Epistasis Can Facilitate the Evolution of Reproductive Isolation by Peak Shifts: A Two-Locus Two-Allele Model

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ABSTRACT

The influence of epistasis on the evolution of reproductive isolation by peak shifts is studied in a two-locus two-allele model of a quantitative genetic character under stabilizing selection. Epistasis is introduced by a simple multiplicative term in the function that maps gene effects onto genotypic values. In the model with only additive effects on the trait, the probability of a peak shift and the amount of reproductive isolation are always inversely related, *i.e.*, the higher the peak shift rate, the lower the amount of reproductive isolation caused by the peak shift. With epistatic characters there is no consistent relationship between these two values. Interestingly, there are cases where both transition rates as well as the amount of reproductive isolation of the transition point, and the hybrids between the two alternative optimal genotypes have lower average fitness in the epistatic case. A review of the empirical literature shows that the fitness relations resulting in higher peak shift rates and more reproductive isolation are qualitatively the same as those observed for genes causing hybrid inferiority.

FOR sexually reproducing populations, speciation consists in the acquisition of genetic differences that cause reproductive isolation of one such population from other populations. Of all the possible modes of speciation genetic differentiation of isolated populations seems to be prevalent in animals [MAYR (1942); see also COYNE (1992) for a recent review]. In this report, we consider a scenario in which a small population gets separated from the main population without undergoing a founder event or several crash/flush cycles. We further assume that genetic differentiation is mainly caused by random drift, *i.e.*, there is no difference in selection on the main population and the daughter population. In this case, genetic differences are either neutral and therefore irrelevant for speciation, or they constitute transitions among adaptively equivalent genotypes. In the latter case, the population has to cross an adaptive valley (a "peak shift" occurs) (WRIGHT 1952). Such a transition event will cause a reproductive barrier between the source population and its isolate. This is because not all of the possible hybrid and back cross phenotypes can be adaptively optimal, otherwise the difference would be neutral.

Genetic analysis suggests that initial stages of speciation may be caused by a small number (mostly pairs) of interacting loci (ORR 1987, 1989; ORR and COYNE 1989). Therefore, peak shifts among alternative genotypes are likely to involve only few genes, if genetic differentiation is due to drift. We model this process in the framework of a two-locus two-allele model. We will ask how the genetic architecture influences both, the rate of transition

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between alternative optimal genotypes as well as the amount of reproductive isolation between those genotypes.

Considerable effort has been devoted to obtaining estimates of the peak-shift rates by modeling specific evolutionary scenarios (BARTON and CHARLESWORTH 1984; BARTON and ROUHANI 1987; LANDE 1985). In principle, two kinds of models can be distinguished: In "phenotypic" models distinct phenotypes can occupy local maxima in the fitness landscape. In "genotypic" models, on the other hand, different combinations of genes may lead to the same, optimal phenotype. The model studied below is an example for the latter kind of models.

Assumptions about modes of interactions between gene effects are essential for genotypic models. The most elementary of these assumptions is that genes have linear (additive) effects on the genotypic value of a quantitative character. Peak-shift scenarios under the assumption of purely additive gene effects have been extensively studied (LANDE 1985; FOLEY 1987; BÜRGER 1988; CHARLESWORTH and ROUHANI 1988; BARTON 1989a). BARTON (1989a), for example, showed that peak shifts can occur at an appreciable rate, although the amount of reproductive isolation obtained per peak shift is small. The overall rate of accumulation of reproductive isolation has been estimated to be of the order of the mutation rate.

To what extent the slow pace of evolution predicted by additive models carries over to epistatic models is unclear [for a review, see BARTON (1989b)]. The discussion is mostly framed in terms of the contrast between

type I architectures, where many genes have approximately additive effects, and type II architectures, where there are few genes with strongly epistatic effects and many "modifier" loci. The results are difficult to generalize, since there are countless many ways to model epistatic gene interactions. In the present paper we concentrate on an epistatic model of a quantitative character under stabilizing selection. The relative strength of epistasis can be adjusted by changes in one parameter (see below). Thus, a one parameter class of models with different degrees of epistasis in the quantitative character is defined. This class includes a purely additive case. A member of this class which shows a high rate of evolution of reproductive isolation is analyzed in detail and compared to the additive case. A comparison of this member to data about genes causing hybrid inferiority suggests that it is representative of many genes involved in the emergence of reproductive isolation.

THE MODEL

We consider a diploid randomly mating population with overlapping generations that is either dioecious or monoecious with the same pattern of selection acting on both sexes. Heritable fitness differences are assumed to be due to the variation in one quantitative character P. No genotype-environment interaction is assumed to be present, such that the genotypic value G and the environmental contribution E are independent:

$$P = G + E. \tag{1}$$

The environmental effect E is supposed to be normally distributed with mean zero and variance one.

Selection is supposed to be stabilizing with P = 0 as the optimal phenotype. More precisely, we assign to each phenotypic value P a fitness value $m_p(P)$, defined as

$$m_p(P) = 1 - sP^2,$$
 (2)

where s denotes a measure for the strength of stabilizing selection. However, since the environmental effect E is assumed to be superimposed onto G, it is necessary to evaluate the mean fitness $\overline{m}(G)$ of a genotype with genotypic value G. By using (2) and the above assumptions about the distribution of E, $\overline{m}(G)$ becomes

$$\bar{m}(G) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{\infty} m_p(G+E) e^{-(E^2/2)} dE$$

$$= 1 - s - sG^2.$$
(3)

Because the selection dynamics with overlapping generations is invariant to the addition of a constant to the fitness, we can ignore the term s in $\overline{m}(G)$.

Furthermore, we assume that the genotypic value G of the quantitative character under consideration is determined solely by the genetic composition of two loci X and Y, with two alleles each: X_0 and X_1 at locus X and Y_0 and Y_1 at locus Y. Contributions to G by the underlying variables which are influenced by locus X are denoted by the lowercase letters x_0 , x_1 , x_2 for genotypes X_0X_0 , X_0X_1 and X_1X_1 , respectively. An analogous notation is used for contributions y_{k+1} of the genotypes Y_kY_l at the locus Y. The genotypic values for the underlying variables are arbitrarily chosen to be $x_0 = y_0 = 3$, $x_1 = y_1 = 2$ and $x_2 = y_2 = 1$. Additionally, we suppose that there exists a smooth function g(x,y) of the underlying variables x and y which determines the genotypic value G, G := g(x, y). In this paper we will be concerned only with two special cases of such a function, a linear (additive) one, and a "mildly" non-linear (epistatic) one.

The linear function g_1 is given by $g_1(x, y) := c_0 + c_1x + c_2y$, c_0 , c_1 and c_2 being arbitrary real numbers. To specify the coefficients c_i in the above functions, we introduce the following three assumptions. First, since we want to study the transition between alternative genetic adaptations, it is assumed that two complementary double homozygous genotypes have the same genotypic value zero, *i.e.*, $g_1(x_0, y_2) := 0$ and $g_1(x_2, y_0) := 0$. Further, we assume that the contributions of the loci are symmetrical, *i.e.*, $c_1 = c_2$. These assumptions specify the additive genotype phenotype map up to a multiplicative constant:

$$g_1(x, y) := c (x + y - 4).$$
 (4a)

Since fitness only depends on the product of sc^2 the constant c can be chosen arbitrarily without loss of generality as c = 1.

As a model of the epistatic genotype phenotype map $g_2(x, y)$ we use a modification of GIMELFARB's (1989) additive/multiplicative model, which one obtains by adding a multiplicative term to the additive model:

$$g_2(x, y) = g_1(x, y) + v(x, y),$$

where

$$v(x, y) = c_3 xy + c_4.$$

Since we want to maintain that the two complementary double homozygous genotypes have the same genotypic value zero in order to have the same optimal genotypes in both models, the interaction term v(x, y)has to be zero for these two genotypes too. This specifies its coefficients up to a multiplicative constant: v(x, y) = b(xy - 3). In the resulting model for the epistatic character

$$g_2(x, y) := c'(x + y - 4) + b(xy - 3)$$

the strength of epistasis is determined by the ratio $\beta = b/c'$. It is thus convenient to rewrite $g_2(x,y)$ as

$$g_2(x, y) := c'[(x + y - 4) + \beta (xy - 3)].$$
 (4b)

As in the linear model, c' only enters the fitness as sc'^2 ,

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$$\begin{array}{c} G_1 & Y_0Y_0 & Y_0Y_1 & Y_1Y_1 \\ & X_0X_0 \\ & X_0X_1 \\ & 1 & 0 & -1 \\ & X_1X_1 \\ \end{array} \right) \\ (b) \\ (b) \\ (c) \\ \begin{array}{c} G_2 & Y_0Y_0 & Y_0Y_1 & Y_1Y_1 \\ & X_0X_0 \\ & X_0X_1 \\ & X_1X_1 \\ \end{array} \right) \\ (c) \\ (c) \\ M_2 & Y_0Y_0 & Y_0Y_1 & Y_1Y_1 \\ & X_1X_1 \\ \end{array} \right) \\ (c) \\ M_2 & Y_0Y_0 & Y_0Y_1 & Y_1Y_1 \\ & X_0X_0 \\ & (1 - 4s(1 + 3\beta)^2 & 1 - s(1 + 3\beta)^2 & 1 \\ & 1 - s(1 + 3\beta)^2 & 1 - s(\beta^2 & 1 - s(1 + \beta)^2 \\ & 1 & 1 - s(1 + \beta)^2 & 1 - 4s(1 + \beta)^2 \\ & 1 & 1 - s(1 + \beta)^2 & 1 - 4s(1 + \beta)^2 \\ \end{array} \right) \\ (d) \\ (d) \\ \begin{array}{c} M_2 & Y_0Y_0 & Y_0Y_1 & Y_1Y_1 \\ & X_0X_0 \\ & (1 - 36s & 1 - 9s & 1 \\ & X_0X_1 \\ & X_0X_1 \\ & X_1X_1 \\ \end{array} \right) \\ (d) \\ \end{array}$$

FIGURE 1.—Genotype and fitness values. (a) Genotype values, G_1 , for an additive character G_1 resulting from (4a), or from (4b) with $\beta = 0$ (c = 1). (b) Genotype values, G_2 , for an epistatic model resulting from (4b) (c = 1). (c) Fitness matrix M_2 resulting from (4b) (c = 1). (d) Fitness matrix M_2 , as in (c), but for $\beta = -\frac{4}{3}$. See text for details.

and can be treated as an arbitrary constant c' = 1 without loss of generality. The factor β defines a class of models where the amount of epistasis in the genotype-phenotype map depends on the parameter β (N. BARTON, personal communication).

The resulting matrices for genotypic values, G_1 for the additive model ($\beta = 0$) and G_2 ($\beta \neq 0$) for the epistatic model, are shown in Figure 1a and 1b, respectively. Applying (3) to the genotype matrices $G_1 := (g_{ij}^{(1)})$ and $G_2 := (g_{ij}^{(2)})$, and setting the maximum fitness equal to one, we obtain a set of fitness matrices denoted as $M_k = (m_{ij}^{(k)})$, where $m_{ij}^{(k)} = 1 - s_k (g_{ij}^{(k)})^2$ ($k \in \{1, 2\}, i, j \in \{0, 1, 2\}$). M_2 is depicted in Figure 1c.

Note that we use here a coefficient s_k instead of s to specify the intensity of stabilizing selection. Since the additive and the epistatic character model lead to different average allelic effects, they also lead to different selection intensities at the genic level. When these two models are going to be compared, these differences have to be taken into account. Since there are several ways to correct for these effects, we will maintain different coefficients for the selection on the additive and the epistatic character.

For investigating the selection forces that act on the gamete frequencies we will use the following standard model of ordinary differential equations (CROW and KIMURA 1970).

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$$p_1 = \frac{dp_1}{dt} = p_1(m_1^{(j)} - \bar{m}^{(j)}) - nD + \mu(p_2 + p_3 - 2p_1) \quad (5a)$$

$$p_2 = \frac{dp_2}{dt} = p_2(m_2^{(j)} - \bar{m}^{(j)}) + nD + \mu(p_1 + p_4 - 2p_2)$$
(5b)

$$\dot{p}_3 = \frac{dp_3}{dt} = p_3(m_3^{(j)} - \bar{m}^{(j)}) + nD + \mu(p_1 + p_4 - 2p_3) \quad (5c)$$

$$p_4 = \frac{dp_4}{dt} = p_4(m_4^{(j)} - \bar{m}^{(j)}) - nD + \mu(p_2 + p_3 - 2p_4), \tag{5d}$$

where p_1 , p_2 , p_3 , p_4 denote the frequencies of gametes X_0Y_0 , X_0Y_1 , X_1Y_0 , X_1Y_1 , respectively. Linkage disequilibrium is denoted by $D := p_1p_4 - p_2p_3$ and the recombination rate between loci is denoted by r. Forward and backward mutations at each locus are assumed to occur at the same frequency, μ . Furthermore,

$$m_k^{(j)} := \sum_{l=1}^4 m_{kl}^{(j)} p_l \tag{6}$$

is the marginal mean fitness of the gamete p_k , and

$$\bar{m}^{(j)} = \sum_{k=1}^{4} m_k^{(j)} p_k \tag{7}$$

represents the mean fitness of the population.

Certain restrictions apply to the usage of equations (5) (CROW and KIMURA 1970; CHARLESWORTH 1970). First, selection has to be weak with no dominance in the death rates and small differences in the birth rates. Furthermore it is assumed that the interaction between mutation and selection can be neglected, allowing for an additive contribution of the change of p_i due to mutation to the total change of p_i . Also, in a continuous time model the parameter r is in fact the product of the recombination fraction and the birth rate of the double heterozygote. Therefore, $r \leq 0.5$ need not necessarily hold.

The results are presented in four parts: first, the structure of the fitness matrices resulting from the assumption of epistasis on the character will be discussed, which leads to the identification of a special case that is analyzed in detail; second, the amount of reproductive isolation between alternative optimal genotypes is calculated and compared to the additive case; third, a deterministic analysis of the epistatic model sets the stage for a numerical estimation of the rates of peak shifts between alternative genotypes, which is the fourth part of the results.

RESULTS

Qualitative comparison between additive and epistatic character models: Epistasis is introduced as a multiplicative term in the function g specifying the genetic

(a)

effects on the variation of the quantitative character.

$$g_1(x,y) := (x + y - 4)$$

$$g_2(x,y) := [(x + y - 4) + \beta(xy - 3)].$$

The parameter β regulates the strength of epistasis at the character level such that the additive model can be considered a special case ($\beta = 0$) of the epistatic model. Epistasis on the level of the quantitative character is to be distinguished from epistasis in fitness. Whereas in the additive model there are only additive effects of the genetic level on the quantitative character, the quadratic fitness function we use to model stabilizing selection introduces negative epistasis in fitness, E < 0. The measure for the amount of epistasis we use here is the coefficient of epistasis in fitness, $E := m_1 - m_2 - m_3 + m_4$, introduced by CROW and KIMURA (1970). (Note that this Ediffers from the E in (1).) The epistatic model, on the other hand, incorporates epistasis also on the level of the character, such that an increase in $|\beta|$ leads to an increase in epistasis on this level. The outcome in terms of the amount of epistasis in fitness is no longer a monotonic function of β , as can be seen from Figure 2, which shows the coefficient of epistasis E in fitness as a function of the parameter β . It indicates that for $\beta = 0$ (additive character) epistasis for fitness is strong $(E \neq 0)$ and that it approaches zero from below, as β approaches -0.4(for $p_i = \frac{1}{4}$). For $\beta > -0.4$ it deviates from zero again. For positive values of β , |E| always increases.

For all values of β the two homozygous genotypes $X_0X_0Y_1Y_1$ and $X_1X_1Y_0Y_0$ have the highest fitness $m_{22} = m_{33} = 1$. Further, in the case of an additive character, the double heterozygous genotype also has maximal fitness. This is the genotype of the F_1 hybrid between the alternative optimal genotypes. Whenever β is unequal to zero, the double heterozygous genotype is less fit than the two optimal homozygous genotypes.

The fitness matrix in the additive character model is symmetric. In particular, $m_{22} = m_{33} = 1$ and $m_{11} = m_{44}$ < 1 holds. As epistasis is introduced, this symmetry of m_{11} and m_{44} does in general not hold. For $\beta \in (-\frac{1}{2}, 0)$, m_{44} $< m_{11}$ and for $\beta < -\frac{1}{2}, m_{44} > m_{11}$. Interestingly, for $\beta =$ $-\frac{1}{2}$, $m_{11} = m_{44}$ as in the additive case, and the fitness landscape for this parameter value resembles the fitness landscape with an additive quantitative character. Most importantly, the fitness of m_{11} or m_{44} (depending on β) can be larger than the fitness of the double heterozygous genotype (Figure 3). Consider, for example, the difference between m_{44} and m_{14} , $m_{44} - m_{14}$. This value is larger than zero in the interval $-2 \le \beta \le -\frac{2}{3}$; it is maximal for $\beta = -\frac{4}{3}$. Similarly, there exist values for β for which m_{11} is larger than the fitness of the double heterozygote genotype. Hence, depending on β there may be genotypes intermediate to the two alternative optimal genotypes, which have higher fitness than the F_1 hybrid. This means that the fitness valley which has to be crossed to



FIGURE 2.—Coefficient of epistasis in fitness E as a function of β . The coefficient of epistasis in fitness, E (CROW and KIMURA 1970), defined as $m_1 - m_2 - m_3 + m_4$ is shown as a function of β in the center of the simplex ($p_1 = p_2 = p_3 = p_4 = \frac{1}{4}$). It is closest to zero for $\beta = -0.4$. Note that, since the fitness function used is nonlinear, E for a completely additive character ($\beta = 0$) is not equal to zero.

reach the alternative genotype can be less deep than the fitness valley in which the hybrids are located. Below, we will use the special case of $g_2(x, y)$ with $\beta = -\frac{4}{3}$ as example for the deterministic analysis and the Monte-Carlo simulations. This case will allow us to demonstrate most clearly the difference between the additive character case and the epistatic character case. The fitness matrix M_2 for $\beta = -\frac{4}{3}$ is shown in Figure 1d.

One further remark seems appropriate. The existence of genotypes with high fitness between the alternative homozygous genotypes does not imply that there is no adaptive valley separating them. For instance, in the case of an additive character under stabilizing selection, the double heterozygous genotype has maximal fitness. However, there exists an adaptive valley between the two optimal homozygous genotypes, because the offspring of double heterozygous individuals have a high segregation variance and therefore low average fitness under stabilizing selection. The existence of intermediate genotypes with high fitness alone is therefore not sufficient to predict how easy an alternative optimum genotype can be reached.

The amount of reproductive isolation: In this section it is discussed how epistasis in the character influences the amount of reproductive isolation between the alternative optimal genotypes. Since our model is based on viability selection, only the evolution of postzygotic isolation can be considered here. In this case, the amount of gene flow between partially isolated populations depends on the intensity of selection against hybrids. We analyze the fitness of the F_1 hybrids and the genotypes that result from back crosses *B* into one of the parental populations. These values directly measure the selection against the most frequent hybrid genotypes (F_1 and B). An alternative would be to use the mean fitness of a hybrid population interbreeding among themselves

$$max(m_{11}, m_{44}) - m(F_1)$$



FIGURE 3.—Comparison of fitness of F_1 hybrid (m_{23}) with m_{11} and m_{44} . The difference between m_{11} or m_{44} , whichever is larger, and the fitness, m_{23} , of the F_1 hybrid between the two optimal genotypes, *i.e.*, $max(m_{11}, m_{44}) - m_{23}$, is shown as a function of β . Positive values indicate that there are genotypes intermediate between the two alternative optimal genotypes which have higher fitness than the F_1 hybrids. These are the cases where the population has to cross an adaptive valley which is less deep than the fitness of the hybrids. For additive characters, this value is zero. In the case of $\beta = -\frac{4}{3}$, m_{44} is maximal compared to the hybrid fitness, and the discrepancy between the adaptive valley and the hybrid fitness is largest. This is also the case which is analyzed in detail below.

(BARTON 1989a). However, hybrids usually do not exist in isolated populations, but are part of a hybrid zone interbreeding with the two parental populations. Gene flow between parental populations is caused by matings between hybrids and members of the parental populations (back crosses). We therefore think that the fitness of hybrid genotypes is a more adequate measure of reproductive isolation than the mean fitness of a isolated hybrid population.

Because the two alternative adaptive genotypes are the double homozygous genotypes $X_1X_1Y_0Y_0$ and $X_0 X_0 Y_1 Y_1$, the F_1 hybrids are the double heterozygous genotypes $X_0X_1Y_0Y_1$. For the additive character model, these genotypes have always the same genotypic values as the optimal ones. In the epistatic case, the mean fitness in the F_1 generation is $1 - s_2\beta^2$, because the epistatic effects cause a displacement from the optimum of the mean phenotype of the F_1 hybrids. The mean fitness of the back crosses B with one of the parental populations depends on the recombination rate, because the F_1 hybrids produce all four possible gametes by recombination. Consequently, four genotypes have to be taken into account to estimate selection against the back cross genotypes with, say, the population consisting of $X_1 X_1 Y_0 Y_0$ genotypes:

$$\bar{m}(B) = \frac{1-r}{2}m_{22} + \frac{1-r}{2}m_{23} + \frac{r}{2}m_{24} + \frac{r}{2}m_{12}.$$

For the additive character case the mean fitness of back

crosses is

$$\bar{m}(B) = 1 - rs_1$$

and in the epistatic case it is

$$\bar{m}(B) = 1 - s_2 \left(r + 4\beta r + \frac{\beta^2}{2} + \frac{9\beta^2 r}{2} \right).$$

In both cases, recombination between the two interacting loci increases the amount of reproductive isolation, because it produces unbalanced genotypes. Furthermore, if $s_1 = s_2$ the mean fitness of the back cross genotypes is lower in the case of an epistatic character than for an additive character, whenever $\beta > 0$ or $\beta < -8/(1$ + 9r). For $\beta = -\frac{4}{3}$ the mean fitness of the back cross genotypes is

$$\bar{m}(B) = 1 - s_2\left(\frac{8}{9} + \frac{11r}{3}\right)$$

which is much less than for additive characters, even if s_1 is larger than s_2 by a factor of four to five.

Both the F_1 hybrids and the back crosses are less fit in the epistatic case than in the additive model. Consequently, for a wide range of values of the ratio s_1/s_2 , the amount of reproductive isolation caused by peak shifts is higher in the epistatic character model than in the additive character model.

Deterministic analysis: The fitness matrix M_1 generated by the genotype matrix G_1 is a special case of the fitness matrix of the so-called symmetric viability model, which has found considerable attention since it has been first investigated by WRIGHT (1952). Rigorous analytical work in the case of $\mu = 0$ has been carried out by KARLIN and FELDMAN (1970) as well as by BODMER and FELSEN-STEIN (1967). More recently, BÜRGER (1989) has carried out a global analysis of exactly the dynamics generated by M_1 using (5). Since his results for the special case of $\mu = 0$ are of interest to our analysis and since they will be used in the sequel, we shall briefly recapitulate them using the notation introduced above. First, it has been shown that all orbits in the linear model converge to the plane $p_1 = p_4$. Second, there exists an unstable equilibrium point F1 in this plane, given by

$$\hat{p}_1 = \hat{p}_4 = \frac{1}{4} + D_1, \qquad \hat{p}_2 = \hat{p}_3 = \frac{1}{4} - D_1,$$

where

$$\hat{D}_1 = -\frac{s_1}{4} \frac{1}{\sqrt{s_1^2 + r^2} + r}.$$

Orbits starting in the interior of the manifold defined by $p_2 = p_3$ converge to F1. Third, two locally stable "vertex" equilibria, F2(F3), exist with coordinates $\hat{p}_2 = 1$ ($\hat{p}_3 = 1$). Their domain of attraction is the set where $p_2 > p_3$ ($p_2 < p_3$). The above results imply that the equilibrium state of the population is influenced by its initial state. Transitions from the region of *S* where $p_2 < p_3$ holds, to the



FIGURE 4.—Phase diagrams for epistatic and additive model. Numerical integration of (5) for a series of initial conditions close to the intersection of the plane where $p_2 = p_3$ (gray shading) and the plane where $p_1 = 0$ in the domain $p_2 > p_3$. s = 0.001; r = 0.01; $\mu = 0$; (a) Additive model; (b) Epistatic model; In the additive case, the trajectories approach the (invisible) plane $p_1 = p_4$ before converging to $p_2 = 1$, whereas in the epistatic case trajectories are approaching $p_4 = 1$ before converging to $p_2 = 1$ very close to the edge where $p_2 + p_4 = 1$.

region where $p_2 > p_3$ can only be expected if there is also a stochastic component that influences the gamete frequencies, such as genetic drift.

Analysis of the dynamics of (5) with $\mu = 0$ and the fitness matrix M_2 with $\beta = -\frac{4}{3}$ (Figure 1d), *i.e.*, the epistatic case, reveals dynamics that are qualitatively different from the additive case. Here we only present a summary of a more detailed analysis which is carried out in the APPENDIX. In the epistatic case there also exist two locally stable vertex equilibria $p_2 = 1$ ($p_3 = 1$) with the set $p_2 > p_3(p_2 < p_3)$ as domain of attraction, and one unstable equilibrium point within the plane $p_2 = p_3$. The latter equilibrium is a saddle, i.e., it has a twodimensional stable manifold that is located within that plane $p_2 = p_3$. Thus, the number of equilibria and their stability properties are very similar in the additive and in the epistatic model. However, an important difference between the additive and the epistatic model is that the respective equilibrium points in $p_2 = p_3$ are "semisymmetrical" $(p_1 \neq p_4)$ in the epistatic case (see APPEN-DIX), but "symmetrical" ($p_1 = p_4$) in the additive case (BÜRGER 1989). In fact, the saddle point within the $p_2 =$ p_3 plane is shifted towards the vertex $p_4 = 1$ in the epistatic case. A further, qualitative difference can be seen in the path that trajectories leading to the vertex equilibria take in the two models. Trajectories in the epistatic model do in general not approach the plane $p_1 = p_4$ but

cross it. They spend more time in the vicinity of $p_4 = 1$ than those in the additive model. This becomes evident by numerically integrating (5) for different initial conditions, as shown in Figure 4 for the additive and for the epistatic case, respectively. Although the final outcome for both models in the absence of mutation will be the same (in that the stable equilibria in this case reduce to $p_2 = 1$ or $p_3 = 1$), these differences in the dynamics of the two models are important for the stochastic analysis carried out below, since it is the location of the saddle points within the plane $p_2 = p_3$, as well as the path of the trajectories that define the region where peak shifts take place and the above differences are responsible for the difference between the additive and the epistatic model.

Peakshift probabilities estimated by Monte-Carlo simulations: Stochastic perturbations of the deterministic dynamical system defined in (5) were used to compare transition rates for the additive and the epistatic model. The differential equations used are identical to those in (5), except for an additive stochastic term $\vec{v} := (v_1, \ldots, v_4)$, *i.e.*, they are given by $(\delta \not{p} / \delta t)_{\text{stoch}} :=$ $(\delta \not{p} / \delta t)_{\text{det}} + \vec{v}$, where $(\delta \not{p} / \delta t)_{\text{det}}$ represents the right hand side of (5). The stochastic term \vec{v} represents the effects of genetic drift. It is generated as a pseudorandom multidimensional Gaussian deviate that has the exact co-variance matrix, *i.e.*, the one corresponding to a multinomial distribution

where N_e is the effective population size. This Gaussian approximation is adequate provided the components of \vec{p} are not too small. Because the equations used here are continuous-valued approximation of a discrete \vec{p} , allele fixation has to be enforced for small p_i . In order to represent the effects of mutations correctly, the following algorithm was used: if $p_i \in [0, 1/2N_e]$, it is reset to $1/2N_e$ with probability $2N_e p_i$ and to 0 with probability $1 = 2N_e p_i$. After any such fixation step, normalization of gamete frequencies to a sum of 1 was performed.

For estimates of shift times between $p_2 > p_3$ and $p_2 < p_3$ a population was initialized at the optimum genotype $(p_2 = 1)$ and let to evolve until genetic drift caused it to cross the plane of symmetry corresponding to the valley *that separates the two basins of attractions in the adap*-tive landscape $(p_2 = p_3)$. Crossing time and crossing coordinates in the simplex were recorded and the system was reinitialized. The following results were derived from the statistical distribution of crossing events thus obtained.

Simulations were carried out with large or small population sizes $(N_{e}s_{k} > 1 \text{ or } N_{e}s_{k} < 1)$ in the regime of small



FIGURE 5.—Comparison of transition point distributions. Histograms of the frequency p_4 at the crossing point ($p_2 = p_3$). (a) Additive model: $N_e s_1 = 2.34$; r = 0.5; $N_e \mu = 0.06$. (b) Epistatic model: $N_e s_2 = 15.6$; r = 0.5; $N_e \mu = 0.4$. Standard errors for all values given are 2%. Note that in the epistatic model the transitions occur at much higher frequencies of p_4 than in the additive model (see text for explanation).

mutation rates $(N_e\mu \ll 1)$. Histograms of the distribution of p_4 -coordinates of the crossing points are presented in Figure 5, a and b, for the additive and the epistatic character, respectively. They show that, provided that $N_e s_k$ is large enough, the trajectories tend to cross the dividing plane $p_2 = p_3$ near the unstable equilibrium points. Note that the locations of the saddle points are very different for the two models, as predicted above.

It follows from examination of the Kolmogorov-Fokker-Planck equation (EWENS 1979) which describes the evolution of the probability distribution of the population state that the shift frequency $\Gamma = 1/T$ is a homogeneous function of order (+1) in the four arguments $(\mu, s, 1/N_{e}, r)$. One can deduce from this symmetry that Γ/μ is a function of three arguments only, for instance, $(N_{e}s, \mu/s_{k}, s_{k}/r)$. If r is much larger than s_{k} one can argue that recombination will enforce linkage equilibrium but will not further affect the solution, since the regime will have entered the asymptotic region where $s_{\rm b}/r$ is nearly null. Under this condition, the shift time normalized to the mutation rate will depend asymptotically on two arguments only, $N_k s_k$ and μ/s_k . We were able to verify numerically that this asymptotic regime was reached, since Γ/μ was not affected by varying N_{μ} , μ and



FIGURE 6.—Comparison of peak shift frequencies. Transition frequency Γ normalized to mutation rate μ as a function of $N_c s_k$. (a) Additive model: $s_1 = 0.156$; r = 0.5. (b) Epistatic model: $s_2 = 0.156$; r = 0.5. Standard errors for all values given are 2%. Note that the exponential approximation of Γ as a function of $N_c s_k$ only holds for small mutation rates.

 s_k within an order of magnitude while keeping $N_e s_k$ and μ/s_k constant (results not shown).

In Figures 6, a and b, for the additive and the epistatic case, respectively, crossing times T are plotted as a function of effective population size N_e , selection coefficient s_k , and mutation rate μ . More precisely, crossing rates normalized to the mutation rate, Γ/μ , are shown.

Our numerical results show that the transition frequency is well approximated by an exponential function of $N_e s_k$. One obtains for the additive model

$$\Gamma_1/\mu \approx 0.6 \exp(-0.96 N_e s_1)$$

with a mean fitness at the saddle point of $\bar{m}^{(1)} \approx 1 - 0.85s_1$. In the epistatic case one finds

$$\Gamma_9/\mu \approx 1.2 \exp(-0.2 N_s s_9)$$

and a mean fitness at the saddle point of $\bar{m}^{(2)} \approx 1 - 0.23s_2$. Note the dependence of Γ on the mutation rate (Figure 6b). For small $N_e s_k$, Γ is proportional to μ . However, for larger values of $N_e s$, Γ is proportional to a power of μ higher than one: according to the analytical results given by BARTON and ROUHANI (1987), Γ should be proportional to μ^2 for very large values of $N_e s$.

The ratio of the transition probabilities R is

$$R = \frac{\Gamma_2}{\Gamma_1} \approx 2.0 \, \exp(N_e(0.96s_1 - 0.2s_2)) > 1.$$

As mentioned above, the effect of a gene substitution is different in the additive and the epistatic character model. Therefore, the intensity of stabilizing selection has to be scaled such that the transition probabilities can be compared. Below we will discuss three ways of scaling, one with $s_1 = s_2$, one where the average effect of a gene substitution is held constant and one where the fitness at the transition point is kept the same for the two models. The ratio of the transition rates *R* implies that for s_2 < 4.8 s_1 peak shifts are more likely in the epistatic character case than in the additive case. The exact magnitude of the advantage depends on how one scales the selection intensities on the additive and the epistatic character and what values of $N_c s$ are reasonable.

Values for the intensity of stabilizing selection have been compiled by ENDLER (1986). He uses the effects of stabilizing selection on phenotypic variance to measure the intensity of stabilizing selection

$$j = \frac{V_{Pw} - V_P}{V_P}$$

where V_P and V_{Pw} denote the phenotypic variance before and after selection, respectively. In terms of our model and using $V_E = 1$ one obtains

$$s_k = \frac{-j}{j + V_P(1+j)}$$

Assuming a heritability of about 0.5, one obtains

$$s_k = \frac{-j}{5j+3}.$$

Given the values of *j* compiled by ENDLER, $s_k = 0.1$ is quite realistic in wild populations. This selection coefficient easily leads to values for $N_e s_k$ that are of the order of 10. If selection on the epistatic character is as strong as on the additive character, $s_1 = s_2$, then the predicted ratio of peak shift probabilities easily exceeds three orders of magnitude.

Another way to adjust for the differences in the epistatic and the additive character model is to hold the average effect on the character of a mutation at one of the loci constant. For $\beta = -\frac{4}{3}$, the appropriate adjustment is $s_2 = 0.64s_1 = s$. Under these conditions, the ratio of the transition probabilities exceeds four orders of magnitudes as N_s exceeds a value of 11. Finally, it is possible to adjust the selection intensity such that the mean fitness at the saddle point is the same for the epistatic and the additive character $(s_2 = 3.7s_1)$. This is the most conservative assumption. Under these conditions, the ratio still exceeds one order of magnitude. Hence, for moderately large populations and realistic strengths of stabilizing selection (ENDLER 1986) epistasis in the genotype phenotype map is expected to have a substantial influence on the rate of peak shifts as compared to an additive character.

DISCUSSION

The question considered in this contribution is: how does the genetic architecture of a quantitative character

under stabilizing selection influence the rate of accumulation of reproductive isolation by peak shifts in a small and isolated, but stable population. More specifically, we are interested in the influence of epistatic interactions among quantitative trait loci on the rate of evolution of reproductive isolation. A class of two-locus two-allele models was analyzed, for which the degree of epistasis among quantitative trait loci was adjustable via a parameter, β . $\beta = 0$ results in a completely additive character, whereas deviations from $\beta = 0$ yield continuously varying degrees of epistasis. The value $\beta = -\frac{4}{3}$, as discussed above, allows us to illustrate most clearly our central claim, namely that epistasis may allow for a considerable increase in peak shift rate, in comparison to an additive trait. We therefore focused on a comparison of the cases $\beta = 0$ and $\beta = -\frac{4}{3}$, referring to them in the following as the additive model and the epistatic model, respectively. It has to be pointed out that this property of increased peak shift rates is not a property of epistatic interactions in and by themselves, but rather of a certain type of epistasis. Cases are conceivable where epistasis will decrease peakshift rates. However, it will be argued below that there is empirical evidence in favor of the fitness scenario presented here.

The impact on speciation of the architecture of the genetic system has been discussed mainly with reference to the contrast between the so-called type I and type II architectures (TEMPLETON 1982; BARTON and CHARLES-WORTH, 1984; CARSON and TEMPLETON 1984; BARTON 1989b). Type I architecture assumes many genes with small and approximately additive effects, while type II architecture assumes strong epistasis between genes and genes with unequal effects (TEMPLETON 1982). The implications of type I architecture for the accumulation of reproductive isolation are quite well understood (BARTON and CHARLESWORTH 1984; BARTON 1986, 1989a,b), and essentially state that slow accumulation of small contributions to postzygotic isolation is the most likely mode of speciation with type I architecture. While there is ample evidence for the involvement of epistatically interacting genes in species differences [see reviews by CARSON and TEMPLETON (1984) and COYNE (1992)], the importance of epistasis for the speciation process is controversial. It has been shown that certain type II models predict approximately the same rate of accumulation of reproductive isolation as the type I model (BARTON 1989b). Below, it will be discussed how the higher rate of divergence, predicted by the epistatic model analyzed here, is related to the genetic architecture assumed in the model.

The genetic architecture of the trait considered in the epistatic model results from two assumptions. First, it is assumed that the effect of the two genes on the phenotypic characters is mediated by their independent effects on two underlying physiological or developmental traits. Second, it is assumed that these underlying variables interact nonlinearily to produce the phenotypic character, which leads to epistatic interactions between the genes. In the epistatic model analyzed here, we assume the lowest possible degree of nonlinearity, namely a mixed second order term of a polynomial. Two differences to the additive model in the genetic architecture are thereby introduced. First, the double heterozygote genotype, *i.e.*, the hybrids between the two alternative adaptations $X_0X_0Y_1Y_1$ and $X_1X_1Y_0Y_0$, are not optimal. In the additive case the double heterozygote has the same phenotype as the two alternative homozygote genotypes due to the mathematical properties of additivity. The second difference is the effect of a gene-substitution at one of the optimal genotypes. In the additive model used for comparison, the allele substitution at either locus has the same effect on the phenotype and is thus a simple model of type I architecture. In the epistatic model, effects of substitutions at the X and the Y locus are not the same, representing a type II architecture. For $\beta = -\frac{4}{3}$, if one considers the effect of allele substitutions at the genotype $X_0 X_0 Y_1 Y_1$, the substitution of X_0 by X_1 would have an effect of $-\frac{1}{3}$ on the character *p*, while a substitution at the Y locus would have the effect 3. Hence, Y may be called the major locus and X the minor locus in this case. However, the role of the major and the minor locus switches if we consider the alternative genotype $X_1X_1Y_0Y_0$. In this case the X locus has a much greater effect than the Y locus. Hence the nonlinear genotypephenotype map induces a context dependent type II architecture of the trait p. The role of the major and the minor locus depends on the genotype we consider. This context-dependent type II architecture of a quantitative trait resembles, if combined with stabilizing selection, the phenomenon of complementary deleterious alleles [see, e.g., SAUNDERS (1952)]: in the simplest case the two populations have the complementary two-locus genotypes $L_1L_1l_2l_2$ and $l_1l_1L_2L_2$, where in the hybrids each genotype containing both L_1 and L_2 alleles are lethal or have reduced viability, while the genotypes $l_1 l_1 L_2 l_2$, $L_1 l_1 l_2 l_2$ and $l_1 l_1 l_2 l_2$ are less affected or not at all affected. This context dependent type II architecture is the major difference of the present epistatic model to the epistatic models criticized by BARTON (1989b). In BARTON's model the identity of minor loci and major loci is predetermined by the model and epistasis only defines which gene combination is "coadapted." Due to the multiplicative interaction between the primary gene effects in our model, however, these roles are context dependent.

The key feature of the epistatic model considered here is that a chain of genotypes with high fitness exists that connects the two alternative optimal genotypes. In our notation, these genotypes are $X_1X_0Y_1Y_1$, $X_1X_1Y_1Y_1$, and $X_1X_1Y_0Y_1$ (see Figure 1d). These genotypes differ only by one allele substitution per step and connect the alternative genotypes $X_0X_0Y_1Y_1$ and $X_1X_1Y_0Y_0$. All these genotypes are much more fit than the double heterozygote or the other genotypes, *e.g.*, the $X_0X_0Y_0Y_0$ genotype. Hence, peak shifts can trace this chain of relatively fit genotypes to reach the alternative genetic adaptation. The fitness of the intermediate stages in a peak shift is independent of the fitness of the inter-population hybrids or the backcrosses between the F_1 and one of the parental populations. The existence of such a chain of relatively fit genotypes provides a qualitative explanation of the mathematical results presented in this paper. For instance, in our epistatic model the saddle point in the plane $p_2 = p_3$ is displaced towards the vertex $p_4 = 1$ of the simplex, as opposed to the additive model where the corresponding fixed point occupies a location close to the center of the simplex. The displacement of this fixed point in the epistatic model is due to much stronger selection against the gamete $X_0 Y_0$ as compared to the gamete $X_1 Y_1$. (In the additive model, selection against these two gametes is equally strong.) This can be seen from the lower fitness of the genotype $X_0 X_0 Y_0 Y_0$ relative to the fitness $X_1X_1Y_1Y_1$ (Figure 1d). Hence, selection pushes the population towards higher frequencies p_4 of X_1Y_1 , *i.e.*, towards the vertex $p_4 = 1$ of the simplex. The location of the saddle point within $p_2 = p_3$ is important, since peak shifts occur in its neighborhood (Figure 5). Its displacement in the epistatic case avoids the production of genotypes with very low fitness, such as $X_0X_0Y_0Y_0$, during the peak shift. Metaphorically speaking, the population shifting between peaks follows a path around the adaptive valley.

The presence of context dependent type II architecture is detectable by the genetic techniques used by ORR and COYNE (1989) for the analysis of species hybrids. The prediction is that the epistatic interaction between pairs of loci causing postzygotic isolation leads to an inversion of the relative magnitude of effects of gene substitutions at the different loci in the two parental genotypes. Epistatic models have been used by DOBZHANSKY (1937) and MULLER (1942) to show that there is no necessity for crossing an adaptive valley during the evolution of incompatible genotypes. The model assumes epistatic interaction between two loci A and B which diverge independently in two isolated populations from $A_1A_1B_1B_1$ to $A_2A_2B_1B_1$ and $A_1A_1B_2B_2$, respectively. Reproductive isolation occurs if the alleles A_2 and B_2 are incompatible. In this case no adaptive valley has to be crossed to evolve reproductive isolation. The epistatic model analyzed in this paper is similar to the DOBZHANSKY-MULLER model, as it involves epistatic interactions and does not require the populations to cross an adaptive valley that is as deep as the fitness of the inter-population hybrids. The differences are that, in our model, the two gene substitutions required to get reproductive isolation take place in the same population and that the build-up of reproductive isolation occurs by peak shifts.

Both, the DOBZHANSKY-MULLER model as well as the present model assume that reproductive isolation is primarily due to a few epistatic loci. Not much is known about the genetic basis of reproductive isolation, but there are several examples that demonstrate strong epistasis among a limited number of loci causing reduced hybrid fitness and hybrid break down (WIEBE 1934; SAUNDERS 1952; HERMSEN 1963; OKA 1974; MACNAIR and CHRISTIE 1983; CHRISTIE and MACNAIR 1984; ORR 1987, 1989; ORR and COYNE 1989). Furthermore, it has been demonstrated in five cases that the loci involved act as complementary deleterious/lethal genes with fitness relations qualitatively similar to our case $\beta = -\frac{4}{3}$ (WIEBE 1934; SAUNDERS 1952; CHRISTIE and MACNAIR 1984; ANDERS 1952; CHRISTIE and MACNAIR 1984; ANDERS *et al.* 1984; TEMPLETON *et al.* 1985).

Of particular interest is tumorigenesis in hybrids between Xiphophorus maculatus and Xiphophorus helleri (GORDON 1927; HÄUSSLER 1928; KOSSWIG 1928) [for review see ANDERS et al. (1984)], because its molecular basis is well understood in comparison to other systems. This form of hybrid inviability is caused by the interaction between a dominant oncogen T_{μ} , which is a tyrosine kinase gene, and a regulatory gene R (WITTBRODT *et al.* 1989). Melanoma formation occurs whenever the T_{u} allele is separated by recombination from its regulator gene at the R locus. This system exhibits the same kind of context dependent type II architecture that is characteristic of the model analyzed here. Starting with genotype $T_{\mu}T_{\mu}RR$ a substitution of the R allele has a major effect on viability while a substitution of T_u has at most a minor effect. In contrast, if we start with the complementary genotype that is fully viable, $t_u t_u rr$, a substitution at the T_{ij} locus, replacing t_{ij} by T_{ij} , has a major effect, while a substitution of r by R has only minor effects. Hence, epistasis that results from interactions between regulatory genes and primary genes are a realization of the model analyzed in this report.

Another example for which the molecular basis of a context dependent type II architecture is known, is the abnormal abdomen syndrome (aa) of Drosophila mercatorum (TEMPLETON et al. 1985). Two loci interact in causing the aa syndrome. One is a 5-kb insertion into some copies of the 28S rRNA genes, the second is an allele at a different locus responsible for differential replication of the noninserted copies of the 28S rRNA genes during polytenization. The aa phenotype requires the presence of inserts in the rRNA genes as well as a failure to replicate the noninserted rRNA genes differentially. There are two optimal homozygous genotypes, one with the insertions and the gene for differential replication of the noninserted genes and one with neither the insertion nor the differential replication allele. However, the genotype without insertions and with the differential replication gene is also viable. Here, again, two alternative genotypes are producing imbalanced hybrids (with the *aa* syndrome), but are nevertheless connected by a chain of viable genotypes.

In summary, according to the results presented here, epistatic gene interactions are likely to contribute to the evolution of reproductive isolation. They may lead to a context-dependent type II architecture, in which a chain of viable genotypes connects alternative optimal states, while F_1 hybrids between these optimal genotypes are inviable or lethal. This ultimately allows a much higher rate of accumulation of postzygotic isolation than for other genetic systems. However, the question remains whether at all peak shifts are a reasonable model for the evolution of reproductive isolation. This question has to be raised, since the rate of transitions in the epistatic model is still only of the order of the mutation rate (see RESULTS).

To evaluate the plausibility of the peak shift model as an explanation of speciation we use the data of COYNE and ORR (1989) on the degree of reproductive isolation between closely related species of Drosophila. They have shown that the degree of postzygotic isolation increases approximately linearly with the NEI's genetic distance D. Postzygotic isolation reaches a value of 1 (total isolation) among species pairs with an average D of 1 (COYNE and ORR 1989, Tab. 2). NEI (1987) suggests that in many species D = 1 corresponds on the average to a divergence time of 5,000,000 years, which is also in agreement with molecular, biogeographic and paleontological data for Drosophila (Powell and Desalle 1994). Taking into account the generation time of Drosophila, this easily leads to a number of generations in excess of 107. Hence, in Drosophila, postzygotic isolation evolves during a period of more than 10⁷ generations in allopatry.

The additive model can not be compared to this data since it always predicts optimal phenotypes for the F1 hybrids. Our epistatic model assumes that each peak shift reduces the fitness of the F1 hybrids by about $-s_{\mu}\beta^2$. With our value of $\beta = -\frac{4}{3}$ and a s_2 value of 0.05 (see above for estimates), it takes about 10 peak shifts to reach total postzygotic isolation. Thus, the question is how large the transition probability has to be in order to expect about 10 transitions in 10^7 generations? Obviously, any transition probability of the order of 10^{-6} is sufficient to reach total postzygotic isolation within the time frame observed for Drosophila. Assuming a mutation rate at the relevant loci of about 10^{-5} to 10^{-6} , the predictions of our epistatic simulation model are compatible with the Drosophila data. Even though one should not put too much weight on the exact numerical values, the calculations show that the model is in qualitative agreement with observed rates of speciation.

The reason why low transition rates are compatible with the observed rates of divergence is that a peak shift model has to assume the existence of several pairs of loci able to undergo a peak shift to an alternative optimal genotype, each contributing a fraction of the total reproductive isolation. In our example we have to assume that there are at least 10 independent pairs of interacting loci contributing to total postzygotic isolation. If there are ten pairs of loci, and the transition probability at each locus is of the order of the mutation rate, the total probability to get any transition is approximately ten times as large. Hence, due to the fact that a peak shift model has to assume the existence of many genes contributing to postzygotic isolation, the probability of any transition taking place is higher than the probability for each locus.

The scenario analyzed above is one where two stable, moderately large populations exist for a long time in allopatry. The present model does not predict a higher rate of speciation in the case of bottle necks or founder events. The reason is that the amount of polymorphisms existing in mutation selection equilibrium is not much higher in our epistatic model than in the additive model (A. WAGNER, unpublished results). Hence, the likelihood that a founder population is shifting to a different peak is roughly the same in the additive and the epistatic model.

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APPENDIX

In the sequel, we use an approach based on Ljapunov functions (*cf.* HOFBAUER and SIGMUND 1988) in order to qualitatively determine the global dynamical behavior of (5) in the epistatic case ($\beta = -\frac{4}{3}$), using the fitness matrix M₂. The specific Ljapunov functions used throughout have been first introduced by BÜRGER (1983a-c) and used by BÜRGER (1989) to carry out the global analysis in the linear case.

Using the matrix of genotypic values M_2 shown in Figure 1d, we rescale, purely for technical convenience, the selection parameter s such that s' := 9s/16. The qualitative results presented below do not depend on the magnitude of s. The rescaling leads to a convenient algebraic form for the marginal mean fitnesses m_i of gamete p_i , in which the terms m_{23} , m_{32} , m_{14} and m_{41} are equal to 1 - s'. The marginal mean fitness values become

$$m_1^{(2)} = 1 - s' \left(\frac{81}{4} p_1 + \frac{81}{16} (p_2 + p_3) + p_4 \right)$$
 (A1a)

$$m_2^{(2)} = 1 - s' \left(\frac{81}{16} p_1 + p_3 + \frac{1}{16} p_4 \right)$$
 (A1b)

$$m_3^{(2)} = 1 - s' \left(\frac{81}{16} p_1 + p_2 + \frac{1}{16} p_4 \right)$$
 (A1c)

$$m_4^{(2)} = 1 - s' \left(p_1 + \frac{1}{16} \left(p_2 + p_3 \right) + \frac{1}{4} p_4 \right),$$
 (A1d)

and the mean fitness of the population

$$\bar{m}^{(2)} = 1 - s' \left[\frac{81}{4} p_1^2 + \frac{1}{4} p_4^2 + \left(\frac{81}{8} p_1 + \frac{1}{8} p_4 \right) (p_2 + p_3) + 2p_1 p_4 + 2p_2 p_3 \right].$$
(A2)

In the first place, we observe by inspection of (A1), that no interior equilibrium point $\hat{\vec{p}}$ can occur if r = 0 and $\mu = 0$, since there is no $\hat{\vec{p}} \in intS$, such that the necessary and sufficient condition $m_k^{(2)}(\hat{\vec{p}}) = m_l^{(2)}(\hat{\vec{p}}), \forall k, l \in$ $\{1, 2, 3, 4\}$ for the existence of an interior equilibrium point is met. An analogous argument applies to the boundary faces of S.

The flow along the edges of S behaves as follows: Along the edges $p_1 + p_2 = 1$ and $p_2 + p_4 = 1$ it points towards the vertex $p_2 = 1$, along $p_1 + p_3 = 1$ and $p_4 + p_3 = 1$ $p_3 = 1$ it points towards $p_3 = 1$ and along $p_1 + p_4 = 1$ it points towards $p_4 = 1$. An unstable equilibrium exists at $p_3 + p_2 = 1$ with $p_2 = p_3 = \frac{1}{2}$. At this edge the flow points towards $p_3 = 1$ for $p_3 > \frac{1}{2}$ and into the opposite direction for $p_3 < \frac{1}{2}$. This equilibrium vanishes as soon as r > 0. Furthermore, one can exclude the occurrence of a symmetric interior equilibrium point even if $r \neq 0$, *i.e.*, an equilibrium where $\hat{p}_1 = \hat{p}_4$ and $\hat{p}_2 = \hat{p}_3$ holds. This is due to the fact that for all $\hat{p} \in \text{intS}$, $m_1^{(2)} \neq m_4^{(2)}$ holds, so that there is no $\vec{p} \in \text{int}S$ with $\vec{p}_1 = p_1(m_1 - \bar{m}) - rD$ $= p_4(m_4 - \bar{m}) - rD = p_4$, this also representing a fundamental difference to the linear case ($\beta = 0$) analyzed in the main text. Since $m_2^{(2)} = m_3^{(2)}$ iff $p_2 = p_3$, the plane

 $p_2 = p_3$ represents an invariant manifold that divides the simplex into two disjoint domains of attraction. We focus our attention now on orbits starting in the interior of $p_2 > p_3$ and show that every orbit converges to $p_2 = 1$. Symmetric arguments hold for $p_2 < p_3$. Orbits starting at a point \vec{p}^0 , where $p_2^0 > p_3^0$ holds, cannot reach the domain of S where $p_2 < p_3$ and vice versa.

Let us assume that there exists a stationary equilibrium $\vec{p} \in \text{int}S$ for some initial condition $\vec{p}^0 \in \text{int}S$. First we consider the function $Z = p_2 p_3 / p_1 p_4$, observing that $D = p_1 p_4 (1 - Z)$. Given Z, it is easy to show that

$$\dot{Z} = Z(m_2^{(2)} + m_3^{(2)} - m_1^{(2)} - m_4^{(2)}) + \frac{r(1-Z)}{p_1 p_4} T(p)$$
(A3)

with

$$m_2^{(2)} + m_3^{(2)} - m_1^{(2)} - m_4^{(2)}$$

= $s' \left(\frac{89}{8} p_1 + \frac{33}{8} (p_2 + p_3) + \frac{9}{8} p_4 \right) > 0$

and

$$T(p) = p_1 p_2 p_3 + p_1 p_2 p_4 + p_1 p_3 p_4 + p_2 p_3 p_4 > 0$$

By the above relations we conclude that, starting in $Z \le 1$, *i.e.*, D > 0, $\dot{Z} > 0$ holds and for orbits starting anywhere in int S Z > 1 will eventually hold, so that D < 0 holds if the trajectory remains in int S. Next we show that if D < 0, then $d/dt(p_2/p_3 - 1)^2 > 0$ holds. Indeed, if D < 0

$$\frac{d}{dt} \left(\frac{p_2}{p_3} - 1\right)^2 = 2\left(\frac{p_2}{p_3} - 1\right) \frac{d}{dt} \left(\frac{p_2}{p_3}\right)$$
$$= 2\left(\frac{p_2}{p_3} - 1\right) \left[\frac{p_2 p_3 - p_2 p_3}{p_3^2}\right] \qquad (A4)$$
$$= 2\left(\frac{p_2}{p_3} - 1\right)^2 \left(s' p_2 - \frac{nD}{p_3}\right) > 0$$

holds. Thus, provided there is negative linkage disequilibrium, the distance of each orbit to the plane $p_2 = p_3$ increases. But this is in contradiction to our assumption of the existence of an internal equilibrium point, since at any such point \hat{p} , D < 0 must hold, which in turn implies that $d/dt(p_2/p_3 - 1)^2|_{\hat{p}} > 0$. Therefore \hat{p} can not be an equilibrium point and any orbit starting in $p_2 > p_3$ approaches one of the vertex equilibria. Inspection of the Jacobian matrix $A = (a_{k1}) = \partial p_k/\partial p_l$ of (5) shows that its eigenvalues evaluated at the vertex equilibrium $p_4 = 1$ are

$$\lambda_{1} = -\frac{3's}{4} - r < 0$$

$$\lambda_{2} = \lambda_{3} = \frac{3's}{16} > 0$$
(A5)
$$\lambda_{4} = \frac{s'}{4} - 1 < 0.$$

 λ_4 is irrelevant here, since it corresponds to trajectories outside the simplex S. The signs of λ_1 , λ_2 and λ_3 imply that there exists only a one-dimensional stable manifold for the vertex equilibrium $p_4 = 1$. It is therefore not locally stable. That $p_1 = 1$ can also not be a locally stable equilibrium point can be seen by analyzing the behavior of (5a) with m_1 specified by (A1a) and \bar{m} specified by (A2) in a sufficiently small neighborhood of $p_1 = 1$. In such a neighborhood $p_i^2 \approx 0$, $i \in \{2, 3, 4\}$ and by using $p_1 = 1 - p_2 - p_3 - p_4$ one observes that $p_1^2 \approx 1 - 2p_2 - 2p_3 - 2p_4$ holds. Thus, (5a) becomes

$$p_1 \approx -s' \frac{243}{16}(p_2 + p_3) - \left(\frac{77}{4}s' + r\right)p_4 < 0,$$
 (A6)

which shows that in this neighborhood p_1 is decreasing. Therefore we can conclude that starting in $\{\vec{p} \in S | p20 > p30\}$ trajectories will converge to $p_2 = 1$. Completely analogous arguments show that for initial conditions in $\{\vec{p} \in S | p20 < p30\}$ all orbits will converge to $p_3 = 1$.

The case of $p_2 = p_3$ is of less importance for the equilibrium behavior of the system, since it is only an unstable set of measure zero within the simplex and small stochastic perturbations would immediately lead the dynamics away from it and to one of the equilibrium points $p_2 = 1$ or $p_3 = 1$. Within this plane, however, there exists a further equilibrium point, which can be explicitly calculated for r = 0 and is given by $\hat{p}_1 = 0$, $\hat{p}_2 = \hat{p}_3 = \frac{3}{20}$, and $\hat{p}_4 = \frac{7}{10}$. For r > 0 no analytical solution for the equilibrium point within $p_2 = p_3$ was obtained. However, the existence of an internal fixed point for r > 0 follows from a stability analysis of $p_4 = 1$. For examining the stability of $p_4 = 1$ within the plane $p_2 = p_3$ the differential equation describing the dynamics of p_4 is substituted by $p := p_2 = p_3$ and in an approach similar to (A6) one arrives at

$$\dot{p}_4 \approx p_1 \left(\frac{3s'}{4} - r\right) - p \frac{3s'}{8}$$

If r > 3s'/4, p_4 will be negative and p_4 will therefore be unstable. Since there is no other equilibrium point on the boundary of the plane, there has to be an equilibrium point in the interior of $p_2 = p_3$. No analytical results regarding stability of this equilibrium point within $p_2 = p_3$ have been obtained, although we have calculated its approximate coordinates numerically for specific values of r and s, and numerical integration of the system (5) within this manifold indicated its stability (results not shown).