Efficient and Robust Model Selection for Quantitative Trait Loci Analysis in Inbred Lines

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Goals

- model selection with one QTL
  - review interval mapping basics
  - extensions of phenotype model
    - how to map non-normal data?
  - brief digression to multiple crosses
  - Bayesian interval mapping
    - how to sample from the posterior?
- model selection over multiple QTL
  - how many QTL are supported by data?
  - how to sample complicated model space?

Main Topics

away from normality

- fewer assumptions
  - semi-parametric
  - non-parametric
- extended phenotypes
- check robustness
- multiple crosses

how many QTL?

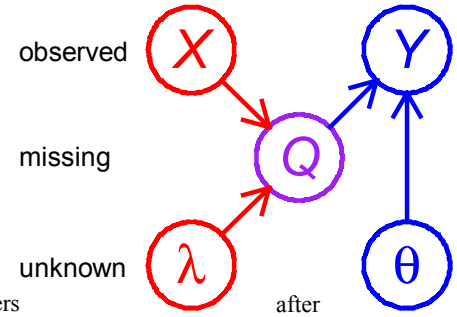
- inferring the number
- sampling all QT loci
- Bayesian analysis
- MCMC methodology
- estimating heritability

Overview

- I: IM basics (review)
- II: Beyond normal data
- III: Bayesian idea
  - Bayes theorem
  - posterior & likelihood
- IV: MCMC samples
  - Monte Carlo idea
  - study posterior
- V: Multiple QTL
- VI: How many QTL?
  - Reversible Jump
  - analog to regression
- VII: RJ-MCMC details
- VII: Model assessment
- IX: References
  - Software
  - Articles
- X: Multiple crosses

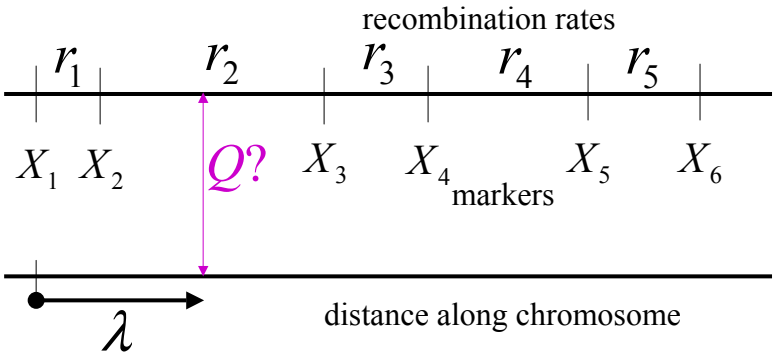
Part I: Interval Mapping Basics

- 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
  - λ = QT locus (or loci)
  - θ = phenotype model parameters
- pr($Q|X,\lambda$) recombination model
  - grounded by linkage map, experimental cross
  - recombination yields multinomial for Q given X
- pr($Y|Q,\theta$) phenotype model
  - distribution shape (could be assumed normal)
  - unknown parameters θ (could be non-parametric)



after Sen Churchill (2001)

recombination model components

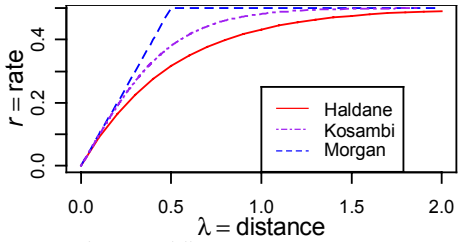


Recombination and Distance

- assume map and marker distances are known
- useful approximation for QTL linkage
  - Haldane map function: no crossover interference
  - independence implies crossover events are Poisson
- all computations consistent in approximation
  - rely on given map with known marker locations
  - 1-to-1 relation of distance to recombination
  - all map functions are approximate anyway

$$r = \tfrac{1}{2}\left(1 - e^{-2\lambda}\right)$$

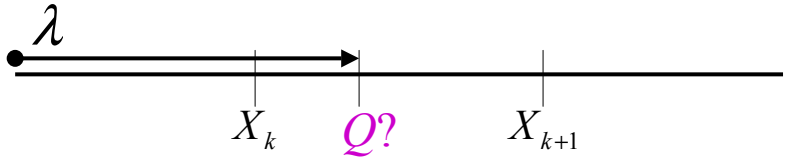
$$\lambda = -\tfrac{1}{2}\log(1-2r)$$



recombination model $\text{pr}(Q|X,\lambda)$

- locus λ is distance along linkage map
  - identifies flanking marker region
- flanking markers provide good approximation
  - map assumed known from earlier study
  - inaccuracy slight using only flanking markers
    - extend to next flanking markers if missing data
  - could consider more complicated relationship
    - but little change in results

$$\text{pr}(Q|X,\lambda) = \text{pr}(\text{geno} \mid \text{map, locus}) \approx \text{pr}(\text{geno} \mid \text{flanking markers, locus})$$



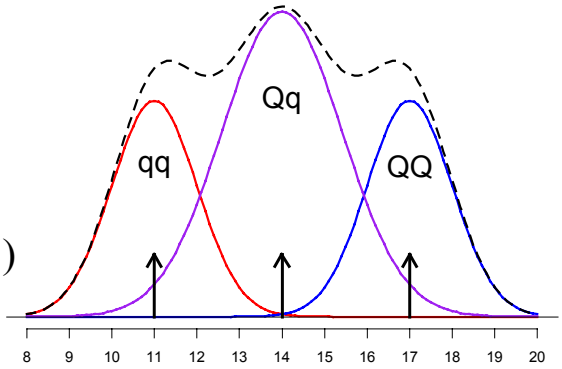
idealized phenotype model

- trait = mean + additive + error
- trait = effect_of_geno + error
- pr(trait | geno, effects)

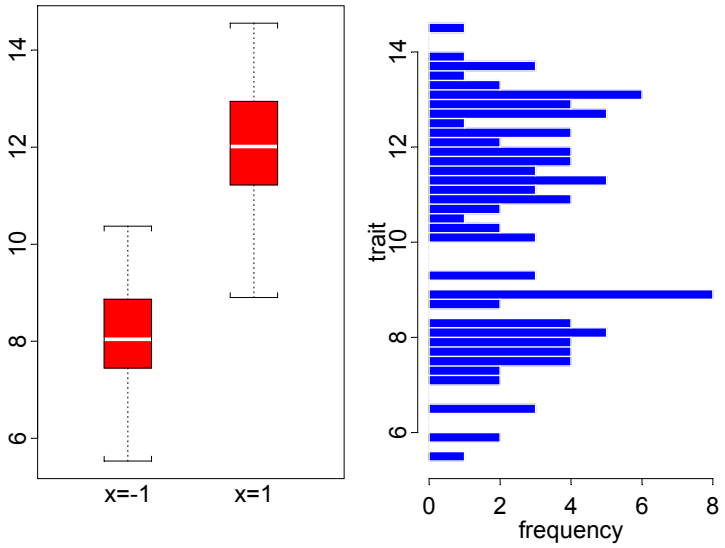
$$Y = G_Q + E$$

$$\text{pr}(Y \mid Q, \theta) =$$

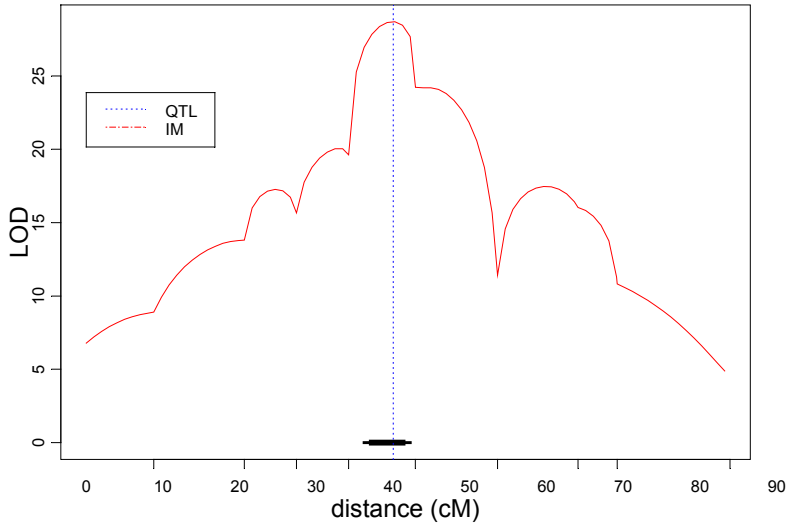
$$\text{normal}(G_Q, \sigma^2)$$



Simulated Data with 1 QTL



Profile LOD for 1 QTL



Interval Mapping Likelihood

- likelihood: basis for scanning the genome
  - product over $i = 1,\ldots,n$ individuals

  $L(\theta,\lambda|Y) = \text{product}_i \text{ pr}(Y_i|X_i,\lambda)$

  $= \text{product}_i \text{ sum}_Q \text{ pr}(Q|X_i,\lambda) \text{ pr}(Y_i|Q,\theta)$
  - complicated procedure to get estimates
- null likelihood: no QTL

  $L(\theta|Y) = \text{product}_i \text{ pr}(Y_i|\theta) = \text{product}_i \text{ N}(Y_i|\mu,\sigma^2)$
  - usual mean and variance estimates

Interval Mapping for Quantitative Trait Loci

- profile likelihood (LOD) across QTL
  - scan whole genome locus by locus
    - use flanking markers for interval mapping
  - maximize likelihood ratio (LOD) at locus
    - best estimates of effects for each locus
    - EM method (Lander & Botstein 1989)

$$LOD(\lambda) = \text{sum}_i \log_{10}\left(\frac{\text{sum}_Q \ \text{pr}(Y_i \mid Q, \hat{\theta}) \ \text{pr}(Q \mid \lambda)}{\text{pr}(Y_i \mid \widetilde{\theta})} \right)$$

Interval Mapping Tests

- profile LOD across possible loci in genome
  - maximum likelihood estimates of effects at locus
  - LOD is rescaling of *L*(effects, locus|y)
- test for evidence of QTL at each locus
  - LOD score (*LR* test)
  - adjust (?) for multiple comparisons

Interval Mapping Estimates

- confidence region for locus
  - based on inverting test of no QTL
  - 2 LODs down gives approximate CI for locus
  - based on chi-square approximation to *LR*
- confidence region for effects
  - approximate CI for effect based on normal
  - point estimate from profile LOD

$$\text{locus CI} = \left\{\lambda \mid LOD(\hat{\lambda}) - LOD(\lambda) < 2\right\}$$

$$\text{genetic effects } CI = \hat{G}_Q \pm 1.96 \times \text{se}(\hat{G}_Q)$$

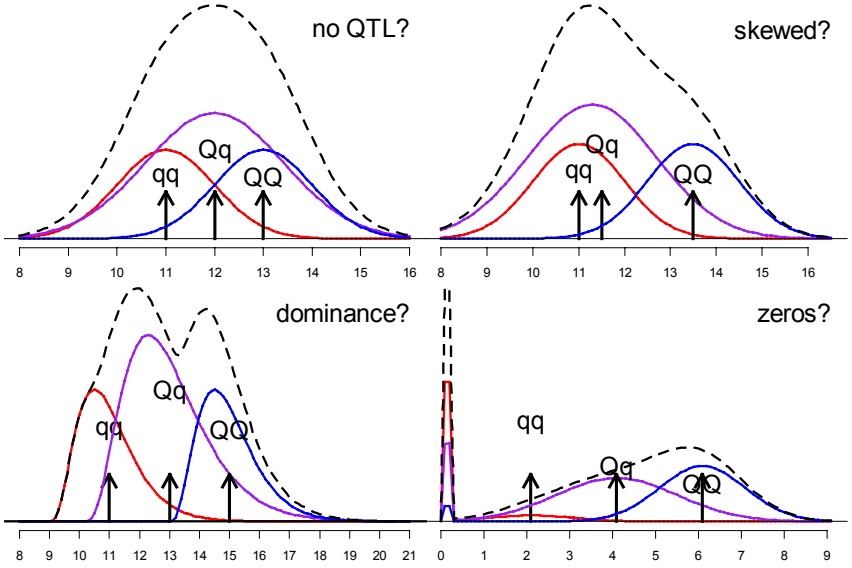
Part II: Extension of Phenotype Model

- limitations of parametric models
- quick fixes (but watch out!)
- semi-parametric approaches
- non-parametric approaches
- bottom line:
  - normal phenotype model works well to pick up loci, but may be poor at estimates of effects

Limitations of Parametric Models

- measurements not normal
  - counts (*e.g.* number of tumors)
  - survival time (*e.g.* days to flowering)
- false positives due to miss-specified model
  - check model assumptions?
- want more robust estimates of effects
  - parametric: only center (mean), spread (SD)
  - shape of distribution may be important

What if data are far away from ideal?



What shape is your histogram?

- histogram conditional on known QT genotype
  - pr(Y|qq, θ) model shape with genotype qq
  - pr(Y|Qq, θ) model shape with genotype Qq
  - pr(Y|QQ, θ) model shape with genotype QQ
- is the QTL at a given locus λ?
  - no QTL pr(Y|qq, θ) = pr(Y|Qq, θ) = pr(Y|QQ, θ)
  - QTL present mixture if genotype unknown
- mixture across possible genotypes
  - sum over Q = qq, Qq, QQ
  - pr($Y|X,\lambda,\theta$) = sum_Q pr($Q|X,\lambda$) pr($Y|Q,\theta$)

Interval Mapping Likelihood

- likelihood: basis for scanning the genome
  - product over $i = 1,\ldots,n$ individuals

$$L(\theta,\lambda|Y) = \text{product}_i \text{ pr}(Y_i|X_i,\lambda)$$
$$= \text{product}_i \text{ sum}_Q \text{ pr}(Q|X_i,\lambda) \text{ pr}(Y_i|Q,\theta)$$

- problem: unknown phenotype model
  - parametric pr($Y|Q,\theta$) = normal(G_Q,σ^2)
  - semi-parametric pr($Y|Q,\theta$) = $f(Y)\exp(Y\beta_Q)$
  - non-parametric pr($Y|Q,\theta$) = $F_Q(Y)$

Useful Models & Transformations

- binary trait (yes/no, hi/lo, …)
  - map directly as another marker
  - categorical: break into binary traits?
  - mixed binary/continuous: condition on $Y > 0$?
- known model for biological mechanism
  - counts Poisson
  - fractions binomial
  - clustered negative binomial
- transform to stabilize variance
  - counts $\sqrt{Y}$ = sqrt(Y)
  - concentration log(Y) or log($Y+c$)
  - fractions arcsin($\sqrt{Y}$)
- transform to symmetry (approx. normal)
  - fraction log(Y/(1-Y)) or log(($Y+c$)/(1+c-Y))
- empirical transform based on histogram
  - watch out: hard to do well even without mixture
  - probably better to map untransformed, then examine residuals

Semi-parametric QTL

- phenotype model $\text{pr}(Y|Q,\theta) = f(Y)\exp(Y\beta_Q)$
  - unknown parameters $\theta = (f, \beta)$
    - $f(Y)$ is a (unknown) density if there is no QTL
    - $\beta = (\beta_{qq}, \beta_{Qq}, \beta_{QQ})$
    - $\exp(Y\beta_Q)$ `tilts' f based on genotype Q and phenotype Y
- test for QTL at locus λ
  - $\beta_Q = 0$ for all Q, or $\text{pr}(Y|Q,\theta) = f(Y)$
- includes many standard phenotype models

  normal $\text{pr}(Y|Q,\theta) = N(G_Q,\sigma^2)$

  Poisson $\text{pr}(Y|Q,\theta) = \text{Poisson}(G_Q)$

  exponential, binomial, …, but not negative binomial

Semi-parametric Empirical Likelihood

- phenotype model $\text{pr}(Y|Q,\theta) = f(Y)\exp(Y\beta_Q)$
  - "point mass" at each measured phenotype Y_i
  - subject to distribution constraints for each Q:
    $1 = \text{sum}_i f(Y_i)\exp(Y_i\beta_Q)$
- non-parametric empirical likelihood (Owen 1988)

$$\begin{aligned} L(\theta,\lambda|Y,X) &= \text{product}_i\,[\text{sum}_Q\,\text{pr}(Q|X_i,\lambda)\,f(Y_i)\exp(Y_i\beta_Q)] \\ &= \text{product}_i\,f(Y_i)\,[\text{sum}_Q\,\text{pr}(Q|X_i,\lambda)\exp(Y_i\beta_Q)] \\ &= \text{product}_i\,f(Y_i)\,w_i \end{aligned}$$

  - weights $w_i = w(Y_i|X_i,\beta,\lambda)$ rely only on flanking markers
    - 4 possible values for BC, 9 for F2, etc.
- profile likelihood: $L(\lambda|Y,X) = \max_\theta L(\theta,\lambda|Y,X)$

Semi-parametric Formal Tests

- clever trick: use partial empirical LOD
  - Zou, Fine, Yandell (2002 *Biometrika*)
  - $\text{LOD}(\lambda) \approx \log_{10} L(\lambda|Y,X)$
- has same formal behavior as parametric LOD
  - single locus test: approximately χ^2 with 1 d.f.
  - genome-wide scan: can use same critical values
  - permutation test: possible with some work
- can estimate cumulative distributions
  - nice properties (converge to Gaussian processes)

log empirical likelihood details

$\log(L(\theta,\lambda|Y,X)) = \text{sum}_i \log(f(Y_i)) + \log(w_i)$

now profile with respect to β,λ

$\log(L(\beta,\lambda|Y,X)) = \text{sum}_i \log(f_i) + \log(w_i)$

$+ \text{sum}_Q \alpha_Q(1-\text{sum}_i f_i \exp(Y_i\beta_Q))$

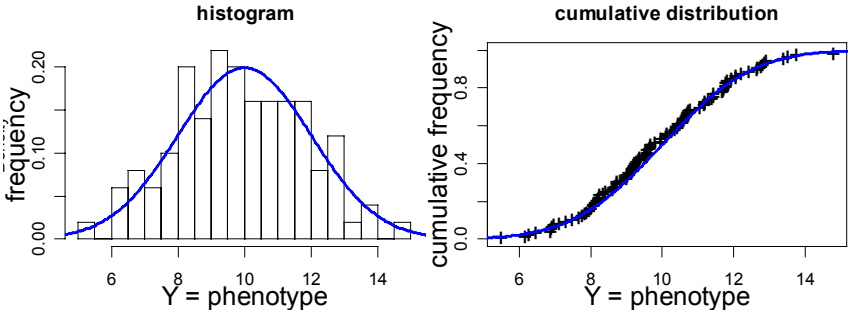
partial likelihood: set Lagrange multipliers α_Q to 0

point mass density estimates

$$f_i = \left[\text{sum}_Q \exp(Y_i\beta_Q)\, p(Q \mid X, \lambda)\right]^{-1}$$

with $p(Q \mid X, \lambda) = \text{sum}_i \text{pr}(Q \mid X_i, \lambda)$

Histograms and CDFs

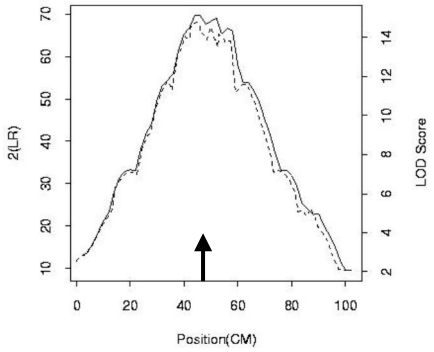


histograms capture shape but are not very accurate

CDFs are more accurate but not always intuitive

Rat study of breast cancer
Lan *et al.* (2001 *Genetics*)

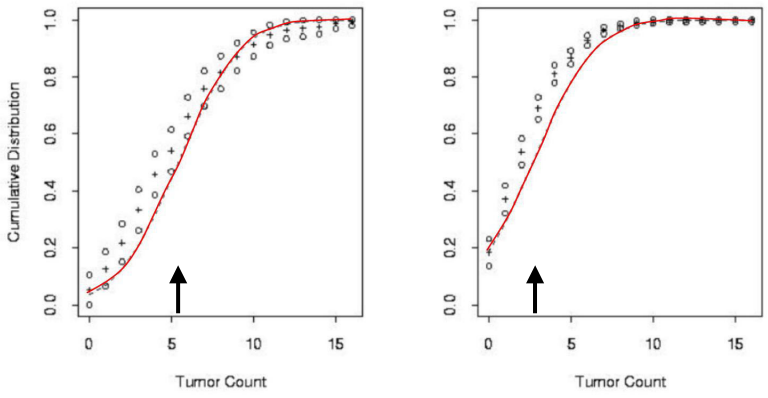
- rat backcross
  - two inbred strains
    - Wistar-Furth susceptible
    - Wistar-Kyoto resistant
  - backcross to WF
  - 383 females
  - chromosome 5, 58 markers
- search for resistance genes
- Y = # mammary carcinomas
- where is the QTL?



dash = normal
solid = semi-parametric

What shape histograms by genotype?

WF/WF WKy/WF



line = normal, + = semi-parametric, o = confidence interval

Non-parametric Methods

- phenotype model $\text{pr}(Y|Q,\theta) = F_Q(Y)$
  - $\theta = F = (F_{qq},F_{Qq},F_{QQ})$ arbitrary distribution functions
- Kruglyak Lander (1995)
  - interval mapping rank-sum test, replacing Y by rank(Y)
  - claimed no estimator of QTL effects
- estimators are indeed possible
  - semi-parametric shift (Hodges-Lehmann)
    - Zou (2001) thesis, Zou, Yandell, Fine (2002 in review)
  - non-parametric cumulative distribution
    - Fine, Zou, Yandell (2001 in review)

Rank-Sum QTL Methods

- phenotype model $\text{pr}(Y|Q,\theta) = F_Q(Y)$
- replace Y by rank(Y) and perform IM
  - extension of Wilcoxon rank-sum test
  - fully non-parametric
- Hodges-Lehmann estimator of shift β
  - most efficient if $\text{pr}(Y|Q,\theta) = F(Y+Q\beta)$
  - find β that matches medians
    - problem: genotypes Q unknown
    - resolution: Haley-Knott (1992) regression scan
  - works well in practice, but theory is elusive
    - Zou, Yandell Fine (*Genetics*, in review)

Non-Parametric QTL CDFs

- estimate non-parametric phenotype model
  - cumulative distributions $F_Q(y) = \text{pr}(Y \le y \,|Q)$
  - can use to check parametric model validity
- basic idea:

  $\text{pr}(Y \le y \,|X,\lambda) = \text{sum}_Q \text{pr}(Q|X,\lambda)F_Q(y)$
  - depends on X only through flanking markers
  - few possible flanking marker genotypes
    - 4 for BC, 9 for F2, etc.

Finding NP QTL CDFs

- cumulative distribution $F_Q(y) = \text{pr}(Y \le y \,|Q)$
- $F = \{F_Q$, all possible QT genotypes $Q\}$
  - BC with 1 QTL: $F = \{F_{QQ}, F_{Qq}\}$
- find F to minimize over all phenotypes y

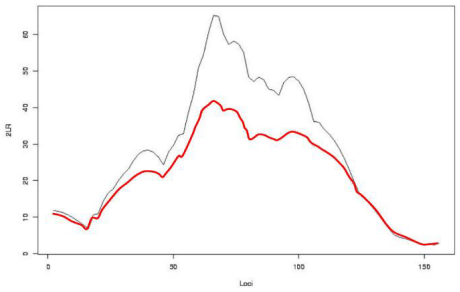
  $\text{sum}_i [I(Y_i \le y) - \text{sum}_Q \text{pr}(Q|X,\lambda)F_Q(y)]^2$
- looks complicated, but simple to implement

Non-parametric CDF Properties

- readily extended to censored data
  - time to flowering for non-vernalized plants
- nice large sample properties
  - estimates of $F(y) = \{F_Q(y)\}$ jointly normal
  - point-wise, experiment-wise confidence bands
- more robust to heavy tails and outliers
- can use to assess parametric assumptions

What QTL influence flowering time? no vernalization: censored survival

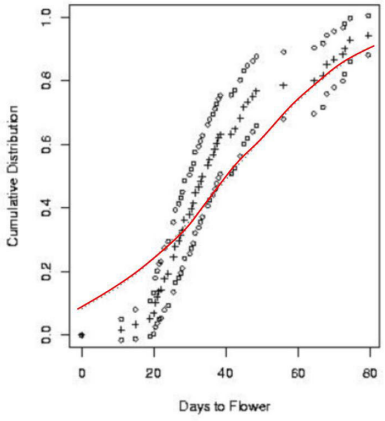
- *Brassica napus*
  - Major female
    - needs vernalization
  - Stellar male
    - insensitive
  - 99 double haploids
- Y = log(days to flower)
  - over 50% Major at QTL never flowered
  - log not fully effective



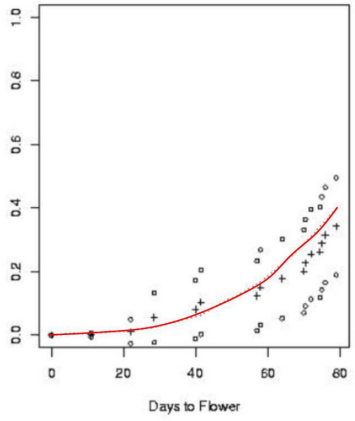
grey = normal, red = non-parametric

What shape is flowering distribution?

B. napus Stellar



B. napus Major



line = normal, + = non-parametric, o = confidence interval

Part III: Bayesian Idea

- Thomas Bayes and the original idea
- Bayes theorem
- How do frequentist & Bayesian approaches differ?
- Choice of Bayesian priors
  - normal data phenotype model
  - empirical Bayes
- Bayesian interval mapping basics

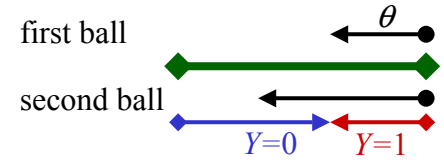
Bayesian QTL Model Selection

- Bayesian perspective
  - common in animal model
  - use "prior" information
    - previous experiments
    - related genomes
- inbred lines "easy"
  - can check against *IM
  - ready extension
    - multiple experiments
    - pedigrees
    - non-normal data
    - epistasis
- resampling from data
  - permutation tests
  - bootstrap, jackknife
  - MCMC
    - special Markov chain
    - Monte Carlo sampling
- show MCMC ideas
  - Gibbs sampler
  - Metropolis-Hastings
  - reversible jump MCMC

Who was Bayes?

- Reverend Thomas Bayes (1702-1761)
  - part-time mathematician
  - buried in Bunhill Cemetary, Moongate, London
  - famous paper in 1763 *Phil Trans Roy Soc London*
    - Barnard (1958 *Biometrika*), Press (1989) *Bayesian Statistics*
    - Stigler (1986) *History of Statistics*
    - Carlin Louis (1996); Gelman et al. (1995) books
  - Was Bayes the first with this idea? (Laplace)
- billiard balls on rectangular table
  - two balls tossed at random (uniform) on table
  - where is first ball if the second is to its right (left)?

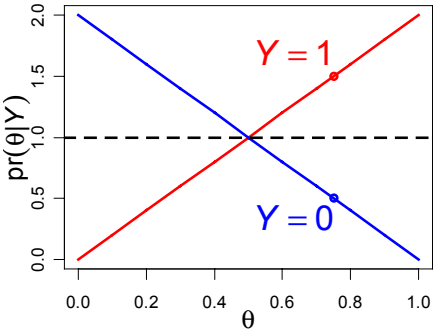
Where is the first ball?



prior $\quad \text{pr}(\theta) \quad = 1$

likelihood $\quad \text{pr}(Y|\theta) = \theta^{Y}(1-\theta)^{1-Y}$

posterior $\quad \text{pr}(\theta|Y) = ?$



$$\text{pr}(\theta|Y) = \frac{\text{pr}(Y|\theta)\text{pr}(\theta)}{\text{pr}(Y)}$$

$$\text{pr}(Y) = \int_0^1 \theta^{Y}(1-\theta)^{1-Y}\,d\theta = \frac{1}{2}$$

$$\text{pr}(\theta|Y) = \begin{cases} 2\theta & Y = 1 \\ 2(1-\theta) & Y = 0 \end{cases}$$

(now throw second ball *n* times)

What is Bayes Theorem?

- before and after observing data
  - prior: $\text{pr}(\theta)$ = pr(parameters)
  - posterior: $\text{pr}(\theta|Y)$ = pr(parameters|data)
- posterior = likelihood * prior / constant
  - usual likelihood of parameters given data
  - normalizing constant pr(*Y*) depends only on data
    - constant often drops out of calculation

$$\text{pr}(\theta|Y) = \frac{\text{pr}(\theta, Y)}{\text{pr}(Y)} = \frac{\text{pr}(Y|\theta)\times\text{pr}(\theta)}{\text{pr}(Y)}$$

What is Probability?

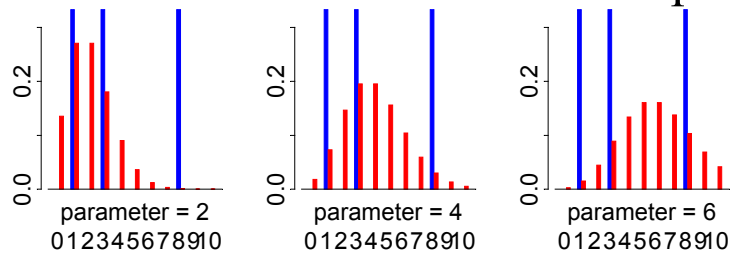
Frequentist analysis

- chance over many trials
  - long run average
    - estimates
    - confidence intervals
  - long term frequency
    - hypothesis tests
    - *p*-values
- Type I error rate
  - reject null when true
  - chance of extreme result

Bayesian analysis

- uncertainty of true value
- prior
  - uncertainty before data
  - incorporate prior knowledge/experience
- posterior
  - uncertainty after analyzing current data
  - balance prior and data

Likelihood and Posterior Example



$$\text{data} : Y = 1,3,8$$

$$\text{parameter} : \theta = ?$$

$$\text{pr}(Y = y \mid \theta) = \frac{\theta^y e^{-\theta}}{y!}$$

(M. Newton, pers. comm.)

Frequentist or Bayesian?

- Frequentist approach
  - fixed parameters
    - range of values
  - maximize likelihood
    - ML estimates
    - find the peak
  - confidence regions
    - random region
    - invert a test
  - hypothesis testing
    - 2 nested models
- Bayesian approach
  - random parameters
    - distribution
  - posterior distribution
    - posterior mean
    - sample from dist
  - credible sets
    - fixed region given data
    - HPD regions
  - model selection/critique
    - Bayes factors

Frequentist or Bayesian?

- Frequentist approach
  - maximize over mixture of QT genotypes
  - locus profile likelihood
    - max over effects
  - HPD region for locus
    - natural for locus
      - 1-2 LOD drop
    - work to get effects
      - approximate shape of likelihood peak
- Bayesian approach
  - joint distribution over QT genotypes
  - sample distribution
    - joint effects & loci
  - HPD regions for
    - joint locus & effects
    - use density estimator

Choice of Bayesian priors

- elicited priors
  - higher weight for more probable parameter values
    - based on prior empirical knowledge
  - use previous study to inform current study
    - weather prediction, previous QTL studies on related organisms
- conjugate priors
  - convenient mathematical form
  - essential before computers, helpful now to simply computation
  - large variances on priors reduces their influence on posterior
- non-informative priors
  - may have "no" information on unknown parameters
  - prior with all parameter values equally likely
    - may not sum to 1 (improper), which can complicate use
- always check sensitivity of posterior to choice of prior

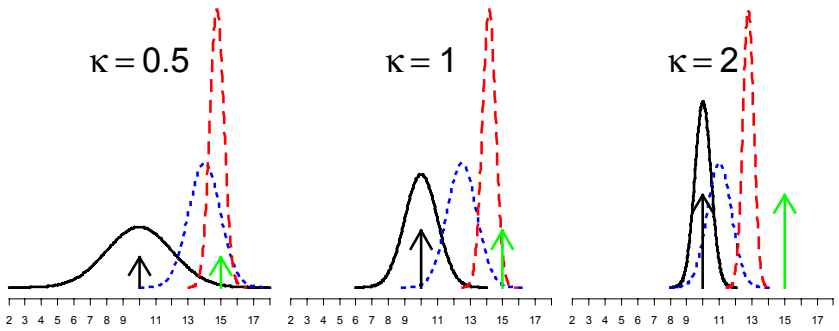
Bayes for normal data

$Y = G + E$	posterior for single individual
environ	$E \sim \mathrm{N}(0, \sigma^2)$, σ^2 known
likelihood	$\mathrm{pr}(Y \mid G, \sigma^2) = \mathrm{N}(Y \mid G, \sigma^2)$
prior	$\mathrm{pr}(G \mid \sigma^2, \mu, \kappa) = \mathrm{N}(G \mid \mu, \sigma^2/\kappa)$
posterior	$\mathrm{N}(G \mid \mu + B_1(Y - \mu), B_1\sigma^2)$
$Y_i = G + E_i$	posterior for sample of n individuals
	shrinkage weights B_n go to 1

$$\mathrm{pr}(G \mid Y, \sigma^2, \mu, \kappa) = \mathrm{N}\left(G \middle| \mu + B_n(\overline{Y}_\bullet - \mu), B_n \frac{\sigma^2}{n}\right)$$

$$\text{with } \overline{Y}_\bullet = \mathrm{sum}\frac{Y_i}{n}, B_n = \frac{n}{\kappa + n} \to 1$$

effect of prior variance on posterior



normal prior, posterior for $n = 1$, posterior for $n = 5$, true mean

posterior by QT genetic value

$Y_i = G(Q_i) + E_i$ genetic Q_i = qq,Qq,QQ

environ $E \sim N(0,\sigma^2)$, σ^2 known

parameters $\theta = (G,\sigma^2)$

likelihood $\text{pr}(Y_i \mid Q_i,G,\sigma^2) = N(Y_i \mid G(Q_i),\sigma^2)$

prior $\text{pr}(G_Q \mid \sigma^2,\mu,\kappa) = N(G_Q \mid \mu,\sigma^2/\kappa)$

posterior:

$$\text{pr}(G_Q \mid Y,Q,\sigma^2,\mu,\kappa) = N\left(G_Q \middle| \mu + B_Q(\bar{Y}_Q - \mu), B_Q\frac{\sigma^2}{n_Q}\right)$$

$$n_Q = \text{count}\{Q_i = Q\}, \bar{Y}_Q = \underset{\{i:Q_i=Q\}}{\text{sum}} \frac{Y_i}{n_Q}, B_Q = \frac{n_Q}{\kappa + n_Q} \to 1$$

Empirical Bayes: choosing hyper-parameters

How do we choose hyper-parameters μ, κ?

Empirical Bayes: marginalize over prior

estimate μ, κ from marginal posterior

likelihood $\quad \text{pr}(Y_i \mid Q_i, G, \sigma^2) = \text{N}(Y_i \mid G(Q_i), \sigma^2)$

prior $\quad \text{pr}(G_Q \mid \sigma^2, \mu, \kappa) = \text{N}(G_Q \mid \mu, \sigma^2/\kappa)$

marginal $\quad \text{pr}(Y_i \mid \sigma^2, \mu, \kappa) = \text{N}(Y_i \mid \mu, \sigma^2 (\kappa + 1)/\kappa)$

estimates $\quad \hat{\mu} = \overline{Y}_\bullet, s^2 = \text{sum}_i (Y_i - \overline{Y}_\bullet)^2 / n$

$\kappa \le 1$ or $\kappa = \sigma^2 / s^2$

EB posterior $\quad \text{pr}(G_Q \mid Y) = \text{N}\left(G_Q \middle| \overline{Y}_\bullet + \hat{B}_Q (\overline{Y}_Q - \overline{Y}_\bullet), \hat{B}_Q \frac{\sigma^2}{n_Q} \right)$

What if variance σ^2 is unknown?

- recall that sample variance is proportional to chi-square
  - $\text{pr}(s^2 \mid \sigma^2) = \chi^2 (ns^2/\sigma^2 \mid n)$
  - or equivalently, $ns^2/\sigma^2 \mid \sigma^2 \sim \chi_n^2$
- conjugate prior is inverse chi-square
  - $\text{pr}(\sigma^2 \mid \nu, \tau^2) = \text{inv-}\chi^2 (\sigma^2 \mid \nu, \tau^2)$
  - or equivalently, $\nu\tau^2/\sigma^2 \mid \nu, \tau^2 \sim \chi_\nu^2$
  - empirical choice: $\tau^2 = s^2/3$, $\nu = 6$
    - $\text{E}(\sigma^2 \mid \nu, \tau^2) = s^2/2$, $\text{Var}(\sigma^2 \mid \nu, \tau^2) = s^4/4$
- posterior given data
  - $\text{pr}(\sigma^2 \mid Y, \nu, \tau^2) = \text{inv-}\chi^2 (\sigma^2 | \nu + n, (\nu\tau^2 + ns^2)/(\nu + n))$

joint effects posterior details

$Y_i = G(Q_i) + E_i$

genetic Q_i = qq,Qq,QQ

environ $E \sim N(0,\sigma^2)$

parameters $\theta = (G,\sigma^2)$

likelihood $\text{pr}(Y_i \mid Q_i, G, \sigma^2) = N(Y_i \mid G(Q_i), \sigma^2)$

prior $\text{pr}(G_Q \mid \sigma^2, \mu, \kappa) = N(G_Q \mid \mu, \sigma^2/\kappa)$

$\text{pr}(\sigma^2 \mid \nu, \tau^2) = \text{inv-}\chi^2(\sigma^2 \mid \nu, \tau^2)$

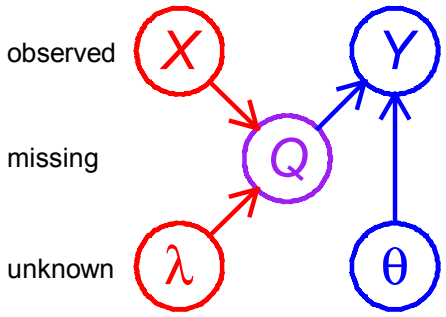
posterior: $\text{pr}(G_Q \mid Y, Q, \sigma^2, \mu, \kappa) = N\left(G_Q \middle| \bar{Y}_\cdot + B_Q(\bar{Y}_Q - \bar{Y}_\cdot), B_Q \frac{\sigma^2}{n_Q}\right)$

$$\text{pr}(\sigma^2 \mid Y, Q, G_Q, \nu, \tau^2) = \text{inv-}\chi^2\left(\sigma^2 \middle| \nu + n, \frac{\nu\tau^2 + n s_Q^2}{\nu + n}\right)$$

with $B_Q = \frac{n_Q}{\kappa + n_Q}, s_Q^2 = \text{sum}_i (Y_i - G(Q_i))^2 / n$

Bayesian Idea for QTLs

- key idea
  - sample missing genotypes Q
    - using recombination model
  - phenotype model given Q
    - see previous slides
- methods and philosophy
  - EM & MCMC
  - Frequentists & Bayesians



- review interval maps & profile LODs
- case study: simulated single QTL

QTL Full Posterior

- posterior = likelihood * prior / constant
- posterior(paramaters | data)

pr(loci, genos, effects | trait, map)

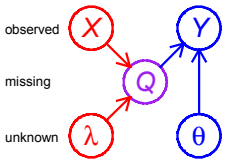
$$\text{pr}(\lambda, Q, \theta \mid Y, X) = \frac{\text{pr}(\theta)\text{pr}(\lambda)\text{pr}(Q \mid X, \lambda)\text{pr}(Y \mid Q, \theta)}{\text{constant}}$$

$$\text{constant} = \text{pr}(Y) = \text{sum}_{\{\lambda, Q, \theta\}} \text{pr}(\theta)\text{pr}(\lambda)\text{pr}(Q \mid X, \lambda)\text{pr}(Y \mid Q, \theta)$$

$$\text{pr}(Q \mid X, \lambda)\text{pr}(Y \mid Q, \theta) = \text{product}_i \left[\text{pr}(Q \mid X_i, \lambda)\text{pr}(Y_i \mid Q, \theta)\right]$$

marginal posteriors

- joint posterior
  - pr($\lambda, Q, \theta \mid Y, X$) = pr($\theta$)pr($\lambda$)pr($Q \mid X, \lambda$)pr($Y \mid Q, \theta$) /constant
- genetic effects
  - pr($\theta \mid Y, X$) = sum$_Q$ pr($\theta \mid Y, Q$) pr($Q \mid Y, X$)
- QTL locus
  - pr($\lambda \mid Y, X$) = sum$_Q$ pr($\lambda \mid X, Q$) pr($Q \mid Y, X$)
- QTL genotypes more complicated
  - pr($Q \mid Y, X$) = sum$_{\lambda, \theta}$ pr($Q \mid Y, X, \lambda, \theta$) pr($\lambda, \theta \mid Y, X$)
  - impossible to separate λ and θ in sum



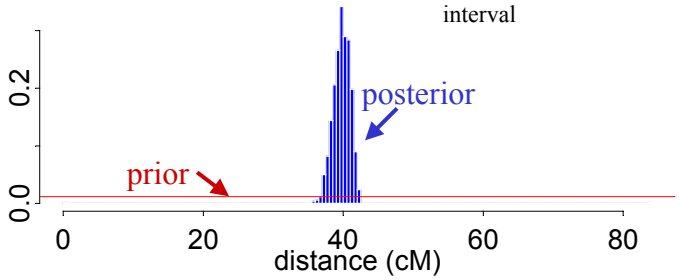
prior & posterior for genotypes Q

- prior is recombination model
  $\text{pr}(Q|X_i,\lambda)$
- can explicitly decompose by individual i
  - binomial (or trinomial) probability
- posterior for genotype depends on
  - effects via trait model
  - locus via recombination model
- posterior agrees exactly with interval mapping
  - used in EM: estimation step
  - but need to know locus λ and effects θ

$$P_{Qi} = \text{pr}(Q \mid Y_i, X_i, \lambda, \theta) = \frac{\text{pr}(Y_i \mid Q, \theta)\text{pr}(Q \mid X_i, \lambda)}{\text{sum}_Q \left[\text{pr}(Y_i \mid Q, \theta)\text{pr}(Q \mid X_i, \lambda)\right]}$$

prior & posterior for QT locus

- prior information from other studies
  - •concentrate on credible regions
  - •use posterior of previous study as new prior
- no prior information on locus
  - uniform prior over genome
  - use framework map
    - •choose interval proportional to length
    - •then pick uniform position within interval



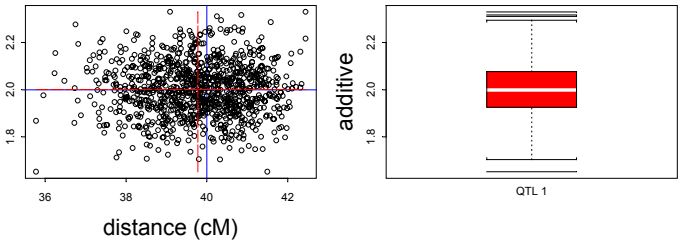
QTL Bayesian Inference

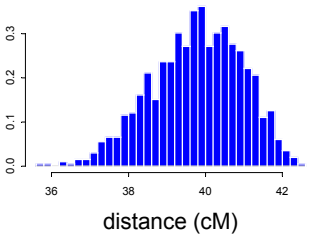
- study posterior distribution of locus & effects
  - sample joint distribution
    - locus, effects & genotypes
  - study marginal distribution of
    - locus
    - effects
      - overall mean, genotype difference, variance
    - locus & effects together
- estimates & confidence regions
  - histograms, boxplots & scatter plots
  - HPD regions

Marginal Posterior Summary

- marginal posterior for locus & effects
- highest probability density (HPD) region
  - smallest region with highest probability
  - credible region for locus & effects
- HPD with 50,80,90,95%
  - range of credible levels can be useful
  - marginal bars and bounding boxes
  - joint regions (harder to draw)

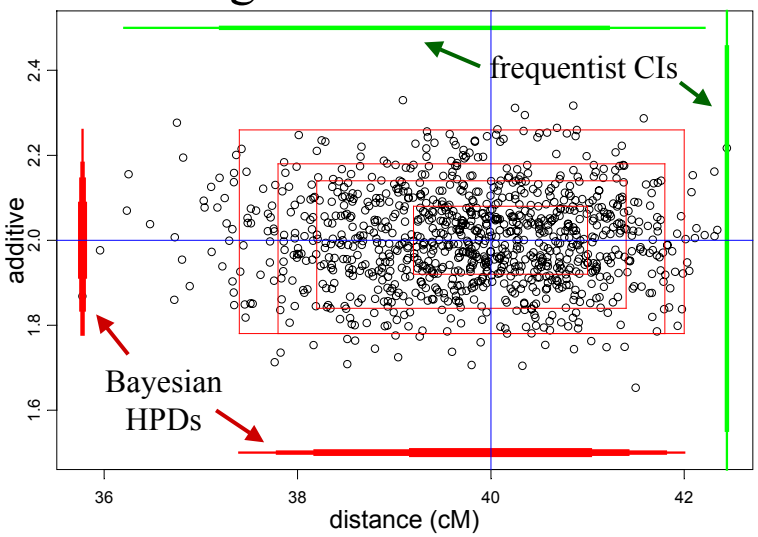
Posterior for locus & effect





summaries of MC samples
joint scatter plot
(lines for true, estimates)
marginal histogram
marginal box-plot

HPD region for locus & effect



Part IV: Monte Carlo Sampling from the Bayesian posterior

- How can we study Bayesian posteriors?
  - frequentist & Bayesian methods
  - EM & MCMC duality
- What is a Markov chain?
- How does Markov chain Monte Carlo work?
  - use Markov chain to sample from posterior
  - Gibbs sampler for effects θ, genotypes Q
  - Metropolis-Hastings for loci λ

How can we study Bayesian posteriors?

- exact methods if possible
  - manipulate math formula
  - can be difficult or impossible to analyze
- approximate methods
  - importance sampling
  - numerical integration
  - Monte Carlo & other
- Monte Carlo methods
  - easy to implement
  - independent samples
  - just draw large sample
- MCMC methods
  - handle hard problems
  - art to efficient use
  - iterative: Markov chain
  - correlated samples

How to study the QTL likelihood?

- frequentist approach
  - maximize (*IM)
    - find the peak
    - avoid local maxima
  - profile LOD across locus
    - maximize for effects
- approximate methods
  - EM (Lander Botstein 1989)
  - MCMC (Guo Thompson 1994)
- Bayesian approach
  - sample from posterior
  - examine whole posterior
    - summarize later
    - joint locus & effects
- approximate methods
  - MCMC (Satagopan et al. 1996)
  - imputation (Sen Churchill 2001)

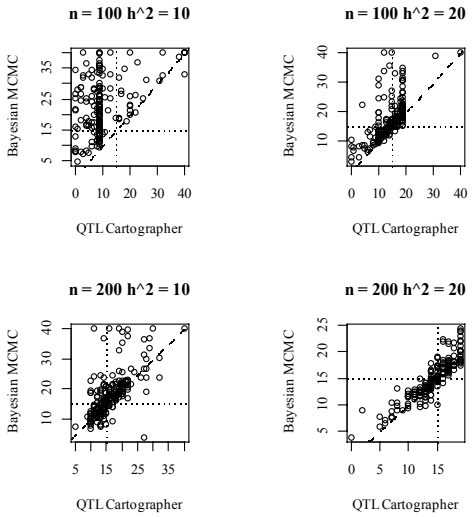
EM-MCMC duality

- EM approaches can be redone with MCMC
  - EM estimates & maximizes
  - MCMC draws random samples
    - simulated annealing: gradually cool towards peak
  - both can address same problem
- sometimes EM is hard (impossible) to use
- MCMC is tool of "last resort"
  - use exact methods if you can
  - try other approximate methods
  - be clever! (math, computing tricks)
  - very handy for hard problems in genetics

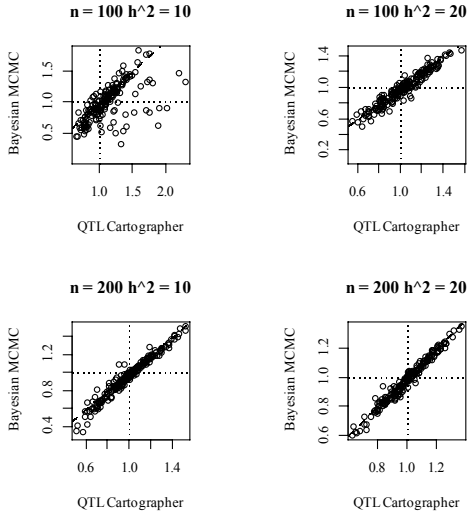
Simulation Study

- 200 simulation runs
- n = 100, 200; h^2 = 10, 20%
- 1 QTL at 15cM
- markers at 0, 10, 20, 40, 60, 80
- effect = 1
- variance depends on heritability h^2

200 Simulations: Locus



200 Simulations: Effect



Why not Ordinary Monte Carlo?

- independent samples of joint distribution
- chaining (or peeling) of effects

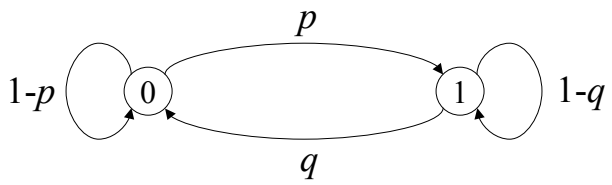
$$\text{pr}(\theta|Y,Q) = \text{pr}(G_Q \mid Y,Q,\sigma^2)\ \text{pr}(\sigma^2 \mid Y,Q)$$

- possible analytically here given genotypes Q
- Monte Carlo: draw N samples from posterior
  - sample variance σ^2
  - sample genetic values G_Q given variance σ^2
- but we know markers X, not genotypes Q!
  - would have messy average over possible Q
  - $\text{pr}(\theta|Y,X) = \text{sum}_Q\ \text{pr}(\theta|Y,Q)\ \text{pr}(Q|Y,X)$

What is a Markov chain?

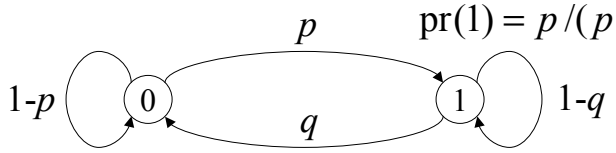
- future given present is independent of past
- update chain based on current value
  - can make chain arbitrarily complicated
  - chain converges to stable pattern $\pi()$ we wish to study

$$\text{pr}(1) = p/(p+q)$$



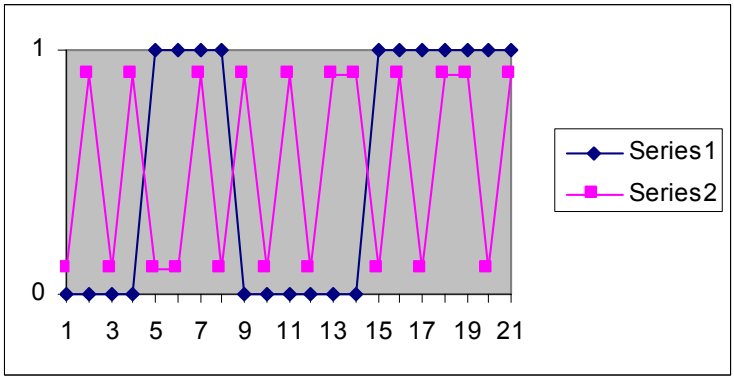
Markov chain idea

$$\text{pr}(1) = p/(p+q)$$



Mitch's

other pubs



Markov chain Monte Carlo

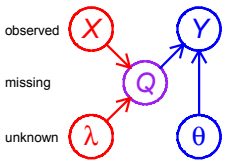
- can study arbitrarily complex models
  - need only specify how parameters affect each other
  - can reduce to specifying full conditionals
- construct Markov chain with "right" model
  - joint posterior of unknowns as limiting "stable" distribution
  - update unknowns given data and all other unknowns
    - sample from full conditionals
    - cycle at random through all parameters
  - next step depends only on current values
- nice Markov chains have nice properties
  - sample summaries make sense
  - consider almost as random sample from distribution
  - ergodic theorem and all that stuff

MCMC Idea for QTLs

- 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 components from full conditionals
  - update effects θ given genotypes & traits
  - update locus λ given genotypes & marker map
  - update genotypes Q given traits, marker map, locus & effects

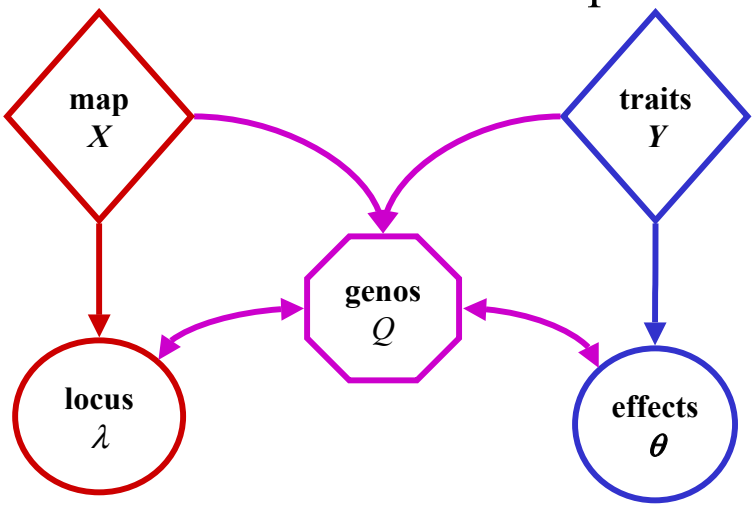
$$(\lambda, Q, \theta) \sim \text{pr}(\lambda, Q, \theta \mid Y, X)$$
$$(\lambda, Q, \theta)_1 \rightarrow (\lambda, Q, \theta)_2 \rightarrow \cdots \rightarrow (\lambda, Q, \theta)_N$$

sample from full conditionals



- hard to sample from joint posterior
  - $\text{pr}(\lambda, Q, \theta \mid Y, X) = \text{pr}(\theta)\text{pr}(\lambda)\text{pr}(Q \mid X, \lambda)\text{pr}(Y \mid Q, \theta)$ /constant
- easy to sample parameters from full conditionals
  - full conditional for genetic effects
    - $\text{pr}(\theta \mid Y, X, \lambda, Q) = \text{pr}(\theta \mid Y, Q) = \text{pr}(\theta)\ \text{pr}(Y \mid Q, \theta)$ /constant
  - full conditional for QTL locus
    - $\text{pr}(\lambda \mid Y, X, \theta, Q) = \text{pr}(\lambda \mid X, Q) = \text{pr}(\lambda)\ \text{pr}(Q \mid X, \lambda)$ /constant
  - full conditional for QTL genotypes
    - $\text{pr}(Q \mid Y, X, \lambda, \theta) = \text{pr}(Q \mid X, \lambda)\ \text{pr}(Y \mid Q, \theta)$ /constant

MCMC full conditional updates



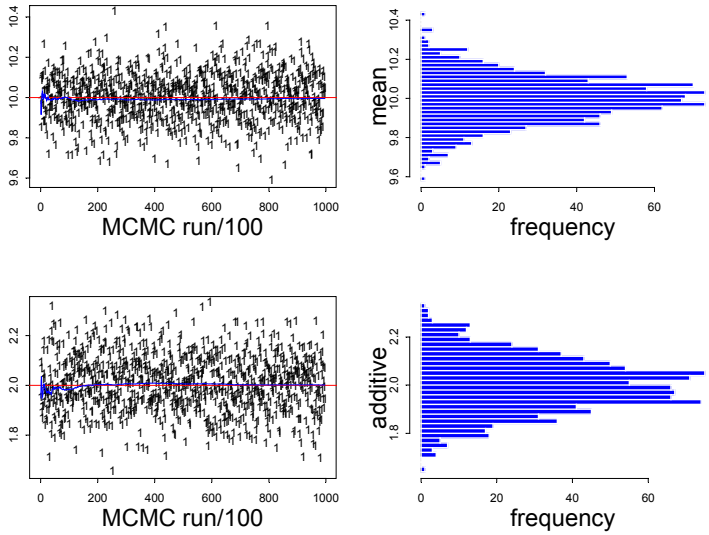
Gibbs Sampler: effects & genotypes

- for given locus λ, can sample effects θ and genotypes Q
  - effects parameter vector $\theta = (G,\sigma^2)$ with $G=(G_{qq},G_{Qq},G_{QQ})$
  - missing genotype vector $Q = (Q_1,Q_2,\ldots,Q_n)$
- Gibbs sampler: update one at a time via full conditionals
  - randomly select order of unknowns
  - update each given current values of all others, locus λ and data (Y,X)
    - sample variance σ^2 given Y,Q and genetic values G
    - sample genotype Q_i given markers X_i and locus λ
  - can do block updates if more efficient
    - sample all genetic values G given Y,Q and variance σ^2

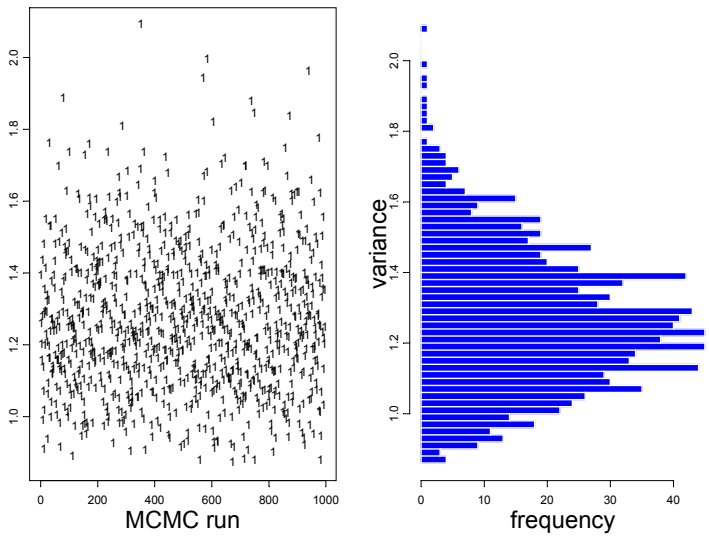
phenotype model: alternate form

- genetic value $G(Q)=G_Q$ in "cell means" form easy
- but often useful to model effects directly
  - sort out additive and dominance effects
  - useful for reduced models with multiple QTL
    - QTL main effects and interactions (pairwise, 3-way, etc.)
- we only consider additive effects here
  - $G_{qq} = \mu - a$, $G_{Qq} = \mu$, $G_{QQ} = \mu + a$
- recoding for regression model
  - $Q_i = -1$ for genotype qq
  - $Q_i = 0$ for genotype Qq
  - $Q_i = 1$ for genotype QQ
  - $G(Q_i) = \mu + aQ_i$

MCMC run of mean & additive



MCMC run for variance



missing marker data

- sample missing marker data a la QT genotypes
- full conditional for missing markers depends on
  - flanking markers
  - possible flanking QTL
- can explicitly decompose by individual *i*
  - binomial (or trinomial) probability

$$X_{ik} = \text{aa}, \text{Aa} \text{ or } \text{AA}$$

$$\text{pr}(X_{ik} \mid Y_i, X_i, Q_i, \theta, \lambda) = \text{pr}(X_{ik} \mid X_i, Q_i, \lambda)$$

full conditional for locus

- cannot easily sample from locus full conditional

$$\begin{aligned} \text{pr}(\lambda \mid Y, X, \theta, Q) &= \text{pr}(\lambda \mid X, Q) \\ &= \text{pr}(\lambda)\ \text{pr}(Q \mid X, \lambda)\ /\text{constant} \end{aligned}$$

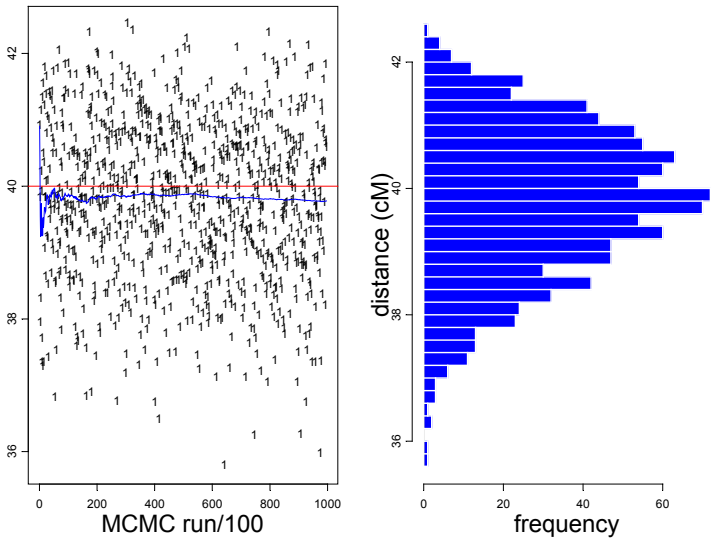
- cannot explicitly determine full conditional
  - difficult to normalize
  - need to average over all possible genotypes over entire map
- Gibbs sampler will not work
  - but can use method based on ratios of probabilities…

Metropolis-Hastings Step

- pick new locus based upon current locus
  - propose new locus from distribution $q(\ )$
    - pick value near current one?
    - pick uniformly across genome?
  - accept new locus with probability $a()$
- Gibbs sampler is special case of M-H
  - always accept new proposal
- acceptance insures right stable distribution
  - accept new proposal with probability A
  - otherwise stick with current value

$$A(\lambda_{old}, \lambda_{new}) = \min\left(1, \frac{\pi(\lambda_{new} \mid \mathbf{x}^*) q(\lambda_{new}, \lambda_{old})}{\pi(\lambda_{old} \mid \mathbf{x}^*) q(\lambda_{old}, \lambda_{new})}\right)$$

MCMC Run for 1 locus at 40cM



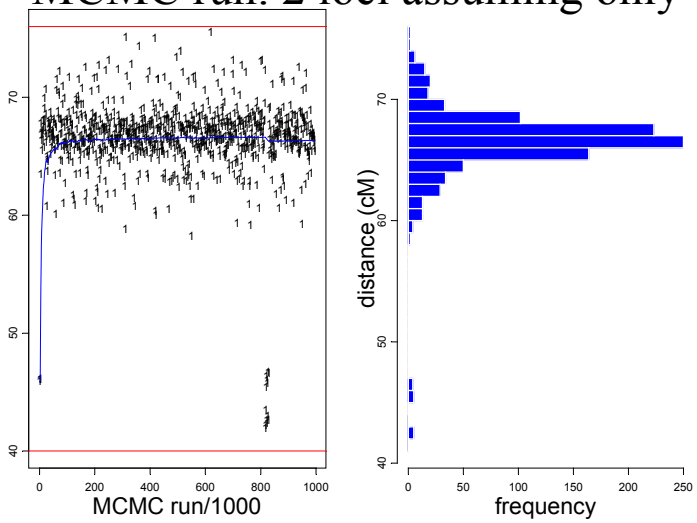
Care & Use of MCMC

- sample chain for long run (100,000-1,000,000)
  - longer for more complicated likelihoods
  - use diagnostic plots to assess "mixing"
- standard error of estimates
  - use histogram of posterior
  - compute variance of posterior--just another summary
- studying the Markov chain
  - Monte Carlo error of series (Geyer 1992)
    - time series estimate based on lagged auto-covariances
  - convergence diagnostics for "proper mixing"

Part V: Multiple QTL

- multiple QTL phenotype model
- issues for 2 QTL
- MCMC sampling from the posterior
- Simulated data for 0,1,2 QTL
- *Brassica* data on days to flowering

MCMC run: 2 loci assuming only 1



Multiple QTL model

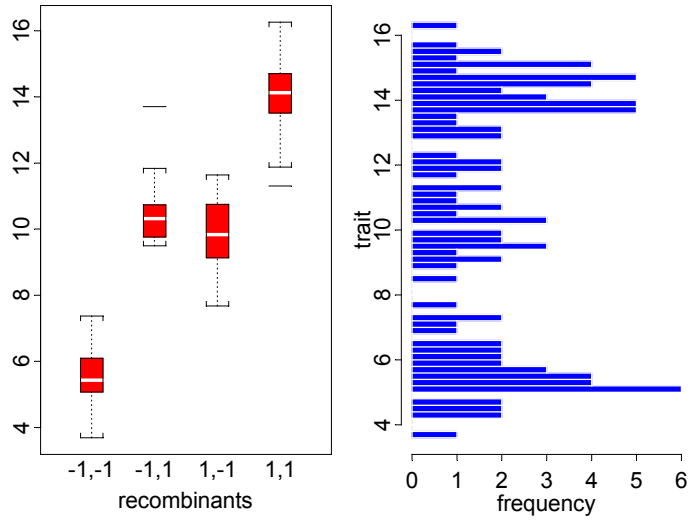
- trait = mean + add1 + add2 + error
- trait = genetic effect + error
- pr(trait | genos, effects)

$$Y_i = \mu + a_1 Q_{1i} + a_2 Q_{2i} + e_i$$

$$Y_i = \mu + \sum_{r=1}^{m} a_r Q_{ri} + e_i$$

$$\mu \sim \mathrm{N}(\overline{Y}_\cdot, s^2), a_r \sim \mathrm{N}(0, 2\beta s^2 / m), \beta = ?$$

Simulated Data with 2 QTL

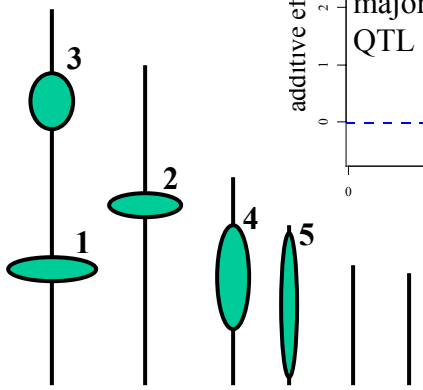


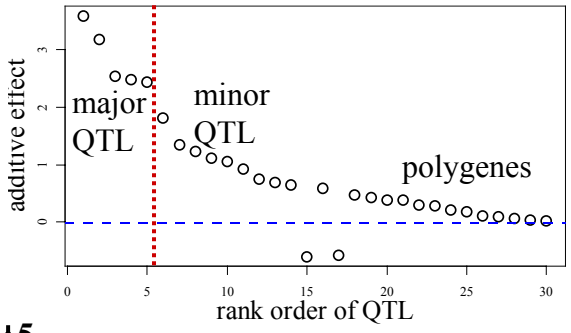
Issues for Multiple QTL

- how many QTL influence a trait?
  - 1, several (oligogenic) or many (polygenic)?
  - or do *most* genes influence most complex traits?
  - how many are supported by the data?
    - effects can be localized
- searching for 2 or more QTL
  - conditional search (IM, CIM)
  - simultaneous search (MIM)
- epistasis (inter-loci interaction)
  - many more parameters to estimate
  - effects of ignored QTL

Pareto diagram of QTL effects

major QTL on linkage map

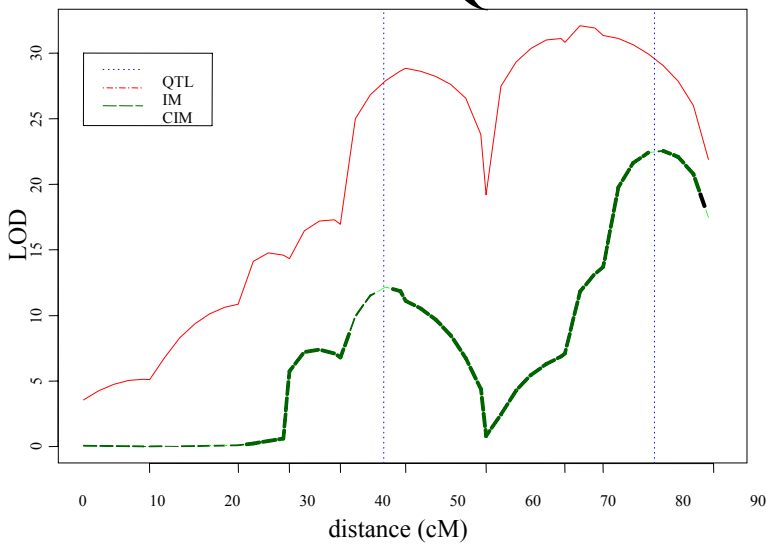




interval mapping approach

- interval mapping (IM)
  - scan genome for 1 QTL
- composite interval mapping (CIM)
  - scan for 1 QTL while adjusting for others
  - use markers as surrogates for other QTL
- multiple interval mapping (MIM)
  - use CIM as basic model
  - forward selection/backward elimination

LOD for 2 QTL



Bayesian approach

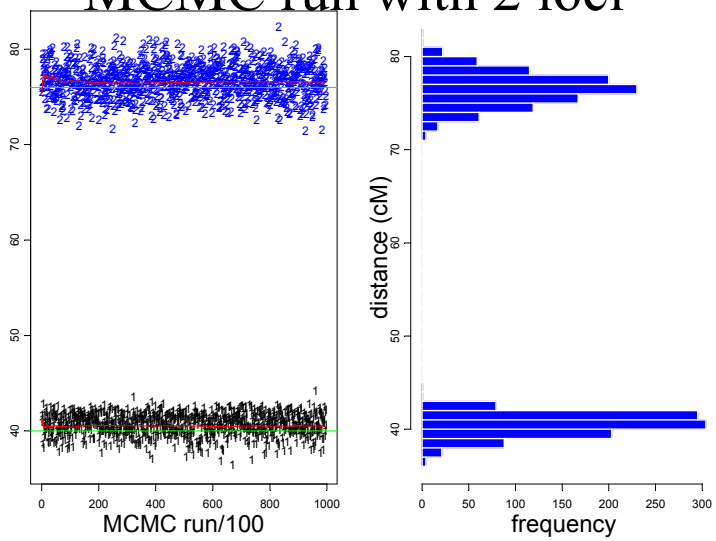
- simultaneous search for multiple QTL
- use Bayesian paradigm
  - easy to consider joint distributions
  - easy to modify later for other types of data
    - counts, proportions, etc.
  - employ MCMC to estimate posterior dist
- study estimates of loci and effects
- model selection and assessment
  - Bayes factors for number of QTL
  - posterior model averaging for loci

MCMC for multiple QTLs

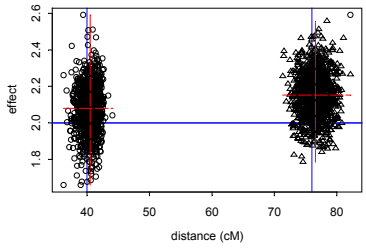
- posterior now has *m* loci rather than 1 locus
  - just change interpretation of unknowns
  - add extra subscript to keep track of loci
- construct Markov chain around posterior
  - "easy" extension of 1 QTL approach
  - now randomly pick which loci to update
- update all terms for each locus at one time?
  - open questions of efficient mixing

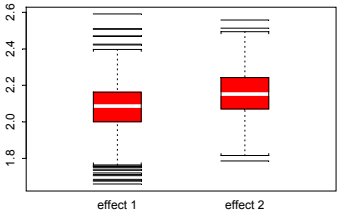
$$(\lambda, Q, \theta) \sim \text{pr}(\lambda, Q, \theta \mid Y, X)$$
$$(\lambda, Q, \theta)_1 \rightarrow (\lambda, Q, \theta)_2 \rightarrow \cdots \rightarrow (\lambda, Q, \theta)_N$$

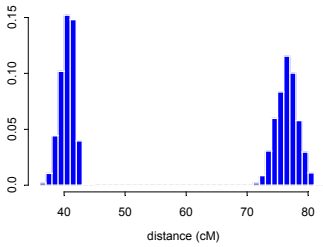
MCMC run with 2 loci



effects for 2 simulated QTL





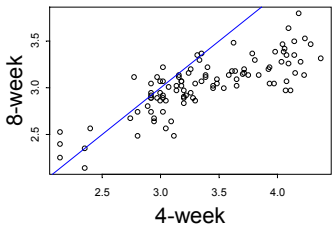


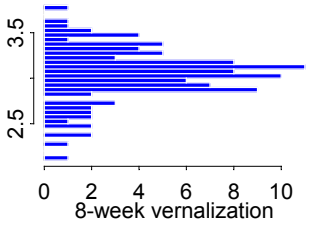
summaries of MC samples
joint scatter plots by loci
(lines for true, estimates)
marginal histograms
marginal box-plots

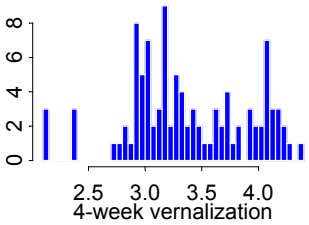
Brassica napus data

- 4-week & 8-week vernalization effect
  - log(days to flower)
- genetic cross of
  - Stellar (annual canola)
  - Major (biennial rapeseed)
- 105 F1-derived double haploid (DH) lines
  - homozygous at every locus (*QQ* or *qq*)
- 10 molecular markers (RFLPs) on LG9
  - two QTLs inferred on LG9 (now chromosome N2)
  - corroborated by Butruille (1998)
  - exploiting synteny with *Arabidopsis thaliana*

Brassica 4- & 8-week data

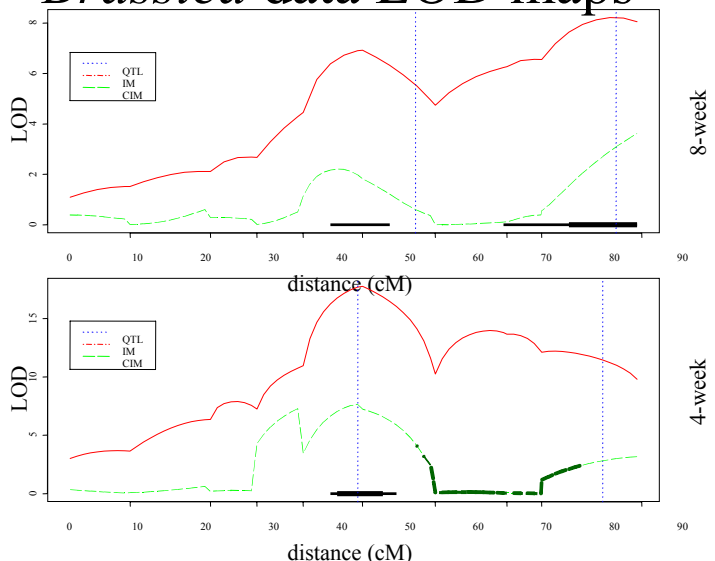




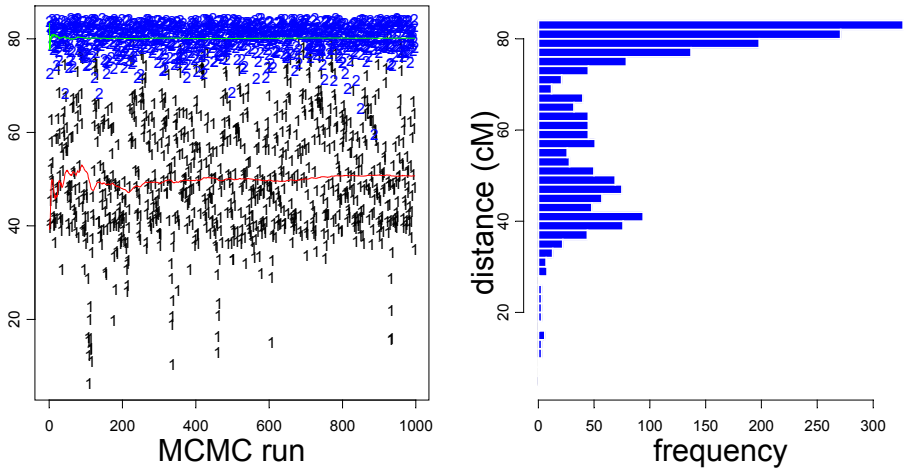


summaries of raw data
joint scatter plots
(identity line)
separate histograms

Brassica data LOD maps



Brassica 8-week data locus MCMC with *m*=2



4-week vs 8-week vernalization

4-week vernalization

- longer time to flower
- larger LOD at 40cM
- modest LOD at 80cM
- loci well determined

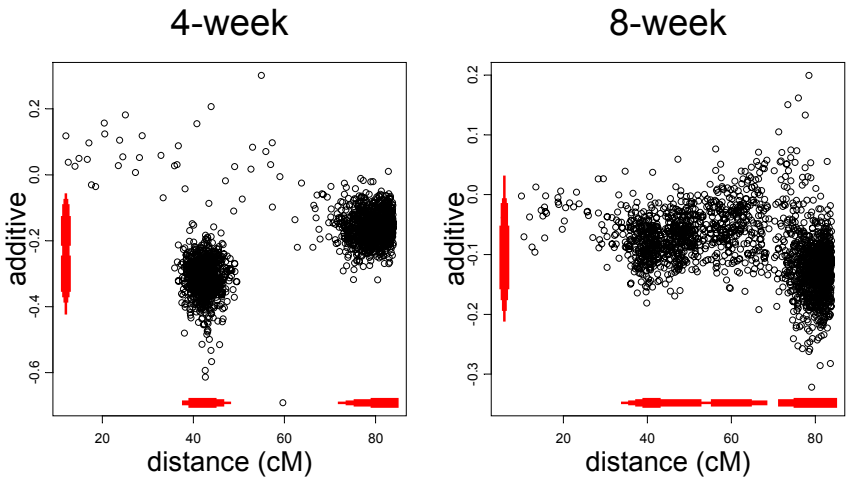
cM	add
40	.30
80	.16

8-week vernalization

- shorter time to flower
- larger LOD at 80cM
- modest LOD at 40cM
- loci poorly determined

cM	add
40	.06
80	.13

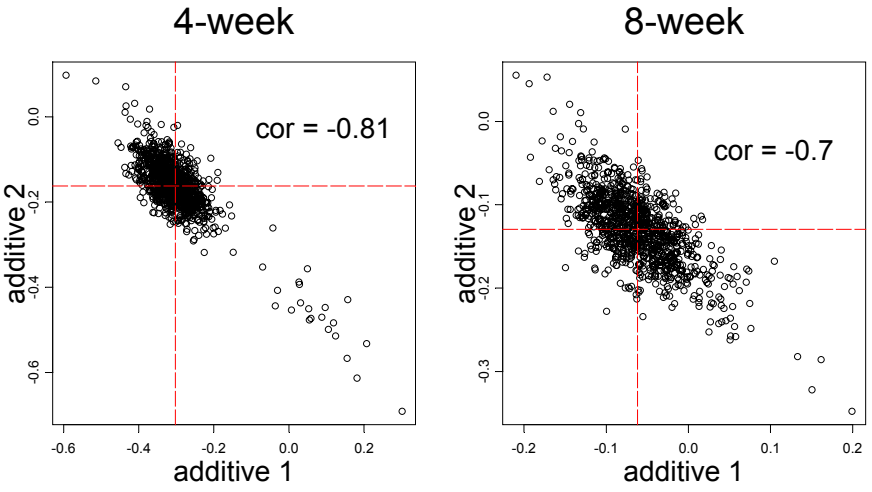
Brassica credible regions



collinearity of QTLs

- multiple QT genotypes are correlated
  - QTL linked on same chromosome
  - difficult to distinguish if close
- estimates of QT effects are correlated
  - poor identifiability of effects parameters
  - correlations give clue of how much to trust
- which QTL to go after in breeding?
  - largest effect?
  - may be biased by nearby QTL

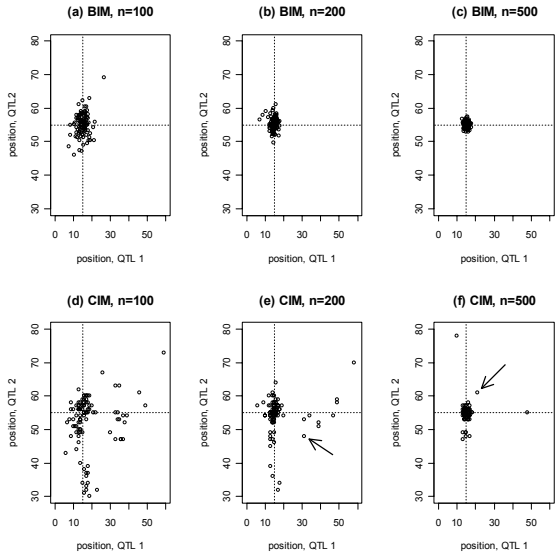
Brassica effect correlations



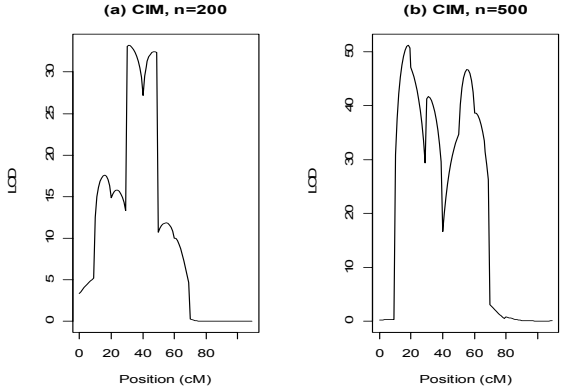
simulation: Bayesian vs composite IM

- 11 markers at 10cM spacing
- 2 QTL at 15cM, 55cM
  - effect size 1, variance 1, heritability 74%
- sample sizes n = 100, 200, 500
  - 100 independent trials
- comparison of methods
  - Bayesian interval mapping, 400,000 scans
  - composite interval mapping (QTL Cart)

Bayesian vs. composite IM: 2 QTL



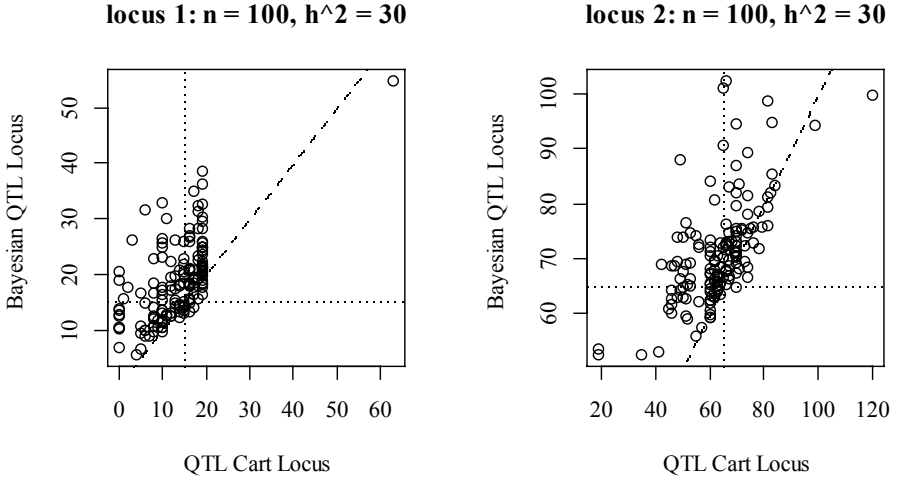
ghost QTL detected with CIM two selected examples



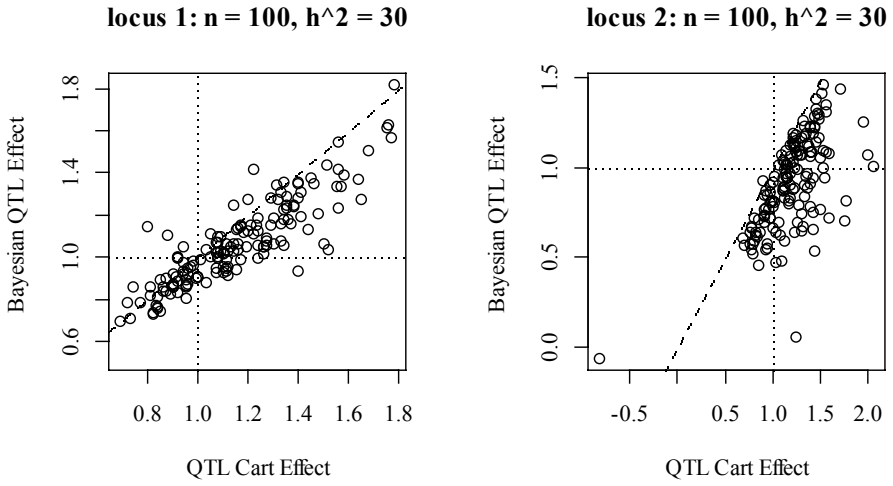
another 2-QTL simulation

- CIM vs. Bayesian QTL estimates
  - locus: 15, 65cM
  - effect: 1, 1
- sample sizes and heritabilities
  - $n = 100$, $h^2 = 30$
  - $n = 200$, $h^2 = 25, 30, 40$
  - 100 independent trials
- examine loci and effects

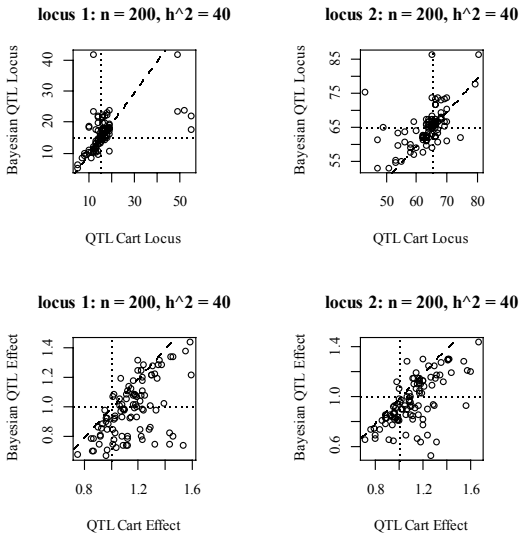
2 QTL: loci estimates



2 QTL: effect estimates



2 QTL: loci and effects



Part VI: How many QTLs?

- How many QTLs?
  - number of QTL is uncertain
  - estimate the number *m*
- What is the genetic architecture?
  - model architecture is uncertain
    - number, gene action, interaction among QTL
  - estimate the model *M*
- How does reversible jump MCMC work?
  - basic idea of Green(1995)
  - model selection in regression

QTL Full Posterior

- posterior = likelihood * prior / constant
- posterior(paramaters | data)

pr(loci, genos, effects, model | trait, map)

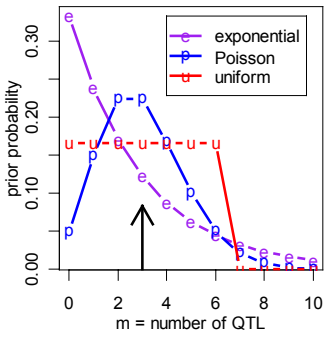
$$\text{pr}(\lambda, Q, \theta, M \mid Y, X) = \frac{\text{pr}(\theta \mid M)\text{pr}(\lambda \mid M)\text{pr}(Q \mid X, \lambda, M)\text{pr}(Y \mid Q, \theta, M)\text{pr}(M)}{\text{constant}}$$

$$\text{constant} = \text{pr}(Y) = \text{sum}_M \text{pr}(Y \mid M)$$

$$\text{pr}(Q \mid X, \lambda, M)\text{pr}(Y \mid Q, \theta, M) = \text{product}_i \left[\text{pr}(Q \mid X_i, \lambda, M)\text{pr}(Y_i \mid Q, \theta, M)\right]$$

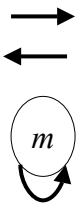
jumping the number of QTL

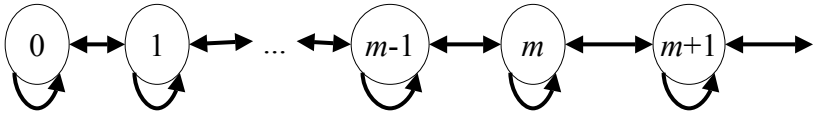
- model changes with number of QTL
  - analogous to stepwise regression if Q known
  - use reversible jump MCMC to change number
    - book keeping to compare models
    - change of variables between models
- what prior on number of QTL?
  - uniform over some range
  - Poisson with prior mean
  - exponential with prior mean



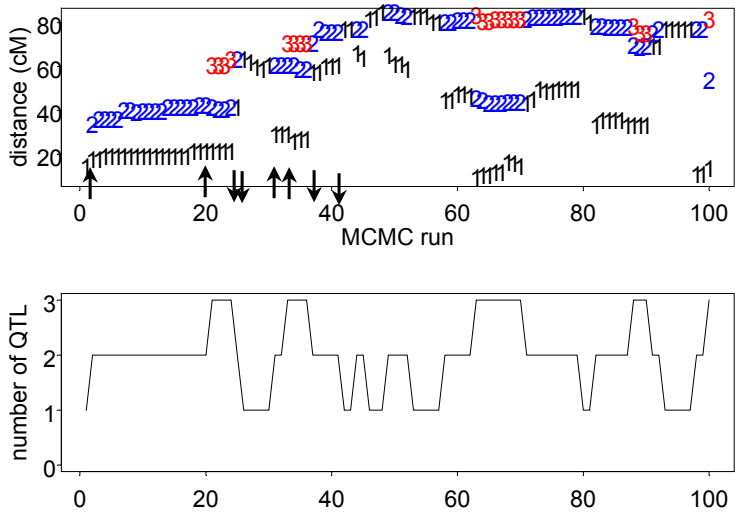
Markov chain for number m

- add a new locus
- drop a locus
- update current model

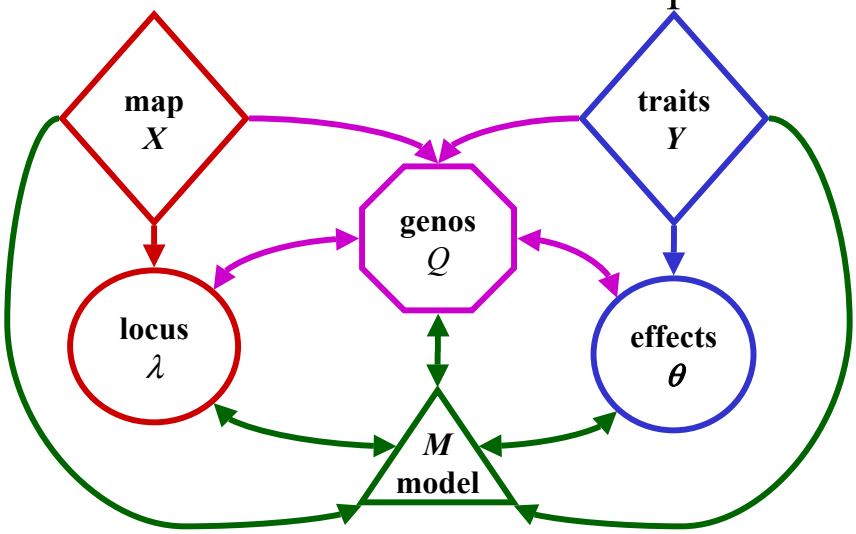




jumping QTL number and loci



RJ-MCMC full conditional updates

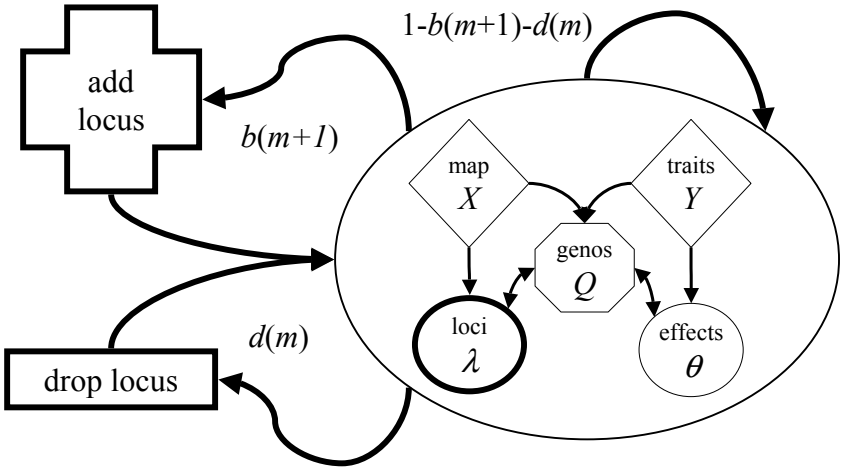


reversible jump choices

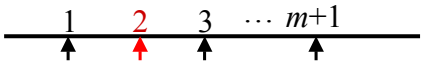
action step: draw one of three choices
(m = number of QTL in model)

- update step with probability 1-$b(m+1)$-$d(m)$
  - update current model
  - loci, effects, genotypes as before
- add a locus with probability $b(m+1)$
  - propose a new locus
  - innovate effect and genotypes at new locus
  - decide whether to accept the "birth" of new locus
- drop a locus with probability $d(m)$
  - pick one of existing loci to drop
  - decide whether to accept the "death" of locus

RJ-MCMC updates



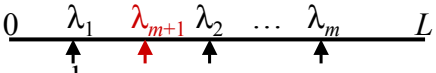
propose to drop a locus



- choose an existing locus
  - equal weight for all loci ?
  - more weight to loci with small effects?
- "drop" effect & genotypes at old locus
  - adjust effects at other loci for collinearity
  - this is reverse jump of Green (1995)
- check acceptance …
  - do not drop locus, effects & genotypes
  - until move is accepted

$$q_d(r;m+1)=\frac{1}{m+1}$$

propose to add a locus



- propose a new locus
  - uniform chance over genome
  - actually need to be more careful (R van de Ven, pers. comm.)
    - choose interval between loci already in model (include 0,L)
      - probability proportional to interval length $(\lambda_2-\lambda_1)/L$
    - uniform chance within this interval $1/(\lambda_2-\lambda_1)$
  - need genotypes at locus & model effect
- innovate effect & genotypes at new locus
  - draw genotypes based on recombination (prior)
    - no dependence on trait model yet
  - draw effect as in Green's reversible jump
    - adjust for collinearity: modify other parameters accordingly
- check acceptance ...

$$q_b(\lambda)=1/L$$

acceptance of reversible jump

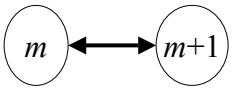
- accept birth of new locus with probability
$\min(1, A)$
- accept death of old locus with probability
$\min(1, 1/A)$

$$A = \frac{\text{pr}(\theta_{m+1}, m+1 \mid Y, X)}{\text{pr}(\theta_m, m \mid Y, X)} \times \frac{d(m+1)}{b(m)} \frac{q_b(\lambda_{m+1})}{q_d(r; m+1)} \frac{1}{J}$$

$$\theta_m = (Q, \theta, \lambda, m)$$

acceptance of reversible jump

- move probabilities



$$\frac{d(m+1)}{b(m)}$$

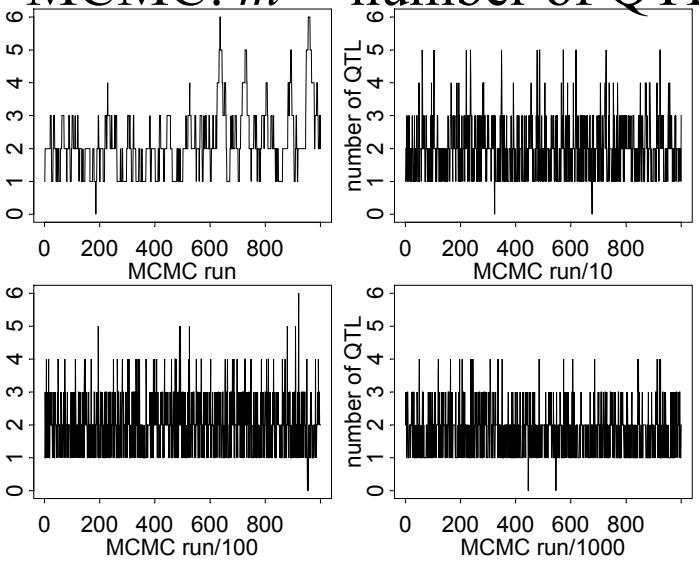
- birth & death proposals

$$\frac{q_b(\lambda_{m+1})}{q_d(r; m+1)}$$

- Jacobian between models
  - –fudge factor
  - –see stepwise regression example

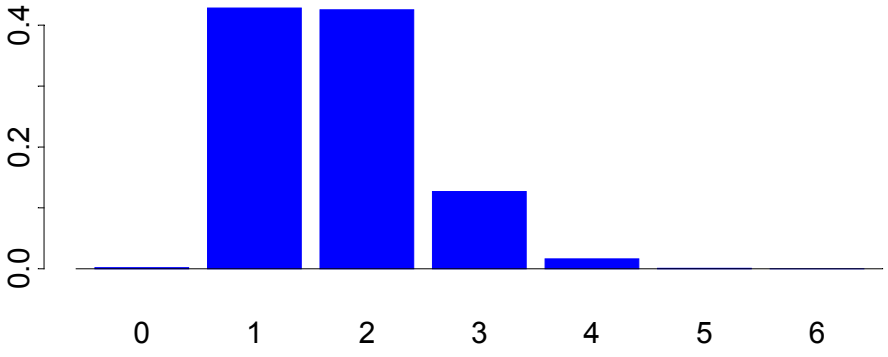
$$J = \frac{\sigma}{s_{r|others}\sqrt{n}}$$

RJ-MCMC: m = number of QTL



posterior for m for 8-week data

98% credible region for m: (1,3)
based on 1 million steps
Poisson prior with mean 3



Part VII: Reversible Jump Details

- reversible jump MCMC details
  - can update model with *m* QTL
  - have basic idea of jumping models
  - now: careful bookkeeping between models
- RJ-MCMC & Bayes factors
  - Bayes factors from RJ-MCMC chain
  - components of Bayes factors

reversible jump idea

- expand idea of MCMC to compare models
- adjust for parameters in different models
  - augment smaller model with innovations
  - constraints on larger model
- calculus "change of variables" is key
  - add or drop parameter(s)
  - carefully compute the Jacobian
- consider stepwise regression
  - Mallick (1995) & Green (1995)
  - efficient calculation with Hausholder decomposition

model selection in regression

- known regressors (e.g. markers)
  - models with 1 or 2 regressors
- jump between models
  - centering regressors simplifies calculations

$$m = 1 : Y_i = \mu + a(Q_{i1} - \overline{Q}_1) + e_i$$

$$m = 2 : Y_i = \mu + a_1(Q_{i1} - \overline{Q}_1) + a_2(Q_{i2} - \overline{Q}_2) + e_i$$

slope estimate for 1 regressor

recall least squares estimate of slope
note relation of slope to correlation

$$\hat{a} = \frac{r_{1y}\, s_y}{s_1}, \quad r_{1y} = \frac{\sum_{i=1}^{n}(Q_{i1} - \overline{Q}_1)(Y_i - \overline{Y})/n}{s_1\, s_y}$$

$$s_1^2 = \sum_{i=1}^{n}(Q_{i1} - \overline{Q}_1)^2/n, \; s_y^2 = \sum_{i=1}^{n}(Y_i - \overline{Y})^2/n$$

2 correlated regressors

slopes adjusted for other regressors

$$\hat{a}_1 = \frac{(r_{1y} - r_{12}r_{2y})s_y}{s_1} = \hat{a} - \frac{r_{2y}s_y}{s_2}c_{21}, \quad c_{21} = \frac{r_{12}s_2}{s_1}$$

$$\hat{a}_2 = \frac{(r_{2y} - r_{12}r_{1y})s_y}{s_2}, s^2_{2\cdot 1} = \frac{\sum_{i=1}^{n}(Q_{i2} - \overline{Q}_2 - c_{21}(Q_{i1} - \overline{Q}_1))^2}{n}$$

Gibbs Sampler for Model 1

- mean $$\mu \sim \phi\left(\eta + B_n(\overline{Y}_\cdot - \eta), B_n\frac{\sigma^2}{n}\right), B_n = \frac{n}{n+\kappa}$$
- slope $$a \sim \phi\left(B_n\frac{\sum_{i=1}^{n}(Q_{i1} - \overline{Q}_1)(Y_i - \overline{Y}_\cdot)}{ns_1^2}, B_n\frac{\sigma^2}{ns_1^2}\right)$$
- variance $$\sigma^2 \sim \text{inv-}\chi^2\left(\nu + n, \frac{\nu\tau^2 + \sum_{i=1}^{n}\left(Y_i - \overline{Y}_\cdot - a(Q_{i1} - \overline{Q}_1)\right)^2}{\nu + n}\right)$$

Gibbs Sampler for Model 2

- mean $\mu \sim \phi\left(\eta + B_n(\overline{Y}_\cdot - \eta), B_n \frac{\sigma^2}{n}\right)$
- slopes $a_2 \sim \phi\left(B_n \frac{\sum_{i=1}^{n}(Q_{i2} - \overline{Q}_2)(Y_i - \overline{Y}_\cdot - a_1(Q_{i1} - \overline{Q}_1))}{ns_{2\cdot 1}^2}, B_n \frac{\sigma^2}{ns_{2\cdot 1}^2}\right)$
- variance $\sigma^2 \sim \text{inv-}\chi^2\left(v + n, \frac{v\tau^2 + \sum_{i=1}^{n}\left(Y_i - \overline{Y}_\cdot - \sum_{k=1}^{2} a_k(Q_{ik} - \overline{Q}_k)\right)^2}{v+n}\right)$

updates from 2->1

- drop 2nd regressor
- adjust other regressor

$$a \rightarrow a_1 + a_2 c_{21}$$
$$a_2 \rightarrow 0$$

updates from 1->2

- add 2nd slope, adjusting for collinearity
- adjust other slope & variance

$$z \sim \phi(0,1), \qquad J = \frac{\sigma}{s_{2\cdot1}\sqrt{n}}$$

$$a_2 \to \hat{a}_2 + z \times J, \quad \hat{a}_2 = \frac{\sum_{i=1}^{n} (Q_{i2} - \overline{Q}_2)\left(Y_i - \hat{\mu} - \hat{a}_1 (Q_{i1} - \overline{Q}_1)\right)}{n s_{2\cdot1}^2}$$

$$a_1 \to a - a_2 c_{21} = a - z \times c_{21} J - \hat{a}_2 c_{21}$$

model selection in regression

- known regressors (e.g. markers)
  - models with 1 or 2 regressors
- jump between models
  - augment with new innovation z

m	parameters	innovations	transformations
$1 \to 2$	$(\mu, a, \sigma^2; z)$	$z \sim \phi(0,1)$	$\begin{Bmatrix} a_2 \to \hat{a}_2 + z \times J \\ a_1 \to a - a_2 c_{21} \end{Bmatrix}$
$2 \to 1$	$(\mu, a_1, a_2, \sigma^2)$		$\begin{Bmatrix} a \to a_1 + a_2 c_{21} \\ z \to 0 \end{Bmatrix}$

change of variables

- change variables from model 1 to model 2
- calculus issues for integration
  - need to formally account for change of variables
  - infinitessimal steps in integration (*db*)
  - involves partial derivatives (next page)

$$\begin{pmatrix} a_1 \\ a_2 \end{pmatrix} = \begin{bmatrix} 1 & -c_{21}J & -c_{21} \\ 0 & J & 1 \end{bmatrix} \times \begin{pmatrix} a \\ z \\ \hat{a}_2 \end{pmatrix} = g(a;z \mid Y, Q_1, Q_2)$$

$$\int \pi(a_1, a_2 \mid Y, Q_1, Q_2) da_1 da_2 = \int \pi(a;z \mid Y, Q_1, Q_2) J da dz$$

Jacobian & the calculus

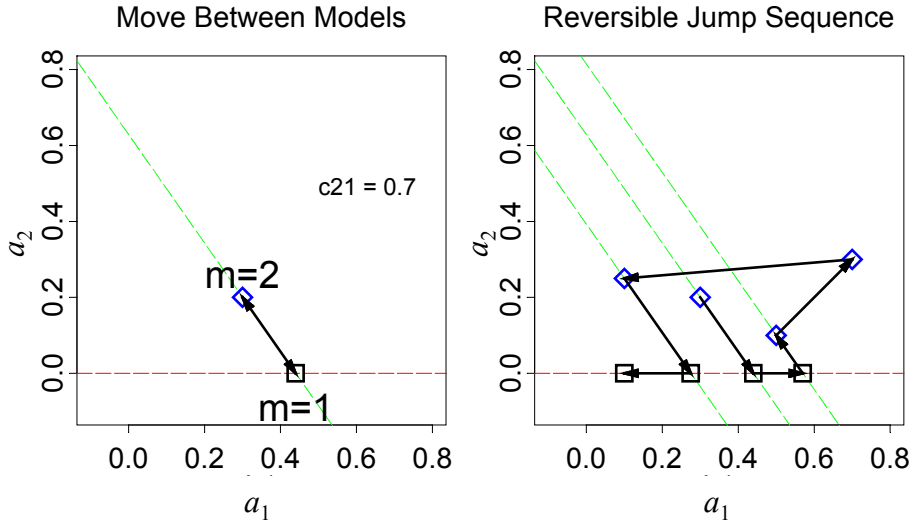
- Jacobian sorts out change of variables
  - careful: easy to mess up here!

$$g(a;z) = (a_1, a_2), \quad \frac{\partial g(a;z)}{\partial a \partial z} = \begin{bmatrix} 1 & -c_{21}J \\ 0 & J \end{bmatrix}$$

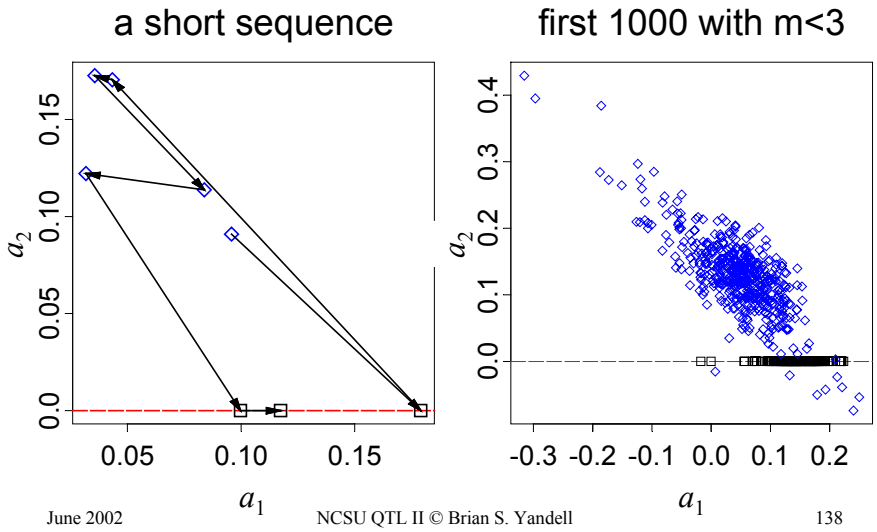
$$\left| \det\left(\begin{bmatrix} 1 & -c_{21}J \\ 0 & J \end{bmatrix} \right) \right| = \left| 1 \times J - 0 \times (-c_{21}J) \right| = J$$

$$da_1 da_2 = \left| \det\left(\frac{\partial g(\mu, a, \sigma^2; z)}{\partial a \partial z} \right) \right| da_1 da_2 = J da dz$$

geometry of reversible jump



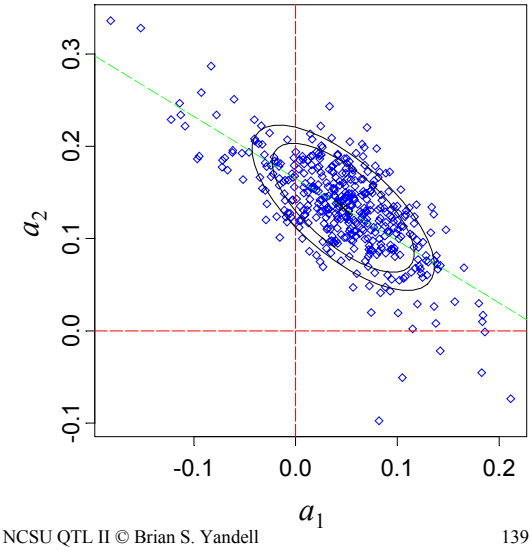
QT additive reversible jump



credible set for additive

90% & 95% sets based on normal

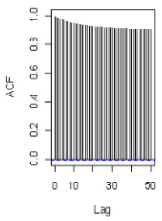
regression line corresponds to slope of updates



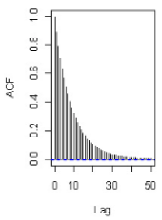
multivariate updating of effects

- more computations when $m > 2$
- avoid matrix inverse
  - Cholesky decomposition of matrix
- simultaneous updates
  - effects at all loci
- accept new locus based on
  - sampled new genos at locus
  - sampled new effects at all loci
- also long-range positions updates

before



after



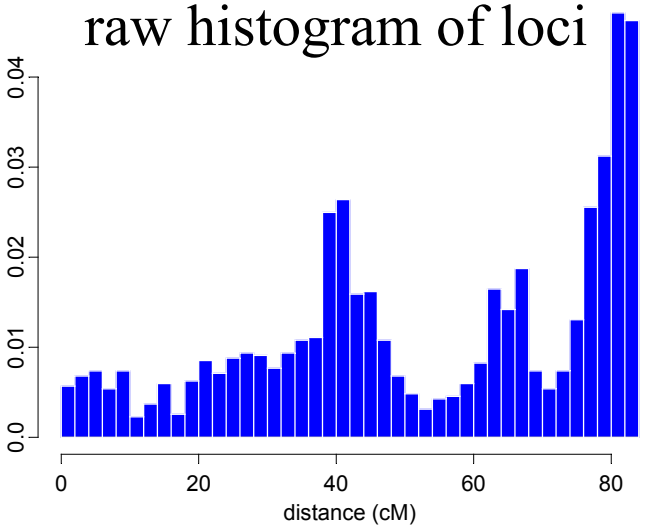
Part VII: Model Assessment

- posterior histograms
  - number of QTL
    - effect of prior on posterior
  - genetic architecture across genome
  - model averaging: loci and effects
- Bayes factors
  - What are Bayes factors?
  - Bayes factors from RJ-MCMC chain
  - components of Bayes factors

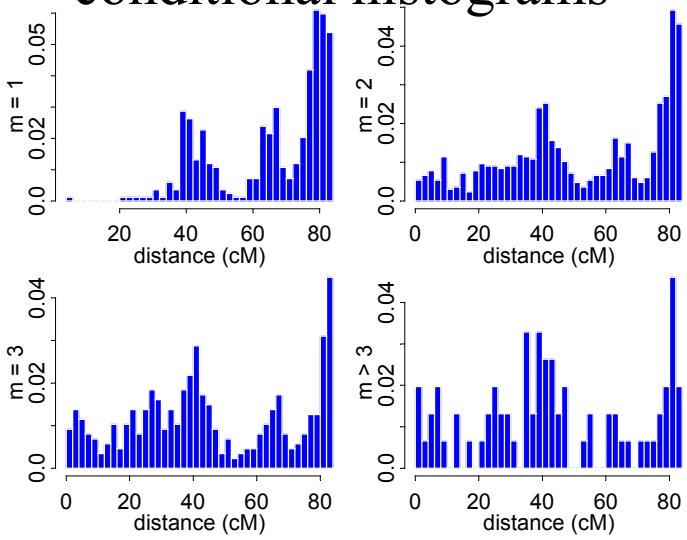
model selection and assessment

- how many QTL are supported by data?
  - parsimony: balance model fit to model complexity
- posterior as tool for model insight
  - number and chromosome distribution of QTL
  - loci and effects across genome
  - heritability, variance and LOD by number of QTL
- Bayes factors
  - advantages
    - related to likelihood ratio test
    - modest sensitivity to prior
    - intuitive interpretation
  - disadvantages/criticisms
    - do not work for improper priors
    - theoretical problems (Gelfand Day 1994; Draper 1995)

8-week vernalization raw histogram of loci



conditional histograms



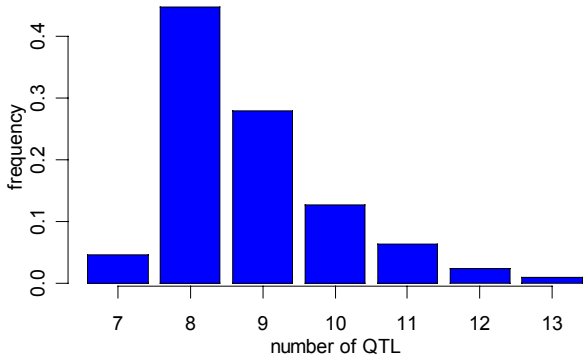
8 QTL simulation (Stevens Fisch 1998)

- $n = 200$, $h^2 = .5$
  - SF detected 3 QTL
- Bayesian IM

n	h^2	detect
200	.5	2
200	.8	4
500	.9	7
500	.97	8

QTL No. j	Location, λ_j			Additive effect α_j	Dominance Effect δ_j
	Chrom. λ_j^c	Marker λ_j^m	Position (cM)		
1	1	1	11	-3	0
2	1	3	10	-5	0
3	3	4	2	2	0
4	6	6	7	-3	0
5	6	8	12	3	0
6	8	2	12	-4	0
7	8	3	14	1	0
8	9	10	15	2	0

posterior number of QTL

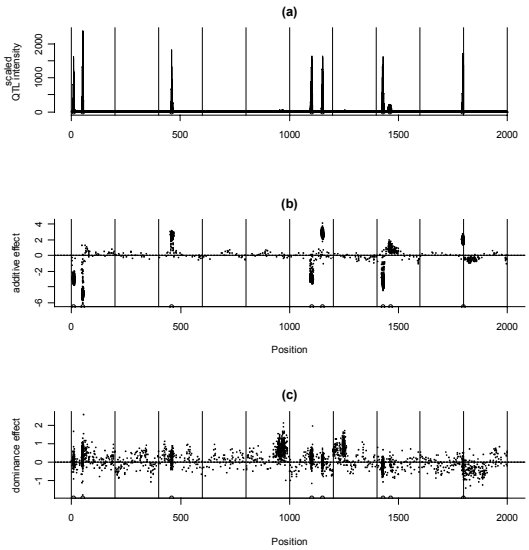


geometric prior with mean 0.5
seems to have no influence on posterior here

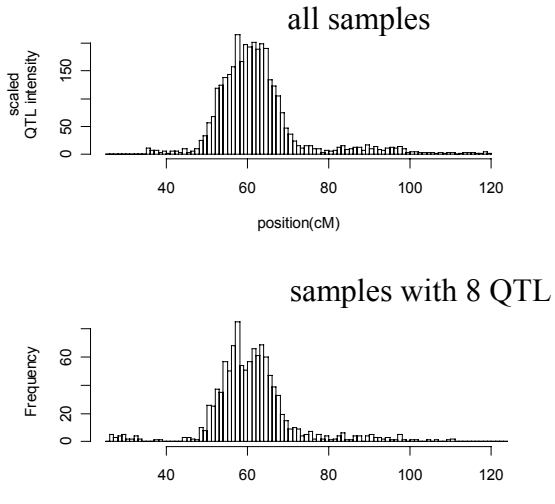
posterior genetic architecture

	Chromosome count vector										
m	1	2	3	4	5	6	7	8	9	10	Count
8	2	0	1	0	0	2	0	2	1	0	3371
9	*3*	0	1	0	0	2	0	2	1	0	751
7	2	0	1	0	0	2	0	*1*	1	0	377
9	2	0	1	0	0	*3*	0	2	1	0	218
9	2	0	1	0	0	2	0	2	*2*	0	198

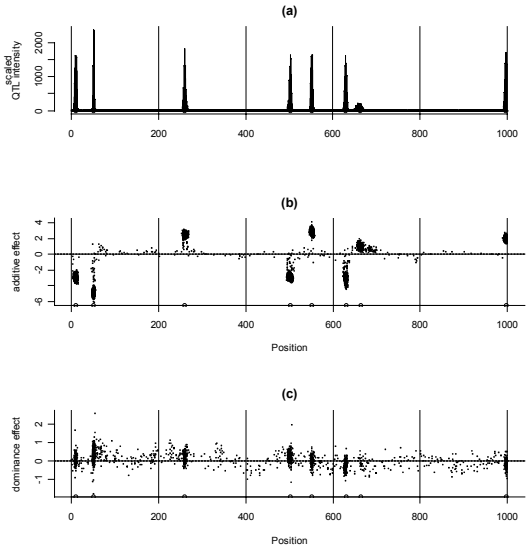
model averaging for 8 QTL



model averaging: focus on chr. 8



focus on key chromosomes



B. napus 8-week vernalization whole genome study

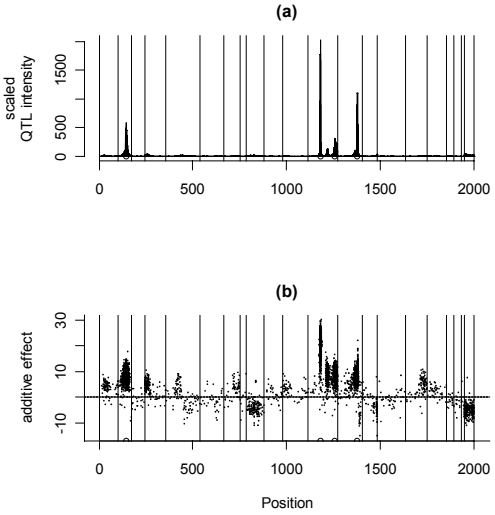
chrom	position	LOD	effect
n2	66.4	25.87	21.3
n3	106.8	13.33	12.95
n10	43.3	13.14	12.77
n2	154.0	10.69	11.3
n13	126.7	32.4	-5.78

Table 8.5: Result of CIM analysis for *B. napus dataset.*

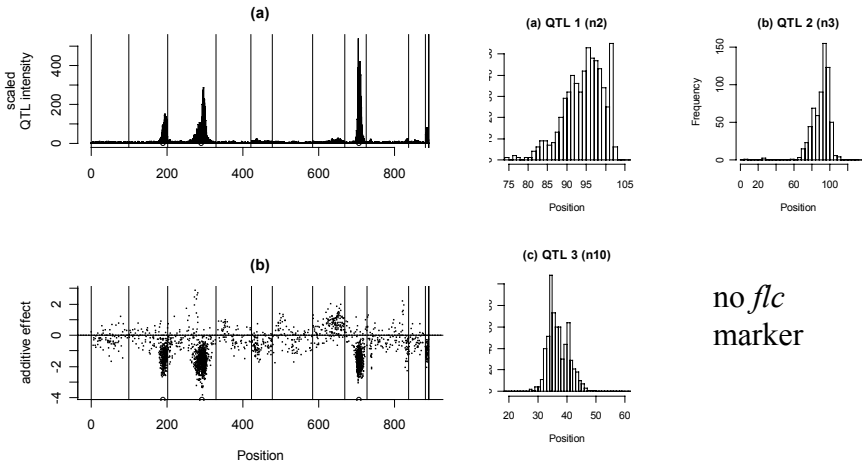
chrom	position	effect
n10	45.0	9.24
n2	66.9	22.4
n2	142.6	9.01
n3	103.4	8.36

Table 8.6: Estimates of QTL location and effect using BIM.

8-week vern: model averaging

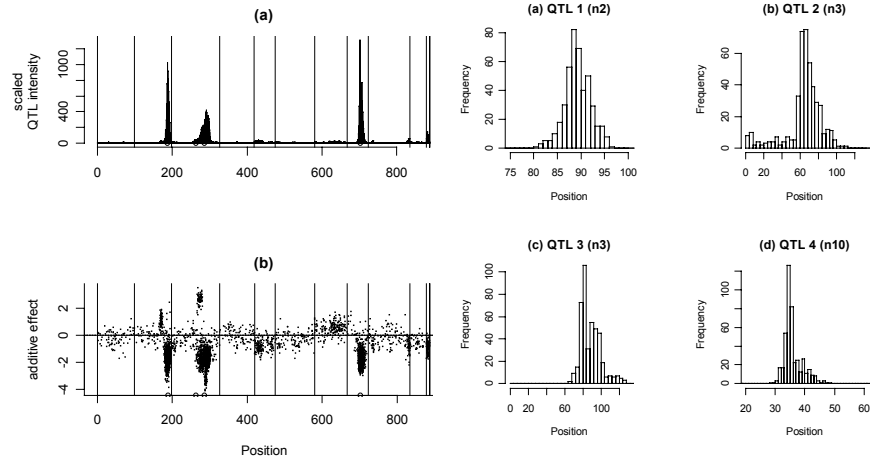


B. rapa: effect of *flc* marker
Kole et al. (1997)



no *flc* marker

B. rapa with added *flc* marker



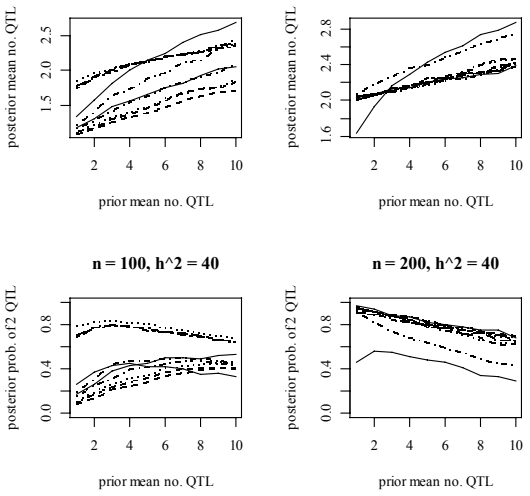
How sensitive is posterior to choice of prior?

- simulations with 0, 1 or 2 QTL
  - strong effects (additive = 2, variance = 1)
  - linked loci 36cM apart
- differences with number of QTL
  - clear differences by actual number
  - works well with 100,000, better with 1M
- effect of Poisson prior mean
  - larger prior mean shifts posterior up
  - but prior does not take over

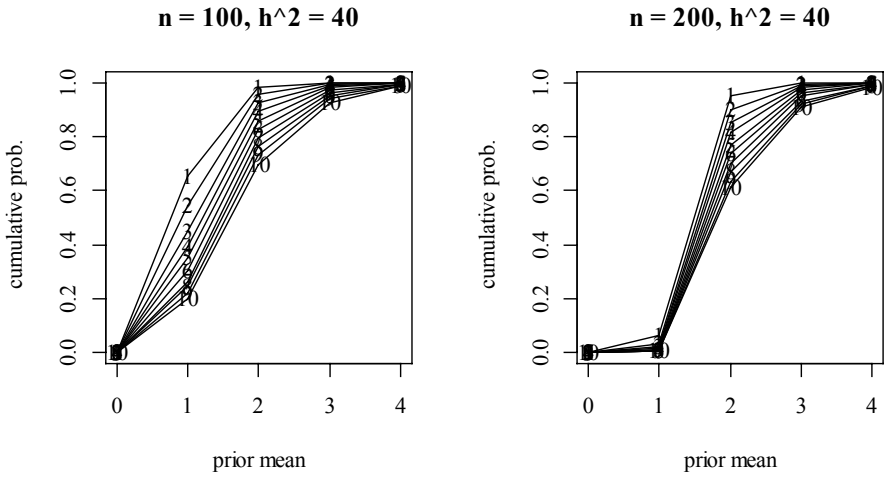
simulation study: prior

- 2 QTL at 15, 65cM
- n = 100, 200; h^2 = 40%
- vary prior mean from 1 to 10 QTL
  - Poisson prior
- 10 independent simulations
- examine posterior mean, probability

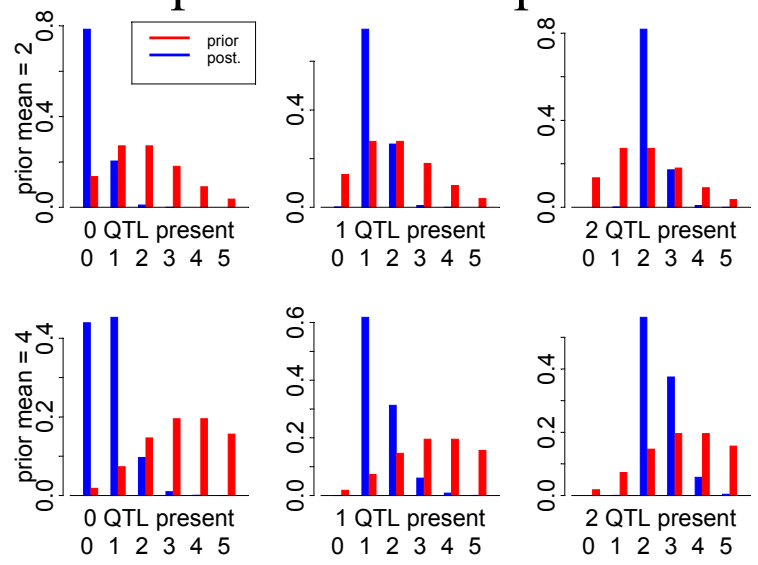
posterior *m* depends on prior



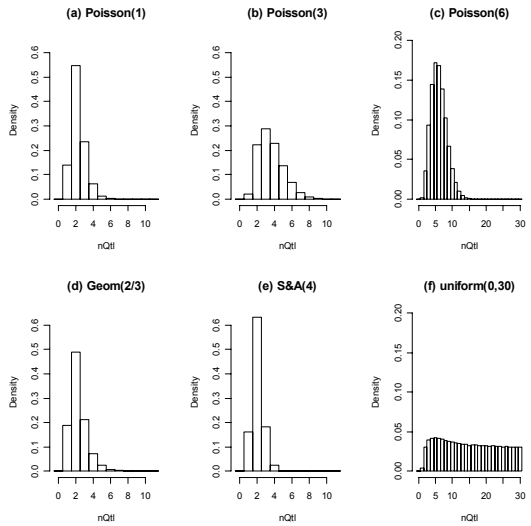
cumulative posterior as prior mean changes



effect of prior mean on posterior *m*



prior effect on posterior



Bayes factors

Which model (1 or 2 or 3 QTLs?) has higher probability of supporting the data?

- ratio of posterior odds to prior odds
- ratio of model likelihoods

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

BF(1:2)	2log(BF)	evidence for 1st
< 1	< 0	negative
1 to 3	0 to 2	negligible
3 to 12	2 to 5	positive
12 to 150	5 to 10	strong
> 150	> 10	very strong

computing marginal means

$$\text{pr}(Y \mid \text{model}_k) = \int \text{pr}(Y \mid \theta_k, \text{model}_k)\text{pr}(\theta_k \mid \text{model}_k)d\theta_k$$

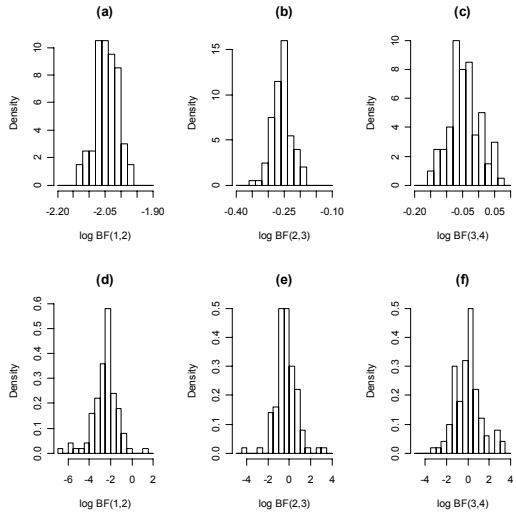
- very difficult based on separate model runs
  - run MCMC for model k
  - average pr(Y|θ_k) across model parameters θ_k
    - arithmetic mean
      - can be inefficient if prior differs from posterior
    - weighted harmonic mean
      - more efficient but less stable
    - stabilized harmonic mean (SHM)
      - average over "nuisance parameters" (*e.g.* variance)
      - more work, but estimate is more stable (Satagopan et al. 2000)
- easy when model itself is a parameter
  - RJ-MCMC: marginal summaries of number of QTL
  - posterior/prior provides Bayes factor yardstick

estimating Bayes factors

combined RJ-MCMC
posterior freq/prior

8-wk vern data
100 MCMC repeats
(note different scales)

separate MCMCs
stabilized
harmonic mean



Bayes factors & likelihood ratio

- equivalent to *LR* statistic when
  - comparing two nested models
  - simple hypotheses (e.g. 1 vs 2 QTL)
- Bayes Information Criteria (BIC) in general
  - Schwartz introduced for model selection
  - penalty for different number of parameters *p*

$$-2\log(B_{12}) = -2\log(LR) - (p_2 - p_1)\log(n)$$

Bayesian LOD

- Bayesian "LOD" computed at each step
  - based on *LR* given sampled genotypes and effects
  - can be larger or smaller than profile LOD
  - informal diagnostic of fit
  - geometric marginal means for pr(*Y*|model)
  - log posterior odds (LPD; see Sen Churchill 2000)

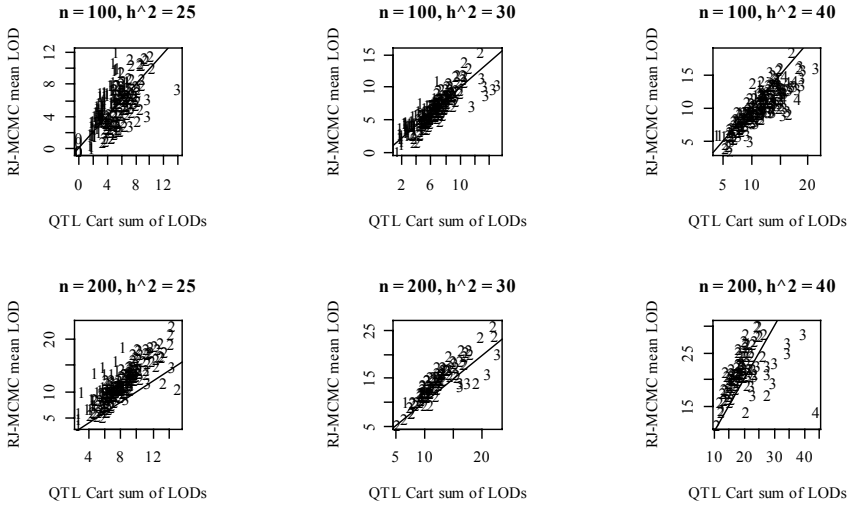
$$LOD(\lambda) = (\log_{10} e)\sum_{i=1}^{n} \ln\left(\frac{\sum_{Q} \Pr(Y_i \mid Q;\hat{\theta})\Pr(Q \mid X_i,\lambda)}{\Pr(Y_i \mid \tilde{\theta})} \right)$$

$$BLOD = (\log_{10} e)\sum_{i=1}^{n} \ln\left(\frac{\Pr(Y_i \mid Q_i,\theta)}{\Pr(Y_i \mid \tilde{\theta})} \right)$$

compare LODs

- 200 simulations (only 100 for some)
- n = 100, 200; h^2 = 25, 30, 40%
- 2 QTL at 15, 65cM
- Bayesian vs. CIM-based LODs
  - Bayesian for simultaneous fit
  - classical for sum of CIM LODs at peaks
- plot symbol is number of CIM peaks

comparing LODs



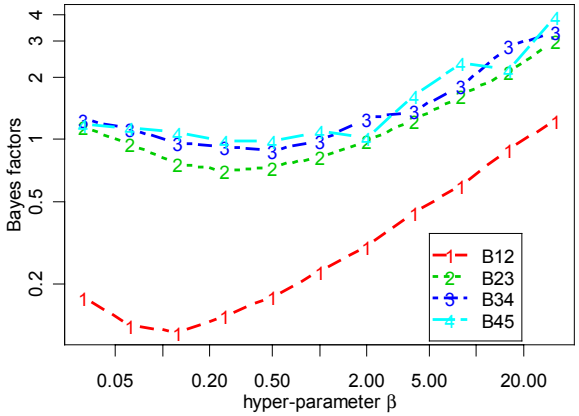
prior sensitivity of Bayes factor

- adjust effects prior as *m* grows
  - otherwise prior dominates for large models
- BF sensitive to fixed prior for effects
  - use hyperprior to soften effect

$$Y_i = \mu + \sum_{r=1}^{m} a_r Q_{ri} + e_i$$

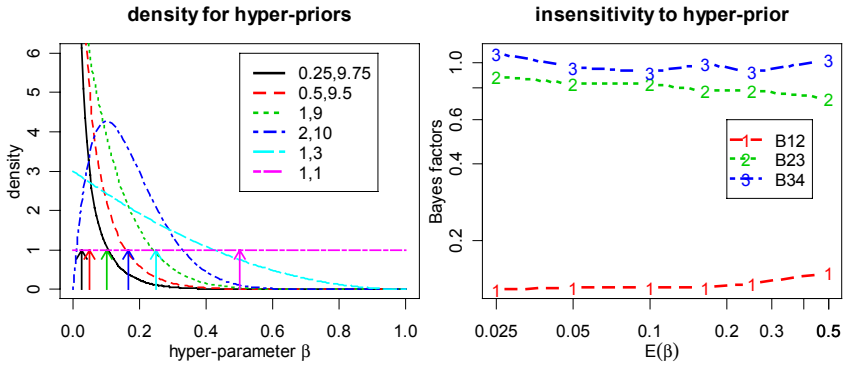
$$a_r \sim \mathrm{N}(0, 2\beta s^2 / m), \beta \sim \mathrm{Beta}(?, ?)$$

BF sensitivity to fixed prior for effects



Bayes factors for 8-week vernalization data

BF insensitivity to random effects prior



$$a_r \sim \mathrm{N}(0, 2\beta s^2/m), \beta \sim \mathrm{Beta}(?,?)$$

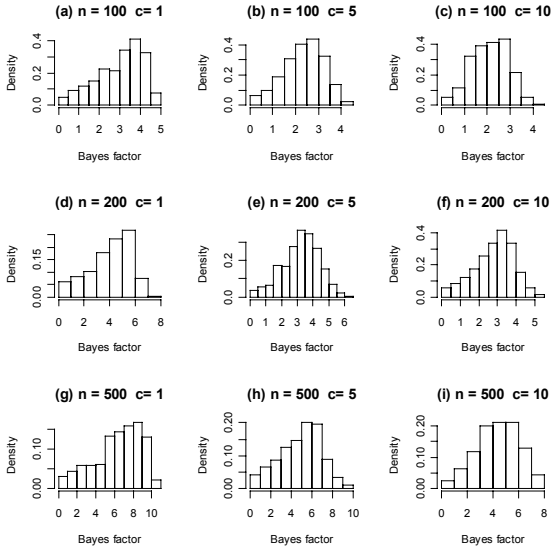
BF approximately invariant to form of prior

Prior, pr(*m*)	B_{12}	B_{23}	B_{34}	B_{45}
Geometric(2/3)	0.129	0.773	0.954	1.019
Poisson(1)	0.128	0.775	0.941	1.013
Poisson(3)	0.130	0.766	0.954	1.003
Poisson(6)	0.132	0.775	0.963	1.009
Fast-decay poisson(1)	0.128	0.764	0.941	1.022
Fast-decay Poisson(4)	0.129	0.773	9.963	1.032
Uniform	0.133	0.774	0.960	0.99

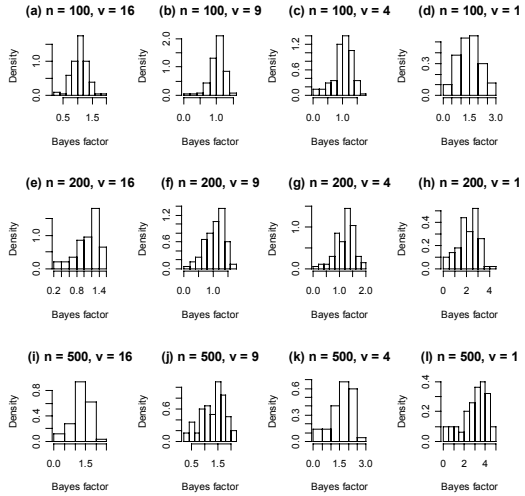
power study of Bayes factor

- large B_{01} favors model with 1 QTL
- n = 100, 200, 500
- size of genome
  - c = 1, 5, 10 number of chromosomes
- environmental variance
  - V = 1, 4, 9 with effect of size 1
- 11 markers per chromosome, 10cM apart
- 100 independent trials

B_{01} "power" vs. n & genome size c



B_{12} "size of test" vs. n & variance v



Part IX: Software & References

- MCMC software
  - general
  - specific to QTL problems
- References
  - MCMC, reversible jump
  - Bayesian approach
  - Bayesian QTL analysis

RJ-MCMC software

- General MCMC software
  - U Bristol links
    - www.stats.bris.ac.uk/MCMC/pages/links.html
  - BUGS (Bayesian inference Using Gibbs Sampling)
    - www.mrc-bsu.cam.ac.uk/bugs/
- MCMC software for QTLs
  - Bmapqtl (Satagopan Yandell 1996; Gaffney 2001)
    - www.stat.wisc.edu/~yandell/qtl/software/Bmapqtl
  - Bayesian QTL / Multimapper (Sillanpää Arjas 1998)
    - www.rni.helsinki.fi/~mjs
  - Yi, Xu (shxu@citrus.ucr.edu)
  - Stephens, Fisch (email)

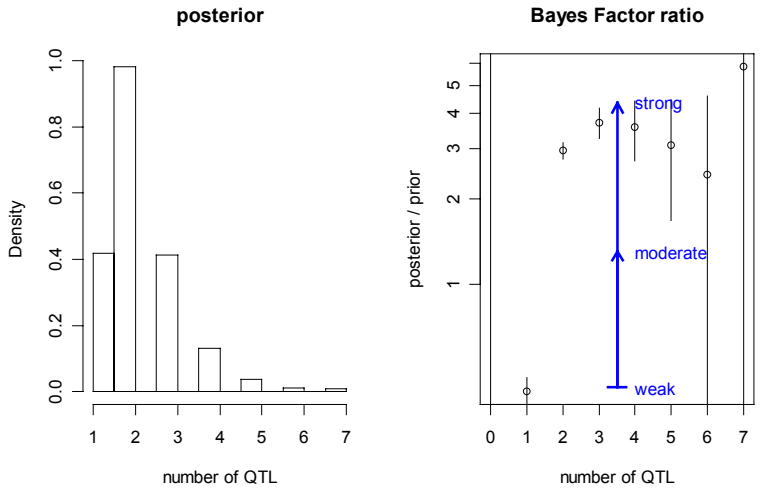
Bmapqtl: our RJ-MCMC software

- www.stat.wisc.edu/~yandell/qtl/software/Bmapqtl
  - module using QtlCart format
  - compiled in C for Windows/NT
  - extensions in progress
  - R post-processing graphics (Yandell)
- Bayes factor and reversible jump MCMC computation
- enhances MCMCQTL and revjump software
  - 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

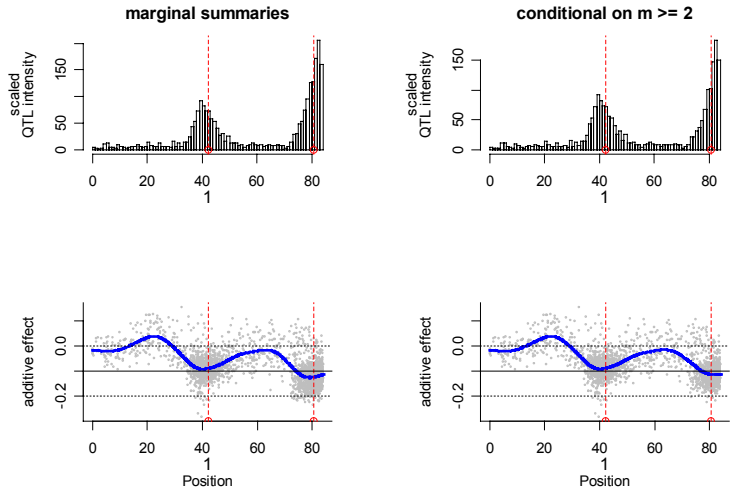
R library(Bmapqtl)

```
> library(Bmapqtl)
> Bmapqtl.plot( vern8.exp, "exp", nqtl = 2 )
posterior for number of QTL
   1    2    3    4    5    6    7
0.21 0.49 0.21 0.07 0.02 0.00 0.00
Loading required package: modreg
2 estimated loci: 42.22 80.64
marginal heritability 0.356
conditional heritability
    1     2     3     4     5     6     7
0.325 0.360 0.373 0.363 0.361 0.368 0.357
marginal LOD 9.726
conditional LOD
     1      2      3      4      5      6      7
 8.576  9.933 10.193 10.079 10.233 10.823  9.489
```

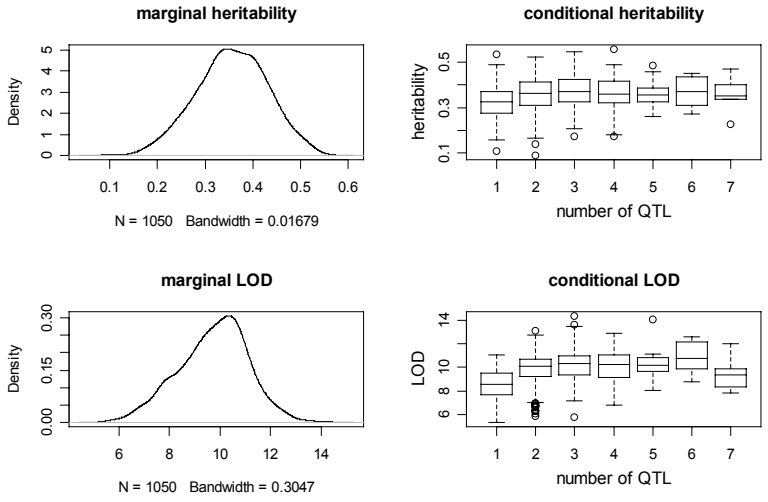
Bmapqtl.nqtl(data, prior)



Bmapqtl.loci(data, nqtl)



Bmapqtl.hist(data, histograms, mains)



the art of MCMC

- convergence issues
  - burn-in period & when to stop
- proper mixing of the chain
  - smart proposals & smart updates
- frequentist approach
  - simulated annealing: reaching the peak
  - simulated tempering: heating & cooling the chain
- Bayesian approach
  - influence of priors on posterior
  - Rao-Blackwell smoothing
- bump-hunting for mixtures (e.g. QTL)
  - model averaging

Bayes factor references

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QTL reversible jump MCMC: inbred lines

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QTL references

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Part X: Combining Multiple Crosses

- combining inbred lines in search of QTL
  - most IM methods limited to single cross
  - animal model largely focuses on polygenes
  - individuals no longer independent given Q
- recent work in plant sciences
  - Bernardo (1994) Wright's relationship matrix A
  - Rebai *et al.* (1994) regression method
  - Xu, Atchley (1995) IBD & A for QTLs & polygenes
  - Liu, Zeng (2000) multiple inbred lines, fixed effect IM
  - Zou, Yandell, Fine (2001 *Genetics*) power, threshold
  - Yi, Xu (2002) *Genetica*

thresholds for multiple crosses

- permutation test
  - Churchill Doerge (1994); Doerge Churchill (1996)
  - computationally intensive
  - difficult to compare different designs
- theoretical approximation
  - Lander Botstein (1989) Dupuis Siegmund (1999)
    - single cross, dense linkage map
  - Rebai *et al.* (1994, 1995) approximate extension
    - Piepho (2001) improved calculation of efficiency
  - Zou, Yandell, Fine (2001) extend original theory

extension of threshold theory

- likelihood for multiple crosses of inbred lines with m founders
  - approximately χ^2 with m degrees of freedom
  - genome-wide threshold theory
    - extends naturally based on Ornstein-Uhlenbeck
  - threshold based on dense or sparse linkage map
- some calculations based on BC1, F2, BC2
  - Liu Zeng (2000) ECM method to estimate $Y_j \sim \text{Normal}(G_{Qj}, \sigma_j^2), j = \text{cross}$

literature on outbred studies

- Interval Mapping for Outbred Populations
  - Haley, Knott & Elsen (1994) *Genetics*
  - Thomas & Cortessis (1992) *Hum. Hered.*
  - Hoeschele & vanRanden (1993ab) *Theor. Appl. Genet.* (etc.)
  - Guo & Thompson (1994) *Biometrics*
- Experimental Outbred Crosses (BC, F2, RI)
  - collapse markers from 4 to 2 alleles
- Multiple Cross Pedigrees
  - polygenic effects not modeled here
  - related individuals are correlated (via coancestry)
  - Liu & Zeng (2000) *Genetics*
  - Zou, Yandell & Fine (2001) *Genetics*

QTL reversible jump MCMC: pedigrees

- S Heath (1997) Markov chain Monte Carlo segregation and linkage analysis for oligenic models, *Am J Hum Genet* 61: 748-760.
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