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The Evolutionary Development of Modifier Genes

(linkage development/mutation reduction/assortment/selfing)

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ABSTRACT **The main findings of a study of the evolution of modifier gene frequencies in models of deterministic population genetics are presented. A wide variety of random mating systems are subject to selection with modifiers operating, in different cases, on mutation rates, dominance, migration between subpopulations, and linkage between other loci. In all these instances the modifier frequencies evolve in such a way as to maximize the mean fitness of the population at equilibrium. This is remarkable since, except for the dominance modifier, the modifier genes are selectively neutral in the sense that they do not affect the fitness of their individual carriers. In nonrandom mating systems the mean fitness concept is not well defined, and there does not appear to be such a simple principle governing the evolution of modifier frequencies. In assortative mating systems modifiers favoring reduced assortment propensities tend to increase. In contrast, for selfing-outcrossing systems modifiers favoring increased selfing tend to increase.**

This paper highlights several results and qualitative findings (based on a study to be published) concerning the fate of genes that modify parameters that determine the main effects of genes at other loci. The modifier model considered has the following structure. There is a set of primary loci subject to the usual genetic influences of natural selection forces, mutation and migration rates, recombination fraction, and mating behavior and pattern; e.g., as assortment propensities and degree of outcrossing, etc. The genotypes at the secondary (modifier) loci alter the determination of the parameter values delimiting the genetic system and mechanisms corresponding to the primary loci. Linkage relationships may exist between the primary and secondary loci. It is useful to refer to the following specific modifier models.

(*i*) *Linkage Modification.* The existence of genes finely controlling recombination at specific sites are well and increasingly documented (see refs. 1 and 2 for literature cited). In recent years considerable effort has been put forth in the investigation of the fate of modifier alleles that modify linkage between other loci (2–4). These authors mainly deal with an infinite population in which there is a pair of loci, subject to selection and reproduction by random mating. A secondary locus (or actual third locus in the specific genetic system at hand) controls the recombination fraction between the two primary loci while generally not directly altering or affecting the selection regime, operating on the controlled loci. Thus the third locus involving, say, three genotypes MM, Mm, and mm, respectively, determine the recombination fractions r_1, r_2, and r_3 between the primary loci.

(*ii*) *Modification of Mutation Rate.* The existence of genes affecting and/or controlling the mutation rate at an alternative specific locus are well established. A mutation modifier model stipulates that at a primary locus with two alleles, A and a, a deleterious recessive allele, a, is maintained at low frequency by selection–mutation balance where recurrent mutation transforms A to a. The modifier locus with genotypes MM, Mm, and mm determines only that the mutation rate of $A \rightarrow a$ is μ_1, μ_2, and μ_3, respectively.

(*iii*) *Modification of Migration Factors.* Consider a population comprised of two subpopulations (niches) or demes. In each deme there is reproduction by random mating, selection in the form of differential viabilities or fertilities, and a small to moderate gene flow between demes mediated by migration. Suppose also there is a separate modifier gene that determines the migration rate and only in this way influences the development of the primary trait. The concept of migration rates under genetic control is exemplified by genes determining flagella in protozoa, migration patterns in *Hydra*, and other phenomena.

(*iv*) *Modification of Fitness Coefficients.* The secondary locus determines the nature and magnitudes of differential viability, fertility, and segregation distortion factors applicable at the primary loci. Perhaps the first mathematical model with a modifier locus arose from Fisher's theory of evolution of dominance of the sort involving modification of selection coefficients.

(*v*) *Modification of Assortment Parameters or Selfing Rates in Mating Pattern.* Here we have a secondary locus where the various modifier genotypes may alter the parameters of assortment or rates of selfing operating at the primary locus such that the assortment rates are under fine genetic control. The feasibility of such genes has been documented (5).

In the general formulation, the modifier and primary genes are distinguished by the degree of direct selection exerted. More specifically, a modifier trait does not contribute in a direct, essential way to the fitness of its carrier. In the examples (*i*), (*ii*), and (*iii*) the modifier genotypes can be regarded as "neutral," whereas in model (*iv*) the expression of the various modifier genotypes actually alters fitnesses. The concept of fitness in model (*v*) is ambiguous since mating preferences themselves impose a form of selection (commonly called sexual selection).

The gamete or genotype frequencies $p_1, p_2, \ldots, p_m$ that describe the state of the population admit some locally *stable equilibrium* $p^* = (p_1^*, p_2^*, \ldots, p_m^*) = p^*(\theta)$ that depend on a (or a set of) parameter(s) θ where the parameter is subject to control by alleles at a modifier locus. (The parameter θ may

prescribe a set of viabilities, a recombination fraction, a mutation rate, etc.)

The problem concerning evolution of modifier alleles in a genetic system involving primary and modifier loci can be given the following more precise formulation. We assume the system has been at equilibrium with the modifier locus homozygous MM, corresponding to a parameter value θ_1. The stable equilibrium state of frequency vector $p^*(\theta_1)$ is that expressed at the primary loci. A new modifier allele, m, is introduced at low frequency, with the property that the genotypes Mm and mm correspond to parameter values θ_2 and θ_3, respectively. Provided θ_2 does not differ much from θ_1, there will be a nearby equilibrium $p^*(\theta_2)$. The fact that the parameter values θ_1 are stipulated to be close tacitly implies that the modifier locus is of a kind mainly exercising fine control.

From our study of numerous cases, it has become convincingly clear that the fate of modifier alleles is governed by secondary selection and the direction of the modifier process can be determined by examination of the mean fitness function at suitable frequency states of the genetic system at the primary loci. The *mean fitness* W(p) of a population configuration corresponding to p, the frequency vector of parental types at maturation in the current generation, is the expected number of mature types in the next generation measured relative to $W(e)$ (normalized to 1) with e the particular frequency vector $e = (1/m, 1/m, \ldots, 1/m)$.

The following principle, relevant in the circumstance of random mating, appears to be operative in a wide host of models of neutral modifier loci. {We use the notation $W[p^*(\theta)] = F(\theta)$; the mean fitness at $p^*(\theta)$.}

The mean fitness principle

The modifier allele, m, *will increase in frequency when* $F(\theta_2) > F(\theta_1)$ *and will go extinct if* $F(\theta_2) < F(\theta_1)$. A succinct representation of the principle is in terms of a secondary selection factor, effective at the modifier locus. Consider the two-allele, one-locus array with the assigned fitness coefficients as indicated.

MM	Mm	mm		
$F(\theta_1)$	$F(\theta_2)$	$F(\theta_3)$	Fitness coefficients	[1]
z_1	z_2	z_3	Population frequencies	

Our principle asserts that the fate at the modifier gene is determined qualitatively (not quantitatively) in the manner of a one-locus, two-allele population subject to the indicated viability scheme. In particular, the qualitative behavior at the modifier locus obeys the following precepts: $F(\theta_1) < F(\theta_2) < F(\theta_3)$ entails fixation of the m allele, while the reversed inequality entails fixation of the M allele; $F(\theta_2) > \max [F(\theta_1), F(\theta_3)]$ implies the existence of a balanced polymorphism with both m and M alleles maintained; $F(\theta_2) < \max [F(\theta_1), F(\theta_3)]$ implies that for z_1 near 1 the M allele becomes fixed, while for z_3 near 1 the m allele becomes fixed.

We do not claim that the actual frequencies at the M–m locus are those deduced from one-locus theory. Only the qualitative conclusion of a balanced M–m locus is assured. The precise quantitative analysis of the global process involving both the primary and modifier loci is formidable. The explicit determination of the attained equilibrium would involve tractability of a multilocus viability model.

The general principle enunciated above and the results implicit to the reduction to the one-locus set up is operative in all of the particular models of random mating examined for modification of mutation, migration, and recombination rates. It seems evident that the principle will apply to other cases of substantially greater complexity, in particular to cases where the parameter θ is itself a vector of real valued parameters.

Our fitness principle asserts that the modifier locus leads ultimately to an increased mean fitness value, but it should be emphasized that the actual path of evolution is usually not one where the mean fitness function increases over successive generations. Stable equilibrium points are not local maxima of the fitness function (especially in multilocus phenomena), and it frequently happens that fitness may decrease at first, but the inevitable outcome manifests a higher mean fitness over its initial value.

The fitness principle for characterizing the pattern of evolution of modifier genes does not apply to mating systems other than random mating and the guiding criteria for such systems are as yet unresolved.

Method of analysis

To study a modifier process it is first necessary to carefully analyze the behavior of the population when the modifier locus is homozygous MM. It is assumed that the gene frequencies of the population are at stable equilibrium values, where the stability refers to perturbations of the gene frequencies at the primary loci but not at the modifier locus. The dominant eigenvalue for this system we denote by λ, and it can be viewed as a function of θ, $\lambda = \lambda(\theta)$, the parameter that will be subject to modifier influence. We suppose the equilibrium stable in the sense that $|\lambda(\theta_1)| < 1$, where θ_1 is the parameter value corresponding to the homozygous MM modifier locus. Introduction of the modifier allele, m, at low frequency constitutes a perturbation of a kind not contemplated in the stability considerations described above. The question of whether these new perturbations result in return to the equilibrium (m eliminated) or not (m increases) is determined by a new dominant eigenvalue, λ^*, referring to the coupled system involving both the primary and the modifier loci. Our findings from investigation of the various models (only for random mating with neutral modifier alleles) can be summarized as follows. Let θ_2 be the parameter value corresponding to genotype Mm, and $F(\theta)$ be the mean fitness function at equilibrium. Then $\lambda^* < 1$ if $F(\theta_2) < F(\theta_1)$ but $\lambda^* > 1$ if $F(\theta_2) > F(\theta_1)$. On more careful study we find that λ^* is approximately of the form

$$\lambda^* = 1 + \gamma \cdot (\theta_2 - \theta_1) \qquad [2]$$

Here γ is a constant that depends on the makeup of the genetic system at the primary locus and sign γ = sign-$[F(\theta_2) - F(\theta_1)]$ as asserted in the mean fitness principle. It is also correct that γ vanishes when $F(\theta_2) = F(\theta_1)$, even where θ_1 could differ from θ_2. Numerical computations indicate that the process of change of modifier frequency is quite slow, not only in its initial and final phases, but throughout all its phases.

Summary and qualitative implications of results

Neutral Alleles and Induced Selection. In the examples of modification of mutation and migration rates, and in models of recombination fraction modifiers, the modifier alleles do not affect the fitness of their carriers and, hence, must be viewed as selectively neutral alles. In these neutral cases, when a modifier allele is introduced at low frequency into a population previously at equilibrium, as already asserted, the fate of the allele, whether it will increase or decrease in frequency, is

determined by mean fitness relationships; this may appear somewhat paradoxical. It has been argued vigorously recently by some authors that selectively neutral genes could only progress in small finite populations, and there under the influence of random drift. It appears from our investigation that modifier genes, which are truly selectively neutral at the level of the individual, evolve under the direction of Darwinian selection, actually a kind of secondary selection. Analogous arguments were advanced by Feldman (4).

Slow Rates of Evolution of Modifier Alleles. Modifier genes are most easily detected in natural populations when they have pronounced discrete effects, corresponding in the models to large values of the parameter change $\theta_2 - \theta_1$. On the other hand, the parameters θ under modification will most often be inherited as quantitative characters subject to control by modifying genes at many different loci with individually minute effects (small $\theta_2 - \theta_1$). The rate of progress of the frequencies of modifier alleles is governed by the dominant eigenvalue $\lambda^* = 1 + \gamma(\theta_2 - \theta_1)$, displayed in [2], and will be slow if λ^* is nearly equal to 1. Thus in the most common case of modifiers with small effects, the evolutionary process will proceed extremely slowly as partially effective modifiers are accumulated at different loci. On this theme three salient facts emanating from the analyses of models of mutation, migration, or recombination modification are now highlighted.

(*i*) When dominance of M to m occurs such that $\theta_2 = \theta_1$, then automatically $\lambda^* = 1$ and the fate of the modifier m allele is generally undetermined. Whether the m allele initially at low frequency increases in frequency or is lost from the population can only be discerned from analysis of the full transformation equations of the total genetic systems. In all events, since $\lambda^* = 1$, the changes in the process are very slow, transpiring at most at an algebraic rate.

(*ii*) When $F(\theta_1) = F(\theta_2)$ (with possibly $\theta_1 \neq \theta_2$) so that dominance occurs in the guise of the induced selection force by way of the mean fitness function, we find that $\gamma = 0$ (see [2]) and again $\lambda^* = 1$. Usually in this case, for the coupled genetic system (primary and modifier loci combined), a curve of equilibria can be identified. The population dynamics of the process are such that slight departure from the curve induces rapid return of the frequency vector to the curve (not necessarily converging to the same point at which the perturbation emanated).

Cases of $F(\theta_1) = F(\theta_2)$ with $\theta_1 \neq \theta_2$ are manifested in the recombination modification model where θ determines a recombination rate at the primary loci corresponding to a nonepistatic stable equilibrium point (i.e., an equilibrium with zero linkage disequilibrium).

(*iii*) Another case of slow evolution (actually $\lambda^* = 1$) of the modifier allele arises when the parameter value θ_1 determines the smallest permissible value of its range. In particular, for the recombination modifier model, departure or approach to zero recombination is for all selection regimes always extremely slow (at best at an algebraic rate), even when the heterozygote Mm corresponds to a recombination rate r_2 substantially larger than zero.

Balanced Polymorphism at the Modifier Locus. Concentrating on a neutral modifier gene, recall that provided $F(\theta_2) > \max [F(\theta_1), F(\theta_3)]$ a balanced polymorphism is expected to be established at the modifier locus. In particular, we may have a situation where the modifier locus controls the mutation rate at a primary locus such that the mutation rate varies among the values μ_1, μ_2, and μ_3 in polymorphic balance. Similarly, migration rate polymorphisms are feasible, and for $F(r_2) > \max [F(r_1), F(r_3)]$, recombination rate for a specific site may be in polymorphic equilibrium. Feldman and Balkau have calculated for a quite special model of two-locus, symmetric viability selection the explicit frequencies attained with the recombination balance (manuscript in preparation).

Effects of Linkage Between the Modifier and Primary Loci on Evolutionary Development of the Modifier Locus. For the modifier models investigated we have found generally no decisive influence on the fate of alleles at the modifier locus due to linkage relationships between modifier and primary loci. Linkage between modifier and primary loci appears to affect only the speed of fixation or convergence to polymorphism, but not the qualitative nature of the outcome. The above assertion applies to all the neutral modification models studied involving panmictic mating. On the other hand, Feldman and Balkau (6) have constructed examples to show that for selfing, the state of linkage and position of the linkage modification locus relative to the primary loci actually effects the ultimate state of various modifier alleles.

Modification of Parameters Tend Towards Zero Values; A Seeming Paradox. The models of modification of recombination, mutation, or migration rates analyzed all indicate tendencies for reduction in their parameter values. This fact poses the following questions. Why does not linkage tighten completely to zero recombination? Why does not mutation expression cease? Why does not complete isolation between demes (migration rate zero) persistently evolve? These dilemmas can be partly averted by the following considerations:

(*i*) For zero rates the dominant eigenvalue is 1, which means that the evolution is exceptionally slow in such extreme cases.

(*ii*) Moreover, as the rates become sufficiently small, it is conceivable that the pertinent selection regimes change countering the reduction of these parameters, since small parameters diminish potential for adaptation to varying environments.

(*iii*) There is commonly manifested a discontinuity or degeneracy in the stable configurations of the models for zero parameter value that precludes the attainment and realization of a single stable state for these extreme parameter specifications.

Contrasts in Models for Modification of Rates of Some Inbreeding Systems. There appears to be no single criterion that characterizes the evolution of alleles controlling selfing or assortment rates associated with a given locus. The following results specifically attest to this conclusion.

(*i*) Modifier alleles that favor reduced propensities for assortment tend to increase.

(*ii*) In sharp contrast to modification of assortment propensities, modification of selfing patterns appears to go in the direction of increased selfing rates. It is puzzling and challenging to try to explicate the markedly different results deduced for modification of assortment against selfing rates, especially in that the one-locus equations describing changes in genotype frequencies for assortment and selfing populations coincide. The differences in the transformation equations for these two mating systems become pronounced only in describing the mating patterns involving two or more loci.

(*iii*) For very low or high parameters under modification of selfing or assortment rates, the gene frequency of modifier alleles change very slowly at an algebraic rate.

An analog of the mean fitness principle is lacking for the modifier models of nonrandom mating discussed in this paragraph. The general problem of introducing an evaluation of "selection effects" associated with mating structure or behavior remains insufficiently analyzed. It appears that ordering relations among several quantities may be needed to provide an appropriate concept for determination of the fate of modifier alleles controlling propensities for various forms of inbreeding.

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