ACADEMIC
PRESS

Available online at www.sciencedirect.com
SCIENCE DIRECT®

Theoretical Population Biology 64 (2003) 101–117

Theoretical Population Biology

http://www.elsevier.com/locate/ytpbi

The two-locus model of Gaussian stabilizing selection

Martin Willensdorfer and Reinhard Bürger*

Department of Mathematics, University of Vienna, Vienna, Austria

Received 27 June 2002

Abstract

We study the equilibrium structure of a well-known two-locus model in which two diallelic loci contribute additively to a quantitative trait that is under Gaussian stabilizing selection. The population is assumed to be infinitely large, randomly mating, and having discrete generations. The two loci may have arbitrary effects on the trait, the strength of selection and the recombination rate may also be arbitrary. We find that 16 different equilibrium patterns exist, having up to 11 equilibria; up to seven interior equilibria may coexist, and up to four interior equilibria, three in negative and one in positive linkage disequilibrium, may be simultaneously stable. Also, two monomorphic and two fully polymorphic equilibria may be simultaneously stable. Therefore, the result of evolution may be highly sensitive to perturbations in the initial conditions or in the underlying genetic parameters. For the special case of equal effects, global stability results are proved. In the general case, we rely in part on numerical computations. The results are compared with previous analyses of the special case of extremely strong selection, of an approximate model that assumes linkage equilibrium, and of the much simpler quadratic optimum model.

Keywords: Quantitative genetics; Stabilizing selection; Two-locus model; Recombination; Linkage disequilibrium; Symmetric viability model; Stable polymorphism

1. Introduction

Understanding the nature of quantitative genetic variation and the forces by which it is maintained is one of the most important goals in evolutionary genetics. Through the abundance of molecular markers, experimental approaches to identify quantitative trait loci, and thus to elucidate the genetic basis of quantitative traits, have been increasingly successful. Nevertheless, it is yet unknown if typically many genes, each with individually small effect (the classical view), or few genes with large effect, possibly assisted by a larger number of genes of small effect, are responsible for the observed genetic variation. Experimental evidence indicates that this may depend on the trait and, perhaps, even on the species, but identifying genes of small effect still poses enormous difficulties. However, even knowledge of all the genes and their interactions in producing the phenotype is not sufficient to understand how genetic variation is maintained. Understanding these mechanisms would be important not only for many topics in evolutionary biology, but also for the improvement of economically important traits in animals and plants, and maybe even for human and medical genetics (for recent reviews, see Mackay, 2001; Barton and Keightley, 2002).

A central paradox is that many quantitative characters show relatively high levels of genetic variation although they are subject to various forms of selection, such as stabilizing, directional, or disruptive selection. The first two are generally believed to deplete genetic variation, yet they may be the most frequent ones (Endler, 1986). In particular, stabilizing selection, i.e., selection toward an intermediate phenotypic optimum, is likely to be very common, also on evolutionary time scales (Charlesworth et al., 1982). Empirical evidence, however, is not yet conclusive (Kingsolver et al., 2001). Almost all theoretical studies of stabilizing selection have employed either a quadratic or a Gaussian fitness function. The first choice requires sufficiently weak selection because fitnesses have to be nonnegative, but it often simplifies the analysis.

Many different mechanisms have been suggested in the past 50 years by which genetic variation could be

---

*Corresponding author. Institut für Mathematik, Universität Wien, Strudlhofgasse 4, A-1090 Wien, Austria. Fax: +43-1-4277-506-50.
E-mail address: reinhard.buerger@univie.ac.at (R. Bürger).

0040-5809/03/$ - see front matter © 2003 Elsevier Science (USA). All rights reserved.
doi:10.1016/S0040-5809(03)00049-2

maintained despite selection. Among these are mutation–selection balance, overdominance, genotype–environment interaction, frequency-dependent selection, temporally or spatially varying selection, or indirect mechanisms based on pleiotropy. All of them have their appeal in special situations but, apart from mutation–selection balance maybe combined with pleiotropy, none seems to be a convincing candidate for explaining the ubiquity of heritable variation. Unfortunately, given our current empirical knowledge about the genetics of quantitative traits, theoretical models predict that also mutation–selection balance can explain only a relatively small fraction of the variability observed (for comprehensive reviews, see Barton and Turelli, 1989; Falconer and Mackay, 1995; Bürger, 2000; Barton and Keightley, 2002).

The view that stabilizing selection depletes genetic variation was established by analyses based on the study of a single locus (Fisher, 1930; Robertson, 1956; Bulmer, 1971; Kimura, 1981; Nagylaki, 1984) and by a two-locus study of Wright (1935). The latter was extended by Hastings (1987), who proved that for loci of equal effects, arbitrary recombination rates, and arbitrary symmetric fitness functions with optimum at the value of the double heterozygote, both loci are eventually fixed. Also various models of mutation–selection balance, in particular with a continuum of possible alleles per locus or with many loci of small effect, indicate that without mutation no genetic variation is maintained (Latter, 1960; Bulmer, 1972; Lande, 1975; Turelli, 1984; Bürger, 1986, 2000).

By contrast, some early numerical studies of models in which only two or a few loci contribute to a trait under quadratic stabilizing selection revealed that multilocus polymorphisms could be maintained if there is partial dominance (Kojima, 1959; Lewontin, 1964; Singh and Lewontin, 1966), and Gale and Kearsey (1968), and Kearsey and Gale (1968) found stable two-locus polymorphisms in a completely additive model. The latter authors, however, used a triangular fitness function. Detailed analytical studies of a diallelic two-locus model of stabilizing selection were performed by Gavrilets and Hastings (1993, 1994b) and Bürger and Gimelfarb (1999) by assuming quadratic stabilizing selection with the optimum at the double heterozygote, thus inducing certain symmetries, but arbitrary allelic effects and recombination rate. It was proved that for sufficiently tight linkage both loci can be maintained polymorphic and, depending on the recombination rate, one or two interior polymorphic equilibria, exhibiting negative linkage disequilibrium, can be stable if the effects of the loci are unequal.

For the most natural choice of a fitness function, the Gaussian, only few results for specific cases have been derived. For instance, Nagylaki (1989) showed that if recombination is strong enough to ignore linkage disequilibrium, then five convergence patterns can occur, including global stability of the central symmetric equilibrium. Gavrilets and Hastings (1993, 1994b) found that under strong selection a stable interior equilibrium with positive linkage disequilibrium can exist, and Gimelfarb (1996) showed that two stable interior equilibria can exist, one in positive, the other in negative linkage disequilibrium. It is the purpose of this article to fully explore the equilibrium structure of the two-locus two-allele model of Gaussian stabilizing selection under the assumption of additive gene action and symmetry of the fitness function with respect to the double heterozygous phenotype. Effects of the loci, hence strength of selection, and recombination rate are arbitrary.

2. The model

We consider a quantitative trait that is controlled additively (no dominance or epistasis) by two diallelic loci. The alleles at the first locus are labeled A_1 and A_2, those at the second, B_1 and B_2. Let their contributions to the genotypic value G of the trait be $-\frac{1}{2}\gamma_1$, $\frac{1}{2}\gamma_1$, $-\frac{1}{2}\gamma_2$, and $\frac{1}{2}\gamma_2$. Because the alleles determine the genotypic value purely additively, the contributions of the gametes A_1B_1, A_1B_2, A_2B_1, A_2B_2 are $-\frac{1}{2}(\gamma_1+\gamma_2)$, $-\frac{1}{2}(\gamma_1-\gamma_2)$, $\frac{1}{2}(\gamma_1-\gamma_2)$, $\frac{1}{2}(\gamma_1+\gamma_2)$, respectively, and the resulting genotypic values are given by

$$\begin{array}{c c} & \begin{array}{ccc} B_1B_1 & B_1B_2 & B_2B_2 \end{array} \\ \begin{array}{c} A_1A_1 \\ A_1A_2 \\ A_2A_2 \end{array} & \begin{pmatrix} -\gamma_1-\gamma_2 & -\gamma_1 & -\gamma_1+\gamma_2 \\ -\gamma_2 & 0 & \gamma_2 \\ \gamma_1-\gamma_2 & \gamma_1 & \gamma_1+\gamma_2 \end{pmatrix} \end{array}. \tag{2.1}$$

For definiteness, we assume $\gamma_1 \geqslant \gamma_2 > 0$ and refer to these loci as major and minor, respectively. We call γ_1 and γ_2 the effects of the loci.

The trait is assumed to be under stabilizing selection toward an intermediate phenotypic optimum. The relative fitness of individuals with genotypic value G is designated as $W(G)$. In this paper, we are mainly interested in so-called Gaussian stabilizing selection, i.e.,

$$W(G) = \exp(-sG^2), \tag{2.2}$$

but we shall also discuss the relation to models that are based on other fitness functions. In particular, it is assumed that the fitness function has its optimum at zero, the genotypic value of the double heterozygote. This simplification makes the model analytically tractable and has been used in most previous analyses (for a review, see Bürger, 2000).

Combining (2.1) and (2.2), the fitnesses of all genotypes can be calculated and represented as

$$\begin{array}{cc} & \begin{array}{ccc} B_1B_1 & B_1B_2 & B_2B_2 \end{array} \\ \begin{array}{c} A_1A_1 \\ A_1A_2 \\ A_2A_2 \end{array} & \begin{pmatrix} 1-d & 1-b & 1-a \\ 1-c & 1 & 1-c \\ 1-a & 1-b & 1-d \end{pmatrix} \end{array}, \tag{2.3}$$

where $a=1-W(\gamma_1-\gamma_2)$, $b=1-W(\gamma_1)$, $c=1-W(\gamma_2)$, and $d=1-W(\gamma_1+\gamma_2)$. Therefore, the present model is a special case of the symmetric viability model that has received much attention in population genetics (e.g., Bodmer and Felsenstein, 1967; Karlin and Feldman, 1970; Christiansen, 1999; Bürger, 2000). Defining

$$\alpha_i = W(\gamma_i) = \exp(-s\gamma_i^2), \quad i = 1,2 \tag{2.4}$$

and

$$\alpha_{12} = \exp(-2s\gamma_1\gamma_2) = \exp(-2\sqrt{\ln\alpha_1 \ln\alpha_2}), \tag{2.5}$$

we obtain

$$a = 1-\alpha_1\alpha_2/\alpha_{12}, \quad b = 1-\alpha_1, \quad c = 1-\alpha_2, \quad d = 1-\alpha_1\alpha_2\alpha_{12}. \tag{2.6}$$

Obviously, α_1 and α_2 are sufficient to describe the fitnesses. They satisfy $0<\alpha_1^2 \leqslant \alpha_{12} \leqslant \alpha_2^2 < 1$. It may be noted that without loss of generality the selection coefficient s in (2.2) can be set to unity. The parameters a, b, c, d satisfy the relations

$$0 \leqslant a, c \leqslant b < d \leqslant 1, \quad c > 0, \quad \text{and} \quad b > a. \tag{2.7}$$

We label the gametes A_1B_1, A_1B_2, A_2B_1, A_2B_2 by $i = 1,2,3,4$, and denote their relative frequencies measured among zygotes by x_i. We assume random mating, hence the zygotes are in Hardy–Weinberg proportions and the evolutionary dynamics can be described by the gamete frequencies. If recombination (at rate r) occurs after selection, the gamete frequencies in the next generation are given by the standard system of recursion relations

$$\overline{W}x_i' = x_iW_i - \eta_i rD, \quad i = 1,\dots,4, \tag{2.8}$$

where $\eta_1 = \eta_4 = 1$, $\eta_2 = \eta_3 = -1$, $D = x_1x_4 - x_2x_3$ measures linkage disequilibrium, W_i is the marginal fitness of gamete i, and $\overline{W}$ is the mean fitness. The marginal fitnesses can be written as

$$\begin{aligned} W_1 &= 1 - dx_1 - bx_2 - cx_3, \\ W_2 &= 1 - bx_1 - ax_2 - cx_4, \\ W_3 &= 1 - cx_1 - ax_3 - bx_4, \\ W_4 &= 1 - cx_2 - bx_3 - dx_4, \end{aligned}$$

and the mean fitness is

$$\begin{aligned} \overline{W} = 1 &- d(x_1^2 + x_4^2) - a(x_2^2 + x_3^2) \\ &- 2b(x_1x_2 + x_3x_4) - 2c(x_1x_3 + x_2x_4) \end{aligned}$$

(e.g., Bürger, 2000, pp. 46–51).

The three parameters $\alpha_1 = W(\gamma_1)$, $\alpha_2 = W(\gamma_2)$, and r fully determine the model. Throughout, we assume $0 < r \leqslant \frac{1}{2}$, i.e., we exclude complete linkage. At several occasions, it will be useful to employ the symmetric coordinates

$$x = x_1 - x_4, \quad y = x_2 - x_3, \quad z = x_1 + x_4 - x_2 - x_3 \tag{2.9}$$

instead of the gamete frequencies.

In the following three sections, our aim is to find the possible equilibrium patterns and to investigate how their existence depends on the parameters (α_1, α_2, r). We start with some general analytical results, then derive global stability results for the special case of loci of equal effects and present a comprehensive numerical study of the general case in Section 5.

3. General results

Because the present model is a special case of the symmetric viability model, only the following four types of equilibria can exist (Karlin and Feldman, 1970).

1. Four corner, or monomorphic, equilibria (denoted by $\mathscr{C}_i$, $i = 1,2,3,4$) with only one gamete present (i.e., $x_i = 1$ at $\mathscr{C}_i$).
2. Four equilibria at the edges of the simplex with one of the loci polymorphic (denoted by $\mathscr{E}_i$, $i = 1,2,3,4$).
3. Up to three symmetric interior equilibria (denoted by $\mathscr{S}_i$, $i = 1,2,3$) characterized by the conditions $x_1 = x_4$ and $x_2 = x_3$;
4. Up to four unsymmetric interior equilibria, i.e., $x_1 \neq x_4$ or $x_2 \neq x_3$ (denoted by $\mathscr{U}_i$, $i = 1,2,3,4$).

Obviously, the monomorphic equilibria exist always. Also one symmetric equilibrium ($\mathscr{S}_1$) exists always. It satisfies $D<0$. In the present model, at most two edge equilibria can exist. They, as well as the interior equilibria $\mathscr{S}_2$, $\mathscr{S}_3$, and $\mathscr{U}_i$ $(i = 1,2,3,4)$ exist only in certain regions of the parameter space (see below). Since we assume $r>0$, no boundary equilibria involving exactly three gametes can exist.

We begin by determining the stability conditions of the corner (monomorphic) equilibria in the general case. They yield simple necessary and sufficient conditions under which at least one locus is maintained polymorphic at equilibrium. Then some general results about the edge and the symmetric equilibria are derived. Computations are most efficiently performed by using the symmetric coordinates (2.9).

3.1. Stability of monomorphic equilibria

Linearization of system (2.8) at the corner equilibria $\mathscr{C}_i$ is straightforward. Asymptotic stability, i.e., convergence from a sufficiently small neighborhood, is guaranteed if all eigenvalues are less than 1 in modulus. The eigenvalues at $\mathscr{C}_2$ and $\mathscr{C}_3$, the equilibria at which one of the gametes with smallest effect is present (A_1B_2, A_2B_1), are $\lambda_1 = \frac{1-r}{1-a}$, $\lambda_2 = \frac{1-c}{1-a}$, and $\lambda_3 = \frac{1-b}{1-a}$

(cf. Bodmer and Felsenstein, 1967). Because $a<b$ holds by our general assumptions (2.7), we have always $|\lambda_3|<1$. The other two eigenvalues are less than 1 (in modulus) if and only if

$$a<r \quad \text{and} \quad a<c. \tag{3.1}$$

Therefore, under Gaussian selection the corner equilibria $\mathscr{C}_2$ and $\mathscr{C}_3$ are asymptotically stable if and only if

$$1-\alpha_1\alpha_2\exp(2\sqrt{\ln\alpha_1\ln\alpha_2})\leqslant r \tag{3.2a}$$

and

$$\alpha_2^4\leqslant\alpha_1 \tag{3.2b}$$

are fulfilled (that equality can be admitted in both cases is shown by a simple additional argument). Condition (3.2a) is satisfied if selection on the double homozygous genotypes A_1B_2/A_1B_2 and A_2B_1/A_2B_1 is weak relative to recombination. If the effects of the loci are very similar, then a is close to zero, and (3.2a) is valid for all but very low recombination rates. The second condition, (3.2b), holds if and only if

$$\gamma_1\leqslant 2\gamma_2, \tag{3.3}$$

i.e., if the effect of the major locus is less than twice as large as that of the minor locus.

The equilibria $\mathscr{C}_1$ and $\mathscr{C}_4$ are always unstable; two eigenvalues are always $\geqslant 1$ and the third is $\geqslant 1$ if $d\geqslant r$.

3.2. *The edge equilibria*

It is straightforward to calculate the coordinates of the possible equilibria with one locus monomorphic and the other polymorphic. Because our parameters satisfy $b>a$ (2.7), only the equilibria $\mathscr{E}_1$ and $\mathscr{E}_2$ can exist. They are given by

$$\mathscr{E}_1: x_1=x_3=0, \quad x_2=\frac{1}{1+\frac{a-c}{d-c}}, \quad x_4=1-x_2, \tag{3.4a}$$

$$\mathscr{E}_2: x_2=x_4=0, \quad x_1=\frac{1}{1+\frac{d-c}{a-c}}, \quad x_3=1-x_1. \tag{3.4b}$$

Indeed, they exist if and only if $a>c$, which is equivalent to $\alpha_1<\alpha_2^4$ and, hence, to $\gamma_1>2\gamma_2$. Therefore, existence of the edge equilibria implies instability of the monomorphic equilibria (but not vice versa).

The eigenvalues of the edge equilibria $\mathscr{E}_1$ and $\mathscr{E}_2$ are

$$\lambda_1=\frac{a+d-2c+ac+cd-2ad}{a+d-2c+c^2-ad} =\frac{\alpha_1(1-\alpha_1^2)+\alpha_1(\alpha_1-\alpha_{12})^2}{(1-\alpha_1^2)\alpha_2} \tag{3.5}$$

and

$$\lambda_\pm=\frac{(a+d-2c)(2-b-r)\pm\sqrt{(d-a)^2(b-r)^2+4r^2(d-c)(a-c)}}{2(a+d-2c+c^2-ad)}. \tag{3.6}$$

It follows easily that for Gaussian stabilizing selection, $0<\lambda_1<1$ holds always. The stability conditions ensuing from (3.6) are not simple. However, because $c<a\leqslant b\leqslant d$ holds whenever the boundary equilibria exist, $c>r$ implies that the numerator of λ_+ is greater than $(a+d-2c)(2-b-c)+(d-a)(b-c)$, whence we obtain

$$\lambda_+>1+\frac{(d-b)(a-c)}{a+d-2c+c^2-ad}\geqslant 1. \tag{3.7}$$

Therefore, a simple sufficient condition for instability is $r<c=1-\alpha_2$. Hence, the edge equilibria are never stable if linkage is sufficiently tight. Put otherwise, if selection is sufficiently strong, e.g., such that $\alpha_1^{1/4}<\alpha_2<\frac{1}{2}$, then the edge equilibria are unstable for any recombination rate.

Combining these results with those for the monomorphic equilibria, we can conclude that no boundary equilibrium can be stable if

$$r<\min(a,c)=\min(1-\alpha_1\alpha_2/\alpha_{12},1-\alpha_2). \tag{3.8}$$

In Appendix A it is proved that if the single-locus polymorphisms $\mathscr{E}_1$ and $\mathscr{E}_2$ are stable, then only one symmetric equilibrium ($\mathscr{S}_1$) can exist.

3.3. *Symmetric equilibria*

The symmetric equilibria are best expressed in terms of the symmetric coordinates because they satisfy $x=y=0$. The equilibrium coordinates z are the solutions of the cubic equation

$$(a-2(b+c)+d)z^3+(d-a)z^2 - (a-2(b+c)+d+8r)z+a-d=0. \tag{3.9}$$

If $b+c>d$ and r is sufficiently small, then there are three valid solutions ($-1\leqslant z\leqslant 1$); otherwise, there is exactly one (Karlin and Feldman, 1970). In the present model, the condition $b+c>d$ is equivalent to $W(0)+W(\gamma_1+\gamma_2)>W(\gamma_1)+W(\gamma_2)$, i.e., to

$$b+c-d=1+\alpha_1\alpha_2\alpha_{12}-\alpha_1-\alpha_2>0. \tag{3.10}$$

Trivially, this condition is always satisfied if $\alpha_1+\alpha_2<1$. Actually, this is a quite accurate estimate because for given $\alpha_1+\alpha_2$ the left-hand side of (3.10) achieves its maximum if $\alpha_1=\alpha_2=\alpha$. Then (3.10) simplifies to

$$1-2\alpha+\alpha^4=(1-\alpha)(1-\alpha-\alpha^2-\alpha^3)>0, \tag{3.11}$$

which is satisfied if $\alpha<\alpha_c\approx 0.544$. Therefore, (3.10) can never be valid if

$$\alpha_1+\alpha_2>2\alpha_c\approx 1.088. \tag{3.12}$$

Hence, (3.12) is a sufficient condition for the existence of a single symmetric equilibrium for all $r>0$, whereas $\alpha_1+\alpha_2<1$ implies the existence of three symmetric equilibria for small recombination rates. In terms of locus effects, (3.12) is fulfilled if $\gamma_1+\gamma_2<1.561$. No lower bound on $\gamma_1+\gamma_2$ exists that guarantees validity of (3.10). For various ratios of α_1/α_2, Fig. 2 displays the critical recombination rate below which three symmetric equilibria exist.

The symmetric equilibrium that always exists satisfies $0 < x_1 < \frac{1}{4}$ $(-1 < z < 0)$, hence exhibits negative linkage disequilibrium. It is denoted by $\mathscr{S}_1$. The other two equilibria, provided they exist, have larger x_1 values and are denoted by $\mathscr{S}_2$ and $\mathscr{S}_3$, where $\mathscr{S}_3$ is the equilibrium with the largest value of x_1 (and D). Both satisfy $D > 0$, but $\mathscr{S}_2$ is always unstable. In Appendix B it is proved that $\mathscr{S}_3$ is asymptotically stable whenever it exists. If $\mathscr{S}_3$ exists, then the single-locus polymorphisms $\mathscr{E}_i$ cannot be stable (Appendix A).

3.4. *Unsymmetric equilibria*

Their existence conditions and coordinates can be determined by first solving a quadratic equation in z which, however, is unwieldy. This is equation (A.7) of Karlin and Feldman (1970). From (A.4) and (2.8a) of the same paper, the two other coordinates x and y can then be determined. It has to be checked if this yields a solution within the simplex. These equilibria and their stability conditions are calculated only numerically.

4. Equilibria and dynamics for loci of equal effects

For loci of equal effects, the parameters of the symmetric viability model satisfy $a = 0$ and $b = c$. In this case, Gavrilets and Hastings (1994b) proved the following result:

> If $2b \leqslant d$, then the only possible stable equilibria are the monomorphic equilibria $\mathscr{C}_2$ *and* $\mathscr{C}_3$. If $2b > d$ and selection is sufficiently strong relative to linkage, then in addition to these fixation equilibria which remain asymptotically stable, the equilibrium $\mathscr{S}_3$ exists and is asymptotically stable. The symmetric equilibrium $\mathscr{S}_1$ exists always and is unstable. Also $\mathscr{S}_2$ is unstable whenever it exists.

In Appendix C, the following stronger result is proved for loci of equal effects and a large class of fitness functions that describe stabilizing selection and includes the Gaussian:

> All trajectories starting in the region $\{D \leqslant 0\} \cup \{z \leqslant \frac{1}{3}\}$ converge to $\mathscr{C}_2$ if initially $x_2 > x_3$, and to $\mathscr{C}_3$ if $x_3 > x_2$. If $\mathscr{S}_3$ does not exist, then all trajectories initially satisfying $x_2 > x_3$ converge to $\mathscr{C}_2$, those with $x_3 > x_2$ to $\mathscr{C}_3$. Trajectories starting in the plane $x_2 = x_3$ may converge to $\mathscr{S}_3$ or to $\mathscr{S}_1$. If $\mathscr{S}_3$ exists, a trajectory converging neither to $\mathscr{C}_2$ nor to $\mathscr{C}_3$ converges to $\mathscr{S}_3$ unless it starts in the plane $x_2 = x_3$, when it may converge to $\mathscr{S}_1$.

For the Gaussian fitness function, we can derive more detailed results about the existence and, hence, stability of the symmetric equilibrium $\mathscr{S}_3$. Because for equal effects, $\alpha_1 = \alpha_2 = \alpha$ $(0 < \alpha < 1)$ and $\alpha_{12} = \alpha^2$ holds, we have $a = 0$, $b = c = 1 - \alpha$, $d = 1 - \alpha^4$. Therefore, the equilibrium condition (3.9) for the symmetric equilibria becomes

$$g(x_1) = 2(3 - 4\alpha + \alpha^4)x_1^3 - (5 - 6\alpha + \alpha^4)x_1^2 + (1 + r - \alpha)x_1 - \tfrac{1}{4}r = 0, \qquad (4.1)$$

where $0 \leqslant x_1 = (1 + z)/4 \leqslant \frac{1}{2}$. As already noted below (3.11), three symmetric equilibria may exist if and only if $\alpha < \alpha_c \approx 0.544$. Solving $g(x_1) = 0$ with respect to r produces

$$r = r(x_1, \alpha) = \frac{2(3 - 4\alpha + \alpha^4)x_1^3 - (5 - 6\alpha + \alpha^4)x_1^2 + (1 - \alpha)x_1}{\frac{1}{4} - x_1}. \qquad (4.2)$$

Fig. 1 displays the graph of (4.2) for different values of α and, thus, shows the relation between r and the position of the symmetric equilibria, which is uniquely determined by x_1. For weak selection (e.g., the dotted line) only one symmetric equilibrium ($\mathscr{S}_1$) exists. Note that the equilibria $\mathscr{S}_2$ and $\mathscr{S}_3$ exhibit positive linkage disequilibrium because they obviously satisfy $x_1 > \frac{1}{3}$. From Appendix B, Eq. (B.2), we can even infer that the x_1 coordinates of $\mathscr{S}_2$ and S_3 both satisfy $x_1 > (3 - \alpha - \alpha^2 - \alpha^3)^{-1}$ for all $r > 0$.

By determining the local maximum of the function $r(., \alpha)$, the critical recombination rate $r_c = r_c(\alpha)$ can be computed below which three symmetric equilibria exist. The expressions are complicated, therefore the function r_c is displayed in Fig. 2 together with other such critical recombinations rates for various ratios of α_1/α_2. The domain of attraction of $\mathscr{S}_3$ is quite small (results not

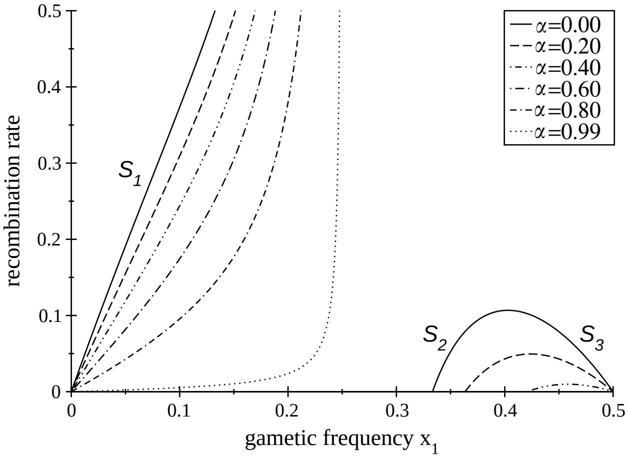

Fig. 1. Position of the symmetric equilibria for loci of equal effects. For the six indicated values of α, the lines display the function $r(x_1)$ given by (4.2), i.e., position and corresponding value r of the symmetric equilibria.

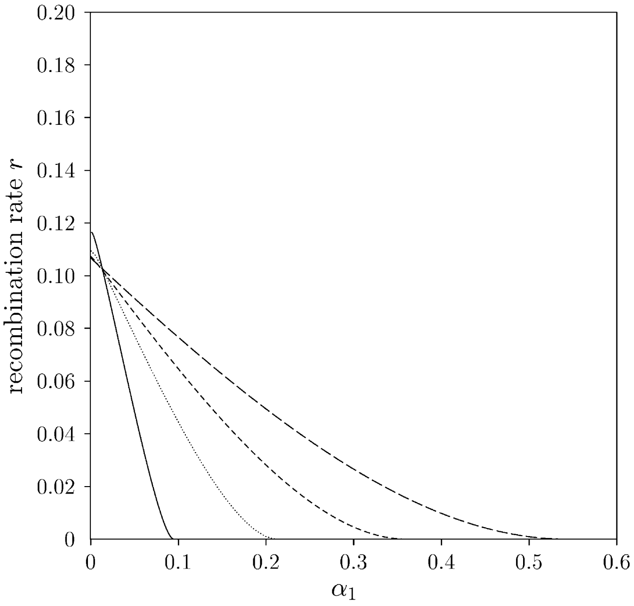

Fig. 2. Regions of existence of three symmetric equilibria. Three symmetric equilibria exist below the displayed lines. The long-dashed line is for $\alpha_1 = \alpha_2$, the short-dashed line for $\alpha_1 = \frac{1}{2}\alpha_2$, the dotted line for $\alpha_1 = \frac{1}{4}\alpha_2$, and the solid line for $\alpha_1 = \frac{1}{10}\alpha_2$.

shown). If $r > r_c(0) \approx 0.107$, then only one symmetric equilibrium ($\mathscr{S}_1$) can exist for any α.

5. Equilibrium structure for loci of unequal effects

Now we study the general case of unequal effects and henceforth assume $\alpha_1 \leqslant \alpha_2$. Although in principle all equilibria and their eigenvalues can be determined analytically, at least as solutions of quadratic or cubic equations, the resulting expressions are often awkward and reasonably simple existence and stability conditions are in general not obtainable. Therefore, we pursued a numerical approach and calculated the equilibria and their eigenvalues from the explicit expressions that have been obtained (Section 3).

We systematically explored the parameter space $\{(r, \alpha_1, \alpha_2) : 0.001 \leqslant r \leqslant 0.5,\ 0.001 \leqslant \alpha_1 < \alpha_2 \leqslant 0.999\}$ by choosing a grid with increments of 0.001 in all three dimensions. In addition, the smaller value $r = 0.0005$ in combination with all pairs (α_1, α_2) as above was included. For each of these points we determined the existence and the local stability properties of the possible equilibria. For each r, we examined the resulting equilibrium patterns. Particularly interesting and representative cases are presented in Figs. 3–7 which display the numerically determined equilibrium patterns for $r =$ 0.5, 0.38, 0.215, 0.085, and 0.0005, respectively. These figures contain 15 of the 16 equilibrium patterns that we found, although only 13 are visible. For selected values of r, subregions of the (α_1, α_2) space were examined on a much finer grid for additional equilibrium patterns that were not found on the 1000×1000 grid, or occurred only spuriously, but were expected to exist as transient patterns by topological considerations. All 16 equilibrium patterns that were found are listed in Table 1.

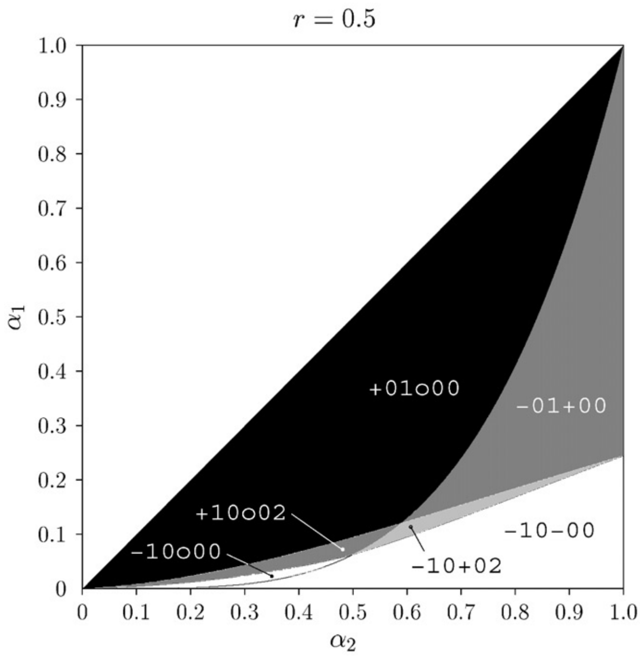

Fig. 3. Case map for $r = 0.5$. For free recombination, six equilibrium patterns exist. The transitory nature of the patterns with a pair of unstable unsymmetric equilibria (+10o02, −10+02) is clearly visible. Using α_1 as the bifurcation parameter, the transition occurring from +01o00 via +10o02 to −10o00 corresponds to the bifurcation pattern a_1 of Fig. 8, that from −01+00 via −10+02 to −10−00 to pattern a_2 of Fig. 8.

To distinguish and characterize the equilibrium patterns, we introduce a six-letter code according to the following rules. The first character refers to the stability of the corner equilibria and is a "+" if $\mathscr{C}_2$ and $\mathscr{C}_3$ are stable, and a "−", otherwise (recall that the corner equilibria $\mathscr{C}_1$ and $\mathscr{C}_4$ are always unstable). The second and the third character indicate the number of stable and unstable symmetric equilibria, respectively. The fourth letter refers to the edge equilibria $\mathscr{E}_1$ and $\mathscr{E}_2$. If they do not exist, the fourth letter is an "o". The existence of the edge equilibria is indicated by a "+" if they are stable, and by a "−" if they are unstable. The last two characters refer to the number of stable and unstable unsymmetric equilibria; the fifth letter gives the number of stable unsymmetric equilibria and the sixth letter the number of unstable unsymmetric equilibria. For example, the equilibrium pattern labeled +10o02 has two stable corner equilibria ($\mathscr{C}_2, \mathscr{C}_3$), one stable symmetric equilibrium ($\mathscr{S}_1$), $\mathscr{E}_1$ and $\mathscr{E}_2$ do not exist, and it has two unstable unsymmetric equilibria. Similarly, the pattern denoted by −21−00 has no stable monomorphic equilibria, two stable symmetric equilibria ($\mathscr{S}_1, \mathscr{S}_3$), one unstable symmetric equilibrium ($\mathscr{S}_2$), two unstable edge equilibria, and no unsymmetric

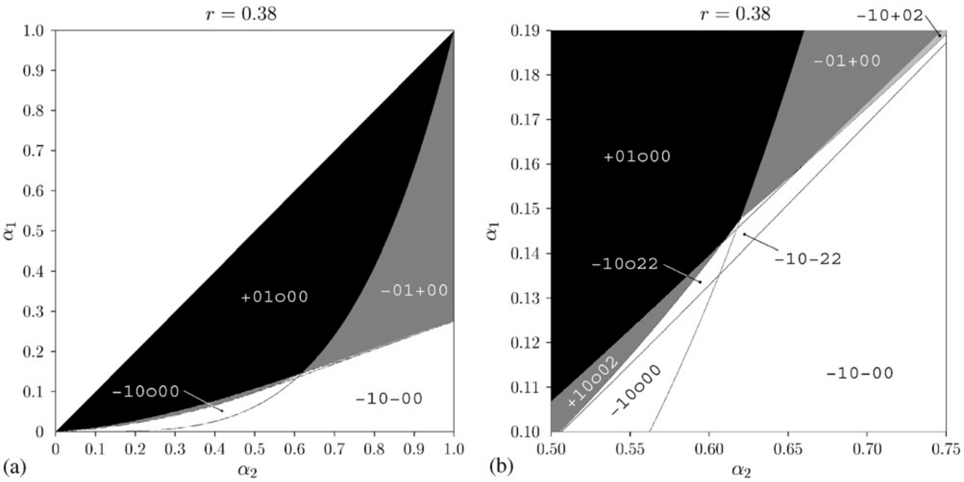

Fig. 4. Case map for $r = 0.38$. (a) The four main equilibrium patterns are the same as in Fig. 3, but the white regions (only polymorphic stable equilibria) are extended to somewhat larger α_1. The main difference is that six equilibrium patterns involving unsymmetric equilibria occur, thus in total 10 patterns exist. (b) Displays a zoomed-in picture. The two transitory regions +10o02 and −10+02 from Fig. 3 still exist, but are smaller. Four new equilibrium patterns have emerged, two with a pair of stable and a pair of unstable unsymmetric equilibria (−10o22, −10−22), and two tiny regions near the center, namely, −01o20 and −01−20. Between the black (+01o00) and the white (−10o00) region, the bifurcation patterns a_1 (for $\alpha_2 < 0.5$), b_1, and c_1 occur for increasingly large α_2 (the complete last one actually only parallel to the curve $\alpha_1^4 = \alpha_2$, but not vertically). To the right of this curve, the patterns c_2, b_2, a_2 of Fig. 8 occur for increasing α_2 (the last one only for $\alpha_2 > 0.85$).

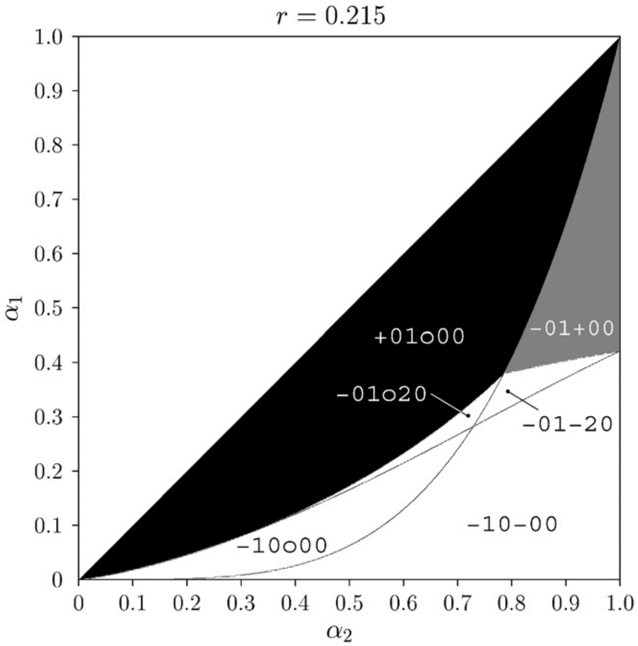

Fig. 5. Case map for $r = 0.215$. The four main regions are similar to those in Figs. 3 and 4, but the size of the regions in which $\mathscr{S}_1$ is the only stable equilibrium is much larger. The main transitory regions are now −01o20 and −01−20, the tiny ones from Fig. 4b. In total, there are eight equilibrium patterns. The regions −10−22 and −10+20 have disappeared and are "substituted" by −01−20 (bifurcation pattern d_1 of Fig. 8). The patterns +10o02 and −10o22 still exist between +01o00 and −10o00 (similarly as in Fig. 4), but only for small values of α_2 and an extremely narrow range of α_1 values, so that they remain invisible. Thus, from left to right, the bifurcation patterns a_1, b_1, c_1, and d_2 occur between the shaded and white regions using α_1 as bifurcation parameter.

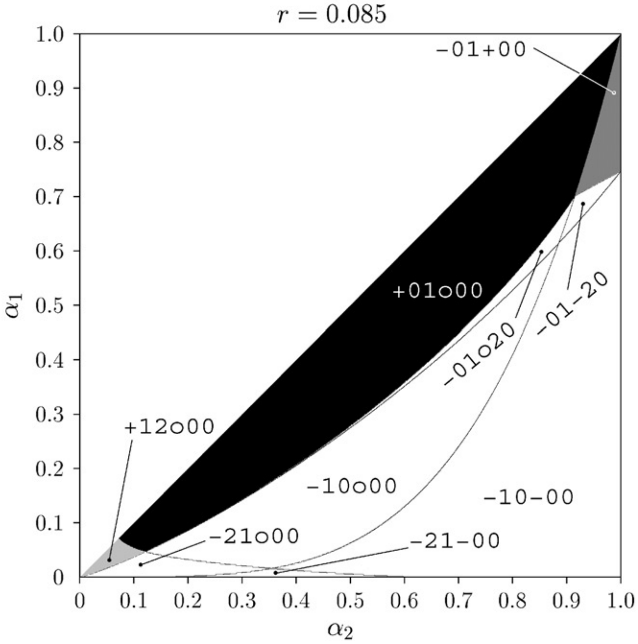

Fig. 6. Case map for $r = 0.085$. The right upper corner is similar to Fig. 5. Between +01o00 and −10o00 the pattern +10o02 still exists but is invisible (bifurcation pattern a_1 of Fig. 8), whereas −10o22 has disappeared. However, four new patterns, all involving three symmetric equilibria have arisen. Three are visible and indicated, one (+21o02) is invisible and located between +12o00 and −21o00 (bifurcation pattern a_3). Thus, in total there are 11 equilibrium patterns for this value of r, the maximum number we found for a given r.

equilibria. We note that in the equilibrium patterns +12o00 and −12o20, the symmetric equilibrium $\mathscr{S}_3$ is stable and $\mathscr{S}_1$ is unstable because $\mathscr{S}_3$ is stable whenever

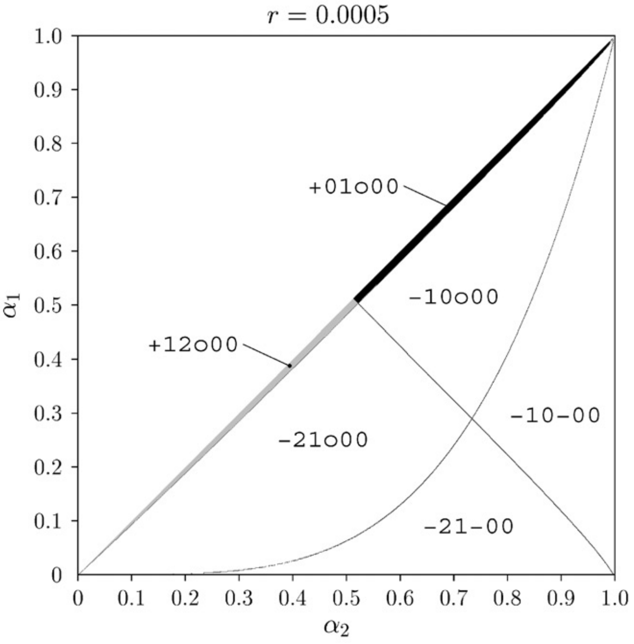

Fig. 7. Case map for $r = 0.0005$. Unless the effects of the loci are nearly equal, only fully polymorphic stable equilibria exist. For strong selection on at least one locus three symmetric equilibria exist (+12o00, −21o00, −21−00). In addition to the six indicated equilibrium patterns, there are four that are invisible. For very weak selection, near $\alpha_1 = \alpha_2 = 1$, there exist the patterns −01+00 and −01−20. Their location becomes obvious by comparison with Fig. 6. Moreover, −12o20 is located between +12o00 and −21o00 (bifurcation pattern d_3 of Fig. 8) and −01o20 occurs between +01o00 and −10o00 (pattern d_1).

it exists (Appendix B). Table 2 summarizes which types of equilibria can be simultaneously stable.

In the figures, the black area always signifies the equilibrium pattern +01o00 which is the only one that does not maintain any polymorphism. By contrast, white regions are those in which the only stable equilibria are two-locus polymorphisms, thus giving rise to a protected polymorphism. All other regions are in various shadings of grey. In all figures, the curve $\alpha_1 = \alpha_2^4$ is clearly visible. It delineates the region in which the single-locus polymorphisms ($\mathscr{E}_1, \mathscr{E}_2$) do not exist (above the curve) from the region in which they exist (below the curve); cf. Sections 3.1 and 3.2. Crossing this curve from above to below, the edge equilibria, $\mathscr{E}_1$ and $\mathscr{E}_2$, move into the simplex through the monomorphic equilibria $\mathscr{C}_2$ and $\mathscr{C}_3$, respectively. If the latter are stable above this curve (i.e., if r is sufficiently large), then the edge equilibria are stable right below this curve (but may become unstable if α_1 decreases further).

Interestingly, a stable two-locus polymorphism can be maintained for every recombination rate. The figures show that with decreasing r, the parameter region in which (only) completely polymorphic equilibria are stable grows, and the regions in which no or only one locus can be maintained polymorphic shrink accordingly. For free recombination, unequal effects and strong selection on at least one locus are necessary to maintain a two-locus polymorphism (Fig. 3). Two stable symmetric equilibria ($\mathscr{S}_1$ and $\mathscr{S}_3$) can occur only for tight or moderate linkage ($r \leqslant 0.144$, Table 1) and strong selection (Figs. 6 and 7; Section 3.3). A pair of stable unsymmetric equilibria, together with stable or unstable $\mathscr{S}_1$, can exist in a much larger range of values r ($r \leqslant 0.439$, Table 1), however, the region of (α_1, α_2) values in which they exist may be extremely small (Figs. 4–6). Unstable unsymmetric equilibria exist at least for $r \geqslant 0.046$, maybe even for all r as suggested by the spurious occurrence of pattern −21o22 (Table 1). For tightly linked loci ($r = 0.0005$, Fig. 7), there always exists a stable interior polymorphism unless the loci have nearly equal effects (along the diagonal), cf. (3.8), and two stable symmetric equilibria coexist for about half of the parameter space. The boundary of this region is closely approximated by the line $\alpha_1 + \alpha_2 = 1$ (Section 3.3).

Table 1
The equilibrium patterns and some of their properties

Pattern	(SPE)	(SE)	(PE)	(E)	[%]	quad sel	$[r_1, r_2]$
+01o00	0	2	1	5	46.4	Yes	$[0, 0.5]$
−01+00	0	2	1	7	12.1	Yes	$[0, 0.5]$
−10o00	1	1	1	5	10.2	Yes	$[0, 0.5]$
−10−00	1	1	1	7	26.1	Yes	$[0, 0.5]$
+12o00	1	3	3	7	0.4	No	$[0, 0.111]$
+10o02	1	3	3	7	0.4	No	$[0.084, 0.5]$
−10+02	1	3	3	9	0.2	No	$[0.361, 0.5]$
−21o00	2	2	3	7	1.8	No	$[0, 0.145]$
−01o20	2	2	3	7	0.8	Yes	$[0, 0.382]$
−01−20	2	2	3	9	0.7	Yes	$[0, 0.383]$
−21−00	2	2	3	9	0.7	No	$[0, 0.144]$
+21o02	2	4	5	9	3×10^{-5}	No	$[0.046, 0.107]$
−10o22	3	3	5	9	0.01	No	$[0.096, 0.438]$
−12o20	3	3	5	9	4×10^{-3}	No	$[0, 0.077]$
−10−22	3	3	5	11	0.01	No	$[0.319, 0.439]$
−21o22	4	4	7	11	$< 10^{-8}$	No	$[0.005, 0.007]$

The six-letter code used to label the equilibrium patterns is explained in the text. The columns entitled #(SPE), #(SE), #(PE), #(E) contain the number of stable polymorphic equilibria, the number of stable equilibria, the number of polymorphic equilibria, and the number of existing equilibria, respectively. The column entitled [%] contains the proportion of the given equilibrium pattern among all equilibrium patterns as calculated using the grid with increments 0.001 on the parameter-space $\{(r, \alpha_1, \alpha_2) : 0.001 \leqslant r \leqslant 0.5,\ 0.001 \leqslant \alpha_1 < \alpha_2 \leqslant 0.999\}$. The column "quad sel" signifies the equilibrium patterns that exist under quadratic stabilizing selection (Section 6), and $[r_1, r_2]$ gives the range of recombination rates for which the given equilibrium pattern exists (a lower bound of 0 indicates that it exists for $r = 0.0005$, the smallest value investigated, and we expect it to exist for all $r > 0$). For some patterns, the range may be somewhat larger than indicated if they exist only for an extremely narrow range of values α_1 and α_2, so that our grid was too coarse to detect them.

The unsymmetric equilibria occur only as transient states between equilibrium patterns for which boundary equilibria ($\mathscr{C}_i$ or $\mathscr{E}_i$) are stable and equilibrium patterns

Table 2
Stable coexistence of equilibria

	$\mathscr{C}_2\&\mathscr{C}_3$	$\mathscr{E}_1\&\mathscr{E}_2$	$\mathscr{S}_1$	$\mathscr{S}_3$	$\mathscr{S}_1\&\mathscr{S}_3$	$\mathscr{U}_1\&\mathscr{U}_2$
$\mathscr{C}_2\&\mathscr{C}_3$	$\oplus$	$-$	$\pm$	$\pm$	$\pm$	$-$
$\mathscr{E}_1\&\mathscr{E}_2$		$\oplus$	$\pm$			$-$
$\mathscr{S}_1$	$\pm$	$\pm$	$\oplus$			$-$
$\mathscr{S}_3$	$+$			$\ominus$		$+$
$\mathscr{S}_1\&\mathscr{S}_3$	$+$				$\oplus$	
$\mathscr{U}_1\&\mathscr{U}_2$	$-$	$-$	$-$	$+$	$-$	$\oplus$
$\mathscr{U}_1-\mathscr{U}_4$			$\exists$		$\exists$	

A "+" indicates that the equilibrium/a indicated on the left can be asymptotically stable if the equilibrium indicated on top is stable. A "−" indicates that this equilibrium combination may exist but if it exists, then the equilibrium indicated on the left is unstable if that on top is stable. A "±" indicates that the equilibrium on the left can be stable or unstable if that on top is stable. No entry signifies that this combination never exists (under the condition that the equilibrium on top is stable). Thus, the equilibria indicated on top of the columns are assumed to be stable. $\mathscr{U}_1\&\mathscr{U}_2$ indicates existence (and stability/instability) of exactly two unsymmetric equilibria. The sign $\exists$ in the line $\mathscr{U}_1-\mathscr{U}_4$ indicates that four unsymmetric equilibria can exist, in which case two are stable and two are unstable. The column (or line) label $\mathscr{S}_1$ indicates that $\mathscr{S}_1$ is stable (exists or is stable/unstable) but $\mathscr{S}_3$ does no exist. Similarly, $\mathscr{S}_3$ indicates stability of $\mathscr{S}_3$ if $\mathscr{S}_1$ is unstable (recall that $\mathscr{S}_3$ is stable whenever it exists and $\mathscr{S}_1$ exists always). The entry "$\oplus$" in the diagonal indicates that this equilibrium(type) can be the only stable one, a "$\ominus$" that it cannot.

for which one or two symmetric equilibria are stable. The four observed types of transitions (bifurcations) are displayed in Fig. 8. The figure captions to Figs. 3–7 indicate which of these bifurcations occur. An example with four unsymmetric equilibria that also shows their range of attraction is shown in Fig. 11. Bifurcations that do not affect the unsymmetric equilibria are very straightforward: As already described above, the single-locus polymorphisms $\mathscr{E}_1, \mathscr{E}_2$ move into the simplex through the vertices $\mathscr{C}_2, \mathscr{C}_3$, respectively. The symmetric equilibria $\mathscr{S}_2$ and $\mathscr{S}_3$ approach and, ultimately, extinguish each other if, for given (α_1, α_2), r increases to the critical value above which only $\mathscr{S}_1$ exists.

An equilibrium pattern that is never visible in these figures is −21o22, the last one in Table 1. It consists of four stable interior equilibria (two symmetric and two unsymmetric), three unstable interior equilibria, and the four unstable corners. Apparently, it exists only in an extremely small parameter region, e.g., for $r = 0.006$ and $0.02264 \leqslant \alpha_1 \leqslant 0.02267$ in very narrow intervals of length $\leqslant 10^{-9}$ within $0.016636 \leqslant \alpha_2 \leqslant 0.016662$. For instance, if $\alpha_1 = 0.2265$, the pattern −21o22 occurs if $10^{10}(\alpha_2 - 0.0166463002) \in (0.85, 0.90)$. We found both corresponding bifurcation patterns, i.e., b_3 and c_3 of Fig. 8. Also the second equilibrium pattern with four stable equilibria, +21o02, occurs only in a very narrow parameter region (Table 1).

We have not proved that the 16 observed equilibrium patterns are all that can occur. However, there is no reason to assume that additional patterns should exist because no bifurcation patterns are missing. For instance, our general results of Section 3 imply that any feasible additional pattern had to differ from one of the listed patterns solely by the number of stable or unstable unsymmetric equilibria. Moreover, by calculating the indices of the monomorphic, the edge, and the symmetric equilibria (when possible), some further equilibrium patterns can be excluded through the Poincarè–Hopf theorem (Hofbauer and Sigmund, 1998). For example, such an argument shows that −10+00 cannot exist, hence −01+00 is the only possible equilibrium pattern with stable edge equilibria and no unsymmetric equilibria. In any case, if additional patterns exist, their range of existence has to be extremely small.

6. Comparison with quadratic stabilizing selection

In contrast to Gaussian stabilizing selection, quadratic stabilizing selection, i.e.,

$$W(G) = 1 - sG^2, \tag{6.1}$$

has been studied analytically and all possible equilibrium patterns have been determined (Gavrilets and Hastings, 1993; Bürger and Gimelfarb, 1999; for a review see Bürger, 2000, pp. 204–210). If selection is sufficiently weak, or the genotypic effects sufficiently small, then quadratic stabilizing selection can be used as an approximation for Gaussian stabilizing selection. Because negative fitnesses cannot occur, the quadratic fitness function can be used only if $s(\gamma_1 + \gamma_2)^2 \leqslant 1$. Setting, as in (2.4), $\alpha_i = W(\gamma_i) = 1 - s\gamma_i^2$ $(i = 1, 2)$, this condition is translated to

$$\alpha_1 \geqslant \alpha_2 - 1 + 2\sqrt{1 - \alpha_2}. \tag{6.2}$$

We note that the condition $\gamma_1 \leqslant 2\gamma_2$ is equivalent to

$$\alpha_1 \geqslant 4\alpha_2 - 3 \tag{6.3}$$

which, for weak selection (α_1 and α_2 close to 1), approximates the Gaussian equivalent (3.2b).

The following critical recombination rates play an important role in the quadratic selection model (Bürger, 2000, p. 205):

$$\begin{aligned} r_1 = &\tfrac{1}{3}(\alpha_1 + \alpha_2 - 2 \\ &+ 2\sqrt{1 + \alpha_1^2 + \alpha_2^2 - \alpha_1 - \alpha_2 - \alpha_1\alpha_2}), \end{aligned} \tag{6.4}$$

$$r_2 = \min\{(\sqrt{1 - \alpha_1} - \sqrt{1 - \alpha_2})^2, \tfrac{1}{3}(\alpha_2 - \alpha_1)\}, \tag{6.5}$$

where $r_2 = (\sqrt{1 - \alpha_1} - \sqrt{1 - \alpha_2})^2$ if and only if (6.3) holds. With quadratic stabilizing selection, only six equilibrium patterns exist (indicated in Table 1). Three symmetric equilibria can never exist, and at most two unsymmetric equilibria exist which are stable in that case. If the effects of the loci are similar, i.e., if (6.3) holds, then the monomorphic equilibria $\mathscr{C}_2$, $\mathscr{C}_3$ are the

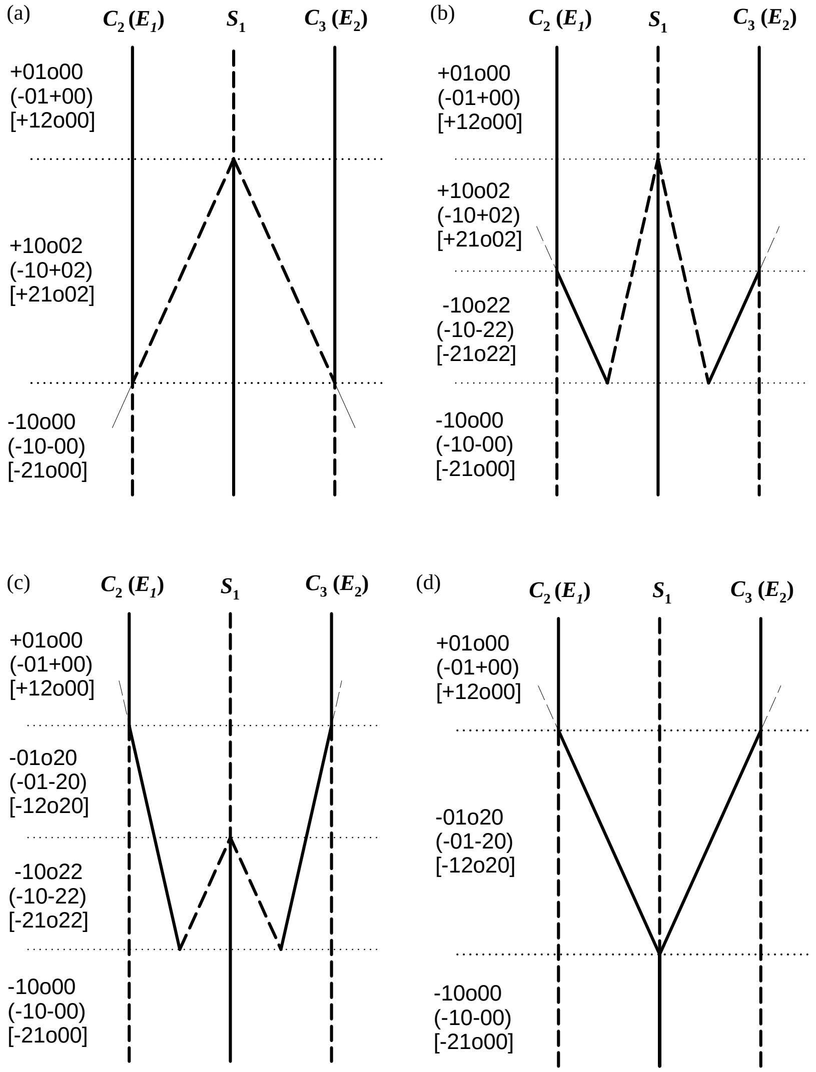

Fig. 8. Bifurcation patterns involving the unsymmetric equilibria. As bifurcation parameter, α_1 may be used (large α_1 on top). Each of the four patterns (a)–(d) can occur with three different types of equilibrium configurations: (1) $\mathscr{C}_2$ and $\mathscr{C}_3$ stable on top (indicated to the left without parentheses); (2) $\mathscr{E}_1$ and $\mathscr{E}_2$ stable on top (indicated to the left in parentheses); or (3) $\mathscr{C}_2$, $\mathscr{C}_3$ stable on top, and $\mathscr{S}_3$ always stable (indicated to the left in square brackets). Vertical lines symbolize equilibria. A pair of unsymmetric equilibria (indicated by diagonal lines) enters or exits the simplex by exchange of stability through $\mathscr{C}_2$ and $\mathscr{C}_3$ in the equilibrium patterns given without parentheses or in brackets, and through $\mathscr{E}_1$ and $\mathscr{E}_2$ for the equilibrium patterns in parentheses. Unsymmetric equilibria may also arise or disappear by a pitchfork bifurcation from $\mathscr{S}_1$ or (as in (b) and (c)) by a blue sky bifurcation, i.e., a stable and an unstable unsymmetric equilibrium may extinguish each other. Bold lines indicate stable, dashed lines unstable equilibria. We use the convention to refer to the bifurcation pattern occurring in, e.g., (c) in parentheses, i.e., −01+00 → −01−20 → −10−22 → −10−00, as bifurcation pattern c_2, to that in brackets as c_3, etc. As r decreases, the bifurcation patterns (a), (b), (c), (d) occur (and disappear) in this order, but the three different subtypes occur in different ranges of r (see Table 1).

only stable ones if $r \geqslant r_2 = (\sqrt{1-\alpha_1} - \sqrt{1-\alpha_2})^2$ (equilibrium pattern +01o00), the unsymmetric equilibria exist and are stable if and only if $r_1 < r < r_2$ (−01o20), and the symmetric equilibrium $\mathscr{S}_1$ is the only stable one if $r \leqslant r_1$ (−10o00). If the locus effects are sufficiently different, i.e., (6.3) is invalid, then the single-locus polymorphisms $\mathscr{E}_1$, $\mathscr{E}_2$ exist and the monomorphic equilibria are always unstable. The single-locus polymorphisms are the only stable equilibria if $r \geqslant r_2 = \frac{1}{3}(\alpha_2 - \alpha_1)$ (pattern −01+00), they are unstable and the unsymmetric equilibria exist and are the only stable ones if $r_1 < r < r_2$ (pattern −01−20), and the symmetric equilibrium $\mathscr{S}_1$ is the only stable one if $r \leqslant r_1$ (−10−00).

Because $r_2 \leqslant \frac{1}{3}$ holds always, no fully polymorphic equilibria can exist if $r \geqslant \frac{1}{3}$, thus +01o00 and −01+00 are the only possible equilibrium patterns in this case. In addition, from $r_2 = 1 - \alpha_2$ if $\alpha_1 = 4\alpha_2 - 3$ and the constraint (6.2) it follows easily that for loci of similar effect ($\gamma_1 \leqslant 2\gamma_2$), the only possible equilibrium pattern is +01o00 if $r \geqslant 0.128$. Using $r \leqslant r_1$, it can be shown in a similar way that the pattern −10o00 can occur only if $r \leqslant 0.094$. For loci of sufficiently different effects, so that (6.3) is invalid, it is easily shown that stable polymorphic

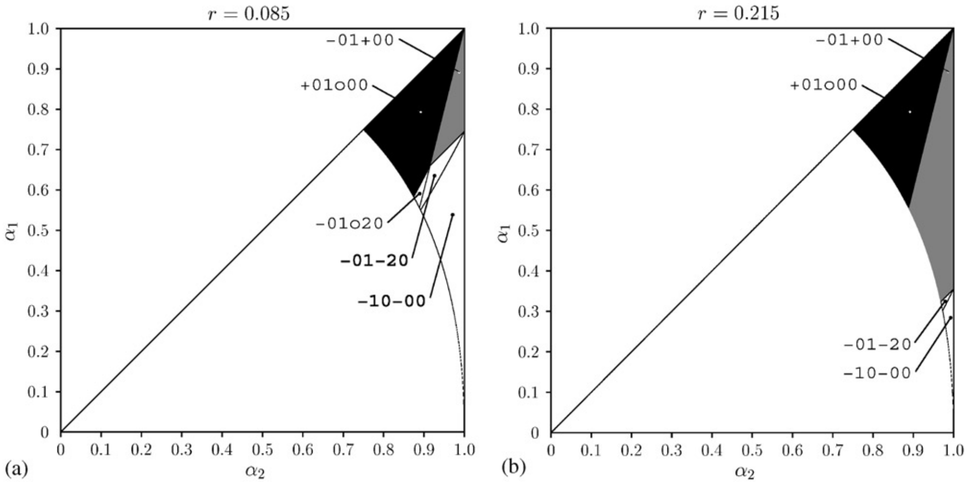

Fig. 9. Case maps for quadratic stabilizing selection. (a) ($r = 0.085$) All six possible equilibrium patterns occur. (b) ($r = 0.215$) Only four equilibrium patterns are possible (see main text). The curved line indicates the restriction (6.2) on the parameters (α_1, α_2) in this model.

equilibria (patterns −01−20 or −10−00) exist only if $\alpha_1 < 1 - 3r$ (because r_2 is monotone decreasing in α_2). Equivalently, the pattern −01+00 occurs whenever $\alpha_1 \geqslant 1 - 3r$. It cannot exist if $\alpha_1 < \frac{1}{2}(\sqrt{2 - 9r^2} - 3r)$. In summary, all six equilibrium patterns can occur together only if $r \leqslant 0.094$.

Fig. 9 displays the case maps under quadratic stabilizing selection for the two indicated recombination rates. Thus, Fig. 9a corresponds to Fig. 6 and Fig. 9b to Fig. 5. The similarities and differences are clearly visible.

7. Discussion

A Gaussian fitness function seems to be the most natural choice for modeling stabilizing selection on a quantitative trait and has been widely used. In particular, in models of phenotypic evolution it often yields results that are easy to interpret and in accordance with biological intuition (e.g., Lande, 1976). However, already previous studies of two-locus models of a trait under Gaussian stabilizing selection yielded some counter-intuitive results beyond the fact that some forms of stabilizing selection can maintain more than one locus polymorphic under certain conditions on the underlying genetics. For instance, Gavrilets and Hastings (1993, 1994b) showed that for linked loci with equal effects and for sufficiently strong selection, a stable symmetric equilibrium with positive linkage disequilibrium can be maintained, thus stabilizing selection may “inflate” the genetic variance above the level expected in linkage equilibrium (cf. Section 4). In our notation, they detected the equilibrium pattern +12o00. This pattern exists only for loci of very similar effects (see Figs. 6 and 7) and occurs for about 0.4% of all admissible parameter combinations (r, α_1, α_2) (Table 1). Gimelfarb (1996) showed that for unequal effects and sufficiently strong selection relative to recombination, two symmetric equilibria may be simultaneously stable, one exhibiting negative, the other positive linkage disequilibrium ($\mathcal{S}_1$ and $\mathcal{S}_3$ in our notation). As may be seen from Table 1, this also is a fairly rare event that occurs in about 2.3% of the parameter space. It may be realized by four different equilibrium patterns, namely −21o00, −21−00, +21o02, and −21o22.

Nagylaki (1989) examined general forms of symmetric stabilizing selection on traits determined by two diallelic loci subject to the constraint that the double heterozygote coincides with the fitness optimum. Thus, his sole restrictions on the genotypic fitnesses are exactly those stated in (2.7). He determined all possible equilibrium patterns under the assumption that recombination is strong enough relative to selection that linkage disequilibrium can be ignored. Among others, he applied his general results to Gaussian stabilizing selection, derived all equilibrium patterns and determined analytically their regions of existence. For comparison with our results, they are displayed in Fig. 10, which may be compared with Fig. 3. Overall, the equilibrium structure obtained by ignoring linkage disequilibrium looks quite similar to the exact one but closer inspection shows that the equilibrium pattern −10o00 does not exist in Nagylaki’s model. This is not really surprising because it occurs only under very strong selection on the major locus (very small α_1), thus violating the assumption of weak selection relative to recombination. Further comparison of the two figures reveals that in the full model (Fig. 3) the regions in which stable two-locus polymorphisms exist are larger (extend to higher values of α_1) than when linkage disequilibrium is neglected (Fig. 10). Thus, as predicted by Nagylaki (1989), inclusion of linkage disequilibrium relaxes the conditions for the existence of stable two-locus polymorphisms. Clearly, the conditions for the existence of the edge

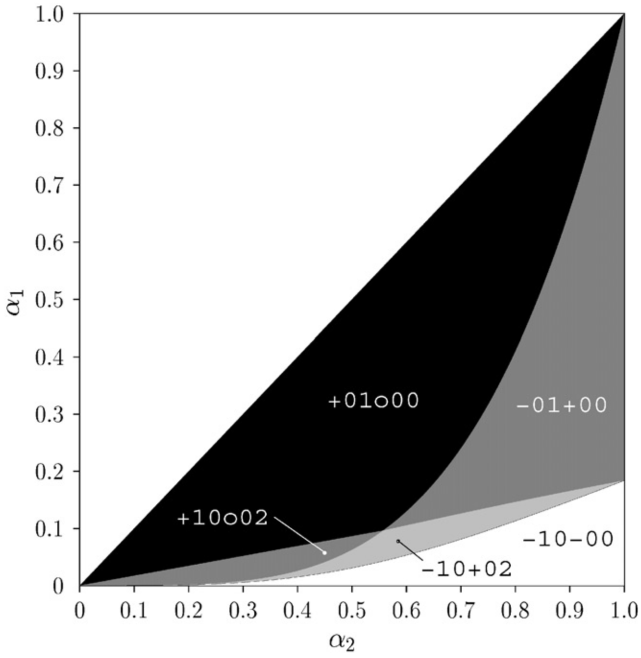

Fig. 10. Case map of Nagylaki's model which neglects linkage disequilibrium. Only five equilibrium structures can occur.

equilibria (3.2a) are identical in both models but the stability conditions are not.

Our results demonstrate that the equilibrium structure under the full two-locus model of Gaussian stabilizing selection is much richer than might be expected from the previous studies of special cases or from the studies of quadratic stabilizing selection (Section 6). In particular, it reveals a remarkable sensitivity of the endresult of evolution to the initial conditions, to the genetic parameters, and the strength of selection. However, only few of the 16 equilibrium patterns are common, i.e., occur in a reasonably wide range of parameters, some are extremely rare (see Table 1). We found that up to four stable fully polymorphic equilibria may coexist, although this occurs only in an extremely narrow parameter range. For about 48% of all parameter combinations (r, α_1, α_2), monomorphic equilibria are the only stable ones, and for another 12% only single-locus polymorphisms are stable. For quadratic stabilizing selection, about 46% of all parameter combinations yield only stable monomorphic equilibria, but about 39% yield a stable single-locus polymorphism, and the rest, about 14%, a two-locus polymorphism. (This can be calculated directly from Eqs. (6.2) to (6.5).) In contrast to quadratic stabilizing selection, for Gaussian selection equilibria with different degree of polymorphism may be simultaneously stable, and interior equilibria can be stable for free recombination (see Fig. 3). This, however, requires very strong selection on the major locus. Two or more stable interior equilibria exist for every recombination rate $r \leqslant 0.439$, yet for only about 4% of all parameter combinations (r, α_1, α_2). For loose linkage (e.g. $r > 0.2$), this requires very strong selection on at least one locus and occurs only if two unsymmetric equilibria are stable. If the locus effects are different and r is sufficiently small, then no boundary equilibrium can be stable (3.8). The range of attraction of $\mathscr{S}_3$ is always small. The range of attraction of the unsymmetric equilibria may be large or small, depending on the parameters (for an example, see Fig. 11). For weak selection on both loci (say, $\alpha_1, \alpha_2 \geqslant 0.8$), genetic variability at both loci can be maintained only for tight linkage (see Figs. 6 and 7).

Only one other example of a two-locus two-allele model with four stable interior equilibria has been published (Hastings, 1985). The present one appears to be the first example showing that two symmetric equilibria can stably coexist with unsymmetric equilibria. It seems to be unknown if more than four stable interior equilibria can coexist in diallelic two-locus models. An example of four stable boundary equilibria and two stable interior equilibria was given by Feldman and Liberman (1979).

The present model rests on some simplifying assumptions. Genes are assumed to have additive effects on the trait, thus dominance and epistasis are ignored; and the fitness function has its optimum at zero, the value of the double heterozygote, which induces symmetry. For Gaussian stabilizing selection nothing is known about the effect inclusion of one or some of these generalizations would have. For quadratic stabilizing selection more is known. Numerical results of Kojima (1959), Lewontin (1964), and Singh and Lewontin (1966) show that even with equal effects, genetic variation can be maintained if there is partial dominance and the

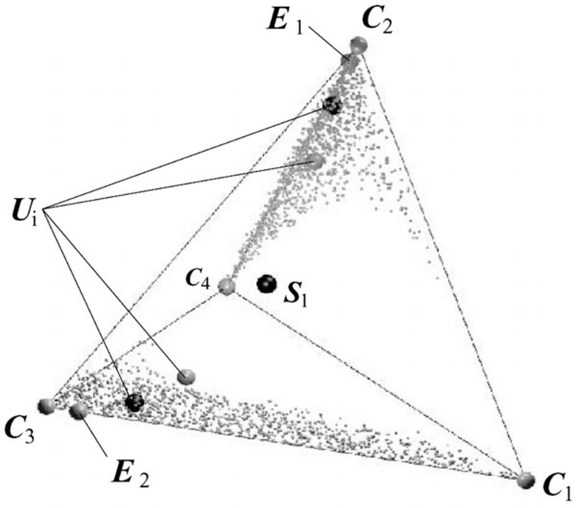

Fig. 11. Position and region of attraction of unsymmetric equilibria for the equilibrium pattern −10−22. Black spheres indicate locally stable equilibria, grey spheres unstable equilibria. The small grey spheres display initial points for which the trajectories converge to one of the unsymmetric equilibria. The overall number of initial points was 10 000. The parameters are $\alpha_1 = 0.645$, $\alpha_2 = 0.150$, $r = 0.38$.

optimum is shifted towards the extreme phenotypes. Gimelfarb (1989) showed numerically that in the symmetric model and in the absence of dominance, moderate or strong epistasis can maintain much genetic variation. For additive loci but with the position of the optimum shifted to an arbitrary point, some analytical results were derived by Hastings and Hom (1990) and Gavrilets and Hastings (1993). A review together with some additional numerical results can be found in Bürger (2000, pp. 213–216). Not unexpectedly, a small shift in the optimum leads to only a slight change; but a large shift, such that both loci are effectively under directional selection, may lead to a major change and always to depletion of all genetic variability. In between, equilibrium patterns may exist that cannot occur in the symmetric model. It seems likely that qualitatively similar conclusions will be valid for Gaussian selection.

It is unknown how the equilibrium structure depends on the shape of the fitness function. For functions that decrease monotonically from an optimum that coincides with the double heterozygote and that are symmetric with respect to this optimum, i.e., satisfy (2.7), Nagylaki (1989) classified all possible equilibrium structures under the assumption of linkage equilibrium, thus requiring selection to be sufficiently weak relative to recombination. His analysis shows that with a triangular or a double exponential fitness function, a stable two-locus polymorphism can be maintained for arbitrarily weak selection on both loci if the locus effects are sufficiently different. Therefore, the possible equilibrium patterns depend not only on the behavior of the fitness function near its tails (as exemplified by the differences between Gaussian and quadratic stabilizing selection), but also on its shape near the optimum. But even more sophisticated details may matter (see Nagylaki's example for his Case a). Therefore, although all possible equilibria have been identified (Karlin and Feldman, 1970) and all but two boundary equilibria occur with Gaussian stabilizing selection, there seems to be little hope for a complete classification of equilibrium patterns in the general case.

A further open problem concerns the extension to multiple loci. Because of the complexity of the resulting model, the derivation of analytical results is rather cumbersome and very little is known. Gavrilets and Hastings (1994a) derived the stability conditions of the monomorphic equilibria in a general multilocus multiallele system. They also performed a perturbation analysis on the location and stability of polymorphic equilibria involving two gametes under the assumption that selection is very strong relative to recombination. However, these results do not immediately yield insight into the equilibrium structure or the potential of stabilizing selection to maintain genetic variation in traits determined by many loci. An extensive numerical study of a model in which up to five diallelic loci contribute to a trait under quadratic stabilizing selection was performed by Bürger and Gimelfarb (1999). The principal conclusion of this investigation is that the expected number of loci maintained polymorphic at a stable equilibrium and the expected genetic variance of the trait at equilibrium decrease rapidly to very low levels as the number of loci increases from two to five. These results were obtained by iterating the recursion relations for 20 randomly chosen initial distributions per parameter set and 4000 parameter sets of randomly chosen recombination rates and locus effects. For strong to moderate stabilizing selection, the probability of maintaining two loci polymorphic was found to be about 17%, 3%, 1%, and less than 0.5% in a 2-, 3-, 4-, and 5-locus model, respectively. Although our analysis shows that under Gaussian stabilizing selection, stable two-locus polymorphisms are maintained in a wider region of the parameter space than under quadratic selection, there is little doubt that for Gaussian stabilizing selection the probability of maintaining a polymorphism in at least two loci will also decrease rapidly with increasing number of contributing loci. The reason is that as the number of loci or the number of alleles per locus increases the optimum phenotype can be matched easier by a homozygous genotype. Still, no systematic study has been performed yet.

Summarizing, we may conclude that stabilizing selection per se has the potential to maintain more than one locus polymorphic, and two-locus polymorphisms become likely if a trait is determined by two or very few linked loci of large effect so that selection is strong relative to recombination. If, however, many loci of small effect contribute to a trait, other forces must be responsible for the genetic variation of this trait.

Acknowledgments

We thank J. Hofbauer for a useful hint that led to the proof of Lemma 2 in Appendix B. This work was finished during the program on Mathematical Population Genetics and Statistical Physics funded by the Erwin Schrödinger International Institute of Mathematical Physics.

Appendix A. Stability of the edge equilibria excludes existence of $\mathcal{S}_3$

Here we prove that if the edge equilibria are stable, then only one symmetric equilibrium can exist. If the edge equilibria are stable, then we have $0<c<a<b<d<1$ and $r>c$. The symmetric equilibria are the solutions of Eq. (3.9), which we rewrite as

$$h(z) = 8rz, \tag{A.1}$$

where

$$h(z) = (1 - z^2)(z(2b + 2c - a - d) - (d - a)). \qquad \text{(A.2)}$$

Then $h(z) = 0$ if $z = \pm 1$ or $z = z_c = (d - a)/(2b + 2c - a - d)$, where $z_c < 1$ if and only if $b + c > d$. In this case, $h(z) > 0$ if $z_c < z < 1$ and, as is well known, three solutions of (A.1) and (3.9) exist for sufficiently small r. Here we show that this is impossible if $r \geqslant c$. We observe that $h''(z) = 2(d - a - 3z(2b + 2c - a - d))$ is negative for $z_c \leqslant z \leqslant 1$ because $d > a$ and $b + c > d$. Therefore, $h(z)$ and $8rz$ cannot intersect on this interval (and hence on $(0, 1)$) if $h'(z_c) < 8c < 8r$. The inequality $h'(z_c) < 8c$ is always fulfilled because

$$\begin{aligned} h'(z_c) - 8c = {} & \frac{-4}{2b + 2c - a - d}[(d - b)(b - a) \\ & + c(2b + 3c - a - d)] < 0. \end{aligned} \qquad \text{(A.3)}$$

Appendix B. Stability of $\mathscr{S}_3$

Here we prove that under Gaussian stabilizing selection the symmetric equilibrium $\mathscr{S}_3$ is asymptotically stable whenever it exists, i.e., if $b + c > d$ holds. We set $u = 1 - z$ and $e = b + c - d$. Then $e > 0$ and a symmetric equilibrium with $D > 0$ exists if and only if

$$-8r(1 - u) + u(2 - u)(2e - u(d - a + 2e)) = 0 \qquad \text{(B.1)}$$

has a solution $0 < u < 1$. In this case, actually two solutions in $[0, 1]$ exist, giving rise to $\mathscr{S}_2$ and $\mathscr{S}_3$ (the latter with the smaller value of u). Consequently, the coordinate u of $\mathscr{S}_3$ (and also of $\mathscr{S}_2$) satisfies $0 < u < u_*$, where u_* is the third solution of (B.1) if $r = 0$, i.e.,

$$u_* = \frac{2e}{d - a + 2e} = \frac{2(b + c - d)}{2(b + c) - a - d} < 1. \qquad \text{(B.2)}$$

In terms of z, this means

$$1 > z > \frac{d - a}{2(b + c) - a - d} > 0.$$

From the defining equation (3.9), or (B.1), it is readily shown that $\mathscr{S}_3$ is locally stable on the symmetric line $\{x = y = 0\}$. Therefore, to prove local stability of $\mathscr{S}_3$, it has to be shown that the two other eigenvalues, obtained from linearization of (2.8) using the coordinates x, y, and z, are less than one in modulus. These eigenvalues are computed to be

$$\lambda_{2,3} = \frac{2(A \pm \sqrt{B})}{C}, \qquad \text{(B.3)}$$

where

$$A = 4 - b - c - 2d + u(d - a),$$

$$\begin{aligned} B = {} & (b + c - d)^2 - 2u[(a + d - 2b)(d - c) \\ & + (a + d - 2c)(d - b)] \\ & + u^2(a + d - 2b)(a + d - 2c), \end{aligned}$$

$$C = 4(2 - d) - 4u(b + c - d) + u^2(2b + 2c - a - d),$$

and u denotes the coordinate of the equilibrium. The general conditions (2.7) imply that $A > 0$ because $u > 0$. Furthermore, we have $C > 0$ if $0 \leqslant u \leqslant 1$ because C is convex and attains it minimum at $u_m = 2e/(d - a + 2e) \in (0, 1)$ and the value of C is

$$\begin{aligned} C|_{u=u_m} = {} & \frac{4}{d - a + 2e} \\ & \times [(d - a)(2 - d) + e(4 - b - c - d)] > 0. \end{aligned}$$

Positivity of B is slightly more delicate. We have $B|_{u=0} > 0$ and $B|_{u=1} = (b - c)^2 + (a - d)^2 > 0$. If the coefficient $\beta_2 = (a + d - 2b)(a + d - 2c)$ of u^2 is negative, the polynomial is concave and we are finished. Otherwise, we show that the location of the minimum of B, given by β_1/β_2, where $\beta_1 = (a + d - 2b)(d - c) + (a + d - 2c)(d - b)$, is not in $[0, 1]$. Indeed, if $a + d > 2b \geqslant 2c$, then $\beta_2 > 0$, $\beta_1 - \beta_2 = (d - a)(a + d - b - c) > 0$, and $\beta_1/\beta_2 > 1$; if $a + d < 2c \leqslant 2b$, then $\beta_2 > 0$ and $\beta_1 < 0$.

Consequently, we have $\lambda_2 \geqslant \lambda_3$.

Now we show $\lambda_3 \geqslant 0$. This is the case if and only if $A^2 - B \geqslant 0$. Indeed, we have

$$\begin{aligned} A^2 - B = {} & 8(1 - d)(2 - b - c) \\ & + 8u[(d - a)(1 - d) + (d - b)(d - c)] \\ & + u^2[(b - a)(d - c) + (c - a)(d - b)] > 0, \end{aligned}$$

because $A^2 - B|_{u=0} > 0$,

$$\begin{aligned} A^2 - B|_{u=1} = {} & 2(2 - a - d)(2 - b - c) + 2(1 - b)(1 - c) \\ & + 2(1 - a)(1 - d) > 0, \end{aligned}$$

and the coefficient $(d - a)(1 - d) + (d - b)(d - c)$ of u is positive.

It remains to demonstrate $\lambda_2 < 1$. Because $C - 2A = 2(b + c)(1 - u)^2 + (a + d)(2 - u)u > 0$, we have to prove

$$\tfrac{1}{4}[(C - 2A)^2 - 4B] = p(u) = p_0 - 2p_1 u + p_2 u^2 > 0$$

for $0 \leqslant u \leqslant u_*$, where

$$p_0 = 4d(b + c - d),$$

$$p_1 = 2(b^2 + c^2 - ad + d(b + c - d)),$$

$$p_2 = 3(b + c - d)(b + c - a) + 3(b^2 + c^2 - ad) + 2bc.$$

Obviously, we have $p_0 > 0$. Lemma B.1 (see below) shows $b^2 + c^2 - ad > 0$ which implies $p_1 > 0$ and $p_2 > 0$.

Next we observe $p(0) = p_0 > 0$ and

$$\begin{aligned} p(u_*) = {} & \frac{4e}{(d - a + 2e)^2}\Big[(b + c - a)[ad - (b - c)^2] \\ & + 2e^2(b + c - a) + e^3\Big] > 0, \end{aligned}$$

because for Gaussian selection $ad - (b - c)^2 \geqslant 0$ holds (see Lemma B.2 below). In order to prove that $p(u) > 0$ between 0 and u_*, we show that if the minimum $u_{\min} =$

$p_1/p_2 \in (0, u_*)$, then

$$p(u_{\min}) = \frac{p_0 p_2 - p_1^2}{p_2} > 0.$$

Because $p_1 > 0$ and $p_2 > 0$, we have $u_{\min} \in (0, u_*)$ if and only if $u_* p_2 > p_1$. In this case, we obtain

$$p_0 p_2 - p_1^2 > \frac{p_1}{u_*}(p_0 - u_* p_1),$$

whence $p(u_{\min}) > 0$ if $p_0 - u_* p_1 > 0$. This, however, follows from

$$p_0 - u_* p_1 = \frac{4e}{d - a + 2e}[2d(b + c - d) + d(b + c - a) + b^2 + c^2 - ad] > 0,$$

because each of the terms is nonnegative (by Lemma B.1 and because $b + c > d$). This finishes the proof.

Lemma B.1. *For Gaussian stabilizing selection,* $b^2 + c^2 - ad > 0$ *holds.*

Proof. Let

$$h(\gamma_1, \gamma_2) = b^2 + c^2 - ad = (1 - e^{-\gamma_1^2})^2 + (1 - e^{-\gamma_2^2})^2 - (1 - e^{-(\gamma_1 - \gamma_2)^2})(1 - e^{-(\gamma_1 + \gamma_2)^2}).$$

Then, $h(\gamma_1, \gamma_1) = 2(e^{-\gamma_1^2} - 1)^2$, $h(\gamma_1, 0) = 0$, and we shall prove that h is monotone increasing for fixed γ_1 in direction of increasing γ_2. A straightforward calculation yields

$$\frac{\partial h}{\partial \gamma_2} = 2e^{-2(\gamma_1^2 + \gamma_2^2)}[(\gamma_1 - \gamma_2)e^{(\gamma_1 + \gamma_2)^2} - (\gamma_1 + \gamma_2)e^{(\gamma_1 - \gamma_2)^2} + 2\gamma_2 + 2\gamma_2 e^{2\gamma_1^2}(e^{2\gamma_2^2} - 1)].$$

To show that this is positive for $0 < \gamma_2 \leqslant \gamma_1$, we need to prove

$$\varphi(\gamma_1, \gamma_2) = (\gamma_1 - \gamma_2)e^{(\gamma_1 + \gamma_2)^2} - (\gamma_1 + \gamma_2)e^{(\gamma_1 - \gamma_2)^2} + 2\gamma_2 > 0$$

for such γ_2. Indeed, $\varphi(\gamma_1, \gamma_2) = 0$ if $\gamma_2 = 0$ or if $\gamma_1 = \gamma_2$, and

$$\frac{\partial \varphi}{\partial \gamma_1} = (e^{(\gamma_1 + \gamma_2)^2} - e^{(\gamma_1 - \gamma_2)^2})(1 + 2\gamma_1^2 - 2\gamma_2^2) > 0.$$

This finishes the proof of the lemma.

Lemma B.2. *For Gaussian stabilizing selection,* $ad - (b - c)^2 > 0$ *holds.*

Proof. We set $\gamma = \gamma_1 + \gamma_2$, $v = \gamma_1 - \gamma_2$, $x = v/\gamma$, and define

$$f(\gamma, x) = \frac{ad}{(b - c)^2} = e^{\frac{1}{2}\gamma^2(1 - x)^2} \frac{(1 - e^{-\gamma^2})(1 - e^{-\gamma^2 x^2})}{(1 - e^{-\gamma^2 x})^2},$$

where $0 < \gamma < \infty$ and $0 < x \leqslant 1$. Then $\lim_{x \to 0} f(\gamma, x) = \gamma^{-2}\sinh(\frac{1}{2}\gamma^2) > 1$ and $f(\gamma, 1) = 1$. We show that $f(\gamma, x)$ is monotone decreasing in x. It is straightforward to check that

$$\frac{\partial f(\gamma, x)}{\partial x} = \gamma^2 x^2 [g(\gamma, x) - g(\gamma, x^2)] \times \frac{\sinh(\frac{1}{2}\gamma^2)\cosh(\frac{1}{2}\gamma^2 x)\cosh(\frac{1}{2}\gamma^2 x^2)}{[\sinh(\frac{1}{2}\gamma^2 x)]^3},$$

where

$$g(\gamma, x) = \frac{1}{x}\tanh(\frac{1}{2}\gamma^2 x).$$

To prove that $f(\gamma, x)$ is monotone decreasing in x, it is sufficient to show that $g(\gamma, x)$ is monotone decreasing in x. Differentiation of g with respect to x yields

$$\frac{\partial g(\gamma, x)}{\partial x} = \frac{1 - e^{2\gamma^2 x} + 2x\gamma^2 e^{\gamma^2 x}}{x^2(1 + e^{\gamma^2 x})^2}.$$

This is indeed nonpositive for $0 \leqslant x \leqslant 1$, because the nominator is zero at $x = 0$ and its derivative is negative in $(0, 1)$. This proves Lemma B.2.

Appendix C. Global results for loci of equal effects

Here we derive global stability results for the case of equal effects. Actually, we deal with more general fitness functions than Gaussian stabilizing selection. We assume the general conditions (2.7), equal effects, i.e., $a = 0$ and $c = b$, and

$$d \geqslant 2b - b^2. \qquad \text{(C.1)}$$

Condition (C.1) is satisfied not only by the Gaussian fitness function, but also by the quadratic, triangular, or double exponential fitness function. It is not satisfied, for instance, if $W(G) = 1 - |G|^{1/2}$. In Bürger (2002), it is proved that the region $D \leqslant 0$ is positively invariant for every fitness scheme satisfying (2.7) and (C.1). Actually, $D' < 0$ holds if $D \leqslant 0$, except when one of the loci is monomorphic. For the Gaussian and the above-mentioned fitness functions, this is true even for loci with unequal effects (see Bürger, 2002).

In the following, however, we assume equal effects and the inequalities (2.7) and (C.1). First, we demonstrate that the region $\{D \leqslant 0\} \cup \{z \leqslant \frac{1}{3}\}$ is positively invariant. Because we already know that $D \leqslant 0$ is positively invariant, it is sufficient to show $z' \leqslant \frac{1}{3}$ if $z \leqslant \frac{1}{3}$ and $D \geqslant 0$. This follows from

$$\overline{W}(z' - \tfrac{1}{3}) = -4rD - \tfrac{1}{3}dx^2 - \tfrac{1}{12}[(3 - z)(1 - 3z) + (1 + z) \times (1 + d - 2b - z(3 - d - 2b))] \leqslant 0$$

because the expression in brackets is nonnegative if $z \leqslant \frac{1}{3}$.

The assumption of equal effects implies $W_2 = W_3$, so we obtain from the recursion relations

$$\frac{x_2'}{x_3'} = \frac{x_2 W_2 + rD}{x_3 W_2 + rD}. \tag{C.2}$$

We can conclude that each of the regions $x_2 > x_3$, $x_2 = x_3$, $x_2 < x_3$ is invariant under the dynamics. In addition, it follows that

$$\left(\frac{x_2'}{x_3'} - 1\right)^2 \geqslant \left(\frac{x_2}{x_3} - 1\right)^2 \tag{C.3}$$

if $D \leqslant 0$, and equality holds only if $x_2 = 1$ or $x_3 = 1$ or $D = 0$. Because $D \leqslant 0$ is positively invariant, this implies that all trajectories starting in $D \leqslant 0$ (except in $\mathscr{C}_1$ or $\mathscr{C}_4$) converge to either $\mathscr{C}_2$ or $\mathscr{C}_3$, depending on the initial fraction x_2/x_3 (except when $x_2 = x_3$; see below). This conclusion is also valid for trajectories starting in $D = 0$. It may be noted that the "$\geqslant$" sign in (C.3) can be replaced by a "$\leqslant$" sign if $D \geqslant 0$. Because $D \geqslant 0$ is not positively invariant, this does not imply that x_2/x_3 eventually converges to 1, but implies that the dynamics is simple, i.e., no limit cycles or more complex behavior can occur. A further consequence is that all trajectories starting in the positively invariant region $\{D \leqslant 0\} \cup \{z \leqslant \frac{1}{3}\}$ will enter the positively invariant region $D \leqslant 0$ because $(x_2/x_3 - 1)^2$ is a Lyapunov function on $\{D \geqslant 0\} \cap \{z \leqslant \frac{1}{3}\}$.

Hastings (1987) showed that $|x_1 - x_4| \to 0$, hence all trajectories converge to the plane $x_1 = x_4$.

Putting all this together, we have demonstrated that all trajectories starting in the region $\{D \leqslant 0\} \cup \{z \leqslant \frac{1}{3}\}$ converge to $\mathscr{C}_2$ if initially $x_2 > x_3$, and to $\mathscr{C}_3$ if $x_3 > x_2$. All others must also converge to an asymptotically stable equilibrium ($\mathscr{C}_2$, $\mathscr{C}_3$, or $\mathscr{S}_3$; trajectories with $x_2 = x_3$ may also converge to $\mathscr{S}_1$). The reason is that all trajectories converge to the plane $x_1 = x_4$, and the Lyapunov function $(x_2/x_3 - 1)^2$ on $D \geqslant 0$ implies that trajectories that do not enter $D \leqslant 0$ must converge to an asymptotically stable equilibrium, the only possibility being $\mathscr{S}_3$. If $\mathscr{S}_3$ does not exist, then all trajectories converge to either $\mathscr{C}_2$ or $\mathscr{C}_3$ (except those starting in the plane $x_2 = x_3$).

References

Barton, N., Keightley, P., 2002. Understanding quantitative genetic variation. Nat. Rev. Genet. 3, 11–21.

Barton, N.H., Turelli, M., 1989. Evolutionary quantitative genetics: how little do we know? Annu. Rev. Genet. 23, 337–370.

Bodmer, W.F., Felsenstein, J., 1967. Linkage and selection: theoretical analysis of the deterministic two locus random mating model. Genetics 57, 237–265.

Bulmer, M.G., 1971. The stability of equilibria under selection. Heredity 27, 157–162.

Bulmer, M.G., 1972. The genetic variability of polygenic characters under optimizing selection, mutation and drift. Genet. Res. 19, 17–25.

Bürger, R., 1986. On the maintenance of genetic variation: global analysis of Kimura's continuum-of-alleles model. J. Math. Biol. 24, 341–351.

Bürger, R., 2000. The Mathematical Theory of Selection, Recombination, and Mutation. Wiley, Chichester.

Bürger, R., 2002. Linkage disequilibria in two-locus models of stabilizing selection. Manuscript.

Bürger, R., Gimelfarb, A., 1999. Genetic variation maintained in multilocus models of additive quantitative traits under stabilizing selection. Genetics 152, 807–820.

Charlesworth, B., Lande, R., Slatkin, M., 1982. A neo-Darwinian commentary on macroevolution. Evolution 36, 474–498.

Christiansen, F.B., 1999. Population Genetics of Multiple Loci. Wiley, Chichester.

Endler, J.A., 1986. Natural Selection in the Wild. Princeton University Press, Princeton, NJ.

Falconer, D.S., Mackay, T.F.C., 1995. Introduction to Quantitative Genetics, 4th Edition. Addison–Wesley, Longman, NY.

Feldman, M.W., Liberman, U., 1979. On the number of stable equilibria and the simultaneous stability of fixation and polymorphism in two-locus models. Genetics 92, 1355–1360.

Fisher, R.A., 1930. The Genetical Theory of Natural Selection. Clarendon Press, Oxford.

Gale, J.S., Kearsey, M.J., 1968. Stable equilibria under stabilising selection in the absence of dominance. Heredity 23, 553–561.

Gavrilets, S., Hastings, A., 1993. Maintenance of genetic variability under strong stabilizing selection: a two-locus model. Genetics 134, 377–386.

Gavrilets, S., Hastings, A., 1994a. Maintenance of multilocus variability under strong stabilizing selection. J. Math. Biol. 32, 287–302.

Gavrilets, S., Hastings, A., 1994b. Dynamics of genetic variability in two-locus models of stabilizing selection. Genetics 138, 519–532.

Gimelfarb, A., 1989. Genotypic variation for a quantitative character maintained under stabilizing selection without mutations: epistasis. Genetics 123, 217–227.

Gimelfarb, A., 1996. Some additional results about polymorphisms in models of an additive quantitative trait under stabilizing selection. J. Math. Biol. 35, 88–96.

Hastings, A., 1985. Four simultaneously stable polymorphic equilibria in two-locus two-allele models. Genetics 109, 255–261.

Hastings, A., 1987. Monotonic change of the mean phenotype in two-locus models. Genetics 117, 583–585.

Hastings, A., Hom, C.L., 1990. Multiple equilibria and maintenance of additive genetic variance in a model of pleiotropy. Evolution 44, 1153–1163.

Hofbauer, J., Sigmund, K., 1998. Evolutionary Games and Population Dynamics. Cambridge University Press, Cambridge.

Karlin, S., Feldman, W.M., 1970. Linkage and selection: two locus symmetric viability model. Theor. Popul. Biol. 1, 39–71.

Kearsey, M.J., Gale, J.S., 1968. Stabilising selection in the absence of dominance: an additional note. Heredity 23, 617–620.

Kimura, M., 1981. Possibility of extensive neutral evolution under stabilizing selection with special reference to nonrandom usage of synonymous codons. Proc. Natl Acad. Sci. USA 78, 5773–5777.

Kingsolver, J.G., Hoekstra, H.E., Hoekstra, J.M., Berrigan, D., Vignieri, S.N., Hill, C.E., Hoang, A., Gibert, P., Beerli, P., 2001. The strength of phenotypic selection in natural populations. Amer. Nat. 157, 245–261.

Kojima, K.-I., 1959. Stable equilibria for the optimum model. Proc. Natl Acad. Sci. USA, 78.

Lande, R., 1975. The maintenance of genetic variability by mutation in a polygenic character with linked loci. Genet. Res. 26, 221–235.

Lande, R., 1976. Natural selection and random genetic drift in phenotypic evolution. Evolution 30, 314–334.

Latter, B.D.H., 1960. Natural selection for an intermediate optimum. Aust. J. Biol. Sci. 13, 30–35.

Lewontin, R.C., 1964. The interaction of selection and linkage. II. Optimum models. Genetics 50, 757–782.

Mackay, T.F.C., 2001. Quantitative trait loci in *Drosophila*. Nat. Rev. Genet. 2, 11–20.

Nagylaki, T., 1984. Selection on a quantitative character. In: Chakravarti, A. (Ed.), Human Population Genetics: The Pittsburgh Symposium. Van Nostrand, New York, pp. 275–306.

Nagylaki, T., 1989. The maintenance of genetic variability in two-locus models of stabilizing selection. Genetics 122, 235–248.

Robertson, A., 1956. The effect of selection against extreme deviants based on deviation or homozygosis. J. Genet. 54, 236–248.

Singh, M., Lewontin, R.C., 1966. Stable equilibria under optimizing selection. Proc. Natl Acad. Sci. USA 56, 1345–1348.

Turelli, M., 1984. Heritable genetic variation via mutation-selection balance: lerch's zeta meets the abdominal bristle. Theor. Popul. Biol. 25, 138–193.

Wright, S., 1935. Evolution in populations in approximate equilibrium. J. Genet. 30, 257–266.