Chinese Science Bulletin 2006 Vol. 51 No. 15 1857—1862

DOI: 10.1007/s11434-006-2050-z

Composite interval mapping of QTL for dynamic traits

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Received January 9, 2006; accepted June 2, 2006

Abstract Many economically important quantitative traits in animals and plants are measured repeatedly over time. These traits are called dynamic traits. Mapping QTL controlling the phenotypic profiles of dynamic traits has become an interesting topic for animal and plant breeders. However, statistical methods of QTL mapping for dynamic traits have not been well developed. We develop a composite interval mapping approach to detecting QTL for dynamic traits. We fit the profile of each QTL effect with Legendre polynomials. Parameter estimation and statistical test are performed on the regression coefficients of the polynomials under the maximum likelihood framework. Maximum likelihood estimates of QTL parameters are obtained via the EM algorithm. Results of simulation study showed that composite interval mapping can improve both the statistcial power of QTL detecting and the accuracy of parameter estimation relative to the simply interval mapping procedure where only one QTL is fit to each model. The method is developed in the context of an F_2 mapping population, but extension to other types of mapping populations is straightforward.

Keywords: composite interval mapping, dynamic trait, EM algorithm, Legendre polynomial, maximum likelihood.

The theoretical foundation for mapping quantitative trait loci (QTL) was laid by Sax[1] who discovered the association between the segregation pattern of pigment markers with seed size of bean. However, statistical methods were not well developed until the pioneering work of interval mapping by Lander and Botstein's[2], and Haley and Knott's[3]. The interval mapping procedure is a single QTL model approach, which can lead to biased estimates of QTL positions and effects when multiple QTL are present in the same linkage group[2−4]. On the basis of interval mapping, Jansen[5] and Zeng[4] independently proposed the idea of composite interval mapping in which mapping in a particular interval is combined with multiple regressions on markers in other chromosomal regions to absorb effects of background QTL. The ultimate goals were to eliminate the bias in QTL parameter estimation and reduce the residual error variance, and eventually increase the power of QTL detection.

As an effective and practical method of mapping QTL, the composite interval mapping procedure has always been applied to QTL mapping for a single trait. When applied to dynamic trait, phenotypes measured at different time points are usually treated as different traits. These traits are either analyzed separately or jointly[6 − 11]. Some investigators proposed to fit a growth trajectory for the trait value as a function of time in the first step and then map QTL for the growth parameters in the second step[12,13]. Fitting a Logistic curve to the QTL effect on the growth process of trees, Ma *et al.*[14] and Wu *et al.*[15,16] constructed the mathematical model and developed the functional mapping strategy to map dynamic trait loci in a single step. The functional mapping strategy is neither suitable to arbitrary dynamic traits, nor extendable to composite interval mapping. Therefore, we used the orthogonal Legendre polynomial approach to fitting the growth trajectory to each effect of the QTL model[17,18]. The current status of QTL mapping for dynamic traits remains in the stage of interval mapping. The objectives of this study are to develop the basic principle of composite interval mapping and demonstrate its applicability to mapping for dynamic traits using a series of simulation experiments.

1 Theory and method

1.1 Genetic model

We now use an F_2 mating design as an example to describe the genetic model of composite interval mapping for dynamic traits. Based on Mendel's law of inheritance, there are three possible genotypes in an F_2 population at any given locus, denoted by QQ (MM), Qq (Mm) and qq (mm), respectively, for the three genotypes. Assume that there are h+2 molecular markers with known positions on the genome. To detect QTL located between marker i and marker i+1, markers outside the scanning interval are treated as cofactors. The phenotypic values of a dynamic trait are measured

from n individuals of an F_2 population. Let m be the number of time points measured for the dynamic trait of interest. In practice, not all individuals may have the same m because of uncontrolled factors causing individuals to fail to be measured at some time points. Therefore, m may vary across individuals, denoted by m_j for the ith individual. If we use a Legendre polynomial of order s to describe the changes in the population mean, the QTL effect and each of the cofactors on the dynamic trait, the phenotypic value y_{ij} of individual i measured at time point t_j may be expressed using the following linear model:

$$y_{ij} = T_{ij}\mu + z_i T_{ij} a + w_i T_{ij} d + \sum_{l=1}^{h} z_{il} T_{ij} a_l + \sum_{l=1}^{h} w_{il} T_{ij} d_l + e_{ij} \quad (1)$$

for $i = 1, 2, \cdots, n$ and $j = 1, 2, \cdots, m$. Parameter μ is an $(s + 1)\times 1$ vector for the population means. Variable a denotes an $(s + 1)\times 1$ vector for the additive effects. Variable d is another $(s + 1)\times 1$ vector for the dominant effects. Variable z_i is an indicator variable (defined as 1 for QQ (MM), 0 for Qq (Mm) and −1 for qq (mm)) for the ith individual at the QTL or markers, and w_i is a dominance indicator variable defined as 1 for heterozygote and 0 for homozygotes. $a_l$and d_l are the vectors for the additive and dominant regression effects of the lth cofactor. Variable T_{ij} is defined as $T_{ij} = [L_{i0}(\tau_{ij})\ L_{i1}(\tau_{ij})\cdots L_{is}(\tau_{ij})]$ with the general form of Legendre polynomial covariable

$$L_k(\tau) = \frac{1}{2^k}\sum_{r=0}^{k/2}\frac{(-1)^r(2k-2r)!}{r!(k-r)!(k-2r)!}\tau^{k-2r} \quad (k = 0, 1, \cdots, s)$$

and $\tau = -1 + 2\times\dfrac{t - \min\{t\}}{\max\{t\} - \min\{t\}}$. The residual error is denoted by e_{ij} which follows a $N(0, \sigma_j^2)$ distribution and is mutually independent among different test days.

1.2 Maximum likelihood estimation

Let $y_i = [y_{i1}\ y_{i2}\ \cdots\ y_{imi}]^T$ and $T_i = [T_{i1}^T\ T_{i2}^T\ \cdots\ T_{imi}^T]^T$. In matrix notation, model (1) can then be rewritten as

$$y_i = T_i\mu + z_i T_i a + w_i T_i d + \sum_{l=1}^{h} z_{il} T_i a_l + \sum_{l=1}^{h} w_{il} T_i d_l + e_i. \quad (2)$$

The phenotypic values belonging to the kth genotype of QTL for individual i has an m-dimensional multiple normal distribution, denoted by

$$f_k(y_i) = \frac{1}{(2\pi)^{mi/2}|R_i|^{1/2}} \times \exp\left\{-\frac{1}{2}\left(y_i - \left[T_i\mu + z_i T_i a + w_i T_i d + \sum_{l=1}^{h} z_{il} T_i a_l + \sum_{l=1}^{h} w_{il} T_i d_l\right]\right)^T \times R_i^{-1}\left(y_i - \left[T_i\mu + z_i T_i a + w_i T_i d + \sum_{l=1}^{h} z_{il} T_i a_l + \sum_{l=1}^{h} w_{il} T_i d_l\right]\right)\right\},$$

where, $R = \mathrm{diag}\{\sigma_1^2\ \ \sigma_2^2\ \ \cdots\ \ \sigma_{mi}^2\}$ is the residual covariance matrix corresponding to m_i phenotypic values for the ith individual.

The conditional probabilities of the three QTL genotypes, denoted by p_{ik} (k = 1, 2, 3), are calculated using information from two flanking markers[2] or all markers[19]. The likelihood function is

$$L(\theta) = \prod_{i=1}^{n}\left[\sum_{k=1}^{3} p_{ik} f_k(y_i)\right],$$

where, $\theta = [\mu\ a\ d\ a_l\ d_l\ R\ \lambda]$ is a vector for the estimated parameters, l = 1, 2, $\cdots$, h, and λ is the current position of the QTL.

The log-likelihood function is

$$\ln L(\theta) = \sum_{i=1}^{n}\ln\left[\sum_{k=1}^{3} p_{ik} f_k(y_i)\right].$$

The solution for $\ln L(\theta)$ can be found using the EM algorithm[20], which is summarized as follows:

(1) Set all parameters to values in their legal domain, denoted by $\theta^{(0)}$;

(2) calculate the posterior probabilities of each QTL genotype:

$$p_{ik}^* = \frac{p_k f_k(y_i)}{\sum_{k=1}^{3} p_k f_k(y_i)} \quad (k = 1, 2, 3);$$

(3) update the additive and dominance regression effects for the QTL:

$$\begin{bmatrix} a^{(1)} \\ d^{(1)} \end{bmatrix} = \begin{bmatrix} \sum_{i=1}^{n}(p_{i1}^* + p_{i3}^*)T_i^T R^{-1} T_i & 0 \\ 0 & \sum_{i=1}^{n} p_{i2}^* T_i^T R^{-1} T_i \end{bmatrix}^{-1} \bullet \begin{bmatrix} \sum_{i=1}^{n}(p_{i1}^* - p_{i3}^*)T_i^T R^{-1}(y_i - T_i\mu^{(0)} - \sum_{l=1}^{h} z_{il} T_i a_l^{(0)} + \sum_{l=1}^{h} w_{il} T_i d_l^{(0)}) \\ \sum_{i=1}^{n} p_{i2}^* T_i^T R^{-1}(y_i - T_i\mu^{(0)} - \sum_{l=1}^{h} z_{il} T_i a_l^{(0)} + \sum_{l=1}^{h} w_{il} T_i d_l^{(0)}) \end{bmatrix};$$

(4) update additive and dominance regression effects for h cofactors:

$$\begin{bmatrix}\mu^{(1)}\\ a_1^{(1)}\\ d_1^{(1)}\\ \cdots\\ a_h^{(1)}\\ d_h^{(1)}\end{bmatrix}=\begin{bmatrix}\sum_{i=1}^{n}T_i^TR^{-1}T_i & \sum_{i=1}^{n}z_{i1}T_i^TR^{-1}T_i & \sum_{i=1}^{n}w_{i1}T_i^TR^{-1}T_i & \cdots & \sum_{i=1}^{n}z_{ih}T_i^TR^{-1}T_i & \sum_{i=1}^{n}w_{ih}T_i^TR^{-1}T_i\\ & \sum_{i=1}^{n}z_{i1}^2T_i^TR^{-1}T_i & 0 & \cdots & \sum_{i=1}^{n}z_{i1}z_{ih}T_i^TR^{-1}T_i & \sum_{i=1}^{n}z_{i1}w_{ih}T_i^TR^{-1}T_i\\ & & \sum_{i=1}^{n}w_{i1}^2T_i^TR^{-1}T_i & \cdots & \sum_{i=1}^{n}w_{i1}z_{ih}T_i^TR^{-1}T_i & \sum_{i=1}^{n}w_{i1}w_{ih}T_i^TR^{-1}T_i\\ & & & \cdots & \cdots & \cdots\\ & & & & \sum_{i=1}^{n}z_{ih}^2T_i^TR^{-1}T_i & 0\\ & sym. & & & & \sum_{i=1}^{n}w_{ih}^2T_i^TR^{-1}T_i\end{bmatrix}^{-1}\bullet\begin{bmatrix}\sum_{i=1}^{n}T_i^TR^{-1}y_i\\ \sum_{i=1}^{n}z_{i1}T_i^TR^{-1}[y_i-(p_{i1}^*-p_{13}^*)T_ia^{(1)}-p_{i2}^*T_id^{(1)}]\\ \sum_{i=1}^{n}w_{i1}T_i^TR^{-1}[y_i-(p_{i1}^*-p_{13}^*)T_ia^{(1)}-p_{i2}^*T_id^{(1)}]\\ \cdots\\ \sum_{i=1}^{n}z_{ih}T_i^TR^{-1}[y_i-(p_{i1}^*-p_{13}^*)T_ia^{(1)}-p_{i2}^*T_id^{(1)}]\\ \sum_{i=1}^{n}w_{ih}T_i^TR^{-1}[y_i-(p_{i1}^*-p_{13}^*)T_ia^{(1)}-p_{i2}^*T_id^{(1)}]\end{bmatrix};$$

(5) update the residual variance:

$$\begin{aligned}\sigma_j^2=\frac{1}{n}\sum_{i=1}^{n}\Bigg[&p_{i1}^*\left(y_i-T_i\mu-T_ia-\sum_{l=1}^{h}z_{il}T_ia_l-\sum_{l=1}^{h}w_{il}T_id_l\right)^T\left(y_i-T_i\mu-T_ia-\sum_{l=1}^{h}z_{il}T_ia_l-\sum_{l=1}^{h}w_{il}T_id_l\right)\\&+p_{i2}^*\left(y_i-T_i\mu-T_id-\sum_{l=1}^{h}z_{il}T_ia_l-\sum_{l=1}^{h}w_{il}T_id_l\right)^T\left(y_i-T_i\mu-T_id-\sum_{l=1}^{h}z_{il}T_ia_l-\sum_{l=1}^{h}w_{il}T_id_l\right)\\&+p_{i3}^*\left(y_i-T_i\mu+T_ia-\sum_{l=1}^{h}z_{il}T_ia_l-\sum_{l=1}^{h}w_{il}T_id_l\right)^T\left(y_i-T_i\mu+T_ia-\sum_{l=1}^{h}z_{il}T_ia_l-\sum_{l=1}^{h}w_{il}T_id_l\right)\Bigg].\end{aligned}$$

Replace $\theta^{(0)}$ by $\theta^{(1)}$ and repeat (1)—(5) until a certain criterion of convergence is reached.

1.3 Hypothesis test

Hypothesis test is carried out via the likelihood ratio test statistics. The null hypothesis is "no segregation of a QTL at the current position tested," which is denoted by H_0: $a = d = 0$. The test statistic for this hypothesis is

$$LR = -2[\ln L(\hat{\theta}_0) - \ln L(\hat{\theta}_1)],$$

where $\ln L(\hat{\theta}_1)$ is the log likelihood function evaluated at $\hat{\theta}_1 = [\mu\ a\ d\ a_l\ d_l\ R\ \lambda]$ and $\ln L(\theta_0)$ is the log likelihood under the null model evaluated at $\hat{\theta}_0 = [\mu\ a_l\ d_l\ R\ \lambda]$.

The above statistics are conditional on a fixed position (λ) of the QTL in question. The maximum likelihood estimate of λ takes the position of the genome where the maximum value of the likelihood occurs.

2 Simulation studies

The purposes of the simulation studies are to investigate the efficiency and behavior of the composite interval mapping relative to those of the simple interval mapping. We are particularly interested in comparing the statistical power of the composite mapping to the interval mapping for detecting QTL for dynamic traits.

We simulated an F_2 population with 200 individuals. A single chromosome segment of length 150 cM was covered by 16 evenly spaced markers (10 cM/interval). Four QTL were placed at positions 15, 36, 62 and 104 cM measured from the left end of the chromosome. The test day ranged from 1 to 150 d. Five test day records for the dynamic trait of interest were measured from every individual, which were randomly sampled from five even intervals between 1 and 150 d. Legendre polynomial of order 3 was used to describe the changes in the population mean, effects of QTL and cofactors on the dynamic trait with time. $\mu = [45\ 44\ -1\ -7]$. The simulated additive and dominant regression effects for the 4 QTL are listed in Table 1. Cumulative heritabilities of the 4 QTL were 0.2972, 0.0698, 0.1371 and 0.1458, respectively. The overall proportion of phenotypic variance contributed by the 4 QTL was about 0.65. In order to design the residual variance of different test day, we also divided the measuring time interval [1,150] into three successive subintervals of [1,30], [31,80] and [81,150], and then fixed the residual variances of the first two subintervals at 5.0 and 11.5, leading to a value of 15.0 as the residual variance for the last subinterval. Given μ, the genetic effects of the four QTL and the residual variances of the test days, vector y_i for phenotypic value of individual i measured at t was generated using

$$y_i(\tau) = T(\tau)\mu + \sum_{j=1}^{4} z_i T(\tau) a_j + \sum_{j=1}^{4} w_i T(\tau) d_j + \xi\sigma(\tau),$$

where $T(\tau) = [1\ L_1(\tau)\ L_2(\tau)\ L_3(\tau)]$, τ is the standardized t and ranges between -1 and $+1$, $L_1(\tau) = \tau$, $L_2(\tau) = \frac{1}{2}(3\tau^2 - 1)$; $L_3(\tau) = \frac{1}{2}(5\tau^3 - 3\tau)$; ξ is a random number sampled from the standardized normal distribution, $\sigma^2(\tau) \in \sigma_i^2$.

We chose several different numbers of cofactors: 0, 3, 4, 6 and 14, corresponding to five different models of the composite interval mapping designated as model_0, model_3, model_4, model_6 and model_14, respectively.

The empirical critical values of the likelihood ratio statistics for testing the presence of a QTL were obtained by simulating 500 additional samples under the null model. Under the alternative model, the simulations were replicated 100 times. Empirical power was calculated by counting the number of runs in which the test statistics were greater than the critical values.

Calculating the averages of likelihood ratios at every scanning point over the segment of chromosome, we depicted the statistic profiles for the five models in Figs. 1 and 2. There is only one peak on the whole chromosome segment in Fig. 1, showing that only one simulated QTL was detected with the interval mapping approach. However, the composite interval mapping detected at least two QTL. As the number of cofactors increased, more QTL were detected and the resolution of QTL detection also increased.

Based on the approximate positions of QTL detected, the chromosome was divided into several intervals, each interval including one QTL only. The statistical power, the means and standard deviations of the estimated QTL parameters for the five models are listed in

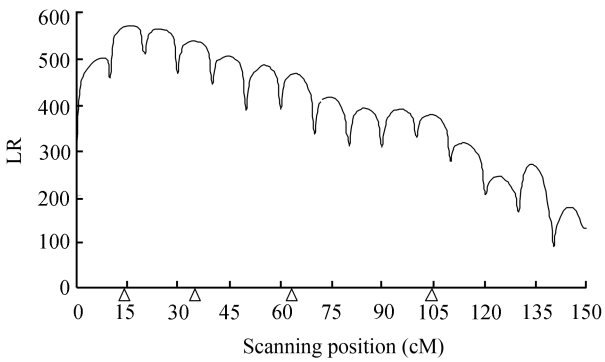

Fig. 1. The statistic profile of interval mapping.

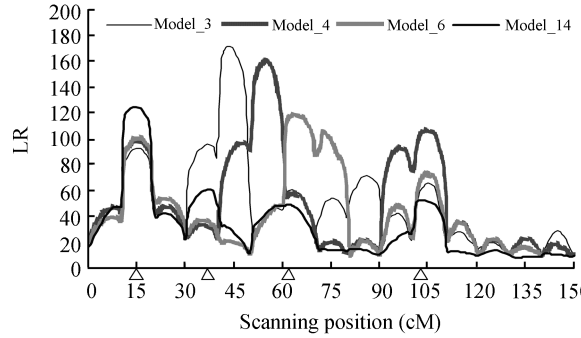

Fig. 2. The statistic profiles of composite interval mapping with different cofactors.

Tables 1 and 2. Compared to the interval mapping procedure, the composite interval mapping has significantly increased the number of QTL detected; in the meantime, it has also improved the efficiency of estimation for the QTL positions and effects. In addition, the accuracy of estimates for the QTL positions and effects has been improved as the number of cofactors increases, but the statistical powers appears to have declined as the number of cofactors increases. In our simulation study, the composite interval mapping with 6 cofactors seems to be ideal for the Legendre polynomial of order 3. In practice, the number of cofactor should be chosen on the basis of the type of dynamic traits and the cost of calculation. As for regular quantitative traits, QTL with higher heritability are easier to be detected than QTL with lower heritability for dynamic traits.

3 Discussions

The reason that the current functional mapping strategy has not been extended to composite interval mapping is that the model describing the genotypic effect of QTL is nonlinear and non-additive. The Legendre polynomial curve is actually linear on the parameters, although it is non-linear on time. The polynomial bears the additive property, i.e. the sum of two polynomials is still polynomial. This property allows us to partition not only the phenotypic value into various environmental effects (including the population means), but also the total genotypic effect into additive, dominance effects and interactions between QTL. This would not be possible using the non-linear model. With regard to the biological meanings of the parameters in the Legendre polynomial, we can estimate the parameters in the model by using the estimated polynomial[21] and infer the biological meanings of the characters of the dynamic traits.

Table 1 Averages and standard deviations (in parenthesis) of additive and dominance regression effects with the five models

QTL	model	a_0	a_1	a_2	a_3	d_0	d_1	d_2	d_3
True value		2.58	1.65	1.02	0.82	1.77	1.27	1.71	1.14
1	_0	3.880 (0.246)	0.789 (0.439)	1.195 (0.393)	1.673 (0.510)	2.887 (0.250)	1.411 (0.305)	2.249 (0.376)	3.155 (0.453)
	_3	2.721 (0.530)	1.592 (0.717)	1.105 (0.725)	1.072 (1.001)	1.914 (0.522)	1.231 (0.812)	1.659 (0.813)	1.270 (1.148)
	_4	2.658 (0.597)	1.517 (0.567)	1.047 (0.796)	0.917 (1.202)	1.969 (0.574)	1.385 (0.816)	1.740 (0.937)	1.038 (0.969)
	_6	2.703 (0.544)	1.616 (0.628)	1.125 (0.875)	0.922 (0.850)	1.870 (0.531)	1.239 (0.700)	1.552 (0.871)	1.183 (0.941)
	_14	2.575 (0.285)	1.620 (0.560)	1.129 (0.643)	0.808 (0.878)	1.774 (0.403)	1.283 (0.644)	1.792 (0.710)	1.121 (0.850)
True value		0.65	0.58	0.65	0.11	1.36	0.27	1.27	0.68
2	_0								
	_3	2.727 (0.427)	1.591 (1.142)	1.371 (0.667)	0.967 (0.669)	2.526 (0.700)	1.110 (0.757)	2.123 (0.914)	1.499 (0.699)
	_4								
	_6	1.041 (0.552)	0.749 (0.614)	0.782 (0.802)	0.121 (0.983)	1.715 (0.597)	0.538 (0.675)	1.389 (0.866)	0.947 (1.040)
	_14	1.013 (0.407)	0.587 (0.690)	0.672 (0.881)	0.140 (0.735)	1.438 (0.586)	0.250 (0.802)	1.137 (0.781)	0.862 (0.966)
True value		1.02	−2.65	−1.04	1.41	−0.71	−1.36	−1.42	1.56
3	_0								
	_3								
	_4	3.174 (0.629)	0.461 (0.443)	1.092 (0.592)	0.513 (0.724)	1.984 (0.708)	2.047 (0.525)	1.670 (0.688)	1.795 (0.861)
	_6	1.589 (0.750)	−2.311 (0.877)	−0.670 (0.762)	1.902 (0.824)	−0.420 (0.837)	−0.659 (0.697)	−0.653 (00931)	1.787 (0.865)
	_14	0.964 (0.275)	−2.556 (0.656)	−0.899 (0.839)	1.425 (0.302)	−0.701 (0.348)	−1.208 (0.797)	−1.405 (0.864)	1.485 (0.361)
True value		1.65	0.12	0.79	0.24	1.27	1.71	1.14	1.46
4	_0								
	_3	2.179 (1.302)	0.255 (0.621)	0.812 (0.824)	0.651 (1.269)	1.877 (0.493)	1.366 (0.849)	1.209 (1.010)	1.683 (1.349)
	_4	2.175 (0.444)	0.461 (0.443)	1.092 (0.592)	0.513 (0.724)	1.984 (0.708)	1.874 (0.525)	1.470 (0.688)	1.795 (0.861)
	_6	1.927 (0.864)	0.545 (0.741)	1.170 (0.866)	0.340 (0.956)	1.478 (0.874)	1.833 (0.779)	1.632 (1.026)	1.681 (1.098)
	_14	1.722 (0.426)	0.162 (0.683)	0.726 (0.684)	0.307 (0.937)	1.295 (0.433)	1.801 (0.786)	1.264 (0.832)	1.532 (0.727)

Table 2 Estimates of QTL position and statistical powers with the five models

Model	Item	Estimates（standard deviation）			
	True value	15	36	62	104
_0	position (cM)	20.46(7.21)			
	95% power	100			
_3	position (cM)	15.71(3.55)	43.79(5.61)		101.99(13.17)
	95% power	100	100		100
_4	position (cM)	15.14(3.07)		54.30(2.10)	102.94(4.28)
	95% power	100		100	100
_6	position (cM)	15.10(3.38)	34.97(4.43)	67.89(4.86)	103.78(5.41)
	95% power	100	94	100	99
_14	position (cM)	14.910(1.35)	36.02(4.49)	61.08(2.25)	103.62(2.08)
	95% power	100	91	100	99

The proposed composite interval mapping for dynamic traits differs from the conditional mapping approach proposed by Zhu *et al*.[14−16]. Our composite interval mapping is to map QTL responsible for the change in trajectory of dynamic traits under the framework of functional mapping, although it can also detect QTL for dynamic point by choosing a proper hypothesis test. The method of Zhu *et al*.[14−16], however, is to analyze every observed point in the dynamic process based on the interval mapping or the composite interval mapping strategy. For any dynamic points, the functional mapping procedure is superior to the interval mapping or the composite interval mapping in terms of high statistical power. This implies that our method is better than the conditional mapping of Zhu *et al*.[14−16].

The current methods of interval mapping for dynamic traits fit QTL effects outside the scanning interval and residual errors to a model with a different covariance structure depending on time, such as heterogeneity for the residual variance but no correlation among residuals at different test days[17]; the stationary or non stationary time series model[14−16,22]; every individual residual being modeled by a Legendre polynomial[23]. None of these methods are more reasonable than the proposed composite interval mapping where cofactors are used to absorb effects of other QTL and the genetic background. Of course, it is necessary to compare these methods with composite interval mapping. The optimal method may be the Bayesian mapping in which the number, positions and effects of QTL are estimated simultaneously.

Acknowledgements We thank Prof. Shizhong Xu at University California (Riversider) for correcting English version of the manuscript. This work was supported by the National Natural Science Foundation of China (Grant No. 30471236).

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