CENTRAL EQUILIBRIA IN MULTILOCUS SYSTEMS. I. GENERALIZED NONEPISTATIC SELECTION REGIMES‡

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ABSTRACT

The generalized nonepistatic selection regime encompasses combinations of multiplicative and neutral viability effects distributed across a set of loci. These subsume, in particular, mixtures of the classical modes of multiplicative and additive fitness evaluations for multilocus traits. Exact analytic conditions for existence and stability of a multilocus Hardy-Weinberg (H-W) polymorphic equilibrium configuration are ascertained. It is established that the central H-W polymorphism is stable only if the component loci are "overdominant" and sufficient recombination is in force. The H-W central equilibrium is never stable for tight linkage whenever some multiplicative selection effects are contributed by at least two of the loci involved. In the case of additive selection expression and individual overdominant loci, the H-W polymorphism is stable independently of the level of recombination. In the context of "natural" recombination schemes, "more recombination" enhances the stability of the H-W polymorphic equilibrium.

A basic problem of population genetics theory today pertains to multilocus models; specifically, the extension of the analysis from two loci to n loci. The theory attempts to delineate the dynamic and equilibrium nature of gamete frequency realizations conforming with various classes of fitness regimes and recombination distributions. This paper is part of a series (see KARLIN 1977, 1978; KARLIN and LIBERMAN 1979a,b), elaborating a quantitative theory of multigene interactions and means of measurement and interpretation of gene frequency associations.

The studies of linkage and selection in multilocus systems centers on four main categories of models: (1) selection expression of "nonepistatic" effects across loci; (2) phenotype selection forms based on certain classes of phenotypic-genotypic associations; (3) genotype fitness evaluations invariant under natural group transformations; and (4) hybrid versions of the selection regimes of (1) to (3).

In order to assess the significance and consequences of epistasis, it is essential to delimit properly the range of nonepistasis and characterize the associated gamete frequency realizations. The essential features of a multilocus concept of nonepistasis are as follows: (a) each locus has an intrinsic fitness matrix of its

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own, which specifies the fitness values of the marginal diplotypes; (b) each locus can express its intrinsic fitness values or be neutral; and (c) the fitness of a genotype is obtained by adding or multiplying the marginal viabilities or neutral values associated with the constituent loci diplotypes.

A relevant class of generalized nonepistatic fitness matrices occurs as a weighted combination of the classical nonepistatic regimes composed from multiplicative, additive and neutral viability forms based on the same intrinsic loci fitness matrices. Another manifestation of "generalized nonepistasis" involves fitness contributions that accumulate additively with respect to a prescribed subset of loci and multiplicatively with respect to the complementary loci involved, while the two loci sets interact multiplicatively or additively. With these representations in mind, we proceed to describe, first in qualitative terms, and later a generalized construction of nonepistatic interaction.

The generalized nonepistatic selection model has the following structure: consider all 2^n possible partitions of the component n loci into two disjoint collections of loci I_1 and I_2. With each such partition we associate a modified multiplicative nonepistatic fitness matrix determined such that at the loci in I_1 differential selection operates in accordance with the intrinsic fitness matrices of these loci, while the complementary loci, those of I_2, act as neutral loci. Thus, corresponding to the partition I_1,I_2, a given genotype carries fitness values such that only the loci of I_1 exercise selection accruing as multiplicative factors conforming with the intrinsic fitness matrices of I_1. The generalized nonepistatic model entails a fitness regime composed of a weighted sum of these (2^n) modified multiplicative forms.

The existence of epistasis as against nonepistasis for our purposes will be understood to signify that fitness cannot be partitioned as appropriate mixtures of multiplicative and neutral selection effects accruing from the component loci in the sense described above.

Orders of genic associations pertain to characterizations and classifications of gamete frequency configurations. A number of relevant indices have been worked on; *e.g.*, BENNETT (1954), FELDMAN, FRANKLIN and THOMSON (1974), HILL (1974, 1976) and SLATKIN (1972). These measurements relate to statistical procedures for evaluating the significance of linkage disequilibrium and higher order associations attendant to observed gamete-frequency data. The defining feature of nonassociation affirms that all pairwise and higher order linkage disequilibrium values are zero. In this vein, the notion of a Hardy-Weinberg (H-W) state is relevant. The Hardy-Weinberg property *across loci* signifies that a population gamete-frequency state has components determined as products of their respective gene frequencies. (Although the H-W attribute is classically understood as an intralocus property, the concept described above across loci is now commonly used.) Generally, a H-W multilocus polymorphism involves all genotypes occurring with moderate frequency and exhibiting random association of its constituent gene frequencies. For the two-locus, two-allele model the H-W property is synonomous with that of linkage equilibrium (D=0). A H-W state in the multilocus context is characterized by the vanishing of a hierarchy of higher-order indices of associations. Measures of associations and concomitant indices are

used also to assess degrees and levels of symmetry, complementarity, and in establishing distance measurements to H-W representations.

Our objective in this work is the elucidation of conditions for existence and stability of H-W equilibrium configurations in the context of the generalized nonepistatic selection models. A particular focus concerns the role of linkage and the quantification of the extent of recombination entailing a stable H-W polymorphism. Apart from their innate interest these studies can help serve as a control for evaluating and interpreting gamete frequency outcomes relevant to classes of more complex epistatic multilocus selection models. A number of specific topics and problems dealt with in this work concern: (1) Ascertainment of the range of recombination rates that guarantee the stability of a H-W polymorphism for various levels and forms of nonepistasis. (2) Discussion of the problem: Does "more recombination" favor the attainment of a H-W stable polymorphism? (3) The relative roles of multiplicative and additive selection effects distributed over the loci bearing on the amount of recombination needed to maintain a stable H-W equilibrium. (4) The influence of position effects, that is, those combinations of loci acting neutrally as against the remaining loci possessing selection differentials.

The analysis and pertinence of H-W equilibrium states for bisexual nonepistatic patterns is covered in KARLIN and LIBERMAN (1979a). The study of H-W configurations in the framework of a multideme population subject to local nonepistatic selection, coupled to migration flow, is dealt with in KARLIN and CAMPBELL (1978).

Results on the two-locus, two-allele multiplicative and additive models have been reported by a number of authors. In the additive case, KARLIN and FELDMAN (1970) have shown that there is a unique polymorphism of the H-W type that is globally stable provided both loci are heterotic (heterozygote advantage at the separate loci) and non-zero recombination operates between the loci. The result was extended to the multiallele two-locus setup in KARLIN and LIBERMAN (1978a). For the multiplicative two-locus, two-allele model, MORAN (1968) proved that under free recombination, the presence of marginal heterosis guarantees global stability of the H-W polymorphism. BODMER and FELSENSTEIN (1967) ascertained the exact conditions for local stability of the H-W polymorphism for the two-locus multiplicative selection model. ROUX (1974) considered other aspects of the multiplicative selection model employing a natural representation of the transformation equations of the process. An extensive review, plus further developments on the two-locus multiplicative-additive models *inter alia*, is covered in KARLIN (1975, 1977).

1. THE GENERAL MULTILOCUS, MULTIALLELE MODEL

Consider in a large diploid monoecious population a trait determined at n loci with m_k possible alleles $A_1^{(k)}, A_2^{(k)}, \ldots, A_{m_k}^{(k)}$, at locus k $(k = 1,2, \ldots, n)$. In developing a framework that is tractable for delineating and interpreting recombination and selection effects, it is essential to operate with a natural coordinate system. We cannot just order all the gamete types $1,2, \ldots, R$, $R = m_1 m_2 \ldots m_n$,

as is customary in the two-locus, two-allele model. Without recognizing the inherent intra- and interlocus symmetries in the n-locus context, the transformation equations and their analyses become prohibitive. In the natural parameterization, the analysis is substantially forthcoming and revealing.

Let $i_0^{(k)}, i_1^{(k)}$ index the possible alleles at the k^{th} locus. Associated gametes (haplo or chromosomal types) are described by the n-tuples.

$$\mathbf{i}_0 = (i_0^{(1)}, i_0^{(2)}, \ldots, i_0^{(n)}) \text{ and } \mathbf{i}_1 = (i_1^{(1)}, i_1^{(2)}, \ldots, i_1^{(n)}). \tag{1}$$

A typical genotype composed of the two gametes above is displayed in the form

$$\frac{\mathbf{i}_0}{\mathbf{i}_1} = \frac{i_0^{(1)}, i_0^{(2)}, \ldots, i_0^{(n)}}{i_1^{(1)}, i_1^{(2)}, \ldots, i_1^{(n)}} \tag{2}$$

signifying that the allelic composition at locus k consists of alleles $i_0^{(k)}$ and $i_1^{(k)}$. We do not preclude that $i_0^{(k)}$ and $i_1^{(k)}$ refer to the same alleles at locus k.

The fitness value of the genotype (2) is denoted by

$$w\left(\frac{\mathbf{i}_0}{\mathbf{i}_1}\right) = w\left[\frac{i_0^{(1)}, \ldots, i_0^{(n)}}{i_1^{(1)}, \ldots, i_1^{(n)}}\right] = w(\mathbf{i}_0, \mathbf{i}_1). \tag{3}$$

The array (3), where $\mathbf{i}_0 = (i_0^{(1)}, \ldots, i_0^{(n)})$ and $\mathbf{i}_1 = (i_1^{(1)}, \ldots, i_1^{(n)})$ cover all gamete combinations, generates the fitness matrix of order $(\prod_{k=1}^{n} m_k) \times (\prod_{k=1}^{n} m_k)$.

The recombination-segregation distribution depicts the frequency rates of the gamete output resulting from recombination and segregation. The outcome of meiosis involving the "male" gamete $(i_0^{(1)}, i_0^{(2)}, \ldots, i_0^{(n)})$ and the "female" gamete $(i_1^{(1)}, i_1^{(2)}, \ldots, i_1^{(n)})$ can be any of the 2^n gametes $(i_{\varepsilon_1}^{(1)}, i_{\varepsilon_2}^{(2)}, \ldots, i_{\varepsilon_n}^{(n)})$, where each $\varepsilon_k = 0$ or 1, $k = 1,2,\ldots,n$. The recombination-segregation distribution $\mathbf{R}$ prescribes probabilities to these 2^n mutually exclusive events, and, thus it consists of the 2^n nonnegative parameters $\{R(\varepsilon)\}$, where

$$R(\varepsilon) = R(\varepsilon_1, \varepsilon_2, \ldots, \varepsilon_n), \tag{4}$$

stands for the probability of the recombination-segregation gamete product $(i_{\varepsilon_1}^{(1)}, i_{\varepsilon_2}^{(2)}, \ldots, i_{\varepsilon_n}^{(n)})$ and $\varepsilon = (\varepsilon_1, \varepsilon_2, \ldots, \varepsilon_n)$. The representation (4) for the combined recombination-segregation distribution was formalized in this manner first by GEIRINGER (1944). As the two parental gametes contribute symmetrically to the gamete product and since the parameters $\{R(\varepsilon)\}$ correspond to mutually exclusive recombination events, we have the two intrinsic relations

$$R(\varepsilon) = R(\mathbf{1} - \varepsilon), \quad \sum_{\varepsilon} R(\varepsilon) = 1 \quad (\text{Here } \mathbf{1} = (1,1,\ldots,1)). \tag{5}$$

Mostly, we refer to $\mathbf{R} = \{R(\varepsilon)\}$ simply as the recombination distribution.

In order to operate the multilocus diploid recombination mechanism, the description of the gametes in terms of the 0 and 1 subscripts is natural.

The two-locus case: In the case of two loci, if r is the probability of recombination between the two loci, then

$$R(0,0) = R(1,1) = \frac{1-r}{2}, \quad R(0,1) = R(1,0) = \frac{r}{2} \tag{6}$$

The three-locus case: The recombination distribution is determined by three parameters r,s and t defined by

$$\begin{aligned} R(0,0,0) = R(1,1,1) &= \frac{1-r-s-t}{2}, \quad R(0,0,1) = R(1,1,0) = \frac{s}{2} \\ R(0,1,1) = R(1,0,0) &= \frac{r}{2}, \qquad\quad R(0,1,0) = R(1,0,1) = \frac{t}{2}. \end{aligned} \tag{7}$$

A different parameterization of the recombination scheme is more traditionally used with r_1 as the recombination rate between loci 1 and 2, r_2 as that between loci 2 and 3, and r_3 as that between loci 1 and 3. The parameters in the two notations are connected by the relations $r_1 = r+t$, $r_2 = s+t$, $r_3 = r+s$.

The case of no interference is characterized by the equation $t = (r+t)(s+t)$ or equivalently by the relation $r_3 = r_1(1-r_2) + r_2(1-r_1) = r_1 + r_2 - 2r_1r_2$. The situation where recombination between two adjacent positions precludes recombination in the next segment (the complete interference model) corresponds to the stipulation $t = 0$.

We single out next, in the context of the general n-locus model, a number of relevant recombination distributions. Absolute linkage (no recombination) $\mathbf{R}^{(0)}$ is defined by

$$R(\mathbf{0}) = R(\mathbf{1}) = \frac{1}{2}, \quad R(\varepsilon) = 0 \text{ for } \varepsilon \neq \mathbf{0} \text{ or } \mathbf{1} \tag{8}$$

where $\mathbf{0} = (0,0,\ldots,0)$ and $\mathbf{1} = (1,1,\ldots,1)$ reflect no effective exchange of genetic material.

Free recombination, $\mathbf{R}^{(f)}$: Here, in the case of n segregating loci,

$$R(\varepsilon) = \frac{1}{2^n} \text{ independent of } \varepsilon. \tag{9}$$

Where the individual loci are all located on different chromosomes, then (9) assuredly applies.

Recombination arrays reflecting specific physical characteristics of loci: Suppose the loci are endowed with a physical arrangement along a single chromosome. We can consider independent probabilities of breaks between successive positions (the no interference postulate). Let r_i be the probability of a break between loci i and $i+1$. Then,

$$R(\varepsilon) = \frac{1}{2} \prod_{i=1}^{n-1} r_i^{|\varepsilon_i - \varepsilon_{i+1}|} (1-r_i)^{1-|\varepsilon_i - \varepsilon_{i+1}|}.$$

It is possible to generate a hierarchy of recombination-segregation distributions that take account of the physical ordering in the loci using concepts of renewal and counter processes, *e.g.*, see OWEN (1950), BAILEY (1961) and KARLIN and LIBERMAN (1978b).

The gamete frequency transformation equations: Let $x(\mathbf{i}_0) = x(i_0^{(1)}, \ldots, i_0^{(n)})$ denote the frequency of the general gamete type $\mathbf{i}^0 = (i_0^{(1)}, \ldots, i_0^{(n)})$ in the population of the current generation. Under random mating, subject to the

effects of viability selection, the relative proportion of the genotype (2) among mature individuals is $w\left(\frac{\mathbf{i}_0}{\mathbf{i}_1}\right) x(\mathbf{i}_0)x(\mathbf{i}_1)$. The segregation process joined with the recombination contingencies leads to the frequency of the gamete type $x'(\mathbf{i}_0) = x'(i_0^{(1)}, \ldots, i_0^{(n)})$ in the next generation computed by the formula

$$w(\mathbf{x})x'(\mathbf{i}_0) = \sum_{\mathbf{i}_1} \sum_{\varepsilon} R(\varepsilon)\, w\left(\frac{\mathbf{i}_\varepsilon}{\mathbf{i}_{1-\varepsilon}}\right) x(\mathbf{i}_\varepsilon)x(\mathbf{i}_{1-\varepsilon}) \tag{10}$$

(the sum $\sum_{\mathbf{i}_1}$ extends over all possible $R = m_1 m_2 \ldots m_n$ gamete types $\mathbf{i}_1 = (i_1^{(1)}, i_1^{(2)}, \ldots, i_1^{(n)})$.) where $w(\mathbf{x})$ is the mean fitness function for the population state $\mathbf{x}$, namely

$$w(\mathbf{x}) = \sum_{\mathbf{i}_0, \mathbf{i}_1} w\left(\frac{\mathbf{i}_0}{\mathbf{i}_1}\right) x(\mathbf{i}_0)x(\mathbf{i}_1) \ .$$

It may be helpful to illustrate the procedure underlying formula (10) and the formula itself for the two-locus, two-allele case with alleles A,a at the first locus and B,b at the second. Let $\mathbf{i}_0 = (i_0^{(1)}, i_0^{(2)})$ refer to the gamete ab. There are four classes of genotypes that can produce by recombination-segregation the gamete ab. They are listed next with their corresponding frequencies.

Genotype class:	$\frac{(a,b)}{(i_1^{(1)}, i_1^{(2)})}$	$\frac{(a, i_1^{(2)})}{(i_1^{(1)}, b)}$	$\frac{(i_1^{(1)}, b)}{(a, i_1^{(2)})}$	$\frac{(i_1^{(1)}, i_1^{(2)})}{(a,b)}$
Frequency of ab:	$R(0,0)$	$R(0,1)$	$R(1,0)$	$R(1,1)$

where $(i_1^{(1)}, i_1^{(2)})$ runs over the four possible gametes AB, Ab, aB, ab. Accordingly, the resulting frequency of the ab gamete $x'(a,b)$ in the next generation is

$$\begin{aligned} w(\mathbf{x})x'(a,b) = {} & R(0,0) \sum_{(i_1^{(1)}, i_1^{(2)})} w\left(\frac{a,b}{i_1^{(1)}, i_1^{(2)}}\right) x(a,b)x(i_1^{(1)}, i_1^{(2)}) \\ & + R(1,0) \sum_{(i_1^{(1)}, i_1^{(2)})} w\left(\frac{a, i_1^{(2)}}{i_1^{(1)}, b}\right) x(a, i_1^{(2)})x(i_1^{(1)}, b) \\ & + R(0,1) \sum_{(i_1^{(1)}, i_1^{(2)})} w\left(\frac{i_1^{(1)}, b}{a, i_1^{(2)}}\right) x(i_1^{(1)}, b)x(a, i_1^{(2)}) \\ & + R(1,1) \sum_{(i_1^{(1)}, i_1^{(2)})} w\left(\frac{i_1^{(1)}, i_1^{(2)}}{a,b}\right) x(i_1^{(1)}, i_1^{(2)})x(a,b) \ , \end{aligned}$$

which is exactly (10).

2. THE GENERALIZED NONEPISTATIC MULTILOCUS SELECTION MODEL

The generalized nonepistatic selection construction encompasses combinations of multiplicative and neutral viability effects across loci. It is instructive and of independent interest to set forth first the two-locus, two-allele case. Let the intrinsic fitness values for the indicated genotypes at the first locus be

$$AA\colon\ w_{11}^{(1)} \quad Aa\colon\ w_{12}^{(1)} = w_{21}^{(1)} \quad aa\colon\ w_{22}^{(1)} \ , \tag{11a}$$

and at the second locus

$$BB\colon\ w_{11}^{(2)} \cdot Bb\colon\ w_{12}^{(2)} = w_{21}^{(2)} \quad bb\colon\ w_{22}^{(2)} \tag{11b}$$

In the present context, there are four basic selection forms that may be joined in constructing the generalized nonepistatic selection regime. Two of them, $W(1,0)$ and $W(0,1)$, are fitness prescriptions carrying selection effects expressed only at the first and second loci, respectively, following the two marginal fitness matrices. The third basic regime, $W(1,1)$ manifests independent multiplicative effects coupling the loci; *i.e.*, the fitness of a genotype is the product of the marginal fitnesses conferred by each locus. The fourth form, $W(0,0)$, entails no selection differentials among genotypes, *i.e.*, total neutrality. It is useful for regulating the selection intensities of the other terms.

It is convenient to display these four basic nonepistatic regimes, conforming to the gamete arrangement AB, Ab, aB, ab, associated with the marginal fitness parameters of (11a, 11b).

$$W(1,1) = \begin{Vmatrix} w_{11}^{(1)} \cdot w_{11}^{(2)}, w_{11}^{(1)} \cdot w_{12}^{(2)}, w_{12}^{(1)} \cdot w_{11}^{(2)}, w_{12}^{(1)} \cdot w_{12}^{(2)} \\ w_{11}^{(1)} \cdot w_{21}^{(2)}, w_{11}^{(1)} \cdot w_{22}^{(2)}, w_{12}^{(1)} \cdot w_{21}^{(2)}, w_{12}^{(1)} \cdot w_{22}^{(2)} \\ w_{21}^{(1)} \cdot w_{11}^{(2)}, w_{21}^{(1)} \cdot w_{12}^{(2)}, w_{22}^{(1)} \cdot w_{11}^{(2)}, w_{22}^{(1)} \cdot w_{12}^{(2)} \\ w_{21}^{(1)} \cdot w_{21}^{(2)}, w_{21}^{(1)} \cdot w_{22}^{(2)}, w_{22}^{(1)} \cdot w_{21}^{(2)}, w_{22}^{(1)} \cdot w_{22}^{(2)} \end{Vmatrix} \quad W(0,0) = \begin{Vmatrix} 1 & 1 & 1 & 1 \\ 1 & 1 & 1 & 1 \\ 1 & 1 & 1 & 1 \\ 1 & 1 & 1 & 1 \end{Vmatrix} \tag{12}$$

$$W(1,0) = \begin{Vmatrix} w_{11}^{(1)}, w_{11}^{(1)}, w_{12}^{(1)}, w_{12}^{(1)} \\ w_{11}^{(1)}, w_{11}^{(1)}, w_{12}^{(1)}, w_{12}^{(1)} \\ w_{21}^{(1)}, w_{21}^{(1)}, w_{22}^{(1)}, w_{22}^{(1)} \\ w_{21}^{(1)}, w_{21}^{(1)}, w_{22}^{(1)}, w_{22}^{(1)} \end{Vmatrix} \quad W(1,0) = \begin{Vmatrix} w_{11}^{(2)}, w_{12}^{(2)}, w_{11}^{(2)}, w_{12}^{(2)} \\ w_{21}^{(2)}, w_{22}^{(2)}, w_{21}^{(2)}, w_{22}^{(2)} \\ w_{11}^{(2)}, w_{12}^{(2)}, w_{11}^{(2)}, w_{12}^{(2)} \\ w_{21}^{(2)}, w_{22}^{(2)}, w_{21}^{(2)}, w_{22}^{(2)} \end{Vmatrix}$$

Thus, the fitness of the genotype (AB/Ab) corresponding to $W(1,0)$ has value $w_{11}^{(1)}$ reflecting selection acting only at the first locus. Similarly, the fitness value of (AB/Ab) corresponding to $W(0,1)$ is $w_{12}^{(2)}$ and that of (AB/Ab) associated with $W(1,1)$ is $w_{11}^{(1)}w_{12}^{(2)}$. Finally, the fitness ascribed to (AB/Ab) (in fact to any genotype) by $W(0,0)$ is 1.

In the two-locus context the generalized nonepistatic selection structure founded on the intrinsic fitness parameters of (11a, 11b) consists of the combined fitness expression

$$\Gamma = \alpha W(1,1) + \beta W(1,0) + \gamma W(0,1) + \delta W(0,0), \quad (\alpha,\beta,\gamma,\delta \geqslant 0); \tag{13}$$

that is, a weighted sum of the four basic fitness matrices. Note that Γ for the determination $\beta=\gamma=\delta=0$, $\alpha = 1$ reduces to the classical two-locus, two-allele multiplicative nonepistatic regime, while the specialization $\beta=\gamma=1$, $\alpha=\delta=0$ leads to the classical additive nonepistatic regime.

It is illuminating and helpful to pass next to three loci to help convey the scope and nature of the generalized nonepistatic selection mode. Let the marginal fitness matrix for the k^{th} locus, $k = 1,2,3$, be $W_k = \|w_{ij}^{(k)}\|_{i,j=1}^{m_k}$ specifying the fitnesses

associated with the diplotypes $(A_i^{(k)} A_j^{(k)})$. These matrices combine in eight ways (2^n for n loci) to generate the basic selection regimes underlying generalized nonepistatic selection structures. We highlight these matrices in tabular form indicating the fitness associated with the genotype $(A_i^{(1)}A_j^{(2)}A_k^{(3)})/(A_m^{(1)}A_p^{(2)}A_q^{(3)})$

Matrix	Entry	Description
$W(1,1,1)$	$w_{im}^{(1)}w_{jp}^{(2)}w_{kq}^{(3)}$	Independent multiplicative factors from all three loci
$W(1,1,0)$	$w_{im}^{(1)}w_{jp}^{(2)}$	Loci 1 and 2 interact multiplicatively, while locus 3 manifests neutrality
$W(1,0,1)$	$w_{im}^{(1)}w_{kq}^{(3)}$	Loci 1 and 3 interact multiplicatively, while locus 2 manifests neutrality
$W(0,1,1)$	$w_{jp}^{(2)}w_{kq}^{(3)}$	Loci 2 and 3 interact multiplicatively, while locus 1 manifests neutrality
$W(1,0,0)$	$w_{im}^{(1)}$	Selection only acting at locus 1
$W(0,1,0)$	$w_{jp}^{(2)}$	Selection only acting at locus 2
$W(0,0,1)$	$w_{kq}^{(3)}$	Selection only acting at locus 3
$W(0,0,0)$	1	Neutral

With this notation generalized nonepistasis induces a fitness matrix of the form

$$\begin{aligned}\Gamma = {} & c_{111}W(1,1,1) + c_{110}W(1,1,0) + c_{101}W(1,0,1) + c_{011}W(0,1,1) \\ & + c_{100}W(1,0,0) + c_{010}W(0,1,0) + c_{001}W(0,0,1) + c_{000}W(0,0,0) \ .\end{aligned} \tag{14}$$

As with two loci, the standard multiplicative nonepistatic form ensues from the choice $c_{111} = 1$ with all other c's equal to zero. Additive nonepistasis results from the specification $c_{100} = c_{010} = c_{001} = 1$, and all other c's zero. Other interesting specializations of (14) reflect a mixed additive-multiplicative interaction among the loci. For example, the choice $c_{110} = c_{001} = 1$ (with the remaining c's equal to zero) entails multiplicative nonepistasis between the first two loci, but additive nonepistasis between the gene complex consisting of the first two loci and the third locus.

We now pass to the formulation of the n-locus generalized nonepistatic selection regime. For pure multiplicative nonepistatic selection we have the familiar construction:

$$w\left(\frac{i_0^{(1)}, i_0^{(2)}, \ldots, i_0^{(n)}}{i_1^{(1)}, i_1^{(2)}, \ldots, i_1^{(n)}}\right) = \prod_{k=1}^{n} w_{i_0^{(k)}, i_1^{(k)}}^{(k)} \tag{15}$$

where $W_k = \|w_{ij}^{(k)}\|_{i,j=1}^{m_k}$ is the intrinsic fitness matrix associated with locus k.

For pure additive nonepistatic selection, the evaluation on the right side of (15) replaces product by sum, so that

$$w\left(\frac{i_0^{(1)}, \ldots, i_0^{(n)}}{i_1^{(1)}, \ldots, i_1^{(n)}}\right) = \sum_{k=1}^{n} w_{i_0^{(k)}, i_1^{(k)}}^{(k)} \ . \tag{16}$$

We need the mathematical concept of Kronecker products of matrices and vectors. Let A be an $m \times n$ matrix and B an $l \times k$ matrix. We denote by $A \otimes B$ the Kronecker product of A and B namely, the partitioned matrix

$$A \otimes B = \begin{Vmatrix} a_{11}B & a_{12}B & \cdots & a_{1n}B \\ a_{21}B & a_{22}B & \cdots & a_{2n}B \\ \vdots & & & \vdots \\ a_{m1}B & a_{m2}B & \cdots & a_{mn}B \end{Vmatrix}$$

A Kronecker product of vectors $x \otimes y$ is calculated as the Kronecker product of the (single) row matrices regarding the vectors x and y as matrices.

Employing the construction of Kronecker products of matrices, we can write the multiplicative fitness matrix (15) in the Kronecker product form

$$M = W_1 \otimes W_2 \otimes \ldots W_n \tag{17}$$

In the additive case, we denote by E_k, $k = 1,2,\ldots,n$, the $m_k \times m_k$ matrix whose elements are all unity. In this notation, we may identify the summand $w^{(k)}_{i_0^{(k)}, i_1^{(k)}}$ with the n-locus fitness matrix $S_k = E_1 \otimes E_2 \otimes \ldots \otimes W_{k-1} \otimes W_k \otimes E_{k+1} \otimes \ldots \otimes E_n$. Therefore, we can represent (16) as the special sum of Kronecker products

$$S = \sum_{k=1}^{n} S_k \tag{18}$$

When selection is globally neutral, then the fitness matrix is simply

$$E = E_1 \otimes E_2 \otimes \ldots \otimes E_n \tag{19}$$

A generalized nonepistatic selection model extending (13) and (14) has the following construction. There is defined for each locus an intrinsic fitness matrix W_k of order $m_k \times m_k$ for locus k, admitting m_k possible alleles. Let E_k as before be the fitness matrix of size $m_k \times m_k$ composed of all unit elements. A generalized notion of nonepistasis of an n-locus trait with associated fitness matrix Γ of order $R \times R$ $(R = \prod_{k=1}^{n} m_k)$ has the form

$$\Gamma = \sum_{\eta} c(\eta)\ (W_1^{(\eta_1)} \otimes W_2^{(\eta_2)} \otimes \ldots \otimes W_n^{(\eta_n)}) \tag{20}$$

where the sum is extended over all n-tuples $\eta = (\eta_1,\eta_2,\ldots,\eta_n)$, $\eta_k = 0$ or 1, subject to the special convention

$$W_k^{(1)} = W_k, \quad W_k^{(0)} = E_k \tag{21}$$

Accordingly, for each η, the matrix $W(\eta) = W_1^{(\eta_1)} \otimes W_2^{(\eta_2)} \otimes \ldots \otimes W_n^{(\eta_n)}$ describes an ordinary multiplicative nonepistatic fitness matrix with marginal selection forces operating at those component loci where $\eta_k = 1$ while no selection differentials are contributed from the other loci. The collection of fitness matrices, $\{W(\eta)\}$, combined as in (20) induce a generalized nonepistatic regime based on the intrinsic fitness matrices $\{W_k\}_1^n$. The coefficients $c(\eta)$ contrast specific

combinations of nonepistatic selection differentials and neutral effects distributed among groupings of loci. We will write (21) more compactly as (*cf.*, (13), (14))

$$\Gamma = \sum_{\eta} c(\eta) W(\eta) \ . \tag{22}$$

Where $c(\mathbf{1}) = c(1,1,\ldots,1) = 1$ and all other $c(\eta)$'s equal zero, we have the pure multiplicative nonepistatic selection mode W of (17). If $c(1,0,\ldots,0) = c(0,1,\ldots,0) = \ldots = c(0,\ldots,0,1) = 1$ and all other $c(\eta)$'s equal zero then (22) represents additive nonepistatic selection S, whereas if $c(0,0,\ldots,0) = 1$ and all other $c(\eta)$'s are zero we get neutral selection E. We obtain the mixture

$$\Gamma = \alpha M + \beta S + \gamma E$$

of these three selection patterns by prescribing

$$c(\mathbf{1}) = \alpha,\ c(1,0,\ldots,0) = c(0,1,\ldots,0) = \ldots = c(0,\ldots,0,1) = \beta,\ c(\mathbf{0}) = \gamma. \tag{23}$$

and the remaining $c(\eta) = 0$.

The gamete frequency transformation equations with generalized nonepistatic selection: In the important case where the underlying fitness matrix has the multiplicative structure (17), (10) can be succinctly expressed in terms of Kronecker and Schur products.

Schur product: Let $\mathbf{x} = (x_1,\ldots,x_m)$ and $\mathbf{y} = (y_1,\ldots,y_m)$ be two vectors. The Schur product of $\mathbf{x}$ and $\mathbf{y}$ denoted $\mathbf{x} \circ \mathbf{y}$ is the vector

$$\mathbf{x} \circ \mathbf{y} = (x_1y_1, x_2y_2, \ldots, x_my_m) \ .$$

Let $\mathbf{x}$ designate the population state (gamete frequency array) in the current generation and $\mathbf{x}'$, the population state of the next generation.

With multiplicative nonepistatic selection and intrinsic fitness matrices $W_1, W_2, \ldots, W_n$, the transformation of gamete frequencies (10) expressed in vector form becomes

$$w(\mathbf{x})x' = \sum_{\varepsilon} R(\varepsilon)\,(W_1^{\varepsilon_1} \otimes W_2^{\varepsilon_2} \otimes \ldots \otimes W_n^{\varepsilon_n})\,\mathbf{x} \circ (W_1^{1-\varepsilon_1} \otimes W_2^{1-\varepsilon_2} \otimes \ldots \otimes W_n^{1-\varepsilon_n})\mathbf{x} \tag{24}$$

where $w(\mathbf{x})$ is the mean fitness at the population state $\mathbf{x}$. The exponents ε_k and $1-\varepsilon_k$ indicate powers such that $W_k{}^0 = I_k$ (the identity matrix of order m_k) and $W_k{}^1 = W_k$.

It is helpful to exhibit the form of (24) in the case of two and three loci. For the two-locus multiplicative model, (24) reads as

$$w(\mathbf{x})\mathbf{x}' = (1-r)\,(I \otimes I)\mathbf{x} \circ (W_1 \otimes W_2)\mathbf{x} + r(W_1 \otimes I)\mathbf{x} \circ (I \otimes W_2)\mathbf{x} \ .$$

For the three-locus multiplicative model with recombination parameters r,s,t as defined in (7), (24) becomes

$$\begin{aligned} w(\mathbf{x})\mathbf{x}' = {} & (1-r-s-t)\,(I \otimes I \otimes I)\mathbf{x} \circ (W_1 \otimes W_2 \otimes W_3)\mathbf{x} \\ & + r(W_1 \otimes I \otimes I)\mathbf{x} \circ (I \otimes W_2 \otimes W_3)\mathbf{x} \\ & + s(W_1 \otimes W_2 \otimes I)\mathbf{x} \circ (I \otimes I \otimes W_3)\mathbf{x} \\ & + t(W_1 \otimes I \otimes W_3)\mathbf{x} \circ (I \otimes W_2 \otimes I)\mathbf{x} \ . \end{aligned}$$

We underscore that the recombination frequencies r,s,t enter into the transformation equations symmetrically. This would not be the case if the traditional crossover parameters r_1,r_2, and r_3 were used (see after equation 7).

As the fitness matrix for the extended nonepistatic model (20) is a sum of multiplicative fitness regimes, the attendant transformation equations of gamete frequencies are derived by applying the formula (24) to each of the terms in (20).

3. EXISTENCE AND STABILITY OF HARDY-WEINBERG POLYMORPHIC EQUILIBRIUM

An important ingredient of the generalized nonepistatic selection model concerns the existence of a "central" Hardy-Weinberg equilibrium frequency state. Formally, a vector $\mathbf{x}$ of $\prod_{k=1}^{n} m_k = R$ coordinates is said to be of the H-W type if $\mathbf{x}$ admits the Kronecker product representation

$$\mathbf{x} = \mathbf{x}_1 \otimes \mathbf{x}_2 \otimes \ldots \otimes \mathbf{x}_n \tag{25}$$

where $\mathbf{x}_k$ is a vector of size m_k. The representation (25) entails that the components of $\mathbf{x}$ are determined by multiplicative contributions from the components of $\mathbf{x}_1,\mathbf{x}_2,\ldots,\mathbf{x}_n$. That is, the gamete frequencies (the components of $\mathbf{x}$) result as the products of their respective gene frequencies (the components of the $\mathbf{x}_k$'s). It is helpful to discuss some examples.

In the model of two loci with two alleles at each locus (alleles A,a at locus 1 and alleles B,b at locus 2), then $\mathbf{x} = (\xi_1,\xi_2,\xi_3,\xi_4)$ is H-W if and only if the disequilibrium expression $D(\mathbf{x}) = \xi_1\xi_4 - \xi_2\xi_3$ vanishes (*i.e.*, $\mathbf{x}$ is in linkage equilibrium). This fact is manifest on the basis of the familiar representation

$$\begin{aligned} \xi_1 &= \text{freq}(AB) = p_A p_B + D_{AB}, \quad \xi_2 = \text{freq}(Ab) = p_A p_B - D_{AB} \\ \xi_3 &= \text{freq}(aB) = p_a p_B - D_{AB}, \quad \xi_4 = \text{freq}(ab) = p_a p_b + D_{AB} \ , \end{aligned} \tag{26}$$

where $p_A = \xi_1 + \xi_2$ is the marginal frequency of A for the population state $\mathbf{x}$, $p_B = \xi_1 + \xi_3$, etc., and $D(\mathbf{x}) = D_{AB}(\mathbf{x}) = \xi_1\xi_4 - \xi_2\xi_3$ is the linkage disequilibrium function. The marginal frequency vectors $\mathbf{x}_1$ and $\mathbf{x}_2$ corresponding to the two loci in explicit components are $\mathbf{x}_1 = (p_A,p_a)$ and $\mathbf{x}_2 = (p_B,p_b)$. A compact writing of (26) as sums of Kronecker products gives

$$\mathbf{x} = \mathbf{x}_1 \otimes \mathbf{x}_2 + D(\mathbf{x})\mathbf{e} \otimes \mathbf{e} \tag{27}$$

where $\mathbf{e} = (1,-1)$, which shows that $\mathbf{x}$ projects in the direction of $\mathbf{e} \otimes \mathbf{e}$ an amount of $D(\mathbf{x})$ to achieve the Kronecker product vector composed from its component gene frequency vectors.

Consider next the case of three loci with two alleles at each locus, say $\{A,a\}$, $\{B,b\}$, and $\{C,c\}$ at the respective loci. Let $p_A, p_a, p_B \ldots$, denote the marginal frequencies of the alleles $A,a,B,\ldots$, respectively. We focus on the frequency state $\mathbf{x} = (\xi_1,\xi_2,\ldots,\xi_8)$, where $\xi_1 =$ frequency of the gamete type (ABC), $\xi_2 =$ freq(ABc), etc. It is convenient to operate with the random variables X,Y,Z defined for each gamete type, such that $X = 1\,(0)$ if allele $A\,(a)$ occurs at locus

1; $Y = 1$ or 0; $Z = 1$ or 0 according as B or b and C or c occurs at loci 2 and 3, respectively. We recall the following functionals and measures of association (apparently introduced originally by BENNETT 1954);

$E(X)$ = expectation of X = frequency of $A = p_A$,

$E(Y)$ and $E(Z)$ are defined similarly;

pairwise linkage disequilibrium values (or second order associations)

$$D_{AB} = E[X\text{-}E(X)][Y\text{-}E(Y)] = E(XY) - E(X)E(Y) = \text{freq}(AB)\text{-}p_A p_B,$$
$$D_{BC} \text{ and } D_{AC} \text{ defined analogously;} \tag{28}$$

third order association,

$$D_{ABC} = E[(X\text{-}E(X))(Y\text{-}E(Y))(Z\text{-}E(Z))]$$
$$= \text{freq}(ABC) - p_A \text{freq}(BC) - p_B \text{freq}(AC) - p_C \text{freq}(AB) + 3\, p_A p_B p_C.$$

An extension of (26) employs the representation

$$\begin{aligned}
\xi_1 &= \text{freq}(ABC) = p_A p_B p_C + p_A D_{BC} + p_B D_{AC} + p_C D_{AB} + D_{ABC} \\
\xi_2 &= \text{freq}(ABc) = p_A p_B p_c - p_A D_{BC} - p_B D_{AC} + p_c D_{AB} - D_{ABC} \\
\xi_3 &= \text{freq}(AbC) = p_A p_b p_C - p_A D_{BC} + p_b D_{AC} - p_C D_{AB} - D_{ABC} \\
\xi_4 &= \text{freq}(Abc) = p_A p_b p_c + p_A D_{BC} - p_b D_{AC} - p_c D_{AB} + D_{ABC} \\
\xi_5 &= \text{freq}(aBC) = p_a p_B p_C + p_a D_{BC} - p_B D_{AC} - p_C D_{AB} - D_{ABC} \\
\xi_6 &= \text{freq}(aBc) = p_a p_B p_c - p_a D_{BC} + p_B D_{AC} - p_c D_{AB} + D_{ABC} \\
\xi_7 &= \text{freq}(abC) = p_a p_b p_C - p_a D_{BC} - p_b D_{AC} + p_C D_{AB} + D_{ABC} \\
\xi_8 &= \text{freq}(abc) = p_a p_b p_c + p_a D_{BC} + p_b D_{AC} + p_c D_{AB} - D_{ABC}
\end{aligned} \tag{29}$$

The marginal frequency vectors, at the population state $\mathbf{x}$, are

$$\mathbf{x}_1 = (p_A, p_a),\ \mathbf{x}_2 = (p_B, p_b),\ \mathbf{x}_3 = (p_C, p_c)\ .$$

In line with (27), we can condense (29) to the form

$$\mathbf{x} = \mathbf{x}_1 \otimes \mathbf{x}_2 \otimes \mathbf{x}_3 + D_{BC}(\mathbf{x})(\mathbf{x}_1 \otimes \mathbf{e} \otimes \mathbf{e}) + D_{AC}(\mathbf{x})(\mathbf{e} \otimes \mathbf{x}_2 \otimes \mathbf{e}) + D_{AB}(\mathbf{x})(\mathbf{e} \otimes \mathbf{e} \otimes \mathbf{x}_3) + D_{ABC}(\mathbf{x})(\mathbf{e} \otimes \mathbf{e} \otimes \mathbf{e}) \tag{30}$$

where $\mathbf{e}$ stands for the canonical vector $\mathbf{e} = (1, -1)$ as in (27).

It is easy to infer on the basis of (30) that $\mathbf{x}$ reduces to $\mathbf{x} = \mathbf{x}_1 \otimes \mathbf{x}_2 \otimes \mathbf{x}_3$, that is the gamete frequencies occur as products of their gene frequencies if and only if

$$D_{BC}(\mathbf{x}) = D_{AC}(\mathbf{x}) = D_{AB}(\mathbf{x}) = D_{ABC}(\mathbf{x}) = 0\ . \tag{31}$$

When multiple (more than two) alleles are present, the measures akin to (28) are determined by distinguishing an allele at each locus and lumping the remaining alleles, reducing the system to two alleles per locus. In this way, corresponding to each gamete, an array of second, third, etc., association indices are computed. With these concepts established, we secure the fact that a vector of the Kronecker product form (25) manifests zero associations of all orders. Conversely, a complete set of zero association values for $\mathbf{x}$ characterize vectors repre-

sented as Kronecker products composed from the component gene frequency vectors.

The important Result I below applies to the generalized nonepistatic fitness regimes (22). The precise quantitative conditions ensuring stability of the H-W polymorphic equilibrium are delineated in Result III subsequently.

Result I: If each marginal fitness matrix W_k admits an equilibrium, $\mathbf{x}_k$ then the Kronecker product vector

$$\hat{\mathbf{x}} = \hat{\mathbf{x}}_1 \otimes \hat{\mathbf{x}}_2 \otimes \ldots \otimes \hat{\mathbf{x}}_n \tag{32}$$

constitutes an equilibrium of the extended nonepistatic fitness regime (22), independent of the weights $\{c(\eta)\}$, persisting for any recombination distribution. The equilibrium mean fitness is given by

$$\hat{w} = \sum_{\eta} c(\eta)\hat{w}(\eta) \quad \text{where } \hat{w}(\eta) = \hat{w}_1^{\eta_1}\hat{w}_2^{\eta_2} \ldots \hat{w}_n^{\eta_n} .$$

It is revealing to present in qualitative terms (*cf.*, 36, below) the stability conditions for the central H-W equilibrium in the cases of the pure multiplicative and pure additive selection forms. The facts on this matter are juxtaposed and highlighted as the content of Result II.

Result II: For multiplicative nonepistasis, the H-W vector (32) can be stable only under the condition that "heterosis" ("overdominance") prevails at each component locus (*i.e.*, each $\mathbf{x}_k$ is stable for the one-locus fitness matrix, W_k), and provided the recombination frequencies are large enough (*e.g.*, free recombination is more than enough); whereas in the additive nonepistatic case, heterosis at each separate locus already assures that the H-W polymorphism is stable, probably globally stable, for any degree of non-zero recombination.

In the general model (22), where the fitness values are not purely additive over loci, stability for the H-W equilibrium still requires enough positive recombination frequency among the loci, but at a reduced rate compared to the pure multiplicative model. Our experience, based on numerical computations, pertaining to Result II, indicates that generally moderate recombination suffices to insure a stable H-W polymorphism for multiplicative fitnesses.

Exact conditions for stability of the H-W polymorphism: *Suppose* $\hat{\mathbf{x}}_k$ is a polymorphic equilibrium with respect to locus k associated with the marginal fitness matrix W_k. Let $w_k(\mathbf{z})$ denote the mean fitness of the frequency state $\mathbf{z}$ with respect to the fitness matrix W_k. The standard one-locus theory (*e.g.*, KINGMAN 1961), tells us that $\hat{\mathbf{x}}_k$ is stable if and only if the eigenvalues $\{\lambda_{k,i}\}_{i=1}^{m_k}$ of the matrix $\widetilde{W}_k$ defined in (34) below satisfy

$$1 = \lambda_{k,1} > 0 > \lambda_{k,2} \geqslant \ldots \geqslant \lambda_{k,m_k} . \tag{33}$$

The matrix $\widetilde{W}_k$ is constructed as the matrix W_k multiplied on the left by the diagonal matrix having the components of the vector $\hat{\mathbf{x}}_k/w_k(\hat{\mathbf{x}}_k)$ on the diagonal, or in symbols

$$\widetilde{W}_k = \frac{\hat{\mathbf{x}}_k \circ W_k}{w_k(\hat{\mathbf{x}}_k)} . \tag{34}$$

Because the factors E_k occur intrinsically in (20) – (21), we also need to work with the matrix

$$\tilde{E}_k = \hat{\mathbf{x}}_k \circ E_k \ . \tag{35}$$

(This is E_k multiplied on the left by the diagonal matrix with the components of $\hat{\mathbf{x}}_k$ on the diagonal.) The eigenvalues of E_k, designated by $\{\mu_{k,i}\}_{i=1}^{m_k}$, assume two values $\mu_{k,1} = 1$, $\mu_{k,i} = 0$, $i = 2,3,\ldots,m_k$. We are now prepared to exhibit the exact stability conditions.

Result III: The H-W polymorphism $\mathbf{x} = \mathbf{x}_1 \otimes \mathbf{x}_2 \otimes \ldots \mathbf{x}_n$ is locally stable for the generalized nonepistatic selection regime (22) provided the quantities

$$\frac{2}{\hat{w}} \sum_{\eta} c(\eta)\hat{w}(\eta) \sum_{\varepsilon} R(\varepsilon) \left(\prod_{k=1}^{m_k} [\lambda_{k,i_k}^{\eta_k} \mu_{k,i_k}^{1-\eta_k}]^{\varepsilon_k} \right) \tag{36}$$

for all possible specifications of $i_1, i_2, \ldots, i_n$ precluding $i_1 = i_2 = \ldots = i_n = 1$, are less than one in magnitude. The rate of approach to the "central" H-W equilibrium is the largest magnitude of the quantities (36). (The strength of stability can be defined as 1 – rate of approach).

These criteria impose $(\prod_{k=1}^{n} m_k) - 1 = R-1$ requirements that often can be reduced by assuming additional structure on the model, usually of the nature of further relations satisfied by the coefficients $\{c(\eta)\}$ defining the selection regime. It is illuminating to elaborate a number of important cases of Result III. In the sequel, unless stated otherwise, we assume the hypothesis of Result I and that each individual locus is overdominant (see Result II).

1. *Two-locus stability of a H-W polymorphic equilibrium*: In this case the generalized nonepistatic fitness matrix has the form

$$c(1,1)W_1 \otimes W_2 + c(1,0)W_1 \otimes E_2 + c(0,1)E_1 \otimes W_2 + c(0,0)E_1 \otimes E_2 \ . \tag{37}$$

The conditions of (36) are of two types. The first merely affirms the stability requirements for the marginal equilibrium vectors, $\hat{\mathbf{x}}_1$ and $\hat{\mathbf{x}}_2$, equivalent to the relations (33) for the eigenvalues $\{\lambda_{1,i}\}_1^{m_1}$ and $\{\lambda_{2,i}\}_1^{m_2}$, that is, loci 1 and 2 are individually "overdominant". For typographical convenience we abbreviate the notation to

$$\lambda_{1,i} = a_i, \ i=1,2,\ldots,m_1 \text{ and } \lambda_{2,j} = b_j, \ j=1,2,\ldots,m_2$$

The further requirements embedded in (36) involve the recombination rate r between the two loci. This second set of conditions can be condensed to the single inequality

$$r > r_0 = \max_{\substack{2\leqslant i\leqslant m_1 \\ 2\leqslant j\leqslant m_2}} R_{ij} \quad , \text{ where } R_{ij} = \frac{c(1,1)\hat{w}_1\hat{w}_2 a_i b_j}{c(1,1)\hat{w}_1\hat{w}_2(1-a_i)(1-b_j)+c(1,0)\hat{w}_1(1-a_i)+c(0,1)\hat{w}_2(1-b_j)+c(0,0)} \tag{38}$$

where $\hat{w}_1 = w_1(\hat{\mathbf{x}}_1)$ and $\hat{w}_2 = w_2(\hat{\mathbf{x}}_2)$ calculate the marginal mean fitnesses at equilibrium.

Inspection of (38) reveals that if $c(1,1) > 0$, then some positive recombination is indispensable for stability of the H-W polymorphic equilibrium. In the pure multiplicative selection model, *viz*,

$$c(1,1) > 0,\ c(0,1) = c(1,0) = c(0,0) = 0,\ \text{then}$$
$$r_0 = \max_{\substack{2 \leqslant i \leqslant m_1 \\ 2 \leqslant j \leqslant m_2}} \left[\left(\frac{a_i}{1-a_i} \right) \left(\frac{b_j}{1-b_j} \right) \right] \quad \text{(Roux 1974)}. \tag{39}$$

Notice that with two loci, if $c(1,1) = 0$, such that the generalized nonepistatic selection regime is lacking a pure multiplicative contribution, then $r_0 = 0$, and any degree of positive recombination entails stability of the H-W polymorphic equilibrium, provided the two loci are heterotic. We add the note that if $c(1,1) = 0$, the selection mode is not the additive case unless $c(1,0) = c(0,1)$.

Since $-1 < a_i < 0, i = 2, \ldots, n$ (see 33), it follows that $\frac{a_i}{1-a_i} < \frac{1}{2}$ On this basis we deduce that $r_0 < \frac{1}{4}$ for all circumstances of two-locus generalized nonepistatic selection provided only that $c(\eta) \geqslant 0$ for all η. In particular, the central H-W equilibrium is stable in the presence of free recombination, even for $r > \frac{1}{4}$ (and in most practical cases for $r > 0.1$).

Felsenstein (1974) studied a two-locus fitness model with viability regime

	BB	*Bb*	*bb*
AA	$1-s-u+ksu$	$1-s$	$1-s-v+ksv$
Aa	$1-u$	1	$1-v$
aa	$1-t-u+ktu$	$1-t$	$1-t-v+ktv$

(40)

subject to $0 < s,t,u,v,k < 1$. If we prescribe the marginal fitness matrices

$$\begin{array}{c} \\ A \\ a \end{array} \begin{array}{c} \begin{array}{cc} A & a \end{array} \\ \left\| \begin{array}{cc} 1-s & 1 \\ 1 & 1-t \end{array} \right\| \end{array} = W_1, \qquad \begin{array}{c} \\ B \\ b \end{array} \begin{array}{c} \begin{array}{cc} B & b \end{array} \\ \left\| \begin{array}{cc} 1-u & 1 \\ 1 & 1-v \end{array} \right\| \end{array} = W_2,$$

then the fitness matrix associated with (40) can be represented as

$$kW_1 \otimes W_2 + (1-k)W_1 \otimes E_2 + (1-k)E_1 \otimes W_2 - (1-k)E_1 \otimes E_2, \tag{41}$$

which is of the structure (22).

In this special case the two-locus H-W polymorphism is locally stable by (38), provided the recombination frequency r satisfies

$$r > k \frac{st}{s+t} \quad \frac{uv}{u+v} \tag{42}$$

2. *Pure multiplicative nonepistasis*: In (22) we set $c(\mathbf{1}) = 1$, $c(\eta) = 0$ for all $\eta \neq 1$, so that the conditions of (36) reduce to:

the polymorphism $\hat{\mathbf{x}} = \hat{\mathbf{x}}_1 \otimes \hat{\mathbf{x}}_2 \otimes \ldots \otimes \hat{\mathbf{x}}_n$, is locally stable provided the inequalities

$$\left| 2 \sum_{\varepsilon} R(\varepsilon) (\lambda_{1,i_1}^{\varepsilon_1} \cdot \lambda_{2,i_2}^{\varepsilon_2} \cdots \lambda_{n,i_n}^{\varepsilon_2}) \right| < 1 \tag{43}$$

prevail for all choices of $\{\lambda_{k,i}\}_{i=1}^{m_k}$, $k=1,2,\ldots,n$ omitting the specification $\{\lambda_{1,1},\lambda_{2,1},\ldots,\lambda_{n,1}\}$.

The finding (43) for pure multiplicative nonepistasis was first uncovered by ROUX (1974).

3. *Mixed nonepistasis selection effects*: Based on case (1), one might have the impression that the stability of H-W polymorphic equilibrium needs some recombination only when the fitness matrix involves a pure multiplicative term. To illustrate that this is wrong, we discuss the case of three loci, with two alleles per locus, where the fitness matrix is given by

$$W_1 \otimes E_2 \otimes E_3 + E_1 \otimes W_2 \otimes W_3 \ . \tag{44}$$

This fitness matrix represents a generalized nonepistatic selection mode where the fitness contributions are conferred additively with respect to the first locus and the other two loci, while the fitnesses due to the second and third loci are multiplicative. This selection mode does not involve any straight multiplicative term. But applying the stability conditions (36) we find that the H-W polymorphism is stable when the three loci are heterotic and the recombination parameters r,s,t (of (7)) satisfy

$$0 < r \leqslant 1/2, \ \alpha^* < s+t < 1/2 \ , \tag{45}$$

where α^* is a calculable positive number determined by the actual fitness values at the three loci.

4. THE INFLUENCE OF "MORE RECOMBINATION" ON THE STABILITY OF A HARDY-WEINBERG POLYMORPHISM

For a system of two loci there are two natural bounds for the range of the recombination rate, r. On the one extreme there occurs the phenomenon of absolute linkage (no recombination), corresponding to $r=0$. The traditional upper bound refers to free recombination, $r=1/2$. Although mechanisms for recombination rates exceeding $1/2$ are conceivable in the context of some degree of chromatid interference, one usually takes the "natural" recombination range to be the interval $0 \leqslant r \leqslant 1/2$.

The theoretical analysis of two-locus selection balance often compels the intrinsic restriction $r \leqslant 1/2$. For example, the special position of free recombination relates to the scope of stability for a H-W equilibrium in the presence of a general viability scheme. Let $\mathbf{x}^* = (\xi_1^*,\xi_2^*,\xi_3^*,\xi_4^*)$ be an equilibrium for a general two-locus, two-allele viability regime. Suppose that $D(\mathbf{x}^*) = \xi_1^*\xi_4^* - \xi_2^*\xi_3^* = 0$ and $\mathbf{x}^*$ is stable for some recombination ($r = r_0$). Then it is established (KARLIN 1979) that $\mathbf{x}^*$ persists as a stable equilibrium for r through the range $r_0 \leqslant r \leqslant 1/2$. On the other hand, although $\mathbf{x}^*$ exists as an equilibrium for all $0 \leqslant r \leqslant 1$, this equilibrium state need not be stable when r somewhat exceeds $1/2$.

The ordering of more or less recombination in the case of two loci is unambiguous since a single real recombination parameter is involved. For three or more loci, the recombination process is characterized by a vector of rates (3 for three loci, 7 for four loci, etc.). Because of this multivariate setting, two recombination

frequency distributions $\mathbf{R} = \{R(\varepsilon)\}$ and $\mathbf{R}' = \{R'(\varepsilon)\}$ are not always comparable. However, any partial ordering relation among natural recombination distributions certainly compels the view that absolute linkage $\mathbf{R}^{(0)}$ [see (8)] is a minimal recombination distribution, whereas free recombination $\mathbf{R}^{(f)}$ [see (9)] should correspond to a "maximal" natural recombination distribution. A possible characterization of what is "more recombination" in a multilocus framework can be based on the following idea. Suppose that n loci are ordered, and let Δ_i for $i = 1,2,\ldots,n-1$ denote the chromosome segment connecting loci i and $i+1$. With respect to each subcollection of such segments, we ascertain the probability of an odd number of crossover events. These quantities are called "generalized recombination values" evaluated for every union of genomic segments connecting the various loci. For a single segment, Δ_i, the generalized recombination value coincides with the actual recombination rate between loci i and $i+1$. These generalized recombination values are estimable just as ordinary recombination rates (actually, independent of the order of the loci involved).

In terms of this array of generalized recombination values, the notions of "natural recombination" and "more recombination" can be coherently defined. Accordingly, relative to the n loci genome region we say that: (1) the recombination distribution $\mathbf{R}$ induces a "natural recombination" scheme if all the associated "generalized recombination values" are confined to the range [0,1/2] and (2) under the meaningful constraint that the recombination distributions $\mathbf{R}$ and $\mathbf{R}'$ are both natural, we say that $\mathbf{R}$ involves "more recombination" than $\mathbf{R}'$, provided all the generalized recombination values associated with $\mathbf{R}$ exceed, respectively, those associated with $\mathbf{R}'$.

With respect to these concepts, the recombination distribution referring to absolute linkage and free recombination are both natural, and they serve as "minimal" and "maximal" natural recombination distributions, such that other natural recombination distributions are constrained between them. To introduce these notions formally we define the multilocus linkage values associated with a recombination distribution, $\mathbf{R}$.

Definition 1: Let $\mathbf{R} = \{R(\varepsilon)\}$ be an n locus recombination distribution and let $\delta = (\delta_1,\delta_2,\ldots,\delta_n)$ be such that $\delta_i = 0$ or $\delta_i = 1$ for $i = 1,2,\ldots,n$ and $|\delta| = \sum_{i=1}^{n} \delta_i$ is even. The linkage value $\rho(\delta; \mathbf{R})$ associated with δ is defined as

$$\rho(\delta; \mathbf{R}) = \sum_{\varepsilon} R(\varepsilon)\,(-1)^{\sum_{i=1}^{n} \varepsilon_i \delta_i}, \tag{46}$$

where the sum extends over all $\varepsilon = (\varepsilon_1,\varepsilon_2,\ldots,\varepsilon_n)$, and each ε_i is independently 0 or 1. (The linkage value concept was first introduced by SCHNELL (1961) for purposes of computing identity-by-descent measures of various regular inbreeding systems in the multilocus framework.)

Definition 2: (1) The recombination distribution $\mathbf{R}$ is natural if the associated linkage values $\rho(\delta; R)$ are nonnegative for all δ. (2) If $\mathbf{R}$ and $\mathbf{R}'$ are two natural recombination distributions, we say that $\mathbf{R}$ involves more recombination than $\mathbf{R}'$ if

$$\rho(\delta; \mathbf{R}) \leqslant \rho(\delta; \mathbf{R}') \text{ for all } \delta. \tag{47}$$

With two loci, a check of (46) shows that a recombination scheme is natural if $0 \leqslant r \leqslant 1/2$. In view of (46), the comparison (47) reduces to $r > r'$. For the case of absolute linkage $\mathbf{R}^{(0)}$, the linkage values are all identically 1, while for the case of free recombination, all the linkage values vanish except for the $\delta = \mathbf{0}$ component.

With Definition 2 at hand the following result emerges:

Result IV: Under a generalized nonepistatic selection regime with "natural" recombination, if the H-W polymorphism is stable for some recombination level, then it is stable if "more" recombination is in force.

In the two-locus case, the foregoing result simply states that if the recombination rate ranges from 0 to 1/2, then the stability conditions on r are of the form $r > r_0$, where r_0 is explicitly ascertained (in terms of the nonepistatic fitness coefficients [*cf.*, (38)]. For any noninterference recombination structure with natural (between 0 and 1/2) pairwise recombination rates, stability of the H-W polymorphism is maintained only if the pairwise recombination rates are sufficiently large.

5. FURTHER DISCUSSION AND GRAPHICAL ANALYSIS OF SOME EXAMPLES

We attempt herewith to pinpoint the consequences of different forms of nonepistasis with respect to the "critical" levels of recombination needed in establishing a stable central H-W polymorphism. In order to discern these effects as separated from the influences attributable to variant marginal selection parameters, we assume that the marginal fitness matrices across loci are the same. Furthermore, in the comparisons we can assume without loss of generality that each locus carries two alleles such that the marginal heterozygote fitness value is 1.

The two-locus case: Let r_0 be the minimum level of recombination essential for stability of the H-W polymorphism, when selection forces are straight multiplicative. Then, the critical recombination frequencies corresponding to the extended nonepistatic selection regime

$$c(1,1)W_1 \otimes W_2 + c(1,0)W_1 \otimes E_2 + c(0,1)E_1 \otimes W_2 + c(0,0)E_1 \otimes E_2 \text{ is}$$

$$\left(\frac{c(1,1)}{c(1,1) + c(1,0) + c(0,1) + c(0,0)}\right) \cdot r_0 , \tag{48}$$

namely, the part of r_0 determined by the proportion of pure multiplicative viability effects relative to the conglomerate nonepistatic selection regime. Accordingly, with the superposition of increased multiplicative selection expression relative to additive selection expression, the opportunities for observing a stable H-W polymorphic equilibrium are diminished.

The three-locus case: Let $r_1 = r+t$, $r_2 = s+t$, $r_3 = r+s$ (see Section 1) be the pairwise recombination rates between loci 1 and 2, 2 and 3, and 1 and 3, respectively. Let r_0 denote, as above, the critical extent of pairwise loci recombination rates necessary for establishing the H-W polymorphism stable under pure multiplicative selection (r_0 coincides for the three pairs of loci as the marginal fitness

matrices coincide). Thus, for extended nonepistatic selection regimes of the form [*cf.*, (14)]

$c(1,1,1)W_1 \otimes W_2 \otimes W_3 + c(1,1,0)W_1 \otimes W_2 \otimes E_3 + \ldots + c(0,0,0)E_1 \otimes E_2 \otimes E_3$,

the stability of the H-W polymorphism requires overdominance at each locus and pairwise recombination rates large enough to the extent of

$$r_1 > r_0 \cdot \frac{c(1,1,0)+\hat{w}c(1,1,1)}{[c(1,1,0)+c(1,0,0)+c(0,1,0)+c(0,0,0)]+\hat{w}[c(1,1,1)+c(1,0,1)+c(0,1,1)+c(0,0,1)]}$$

$$r_2 > r_0 \cdot \frac{c(0,1,1)+\hat{w}c(1,1,1)}{[c(0,1,1)+c(0,1,0)+c(0,0,1)+c(0,0,0)]+\hat{w}[c(1,1,1)+c(1,1,0)+c(1,0,1)+c(1,0,0)]} \tag{49}$$

$$r_3 > r_0 \cdot \frac{c(1,0,1)+\hat{w}c(1,1,1)}{[c(1,0,1)+c(1,0,0)+c(0,0,1)+c(0,0,0)]+\hat{w}[c(1,1,1)+c(1,1,0)+c(0,1,1)+c(0,1,0)]}$$

We propose to provide a comparison along the lines of the two-locus case. In this vein, we compare the stability conditions (49) for the three classes of selection forms

$\mathcal{C}_{[3]}$ — Pure multiplicative selection $c(1,1,1) = 1$ and other c's zero.
$\mathcal{C}_{[2]}$ — $c(1,1,0) = c(0,1,1) = c(1,0,1) = 1$ and all other c's zero.
$\mathcal{C}_{[1]}$ — Pure additive selection $c(1,0,0) = c(0,1,0) = c(0,0,1) = 1$

and all other c's zero.

For each of these nonepistatic viability regimes, the weights $\{c(\eta)\}$ depend on the number of loci exhibiting differential selection (one in pure additive selection, two in the class $\mathcal{C}_{[2]}$ and three where pure multiplicative selection operates). Comparing the stability conditions in these three classes, we obtain the following:

For a given set of recombination rates, then with more loci expressing differential selection the H-W polymorphism is less likely to be stable. Equivalently, if the H-W polymorphism is stable with respect to multiplicative selection ($\mathcal{C}_{[3]}$), it is also stable with respect to the class $\mathcal{C}_{[2]}$, and when stable with respect to $\mathcal{C}_{[2]}$, it is also stable for additive selection $\mathcal{C}_{[1]}$.

We render this result in schematic form in two cases of recombination patterns:

(1) no interference between the three loci
$r_3 = r_1(1-r_2) + r_2(1-r_1) = r_1 + r_2 - 2r_1r_2$;

(2) complete interference between the three loci, *i.e.*, $r_3 = r_1 + r_2$.

In both cases there are only two effective recombination frequencies, which we observe to be r_1 and r_2. Where r_1 and r_2 obey (49), the same holds for r_3. The stability domains in both cases are displayed in Figure 1.

SUMMARY AND DISCUSSION

There are two classical prototype forms of nonepistatic selection—the multiplicative and the additive models. The fitness value of a given genotype is attributable to the independent effects conferred by the separate loci in either a multiplicative or additive sense. The dynamic and equilibrium behavior for the multiplicative as against the additive model is significantly divergent, especially

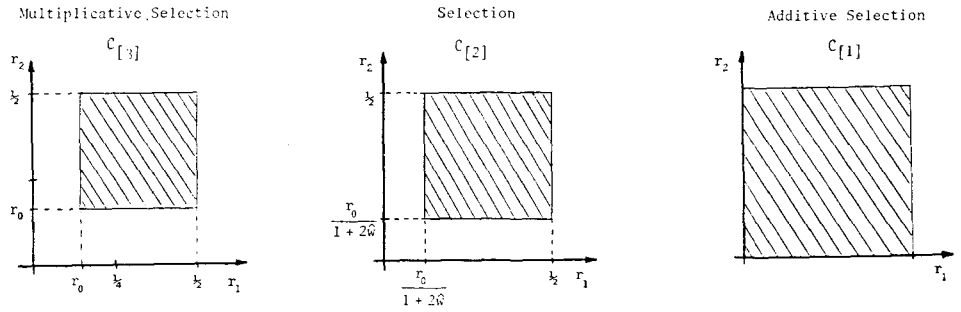

FIGURE 1.—The shaded area is a schematic comparison of the domains of recombination frequencies (r_1, r_2) for which the H-W polymorphism is stable with respect to the specified selection regime ($\mathcal{C}_{[1]}$, $\mathcal{C}_{[2]}$ and $\mathcal{C}_{[3]}$).

in the presence of tight linkage (see KARLIN 1975, 1977). The existence of epistasis is generally understood to signify that the fitness of a genotype cannot be partitioned into contributions of mixed additive and multiplicative effects along a series of loci. We introduced (detailed in section 2) a generalized formulation of nonepistasis that embraces mixed multiplicative and additive regimes where the fitness expression involves combinations of nonepistatic selection differentials and neutral effects distributed among groupings of loci. In this framework, measures of epistasis should refer to the degree of departure from the generalized nonepistatic selection mode.

Nonepistasis (referring to a class of selection regimes) and genic nonassociations (pertaining to characterizations and classifications of gamete configurations) convey activities and measurements at different levels of the genetic process. Nevertheless, these concepts are intimately connected. In particular, we have established (Results 1 to 3 of section 3) that H-W equilibria arise for nonepistatic selection models, under conditions of loose linkage.

The precise stability criterion of a H-W polymorphic equilibrium generally depends on the type of nonepistasis operating and the extent of recombination involved. For straight multiplicative nonepistasis, a H-W polymorphism can be stable only under the condition that "heterosis" (the existence of a stable polymorphism) prevails at each component locus and provided that the recombination rates are sufficiently large (Result II). On the other hand, in the additive case heterosis at each separate locus already assures that the H-W equilibrium is stable for any set of non-zero recombination frequencies. For the generalized nonepistatic selection regime where the effects are not exclusively multiplicative over loci, stability for a H-W polymorphic equilibrium generally still requires positive recombination among the loci, but at a reduced rate compared to the straight multiplicative model.

The nature of stable equilibria with tight linkage for multiplicative nonepistasis, in sharp contrast to H-W type of equilibria, usually entails a partial group of gamete types each represented in moderate frequencies, while the remaining gamete types appear in trace amounts. The precise results fall back on a careful

description of the nature of the stable equilibria extant for certain multiallele one-locus selection models. When the H-W equilibrium is not stable for absolute linkage, the multiallele one-locus theory points up the existence of a multiplicity of stable boundary and approximate boundary equilibria (see KARLIN 1977).

Subject to an extended nonepistatic fitness selection form, the H-W polymorphism is always stable for free recombination, but never stable with tight linkage when the fitness regime involves at least two loci contributing multiplicative fitness factors. The contrapositive form of this statement conveys the following implication. Where a population equilibrium exhibits approximately H-W proportions and there is evidence that the loci involved are tightly linked, and if some selection balance is implicated, then the selection operating entails some degree or form of epistasis.

Additive and/or neutral components of the generalized nonepistatic fitness regime, relative to a straight multiplicative term, require a diminished recombination mechanism in order to maintain a stable H-W polymorphism. Equivalently, the addition of more contrast to the pure multiplicative selection component with the same level of recombination can have a destabilizing effect relative to the H-W equilibrium.

Another facet of interest concerns the rate of convergence to a stable H-W polymorphism. One might expect the introduction of neutral terms to decelerate the rate of convergence. This inference is generally not valid. Already in the simplest two-locus case, we can produce examples entailing an interval of recombination frequencies in which the H-W polymorphism is stable, whereas with the introduction of "more" neutral effects, the rate of convergence to the polymorphism is slowed.

A H-W equilibrium array is characterized by zero associations of all orders. A possible implication of this fact is as follows. A recorded set of gamete frequencies entailing significant non-zero associations, coupled to some independent evidence of loose linkage among the loci involved, essentially abrogates a generalized nonepistatic selection linkage balance as a mechanism to account for the observed population state. Of course, there are other possible causes for linkage disequilibrium that need to be weighed in the total picture. These include random genetic drift effects, admixture and migration among two or more populations, nonrandom mating patterns, etc.

A stable H-W polymorphic equilibrium for some recombination level remains stable with "more recombination". This concept is circumscribed in Definitions 1 and 2 of Section 4.

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