Bayesian Inference for QTLs in Inbred Lines

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USDA Hatch Grants

What is the Goal Today?

- show MCMC ideas
  - Gibbs sampler
  - Metropolis-Hastings
- handle hard problems
  - image analysis
  - genetics
  - large dependent data
- resampling our data
  - permutation tests
  - MCMC
  - other (bootstrap,...)
- 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

Note on Outbred Studies

- Interval Mapping
  - Haley, Knott & Elsen (1994) *Genetics*
  - Thomas & Cortessis (1992) *Hum. Hered.*
  - Hoeschele & vanRanden (1993ab) *Theor. Appl. Genet.* (etc.)
  - Guo & Thompson (1994) *Biometrics*
- Nuances -- faking it
  - experimental outbred crosses
    - collapse markers from 4 to 2 alleles
  - pedigrees
    - polygenic effects not modeled here
    - related individuals are correlated (via coancestry)

Overview

- I: Single QTL
- II: Bayesian Idea
  - Bayes rule
  - posterior & likelihood
- III: MCMC Samples
  - Monte Carlo idea
  - study posterior
- IV: MCMC Details
- V: Multiple QTL
- VI: How many QTL?
  - Reversible Jump
  - analog to regression
- VII: RJ-MCMC Details
- VIII: Bayes Factors
- IX: References
  - Software
  - Articles

Part I: Interval Mapping

- Modelling a `trait` with a QTL
  - linear model for `trait` given genotype
  - recombination near `loci` for genotype
- Likelihoods
- Review Interval Maps & Profile LODs

QTL Components

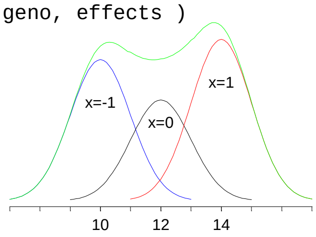
- observed data on individual
  - trait: field or lab measurement
    - log(days to flowering) , yield, …
  - markers: from wet lab (RFLPs, etc.)
    - linkage map of markers assumed known
- unobserved data on individual
  - geno: genotype (QQ=1/Qq=0/qq=-1)
- unknown model parameters
  - effects: mean, difference, variance
  - locus: quantitative trait locus (QTL)

Single QTL trait Model

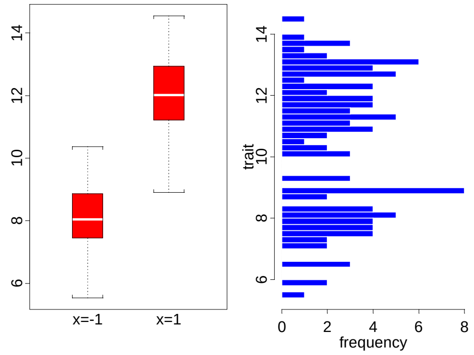
- trait = mean + additive + error
- trait = effect_of_geno + error
- *prob*(trait | geno, effects)

$$y_j=\mu+b^*x_j^*+e_j$$

$$\pi(y_j\mid x_j^*;\mu,b^*,\sigma^2)=\phi\left(\frac{y_j-\mu-b^*x_j^*}{\sigma}\right)$$



Simulated Data with 1 QTL

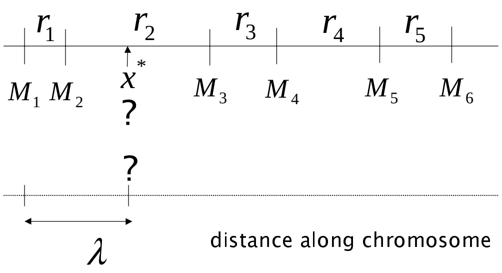


Recombination and Distance

- no interference--easy approximation
  - Haldane map function
  - no interference with recombination
- all computations consistent in approximation
  - rely on given map
    - marker loci assumed known
  - 1-to-1 relation of distance to recombination
  - all map functions are approximate
- assume marker positions along map are known

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

markers, QTL & recombination rates



distance along chromosome

Interval Mapping of QT genotype

- can express probabilities in terms of distance
  - locus is distance along linkage map
  - flanking markers sufficient if no missing data
  - could consider more complicated relationship

prob(geno | locus, map)
= *prob*(geno | locus, flanking markers)

$$\pi(x_j^*\mid\lambda)=\pi(x_j^*\mid\lambda,M_{j,k},M_{j,k+1})$$

Building trait Likelihood

- likelihood is mixture across possible genotypes
- sum over all possible genotypes at locus

like(effects, locus | trait)
= sum of *prob*(trait, genos | effects, locus)

$$L(\mu,b^*,\sigma^2,\lambda\,|\,y_j)=\pi(y_j\,|\,\mu,b^*,\sigma^2;\lambda)$$

$$=\sum_{x=-1,0,1}\pi(y_j\,|\,x;\mu,b^*,\sigma^2)\pi(x\,|\,\lambda)$$

Likelihood over Individuals

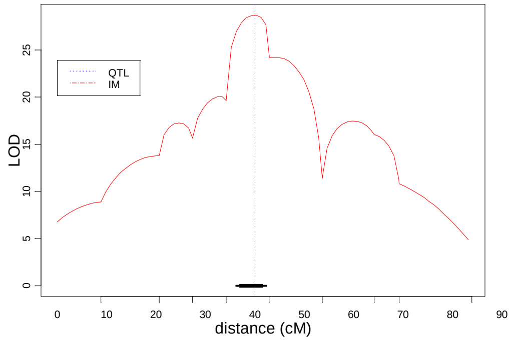
- product of trait probabilities across individuals
  - product of sum across possible genotypes

like(effects, locus | traits, map)
= product of *prob*(trait | effects, locus, map)

$$L(\mu,b^*,\sigma^2;\lambda\,|\,\mathbf{y})=\prod_{j=1}^{n}\pi(y_j\,|\,\mu,b^*,\sigma^2;\lambda)$$

$$=\prod_{j=1}^{n}\sum_{x=-1,0,1}\pi(y_j\,|\,x;\mu,b^*,\sigma^2)\pi(x\,|\,\lambda)$$

Profile LOD for 1 QTL



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)

$$LOD(\lambda)=(\log_{10}e)\sum_{j=1}^{n}\ln\left(\frac{\sum_{x=-1,0,1}\pi(y_j\,|\,x;\hat{\mu},\hat{b}^*,\hat{\sigma}^2)\pi(x\,|\,\lambda)}{\pi(y_j\,|\,\hat{\mu},b^*=0,\hat{\hat{\sigma}}^2)}\right)$$

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

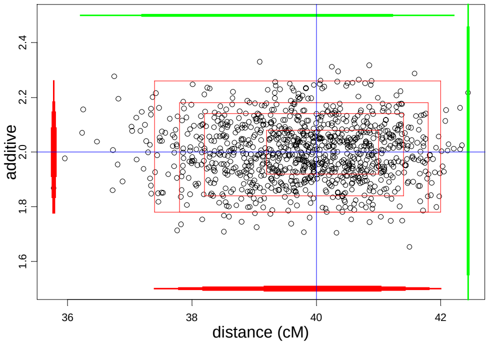
Interval Mapping Estimates

- 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

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

$$effect\ CI=\hat{b}^*\pm 1.96se(\hat{b}^*)$$

IM Confidence Region



Part II: Bayesian Idea

- joint distribution of known & unknown
  - known: trait, markers, linkage map
  - unknown: locus, genotype, effect, variance
- Use Same Likelihood Components
  - trait given genotype
    - follows linear model
    - depends on size of effect, variance
  - genotype given locus, markers & map
    - depends on recombination near locus
- Inference about unknowns
  - Bayes theorem

Bayes Theorem

- posteriors and priors
  - prior: *prob*(parameters)
  - posterior: *prob*(parameters | data)
- posterior = likelihood * prior / constant
- posterior distribution is proportional to
  - likelihood of parameters given data
  - prior distribution of parameters

$$\pi(param|data)=\frac{\pi(param,data)}{\pi(data)}=\frac{\pi(data|param)\times\pi(param)}{\pi(data)}$$

$$\pi(param|data)=\pi(data|param)\times\pi(param)/C$$

What is Probability?

Frequentist Analysis

repeat experiment

- many times
- hypothetical

long term frequency

- Type I error rate
- reject null when true

Bayesian Analysis

uncertainty about true value

prior

- uncertainty before examining data
- incorporate prior knowledge/experience

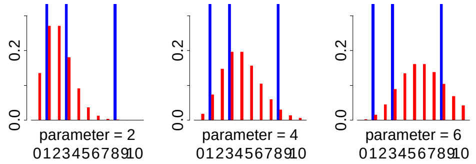
posterior

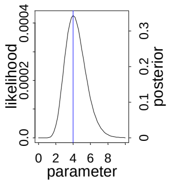
- uncertainty after analyzing current data
- balance prior & current

Bayesian Prior

- “prior” belief used to infer “posterior” estimates
  - higher weight for more probable parameter values
    - based on prior knowledge
  - use previous study to inform current study
    - weather prediction: tomorrow is much like today
    - previous QTL studies on related organisms
  - historical criticism: can get “religious” about priors
- often want negligible effect of prior on posterior
  - pick non-informative priors
    - all parameter values equally likely
    - large variance on priors
  - always check sensitivity to prior

Likelihood & Posterior Example





$$data: y = 1,3,8$$

$$parameter: t = ?$$

$$prob\{y = k \mid t\} = \frac{t^k e^{-t}}{k!}$$

Bayesian Idea for QTLs

- Modelling a `trait` with a QTL
  - linear model for `trait` given genotype
  - recombination near `loci` for genotype
- Bayesian Posterior
- Likelihoods
  - EM & MCMC
  - Frequentists & Bayesians
- Review Interval Maps & Profile LODs
- Case Study: Simulated Single QTL

QTL Effect Posterior

- posterior = likelihood * prior / constant

- posterior distribution is proportional to
  - prior distribution of `effect`
  - likelihood of `traits` given `effect` & genos

$$\pi(b^* \mid \mathbf{y})$$

is proportional to

$$\pi(b^*)\prod_{j=1}^{n}\pi(y_j \mid x_j^*; \mu, b^*, \sigma^2)$$

QTL Full Posterior

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

  prob`( genos, effects, loci | trait, map )`

$$\pi(\mathbf{x}^*; \mu, b^*, \sigma^2; \lambda \mid \mathbf{y})$$

is proportional to

$$\pi(\mu)\pi(b^*)\pi(\sigma^2)\pi(\lambda)\prod_{j=1}^{n}\pi(x_j^* \mid \lambda)$$

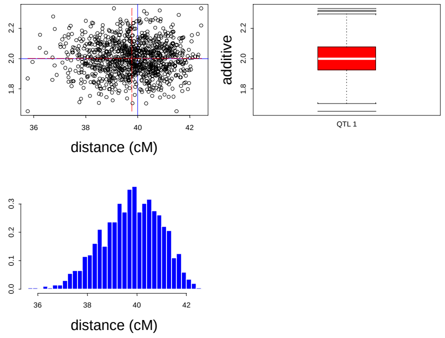
$$\times\prod_{j=1}^{n}\pi(y_j \mid x_j^*; \mu, b^*, \sigma^2)$$

How to Study Posterior?

- exact methods
  - exact if possible
  - can be difficult or impossible to analyze
- approximate methods
  - importance sampling
  - numerical integration
  - Monte Carlo & other

- Monte Carlo methods
  - easy to implement
  - independent samples
- MCMC methods
  - handle hard problems
  - art to efficient use
  - correlated samples

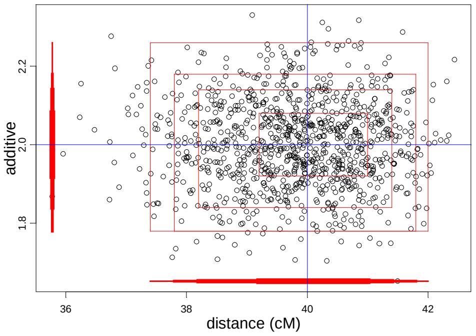
Posterior for `locus` & `effect`



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)

HPD Region for locus & effect



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

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

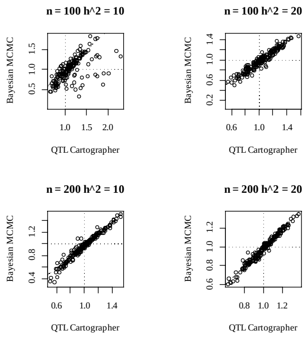
Frequentist or Bayesian?

- 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

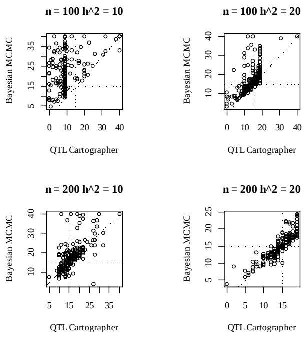
Simulation Study

- 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 h^2

200 Simulations: Effect



200 Simulations: Locus



Basic Idea of Likelihood Use

- build likelihood in steps
  - build from trait & genotypes at locus
  - likelihood for individual *i*
  - log likelihood over individuals
- maximize likelihood (interval mapping)
  - EM method (Lander & Botstein 1989)
  - MCMC method (Guo & Thompson 1994)
- study whole likelihood as posterior (Bayesian)
  - analytical methods (e.g. Carlin & Louis 1998)
  - MCMC method (Satagopan et al 1996)

Studying the Likelihood

- maximize (*IM)
  - find the peak
  - avoid local maxima
  - profile LOD
    - across locus
    - max for effects
- sample (Bayes)
  - get whole curve
  - summarize later
  - posterior
    - locus & effects together
- EM method
  - always go up
  - steepest ascent
- MCMC method
  - jump around
  - go up if you can
  - sometimes go down
  - cool down to find peak
    - simulated annealing
    - simulated tempering

EM-MCMC duality

- EM approach can be redone with MCMC
  - EM estimates & maximizes
  - MCMC draws random samples
  - 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!
  - very handy for hard problems in genetics

Part III: MCMC Sampling

- Study the Bayesian Posterior
  - use Markov chain to sample
    - Markov chain Monte Carlo
    - Gibbs sampler for effects
    - Metropolis-Hastings for loci
- *Brassica* data on days to flowering

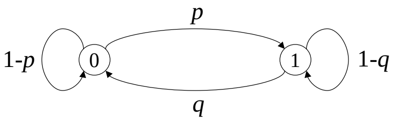
How to Proceed?

- want to study π(parameters|data)
- run Markov chain with stable pattern π()
- study properties of Markov chain to learn about posterior π(parameters|data)
  - Markov chain Monte Carlo
- summarize results in graphical form
- diagnostics

Markov chain idea

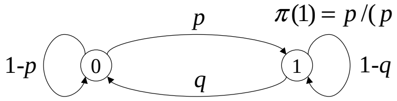
- future given present is independent of past
- update chain based on current value
  - can make chain arbitrarily complicated
  - chain converges to stable pattern π() we wish to study

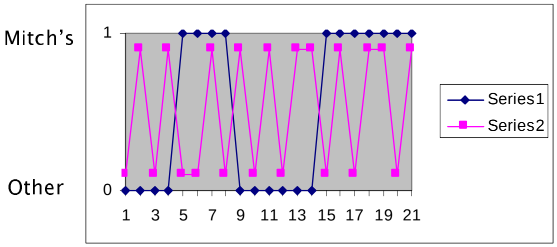
$$\pi(1) = p/(p+q)$$



Markov chain idea

$$\pi(1) = p/(p+q)$$

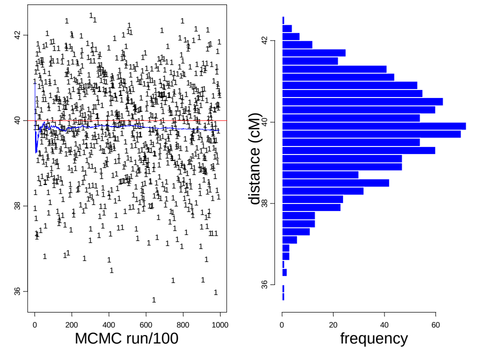




Markov chain Monte Carlo

- 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
  - update some parameters given data and others
  - can fudge on "right" (importance sampling)
  - next step depends only on current estimates
- nice Markov chains have nice properties
  - sample summaries make sense
  - consider almost as random sample from distribution

MCMC Run for 1 locus Data



Why not Ordinary Monte Carlo?

- independent samples of joint distribution
- chaining (or peeling) of effects
- requires numerical integration
  - possible analytically here
  - very messy in general

$$\pi(\mu,b^*,\sigma^2 \mid \mathbf{y},\mathbf{x}^*) =$$
$$\pi(\sigma^2 \mid \mathbf{y},\mathbf{x}^*;\mu,b^*)\times\pi(b^* \mid \mathbf{y},\mathbf{x}^*;\mu)\times\pi(\mu \mid \mathbf{y},\mathbf{x}^*)$$

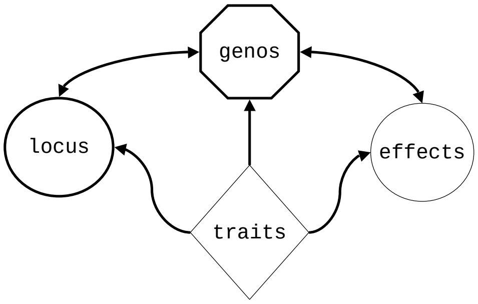
$$\pi(\mu \mid \mathbf{y},\mathbf{x}^*) = E_{(b^*,\sigma^2)}\left(\pi(\mu,b^*,\sigma^2 \mid \mathbf{y},\mathbf{x}^*)\right)$$

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 one (or several) components at a time
  - update effects given genotypes & traits
  - update locus given genotypes & traits
  - update genotypes give locus & effects

$$\theta = (\mathbf{x}^*;\mu,b^*,\sigma^2;\lambda) \sim \pi(\mathbf{x}^*;\mu,b^*,\sigma^2;\lambda \mid \mathbf{y})$$
$$\theta_1 \to \theta_2 \to \cdots \to \theta_N$$

Markov chain updates



Gibbs Sampler for effects

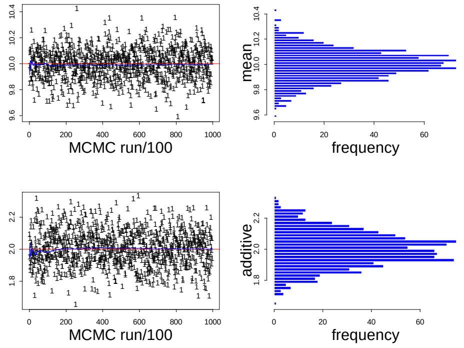
- set up Markov chain around posterior for effects
- sample from posterior by sampling from full conditionals
  - conditional posterior of each parameter given the other
  - update parameter by sampling full conditional

update mean $\pi(\mu \mid \mathbf{y},\mathbf{x}^*;b^*,\sigma^2) = \pi(\mu)\pi(\mathbf{y} \mid \mathbf{x}^*;\mu,b^*,\sigma^2)/c$

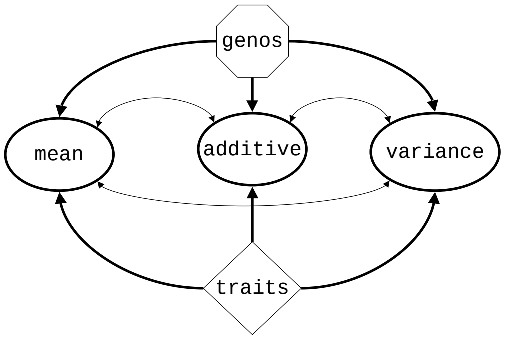
update additive $\pi(b^* \mid \mathbf{y},\mathbf{x}^*;\mu,\sigma^2) = \pi(b^*)\pi(\mathbf{y} \mid \mathbf{x}^*;\mu,b^*,\sigma^2)/c$

update variance $\pi(\sigma^2 \mid \mathbf{y},\mathbf{x}^*;\mu,b^*) = \pi(\sigma^2)\pi(\mathbf{y} \mid \mathbf{x}^*;\mu,b^*,\sigma^2)/c$

MCMC run of mean & effect



Markov chain details



Full Conditional for genos

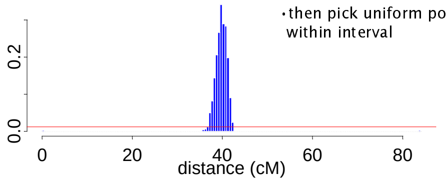
- full conditional for genotype depends on
  - `effects` via `trait` model
  - `locus` via recombination model
- can explicitly decompose by individual *j*
  - binomial (or trinomial) probability

$$x_j^* = -1, 0, or\, 1$$

$$P_j = \pi(x_j^* \mid y_j; \mu, b^*, \sigma^2; \lambda) = \frac{\pi(y_j \mid x_j^*; \mu, b^*, \sigma^2)\pi(x_j^* \mid \lambda)}{\sum_{x=-1,0,1} \pi(y_j \mid x; \mu, b^*, \sigma^2)\pi(x \mid \lambda)}$$

Prior for `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

Full Conditional for `locus`

- cannot easily sample from `locus` full conditional
- cannot explicitly determine full conditional
  - difficult to normalize
  - need to consider all possible genotypes over entire `map`
- Gibbs sampler will not work
  - but can get something proportional ...

$$\pi(\lambda \mid \mathbf{y}, \mathbf{x}^*; \mu, b^*, \sigma^2) = \pi(\lambda \mid \mathbf{x}^*)$$
$$= \pi(\lambda) \prod_{j=1}^{n} \pi(x_j^* \mid \lambda) / c$$

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

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

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”

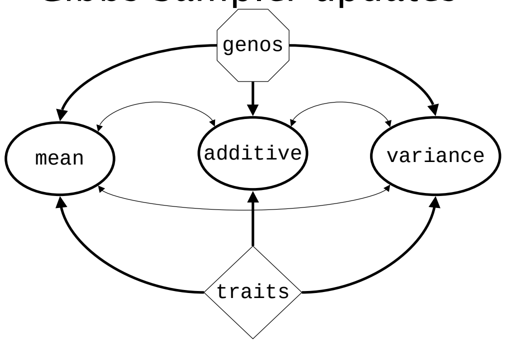
Part IV: MCMC Details

- quick review of trait model
  - single & multiple QTL
  - details of Gibbs sampler full conditionals
  - vector notation

Quick Review of `trait` Model

- single QTL details of Gibbs sampler
  - normal priors & likelihoods
    - mean, additive effects
  - inverse gamma prior for variance
    - or inverse chi-square
  - vague priors lead to usual estimates as posterior means
- multiple QTL `trait` model
  - model with vector notation

Gibbs Sampler updates



Full Conditional for `mean`

- normal prior with large variance τ^2

$$\pi(\mu \mid \mathbf{y},\mathbf{x}^*;b^*,\sigma^2) \propto \phi\left(\frac{\mu-\eta}{\tau}\right)\prod_{j=1}^{n}\phi\left(\frac{y_j-\mu-b^*x_j^*}{\sigma}\right)$$

- leads to normal posterior
- posterior mean

$$E(\mu \mid \mathbf{y},\mathbf{x}^*;b^*,\sigma^2)=\frac{\sum_{j=1}^{n}(y_j-b^*x_j^*)+\eta\frac{\sigma^2}{\tau^2}}{n+\frac{\sigma^2}{\tau^2}}\approx\frac{\sum_{j=1}^{n}(y_j-b^*x_j^*)}{n}$$

- posterior variance

$$V(\mu \mid \mathbf{y},\mathbf{x}^*;b^*,\sigma^2)=\frac{\sigma^2}{n+\frac{\sigma^2}{\tau^2}}\approx\frac{\sigma^2}{n}$$

Full Conditional for `additive` Effect

- normal prior with large variance τ^2

$$\pi(b^* \mid \mathbf{y},\mathbf{x}^*;\mu,\sigma^2) \propto \phi\left(\frac{b^*}{\tau}\right)\prod_{j=1}^{n}\phi\left(\frac{y_j-\mu-b^*x_j^*}{\sigma}\right)$$

- leads to normal posterior
- posterior mean

$$E(b^* \mid \mathbf{y},\mathbf{x}^*;\mu,\sigma^2)=\frac{\sum_{j=1}^{n}x_j^*(y_j-\mu)}{\sum_{j=1}^{n}(x_j^*)^2+\frac{\sigma^2}{\tau^2}}\approx\frac{\sum_{j=1}^{n}x_j^*(y_j-\mu)}{\sum_{j=1}^{n}(x_j^*)^2}$$

- posterior variance

$$V(b^* \mid \mathbf{y},\mathbf{x}^*;\mu,\sigma^2)=\frac{\sigma^2}{\sum_{j=1}^{n}(x_j^*)^2+\frac{\sigma^2}{\tau^2}}\approx\frac{\sigma^2}{\sum_{j=1}^{n}(x_j^*)^2}$$

Full Conditional for `variance`

- inverse gamma prior with large *v/a*

$$\sigma^2 \sim Inv\Gamma(a,v) \propto (\sigma^2)^{-(a+1)}e^{-v/\sigma^2}$$

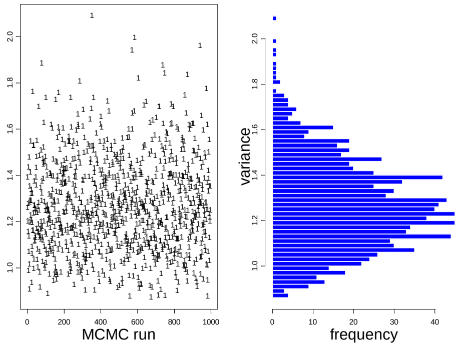
- posterior distribution

$$\sigma^2 \mid \mathbf{y},\mathbf{x}^*;\mu,b^* \sim Inv\Gamma\left(a+\tfrac{n}{2},v+\tfrac{n}{2}\hat{\sigma}^2\right)$$

- posterior mean

$$E(\sigma^2 \mid \mathbf{y},\mathbf{x}^*;\mu,b^*)=\frac{v+\frac{n}{2}\hat{\sigma}^2}{a+\frac{n}{2}-1}\approx\hat{\sigma}^2=\frac{\sum_{j=1}^{n}(y_j-\mu-b^*x_j^*)^2}{n}$$

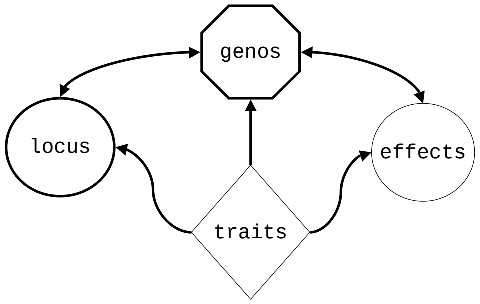
MCMC run for `variance`



Alternative for Variance: use Inverse Chi-square

- inverse chi-square prior with large *d,v* $\sigma^2 \sim Inv\chi^2(d,v) = \frac{vd}{\chi_d^2}, \text{or} \frac{vd}{\sigma^2} \sim \chi_d^2$
- posterior distribution $\sigma^2 \mid \mathbf{y},\mathbf{x}^*;\mu,b^* \sim Inv\chi^2\left(d+n, \frac{vd+\sum_{j=1}^{n}(y_j-\mu-b^*x_j^*)^2}{d+n} \right)$

Markov chain updates



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

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

Full Conditional for `genos`

- full conditional for genotype depends on
  - `effects` via `trait` model
  - `locus` via recombination model
- can explicitly decompose by individual *j*
  - binomial (or trinomial) probability

$$x_j^* = -1, 0, or\, 1$$

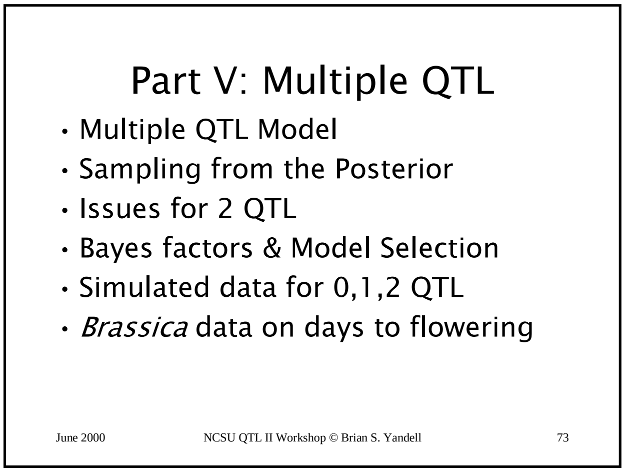
$$\pi(x_j^* \mid y_j;\mu,b^*,\sigma^2;\lambda) = \frac{\pi(y_j \mid x_j^*;\mu,b^*,\sigma^2)\pi(x_j^* \mid \lambda)}{\sum_{x=-1,0,1}\pi(y_j \mid x;\mu,b^*,\sigma^2)\pi(x \mid \lambda)}$$

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 *j*
  - binomial (or trinomial) probability

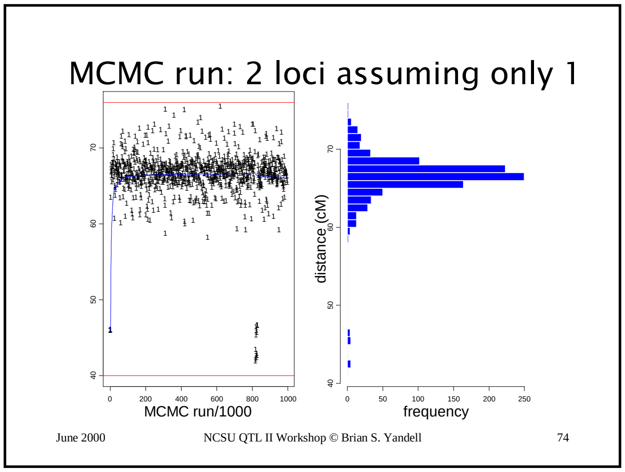
$$M_{kj} = -1, 0, or\, 1$$

$$\pi(M_{kj} \mid x_j^*, y_j;\mu,b^*,\sigma^2;\lambda;\mathbf{M}_j) = \pi(M_{kj} \mid x_j^*;\mathbf{M}_j)$$

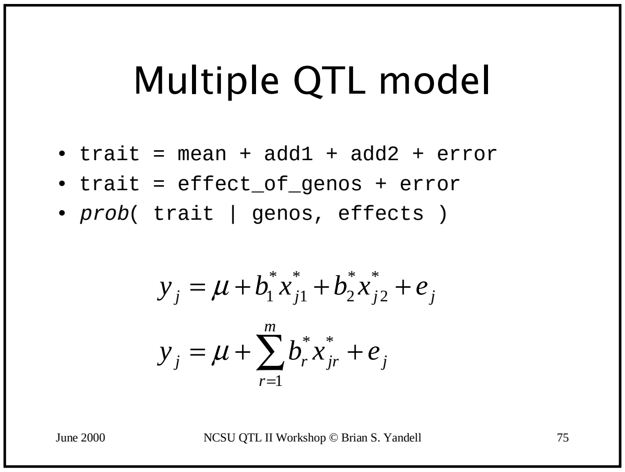


Part V: Multiple QTL

- Multiple QTL Model
- Sampling from the Posterior
- Issues for 2 QTL
- Bayes factors & Model Selection
- Simulated data for 0,1,2 QTL
- *Brassica* data on days to flowering



MCMC run: 2 loci assuming only 1

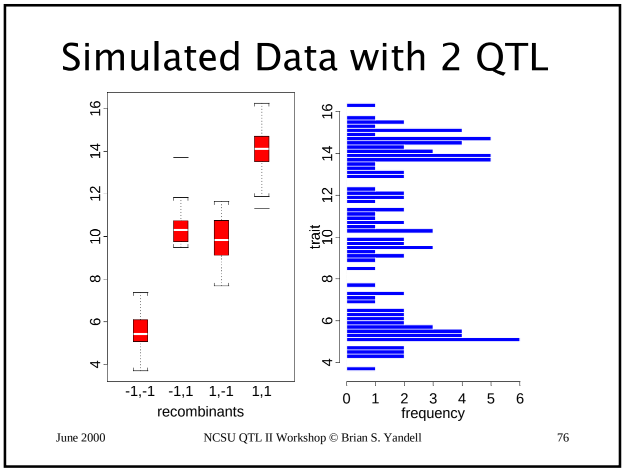


Multiple QTL model

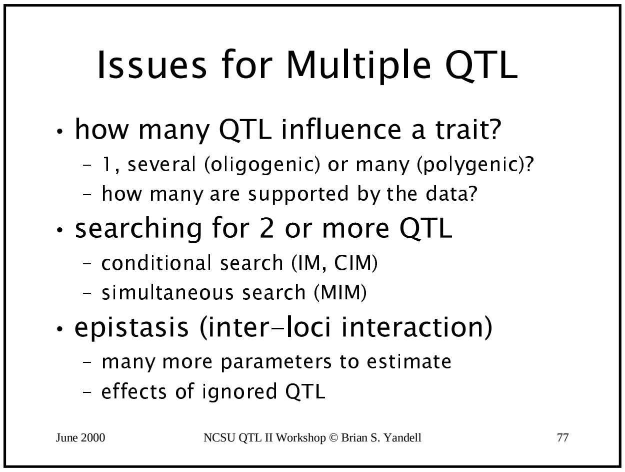
- trait = mean + add1 + add2 + error
- trait = effect_of_genos + error
- *prob*(trait | genos, effects)

$$y_j = \mu + b_1^* x_{j1}^* + b_2^* x_{j2}^* + e_j$$

$$y_j = \mu + \sum_{r=1}^{m} b_r^* x_{jr}^* + e_j$$

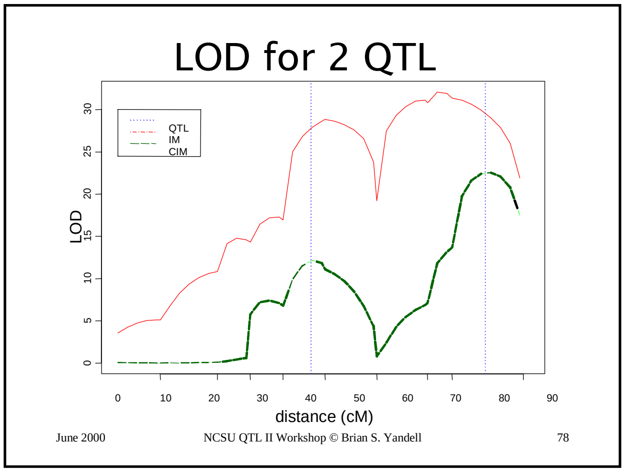


Simulated Data with 2 QTL



Issues for Multiple QTL

- how many QTL influence a trait?
  - 1, several (oligogenic) or many (polygenic)?
  - how many are supported by the data?
- 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



LOD for 2 QTL

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)
  - search for multiple QTL

Multiple QTL model

- `trait = mean + add1 + add2 + error`
- `trait = effect_of_genos + error`
- *`prob`*`( trait | genos, effects )`

$$y_j = \mu + b_1^* x_{j1}^* + b_2^* x_{j2}^* + e_j$$

$$y_j = \mu + \sum_{r=1}^{m} b_r^* x_{jr}^* + e_j$$

Vector Notation for QTLs

- inner product for sum
- condense notation

$$\sum_{r=1}^{m} b_r^* x_{jr}^* = < \mathbf{b}^*, \mathbf{x}_j^* >$$

$$\mathbf{b}^* = \begin{pmatrix} b_1^* \\ \vdots \\ b_m^* \end{pmatrix}, \mathbf{x}_j^* = \begin{pmatrix} x_{j1}^* \\ \vdots \\ x_{jm}^* \end{pmatrix}, \mathbf{X}^* = \left(\mathbf{x}_1^*, \cdots, \mathbf{x}_n^*\right)$$

Multiple `loci`

- vector of `loci` across linkage map
- careful bookkeeping during update
  - identifiability & bump hunting
  - possibility of two loci in one marker interval
- ordered `loci` are sufficient

$$\pi(\Lambda \mid \mathbf{X}^*) = \prod_{r=1}^{m} \pi(\lambda_r \mid \mathbf{X}^*), \Lambda = (\lambda_1, \cdots, \lambda_m)$$

$$\pi(\lambda_r \mid \mathbf{X}^*) \propto \pi(\lambda_r) \prod_{j=1}^{n} \pi(x_{jr}^* \mid \lambda_r)$$

Posterior: Multiple QTLs

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

  `prob``( genos, effects, loci | traits, map )`

$$\pi(\mathbf{X}^*; \mu, b^*, \sigma^2; \Lambda \mid \mathbf{y})$$

is proportional to

$$\pi(\mu)\pi(\sigma^2) \prod_{r=1}^{m} \left(\pi(b_r^*) \pi(\lambda_r) \prod_{j=1}^{n} \pi(x_{jr}^* \mid \lambda_r) \right)$$

$$\times \prod_{j=1}^{n} \pi(y_j \mid \mathbf{x}_j^*; \mu, \mathbf{b}^*, \sigma^2)$$

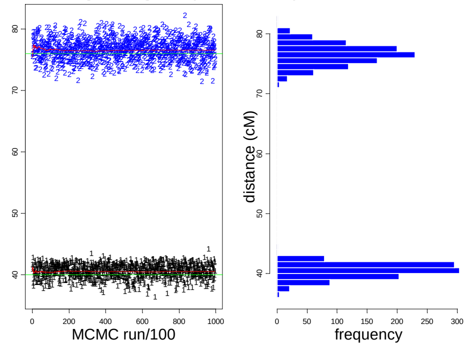
MCMC for Multiple QTLs

- construct Markov chain around posterior
- update one (or several) components at a time
  - update `effects` given genotypes & `traits`
  - update `loci` given genotypes & `traits`
  - update genotypes give `loci` & `effects`
- update all terms for each `locus` at one time?
  - open questions of efficient mixing

$$\theta = (\mathbf{X}^*; \mu, \mathbf{b}^*, \sigma^2; \Lambda) \sim \pi(\mathbf{X}^*; \mu, \mathbf{b}^*, \sigma^2; \Lambda \mid \mathbf{y})$$

$$\theta_1 \to \theta_2 \to \cdots \to \theta_N$$

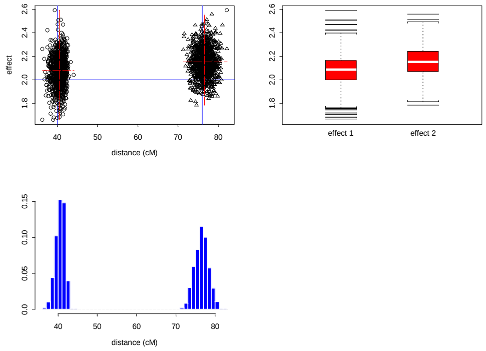
MCMC run with 2 loci



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 & effects
- use Bayes factors for model selection
  - number of QTL

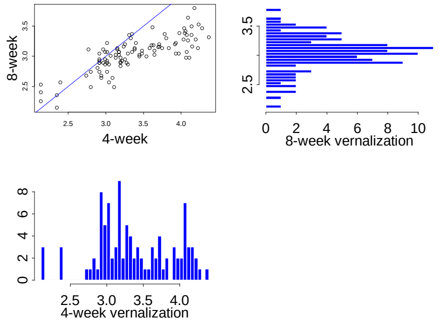
Effects for 2 Simulated QTL



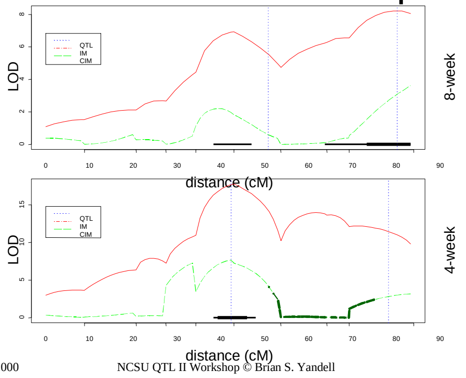
Brassica napus Data

- 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



Brassica Data LOD Maps



4-week vs 8-week vernalization

4-week vernalization

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

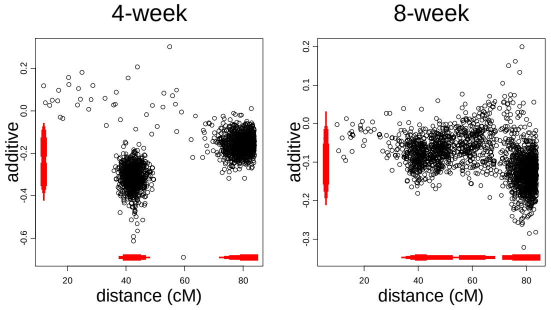
cM	add
40	.30
80	.16

8-week vernalization

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

cM	add
40	.06
80	.13

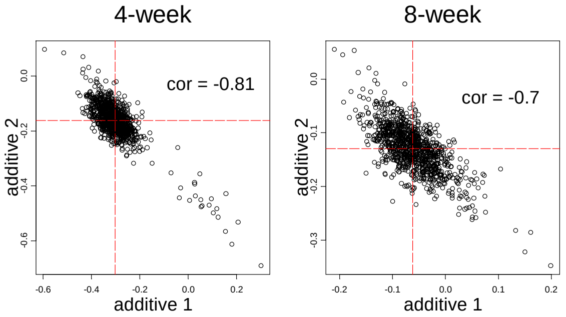
Brassica Credible Regions



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

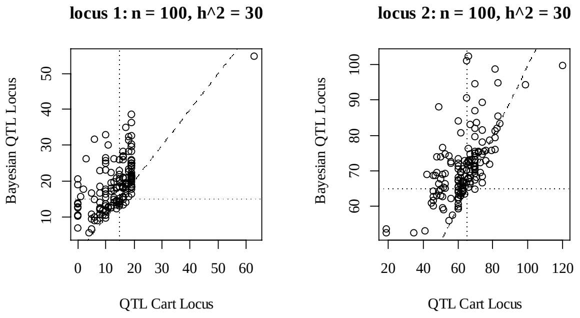
Brassica `effect` Correlations



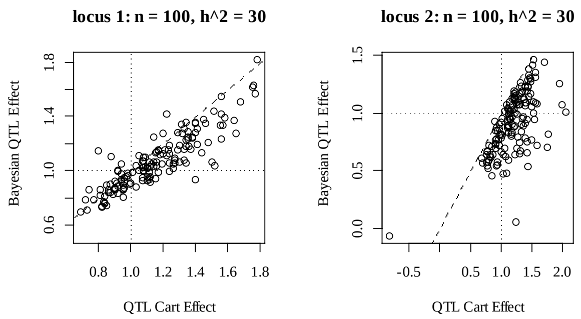
Simulation Study

- 2 linked QTL
- QTL Cart vs. Bayesian QTL estimates
  - locus: 15, 65cM
  - effect: 1, 1
- n = 100, h^2 = 30
- also considered
  - n = 200, h^2 = 25, 30, 40

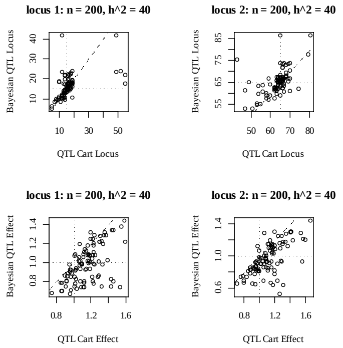
2 QTL: Loci Estimates



2 QTL: Effect Estimates



2 QTL: Loci & Effects



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

$$B_{12} = \frac{\pi(\text{model}_1 \mid \mathbf{y})/\pi(\text{model}_2 \mid \mathbf{y})}{\pi(\text{model}_1)/\pi(\text{model}_2)} = \frac{\pi(\mathbf{y} \mid \text{model}_1)}{\pi(\mathbf{y} \mid \text{model}_2)}$$

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

Bayes Factors & *LR*

- 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*

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

Model Determination using Bayes Factors

- pick most plausible model
  - histogram for range of models
  - posterior distribution of models
  - use Bayes theorem
  - often assume flat prior across models
- posterior distribution of number of QTLs

Brassica Bayes Factors

- compare models for 1, 2, 3 QTL
- Bayes factor and $-2\log(LR)$
- large value favors first model
- 8-week vernalization only here

i vs. *j*	Bayes Factor	-log(*LR)*
2 vs. 1	2.49	7.82
3 vs. 1	.005	7.41
3 vs. 2	.002	4.17

Computing Bayes Factors

- arithmetic mean
  - using samples from prior
  - mean across Monte Carlo or MCMC runs
  - can be inefficient if prior differs from posterior

$$\pi(\mathbf{y}\,|\,\text{model}_k) = \int \pi(\mathbf{y}\,|\,\theta_k;\text{model}_k)\pi(\theta_k\,|\,\text{model}_k)d\theta_k$$

- harmonic mean
  - using samples from posterior
  - more efficient but less stable
  - careful choice of weight $h()$ close to posterior

$$\hat{\pi}(\mathbf{y}\,|\,\text{model}_k) = G\left[\sum_{g=1}^{G}\frac{h(\theta_k)}{\pi(\mathbf{y}\,|\,\theta_k;\text{model}_k)\pi(\theta_k\,|\,\text{model}_k)}\right]^{-1}$$

Part VI: How many QTLs?

- Reversible Jump MCMC
  - basic idea of Green(1995)
  - model selection in regression
- how many QTLs?
  - number of QTL is random
  - estimate the number *m*
- RJ-MCMC vs. Bayes factors
- other similar ideas

Jumping the Number of QTL

- model changes with number of QTL
  - almost analogous to stepwise regression
  - use reversible jump MCMC to change number
    - book keeping helps in comparing models
    - change of variables between models
- prior on number of QTL
  - uniform over some range
  - Poisson with prior mean

$$\pi(m\,|\,\ell) = \frac{\ell^m e^{-\ell}}{m!}$$

Posterior: Number of QTL

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

```
*prob*( genos, effects, loci, *m* | traits, map )
```

$$\pi(\mathbf{X}^*;\mu,b^*,\sigma^2;\Lambda,m\,|\,\mathbf{y})$$

is proportional to

$$\prod_{j=1}^{n}\pi(y_j\,|\,\mathbf{x}_j^*;\mu,\mathbf{b}^*,\sigma^2;m)\times$$

$$\pi(m)\pi(\mu)\pi(\sigma^2)\prod_{r=1}^{m}\left(\pi(b_r^*)\pi(\lambda_r)\prod_{j=1}^{n}\pi(x_{jr}^*\,|\,\lambda_r)\right)$$

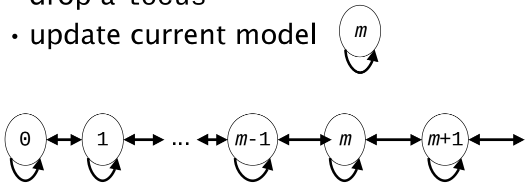
Reversible Jump Choices

action step: draw one of three choices

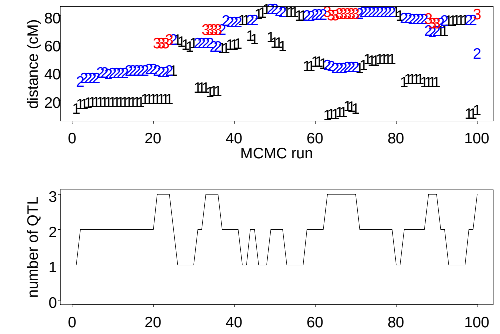
- update step with probability $1\text{-}b(m+1)\text{-}d(m)$
  - update current model
  - `loci`, `effects`, genotypes as before
- add a locus with probability $b(m+1)$
  - propose a new `locus`
  - innovate `effect` and genotypes at new `locus`
  - decide whether to accept the “birth” of new `locus`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

Markov chain for number *m*

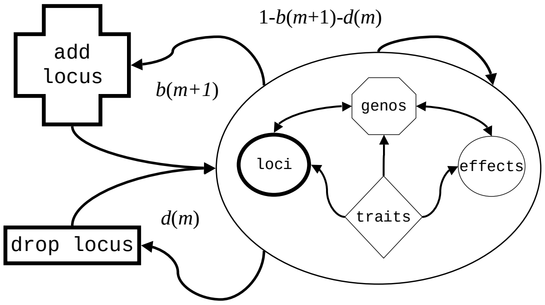
- add a new locus →
- drop a locus ←
- update current model



Jumping QTL number & loci



RJ-MCMC Updates



Propose to Add a locus

- propose a new locus
  - similar proposal to ordinary update $q_b(\lambda) = 1/D$
    - uniform chance over genome
    - easier to avoid interval with another QTL
  - 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 …

Propose to Drop a locus

- choose an existing locus $q_d(r;m) = 1/m$
  - 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

Acceptance of Reversible Jump

- accept birth of new locus with probability

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

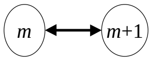
  $\min(1,1/A)$

$$A = \frac{\pi(\theta_{m+1}, m+1 \mid \mathbf{y})}{\pi(\theta_m, m \mid \mathbf{y})} \times \frac{d(m+1)}{b(m)} \frac{q_b(\lambda_{m+1})}{q_d(r; m+1)} \frac{1}{J}$$

$$\theta_m = \left(\mathbf{X}^*; \mu, \mathbf{b}^*, \sigma^2; \Lambda, m\right)$$

Acceptance of Reversible Jump

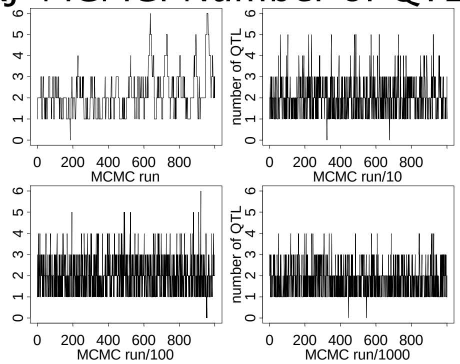
- move probabilities $\dfrac{d(m+1)}{b(m)}$



- birth & death proposals $\dfrac{q_b(\lambda_{m+1})}{q_d(r;m+1)}$

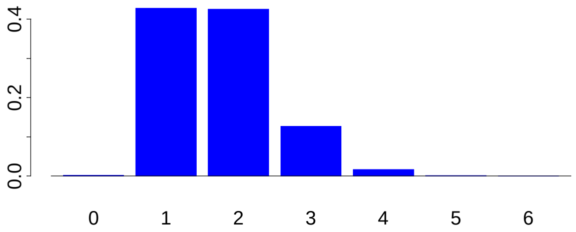
- Jacobian between models $J = \dfrac{\sigma}{s_{r|others}\sqrt{n}}$
  - –fudge factor
  - –see stepwise regression example

RJ-MCMC: Number of QTL



Posterior # QTL for 8-week Data

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



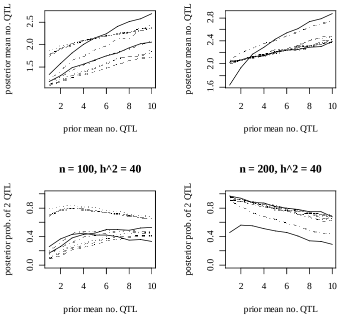
How Good is RJ-MCMC?

- 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

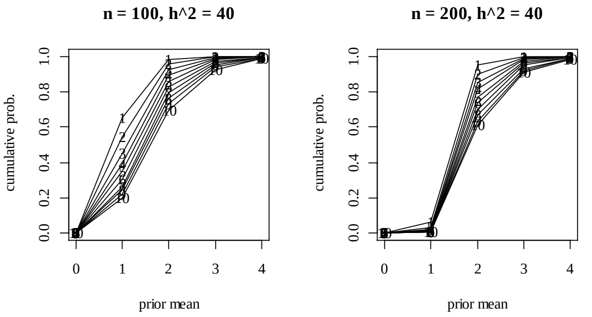
Simulation Study: Prior

- 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

Prior on Number of QTL



Prior on Number of QTL



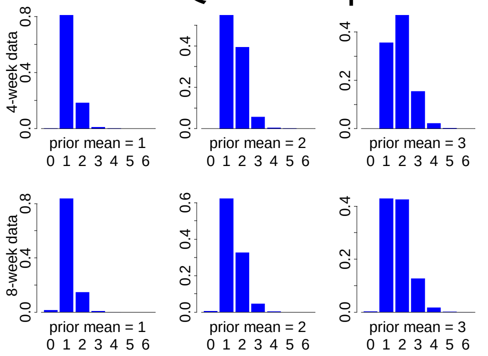
QTL in *Brassica* Data

- 4-week & 8-week vernalization
  - log(days to flower)
  - 105 lines, 10 markers
  - modest effects
  - evidence of 1 or 2 QTL using Bayes factors
- histograms of posterior number of QTL
  - depends somewhat on prior
  - mode is 1 or 2 QTL
- 90% credible sets
  - all include 2 QTL
  - include 1 QTL if prior not huge

Brassica #QTL 90% Credible Sets

	8-week			4-week		
prior	lo	hi	level	lo	hi	level
1	1	2	0.98	1	2	0.99
2	1	2	0.95	1	2	0.94
3	1	3	0.98	1	3	0.98
4	1	3	0.95	1	3	0.93
6	1	4	0.96	1	4	0.94
10	2	5	0.90	2	6	0.97

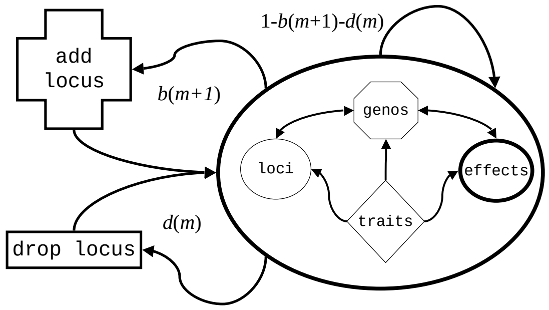
Brassica #QTL Comparison



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

RJ-MCMC Updates



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

$$m = 1 : y_j = \mu + b(x_{j1} - \bar{x}_1) + e_j$$

$$m = 2 : y_j = \mu + b_1(x_{j1} - \bar{x}_1) + b_2(x_{j2} - \bar{x}_2) + e_j$$

Slope Estimate for 1 Regressor

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

$$\hat{b} = \frac{r_{1y}\, s_y}{s_1}, \quad r_{1y} = \frac{\sum_{j=1}^{n}(x_{j1} - \bar{x}_1)(y_j - \bar{y})/n}{s_1\, s_y}$$

$$s_1^2 = \sum_{j=1}^{n}(x_{j1} - \bar{x}_1)^2/n, s_y^2 = \sum_{j=1}^{n}(y_j - \bar{y})^2/n$$

2 Correlated Regressors

slopes adjusted for other regressors

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

$$\hat{b}_2 = \frac{(r_{2y} - r_{12}r_{1y})s_y}{s_2}$$

Gibbs Sampler for Model 1

- mean $\mu \sim \phi\left(\frac{n\bar{y} + \eta\frac{\sigma^2}{\tau^2}}{n + \frac{\sigma^2}{\tau^2}}, \frac{\sigma^2}{n + \frac{\sigma^2}{\tau^2}}\right)$
- slope $b \sim \phi\left(\frac{\sum_{j=1}^{n}(x_{j1} - \bar{x}_1)(y_j - \mu)}{ns_1^2 + \frac{\sigma^2}{\tau^2}}, \frac{\sigma^2}{ns_1^2 + \frac{\sigma^2}{\tau^2}}\right)$
- variance $\sigma^2 \sim Inv\Gamma\left(a + \frac{n}{2}, v + \frac{1}{2}\sum_{j=1}^{n}\left(y_j - \mu - b(x_{j1} - \bar{x}_1)\right)^2\right)$

Gibbs Sampler for Model 2

- mean $\mu \sim \phi\left(\frac{n\bar{y} + \eta\frac{\sigma^2}{\tau^2}}{n + \frac{\sigma^2}{\tau^2}}, \frac{\sigma^2}{n + \frac{\sigma^2}{\tau^2}}\right)$
- slopes $b_2 \sim \phi\left(\frac{\sum_{j=1}^{n}(x_{j2} - \bar{x}_2)(y_j - \mu - b_1(x_{j1} - \bar{x}_1))}{ns_{2|1}^2 + \frac{\sigma^2}{\tau^2}}, \frac{\sigma^2}{ns_{2|1}^2 + \frac{\sigma^2}{\tau^2}}\right)$

$$s_{2|1}^2 = \sum_{j=1}^{n}(x_{j2} - \bar{x}_2 - c_{21}(x_{j1} - \bar{x}_1))^2/n$$

- variance $\sigma^2 \sim Inv\Gamma\left(a + \frac{n}{2}, v + \frac{1}{2}\sum_{j=1}^{n}\left(y_j - \mu - \sum_{k=1}^{2}b_k(x_{jk} - \bar{x}_k)\right)^2\right)$

Updates from 2->1

- drop 2nd regressor
- adjust other regressor

$$b \to b_1 + b_2 c_{21}$$

$$b_2 \to 0$$

Updates from 1->2

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

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

$$b_2 \to \hat{b}_2 + z \times J, \quad \hat{b}_2 = \frac{\sum_{j=1}^{n} (x_{j2} - \bar{x}_2)\left(y_j - \hat{\mu} - \hat{b}_1 (x_{j1} - \bar{x}_1)\right)}{n s_{2\cdot1}^2}$$

$$b_1 \to b - b_2 c_{21} = b - z \times c_{21} J - \hat{b}_2 c_{21}$$

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*
$1 \to 2$	$(\mu, b, \sigma^2; z)$	$z \sim \phi(0,1)$	$\begin{Bmatrix} b_2 \to \hat{b}_2 + z \times J \\ b_1 \to b - b_2 c_{21} \end{Bmatrix}$
$2 \to 1$	$(\mu, b_1, b_2, \sigma^2)$		$\begin{Bmatrix} b \to b_1 + b_2 c_{21} \\ z \to 0 \end{Bmatrix}$

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)

$$\begin{pmatrix} b_1 \\ b_2 \end{pmatrix} = \begin{bmatrix} 1 & -c_{21}J & -c_{21} \\ 0 & J & 1 \end{bmatrix} \times \begin{pmatrix} b \\ z \\ \hat{b}_2 \end{pmatrix} = g(b; z \mid \mathbf{y}, \mathbf{x}_1, \mathbf{x}_2)$$

$$\int \pi(b_1, b_2 \mid \mathbf{y}, \mathbf{x}_1, \mathbf{x}_2) db_1 db_2 = \int \pi(b; z \mid \mathbf{y}, \mathbf{x}_1, \mathbf{x}_2) J db dz$$

Jacobian & the Calculus

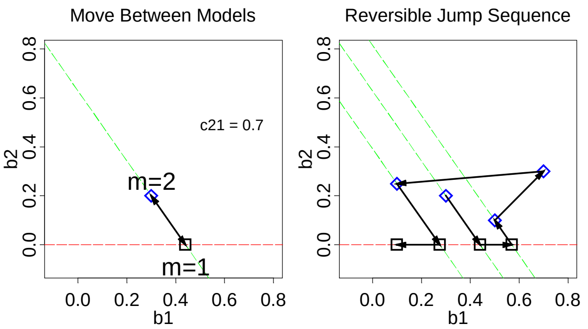
- Jacobian sorts out change of variables
  - <u>careful</u>: easy to mess up here!

$$g(b; z) = (b_1, b_2), \ \frac{\partial g(b; z)}{\partial b \partial z} = \begin{bmatrix} 1 & -c_{21}J \\ 0 & J \end{bmatrix}$$

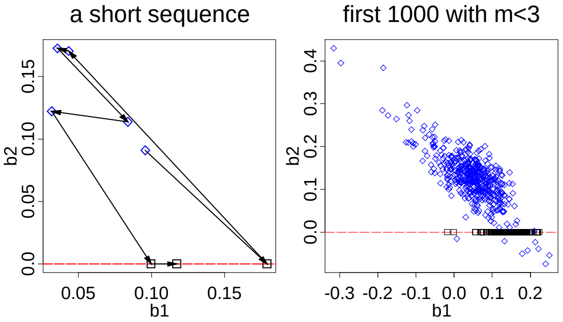
$$\left|\det\left(\begin{bmatrix} 1 & -c_{21}J \\ 0 & J \end{bmatrix}\right)\right| = \left|1 \times J - 0 \times (-c_{21}J)\right| = J$$

$$db_1 db_2 = \left|\det\left(\frac{\partial g(\mu, b, \sigma^2; z)}{\partial b \partial z}\right)\right| db_1 db_2 = J db dz$$

Geometry of Reversible Jump



QT additive Reversible Jump

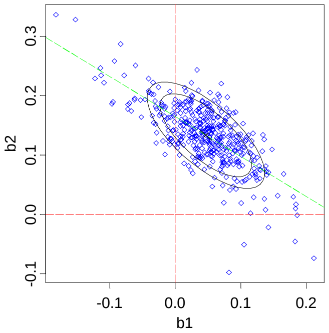

a short sequence

first 1000 with m<3

Credible Set for additive

90% & 95% sets
based on normal

regression line
corresponds to
slope of updates



Efficient Updating of additive

- more computations when $m > 2$
- want to avoid matrix inverses
  - decompose matrix instead
  - solve linear system of equations
- use linear algebra
  - Hausholder (QR) decomposition
  - *LAPACK User's Guide* (1995, 2nd ed) Anderson et al., SIAM.

Hausholder (QR) Decomposition

- decomposition
  - G is upper triangular
  - F is orthogonal

$$\mathbf{X} = \mathbf{F}\mathbf{G} = [\mathbf{F}_1 : \mathbf{F}_2]\begin{bmatrix}\mathbf{G}_1 \\ \mathbf{0}\end{bmatrix} = \mathbf{F}_1\mathbf{G}_1$$

- orthogonality

$$\mathbf{F}^T\mathbf{F} = \begin{bmatrix}\mathbf{F}_1^T\mathbf{F}_1 & \mathbf{F}_1^T\mathbf{F}_2 \\ \mathbf{F}_2^T\mathbf{F}_1 & \mathbf{F}_2^T\mathbf{F}_2\end{bmatrix} = \mathbf{I}_n$$

$$\mathbf{F}_1^T\mathbf{F}_1 = \mathbf{I}_m, \mathbf{F}_2^T\mathbf{F}_2 = \mathbf{I}_{n-m}$$

$$\mathbf{F}_1^T\mathbf{F}_2 = \mathbf{0}, \mathbf{F}_2^T\mathbf{F}_1 = \mathbf{0}$$

- design matrix

$$\mathbf{F}_2^T\mathbf{X} = \mathbf{0}$$

QR & Regression

- model

$$\mathbf{y} = \mathbf{X}\mathbf{b} + \mathbf{e}$$

- error piece

$$\mathbf{F}_2^T\mathbf{y} = \mathbf{F}_2^T\mathbf{X}\mathbf{b} + \mathbf{F}_2^T\mathbf{e} = \mathbf{F}_2^T\mathbf{e}$$

$$\mathbf{y}^T\mathbf{F}_2\mathbf{F}_2^T\mathbf{y} = SS_{ERROR}$$

- model piece

$$\mathbf{F}_1^T\mathbf{y} = \mathbf{F}_1^T\mathbf{X}\mathbf{b} + \mathbf{F}_1^T\mathbf{e} = \mathbf{G}_1\mathbf{b} + \mathbf{F}_1^T\mathbf{e}$$

$$\mathbf{y}^T\mathbf{F}_1\mathbf{F}_1^T\mathbf{y} = SS_{MODEL}$$

- estimators

$$\hat{\mathbf{b}} = (\mathbf{X}^T\mathbf{X})^{-1}\mathbf{X}^T\mathbf{y} = \mathbf{G}_1^{-1}\mathbf{F}_1^T\mathbf{y} = \frac{r_{1y}s_y}{r_1}$$

Absorbing Old Model

- *old* model
  - *m* regressors
  - QR decomposition

$$\mathbf{y} = \mathbf{X}\mathbf{b}_{old} + \mathbf{e}$$

$$\mathbf{X} = \mathbf{F}\mathbf{G} = \mathbf{F}_1\mathbf{G}_1$$

- *new* model
  - *m*+1 regressor
  - use QR to absorb old model

$$\mathbf{y} = \mathbf{X}\mathbf{b}_{old} + \mathbf{x}_{m+1}b_{m+1} + \mathbf{e}$$

$$\mathbf{F}_2^T\mathbf{y} = \mathbf{F}_2^T\mathbf{x}_{m+1}b_{m+1} + \mathbf{F}_2^T\mathbf{e}$$

Adjusted Slope Estimators

- *old* slopes
  - note m=1 case

$$\hat{\mathbf{b}}_{old} = \mathbf{G}_1^{-1}\mathbf{F}_1^T\mathbf{y} = \frac{r_{1y}s_y}{s_1}$$

- added slope
  - note sum of squares

$$\hat{b}_{m+1} = V^{-1}\mathbf{x}_{m+1}^T\mathbf{F}_2\mathbf{F}_2^T\mathbf{y} = \frac{(r_{2y} - r_{12}r_{1y})s_y}{s_2}$$

$$V = \mathbf{x}_{m+1}^T\mathbf{F}_2\mathbf{F}_2^T\mathbf{x}_{m+1} = ns_{2|1}^2$$

- variance
  - note Jacobian

$$V(\hat{b}_{m+1}) = \sigma^2 / V = J^2$$

- *new* slopes

$$\hat{\mathbf{b}}_{new} = \mathbf{G}_1^{-1}\mathbf{F}_1^T(\mathbf{y} - \mathbf{x}_{m+1}\hat{b}_{m+1})$$

$$\hat{\mathbf{b}}_{new} = \hat{\mathbf{b}}_{old} - \mathbf{G}_1^{-1}\mathbf{F}_1^T\mathbf{x}_{m+1}\hat{b}_{m+1}$$

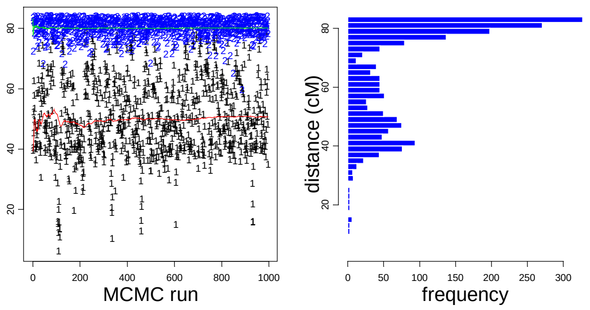
VIII: RJMCMC & Bayes Factors

- RJ-MCMC & Bayes factors
  - Bayes factors from RJ-MCMC chain
  - components of Bayes factors

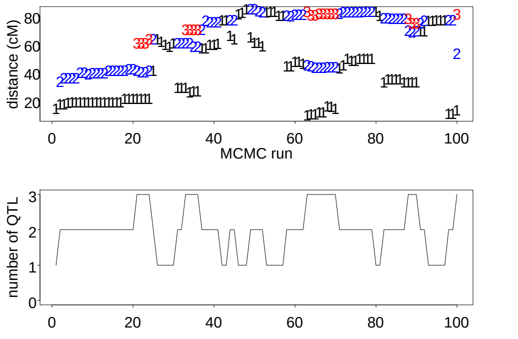
How To Infer `loci`?

- if m is known, use fixed MCMC
  - histogram of loci
  - issue of bump hunting
- combining loci estimates in RJ-MCMC
  - some steps are from wrong model
    - too few loci (bias)
    - too many loci (variance/identifiability)
  - condition on number of loci
    - subsets of Markov chain

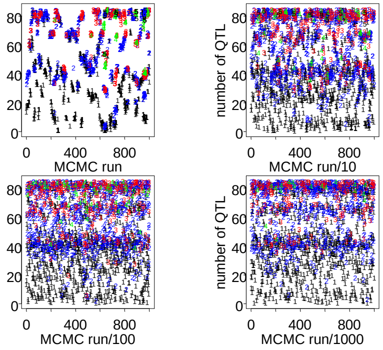
Brassica 8-week Data `locus` MCMC with m=2



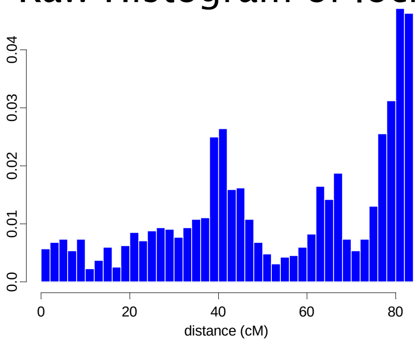
Jumping QTL number & `loci`



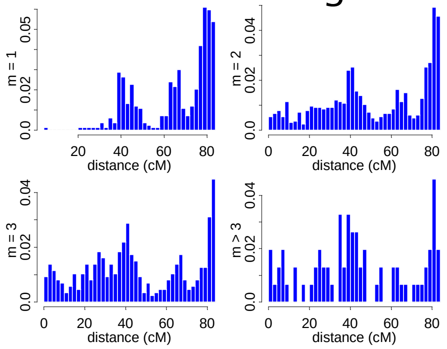
RJ-MCMC `loci` chain



Raw Histogram of loci



Conditional Histograms



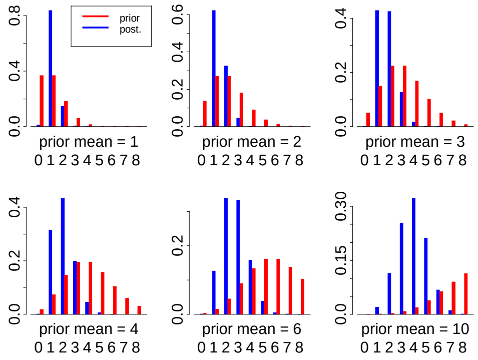
Bayes Factors

- ratio of posterior odds to prior odds
  - RJ-MCMC gives posterior on number of QTL
  - prior is Poisson

$$B_{12} = \frac{\pi(\text{model}_1 \,|\, \mathbf{y}) / \pi(\text{model}_2 \,|\, \mathbf{y})}{\pi(\text{model}_1) / \pi(\text{model}_2)} = \frac{\pi(\mathbf{y} \,|\, \text{model}_1)}{\pi(\mathbf{y} \,|\, \text{model}_2)}$$

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

#QTL for *Brassica* 8-week



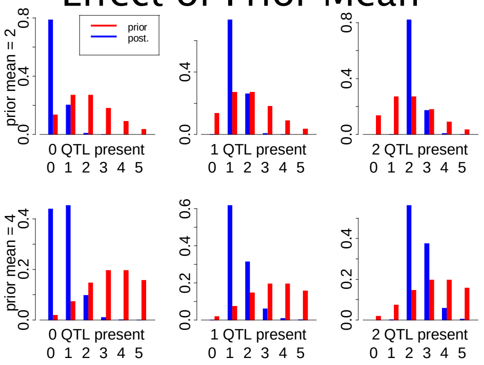
RJ-Bayes Factors (8-week Brassica data)

prior mean	1	2	3	4	6	10
ratio						
1:2	2.87	1.91	1.51	1.45	1.12	0.85
1:3	27.62	9.10	5.06	4.22	2.28	1.28
1:4	1743.29	81.30	28.85	18.51	7.17	2.51
2:3	9.63	4.76	3.35	2.91	2.04	1.5
2:4	608.00	42.51	19.09	12.75	6.41	2.95
3:4	63.13	8.93	5.70	4.39	3.15	1.96

Simulation Study of Prior Effect

- how dramatic is the effect of prior?
- simulations of 0, 1 or 2 QTL
  - QTL have large effect
    - additive = 2, variance = 1
  - 2 QTL spaced 36cM apart
  - sample sized of 105
- RJ-MCMC runs of 100,000

Effect of Prior Mean



Bayes Factor

prior of 2

m ratio	0	1	2
0:1	3.85	0	0
0:2	50.93	0	0
0:3	569.11	0.03	0
1:2	13.22	1.87	0
1:3	147.75	30.09	0
2:3	11.17	16.05	2.38

prior of 4

m ratio	0	1	2
0:1	0.97	0	0
0:2	3.02	0	0
0:3	15.07	0	0
1:2	3.12	1.32	0
1:3	15.54	3.04	0
2:3	4.99	2.58	0.75

Bayes Factors & LODs

- others have tried arithmetic & harmonic mean
- why not geometric mean?
- terms that are averaged are log likelihoods...

$$\hat{\pi}(\mathbf{y}\,|\,\text{model}_k) = \exp\left(\frac{\sum_{g=1}^{G} \log \pi(\mathbf{y}\,|\,\theta_k;\text{model}_k)}{G}\right)$$

$$g = 1,\cdots,G \quad \textit{MCMC runs}$$

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
  - combine to for geometric estimates of Bayes factors

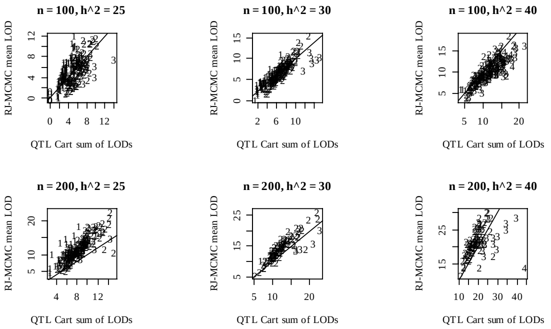
$$LOD(\lambda) = (\log_{10} e)\sum_{j=1}^{n} \ln\left(\frac{\sum_{x=-1,0,1} \pi(y_j\,|\,x;\hat{\mu},\hat{b}^*,\hat{\sigma}^2)\pi(x\,|\,\lambda)}{\pi(y_j\,|\,\hat{\mu},b^*=0,\hat{\hat{\sigma}}^2)}\right)$$

$$BLOD = (\log_{10} e)\sum_{j=1}^{n} \ln\left(\frac{\pi(y_j\,|\,x_j^*;\mu,b^*,\sigma^2)}{\pi(y_j\,|\,\mu,b^*=0,\sigma^2)}\right)$$

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



IX: RJ-MCMC Software

- General MCMC software
  - U Bristol links
    - http://www.stats.bris.ac.uk/MCMC/pages/links.html
  - BUGS (Bayesian inference Using Gibbs Sampling)
    - http://www.mrc-bsu.cam.ac.uk/bugs/
- Our MCMC software for QTLs
  - C code using LAPACK
    - ftp://ftp.stat.wisc.edu/pub/yandell/revjump.tar.gz
  - coming soon:
    - perl preprocessing (to/from QtlCart format)
    - Splus post processing
    - Bayes factor computation

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)

Bayes Factor References

- MA Newton & AE Raftery (1994) “Approximate Bayesian inference with the weighted likelihood bootstrap”, *J Royal Statist Soc B* 56: 3-48.
- RE Kass & AE Raftery (1995) “Bayes factors”, *J Amer Statist Assoc* 90: 773-795.
- JM Satagopan, MA Newton & AE Rafter (1999) “On the harmonic mean estimator of marginal probability”, ms in prep, mailto:satago@biosta.mskcc.org.

Reversible Jump MCMC References

- PJ Green (1995) “Reversible jump Markov chain Monte Carlo computation and Bayesian model determination”, *Biometrika* 82: 711-732.
- S Richardson & PJ Green (1997) “On Bayesian analysis of mixture with an unknown of components”, *J Royal Statist Soc B* 59: 731-792.
- BK Mallick (1995) “Bayesian curve estimation by polynomials of random order”, TR 95-19, Math Dept, Imperial College London.
- L Kuo & B Mallick (1996) “Bayesian variable selection for regression models”, *ASA Proc Section on Bayesian Statistical Science*, 170-175.

QTL Reversible Jump MCMC: Inbred Lines

- JM Satagopan & BS Yandell (1996) “Estimating the number of quantitative trait loci via Bayesian model determination”, *Proc JSM Biometrics Section*.
- DA Stephens & RD Fisch (1998) “Bayesian analysis of quantitative trait locus data using reversible jump Markov chain Monte Carlo”, *Biometrics* 54: 1334-1347.
- MJ Sillanpaa & E Arjas (1998) “Bayesian mapping of multiple quantitative trait loci from incomplete inbred line cross data”, *Genetics* 148: 1373-1388.
- R Waagepetersen & D Sorensen (1999) “Understanding reversible jump MCMC”, mailto:sorensen@inet.uni2.dk.

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.
- I Hoeschele, P Uimari , FE Grignola, Q Zhang & KM Gage (1997) “Advances in statistical methods to map quantitative trait loci in outbred populations”, *Genetics* 147:1445-1457.
- P Uimari and I Hoeschele (1997) “Mapping linked quantitative trait loci using Bayesian analysis and Markov chain Monte Carlo algorithms”, *Genetics* 146: 735-743.
- MJ Sillanpaa & E Arjas (1999) “Bayesian mapping of multiple quantitative trait loci from incomplete outbred offspring data”, *Genetics* 151, 1605-1619.

Bayes & MCMC References

- CJ Geyer (1992) “Practical Markov chain Monte Carlo”, *Statistical Science* 7: 473-511
- L Tierney (1994) “Markov Chains for exploring posterior distributions”, *The Annals of Statistics* 22: 1701-1728 (with disc:1728-1762).
- A Gelman, J Carlin, H Stern & D Rubin (1995) *Bayesian Data Analysis*, CRC/Chapman & Hall.
- BP Carlin & TA Louis (1996) *Bayes and Empirical Bayes Methods for Data Analysis*, CRC/Chapman & Hall.
- WR Gilks, S Richardson, & DJ Spiegelhalter (Ed 1996) *Markov Chain Monte Carlo in Practice*, CRC/Chapman & Hall.

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  - coming soon:
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QTL References

- D Thomas & V Cortessis (1992) “A Gibbs sampling approach to linkage analysis”, *Hum. Hered.* 42: 63-76.
- I Hoeschele & P vanRanden (1993) “Bayesian analysis of linkage between genetic markers and quantitative trait loci. I. Prior knowledge”, *Theor. Appl. Genet.* 85:953-960.
- I Hoeschele & P vanRanden (1993) “Bayesian analysis of linkage between genetic markers and quantitative trait loci. II. Combining prior knowledge with experimental evidence”, *Theor. Appl. Genet.* 85:946-952.
- SW Guo & EA Thompson (1994) “Monte Carlo estimation of mixed models for large complex pedigrees”, *Biometrics* 50: 417-432.
- JM Satagopan, BS Yandell, MA Newton & TC Osborn (1996) “A Bayesian approach to detect quantitative trait loci using Markov chain Monte Carlo”, *Genetics* 144: 805-816.