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Bayesian mapping of genome-wide epistatic imprinted loci for quantitative traits

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Abstract Genomic imprinting, an epigenetic phenomenon of parent-of-origin-specific gene expression, has been widely observed in plants, animals, and humans. To detect imprinting genes influencing quantitative traits, the least squares and maximum likelihood approaches for fitting a single quantitative trait locus (QTL) and Bayesian methods for simultaneously modeling multiple QTL have been adopted, respectively, in various studies. However, most of these studies have only estimated imprinting main effects and thus ignored imprinting epistatic effects. In the presence of extremely complex genomic imprinting architectures, we introduce a Bayesian model selection method to analyze the multiple interacting imprinted QTL (iQTL) model. This approach will greatly enhance the computational efficiency through setting the upper bound of the number of QTLs and performing selective sampling for QTL parameters. The imprinting types of detected main-effect QTLs can be estimated from the Bayes factor statistic formulated by the posterior probabilities for the genetic effects being compared. The performance of the proposed method is demonstrated by several simulation experiments. Moreover, this method is applied to dissect the imprinting genetic architecture for body weight in mouse and fruit weight in tomato. Matlab code for implementing this approach will be available from the authors upon request.

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Introduction

Through molecular mechanisms such as DNA methylation, histone modification, noncoding RNAs (ncRNA), and long-distance interchromosomal interactions (Allis et al. 2007; Kiefer 2007; Pauler and Barlow 2006; Wood et al. 2008), genes may exhibit distinct expression patterns, depending on the parent who passes on the alleles. Such a parent-of-origin effect on allele activities and phenotypes is a type of epigenetic processes, or genomic imprinting, which has been widely observed in plants (Alleman and Doctor 2000) and animals (Falls et al. 1999; Jeon et al. 1999; McInnis et al. 2003; McKeigue and Wild 1997; Nezer et al. 1999; Paterson et al. 1999; Tuiskula-Haavisto et al. 2004; Van Laere et al. 2003) and has been unanimously recognized for its role in shaping organisms' developmental processes (Constancia et al. 2004; Isles and Holland 2005; Tycko and Morison 2002). In addition to single imprinted genes, evidence of interaction between

imprinted genes has been also reported (Cattanach et al. 2004; Wolf and Cheverud 2009). Different types of imprinting effects on traits of interest have been defined. Based on the parental origin of the expressed allele, imprinting can be classified into paternal imprinting and maternal imprinting, whereas based on the extent of expression difference, imprinting can then be categorized as either complete imprinting when only one parental allele is expressed or partial imprinting when both parental alleles are expressed but in different levels (Naumova and Croteau 2004; Sandovici et al. 2003, 2005). Aiming to provide a comprehensive classification scheme, a recent study (Cheverud et al. 2008) classified imprinting types into either parental expression or dominance imprinting.

Genetic mapping approaches have been developed to detect the epigenetic modification of an imprinted gene on quantitative traits in populations with different structures. For a complex pedigree, the iQTLs can be identified using identical-by-descent-based random models (Haghighi and Hodge 2002; Hanson et al. 2001; Shete and Amos 2002; Shete et al. 2003). For the controlled crosses between outbred parents (de Koning et al. 2000, 2002; Knott et al. 1996; Tuiskula-Haavisto et al. 2004), tracing parental origins of alleles from the offsprings to the parents can be used to study genomic imprinting (Knott et al. 1998). Note that when the reciprocal heterozygotes are fully informative or distinguishable, imprinted effects of QTLs can be uniquely tested and estimated by means of genetic association of phenotype with markers (Cheverud et al. 2008; Hager et al. 2009; Wolf et al. 2008) or interval mapping with conditional probabilities of QTL genotypes on given flanking marker genotypes (Cheverud et al. 2008; Hager et al. 2009; Mantey et al. 2005). On the other hand, when the reciprocal heterozygotes are not fully informative or distinguishable, the information of sex-specific differences in recombination fraction (De Vicente and Tanksley 1991; Dib et al. 1996; Dietrich et al. 1996; Groover et al. 1995; Haldane 1992; Huxley 1928; Knott et al. 1998; Neff et al. 1999) can be used to make imprinted effects of QTLs estimable, allowing us to infer the inheritance patterns of quantitative traits in the genetically designed population with only one heterozygote, such as inbred F_2 population.

Some available methods for detecting imprinting locus have been extended from methods for interval mapping of Mendelian QTLs. Imprinting effects can be estimated using either least squares (de Koning et al. 2000, 2002; Knott et al. 1996; Tuiskula-Haavisto et al. 2004) or maximum likelihood methods (Cui et al. 2006). Multiple step tests for contrast models have been also proposed to identify the imprinting pattern (de Koning et al. 2000, 2002; Knott et al. 1996; Tuiskula-Haavisto et al. 2004). All those mapping approaches are based on a single QTL model, i.e. estimating and testing one locus at a time. Bayesian mapping, on the other hand, is able to simultaneously map multiple QTLs and plays an important role in detecting iQTLs and distinguishing between Mendelian and imprinting expressions of QTLs (Hayashi and Awata 2008). Although the Bayesian mapping approach improves statistical power of QTL detection, its attempt to estimate the number of QTLs using a reversible-jump MCMC procedure may result in lower convergence efficiency and poor mixing. Given maximum number of QTLs, therefore, Yang et al. (2010) have adopted Bayesian model selections to estimate the iQTLs and estimated their imprinting types in a computationally efficient manner. However, these Bayesian mapping methods mainly focus on main effects of iQTLs, without considering the interactions between iQTLs, which is largely due to the fact that statistical analyses for interacting iQTLs can be more complex in the presence of various factors, such as unknown number of iQTLs and the huge number of possible epistatic effects. To better understand genomic imprinting architecture of quantitative traits, in this study, we extend Bayesian model selection for analyzing epistatic QTLs inherited in Mendelian fashion (Yi et al. 2005) to interacting iQTLs. We demonstrate the performance of the proposed method using computer simulation experiments and apply the method to studying the genetic controls of body weight in mouse and fruit weight in tomato.

Theory and method

Genetic model

We take an F_2 mating design as an example to describe the imprinting genetic model for quantitative traits. To locate the iQTLs, we measure genotypes of a set of codominant molecular markers with a known genetic linkage map as well as phenotypes for the trait of interest on n individuals. Suppose there are m QTLs controlling a trait of interest. The phenotypic value y_k of individual k can be represented by the following multiple interacting QTL model:

$$y_k = \mu + \sum_{j=1}^{m} M_{kj} + \sum_{h>j}^{m} \Delta_{kjh} + e_k \quad (1)$$

where μ is the population mean, and e_k is a random environmental error, distributed as $N(0, \sigma^2)$ with σ^2 being residual variance; in particular, M_{kj} denotes the main effect of the jth QTL, and $\Delta_{kjh}$is the interaction between the jth QTL and the hth QTL for the kth individual. M_{kj} and Δ_{kjh} will be formulated based on the genetic imprinting theory.

For two alleles Q and q of a QTL in an F_2 population, their parental origins are represented by Q_M and q_M when they are derived from the F_1 maternal parent, and Q_P and

q_P when from F_1 paternal parent. Therefore, there are four possible imprinted genotypes: Q_MQ_P, Q_Mq_P, q_MQ_P, and q_Mq_P. Different from traditional Mendelian inheritance, genetic imprinting theory suggests that the two reciprocal heterozygotes, Q_Mq_P, and q_MQ_P, are distinguishable, because the alleles inherited from one parent are not completely expressed. Thus, the main effects of the jth iQTL can be decomposed as

$$M_{kj} = c_{kj}a_j + z_{kj}d_j + s_{kj}i_j \quad (2)$$

for $j = 1, 2,\ldots, m$, where a_j, d_j, and i_j are additive, dominance, and imprinting effects, respectively, for the jth QTL. Variable c_{kj}, z_{kj}, and s_{kj} are the genotype indicators for individual k at locus j and are defined as (Mantey et al. 2005)

$$c_{kj} = \begin{cases} +1 \\ 0 \\ 0 \\ -1 \end{cases}, \quad z_{kj} = \begin{cases} 0 \\ +1 \\ +1 \\ 0 \end{cases} \quad \text{and} \quad s_{kj} = \begin{cases} 0 & \text{for } Q_MQ_P \\ +1 & \text{for } q_MQ_P \\ -1 & \text{for } Q_Mq_P \\ 0 & \text{for } q_Mq_P \end{cases}$$

The relationship of interactions among iQTLs is very complicated because of the complex types of their main effects. For simplicity, only pairwise interactions between main effects from different QTLs are considered. We form the interactions between the jth QTL and the hth QTL by pairing the components from main-effect M_j and M_h (Wolf and Cheverud 2009); the interaction of the two QTLs for individual i can be then written as

$$\begin{aligned}\Delta_{kjh} = {} & w^{aa}_{kjh}\delta^{aa}_{jh} + w^{ad}_{kjh}\delta^{ad}_{jh} + w^{ai}_{kjh}\delta^{ai}_{jh} + w^{da}_{kjh}\delta^{da}_{jh} + w^{dd}_{kjh}\delta^{dd}_{jh} \\ & + w^{di}_{kjh}\delta^{di}_{jh} + w^{ia}_{kjh}\delta^{ia}_{jh} + w^{id}_{kjh}\delta^{id}_{jh} + w^{ii}_{kjh}\delta^{ii}_{jh} \end{aligned} \quad (3)$$

where δ^{aa}_{jh}, δ^{ad}_{jh}, δ^{ai}_{jh}, δ^{da}_{jh}, δ^{dd}_{jh}, δ^{di}_{jh}, δ^{ia}_{jh}, δ^{id}_{jh}, and δ^{ii}_{jh} are the epistatic (interactive) effects between the jth QTL and the hth QTL, corresponding to additive × additive, additive × dominant, additive × imprinting, dominant × additive, dominant × dominant, dominant × imprinting, imprinting × additive, imprinting × dominant and imprinting × imprinting, respectively. The dummy variables are

$$\begin{aligned} & w^{aa}_{kjh} = c_{kj}c_{kh},\ w^{ad}_{kjh} = c_{kj}z_{kh},\ w^{ai}_{kjh} = c_{kj}s_{kh}, \\ & w^{da}_{kjh} = z_{kj}c_{kh},\ w^{dd}_{kjh} = z_{kj}z_{kh},\ w^{di}_{kjh} = z_{kj}s_{kh}, \\ & w^{ia}_{kjh} = s_{kj}c_{kh},\ w^{id}_{kjh} = s_{kj}z_{kh} \quad \text{and} \\ & w^{ii}_{kjh} = s_{kj}s_{kh},\ \text{respectively.} \end{aligned}$$

Bayesian model selection for QTL parameters

To facilitate our description below, we also transform the model (1) to a simple linear model:

$$y_k = \mu + \mathbf{x}_k\boldsymbol{\beta} + e_k \quad (4)$$

As compared with multiple main-effect QTL model in Yang et al. (2010), the components in $\mathbf{x}_k$ include not only indicator variables or dummy variables of main-effect iQTLs, but also that of interactions between iQTLs, and $\boldsymbol{\beta}$ consists of corresponding main and epistatic effects. Different from a common linear model, the number of independent variables in the model (4) are unknown and the associated design matrix are unobservable due to the number of QTLs and QTL positions being estimated.

It is hypothesized in quantitative genetics that, the genetic variation of most quantitative traits is actually controlled by a few loci with large effects and a large number of loci with small effects (Lynch and Walsh 1998). This suggests that among those estimated genetic effects, only a few are large or significant and most of them are small or negligible. Therefore, Bayesian model selection based on a composite space representation (Carlin and Chib 1995; Yi 2004; Yi et al. 2005, 2007) provides a simple and efficient way to identify a small number of large or significant genetic effects in multiple interacting QTL model.

Bayesian model selection approach for mapping QTLs starts with specifying the upper bound of the number of QTLs included in the model (Yi et al. 2005), which is greater than the number of detectable QTLs in a given data set. Given the upper bound of the number of QTLs, QTLs will be randomly drawn from all possible spaced loci across the genome. Even with a moderate value of the upper bound, there are many genetic effects being estimated in the model (4). To test of the existence of these effects, a random binary variable γ_j is introduced to indicate which genetic effects are included ($\gamma_j = 1$) in or excluded from ($\gamma_j = 0$) the model (George and McMullochr 1997; Kuo and Mallick 1998). Let $\boldsymbol{\Gamma}$ be a diagonal matrix consisting of all binary variables; the model (4) becomes

$$y_k = \mu + \mathbf{x}_k\boldsymbol{\Gamma}\beta + e_k \quad (5)$$

Unknown parameters in the model, which include μ, $\boldsymbol{\Gamma}$ and $\boldsymbol{\beta}$, are estimated by the implementation of MCMC algorithms. During the MCMC sampling, the real sampling value for γ in the matrix $\boldsymbol{\Gamma}$ within one sampling cycle determines which genetic effect and position of QTL will be drawn or estimated in next sampling cycle. As a rule, QTLs with larger genetic effects are included in the model with higher probabilities than those with smaller genetic effects. This will greatly reduce the computational time, since only a few large main and epistatic effects are drawn in each MCMC iteration.

In fact, Bayesian mapping of iQTLs has the same form of likelihood function, the same method for specifying the priors, and the same forms of conditional posteriors as QTLs inherited under Mendelian law (Yi et al. 2005, 2007). The difference between two models is that the iQTL involves more types of main and epistatic effects than the

inherited QTL under Mendelian law with the same genetic design. This distinction may result in a decreased prior inclusion probability for each genetic effect and an increased computational cost. We specify the prior distribution for each QTL parameter (see Appendix A) and derive the conditional posterior distribution for each QTL parameter from the joint posterior distribution for all unknown parameters (see Appendix B). According to these conditional posterior distributions, full Bayesian sampling for all known parameters is implemented via the MCMC algorithm. Specifically, the associated design matrix is jointly sampled along with QTL positions, instead of the expectation of prior conditional probabilities for QTL genotypes as in Yi et al. (2005, 2007).

Bayesian inference for imprinting patterns

As usual, the mixing behavior and convergence rates of MCMC processes are monitored by visually inspecting trace plots of the sample values for scalar quantities of interest or by using formal diagnostic methods provided in the package R/coda (Plummer et al. 2004). Characteristics of the imprinting genetic architecture are assessed through model averaging (Raftery et al. 1997; Sillanpää and Corander 2002). The posterior inclusion probability of each locus or effect is estimated as its frequency in the posterior samples. Bayes factor (BF), used as the criterion for including each QTL locus or effect (Kass and Raftery 1995; Yi et al. 2005), is defined as

$$\mathrm{BF}_\theta = \frac{p_\theta}{1-p_\theta} \times \frac{1-p_\theta^*}{p_\theta^*}$$

where $\theta = \lambda$, a, d, i and δ, corresponding to the QTL position, additive, dominant, imprinting, and epistatic effects, respectively, conditional on which p_θ is the prior probability and p_θ^* is the posterior probability. Here, when $\theta = a$, d, i and δ, p_θ^* is calculated as the proportion of samples with corresponding $\gamma = 1$, but when $\theta = \lambda$, p_θ^* is calculated as the proportion of samples with $\gamma = 1$ for a, d, i or δ in the whole MCMC sampling iterations. Generally, a threshold of BF for declaring statistical significance is empirically determined as 3, or 2 $\ln\mathrm{BF} = 2.197$.

Next, we need to test whether the QTL exists, which fashion the detected QTL inherits in and which imprinting pattern of the iQTL. Given the existence of a QTL, if the imprinting effect is not significant, the detected QTL inherits in Mendelian fashion; otherwise, it is imprinted. The imprinting patterns can be defined as either additive imprinting or dominance imprinting. Furthermore, the additive imprinting is composed of four subtypes, namely, the complete or partial paternal additive imprinting, corresponding to hypothesis $d = 0$ and $a = i$ or $d = 0$ and $a \neq i$, respectively, and the complete or partial maternal additive imprinting, corresponding to hypothesis $d = 0$ and $a = -i$ or $d = 0$ and $a \neq -i$, respectively. Finally, the dominance imprinting is further classified into bipolar dominance (H_0: $a = 0$ and $d = 0$), polar over-dominance (H_0: $a = 0$ and $d = i$), and polar under-dominance (H_0: $a = 0$ and $d = -i$). Following the definition of imprinting types and the corresponding null hypothesis (Cheverud et al. 2008; Wolf et al. 2008; Yang et al. 2010), the imprinting pattern for the detected QTL depends on whether genetic effect a or d equals imprinting effect i and can also be statistically inferred by BF, which is defined as the ratio of posterior probabilities for the genetic effects being compared. Imprinting patterns, hypotheses, and corresponding statistical criteria for the iQTLs are detailed in Yang et al. (2010).

Real data analysis

Body weight in mouse

An F_2 mating population was derived from two strains, the Large (LG/J) strain and the Small (SM/J) strain (Cheverud et al. 1996). A total of 502 F_2 mice were genotyped for 96 microsatellite markers across 19 autosomal chromosomes. A linkage map of a total length of 1,780 cm has been constructed (Vaughn et al. 1999). The body mass was measured on each mouse at 10-week intervals starting at the age of 7 days. The raw weights were adjusted for several covariates such as dam, litter size at birth and parity, and sex (Vaughn et al. 1999).

We take the body weight growth at the fifth time point as the mapping subject to illustrate our method. Female-to-male recombination rate of 1.25:1 is incorporated into mapping analysis due to no distinguishable reciprocal heterozygotes for measured maker genotypes. In Bayesian mapping analysis, the prior number of main-effect QTLs is set at $l_\mathrm{m} = 3$ according to a previous interval mapping results (Yang et al. 2010). Since the prior expected number of all QTLs (l_0) is set to $l_\mathrm{m} + 5$, the upper bounds of the number of QTLs, L, are 8 for non-epistatic analysis and 16 for epistatic analysis. The initial values of all unknown parameters are the same as what has been done in the simulation study. Since the number of QTLs is prespecified and is not sampled in Bayesian model selection, MCMC sampling easily reaches convergence without any mixing problem. Since the research interest here is not the determination of MCMC convergence, the length of burn-in period is empirically determined by visually inspecting the posterior samples of the plots and then is set to a sufficiently large number to ensure convergence. Here, the MCMC sampling is run for 200,000 cycles after a burn-in period of 6,000 cycles.

There are the five QTLs detected on chromosomes 6, 7, 10, 13, and 15, which all show significant imprinting

effects. Their imprinting types are statistically identified and summarized in Table 1 along with parameter estimates. These detectable QTLs are completely consistent with our previous findings using Bayesian non-epistatic analysis (Yang et al. 2010). In comparison, maximum likelihood method (Cui et al. 2006) only identifies three of the five QTLs detected by the Bayesian method. Moreover, the imprinting types for the three QTLs detected (shown in the final column of Table 1) are quite different from those identified by the Bayesian method, which may be mainly due to the difference of the models used in two mapping methods. Because Cui's method is based on an additive QTL model, the method is not able to estimate dominance and imprinting effects and distinguish between different types of dominance imprinting, as stated in the section of discussion.

Bayesian epistatic analysis also found 8 pairs of epistatic QTLs, some of which depend on both main-effect QTLs, such as the first and the fourth pairs of QTLs, some of which depend on one main-effect QTL, such as the third, the seventh, and the eighth pairs of QTLs, and the others do not depend on any main-effect QTLs. Interestingly, these interactions mainly occur between additive and dominant effects, and only one pair of epistatic QTLs is detected as additive by additive interaction. No interaction with imprinting effect is found. Parameter estimates for epistatic QTLs obtained by the Bayesian epistatic analysis for body weight in mouse are listed in Table 2.

To assess the influence of the sex-biased recombination rates, we re-analyze the dataset by specifying the female-to-male recombination rates of 1.30:1 and 1.20:1. As a result, detected QTLs are the same as what are found above. Moreover, if female-to-male recombination rates are set between 1.30:1 and 1.25:1 or between 1.20:1 and 1.25:1, the imprinting types are exactly the same for main-effect QTLs, and the estimated genetic effects are very close for either main effect or epistatic QTLs. Therefore, we conclude that the proposed Bayesian mapping method is not sensitive to a small change in the sex-specific recombination fraction (simulation results are not shown).

Fruit weight in tomato

To map the QTLs for yield traits in tomato, an F_2 population with 142 progenies was generated by crossing of *Lycopersicon esculentum* Mill.XF98-7 and *Lycopersicon pimpinellifolium* LA2184 (Liu et al. 2005). Based on this population, a genetic linkage map panning 808.4 cm of the tomato genome has been constructed using 112 SSR markers distributed on 16 linkage groups. Fruit weight, as the trait analyzed, was measured by the average of ten representative ripe fruits at the end of the growth season.

We locate the iQTLs for fruit weights using maximum likelihood methods of Cui et al. (2006), Bayesian method of Yang et al. (2010), and our proposed method, respectively. The female-to-male recombination rates of 1.19:1 (de Vicente and Tanksley, 1991) are used to distinguish from reciprocal heterozygotes. Maximum likelihood method identifies 5 QTLs on chromosomes 1, 2, 3, and 12, among which three are imprinted. Based on this result, the expected number of main-effect QTLs in Bayesian mapping is specified as 5 and the prior expected number of all QTLs is specified as 10, leading to the maximum number of QTLs being 19. Initial values of other parameters and sampling scheme are as the same as those appearing in the real data analysis. Table 3 tabulates parameter estimates as well as imprinting types for main-effect QTLs detected by Bayesian non-epistatic analysis. Actually, both Bayesian non-epistatic analysis and Bayesian epistatic analysis identify the same 5 main-effect QTLs. Only one of them is inherited in Mendelian fashion and all others are imprinted in different imprinting types, which are considerably different from those estimated by Cui's maximum likelihood method (see final column of Table 3). What is more, our method further detects five pairs of epistatic QTLs (see Table 4). Additionally, we also re-analyze the dataset by adjusting the female-to-male recombination rate to 1.25:1 and again confirm that a small change in sex-specific recombination fraction does not produce more QTLs other than those detected above and does not affect the size of

Table 1 Estimates for main-effect iQTL parameters and statistical inference for Inheritance modes with Bayesian epistatic analysis for body weight in mouse

QTL	Bayesian method					Cui's method
	Chr-position	*a*	*d*	*i*	Inheritance mode	Inheritance mode
1	6–73.2	0.62 (6.21)	0.57 (0.00)	0.15 (6.62)	Complete paternal	Complete maternal
2	7–63.1	0.78 (9.25)	0.33 (0.00)	−0.35 (8.54)	Complete maternal	Mendelian
3	10–72.7	0.21 (0.00)	0.46 (5.73)	0.29 (7.34)	Polar over-dominance	–
4	13–26.3	0.34 (0.00)	0.66 (3.61)	0.54 (3.81)	Polar over-dominance	–
5	15–12.7	0.51 (4.12)	0.16 (0.00)	−0.19 (3.54)	Complete maternal	Complete paternal

Numbers in the parentheses are 2lnBF values for the corresponding iQTL effects

Table 2 Estimates for epistatic iQTL parameters obtained with Bayesian epistatic analysis for body weight in mouse

QTL no.	QTL type	Chr-position	Effect
1	$a \times a$	6–73.1 × 7–63.1	2.19 (4.06)
2	$a \times d$	2–104.3 × 9–50.1	2.17 (4.95)
3	$a \times d$	5–50.8 × 10–72.7	0.82 (3.08)
4	$a \times d$	7–63.1 × 10–72.7	1.24 (3.29)
5	$a \times d$	9–50.1 × 13–82.7	1.20 (2.89)
6	$d \times a$	2–104.3 × 3–10.2	−0.83 (2.91)
7	$d \times a$	2–104.3 × 7–63.1	1.54 (3.81)
8	$d \times a$	6–73.2 × 16–23.7	1.49 (4.12)

Numbers in the parentheses are 2lnBF values for the corresponding QTL effects

estimated QTL effects as well as detected QTL positions (result not shown).

Simulation studies

The statistical properties of the proposed model are also investigated through simulation studies. In particular, we assume that there are 61 equally spaced codominant markers on a single large chromosome with a length of 500 cm. Three QTLs are assumed on this chromosome, among which two pairwise interactions exist. We simulate these QTLs and maker genotypes for individuals in an F_2 population, with sample size being 250 or 500, where the marker and QTL genotypes are generated by mimicking sex-specific recombination fractions of 1.25:1 in mouse. The imprinting type of each QTL depends on the additive or dominant effect (listed in Table 5). The proportion of phenotypic variance contributed by an individual QTL ranges from 4.14 to 28.54%, and the population mean and residual variance are $\mu = 5.0$ and $\sigma^2 = 5.0$, respectively. Given these parameters, the phenotypic value of the quantitative trait is randomly generated for each individual according to model (1).

Table 4 Estimates for epistatic QTL parameters obtained with Bayesian epistatic analysis for fruit weight in tomato

QTL no.	QTL type	Chr-position	Effect
1	$a \times a$	3–67.8 × 1–10.5	0.18 (4.43)
2	$a \times a$	7–20.3 × 8–15.4	−0.21 (4.98)
3	$a \times d$	3–67.8 × 12–20.2	0.16 (4.76)
4	$a \times d$	2–8 × 12–20.2	0.26 (4.72)
5	$d \times a$	1–10.5 × 12–20.2	0.04 (3.69)

Numbers in the parentheses are 2lnBF values for the corresponding QTL effects

Prior to Bayesian sampling, we set the prior number of main-effect QTLs as $l_m = 3$ and the prior expected number of epistatic QTLs as 3, which implies the upper bound of the number of QTLs is $L = 6 + 3\sqrt{6} = 13$. The values of hyperparameters are taken as $v_e = 0$ and $s_e = 1$. The initial values of all variables are sampled from their prior distributions. The MCMC procedure run for 6,000 cycles as a burn-in period (discarded) and then run additional 100,000 cycles after the burn-in period. To reduce serial correlation, we save one observation out of every 40 cycles and therefore obtain independent posterior sample of 2,500 observations for the post-MCMC analysis. Fifty simulations of the same setting are carried out to evaluate statistical power of QTL detection.

The identified imprinting loci positions, estimated effects as well as relative statistical powers of these iQTLs detection based on Bayesian epistatic analysis are shown in Table 5. Using BF statistic, the imprinting type of the detected locus can be identified more completely and accurately. Bayesian mapping of genome-wide imprinting interacting loci is able to better estimate the effects and positions of detected QTLs. As expected, the estimation precision of parameters and the statistical power of QTL detection increase as the genetic contribution of QTL measured by true effect and sample size increase. In addition, we notice that the Bayesian model selection is more sensitive to the iQTLs with relatively small genetic

Table 3 Estimates for main-effect QTL parameters and statistical inference for Inheritance modes with Bayesian epistatic analysis for fruit weight in tomato

QTL No.	Bayesian method					Cui's method
	Chr-position	a	d	i	Inherence node	Inherence mode
1	1–10.5	−1.38 (9.13)	0.12 (0.00)	1.17 (8.73)	Complete paternal	Complete paternal
2	2–8.0	0.07 (0.00)	1.15 (3.318)	−1.83 (2.28)	Polar over-dominance	Mendelian
3	2–28.3	−1.13 (7.75)	0.09 (0.00)	0.98 (7.93)	Partial paternal	Mendelian
4	3–67.8	1.04 (10.47)	−0.05 (0.00)	0.87 (9.73)	Complete paternal	Partial paternal
5	12–20.2	0.06 (0.00)	1.21 (8.96)	−0.31 (0.00)	Mendelian dominance	Mendelian

Numbers in the parentheses are 2lnBF values for the corresponding QTL effects

Table 5 Parameter estimates (standard deviations) and statistical powers of QTLs detection obtained with Bayesian epistatic analysis for the simulated data under sex-specific differences in recombination rate of human and mouse (1.60:1 and 1.25:1)

Sample size	Sex specific	QTL parameter	QTL No.							
			1		2		3		4	5
			Additive	Imprinting	Dominant	Imprinting	Additive	Dominant	Additive × dominant	Imprinting × additive
True		Position	23		148		308		23 × 148	148 × 308
		Effect	1.3	1.3	0.6	0.6	0.5	−1.0	1.0	−0.7
		Heritability	0.29		0.06		0.11		0.08	0.04
250	Mouse	Position	21.8 (2.53)		145.3 (3.92)		305.6 (6.87)		24.9 (2.97) × 146.1 (3.96)	147.2 (3.73) × 310.2 (6.85)
		Effect	1.26 (0.34)	1.33 (0.35)	0.46 (0.21)	0.69 (0.27)	0.42 (0.33)	−1.09 (0.29)	0.89 (0.26)	−0.67 (0.26)
		Heritability	0.28		0.06		0.12		0.07	0.04
		Power	100%		82%		90%		84%	80%
	Human	Heritability	0.29		0.07		0.11		0.07	0.04
		Power	100%		86%		90%		84%	84%
500	Mouse	Position	22.1 (2.31)		146.7 (3.07)		306.2 (5.26)		23.8 (2.56) × 146.9 (3.28)	149.3 (3.31) × 308.6 (5.97)
		Effect	1.33 (0.27)	1.31 (0.26)	0.52 (0.17)	0.61 (0.26)	0.45 (0.28)	−0.97 (0.22)	0.95 (0.21)	−0.76 (0.18)
		Heritability	0.29		0.06		0.11		0.08	0.04
		Power	100%		88%		96%		90%	86%
	Human	Heritability	0.29		0.06		0.11		0.08	0.04
		Power	100%		92%		96%		92%	90%

Table 6 Parameter estimates (standard deviations) and statistical powers of QTLs detection obtained with Bayesian nonepistatic analysis for the simulated data by mimicking sex-specific recombination fraction of 1.25:1 in mouse

Sample size	QTL parameter	QTL No.					
		1		2		3	
		Additive	Imprinting	Dominant	Imprinting	Additive	Dominant
True	Position	23		148		308	
	Effect	1.3	1.3	0.6	0.6	0.5	−1.0
250	Position	22.8 (2.03)		146.8 (3.42)		306.9 (6.01)	
	Effect	1.36 (0.33)	1.39 (0.25)	0.76 (0.26)	0.79 (0.29)	0.62 (0.33)	−1.17 (0.39)
	Power	100%		84%		92%	
500	Position	23.3 (1.79)		147.5 (2.98)		308.4 (4.96)	
	Effect	1.40 (0.27)	1.37 (0.18)	0.66 (0.19)	0.69 (0.23)	0.65 (0.27)	−1.21 (0.29)
	Power	100%		94%		98%	

contribution, as opposed to Mendelian QTLs (Yi et al. 2005, 2007). The same datasets simulated are also analyzed using Bayesian non-epistatic analysis. The results show that Bayesian non-epistatic analysis can also precisely map all the main-effect iQTLs simulated with the same or slightly higher power than Bayesian epistatic analysis, but effects of iQTLs are somewhat overestimated (see Table 6). Additionally, simulations specifying various expected numbers of iQTLs consistently support the statistical power and robustness of our method in estimating parameters of iQTLs (results not shown).

By increasing the sex-specific difference in recombination fractions to 1.6:1, which is a reasonable estimate for humans, we perform additional simulation experiments to investigate the impact of difference in sex-specific recombination fraction on iQTLs detections of our method. Comparison of simulation results in Table 5 indicates that statistical power to detect iQTLs and the estimating precision of effects of iQTLs increase moderately as the difference in sex-specific recombination increases, but this improvement is more evident to the iQTL than that inherited in Mendelian fashion. This suggests that larger sex-specific difference in recombination fraction contributes to better distinguishing between two different formations of QTL heterozygotes based on the two flanking markers.

Discussion

In this study, we extend Bayesian mapping for multiple main-effect iQTLs (Yang et al. 2010) to interacting iQTLs. Bayesian model selection for mapping interacting Mendelian QTLs (Yi et al. 2005) is employed to analyze the interacting iQTLs for quantitative traits. Our proposed approach is not only capable of identifying the main effect of iQTLs, but also capable of estimating the pairwise interactions among iQTLs, even if the interactions among iQTLs cannot be well explained with our current knowledge of biological processes and metabolic pathways. The imprinting types of main-effect QTLs detected by our model can be estimated based on the BF statistic formulated by the posterior probabilities for various imprinting genetic effects. Simulation studies demonstrate the performance of this method under different experimental designs, where various genetically contributed proportion by iQTL and different sample sizes are considered. A real data analysis validates the flexibility of our method by comparing the result of our approach with the results from a full model containing only main effect and another model based on maximum likelihood.

Cui et al. (2006) have proposed the single imprinting QTL model within the framework of maximum likelihood, which may better detect which parent the imprinting effect was originated from according to respective estimators for the paternally and maternal inherited effects. In fact, the imprinting can also lead to the change of interaction between alleles. Cheverud et al. (2008) illustrated a scheme for characterizing the potential diversity of imprinting patterns, where imprinting patterns were classified as either parental expression (paternal or maternal) or dominance (bipolar and polar). The model by Cui et al. (2006) can also estimate the dominant effect, but such a dominant effect was merely an interaction between the paternally and maternally inherited effects (see assigned values for the indicator variables in formula (3)). Therefore, their model can be treated as additive genetic effect model and thus cannot be used to adjudge the imprinting type related to dominance.

Most imprinted genes play important roles in controlling embryonic and postnatal growth and development in mammal (Constancia et al. 2004; Isles and Holland 2005; Tycko and Morison 2002). As a highly complex process, genomic imprinting is involved in a number of growth axes operating coordinately at different developmental stages (Bartolomei and Tilghman 1997), and shows time-varying

effect during development (Villar et al. 1995). The unbalanced expression of an imprinted gene that occurs during a developmental stage challenges the traditional paradigm of inheritance and mapping methods. Since our Bayesian mapping method treats a trait measured at a certain developmental stage as mapping subject, and does not consider the correlation information at different developmental stages, it is less powerful in dissecting the dynamic iQTL effects. Cui et al. (2008) recently proposed a functional iQTL mapping framework underlying developmental characteristics, which incorporated a mathematical function that best describes a developmental feature into an iQTL mapping framework. Such approach can estimate and test time-specific imprinting effect at specific developmental stages, and is expected to display several merits over traditional iQTL mapping methods. Nevertheless, this mapping procedure is still a single QTL model that estimates and tests one locus at a time without considering the effects of other QTLs. Hence, it is necessary to develop a Bayesian mapping method that can simultaneously map multiple QTLs for growth trajectory or developmental pattern in the spirit of our approach.

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Appendix A: Specification of priors

The maximal number of QTLs is estimated as $L = l_0 + 3\sqrt{l_0}$, where l_0 is the prior expected number of all QTLs including main-effect (l_m) and epistatic QTLs that are determined based on Bayesian model proposed by Yi et al. (2005).

The binary indicator $\gamma$for each genetic effect is assigned to be independent prior $p(\gamma) = \prod w^{\gamma}(1-w)^{(1-\gamma)}$, where $w = p(\gamma = 1)$ is the prior inclusion probability for the jth effect. According to derivation of Yi et al. (2005), given the prior expected numbers of main-effect and all QTLs we obtain $w_\mathrm{m} = 1 - \left[1 - \frac{l_\mathrm{m}}{L}\right]^{1/K}$for main effect and $w_\mathrm{e} = 1 - \left[\frac{1-l_0/L}{(1-w_\mathrm{m})^K}\right]^{1/K^2(L-1)}$ for epistatic effect, where $K = 3$ is the number of possible main effects for each QTL and $K^2 = 9$ is the number of possible epistatic effects of any two QTLs.

The population mean μ is assumed to have a prior which is proportional to a constant. The prior distribution for each genetic effect is proposed as $\beta_j\big|(\gamma_j, \sigma^2, x_{\cdot j}) \sim N\left(0, \gamma_j c\sigma^2\left(\sum_{k=1}^n x_{kj}^2\right)^{-1}\right)$, where c takes to be n. A scaled inverse-χ^2 distribution with hyper-parameters v_e and s_e is adopted as a prior forσ^2, i.e., $\sigma^2|v_\mathrm{e}, s_\mathrm{e} \sim \mathrm{IC}\left(v_\mathrm{e}, (v_\mathrm{e}s_\mathrm{e})^{-1}\right)$.

Prior probabilities of genotypes for each possible locus can be inferred from two flanking markers (Rao and Xu 1998), denoted as $p(G_g)$ for $g = 1, 2, 3, 4$ corresponding to $Q_\mathrm{M}Q_\mathrm{P}$, $Q_\mathrm{M}q_\mathrm{P}$, $q_\mathrm{M}Q_\mathrm{P}$, and $q_\mathrm{M}q_\mathrm{P}$.

Appendix B: Derivation of conditional posterior distribution

Given unknown parameters, the conditional density of all phenotypes, called likelihood of model (5), is

$$p(\mathbf{y}|\mathbf{X}, \boldsymbol{\lambda}, \mu, \boldsymbol{\Gamma}, \boldsymbol{\beta}, \sigma^2) \propto (\sigma^2)^{-\frac{n}{2}} \exp\left[-\frac{1}{2\sigma^2}\sum_{k=1}^{n}\left(y_k - \mu - \mathbf{x}_k\Gamma\beta\right)^2\right]$$

Then, we can form joint posterior density by multiplying priors for all unknown parameters and likelihood. The conditional posterior distributions of all parameters need to be derived from the joint posterior density by keeping other parameters fixed.

The full conditional posterior density of the population mean μ, given all other parameters, follows a normal distribution with mean $\frac{1}{n}\sum_{k=1}^{n}(y_k - \mathbf{x}_k\Gamma\beta)$, and variance $\frac{1}{n}\sigma^2$.

The fully conditional posterior distribution for QTL genetic effect β_j is also normal distribution with mean $\hat{\beta}_j = \frac{c}{c+1}\left(\sum_{k=1}^{n} x_{kj}^2\right)^{-1}\sum_{k=1}^{n} x_{kj}(y_k - \mu - \mathbf{x}_k\Gamma\beta + x_{kj}\beta_j)$ and variance $\hat{\sigma}_j^2 = \frac{c}{c+1}\left(\sum_{k=1}^{n} x_{kj}^2\right)^{-1}\sigma^2$.

For the residual variance σ^2, the corresponding full conditional distribution can be shown to be an inverse χ^2 distribution with parameters $df = v_\mathrm{e} + n$ and $\mathrm{SS} = (v_\mathrm{e} + n)s_\mathrm{e} + \sum_{k=1}^{n}(y_k - \mu - \mathbf{x}_k\Gamma\beta)^2$.

Although a Bernoulli distribution can be constructed as the conditional posterior for γ, for improving sampling efficiency, we adopt an efficient Metropolis–Hastings algorithm (Kohn et al. 2001; Yi et al. 2007) with acceptance rate

$$\begin{aligned}\alpha &= \frac{p(\mathbf{y}\big|\gamma_j = 1, \boldsymbol{\Gamma}_{-\gamma_j}, \mathbf{X}, \boldsymbol{\beta}_{-\beta_j})}{p(\mathbf{y}\big|\gamma_j = 0, \boldsymbol{\Gamma}_{-\gamma_j}, \mathbf{X}, \boldsymbol{\beta}_{-\beta_j})}\cdot\frac{1-w}{w} \\ &= \frac{p(\mathbf{y}\big|\gamma_j = 1, \boldsymbol{\Gamma}_{-\gamma_j}, \mathbf{X}, \boldsymbol{\beta}_{-\beta_j}, \beta_j)p(\beta_j\big|\gamma_j = 1, \boldsymbol{\Gamma}_{-\gamma_j}, \mathbf{X}, \boldsymbol{\beta}_{-\beta_j})}{p(\mathbf{y}\big|\gamma_j = 0, \boldsymbol{\Gamma}_{-\gamma_j}, \mathbf{X}, \boldsymbol{\beta}_{-\beta_j})p(\beta_j\big|\gamma_j = 1, \boldsymbol{\Gamma}_{-\gamma_j}, \mathbf{X}, \boldsymbol{\beta}_{-\beta_j}, \mathbf{y})} \\ &\cdot\frac{1-w}{w} = \sqrt{\frac{c}{c+1}}\exp\left(-\frac{\hat{\beta}_j^2}{2\hat{\sigma}_j^2}\right)\cdot\frac{1-w}{w}\end{aligned} \tag{B1}$$

where $p(\beta_j \big| \gamma_j = 1, \mathbf{\Gamma}_{-\gamma_j}, \mathbf{X}, \boldsymbol{\beta}_{-\beta_j})$ and $p(\beta_j \big| \gamma_j = 1, \mathbf{\Gamma}_{-\gamma_j}, \mathbf{X}, \boldsymbol{\beta}_{-\beta_j}, \mathbf{y}.)$ are prior and posterior probabilities for β_j, respectively. $\mathbf{\Gamma}_{-\gamma_j}$ stands for all elements of $\mathbf{\Gamma}$ except for γ_j and $\boldsymbol{\beta}_{-\beta_j}$ denotes all elements of $\boldsymbol{\beta}$ except for β_j. The fact that $\gamma_j = 1$ is accepted with a probability of min (1, α).

The conditional posterior distribution of QTL genotypes for the kth individual is multinomial with the probabilities

$$p_k^*(G_g) = \frac{p(y_k|\mathbf{x}_{k(-G_g)}, x_{kj|G_g}, \boldsymbol{\lambda}, \mathbf{\Gamma}, \mu, \boldsymbol{\beta}, \sigma^2) p_k(G_g)}{\sum_{l=1}^{4} p(y_k|\mathbf{x}_{k(-G_g)}, x_{kj|G_g}, \boldsymbol{\lambda}, \mathbf{\Gamma}, \mu, \boldsymbol{\beta}, \sigma^2) p_k(G_g)} \quad (g = 1, 2, 3, 4) \tag{B2}$$

where $\mathbf{x}_{k(-G_g)}$ represents all elements of $\mathbf{x}_k$ except those associated with QTL genotype G_g, $\boldsymbol{\lambda}$ is a vector of L QTL positions and $x_{kj|G_g}$ is a vector consisting of known main-effect indicators and relative epistatic dummy variables that are conditional on QTL genotype G_g for the kth individual.

The conditional posterior distribution for position of QTL does not have a closed form, so Metropolis–Hastings algorithm will be used to sample QTL positions. Considering that the genotypes of QTLs closely depend on the QTL positions, we decide to jointly sample QTL position and relative genotype for one locus at a time. Each locus is sampled from a variable interval (Wang et al. 2005; Zhang and Xu 2005) whose boundaries are the positions of adjoining QTLs. It is assumed that not more than one QTL exists in each marker interval. We sample a new position $\lambda_j^* (j = 1, 2, \ldots, L)$ from two placed loci on the left and right of existing position λ_j^0 with the same probability; then the new position is accepted with a probability of min (1, α) with

$$\alpha = \frac{\prod_{k=1}^{n} p(y_k|\lambda_j^*, \ldots) p_k(G_g \big| \lambda_j^0)}{\prod_{k=1}^{n} p(y_k|\lambda_j^0, \ldots) p_k(G_g \big| \lambda_j^*)} \tag{B3}$$

where $p(y_k|\lambda_j, \cdots) = \sum_{g=1}^{4} p(y_k|\mathbf{x}_{k(-G_g)}, x_{kj|G_g}, \lambda_j, \mu, \mathbf{\Gamma}, \boldsymbol{\beta}, \sigma^2) p_k(G_g|\lambda_j)$.

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