A unifying statistical model for QTL mapping of genotype × sex interaction for developmental trajectories

Wei Zhao,1 Changxing Ma,1 James M. Cheverud,2 and Rongling Wu1
1Department of Statistics, University of Florida, Gainesville, Florida 32611; and 2Department of Anatomy and Neurobiology, Washington University School of Medicine, St. Louis, Missouri 63110

Submitted 27 May 2004; accepted in final form 5 August 2004

Zhao, Wei, Changxing Ma, James M. Cheverud, and Rongling Wu. A unifying statistical model for QTL mapping of genotype × sex interaction for developmental trajectories. Physiol Genomics 19: 218–227, 2004. First published August 10, 2004; doi:10.1152/physiolgenomics.00129.2004.—Most organisms display remarkable differences in morphological, anatomical, and developmental features between the two sexes. It has been recognized that these sex-dependent differences are controlled by an array of specific genetic factors, mediated through various environmental stimuli. In this paper, we present a unifying statistical model for mapping quantitative trait loci (QTL) that are responsible for sexual differences in growth trajectories during ontogenetic development. This model is derived within the maximum likelihood context, incorporated by sex-stimulated differentiation in growth form that is described by mathematical functions. A typical structural model is implemented to approximate time-dependent covariance matrices for longitudinal traits. This model allows for a number of biologically meaningful hypothesis tests regarding the effects of QTL on overall growth trajectories or particular stages of development. It is particularly powerful to test whether and how the genetic effects of QTL are expressed differently in different sexual backgrounds. Our model has been employed to map QTL affecting body mass growth trajectories in both male and female mice of an F2 population derived from the large (LG/J) and small (SM/J) mouse strains. We detected four growth QTL on chromosomes 6, 7, 11, and 15, two of which trigger different effects on growth curves between the two sexes. All the four QTL display significant genotype-sex interaction effects on the timing of maximal growth rate curves derived from fundamental biological principles. The implications of our model for studying the genetic architecture of growth trajectories and its extensions to some more general situations are discussed.

EM algorithm; functional mapping; growth trajectories; mice; QTL × sex interaction

FUNCTIONAL MAPPING HAS EMERGED as a powerful statistical method for detecting quantitative trait loci (QTL) that affect complex phenotypes undergoing developmental changes (21, 36, 38, 39). This method integrates mathematical models of growth curves with quantitative and molecular genetics theory within a QTL mapping framework. It does not directly estimate the expected means of different QTL genotypes at different time points, but instead fits these means using time-dependent growth curves derived from fundamental biological principles (2, 32). Thus the estimation of QTL effects on growth is equivalent to the estimation of model parameters describing the shape of growth curves.

Although it is originally conceived to map the dynamic effects of QTL on growth trajectories, functional mapping has been extended to study the genetic mechanisms for many other biological or biomedical processes including allometric scaling, thermal norm reaction, HIV-1 dynamics, tumor progression, biological clock, and drug response (31, 37). The results from real data analyses or computer simulations in each of these extensions indicate that functional mapping displays tremendous power to detect “dynamic” QTL. However, in real life, the influences of specific QTL on biological processes are far more complicated than what we have modeled thus far with gene actions of single QTL. It is impossible that the expression of QTL effects is isolated from the environment in which the organism is reared or from the genetic background of the organism. Mackay (22) documented a considerable body of evidence for genotype × sex, genotype × environment, and gene × gene (epistatic) interactions at the individual QTL level for a number of morphological traits and longevity in Drosophila. Sex- or environment-specific QTL were found to affect growth, morphological and physiological traits, or susceptibility to different diseases in other species, such as humans (25) and mice (4, 13, 23, 30). Although no studies have been able to quantify the impacts of interacting QTL on the developmental process of a trait, these QTL must commonly exist to potentially direct organisinal development toward the best utilization of resources in heterogeneous environments (22).

The motivation of this study is to develop a unifying statistical model for mapping QTL that display interactions with environments, sexes, or genetic backgrounds during ontogenetic growth. By quantifying how QTL effects on growth trajectories vary between males and females, in different environments, and in different genetic backgrounds, this model has power to unravel the genetic architecture of complex phenotypes in a comprehensive context of development, ecology, and evolution. Since the studies of these three “interactions” should be based on different genetic and statistical strategies, we have to report the results separately for each of them. In our earlier work (38), models for epistatic and QTL–environment interaction effects have been described. In this article, we present a different model for studying QTL–sex interaction for developmental trajectories. This article is organized as follows. In the first section, METHODOLOGY, we present basic methodologies for functional mapping of quantitative traits displaying genotype-sex interactions. In the second section, HYPOTHESIS TESTS, we describe a number of hypothesis tests including the molecular genetic basis of genotype-sex interactions. In the third section, RESULTS, we report the results from this model for a worked example in an F2 progeny of...
mice. The advantages of this model and its implications are discussed in the discussion.

**METHODOLOGY**

The finite mixture model. The statistical foundation of functional mapping for growth curves is based on a finite mixture model in which each curve fitted by a finite set of measurements with $\tau$ time points for any individual, arrayed by $y = [y(1), \ldots, y(\tau)]$, is assumed to have arisen from one of a known or unknown number of components, each component being modeled by a multivariate normal distribution density (20). Assuming that there are $J$ genotypes contributing to the variation among different curves, this mixture model is expressed as

$$
\mathbf{y} \sim p(\mathbf{y} | \mathbf{\pi}, \mathbf{\varphi}, \eta) = \pi_1 f_1(\mathbf{y} | \mathbf{\varphi}_1, \eta) + \cdots + \pi_J f_J(\mathbf{y} | \mathbf{\varphi}_J, \eta)
$$

where $\mathbf{\pi} = (\pi_1, \ldots, \pi_J)^T$ are the mixture proportions (i.e., genotype frequencies) which are constrained to be nonnegative and sum to unity; $\varphi = (\varphi_1, \ldots, \varphi_J)^T$ are the component-specific (or genotype-specific) parameters, with $\varphi_j$ being specific to component $j$; and $\eta$ is a parameter which is common to all components.

The likelihood function. Consider a standard $F_2$ design, initiated with two contrasting homozygous inbred lines. This $F_2$ progeny of size $n$ contains two subpopulations, one composed of $n_1$ male siblings and the other composed of $n_2$ female siblings ($n_1 + n_2 = n$), in each of which there are three groups of genotypes at a locus. A composite genetic linkage map that integrates the siblings and the other composed of $n$ individuals.

The determination of QTL using a regression model expressed as

$$
\mathbf{y}_{ik}(t) = x_i \mu_{i(k)}(t) + e_{i(k)}(t)
$$

where $x_i$ is the indicator variable denoted as 1 if a QTL genotype $j$ is considered for subject $i$ and 0 otherwise; $e_{i(k)}(t)$ is the residual error that is iid normal with the mean of zero and the variance of $\sigma_i^2(t)$. The errors at two different time points, $t_1$ and $t_2$, are correlated with the covariance of $\text{cov}_{i(t_1,t_2)}$. These (co)variances comprise a $(\tau \times \tau)$ matrix $\Sigma_i$ whose elements are the common parameter $\eta$ of the mixture model (Eq. 1).

The determination of the value for the indicator variable describing the genotypes of the QTL for progeny $i$ is not obvious. According to the interval mapping theory, it is possible to do so if we use the segregation information of the known flanking markers that bracket the QTL. Suppose this QTL is bracketed by two flanking markers $M_1$ (with alleles $M_1^0$ and $M_1^1$) and $M_{l+1}$ (with alleles $M_{l+1}^0$ and $M_{l+1}^1$). Thus the QTL genotype frequencies in the $F_2$ population (denoted by $\pi_j$) should be expressed as the conditional probabilities of the unknown QTL genotypes given the known marker genotypes. Table 1 tabulates these conditional probabilities, generally expressed as $\pi_{ji}$, where $ji$ stands for QTL genotype $j$ given a particular marker genotype for progeny $i$. We rewrite the likelihood function of sex-specific longitudinal data ($\mathbf{y}_{ik}$) and marker information genotyped for both sexes (K) as

$$
L(\mathbf{\pi}, \mathbf{\varphi}, \eta | \mathbf{y}, K) = \prod_{k=1}^{2} \prod_{i=1}^{n_k} \sum_{j=0}^{2} \pi_{ji} \mathcal{L}_j(\mathbf{\pi}, \mathbf{\varphi}_j, \eta | \mathbf{y}_{ik})
$$

where $\Theta_k$ is a set of sex-specific parameters. Note that Eq. 6 is different from Eq. 3, as the former does not make use of marker information, whereas the latter does.

**Modeling the mean vector and (co)variance matrix.** The estimation of the mean vector $\mu_{i(k)}$ and the (co)variance matrix $\Sigma_k$ is statistically difficult because they involve too many unknown parameters given a possible sample size. Also, such direct estimation does not take into account the biological
principles of growth and development. We incorporate the universal growth law, as described by a logistic equation, into the estimation process of the likelihood function (Eq. 6). Thus the mean value of QTL genotype \( j \) at time \( t \) is expressed by

\[
\mu_{j(t)} = \frac{a_{j(k)}}{1 + b_{j(k)}e^{-c_{j(k)}t}}
\]

where the growth parameter set \( G_{j(k)} = (a_{j(k)}, b_{j(k)}, c_{j(k)}) \) describes the asymptotic growth, initial growth, and relative growth rate, respectively (24). With this growth equation, we only need to estimate the growth parameters, rather than estimate genotypic means at every point, to detect genotypic differences in growth. This can significantly reduce the number of unknown parameters to be estimated, especially when the number of time points is large.

Similarly, the (co)variance matrix can be structured with an appropriate model. Statistical analysis of longitudinal data has established a number of structural models that capture most of the information contained in the matrix (12). Here, we use a first-order autoregressive [AR(1)] model to model the structure of the matrix, which is based on two assumptions: first, the variance \( \sigma^2 \) is constant over time; and second, the correlation decays in a proportion of \( \rho \) with pure time interval. With the AR(1) model, we only need to estimate \( \Theta_k = (\mu_k, \sigma^2_k) \), instead of all elements in the matrix. The advantage of such a matrix-structuring model is to reduce the number of unknown parameters, without losing the information of the matrix. There are many other structural models that may be more advantageous over the stationary AR(1) model, but the choice of an optimal model in a particular situation should be based on statistical tests, as described in Zimmerman and Núñez-Antón (41).

**Computational algorithms.** As classified above, the unknown parameters that build up the likelihood function (Eq. 6) include the curve parameters, matrix-structuring parameters, and the QTL genotype frequencies specified by QTL position measured in terms of the recombination fractions \( (r_1, r_2) \) between the QTL and its flanking markers (see Table 1). Arrayed by \( \Omega = (\Omega_k)_{k=1}^2 = (G_{j(k)}, \Theta_k, r_1, r_2) \), these unknowns can be estimated through differentiating the log-likelihood function of Eq. 2 with respect to each unknown, setting the derivative equal to zero, and solving the log-likelihood equations. This estimation process can be implemented with the EM algorithm as described below.

The log-likelihood function of growth and marker data for sex \( k \) based on Eq. 6 is given by

\[
\log L_4 (\Omega_k | y_{i,j,k}) = \sum_{i=1}^{n_k} \sum_{j=1}^{2} \log \left[ \pi_{j(f_i)} (y_{i,j,k}, G_{j(k)}, \Theta_k) \right]
\]

with the derivative with respect to any element \( \Omega_i \) in \( \Omega_k 

\[
\frac{\partial}{\partial \Omega_i} \log L_4 (\Omega_k | y_{i,j,k}) = \sum_{i=1}^{n_k} \sum_{j=1}^{2} \frac{\partial}{\partial \Omega_i} \log \left[ \pi_{j(f_i)} (y_{i,j,k}, G_{j(k)}, \Theta_k) \right]
\]

where we define

\[
\Pi_{j(f_i)} = \frac{\partial}{\partial \Omega_i} \log f_i (y_{i,j,k}, G_{j(k)}, \Theta_k)
\]
\[
\Pi_{j_i} = \frac{\pi_{j_i} f_j (y_{i,k}, K; G_{j,k}, \Theta_k)}{\sum_{j=0}^{2} \left[ \pi_{j_i} f_j (y_{i,k}, K; G_{j,k}, \Theta_k) \right]}
\]  

which could be thought of as a posterior probability that progeny \(i\) with a particular marker genotype has QTL genotype \(j\). We then implement the EM algorithm with the expanded parameter set \( \{ \Omega, \Pi \} \), where \( \Pi = \{ \pi_{j_i} \} \). Conditional on \( \Pi \) (the E step; Eq. 7), we solve for

\[
\frac{\partial}{\partial \Omega} \log L_k (\Omega | y_{i}, K) = 0
\]

to get the estimates of \( \Omega \) (the M step; Eq. 8). The estimates are then used to update \( \Pi \), and the process is repeated between Eqs. 7 and 8 until convergence. The values at convergence are the maximum likelihood estimates (MLEs) of \( \Omega \). The iterative expressions of estimating \( \Omega \) from the previous step were given in Ma et al. (21) and Wu et al. (39). In Wu et al. (36), approximate estimates of the samplings errors from Fisher’s information matrices were given.

As usual, the QTL position parameter can be viewed as a known parameter, because a putative QTL can be searched at every 1 or 2 cM on a map interval bracketed by two markers known parameter, because a putative QTL can be searched at information matrices were given.

HYPOTHESIS TESTS

Different from traditional mapping approaches, our functional mapping for longitudinal traits allows for the tests of a number of biologically meaningful hypotheses (38). These hypothesis tests can be a “global” test for the existence of significant QTL, a “local” test for the genetic effect on growth at a particular time point, a “regional” test for the overall effect of QTL on a particular period of growth process, or and “interaction” test for the change of QTL expression across times. These tests at different levels can be formulated to test the effects of QTL \( \times \) sex interaction on the shape of growth.

Global test. Testing whether specific QTL exist to affect growth trajectories is a first step toward the understanding of the genetic architecture of growth and development. The genetic control over entire growth processes can be tested by formulating the following hypotheses:

\[
\left\{ \begin{array}{l}
H_0 : G_{j,k} = G_k, k = 1, 2, 3, j = 1, 2, 3 \\
H_1 : \text{Not all the equalities in } H_0 \text{ hold}
\end{array} \right. 
\]

The \( H_0 \) states that there are no QTL affecting growth trajectories and the three genotypic curves in each sex overlap (the reduced model), whereas the \( H_1 \) proposes that such QTL do exist (the full model). The test statistic for testing the hypotheses in Eq. 9 is calculated as the log-likelihood ratio (LR) of the reduced to the full model:

\[
LR = -2 [\log L(\Omega | y; K) - \log L(\hat{\Omega} | y; K)]
\]

where \( \hat{\Omega} \) and \( \hat{\Omega} \) denote the MLEs of the unknown parameters under \( H_0 \) and \( H_1 \), respectively. The LR is asymptotically \( \chi^2 \)-distributed with 12 degrees of freedom. An empirical approach for determining the critical threshold is based permutation tests, as advocated by Churchill and Doerge (11). By repeatedly shuffling the relationships between marker genotypes and phenotypes, a series of the maximum LR values are calculated, from the distribution of which the critical threshold is determined.

After a significant QTL is detected, the next test is about the effect of this QTL on growth in each sex. This will use the same form as shown in Eq. 9, but focusing on a sex. It is interesting to test whether the QTL interacts with sex to affect growth trajectories. Such a null hypothesis test can be formulated as

\[
G_{j(1)} = G_{j(2)}, j = 2, 1, 0
\]

which states that any two curves between the same QTL genotype from different sexes overlap. However, when two sex-specific curves with the same QTL genotype are approximately parallel to each another, the area under the curve (\( A_j \)) is an appropriate criterion for this QTL \( \times \) sex interaction test, expressed as

\[
A_{j(k)} = \int_{t_1}^{t_2} \frac{a_{j(k)}}{1 + b_{j(k)} e^{-c_{j(k)} t}} dt
\]

In this case, the null hypothesis for testing QTL \( \times \) sex interaction can be formulated as

\[
A_{j(1)} - A_{j(2)} = A_1 - A_2, j = 2, 1, 0
\]

i.e., the difference between the areas under curves for different sexes is set equal for the three QTL genotypes.

In addition to testing overall genetic effects on growth trajectories, our model allows for the tests of the additive and dominant effect as well as their interaction effects with sexes. Wu et al. (38) proposed detailed procedures for making these specific tests, all of which can be directly used or modified for this study.

Local test. The local test can test for the significance of the genetic effect of QTL and QTL \( \times \) sex interaction effect on growth traits measured at a time point (\( t^* \)) of interest. For example, the hypothesis for testing the effect of QTL on growth at a given time \( t^* \) can be formulated as

\[
\left\{ \begin{array}{l}
H_0 : \mu_{j(1)} (t^*) = \mu_{j(2)} (t^*), \mu_{j(2)} (t^*) = \mu_{j(3)} (t^*) \\
H_1 : \text{Not all the equalities in } H_0 \text{ hold}
\end{array} \right. 
\]

which is equivalent to testing the difference of the full model with no restriction and the reduced model with a restriction as set in the null hypothesis.

Regional test. Sometimes we are interested in testing the difference of growth trajectories in a time interval rather than simply at a time point. The question of how a QTL exerts its effects on a period of growth trajectories \( [t_1, t_2] \) can be tested using a regional test approach based on the areas,  

\[
A_{j(k)} = \int_{t_1}^{t_2} \frac{a_{j(k)}}{1 + b_{j(k)} e^{-c_{j(k)} t}} dt
\]

where

\[
\frac{a_{j(k)}}{c_{j(k)}} \left[ \ln (b_{j(k)} + e^{c_{j(k)} t^*}) - \ln (b_{j(k)} + e^{c_{j(k)} t^*}) \right]
\]
covered by load curves. The hypothesis test for the genetic effect on a period of growth process is equivalent to testing the difference between the full model without no restriction and the reduced model with a restriction.

Interaction test. The effects of QTL may change with time, which suggests the occurrence of QTL \times time interaction effects on growth trajectories. The differentiation of growth with respect to time \( t \) represents growth rate. If the growth rates at a particular time point \( t^* \) are different between the curves of different QTL genotypes, then this means that significant QTL \times time interaction occurs between this time point and next.

Test for biologically important parameters. There are a number of biological parameters that can be used to evaluate the developmental characteristics of growth. The logistic growth curve can be used to determine the coordinates of a biologically important point in the entire growth trajectory, the “inflection point,” where the exponential phase ends and the asymptotic phase begins (24). The time at the inflection point corresponds to the time point at which a maximum growth rate occurs. The time

\[ t_{\text{inf}}(k) \]

and growth

\[ \mu(t_{\text{inf}}(k)) \]

at the inflection point for QTL genotype \( j \) from sex \( k \) can be derived as

\[
\begin{align*}
  t_{\text{inf}(k)} &= \frac{\ln b_{(k)}}{c_{(k)}} \\
  \mu(t_{\text{inf}(k)}) &= \frac{a_{(k)}}{2}
\end{align*}
\]  

(14)

Fig. 1. Plots of body mass vs. age for 259 male (A) and 243 female (B) mice in an F\(_2\) progeny derived from LG/J and SM/J strains (30). To display sex-specific differences, body mass was not corrected for the sex effect. The log-transformed data are plotted separately (C and D).
The difference in the coordinates between different genotypes provides important information about the genetics and evolution of growth trajectories (24). The genotypic differences in time and growth at the inflection point of maximum growth rate can be tested. The test for the genotypic difference is based on the restriction

$$\frac{\ln b_{(j1)}}{c_{(j1)}} = \frac{\ln b_{(j2)}}{c_{(j2)}} = \frac{\ln b_{2j}}{c_{2j}} = 2,1,0 \quad \text{for } t_{(jkl)}$$

and

$$a_{j(1)} = a_{1}, \quad a_{j(2)} = a_{2}, \quad j = 2,1,0 \quad \text{for } \mu_{(l(jkl))}.$$  

RESULT

We used the joint statistical model to map sex-specific QTL that affect growth trajectories in an animal model system: the mouse. Cheverud et al. (8) constructed a linkage map with 75 microsatellite markers for 535 F2 mice derived from two strains, the large (LG/J) and small (SM/J). The same cross experiment was replicated by Vaughn et al. (30) to produce a new F2 population of 259 male and 243 female mice. A molecular linkage map based on the new F2 population was constructed from 96 polymorphic loci. Vaughn et al. (30) reported the construction of this map with a total map distance of ~1,780 cM (in Haldane units) and an average interval length of ~23 cM.

The F2 progeny were measured for their body mass at 10 weekly intervals starting at age 7 days. The raw weights were corrected for the effects of each covariate due to dam, litter size at birth, and parity (30). To study the genetic architecture of sexual differences in body mass growth, the raw weights were not corrected for the effect due to sex. Figure 1 illustrates growth curves of body weights separately for the male (Fig. 1A) and female F2 mice (Fig. 1B). On average, males display different growth trajectories than females, with the former being heavier at all time points than the latter. Substantial variation in growth curve among different animals in each sex suggests that specific QTL may be involved in shaping developmental trajectories.
Our model is employed to search for growth QTL through a genome-wide scanning approach. The assumption of constant variance for the AR(1) model may not be true in our data, as indicated by increased variance with ages in both males and females (Fig. 1). Wu et al. (39) proposed a transformation approach, called the “transform-both-sides” (TBS) model by Carroll and Ruppert (5), to reduce variance heteroscedasticity and, therefore, increase the power of the model. This TBS-based mapping model can also preserve the biological meanings of curve parameters. In this study, we incorporate the TBS-based model through log transformation into the functional mapping framework for analyzing QTL/sx interactions. As shown in Fig. 1, C and D, the log transformation can lead to relatively constant variances in body mass growth for both males and females, although a more effective transformation approach should be estimated simultaneously with the model parameters (3, 5). Four peaks of the LR profile throughout the genome were found on chromosomes 6, 7, 11, and 15 (Fig. 2). The LR values at these peaks were detected to be greater than the genome-wide critical threshold value at the α = 0.05 significance level determined on the basis of 100 permutation tests. This thus suggests the existence of significant QTL for growth curves at the corresponding LR peaks on these chromosomes.

The three growth curves each determined by a genotype at each of these significant QTL are drawn separately for males and females (Fig. 3) using the MLEs of curve parameters (̂Gk,̂θ; Table 2) from our model. The growth trajectories of the same QTL genotype are different between the two sexes, suggesting that the genetic expression of QTL is affected by sex-related background. In general, these four QTL start to exert their effects on growth when the mice age 3 or 4 wk. These ages are just the timing at which maximal growth rate occurs (inflection point; Fig. 3). After the inflection point, the QTL effects tend to increase with age.

We further tested how the QTL interact with sex to affect growth trajectories. Based on the hypothesis test given in Eq. 12, we calculate the LR values for QTL sex interaction effects...
for all the four QTL (Table 3). Significant interactions were detected for QTL on chromosomes 6 and 11. The QTL on chromosome 6 is significant for both males and females (Fig. 3A), but the modes of gene action are different between the two sexes. In males, this QTL appears to be over-dominant because the heterozygote (Qq) outgrows the better homozygote (QQ). But in females, this QTL operates in a partial dominant fashion since the heterozygote is between the two homozygotes. Given these analyses, the QTL on chromosome 6 triggers significant interaction effects with sex through a so-called “allelic sensitivity” mechanism in which phenotypic changes result from differential expression of the same QTL (35). The second interacting QTL on chromosome 11 has a different mechanism. It exerts an effect on growth only in one sex (Fig. 3C). Although this QTL affects growth trajectories in a dominant fashion in males, it displays a non-significant effect in females. Thus this QTL may use a “regulatory mechanism” to affect differentiation in growth curves in that phenotypic changes rely upon the formation of novel genes.

Males reach the inflection point 3–5 days earlier than females. As demonstrated in Fig. 3, the QTL with significant effects on overall growth curves also affect the timing of the occurrence of maximal growth rate. Moreover, these QTL interact significantly with sexes to affect the timing of the inflection point, as shown by the LR values calculated according to the section Test for biologically important parameters (in Hypothesis Tests, above) (Table 3). With different growth curves, each corresponding to a QTL genotype, we can investigate possible pleiotropic effects of each of these growth QTL on many other developmental events, such as the timing of sexual maturity and reproductive fitness, or biomedically important traits, such as metabolic rate and fatness. We can therefore integrate growth and development, which are historically regarded as two different biological problems, into a comprehensive framework under which their common or unique underlying genetic machineries are identified.

**DISCUSSION**

From a developmental perspective, the sexes are an important force to generate different optimal reproductive phenotypes (26). However, because the sexes represent different environmental in which homologous traits are expressed, a conflict that cause genotype sex interactions may arise (6). It has now been recognized that the interaction between genotype and sex plays a central role in creating and maintaining extensive genetic variation for quantitative traits in heterogeneous environments (22). The statistical estimation of genotype × sex interaction at the individual QTL level, although extremely important in genetic and evolutionary studies, is difficult, due to the fact that the phenotype may not replicate across sexes. Cheverud and colleagues (9, 13, 30) used the general linear model to make a genome-wide scan for genotype × sex interactions at the QTL affecting a quantitative trait. While most quantitative traits undergo distinct developmental changes and, thus, should be described by multiple phenotypes measured at different time points (1, 7), the understanding of QTL × sex interaction effects on developmental trajectories has become a fundamental theme for evolutionary and developmental genetics.

Thanks to the recent development of functional mapping models for QTL mapping of longitudinal traits (21, 36, 38, 39), we have been able to develop a joint statistical framework for addressing this basic question of how QTL genomewide scan for genotype × sex interactions at the QTL affecting a quantitative trait. While most quantitative traits undergo distinct developmental changes and, thus, should be described by multiple phenotypes measured at different time points (1, 7), the understanding of QTL × sex interaction effects on developmental trajectories has become a fundamental theme for evolutionary and developmental genetics.
phenomena of interest that have been established from fundamental biochemical or physiological principles. For example, change in the size of any biological entity as a function of time follows a particular growth law that can be described by sigmoid or logistic curves (32). The incorporation of such a growth law does not only reduce the number of unknown parameters, but also, more importantly, can be well supported by biological principles. The results from such analyses are expected to be more biologically relevant.

Some specific patterns occur for the structure of a (co)variance matrix for longitudinal traits (12, 41). A considerable body of statistical literature has documented the parametricance matrix for longitudinal traits (12, 41). A considerable body of statistical literature has documented the parametricance matrix for longitudinal traits (12, 41). A considerable body of statistical literature has documented the parametricance matrix for longitudinal traits (12, 41). A considerable body of statistical literature has documented the parametricance matrix for longitudinal traits (12, 41). Although the simple AR(1) model through TBS transformation (5) works well for the age-dependent (co)variance matrix in our example, it can be readily extended to implement more sophisticated structural models within our functional mapping framework. In particular, nonparametric or semiparametric approaches will be likely to substantially contribute to the structuring of (co)variance matrices (40).

Second, well beyond existing models, our model allows for tests of a number of developmentally or ecologically meaningful questions at the interplay among different biological disciplines. Our earlier model incorporating epistatic effects due to different QTL can shed light on the genetic control mechanisms over developmental aspect of growth (38). The model proposed in this article preserves all favorable features of the model of Wu et al. (38). The current model allows for integration between genetics, ecology, and development. More specifically, it can test when a sex-specific QTL starts to trigger an effect on growth, how long this effect takes during the time course of growth, and in which gene action mode it can alter developmental trajectories. These questions, once incorporated into an evolutionary genetic model, will help to address some long-standing debates regarding organismal development and evolution (17, 29).

Our model was used to reanalyze published data on body mass growth in an F2 progeny population derived from large and small strains. We have successfully detected four QTL that affect growth trajectories. Statistical tests suggest that two of them on chromosomes 6 and 11 are sex-specific in trait control over overall growth curves. These two QTL use different mechanisms to alter growth patterns between the two sexes. In general, our results from the joint functional mapping model support the previous findings using single-trait mapping models (30). For example, two QTL on chromosomes 6 and 7 were detected in both studies. More QTL detected in Vaughn et al. (30) may be due to their doubled sample size and less stringent thresholds they used to reduce the type II error rate. Compared with single-trait approaches, our functional mapping that capitalizes on biological principles and correlated information has proved to be more powerful for detecting significant QTL and to provide biologically more relevant results (21).

It should be pointed out that the power of our model is affected by the ways in which to model the mean vector and the structure of the residual (co)variance matrix. Preliminary tests are needed for the goodness-of-fit of observed growth data to a particular growth equation and (co)variance structuring model. The model presented in this article can be further extended to incorporate other development- or reproduction-related traits. Growth cannot be viewed as a trait isolated from morphological architecture, developmental timing, or reproductive fitness. Cheverud et al. (9) investigated the genetic control of adiposity. The influences of QTL on the size and shape of mandibular molars were analyzed in some detail (10, 18, 19, 34). It is possible to integrate the genetic control of other traits into our functional mapping framework, which will allow for the identification of pleiotropic QTL on different traits. In the model reported here, we assume that single QTL controls the differentiation in growth trajectories between the two sexes. Given the ubiquity of epistatic effects on development, however, it is essential to model QTL-QTL interactions in this sex-specific mapping model. Also, such QTL-QTL interactions are not necessarily derived from the same genome rather than from different genomes (male and female), as pointed out in a recent study by Wolf (33). The QTL-QTL interaction from different genomes, called genome-genome or individual-individual interaction, should be considered in our model to gain greater insights into the genetic and developmental aspects of ontogenetic growth.

ACKNOWLEDGMENTS

The publication of this manuscript is approved as journal series R-09205 by the Florida Agricultural Experiment Station.

GRANTS

This work is partially supported by National Institutes of Health Grant DK-52514 to J. M. Cheverud and by an Outstanding Young Investigators Award (no. 30128017) of the National Natural Science Foundation of China and the University of Florida Research Opportunity Fund (no. 02050259) to R. Wu.

REFERENCES

13. Ehrlich TH, Vaughn TT, Koreishi S, Linsey RB, Pletscher LS, and Cheverud JM. Pleiotropic effects on mandibular morphology. I. Devel-
opmental morphological integration and differential dominance. J Exp Zoo
14. Kirkpatrick M and Heckman N. A quantitative genetic model for
growth, shape, reaction norms, and other infinite-dimensional characters.
structure of traits during growth and aging, illustrated with lactation in
16. Kirkpatrick M, Loefvold D, and Bulmer M. Analysis of the inheritance,
selection and evolution of growth trajectories. Genetics 124: 979–993,
1990.
17. Klingenberg CP. Heterochrony and allometry: the analysis of evolution-
18. Klingenberg CP, Leamy LJ, Routman EJ, and Cheverud JM. Genetic
architecture of mandible shape in mice: effects of quantitative trait loci
19. Klingenberg CP, Leamy LJ, and Cheverud JM. Integration and mod-
ularity of quantitative trait locus effects on geometric shape in the mouse
20. Lander ES and Botstein D. Mapping Mendelian factors underlying
quantitative traits using RFLP linkage maps. Genetics 121: 185–199,
1989.
21. Ma CX, Casella G, and Wu RL. Functional mapping of quantitative trait
loci underlying the character process: a theoretical framework. Genetics
22. Mackay TFC. Quantitative trait loci in Drosophila. Nat Rev Genet 2:
23. Mogil JS, Richards SP, O’Toole LA, Helms ML, Mitchell SR, Kest B,
and Belknap JK. Identification of a sex-specific quantitative trait locus
mediating nonopiod stress-induced analgesia in female mice. J Neurosci
24. Niklas KL. Plant Allometry: The Scaling of Form and Process. Chicago,
25. North KE, Martin LJ, Dyer T, Comuzzie AG, and Williams JT. HDL
cholesterol in females in the Framingham Heart Study is linked to a region
26. Nuzhdin SV, Pasyukova EG, Dilda C, and Mackay TFC. Sex-specific
quantitative trait loci affecting longevity in Drosophila melanogaster.
27. Pletcher SD and Geyer CJ. The genetic analysis of age-dependent traits:
28. Pletcher SD and Jaffrezic F. Generalized character process models:
estimating the genetic basis of traits that cannot be observed and that
change with age or environmental conditions. Biometrics 58: 157–162,
2002.
29. Rice SH. The analysis of ontogenetic trajectories: when a change in size
30. Vaughn TT, Pletcher LS, Peripato A, King-Ellison K, Adams E, Eriksen C,
and Cheverud JM. Mapping quantitative trait loci for murine growth: a closer look at genetic architecture. Genet Res 74: 313–322,
1999.
31. Wang ZH and Wu RL. A statistical model for high-resolution mapping
of quantitative trait loci determining human HIV–1 dynamics. Stat Med
32. West GB, Brown JH, and Enquist BJ. A general model for ontogenetic
33. Wolf JB. Genetic architecture and evolutionary constraint when the
environment contains genes. Proc Natl Acad Sci USA 100: 4655–4660,
2003.
34. Workman MC, Leamy LJ, Routman EJ, and Cheverud JM. Analysis of
quantitative trait locus effects on the size and shape of mandibular molar
35. Wu RL. The detection of plasticity genes in heterogeneous environments.
36. Wu RL, Ma CX, Chang M, Littell RC, Wu SS, Yin TM, Huang MR,
Wang MX, and Casella G. A logistic mixture model for characterizing
 genetic determinants causing differentiation in growth trajectories. Genet
37. Wu RL, Ma CX, Littell RC, and Casella G. A statistical model for the
38. Wu RL, Ma CX, Lin M, and Casella G. A general framework for
analyzing the genetic architecture of developmental characteristics. Ge-
39. Wu RL, Ma CX, Lin M, Wang ZH, and Casella G. Functional mapping
of quantitative trait loci underlying growth trajectories using a transform-
40. Wu WB and Pourahmadi M. Nonparametric estimation of large covari-
41. Zimmerman DL and Núñez-Antón V. Parametric modeling of growth