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# THE EFFECTS OF LINKAGE DISEQUILIBRIUM ON THE ADDITIVE AND DOMINANCE VARIANCES IN A RANDOM MATING SMALL POPULATION

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## ABSTRACT

In a random mating small population components of genetic variance of a quantitative trait are studied as a stochastic process over discrete generations for a two-locus dominance model. Single-locus and two locus terms in the expected values of the components are defined and solved by using the marginal and simultaneous distributions of two locus gene frequencies.

Theoretical expectations of the variances are obtained for a genetic system simulated previously. These expectations are compared with the results in simulation. A faster decrease in genetic variance components is observed in simulation. Probable reasons for this are discussed.

In theoretical expecetations the effect of linkage disequilibrium on both additive and dominance variances is found to be significant. Even in the case of initial linkage equilibrium there is an increase in dominance variance in early generations since some expectations related to the joint distributions of two genes are not zero in replicate lines.

## INTRODUCTION

The genetic variance and its components for a quantitative trait are among the most important subjects in animal and plant breeding. In order to make decisions about the breeding plan the genetic variance present in the population should be estimated and analyzed. If its additive component large enough proportional to the total phenotypic variance, selection for high phenotypes is thought to be the method to increase the population mean. If non-additive part is important, other methods such as crosses between lines together with or without selection will be more convenient. In the case of genetic variance being small, one should increase it first of all.

The genetic variance is an important problem also in the theory of evolution, especially with respect to studying fitness as a quantitative trait which is the measure variable of the natural selection acting for a phenotype contolled by presumably all loci included in whole genotype.

There are some methods of estimating genetic variance and its components in an agricultural or natural population. These methods are based on, in general, single–locus model in which no correlation are assumed between the effects of non–allelic genes. But this correlation may not be zero due to linkage disequilibrium. This effect of linkage disequilibrium on the genetic variance has tended to be ignored for quite a long time and recently started to be studied (Avery & Hill, 1979). There are some observations that the two–locus model (a name indicating that the linkage disequilibrium is included) is sufficient to explain the genetic variation in many quantitative trait (Avery & Hill, 1979). When there are some interaction effects of two or more non–allelic genes it becomes necessary to consider the joint distributions of the genes at more than two loci.

Whether single–locus or two–locus model is considered the process of genetic variance over generations in a small population is subject to chance effects. In last three decades this process has been studied in terms of distribution of gene frequencies (Wright, 1969; Crow & Kimura, 1970; Ewens, 1979). In more recent studies the terms related to the distribution of linkage disequilibrium has been taken into account (Avery & Hill, 1979; Kavuncu,1984; Golding, 1984; Hudson, 1985).

In this study the theory about the expected values of the additive and dominance variances in a quantitative trait in t-th generation of a random meting small population are reviewed. Then some numerical results for a genetic system simulated before (Kavuncu & Kesici, 1980) are compared with theoretical results.

## THEORY

Here fist the model is described, then the distribution of a gene frequency in a small population is defined and, finally two–locus expectations required in the expected values of the genetic variance components are given.

### *Model*

Consider a diploid organism. For the purpose here diploidy may be defined as possesing two genes at each locus, each of which come through one parental gamete. In a biallelic locus which is the case here the two genes may be either A or a, so the possible genotypes at that particular locus are AA, Aa and aa. Further assume that the probability of a gene being A at the paternal gamete is equal to that of the gene at the maternal gamete.

In this study a quantitative trait controlled by the genes at n loci is considered. The gene at i-th locus of a gamete may be $A_i$ with the probability of $p_i$ or $a_i$ with the probability of $1-p_i$. Assume that two gametes uniting to give an offspring are taken at random from the infinite gametic output produced by equal contributions of N parents. This means that we have an organism whose reproductive system includes selfing with the probability of $1/2N$. This model is called *random union of gametes*. The number of individuals is constant over generations. That is, the number of gametes sampled at random each generation is 2N. Selection, mutation, and migration are absent.

Genotypic value of an individual for the quantitative trait studied is given by

$$G = \sum_{1=i}^{n} X_i \qquad (1)$$

with the assumption that there is no epistasis, i.e. no interaction between the effects of different loci. Here $X_i$ is the effect of genotype at i-th locus. It is conventionally defined as deviation from midpoint of two homozygotes and can take the values $a_i$, $d_i$ or $-a_i$ for the genotypes $A_iA_i$, $A_ia_i$ or $a_ia_i$, respectively. The variance of G is, by definition

$$V_G = \sum^{n} V(X_i) + 2 \sum_{i<j}\sum \mathrm{cov}\,(X_i, X_j) \qquad (2)$$

When there is a dependence in the joint distribution of $X_i$ and $X_j$, the genetic variance includes the covariances. The measure of dependence is so-called the coefficient of linkage disequilibrium. For the loci i and j it is defined as

$$D_{ij} = f(A_iA_j).\ f(a_ia_j) - f(A_ia_j)\ f(a_iA_j) \qquad (3)$$

One can show that the covariance of $X_i$ with $X_j$ becomes zero if $D_{ij}$ is zero in an infinitely large population. For such a population Hardy Weinberg frequencies do not change over generations and the genetic variance remains constant. But for a small population gene frequencies are subject to random fluctuations. Starting from a reference population from which many replicate lines are sampled, additive genetic variance in a replicate line after t generations of random mating is expected to be

$$E_t(V_A) = 2\ \Sigma a^2 E_t(p_i(1-p_i)) + 4\ \Sigma\ a_i d_i E_t\ (p_i\ (1-pi)\ (1-2p_i)) +$$
$$2\ \Sigma\ d_i\ {}^2E_t\ (p_i\ (1-p_i)\ (1-p_i)^2) + 4 \sum_{i<j}\sum a_i a_j E_t\ (D_{ij}) + \tag{4a}$$
$$4 \sum_{i\neq j}\sum a_i d_j E_t\ (D_{ij}\ (1-2p_i)) + 4 \sum_{i<j}\sum d_i d_j E_t\ (D_{ij}\ (1-2p_i)\ \ (1-2p_j))$$

and the variance of dominance deviations for the same situation is

$$E_t\ (V_D) = 4\ \Sigma\ \ d_i\ {}^2E_t\ (p_i^2\ \ (1-p_i)^2) + 8 \sum_{i<j}\sum\ d_i d_j E_t\ (D_{ij}^2) \tag{4b}$$

The sum of two components is total genetic variance designated by $V_G$. Its actual value may be different from the summation due to the correlation between additive and dominance effects at a given locus. But this correlation may be ignored in a random mating population. Both eqs. (4a) and (4b) are given by Avery &Hill (1979).

The right hand side terms in eqs. (4a) and (4b) can be divided into two groups: single–locus expectations and two–locus expectations. Now we are going to discuss about these expectations in connection with their distributions.

### *Single-Locus Expectations*

Let the frequency of the gene A be p in a reference population. 2N gametes to reproduce the offspring are taken at random. Let among 2N gametes the number of those having the gene A be Y. Y is a binominal random variable and the probability that it takes a value y is

$$P\ (Y = y) = \binom{2N}{y} p^y\ (1-p)^{2N-y} \tag{5}$$

In order to get a solution to eqs (4a) and (4b) given that initial $p_i$ is known, we need first four moments of this distribution. By using moment generating function of Y these are obtained as

$$E\ (Y) = 2Np \tag{6a}$$

$$E\ (Y^2) = 2Np + 2N\ (2N-1)\ p^2 \tag{6b}$$

$$E(Y^3) = 2Np + 6N(2N-1)p^2 + 2N(2N-1)(2N-2)p^3 \qquad (6c)$$

$$E(Y^4) = 2Np + 14N(2N-1)p^2 + 12N(2N-1)(2N-2)p^3 + 2N(2N-1)(2N-2)(2N-3)p^4 \qquad (6d)$$

The k–th moment of p can now be obtained by dividing corresponding moments of Y by $(2N)^k$ since $p = Y/2N$. Thus, given that the frequency of gene A in generation t–1 is $E_{t-1}(p)$, the expected values we need in generation t are

$$E_t(p) = E_{t-1}(p) \qquad (7a)$$

$$E_t(p^2) = \frac{1}{2N} E_{t-1}(p) + \left(1-\frac{1}{2N}\right) E_{t-1}(p^2) \qquad (7b)$$

$$E_t(p^3) = \frac{1}{4N^2} E_{t-1}(p) + \frac{3}{2N}\left(1-\frac{1}{2N}\right) E_{t-1}(p^2) + \left(1-\frac{1}{2N}\right)\left(1-\frac{2}{2N}\right) E_{t-1}(p^3) \qquad (7c)$$

$$E_t(p^4) = \frac{1}{8N^3} E_{t-1}(p) + \frac{7}{4N^2}\left(1-\frac{1}{2N}\right) E_{t-1}(p^2) + \frac{6}{2N}\left(1-\frac{1}{ZN}\right)\left(1-\frac{2}{2N}\right) E_{t-1}(p^3) + \left(1-\frac{1}{2N}\right)\left(1-\frac{2}{2N}\right)\left(1-\frac{3}{2N}\right) E_{t-1}(p^4)$$

Given that the gene frequency in the reference population is p the difference eqs. 7a–d are solved as

$$E_t(p) = p \qquad (8a)$$

$$E_t(p^2) = p - \left(1-\frac{1}{2N}\right)^t p(1-p) \qquad (8b)$$

$$E_t(p^3) = p - \frac{3}{2}\left(1-\frac{1}{2N}\right)^t p(1-p) + \frac{1}{2}\left[\left(1-\frac{1}{2N}\right)\left(1-\frac{2}{2N}\right)\right]^t p(1-p)(1-2p) \qquad (8c)$$

$$E_t(p^4) = p - \frac{18N-11}{10N-6}\left(1-\frac{1}{2N}\right)^t p(1-p) + \left[\left(1-\frac{1}{2N}\right)\left(1-\frac{1}{2N}\right)\right]^t p(1-p)(1-2p) + \left[\left(1-\frac{1}{2N}\right)\left(1-\frac{2}{2N}\right)\left(1-\frac{3}{2N}\right)\right]^t p(1-p)\left[p(1-p) - \frac{2N-1}{10N-6}\right] \qquad (8d)$$

The variance of gene froquency in generation t can be given as

$$V_t(p) = E_t(p^2) - [E_t(p)]^2 = \left[1-\left(1-\frac{1}{2N}\right)^t\right] p(1-p) \tag{9}$$

The variance in eq. 9 is a measure of variation between replicate lines in generation t. According to the eq. 8a the average gene frequency over lines is equal to the initial gene frequency in the reference population. Eventual result of eq. 9 as t goes to infinity is p (1–p) which is the variance between replicate lines whose gene frequency is either 0 or 1. This means that the ultimate variance within lines is zero. From an evolutionary point of view one can say, as Fisher points out, that dispersive agent of evolution is not enough to maintain a population in a polymorpic state.

It is shown by Wright (1969) that epistatic selection and/or migration whose pressures can vary from generation to generation, together with chance itself, provide multiple peaks, i.e. many possible equilibrium points, in the state space of the system. Epistatic selection acts interactively over many loci. This theory has been known as

Wright's shifting balance theory. According to the theory in the state space of the population a small departure from an equilibrium point may cause it go away and approach to another point, it may turn back to the old one as well.

Fisher, on the other hand, thinks of random drift, a name implying all the stochastic effects, as a-making-noise-agent that makes the deterministic processes directed by systematic agents of evolution less efficient. In other words Fisher assumes that the only effect of random drift is to delay the ultimate fate of the population mainly determined by the systematic agents. Some evidence from molecular biology indicates that random drift may have a role more important than what Fisher thinks (Crow & Kimura. 1970).

Another way to discuss the eventual fate of a replicate line is to look at the proportions of the genotypes AA, Aa, aa. In the reference pupulation these proportions are $p^2$, $2p(1-p)$, $(1-p)^2$. In t-th generation the proportion of the homozygotes AA within a replicate line is expected to be, by definition,

$$E_t(p^2) = p^2 + V(p_t) \qquad (10a)$$

and the proportion of aa is

$$E_t((1-p)^2) = (1-p)^2 + V(p_t) \qquad (10b)$$

since $V(p) = V(1-p)$ in a binomial distribution. The residual is, then, the proportion of heterozygotes:

$$E_t(2p(1-p)) = 2p(1-p)(1-1/2N)^t \qquad (10c)$$

One may ignore the deviation from Hardy Weinberg frequencies within a line in generation t. But this is not true when all lines considered as a whole population (Falconer, 1981). The genotype frequencies in eqs. 10a, b, c are the averages of all lines. It is clear that these are not Hardy–Weinberg frequencies with respect to p, the average gene frequency over replicate lines.

### *Two–Locus Terms*

The genetic variance of a quantitative trait whose components are given by eqs (4a) and (4b) includes the covariances of genotypic values at two different loci. In the absence of linkage disequilibrium this term dissappears in the reference population. But the assumption that there is no effect of linkage disequilibrium on the genetic variance in a replicate line in generation t may not hold, even if an initial linkage equilibrium exists as it is one of the cases for numerical results given at next section in this paper.

The two–locus expressions in eqs. (4a) and (4b) can be obtained by using the multinomial distribution of gametes for two loci. For the loci i and j the possible gametes are $A_iA_j$, $A_ia_j$, $a_iA_j$, $a_ia_j$ designated here, for simplicity, by the numbers 1, 2, 3, and 4, respectively. Let a replicate line in generation t consists of N individuals. This means that it is constructed by 2N gametes with the frequencies $c_1$, $c_2$, $c_3$ and $c_4$. Given that the population size remains constant from generation to generation individuals reproduce gametic output in proportions

$$\varphi_l = c_l + \delta_l r_{ij} D_{ij}$$

from which 2N are taken at random in order to make up N offspring in next generation. Here $r_{ij}$ is the recombination fraction, $\delta_1 = \delta_4 = -1$ and $\delta_2 = \delta_3 = +1$. The probability that the number of gametes will be $n_1$, $n_2$, $n_3$ and $n_4$ is given by

$$P\ (n_1, n_2, n_3, n_4) = \frac{(2N)!}{\prod\limits_{i=1}^{4} n_i!} \prod_{i=1}^{4} \varphi_i^{n_i} \tag{12}$$

The expected values of two–locus terms in eqs. 4a and 4b can be solved by using moment generating function of eq. 12. Derivations of the formulae can be found in literature (Karlin and McGregor 1968; Hill and Robertson 1968; Avery and Hill 1979):

$$E_{t+1}\ (D) = \left(1- \frac{1}{2N}\right) (1-r)\ E_t(D) \tag{13a}$$

$$E_{t+1}\ [D\ (1-2p_i)] = \left(1- \frac{1}{2N}\right) \left(1- \frac{2}{2N}\right) (1-r)\ E_t[D(1-2p_i)] \tag{13b}$$

$$E_{t+1}[D\ (1-2p_i)\ \ (1-2p_j)] = \left(1- \frac{1}{2N}\right) \left(1- \frac{1}{2N}\right)^2 (1-r)\ E_t\,[D\ (1-2p_i)$$

$$(1-2p_j)] + \frac{2}{N} \left(1- \frac{1}{2N}\right) \left(1- \frac{2}{2N}\right) (1-r)^2\ E_t\ (D^2) \tag{13c}$$

$$E_{t+1}(D^2) = \frac{1}{2N} \left(1- \frac{1}{2N}\right) E_t[p_i(1-p_i)p_j(1-p_j)] + \frac{1}{2N} \left(1- \frac{1}{2N}\right)^2$$

$$E_t[(D\ \ (1-2p_i)\ \ (1-2p_j)] + \left(1- \frac{2}{2N}\right) \left(1- \frac{1}{2N}\right) \left[\frac{1}{4N^2} + \right.$$

$$\left.\left(1- \frac{1}{2N}\right)^2\right] (1-r)^2\ E_t\ (D^2) \tag{13d}$$

The new term $E_{t+1}\ (p_i\ (1-p_i)\ p_j\ (1-p_j))$ is equal to

$$E_{t+1}[p_i(1-p_i)\ \ p_j\ (1-p_j)] = \left(1- \frac{1}{2N}\right)^2 E_t\ [p_i\ (1-p_i)\ p_j\ (1-p_j)] +$$

$$\frac{1}{2N} \left(1- \frac{1}{2N}\right) (1-r)\ E_t\ [D(1-p_i)\ (1-2p_j)] + \frac{1}{2N^2} \left(1- \frac{1}{2N}\right)$$

$$(1-r)^2\ E_t\ (D^2) \tag{13e}$$

Difference eps. 13a and b are solved immediately. The system of difference eps. 13c, d, and e has been solved for $r_{ij} = 0$ by Avery and Hill (1979). A complete analytic solution to the system has not appear yet, nor the distribution of linkage disequilibrium was obtained analytically. Kavuncu and Düzgüneş (1983) pointed out that a function of the square of D might have a chi–square distribution with 1 degree of freedom in the samples drawn at random from a reference population in linkage equilibrium. In more recent simulation studies the distribution has been evaluated emprically (Golding 1984; Hudson 1985).

## RESULTS

In 1977 a genetic system was simulated for five generations of random mating (Kavuncu and Kesici, 1980). The simulation results were the averages of three replicates. The system studied was 16 loci distributed equally into four chromosomes. The values of $A_iA_i$, $A_ia_i$ and $a_ia_i$ were 1, 1,–1 respectively ($a_i = d_i = 1$ in eqs 4a and 4b, complete dominance model) at eight loci in two chromosomes, while eight loci in the other two had only additive effects, the value of the genotypes $A_iA_i$, $A_ia_i$ and $a_ia_i$ are 1, 0,–1 respectively ($a_i = 1$, $d_i = 0$ in eqs 4a and 4b, additive model). Two recombination values were .5 and .01 between adjacent loci in the same chromosome. Two homozygote lines with the genotypes $A_1A_2 \ldots A_{16} / A_1A_2 \ldots A_{16}$ and $a_1a_2 \ldots a_{16} / a_1a_2 \ldots a_{16}$ were crossed and the offsprings of hybrids were taken at random, so, $F_2$ was the initial generation and $p_i = .5$ was the expected frequency of the gene A for all i. In $F_2$ generation the linkage disequilibrium coefficient was expected to be zero for all pairs of loci whose recombination values were .5, while in the case of $r = .01$ between adjacent loci it was .2450, .2401 and .2353 respectively, for the pairs i and i + 1; i and 1 + 2; i and i + 3 of the loci at the same chromosome. Two population size treated were 100 and. 450 with equal numbers of two sexes. But parents were selected at randeom with 40 percent intensity in females and 10 percent in males. Thus effective population sizes by which 2N is replaced in eqs. 7s, 8s and 13s were calculated as 16 and 72 approximately from the relation

$$Ne = \frac{4\, N_m\, Nf}{N_m + Nf}$$

where $N_m$ and Nf are the numbers of male and female parents respectively. Ne is the harmonic mean of the numbers of male and female gametes ($2N_m$ and 2Nf here) contributing to the next generation. It is equivalent to the number of gametes in the random union of gametes model.

Genetic variance expectations for the same genetic system used in the simulation are calculated by using eqs. 4a and 4b. According to these results the effect of linkage disequilibrium on the dominance variance is observable in all of the four system while its effect on the additive variance is noticeable only in the systems initial linkage disequilibrium exists. In the case of $D_{ij} = 0$ in the reference population an increase in dominance variance is observed in early generations, since some expectations related to $D_{ij}$ are not zero in replicate lines even in this case, as it can be seen in eqs. 13c, d and, e. The larger the population size, the slower increase in the genetic variance.

The results of simulation and those obtained by using eqs. 4a and 4b are compared in tables 1, 2, 3 and 4. The decrease are faster in simulation results than in theoretical expectations. Some immediate reasons for this could be mentioned as

Table 1. Simulation Results and Theoretical Expectations Ne $= 16$, r $= .50$

|  | $V_A$ |  | $V_D$ |  |
|---|---|---|---|---|
| t | sim. | theor. | sim. | theor. |
| 0 | 10.16 | 8.00 | 1.94 | 2.00 |
| 1 | 8.57 | 7.71 | 1.95 | 3.41 |
| 2 | 7.28 | 7.40 | 1.95 | 3.37 |
| 3 | 8.41 | 7.05 | 1.84 | 3.09 |
| 4 | 6.96 | 6.68 | 1.87 | 2.78 |
| 5 | 4.57 | 6.30 | 1.87 | 2.51 |

Table 2. Simulation Results and Theoretical expectations Ne $= 16$, r $= .01$

|  | $V_A$ |  | $V_D$ |  |
|---|---|---|---|---|
| t | sim. | theor. | sim. | theor. |
| 0 | 28.80 | 31.21 | 7.86 | 7.61 |
| 1 | 24.35 | 29.66 | 5.78 | 7.91 |
| 2 | 24.66 | 28.03 | 5.27 | 7.46 |
| 3 | 19.71 | 26.35 | 5.01 | 6.91 |
| 4 | 16.39 | 24.68 | 3.82 | 6.40 |
| 5 | 14.70 | 23.06 | 4.49 | 5.93 |

Table 3. Simulation Results and Theoretical Expectations Ne = 72, r = . 50.

| t | $V_A$ |  | $V_D$ |  |
|---|---|---|---|---|
|  | sim. | theor. | sim. | theor. |
| 0 | 10.06 | 8.00 | 1.89 | 2.00 |
| 1 | 8.95 | 7.94 | 2.02 | 2.33 |
| 2 | 8.49 | 7.88 | 2.07 | 2.36 |
| 3 | 7.80 | 7.82 | 2.05 | 2.32 |
| 4 | 8.06 | 7.75 | 1.96 | 2.27 |
| 5 | 7.31 | 7.68 | 2.01 | 2.21 |

Table 4. Simulation Results and Theoretical Expectations Ne = 72, r = .01

| t | $V_A$ |  | $V_D$ |  |
|---|---|---|---|---|
|  | sim. | theor. | sim. | theor. |
| 0 | 31.15 | 31.21 | 7.69 | 7.61 |
| 1 | 29.96 | 30.60 | 6.04 | 7.54 |
| 2 | 24.24 | 29.99 | 4.93 | 7.31 |
| 3 | 22.59 | 29.38 | 4.87 | 7.06 |
| 4 | 19.46 | 28.78 | 4.37 | 6.82 |
| 5 | 17.67 | 28.18 | 4.20 | 6.59 |

1. The variance in simulation are those of progeny while theoretical expectations belong to the individuals selected as parents from that progeny. So in theoretical expectations two step sampling which is the case in most agricultural populations was not carried out. Such a consideration was done in a previous study on additive variance and approach was found to be better than the classical one is, although simulation results still showed faster decrease (Kavuncu, 1984). It may be worthwhile to study whether the sampling step to get the parents of next generation may have non–trivial effects on the expected value of dominance variance as well.

2. The variation in the number of offspring per mating was realized in simulation, but not in theoretical expectations. This realization must be made also in theoretical studies on quantitative genetic processes (see Wright 1969, p. 215, for an evaluation).

3. The reference population was subject to sampling in simulation, whereas the theoretical expectations was calculated deterministically.

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