Linkage Analysis With an Alternative Formulation for the Mixed Model of Inheritance: The Finite Polygenic Mixed Model

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ABSTRACT

This paper presents an extension of the finite polygenic mixed model of FERNANDO *et al.* (1994) to linkage analysis. The finite polygenic mixed model, extended for linkage analysis, leads to a likelihood that can be calculated using efficient algorithms developed for oligogenic models. For comparison, linkage analysis of 5 simulated 4021-member pedigrees was performed using the usual mixed model of inheritance, approximated by HASSTEDT (1982), and the finite polygenic mixed model extended for linkage analysis presented here. Maximum likelihood estimates of the finite polygenic mixed model could be inferred to be closer to the simulated values in these pedigrees.

MOST traits of economic importance in livestock, such as milk production in dairy cattle and average daily gain in beef cattle, are assumed to be controlled by genes at a large number of loci. Such loci are referred to as quantitative trait loci (QTL). Until recently, the effect of individual QTL had not been studied. However, with the availability of genetic markers, their study has become feasible. The search for QTL has been most successful in plants and laboratory species where data are available for backcross and F_2 populations from inbred lines. With such data and the assumption that they follow a mixture of univariate normal densities, maximum likelihood techniques have been used to estimate the recombination fraction between the marker and the QTL and to investigate the mode of inheritance at the QTL (*e.g.*, ZENG 1994; ZHUCHENKO *et al.* 1979; WELLER *et al.* 1988).

In most livestock species, inbred lines are not available. Thus backcross or F_2 populations from inbred lines cannot be formed. In the absence of such data, marker-QTL analyses must be based on pedigree data. If a trait is controlled by only one QTL, the likelihood for a general pedigree can be efficiently calculated by methods based on the ELSTON-STEWART algorithm (ELSTON and STEWART 1971; LANGE and ELSTON 1975; CANNINGS *et al.* 1976; LANGE and BOEHNKE 1983; JANSS *et al.* 1992; FERNANDO *et al.* 1993). The reason for this is that if a trait is controlled only by one QTL, the phenotypic values of pedigree members are conditionally independent, given the genotypes of the pedigree members at that one locus. Also, the genotype of an individual is conditionally independent of those of all ancestors and sibs, given the genotypes of the parents. Suppose, however, that the trait is controlled both by a marker-linked QTL (MQTL) and by other residual QTL (RQTL) that are not linked to the marker (mixed inheritance). Such traits have been analyzed by assuming that the additive effect of the RQTL is normally distributed, giving rise to a multivariate normal mixture distribution for the trait (ELSTON and STEWART 1971; MORTON and MACLEAN 1974; HASSTEDT 1982, 1991). This assumption implies an infinite number of RQTL. Furthermore, because the phenotype is also influenced by the RQTL, the phenotypic values of pedigree members cannot be assumed to be conditionally independent, given the genotypes at the MQTL. Thus, under this assumption, fast algorithms to calculate the exact likelihood for extended pedigrees do not exist (ELSTON 1990; BONNEY 1992). The problem encountered here is identical to that in computing the likelihood for pedigree data in segregation analysis. Since the likelihood of such a marker-QTL model cannot be efficiently calculated for a general pedigree, most of the marker-QTL studies in livestock species have been limited to the detection of associations between markers and quantitative traits using the analysis of variance and related methods (BEEVER *et al.* 1990; COWAN *et al.* 1990; HOESCHELE and MEINERT 1990). These methods, however, are not as desirable as maximum likelihood to estimate both the recombination fraction between the marker and the QTL and the mode of inheritance at the QTL (LANDER and BOTSTEIN 1989).

For segregation analysis under mixed inheritance, FERNANDO *et al.* (1994) introduced the "finite polygenic mixed model" (FPMM) and showed how to compute the corresponding likelihood using fast algorithms developed for oligogenic traits. The objective of this paper

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is to describe how linkage analysis between a marker and a QTL can be conducted by maximum likelihood when an MQTL and several RQTL are segregating for the observed trait. The approach taken is to assume an FPMM, *i.e.*, a finite number of RQTL, and hence to compute the likelihood using fast algorithms developed for oligogenic traits.

THEORY

The probability density of the phenotypic values of the pedigree members, expressed as a function of the unknown parameters of the density, is the likelihood for the pedigree. In order to introduce how to compute the likelihood of a MQTL and several RQTL, consider first the computation of the likelihood of a single MQTL without RQTL, *i.e.*, an oligogenic model. Under oligogenic inheritance, phenotypic values are assumed to be conditionally independent, given the genotypes. Furthermore, it is assumed that the marker genotype has no effect upon the phenotype. Thus, the conditional density of the phenotypic values given z, the vector of joint genotypes at the MQTL and the marker locus, can be written for the n pedigree members as

$$\Pr(\mathbf{y}|z) = \Pr(\mathbf{y}|\mathbf{g}) = \prod_{i=1}^{n} \Pr(y_i|g_i), \qquad (1)$$

where $\mathbf{y}$ is the vector of n phenotypic values, $\mathbf{g}$ is the vector of n genotypes at the MQTL, and $\Pr(y_i|g_i)$ is the penetrance function or the conditional density of the phenotypic value given the genotype at the MQTL. Under mendelian inheritance, the probability of the joint genotypes z at the MQTL and the marker locus can be written as

$$\Pr(z) = \prod_{i=1}^{n_1} \Pr(z_i) \prod_{i=n_1+1}^{n} \Pr(z_i|z_m, z_f), \qquad (2)$$

where pedigree members 1 through n_1 are founders and the rest are non-founders. $\Pr(z_i)$ is the population frequency of the joint genotype at the MQTL and the marker locus. $\Pr(z_i|z_m, z_f)$ is the transition probability or the conditional probability that an offspring will have the joint genotype z_i given the mother m has the joint genotype z_m and the father f has the joint genotype z_f (ELSTON and STEWART 1971). Let T_b, T_d be alleles at the MQTL, M_c, M_e alleles at the marker locus, $\Pr(T_bT_d)$ the marginal probability of the genotype at the MQTL in the population, and $\Pr(M_cM_e)$ be the marginal probability of the marker genotype in the population. Then, $\Pr(z_i)$, the probability of the joint genotype in the population, can be computed as (*cf.*, ELSTON and STEWART 1971)

$$\Pr(z_i) = \Pr\left[\frac{T_bM_c}{T_dM_e}\right] = C \cdot \Pr(T_bT_d) \cdot \Pr(M_cM_e),$$

where

$$C = \begin{cases} 1, & \text{if } T_b = T_d \quad \text{or} \quad M_c = M_e \\ \tfrac{1}{2}, & \text{otherwise.} \end{cases}$$

To compute the transition probability $\Pr(z_i|z_m, z_f)$, or the conditional probability that an offspring will have the joint genotype z_i, given its parents have the joint genotypes z_m and z_f, respectively, we first define the transmission probabilities $\tau_s[(T_bM_c/T_dM_e) \rightarrow T_fM_g]$ following ELSTON and STEWART (1971): $\tau_s[(T_bM_c/T_dM_e) \rightarrow T_fM_g]$ is the probability that a parent of sex s with joint genotype $[T_bM_c/T_dM_e]$ will transmit the haplotype $[T_fM_g]$ to the offspring. These transmission probabilities are computed as

$$\tau_s\left[\frac{T_bM_c}{T_dM_e} \rightarrow T_fM_g\right] = \frac{(1-\theta_s)(\delta_{T_bT_f}\delta_{M_cM_g} + \delta_{T_dT_f}\delta_{M_eM_g})}{2} + \frac{\theta_s(\delta_{T_bT_f}\delta_{M_eM_g} + \delta_{T_dT_f}\delta_{M_cM_g})}{2},$$

where θ_s is the sex-dependent recombination fraction between the trait and the marker locus and δ_{xy} equals 1 if $x = y$, 0 otherwise. Using these transmission probabilities, the transition probability $\Pr(z_i|z_m, z_f)$ can be calculated as (ELSTON and STEWART 1971)

$$\Pr(z_i|z_m, z_f) = \Pr\left[\frac{T_fM_g}{T_hM_j} \,\middle|\, \frac{T_rM_s}{T_uM_v}, \frac{T_bM_c}{T_dM_e}\right]$$

$$= \begin{cases} \tau_m\left[\dfrac{T_rM_s}{T_uM_v} \rightarrow T_hM_j\right] \cdot \tau_f\left[\dfrac{T_bM_c}{T_dM_e} \rightarrow T_fM_g\right], \\ \qquad\qquad \text{if } T_f = T_h \quad \text{and} \quad M_g = M_j, \\ \tau_m\left[\dfrac{T_rM_s}{T_uM_v} \rightarrow T_hM_j\right] \cdot \tau_f\left[\dfrac{T_bM_c}{T_dM_e} \rightarrow T_fM_g\right] \\ \quad + \tau_m\left[\dfrac{T_rM_s}{T_uM_v} \rightarrow T_fM_g\right] \cdot \tau_f\left[\dfrac{T_bM_c}{T_dM_e} \rightarrow T_hM_j\right], \\ \qquad\qquad \text{otherwise.} \end{cases}$$

The likelihood for the pedigree can then be computed as

$$\Pr(\mathbf{y}) = \sum_{z_1} \sum_{z_2} \cdots \sum_{z_n} \prod_{i=1}^{n} \Pr(y_i|g_i) \times \prod_{i=1}^{n_1} \Pr(z_i) \prod_{i=n_1+1}^{n} \Pr(z_i|z_m, z_f). \qquad (3)$$

The summations in (3) are over the joint genotypes. For founders, let $f(z_i) = \Pr(y_i|g_i)\Pr(z_i)$, and for non-founders, let $h(z_i, z_m, z_f) = \Pr(y_i|g_i) \cdot \Pr(z_i|z_m, z_f)$. Then, the likelihood can be written as

$$\Pr(\mathbf{y}) = \sum_{z_1} \sum_{z_2} \cdots \sum_{z_n} \prod_{i=1}^{n_1} f(z_i) \prod_{i=n_1+1}^{n} h(z_i, z_m, z_f). \qquad (4)$$

If the summations are over m joint genotypes, the num-

ber of calculations required to compute the likelihood as indicated by (4) is proportional to m^n. However, because the function $f(z_i)$ involves the joint genotype of only a founder and the function $h(z_i, z_m, z_f)$ involves the joint genotypes of only a non-founder and parents m and f, the order of adding and multiplying in (4) can be rearranged such that the number of calculations required to compute the likelihood is proportional to n (ELSTON and STEWART 1971; LANGE and ELSTON 1975; CANNINGS *et al.* 1976, 1978; LALOUEL 1980; LANGE and BOEHNKE 1983; GORADIA *et al.* 1992; FERNANDO *et al.* 1993). If two alleles at each of the MQTL and the marker locus are assumed, 10 joint genotypes at the MQTL and the marker locus have to be considered, because the doubly heterozygous genotype exists in two phases. Thus, each summation in (4) is over these 10 joint genotypes. LANGE and BOEHNKE (1983) showed how the amount of necessary summations may be reduced using genotype and phase elimination. If the marker genotypes can be observed for all n pedigree members, then the likelihood can be written as

$$\Pr(\mathbf{y}) = \sum_{g_1}\sum_{g_2}\cdots\sum_{g_n}\prod_{i=1}^{n_1} f(z_i)\prod_{i=n_1+1}^{n} h(z_i, z_m, z_f), \quad (5)$$

i.e., only the summations over the genotypes $\mathbf{g}$ at the MQTL have to be carried out, provided we distinguish between the maternal and paternal alleles of all marker heterozygotes.

Now consider the segregation of a MQTL and several RQTL in a pedigree, *i.e.*, a mixed model of inheritance (ELSTON and STEWART 1971; MORTON and MACLEAN 1974). The conditional density of the phenotypic value given z, the vector of the joint genotypes at the MQTL and the marker locus, cannot be written as (1) because of the remaining segregating RQTL. Several approaches have been taken to compute the likelihood of such a model (HASSTEDT 1982, 1991; BONNEY 1984, 1992; FERNANDO *et al.* 1994). Following the theory of FERNANDO *et al.* (1994), consider a mixed model where the genotypic value is determined by a MQTL and by a finite number k of unlinked polygenic loci, rather than an infinite number of polygenic loci as implied by the assumption of normality for the polygenic component in the usual mixed model. Further, assume that the polygenic component of the genotypic value is additive and that the aggregate genotypic value is the sum of the genotypic values of the MQTL and of the polygenic component. With this formulation of the mixed model, the conditional distribution of the phenotypic values given the genotypes determined by the MQTL and the polygenic loci, can be written as (1), *i.e.*,

$$\Pr(\mathbf{y}|z, \mathbf{v}) = \Pr(\mathbf{y}|\mathbf{g}, \mathbf{v}) = \prod_{i=1}^{n}\Pr(y_i|g_i, v_i)$$

where $\mathbf{g}$ is the vector of genotypes at the MQTL and $\mathbf{v}$ is the vector of genotypes at the polygenic loci, as explained in FERNANDO *et al.* (1994). Thus, algorithms applicable to oligogenic traits can be used to calculate the likelihood. A problem with this approach, however, is that the number of genotypes, and hence also the computing time, increases exponentially with the number of loci. For example, suppose there are two alleles at the MQTL, at the marker locus and at each of k polygenic loci. Then, the number of genotypes that have to be summed over is $10 \cdot 3^k$. To reduce the computations in calculating the likelihood, the same assumptions and definitions are made as in FERNANDO *et al.* (1994), allowing us to write the likelihood as

$$\Pr(\mathbf{y}) = \sum_{z_1}\sum_{v_1}\sum_{z_2}\sum_{v_2}\cdots\sum_{z_n}\sum_{v_n}\prod_{i=1}^{n}\Pr(y_i|g_i, v_i) \times \prod_{i=1}^{n_1}\Pr(z_i)\Pr(v_i)\prod_{i=n_1+1}^{n}\Pr(z_i|z_m, z_f)\Pr(v_i|v_m, v_f) \quad (6)$$

which can be rearranged as

$$\Pr(\mathbf{y}) = \sum_{z_1}\sum_{v_1}\sum_{z_2}\sum_{v_2}\cdots\sum_{z_n}\sum_{v_n}\prod_{i=1}^{n_1} f(z_i, v_i) \times \prod_{i=n_1+1}^{n} h(z_i, v_i, z_m, v_m, z_f, v_f).$$

Further, by the assumptions 1 and 2 in FERNANDO *et al.* (1994), the summation over each v is over only $2k + 1$ polygenic numbers. (In contrast, there are 3^k possible genotypes for the polygenic loci). Suppose, for example, there are two alleles at each of the MQTL and the marker locus. Then, the number of calculations to compute (6) is equivalent to that for computing the likelihood of a monogenic model with $10 \cdot (2k + 1)$ possible genotypes.

If the marker genotypes can be observed on all n pedigree members, then, analogous to (5) the likelihood can be written as

$$\Pr(\mathbf{y}) = \sum_{g_1}\sum_{v_1}\sum_{g_2}\sum_{v_2}\cdots\sum_{g_n}\sum_{v_n}\prod_{i=1}^{n_1} f(z_i, v_i) \times \prod_{i=n_1+1}^{n} h(z_i, v_i, z_m, v_m, z_f, v_f)$$

DATA ANALYSIS

Linkage analysis by maximum likelihood under an FPMM, using the computer package SALP (STRICKER *et al.* 1995) will be compared with that under the usual mixed model (UMM), where the likelihood under the UMM is approximated as described by HASSTEDT (1982) and implemented in the subroutine PAPENP of the computer package PAP Rev. 3.0 (HASSTEDT 1989). An attempt was also made to apply to the same dataset the approach of HASSTEDT (1991), implemented in the computer package PAP Rev. 4.0 (HASSTEDT 1994), to compute the likelihood of the UMM. Whereas HAS-

TABLE 1

Maximum likelihood estimates under the UMM

Pedigree	Difference between homozygotes	Allele frequency		Recombination fraction	Variance		
		Major locus	Marker locus		Major locus	Polygenic	Residual
A	2.74	0.38	0.51	0.07	0.9	5.02	7.66
B	1.76	0.43	0.49	0.0*	0.4	6.92	6.76
C	4.11	0.44	0.51	0.23	2.1	5.54	6.32
D	0.77	0.52	0.51	0.0*	0.1	6.34	7.07
E	2.05	0.58	0.50	0.0*	0.5	6.41	6.57
True parameter values	4.00	0.50	0.50	0.10	2.0	5.00	7.00

* Likelihood maximized at lower boundary.

STEDT (1982) (and PAP Rev. 3.0) computes the likelihood of the UMM by numerical integration, the approach of HASSTEDT (1991) (and PAP Rev. 4.0) inverts the variance-covariance matrix that is determined by the relationships between individuals. In the context of large pedigrees, the latter approach becomes prohibitively time consuming, as indicated below.

Material and methods: Five three-generational pedigrees of the same structure comprising 4021 individuals each were simulated. The structure of each pedigree was generated by the following matings: 1 grandfather was mated to 10 unrelated grandmothers to produce 1 son each. These 10 halfsibs were mated each to 10 unrelated female individuals to produce 3 daughters each. The genotypic value for the simulated trait was additively determined by a major locus and 40 polygenic loci, with two alleles of equal frequencies at the major locus and at each of the polygenic loci. The difference between homozygotes was 4 at the major locus and 1 at each of the polygenic loci. This gives a variance of 2 for the major locus and of 5 for the polygenic component. The phenotype was simulated by adding a normally distributed residual with mean 0 and variance 7 to the genotypic value. A marker locus with two alleles of equal frequencies was simulated to be unlinked to the polygenic loci and linked to the major locus with a recombination fraction of 0.1. Whereas all individuals were genotyped with respect to the marker locus, all male individuals were assigned a missing trait phenotype.

The same number of parameters were estimated from each pedigree under both the FPMM and the UMM. It should be noted that SALP uses the Downhill Simplex method (NELDER and MEAD 1965) to maximize the likelihood, whereas PAP maximizes the likelihood function using the variable metric method (GEMINI; LALOUEL 1979). As mentioned above, the program package PAP Rev. 4.0 (HASSTEDT 1994) was not considered further, due to high requirements in terms of computer time for the size of pedigrees generated here (around 5 CPU-hours for the computation of a single likelihood on a DEC AXP 4000/710 Alpha-Workstation).

Results and discussion: The maximum likelihood estimates for each of the five pedigrees are listed in Table 1 for the UMM and in Table 2 for the FPMM, assuming 5 polygenic loci. The calculation, and thus also the maximization, of the exact likelihood (of the model that was used to simulate the pedigree data) was not computationally feasible. Thus it was not possible to obtain maximum likelihood estimates for the parameters under the true model used to simulate the pedigrees. However, because we simulated five large pedigrees, the differences between the parameter estimates under the true model and the true parameter values used to generate the pedigrees could be expected to be small.

TABLE 2

Maximum likelihood estimates under the FPMM

Pedigree	Difference between homozygotes	Allele frequency		Recombination fraction	Variance		
		Major locus	Marker locus		Major locus	Polygenic	Residual
A	3.81	0.54	0.48	0.02	1.8	4.39	7.82
B	3.17	0.57	0.49	0.03	1.2	6.22	6.69
C	3.78	0.44	0.51	0.13	1.8	5.19	6.90
D	4.01	0.54	0.51	0.08	2.0	4.48	7.10
E	4.51	0.56	0.50	0.15	2.5	4.46	6.74
True parameter values	4.00	0.50	0.50	0.10	2.0	5.00	7.00

When the approximate likelihood of the UMM was maximized with the program package PAP Rev. 3.0, the estimate for the recombination fraction was at its lower boundary zero in pedigrees *B*, *D* and *E* (indicated by asterisks in Table 1). To examine if other maxima exist for these pedigrees within the parameter space of the recombination fraction, the maximization process was restarted at the previous maximum but with the initial value for the recombination fraction set to 0.1. Since the likelihoods for pedigrees *B*, *D* and *E* were again maximized at the same boundary, the lower boundary for the recombination fraction was increased from 0.0 to 0.0001 and the maximization process was restarted again. Because all these restarted maximization processes converged to the boundary 0.0 or 0.0001 for the recombination fraction, respectively, for all three pedigrees, it was concluded that there was no other maximum within the parameter space for pedigrees *B*, *D* and *E*. The maximum likelihood estimates under the FPMM show only relatively small differences among the five simulated pedigrees and are within close range of the parameters that were used to simulate the pedigree data (Table 2).

The maximum likelihood estimates under the UMM approximated by HASSTEDT (1982) showed more variability among the 5 pedigrees, especially for the parameters recombination fraction, major gene frequency and major genotypic means. As a consequence of the parameter estimates for the major genotypic means and frequencies under the UMM approximated by HASSTEDT (1982), the amount of variation the model fitted to the major locus within each pedigree is also different and deviates considerably from the values obtained by the FPMM and those used to simulate the pedigree data.

The CPU time to compute a single likelihood by SALP was around 5–10 min depending on the machine used and thus was considerably higher than by PAP Rev. 3.0. An exact comparison was not possible because the likelihoods were computed on different machines, due to higher memory requirements of the FPMM approach. For the FPMM approach, memory requirements increase approximately linear with the number of individuals, the analysis of a 4021-member pedigree, as presented here, took around 70 megabytes. Even if the two likelihoods were computed on the same machine, it would be necessary to assume the same degree of efficiency in programming between SALP and PAP to make a fair comparison between the two approaches. Because the two packages are programmed in different programming languages, each using specific features of that language, compiled by different compilers, and may thus be optimized to a different degree, a comparison in terms of CPU-time between the two algorithms, as implemented in PAP Rev. 3.0 and SALP, would be meaningless (see *e.g.*, COTTINGHAM *et al.* 1993). Furthermore, the time used to compute a single likelihood also depends upon the number of polygenic loci used in SALP. For linkage analysis, we have shown in this paper that a FPMM, as implemented in SALP, assuming 5 polygenic loci, gives a better approximation to the simulated data than does the approximate UMM implemented in the subroutine PAPEND of PAP rev. 3.0.

The analysis under either the UMM or FPMM may also be conducted using a Monte Carlo approach such as Gibbs Sampling (THOMPSON and GUO 1991; GUO and THOMPSON 1992). This requires less memory than the FPMM approach presented here, but due to repeated conditional sampling, Gibbs Sampling is intensive with respect to CPU-time. It should be noted that Monte Carlo methods yield approximate results, though the approximations can always be improved by increasing the amount of sampling performed if sufficient CPU-time is available.

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