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Evolution

An evolutionary reduction principle for genetic modifiers

(recombination/mutation/migration/evolutionarily stable strategy/evolutionary genetic stability)

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ABSTRACT **The joint evolution of major genes under viability selection and a modifier locus that controls recombination between the major genes, mutation at the major gene, or migration between two demes is studied. The modifying locus is selectively neutral and may have an arbitrary number of alleles. For each case a class of polymorphic equilibria exists in which the frequencies of the modifying alleles are those computed by assuming that the recombination, mutation, or migration rates were viabilities and in which the major and modifier loci are not statistically associated. These are called *viability-analogous Hardy–Weinberg* (VAHW) equilibria. A new allele introduced near these equilibria will enter the population if its marginal average rate of recombination, mutation, or migration (whichever applies) is less than the population average prior to its introduction. Stability properties of these VAHW equilibria are also reported.**

This paper reports a class of results in the evolutionary theory of recombination, mutation, and migration. Each of these has been the subject of investigation from both the point of view of evolutionarily stable strategy (ESS) and that of population genetics. The population genetic theory we describe here has its origin in Nei's study (1, 2) of selectively neutral modifiers of recombination between two major genes under selection. Nei's approach has been recast and applied to the evolution of mutation and migration also (3–8). This reformulation has the following three components: (*i*) The modifying locus is originally fixed on allele M_1. (*ii*) There is an equilibrium due to the balance between selection on the major genes and whichever one of recombination, mutation, or migration is under study, and this equilibrium is a function of the modified parameter. (*iii*) A new allele, M_2, at the modifying locus is introduced near this equilibrium. We then seek the conditions on the heterozygote M_1M_2 that entail its initial increase.

It has been shown in the case of recombination (3, 4), mutation (5, 6), and migration (5, 7, 8) that under assumptions (*i*) and (*ii*) above the frequency of the new allele M_2 increases initially, provided it reduces the value of the recombination fraction, mutation rate, or migration rate. While this reduction often entails an increase in the population mean fitness (5, 9), the two properties do not necessarily coincide (10, 11).

The fate of the new modifying allele subsequent to its initial increase depends on all of the parameters at the modifier locus. Feldman and Balkau (12) exhibited a polymorphic equilibrium for a recombination modifier when M_1M_2 had a lower recombination rate than either M_1M_1 or M_2M_2. The stability of the polymorphism was shown to depend on the linkage of the major genes to the modifier, in marked contrast to the initial increase results, which showed no such dependence. A general form for such two-allele modifier polymorphisms was exhibited by Feldman and Krakauer (13), and its extension will be the subject of the following presentation.

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Our aim here is to describe the generalization of this entire theory to allow an arbitrary number of alleles at the modifying locus. Such an extension would then apply to the situation of a number of tightly linked modifying loci. In the process we shall characterize the joint equilibria of the modifier and major genes and show that a new modifying allele, introduced near an important class of these equilibria, succeeds only if it reduces the parameter it modifies. We call this the *evolutionary reduction principle*.

Models of Neutral Modifiers

The theory concerns randomly mating diploids with nonoverlapping generations. Selection is at the level of viability and is constant over time. The populations are large.

Mutation. At the major locus there are alleles A and a, and the relative viabilities of AA, Aa, and aa are w_{11}, w_{12}, and w_{22}, respectively. At the mutation-modifying locus there are n alleles $M_1, M_2, \ldots, M_n$ such that if the genotype at this locus is M_iM_j, the mutation rate is μ_{ij} for mutation from A to a and ν_{ij} from a to A. The genotype at the modifying locus has no effect on the fitnesses of the genotypes at the major gene. Denote the matrices $\|\mu_{ij}\|$ and $\|\nu_{ij}\|$ by $\mathbf{M}$ and $\mathbf{N}$, respectively. Although we have proved (14) some results without further assumptions on $\mathbf{M}$ and $\mathbf{N}$, the majority of the results reported below require that $\mathbf{N} = b\mathbf{M}$, where b is a scalar constant that we may assume satisfies $0 \le b \le 1$. It will be clear where this assumption is required. The recombination rate between the major and modifying loci is R ($0 \le R \le \frac{1}{2}$).

After random union of gametes, viability selection, mutation, recombination, and Mendelian segregation occur, in that order, after which gametes are censused. The frequencies of A and a are x_1 and x_2 ($= 1 - x_1$), respectively. Then denote by x_1p_i and x_2q_i the frequencies of AM_i and aM_i, respectively, with $0 \le p_i, q_i \le 1$; $\Sigma_{i=1}^n p_i = \Sigma_{i=1}^n q_i = 1$. We write $\mathbf{p} = (p_1, p_2, \ldots, p_n)$, $\mathbf{q} = (q_1, q_2, \ldots, q_n)$, and $\mathbf{x} = (x_1, x_2)$. This frequency representation has been used by Lessard (15).

Recombination. The major genes have alleles A and a at the first locus and B and b at the second. The chromosomes AB, Ab, aB, and ab are indexed as 1, 2, 3, and 4, respectively, with w_{ij} the viability of the i,j two-locus genotype. The alleles M_1, M_2, ..., M_n at the modifying locus are such that when the genotype is M_iM_j at the modifier, the recombination fraction between A/a and B/b is R_{ij} with $\mathbf{R} = \|R_{ij}\|$. The extent of linkage between the modifier locus and the major loci is arbitrary. The order of the three genes and the nature of the interference between them are immaterial, although for some results we shall require no interference among the genes.

The order of events is random mating, recombination, Mendelian segregation, and viability selection, in that order, after which the chromosome frequencies are censused. The frequencies of the chromosomes AB, Ab, aB, and ab are x_1, x_2, x_3, and x_4, respectively, and those of ABM_i, AbM_i, aBM_i, and abM_i are x_1p_i, x_2q_i, x_3r_i, and x_4s_i, respectively, with $0 \le p_i, q_i, r_i, s_i \le 1$; $\Sigma_{i=1}^n p_i = \Sigma_{i=1}^n q_i = \Sigma_{i=1}^n r_i = \Sigma_{i=1}^n s_i = 1$, and we

Abbreviation: VAHW, viability-analogous Hardy–Weinberg.

set $\mathbf{p} = (p_1, p_2, \ldots, p_n)$, $\mathbf{q} = (q_1, q_2, \ldots, q_n)$, $\mathbf{r} = (r_1, r_2, \ldots, r_n)$, $\mathbf{s} = (s_1, s_2, \ldots, s_n)$, and $\mathbf{x} = (x_1, x_2, x_3, x_4)$.

Migration. There are two demes with individuals defined by two genes. At the first locus there are two alleles A and a, and the genotypes AA, Aa, and aa have relative viabilities w_{11}, w_{12}, and w_{22} in the first deme, and v_{11}, v_{12}, and v_{22} in the second. The second locus, with alleles M_1, M_2, ..., M_n, controls the rate of migration between demes so that an individual of genotype M_iM_j migrates from one deme to the other with probability m_{ij} and remains in the same deme with probability $1 - m_{ij}$. We write $\mathbf{M} = \|m_{ij}\|$. The sequence of events is random union of gametes in each deme separately, viability selection on the zygotes in each deme, migration of the survivors of selection, recombination, and Mendelian segregation in each deme, in that order, after which the census of gametes occurs. It will be clear from the context whether $\mathbf{M}$ refers to the mutation or migration matrix.

Again x_1 and x_2 $(= 1 - x_1)$ [y_1 and y_2 $(= 1 - y_1)$] are the frequencies of A and a in deme I (deme II) and in deme I we set x_1p_i and x_2q_i to be the frequencies of AM_i and aM_i, respectively. y_1r_i and y_2s_i are the corresponding frequencies in deme II. Here $0 \le p_i, q_i, r_i, s_i \le 1$; $\Sigma_i p_i = \Sigma_i q_i = \Sigma_i r_i = \Sigma_i s_i = 1$ and $\mathbf{x} = (x_1, x_2)$, $\mathbf{y} = (y_1, y_2)$ with $\mathbf{p}$, $\mathbf{q}$, $\mathbf{r}$, and $\mathbf{s}$ as before.

The theory that we shall develop for these models has three parts. We first exhibit a class of equilibria that is polymorphic at the major and modifying loci and has a similar structure for all three models. This structure is characterized by statistical independence of the major and modifying loci. Second, we enunciate the *reduction principle*—namely, that such a polymorphism with n modifying alleles is unstable to invasion by the allele M_{n+1} if the parameter under modification is initially decreased in genotypes with M_{n+1}. Third, we report some stability properties of the n-allele polymorphism in the usual interior sense.

Viability-Analogous Hardy–Weinberg (VAHW) Equilibria

For each of the three models a class of equilibria of the evolutionary dynamic system exists. Although there is a major core of similarity among the cases, it is useful to separate them as follows. The details of the analyses are reported for mutation in ref. 14 and recombination in ref. 16 and will be reported elsewhere for migration.

Mutation.

RESULT I. *At equilibrium either* $\mathbf{p} = \mathbf{q}$ *or the equilibrium frequencies of* A *and* a *do not depend on the mutation matrices* $\mathbf{M}$ *and* $\mathbf{N}$.

Since our subsequent analysis is relevant only to equilibria for which the frequencies are functions of the mutation rate, we assume $\mathbf{p} = \mathbf{q}$. Then we have

RESULT II. *Suppose that the mutation matrices* $\mathbf{M}$ *and* $\mathbf{N}$ *are such that there exists a frequency vector* p^* *for which* $\mathrm{p}\circ\mathbf{M}\mathrm{p}^* = \mu^*\mathrm{p}^*$ *and* $\mathrm{p}^*\circ\mathbf{N}\mathrm{p}^* = \nu^*\mathrm{p}^*$, *where* $\mu^* = (\mathrm{p}^*, \mathbf{M}\mathrm{p}^*)$ *and* $\nu^* = (\mathrm{p}^*, \mathbf{N}\mathrm{p}^*)$. *Then there is at least one (and at most three) equilibrium of the two-locus system having the form* $\mathrm{x}^*\otimes\mathrm{p}^*$, *where* $\mathrm{x}^* = (\mathrm{x}_1^*, \mathrm{x}_2^*)$ *is an equilibrium of the major locus (considered in the absence of the modifying gene) under the specified selection regime and with mutation rates* μ^* *and* ν^*. *The equilibrium* $\mathrm{x}^*\otimes\mathrm{p}^*$ *is called a viability-analogous Hardy–Weinberg (VAHW) equilibrium of the two-locus system.*

Remarks: (*i*) The terminology "viability-analogous" (18) reflects the fact that $\mathbf{p}^*$ has the form of a polymorphic n-allele equilibrium under viability selection with viability matrix $\mathbf{M}$. It should not be interpreted in terms of the actual viabilities at the major locus. Such a viability-analogous equilibrium exists if a valid frequency vector solves the linear system specified by the equality of the n marginal average mutation rates for M_1, M_2, ..., M_n. Existence properties of such systems have been studied extensively in population genetics (19, 20).

(*ii*) The descriptor "Hardy–Weinberg" has been used (21) to indicate that at equilibrium the two loci are in linkage equilibrium, so that each gamete frequency is simply the product of its constituent allele frequencies. No relationship with the Hardy–Weinberg law for one locus is implied by this terminology.

(*iii*) μ^* and ν^* are the population average mutation rates computed at the viability-analogous values for the frequencies of M_i. *Result I* requires no assumptions on $\mathbf{M}$ and $\mathbf{N}$. In what follows we shall assume that $\mathbf{N} = b\mathbf{M}$, where b is a scalar and $0 \le b \le 1$, so that $\nu^* = b\mu^*$. *Result II* holds in this case, and models with $b = 0$ and $b = 1$ have been studied previously (e.g., ref. 6). It is likely that the following results about mutation modifiers may be qualitatively true more generally.

Recombination.

RESULT III. *Suppose that the vector* y^* *satisfies* $\mathrm{y}^*\circ\mathbf{R}\mathrm{y}^* = \mathrm{r}^*\mathrm{y}^*$, *where* $\mathrm{r}^* = (\mathrm{y}^*, \mathbf{R}\mathrm{y}^*)$. *Suppose also that* x^* *is an equilibrium of the two-locus system with viabilities* $\|\mathrm{w}_{ij}\|$ *and recombination fraction* r^*, *considered in the absence of the modifying locus. Then there is an equilibrium of the form* $\mathrm{p} = \mathrm{q} = \mathrm{r} = \mathrm{s} = \mathrm{y}^*$ *with the* 4n *gamete frequencies specified by* $\mathrm{x}^*\otimes\mathrm{y}^*$.

Remark: Again this is a VAHW equilibrium. $\mathbf{r}^*$ is the population average recombination frequency at $\mathbf{y}^*$ and, although the two major loci may be in linkage disequilibrium, they are in linkage equilibrium with the modifier.

Migration.

RESULT IV. *Suppose that the vector* z^* *satisfies* $\mathrm{z}^*\circ\mathbf{M}\mathrm{z}^* = \mathrm{m}^*\mathrm{z}^*$, *where* $\mathrm{m}^* = (\mathrm{z}^*, \mathbf{M}\mathrm{z}^*)$. *Suppose also that* $\mathrm{x}^* = (\mathrm{x}_1^*, \mathrm{x}_2^*)$ *and* $\mathrm{y}^* = (\mathrm{y}_1^*, \mathrm{y}_2^*)$ *are equilibria of the one-locus two-deme model with selection regimes* w_{11}, w_{12}, w_{22} *and* v_{11}, v_{12}, v_{22} *described earlier, and migration rate* m^*. *Then there is an equilibrium of the complete system of the form* $\mathrm{p} = \mathrm{q} = \mathrm{r} = \mathrm{s} = \mathrm{z}^*$ *with the gamete frequencies specified by* $\mathrm{x}^*\otimes\mathrm{z}^*$ *in deme I and* $\mathrm{y}^*\otimes\mathrm{z}^*$ *in deme II.*

In each of the three models the results describe one class of equilibria. They do not address the existence of other equilibria, which has been demonstrated in special cases (12). The two-allele form of the above existence propositions was suggested previously by Feldman and Krakauer (13). In the next two sections we consider the stability of the VAHW equilibrium in two senses, first to invasion by a new modifying allele M_{n+1} and second in the usual sense of a polymorphic equilibrium subject to perturbation of the frequencies of gametes already present.

The Reduction Principle Near VAHW Equilibria

The population is assumed to be very close to a VAHW equilibrium at which the frequencies of the n modifying alleles are given by the vector $\mathbf{p}^*$ in terms of the matrix $\mathbf{T} = \|\tau_{ij}\|$ of parameter values τ_{ij} for M_iM_j $(i,j = 1, 2, \ldots, n)$. Here τ_{ij} refers to any of the three models. In the mutation case we assume (from now on) that $\mathbf{N} = b\mathbf{M}$ so that τ_{ij} refers to μ_{ij}. Write $\tau^* = \Sigma_{i=1}^n \Sigma_{j=1}^n \tau_{ij} p_i^* p_j^*$ for the population average parameter value at the VAHW point.

A new allele M_{n+1} arises at the modifying locus in this neighborhood of the VAHW point. The genotypes M_iM_{n+1} give rise to parameter values $\tau_{i,n+1}$. The following result is true for all three models (under the assumption that $\mathbf{N} = b\mathbf{M}$ in the mutation case) and specifies the conditions on $\tau_{i,n+1}$ under which M_{n+1} will initially increase.

RESULT V. Reduction principle. *Let* $\hat{\tau} = \Sigma_{i=1}^n p_i^*\tau_{i,n+1}$ *be the marginal average parameter value for the new allele* M_{n+1} *introduced near a VAHW equilibrium at which the frequencies of* $\mathrm{M}_1, \mathrm{M}_2, \ldots, \mathrm{M}_n$ *are given by* $\mathrm{p}_1^*, \mathrm{p}_2^*, \ldots, \mathrm{p}_n^*$ *in terms of* $\mathbf{T}_{n\times n}$. *Suppose also that at the VAHW equilibrium the gamete frequencies at the major locus (or loci) depend on* τ^*. *Then*

this VAHW equilibrium is unstable to the introduction of M_{n+1} *if* $\hat{\tau} < \tau^*$ *and it is stable to the introduction of* M_{n+1} *if* $\hat{\tau} > \tau^*$. Thus, in each model there is induced selection on the modifying locus to reduce the population average parameter value.

Remark: The result is independent of the degree of linkage of the major and modifying loci. In the case of recombination, it is independent of the presence of interference (16). If M_{n+1} is introduced near an equilibrium that is not a function of the modified parameter values, the rate of change of M_{n+1} is at most algebraic. Such a case arises, for example, in the linkage modification case when there is linkage equilibrium (see ref. 3).

Internal Stability of VAHW Equilibrium

We seek conditions under which a VAHW equilibrium is locally stable to perturbations among the resident genotypes. Such perturbations are in the interior of the simplex described by the *n* original modifying alleles and the major locus; it is therefore called *internal stability*. Our interest is only in those VAHW equilibria that actually depend on the parameter affected by the modifier locus. Thus, for example, in the case of recombination modification the major loci must be in linkage disequilibrium. For the mutation case we again assume $\mathbf{N} = b\mathbf{M}$. In the case of recombination we assume that there is no interference. Then for all three models we have

RESULT VI. Necessary condition for internal stability. *Suppose that the frequencies of* M_i *at the VAHW equilibrium with respect to* $\mathbf{T} = \|\tau_{ij}\|$ *are* p_i^* $(i = 1, 2, \ldots, n)$. *Then for the VAHW equilibrium to be stable it is necessary that all of the eigenvalues of the matrix* $\mathbf{p}^* \circ \mathbf{T}$ *be positive.*

From the well-known result of Kingman (22), *Result VI* implies that $\mathbf{p}^*$, considered as the polymorphic equilibrium of the viability matrix $\mathbf{T}$, would be unstable. In the same sense it would be stable with respect to the matrix $\mathbf{E} - \mathbf{M}$, where $\mathbf{E}$ is the matrix whose entries are all units. For further details concerning internal stability the three cases are treated separately.

RESULT VII. *In the mutation case with* $\mathbf{N} = b\mathbf{M}$ *suppose that all eigenvalues of* $\mathbf{p}^* \circ \mathbf{M}$ *are positive and that the equilibrium* x^* *at the major locus is stable as a one-locus equilibrium. Then* $x^* \otimes p^*$ *is locally stable under any of the following conditions:*

(i) $b = 1$; *i.e.*, $\mathbf{N} = \mathbf{M}$.

(ii) *The major and modifying genes are sufficiently loosely linked.*

(iii) μ^* *(and hence* ν^**) are sufficiently small with respect to* w_{11}, w_{12}, *and* w_{22}.

Remark: Condition *iii* is generally considered to be biologically reasonable. *Result VII* holds more generally than stated. For example, if $w_{11}w_{22} > w_{12}^2$ the result is true for arbitrary linkage between the loci. Further, we have numerically explored the parameter space for two modifying alleles M_1M_2 under the condition $\mu_{12} < \mu_{11}, \mu_{22}$ (so that the condition of *Result VI* holds) with $b = 0$ and the two loci *absolutely linked*, and $w_{12}^2 > w_{11}w_{22}$ has failed to produce a case in which the VAHW polymorphism is unstable.

RESULT VIIIA. Recombination case. *When the modifier locus and major locus are tightly linked the VAHW polymorphism is internally unstable.*

RESULT VIIIB. Recombination case. *Suppose that all eigenvalues of* $y^* \circ \mathbf{R}$ *are positive and that* x^*, *considered as an equilibrium of the two major loci, is stable. Then* $x^* \otimes y^*$ *is internally locally stable if the linkage between the major loci and the modifier is sufficiently loose.*

RESULT IX. Migration case. *Suppose that all eigenvalues of* $z^* \circ \mathbf{M}$ *are positive and that* $m^* \leq \frac{1}{2}$. *Suppose also that* x^* *in deme I and* y^* *in deme II constitute a stable one-locus two-deme polymorphism with migration rate* m^*. *Then the VAHW equilibrium specified by* $x^* \otimes z^*$ *and* $y^* \otimes z^*$ *is internally locally stable, provided that the two loci are sufficiently loosely linked.*

Remark: Again *Result IX* is not the best possible for the migration case. Numerical studies (K. E. Holsinger, M.W.F., and U.L., unpublished manuscript) have produced many examples in which the two loci are absolutely linked and, in contrast to the recombination case, the VAHW equilibrium is stable.

Discussion

The VAHW equilibria constitute but one class of polymorphisms that may exist in these models. In the recombination and mutation cases we know that other polymorphic equilibria may be locally stable for ranges of parameters that may overlap those for which the VAHW points are stable. It is reasonable to conjecture that these other points also satisfy the reduction principle. In other words, our conjecture is that the parameter value zero has the property of evolutionary genetic stability (EGS). EGS was introduced by Eshel and Feldman (24) as an alternative conceptual view of long-term evolution to evolutionarily stable strategy in the presence of genetic polymorphism.

The results we have reported are "local" in the sense that they refer to the reduction of the population's average parameter value in the neighborhood of the VAHW equilibrium. S. Karlin, U.L., and M.W.F. (unpublished results) have shown that there is a global consequence—namely, that the ultimate mean population value of the modified parameter will be smaller than the original value prior to the introduction of M_{n+1}. The suggestion is, then, that genetic modifiers of mutation, recombination, and migration should evolve to the lowest value compatible with selective neutrality, at least at the viability level.

When does the reduction principle fail? It is well known that, with finite population size or fluctuating viabilities over time, modifiers that increase the parameters studied here may succeed (17, 25, 26). It is not so widely known that, in constant selection regimes, increase may occur when (*i*) both gametic and zygotic selection occur (11); (*ii*) when the modifier affects one of the parameters, recombination, but there is also mutation at the major loci (4); or (*iii*) when mating is not at random (7). We have also recently found cases in which, with constant selection, but at the level of fertility rather than viability, mutation may increase (23). The bounds on the class of models that allow VAHW equilibria and on parameters that are subject to our reduction principle remain an open question.

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