REMARKS ON THE EVOLUTIONARY EFFECT OF NATURAL SELECTION

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ABSTRACT

The so-called "Fundamental Theorem of Natural Selection", that the mean fitness of a population increases with time under natural selection, is known not to be true, as a mathematical theorem, when fitnesses depend on more than one locus. Although this observation may not have particular biological relevance, (so that mean fitness may well increase in the great majority of interesting situations), it does suggest that it is of interest to find an evolutionary result which is correct as a mathematical theorem, no matter how many loci are involved. The aim of the present note is to prove an evolutionary theorem relating to the variance in fitness, rather than the mean: this theorem is true for an arbitrary number of loci, as well as for arbitrary (fixed) fitness parameters and arbitrary linkage between loci. Connections are briefly discussed between this theorem and the principle of quasi-linkage equilibrium.

The "Fundamental Theorem"

THE "Fundamental Theorem of Natural Selection" (FTNS: FISHER 1930) that the mean fitness of a population increases with time (at least under certain assumptions, most notably that fitness depends on the genetic constitution at a single locus) has had considerable influence in population genetics, since it appears to quantify a central theme of the Darwinian theory. The theorem is, however, open to criticism in two ways. First, it is no longer necessarily true as a mathematical theorem when fitness depends, as it surely must, on the genetic constitution at two or more loci (LEWONTIN and KOJIMA 1960; MORAN 1964. FISHER's so-called multi-locus proof (1958) is quite vacuous, and many multi-locus counter-examples to the FTNS are now available). Second, when total population size is held approximately constant by extrinsic factors, it is not at all evident (CROW and KIMURA, 1970) what the biological content of the theorem, even if it were true mathematically, really is.

In order to maintain the FTNS, at least in part, one might attempt to prove it under certain, perhaps biologically realistic, assumptions. The principle of quasi-linkage equilibrium (QLE) (KIMURA, 1965) is such an attempt. This principle states, for two loci with two alleles per locus, that with small selective differences and rather loose recombination, a function of gametic frequencies (denoted by Z later in this paper) soon reaches effective constancy. When this situation obtains, the rate of change of mean fitness is essentially equal to the additive gametic variance. Since the latter must be non-negative, the FTNS prevails. A precise definition of this principle has recently been given by NAGYLAKI (1976), and later in this paper we touch upon the relation between NAGYLAKI's results and that given in the following section.

A second approach to saving the FTNS in part is to show that it is true under certain restrictions on the fitness values (EWENS 1969; KARLIN 1975). This approach is of limited usefulness since difficulties arise in showing that if the fitness restrictions "almost" hold, then the theorem is "almost" true. Altogether there seems to be considerable difficulty in finding a rigorously mathematically correct version of the FTNS which is true in a broad range of biological situations. Thus while the mathematical validity of a theorem is not necessarily related to its biological usefulness, it is of some interest to find some mathematical theorem which is true for an arbitrary number of loci, at least under certain conditions.

In this paper we prove such a theorem. It concerns the evolutionary effect of natural selection on the *variance* in fitness, rather than the *mean*. The theorem relates to the additive gametic variance, which plays a central role, as noted above, in the QLE concept. The theorem is already well known for one and two loci.

Additive gametic variance principle

We consider an indefinitely large population mating at random, with fixed fitness values, with time considered as "discrete."

THEOREM. No matter how many loci fitness depends on, how many alleles exist at each locus, or what the recombination fraction is between loci, the effect of natural selection is always to make the additive gametic variance ultimately zero.

PROOF. Although the proof of this theorem is known for two loci with two alleles at each locus, we outline first a form of proof for this case which extends readily to an arbitrary number of loci.

It is useful to adopt a non-standard notation and label the loci A_1 and A_2, with alleles A_{11} and A_{12} at the locus A_1 and alleles A_{21} and A_{22} at the locus A_2. Let gamete frequencies be x_1 (of A_{11} A_{21}), x_2 (of A_{11} A_{22}), x_3 (of A_{12} A_{21}) and x_4 (of A_{12} A_{22}). The standard recurrence relations for these frequencies can most usefully be written (see KARLIN 1975, p. 366) as

$$\begin{aligned} \bar{W} x_1' &= w_1 x_1 + D, \\ \bar{W} x_2' &= w_2 x_2 - D, \\ \bar{W} x_3' &= w_3 x_3 - D, \\ \bar{W} x_4' &= w_4 x_4 + D. \end{aligned} \tag{1}$$

Here $\bar{W}$ is the mean fitness of the population, the w_i are the so-called "marginal gametic fitness" and D is a term which involves gamete frequencies, the fitness of the double heterozygote and the recombination fraction between the two loci. At equilibrium, $x_i' = x_i$: appropriate summations if (1) then yield, for the equilibrium frequencies,

$$\begin{aligned} &\Sigma x_i (w_i - \bar{W}) &&= 0, &&\text{(2a)}\\ &x_2 (w_2 - \bar{W}) + x_4 (w_4 - \bar{W}) &&= 0, &&\text{(2b)}\\ &x_3 (w_3 - \bar{W}) + x_4 (w_4 - \bar{W}) &&= 0. &&\text{(2c)} \end{aligned}$$

We consider now variances in fitness. The total gametic variance $\sigma^2{}_{TG}$ is defined as

$$\sigma^2{}_{TG} = 2\Sigma x_i (w_i - \bar{W})^2. \tag{3}$$

This may be partitioned into an additive and a non-additive component, as follows. Define V by

$$\begin{aligned} \tfrac{1}{2}V = x_1 (w_1 - \bar{W} - m)^2 + x_2 (w_2 - \bar{W} - m - a)^2 + x_3 (w_3 - \bar{W} - m - b)^2 \\ + x_4 (w_4 - \bar{W} - m - a - - b)^2. \end{aligned} \tag{4}$$

For any values of x_2, x_2, x_3 and x_4, we may minimize V with respect to m, a and b. The minimum value is the non-additive component $\sigma^2{}_{NAG}$ of the total gametic variance; the additive component $\sigma^2{}_{AG}$ is then found by subtraction: $\sigma^2{}_{AG} = \sigma^2{}_{TG} - \sigma^2{}_{NAG}$. Note that if the minimum value of V occurs at $m = a = b = 0$, then $\sigma 2_{TG} = \sigma^2{}_{NAG}$ and thus $\sigma^2{}_{AG} = 0$. Now the minimizing equations $\partial V / \partial a = \partial V / \partial b = 0$ yield

$$\begin{aligned} \Sigma x_i (w_i - \bar{W}) - m - a (x_2 + x_4) - b (x_3 + x_4) &= 0,\\ x_2 (w_2 - \bar{W}) + x_4 (w_4 - \bar{W}) - m (x_2 + x_4) - a (x_2 + x_4) - b x_4 &= 0,\\ x_3 (w_3 - \bar{W}) + x_4 (w_4 - \bar{W}) - m (x_3 + x_4) - a x_4 - b (x_3 + x_4) &= 0. \end{aligned} \tag{5}$$

Using equations (2), we see that at any equilibrium point of the recurrence system (1), equations (5) reduce to

$$\begin{aligned} m + a (x_2 + x_4) + b (x_3 + x_4) &= 0,\\ m (x_2 + x_4) + a (x_2 + x_4) + b x_4 &= 0,\\ m (x_3 + x_4) + a x_4 + b (x_3 + x_4) &= 0. \end{aligned} \tag{6}$$

If we assume $x_i > 0$ at the equilibrium point, there is a unique solution, (clearly $m = a = b = 0$) to equations (6). This implies immediately that $\sigma^2{}_{AG} = 0$ at equilibrium. (Before proceeding it is of value to discuss the uniqueness of the solution of (6). In the present case this can be shown easily by checking that the determinant of the matrix of coefficients is non-zero when $x_i > 0$. An alternative approach, which we use when generalizing the above result, is to note that, if $x_i > 0$, V is a nondegenerate quadratic form in m, a and b and hence admits a unique minimum value).

The proof in the general case follows similar lines. Suppose we have l loci with n_j alleles possible at the j^{th} locus. Follow the notation established above and A_{jk} be the k^{th} allele at the j^{th} locus. Suppose the $T = n_1 n_2 \ldots n_l$ gametes are labelled in some dictionary order and let the frequency of the i^{th} such gamete be x_i. Then the recurrence relations generalizing (1) are of the form

$$\bar{W} x_i' = w_i x_i \pm D_{i1} \pm \ldots, i = 1,2,.., T. \tag{7}$$

Here, as above, $\bar{W}$ is the mean fitness and w_i a "marginal gametic fitness." The quantities D_{i1}, D_{i2}, ... , involve gamete frequencies, recombination fractions between the various loci and multiple heterozygote fitnesses, (see, for example, FELDMAN, FRANKLIN and THOMSON 1974, Table 1, for the case of three loci). The D values have the property that if the recurrence relations (7) are summed over all gametes containing any specified allele A_{jk}, the quantities D_{11}, D_{12}, ... cancel exactly and an equation of the form

$$\bar{W} \Sigma x_i' = \Sigma w_i x_i \tag{8}$$

is obtained, where both summations are over all gametes containing the allele A_{jk}. (The easiest way to see why such a cancellation occurs is to note that $\Sigma x_i'$ is the new frequency of A_{jk} and that recombinational events, once x_1, x_2, ... , x_T are given, will change gamete frequencies but not allele frequencies). Thus at equilibrium

$$\sum_{\text{all}} x_i (w_i - \bar{W}) = 0, \tag{9a}$$

$$\sum_{\text{allele}} x_i (w_i - \bar{W}) = 0. \tag{9b}$$

Here the summation "all" is over all T gametes while the summation over "allele" is over all gametes containing any specified allele: if this allele is at the j^{th} locus, there will be T/n_j terms in this sum. Equation (9a) is the direct generalization of (2a) and equation (9b) generalizes (2b) and (2c), in (2b) the allele summed over being A_{22} and in (2c), A_{12}. We may suppose without loss of generality that all alleles at all loci occur with positive frequency at the equilibrium point: (if they do not, we simply restrict our consideration to those which do).

We now turn to the additive gametic variance. The total gametic variance is

$$\sigma^2_{TG} = 2 \sum_{\text{all}} x_i (w_i - \bar{W})^2, \tag{10}$$

and, as for two loci, may be partitioned into an additive and a non-additive component. Suppose the first gamete is taken as a reference and with respect to it define additive components a_{1p}, a_{2q}, ... , for the i^{th} gamete (where it is assumed that the i^{th} gamete is A_{1p} A_{2q} . . . .). We minimize the expression V, defined by

$$\tfrac{1}{2} V = \sum_{\text{all}} x_i (w_i - \bar{W} - m - a_{1p} - a_{2q} - \ldots)^2 \tag{11}$$

with respect to m and the a_{jk}'s. The minimizing equations yield

$$\sum_{\text{all}} x_i (w_i - \bar{W} - m - a_{1p} - a_{2q} \ldots) = 0 \tag{11a}$$

$$\sum_{\text{allele}} x_i (w_i - \bar{W} - m - \ldots) = 0 \tag{11b}$$

where the first summation is over all T gametes and the second is over all those containing any specified allele A_{jk} (it is difficult to devise a simple notation for the constants a_{rs} which arise in the second summation). Under the assumption that only those alleles which arise with positive frequency at the equilibrium point are considered, V is a nondegenerate quadratic form in m, a_{11}, a_{12}, ... , and hence has a unique minimum with respect to those parameters. Comparison of (9) with (11) then shows that, at any equilibrium point of the system, the (unique) solution of (11) is $m = a_{11} = a_{12} \ldots . = 0$. Thus at any equilibrium point the additive gametic variance is zero and the theorem is proved.

Remark TURNER (1969) has directed attention verbally to the possibility that an interesting effect of natural selection is to make certain components of the genetic variance zero. The above may be thought of as a quantification of TURNER's statement.

If we adopt the usual definition of heritability in the narrow sense as the ratio of the additive gametic variance to the total variance, the theorem may be restated thus: no matter how many loci fitness depends on, how many alleles appear at each locus, or what the linkage arrangement between loci, natural selection always acts so at ultimately to make heritability zero. (This is again well known when fitness depends on one or two loci). Note that, as with the above theorem, this conclusion assumes random mating, discrete time and fixed fitness values.

Remarks on QLE

In the above it has been remarked that there is some relation between the QLE principle and the result of the theorem just proved.

There has been a recent tendency to word the QLE principle thus: for two loci and two alleles at each locus, when linkage is loose and selective differences small, a state (of QLE) soon emerges in the evolution of the system (1) where the quantity $Z = x_1\ x_4/x_2\ x_3$ becomes essentially constant. But when Z is constant the change in mean fitness equals the additive gametic variance. Thus in general we may normally expect the change in Z to be sufficiently small so that the change in mean fitness is very close to the additive gametic variance, and is hence positive.

To check the theorem of the preceding section numerically I computed iterations of the recurrence relation (1) in a variety of different circumstances. In each generation various statistics, including Z and the additive gametic variance, were computed. In not one case did the QLE principle, as stated loosely above, hold. More precisely, the change in mean fitness, both absolutely and relatively, was normally considerably less than the change in Z itself, (sometimes by a factor of 100 or 1000).

Clearly a more precise definition of QLE is desirable. This has recently been given by NAGLYAKI (1976), and is best discussed by using the "continuous time" equation for change in mean fitness (FELDMAN and CROW 1975):

$$\frac{d\bar{W}}{dt} = \sigma^2_{AG} + \frac{2E}{PZ}\ \frac{dZ}{dt} \tag{12}$$

Here E is a measure of epistasis and P a function of gamete frequencies whose exact definition is not important for the present argument. Whether or not the mean fitness increases depends on the relative magnitudes of the two terms on the right-hand side of (12), since the first term is non-negative and the second term is unrestricted in sign. This remark was made by FELDMAN and CROW (1970, p. 386) and the present approach really stems from this observation.

The crucial contribution of NAGYLAKI (1975) is to show that if the parameter s is a measure of the selective differences between genotypes, then during most of the gene frequency change σ^2_{AG} and dZ/dt are of order s^2, while E is of order s. (P and Z are of order unity and are not central to the present argument). This implies, assuming s to be small, that during most of the time that gene frequency changes are substantial the second term on the right-hand side of (12) is of an order of magnitude less than the first term, so that approximately

$$\frac{d\bar{W}}{dt} \approx \sigma^2_{AG} \,. \tag{13}$$

This is NAGYLAKLI's more precise statement of the QLE principle and should be used instead of the inaccurate statement that (13) holds because dZ/dt is small compared to $d\bar{W}/dt$.

The result of this paper implies a second order-of-magnitude argument. Suppose the system (1) is moving towards an equilibrium point at which Z is not unity. Let δ be a measure of the deviations of the gamete frequencies from their equilibrium values. Then the theorem proved above shows that σ^2_{AG} is of order δ^2, whereas the other two terms in (12) are of order δ. Thus near an equilibrium point the second term on the right-hand side of (12) will dominate the first term, despite the order-of-magnitude arguments relating to fitness differentials just outlined. Thus near an equilibrium point $\bar{W}$ may decrease, (a result already explicit in NAGYLAKI's argument). More generally, the three terms in (12) are respectively of order $s^2\delta$, $s^2\delta^2$ and $s^3\delta$ so that possible decreases in the mean fitness will arise when δ and s are of the same order of magnitude.

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