Chapter 3

The Evolution of Transformations

from

A Generalization of Theory on the Evolution of Modifier Genes

Stanford University Doctoral Thesis

by Lee Altenberg ©1984

CHAPTER 3

THE EVOLUTION OF TRANSFORMATIONS

In the previous sections I developed general formulations for the evolution of the frequencies of types in a population undergoing selection and transformation. In this chapter, the evolution of the transformations themselves will be explored, by including in the models transmissible variation for the transformations. Actually, this is not so much an augmentation of the models in the previous chapter as a structuring of the variation between different types. We must now define two, and sometimes three independent dimensions in the specification of an individual's type: the selection type, the transformation type, and the "structural" type.

The selection type determines the selection that acts on the individual. The transformation type determines the frequencies of different selection types among the offspring of the individual given its own selection type (or of the mated pair, given their two selection types). The additional dimension for which transmissible variation may exist is in how the transformation types may be co-transformed or associated with the selection types in the offspring; this is what I call the individual's "structural" type.

The classic modifier model requires each of these three kinds of information. In the modifier model, a new locus, the modifier, is added to a set of other genes under selection. Different alleles at the

modifier locus produce different parameters for the transformation processes acting on the selected loci. In diploid models, in order to know how the modifier alleles are associated with the newly transformed alleles at the selected loci, we need to know the linkage phase of the modifier alleles in the diploid. This is its structural type.

I will not attempt an analysis which deals in complete generality with the forms of the selection, transformation, and structural types. The models I will treat will for the most part assume that the transformation types themselves are not being transformed, but are faithfully transmitted. I will investigate the evolution of transformation types in populations with pure branching descent, and in several models of populations with pair-mating descent.

This formulation of types partitions the variation for fitness and transformation into two independent pieces of information about the organism. However, in the actual variation among organisms, this separation may be bridged by pleiotropy. Wright (1964), discussing his criticism of Fisher's (1928) modifier theory for the evolution of dominance, showed that very small intrinsic fitness differences between the modifier alleles due to pleiotropic effects would dominate over the selection on the modifier alleles due to their effects on dominance. If we were to include pleiotropic fitness effects in the transformation types and pleiotropic transformation effects in the selection types we might obtain a more realistic model, but it returns then to the general form for evolution under selection and transformation discussed in Chapter 2. Short of this, I will examine cases where there are intrinsic fitness differences between the transformation types, where these differences interact multiplicatively with the fitnesses

determined by the selection type. Thus some of the questions regarding the effects of pleiotropy of modifiers can be investigated. Transformation types which have no intrinsic fitness effects will be called neutral.

1. THE SELECTIVE FORCES ON TRANSFORMATION TYPES

When the transformation types are not being transformed, they constitute a "conserved particle" within the type, which was discussed in section 3.(2) of the last chapter. Their growth rate in the population will be determined by their marginal fitnesses relative to the mean fitness of the population. In the case where the transformation type is neutral, its marginal fitness will simply be the average of the fitnesses of the selected types with which it is associated.

These marginal fitnesses would clearly be the same for all of the transformation types if they were randomly associated with the selected types. In such a case, there would be no change in the overall frequencies of the transformation types in the population. The essential feature of transformation types that allows them to evolve is that, through their effects on transformation, they may be able to create a non-random association between themselves and the selected types. Those transformation types which have induced their marginal fitnesses to be greater that the mean fitness of the population by causing themselves to occur more frequently with the fitter types in the population, will increase in overall frequency. Hitchhiking, then, is

the essential mechanism by which neutral, perfectly transmitted transformation types evolve.

For evolution by hitchhiking, the nature of the dynamics is quite different between populations that are in a transient phase of their evolution and populations that have reached an equilibrium. In fact, one might expect that at an equilibrium, because there are no changes in the frequencies, there could be no hitchhiking effects at all. However, recall that when transformation is occurring, there may be differences in the marginal fitnesses among the types present, and that this requires a constant net "flow" by transformation from the fitter types to the less fit. By altering this "flow", a transformation type can come to be non-randomly associated with the selected types, and may therefore aquire a marginal fitness different from the mean of the population. We would expect, therefore, that a prerequisite for evolution to occur among transformation types when the population is at equilibrium is that there be a standing variance in the marginal fitnesses of the types present, and this will be seen to be true. To be more precise, in order for a transformation type to have a geometric, rather than algebraic, asymptotic rate of change in frequency, there must be a variance in the marginal fitnesses at equilibrium. When we consider situations where there is transformation acting on the transformation types, this no longer need be true, as will be seen in the case of modifiers of segregation distortion.

In the literature, a dichotomy can be drawn between studies of the evolution modifier genes where the population is allowed to converge to equilibrium, and conversely, where the population is continually placed back in a transient phase of its evolution by fluctuations in selection,

sampling error due to finite population size, or the introduction of novel, fitter types. Examples of modifier models with transient dynamics include Leigh (1970, 1973), Eshel (1973), Painter (1975), Strobeck et al. (1976), Felsenstein and Yokoyama (1976), Charlesworth (1976), Charlesworth et al. (1977), Gillespie (1981 a,b,c). This thesis will deal solely with the nature of modifier hitchhiking in populations near equilibrium.

Any features of the organism which affect the maintenance of association between the transformation types and the selected types would be expected to influence the evolutionary dynamics of modifier hitchhiking. This is why the structural type can play an important role, because it determines the association of transformation and selected types in the offspring. In modifier gene models, it is the recombination between the modifier gene and the selected loci that will play this role. In cultural transmission models, the structural type has no single embodiment. One would include any covariance in transmission of different independent traits. Boyd and Richerson (1985) have modeled an example of this, where several traits may be simultaneously acquired from individuals chosen as models, hence their particular association in an individual model will be passed on. We would expect that the less the associations are maintained, the weaker the selection on the transformation types will be. This will be seen to be true where analysis is possible.

2. THE NATURE OF THE VARIATIONS IN TRANSFORMATIONS

One of the major results that will be found is that the evolution of transformations depends greatly on how the underlying biological processes involved in transformation constrain the variation in the transformation probabilities. The variation in the transformation processes in nature that have been characterized, such as mutation, recombination, and migration, is usually conceived not as adjusting each transformation probability individually, but rather as changing parameters in underlying processes which generate the transformations. The variation therefore has much fewer degrees of freedom than the number of types in the population. In the cases of mutation, recombination, gene conversion or other changes in the genetic material, it is changes in the basic rates of the underlying processes due to variation in enzymes, concentrations or other conditions. In processes such as dispersal, where location is the type, behavioral variables or morphological differences change the overall migration probabilities.

UNIFORM VARIATION

The model which is frequently used for variation in transformations, and is fairly well justified when transformations consist of single events, is that the relative probabilities of each transformation event are changed uniformly by changes in a parameter of some underlying process generating the transformations. By this I mean that the matrix of transformation probabilities contains a term mT_1, where all the variation occurs in the parameter m, and T_1 is a fixed matrix of the relative transformation probabilities. To illustrate, T_1

could represent the probabilities that a gene, given that it mutates, changes from one allelic state to another, while m represents the base line chance that it will mutate.

The process that m and T_1 represent need not be the only process involved in transformation. How this process relates to any other transformation processes occurring will affect how m and T_1 are incorporated into the transformation matrix. Several possibilities are given below:

1) m controls the rate of the only transformation process occurring. Then

$$T = (1-m)T_{id} + mT_1 .$$

2) m controls transformations that interact additively with others that are occurring. Then

$$T = (1-\alpha-m)T_{id} + \alpha T_2 + mT_1 ,$$

where αT_2 represents the other processes.

3) m changes the relative probabilities of different transformations, but not the overall rate. Then

$$T = (1-\alpha)T_{id} + \alpha\left((1-m)T_2 + mT_1\right) .$$

4) m changes the relative probabilities and the overall rate of transformation. Then

$$T = (1-m)\left((1-\alpha_2)T_{id} + \alpha_1 T_2\right) + m\left((1-\alpha_1)T_{id} + \alpha_1 T_1\right) ,$$

$$\text{with } \alpha_1 \neq \alpha_2 \text{ and } T_1 \neq T_2 .$$

5) m controls the rate of one step in a sequence of transformations. Then

$$T = \left((1-\alpha_1)T_{id} + \alpha T_2 \right) \left((1-m)T_{id} + mT_1 \right) \left((1-\alpha_2)T_{id} + \alpha_2 T_3 \right) ,$$

where the two outside matrices represent the transformations occurring before and after the one controlled by m .

For this case, if one of the transformations is from mated pairs to individuals, the changes in dimension require that the matrices have the appropriate size.

6) m changes the rate of events which can occur independently multiple times. Then

$$T = \left((1-m)I + mT_1 \right)^n .$$

This case is not defined for transformations from mated pairs to individuals, but only for transformations within the same phase of the life cycle, which is why in this case, $T_{id} = I$.

I will make several definitions to characterize the variation in the transformations for these different cases.

DEFINITION 1: Case 1) is defined as LINEAR variation, because the transformation matrices form a line that intersects the perfect transmission matrix.

DEFINITION 2: Cases 2) through 5) are defined as AFFINE variation, because the transformation matrices form a line that does not intersect the perfect transmission matrix.

DEFINITION 3: LINEAR and AFFINE variation comprise what is defined as UNIFORM variation, that is, variation where the transformation matrices all lie on a line. In case 6), the transformation matrices do not lie on a line, so it is an example of NON-UNIFORM variation.

A general form for uniform variation is

$$T = T_{id} + A + mB \quad , \qquad (3.1)$$
$$\text{where } \underline{e}^T A = \underline{e}^T B = 0 \ .$$

When $A = 0$ it is linear, and when $A \neq 0$ it is affine, unless A is proportional to B, in which case the variation is really linear, where the variable parameter now is defined as $\tilde{m} = m + \gamma$ if $A = \gamma B$, giving

$$T = T_{id} + \tilde{m}B \ .$$

Under some special relations between T_1, T_2, and T_{id}, which can be readily derived, cases 2) through 5) are actually linear variation.

An alternative form for uniform variation is

$$T = (1-m)T_1 + mT_2 \ , \qquad (3.2)$$

where T_1 and T_2 are transformation matrices.

For the first form, m can range from 0 up to a value that depends on the scaling of B, which is arbitrary, which keeps T within the hull of stochastic matrices, and in the second form it depends in detail on the entries of the matrices T_1 and T_2, and may range below 0 or above 1 under some circumstances; I mention this only to avoid confusion later. It will be clear from the particular matrices used what the range of m is, and it does not enter into any of the results.

When the variation in transformations consists of a one parameter family of transformation matrices as it has been characterized here, then the phenotype of the transformation type is simply the value of m that it determines. When the transformation is in a pure branching phase of a life cycle, each transformation type a determines a parameter m_a. When the transformation is from mated pairs to individuals, then a pair of individuals of transformation types a and b will determine a parameter $m_{a,b}$.

In nearly all of the random mating models of recombination, mutation, and migration modifiers in the literature, the variation in transformations due to modifier genes is uniform. An exception is the model of a modifier acting on recombination between multiple loci by Charlesworth (1976) and Charlesworth and Charlesworth (1979a). In this case, as the basic recombination rate increases, the relative frequency of multiple recombinants increases faster than that of single recombinants. In the presence of complete interference in recombination between loci, recombination occurs as only a single event for each individual and the variation becomes uniform.

Examples of affine variation include the model of Feldman et al. (1980) where a modifier controls recombination between two selected loci which are also undergoing mutation, the model of Charlesworth and Charlesworth (1979b) where a modifier controls recombination in a population also undergoing migration, and the model of Christiansen and Feldman (1975) where a modifier controls either recombination or migration in a population undergoing recombination and migration.

In the analyses to follow, these distinctions in the nature of the variation in transformations will be found to be fundamental in determining the evolution of the transformations.

3. THE EVOLUTION OF TRANSFORMATION TYPES UNDER PURE BRANCHING DESCENT

The biological situations in which pure branching descent occurs include both asexual organisms and purely-selfing organisms, as shown in Table 2. In purely-selfing diploids, organisms heterozygous at a modifier locus will produce homozygous offspring, which constitutes a transformation on transformation types, which I am excluding from the present analysis. Hence, I shall be considering only asexual organisms here.

The full type of an asexual organism will be specified by its transformation type a, and its selection type, j. No structural type need be specified since all of a type a's offspring will be type a.

The transformation probabilities will be expressed as $T_{aj \to ai}$. The recursion on the frequencies, z_{ai}, of types (ai), after a life cycle of selection and transformation is:

$$z'_{ai} = \sum_j z_{aj} \frac{w_j}{\bar{w}} T_{aj \to ai}, \quad \text{where} \quad \bar{w} = \sum_{ai} z_{ai} w_i .$$

In vector form this is:

$$\underline{z}' = \frac{1}{\bar{w}} \tilde{\tilde{T}} \tilde{\tilde{W}} \underline{z} ,$$

where

$$\tilde{\tilde{T}} = \begin{Vmatrix} T_1 & & 0 \\ & T_2 & \\ 0 & & \ddots \end{Vmatrix}, \quad \text{with} \quad T_a = \| T_{aj \to ai} \| ,$$

$$\tilde{\tilde{W}} = I_1 \otimes W , \quad \text{with} \quad W = \text{diag}(w_i),$$

$$\underline{z} = \begin{pmatrix} \underline{z}_1 \\ \underline{z}_2 \\ \vdots \end{pmatrix}, \text{ with } \underline{z}_a = \begin{pmatrix} z_{a1} \\ z_{a2} \\ \vdots \end{pmatrix}, \text{ and}$$

$$\bar{w} = \left(\underline{e}^T \underline{e}^T\right) \tilde{W} \underline{z} .$$

This is, therefore, a special case of the general model of evolution under selection and transformation (Chapter 2, Section 1.(1)) where the matrix $\tilde{\tilde{T}}\tilde{W}$ is completely decomposable into diagonal blocks T_aW. The recursion therefore can be separated into recursions on the vector of frequencies for each transformation type a:

$$\underline{z}'_a = \frac{1}{\bar{w}} T_a W \underline{z}_a .$$

(1) CONVERGENCE BEHAVIOR

From the considerations of Section 2.(2) of Chapter 2, the convergence behavior of the population may depend on the initial frequencies of the types. What is of interest is the long term evolution of transformations in the population, so I will assume that each transformation type eventually gets tested in the population in combination with each of the selected types. This means that eventually the frequency vector of types will contain some component of eigenvectors or their principal vectors whose eigenvalues are of modulus equal to the spectral radius of T_aW. Assuming that the fitnesses and transformations are frequency independent, the asymptotic marginal fitness of transformation type a will then be the spectral radius of T_aW. The population will then fix on the transformation type with the largest spectral radius. If several types have the maximal spectral

radius, then they can be present in a polymorphism. This polymorphism will be neutral, however. That is, the total frequency of each transformation type is unconstrained and will not resist perturbation to other values, regardless of how the frequencies of selected types associated with a given transformation type converge. The situation described in Chapter 2, section 2.(2) 2)a. applies here.

1. POPULATION LEVEL CONSEQUENCES: MEAN FITNESS AND FITNESS LOAD

Two consequences for the population can be derived from these results. Once the population is fixed on the transformation types yielding the maximal spectral radius, its mean fitness is simply this spectral radius. Therefore, if a new transformation type is to increase when introduced to the population, it must result in an eventual increase in the mean fitness of the population. This is the Mean Fitness Principle of Karlin and McGregor (1974). In the absence of frequency dependence, the Mean Fitness Principle therefore holds in the case of populations with asexual descent (pointed out to me by Kent Holsinger, personal communication).

Another consequence can be seen to directly follow from this. Because the fitnesses are constant and the eventual mean fitness increases, the eventual fitness load,

$$\frac{\max_i(w_i)}{\hat{\bar{w}}} - 1 ,$$

must decrease after the substitution of any new transformation types.

In case of frequency independence, these two consequences coincide. However, in an example of frequency dependent selection

discussed later, these two will not coincide, and this will be the basis of a new principle I will conjecture about the evolution of transformations.

2. DETERMINANTS OF THE SPECTRAL RADIUS

Of primary importance then is the spectral radius of $T_a W$. If the fitnesses of all the selected types are equal, then $\frac{1}{\bar{w}} W = I$, and the spectral radii for all transformation types are equal to one. This yields the following result:

RESULT 3.1:

When there is no selection on selected types, there can be no selection on transformation types.

The frequencies of the transformation types will remain at their initial values thoughout, while concurrently the frequencies of the selected types associated with each transformation type a will converge to equilibria or cycles in the spectral radius space of T_a.

When the fitnesses of the selected types are different, so that $\frac{1}{\bar{w}} W \neq I$, then different transformation matrices will yield different spectral radii. It is not possible to say in general which of any two transformation matrices will yield the larger spectral radius. However, the following specific results can be shown:

1. The highest spectral radius occurs for transformation types yielding perfect transmission, and the spectral radius is the maximum fitness

of the selected types. The other transformations which have this maximal spectral radius are those for which no types with the maximal fitness are transformed to any types with lesser fitness.

2. For a set of matrices T_a that vary linearly away from perfect transmission, the spectral radius $\rho(T_a W)$ is non-increasing, and strictly decreasing if T_a is irreducible.

Result 1. can be seen to be a consequence of result 2., which is Theorem 5.2 in Karlin (1982). The implications of these results for the evolution of transformations makes us examine the nature of variation in transformations.

a. LINEAR VARIATION

As described above, if what is varying is the overall rate of single event transformations in the absence of any other transformation processes, then the variation in transformations is expected to be linear. The transformation matrices will be of the form

$$T_a = (1-m_a)I + m_a T_1 .$$

Theorem 5.2 of Karlin (1982) states that

$$\text{if } m_a < m_b \text{ then } \rho(T_a W) > \rho(T_b W) ,$$

and if T_1 is irreducible, then the the right hand inequality is strict. In this case, therefore, evolution toward perfect transmission is the evolutionary outcome.

EFFECT ON THE FITNESS LOAD

An upper bound on the fitness load is $\frac{m_a}{1-m_a}$; therefore, as

transformation types with succeedingly smaller values of m_a substitute in the population, the fitness load is forced to go to zero.

b. AFFINE VARIATION

If the variation is not linear, other evolutionary outcomes are possible. There is no theorem comparable to Karlin's for affine or non-uniform variation, but in one special case the local rate of change of the spectral radius can be calculated. This is for transformations with memoriless distributions, defined as follows:

DEFINITION 4: A transformation with a MEMORILESS DISTRIBUTION is one whose transformation matrix is of the form

$$T = (1-\beta)T_{id} + \beta T_1 ,$$

where for pure branching descent,

$$T_1 = \mathrm{diag}(t_i)U ,$$

U is a matrix of ones, and $\sum_i t_i = 1$.

Therefore, all types have the same probability of undergoing a transformation processes in which their former type has no influence on the type they become. This has been called "house of cards" mutation by Kingman (1980).

The general affine form for transformations incorporating memoriless distributions is

$$T_a = (1-m_a)\left((1-\alpha)I + \alpha S\right) + m_a\left((1-\beta)I + \beta P\right) ,$$

where S and P are the rank one matrices

$$S = \mathrm{diag}(s_i)U, \quad \text{and} \quad P = \mathrm{diag}(p_i)U .$$

THEOREM 3.2a:

Assume that the normalized leading eigenvector $\hat{\underline{v}}$ where $\hat{\rho}\hat{\underline{v}} = \hat{T}\hat{W}\hat{\underline{v}}$, spans the eigenspace for the spectral radius $\hat{\rho} = \sum_i \hat{v}_i w_i$ and therefore is an isolated point, and satisfies the requirements for differentiability with respect to changes in T.

Then the spectral radius $\rho(T_a W)$ for m_a near $\hat{m}$ is approximately

1)

$$\tilde{\rho} = \hat{\rho} + (m_a - \hat{m}) \frac{\alpha - \beta}{1-(1-\hat{m})\alpha - \hat{m}\beta} \hat{\rho} ,$$

if for some i, $\alpha s_i = \beta p_i = 0$,

or otherwise,

2)

$$\tilde{\rho} = \hat{\rho} + (m_a - \hat{m})\Big(\sum_i \frac{1}{\gamma_i} \hat{v}_i^2 w_i\Big)^{-1} \frac{1}{\gamma^2} \cdot \Big[(\alpha-\beta)\sum_i \frac{1}{\gamma_i} \hat{v}_i^2 (w_i - \hat{\rho})^2 + \hat{\rho}\,\alpha\beta\Big((1-\gamma)\sum_i \hat{v}_i (w_i - \hat{\rho})\Big(\frac{p_i - s_i}{\gamma_i}\Big) + \gamma\ \mathrm{cov}\Big(w_i, \frac{p_i - s_i}{\gamma_i}\Big)\Big)$$

(3.4)

where $\gamma_i \overset{\Delta}{=} (1-\hat{m})\alpha s_i + \hat{m}\beta p_i$, and $\gamma \overset{\Delta}{=} \sum_i \gamma_i = (1-\hat{m})\alpha + \hat{m}\beta$.

The full derivation of these results is given later, under Theorem 3.2b in Section 4. (1) on diploid modifiers, where the same forms appear.

In 1), evolution proceeds in the direction lowering the overall rate of transformation $(1-m_a)\alpha + m_a\beta$.

In 2), three terms contribute to determining whether the spectral radius increases or decreases with m_a . The first term in the brackets is the contribution from lowering the overall rate of transformation. This term is zero if and only if the fitness load is zero, for then

$$\hat{\rho} = w_i \quad \forall\, i \qquad \text{and} \qquad \hat{v}_i = \frac{\gamma_i}{\gamma} \quad \forall\, i \,.$$

The second two terms in the brackets are the contribution from shifting the transformation probabilities toward the more fit types. This term is zero if the fitness load is zero or if the variation is linear, requiring $\alpha = 0, \beta = 0$, or $S = P$.

From this one can say that there are two "forces" acting on the evolution of transformations, one toward more perfect transmission, and one toward producing more of the fitter types. If α is close to β , then an increase in the overall transformation can evolve if it sufficiently increases the probability of transformations to the fitter types, which may result in the extinction of lesser fit types. When the fitness load is zero, then there is no more selective opportunity for the evolution of new transformation types, unless these can cause the creation of novel, fitter types.

(2) "BALANCED MIXTURE" TRANSFORMATION POLYMORPHISMS

In the absence of frequency dependent selection or transformation, it was seen that any polymorphisms in transformation types present in

the population will be essentially neutral. With frequency dependence however, transformation type polymorphisms which are stable to perturbation may be possible. I will not consider this question generally here, but will examine the case where the fitness of each selected type increases as the type become more rare, which is the kind of frequency dependence often proposed for situations with intraspecific competition.

Suppose that the fitness of each selected type strictly increases without bound, as it decreases in frequency. Then in the absence of transformation, there will be a unique, globally stable polymorphic equilibrium where all the fitnesses have equilibrated. Call the frequency vector of this equilibrium $\hat{\underline{v}}$. Whenever the frequency of the selected haplotypes equals $\hat{\underline{v}}$, the fitness matrix will be

$$W = \bar{w} I .$$

So at equilibrium,

$$T_a \hat{\underline{z}}_a = \hat{\underline{z}}_a .$$

Therefore, all transformation matrices will produce spectral radius one. However, the eigenvectors $\hat{\underline{z}}_a$ must satisfy

$$\sum_a \hat{z}_{ai} = \hat{v}_i \text{ , where } \sum_j T_{a\, j \to i}\, \hat{z}_{aj} = \hat{z}_{ai} .$$

(To avoid the complications of possible cycling, I will assume that each transformation matrix is primitive, yielding one strictly positive, unique eigenvector with eigenvalue 1.)

Let us rewrite each eigenvector $\hat{\underline{z}}_a$ as

$$\hat{\underline{z}}_a = x_a \hat{\underline{v}}(a) ,$$

where x_a is the total frequency of transformation type a and $\hat{\underline{v}}(a)$ is the frequency of the selected types among that transformation type, simply $\hat{\underline{z}}_a$ normalized.

Then the equilibrium requirement is

$$\hat{\underline{v}} = \sum_a x_a \hat{\underline{v}}(a) .$$

Thus, $\hat{\underline{v}}$ must be a linear combination of the eigenvectors of each transformation matrix. If there are fewer transformation types than selected types, it is not even guaranteed that $\hat{\underline{v}}$ will be in the space spanned by $\{\hat{\underline{v}}(a)\}$. There must be as many different $\hat{\underline{v}}(a)$ as there are selected types to guarantee that any $\hat{\underline{v}}$ is in the space they span. But there is a further requirement, that the convex hull of $\{\hat{\underline{v}}(a)\}$ contain $\hat{\underline{v}}$. This restricts the possible sets of transformation matrices that can allow this equilibrium to be reached to various "balanced mixtures" of complementary sets. I will refer to these equilibria where all types have the same fitnesses as "balanced mixture" polymorphisms. It is important to note that these generally require that the variation in the transformations not be linear: when the variation is linear, there is only one eigenvector for all the transformations. If the set of transformation types is not sufficient to yield a balanced mixture polymorphism, then there will be a variance in fitnesses at equilibrium.

A NUMERICAL EXAMPLE: MIGRATION WITH SOFT SELECTION

I have not analyzed the stability of these "balanced mixture" polymorphisms in general for this situation. But I have examined numerically an example of this situation, where there are two demes and transformation consists of individuals changing demes. Soft selection resets each deme i to a constant proportion c_i of the total population. The fitness of an individual in deme i therefore is

$$w_i(\underline{v}) = \frac{c_i}{v_i} .$$

Three evolutionary outcomes seem possible:

1) If the resident transformation type has a migration matrix whose leading eigenvector is not $\underline{c} = (c_i)$, then there will be a fitness variance at equilibrium, and any new transformation type with linearly less migration will be able to invade and displace it.

2) In the same circumstance as 1), any new transformation type whose migration matrix has as its leading eigenvector $\underline{c}$ will be able to invade and displace the resident, regardless of the overall rate of migration it causes.

3) In the same circumstance as 1), where the resident transformation type yields matrix T^*, any new transformation type whose migration matrix, T, satisfies

$$c_1T_{1\to 2} > c_2T_{2\to 1} \quad \text{if} \quad c_1T^*_{1\to 2} < c_2T^*_{2\to 1} , \text{ or}$$
$$c_1T_{1\to 2} < c_2T_{2\to 1} \quad \text{if} \quad c_1T^*_{1\to 2} > c_2T^*_{2\to 1} ,$$

will be able to invade, and the two transformation types will go to a balanced mixture polymorphism where the portions of the population in the demes after migration are $\underline{c}$.

In each of these outcomes, the net effect is that the fitness load is decreased. How the transformations themselves evolve depends upon the nature of the variation in the transformations. This suggests the following conjecture:

CONJECTURE: THE FITNESS LOAD PRINCIPLE:

Transformation types that are not themselves being transformed evolve to reduce the equilibrium fitness load of the population.

If this principle seems vaguely familiar to the reader, it is because this basic idea was proposed 25 years ago by Kimura (1960) in a paper that considers the evolution of mutation rates and dominance. Offered not as a result but as a premise, he states

> "I now assume that, in the course of evolution, ...by the accumulation of modifiers ...[the mean fitness] will be maximized, or more strictly the total genetic load ...will be minimized. This is my view on the course of evolution, and I would like to call it the principle of minimum genetic load."

Whether or not this is true in general for asexual populations I have not determined. If it holds it would be remarkable because the fitness load depends only on the difference between the mean fitness of the population and the maximal fitness in the population. If such a principle is operating, it might instead depend on some function of the fitnesses weighted by their deviation from the upper bound on the fitness load, which is determined by the extent of transformation occurring.

4. THE EVOLUTION OF TRANSFORMATIONS UNDER PAIR-MATING DESCENT

In organisms where the life cycle involves pair mating, there are two points of transformation in the cycle, the transformation from individuals to pairs, and from pairs to individuals. There may be, in addition, transformations within the individual or pair phases. Modifier models for individual-to-pair transformations in the literature include modifiers of assortative mating (Karlin and McGregor, 1974), and selfing (Feldman and Christiansen (1983) and Holsinger and Feldman (1984)). I will not be investigating the evolution of pair-mating transformations here, but will concentrate on pair-to-individual transformations. Most of the modifier models in the literature concern the evolution of pair-to-individual transformations. These include recombination, mutation, segregation distortion, and sex ratio modifiers. Migration constitutes a transformation within the individual phase if the migrant is an individual, or within the pair phase if the migrant is a pair.

When there is pair-mating in producing offpsring, the full three dimensional specification of the type, its selection, transformation, and structural components, must be used. Introducing three indices, structural, transformation, and selection types, to the formulation (2.2) we obtain this general recursion on the population.

$$z'_{s_1 ai} = \sum_{\substack{s_2 s_3 \\ bcjk}} z_{s_2 cj}\, z_{s_3 bk}\, \frac{w_{jk}}{\bar{w}}\, T_{s_2 cj,\, s_3 bk \to s_1 ai}\,,$$

where

$$\bar{w} = \sum_{s_2 cj} z_{s_2 cj} z_{s_3 bk} w_{jk}\,.$$

With the assumption that the transformation types are not themselves transformed we obtain:

$$z'_{s_1ai} = 2 \sum_{\substack{s_2 s_3 \\ bjk}} z_{s_2aj}\, z_{s_3bk}\, \frac{w_{jk}}{\bar{w}}\, T_{s_2aj,\, s_3bk \to s_1ai}$$

$$- \sum_{\substack{s_2 s_3 \\ jk}} z_{s_2aj}\, z_{s_3ak}\, \frac{w_{jk}}{\bar{w}}\, T_{s_2aj,\, s_3ak \to s_1ai} \,. \qquad (3.6)$$

I will investigate a number of models which fit the form of (3.6):

The diploid modifier gene model, with random mating, viability selection or multiplicative fertility selection. The haploid modifier models in the literature are special cases of this.

A model for culturally transmitted selection types and transformation types.

The cases where the transformation type affects the frequencies of pairs formed will not be of the form (3.6). I will, however, examine one variant from (3.6),

A model of a modifier of sexual reproduction, in which pair mating frequencies are variable.

(1) THE DIPLOID MODIFIER GENE MODEL

When a gene in an organism determines the tranformation type, it will be called a modifier locus. In this section, the evolution of

modifier loci in diploid organsisms will be considered. Two aspects must first be addressed: the question of transformation of transformation types, and the nature of the selected types. I wish to exclude the transformation of transformation types from the model. So the alleles at the modifier locus will be transmitted without transformation. Nevertheless, from the consideration in the last chapter of the segregation-syngamy transformation acting in diploid sexual reproduction, we know that the modifier genotypes of some of the offspring of two diploids will not be identical to the parental genotypes (production of heterozygotes from homozygotes, and vice versa), which constitutes a transformation of the transformation types. But recall that the segregation-syngamy transformation decomposes when there is random mating and only multiplicative fertility selection. Assuming these conditions, the recursion can be expressed in terms of haploids and haploid pairs (i.e., diploids). The tranformation type will now be the modifier haplotype, which is inherited without being transformed, thus satisfying the requirement for the analysis here.

Secondly, the selected type undergoing transformation need not be a genotype. In models of recombination and mutation modifiers, the selected type is a genotype at a specific locus or set of loci. The modifier therefore controls intragenomic transformation. In migration modifier models, however, location is part of the selected type. There are models where genes affect the transmission of culturally transmitted traits that determine fitness (Feldman and Cavalli-Sforza, 1976). These models of genetic control over culturally transmitted traits have not previously been called modifier models, but in terms of selection and

transformation, what they are controlling are processes that may result in a transformation between parental and offspring cultural types. Models of genetic modifiers of cultural transmission are generally quite complex, because segregation and syngamy transform the modifier genotypes and because the association between modifier genotype and cultural type in the offspring is quite complex. The analysis therefore requires a more general consideration of structural types and transformation of transformation types. and will not be attempted here. Modifiers of intragenomic transformation and modifiers of migration are simpler and will be analyzed in this section.

I. INTRAGENOMIC TRANSFORMATION

In this section I will analyze the model where the transformation type is determined by a modifier locus, and the selection type is determined by another set of loci. This model includes as special cases the models of Charlesworth (1979 a), Feldman (1972), Feldman and Balkau (1972, 1973), Feldman et al. (1980), Feldman and Krakauer (1973, 1976), Leigh (1973), Liberman (1976), Prout et al. (1973), Teague (1976), Thomson and Feldman (1974, 1976) and others. In this case, the co-transmission of transformation and selection types is determined by the linkage between the modifier and selected loci. In terms of the full haplotypes being transmitted, recombination between the modifier and selected loci constitutes a transformation. This recombination is embedded in the T of (3.6). The transformation that is of interest, however, is the transformation acting just on the selected loci.

Therefore I will redefine T in terms of the recombination between modifier and selected loci and an additional set of T's which represent the transformation acting only on the selected loci. The recombination between modifier and selected loci is taken as a fixed feature of the population, outside the control of the modifier.

Two additional problems for this formulation turn out to have the same solution.

1) Interference between recombination events is a ubiquitous phenomenon for homologous recombination in eukaryotes. If the transformation acting on the selected loci is recombination, then recombination with the modifier locus may change the probabilities of recombinant selected haplotypes. To deal with interference generally, we define two new sets of T's: one for when no recombination occurs with the modifier, and one for when recombination does occur.

2) This specification also solves the problem of the modifier locus being linked in between two selected loci. In this situation, recombination with the modifier also may change the haplotype of the selected loci. But this change can be accounted for simply by defining a different set of T's for when recombination with the modifier occurs, as before.

The new sets of T's will be defined in a slightly different way from the previous definitions:

$$T_{bk}^{aj \to ai}$$

represents the probability that haplotype M_aA_j is transformed to haplotype M_aA_i given that the other haplotype in the diploid genotype is M_bA_k, and there is no recombination between M and A.

Conservation of the modifier allele implies that:

$$T_{\frac{bk}{}}^{aj \to ci} = 0 \quad \text{for all } b,j,k,i \quad \text{if } c \neq a \ .$$

An assumption I will make throughout that is critical when recombination to the modifier locus is occurring is that there is no position effect of the modifier on the transformations acting on the selected loci. In other words, although the linkage phase will affect the association of modifier alleles with the selected haplotypes among the gamete offspring of an individual, it will not affect the frequencies of the selected haplotypes themselves. This assumption would be expected to hold whenever the modifier control of the transformations is mediated through trans acting gene products or other cellular activities. This is expressed as:

$$T_{\frac{bk}{}}^{aj \to ai} = T_{\frac{ak}{}}^{bj \to bi} \ .$$

With this assumption it will not matter whether transformation of the selected haplotypes occurs before recombination with the modifier, or whether recombination with the modifier occurs first.

When recombination with the modifier occurs, then

$$\tilde{T}_{\frac{bj}{}}^{ak \to ai}$$

represents the probability that either:

1) haplotype M_aA_k is transformed to haplotype M_aA_i in genotype $M_aA_j // M_bA_k$ after recombination has occured between M and A ; or

2) haplotype M_bA_k is transformed to haplotype M_bA_i in genotype $M_aA_j // M_bA_k$ and then recombination occurs between M and A.

If for some a,b,j,k,i, $T_{\frac{bk}{}}^{aj \to ai} \neq \tilde{T}_{\frac{bk}{}}^{aj \to ai}$, then there is interference.

In this diploid modifier model, transmission distortion is simply segregation distortion. Assuming that there is no segregation distortion of the modifier alleles, then:

$$0 \leq T_{bk}^{aj \to ai} \leq 1 \text{ , and } \sum_i T_{bk}^{aj \to ai} = 1, \sum_i \tilde{T}_{bk}^{aj \to ai} = 1 .$$

The same applies for $\tilde{T}$.

If segregation distortion does occur on the modifier alleles then this assumption is relaxed to:

$$0 \leq T_{bk}^{aj \to ai} \leq 2 \text{ , and } \sum_i T_{bk}^{aj \to ai} + \sum_i T_{aj}^{bk \to bi} = 2 .$$

The same applies for $\tilde{T}$.

The T in (4.10) can now be defined in terms of the new sets of T's:

Let R be the frequency of recombination between M and A. Then,

$$T_{aj,bk \to ai} = (1-R)\, T_{bk}^{aj \to ai} + R\, \tilde{T}_{bj}^{ak \to ai} \quad \text{for } a \neq b ;$$

$$T_{aj,ak \to ai} = \frac{1}{2}(1-R)\left(T_{ak}^{aj \to ai} + T_{aj}^{ak \to ai}\right) + \frac{1}{2}R\left(\tilde{T}_{aj}^{ak \to ai} + \tilde{T}_{ak}^{aj \to ai}\right) \quad \text{for } j \neq k ;$$

$$T_{aj,aj \to ai} = (1-R)\, T_{aj}^{aj \to ai} + R\, \tilde{T}_{aj}^{aj \to ai} .$$

PERFECT TRANSMISSION:

If the selected haplotype is being perfectly transmitted with a given modifier genotype, then

$$T_{bk}^{aj \to ai} = \delta_{ij} = \begin{cases} 0 \text{ if } i \neq j \\ 1 \text{ if } i = j \end{cases} ,$$

and

$$\tilde{T}_{bj}^{ak \to ai} = \delta_{ki} .$$

Only if $R = 0$, however, will this this will constitute perfect transmission of the full haplotype

FITNESSES:

I will also use the diploid genotype notation to index the fitnesses, so the fitness of genotype

$$\frac{M_aA_i}{M_bA_j} \text{ will be } w_k^j \text{ for all } a,b.$$

THE RECURSION:

Let z_{ai} represent the frequency of haplotype M_aA_i. Then equation (3.6) is the recursion on haplotype frequencies in the population with the substitutions for T and W. Thus we obtain:

$$z'_{ai} = \sum_{bjk} z_{aj}z_{bk}\frac{w_k^j}{\bar{w}}\left((1-R)T_{bk}^{aj\to ai} + RT_{bj}^{\tilde{ak}\to ai}\right) .$$

Because this is a non-linear system, it will not be possible to obtain general global convergence results. Instead, pursuing the approach developed for modifier theory by Feldman (1972), the nature of equilibria and their local stability, and the fate of new modifier alleles introduced to the population at stable equilibria will be explored.

THE EQUILIBRIUM IDENTITY

At any equilibrium for this system, the following identity must be satisfied:

$$\hat{z}_{bi} = \sum_{cjk} \hat{z}_{bj}\hat{z}_{ck}\frac{w_k^j}{\hat{\bar{w}}}\left((1-R)T_{ck}^{bj\to bi} + RT_{cj}^{\tilde{bk}\to bi}\right) \qquad (3.7)$$

This can be written in vector form as follows:

Define

$$\Omega_b \triangleq \| \sum_{ck} \hat{z}_{ck} \frac{w_k^j}{\hat{w}_j} \left((1-R) T^{bj \to bi}_{ck} + R T^{bk \to bi}_{cj} \right) \|_{i,j} ,$$

and

$$D \triangleq \operatorname{diag}\left(\frac{\hat{w}_i}{\hat{\underline{w}}}\right) = \left\| \begin{array}{ccc} \frac{\hat{w}_1}{\hat{\underline{w}}} & & 0 \\ & \ddots & \\ 0 & & \frac{\hat{w}_n}{\hat{\underline{w}}} \end{array} \right\| ,$$

where

$$\hat{w}_i \triangleq \sum_{bj} \hat{z}_{bj} w_j^i .$$

D is the matrix of the relative marginal fitnesses of the selected haplotypes, and will reappear throughout the analyses. If there is no marginal fitness variance, then $D = I$.

The matrix Ω_b is a stochastic matrix, since $\underline{e}^T \Omega_b = \underline{e}^T$. The equilibrium identity becomes

$$\hat{\underline{z}}_b = \Omega_b D \hat{\underline{z}}_b ,$$

where

$$\underline{z}_b \triangleq \begin{pmatrix} z_{b1} \\ z_{b2} \\ \vdots \end{pmatrix} .$$

Therefore, at equilibrium the spectral radius

$$\rho(\Omega_b D) = 1 \text{ for each modifier allele } b .$$

The local stability of equilibria are analyzed by deriving the linearized recursions on perturbations away from the equilibrium. For a polymorphism to be a plausible state of the population at equilibrium, the equilibrium must be stable to perturbations among the types present, having what is called interior stability. This condition is described

Let $\hat{\underline{z}}$ be an equilibrium. The population is perturbed to new frequencies $\underline{z}$ where the difference $\underline{\varepsilon} \triangleq \underline{z} - \hat{\underline{z}}$ is small. Let the difference after one generation be defined $\underline{\varepsilon}' \triangleq \underline{z}' - \hat{\underline{z}}$. Then, ignoring terms on the order of $\|\underline{\varepsilon}\|^2$, the recursion relating $\underline{\varepsilon}'$ to $\underline{\varepsilon}$ is:

$$\underline{\varepsilon}' = \Gamma\underline{\varepsilon} ,$$

where Γ is the local stability matrix. The polymorphic equilibrium will be stable if the spectral radius $\rho(\Gamma) < 1$, and unstable if $\rho(\Gamma) > 1$. If $\rho(\Gamma) = 1$ then a second order analysis is required. In some cases, the technique developed by Lessard and Karlin (1982) might be useful for this analysis, but this is not pursued further here.

To investigate the long term evolutionary fate of the modifier locus, we wish to know characteristics of new modifier alleles that either allow them or prevent them from increasing in the population when introduced at an equilibrium.

Let a new modifier allele, M_a , be introduced to the population at an equilibrium $\hat{\underline{z}}$ at small frequencies $z_{ai} = \varepsilon_{ai}$. The linearized recursion on the ε_a 's, ignoring terms of order ε_a^2 , is:

$$\varepsilon_i' = \frac{1}{\bar{w}} \sum_{bjk} \varepsilon_j \hat{z}_{bk} \frac{w_k^j}{\bar{w}} \left((1-R) T_{bk}^{aj \to ai} + R T_{bj}^{ak \to ai} \right) . \qquad (3.8)$$

With the introduction of the new modifier allele, the frequencies of the pre-existing haplotypes will also be perturbed, and this perturbation will be represented by the vector $\underline{\varepsilon}_r$. The total recursion on the perturbations is:

$$\begin{pmatrix} \underline{\varepsilon}_r' \\ \underline{\varepsilon}_a' \end{pmatrix} = \begin{vmatrix} \Gamma & \Theta \\ 0 & \Omega_a D \end{vmatrix} \begin{pmatrix} \underline{\varepsilon}_r \\ \underline{\varepsilon}_a \end{pmatrix} ,$$

with each entry representing blocks, where Ω_a is defined for M_a as in the equilibrium identity.

The matrix Θ is irrelevant to the stability because of the zero block. Thus the spectral radius of the entire stability matrix is

$$\rho = \max(\rho(\Gamma), \rho(\Omega_a D)) .$$

Since the equilibrium is assumed to have interior stability, $\rho(\Gamma) < 1$. Therefore, the stability of the entire system depends on whether the new modifier allele increases or not when introduced, that is, whether

$$\rho(\Omega_a D) > 1 \quad \text{or} \quad \rho(\Omega_a D) < 1 .$$

This is what is called the exterior stability of the equilibrium. This partition was first established for a selectively neutral recombination modifer by Feldman (1972). Since Ω_a is a stochastic matrix, the spectral radius cannot be different from one unless there is an variance in the marginal fitnesses of the selected haplotypes at equilibrium. This yields the following result:

RESULT 3.3:

SELECTION CANNOT ACT ON A NEW MODIFIER ALLELE TO CHANGE ITS FREQUENCY AT MORE THAN AN ALGEBRAIC RATE UNLESS THERE IS AN EQUILIBRIUM FITNESS LOAD.

This result assumes random mating, populations at equilibrium, discrete non-overlapping generations, and no transformation acting on the modifier, as will all the results for pair mating descent, except where noted.

A NOTE ON FREQUENCY DEPENDENCE

An important property of exterior stability, not shared by interior stability, is the following:

THEOREM 3.4:

The exterior stability of an equilibrium is not affected by frequency dependent selection or frequency dependent transformation given two assumptions:

1) $\rho(\Omega_a D) \neq 1$,

2) both fitnesses and transformations are continuous function of $\underline{z}$.

This is because perturbations in W or T appear as second order terms, which cannot change either inequality

$$\rho(\Omega_a D) < 1 \quad \text{or} \quad \rho(\Omega_a D) > 1 .$$

For the interior stability, however, perturbations in W or T appear as first order terms and alter the matrix Γ .

I.1. THE EXTERIOR STABILITY OF EQUILIBRIA

In this section I derive a number of results about the conditions that allow or prevent the initial increase of a new modifier allele introduced to the population at equilibrium. Although the assumption of the existence of the equilibria may implicitly require unknown constraints on the selection regimes and transformation probabilities, in none of the results do these constraints or closed form solutions of

the equilibrium frequencies appear. The only generic assumptions made are that there be polymorphism in the selected haplotypes, that each selected haplotype and each modifier allele in the recursions occur with positive frequency, and that the marginal fitness of each selected haplotype be greater that zero, since it can be disregarded otherwise.

DEFINITION 4: MODIFIER AND SELECTED HAPLOTYPE FREQUENCIES:

Under some circumstances the total frequencies of selected haplotype or of modifier alleles will appear.

The total frequency of each modifier allele is represented by

$$x_a \triangleq \sum_i z_{ai} .$$

The total frequency of each selected haplotype is represented by

$$v_i = \sum_a z_{ai} .$$

DEFINITION 5: TENSOR PRODUCT FREQUENCIES.

A situation in which the modifier and selected alleles are in linkage equilibrium is described by the frequency vectors of the complete haplotypes being a TENSOR PRODUCT of the respective modifier and selected haplotype frequency vectors:

$$\underline{z} = \underline{x} \otimes \underline{v} .$$

THEOREM 3.5:

A NEW MODIFIER ALLELE WHICH ELIMINATES TRANSFORMATION AT THE SELECTIED LOCI WILL ALWAYS INCREASE WHEN RARE, FOR ANY AMOUNT OF LINKAGE TO THESE LOCI, WHEN THE EQUILIBRIUM BEARS A TRANSFORMATION-INDUCED FITNESS VARIANCE.

PROOF:

Here $T^{aj \to ai}_{bk} = \tilde{T}^{aj \to ai}_{bk} = \delta_{ij}$ $\forall$ i,j,b,k . Therefore the recursion is:

$$\varepsilon'_{ai} = (1 - R)\varepsilon_{ai} \frac{\hat{w}_i}{\bar{\hat{w}}} + R\hat{v}_i \sum_j \varepsilon_{aj} \frac{w_j^i}{\bar{\hat{w}}} .$$

Define $Q \triangleq \text{diag}(\underline{\hat{v}})W \text{ diag}(\frac{1}{\hat{w}_i}) = \| \hat{v}_i \frac{w_j^i}{\hat{w}_j} \|$.

$$\text{Then } \underline{\varepsilon}' = \Omega_a D \underline{\varepsilon} = \left[(1 - R)I + RQ \right] D \underline{\varepsilon} .$$

I will prove that the spectral radius

$$\rho(\Omega_a D) = \rho\left(\left[(1 - R)I + RQ \right] D \right) > 1 , \quad \forall \ 0 < R < \frac{1}{2} .$$

Proof:

1) First it will be shown that (1-R)I + RQ is symmetrizable to a positive semi-definite matrix.

Let us call $\text{diag}(\underline{\hat{v}}) \triangleq D_1$, and $\text{diag}(\frac{1}{\hat{w}_i}) \triangleq D_2$. Thus $Q = D_1 W D_2$.

Since for the eigenvalues λ of Q,

$$\lambda(Q) = \lambda(D_1 W D_2) = \lambda\left((D_1 D_2)^{1/2} W (D_1 D_2)^{1/2} \right) ,$$

and the matrices W and $(D_1 D_2)^{1/2}$ are symmetric, all the eigenvalues of Q are real. Because Q is stochastic, its spectral radius is one, and thus all its eigenvalues are between -1 and 1.

Since $-1 \leq \lambda(Q) \leq 1$, then

$\lambda[(1 - R)I + RQ] \in [(1 - R) - R, (1 - R) + R] = [1 - 2R, 1]$.

Therefore for $0 \leq R \leq \frac{1}{2}$, we have $0 \leq \lambda[(1 - R)I + RQ] \leq 1$. All the eigenvalues are non-negative.

Defining $D_3 = D_1^{-\frac{1}{2}} D_2^{\frac{1}{2}}$, we have

$$\lambda[(1-R)I + RQ] = \lambda[D_3[(1-R)I + RQ]D_3^{-1}]$$

$$= \lambda[(D_1D_2)^{\frac{1}{2}}[(1-R)(D_1D_2)^{-1} + RW](D_1D_2)^{\frac{1}{2}}] \geq 0 .$$

The last matrix is non-negative and symmetric, with all non-negative eigenvalues, and is thus is positive semi-definite.

2) This enables us to use Theorem 5.1 Corollary F.2 of Karlin (1982), which states that $\rho(MD) \geq \sum_i \xi_i D_{(i)}$, where M is symmetrizable to a positive semi-definite matrix, $M\underline{\xi} = \underline{\xi}$, $\underline{e}^T M = \underline{e}^T$, and $\underline{e}^T\underline{\xi} = 1$.

Here, the eigenvector $\underline{\xi}$ is $\hat{D}\underline{v}$, since

$$\sum_j Q_{ij}(\hat{D}\underline{v})_j = \sum_j \hat{v}_i \frac{w_{ij}}{\hat{w}_j}\left(\frac{\hat{w}_j}{\hat{\underline{w}}}\hat{v}_j\right) = \hat{v}_i \sum_j \hat{v}_j \frac{w_{ij}}{\hat{\underline{w}}} = \hat{v}_i \frac{\hat{w}_i}{\hat{\underline{w}}} = (\hat{D}\underline{v})_i$$

$$\text{thus } [(1 - R)I + RQ]\hat{D}\underline{v} = \hat{D}\underline{v} .$$

Therefore,

$$\rho(\,\mathcal{U}_a D\,) = \rho(\,[(1-R)I + RQ]D\,) \;>\; \sum_i \hat{v}_i \frac{\hat{w}_i}{\hat{\bar{w}}} \frac{\hat{w}_i}{\hat{\bar{w}}} = \frac{1}{\hat{\bar{w}}^2} \sum_i \hat{v}_i (\hat{w}_i^{\,2} - \hat{\bar{w}}^2) + 1$$

$$= 1 + \mathrm{var}\left(\frac{\hat{w}_i}{\hat{\bar{w}}}\right) \;>\; 1 \,.$$

Thus, if $\mathrm{var}(w_i) > 0$, then

$$\rho(\,\Omega_a D\,) = \rho(\,[(1-R)I + RQ]\,D\,) > 1 \,,$$

and the new modifier increases when rare.

The result that the new modifier allele can increase even when it is unlinked to the selected loci it is somewhat remarkable in light of the intuitive notions about hitchhiking. Hitchhiking is usually thought to be where an allele at one locus increases in frequency by being linked to an allele at another locus which is increasing in frequency due to selection. In this case, however, the locus that is hitchhiking is neither linked to the selected loci nor are the alleles at the selected loci changing frequency! The linkage disequilibrium between the modifier and the selected loci that is necessary for hitchhiking is generated by selection every generation, and even free recombination can no more than halve this disequilibrium by the next phase of selection.

RESULT 3.6:

> The selective advantage of a new modifier allele eliminating transformation decreases with looser linkage to the selected haplotypes.

This is a direct result from Theorem 5.2 of Karlin (1982).

RESULT 3.7:

The fitness load is always greater than the fitness variance.

This is an incidental implication of Result 3.6, which gives

$$\rho(D) = \hat{L} = \max_i\left(\frac{\hat{w}_i}{\bar{\hat{w}}}\right) > 1 + \mathrm{var}\left(\frac{\hat{w}_i}{\bar{\hat{w}}}\right) .$$

This result does not require the fact that these are equilibrium values, hence this holds for populations in a transient phase of their convergence as well.

RESULT 3.8:

A VALUE CAN BE DERIVED FOR AN UPPER BOUND ON THE RATE OF TRANSFORMATION A NEW MODIFIER ALLELE ALLOWS THAT GUARANTEES IT WILL INCREASE WHEN INTRODUCED INTO A POPULATION WITH A MARGINAL FITNESS VARIANCE AT EQUILIBRIUM.

DERIVATION:

For a new modifier allele M_a, let us define

$$\tilde{m}_i \triangleq 1 - \min_{b,k} T^{ai \to ai}_{bk} ,$$

which is the maximal rate of transformation occurring for selected haplotype i in the presence of the new modifier allele.

From the recursion (3.8) on the new modifier allele, we obtain the inequality:

$$\varepsilon'_{ai} = \sum_{bjk} \varepsilon_{aj} \hat{z}_{bk} \frac{w^j_k}{\hat{\bar{w}}} \left((1-R) T^{aj \to ai}_{bk} + R \tilde{T}^{ak \to ai}_{bj} \right)$$

$$= (1 - R)\varepsilon_{ai} \sum_{bk} z_{bk} \frac{w^i_k}{\hat{\bar{w}}} T^{ai \to ai}_{bk} + R\varepsilon_{ai} \sum_{bk} \hat{z}_{bk} \frac{w^i_k}{\hat{\bar{w}}} \tilde{T}^{ak \to ai}_{bi}$$

$$+ (1 - R) \sum_{\substack{bjk \\ j \neq i}} \varepsilon_{aj} \hat{z}_{bk} \frac{w^j_k}{\hat{\bar{w}}} T^{aj \to ai}_{bk} + R \sum_{\substack{bjk \\ j \neq i}} \varepsilon_{aj} \hat{z}_{bk} \frac{w^j_k}{\hat{\bar{w}}} \tilde{T}^{ak \to ai}_{bj} \qquad (3.9)$$

$$\geq (1 - R)\varepsilon_{ai} \frac{\hat{w}_i}{\hat{\bar{w}}} (1 - \tilde{m}_i) .$$

Therefore, if

$$\tilde{m}_i < 1 - \frac{\hat{\bar{w}}}{(1 - R)\hat{w}_i} \quad \text{then} \quad \varepsilon'_{ai} > \varepsilon_{ai},$$

and haplotype $M_a A_i$ increases when introduced.

Thus whenever transformation induces a fitness variance at equilibrium, it is possible, at least when

$$0 \leq R \leq 1 - \frac{\hat{\bar{w}}}{\max_i(\hat{w}_i)},$$

for a new modifier that puts a certain upper bound on the amount of transformation to increase when introduced into the population. This occurs through hitchhiking with the fitter A haplotypes, by preserving their identity during reproduction.

This condition does not use the last three terms of (3.9); using the second term on the right hand side of (3.9) it can be sharpened so that if

$$0 \leq R < \max_i [(1 - \frac{\hat{\bar{w}}}{w_i})(1 - \frac{\hat{v}_i w^i_i}{\hat{w}_i})^{-1}],$$

then the requirement for the initial increase of M_a is that there exist

$$\tilde{m}_i < 1 - \frac{\hat{\bar{w}}}{\hat{w}_i - R(\hat{w}_i - \hat{v}_i w_i^i)} .$$

This depends on $\hat{\underline{v}}$ however, so the improvement is undetermined without additional assumptions.

I.1a. THE EXTERIOR STABILITY OF FIXED MODIFIERS

Consider a population at a stable equilibrium where the modifier locus is fixed on one allele, M_1, yielding transformations T_1 and $\tilde{T}_1$. The selected haplotype frequencies must satisfy the identity

$$\hat{v}_i = \sum_{jk} \hat{v}_j \hat{v}_k \frac{w_k^j}{\hat{\bar{w}}} \left((1-R) T_{lk}^{lj \to i} + R T_{lj}^{lk \to i} \right) .$$

This can be represented in vector form as

$$\hat{\underline{v}} = \Omega_1 D\hat{\underline{v}} = \left((1-R) Y_1 + R\tilde{Y}_1 \right) D\hat{\underline{v}} ,$$

where

$$Y_1 \triangleq \| \sum_k \hat{v}_k \frac{w_k^j}{\hat{w}_j} T_{lk}^{lj \to i} \|_{i,j} , \qquad \tilde{Y}_1 \triangleq \| \sum_k \hat{v}_k \frac{w_k^j}{w_j} \tilde{T}_{lj}^{lk \to i} \|_{i,j} ,$$

and D is the diagonal matrix of relative marginal fitnesses. Y_1 and $\tilde{Y}_1$ are both stochastic matrices, since $\underline{e}^T Y_1 = \underline{e}^T \tilde{Y}_1 = \underline{e}^T$.

A new modifier allele, M_2, yielding transformations T_2 and $\tilde{T}_2$ as a heterozygote with M_1, is introduced into the population, and

the recursion on the frequencies of the new modifier allele is

$$\varepsilon'_i = \sum_{jk} \varepsilon_j \hat{v}_k \frac{w^j_k}{\hat{w}} \left((1-R) T^{2j \to 2i}_{1k} + R \tilde{T}^{2k \to 2i}_{1j} \right) .$$

This can be represented in vector form as

$$\underline{\varepsilon}' = \Omega_2 D \underline{\varepsilon} = \left((1-R) Y_2 + R \tilde{Y}_2 \right) D \underline{\varepsilon} ,$$

where

$$Y_2 \triangleq \| \sum_k \hat{v}_k \frac{w^j_k}{\hat{w}_j} T^{2j \to 2i}_{1k} \|_{i,j} \quad \text{and} \quad \tilde{Y}_2 \triangleq \| \sum_k \hat{v}_k \frac{w^j_k}{\hat{w}_j} \tilde{T}^{2k \to 2i}_{1j} \|_{i,j} .$$

The matrices Y_2 and $\tilde{Y}_2$ are also stochastic.

What determines whether or not the new modifier allele will increase when rare is whether or not the spectral radius

$$\rho\left(\left[(1-R) Y_2 + R \tilde{Y}_2 \right] D \right) > 1 .$$

Note that the matrix for M_1 , $\Omega_1 D$ has spectral radius equal to one,

$$\rho\left(\left[(1-R) Y_1 + R \tilde{Y}_1 \right] D \right) = 1 . \qquad (3.10)$$

This is known since the eigenvector $\hat{\underline{v}}$ is strictly positive by assumption, and the matrix $\Omega_1 D$ is non-negative: From Gantmacher (1959), non-negative matrices have a non-negative eigenvalue which is the spectral radius, and for which the corresponding eigenvector is non-negative. If $\hat{\underline{v}}$ in this case were not that vector, it would have to be orthogonal to it, being also an eigenvector. But being strictly positive, this is impossible. So $\hat{\underline{v}}$ is the eigenvector whose eigenvalue, 1, is the spectral radius of $\Omega_1 D$.

The question of the initial increase of the new modifier allele therefore reduces to the question of how changes from Ω_1 affects the spectral radius of that matrix when multiplied by D. At this point we need again to consider the nature of the variations in the transformations afforded by the modifier locus.

VARIATION IN DIPLOID INTRAGENOMIC TRANSFORMATIONS

Because there are only two transformation matrices involved here, the variation between them is necessarily uniform; what is of concern is whether the variation is linear or not. Suppose the variation is linear, where the relation between T_1 and T_2 is

$$T_{1k}^{2j \to 2i} = (1-m_1^2)\delta_{ji} + m_1^2 T_{1k}^{1j \to 1i} ,$$

and between $\tilde{T}_1$ and $\tilde{T}_2$ is

$$T_{1j}^{2k \to 2i} = (1-m_1^2)\delta_{ki} + m_1^2 \tilde{T}_{1j}^{1k \to 1i} ,$$

where m_1^2 is a modifier parameter for modifier genotype $\frac{M_2}{M_1}$.

Then the following theorem holds:

THEOREM 3.9:

FOR A TIGHTLY LINKED MODIFIER LOCUS, WHEN A NEW MODIFIER ALLELE IS INTRODUCED TO A POPULATION AT EQUILIBRIUM, FIXED FOR THE MODIFIER, WITH A MARGINAL FITNESS VARIANCE FOR THE SELECTED

TYPES, THEN THE NEW MODIFIER ALLELE WILL INCREASE IF IT BRINGS THE TRANSFORMATION ON THE SELECTED LOCI UNIFORMLY CLOSER TO PERFECT TRANSMISSION, AND IT WILL BE EXCLUDED IF IT TAKES THE TRANSFORMATION UNIFORMLY FURTHER AWAY FROM PERFECT TRANSMISSION.

PROOF:

The recursion on the frequency of M_2 is

$$\underline{\varepsilon}' = \left[(1-m_1^2)(1-R)\| \sum_k \hat{v}_k \frac{w_k^j}{\hat{\bar{w}}} \delta_{ji} \| + R \| \sum_k \hat{v}_k \frac{w_k^j}{\hat{\bar{w}}} \delta_{ki} \| \right] \underline{\varepsilon}$$

$$+ \left[m_1^2 (1-R)\| \sum_k \hat{v}_k \frac{w_k^j}{\hat{\bar{w}}} T_{lk}^{lj} \to 1i \| + R \| \sum_k \hat{v}_k \frac{w_k^j}{\hat{\bar{w}}} \tilde{T}_{lj}^{lk} \to 1i \| \right] \underline{\varepsilon}$$

$$= \left[(1-m_1^2)\left((1-R)I + RQ \right) + m_1^2 \left((1-R)Y_1 + R\tilde{Y}_1 \right) \right] D\,\underline{\varepsilon} \,,$$

where Q, Y_1, $\tilde{Y}_1$ and D are defined as before.

If $m_1^2 = 0$ then we have the situation in Theorem 3.5, where the new modifier brings about perfect transmission, and which therefore increases for any R. If $R = 0$, then the recursion is

$$\underline{\varepsilon}' = \left[(1-m_1^2)I + m_1^2 Y_1 \right] D\,\underline{\varepsilon} \,,$$

and now,

$$\Omega_2 = Y_2 = (1-m_1^2)I + m_1^2 Y_1 \,.$$

In this case, Karlin (1982) Theorem 5.2 can be applied. From (3.10) with $R = 0$, we know that $\rho(Y_1 D) = 1$. Therefore, $\rho(\Omega_2 D) > 1$ if $m_1^2 < 1$ and $\rho(\Omega_2 D) < 1$ if $m_1^2 > 1$.

From the theory of small parameters (Karlin and McGregor, 1972) this holds also for some range of $R > 0$. I cannot determine whether it

holds for all R , however. A substitution of $\Omega_2 D$ into the proof of Karlin (1982) Theorem 5.2 ends with a term that requires additional analysis.

This theorem accounts for why the reduction principle works. In the modifier gene models where the reduction principle works, the transformation process controlled by the modifier, be it recombination, mutation or migration (which will be covered later) is the only transformation acting on the selected types and each transformation occurs as a single event. Therefore, the variation in the transformations is linear, so this theorem applies.

When the difference between the transformations determined by M_1 and M_2 is affine, the same results will be found to hold that held in the analysis of affine variation under asexual descent. The discussion of this is deferred until the next section. As will be seen shortly, this analysis of the exterior stability of fixed modifiers is actually a special case of the exterior stability of broad class of "viability analogous" modifier polymorphisms, and I shall continue the analysis in this broader context.

I.1b. MODIFIER POLYMORPHISMS AND THEIR STABILITY

From Theorem 3.8, it is clear that if the transformation determined by the modifier heterozygote is closer to perfect transmission than either homozygote, then as long as the marginal fitness variance at the equilibrium is not zero, the modifier locus has a protected

polymorphism. In previous work to be found on modifier polymorphisms, Feldman and Balkau (1973), Prout et al. (1973), Thomson and Feldman (1976), and Feldman and Krakauer (1976), two kinds of modifier polymorphisms have been discovered. One kind is distinguished by having zero linkage disequilibrium between the modifier and selected loci, while the other has linkage disequilibrium which can be quite high for tight linkage betweeen the modifier and selected loci. It has not proved possible to obtain explicit solutions generally to the equilibrium identity (3.7) with modifier polymorphisms and selected locus polymorphisms. In this section I will generalize the conditions on the existence of zero disequilibrium polymorphisms and analyze their exterior stability. No general results were obtainable for the polymorphisms with linkage disequilibrium. It will be shown that the "balanced mixture" modifier polymorphisms which were described in the asexual case cannot generally be characterized in diploids.

BALANCED MIXTURE MODIFIER POLYMORPHISMS

In diploids, the existence of balanced mixture polymorphisms cannot generally be shown. Even if we assume that the genotype fitnesses are all equal at equilibrium, the requirements for a balanced mixture modifier polymorphisms are not necessarily possible to satisfy. With equal fitnesses, we must have that

$$\hat{\underline{z}}_a = \left[(1-R)T_a + R\tilde{T}_a \right] \hat{\underline{z}}_a ,$$

where

$$T_a \triangleq \| \sum_{bk} \hat{z}_{bk} T^{aj \to ai}_{bk} \|_{i,j}$$

and

$$\tilde{T}_a \triangleq \| \sum_{bk} \hat{z}_{bk} \tilde{T}^{ak \to ai}_{bk} \|_{i,j} .$$

Because this is a system of quadratic equations, the set of transformation matrices that would satisfy the equilibrium cannot be characterized as in the asexual case.

MODIFIER POLYMORPHISMS WITH ZERO LINKAGE DISEQUILIBRIUM

The work in this thesis was initiated in investigating a conjecture by my major adviser, Dr. Feldman, which was a generalization of the results in Feldman and Krakauer (1976) on modifier polymorphisms with zero linkage disequilibrium between the modifier locus and selected loci. He noted that the equilibrium modifier allele frequencies in these cases had the same form as equilibria in two allele models of viability selection, with the modifier parameters in the place of fitnesses. In analogy to the marginal fitnesses in the case of viability selection at a single locus, this means that the marginal modifier parameters, $m_a \triangleq \sum_b x_b m_b^a$, for each modifier allele, M_a, are equal at equilibrium,

$$\hat{m}_a = m^* \quad \forall\, a \ ,$$

where x_b is the frequency of each modifier allele M_b. From this he made the following conjecture:

THEOREM 3.10:

FELDMAN'S THEOREM ON THE EXISTENCE OF VIABILITY-ANALOGOUS TENSOR PRODUCT MODIFIER POLYMORPHISMS:

When the parameter determined by the modifier locus enters linearly into the recursions on the frequency of selected types, then for any equilbrium where the modifier is fixed on an allele

yielding modifier parameter m^*, and the selected haplotype frequencies are $\hat{\underline{v}}$, there will also exist an equilibrium modifier polymorphism when each modifier allele has m^* as its marginal modifier parameter, with the modifier locus and selected haplotypes in linkage equilibrium, and the selected haplotypes at frequencies $\hat{\underline{v}}$.

Because the modifier locus and selected haplotypes are in linkage equilibrium, the vector for the complete haplotype frequencies can be expressed as the tensor product

$$\hat{\underline{z}} = \hat{\underline{x}} \otimes \hat{\underline{v}} ,$$

where $\hat{\underline{x}}$ is the vector of modifier allele frequencies (Feldman and Krakauer, 1976). Multi-locus haplotypes frequencies which are the product of single locus allele frequencies have been referred to as "central" or "multi-locus Hardy-Weinberg" equilibria (Karlin and Feldman, 1978; Karlin and Liberman, 1979). Here I will refer to such equilbria as "tensor product" equilibria to avoid ambiguity or confusion with populations at equilibria having Hardy-Weinberg proportions among the genotypes.

The property of the modifier parameter entering linearly into the recursions is a basic feature of parameters affecting transformation processes, but not selection, because changes in selection values usually enter in the mean fitness, which appears as a normalizer, so that they enter non-linearly in the recursions, whereas the transformation probabilities enter in linear transformations on the frequency vector. Although Feldman's theorem was framed for uniform

variation in the transformations, being for one parameter families of transformation matrices, the linearity of the recursions in each of the transformation probabilities allows the theorem to be extended to general variation in the transformations.

THEOREM 3.11:

CONDITIONS FOR THE EXISTENCE OF TENSOR-PRODUCT MODIFIER POLYMORPHISMS:

Consider a population where the modifier and selected haplotype frequencies are of a tensor product form:

$$\underline{z} = \underline{x} \otimes \underline{v} .$$

Then the recursion becomes

$$z'_{ai} = x_a \sum_{bjk} v_j v_k \frac{w^j_k}{\bar{w}} x_b \left((1-R) T^{aj \to ai}_{bk} + R \tilde{T}^{ak \to ai}_{bj} \right) .$$

At this point, we need to define the following analog to the marginal fitness of a selected haplotype:

DEFINITION 6: THE MARGINAL TRANSFORMATION OF A MODIFIER ALLELE

Define the marginal transformation of a modifier allele M_a as:

$$T a^{j \to i}_{k} \triangleq \sum_b x_b T^{aj \to ai}_{bk} \quad \text{and} \quad \tilde{T} a^{k \to i}_{j} \triangleq \sum_b x_b \tilde{T}^{ak \to ai}_{bj} .$$

Using this in the recursion gives

$$\underline{z}_a' = x_a \left[(1-R) \left\| \sum_k v_k \frac{w_k^j}{w_j} Ta_k^{j \to i} \right\| + R \left\| \sum_k v_k \frac{w_k^j}{w_j} \tilde{Ta}_j^{k \to i} \right\| \right] D\underline{v}$$

$$= x_a \left[(1-R)Y_a + R\tilde{Y}_a \right] D\underline{v} \quad ,$$

where $Y_a \overset{\Delta}{=} \left\| \sum_k v_k \frac{w_k^j}{w_j} Ta_k^{j \to i} \right\|$ and $\tilde{Y}_a \overset{\Delta}{=} \left\| \sum_k v_k \frac{w_k^j}{w_j} \tilde{Ta}_j^{k \to i} \right\|$. (3.11)

If for all modifier alleles M_a , and for some frequencies $\hat{\underline{x}}$ and $\hat{\underline{v}}$,

$$\left[(1-R)\hat{Y}_a + R\hat{\tilde{Y}}_a \right] \hat{D}\hat{\underline{v}} = \hat{\underline{v}} \quad , \tag{3.12}$$

then we have an equilibrium,

$$\underline{z}' = \hat{\underline{x}} \otimes \hat{\underline{v}} = \hat{\underline{z}} \quad .$$

The only requirement on the marginal transformations is that $\hat{\underline{v}}$ be a leading eigenvector of each matrix

$$\left[(1-R)Y_a + R\tilde{Y}_a \right] D$$

derived from the marginal transformations. So in particular, if all the marginal transformations are identical and $\hat{\underline{v}}$ satisfies (3.12), then the tensor product equilibrium obtains. Although there may be cases where (3.12) is satisfied even when the modifier alleles have different marginal transformations, I cannot generally characterize them.

"Viability-analogous" will refer to the marginal transformations all being equal, since this is the analog of the marginal fitnesses of multiple alleles all being equal at equilibrium under viability selection. In the case of uniform variation in transformations, the transformation are characterized by the modifier parameters. Therefore, in order for the marginal transformations to be identical, the marginal modifier parameters must be identical, which proves Feldman's theorem.

I will use V.A.T.P. as an abbreviation for "viability-analogous, tensor product".

When the variation in the transformations is non-uniform, as in the case of a modifier control recombination between several non-interfering loci, it will not in general be possible for the marginal transformations to be equal. Therefore, viability-analogous, tensor product equilibria should be thought of mainly as a feature of uniform variation in transformations.

I.1c. THE EXTERIOR STABILITY OF TENSOR-PRODUCT MODIFIER POLYMORPHISMS

Let the population be at a tensor product modifier polymorphism

$$\hat{\underline{z}} = \hat{\underline{x}} \otimes \hat{\underline{v}} ,$$

where the marginal transformation probabilities for each modifier allele are

$T^{*}\frac{j}{k} \to i$ and $\tilde{T}^{*}\frac{k}{j} \to i$, which yield matrices Y^{*} and $\tilde{Y}^{*}$ when substituted in (3.11).

Now we introduce a new modifier allele M_a which in a genotype containing modifier allele M_b yields transformation probabilities

$$T\frac{aj}{bk} \to ai \quad \text{and} \quad \tilde{T}\frac{ak}{bj} \to ai .$$

The marginal transformations defined for the new modifier allele are

$$Ta\frac{j}{k} \to i = \sum_b \hat{x}_b T\frac{aj}{bk} \to ai \quad \text{and} \quad \tilde{T}a\frac{k}{j} \to i = \sum_b \hat{x}_b \tilde{T}\frac{ak}{ai} \to ai .$$

The recursion on the frequencies of the haplotypes containing the new modifier allele is

$$\underline{\varepsilon}' = \left[(1-R) \left\| \sum_k \hat{v}_k \frac{w_k^j}{\hat{w}_j} Ta_k^{j \to i} \right\| + R \left\| \sum_k \hat{v}_k \frac{w_k^j}{\hat{w}_j} \tilde{T}a_j^{k \to i} \right\| \right] D \underline{\varepsilon}$$

$$= \left[(1-R) Y_a + R \tilde{Y}_a \right] D\underline{\varepsilon} = \Omega_a D\underline{\varepsilon} \quad .$$

RESULT 3.12:

An important point that can be seen here is that it is only the marginal transformation probabilities of the new modifier allele that are involved in its initial increase behavior. The different transformations it may produce with each of the existing modifier alleles do not appear except as contributions to an average.

RESULT 3.13:

The equilibrium frequencies that the selected haplotypes would reach under the marginal transformation of the new modifier allele must be different from the frequencies at the existing equilibrium for there to be selection for or against the new modifier allele that would change its frequency at a geometric rate. This can be seen by noting that if

$$\hat{\underline{v}} = \Omega_a D\hat{\underline{v}} \quad ,$$

satisfying the equilibrium identity with the same selected haplotype frequencies $\hat{\underline{v}}$, then

$$\rho(\Omega_a D) = 1 \quad ,$$

so the new modifier allele can change frequencies at no more that an algebraic rate.

The necessity for the variation in the transformation to appear in the equilibrium relations of the selected haplotypes in order for there to be selection on the modifier has been shown for recombination by Feldman (1972) and for migration by Christiansen and Feldman (1975). In these cases, since the variation in transformations is uniform, it is the modifier parameter that must appear in the equilibrium identity for there to be selection on the modifier.

VIABILITY-ANALOGOUS, TENSOR PRODUCT EQUILIBRIA

For viability-analogous tensor product equilibria, there is only one marginal transformation among the modifier alleles present at equilibrium. Therefore, the initial increase behavior of a new modifier allele depends only on the relation between the equilibrium marginal transformation and the marginal transformation of the new modifier allele. It is the same as if the new modifier allele were introduced to a population fixed on a modifier, where the fixed modifier homozygote yielded the equilbrium marginal transformation, and the new modifier allele yielded the new marginal transformation as a heterozygote.

So what must now be considered, regardless of the nature of the variation in transformations among the modifier genotypes present at equilibrium, is how the new marginal transformation compares with the equilibrium marginal transformation. When the new marginal transformation is uniformly closer to or further from perfect transmission, Karlin (1982) Theorem 5.2 again applies, so Theorem 3.9 can be extended to viability-analogous, tensor product modifier polymorphisms:

THEOREM 3.14:

FOR A TIGHTLY LINKED MODIFIER LOCUS, WHEN A NEW MODIFIER ALLELE IS INTRODUCED TO A POPULATION AT A STABLE VIABILITY-ANALOGOUS, TENSOR PRODUCT EQUILIBRIUM, WHERE THERE IS A VARIANCE IN THE MARGINAL FITNESS OF THE SELECTED TYPES PRESENT, THEN THE NEW MODIFIER ALLELE WILL INCREASE IF ITS MARGINAL TRANSFORMATION IS UNIFORMLY CLOSER TO PERFECT TRANSMISSION THAN THE EQUILIBRIUM MARGINAL TRANSFORMATION, AND IT WILL BE EXCLUDED IF ITS MARGINAL TRANSFORMATION IS UNIFORMLY FURTHER AWAY FROM PERFECT TRANSMISSION.

I.1d. THE EXTERIOR STABILITY OF VIABILITY-ANALOGOUS, TENSOR PRODUCT MODIFIER POLYMORPHISMS WITH RESPECT TO AFFINE VARIATION.

One of the crucial properties of affine variation in transformations is that Theorem 5.2 of Karlin (1982) no longer applies. When the variation in the transformations is not not simply a shifting of weight between perfect transmission and another transformation matrix, it is possible for an increase in the overall rate of transformation to evolve. This is shown in two examples in the literature where modifiers causing affine variation were studied. In the model by Charlesworth (1979 b), where a modifier controls recombination in a population also undergoing migration, and in the

models by Feldman et al. (1980), where a modifier controls recombination in a genes also undergoing mutation, increases in recombination were able to evolve. Although I cannot give any general condition for when increases in transformation will be able to evolve under affine variation, some limited results can nevertheless be obtained.

First I give an intuitive but trivial result. Suppose that with the new modifier allele, all the selected haplotypes are transformed to a selected haplotype h with probability one,

$$T^{aj \to ai}_{bk} = \tilde{T}^{ak \to ai}_{bj} = \delta_{ih} \quad \forall \ b,j,k,i \ .$$

Then the recursion on the haplotypes with the new modifier is

$$\varepsilon_h' = \sum_j \frac{\hat{w}_j}{\bar{\hat{w}}} \varepsilon_j \quad \text{and} \quad \varepsilon_i' = 0 \quad \text{for} \quad i \neq h \ .$$

Therefore from the second generation on,

$$\varepsilon_h' = \frac{\hat{w}_h}{\bar{\hat{w}}} \varepsilon_h \ .$$

So this new modifier allele can increase when introduced only if selected haplotype h happens to have a marginal fitness greater than the mean fitness of the population. This extreme case serves as an example of a more general property that modifiers that cause an increased production of the fitter selected haplotypes can increase in the population, allowing the evolution of transformations to escape from the inexorable trend toward reduction in the overall amount of transformation which occurs under linear variation.

The balance between reduced transformation and increased production of the fitter types can be described quantitatively for affine variation within one class of transformations, those with memoriless

distributions, which include the "house of cards" mutation model of Kingman (1980). Here it is possible to calculate, for a tightly linked modifier, the amount of selection on new modifier allele as its marginal transformation deviates from the equilibrium marginal transformation.

A transformation with a memoriless distribution was defined (DEFINITION 4) to be one where all types have the same probability of undergoing a transformation process, and when they do, the type that they become has a distribution that is independent of their former type. Familiar examples in models of migration are the Wright island model, the Levene model, and the Deakin model (see Karlin, 1982). In the case of diploid genotypes, a transformation matrix with a memoriless distribution will have elements

$$T_{\overline{k}}^{j \to i} = (1-\alpha)\,\delta_{ij} + \alpha\, t_i \quad \forall\, k \text{ , where } t_i > 0 \text{ and } \sum_i t_i = 1 \text{ .}$$

When there is uniform variation in the transformations, due to any of the reasons discussed in Section 2., the general form for the transformation matrix with a memoriless distribution is

$$T_{\overline{bk}}^{aj \to ai} = (1-m_{\overline{b}}^{a})\left((1-\alpha)\delta_{ji} + \alpha s_i\right) + m_{\overline{b}}^{a}\left((1-\beta)\delta_{ji} + \beta p_i\right) \text{ , } \quad (3.13)$$

where α and β are the overall transformation rates and s_i and p_i are probabilities of producing haplotype i given there is a transformation. The modifier may change, therefore, both the overall rate and the relative distribution of transformations. Here I have assumed there is no interference between recombination with the modifier and the transformation process.

THE RATE OF CHANGE IN THE SPECTRAL RADIUS OF THE STABILITY MATRIX FOR A NEW MODIFIER ALLELE

Suppose that the population is at a viability-analogous, tensor product equilibrium, with an equilibrium marginal modifier parameter of m^*. Substitution of (3.13) into (3.11) yields

$$Y^* = (1-m^*)\left((1-\alpha)I + \alpha S\right) + m^*\left((1-\beta)I + \beta P\right) , \qquad (3.14)$$

where $S = \text{diag}(\underline{s})U$, and $P = \text{diag}(\underline{p})U$.

Here, $\hat{\underline{v}}$ must solve the equilibrium identity:

$$\begin{aligned} \hat{\underline{v}} &= \left[\left((1-m^*)(1-\alpha) - m^*(1-\beta)\right) I + (1-m^*)\alpha S + m^*\beta P\right] D\hat{\underline{v}} \qquad (3.15) \\ &= \left(1 - (1-m^*)\alpha - m^*\beta\right) D\hat{\underline{v}} + (1-m^*)\alpha \underline{s} + m^*\beta \underline{p} , \end{aligned}$$

yielding

$$\left[I - \left(1 - (1-m^*)\alpha - m^*\beta\right) D\right] \hat{\underline{v}} = (1-m^*)\alpha \underline{s} + m^*\beta \underline{p} .$$

Suppose that a new modifier allele, M_a has been intoduced to the population, yielding a marginal modifier parameter m_a. The recursion on the frequencies of the haplotypes bearing M_a is

$$\underline{\epsilon}' = Y_a\left[(1-R)I + RQ\right] D\underline{\epsilon} ,$$

where m_a has been substituted for m^* in (3.14) to yield Y_a, and since there is assumed to be no interference, $\tilde{Y}_a = Y_a Q$. Then the following theorem applies:

THEOREM 3.2b:

CONSIDER THE CASE OF AFFINE VARIATION IN TRANSFORMATIONS WITH MEMORILESS DISTRIBUTIONS (3.14). FOR A TIGHTLY LINKED MODIFIER, THE SPECTRAL RADIUS OF THE STABILITY MATRIX FOR A NEW ALLELE WITH MARGINAL MODIFIER PARAMETER m_a NEAR m^* IS APPROXIMATELY

1.

$$\rho(Y_a D) \tilde{=} 1 + (m_a - m^*)\frac{\alpha-\beta}{1-\gamma} ,$$

if for some i , $\alpha s_i + \beta p_i = 0$,

or otherwise,

2.

$$\rho(Y_a D) \tilde{=} 1 + (m_a - m^*)\Big(\sum_i \frac{1}{\gamma_i}\hat{v}_i^2\hat{w}_i\Big)^{-1}\frac{1}{\gamma^2}$$
$$\cdot\Big[\frac{\alpha-\beta}{\hat{\bar{w}}}\sum_i \frac{1}{\gamma_i}\hat{v}_i^2(\hat{w}_i-\hat{\bar{w}})^2 + \alpha\beta\Big((1-\gamma)\sum_i \hat{v}_i(\hat{w}_i-\hat{\bar{w}})\Big(\frac{p_i-s_i}{\gamma_i}\Big) + \gamma\ \mathrm{cov}\Big(\hat{w}_i,\frac{p_i-s_i}{\gamma_i}\Big)\Big)\Big]$$

where

$$\gamma_i \triangleq (1-m^*)\alpha s_i + m^*\beta p_i \text{ , and } \gamma \triangleq (1-m^*)\alpha + m^*\beta .$$

PROOF:

Suppose that sufficient time has elapsed so that $\underline{\varepsilon}$ has converged to the leading eigenvector of the stability matrix $\Omega_a D$ The general relation for an eigenvector $\hat{\underline{\varepsilon}}$ associated with eigenvalue λ of $\Omega_a D$ is:

$$\lambda\hat{\underline{\varepsilon}} = \big[(1-m_a)\big((1-\alpha)I + \alpha S\big) + m_a\big((1-\beta)I + \beta P\big)\big]\big[(1-R)I + RQ\big]\ D\hat{\underline{\varepsilon}} . \quad (3.16)$$

Assume that the eigenvector is an isolated point, so that implicit

differentiation with respect to m_a is possible.

Define the partial derivitives

$$\overset{\circ}{\lambda} \triangleq \frac{\partial}{\partial m_a}\lambda , \quad \overset{\circ}{\underline{\varepsilon}} \triangleq \frac{\partial}{\partial m_a}\hat{\underline{\varepsilon}} .$$

Then:

$$\overset{\circ}{\lambda}\hat{\underline{\varepsilon}} + \lambda\overset{\circ}{\underline{\varepsilon}} = [(\alpha-\beta)I - \alpha S + \beta P][(1-R)I + RQ]D\hat{\underline{\varepsilon}} + Y_a[(1-R)I + RQ]D\overset{\circ}{\underline{\varepsilon}} . \quad (3.17)$$

At $m_a = m^*$, $\hat{\underline{\varepsilon}} = \hat{\underline{v}}$, and $\lambda = \rho = 1$, these identities can be used:

1) $UD\hat{\underline{v}} = \underline{e}$ 2) $UD\overset{\circ}{\underline{\varepsilon}} = \overset{\circ}{\rho}\underline{e}$ 3) $UQD = UD$ 4) $QD\hat{\underline{v}} = D\hat{\underline{v}}$.

Hence

$$PQD\overset{\circ}{\underline{\varepsilon}} = PD\overset{\circ}{\underline{\varepsilon}} = \mathrm{diag}(\underline{p})UD\overset{\circ}{\underline{\varepsilon}} = \mathrm{diag}(\underline{p})\underline{e}\overset{\circ}{\rho} = \overset{\circ}{\rho}\underline{p} ,$$

and

$$PQD\hat{\underline{v}} = PD\hat{\underline{v}} = \underline{p}.$$

After substituting these in (3.17) and rearranging we have

$$\overset{\circ}{\rho}(\underline{v} - (1-m^*)\alpha\underline{s} - m^*\beta\underline{p}) + [I - (1 - (1-m^*)\alpha - m^*\beta)D]\overset{\circ}{\underline{\varepsilon}} - R(1 - (1-m^*)\alpha - m^*\beta)[Q - I]D\overset{\circ}{\underline{\varepsilon}}$$

$$= \beta\underline{p} - \alpha\underline{s} + (\alpha-\beta)D\hat{\underline{v}} .$$

Evaluating $\overset{\circ}{\rho}$ can be done only when $R=0$, which yields

$$\overset{\circ}{\rho}\left(\hat{\underline{v}} - (1-m^*)\alpha\underline{s} - m^*\beta\underline{p}\right) + \left[I - \left(1 - (1-m^*)\alpha - m^*\beta\right)D\right]\overset{\circ}{\underline{\varepsilon}} = \beta\underline{p} - \alpha\underline{s} + (\alpha-\beta)D\hat{\underline{v}} \tag{3.18}$$

Two cases must be considered:

CASE 1.

$$1 - \left(1 - (1-m^*)\alpha - m^*\beta\right)\frac{w_h}{\hat{\underline{w}}} = 0 \quad \text{for some h.}$$

$$\text{Then} \quad (1-m^*)\alpha s_h + m^*\beta p_h = 0 \ .$$

Let us define

$$\gamma \triangleq (1-m^*)\alpha + m^*\beta \ ,$$

which is the overall transformation rate.

Then $\dfrac{\hat{w}_h}{\hat{\underline{w}}} = \dfrac{1}{1-\gamma}$ and

$$\overset{\circ}{\rho} = \frac{\beta p_h - \alpha s_h}{\hat{v}_h} + \frac{\alpha-\beta}{1-\gamma} \ .$$

1. $0 < m^* < 1$.

Then $\alpha s_i = \beta p_i = 0$, and $\overset{\circ}{\rho} = \dfrac{\alpha-\beta}{1-\gamma}$.

2. $m^* = 0$ or $m^* = 1$.

Then the requirements for differentiability may not satisfied.

For $m^* = 0$, this means $\alpha s_h = 0$, so

$$\overset{\circ}{\rho} = \beta\frac{p_h}{\hat{v}_h} + \frac{\alpha-\beta}{1-\gamma} \ .$$

Because v_h drops out of (3.15), and since $m^* = 0$, p_h does not appear in (3.15), so the value $\frac{p_h}{\hat{v}_h}$ is not uniquely defined.

CASE 2.

$$1 - \left(1 - (1-m^*)\alpha - m^*\beta\right)\frac{\hat{w}_i}{\hat{w}} > 0 \qquad \forall\, i\ .$$

Then the matrix $I - \left(1 - (1-m^*)\alpha - m^*\beta\right)D$ is invertible.

Since

$$1 - \left(1 - (1-m^*)\alpha - m^*\beta\right)\frac{\hat{w}_i}{\hat{w}} = \frac{1}{\hat{v}_i}\left((1-m^*)\alpha s_i + m^*\beta p_i\right) \text{ from (3.15),}$$

then

$$\left[I - \left(1 - (1-m^*)\alpha - m^*\beta\right)D\right]^{-1} = \operatorname{diag}(\hat{\underline{v}})\left[(1-m^*)\alpha \operatorname{diag}(\underline{s}) + m^*\beta \operatorname{diag}(\underline{p})\right]^{-1}\ .$$

Define

$$D_2 \triangleq \left[(1-m^*)\alpha \operatorname{diag}(\underline{s}) + m^*\beta \operatorname{diag}(\underline{p})\right]^{-1}\ .$$

Then

$$\overset{\circ}{\rho}\left(\operatorname{diag}(\hat{\underline{v}})^2 D_2\underline{e} - \hat{\underline{v}}\right) + \overset{\circ}{\underline{\varepsilon}} = \operatorname{diag}(\hat{\underline{v}})\, D_2\left(\beta\underline{p} - \alpha\underline{s} + (\alpha-\beta)D\hat{\underline{v}}\right)\ . \tag{3.19}$$

By multiplying (3.19) by $\underline{e}^T D$, we can use the fact that $\overset{\circ}{\rho} = \underline{e}^T D\overset{\circ}{\underline{\varepsilon}}$ and $\underline{e}^T D\hat{\underline{v}} = 1$ to obtain

$$\overset{\circ}{\rho}\left(\underline{e}^T\operatorname{diag}(\hat{\underline{v}})^2 DD_2\underline{e}\right) = \underline{e}^T\operatorname{diag}(\hat{\underline{v}})DD_2\left(\beta\underline{p} - \alpha\underline{s} + (\alpha-\beta)D\hat{\underline{v}}\right)\ . \tag{3.20}$$

Now define $\gamma_i \triangleq (1-m^*)\alpha s_i + m^*\beta p_i = \left(D_2^{-1}\right)_{ii}$, so $\sum_i \gamma_i = \gamma$.

Then $\overset{\circ}{\rho}$ can be expressed

$$\overset{\circ}{\rho} = \left(\sum_i \frac{1}{\gamma_i} \hat{v}_i^2 \hat{w}_i\right)^{-1} \sum_i \frac{1}{\gamma_i} \hat{v}_i \hat{w}_i \left(\beta p_i - \alpha s_i + (\alpha - \beta) \frac{\hat{v}_i \hat{w}_i}{\hat{\bar{w}}}\right) \qquad (3.21)$$

Further evaluation is possible using the identity

$$\sum_i \frac{\hat{v}_i^2 \hat{w}_i^2}{\gamma_i} = \sum_i \frac{1}{\gamma_i} \left(\hat{v}_i \hat{w}_i - \frac{\gamma_i}{\gamma} \hat{\bar{w}}\right)^2 - \frac{\hat{\bar{w}}^2}{\gamma} + \frac{2\hat{\bar{w}}^2}{\gamma} .$$

Then

$$\sum_i \frac{1}{\gamma_i} \left((\alpha - \beta) \frac{v_i^2 w_i^2}{\hat{\bar{w}}} + \hat{v}_i \hat{w}_i (\beta p_i - \alpha s_i)\right)$$

$$= \frac{\alpha - \beta}{\hat{\bar{w}}} \sum_i \frac{1}{\gamma_i} \left(v_i w_i - \frac{\gamma_i}{\gamma} \hat{\bar{w}}\right)^2 + \sum_i \frac{1}{\gamma_i} \hat{v}_i \hat{w}_i \left(\beta p_i - \alpha s_i + \frac{\gamma_i}{\gamma} (\alpha - \beta)\right) .$$

The first term above can be rewritten:

The equilibrium identity

$$\hat{v}_i \left(1 - (1 - \gamma) \frac{\hat{w}_i}{\hat{\bar{w}}}\right) = \gamma_i ,$$

gives

$$\hat{v}_i (\hat{\bar{w}} - \hat{w}_i + \gamma \hat{w}_i) = \gamma_i \hat{\bar{w}} ,$$

thus

$$\hat{v}_i \hat{w}_i - \frac{\gamma_i}{\gamma} \hat{\bar{w}} = \frac{1}{\gamma} \hat{v}_i (\hat{w}_i - \hat{\bar{w}}) .$$

So

$$\sum_i \frac{1}{\gamma_i} \left(\hat{v}_i \hat{w}_i - \frac{\gamma_i}{\gamma} \hat{\bar{w}}\right)^2 = \frac{1}{\gamma^2} \sum_i \frac{1}{\gamma_i} \hat{v}_i^2 (\hat{w}_i - \hat{\bar{w}})^2 .$$

The second term can be rewritten also, since

$$\beta p_i - \alpha s_i + \frac{\gamma_i}{\gamma}(\alpha-\beta) = \frac{1}{\gamma}\alpha\beta(p_i - s_i) .$$

This yields

$$\overset{\circ}{\rho} = \Big(\sum_i \frac{1}{\gamma_i}\hat{v}_i^2 w_i\Big)^{-1} \frac{1}{\gamma^2}\Big[\frac{\alpha-\beta}{\bar{w}}\sum_i \frac{1}{\gamma_i}\hat{v}_i^2(\hat{w}_i - \bar{\hat{w}})^2 + \alpha\beta\gamma\sum_i \hat{v}_i\hat{w}_i\frac{(p_i-s_i)}{\gamma_i}\Big] .$$

The second term in the brackets can be rewritten as

$$\alpha\beta\gamma\sum_i \hat{v}_i\hat{w}_i\frac{p_i-s_i}{\gamma_i} = \alpha\beta\gamma\Big[\bar{\hat{w}}\,\bar{\delta} + \operatorname{cov}\Big(w_i, \frac{p_i-s_i}{\gamma_i}\Big)\Big]$$

where

$$\operatorname{cov}\Big(\hat{w}_i, \frac{p_i-s_i}{\gamma_i}\Big) \triangleq \sum_i \hat{v}_i(\hat{w}_i - \bar{\hat{w}})\Big(\frac{p_i-s_i}{\gamma_i} - \bar{\delta}\Big) ,$$

and

$$\bar{\delta} \triangleq \sum_i \hat{v}_i\frac{p_i-s_i}{\gamma_i} .$$

Into the expression

$$\bar{\delta} = \sum_i \Big(\hat{v}_i - \frac{\gamma_i}{\gamma}\Big)\frac{p_i-s_i}{\gamma_i}$$

we can substitute the following derivation from the equilibrium identity,

$$\hat{v}_i - \frac{\gamma_i}{\gamma} = \hat{v}_i - \frac{1}{\gamma}\Big(1-(1-\gamma)\frac{w_i}{\bar{\hat{w}}}\Big)\hat{v}_i = \frac{(1-\gamma)}{\gamma\,\bar{\hat{w}}}\hat{v}_i(\hat{w}_i - \bar{\hat{w}}) , \qquad (3.22)$$

to yield

$$\alpha\beta\gamma\sum_i \hat{v}_i\hat{w}_i\frac{p_i-s_i}{\gamma_i} = \alpha\beta\Big[(1-\gamma)\sum_i \hat{v}_i(\hat{w}_i-\bar{\hat{w}})\Big(\frac{p_i-s_i}{\gamma_i}\Big) + \gamma\operatorname{cov}\Big(\hat{w}_i, \frac{p_i-s_i}{\gamma_i}\Big)\Big] .$$

Therefore,

$$\rho(Y_a D) \tilde{=} 1 + (m_a - m^*)\Big(\sum_i \frac{1}{\gamma_i}\hat{v}_i^2 w_i\Big)^{-1}\frac{1}{\gamma^2}$$

$$\cdot\Big[\frac{(\alpha-\beta)}{\bar{\hat{w}}}\sum_i \frac{1}{\gamma_i}\hat{v}_i^2(\hat{w}_i-\bar{\hat{w}})^2 + \alpha\beta\Big((1-\gamma)\sum_i \hat{v}_i(\hat{w}_i-\bar{\hat{w}})\Big(\frac{p_i-s_i}{\gamma_i}\Big) + \gamma\operatorname{cov}\Big(\hat{w}_i, \frac{p_i-s_i}{\gamma_i}\Big)$$

This completes the proof.

In Case 1., a new modifier allele can change frequency at a geometric rate when introduced only if it changes the amount of transformation occurring, i.e. only if

$$(m_a - m^*)(\alpha - \beta) \neq 0 ,$$

and it can increase if and only if it reduces the amount of transformation.

In Case 2. the terms in the brackets show two different forces that contribute to the change in the spectral radius. The first term

$$\frac{\alpha - \beta}{\hat{\bar{w}}} \sum_i \frac{1}{\gamma_i} \hat{v}_i^2 \, (\hat{w}_i - \bar{w})^2$$

is the contribution of the marginal fitness variance to decreasing the overall amount of transformation occurring. It is zero if and only if either

1) the marginal fitness variance is zero, so

$$\hat{w}_i = \hat{\bar{w}} \quad \forall \; i , \text{ or}$$

2) the new modifier paramter m_a does not change the total amount of transformation $(1-m_a)\alpha + m_a\beta$, which requires $\alpha = \beta$.

When the marginal fitness variance is not zero, then the term is positive if increasing m_a decreases the overall amount of transformation, and is negative in the opposite case.

Another interesting feature of this term is seen by substituting from the alternative form of the equilibrium identity (3.22),

$$\frac{\gamma \hat{\bar{w}}}{1-\gamma} (\hat{v}_i - \frac{\gamma_i}{\gamma}) = \hat{v}_i (\hat{w}_i - \hat{\bar{w}}) .$$

The first term becomes

$$(\alpha - \beta) \hat{\bar{w}} \frac{\gamma^2}{(1-\gamma)^2} \sum_i \frac{1}{\gamma_i} (\hat{v}_i - \frac{\gamma_i}{\gamma})^2 .$$

If no selection were acting, then under transformation alone the equilibrium haplotype frequencies would all be

$$\hat{v}_i = \frac{\gamma_i}{\gamma} .$$

So the squared term is the deviation of the selected haplotype frequencies from where they would be under pure transformation. The effect of adding selection to a system of pure transformation is to create selection for decreased amounts of transformation.

The second two terms are the contribution from increasing the transformation probabilities toward the fitter types. Increasing m_a shifts the transformation distribution from the s_i values toward the p_i values. When the higher p_i's are sufficiently more associated with the higher marginal fitnesses than the s_i's , then this term is positive.

If the variation is linear, which occurs if and only if

$$\alpha = 0 \text{ , or } \beta = 0 \text{ , or } s_i = p_i \text{ for all } i ,$$

then the second term is zero. It is also zero if the marginal fitness variance is zero.

The basic conclusion from this derivation is that, at least in this case, whether or not a new modifier allele can increase in the population depends on a combination of how much it reduces the overall amount of transformation occurring, and how much it shifts the transformation distribution toward the production of fitter types.

I cannot say whether the results of this derivation would also hold for transformation with other than memoriless distributions, for loosely linked modifiers, or for new marginal modifier parameters far from m^* .

However, in models of recombination modification where there is also migration (Charlesworth and Charlesworth, 1979), or mutation (Feldman et al., 1980), the variation in the transformation is affine because, as was discussed in Section 2., cases 2) and 5) show that when the modifier has only partial control of the transformations occurring, the variation in the transformations can be affine. In these cases where the addition of mutation or migration makes the variation affine, it is possible for a modifier increasing recombination to increase when introduced into the population. This suggests the following principle:

THE PRINCIPLE OF PARTIAL CONTROL:

When a modifier gene has only partial control over the transformations occurring at selected loci, then it is possible for this part of the transformations to evolve an increase.

THE CO-EVOLUTION OF TRANSFORMATIONS

An interesting question is how different parts of a transformation under the control of different modifiers will coevolve. Is it possible, since each modifier will have only partial control over the transformation, for all these parts to evolve an increase? In other words, by fragmenting the control over the transformation among various modifier genes, is it possible for the transformation to "bootstrap" itself away from perfect transmission? For the case of transformations with memoriless distributions, at least, this appears not to be the case.

Suppose that the transformation acting on the selected haploytpes is composed of several processes, each of which is controlled linearly

be a modifier locus, as in case 5) of Section 2.. Consider when there are two such processes and each has a memoriless distribution. The transformation matrix will be of the form

$$Y = \| T_k^{j \to i} \|_{i,j} = \big((1-a)I + aF\big)\big((1-b)I + bG\big)$$
$$= (1-a)(1-b)I + aF + (1-a)bG \quad , \qquad (3.23)$$

where F and G are rank one stochastic matrices.

Now let a modifier control either a or b. (3.23) can be translated into the form of (3.14) choosing either a or b to be the modifier parameter, with the substitutions as shown in the following table:

TABLE 12

MODIFIER CONTROL OVER TWO LINEARLY VARYING TRANSFORMATIONS

values for:	α	β	αS	βP	$P - S$
MODIFIER CONTROLS a:	b	1	bG	F	F - G
MODIFIER CONTROLS b:	a	1	aF	(1-a)G + aF	(1-a)(G - F)

In each case, $\gamma_i = af_i + (1-a)bg_i$.

Let us look at how Theorem 3.2b. applies. For modifiers of both a and b, the coefficient on the term

$$\sum_i \frac{1}{\gamma_i} \hat{v}_i^2 (\hat{w}_i - \hat{\bar{w}})^2$$

from Theorem 3.2b, case 2., will be negative, contributing toward decreasing both a and b. The only way for both a and b to evolve an increase is for the second two terms in the brackets from case 2. to be sufficiently positive. But the values $p_i - s_i$ for the modifier of a will be of opposite sign of those values for the modifier of b, as seen from the last column of Table 12. Therefore, if the second two terms in the brackets are positive for one modifier they will be negative for the other. This yields the following:

RESULT 3.15:

For transformations with memoriless distributions, where two modifiers each have linear control over only a part of the transformation, if one modifier evolves to increase the part of the transformation it controls, then the other modifier must evolve to decrease the part of the transformation it controls.

It would be of interest to know whether Result 3.15 extends to other forms of transformation.

1.2. THE INTERIOR STABILITY OF VIABILITY-ANALOGOUS, TENSOR PRODUCT EQUILIBRIA FOR MODIFIERS YIELDING UNIFORM VARIATION

Here I will evaluate the local interior stability of a viability-analogous, tensor product modifier polymorphism for a modifier that yields uniform variation in the transformations.

Using the general form for representing uniform variation, the recursion for system is

$$z'_{ai} = \sum_{bjk} z_{aj} z_{bk} \frac{w^j_k}{\bar{w}} \left[(1-R)\left(\delta_{ji} + A^{j\to i}_{k} + m^{a}_{b} B^{j\to i}_{k}\right) + R\left(\delta_{ki} + \tilde{A}^{k\to i}_{j} + m^{a}_{b} \tilde{B}^{k\to i}_{j}\right)\right] .$$

Letting

$$z_{ai} = \hat{z}_{ai} + \varepsilon_{ai} = \hat{x}_a \hat{v}_i + \varepsilon_{ai} ,$$

where the perturbations $\sum_{ai} \varepsilon_{ai} = 0$, we obtain the following linearized recursion on the perturbations:

$$\begin{aligned}
\hat{\bar{w}} \varepsilon'_{ai} = {} & (\varepsilon_{ai} \hat{w}_i + \hat{x}_a \hat{v}_i \sum_{bj} w^i_j \varepsilon_{bj})(1-R) + (\hat{x}_a \hat{w}_i \sum_{b} \varepsilon_{bi} + \hat{v}_i \sum_{j} w^i_j \varepsilon_{aj})\, R \\
& + (\sum_{hj} \hat{v}_h w^h_j A^{j\to i}_{h} \varepsilon_{aj} + \hat{x}_a \sum_{hjb} \hat{v}_h w^h_j A^{h\to i}_{j} \varepsilon_{bj})(1-R) \\
& + (\hat{x}_a \sum_{hjb} \hat{v}_h w^h_j \tilde{A}^{j\to i}_{k} \varepsilon_{bj} + \sum_{hj} \hat{v}_h w^h_j \tilde{A}^{h\to i}_{j} \varepsilon_{aj})\, R \\
& + (m^* \sum_{hj} \hat{v}_h w^h_j B^{j\to i}_{h} \varepsilon_{aj} + \hat{x}_a \sum_{hjb} \hat{v}_j w^h_j B^{h\to i}_{j} m^{a}_{b} \varepsilon_{bj})(1-R) \\
& + (\hat{x}_a \sum_{hjb} \hat{v}_h w^h_j \tilde{B}^{j\to i}_{h} m^{a}_{b} \varepsilon_{bj} + m^* \sum_{hj} \hat{v}_j w^h_j \tilde{B}^{h\to i}_{j} \varepsilon_{aj})\, R \\
& - 2\hat{x}_a \hat{v}_i \sum_{bj} \varepsilon_{bj} \hat{w}_j .
\end{aligned}$$

This can be represented in vector form using tensor products:

$$\underline{\varepsilon}' = \left[\begin{array}{l} I_1 \bullet [(1-R)(I_2 + A + m^*B) + R(Q + \tilde{A} + m^*\tilde{B})] \\ + \operatorname{diag}(\hat{\underline{x}})U_1 \bullet [R(I_2 + A) + (1-R)(Q + \tilde{A})] \\ + \operatorname{diag}(\hat{\underline{x}})M \bullet [RB + (1-R)\tilde{B}] \\ - 2\operatorname{diag}(\hat{\underline{x}})U_1 \bullet \operatorname{diag}(\hat{\underline{v}})U_2 \end{array}\right] (I_1 \bullet D)\underline{\varepsilon}$$

$$\triangleq \Gamma\, \underline{\varepsilon} ,$$

where

$$A \triangleq \left\| \sum_k \hat{v}_k \frac{w_k^j}{\hat{\bar{w}}} A_k^{j \to i} \right\|_{i,j} , \quad \tilde{A} \triangleq \left\| \sum_k \hat{v}_k \frac{w_k^j}{\hat{\bar{w}}} \tilde{A}_j^{k \to i} \right\|_{i,j} ,$$

B and $\tilde{B}$ are defined analogously, and Q and D are defined as before. U_1 is an n_1 by n_1 matrix of ones, where n_1 is the number of modifier alleles, and U_2 is that for n_2, the number of selected-loci haplotypes. M is the matrix of modifier parameters, $M = \| m_j^i \|$. I_1 and I_2 are the appropriate identity matrices.

To begin the analysis, first, let us project the vector $\underline{\varepsilon}$ on to the space of perturbations in the selected haplotypes, by adding up, $\sum_a \varepsilon_{ai}$. This is accomplished by premultiplication with

$$\underline{e}_1^T \bullet I_2 .$$

Since

$$\underline{e}_1^T \operatorname{diag}(\hat{\underline{x}})U_1 = \underline{e}_1^T , \qquad \underline{e}_1^T \operatorname{diag}(\hat{\underline{x}})M = m^* \underline{e}_1^T ,$$

we have

$$\begin{aligned} (\underline{e}_1^T \bullet I_2)\,\underline{\varepsilon}' &= (\underline{e}_1^T \bullet I_2)\Gamma\underline{\varepsilon} \\ &= GD[(\underline{e}_1^T \bullet I_2)\,\underline{\varepsilon}] , \end{aligned} \tag{3.24}$$

where

$$G \triangleq I_2 + Q + A + \tilde{A} + m^*(B + \tilde{B}) - 2\,\mathrm{diag}(\hat{\underline{v}})U_2 .$$

This recursion on the perturbations of the selected haplotype frequencies is identical to the recursion when the modifier is fixed,

$$\underline{\nu}' = GD\,\underline{\nu} .$$

Thus we obtain the following:

THEOREM 3.16:

If the selection-transformation equilibrium is unstable when the modifier is fixed, it is also unstable for the viability-analogous, tensor product modifier polymorphism. For the polymorphism to be stable, at least the equilibrium with fixed modifier must be stable, i.e.,

$$\rho(GD) < 1 .$$

Although this was demonstrated here only for uniform variation, it can be seen to hold for any V.A.T.P. equilibrium.

Vectors which project to 0 under $\underline{e}_1^T \otimes I_2$ form a linear subspace of $\{\underline{\varepsilon}\}$, call it N. It will be of dimension $(n_1 - 1)n_2$, where n_1 is the number of modifier alleles, and n_2 the number of selected haplotype. This is seen because we can use as a basis for N

$$\{\underline{\alpha}_i \otimes \underline{\gamma}_j\} ,$$

where $\underline{\alpha}_i$ are n_1 long vectors, $\underline{\gamma}_j$ are n_2 long vectors, and

$$\underline{e}_1^T\underline{\alpha}_i = 0 \quad \forall\, i = 1 \ldots n_1 - 1 , \quad \underline{\gamma}_j = \begin{pmatrix} 0 \\ \vdots \\ 1 \\ \vdots \\ 0 \end{pmatrix} \leftarrow j\text{th component is 1.}$$

There are assumed to be at least two modifier alleles, for otherwise N would consist of the zero vector. To fill out $\{\underline{\varepsilon}\}$, we define the space H, orthogonal to N. H is of dimension $n_2 - 1$. For all $\underline{\beta} \in H$, we know

$$(\underline{e}_1^T \otimes I_2)\,\underline{\beta} \neq 0 \text{ , and } (\underline{e}_1^T \otimes \underline{e}_2^T)\,\underline{\beta} = 0 .$$

For each $\underline{\varepsilon}$ there is always a unique representation

$$\underline{\varepsilon} = \tilde{\underline{\varepsilon}} + \underline{\beta} \quad \text{where } \tilde{\underline{\varepsilon}} \in N,\ \underline{\beta} \in H .$$

Then, from (3.24),

$$\begin{aligned}(\underline{e}_1^T \otimes I_2)\,\Gamma^n \underline{\varepsilon} &= (GD)\,(\underline{e}_1^T \otimes I_2)\,\Gamma^{n-1}\underline{\varepsilon} = (GD)^n(\underline{e}_1^T \otimes I_2)\,\underline{\varepsilon} \\ &= (GD)^n(\underline{e}_1^T \otimes I_2)(\tilde{\underline{\varepsilon}} + \underline{\beta}) = (GD)^n[(\underline{e}_1^T \otimes I_2)\,\underline{\beta}]\end{aligned}$$

Since we have already required that

$$\lim_{n\to\infty} (GD)^n \underline{x} = 0 \quad \forall\, \underline{x}:\ \underline{e}_2^T \underline{x} = 0 \text{ , we have}$$

$$\lim_{n\to\infty} (\underline{e}_1^T \otimes I_2)\,\Gamma^n \underline{\varepsilon} = 0, \quad \forall\ \underline{\varepsilon} .$$

Therefore, trajectories converge to points in N, all components from H in $\underline{\varepsilon}$ damping out, so we need only consider perturbations $\tilde{\underline{\varepsilon}} \in N$.

Now, for

$$\tilde{\underline{\varepsilon}} = \sum_{ij} a_i b_j\, \underline{\alpha}_i \otimes \underline{\gamma}_j \in N ,$$

we have

$$(I_1 \otimes D)\tilde{\underline{\varepsilon}} = \sum_{ij} a_i b_j \underline{\alpha}_i \otimes D\,\underline{\gamma}_j \in N \text{ also.}$$

So

$$(U_1 \otimes D)\,\tilde{\underline{\varepsilon}} = 0 \quad \forall\, \tilde{\underline{\varepsilon}} \in N ,$$

which gives

$$\begin{aligned}\tilde{\underline{\varepsilon}}' = \Big(& I_1 \otimes [(1-R)(I_2 + A + m^* B) + R(Q + \tilde{A} + m^* \tilde{B})] \\ & + \operatorname{diag}(\hat{\underline{x}})M \otimes [RB + (1-R)\tilde{B}] \Big)\ (I_1 \otimes D)\tilde{\underline{\varepsilon}} .\end{aligned}$$

In the analogy to viability selection, the modifier parameters m_j^i behave as fitnesses except that, whereas a new selected allele must have $w_i > \bar{w}$ to increase, the modifier must have $m_i < m^*$, from the last section. Therefore, the analog to the fitness matrix would be the matrix $U - M$. Pursuing this analogy, we might expect that modifier overdominance would be required to make a modifier polymorphism stable.

Maximal overdominance is attained when

$$M = \text{diag}(m_i^i) .$$

Here, the phenotype that is overdominant is the extent to which perfect transmission of the haplotypes is occurring, rather than the extent of transformation. The best biological example of maximal overdominance is a chromosomal inversion bordered by two loci under selection. The inversion acts as a tightly linked modifier of recombination, which as a heterozygote eliminates recombination between the two loci.

Since $\hat{m}_a = \sum_b m_b^a \hat{x}_b = m_a^a \hat{x}_a = m^*$, this gives $\text{diag}(\hat{\underline{x}})M = m^* I_1$. Substituting, we obtain

$$\tilde{\underline{\varepsilon}}' = \left(I_1 \bullet \left[(1-R)(I_2 + A) + R(Q + \tilde{A}) + m^*(B + \tilde{B}) \right] D \right) \tilde{\underline{\varepsilon}}$$

$$\triangleq (I_1 \bullet JD)\, \tilde{\underline{\varepsilon}} .$$

For this case, the V.A.T.P. equilibrium is stable if $\rho(JD) < 1$, and unstable if $\rho(JD) > 1$.

It is significant that neither the specific modifier parameters nor the modifier allele frequencies appear directly here, which gives the following result:

THEOREM 3.17:

For a maximally overdominant modifier locus, neither the degree of allelic multiplicity at the modifier locus, nor the specific modifier parameters of the modifier homozygotes, are relevant to the stability of a V.A.T.P. modifier polymorphism with uniform variation in the transformation.

Note that $J = (1-R)Y^* + R\tilde{Y}^* + m^*(RB + (1-R)\tilde{B})$,

$G = 2\left(\frac{1}{2}(Y^* + \tilde{Y}^*) - \mathrm{diag}(\hat{\underline{v}})U\right)$,

where Y^* and $\tilde{Y}^*$ are defined as in the exterior stability analysis (I.1c.). Now,

$\rho([(1-R)Y^* + R\tilde{Y}^*]D) = 1 \;\forall\; R$ and $\rho(GD) < 1$ by assumption, thus

$$\rho\left(\left[\frac{1}{2}(Y^* + \tilde{Y}^*) - \mathrm{diag}(\hat{\underline{v}})U\right]D\right) < \frac{1}{2} .$$

We wish to know

$$\rho([(1-R)Y^* + R\tilde{Y}^* + m^*(RB + (1-R)\tilde{B})]D) .$$

I cannot solve this generally, but will consider some special cases.

I.2a. UNLINKED MODIFIERS

Note the following relation:

At $R=1/2$,

$$J = \frac{1}{2}(I_2 + A + Q + \tilde{A}) + m^*(B + \tilde{B}) .$$

In comparison, at $R=1/2$, the stability matrix for the initial increase of a new modifier allele whose marginal transformation falls within the same uniform variation is

$$\Omega_a = \frac{1}{2}(I_2 + A + Q + \tilde{A}) + \frac{m_a}{2}(B + \tilde{B}) .$$

Therefore, we have the very interesting result:

THEOREM 3.18:

For an unlinked modifier, a V.A.T.P. equilibrium with uniform variation in transformations and maximal modifier overdominance will be stable internally if and only if it is stable to the introduction of a new modifier allele having marginal parameter

$$m_a = 2m^* .$$

I do not know what is entailed when $2m^*$ is beyond the feasible range of m_a.

Unfortunately, the exterior stability to the introduction of new modifier alleles with $m_a > 0$ has not been tractible for $R > 0$ in the general case. In the cases in Feldman et al. (1980), analysis for loci with two alleles has been done. In the case of a recombination modifier when there is no mutation, so that the variation in the transformation is linear, their results imply that at $R= 1/2$,

$$\rho(JD) < 1 \quad , \text{ since } \rho(\Omega_a D) < 1 \text{ at } m_a = 2m^* .$$

This yields the following:

RESULT 3.19:

For an unlinked modifier of recombination at two loci, subject to no other transformations, when there are two alleles at each of the selected loci, and an arbitrary number of maximally overdominant alleles at the modifier locus, a viability-analogous, tensor product equilibrium is stable given that polymorphism among the selected loci under the equilibrium recombination rate is stable.

This extends the result of Feldman and Balkau (1973) to arbitrary selection regimes and arbitrary numbers of modifier alleles, which, however, are restricted to being maximally overdominant.

If the reduction principle could be shown to hold also for the general case of linear variation in transformations with unlinked modifiers, in other words, if it could be shown that a new allele linearly increasing transformation is always excluded, then Result 3.19 could be extended generally. Given that a polymorphism among the selected loci under a given transformation is stable, then a V.A.T.P. polymorphism with the same equilibrium transformation, with an unlinked, maximally overdominant modifier, and linear variation in the transformation, is always stable.

Now let us consider affine variation in the transformation. At a V.A.T.P. equilibrium, if a new modifier allele increasing transformation by any amount can get into the population, then Theorem 3.18 implies that the V.A.T.P. polymorphism will be unstable for an unlinked modifier. This would hold for the case of recombination modification with mutation present, in Feldman et al. (1980), provided the critical

value of R at which the exterior stability changes is greater than one half. This is to be expected if the viability analogy is reconsidered for the affine case. In this case, the modifier locus would appear to be underdominant, because lower amounts of transformation are being selected against. In analogy with viability selection, polymorphic equilibria with underdominance are unstable.

I will now consider two special cases of transformation: recombination and mutation. In both these cases, the variation in the transformation will be linear, so $A=0$, and $B=P-I$. I will assume there is no interference. Thus

$$J = (1-R-m^*)I + (R-m^*)Q + m^*(P+\tilde{P}),$$

where

$$T^{aj\to ai}_{bk} = (1-m^a_b)\delta_{ji} + m^a_b P^{j\to i}_k ,$$

$$P \triangleq \| \sum_k \hat{v}_k \frac{w^j_k}{\hat{w}_j} P^{j\to i}_k \|_{i,j} \quad \text{and} \quad \tilde{P} \triangleq \| \sum_k \hat{v}_k \frac{w^j_k}{\hat{w}_j} P^{k\to i}_j \|_{i,j} .$$

I.2b. MUTATION MODIFIERS

For the general mutation transformation, $P^{j\to i}_h = P_{j\to i}\ \forall\ h$.

$$\text{Thus } \tilde{P} = \| \sum_H \hat{v}_h \frac{w^h_j}{\hat{w}_j} P_{h\to i} \| = PQ, \quad P = \| P_{j\to i} \| .$$

$$\text{So } J = (1-R)\ I + RQ + m^*(P-I)(I+Q).$$

I will analyze the case with 2 alleles at the selected locus. In the following derivation, m refers to m^* and w_{ij} refers to $w\frac{i}{j}$.

$$D = \begin{Vmatrix} \frac{\hat{w}_1}{\bar{\hat{w}}} & 0 \\ 0 & \frac{\hat{w}_2}{\bar{\hat{w}}} \end{Vmatrix}, \qquad Q = \begin{Vmatrix} \hat{v}_1 \frac{w_{11}}{\hat{w}_1} & \hat{v}_1 \frac{w_{12}}{\hat{w}_2} \\ \hat{v}_2 \frac{w_{21}}{\hat{w}_1} & \hat{v}_2 \frac{w_{22}}{\hat{w}_2} \end{Vmatrix} = \begin{Vmatrix} q_1 & q_3 \\ q_2 & q_4 \end{Vmatrix},$$

$$P = \begin{Vmatrix} P_1 & P_3 \\ P_2 & P_4 \end{Vmatrix}, \text{ and}$$

$$J = (1-m^*-R)\begin{Vmatrix} 1 & 0 \\ 0 & 1 \end{Vmatrix} + m^*\begin{Vmatrix} P_1 & P_3 \\ P_2 & P_4 \end{Vmatrix}\begin{Vmatrix} 1+q_1 & q_3 \\ q_2 & 1+q_4 \end{Vmatrix} + (R-m^*)\begin{Vmatrix} q_1 & q_3 \\ q_2 & q_4 \end{Vmatrix}.$$

I will drop the superscripts where convenient at this point.

Thus $JD =$

$$\frac{1}{\bar{w}}\begin{Vmatrix} w_1[1-m-R+mp_1+(R-m)q_1+m(p_1q_1+p_3q_2)] & w_2[mp_3+(R-m)q_3+m(p_1q_3+p_3q_4)] \\ w_1[mp_2+(R-m)q_2+m(p_2q_1+p_4q_2)] & w_2[1-m-R+mp_4+(R-m)q_4+m(p_2q_3+p_4q_4)] \end{Vmatrix}$$

To evaluate $\rho(JD)$, we examine the characteristic determinant and its derivative at $\lambda=1$. The characteristic determinant is

$$ch(\lambda) = \frac{1}{\bar{\hat{w}}}\begin{vmatrix} C_{11} - \hat{Rv}_2w_{12} & C_{12} + \hat{Rv}_1w_{12} \\ C_{21} + \hat{Rv}_2w_{12} & C_{22} - \hat{Rv}_1w_{12} \end{vmatrix},$$

where

$$C_{11} = \hat{w}_1 - \hat{\bar{w}}\lambda + m(-\hat{w}_1 p_2 - \hat{v}_1 w_{11} + p_1 \hat{v}_1 w_{11} + p_3 \hat{v}_2 w_{12}) ,$$
$$C_{12} = m(p_3 \hat{w}_2 - \hat{v}_1 w_{12} + p_1 \hat{v}_1 w_{12} + p_3 \hat{v}_2 w_{22}) ,$$
$$C_{21} = m(p_2 \hat{w}_1 - \hat{v}_2 w_{12} + p_2 \hat{v}_1 w_{11} + p_4 \hat{v}_2 w_{12}) ,$$
$$C_{22} = \hat{w}_2 - \hat{\bar{w}}\lambda + m(-p_3 \hat{w}_2 - \hat{v}_2 w_{22} + p_2 \hat{v}_1 w_{12} + p_4 \hat{v}_2 w_{22}) .$$

The R^2 terms all cancel.

The R term is:

$$-Rw_{12}[v_1(C_{11} + C_{21}) + v_2(C_{12} + C_{22})] = -Rw_{12}[v_1(w_1 - \bar{w}\lambda) + v_2(w_2 - \bar{w}\lambda)]$$
$$= -Rw_{12}(1-\lambda)\bar{w} .$$

At $\lambda = 1$, the R term is also zero.

Thus

$$ch(1) = \frac{1}{\hat{\bar{w}}} \begin{vmatrix} C_{11} & C_{12} \\ C_{21} & C_{22} \end{vmatrix} = \frac{1}{\hat{\bar{w}}} \begin{vmatrix} w_1 \hat{-} \bar{w} - m\alpha_1 & m\alpha_2 \\ m\alpha_1 & \hat{w}_2 \hat{-} \bar{w} - m\alpha_2 \end{vmatrix}$$

$$= (\hat{w}_1 - \hat{\bar{w}})(\hat{w}_2 - \hat{\bar{w}}) - m(\alpha_1(\hat{w}_2 - \hat{\bar{w}}) + \alpha_2(\hat{w}_1 - \hat{\bar{w}}))$$

where $\alpha_1 \triangleq p_2(\hat{v}_1 w_{11} + \hat{w}_1) - p_3 \hat{v}_2 w_{12}$, $\alpha_2 \triangleq p_3(\hat{v}_2 w_{22} + \hat{w}_2) - p_2 \hat{v}_1 w_{12}$.

The identities

$$\hat{w}_1 - \hat{\bar{w}} = \hat{v}_2(\hat{w}_1 - \hat{w}_2), \text{ and } w_2 - \bar{w} = -\hat{v}_1(\hat{w}_1 - \hat{w}_2),$$

give

$$ch(1) = -(\hat{w}_1 - \hat{w}_2)^2 \hat{v}_1 \hat{v}_2 - m(\hat{w}_1 - \hat{w}_2)(\hat{v}_2 \alpha_2 - \hat{v}_1 \alpha_1) .$$
$$= -(w_1 - w_2)^2 \hat{v}_1 \hat{v}_2 - 2m(\hat{w}_1 - \hat{w}_2)(p_3 \hat{v}_2 \hat{w}_2 - p_2 \hat{v}_1 \hat{w}_1) .$$

Using one of the equilibrium identities,

$$\bar{w}\hat{v}_2 = v_2 w_2(1 - m) + m(p_2 w_1 v_1 + p_4 w_2 v_2),$$

which gives

$$(\bar{w} - w_2)v_2 = (w_1 - w_2)v_1 v_2 = m(p_2 v_1 w_1 - p_3 v_2 w_2) ,$$

we obtain

$$ch(1) = v_1 v_2 (w_1 - w_2)^2 = (w_1 - \bar{w})(\bar{w} - w_2) .$$

In the general case where there is an equilibrium fitness load, meaning the equilibrium $\hat{\underline{v}}$ is mutation dependent, then $w_1 \neq w_2$, thus $ch(1) > 0$.

The derivative of the characteristic polynomial is:

$$\frac{\partial ch(\lambda)}{\partial \lambda} = \frac{1}{\bar{w}} \left(c_{11} \frac{\partial c_{22}}{\partial \lambda} + \frac{\partial c_{11}}{\partial \lambda} c_{22} \right) - R \frac{w_{12}}{\bar{w}} \left(\hat{v}_2 \frac{\partial c_{22}}{\partial \lambda} + v_1 \frac{\partial c_{11}}{\partial \lambda} \right)$$

$$= R w_{12} - c_{11} - c_{22} .$$

Therefore

$$\frac{\partial ch(\lambda)}{\partial \lambda} \Bigg|_{\lambda = 1} > 0 \quad \forall R \quad \text{iff} \quad c_{11} + c_{22} < 0 \quad \text{at} \quad \lambda = 1 .$$

Now,

$$c_{11} + c_{22} = \hat{w}_1 - \bar{w} + \hat{w}_2 - \bar{w} + m\left(p_2 (\hat{v}_1 w_{12} - \hat{v}_1 w_{11} - \hat{w}_1) + p_3 (\hat{v}_2 w_{12} - \hat{v}_2 w_{22} - \hat{w}_2) \right)$$

The equilibrium identities

$$\hat{\bar{w}} - \hat{w}_2 = \frac{m}{\hat{v}_2} (p_2 \hat{v}_1 \hat{w}_1 - p_3 \hat{v}_2 \hat{w}_2), \text{ and } \hat{\bar{w}} - \hat{w}_1 = \frac{m}{\hat{v}_1} (p_3 \hat{w}_2 \hat{v}_2 - p_2 \hat{w}_1 \hat{v}_1),$$

give

$$c_{11} + c_{22} = \frac{m}{\hat{v}_1 \hat{v}_2} \left[p_2 \hat{v}_1 \left(\hat{v}_1 (v_2 w_{12} - w_1) - \hat{v}_1 \hat{v}_2 w_{11} \right) + p_3 \hat{v}_2 \left(\hat{v}_2 (\hat{v}_1 w_{12} - \hat{w}_2) - \hat{v}_1 \hat{v}_2 w_{22} \right) \right]$$

$$= -(p_2 \hat{v}_1^2 w_{11} + p_3 \hat{v}_2^2 w_{22}) < 0 .$$

Therefore, since

$$ch(1) > 0, \quad \frac{\partial ch(\lambda)}{\partial \lambda} \Bigg|_{\lambda = 1} > 0 ,$$

no eigenvalues are greater than or equal to 1. Since JD is non-

negative, by the Perron-Frobenius theorem we know that $\rho(JD) < 1 \; \forall \; R$. Thus we have:

RESULT 3.20:

The viability-analogous, tensor-product modifier polymorphism has local interior stability for a mutation modifier having maximal overdominance, with two alleles at the selected locus.

I.2c. RECOMBINATION MODIFIERS.

Here, there will be 2 loci under selection, each with 2 alleles, whose recombination rate is controlled by a third, modifier locus, not between the 2 selected loci. The existence and stability of a viability analogous-random association equilibria for this model was worked out by Feldman and Balkau (1973) for the Lewontin-Kojima and Wright symmetric viability regimes, and for 2 modifier alleles with symmetric parameters. Here I analyze the stability for general viability selection, and maximal overdominance at an arbitrary number of modifier alleles.

The four haplotypes at the selected loci,

$$A_1B_1 \; , \; A_1B_2 \; , \; A_2B_1 \; , \; A_2B_2 \; ,$$

will be indexed 1, 2, 3, 4, respectively. The matrix P represents the probabilities, given that a crossover occurs, that each haplotype is produced. The modifier locus, M, will be positioned with A between it and B. Therefore, with no recombination between M and A, a haplotype $M_aA_iB_j$ will always come out M_aA_i with possible change

at B . It will be assumed that there is no interference in recombination among the three loci.

Using the form w_{ij} for the fitnesses of selected genotypes $\frac{(AB)_i}{(AB)_j}$, i,j = 1,2,3,4 , matrices PD and $\tilde{P}D$ have the form:

$$\bar{\hat{w}}\,PD = \begin{Vmatrix} \hat{v}_1w_{11} + \hat{v}_3w_{13} & v_1w_{12} + \hat{v}_3w_{32} & 0 & 0 \\ \hat{v}_2w_{21} + \hat{v}_4w_{14} & \hat{v}_2w_{22} + \hat{v}_4w_{24} & 0 & 0 \\ 0 & 0 & \hat{v}_1w_{13} + \hat{v}_3w_{33} & \hat{v}_1w_{14} + \hat{v}_3w_{34} \\ 0 & 0 & \hat{v}_2w_{23} + \hat{v}_4w_{43} & \hat{v}_2w_{24} + \hat{v}_4w_{44} \end{Vmatrix},$$

$$\bar{\hat{w}}\,\tilde{P}D = \begin{Vmatrix} \hat{v}_1w_{11} + \hat{v}_2w_{12} & 0 & \hat{v}_1w_{13} + \hat{v}_2w_{23} & 0 \\ 0 & \hat{v}_1w_{12} + \hat{v}_2w_{22} & 0 & \hat{v}_1w_{14} + \hat{v}_2w_{24} \\ \hat{v}_3w_{13} + \hat{v}_4w_{14} & 0 & \hat{v}_3w_{33} + \hat{v}_4w_{43} & 0 \\ 0 & \hat{v}_3w_{23} + \hat{v}_4w_{24} & 0 & \hat{v}_3w_{34} + \hat{v}_4w_{44} \end{Vmatrix}.$$

This yields

$$(P - I + \tilde{P} - Q)D = \begin{pmatrix} -1 \\ 1 \\ 1 \\ -1 \end{pmatrix} (\hat{v}_4w_{14} - \hat{v}_3w_{23} - \hat{v}_2w_{23}\,\hat{v}_1w_{14}) \frac{1}{\bar{\hat{w}}}.$$

Since $JD = \left((1 - R)I + RQ + m^*(P - I + \tilde{P} - Q) \right)$, we have

$$ch(\lambda) = \det (JD - \lambda I) \stackrel{\Delta}{=} \det(k) =$$

$$\begin{vmatrix}
\hat{Rv}_1 w_{11} - \hat{mv}_4 w_{14} + \hat{w}_1(1 - R) - \lambda \hat{\bar{w}} & \hat{Rv}_1 w_{12} + \hat{mv}_3 w_{23} & \hat{Rv}_1 w_{13} + \hat{mv}_2 w_{23} & \hat{Rv}_1 w_{14} - \hat{mv}_1 w_{14} \\
\hat{Rv}_2 w_{12} + \hat{mv}_4 w_{14} & \hat{Rv}_2 w_{22} - \hat{mv}_3 w_{23} + \hat{w}_2(1 - R) - \lambda \hat{\bar{w}} & \hat{Rv}_2 w_{23} - \hat{mv}_2 w_{23} & \hat{Rv}_2 w_{24} + \hat{mv}_1 w_{14} \\
\hat{Rv}_3 w_{13} + \hat{mv}_4 w_{14} & \hat{Rv}_3 w_{23} - \hat{mv}_3 w_{23} & \hat{Rv}_3 w_{33} - \hat{mv}_2 w_{23} + \hat{w}_3(1 - R) - \lambda \hat{\bar{w}} & \hat{Rv}_3 w_{34} + \hat{mv}_1 w_{14} \\
\hat{Rv}_4 w_{14} - \hat{mv}_4 w_{14} & \hat{Rv}_4 w_{24} + \hat{mv}_3 w_{23} & \hat{Rv}_4 w_{44} + \hat{mv}_2 w_{23} & \hat{Rv}_4 w_{44} + \hat{mv}_1 w_{14} + \hat{w}_4(1 - R) - \lambda \hat{\bar{w}}
\end{vmatrix}$$

The determinant operations used by Feldman et al. (1980) for the initial increase analysis of recombination modifiers are again appropriate for the interior stability analysis.

The following elementary determinant operations were performed on det(k):

1) $k'_{ij} = \frac{1}{\hat{v}_j} k_{ij} \quad \forall\, i,j$.

2) $k'_{1j} = \sum_{i=1}^{4} k_{ij} \quad \forall\, i$.

3) $k'_{i4} = \sum_{j=1}^{4} k_{ij} \quad \forall\, i$.

4) $k'_{2j} = k_{2j} + k_{4j}$, $k'_{3j} = k_{3j} + k_{4j} \quad \forall\, j$.

Define $\hat{d} \triangleq \hat{v}_1\hat{v}_4w_{14} - \hat{v}_2\hat{v}_3w_{23}$, and $\Pi = \prod_{i=1}^{4}\hat{v}_i$.

This yields

$$\hat{\bar{w}}\,\Pi\ ch(\lambda) =$$

$$\begin{vmatrix}
(\hat{w}_1 - \lambda\ \bar{w})v_1 & (\hat{w}_2 - \lambda\ \bar{w})\hat{v}_2 & (\hat{w}_3 - \lambda\ \bar{w})\hat{v}_3 & (1-\lambda)\hat{\bar{w}} \\
R\hat{v}_1(\hat{v}_2w_{12} + \hat{v}_4w_{14}) & R\hat{v}_2(\hat{v}_2w_{22} + \hat{v}_3w_{23}) + \hat{v}_2(\hat{w}_2(1-R) - \lambda\hat{\bar{w}}) & R\hat{v}_3(\hat{v}_2w_{23} + \hat{v}_4w_{34}) & \hat{v}_2w_2 + \hat{v}_4w_4 - \lambda\hat{\bar{w}}(\hat{v}_2 + \hat{v}_4) \\
R\hat{v}_1(\hat{v}_3w_{13} + \hat{v}_4w_{14}) & R\hat{v}_2(\hat{v}_3w_{23} + \hat{v}_4w_{24}) & R\hat{v}_3(\hat{v}_3w_{33} + \hat{v}_4w_{34}) + \hat{v}_3(\hat{w}_3(1-R) - \lambda\hat{\bar{w}}) & \hat{v}_3\hat{w}_3 + \hat{v}_4\hat{w}_4 - \lambda\hat{\bar{w}}(v_3 + v_4) \\
(R-m)\hat{v}_1\hat{v}_4w_{14} & R\hat{v}_2\hat{v}_4w_{24} + m\hat{v}_2\hat{v}_3w_{23} & R\hat{v}_3\hat{v}_4w_{34} + m\hat{v}_2\hat{v}_3w_{23} & \hat{v}_4\hat{w}_4 - 2m\hat{d} - \lambda\hat{\bar{w}}\hat{v}_4
\end{vmatrix}$$

The equilibrium identity,

$$\hat{v}_i = \frac{1}{\hat{\bar{w}}}\left(\hat{v}_i\hat{w}_i(1 - m^*) + m^*\sum_{hj}\hat{v}_h\hat{v}_j\hat{w}_{hj}\ P_h^{j \to i}\right) ,$$

yields

$$(\bar{w}_1 - \hat{\bar{w}})v_1 = -(\hat{w}_2 - \hat{\bar{w}})\hat{v}_2 = -(\hat{w}_3 - \hat{\bar{w}})\hat{v}_3 = (\hat{w}_4 - \hat{\bar{w}})\hat{v}_4 = m^*\hat{d} .$$

Substituting in the above identities, and defining $\beta = (1 - \lambda)\bar{w}$, this gives

$\Pi \bar{w}\ ch(\lambda) =$

$$\begin{vmatrix} md + \beta & -md + \beta & -md + \beta & \beta \\ Rv_1(v_2w_{12} + v_4w_{14}) & Rv_2(v_2w_{22} + v_3w_{23}) - md + \beta - Rv_2w_2 & Rv_3(v_2w_{23} + v_4w_{34}) & (v_2 + v_4)\beta \\ Rv_1(v_3w_{13} + v_4w_{14}) & Rv_2(v_3w_{23} + v_4w_{24}) & Rv_3(v_3w_{33} + v_4w_{34}) - md + \beta - Rv_3w_3 & (v_3 + v_4)\beta \\ (R - m)v_1v_4w_{14} & Rv_2v_4w_{24} + mv_2v_3w_{23} & Rv_3v_4w_{34} + mv_2v_3w_{23} & -md + \beta \end{vmatrix}$$

(superscripts dropped).

At $R = 0$, $\lambda = 1$, we obtain

$$ch(1) = \frac{1}{\hat{v}_1\hat{v}_2\hat{v}_3\hat{v}_4\bar{w}} \begin{vmatrix} m^*d & -m^*d & -m^*d & 0 \\ 0 & -m^*d & 0 & 0 \\ 0 & 0 & -m^*d & 0 \\ -m^*\hat{v}_1\hat{v}_4w_{14} & 0 & m^*\hat{v}_2\hat{v}_3w_{23} & -m^*d \end{vmatrix}$$

$$= \frac{-(m^*d)^4}{\hat{v}_1\hat{v}_2\hat{v}_3\hat{v}_4\hat{w}} \leq 0 .$$

When $\hat{\underline{v}}$ is m^* dependent, that is, when there is an equilibrium marginal fitness load for the four selected haplotypes, then there is linkage disequilibrium, so $d \neq 0$. Therefore $\rho(JD) > 0$, giving this result:

RESULT 3.21:

The V.A.T.P. equilibrium for a recombination modifier is internally unstable, for two selected loci with two alleles, with one of the selected loci tightly linked to a maximally overdominant modifier locus.

This is the same result as for the cases in Feldman and Balkau (1973), extended to multiple modifier alleles and arbitrary selection regime, but restricted to a maximally overdominant modifier locus.

I do not have results for in the general case for what happens to the population after it diverges away from an unstable V.A.T.P. equilibrium. However, we know that each modifier allele is protected by virtue of its maximal overdominance, as long as there is a marginal fitness load in the population. Therefore, I would guess that the population settles on some high complementarity equilibrium comparable to those found in Feldman and Balkau (1973).

From the result of these two stability analyses, it is apparent that the interior stability of a viability-analogous, tensor product equilibrium depends upon the nature of the transformation occurring. This is the first result derived here in which the form of the transformation plays a role.

I.3. AN EXAMPLE OF TRANSFORMATION ACTING ON THE TRANSFORMATION TYPE: MODIFIERS OF SEGREGATION DISTORTION

Previous treatments of modifiers of segregation distortion have considered them to be modifiers of selection parameters (Karlin and McGregor, 1974), therefore coming under direct selection (Feldman and Krakauer, 1976). However, it is clear from the dichotomization of selection and transformation employed here that segregation distortion is actually a form of transformation. It may be due to selection at the gamete level, but as long as it does not affect an individual's fitness, that is, the number of offspring in the next generation to whose genotype that individual contributes, it will be purely a form of transformation, affecting only the content of an individual's reproductive output. It can be seen that there is no intrinsic selection acting on a modifier of segregation distortion since, when it is in linkage equilibrium with the selected distorting locus, the frequencies of its alleles will not change. It can evolve only through hitchhiking. What is unique about segregation distortion is that when a modifier is linked to a distorting locus, it too will be distorted, a form of transformation, which is a situation I have excluded from the analysis up till now.

Here I consider a model where segration distortion is the only transformation acting on the selected and modifier loci, and the modifier locus controls this segregation distortion. It is an extension to multiple alleles of the model of Prout et al. (1973), treated also by Hartl (1975), Thomson and Feldman (1976), and Liberman (1976).

The transformation matrix for segregation distortion takes the form

$$T_{\overline{bk}}^{aj \to ai} = \begin{cases} T_{\overline{bk}}^{ai \to ai} & \text{for } j=i \\ 0 & \text{for } j \neq i \end{cases}$$

where $T_{\overline{bk}}^{ai \to ai}$ is twice the fraction of gametes from genotype $\frac{M_a A_i}{M_b A_k}$ that are of haplotype $M_a A_i$. Let us use a simpler notation for this,

$$T_{\overline{bj}}^{ai} \triangleq T_{\overline{bj}}^{ai \to ai} .$$

Again I assume no position effect of the modifier, so

$$T_{\overline{bj}}^{ai} = T_{\overline{aj}}^{bi} .$$

Moreover,

$$0 \leq T_{\overline{bj}}^{ai} \leq 2 \quad \text{and} \quad T_{\overline{bj}}^{ai} + T_{\overline{bi}}^{aj} = 2 \quad \forall\ a,b,i,j .$$

Segregation distortion is occurring when $T_{\overline{bj}}^{ai} \neq 1$.

If there is interference between the segregation distortion and recombination between the modifier and selected loci, then a second segregation distortion matrix, $\tilde{T}$ must be specified.

The recursion is

$$z'_{ai} = \sum_{bk} \left((1-R) z_{ai} z_{bk} T_{\overline{bk}}^{ai} + R z_{ak} z_{bi} \tilde{T}_{\overline{bk}}^{ai} \right) \frac{w_{\overline{k}}^{i}}{\bar{w}} .$$

VIABILITY-ANALOGOUS, TENSOR PRODUCT EQUILIBRIA

The viability-analogous, tensor-product equilibrium can be described for this case as before, with an interesting result. Suppose that the population is fixed on a modifier yielding T^* and $\tilde{T}^*$ for segregation distortion matrices, and that the population has reached an equilibrium under selection and segregation distortion. Then

$$\hat{v}_i = \hat{v}_i \sum_j \hat{v}_j \frac{w_{\overline{j}}^{i}}{\hat{\bar{w}}} \left((1-R) T^{*i}_{\overline{j}} + R \tilde{T}^{*i}_{\overline{j}} \right) .$$

In the absence of interference, this yields

$$\sum_j \hat{v}_j w_j^i T^{*i}_j = \hat{\bar{w}} \quad \forall\, i \,.$$

Define the values $\Psi_i = \sum_j v_j w_j^i T^{*i}_j$ to be the "marginal transmission values" for the selected alleles. They form a new set of marginal values for each of the alleles which, for those alleles present, must all be equal to the mean fitness at any equilibrium.

The equilibrium marginal fitnesses of the selected alleles are given by

$$\hat{w}_i = \hat{\bar{w}} + \sum_j \hat{v}_j w_j^i \left(1 - T^{*i}_j\right) \,.$$

The marginal fitnesses of the selected alleles will have a variance at equilibrium unless the marginal amount of segregation distortion acting on each of them is zero:

$$\sum_j \hat{v}_j w_j^i \left(T^{*i}_j - 1\right) = 0 \quad \forall\, i \,.$$

We see that at any polymorphism, alleles with a segregation advantage have a fitness disadvantage, and alleles with a fitness advantage have a segregation disadvantage. Any allele have both advantages would be fixed.

Consider now where the modifier is polymorphic, and in linkage equilibrium with the selected loci, so that

$$z_{ai} = x_a \hat{v}_i \,.$$

The recursion is now

$$z'_{ai} = x_a \hat{v}_i \sum_j \hat{v}_j \frac{w_j^i}{\hat{\bar{w}}} \left((1-R)\hat{T}a^i_j + R\hat{\tilde{T}}a^i_j \right) \,,$$

where

$$\hat{T}a\frac{i}{j} = \sum_b x_b T\frac{ai}{bj} \quad \text{and} \quad \hat{\tilde{T}}a\frac{i}{j} = \sum_b x_b \tilde{T}\frac{ai}{bj}$$

are the marginal transformations for each modifier allele M_a. If the marginal transformations are all equal to T^* and $\tilde{T}^*$,

$$\hat{T}a\frac{i}{j} = T^*\frac{i}{j} \quad \text{and} \quad \hat{\tilde{T}}a\frac{i}{j} = \tilde{T}^*\frac{i}{j} \quad \forall\ a,i,j\ ,$$

then the population is at an equilibrium,

$$z'_{ai} = \hat{x}_a \hat{v}_i = \hat{z}_{ai}\ .$$

INITIAL INCREASE OF A NEW MODIFIER ALLELE

The recursion on the frequency of a new modifier allele introduced at a polymorphic equilibrium is

$$\underline{\varepsilon}' = \Omega_a D \underline{\varepsilon} = \left((1-R)Y_a + R\tilde{Y}_a \right) D \underline{\varepsilon}\ ,$$

where

$$Y_a \triangleq \text{diag}\left(\sum_{bk} \hat{z}_{bk} \frac{w\frac{i}{k}}{\hat{w}_j} T\frac{ai}{bk} \right) \quad \text{and} \quad \tilde{Y}_a \triangleq \left\| \sum_b \hat{z}_{bi} \frac{w\frac{i}{j}}{\hat{w}_j} \tilde{T}\frac{ai}{bj} \right\| \quad i,j\ ,$$

and D is defined as before.

a. A MODIFIER ALLELE ELIMINATING SEGREGATION DISTORTION

If the new modifier allele eliminates segregation distortion at the selected locus, then the initial increase recursion is identical to that for the Theorem 3.5 :

$$\underline{\varepsilon}' = \left((1-R)I + RQ \right) D\underline{\varepsilon}\ ,$$

where Q is defined as before. The previous result then holds:

RESULT 3.22:

When there is a variance in the equilibrium marginal fitnesses, an allele eliminating segregation distortion will always increase when introduced into the population, whether linked or not to the selected locus.

b. A TIGHTLY LINKED MODIFIER LOCUS

For the case where the new modifier allele has a less extreme effect on the segregation distortion, I will assume that the modifier is tightly linked to the selected locus, for tractability, and will assume that the modifier is monomorphic, because for tight linkage, the viability-analogous, tensor-product equilibrium may not generally be stable, as shown in Thomson and Feldman (1976), and I do not have results for the introduction at other polymorphic equilibria. The recursion on a new modifier is now

$$\underline{\varepsilon}' = \mathrm{diag}\Big(\sum_j \hat{v}_j \frac{w_{\underline{j}}^{\underline{i}}}{\tilde{w}} \hat{T}_{a\underline{j}}^{\underline{i}}\Big)\underline{\varepsilon} = \frac{1}{\tilde{w}} \mathrm{diag}\big(\hat{\Psi}_{ai}\big)\underline{\varepsilon} ,$$

where $\hat{T}_{a\underline{j}}^{\underline{i}}$ are the marginal transformation values for the new modifier allele M_a, and $\hat{\Psi}_{ai}$ are the marginal transmission values for the selected alleles in coupling with the new modifier allele. Notice now that

$$\sum_i \hat{v}_i \hat{\Psi}_{ai} = \sum_{ij} \hat{v}_i \hat{v}_j w_{\underline{j}}^{\underline{i}} \hat{T}_{a\underline{j}}^{\underline{i}} = \sum_{ij} \hat{v}_i \hat{v}_j w_{\underline{j}}^{\underline{i}} \Big(\frac{1}{2}\hat{T}_{a\underline{j}}^{\underline{i}} + \frac{1}{2}\big(2 - \hat{T}_{a\underline{i}}^{\underline{j}}\big)\Big) = \tilde{w} + 0 .$$

Therefore, if

$$\underset{i}{\text{var}}(\hat{\Psi}_{ai}) > 0 ,$$

then for some i ,

$$\frac{1}{\hat{\bar{w}}} \hat{\Psi}_{ai} > 1 ,$$

so haplotype $M_a A_i$ increases when introduced. Therefore:

RESULT 3.23:

Unless $\hat{\Psi}_{ai} = \hat{\bar{w}}$ for all i, the new modifier allele will be able to increase in the population when introduced.

This means that a new modifier making any change in the marginal transmission values of the selected alleles (which at equilibrium all equal the mean fitness) will allow the modifier to increase. The new modifier cannot be exluded, at least at a geometric rate. This result is that obtained by Liberman (1976).

What produces this result is that the new modifier allele always becomes associated with the selected allele whose segregation ratio it improves on the average. Therefore, a new modifier that reduces the overall amounts of segregation distortion increases by associating with fitter alleles, which have a segregation disadvantage. A modifier allele that raises the overall rates of segregation distortion increases by associating with alleles having a segregation advantage, which are less fit.

Because segregation distortion acts on the modifier locus itself, which constitutes a form of transformation acting on the transformation type, the evolutionary behavior of the modifier is completely changed. In the absence of segregation distortion, the previous results showed

that the induced selection on a new modifier allele is at most algebraic when it is introduced at an equilibrium with no variance in the marginal fitnesses of the selected haplotypes. For a modifier of segregation distortion, however, the equilibrium variance in the marginal fitnesses of the selected alleles is irrelevant. All that is relevant is the change in the marginal transmission values of the selected alleles.

Recent work by Eshel (personal communication) has shown that for unlinked modifiers of segregation distortion, when modifier alleles causing segregation distortion are introduced to a population at equilibrium without segregation distortion, they cannot increase. Though I obtain no analytical results here for the general case of unlinked modifiers, it is interesting to note that, when there is no interference between recombination with the modifier and the amount of segregation distortion of the selected locus, then at $R = \frac{1}{2}$

$$\Omega_a = \frac{1}{2}(Y_a + \tilde{Y}_a)$$

is stochastic, since

$$\underline{e}^T \Omega_a = \sum_{ibj} \hat{z}_{bj} \frac{w_j^i}{\hat{w}_j} \frac{1}{2}(T^{ai}_{bj} + T^{aj}_{bi}) = \frac{\hat{w}_j}{\hat{w}_j} = 1 ,$$

because

$$\frac{1}{2}(T^{ai}_{bj} + T^{aj}_{bi}) = 1 \quad \forall\ a,b,i,j .$$

It may be when the matrix is stochastic that decreased segregation distortion evolves. However, if there is interference, then Ω_a will not be stochastic, and it is unknown what outcome will result in this case.

Holsinger (personal communication) has obtained results for modifiers of selfing rates in a model for plants that are suggestively reminiscent of the results for modifiers of segregation distortion. In the model with mixed selfing and random mating, selfed plants still

contribute to the pollen pool. Holsinger has pointed out that the situation where selfing plants still contribute to the pollen pool constitutes a form of "transmission distortion". There are some ranges on selection values, recombination values, and selfing rates where a new modifier making any change in the selfing rate will increase when introduced, a result just like that for segregation distortion modifiers.

Further analogy between the behavior of this model and that of segregation distortion models is seen in cases tested numerically where the fitnesses of the two selected homozygotes are different. When a selfing-rate reducing modifier allele is introduced, it increases in association with the allele having the less fit homozygote. When a selfing-rate increasing modifier allele is introduced, it increases in association with the allele having the fitter homozygote. In the former case, outcrossing appears with the allele having most to gain by being heterozygous; in the latter case, selfing appears with the allele having the least to lose by being homozygous. Thus, the new modifier allele has a "choice" like the modifier of segregation distortion associating with the fitter alleles or the alleles with segregation advantage. The behavior of this system may therefore be fundamentally analogous to that of systems with segregation distortion.

Models of modifiers of other transformation processes such as mutation or recombination should also be explored when there is segregation distortion occurring. Thomson and Feldman (1974) have examined one such model, a modifier of recombination between a selected locus undergoing segregation distortion and another locus modifying that distortion. In some cases, it is found that a new recombination

modifier allele causing any change in the amount of recombination will increase when introduced.

These few example suggest the following conjecture:

CONJECTURE 3.24: A PRINCIPLE FOR MODIFIERS UNDER TRANSMISSION DISTORTION:

Whenever the exterior stability of a selection-transformation equilibrium is unstable to the introduction of any new modifier allele that causes any change in transformation, then some form of transmission distortion must be occurring for the modifier locus.

II. MIGRATION MODIFIERS

In this section I analyze the evolution of a modifier gene in a diploid organism that controls a transformation outside of the genotype: the probabilities of individuals migrating between different demes. In the following models, a locus that is under selection will also be included and the selection regime may differ between different demes. These models differs from the previous ones in that in addition to the selected genotype, location is now part of the selected type, and mating is not panmictic over the whole population, but restricted to being within demes. The only transformation that will be occurring is

change in location; the selected locus will be transmitted faithfully. In the models dealt with here, mating will always be within a deme. The life cycle consists of several stages: migration, selection, mating and reproduction. These model will generalize to multiple demes and multiple alleles the models of Balkau and Feldman (1973), Karlin and McGregor (1974), Teague (1977), and Asmussen (1983). In addition, they include mixtures of haploid and diploid determination of both migration and selection.

II.1. DERIVATION OF THE MODELS

In developing the models we must define the following:

n_f is the initial size of deme f.

n_f^s is the size of deme f after selection.

n_f^m is the size of deme f after migration.

n_f^r is the size of deme f after recruitment.

$g_{e\frac{ai}{bj}}$ is the frequency of diploid genotype $\frac{M_a A_i}{M_b A_j}$ in deme e.
(If $ai \neq bj$, then actual frequency is $2g_{e\frac{ai}{bj}}$).
Note that $\sum_{aibj} g_{e\frac{ai}{bj}} = 1 \quad \forall\, e$.

$g_{e\frac{ai}{bj}}$ superscripted by s , m , or x is the frequency of the genotype after selection, migration, or mating, respectively.

$w_{e\frac{i}{j}}$ is the fitness of genotype $\frac{A_i}{A_j}$ in deme e .

How each process in the life cycle -- selection, migration, and mating -- will change the values of n_e and $g_{e\frac{ai}{bj}}$ are derived as follows:

1. SELECTION:

$$g^s_{e\frac{ai}{bj}} = g_{e\frac{ai}{bj}} \frac{w_{e\frac{i}{j}}}{\bar{w}_e} ,$$

where the average fitness of the individuals in deme e is

$$\bar{w}_e = \sum_{aibj} g_{e\frac{ai}{bj}} w_{e\frac{i}{j}} .$$

The only role of n_e is this model is to determine the relative contribution of each deme to the migrant pool. If selection does not affect the size of a deme but acts only to determine <u>which</u> genotypes survive, this is <u>soft selection</u> and can be modeled by assuming n_e after selection is a fixed property of each deme. If selection acts on each individual independently of the others in its deme, this is <u>hard selection</u>, and the contribution of the deme to the migrant pool will be scaled by the mean fitness of the individuals in the deme. Thus:

$$n_e^s = \begin{cases} n_e \bar{w}_e & \text{hard selection} \\ n_e & \text{soft selection} \end{cases} .$$

The models of Balkau and Feldman (1973), Karlin and McGregor (1974) and Asmussen (1983) have hard selection, while the model of Teague (1977) has soft selection.

For organisms with an independent haploid phase in the life cycle, the haploids can come under selection. This situation will be described in detail later, in the model of haploid migration.

2. MIGRATION:

Two cases of migration will be distinguished, diploid migration, and a "sea urchin model" of haploid migration.

1) DIPLOID MIGRATION

When the diploid individuals move from one deme to another, after migration,

$$g^{m}_{e\frac{ai}{bj}} = \frac{1}{n^{m}_{e}} \sum_{f} g_{f\frac{ai}{bj}} n_{f} T^{\frac{a}{b}}_{f \to e} ,$$

where $T^{\frac{a}{b}}_{f \to e}$ is the probability that an individual of modifier genotype $\frac{M_a}{M_b}$ will end up in deme e given it is in deme f, and

$$n^{m}_{e} = \sum_{aibjf} g_{f\frac{ai}{bj}} n_{f} T^{\frac{a}{b}}_{f \to e} ,$$

the size of the migrant pool plus remaining residents in deme e after migration.

2) HAPLOID MIGRATION

In a "sea urchin" model of haploid migration, it is the gametes

that disperse and form pools in each new deme which will unite to form the new diploids.

Define

$$z_{eai}$$

to be the frequency of haplotype M_aA_i in deme e.

Then after dispersal,

$$z^{m}_{eai} = \frac{1}{n^{m}_{e}} \sum_{bjf} \left(g_{f\frac{ai}{bj}} (1 - R) + g_{f\frac{ai}{bi}} R \right) n_f \, T^{a}_{\frac{b}{}}f \rightarrow e \quad .$$

If the dispersal depends only on the haplotype's own modifier allele, then

$$T^{a}_{\frac{b}{}}f \rightarrow e = T^{a}_{\frac{c}{}}f \rightarrow e \quad \forall \quad b,c \; ; \quad \text{possibly}$$

$$T^{a}_{\frac{b}{}}f \rightarrow e \neq T^{b}_{\frac{a}{}}f \rightarrow e \; .$$

If the dispersal depends on some combination of haplotype and parental modifier genotypes, then possibly

$$T^{a}_{\frac{b}{}}f \rightarrow e \neq T^{b}_{\frac{a}{}}f \rightarrow e \quad \text{and} \quad T^{a}_{\frac{b}{}}f \rightarrow e \neq T^{a}_{\frac{c}{}}f \rightarrow e \; .$$

RECRUITMENT

After migration, "recruitment" will occur, where the migrants and residents become established in the deme. As described in Chapter 2, if the deme size after recruitment is proportional to the number of individuals arriving through migration and those remaining, this will be called "hard recruitment", and if the size of the population after recruitment is a constant property of the deme, this will be called "soft recruitment". Thus

$$n^{r}_{e} = \begin{cases} n^{m}_{e} & \text{hard recruitment} \\ n_e & \text{soft recruitment} \end{cases} .$$

Soft recruitment would be expected for organisms such as intertidal barnacles, where high larval densities saturate bare sections of rock with new recruits.

In the case of hard recruitment and hard selection, the deme size itself can evolve as well as the gene frequencies in the population.

Some models of migration, for example those of Motro (1982), consider selective forces acting during the process of migration itself. Within the formal framework developed here, where selection is a function only of type and not its history of transformation, the fact of being a migrant must be included as a part of ones type. Motro's models involve the extra steps of selection on migrants, then erasure of the migrant's history once it is established in its new deme. The models here will not include these extra steps.

3. REPRODUCTION:

In the diploid migration model, diploids will mate randomly and produce offspring through segregation and syngamy. For the haploid migration model, the haplotypes in the pools in each deme will undergo syngamy randomly with the respect to the modifier alleles, but allowing non-random union with respect to selected haplotype. The only reproductive transformation allowed will be recombination between the modifier and selected loci.

After syngamy, for the sexual diploid model we have

$$g^{x}_{e\frac{ai}{bj}} = \left((1 - R) \sum_{ck} g_{e\frac{ai}{ck}} + R \sum_{ck} g_{e\frac{ak}{ci}}\right)\left((1 - R) \sum_{ck} g_{e\frac{bj}{ck}} + R \sum_{ck} g_{e\frac{bk}{cj}}\right)$$

Define the haplotype frequencies $z_{eai} \overset{\Delta}{=} \sum_{bj} g_{e\frac{ai}{bj}}$. Then

$$z^{x}_{eai} = (1 - R) \sum_{ck} g_{e\frac{ai}{ck}} + R \sum_{ck} g_{e\frac{ak}{ci}}, \quad \text{so}$$

$$g^{x}_{e\frac{ai}{bj}} = z^{x}_{eai}\, z^{x}_{ebj} .$$

Thus Hardy-Weinberg proportions obtain.

Define the values $f_{e\frac{i}{j}}$ to incorporate any non-random union of gametes, yielding for the haploid migration model:

$$g^{x}_{e\frac{ai}{bj}} = z_{eai}\, z_{ebj} \frac{f_{e\frac{i}{j}}}{\bar{f}_{e}} ,$$

$$\text{where } \bar{f}_{e} = \sum_{aibj} z_{eai}\, z_{ebj}\, f_{e\frac{i}{j}} .$$

LIFE CYCLES COMPOSED OF THESE PROCESSES:

These phases of the life cycle can be composed in two different orders: selection, migration, reproduction, or migration, selection, reproduction. These two sequences have very different analytical

properties, The second is generally intractable within the methods I have used thus far, and will not be presented here. Previous models of migration modifiers (Balkau and Feldman, 1973; Karlin and McGregor, 1974; Teague, 1976; Asmussen, 1983) all analyze the first sequence order.

I will consider the following life cycles:

1) "Adult Dispersal": diploid selection, diploid migration, random mating, Mendelian reproduction.
2) "Gamete Dispersal": diploid selection, gamete production, gamete migration, syngamy.

In each case, the censusing occurs right after recruitment.

1) Adult Dispersal:

Random mating and the absence of fertility selection allows the recursions to be written in terms of the haplotype frequencies:

$$z'_{eai} = \frac{1}{n_e^m} \sum_{bjf} n_f^s \frac{w_{f\bar{j}}^{i}}{\bar{w}_f} T_{\bar{b}f}^{a} \to e \left((1 - R) z_{fai} z_{fbj} + R z_{faj} z_{fbi} \right) , \quad (3.25)$$

$$n'_e = \begin{cases} n_e^m & \text{hard recruitment} \\ n_e & \text{soft recruitment,} \end{cases}$$

$$\text{where } n_e^m = \sum_{chdkf} z_{fch} z_{fdk} \frac{w_{f\bar{k}}^{h}}{\bar{w}_f} n_f^s T_{\bar{d}f}^{c} \to e ,$$

$$\bar{w}_f = \sum_{abjk} z_{vaj} z_{fbk} w_{f\bar{j}}^{i} ,$$

and

$$n_f^s = \begin{cases} n_f \bar{w}_f & \text{hard selection} \\ \text{constant} & \text{soft selection.} \end{cases}$$

2) Gamete Dispersal, Sea Urchin Model:

The recursion is the same as for the Adult Dispersal Model, except that $T^{a}_{b}{}_{f \to e}$ is allowed the asymmetries discussed earlier. Moreover, gamete selection or non-random union may enter without altering the form of the recursion.

Consider a life cycle consisting of:

1) gamete selection phase 1,
2) syngamy, possibly non-random with respect to the selected loci,
3) diploid selection,
4) recombination and Mendelian segregation,
5) gamete selection phase 2, and
6) migration.

The fitnesses for each selection phase are as follows:

$s^{(1)}_{fi}$ = fitness of gamete haplotype A_i in deme f at phase 1.

$\Phi_{f\frac{i}{j}}$ = the scalar biasing the frequency of new zygotes according to selection-type in deme f, due to non-random syngamy.

$s_{f\frac{i}{j}}$ = fitness of diploid selected genotype $\frac{A_i}{A_j}$ in deme f.

$s^{(2)}_{fi}$ = fitness of gamete haplotype M_i in deme f at phase 2, after meiosis.

The recursion is:

$$z'_{eai} = \frac{1}{n^{m}_{e}} \sum_{bjf} n^{s}_{f} \frac{s^{(2)}_{fi} s^{(1)}_{fi} s^{(1)}_{fj} \Phi_{f\frac{i}{j}} s_{f\frac{i}{j}}}{\bar{s}_{f}} \left(z_{fai} z_{fbj}(1-R) + z_{faj} z_{fbi} R \right) T^{a}_{b}{}_{f \to e}$$

where $\bar{s}_{f}$ is the appropriate normalizer.

Define the lumped fitness values

$$w_{fj}^{\underline{i}} \triangleq s_{fi}^{(2)} s_{fi}^{(1)} s_{fj}^{(1)} \Phi_{fj}^{\underline{i}} s_{fj}^{\underline{i}} .$$

These need not be symmetric, allowing $w_{fj}^{\underline{i}} \neq w_{fi}^{\underline{j}}$.

The recursion becomes

$$z'_{eai} = \frac{1}{n_e^m} \sum_{fbj} \left(z_{fai} z_{fbj} (1-R) + z_{faj} z_{fbi} R \right) \frac{w_{fj}^{\underline{i}}}{\bar{w}_f} n_f^s \, T_{\underline{b}}^{\underline{a}} f \to e ,$$

where $\bar{w}_f = \bar{s}_f$, which again is of the same form as (3.25), with the possible asymmetries

$$w_{fj}^{\underline{i}} \neq w_{fj}^{\underline{i}} \quad \text{and} \quad T_{\underline{b}}^{\underline{a}} f \to e \neq T_{\underline{a}}^{\underline{b}} f \to e .$$

The haploid model of Balkau and Feldman (1973) is a special case of this where

$$s_{fi}^{(1)} = \Phi_{fj}^{\underline{i}} = s_{fj}^{\underline{i}} = 1 \quad \forall \quad f,i,j \text{ and}$$

$$T_{\underline{b}}^{\underline{a}} f \to e \triangleq T_a f \to e \quad \forall \quad a,b,f,e .$$

In each of these cases, the recursions can be defined in terms of haplotypes because there is no fertility selection or non-random mating occuring at the level of diploid pairs, so the segregation-syngamy transformation decomposes.

The results for these models parallel the results for modifiers of intragenomic transformation. Viability-analogous, tensor product modifier polymorphisms can exist (Feldman and Krakauer, 1976), because

migration still enters as a linear transformation. "Tensor product" in this case means that the modifier allele frequencies are the same among the selected haplotypes, and also among the demes, because the deme is also a part of an individual's type.

The initial increase behavior of a new migration modifying allele also parallels the results for modifiers of intra-genomic transformation.

II.2. VIABILITY-ANALOGOUS, TENSOR PRODUCT EQUILIBRIA

It will be shown here how tensor product frequencies can be equilibria for the two life cycles.

Define x_a to be the frequency of modifier allele M_a, and v_{ei} to be the frequency of selected haplotype A_i in deme e. At a tensor product value of frequencies, the frequency of haplotype M_aA_i in deme e will be

$$z_{eai} = x_a v_{ei} ,$$

or in vector form

$$\underline{z} = \underline{x} \bullet \underline{v} ,$$

where $\underline{x}$ is the vector of modifier allele frequencies, and $\underline{v}$ is the vector of the selected haplotype frequencies in the demes. The frequencies of the selected haplotypes may differ between different demes.

Substitution in recursion (3.25) yields

$$z'_{eai} = \frac{1}{n_e^m} x_a \sum_f n_f^s v_{fi} \frac{w_{fi}}{\bar{w}_f} T_{af \to e} ,$$

where

$$n_e^m = \sum_{fa} n_f^s x_a T_{af \to e} ,$$

$$T_{af \to e} \overset{\Delta}{=} \sum_b x_b T^a_{\underline{b} f \to e}$$

are the marginal migration probabilities for modifier alleles M_a, and

$$w_{fi} \overset{\Delta}{=} \sum_j v_{fj} w_{f\underline{j}i}$$

are the marginal fitnesses of selected haplotypes A_i in deme e.

Suppose that the population would be at an equilibrium, $\hat{\underline{v}}$, when fixed on a modifier allele yielding migration matrix T^*. Thus

$$\hat{v}_{ei} = \frac{1}{\hat{n}_e^m} \sum_f \hat{n}_f^s \hat{v}_{fi} \frac{\hat{w}_{fi}}{\hat{\bar{w}}_f} T^*_{f \to e} .$$

Then a modifier polymorphism $\underline{z} = \hat{\underline{x}} \circledcirc \hat{\underline{v}}$ will be an equilibrium if the modifier allele frequencies $\hat{\underline{x}}$ are such that

$$\hat{T}_{af \to e} = T^*_{f \to e}$$

for each modifier allele M_a.

II.3. BALANCED MIXTURE MODIFIER POLYMORPHISMS

In diploids, the only situation in which general conditions for "balanced mixture" modifier polymorphisms can be obtained are where the genotypic fitnesses are equal, in addition to there being no fitness load at equilbrium. In this case, (3.25) at equilibrium yields

$$\hat{\underline{z}}_a = T_a \hat{\underline{z}}_a ,$$

where

$$\underline{z}_a = \begin{pmatrix} z_{i_1 a i_2} \\ \vdots \end{pmatrix} ,$$

$$T_a = \| \sum_b \hat{x}_b \, T^a_{\underline{b}j \to i} \|_{i,j} \text{ , and } x_b = \sum_{fj} z_{fbj} \cdot$$

The situation of interest is where frequency dependent selection would yield a globally stable equilibrium $\hat{\underline{v}}$ of selected haplotype frequencies among the demes in the absence of a modifier polymorphism. The result, discussed in Section 3.(2) is that the normalized forms of the eigenvectors $\hat{\underline{z}}_a$ of the marginal migration matrices of each modifier allele must comprise a convex hull containing $\hat{\underline{v}}$ for the equilibrium to exist. However, there are added constraints. Both T_a and $\hat{\underline{v}}$ depend on the frequency of the modifier alleles, so whether the hull of T_a will be sufficient to include the equilibrium is not readily known.

II.4. EVOLUTION OF THE MODIFIER LOCUS

In this section, the initial increase behavior of a new modifier allele under recursion (3.25), which applies to both the "Adult Dispersal" and "Haploid Dispersal" models. Each of the results derived for modifiers of intragenomic transformation will be shown to hold for modifiers of migration.

THE FITNESS LOAD

The concept of a fitness load in the case of subdivided populations we must consider not only the maximally fit genotype but also the maximally "fit" deme, that is, the deme with the largest bias in contributing to the next generation. Consider a population at equilibrium in the absence of migration. We obtain

$$\hat{v}_{ei} = \frac{1}{n_e^m} \sum_j \hat{v}_{ei} \hat{v}_{ej} \frac{w_{ej}}{\bar{\hat{w}}_e} \hat{n}_e^s ,$$

and

$$\hat{\hat{n}}_e = \hat{n}_e .$$

This gives

$$\frac{\hat{n}_e^s \hat{w}_{ei}}{\hat{n}_e^m \bar{\hat{w}}_e} = 1 \text{ for all } e , i .$$

The fitness load will be defined as

$$L \triangleq \max_{ei} \left(\frac{n_e^s w_{ei}}{n_e^m \bar{w}_e} \right) - 1 .$$

In the absence of migration, then, $L = 0$. If migration is occurring, then at an equilibrium where the maximum probability of migration for each individual in each deme is α , the fitness load will be bounded above by

$$L \leq \frac{\alpha}{1-\alpha} .$$

THEOREM 3.25:

If there is any variance at equilibrium in $\frac{n_e^s \hat{w}_{ei}}{n_e^m \bar{\hat{w}}_e}$ (over e and i), which requires migration be occurring, then the equilibrium fitness load will be greater than zero, that is, there will exist e , and i such that

$$\frac{n_e^s \hat{w}_{ei}}{n_e^m \bar{\hat{w}}_e} > 1.$$

Proof.

Suppose to the contrary that

$$\frac{n_e^s w_{ei}}{n_e^m \bar{w}_e} < 1 \quad \forall\, e,i \quad (\ \hat{}\ \text{'s dropped}).$$

Since

$$\hat{\bar{w}}_e = \sum_i \hat{v}_{ei}\hat{w}_{ei} \quad \text{and} \quad \sum_i \hat{v}_{ei} = 1,$$

we know for each e, there exists an i such that $\hat{w}_{ei} \geq \hat{\bar{w}}_e$.

Therefore,

$$n_e^s \leq n_e^m \quad \forall e.$$

But

$$\sum_e n_e^m = \sum_{\substack{cdhk \\ fe}} z_{fch} z_{fdk} \frac{w_{fk}^h}{\bar{w}_f} n_f^s T_d^c \, f \to e = \sum_f n_f^s .$$

So this would yield $n_e^s = n_e^m \ \forall e$. But this requires $\frac{\hat{w}_{ei}}{\hat{\bar{w}}_e} \leq 1 \ \forall e,i$, thus

$$\hat{w}_{ei} = \hat{\bar{w}}_e \quad \forall e,i,$$

giving finally,

$$\frac{n_e^s w_{ei}}{n_e^m \hat{\bar{w}}_e} = 1 \quad \forall e,i,$$

contrary to there being some variance in $\frac{n_e^s \hat{w}_{ei}}{n_e^m \hat{\bar{w}}_e}$.

We see here that there are two possible sources for the equilibrium fitness load, one due to variance in $\left(\frac{n_e^s}{n_e^m}\right)$, and the other due to variance in $\left(\frac{\hat{w}_{ei}}{\hat{\bar{w}}_e}\right)$.

In the case of hard selection and hard recruitment,

$$\hat{n}_e^s = n_e \hat{\bar{w}}_e \text{ and } \hat{n}_e = \hat{n}_e^m ,$$

hence

$$L = \max_{e,i}(\hat{w}_{ei}) .$$

So the marginal fitnesses of the selected haplotypes must vary between haplotypes or between demes.

When there is soft selection or soft recruitment, then even when the selective regimes on the selected locus are identical in each deme, it is possible that the migration flux alone can induce a fitness load. In this case,

$$L = \max_e \left(\frac{n_e^s}{n_e^m}\right) ,$$

and

$$\hat{n}_e^m = \sum_f \bar{T}_{f \to e} n_f^s ,$$

where

$$\bar{T}_{f \to e} = \sum_{bc} \hat{x}_b \hat{x}_c T^b_{cf \to e} .$$

In vector form this is

$$\hat{\underline{n}}^m = \bar{T} \hat{\underline{n}}^s .$$

For the fitness load to be zero, $\underline{n}^m = \underline{n}^s$ must be a leading eigenvector of $\bar{T}$. Yet under soft selection or soft recruitment, $\underline{n}^s$ or $\underline{n}^m$ will be fixed properties independent of the migration distribution, and so they will not in general be eigenvectors of the migration matrix, and the fitness load will be positive.

THE INITIAL INCREASE BEHAVIOR OF A NEWLY INTRODUCED MODIFIER ALLELE

Suppose the population is at an equilibrium $\hat{\underline{z}}$ and a new modifier allele M_a is introduced.

The recursion on the frequency of haplotypes bearing M_a is

$$\varepsilon'_{ei} = \frac{1}{n_e^m} \sum_{bjf} \left[\varepsilon_{fi}\hat{z}_{fbj}(1-R) + \varepsilon_{fj}\hat{z}_{fbi}R\right] \frac{w_{fj}^{i}}{\bar{\hat{w}}_f} n_f^s \, T_{\bar{b}}^{a}{}_{f \to e} \qquad (3.26)$$

RESULT 3.26:

A VALUE CAN BE DERIVED FOR AN UPPER BOUND ON THE AMOUNT OF MIGRATION A NEWLY INTRODUCED MODIFIER ALLELE ALLOWS THAT GUARANTEES IT WILL INCREASE WHEN INTRODUCED INTO A POPULATION WITH A FITNESS LOAD AT EQUILIBRIUM.

DERIVATION:

Define

$$\tilde{m}_e = 1 - \min_b T_{\bar{b}}^{a}{}_{e \to e} .$$

This is the maximum probability of migrating among any of the individuals in deme e bearing M_a.

Then

$$\varepsilon'_{ei} \geq (1-\tilde{m}_e)(1-R) \frac{n_e^s \hat{w}_{ei}}{n_e^m \bar{\hat{w}}_e} \varepsilon_{ei} .$$

Thus, if there exists e and i such that

$$\tilde{m}_e < 1 - \left((1-R)\frac{n_e^s \hat{w}_{ei}}{n_e^m \bar{\hat{w}}_e}\right)^{-1} ,$$

the haplotype $M_a S_i$ will increase in deme e.

We know that if there is any variance in either $\frac{n_e^s}{n_e^m}$ *or* $\frac{w_{ei}}{\bar{w}_e}$ *then* there will be some e and i such that

$$\frac{n_e^s w_{ei}}{n_e^m \bar{w}_e} > 1 .$$

Define

$$\hat{m} \triangleq 1 - \left(\max_{ei} \frac{n_e^s \hat{w}_{ei}}{n_e^m \hat{\bar{w}}_e} \right)^{-1} = 1 - \frac{1}{1+L} .$$

Therefore

$$\frac{\varepsilon'_{ei}}{\varepsilon_{ei}} \geq (1-\tilde{m}_e) \frac{(1-R)}{1-\hat{m}} .$$

If $R < \hat{m}$, and if $0 \leq \tilde{m}_e < \frac{\hat{m}-R}{1-R}$ for some e, then

$$\frac{\varepsilon'_{ei}}{\varepsilon_{ei}} > 1 ,$$

so it is guaranteed that M_a increases.

RESULT 3.27:

A MODIFIER ALLELE WHICH STOPS ALL MIGRATION WILL ALWAYS INCREASE WHEN INTRODUCED TO A POPULATION WITH AN EQUILIBRIUM FITNESS LOAD, FOR ANY LINKAGE TO THE SELECTED LOCUS.

The recursion on a newly introduced modifier allele M_a which stops all migration in its bearers is

$$\varepsilon'_{ei} = \frac{1}{n_e^m} \sum_{bj} \left((1-R)\, \varepsilon_{ei} \hat{z}_{ebj} + R\, \varepsilon_{ej} \hat{z}_{ebi} \right) \frac{w_{ej}^i n_e^s}{\hat{\bar{w}}_e}$$

$$= (1-R) \frac{n_e^s \hat{w}_{ei}}{n_e^m \hat{\bar{w}}_e} \varepsilon_{ei} + R \frac{n_e^s \hat{v}_{ei}}{n_e^m \hat{\bar{w}}_e} \sum_j w_{ej}^i \varepsilon_{ej} ,$$

or in vector form

$$\underline{\varepsilon}'_e = \left[(1-R)I + RQ_e \right] D_e \underline{\varepsilon}_e \ , \quad \text{where} \tag{3.27}$$

$$Q_e \triangleq \text{diag}(\underline{\hat{v}}_e)\ W_e\ \text{diag}\left(\frac{1}{\hat{\bar{w}}_{ei}}\right) \ ,$$

$$D_e \triangleq \text{diag}\left(\frac{n_e^s \hat{w}_{ei}}{n_e^m \hat{\bar{w}}_e}\right) \ , \text{ and } W_e \triangleq \| w_{ej}^{\ i} \|_{i,j} \ .$$

This recursion has the same form as that for a modifiers stopping intragenomic transformation in Theorem 3.5. When applying the proof of Theorem 3.5 , the appropriate normalized eigenvector of Q is

$$\mu_e D_e \underline{\hat{v}}_e \ , \text{ where } \mu_e = \frac{n_e^m}{n_e^s} \ .$$

This is seen since

$$\underline{e}^T \mu_e D_e \underline{\hat{v}}_e = 1 \ ,$$

and

$$\mu_e (Q_e D_e \underline{\hat{v}}_e)_i = \mu_e \sum_j \frac{\hat{v}_{ei} w_{ej}^{\ i} n_e^s \hat{v}_{ej}}{\hat{\bar{w}}_e n_e^m} = \mu_e \hat{v}_{ei} \frac{\hat{w}_{ei} n_e^s}{\hat{\bar{w}}_e n_e^m} = \mu_e (D_e \underline{\hat{v}}_e)_i \ .$$

Thus

$$\rho\left(\left[(1-R)I + RQ_e \right] D_e \right) > \mu_e \sum_i \hat{v}_{ei} \left(\frac{n_e^s \hat{w}_{ei}}{n_e^m \hat{\bar{w}}_e} \right)^2 = \frac{n_e^s}{n_e^m} \left(1 + \text{var}\left(\frac{\hat{w}_{ei}}{\hat{\bar{w}}_e} \right) \right) \ .$$

The inequality depends on the value $\dfrac{n_e^s}{n_e^m}$.

As was shown before, if migration has induced an overall variance in

$$\frac{n_e^s \hat{w}_{ei}}{n_e^m \hat{\bar{w}}_e} \ ,$$

then either

1) there is some deme e where $n_e^s > n_e^m$, or

2) $n_e^s = n_e^m$ $\forall e$, and then in some deme e, $\mathrm{var}(\frac{\hat{w}_{ei}}{\bar{w}_e}) > 0$.

There is always some deme, therefore, in which the migration stopping allele can increase.

When there is variance in the marginal fitnesses of the selected alleles within in deme, then the selection on the modifier is always non-increasing with looser linkage, as in the case of modifiers of intragenomic transformation, since Karlin (1982) Theorem 5.2 can again be applied to (3.27). If Q is irreducible, then the selection on the modifier strictly decreases with looser linkage to the selected locus.

THE EXTERIOR STABILITY OF VIABILITY-ANALOGOUS, TENSOR PRODUCT EQUILIBRIA

Let the population be at a viability-analogous, tensor product equilibrium

$$\hat{\underline{z}} = \hat{\underline{x}} \bullet \hat{\underline{v}} ,$$

with marginal migration probabilities

$$T^*_{f\to e} = \sum_c \hat{x}_c T^{\underline{b}}_{\underline{c}} f\to e \text{ for all modifier alleles } M_b .$$

From (3.25), the recursion on a new modifier allele M_a introduced to the population is

$$\epsilon'_{ei} = \frac{1}{\hat{n}_e^m} \sum_{fj} \hat{n}_f^s \frac{w^{\underline{i}}_{\underline{fj}}}{\hat{\bar{w}}_f} \left((1-R)\epsilon_{fi}\hat{v}_{fj} + R\epsilon_{fj}\hat{v}_{fi} \right) T_{af\to e} , \qquad (3.28)$$

where

$$T_{af\to e} \overset{\Delta}{=} \sum_b \hat{x}_b T^{\underline{a}}_{\underline{b}} f\to e$$

are the marginal migration probabilities determined by the new modifier allele.

Again I can analyze only the case of tight linkage. With $R = 0$, (3.28) is

$$\varepsilon'_{ei} = \frac{1}{\hat{n}^m_e} \sum_f \hat{n}^s_f \frac{\hat{w}_{fi}}{\bar{\hat{w}}_f} T_{af \to e} \varepsilon_{fi} ,$$

or in vector form, letting i and j index the demes now, and h index the selected haplotypes,

$$\underline{\varepsilon}'_h = D_1 T_a D_2 \underline{\varepsilon}_h ,$$

where

$$D_1 \triangleq \operatorname{diag}\left(\frac{1}{\hat{n}^m_i}\right) , \quad T_a \triangleq \| T_{aj \to i} \|_{i,j} , \text{ and } \quad D_2 \triangleq \operatorname{diag}\left(\frac{\hat{n}^s_i \hat{w}_{ih}}{\bar{\hat{w}}_i}\right) .$$

This is a slightly different form from the previous cases for the matrix on the initial increase of the new modifier, but using the general eigenvalue property that

$$\rho(D_1 T_a D_2) = \rho(T_a D_1 D_2) ,$$

we see that we need to know

$$\rho\left(T_a \operatorname{diag}\left(\frac{\hat{n}^s_i \hat{w}_{ih}}{\hat{n}^m_i \bar{\hat{w}}_i}\right)\right) .$$

From the equilibrium identity on the V.A.T.P. equilibrium,

$$\underline{\hat{v}}_h = \operatorname{diag}\left(\frac{1}{\hat{n}^m_i}\right) T^* \operatorname{diag}\left(\frac{\hat{n}^s_i \hat{w}_{ih}}{\bar{\hat{w}}_i}\right) \underline{\hat{v}}_h ,$$

where

$$T^* \triangleq \| T^*_{j \to i} \|_{i,j} .$$

Therefore, we know

$$\rho\left(T^* D_1 D_2\right) = 1 .$$

This yields the following:

RESULT 3.28:

1) The new modifier allele can change frequency at a geometric rate, that is, $\rho(T_a D_1 D_2) \neq 1$, only if there is an equilibrium fitness load in the population, so that $D_1 D_2 \neq I$.
2) The spectral radius for the new modifier allele depends only on how its marginal migration matrix T_a is related to the equilibrium marginal migration matrix T^* . The results of Theorem 3.13 for linear variation, and of Theorem 3.2b for affine variation among memoriless distributions therefore apply directly.

(2) A MODEL FOR SELECTION ON SEXUAL REPRODUCTION

The evolution of sexual reproduction is a long standing topic of evolutionary investigation. Although the effect of sex on genetic variation has been the major reason forwarded for the evolution of sex, no modifier models have been analyzed to my knowledge that include genetic variation both for selected traits and for the sexual reproduction itself. In the following model, sexual reproduction will be treated as a form of transformation process under genetic control. The organsisms modeled here will have a life cycle like Chlamydomonas, which reproduce clonally as haploids or can fuse to make diploids, which undergo meiosis, recreating the haploid phase. In this model, mitotic replications between times of diploidy will be lumped together,

requiring the assumptions that the population changes phase synchronously, and that the number of mitotic divisions has no effect.

Let z_{ai} represent the frequency of haploids with selected haplotype A_i and modfier allele M_a , M_aA_i. The life cycle will consist of the following:

1) Individual selection biases the frequencies of the haploids by the scalar s_i.
2) With probability $1-m_a$ the haploid will reproduce clonally, without transformation, and with probability m_a it will enter a pair-mating pool.
3) In this pool, it pairs randomly with another haploid, M_bS_k.
4) The fitness of the diploid genotype $\frac{A_i}{A_j}$ is f_{ik} .
5) The diploid then yields haploid progeny through a reproductive transformation T , not affected by the modifier. This reproductive transformation would include processes affecting the selected haplotypes during the diploid phase, such as recombination and gene conversion. Moreover, if recombination occurs between the modifier locus and the selected haplotype, then another transformation $\tilde{T}$ is specified to account for any interfence of this with the reproductive transformation.

This yields the following recursion for the population:

$$z'_{ai} = \frac{1}{\bar{w}}\left[(1-m_a)z_{ai}s_i + \frac{1}{\theta}\sum_{bjk} (z_{aj}s_jm_a)(z_{bk}s_km_b)f_{jk}\, T^{R}_{\frac{j}{k}\,+\,i} \right] ,$$

or in vector form

$$\underline{z}'_a = \left[(1-m_a)I + m_aC(\underline{z}) \right] D(\underline{z})\, \underline{z}_a ,$$

where

$$\underline{z}_a \triangleq \begin{pmatrix} z_{a1} \\ z_{a2} \\ \vdots \end{pmatrix} ,$$

with

$$C(\underline{z}) \triangleq \| \frac{1}{\theta} \sum_{bk} z_{bk} s_k m_b f_{jk} T^{R}_{\frac{j}{k} \to i} \|_{i,j} ,$$

and

$$D(\underline{z}) \triangleq \frac{1}{\bar{w}} \operatorname{diag}(s_i) ;$$

the mean fitness is

$$\bar{w} = \sum_{ai} (1-m_a) z_{ai} s_i + \frac{1}{\theta} \sum_{abjk} (z_{aj} s_j m_a)(z_{bk} s_k m_b) f_{jk} ,$$

the size of the mating pool is

$$\theta = \sum_{ai} z_{ai} s_i m_a ,$$

and the transformation probabilities are

$$T^{R}_{\frac{j}{k} \to i} \triangleq (1 - R) T_{\frac{j}{k} \to i} + R T_{\frac{\tilde{k}}{j} \to i} ,$$

where R is the rate of recombination between modifier and selected loci.

Unless the diploid fitnesses satisfy

$$\sum_{ai} z_{ai} s_i m_a f_{ij} = \sum_{ai} z_{ai} s_i m_a \text{ for all } j ,$$

then the matrix $C(\underline{z})$ will not be stochastic, and varying m_a will change the column sums of $\Omega_a D$.

Clearly, though, if the diploid fitness values f_{jk} are large enough,

$$\rho(\Omega_a D) \text{ will increase with larger } m_a ,$$

and if they are small enough,

$$\rho(\Omega_a D) \text{ will increase with smaller } m_a ,$$

showing that a new modifier allele increasing sexual reproduction gets in if there is a strong fitness advantage of the diploid phase, and is excluded if going through the diploid phase has a strong fitness cost. Therefore:

RESULT 3.29:

Strong selection for or against the diploid organism can dominate the evolution of the probability of sexual reproduction in this model.

Suppose now that there is no selection on the diploid, so $f_{jk} = 1$, for all j and k. Then $C(\underline{z})$ is a stochastic matrix. From Karlin (1982) Theorem 5.2, we see that as long as the fitnesses, s_i, of each selected type i are not all equal, the matrix on the frequencies of the individuals with the modifier allele yielding the smallest value m_a will have the largest spectral radius. This of course will change as the frequencies z_{ai} change, but in the limit, the evolutionary outcome will be:

RESULT 3.30:

The population fixes on the modifier causing the highest rate of asexual reproduction (the lowest m_a). The best that modifiers increasing sexual reproduction can do under any condition is be neutral.

This force of induced selection against sexual reproduction is distinct from Williams's (1975) "cost of meoisis". It is more along the lines of "recombinational load" that Williams (1975) discusses.

In this model, when an organism reproduces asexually, transmission is perfect, so that the variation produced by the modifier is linear. However, in real organisms transformation occurs in the asexual organisms also, due to mutation. Incorporation of mutation into the model would change the variation in transformations that the modifier controls to be affine instead of linear. In this case, it may be possible that sexual reproduction would evolve to increase, and the question of what sorts of additional transformation processes could produce an increase in sexual reproduction poses an interesting question.

(3) A MODEL FOR MODIFIERS IN CULTURAL TRANSMISSION

Because cultural transmission is mediated by complex cognitive processes, the idea of transformation can have some interesting applications in this area. Cultural transmission usually goes on within a context of human relationships. The choice of who will be the transmitters of cultural information may depend on these relationships. More importantly, cultural transmission need not be simply the replication of transmitter traits in the receiver; in cases of personality, religious preference, and politics for example, the traits adopted in the receiver can be as much a reaction to these traits in the transmitters as a replication of them because of the nature of the relationship between them. The theories of "family systems" that have been developed are good example of the transformation of behavior. In these theories, the behavior that offspring adopt is

causally related to the behavior of their parents, but does not necessarily resemble it.

The model I pose here considers how culture itself might evolve to affect the degree to which offspring copy the cultural traits of their parents as opposed to adopting traits that are transformed results of their parents traits.

The model has the following components:

1) Individuals bear two kinds of culturally transmitted trait. One affects the individual fitness of its bearer and the fertility of a mated pair. The other, which I refer to as "traditionalism", affects the transmission of the first.
2) Offspring are produced from two parents. Offspring randomly choose one of their parents with whom they will "identify".
3) The offspring acquire from the parent with whom they identify their degree of traditionalism.
4) This degree of traditionalism determines the probability that they also acquire the same selected cultural trait as the parent with whom they identify. Otherwise, they acquire a selected trait which is some function of the selected traits in both their parents.

To represent this, the following are defined:

z_{ai} is the frequency of individuals with traditionalism type a and selected type i before selection.

w_{ij} is the lumped individual fitness and fertility of parental pairs with selected types i and j.

$1-m_a$ is the probability that an offspring adopts the selected trait of the parent with whom it identifies.

$P_{j,k\to i}$ is the probability that an offspring of parental selected types j and k is of selected type i given that it does not simply copy the parent with whom it identifies. These probabilities do not depend on the traditionalism type.

A most important assumption is that the traditionalism itself is transmitted faithfully, in a particulate fashion. It is transmitted without bias, so it can evolve only through hitchhiking with the selected cultural trait.

For a life cycle consisting of selection, random mating with fertility selection, and cultural transmission, the recursion on the frequencies of types is

$$z'_{ai} = \sum_{bjk} z_{aj} z_{bk} \frac{w_{jk}}{\bar{w}} \left((1-m_a)\delta_{ji} + m_a P_{j,k\to i} \right)$$

$$= (1-m_a)\, z_{ai} \frac{w_i}{\bar{w}} + m_a \sum_{jk} z_{aj} v_k \frac{w_{jk}}{\bar{w}} P_{j,k\to i} ,$$

or in vector form

$$\underline{z}'_a = \left[(1-m_a)I + m_a C(\underline{z}) \right] D(\underline{z})\, \underline{z}_a ,$$

where

$$v_k = \sum_a z_{ak}, \qquad w_j = \sum_k v_k w_{jk},$$

$$C(\underline{z}) \triangleq \left\| \sum_k v_k \frac{w_{jk}}{w_j} P_{j,k\to i} \right\|_{i,j}, \qquad \bar{w} \triangleq \sum_{jk} v_j v_k w_{jk}, \text{ and}$$

$$D(\underline{z}) \triangleq \frac{1}{\bar{w}} \operatorname{diag}(w_j) .$$

The variation in cultural transformation determined by the tranditionalism type is linear, so from Karlin (1982) Theorem 5.2, we see that as long as the marginal fitnesses, w_i, of each selected type i are not all equal, the matrix on the frequencies of the individuals with the traditionalism type yielding the smallest value m_a will have the largest spectral radius. This of course will change as the frequencies z_{ai} change, but in the limit, given that the selected cultural traits still maintain marginal fitness differences the evolutionary outcome will be:

RESULT 3.31:

The population fixes on the highest degree of traditionalism in the population (the lowest m_a). The best that the traditionalism types with larger m_a can do is be neutral, and this can occur only for some cases where C at the limit is a reducible matrix.

This simple model suggests that in populations that are allowed to go to equilibrium, forms of culturally transmitted "traditionalism", or faithfulness in cultural transmission of traits that affect fitness will increase. It shows how the trend toward perfect transmission can be found in other contexts, and how the mathematics of these models follow a similar pattern.

5. THE STRENGTH OF SELECTION ON MODIFIERS AND THE EFFECT OF PLEIOTROPY

In the initial increase analyses throughout this chapter, we obtained results on the spectral radius of the exterior stability matrix. Recall that this spectral radius is actually the induced asymptotic relative marginal fitness of the modifier allele (or transformation type in general). Several of the results yield values on the magnitude of this induced marginal fitness.

In the case of tightly linked modifier alleles stopping all transformation, their induced marginal selective advantage was equal to the equilibrium fitness load. This value decreased with looser linkage but was always greater than the equilibrium fitness variance.

For modifiers with lesser effect on the transformations, the result on affine variation with memoriless distributions gives us an estimate of the amount of selection on the modifier as its marginal transformation deviates from the equilibrium marginal transformation of the population. From Theorem 3.2b we obtain

$$\frac{w_a}{\tilde{w}} = 1 + (m_a - m^*)\Big(\sum_i \frac{1}{\gamma_i}\hat{v}_i^2 w_i\Big)^{-1} \frac{1}{\gamma}_2$$

$$\cdot \Big[\frac{\alpha-\beta}{\tilde{w}} \sum_i \frac{1}{\gamma_i}\hat{v}_i^2(\hat{w}_i - \tilde{w})^2 + \alpha\beta\Big((1-\gamma)\sum_i \hat{v}_i(\hat{w}_i - \tilde{w})\Big(\frac{p_i - s_i}{\gamma_i}\Big) + \gamma \ \mathrm{cov}\Big(\hat{w}_i, \frac{p_i - s_i}{\gamma_i}\Big)$$

The selection for or against the modifier will be on the order of the equilibrium fitness variance in the population times the deviation of its marginal transformation matrix from the equilibrium transformation matrix.

What sort of estimates can be obtained for these values in nature? The upper bound on the equilibrium fitness load,

$$\frac{1}{1-\alpha},$$

increases without limit for populations with larger and larger amounts, α, of transformation occurring. The typical values of α in nature depend on the particular transformation process. In the case of the segregation-syngamy transformation, α equals one. Selection on modifiers that lead to ameiotic parthenogenesis or forms of apomixis with the same result can therefore be quite strong. In the case of mutation, although per-locus mutation rates are quite small, per chromosome or per genome rates can range up to order one. Similarly, per-chromosome recombination rates can be on this order. The amount of selection on modifier genes can therefore be quite strong in typical populations. An interesting example is the following:

RESULT 3.32:

The amount of induced selection on a chromosomal inversion can range up to the map length of the inversion, in units of crossover frequency.

What occurs when there is direct selection on the modifier due to pleiotropic effects it may have beyond its effect on transformation? If the pleiotropic selection interacts multiplicatively with the fitnesses of the selected loci, then this pleiotropic selection on the modifier allele is simply multiplied by the induced selection on the modifier due to its effects on transformation. In the case of modifiers completely stopping transformation, the amount of pleiotropic selection against

it, s_p, that it can withstand and still increase when introduced to the population can be as large as α, where its intrinsic fitness relative to the modifier alleles at equilibrium is $1 - s_p$.

The amount of selection on the modifier will actually be a complex function of the transformation probabilities and the selective values of the types in the population; the very course estimates on the possible strength of selection on modifier alleles shown above were made merely to illustrate that the induced selection on modifiers due to their effects on transformation can be on the order of selection acting directly on selected genes.

If the transformations in the population were to continue evolving to reduce the equilibrium fitness load, then the source of induced selection on the modifier will be gradually eliminated. So when the modifier genes that have various degrees of pleiotropic selective effects, the final stages of evolution of the transformations will come to be dominated by these effects.

CONCLUSIONS

In this chapter, the general framework of selection and transformation has been adopted to study the evolution of transformations. Variation for fitness and for transformations has been partitioned into independent dimensions of an individual's type. Perhaps the most basic statement to be derived from the results of this chapter is that the evolution of transformations is driven by an effect of transformation-- the equilibrium variance in the marginal fitnesses

of the selected types. The general result of evolution in the transformations appears to be the elimination of this variance in fitnesses. The state where all marginal fitnesses are equal may be an evolutionarily attractive state for populations at equilibrium when transformation does not act on the transformation types.

The direction in which the transformations evolve depends, however, on the nature of the variation in transformations in the population. Several kinds of variation in transformation have been described: uniform, consisting of linear and affine variation, and non-uniform variation. Three forces have been identified in the evolution of transformations:

1. Selection due to reduction in the amount of transformation.
2. Selection due to increase in the production of the fitter types.
3. Transformation acting on the transformation types.

Only 1. is available when there is linear variation and no transformation of transformation types. With affine variation, or non-uniform variation, 2. becomes available. With segregation distortion or other transmission distortion, 3. becomes available.

A number of properties of the population do <u>not</u> seem to affect the direction in which transformations evolve, including

the nature of the equilibrium at which the new transformation type is introduced,

the nature of the type being transformed, be it genetic, geographic, or cultural,

the nature of the transformations,

the selection regime,

frequency dependent selection or transformation,

allelic multiplicity, or

topology of descent.

It is unknown whether the linkage of the modifier affects the direction of evolution of the transformations, but other work in the literature suggests that it does not unless transformation is acting on the modifier genotype.

Modifiers were found to be potentially able to resist the effects of direct selection, due to pleiotropy, ranging up to the order of the variance in fitness in the population. But if the population is evolving to minimize this fitness variance, at some point pleiotropic effects can come to dominate.

Modifier genes, like selected genes, can maintain polymorphisms. Three kinds of polymorphism have been identified: viability-analogous, tensor product polymorphisms, high complementarity polymorphisms, and "balanced mixture" polymorphisms. I have explored mainly the behavior of viability-analogous, tensor product polymorphisms. They are a general feature of modifiers giving uniform variation in the transformations in randomly mating populations. The addition of tensor product modifier polymorphisms cannot stabilize an unstable selected-locus polymorphic equilibrium. The stability of these polymorphisms does depend on

the stability of the selected haplotype polymorphism,

the nature of the transformation,

the linkage of the modifier,

frequency and density dependent selection and transformation,

the topology of descent,

and most likely, the overdominance of the modifier locus.

But, except as they affect the features above, the stability does not appear to depend on

the kind of selected haplotype polymorphism,

the selection regime, or

allelic multiplicity.