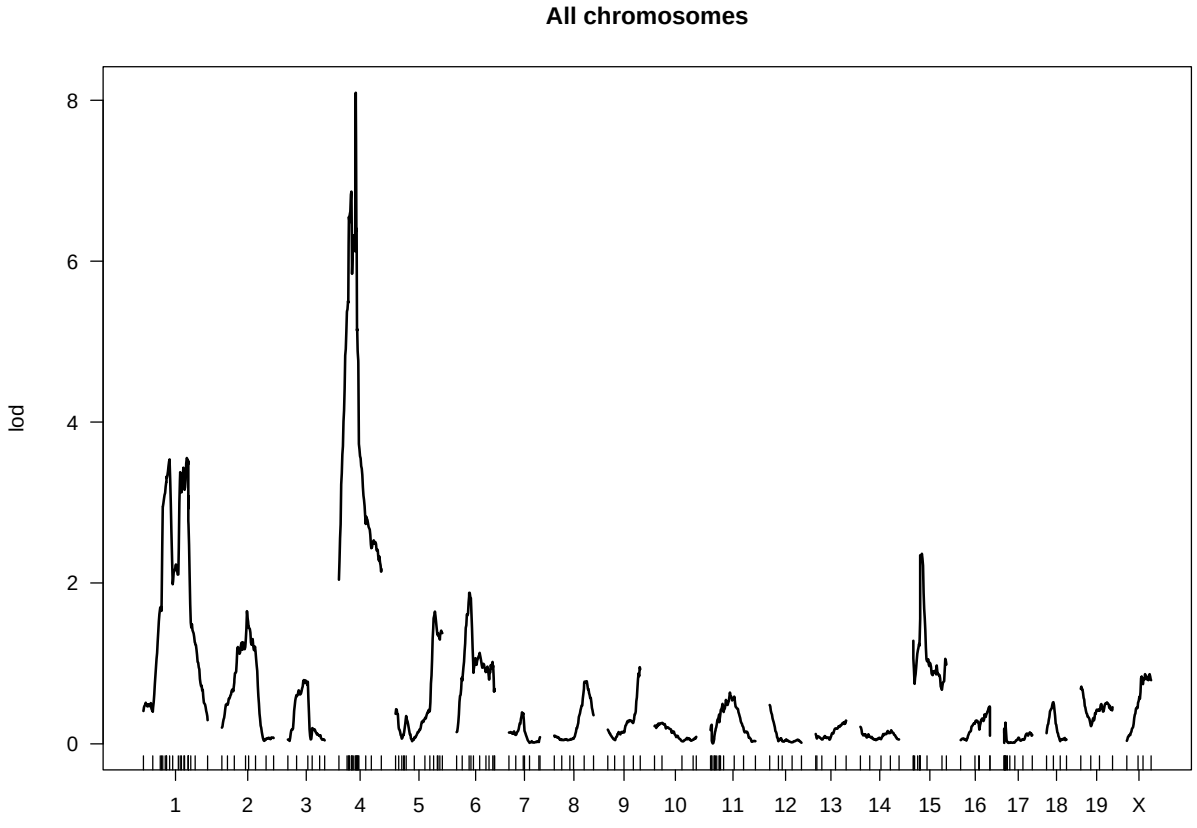
Phenotype distribution

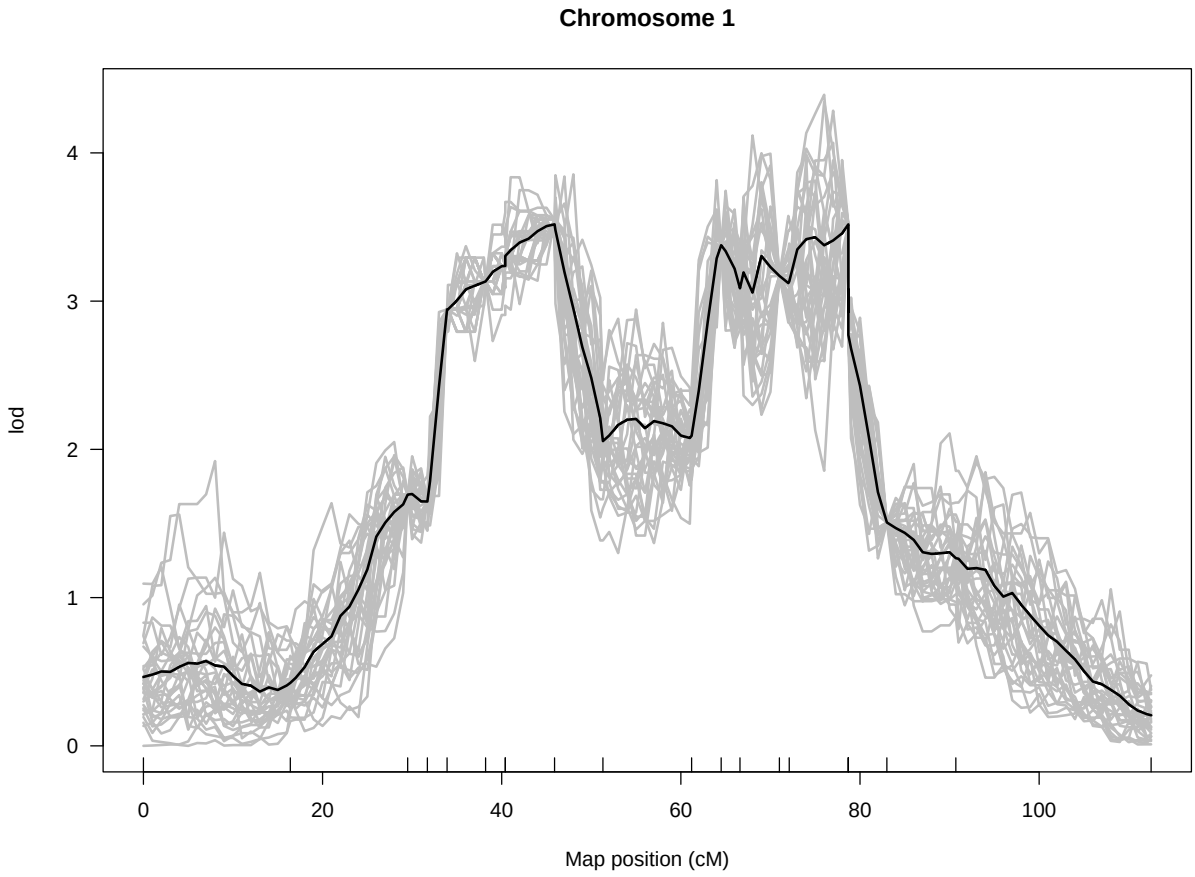


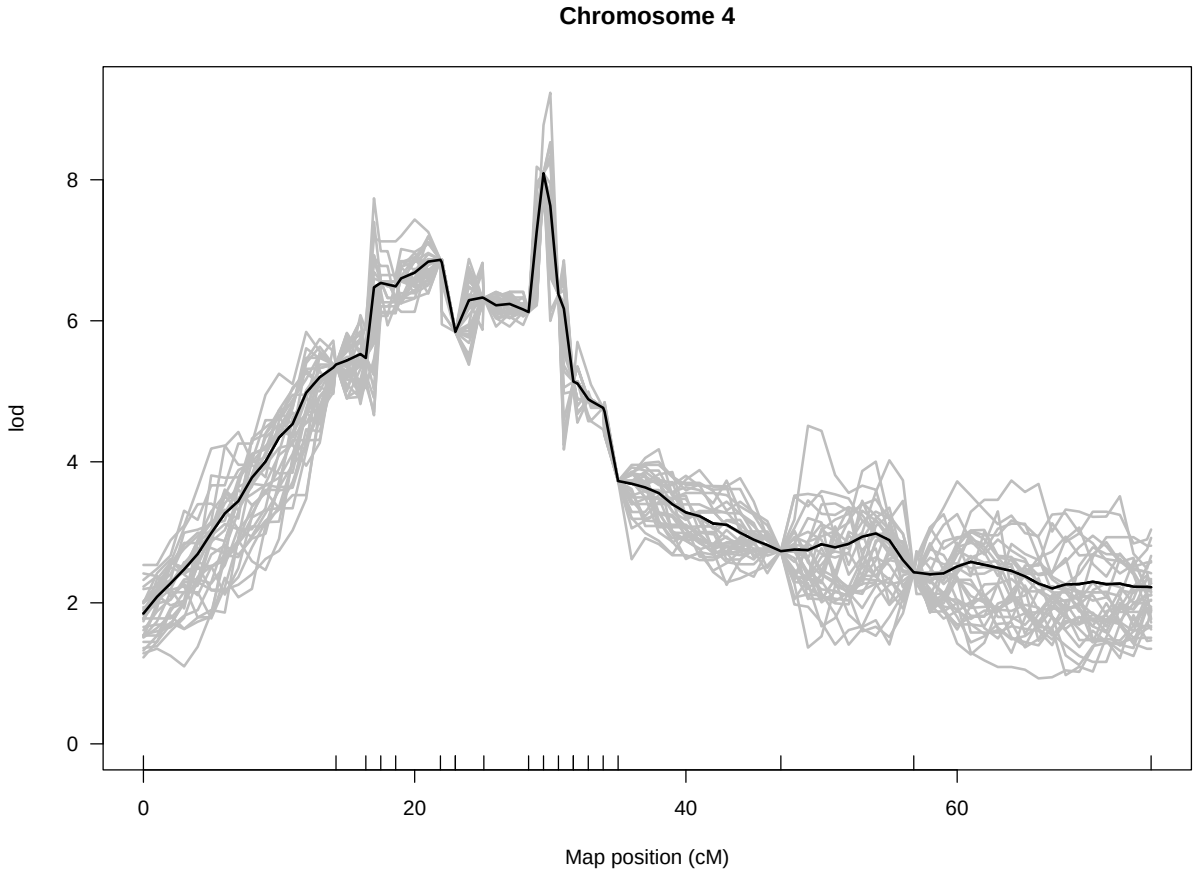
Genetic map

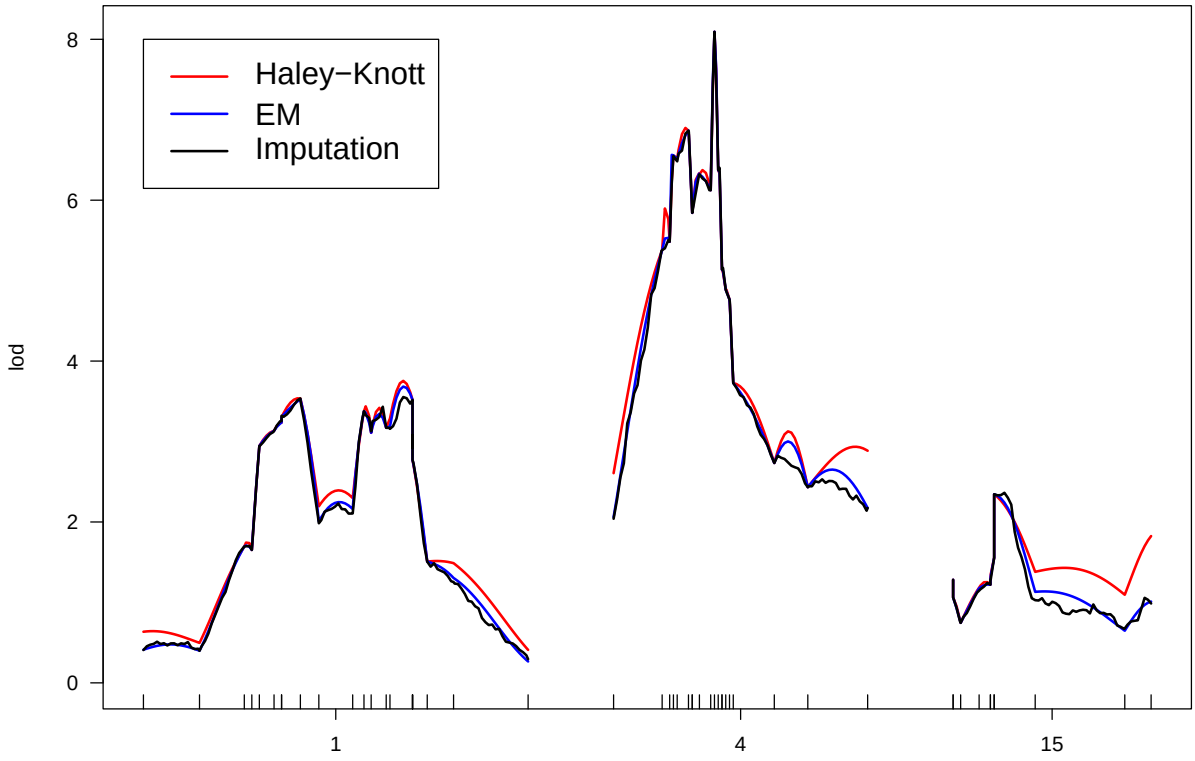



Missing genotypes
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 X
250
200
150
100
50
Individuals
50
100
150
Markers

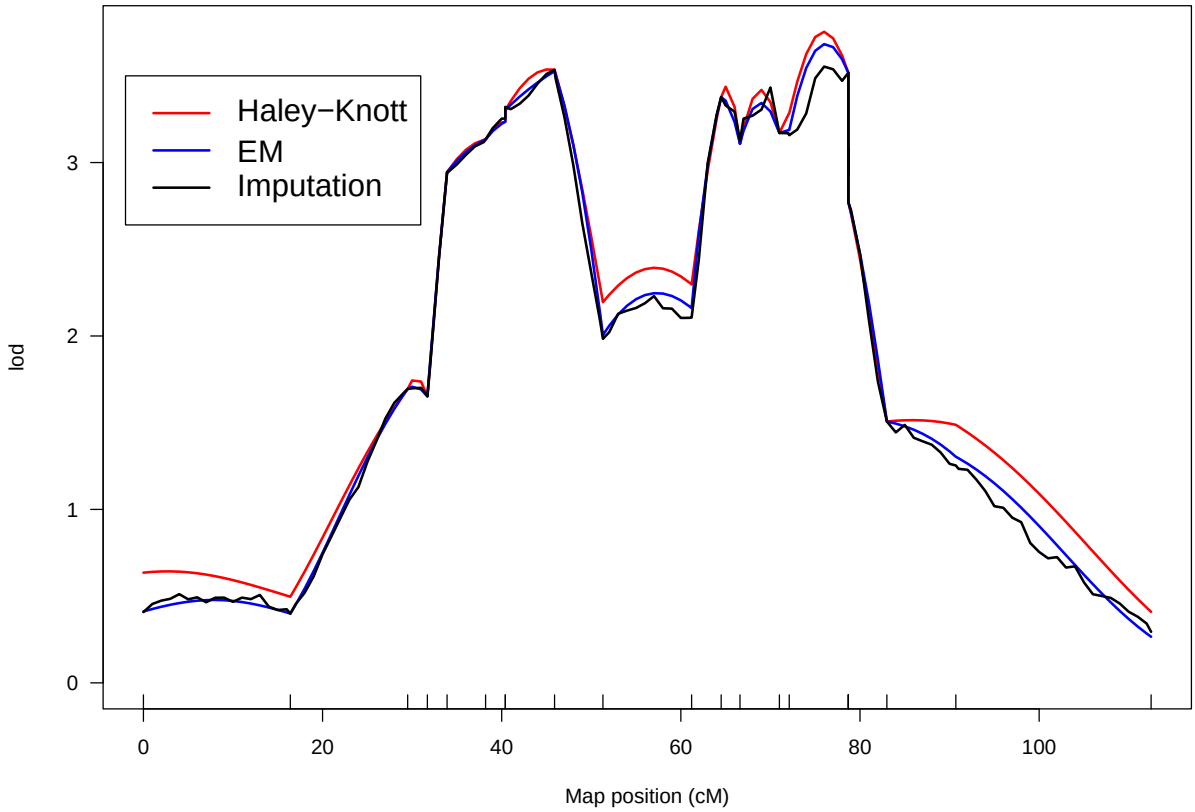

All chromosomes
8
6
4
2
0
lod
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 X

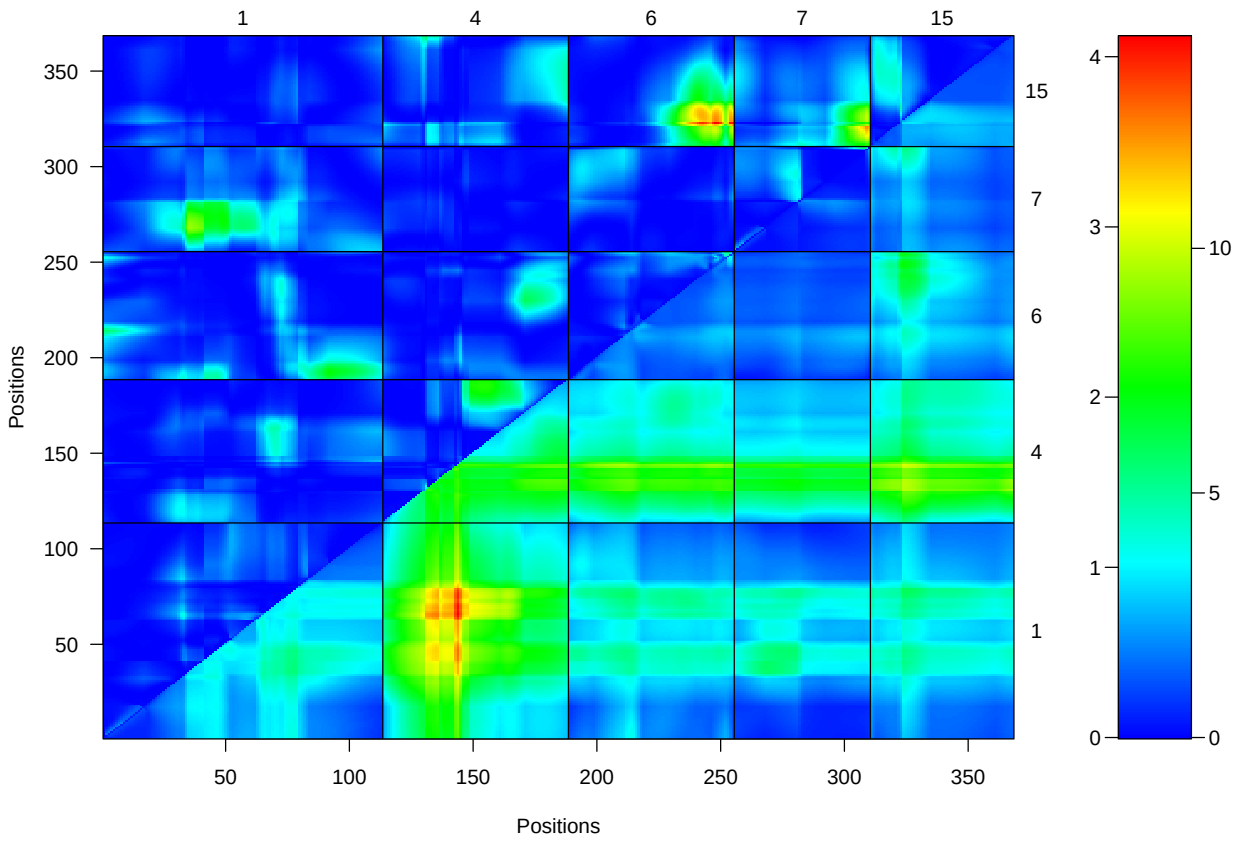

Chromosome 1
lod
0
1
2
3
4
0
20
40
60
80
100
Map position (cM)

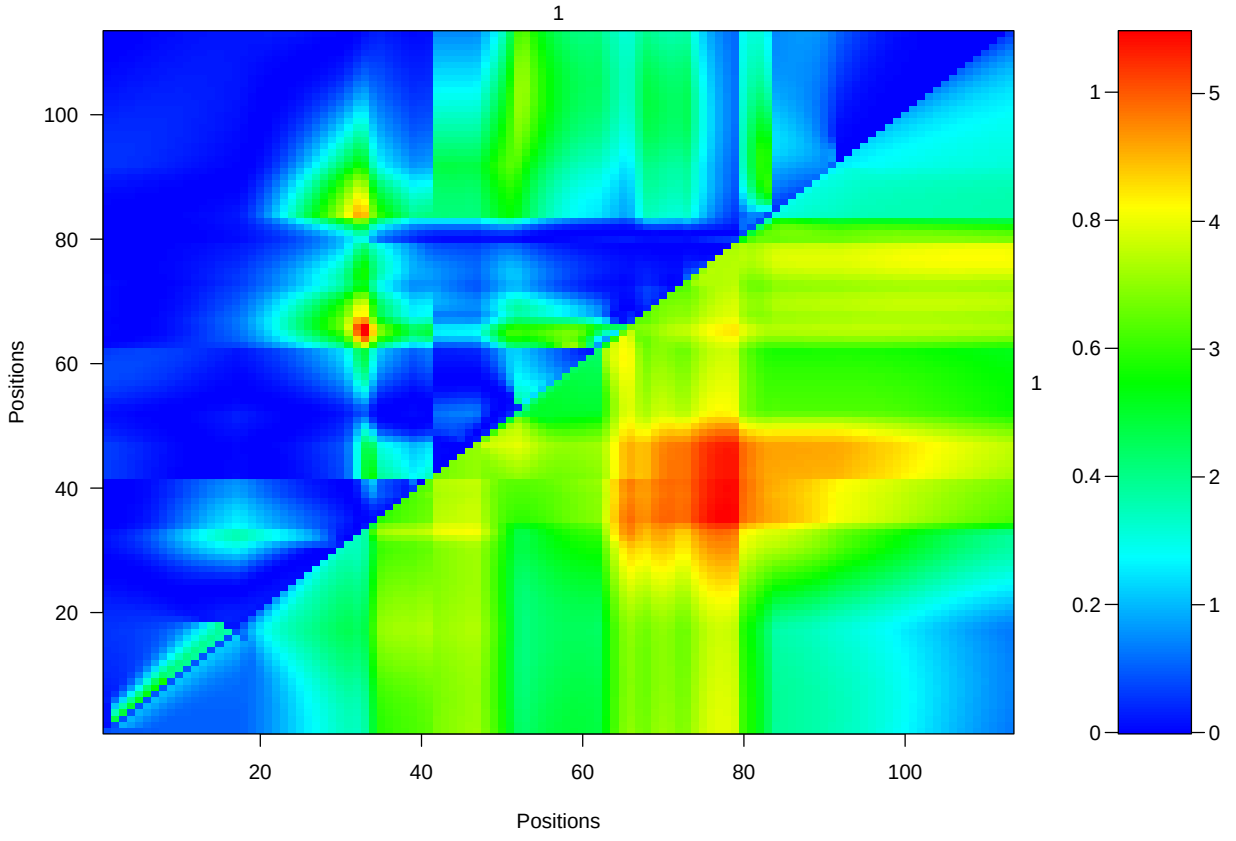

Chromosome 4
lod
0
2
4
6
8
0
20
40
60
Map position (cM)



Chromosome 1




1
4
6
7
15
350
300
250
200
150
100
50
Positions
50
100
150
200
250
300
350
Positions
15
7
6
4
1
4
3
2
1
0
10
5
0


1
100
80
60
40
20
Positions
20
40
60
80
100
Positions
1
1
0.8
0.6
0.4
0.2
0
5
4
3
2
1
0

Drop-one-term table

Term	df	LOD	% variance explained
c1@37	1	1.9	2.3
c1@80	1	3.1	3.8
c4@30	1	9.5	12.3
c6@60	2	5.7	7.1
c7@54	2	2.0	2.4
c15@18	3	7.6	9.6
c6@60 : c15@18	1	3.8	4.6
c7@54 : c15@18	1	1.7	2.1

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