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Introduction to Bayesian Methods for QTL Analysis - 4

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Case Studies

This discussion is based on:

- George, Mengersen and Davis (2000) Localisation of a quantitative trait locus via a Bayesian approach. Biometrics 56, 40-51.
- Baker and Mengersen (2002) Central censoring and selective genotyping, submitted to JABES.
- Various papers as referenced

Leading up to Bayesian methods

- Lander and Botstein 89; Knapp et al 89: Early methods based on assumption of at most one QTL contributing to a trait. Obvious deficiencies with many contributing QTLs.
- Knapp 91; Haley and Knott 92; Martinez and Curnow 92: approximate methods to map several QTLs.
- Jansen 92: general mixture model for multiple QTL.
- Cowen 89; Stam 1991: Multiple regression methods.
- Jansen 93; Zheng 93, 94; Jansen and Stam 94; Jansen 94 : Hybrid methods combining one-QTL mixture model (L&B 1989) with multiple regression, using covariates to correct for neighbouring QTLs and reduce error variation. Output point estimates for number, location and effects of QTLs, approximate critical values for significance tests, inference on parameters via bootstrapping.
- Wu and Li 94, 96: Regression approach to joint mapping of QTLs, allowing comparison of different models for different no’s of QTLs.

Localisation of a QTL

- Specify a genetic model, a statistical model and an analytic technique.
- Focus on half-sib design: large number of half-sib families, missing genotype data from the dams.
- Biallelic QTL

Source of information

- Pedigree structure: K unrelated half-sib families, each family has a single male parent randomly mated to a large number of females, each of which produces a single offspring.
- Marker information: N linked informative (ie heterozygous) markers genotyped on the sires and all progeny but with no information on the dams.
- Phenotypic information: Quantitative trait measured for each offspring and influenced by both genetic and environmental factors.

Models

- Genetic model: Assume the quantitative trait is influenced by a biallelic QTL with alleles Q and q and associated allele frequencies p_Q and $(1-p_Q)$ respectively. Both additive and dominance effects are modelled.

Models

- Statistical model:

$$Y_{ji} = \mu_{G_{ji}} + \varepsilon_{ji}$$

  - Y_{ji} is the trait value for the ith offspring in the jth family
  - $G_{ji} \in \{QQ, Qq, qq\} = \{1,2,3\}$ is the ith offspring's QTL genotype
  - $\mu_{G_{ji}}$ is the expected trait value given the QTL genotype G_{ji}
  - ε_{ji} is the offspring's random deviation from $\mu_{G_{ji}}$. Includes environmental effects and has variance σ_R^2 (residual variance).

  - Trait's phenotypic variance (σ_P^2) is the sum of the between-family (σ_{BF}^2) and the within-family (σ_{WF}^2) variances. For a half-sib design, $\sigma_{WF}^2 = (3/4)\sigma_A^2 + \sigma_D^2 + \sigma_R^2$; $\sigma_{BF}^2 = (1/4)\sigma_A^2$

Notation

y_{ji}: phenotypic value for the ith offspring in the jth family

f_j: set of marker data for the jth family so that fji is the genotype for the N linked marker loci of the *i*th individual in the *j*th family

s: vector of marker genotypes and phase configurations for the K sires

M_{ij} : *j*th allele of the *i*th gene marker M_i

π_j: jth locus on the chromosome, may be a marker locus or a QTL, depending on the locus order

Q: set of recombination rates between locus π_j and π_{j+1}

$\mu=(\mu_1,\mu_2,\mu_3)$, with expected values m+a, m+d, m-a (m is mid homozygote value, a is additive, d is dominance)

z_s : sire's unknown QTL genotype: {QQ,Qq,qQ,qq}={1,2,3,4}

z_f : ith offspring's QTL genotype in the jth family, {QQ,Qq,qq}={1,2,3}

Likelihood

- Likelihood for K half-sib families is equal to a mixture of four within-family likelihoods p_{QQ}, p_{Qq}, p_{qQ}, p_{qq} weighted by the probability of the sire having QTL genotype QQ, Qq, qQ, qq, respectively.

$$
\begin{aligned}
&\prod_{j=1}^{K}\left\{p_Q^2 p_{QQ}(Y_j \mid p_Q, \mu_1, \mu_2, \sigma_R^2\right\} \\
&+ p_Q(1-p_Q)p_{Qq}(Y_j, f_j, s_j \mid \theta, p, p_Q, \mu, \sigma_R^2, \omega_l) \\
&+ (1-p_Q)p_Q)p_{qQ}(Y_j, f_j, s_j \mid \theta, p, p_Q, \mu, \sigma_R^2, \omega_l) \\
&+ (1-p_Q)^2 p_{qq}(Y_j \mid p_Q, \mu_2, \mu_3, \sigma_R^2)
\end{aligned}
$$

Mixture!

This likelihood is conditioned on a specific locus order w_l:
$w_l = QM_1M_2\ldots M_N$; $\omega_l = \ldots M_{l-1}QM_{l+1}$ for $l=2,\ldots,N$;
$w_{N+1} = M_1M_2\ldots M_NQ$.

Single-family likelihood

- For a sire with QTL genotype QQ or qq:
  - Mixture of two Gaussian densities (mean μ_j, variance σ_R^2) weighted by the allele frequencies for Q and q from the dams' contributions.
  - Multiply over the n_j offspring in family j.
  - Genetic information does not feature in p_{QQ} or p_{qq} since the sire's QTL is noninformative.
- For a sire with QTL genotype Qq or qQ:
  - Mixture of three Gaussian densities (offspring's three QTL genotype classes), weighted by the conditional probability of an offspring having genotype f_{ji} and QTL genotype Q_{ji} given the sire's marker genotype and phase s_j, locus order w_l and the sire's QTL genotype Q_j.
  - Multiply over the n_j offspring in family j.

Conditional Probabilities

- Consider *j*th family with assumed paternal QTL qQ and corresponding within-family likelihood $p_{qQ}(.)$
- The conditional probability for an offspring with marker f_{ji} and QTL Q_{ji} has the functional form
- $P(f_{ji},Q_{ji}|\ldots Q_j=qQ)$ – $f_E/\Sigma f_y$

sum over the offspring's QTL genotypes

f_{ji}: expected frequency of A half-sib with marker genotype f_{ji} and QTL genotype Q_{ji}=y -derived from a table of expected and observed genotype numbers

Missing data: dams' genotypes – need to estimate for affected offspring

Priors and posterior

- Model the hidden data structure (individuals' unknown QTL genotypes)
- Can write down:
  - the joint posterior for parameters $\beta=\{\theta,p,p_Q,\mu,\sigma_R,\omega_l\}$ and the missing data z_s and z_f given the observed data and s (marker genotypes and phase configurations for the K sires)
  - The conditional distribution of the offspring's QTL genotypes given the sire's QTL genotypes and β
  - The conditional distribution of the sire's QTL genotype given β

All mixture distributions!

But if we know z, they simplify to a product of terms

Prior for recombination rates θ

- Genotyping errors, recombination hot spots, nonuniformity of recombination events along the chromosomes contribute to errors in the linkage map from which the marker positions are obtained.
- To allow for this uncertainty, estimate the recombination rates in the analysis. Incorporate published marker information through strong priors.
- Assuming independence of recombination rates along the chromosome, the prior for θ is the product of the priors for the between-marker recombination rates. Set these as Gaussian centred around the relevant published value.
- No information on the QTL's position, so place a uniform density on the recombination rate between the QTL and the marker.

Other priors

- Prior for p: set of allele probabilities. Allele probabilities at a given locus do not influence allele probabilities at an alternative locus because of linkage equilibrium, so the prior for p is the product of priors for all individuals. Set a Dirichlet distribution on (p_{i1}, p_{i2}, p_{i3}).
- Prior for p_Q: Strong prior (normal or t-distribution) is possible using information from the design. Here we used a uniform distribution.
- Prior for σ_R^2 (residual variance): must be no larger than the observed phenotypic variance of the quantitative trait σ_P^2. So use uniform $U(0, \sigma_P^2)$.
- Prior for ω_l (locus order): equal weightings to different orders.

Update parameters, given the locus ordering

1. Allocate the z_s: sires are allocated QTL genotypes based on the family's phenotypic and genotypic information and the current set of parameter values.
2. Given the sire's QTL genotype, z_f is allocated: the offspring are allocated QTL genotypes based on the offspring's phenotypic and genotypic information and the current set of parameter values.
3. New parameter values Q,p,p_Q,μ,σ_R^2 are sampled via the M-H algorithm for a specific locus ordering by treating z_s and z_f as known information.

Update locus ordering, given the parameters

Example:

- old values of locus order: $w_2^{\,1}$ = AQBCD and recombination rates: $\theta^1=(0.2,0.4,0.1,0.2)$,
  Q is QTL; A,B,C,D are gene markers
- Convert recombination rates to map distances via the Haldane mapping function ($\delta=0.5\ln(1-2\theta)$), so that $\delta_1=(\delta_{AQ}^{\,1}, \delta_{QB}^{\,1}, \delta_{BC}^{\,1}, \delta_{CD}^{\,1})=(.26,.81,.11,.26)$. (Map distances are easier to work with than recombination rates due to their additive nature.)
- Randomly select a marker to act as a pivot. For a forward or backward move, shift the QTL to the right or left of the pivot, respectively. The distance between the QTL and the pivot remains the same.

- Suppose a forward move is chosen and the pivot marker is B. The new locus order is dependent on the size of δ_{QB}^{1} in relation to δ_{BC}^{1} and δ_{CD}^{1}. For example, $\delta_{QB}^{1} > \delta_{BC}^{1} + \delta_{CD}^{1}$, so δ_5^{2}=ABCDQ.
- The vector of map distances associated with the new locus order is $\delta_{AB}^{2} = \delta_{AQ}^{1} - \delta_{QB1}^{1}$; $\delta_{BC}^{2} = \delta_{BC}^{1}$; $\delta_{CD}^{2} = \delta_{CD}^{1}$; $\delta_{DQ}^{2} = \delta_{QB}^{1} - (\delta_{BC}^{1} + \delta_{CD}^{1})$.
- Obtain θ^2 by applying the inverse of the Haldane mapping function.

- Do a similar trick for a backward move. We can show the reversible nature of these moves.
- These relationships will change depending on the move type, the pivot selected, and the position of the markers on the chromosome, but the principle of shifting the QTL about a randomly selected pivot and adjusting the map distances accordingly is preserved.

Accepting proposed moves

- Proposed move is from old=$(\omega_2^{\ 1},\theta^1)$ to new=$(\omega_5^{\ 2},\theta^2)$
- Accept proposed move with probability

$$\alpha = \min\left(1, \frac{p(new\,|\,\ldots)}{p(old\,|\,\ldots)}\frac{p_B}{p_F}\,|\,J\,|\right)$$

|J| is the determinant of the Jacobian (required because of the way we've moved)

pF: probability of making a forward move

pB: probability of making a backward move.

Complete algorithm

1. Given the locus ordering:
    1. Allocate the sires' QTL genotypes
    2. Allocate the offspring's QTL genotypes
    3. Update the parameter values
2. Update the locus ordering.

Example

- 6 designs:
  - sires = 20, 5
  - offspring = 200, 50
  - σ_R=0.5, 2.0
  - a/σ_P = 1.15a, 0.47a,
  - σ_Q^2/σ_P^2 = 0.67, 0.11
- Design 1:

	q_{M2Q}	p_Q	μ_1	σ_R
True	.10	.50	71.00	0.50
Mean	.10	.48	71.02	0.50
95% CI	(.08,.12)	(.45,.51)	(70.96,71.07)	(.48,.52)

- For each design, the true locus order had the highest posterior probability.
- Use Bayes factors to confirm strength of evidence. Some designs suggested spurious multiple QTL, due to half-sib data.

- Posterior probabilities for the locus order. True locus order is $M_1M_2QM_3M_4$.

	Design 1	Design 2
$Q\ M_1M_2M_3M_4$	0.000	0.020
$M_1QM_2M_3M_4$	0.002	0.346
$M_1M_2QM_3M_4$	0.998	0.365
$M_1M_2M_3QM_4$	0.000	0.233
$M_1M_2QM_3M_4Q$	0.000	0.036

- Average percent of correctly allocated sires and offspring?

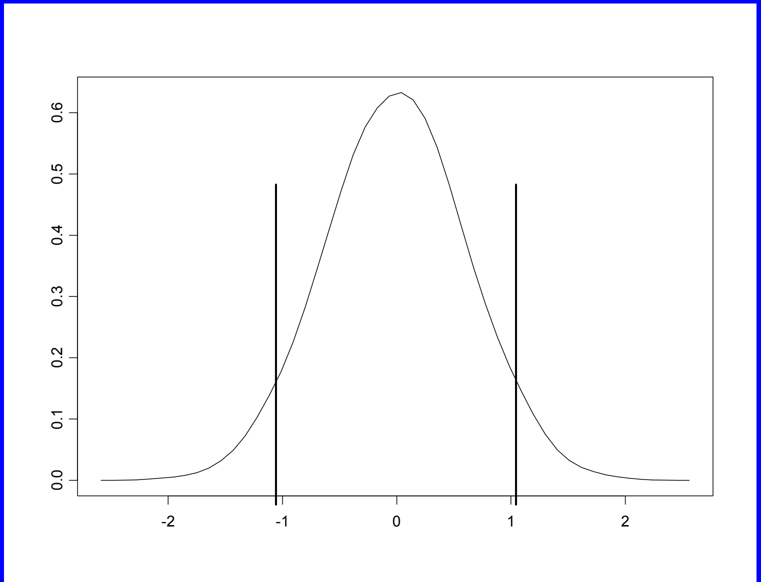
	Design 1	Design 2
Sire allocation:	Design 1: 1.00	Design 2: 0.99
Offspring allocation:	0.77	0.51

Conclusions

- Weak priors result in poor estimation of some parameters.
- Stable estimation of locus ordering takes longer than estimation of parameters within a locus ordering.
- Poor mapping of QTL under some designs, perhaps due to half-sib design.
- Correct allocation of sires is influenced by the size of the QTL and the number of offspring in the half-sib families.
- Correct allocation of the offspring depends only on the strength of the individual's data.
- The size of the QTL has a profound effect on the accuracy of the parameter estimates.
- Family size influences the performance of the sampler: easier to achieve convergence with a small number of large half-sib families compared to a large number of small half-sib families.
- ANIMAP overestimated the additive effect and failed to detect small QTL.

Example: Selective genotyping

- Introduced by Lander & Botstein (1989): increase power to detect QTL of a smaller effect
- Phenotype a population but genotype, via molecular markers, those with extreme phenotypes



Why selective genotyping?

- Lander & Botstein (1989): increase power to detect QTL of a smaller effect
- Darvasi & Soller (1992): for a single marker linked to a QTL, genotyping the upper & lower 25% is nearly as efficient as genotyping the whole population.
- Lin & Ritland (1996): for large linked QTL, may need tails of larger size or genotype all individuals
- Muranty & Goffinet (1997): for a trait other than that used for SG there is no loss of accuracy of QTL detection compared to genotyping a random sample of the same size.

Methods of analysis

- Lander & Botstein (1989): EM approach; need bias adjustment (Darvasi & Soller 1992)

- Baker et al (2000): Bayesian mixture model
  - General Bayesian package BUGS

Cattle mapping study (Davis et al, 1998)

Sire	1	2	3
Progeny:	n=250	n=250	n=250

Phenotype data
(adj. for fixed effects)

4 chromosomes A-D:
5, 5, 4, 4 markers
13 markers heterozygous for Sire 1;
16 for Sire 2
2 linked QTL on A, single QTL on C

Dams: up to
5 markers

Cattle Mapping study (Davis et al, 1998)

- 3 sires 2507, 2508, 2509 each with 250 progeny
- Phenotype data adjusted for fixed effects via linear models
- Four chromosomes A,B,C,E had
  5, 5, 4, 4 markers respectively. Markers were between 20 & 35 cM apart.
- Two linked QTL on chromosome A at approx. 15 & 60 cM from 1st marker and a single QTL on chromosome C at approx 75 cM from 1st marker C1.
- 18 markers: 13 heterozygous for sires 2507 and 2509; 16 heterozygous for sire 2508.

Notation

- Offspring markers labelled as M_1, M_2 if they may have come from the sire or M_3 otherwise
- If a sire has marker alleles M_1 & M_2 and the QTL has 2 alleles Q (positive for the trait) and q, then we assume the sire has marker-QTL genotype M_1Q/M_2q.
- The dams have 3 marker alleles M_1, M_2, M_3 with unknown proportions t_1, t_2, $(1-t_1-t_2)$.

Genetic effects

Genetic effect
Of QTL alleles
$\{\mu_{qq}, \mu_{Qq}, \mu_{QQ})$

Additive (>0)
& dominance
components

$$\begin{pmatrix} G_0 \\ G_1 \\ G_2 \end{pmatrix} = \begin{pmatrix} 1 \\ 1 \\ 1 \end{pmatrix} \mu + \begin{pmatrix} -1 & -1/2 \\ 0 & 1/2 \\ 1 & -1/2 \end{pmatrix} \begin{pmatrix} a \\ d \end{pmatrix} = 1\mu + D \begin{pmatrix} a \\ d \end{pmatrix}$$

Overall
phenotypic
mean

Genetic effects

- Define genetic effect of QTL alleles $\{\mu_{qq}, \mu_{Qq}, \mu_{QQ}\}$ as G_0, G_1, G_2.
- overall phenotypic mean μ
- additive & dominance components $a>0$, d
- Genetic effects written as:

$$\begin{pmatrix} G_0 \\ G_1 \\ G_2 \end{pmatrix} = \begin{pmatrix} 1 \\ 1 \\ 1 \end{pmatrix} \mu + \begin{pmatrix} -1 & -1/2 \\ 0 & 1/2 \\ 1 & -1/2 \end{pmatrix} \begin{pmatrix} a \\ d \end{pmatrix} = 1\mu + D \begin{pmatrix} a \\ d \end{pmatrix}$$

Without marker information

X is design matrix
for fixed effects

Δ is nx3 matrix,
1 = QTL genotype,
0 otherwise

$$y \sim \sum_{k=1}^{3} p_k N\left(X\beta + \Delta_k D \begin{pmatrix} a \\ d \end{pmatrix}, \sigma^2 I \right)$$

Biallelic QTL: Q,q
p is prop'n Q alleles
in dam population

Without marker information

- Define Δ as nx3 matrix with elements 1 to indicate QTL genotype, 0 otherwise
- Define X as design matrix for fixed effects β.
- For observed phenotype data without marker information:

$$y \sim \sum_{k=1}^{3} p_k N\left(X\beta + \Delta_k D \begin{pmatrix} a \\ d \end{pmatrix}, \sigma^2 I \right)$$

- (could replace by skewed *t* or multivariate *t* within clusters)

With marker information

- p_k are conditional on observed marker types
- Let r be recombination rate between the QTL and marker.
- Probabilities of a QTL given a linked marker:

$$R = \begin{array}{cc} & \begin{array}{ccc} QQ & Qq & qq \end{array} \\ \begin{array}{c} M_1M_1 \\ M_1M_2 \\ M_1M_3 \\ M_2M_2 \\ M_2M_3 \end{array} & \begin{pmatrix} p(1-r) & (1-p)(1-r)+rp & (1-p)r \\ \dfrac{t_1pr+t_2p(1-r)}{t_1+t_2} & \dfrac{t_1(p(1-r)+r(1-p))+t_2(pr+(1-p)(1-r))}{t_1+t_2} & \dfrac{t_1(1-p)(1-r)+t_2(1-p)r}{t_1+t_2} \\ p(1-r) & (1-p)(1-r)+rp & (1-p)r \\ pr & p(1-r)+r(1-p) & (1-p)(1-r) \\ pr & p(1-r)+r(1-p) & (1-p)(1-r) \end{pmatrix} \end{array}$$

Likelihood: without SG

- j = 1 for M_1M_2, 2 for M_1M_2, 3 for M_2,M_2 etc
- $\delta_{M(j)}$=1 if offspring has marker type j; 0 otherwise
- δ_l = nx1 vector with l th element 1; 0 otherwise

$$f(y \mid \mu, a, d, r, p, \beta, \sigma) = \prod_{l=1}^{n} \left\{ \sum_{j=1}^{5} \delta_{M(j)} \left(\sum_{k=1}^{3} R_{(jk)} N\left(y_l, \delta_l^T \left(X\beta + \Delta_k D \begin{bmatrix} a \\ d \end{bmatrix} \right), \sigma^2 \right) \right) \right\}$$

Likelihood: with SG

- $\delta_{M(j)}$ is not 0 or 1 if the marker type is not recorded for that individual
- Instead, $\delta_{M(j)}$ is Pr(marker type = j), j=1,..,5) and must be estimated.
- This results in a finite mixture with 15 components for those individuals not genotyped.

Bayesian approach

- Posterior $\propto$ Likelihood x prior

$$f(\mu, a, d, r, p, t_1, t_2, \beta_1, \ldots, \beta_k, \sigma \mid y)$$
$$\propto f(y \mid \ldots) f(\mu) f(a) \ldots f(\sigma)$$

- Marginal posterior distribution of any parameter is found by integrating the joint posterior over all other parameters.
- Use MCMC for computation.

Priors

- No informative prior information, so disperse proper priors were adopted

$$\mu \sim N(0,10^{12}), a \sim N(0,10^{6}) I(a > 0),$$
$$r \sim U(0,0.5), \tau = \sigma^{-2} \sim Ga(.001,.001)$$
$$G \sim Dirichlet(1,2,1)$$

- For selective genotyping, prior on marker types:

$$\delta_{M(j)} \sim Dirichlet(1,\ldots,1)$$

Mixtures as latent variables

- Estimate $\delta_{M(j)}$.
- Then allocate ungenotyped individuals to the 5 marker types.
- For each marker type, estimate $R_{(jk)}$.
- Then allocate individuals to the 3 mixture components.
- Estimate component-specific parameters using those individuals allocated to that component.
- Estimate other parameters.

Results

- Four chromosomes A,B,C,E had 5, 5, 4, 4 markers respectively.
- Markers were between 20 & 35 cM apart.
- Two linked QTL on chromosome A at approx. 15 & 60 cM from 1^{st} marker and a single QTL on chromosome C at approx 75 cM from 1^{st} marker C1.

Sire	Marker	Full Data				S.G. Data			
		Dist (cM)	a	%var	BF	Dist (cM)	a	%var	BF
2509	A3	29	27	33	17.8	29	28	35	15.4
	C1	32	24	24	5.1	31	24	22	4.1
2508	A2				2.0	28	19	15	4.0
	C3	32	20	17	3.9				2.4

Full vs SG datasets: Bayes Factors