THE EVOLUTION OF ONE- AND TWO-LOCUS SYSTEMS[1]

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ABSTRACT

Assuming age-independent fertilities and mortalities and random mating, continuous-time models for a monoecious population are investigated for weak selection. A single locus with multiple alleles and two alleles at each of two loci are considered. A slow-selection analysis of diallelic and multiallelic two-locus models with discrete nonoverlapping generations is also presented. The selective differences may be functions of genotypic frequencies, but their rate of change due to their explicit dependence on time (if any) must be at most of the second order in s, (i.e., $O(s^2)$), where s is the intensity of natural selection. Then, after several generations have elapsed, in the continuous time models the time-derivative of the deviations from Hardy-Weinberg proportions is of $O(s^2)$, and in the two-locus models the rate of change of the linkage disequilibrium is of $O(s^2)$. It follows that, if the rate of change of the genotypic fitnesses is smaller than second order in s (i.e., $o(s^2)$), then to $O(s^2)$ the rate of change of the mean fitness of the population is equal to the genic variance. For a fixed value of s, however, no matter how small, the genic variance may occasionally be smaller in absolute value than the (possibly negative) lower order terms in the change in fitness, and hence the mean fitness may decrease. This happens if the allelic frequencies are changing extremely slowly, and hence occurs often very close to equilibrium. Some new expressions are derived for the change in mean fitness. It is shown that, with an error of $O(s)$, the genotypic frequencies evolve as if the population were in Hardy-Weinberg proportions and linkage equilibrium. Thus, at least for the deterministic behavior of one and two loci, deviations from random combination appear to have very little evolutionary significance.

I. INTRODUCTION

IN 1930 FISHER enunciated the Fundamental Theorem of Natural Selection—that the rate of increase of fitness is equal to the genic variance—and invoked it as the main underpinning of his view of evolution (FISHER 1930). He held that evolution occurs primarily by the deterministic increase in fitness of large populations under the action of natural selection. He recognized that mutation supplies the raw material for genetic diversity, but to random drift he assigned a relatively minor role. WRIGHT (1931, 1970) emphasized that, due to pleiotropy, epistasis, and selection for an intermediate optimum, the fitness surface has many selective peaks. Small populations can "sample" this surface by random drift, sometimes crossing a saddle from a lower selective hill to a higher one. He pointed

out that if a species is divided into many such small populations, which exchange relatively few migrants, selective dispersion may enable it to reach the highest peak on the surface. The neutral theory of KIMURA (1968) and of KING and JUKES (1969) ascribes much of evolution, especially at the molecular level, to mutation and random drift. The ascertainment of the level and range of applicability of these theories and of their comparative importance in the evolution of phenotypes is, if broadly understood, one of the central problems of population genetics.

Another important problem of evolutionary theory has been the assessment of the size of deviations from random combination, i.e., from Hardy-Weinberg proportions and linkage equilibrium. Systems in Hardy-Weinberg ratios and linkage equilibrium are completely described by gene frequencies, and have much simpler dynamics than those for which random combination fails, thereby necessitating the use of genotypic proportions for a full specification. It is of great interest to attack this problem under the biologically common conditions of random mating, loose linkage or independent assortment, and weak selection.

For the continuous-time model employed by FISHER (1930), KIMURA (1958) proved that, even with constant genotypic fitnesses, departures from Hardy-Weinberg proportions and linkage equilibrium will give rise to additional terms in the time-derivative of the mean fitness. Since these terms may sometimes be negative, the mean fitness may decrease. In nearly all biological circumstances, deviations from Hardy-Weinberg proportions and linkage equilibrium will occur in populations unless generations are discrete and nonoverlapping (NAGYLAKI and CROW 1974).

With discrete nonoverlapping generations, provided the fertilities of matings may be expressed as products of factors corresponding to the genotypes, Hardy-Weinberg proportions will be attained in just one generation of random mating (BODMER 1965; KEMPTHORNE and POLLAK 1970). For a single locus with an arbitrary number of alleles, several authors have demonstrated in this Hardy-Weinberg model that the change in mean fitness is nonnegative, being zero only at equilibrium, but it is not exactly equal to the genic variance (SCHEUER and MANDEL 1959; MULHOLLAND and SMITH 1959; ATKINSON, WATTERSON and MORAN 1960; KINGMAN 1961a,b). EWENS (1969a,b) has shown that if fitnesses are additive between loci, the mean fitness is nondecreasing, and observed that this generally implies nondecreasing mean fitness for sufficiently weak additive epistasis. The work of MORAN (1964) and EWENS (1969c, pp. 94–96) shows that even in the general two-locus, two-allele case the mean fitness may decrease.

Since a complete formulation of continuous selective models without age-structure was given only recently (NAGYLAKI and CROW 1974), the effect of deviations from Hardy-Weinberg proportions on the change in fitness could not be evaluated. Considerable attention has been devoted, however, to the departures from the Fundamental Theorem due to linkage disequilibrium in Hardy-Weinberg models, and, as a result, much insight into the dynamics of two-locus systems has been gained. Based on his study of diploid and haploid discrete-time systems, KIMURA (1965) suggested that with small selective differences, and loose linkage

or independent assortment, a population rapidly reaches a state he named "quasi-linkage equilibrium" (hereafter referred to as QLE). Motivated by his work, we shall say a diallelic two-locus system is in QLE if the linkage disequilibrium ratio, Z, varies more slowly than the gametic frequencies. In this condition, the Fundamental Theorem of Natural Selection is generically approximately valid. QLE has been discussed from a slightly different point of view by WRIGHT (1967). KIMURA clearly recognized that it would take several generations to reach QLE, and formulae for the approximate time required in continuous and discrete models have been given (NAGYLAKI 1974). Asymptotic analyses by FELDMAN and CROW (1970) suggested that QLE could *not* be interpreted as the more rapid *ultimate* rate of convergence to equilibrium of Z than of the gametic frequencies. It was later proved generally in all models that *asymptotically* Z and the gametic frequencies have the same time-dependence, and an approximate formula was presented for the beginning of the asymptotic time region (NAGYLAKI 1974).

The first rigorous proof of QLE, as defined above, was obtained by CONLEY (1972) in a continuous Hardy-Weinberg model. Using the qualitative theory of dynamical systems, he showed that after a short time (the same as that given in NAGYLAKI 1974) the time-derivative of the linkage disequilibrium D is at most of the second order in s (i.e., $O(s^2)$), the intensity of natural selection. It follows at once that the same is generally true for Z. CONLEY's treatment was elaborated and generalized to multiple loci and multiple alleles by SHAHSHAHANI (1974). HOPPENSTEADT (1976) simultaneously explored deviations from Hardy-Weinberg proportions and linkage equilibrium in a continuous two-locus, two-allele system by supposing that the fertilities of matings depend only on the female genotype, the male and female genotypic frequencies are the same, and (implicitly) crossovers occur immediately *after* fertilization. He established that for sufficiently slow selection, if the initial linkage disequilibrium is small ,the mean fitness is nondecreasing.

With mathematical techniques similar to HOPPENSTEADT's (1976), we shall investigate departures from Hardy-Weinberg ratios and linkage disequilibrium and their contribution to the change in mean fitness for weak selection. In Section II, we shall consider continuous time models for a single locus with multiple alleles in a diploid organism and two alleles at each of two loci for both diploids and haploids. The models analyzed will be the most general ones possible for a panmictic monoecious population with age-independent fertilities and mortalities. In Section III, we shall carry out the corresponding calculations for Hardy-Weinberg two-locus diallelic and multiallelic models with discrete nonoverlapping generations. Some new expressions for the change in mean fitness will be derived in Sections II and III. The evolution of the genotypic frequencies will be studied in Section IV.

II. CONTINUOUS TIME

We shall rely heavily on the formulation of continuous selective models in NAGYLAKI and CROW 1974. At least for a single locus with multiple alleles, it has

been established that, as long as the mating frequencies and birth and death rates are age-independent, this formulation is completely general (CORNETTE 1975).

1. *Single locus*

Let the alleles at the locus under considering be A_i, $i = 1, 2, \ldots$. We denote the frequencies of the allele A_i and the ordered genotype A_iA_j by p_i and P_{ij} ($=P_{ji}$), and use

$$Q_{ij} \equiv P_{ij} - p_ip_j \tag{1}$$

as measures of the departures from Hardy-Weinberg proportions. We suppose all the fertilities differ from the constant b and all the mortalities from each other by quantities of the order of the constant s. If the selective differences are constant, s can always be taken as the largest selection intensity. Let m_i and m represent the Malthusian parameter of the allele A_i and the mean fitness of the population. With random mating, our basic equations are (NAGYLAKI and CROW 1974)

$$\dot{Q}_{ij} = -bQ_{ij} + sf_{ij}(P,t) \ , \tag{2}$$

$$\dot{p}_i = p_i(m_i - m) \ , \tag{3}$$

where the superior dot signifies the time-derivative, and $f_{ij}(P,t)$ is a complicated function of birth and death rates, genotypic frequencies, and possibly of time, of order unity (i.e., bounded as $s \to 0$).

By the usual variation-of-parameters formula, we may write the solution of (2) as

$$Q_{ij}(t) = Q_{ij}(0)e^{-bt} + se^{-bt} \int_0^t e^{b\tau}f_{ij}[P(\tau) \ , \ \tau]d\tau \ . \tag{4}$$

Let t_1 be the shortest time such that $|Q_{ij}(0)|e^{-bt_1} \leqslant s$ for all i,j. Of course, if the system starts sufficiently close to Hardy-Weinberg proportions, t_1 will be zero. Biology allows us to assume that f_{ij} is uniformly bounded for all $t \geqslant 0$. Then, for $t \geqslant t_1$, $Q_{ij} = O(s)$, so we write $Q_{ij}(t) = sQ^0_{ij}(t)$. Typically, for an approximately stabilized population, b is close to unity, so t_1 will rarely be more than several generations. Thus, the system approaches the Hardy-Weinberg surface $Q_{ij} = 0$ to $O(s)$ very rapidly, but at $t = t_1$ it is still very far from gene frequency equilibrium, the gene frequency change being quite small (crudely, st_1) from $t = 0$ to $t = t_1$. For $t \geqslant t_1$, (2) reads

$$\dot{Q}^0_{ij} = - bQ^0_{ij} + f_{ij}(P , t) \ . \tag{5}$$

From (1), (3), and (5), we conclude that $\dot{P}_{ij} = O(s)$ for $t \geqslant t_1$. We posit that the explicit dependence of the selection coefficients on time, if any, is quite weak, in fact, of $O(s^2)$. This means

$$\frac{\partial f_{ij}}{\partial t} = O(s) \ . \tag{6}$$

Notice that arbitrary dependence on genotypic frequencies is permitted. From (5) and (6), we obtain

$$\frac{d}{dt} [Q^0_{ij} - b^{-1}f_{ij}(P , t)] = - b [Q^0_{ij} - b^{-1}f_{ij}(P , t)] + O(s) \ , \tag{7}$$

whence, by a formula analogous to (4), it follows that

$$Q^0{}_{ij}(t) - b^{-1}f_{ij}[P(t),t] = \{Q^0{}_{ij}(t_1) - b^{-1}f_{ij}[P(t_1),t_1]\}\,e^{-b(t-t_1)} + O(s)\,. \quad (8)$$

We define t_2 ($\geqslant t_1$) as the shortest time such that

$$|Q^0{}_{ij}(t_1) - b^{-1}f_{ij}[P(t_1),t_1]\,|\,e^{-b(t_2-t_1)} \leq s\,. \quad (9)$$

Usually, $t_2 - t_1$ will be several generations. More generally, the order of magnitude of t_1 and t_2 will be $t_1 \approx -b^{-1}\ln s$ and $t_2 \approx 2t_1$. Our results concern the slow evolution of the system near the Hardy-Weinberg surface for $t \geqslant t_2$. Since the population is not close to equilibrium until roughly the much longer time $t_3 \approx 1/s$ has elapsed, the results are not asymptotic, and cannot be deduced by linear analysis. For $t \geqslant t_2$, (8) implies

$$Q^0{}_{ij}(t) = b^{-1}f_{ij}(P,t) + O(s)\,. \quad (10)$$

Therefore, recalling (6) and that $\dot{P}_{ij} = O(s)$, we find $\dot{Q}^0{}_{ij}(t) = O(s)$ or

$$\dot{Q}_{ij}(t) = O(s^2)\,,\quad t \geqslant t_2\,. \quad (11)$$

Equation (11) is the main dynamic result of this subsection. Due to its close biological and mathematical analogy to QLE, we shall designate this approximate constancy of the deviations from Hardy-Weinberg ratios "quasi-Hardy-Weinberg equilibrium" or QHW.

We shall now apply (11) to the Fundamental Theorem. The rate of change of the mean fitness is (KIMURA 1958)

$$\dot{\bar{m}} = V_g + \bar{\dot{m}} + \overline{\overset{\circ}{\theta}d}\,, \quad (12)$$

where V_g is the genic variance, the d_{ij} are the dominance deviations,

$$\theta_{ij} = P_{ij}/(p_ip_j) = Q_{ij}/(p_ip_j) + 1\,, \quad (13)$$

$$\overset{\circ}{\theta} = \frac{d}{dt}\ln\theta\,, \quad (14)$$

and the bars indicate averages over the genotypes. Clearly, $V_g = O(s^2)$. We assume that $\dot{m}_{ij} = o(s^2)$ (i.e., $|\dot{m}_{ij}|/s^2 \to 0$ as $s \to 0$ for all i,j). This means that the variation of the genotypic fitnesses with time, either directly or through the genotypic proportions, must be rather slow. This condition is much stronger than (6), which sufficed for (11). But (11), (13), (14), and the fact that $Q_{ij}(t)$, $p_i(t)$, and d_{ij} are all of $O(s)$ inform us that for $t \geqslant t_2$ the last term in (12) is of $O(s^3)$. Therefore, generally, for sufficiently weak selection the genic variance term dominates in (12), the others being negligible as $s \to 0$, and the mean fitness is nondecreasing.

It is important to realize that, although the above result is generally true, it may fail to hold in some small regions. The genic variance can be *smaller* than a constant of the order of unity times s^2. Then the second and third terms in (12), which may be negative, may dominate. This exception is particularly likely to occur close to an equilibrium. Since they are combinations of time-derivatives, the last two terms in (12) obviously vanish at equilibrium. If μ_i is the average effect of A_i, the genic variance is (KIMURA 1958)

$$V_g = 2\sum_i \mu_i\dot{p}_i\,. \quad (15)$$

Hence, $\dot{V}_g = 0$ at equilibrium. (We may also conclude this because all other terms in (12) are zero at equilibrium.) Therefore, if V_g were to approach zero faster than either $\overset{\circ}{m}$ or $\overline{\theta d}$ as the system tends to a stable equilibrium, $\overset{\circ}{m}$ may be negative sufficiently near that equilibrium. Such exceptions are expected to be local and without much evolutionary significance. While there is substantial gene frequency change, (15) leads us to believe that the genic variance should generally be of the order of s^2.

Our results are easily represented diagrammatically in the two-allele case. For brevity, let us write $p = p_1$, $q = p_2$, $Q = Q_{12}$. It is trivial to see that $Q_{11} = Q_{22} = -Q$. The coordinates Q,p are more convenient than P_{11}, $2P_{12}$, P_{22} of the customary de Finetti plot. The constraints $P_{11} \geqslant 0$, $P_{22} \geqslant 0$, $P_{11} + P_{22} \leq 1$ imply that the system evolves in the region bounded by the three parabolas in Figure 1. Hardy-Weinberg proportions correspond to the dashed line $Q = 0$, $0 \leq p \leq 1$. A typical trajectory is sketched in Figure 1. The times are roughly $t_1 \approx -b^{-1}\ln s$. $t_2 \approx 2t_1$, and $t_3 \approx s^{-1}$. For $0 \leq t \leq t_1$, p changes only by about $st_1 \approx -b^{-1}s\ln s$. while Q is reduced to $O(s)$ in this short time. Hence, the trajectory is nearly horizontal. For $t_1 \leq t \leq t_2$. the changes in p and Q are comparable and small, both being about $-b^{-1}s\ln s$. For $t \geq t_2$. $Q = O(s^2)$, so during $t_2 \leq t \leq t_3$ Q changes by only about $s^2(t_3 - t_2) \approx s^2 t_3 \approx s$, while p approaches equilibrium quite closely. Therefore, during this long time the trajectory is nearly vertical. Note that the rate of motion along the trajectory is much faster on the "horizontal" than the "vertical" portion, though the rate of gene frequency change is always $\dot{p} = O(s)$. The equilibrium satisfies $Q(\infty) = O(s)$. The Fundamental Theorem holds on the "vertical" part, $t \geq t_2$.

2. *Two Loci, Diploids*

We suppose that there are two loci. with alleles A_1, A_2 at one and B_1, B_2 at the other, c is the recombination fraction, and both types of double heterozygotes have the same birth rate, b. Letting the subscripts 1, 2, 3, 4 represent the gametes A_1B_1, A_1B_2, A_2B_1, A_2B_2, we may still use p_i and P_{ij} for gametic and genotypic frequencies and Q_{ij} as an index of departure from Hardy-Weinberg. We define $\varepsilon_i = +1$, $i = 1, 4$; $\varepsilon_i = -1$, $i = 2$. 3 and the actual and Hardy-Weinberg linkage disequilibria, $D = P_{14} - P_{23}$ and $D_0 = p_1p_4 - p_2p_3$. The system evolves governed by the differential equations

$$\dot{Q}_{ij} = -bQ_{ij} + \varepsilon_i\varepsilon_j bc^2D^2 + sf_{ij}(P,t) \; , \tag{16}$$

$$\dot{p}_i = p_i(m_i - \overline{m}) - \varepsilon_i\alpha D \; , \tag{17}$$

$$\dot{\boldsymbol{D}} = -C\boldsymbol{D} + s\boldsymbol{g}(P,t) \; , \tag{18}$$

where $\alpha = bc$ and the matrix C and vector $\boldsymbol{D}$ read

$$C = b \begin{pmatrix} 1+c & -1 \\ c & 0 \end{pmatrix} \qquad \boldsymbol{D} = \begin{pmatrix} D \\ D_0 \end{pmatrix} \tag{19}$$

The selection terms f_{ij} and g correspond to (but, of course, are not equal to) f_{ij} in (2).
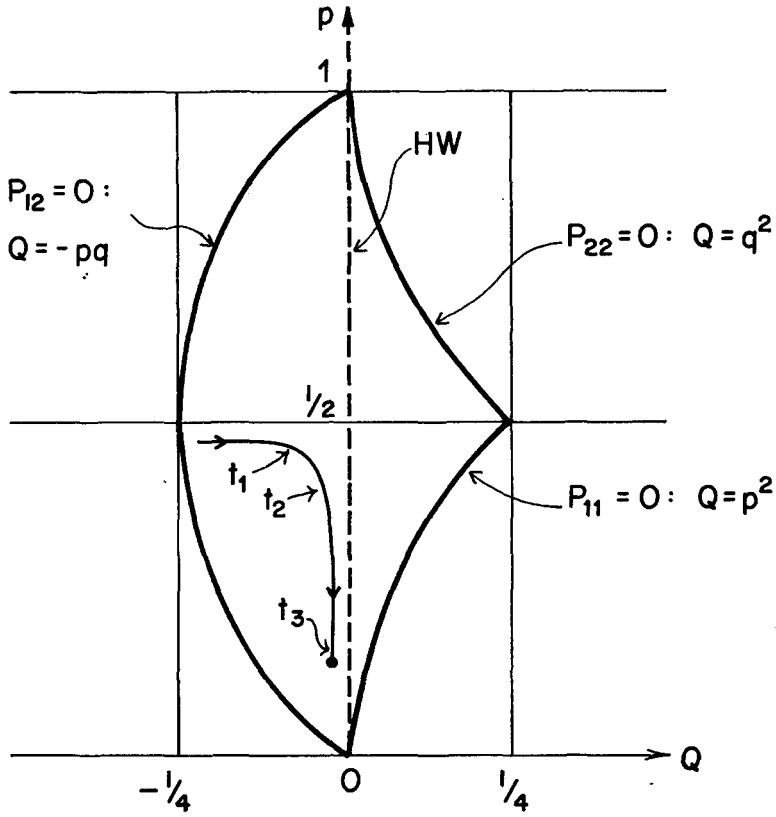
FIG. 1.—The evolution of a typical diallelic single locus system.

Following Subsection II.1, we show directly that we rapidly reach both QLE and QHW. Observing that the eigenvalues of C are b and α, we now define t_1 as the shortest time such that

$$\max[\,|D(0)|e^{-\alpha t_1},\ |D_0(0)|e^{-\alpha t_1},\ |Q_{ij}(0)|e^{-bt_1}] \le s \ . \tag{20}$$

Writing the analogue of (4) for (16) and (18), we see immediately that for $t \ge t_1$ $Q_{ij} \equiv sQ^0{}_{ij}$ and $D \equiv sD^0$ are of $O(s)$. Thus

$$\dot{Q}^0{}_{ij} = -\, bQ^0{}_{ij} + f_{ij}(P,t) + O(s) \ , \tag{21}$$

$$\dot{D}^0 = -\, CD^0 + g(P,t) \ . \tag{22}$$

For $t \ge t_1$, $\dot{P}_{ij} = O(s)$, so with the assumption (6) on f_{ij} and g we find easily that (7) and the equation

$$\frac{d}{dt}\,[D^0 - C^{-1}g(P,t)] = -\,C[D^0 - C^{-1}g(P,t)] + O(s) \tag{23}$$

hold. Let t_2 be the shortest time such that $e^{-\alpha(t_2-t_1)} \le s$. For fairly loose linkage or

independent assortment, this will be only slightly longer than the time defined by (9). Hence, for $t \geq t_2$, we still have (10), as well as

$$\boldsymbol{D}^0(t) = C^{-1}\mathbf{g}(P,t) + O(s) ,\tag{24}$$

from which it follows that

$$\ddot{Q}_{ij}(t) = O(s^2) , \quad \dot{\boldsymbol{D}}(t) = O(s^2) , \quad t \geq t_2 .\tag{25}$$

KIMURA (1958) calculated the derivative of the mean fitness for an arbitrary number of alleles at two loci to be

$$\dot{m} = V_g + \dot{m} + \sum_{n=1}^{2} \overline{\overset{\circ}{\theta}{}^{(n)} d^{(n)}} + \overline{\dot{\phi}E} ,\tag{26}$$

where V_g is the genic variance (for both loci), $\overset{\circ}{\theta}{}^{(n)}$ corresponds to the departure from Hardy-Weinberg at locus n and $d^{(n)}$ to the dominance deviation at that locus, and ϕ and E are measures of linkage disequilibrium and epistasis. We again assume $\overline{\dot{m}} = o(s^2)$. By expressing $\theta^{(n)}$ and ϕ in terms of Q_{ij} and D_0, one can convince oneself that (25) implies for two alleles at each locus $\overset{\circ}{\theta}{}^{(n)} = O(s^2)$ and $\overset{\circ}{\phi} = O(s^2)$. Therefore, the Fundamental Theorem of Natural Selection will again hold for slow selection. As discussed in the previous subsection, where V_g is anomalously small, this conclusion may be false. By the two-locus generalization of (15), $V_g = 0$ where the gene frequencies are constant, so failure will most often occur near equilibrium.

Equation (26) is derived by first decomposing with respect to loci and then with respect to alleles within loci (KIMURA 1958). It is instructive to conform more closely to our dynamical treatment and decompose first with respect to gametes and then relative to alleles within gametes. We may allow an arbitrary number of alleles at each locus. Defining θ_{ij} for gametes as in (13), and writing μ_i for the average effect of a gamete and Δ_{ij} for the "dominance" deviation between gametes, KIMURA's (1958) method yields

$$\dot{\overline{m}} = 2 \sum_i \mu_i p_i + \overline{\dot{m}} + \overline{\overset{\circ}{\theta}\Delta}\tag{27}$$

$$= V_{gam} - 2\alpha D\mathcal{E} + \overline{\dot{m}} + \overline{\overset{\circ}{\theta}\Delta} ,\tag{28}$$

where V_{gam} is the gametic variance, corresponding precisely to the genic variance, and

$$E = \sum_i \varepsilon_i \mu_i\tag{29}$$

represents the epistasis in the average effect of the gametes. Returning to (27) and separating alleles in the first term by the same method leads to

$$\dot{m} = V_g + \overline{\dot{m}} + 2\overline{\overset{\circ}{\psi}I} + \overline{\overset{\circ}{\theta}\Delta} ,\tag{30}$$

in which I is the epistatic deviation within gametes and ψ represents the ratio of the gametic frequencies to the product of the corresponding allelic frequencies. Now (25) shows directly that $\overset{\circ}{\psi} = O(s^2)$ and $\overset{\circ}{\theta} = O(s^2)$ for the two-allele model.

3. *Two Loci, Haploids*

The haploid system evolves according to (17) with $D = D_0$, the Malthusian parameters of the gametes (m_i) prescribed, $\bar{m} = \sum_i p_i m_i$, and

$$\dot{D} = -\alpha D + sf(p,t) \ . \tag{31}$$

We now interpret b as the probability of a conjugation for any gamete, so that $\alpha = bc$ is the probability of recombination. With t_2 defined as in Subsection II.2 and the assumption (6) for f, a much simplified version of the above analysis gives

$$\dot{D}(t) = O(s^2) \ , \quad t \geq t_2 \ . \tag{32}$$

Let

$$E = \sum_i \varepsilon_i m_i$$

measure epistasis, $Z = p_1 p_4 / (p_2 p_3)$ be the linkage disequilibrium ratio, and $R = \sum_i p_i^{-1}$. Then (FELDMAN and CROW 1970)

$$\dot{\bar{m}} = V_g + \dot{\bar{m}} + E(RZ)^{-1} \dot{Z} \ . \tag{33}$$

From (32), we have $\dot{Z} = O(s^2)$ for $t \geq t_2$, and hence the above conclusion concerning the Fundamental Theorem for weak selection still holds.

The common tetrahedral representation of the system with the p_i as coordinates is not as well suited to displaying its dynamics as x and y, the frequencies of A_1 and B_1, and D. The system evolves in a three-dimensional region passing through the horizontal unit square $0 \leq x,y \leq 1$. For $t \leqslant t_1$, the motion is rapid and nearly vertical, while for $t \geqslant t_2$ it is slow, nearly horizontal, and observes the Fundamental Theorem. The detailed description of Figure 1 applies with only trivial and obvious modifications. The same picture may be employed in Section III.

III. DISCRETE TIME

We shall assume that the fertilities of matings are expressible as the products of factors associated with each of the genotypes. Then, with discrete nonoverlapping generations, Hardy-Weinberg ratios are attained in just one generation of random mating (BODMER 1965, KEMPTHORNE and POLLAK 1970). Thus, only the diploid and haploid two-locus models are of interest here.

1. *Diploids*

We employ the notation of Subsection II.2 for alleles and gametic and genotypic frequencies. With fitnesses w_{ij} we have (see, e.g., KIMURA and OHTA 1971, p. 90)

$$\bar{w}\Delta p_i = p_i(w_i - \bar{w}) - \varepsilon_i cD \ , \tag{34}$$

$$\Delta D = -cD + sf(p,t) \ , \tag{35}$$

where the linkage disequilibrium reads

$$D = w_{14} p_1 p_4 - w_{23} p_2 p_3 \ , \tag{36}$$

and the gametic frequencies are measured immediately after fertilization. From (35), we obtain the discrete analogue of (4):

$$D(t) = (1-c)^t D(0) + s(1-c)^t \sum_{t}^{\tau=t} (1-c)^{-\tau} f[p(\tau-1), \tau-1] . \quad (37)$$

(The sum is absent for $t = 0$.) Therefore, t_1 is now the minimum time such that $(1-c)^{t_1}|D(0)| \le s$. Hence, $D(t) = O(s)$ for $t \ge t_1$, and we may write $D(t) = sD^0(t)$ in (35):

$$\Delta D^0 = -cD^0 + f(p,t) . \quad (38)$$

Since $\Delta p_i = O(s)$ for $t \ge t_1$, (38) leads to

$$\Delta[D^0 - c^{-1}f(p,t)] = -c[D^0 - c^{-1}f(p,t)] + O(s) , \quad (39)$$

as long as the explicit time dependence of the selection coefficients is quite weak, in fact, of $O(s^2)$. More precisely, for (39) to follow from (38), the analogue of (6),

$$f[p(t), t+1] - f[p(t), t] = O(s) , \quad (40)$$

must hold. Equation (39) instructs us to define t_2 as the shortest time such that

$$|D^0(t_1) - c^{-1}f[p(t_1),t_1]|(1-c)^{t_2-t_1} \le s . \quad (41)$$

Therefore, for $t \ge t_2$,

$$D^0(t) = c^{-1}f(p,t) + O(s) , \quad (42)$$

from which, with the aid of (40), we deduce $\Delta D^0 = O(s)$ and the desired result,

$$\Delta D(t) = O(s^2) , \quad t \ge t_2 . \quad (43)$$

To see how (43) is reflected in the Fundamental Theorem, it is necessary to derive a suitable expression for the change in the mean fitness. This is

$$\Delta \bar{w} = \sum (w'_{ij}p'_ip'_j - w_{ij}p_ip_j)$$
$$= \overline{\Delta w} + 2\sum_i w_i \Delta p_i + \sum_{ij} w_{ij}\Delta p_i \Delta p_j , \quad (44)$$

where the prime indicates the next generation and

$$\overline{\Delta w} = \sum_{ij} p'_i p'_j \Delta w_{ij} \quad (45)$$

is the change in genotypic fitnesses averaged over the next generation. Substituting (34) into (44) yields

$$\Delta \bar{w} = \bar{w}^{-1}(V_{gam} - 2c\bar{E}D) + \overline{\Delta w} + \bar{w}^{-2}[\sum_{ij} p_i p_j(w_{ij} - \bar{w})$$
$$(w_i - \bar{w})(w_j - \bar{w}) - 2cD\sum_i p_i E_i(w_i - \bar{w}) + c^2\bar{E}D^2] , \quad (46)$$

where

$$V_{gam} = 2\sum_i p_i(w_i - \bar{w})^2 \quad (47)$$

is the gametic variance corresponding to (28), and the epistatic parameters are

$$E_i = \sum_j w_{ij}\varepsilon_j , \quad \bar{E} = \sum_i \varepsilon_i w_i , \quad \bar{\bar{E}} = \sum_i \varepsilon_i E_i . \quad (48)$$

A formula somewhat resembling (46) has been given by TURNER (1970).

Next, we note that (KIMURA 1965)

$$V_{gam} = V_g + 2\bar{E}^2 R^{-1} . \tag{49}$$

All the epistatic parameters are of $O(s)$, and for $t \geqslant t_1$, $D = O(s)$. Consequently, for $t \geqslant t_1$ (46) and (49) give

$$\Delta\bar{w} = V_g + \overline{\Delta w} + 2\bar{E}^2 R^{-1} - 2c\bar{E}D + O(s^3) . \tag{50}$$

Following KIMURA (1965), we compute the change in $Z = p_1 p_4 / (p_2 p_3)$:

$$\begin{aligned}\Delta\ln Z &= \sum_i \varepsilon_i \Delta \ln p_i \\ &= \sum_i \varepsilon_i p_i^{-1} \Delta p_i + O(s^2) .\end{aligned} \tag{51}$$

Equation (51) is valid for $t \geq t_1$ because then $\Delta p_i = O(s)$. Substituting (34) into (51), we find

$$Z^{-1}\Delta Z = \bar{E} - cDR + O(s^2) , \tag{52}$$

whence (50) becomes

$$\Delta\bar{w} = V_g + \overline{\Delta w} + 2\bar{E}(RZ)^{-1}\Delta Z + O(s^3) . \tag{53}$$

Since the factor of 2 in (53) occurs due to diploidy, the analogy with (33) is complete. The crucial feature of (53) is that the last term is not of $O(s^2)$, as might have been expected *a priori*, but of $O(s^3)$.

From (36), we obtain

$$D = p_2 p_3 (w_{14}Z - w_{23}) = p_2 p_3 [Z - 1 + O(s)] . \tag{54}$$

For $t \geqslant t_1$, $\Delta p_i = O(s)$ and $Z - 1 = O(s)$. Therefore,

$$\Delta D = p_2 p_3 \Delta Z + O(s^2) , \tag{55}$$

whence, for $t \geqslant t_2$, (43) allows us to conclude $\Delta Z = O(s^2)$. Thus, the epistatic term in (53) is of $O(s^3)$. If we suppose the genotypic fitnesses change slowly, $\Delta w_{ij} = o(s^2)$, then the genic variance will dominate for slow selection, and the Fundamental Theorem will hold.

As discussed at length in Sec. II, if the allelic frequencies are changing extremely slowly, as is the case very close to an equilibrium, exceptions are possible. This is why, in the heterotic multiplicative model, the existence of the stable $D = 0$ equilibrium, which is not a maximum of the mean fitness (ROUX 1974; KARLIN 1975), does not invalidate our analysis. In the example of MORAN (1964), the mean fitness is decreasing far from equilibrium because the allelic frequencies are constant, and hence the genic variance is identically zero. Since most evolution is likely to be due to substantial gene frequency change, such situations probably have little biological importance.

2. *Haploids*

Measuring the gametic frequencies immediately after conjugation, if w_i are the prescribed gametic fitnesses, the basic equations now read (KIMURA 1965)

$$\bar{w}\Delta p_i = p_i(w_i - \bar{w}) - \varepsilon_i c \bar{w}^{-1} D \ , \tag{56}$$

$$\Delta D = -cD + sf(p,t) \ , \tag{57}$$

where

$$D = w_1 w_4 p_1 p_4 - w_2 w_3 p_2 p_3 \ . \tag{58}$$

Hence, the diploid analysis, (37) to (43), remains valid unaltered. Following (44) to (49), we now find

$$\Delta\bar{w} = \bar{w}^{-1}V_g + \overline{\Delta w} + \bar{w}^{-1}ER^{-1}(E - c\bar{w}^{-1}RD) \ , \tag{59}$$

where

$$E = \sum_i \varepsilon_i w_i \ , \quad \overline{\Delta w} = \sum_i p'_i \Delta w_i \ , \tag{60}$$

and (52) is replaced for $t \geqslant t_1$ by

$$Z^{-1}\Delta Z = \bar{w}^{-1}(E - c\bar{w}^{-1}DR) + O(s^2) \ . \tag{61}$$

Substituting (61) into (59), we obtain

$$\Delta\bar{w} = V_g + \overline{\Delta w} + E(RZ)^{-1}\Delta Z + O(s^3) \ , \tag{62}$$

corresponding to (53). But

$$D = p_2 p_3(w_1 w_4 Z - w_2 w_3) = p_2 p_3[Z - 1 + O(s)] \ , \tag{63}$$

so that (55) still holds, whence $\Delta Z = O(s^2)$ for $t \geqslant t_2$, and the Fundamental Theorem is valid as long as $\Delta w_i = o(s^2)$.

3. *Diploids, Multiple Alleles*

As a small step toward the analysis of the multiple-locus, multiple-allele problem, it is worth considering two loci with multiple alleles. This is most easily done in discrete time because of the Hardy-Weinberg simplification.

Let P_{ij} designate the frequency of the gamete A_iB_j. If $w_{ij,kl}$ and w_{ij} represent the fitnesses of the genotype $A_iA_kB_jB_l$ and gamete A_iB_j, then

$$w_{ij} = \sum_{kl} w_{ij,kl}P_{kl} \ . \tag{64}$$

The difference equations of the model read (KIMURA and OHTA 1971, pp. 92–93)

$$\bar{w}\Delta P_{ij} = P_{ij}(w_{ij} - \bar{w}) - cD_{ij} \ , \tag{65}$$

where the linkage disequilibria are

$$D_{ij} = \sum_{kl} (w_{ij,kl}P_{ij}P_{kl} - w_{il,kj}P_{il}P_{kj}) \ . \tag{66}$$

Observing that

$$\sum_i D_{ij} = 0 \ , \quad \sum_j D_{ij} = 0 \ , \tag{67}$$

we derive from (65) and (66)

$$\Delta D_{ij} = -cD_{ij} + sf_{ij}(P,t) \ . \tag{68}$$

Comparing (65) and (68) to (34) and (35), it is obvious that (37) to (43) apply unaltered if the appropriate subscripts are added.

We turn to the mean fitness,

$$\bar{w} = \sum_{ijkl} w_{ij,kl} P_{ij} P_{kl} \ . \tag{69}$$

Following (44) to (46) leads to

$$\begin{aligned}
\Delta\bar{w} = &\ \bar{w}^{-1}(V_{gam} - 2c\bar{X}) + \overline{\Delta w} \\
&+ \bar{w}^{-2} \Big[\sum_{ijkl} P_{ij} P_{kl} (w_{ij,kl} - \bar{w})(w_{ij} - \bar{w})(w_{kl} - \bar{w}) \\
&- 2c \sum_{ij} X_{ij} P_{ij}(w_{ij} - \bar{w}) + c^2 \sum_{ij} X_{ij} D_{ij} \Big] \ ,
\end{aligned} \tag{70}$$

where

$$V_{gam} = 2 \sum_{ij} P_{ij}(w_{ij} - \bar{w})^2 \ , \tag{71}$$

$$X_{ij} = \sum_{ij} (w_{ij,kl} - \bar{w}) D_{kl} \ , \tag{72}$$

$$\bar{X} = \sum_{ij} P_{ij} X_{ij} = \sum_{ij} (w_{ij} - \bar{w}) D_{ij} \ . \tag{73}$$

Next, we must generalize (49). To decompose V_{gam} into additive (V_g) and epistatic (V_e) components, we set

$$v_{ij} \equiv w_{ij} - \bar{w} = \alpha_i + \beta_j + E_{ij} \ . \tag{74}$$

Minimizing

$$V_e = 2 \sum_{ij} P_{ij} E^2{}_{ij} = 2 \sum_{ij} P_{ij}(v_{ij} - \alpha_i - \beta_j)^2 \tag{75}$$

with respect to the average effects α_i of A_i and β_j of B_j yields

$$\sum_j P_{ij}(v_{ij} - \alpha_i - \beta_j) = \sum_j P_{ij} E_{ij} = 0 \ , \tag{76}$$

$$\sum_i P_{ij}(v_{ij} - \alpha_i - \beta_j) = \sum_i P_{ij} E_{ij} = 0 \ . \tag{77}$$

Introducing the frequencies p_i and q_j and average excesses a_i and b_j of A_i and B_j through the equations

$$p_i = \sum_j P_{ij} \ , \quad q_j = \sum_i P_{ij} \ , \tag{78}$$

$$p_i a_i = \sum_j P_{ij} v_{ij} \ , \quad q_j b_j = \sum_i P_{ij} v_{ij} \ , \tag{79}$$

we obtain from (76) and (77)

$$2 \sum_i p_i a_i \alpha_i + 2 \sum_j q_j b_j \beta_j = 2 \sum_{ij} P_{ij}(\alpha_i + \beta_j)^2 = V_g \ . \tag{80}$$

Substituting (74) into (71) and using (76) and (77) gives

$$V_{gam} = V_g + V_e \ . \tag{81}$$

But we have

$$D_{ij}(t) = O(s) \ , \quad t \geqslant t_1 \ . \tag{82}$$

Therefore, (72), (81), and (82) reduce (70) to the generalization of (50):

$$\Delta \bar{w} = V_g + \overline{\Delta w} + V_e - 2c\bar{X} + O(s^3) \ , \quad t \geqslant t_1 \ . \tag{83}$$

As before, we shall suppose that $\overline{\Delta w} = o(s^2)$. Combining (66) and (82), we find the linkage equilibrium approximation

$$P_{ij} = p_i q_j + O(s) \ , \quad t \geqslant t_1 \ . \tag{84}$$

For $t \geqslant t_1$, we have

$$\Delta D_{ij} = \sum_{kl} (P_{kl} \Delta P_{ij} + P_{ij} \Delta P_{kl} - P_{kj} \Delta P_{il} - P_{il} \Delta P_{kj}) + O(s^2) \ . \tag{85}$$

Substituting (65) into (85) and recalling (67), we get

$$\Delta D_{ij} = \sum_{kl} \{ P_{kl} P_{ij} [(w_{ij} - \bar{w}) + (w_{kl} - \bar{w})] \\ - P_{kj} P_{il} [(w_{il} - \bar{w}) + (w_{kj} - \bar{w})] \} - cD_{ij} + O(s^2) \ . \tag{86}$$

Hence,

$$\begin{aligned}
\Delta D_{ij} &= \sum_{kl} p_i q_j p_k q_l [(w_{ij} - \bar{w}) + (w_{kl} - \bar{w}) \\
&\quad - (w_{il} - \bar{w}) - (w_{kj} - \bar{w})] - cD_{ij} + O(s^2) \\
&= \sum_{kl} p_i q_j p_k q_l (E_{ij} + E_{kl} - E_{il} - E_{kj}) - cD_{ij} + O(s^2) \\
&= \sum_{kl} [P_{kl} P_{ij} (E_{ij} + E_{kl}) - P_{il} P_{kj} (E_{il} + E_{kj})] - cD_{ij} + O(s^2) \\
&= P_{ij} E_{ij} - cD_{ij} + O(s^2) \ ,
\end{aligned} \tag{87}$$

where we employed successively (84), (74), again (84), and (76) and (77). Therefore,

$$2 \sum_{ij} E_{ij} \Delta D_{ij} = 2 \sum_{ij} P_{ij} E^2_{ij} - 2c \sum_{ij} D_{ij} (v_{ij} - \alpha_i - \beta_j) + O(s^3)$$

$$= V_e - 2cX + O(s^3) \ . \tag{88}$$

using (67), (73), (74), and (75). So, (83) becomes

$$\Delta \bar{w} = V_g + \overline{\Delta w} + 2 \sum_{ij} E_{ij} \Delta D_{ij} + O(s^3) \ , \tag{89}$$

which, owing to the fact that $\Delta D_{ij} = O(s^2)$ for $t \geqslant t_2$, proves the Fundamental Theorem.

IV. THE EVOLUTION OF THE GENOTYPIC FREQUENCIES

In Sections II and III it was demonstrated that in a short time t_1 the departures from random combination are reduced to a small quantity of $O(s)$. Geometrically, this means that in time t_1 the distance from the "independence surface" (IS) is reduced to $O(s)$. Furthermore, since we have seen that the rates of change of the deviations from Hardy-Weinberg and linkage equilibrium, after a time $t_2 \approx 2t_1$, are $O(s^2)$, the small distance from the IS changes very slowly. Thus, the trajectory is close and nearly parallel to the IS, as illustrated by the "vertical" portion of the path in Figure 1 for the special case of a single locus with two alleles.

Consider the system at time t_1. The point on the trajectory at that time corresponds to some set of gene frequencies $p_i(t_1)$, which evolve according to some complicated law, $p_i(t)$. On the IS, there is a unique point with gene frequencies $\pi_i(t_1) = p_i(t_1)$, and these evolve according to the much simpler law, $\pi_i(t)$, obtained. in principle, by solving the equations of the system with the assumption of random combination. In Figure 1, of course, $\pi(t_1) = p(t_1)$, a point on the p-axis found by horizontal projection. We shall see that $P_{ij}(t) = \pi_i(t)\pi_j(t) + O(s)$, i.e., the actual evolution of the genotypic frequencies is well approximated, with an error of $O(s)$, by the dynamics of the much simpler system on the IS. In Figure 1, for instance, the motion along the vertical part of the orbit differs only to $O(s)$ from the corresponding evolution on the Hardy-Weinberg line.

The analysis to follow, whose crucial feature is random combination, is the same in all the models considered above. The notation already established is best suited to exposition in terms of the multiallelic single-locus case of Subsection II.1. We display explicitly the possible dependence of the genotypic fitnesses on the genotypic frequencies and the time, and set

$$m_{ij}(P,t) = m(P,t) + sr_{ij}(P,t) \ , \tag{90}$$

where the r_{ij} are of order unity. We calculate

$$p_i m_i = \sum_j m_{ij} P_{ij} = p_i(m + sr_i) \ , \tag{91}$$

$$\bar{m} = \sum_i p_i m_i = m + s\bar{r} \ , \tag{92}$$

in which

$$p_i r_i(P,t) = \sum_j r_{ij}(P,t) P_{ij} \ , \quad \bar{r}(P,t) = \sum_i p_i r_i(P,t) \ . \tag{93}$$

Therefore, (3) becomes

$$\dot{p}_i = sp_i[r_i(P,t) - \bar{r}(P,t)] \ . \tag{94}$$

Recalling (1), we see that

$$r_{ij}(P,t) = r_{ij}(p*p,t) + O(Q) \ , \tag{95}$$

where the asterisk indicates evaluation at $P_{ij} = p_i p_j$. Substituting (1) and (95) into (93) yields

$$r_i(P,t) = c_i(p,t) + O(Q) \ , \tag{96}$$

$$\bar{r}(P,t) = \bar{c}(p,t) + O(Q) \ , \tag{97}$$

where

$$c_i(p,t) = \sum_j r_{ij}(p*p,t) p_j \ ; \quad \bar{c}(p,t) = \sum_i p_i c_i(p,t) \ . \tag{98}$$

Inserting (96) and (97) into (94) gives

$$\dot{p}_i = sp_i[c_i(p,t) - \bar{c}(p,t)] + O(sQ) \ . \tag{99}$$

Let us turn to the trajectories, $\pi_i(t)$, on the Hardy-Weinberg surface. From (99), these obviously satisfy

$$\dot{\pi}_i = s\pi_i[c_i(\pi,t) - \bar{c}(\pi,t)] \ . \tag{100}$$

As is necessary for QHW, we suppose $m = o(s^2)$. On the IS, the third term in (12) is absent and

$$V_g = 2s^2 \sum_i \pi_i[c_i(\pi,t) - \bar{c}(\pi,t)]^2 \ . \tag{101}$$

Consequently, (12) informs us that the system always tends to equilibria, which we suppose to be points (as they are generically if there is no frequency and time-dependence), where (101) vanishes. For $t \geqslant t_1$, $Q_{ij}(t) = O(s)$, which implies that the error term in (99) is of $O(s^2)$. Then (99) and (100) allow us to assert

$$p_i(t) = \pi_i(t) + O(s) \ , \quad t \geqslant t_1 \ . \tag{102}$$

Recalling (1), from (102) we deduce the desired result:

$$P_{ij}(t) = \pi_i(t)\pi_j(t) + O(s) \ , \quad t \geqslant t_1 \ . \tag{103}$$

A conclusion equivalent to (103) has been reached by HOPPENSTEADT (1976) in a particular two-locus, two-allele model by a different method. If, due to unusual frequency or time-dependence, the system does not tend to an equilibrium *point*, (102) and (103) still hold for $t_1 \leq t \leq T$, for any fixed time T.

As a final point, let us establish that the genic variance on the actual trajectory is well approximated for $t \geqslant t_1$ by (101). The average effect of A_i, μ_i, is given by (KIMURA 1958)

$$\mu_i = m_i - \bar{m} - \sum_j p_j\mu_j\theta_{ij}$$

$$= s(c_i - \bar{c}) + O(s^2) - \sum_j p_j\mu_j[1 + O(s)]$$

$$= s[c_i(p,t) - \bar{c}(p,t)] + O(s^2) \ , \tag{104}$$

where in the second step we used (99) and (13), and (104) follows because the mean of the average effects is zero. Substituting (99) and (104) into (15) yields, for $t \geqslant t_1$,

$$V_g = 2s^2 \sum_i p_i[c_i(p,t) - \bar{c}(p,t)]^2 + O(s^3)$$

$$= 2s^2 \sum_i \pi_i[c_i(\pi,t) - \bar{c}(\pi,t)]^2 + O(s^3) \ , \tag{105}$$

as required. It follows from (100) and (105) that V_g is much smaller than s^2 only if the allelic frequencies are changing extremely slowly.

At least for one and two loci, the results of this paper strongly suggest that deviations from random combination have scant evolutionary significance. This appears to be the view of FISHER (1930) and WRIGHT (1969).

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