Bayesian Model Selection for Quantitative Trait Loci with Markov chain Monte Carlo in Experimental Crosses

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outline

1. What is the goal of QTL study?
2. Bayesian priors & posteriors
3. Model search using MCMC
   • Gibbs sampler and Metropolis-Hastings
   • Reversible jump MCMC
   • Fully MCMC approach (loci indicators)
4. Model assessment
   • Bayes factors
   • model selection diagnostics
   • simulation and *Brassica napus* example
1. what is the goal of QTL study?

- uncover underlying biochemistry
  - identify how networks function, break down
  - find useful candidates for (medical) intervention
  - epistasis may play key role
  - statistical goal: maximize number of correctly identified QTL

- basic science/evolution
  - how is the genome organized?
  - identify units of natural selection
  - additive effects may be most important (Wright/Fisher debate)
  - statistical goal: maximize number of correctly identified QTL

- select “elite” individuals
  - predict phenotype (breeding value) using suite of characteristics (phenotypes) translated into a few QTL
  - statistical goal: minimize prediction error
advantages of multiple QTL approach

• improve statistical power, precision
  – increase number of QTL that can be detected
  – better estimates of loci and effects: less bias, smaller intervals

• improve inference of complex genetic architecture
  – infer number of QTL and their pattern across chromosomes
  – construct “good” estimates of effects
    • gene action (additive, dominance) and epistatic interactions
  – assess relative contributions of different QTL

• improve estimates of genotypic values
  – want less bias (more accurate) and smaller variance (more precise)
  – balance in mean squared error = $\text{MSE} = (\text{bias})^2 + \text{variance}$
    • always a compromise…
why worry about multiple QTL?

• many, many QTL may affect most any trait
  – how many QTL are detectable with these data?
    • limits to useful detection (Bernardo 2000)
    • depends on sample size, heritability, environmental variation
  – consider probability that a QTL is in the model
    • avoid sharp in/out dichotomy
    • major QTL usually selected, minor QTL sampled infrequently
• build $M = \text{model} = \text{genetic architecture into model}$
  – $M = \{\text{loci } 1, 2, \ldots, m, \text{ plus interactions } 12, 13, \ldots\}$
  – directly allow uncertainty in genetic architecture
  – model selection over number of QTL, genetic architecture
  – use Bayes factors and model averaging
    • to identify “better” models
Pareto diagram of QTL effects

major QTL on linkage map

- major QTL
- minor QTL
- polygenes

rank order of QTL

additive effect

1 2 3 4 5
interval mapping basics

• observed measurements
  – \( Y \) = phenotypic trait
  – \( X \) = markers & linkage map
    • \( i = \) individual index 1,…,\( n \)

• missing data
  – missing marker data
  – \( Q \) = QT genotypes
    • alleles QQ, Qq, or qq at locus

• unknown quantities
  – \( \lambda \) = QT locus (or loci)
  – \( \theta \) = phenotype model parameters
  – \( m \) = number of QTL

• \( \text{pr}(Q|X,\lambda,m) \) genotype model
  – grounded by linkage map, experimental cross
  – recombination yields multinomial for \( Q \) given \( X \)

• \( \text{pr}(Y|Q,\theta,m) \) phenotype model
  – distribution shape (assumed normal here)
  – unknown parameters \( \theta \) (could be non-parametric)

after Sen Churchill (2001)
2. Bayesian priors for QTL

- genomic region = locus $\lambda$
  - may be uniform over genome
  - $\text{pr}(\lambda \mid X) = 1 / \text{length of genome}$
  - or may be restricted based on prior studies

- missing genotypes $Q$
  - depends on marker map and locus for QTL
  - $\text{pr}( Q \mid X, \lambda )$
  - genotype (recombination) model is formally a prior

- genotypic means and variance $\theta = ( G_q, \sigma^2 )$
  - $\text{pr}( \theta ) = \text{pr}( G_q \mid \sigma^2 ) \text{pr}(\sigma^2 )$
  - use conjugate priors for normal phenotype
    - $\text{pr}( G_q \mid \sigma^2 ) = \text{normal}$
    - $\text{pr}(\sigma^2 ) = \text{inverse chi-square}$
Bayesian model posterior

• augment data \((Y, X)\) with unknowns \(Q\)
• study unknowns \((\theta, \lambda, Q)\) given data \((Y, X)\)
  – properties of posterior \(\text{pr}(\theta, \lambda, Q \mid Y, X)\)
• sample from posterior in some clever way
  – multiple imputation or MCMC

\[
\text{pr}(\theta, \lambda, Q \mid Y, X) = \frac{\text{pr}(Y \mid Q, \theta)\text{pr}(Q \mid X, \lambda)\text{pr}(\theta)\text{pr}(\lambda \mid X)}{\text{pr}(Y \mid X)}
\]

\[
\text{pr}(\theta, \lambda \mid Y, X) = \sum_Q \text{pr}(\theta, \lambda, Q \mid Y, X)
\]
genotype prior model: \( \text{pr}(Q|X, \lambda) \)

- locus \( \lambda \) is distance along linkage map
  - map assumed known from earlier study
  - \( \lambda \) identifies flanking marker interval
- use flanking markers to approximate prior on \( Q \)
  - slight inaccuracy by ignoring multipoint map function
  - use next flanking markers if missing data

\[
\text{pr}(Q|X, \lambda) = \text{pr(geno | map, locus)} \approx \text{pr(geno | flanking markers, locus)}
\]
how does phenotype $Y$ improve posterior for genotype $Q$?

what are probabilities for genotype $Q$ between markers?

recombinants AA:AB all 1:1 if ignore $Y$ and if we use $Y$?
posterior on QTL genotypes

- full conditional of $Q$ given data, parameters
  - proportional to prior $\text{pr}(Q \mid X_i, \lambda)$
    - weight toward $Q$ that agrees with flanking markers
  - proportional to likelihood $\text{pr}(Y_i \mid Q, \theta)$
    - weight toward $Q$ so that group mean $G_Q \approx Y_i$

- phenotype and flanking markers may conflict
  - posterior recombination balances these two weights

$$
\text{pr}(Q \mid Y_i, X_i, \theta, \lambda) = \frac{\text{pr}(Q \mid X_i, \lambda)\text{pr}(Y_i \mid Q, \theta)}{\text{pr}(Y_i \mid X_i, \theta, \lambda)}
$$
idealized phenotype model

- $\text{trait} = \text{mean} + \text{additive} + \text{error}$
- $\text{trait} = \text{effect}_\text{of}_\text{geno} + \text{error}$
- $\text{pr}(\text{trait} | \text{geno}, \text{effects})$

$Y = G_Q + E$

$\text{pr}(Y | Q, \theta) = \text{normal}(G_Q, \sigma^2)$
priors & posteriors: normal data

small prior variance

large prior variance

\[ y = \text{phenotype values} \]
priors & posteriors: normal data

model

\[ Y_i = \mu + E_i \]

environment

\[ E \sim N(0, \sigma^2), \quad \sigma^2 \text{ known} \]

likelihood

\[ Y \sim N(\mu, \sigma^2) \]

prior

\[ \mu \sim N(\mu_0, \kappa\sigma^2), \quad \kappa \text{ known} \]

posterior:

single individual

\[ \mu \sim N(\mu_0 + B_1(Y_1 - \mu_0), B_1\sigma^2) \]

sample of n individuals

\[ \mu \sim N\left(B_n \bar{Y}_n + (1 - B_n)\mu_0, B_n\frac{\sigma^2}{n}\right) \]

with \( \bar{Y}_n = \text{sum} \frac{Y_i}{n} \)

fudge factor

(shrinks to 1)

\[ B_n = \frac{\kappa n}{\kappa n + 1} \rightarrow 1 \]
prior & posteriors: genotypic means $G_Q$

$$y = \text{phenotype values}$$

$n_{\text{small prior}}$

$n_{\text{large}}$

qq  Qq  QQ

6  8  10  12  14  16
prior & posteriors: genotypic means $G_Q$

posterior centered on sample genotypic mean but shrunken slightly toward overall mean

$\kappa$ is related to heritability

prior:  
$$G_Q \sim N(\bar{Y}_*, \kappa\sigma^2)$$

posterior:  
$$G_Q \sim N\left(B_Q \bar{Y}_Q + (1 - B_Q)\bar{Y}_*, B_Q \frac{\sigma^2}{n_Q}\right)$$

$$n_Q = \text{count}\{Q_i = Q\}, \bar{Y}_Q = \sum_{\{i:Q_i=Q\}} \frac{Y_i}{n_Q}$$

fudge factor:  
$$B_Q = \frac{\kappa n_Q}{\kappa n_Q + 1} \to 1$$
What if variance $\sigma^2$ is unknown?

- sample variance is proportional to chi-square
  - $ns^2 / \sigma^2 \sim \chi^2 (n)$
  - likelihood of sample variance $s^2$ given $n, \sigma^2$
- conjugate prior is inverse chi-square
  - $\nu \tau^2 / \sigma^2 \sim \chi^2 (\nu)$
  - prior of population variance $\sigma^2$ given $\nu, \tau^2$
- posterior is weighted average of likelihood and prior
  - $(\nu \tau^2 + ns^2) / \sigma^2 \sim \chi^2 (\nu+n)$
  - posterior of population variance $\sigma^2$ given $n, s^2, \nu, \tau^2$
- empirical choice of hyper-parameters
  - $\tau^2 = s^2/3$, $\nu=6$
  - $E(\sigma^2 | \nu, \tau^2) = s^2/2$, $\text{Var}(\sigma^2 | \nu, \tau^2) = s^4/4$
multiple QTL phenotype model

- phenotype affected by genotype & environment
  \[ \text{pr}(Y|Q=q, \theta) \sim N(G_q, \sigma^2) \]
  \[ Y = G_Q + \text{environment} \]

- partition genotypic mean into QTL effects
  \[ G_q = \mu + \beta_{1q} + \ldots + \beta_{mq} + \beta_{12q} + \ldots \]

- general form of QTL effects for model \( M \)
  \[ G_q = \mu + \sum_{j \in M} \beta_{jq} \]
  \[ |M| = \text{number of terms in model } M < 2^m \]

- can partition prior and posterior into effects \( \beta_{jq} \)
  (details omitted)
prior & posterior on number of QTL

- what prior on number of QTL?
  - uniform over some range
  - Poisson with prior mean
  - geometric with prior mean

- prior influences posterior
  - good: reflects prior belief
    - push data in discovery process
  - bad: skeptic revolts!
    - “answer” depends on “guess”
3. QTL Model Search using MCMC

• construct Markov chain around posterior
  – want posterior as stable distribution of Markov chain
  – in practice, the chain tends toward stable distribution
    • initial values may have low posterior probability
    • burn-in period to get chain mixing well

• update $m$-QTL model components from full conditionals
  – update locus $\lambda$ given $Q,X$ (using Metropolis-Hastings step)
  – update genotypes $Q$ given $\lambda,\theta,Y,X$ (using Gibbs sampler)
  – update effects $\theta$ given $Q,Y$ (using Gibbs sampler)

\[(\lambda,Q,\theta,m) \sim \text{pr}(\lambda,Q,\theta,m \mid Y,X)\]
\[(\lambda,Q,\theta,m)_1 \rightarrow (\lambda,Q,\theta,m)_2 \rightarrow \cdots \rightarrow (\lambda,Q,\theta,m)_N\]
Gibbs sampler idea

- two correlated normals (genotypic means in BC)
  - could draw samples from both together
  - but easier to sample one at a time

- Gibbs sampler:
  - sample each from its full conditional
  - pick order of sampling at random
  - repeat $N$ times

\[
G_{QQ} \sim N(0,1); \quad G_{Qq} \sim N(0,1) \text{ but } cor(G_{QQ}, G_{Qq}) = \rho
\]

\[
G_{QQ} \text{ given } G_{Qq} \sim N\left(\rho G_{Qq}, 1 - \rho^2\right)
\]

\[
G_{Qq} \text{ given } G_{QQ} \sim N\left(\rho G_{QQ}, 1 - \rho^2\right)
\]
Gibbs sampler samples: $\rho = 0.6$

$N = 50$ samples

$N = 200$ samples
How to sample a locus $\lambda$?

- cannot easily sample from locus full conditional
  \[ \text{pr}(\lambda | Y, X, \theta, Q) = \text{pr}(\lambda | X, Q) = \text{pr}(\lambda) \text{pr}(Q | X, \lambda) / \text{constant} \]
- to explicitly determine constant, must average
  - over all possible genotypes
  - over entire map
- Gibbs sampler will not work in general
  - but can use method based on ratios of probabilities
  - Metropolis-Hastings is extension of Gibbs sampler
Metropolis-Hastings idea

- want to study distribution $f(\theta)$
- take Monte Carlo samples
  - unless too complicated
- Metropolis-Hastings samples:
  - current sample value $\theta$
  - propose new value $\theta^*$
    - from some distribution $g(\theta,\theta^*)$
    - Gibbs sampler: $g(\theta,\theta^*) = f(\theta^*)$
  - accept new value with prob $A$
- Gibbs sampler: $A = 1$

\[
A = \min \left( 1, \frac{f(\theta^*)g(\theta^*, \theta)}{f(\theta)g(\theta, \theta^*)} \right)
\]
MCMC realization

added twist: occasionally propose from whole domain
Metropolis-Hastings samples

\[ N = 200 \text{ samples} \]

- narrow \( g \)
- wide \( g \)

\[ N = 1000 \text{ samples} \]

- narrow \( g \)
- wide \( g \)
sampling multiple loci

0 $\lambda_1$ $\lambda_{m+1}$ $\lambda_2$ $\ldots$ $\lambda_m$ L

action steps: draw one of three choices

- **update** $m$-QTL model with probability $1-b(m+1)-d(m)$
  - update current model using full conditionals
  - sample $m$ QTL loci, effects, and genotypes

- **add a locus with probability $b(m+1)$**
  - propose a new locus along genome
  - innovate new genotypes at locus and phenotype effect
  - decide whether to accept the “birth” of new locus

- **drop a locus with probability $d(m)$**
  - propose dropping one of existing loci
  - decide whether to accept the “death” of locus
reversible jump MCMC

- consider known genotypes $Q$ at 2 known loci $\lambda$
  - models with 1 or 2 QTL
- jump between 1-QTL and 2-QTL models
  - adjust parameters when model changes
  - $\alpha$ and $\alpha_1$ differ due to collinearity of QTL genotypes

$$m = 1 : Y = \mu + \beta_{1Q} + e$$
$$m = 2 : Y = \mu + \beta_{1Q} + \beta_{2Q} + e$$
geometry of reversible jump

Move Between Models

Reversible Jump Sequence
geometry allowing $Q$ and $\lambda$ to change

a short sequence

first 1000 with $m<3$
Gibbs sampler with loci indicators

- partition genome into intervals
  - at most one QTL per interval
  - interval = marker interval or large chromosome region
- use loci indicators in each interval
  - $\delta = 1$ if QTL in interval
  - $\delta = 0$ if no QTL
- Gibbs sampler on loci indicators
  - still need to adjust genetic effects for collinearity of $Q$
  - see work of Nengjun Yi (and earlier work of Ina Hoeschele)

$$Y = \mu + \delta_1 \alpha_1 (Q_1 - \overline{Q}_1) + \delta_2 \alpha_2 (Q_1 - \overline{Q}_1) + e$$
epistatic interactions

• model space issues
  – 2-QTL interactions only?
  – Fisher-Cockerham partition vs. tree-structured?
  – general interactions among multiple QTL

• model search issues
  – epistasis between significant QTL
    • check all possible pairs when QTL included?
    • allow higher order epistasis?
  – epistasis with non-significant QTL
    • whole genome paired with each significant QTL?
    • pairs of non-significant QTL?

limits of epistatic inference

• power to detect effects
  – epistatic model size grows exponentially
    • $|M| = 3^m$ for general interactions
  – power depends on ratio of $n$ to model size
    • want $n / |M|$ to be fairly large (say > 5)
    • $n = 100, m = 3, n / |M| \approx 4$

• empty cells mess up adjusted (Type 3) tests
  – missing $q_1 Q_2 / q_1 Q_2$ or $q_1 Q_2 q_3 / q_1 Q_2 q_3$ genotype
  – null hypotheses not what you would expect
  – can confound main effects and interactions
  – can bias AA, AD, DA, DD partition
4. Model Assessment

- balance model fit against model complexity
  - model fit: smaller model miss key features bigger model fits better
  - prediction: may be biased no bias
  - interpretation: easier more complicated
  - parameters: low variance high variance

• information criteria: penalize $L$ by model size $|M|$
  - compare IC = $-2 \log L(M|Y) + \text{penalty}(M)$

• Bayes factors: balance posterior by prior choice
  - compare $\text{pr}(\text{data} \ Y | \text{model} \ M)$
QTL Bayes factors

- BF = posterior odds / prior odds
- BF equivalent to BIC
  - simple comparison: 1 vs 2 QTL
  - same as LOD test
  - general comparison of models
  - want Bayes factor >> 1
- \( m \) = number of QTL
  - indexes model complexity
  - genetic architecture also important

\[
BF_{m,m+1} = \frac{\text{pr}(m|\text{data})/\text{pr}(m)}{\text{pr}(m+1|\text{data})/\text{pr}(m+1)}
\]
Bayes factors to assess models

- Bayes factor: which model best supports the data?
  - ratio of posterior odds to prior odds
  - ratio of model likelihoods

- equivalent to $LR$ statistic when
  - comparing two nested models
  - simple hypotheses (e.g. 1 vs 2 QTL)

- Bayes Information Criteria (BIC)
  - Schwartz introduced for model selection in general settings
  - penalty to balance model size ($p = \text{number of parameters}$)

\[
B_{12} = \frac{\text{pr}(\text{model}_1 \mid Y) / \text{pr}(\text{model}_2 \mid Y)}{\text{pr}(\text{model}_1) / \text{pr}(\text{model}_2)} = \frac{\text{pr}(Y \mid \text{model}_1)}{\text{pr}(Y \mid \text{model}_2)}
\]

\[-2 \log(B_{12}) = -2 \log(LR) - (p_2 - p_1) \log(n)\]
BF sensitivity to fixed prior for effects

\[
\beta_{jq} \sim \mathcal{N}\left(0, \frac{h^2 s^2}{|M|}\right), \quad h^2 \text{ fixed}
\]
BF insensitivity to random effects prior

\[ \beta_{jq} \sim N \left( 0, \frac{h^2 s^2}{|M|} \right), \quad \frac{h^2}{2} \sim \text{Beta}(a, b) \]
simulations and data studies

• simulated F2 intercross, 8 QTL
  – (Stephens, Fisch 1998)
  – $n=200$, heritability = 50%
  – detected 3 QTL

• increase to detect all 8
  – $n=500$, heritability to 97%

<table>
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<th>QTL</th>
<th>chr</th>
<th>loci</th>
<th>effect</th>
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<td>-3</td>
</tr>
<tr>
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<td>1</td>
<td>50</td>
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<td>+2</td>
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<td>107</td>
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<td>195</td>
<td>+2</td>
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loci pattern across genome

- notice which chromosomes have persistent loci
- best pattern found 42% of the time

<table>
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<tr>
<th>Chromosome</th>
<th>Count of 8000</th>
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<td>9</td>
<td>2</td>
</tr>
<tr>
<td>9</td>
<td>2</td>
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</table>
B. napus 8-week vernalization whole genome study

• 108 plants from double haploid
  – similar genetics to backcross: follow 1 gamete
  – parents are Major (biennial) and Stellar (annual)

• 300 markers across genome
  – 19 chromosomes
  – average 6cM between markers
    • median 3.8cM, max 34cM
  – 83% markers genotyped

• phenotype is days to flowering
  – after 8 weeks of vernalization (cooling)
  – Stellar parent requires vernalization to flower

• available in R/bim package
• Ferreira et al. (1994); Kole et al. (2001); Schranz et al. (2002)
Markov chain Monte Carlo sequence

burnin (sets up chain)
mcmc sequence

number of QTL
environmental variance
$h^2 = \text{heritability}$
(genetic/total variance)
LOD = likelihood
MCMC sampled loci

subset of chromosomes N2, N3, N16

points jittered for view
blue lines at markers

note concentration on chromosome N2

includes all models
Bayesian model assessment

<table>
<thead>
<tr>
<th># QTL</th>
<th>pattern</th>
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<tr>
<td>4-5</td>
<td>N2(2-3), N3, N16</td>
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</table>

<table>
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<th>posterior</th>
<th>Bayes factor</th>
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<td>$e^{-0.1}$</td>
<td>1 e+01</td>
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<tr>
<td>$e^{-0.2}$</td>
<td>1 e+01</td>
</tr>
<tr>
<td>$e^{-0.3}$</td>
<td>1 e+01</td>
</tr>
</tbody>
</table>

Evidence suggests 4-5 QTL, N2(2-3), N3, N16.

**Note:** error bars on Bayes factor.
Bayesian estimates of loci & effects
model averaging: at least 4 QTL

histogram of loci
blue line is density
red lines at estimates

estimate additive effects
(red circles)
grey points sampled from posterior
blue line is cubic spline
dashed line for 2 SD
Bayesian model diagnostics

pattern: N2(2),N3,N16
col 1: density
col 2: boxplots by $m$

environmental variance
$\sigma^2 = .008$, $\sigma = .09$

heritability
$h^2 = 52\%$

LOD = 16
(highly significant)

but note change with $m$
Bayesian software for QTLs

- R/bim (Satagopan Yandell 1996; Gaffney 2001)
  - www.stat.wisc.edu/~yandell/qtl/software/Bmapqtl
  - www.r-project.org contributed package
  - version available within WinQTLCart (statgen.ncsu.edu/qtlcart)
- Bayesian IM with epistasis (Nengjun Yi, U AB)
  - separate C++ software (papers with Xu)
  - plans in progress to incorporate into R/bim
- R/qtl (Broman et al. 2003)
  - biosun01.biostat.jhsph.edu/~kbroman/software
  - www.r-project.org contributed package
- Pseudomarker (Sen Churchill 2002)
  - www.jax.org/staff/churchill/labsite/software
- Bayesian QTL / Multimapper
  - Sillanpää Arjas (1998)
  - www.rni.helsinki.fi/~mjs
- Stephens & Fisch (email)
R/bim: our software

• www.stat.wisc.edu/~yandell/qtl/software/Bmapqtl
  – R contributed library (www.r-project.org)
    • library(bim) is cross-compatible with library(qtl)
  – Bayesian module within WinQTLCart
    • WinQTLCart output can be processed using R library

• Software history
  – initially designed by JM Satagopan (1996)
  – major revision and extension by PJ Gaffney (2001)
    • whole genome
    • multivariate update of effects; long range position updates
    • substantial improvements in speed, efficiency
    • pre-burnin: initial prior number of QTL very large
  – upgrade (H Wu, PJ Gaffney, CF Jin, BS Yandell 2003)
  – epistasis in progress (H Wu, BS Yandell, N Yi 2004)
many thanks

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