DIPLOID SEQUENCE SPACE, DOMINANCE, AND EVOLUTION

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ABSTRACT Deterministic models of mutation and selection on the space of (binary) nucleotide-type sequences have been investigated for haploid populations during the past 25 years, and, recently, for diploid populations as well. We consider them here by means of bifurcation theory, which reveals new features of the well-known error threshold phenomenon, on the one hand, and of dynamical properties, on the other.
In a caricature obtained from the original model by neglecting certain small mutation terms, the familiar error threshold of the haploid two-class model turns out to be a simple transcritical bifurcation, whereas its diploid counterpart exhibits an additional saddle node. This corresponds to a second error threshold. Its implications for the evolution of dominance is discussed, and further corroborated by considerations of substitution times.
Three-class models introduce further features. Such are a global bifurcation in haploid populations, and limit cycles in the diploid case.

Keywords: sequence space, selection, mutation, error threshold, bifurcations.

1 Introduction

Several types of sequence space models are now well-established in the theory of (molecular) biological evolution, the most well-known being Kauffman's adaptive walks and Eigen's quasispecies model (for reviews, see Kauffman, 1993, Part I, and Eigen *et al.*, 1989). Their common theme is the movement of a population on (more or less) complex fitness landscapes on the space of (binary) sequences under the influence of mutation and selection; they differ in the way the interplay between selection and mutation is treated.

Kauffman's models describe adaptive walks of homogeneous populations. Every time a mutation occurs, the population as a whole assumes the new genotype if the mutant is fitter, otherwise the mutation is rejected and the population remains unchanged. Thus, the population is genetically homogeneous all the time. The quasispecies model, on the other hand, describes a population made up from different individuals, each of which reproduces according to its own fitness, and may mutate at every such occasion, depending on whether or not the genetic information is copied correctly during the process of replication.

In a previous paper (Baake, 1995), a variant was introduced that models reproduction and mutation as independent processes, mutations being caused by external influences (like radiation) that happen at a constant rate during the life cycle of an organism. We called it the decoupled sequence space model since, unlike in the quasispecies model, mutation is not coupled to reproduction. It should be noted that both the quasispecies model and the decoupled variant are sequence space versions of the classical selection-mutation equations of population genetics (see Crow & Kimura, 1970, Ch. 6, and Hadeler, 1981). It has been shown by Hofbauer (1985) that, for small fitness differences and small mutation rates, both models are essentially equivalent. Moreover, they were demonstrated to have very similar properties even for large mutation rates (Wiehe *et al.*, 1995). It seems thus justified to rely on the decoupled version, which is mathematically simpler. In a few cases at least, this makes possible a complete analysis of the bifurcation structure, for both the classical haploid and the more recent diploid selection regimes (Baake & Wiehe, 1996). This yields a global picture that reveals new features of the well-known error threshold phenomenon, on the one hand, and of dynamical properties, on the other.

After recalling the decoupled selection-mutation equation and its sequence space version, we revisit the haploid and diploid two-class models and show how the latter may give rise to *bistability* and to *two* types of error threshold (Section 3). As a generalization, a three-class model is introduced in Section 4. It exhibits several types of bifurcations, including a global bifurcation in the haploid version, and Hopf bifurcations in the diploid case. We will discuss implications for the evolution of dominance.

2 The model

The independent action of selection and mutation on the composition of an (infinite) diploid population with overlapping generations in Hardy-Weinberg proportions is described by the *decoupled* selection-mutation equation

$$\dot{x}_i \;=\; x_i\,((Wx)_i - (x, Wx)) + (Mx)_i\,, \qquad i = 1, \ldots, n\,, \tag{1}$$

as formulated by Crow & Kimura (1970), and thoroughly investigated by Akin (1979). Here, n is the number of alleles, and x_i denotes the relative frequency of allele A_i (with $\sum_i x_i = 1$). Recall that, in continuous time, Hardy-Weinberg proportions are only an approximation (Hadeler, 1974). W is the symmetric $n \times n$ matrix of (not necessarily positive) Malthusian fitness parameters of (ordered) $\mathrm{A}_i\mathrm{A}_j$ genotypes, and $(Wx)_i := \sum_{j=1}^{n} w_{ij} x_j$ is the marginal fitness of allele A_i. With (x, y) the usual scalar product of vectors x, y, (x, Wx) is the average fitness of the population. M is the mutation matrix with elements $m_{ij} := m_{i \leftarrow j}$ denoting the mutation rate from A_j to A_i for $i \neq j$, and $m_{ii} = -\sum_j m_{ji}$. In a previous paper (Baake, 1995), we introduced a sequence space version of this model. Considering as 'alleles' A_i all possible binary strings of length ν, we have $n = 2^\nu$ and

$$m_{ij} = \begin{cases} \mu\,, & d_{ij} = 1 \\ -\nu\mu\,, & i = j \\ 0\,, & \text{otherwise} \end{cases} \tag{2}$$

where μ is the single digit mutation rate, and $d_{ij} := d(A_i, A_j)$ is the Hamming distance (see, e.g., van Lint, 1982, Ch. 3) between A_i and A_j.

3 The diploid two-class model and error thresholds

A well-established case study in the context of sequence space models is the so-called single-peaked landscape (SPL), a two-class model with one 'fit' allele and competitors of reduced fitness (but equal for all of them). In the haploid context, it has long served to demonstrate the error threshold phenomenon, i.e. the virtual loss of the favourable allele due to accumulation of mutants when a critical mutation rate is surpassed (Eigen *et al.*, 1989). In the context of multi-locus theory, an equivalent fitness landscape has recently been used as a model of complete epistasis (Slatkin, 1995).

As a slight generalization of what has previously been called single-peaked landscape, consider a sequence of length ν with κ 'selected' sites and $\nu - \kappa$ neutral ones. We assume the selective properties of a sequence to depend only on whether it is 'correct' at all κ prescribed positions ('favourable' class B_1) or not ('mutant' class B_2). Denoting by $|B_i|$ the number of sequences in B_i, we obviously have $|B_1| = 2^{\nu-\kappa}$ and $|B_2| = 2^\nu - 2^{\nu-\kappa}$. As long as all mutation terms in (2) are respected, the size of the ODE system (1) remains unchanged. If we consider, however, a caricature of the original model by neglecting mutations from B_2 to B_1 (which is a good approximation if $|B_1| \ll |B_2|$, e.g., $\kappa > 3$), we may lump together as x_1 and x_2 the relative frequencies of all alleles in B_1 and B_2. This yields the equivalent of a classical two allele model (with $x_2 = 1 - x_1$). Denoting by W the corresponding 2×2 fitness matrix, the decoupled equation reads (note the factorization of the right-hand side)

$$\dot{x}_1 = f(x_1) = x_1((Wx)_1 - (x, Wx) - \kappa\mu) = x_1 g(x_1)\,, \tag{3}$$

where

$$g(x_1) := -\phi x_1^2 + (\phi - r)x_1 + r - \kappa\mu$$

and

$$\phi := w_{11} + w_{22} - 2w_{12}\ , \quad r := w_{12} - w_{22}\ .$$

It reduces to the previously-treated model if $\kappa = \nu$. Note that $\phi = 0$ is equivalent to $w_{12} = \frac{1}{2}(w_{11} + w_{22})$, i.e., the diploid model reduces to the haploid case. The case $\phi = r = 0$ corresponds to the case without any fitness differentials and will not be considered here. For $r \geq 0$ and $\phi + r \geq 0$ (but not both quantities zero), we have a single-peaked landscape in the strict sense, i.e., mean fitness is largest in a pure B_1 population.

3.1 Equilibria

For $\phi \neq 0$, the three equilibria of eq. (3) are

$$x_1^{(0)} = 0 \quad \text{and} \quad x_1^{(\pm)} = \frac{1}{2\phi}\left((\phi - r) \pm (\phi + r)\sqrt{1 - \frac{4\kappa\mu\phi}{(\phi + r)^2}}\right) \tag{4}$$

(here and in what follows, singular denominators can be treated properly by l'Hôpital's rule). Thus, the equilibria are the μ-axis, and a parabola in the (μ, x_1)-plane; they intersect at

$$\mu_1 := \frac{r}{\kappa} = \frac{w_{12} - w_{22}}{\kappa}\ ,$$

and the parabola's vertex is at (μ_2, β), where

$$\mu_2 := \frac{(\phi + r)^2}{4\kappa\phi} = \frac{(w_{11} - w_{12})^2}{4\kappa\phi} \quad \text{and} \quad \beta := \frac{1}{2} - \frac{r}{2\phi}\ .$$

For $\mu = 0$, $x_1^{(+)} = 1$, i.e. a pure B_1 population, and

$$x_1^{(-)} = -\frac{r}{\phi} =: \xi \tag{5}$$

is the nontrivial equilibrium. $x_1^{(+)}$ and $x_1^{(-)}$ coalesce when $\phi + r = 0$.

The stability of these equilibria is determined by

$$f'(x_1) = x_1 g'(x_1) + g(x_1)\ . \tag{6}$$

For $x_1^{(0)}$, this reduces to

$$f'(0) = g(0) = r - \kappa\mu\ . \tag{7}$$

For $x_1^{(\pm)}$, we find $f'(x_1^{(\pm)}) = x_1^{(\pm)}\left(-2\phi x_1^{(\pm)} + (\phi - r)\right)$ or, using eq. (5),

$$f'(x_1^{(\pm)}) = \mp x_1^{(\pm)}(1-\xi)\phi\sqrt{1 - \frac{4\kappa\mu}{\phi(1-\xi)^2}} \,.$$

Of course, only equilibria with $0 \leq x_1 \leq 1$ and $\mu \geq 0$ are relevant. It is, however, more instructive to ignore this restriction for the moment.

Let us restrict discussion to $r \geq 0$, $\phi + r \geq 0$. Then, inspection of eqns. (6) and (7) shows that, with μ as the bifurcation parameter, a saddle-node bifurcation occurs at μ_2 and a transcritical bifurcation at μ_1, provided $\phi \neq 0$ and $\mu_1 \neq \mu_2$. For $\mu_1 = \mu_2$ (which is equivalent to $\phi = r$), both bifurcations coalesce into a pitchfork bifurcation, which is supercritical (subcritical) if $\phi > 0$ ($\phi < 0$).

For $\phi = 0$ (but $r > 0$), the situation is characterized by

$$\lim_{\phi \to 0} \frac{\beta}{\mu_2} = -2\frac{\kappa}{r} \,,$$

and the saddle node does not occur (but the transcritical bifurcation remains).

In order to seek nonnegative equilibria, let us specify the fitness scheme

$$w_{11} = 1 + 2s, \quad w_{12} = 1 + 2hs = w_{21}, \quad w_{22} = 1 \,, \tag{8}$$

where $s > 0$ is the selective advantage and h the dominance coefficient ($0 \leq h$). This yields $r = 2sh$, $\phi = 2s(1-2h)$, $\phi + r = 2s(1-h)$, and

$$\mu_1 = \frac{2sh}{\kappa}, \quad \mu_2 = \frac{(1-h)^2 s}{2\kappa(1-2h)} \,.$$

The stability properties of the three equilibria are summarized in Fig. 1 for the various regimes of h. Note that, for $h > 1$ (the so-called overdominant case), $\phi + r < 0$, i.e., we do not have a strict SPL.

The haploid situation corresponds to $h = 1/2$. Obviously, the classical error threshold of the haploid population on a single-peaked landscape emerges as a transcritical bifurcation in the model without back mutation. For $0 \leq h < 1/2$, we find two stable equilibria as long as $\mu_1 < \mu < \mu_2$, with the unstable branch of the parabola separating their domains of attraction. A bistable regime has been observed before by Bürger (1983) for the two-allele selection-mutation equation with one-way mutation. An equivalent situation pertains in the selection-migration equation as treated by Nagylaki (1975) in his 'Island model' (see also Nagylaki, 1992, Ch. 6). We have previously constructed examples of multiple equilibria in the full sequence space model with

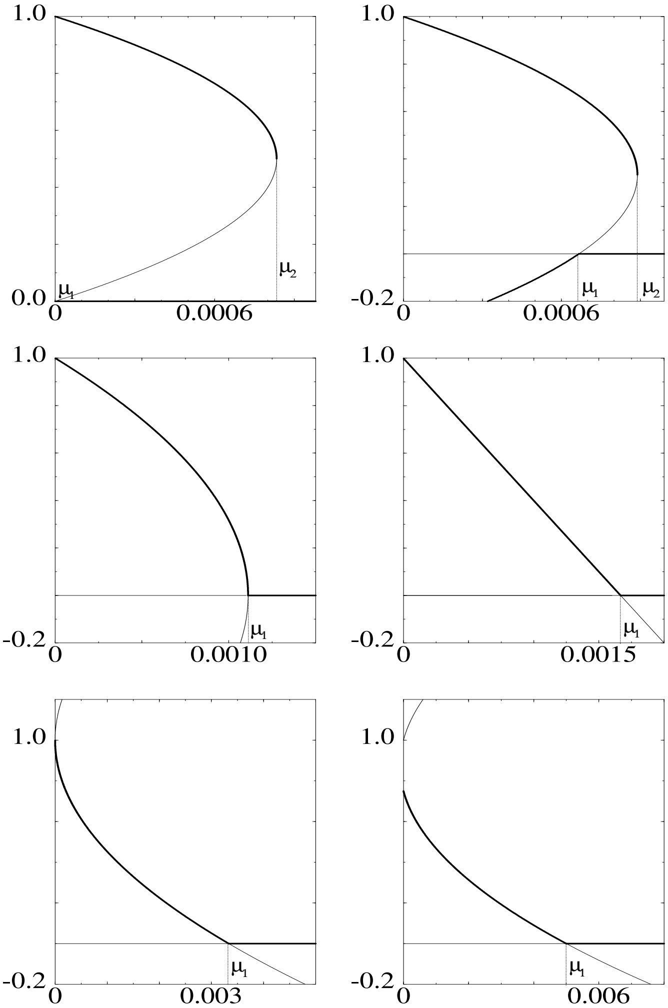

Figure 1: Equilibria of the diploid two–class model, eq. (3), with fitness parameters as in eq. (8) for various values of h. Horizontal axis: μ; vertical axis: x_1. From top left to bottom right $h = 0,\ 1/5,\ 1/3,\ 1/2,\ 1,\ 3/2$. Other parameters: $s = 1/20$, $\nu = 30$. Bold lines: stable equilibria; thin lines: unstable equilibria. Note that there are two (biologically relevant) stable equilibria for $h = 1/5$.

several alleles and back mutation (Wiehe *et al.*, 1995). We may conclude that there are two error thresholds, which depend on initial conditions. This hysteresis illustrates an important difference between haploid and diploid sequence space models. The global stability guaranteed in haploid versions as long as $\mu > 0$ (Moran, 1976; Wiehe *et al.*, 1995) assures the identity between what we would like to call 'static' and 'dynamic' aspects of error thresholds. The static aspect refers to the question how much mutation a population can tolerate once it has found a fitness peak. This is the familiar question behind models of error thresholds (and of Muller's ratchet as well; see Wagner & Krall, 1993). Dynamic aspects, on the other hand, result from the question of how much mutation a new favourable allele can tolerate while still on its way to establish itself. In diploid situations, the answers need not be the same. In the bistable regime, the static error threshold is at μ_2, whereas the dynamic one is at $\mu_1 < \mu_2$. In the extreme case of $h = 0$, the favourable allele is completely recessive and will never manage to establish itself in the population if its initial frequency is low. Thus, during 'evolution' (in its literal sense), a favourable allele may be more vulnerable to mutational loss than in a stationary state—independently of additional stochastic effects.

3.2 Substitution times

The dynamic error threshold may also be understood in terms of substitution times. Assuming that s and the population size N are not too small, we may follow the argument in Stephan *et al.* (1992) to determine the time $\tau_{1-\varepsilon}$ it would take for a newly introduced allele (frequency $\varepsilon := 1/(2N)$) to be substituted in the population (frequency $1 - \varepsilon$) *under the action of selection alone.* For $h = 1/2$, the solution of the pure selection equation,

$$\dot{x}_1 = s x_1 (1 - x_1)\,, \tag{9}$$

with initial condition $x(0) = \varepsilon$ yields

$$\tau_{1-\varepsilon} \;=\; \frac{2}{s}\,(-\ln(\varepsilon) \;+\; \ln(1-\varepsilon)) \;\simeq\; \frac{2}{s}\ln\frac{1}{\varepsilon} \;=\; \frac{2}{s}\ln(2N)\,.$$

In the same way, one obtains $\tau_{2\varepsilon}$, the duration of the initial phase during which the new allele is established in a second copy:

$$\tau_{2\varepsilon} \;=\; \frac{1}{s}\left(\ln(2) \;+\; \ln(1 + \frac{\varepsilon}{1-2\varepsilon})\right) \;\simeq\; \frac{1}{s}\ln(2)\,.$$

These are both relatively short times (remember that s is not 'small'). Let us now examine the situation where the new allele is favourable but recessive. In the extreme case of $h = 0$, the differential equation reads

$$\dot{x}_1 = 2sx_1^2(1 - x_1) \tag{10}$$

and yields

$$\begin{aligned}\tau_{1-\varepsilon} &= \frac{1}{2s}\left(-\frac{1}{1-\varepsilon} + \frac{1}{\varepsilon} + 2\ln(1-\varepsilon) - 2\ln(\varepsilon)\right) \simeq \frac{1}{2s}\left(\frac{1}{\varepsilon} + 2\ln\frac{1}{\varepsilon}\right) \\ &= \frac{1}{s}(N + \ln(2N))\end{aligned}$$

and

$$\tau_{2\varepsilon} \simeq \frac{1}{2s}(N + \ln(2))\,.$$

These are much longer times, and the 'dangerous' initial phase where less than two favourable alleles are present in the population accounts for roughly half the substitution time. This slow increase is intuitively clear from the fact that a completely recessive allele is effectively neutral as long as it is present as a single copy only. It is likely to be hit by a mutation during this long phase – and then it is lost from the population.

Let us recall that a 'long time' in the deterministic equation is to be understood as an average over many (finite) populations, or, equivalently, over many introduction events of a favourable allele into the same population. For a given event, the new allele will either be lost or fixed much faster. In this sense, a long substitution time corresponds to a low fixation probability.

4 Three-class models

We will now turn to situations with two favourable classes, B_1 and B_2, with the class B_3 comprising all other sequences. The ODE then lives on the two-dimensional unit simplex embedded in $\mathbb{R}^3$, which is, in barycentric coordinates,

$$S_2 := \{x \mid x = \sum_{i=1}^{3} x_i \widehat{e}_i\,,\ x_i \geq 0\,,\ \sum_{i=1}^{3} x_i = 1\}\ ,$$

where the $\widehat{e}_i$ are the canonical unit vectors of $\mathbb{R}^3$. For our purposes, however, it turns out more convenient to choose

$$S_2 = \{x | x = \widehat{e}_3 + \sum_{i=1}^{2} y_i(\widehat{e}_i - \widehat{e}_3)\ , y_i \geq 0,\ \sum_{i=1}^{2} y_i \leq 1\}\ ,$$

where it is natural to distinguish the $\widehat{e}_n$ vertex, which corresponds to the pure mutant population. With $y = (x_1, x_2)^t$ as the new vector of variables, the selection terms entering the ODE become

$$(Wx)_i - (x, Wx) = r_i + (\Phi y)_i - (r, y) - (y, \Phi y) \,, \quad i = 1, 2 \,. \tag{11}$$

Here Φ is a symmetric 2×2 matrix and r a vector $\in \mathbb{R}^2$ with elements

$$r_i = w_{i3} - w_{33} \quad \text{and} \quad \phi_{ij} = w_{ij} - w_{i3} - w_{j3} + w_{33} \,. \tag{12}$$

For an interpretation of Φ and r, consider the case of intermediate fitness, i.e., $w_{ij} = \frac{1}{2}(w_{ii} + w_{jj})$. In this case, $\Phi = 0$, and $r_i = \frac{1}{2}(w_{ii} - w_{33})$, $i = 1, 2$. Obviously, the terms involving Φ vanish, and the r_i may be interpreted as haploid fitness parameters (relative to the fitness of the mutant class).

4.1 Haploid populations and mutual exclusion

Let us now consider the decoupled equation describing a haploid situation with two favourable classes B_1, B_2 which comprise all sequences that are correct at κ_1, κ_2 selected positions, and the mutant class B_3 comprising all other sequences. We only consider situations where $d(B_1, B_2) := \min\{d(A_i, A_j), A_i \in B_1, A_j \in B_2, i \neq j\} > 1$, which ensures that B_1 and B_2 are disjoint, and no direct mutation occurs between the two classes in the decoupled system. It also implies that $d(B_1, B_3) = d(B_2, B_3) = 1$, i.e., both B_1 and B_2 mutate to B_3 directly. Using the notation of the previous Section, $\Phi = 0$, and $r_1, r_2 > 0$. Neglecting back mutation makes sense then as long as $|B_1| \ll |B_3|$, $|B_2| \ll |B_3|$, which may be assumed if $\kappa_1, \kappa_2 > 3$.

The model then reads

$$\dot{y}_i = f_i(y) = y_i g_i(y) = y_i \left(r_i - (r, y) - \kappa_i \mu\right) \,, \quad i = 1, 2. \tag{13}$$

Note that the y_1-and y_2-axes are invariant under the flow.

This model can be considered as a special case of Lotka's competition model,

$$\dot{y}_1 = y_1(a - by_1 - cy_2) \tag{14}$$
$$\dot{y}_2 = y_2(d - ey_1 - fy_2) \,, \tag{15}$$

with the choice $a = r_1 - \kappa_1 \mu$, $d = r_2 - \kappa_2 \mu$, $b = e = r_1$, and $c = f = r_2$. Since its behaviour is well known (see, e.g., Hofbauer & Sigmund, 1988, Ch. 8), we can treat it very quickly.

There are, of course, four types of equilibria of the ODE (13):

(A) $y_1 = y_2 = 0$ (pure B_3 population)

(B) $y_1 = 0,\ g_2(y) = 0$ (B_2B_3 population)

(C) $g_1(y) = 0,\ y_2 = 0$ (B_1B_3 population) and

(D) $g_1(y) = g_2(y) = 0$ ('coexistence').
The two nullclines, $g_1(y) = 0$ and $g_2(y) = 0$, are straight lines parallel to each other. They coalesce when $r_1 - \kappa_1\mu = r_2 - \kappa\mu$; then, we have a straight line of equilibria.

In order to summarize the bifurcation behaviour, we assume $r_1 \geq r_2$ without loss of generality. Let us define

$$\mu_0 := \frac{r_1 - r_2}{\kappa_1 - \kappa_2}\ , \quad \mu_1 := \frac{r_1}{\kappa_1}\ , \quad \mu_2 := \frac{r_2}{\kappa_2}\ ,$$

and further assume $\mu_1 \neq \mu_2$ in order to exclude nongeneric cases. Then it is easy to see that, at $\mu = \mu_1 := r_1/\kappa_1$ and $\mu = \mu_2 := r_2/\kappa_2$, the equilibria (C) and (B), respectively, leave the simplex via transcritical bifurcations with the origin, (A). This corresponds to the error-threshold bifurcation of the haploid two-class model. Additionally, at $\mu = \mu_0$, a straight line of equilibria (D) emerges containing (B) and (C), which exchange stabilities *across* this line. This is a *global* bifurcation in the sense that, at $\mu = \mu_0$, the phase portrait is not structurally stable. This is particularly relevant if $\kappa_1 > \kappa_2$ but $\mu_1 < \mu_2$, which is illustrated in Fig. 2. This is the situation where the less fit sequence has a larger number of neutral positions and is thus less vulnerable by mutation. It is inferior to the fittest string as long as mutation rates are small but outcompetes it at higher mutation. The remarkable feature of this transition is the discontinuity in the position of the stable equilibrium, in contrast to the (continuous) transcritical bifurcation of the haploid error threshold. It is also obvious that B_1 and B_2 can only coexist for singular parameter values – mutual exclusion is a generic feature of Lotka's model.

A situation with two favourable sequences, a tall narrow peak in sequence space competing with a less high but broader one has been studied by Schuster & Swetina (1988) with the help of approximations and numerical simulations. In the latter, they observe the transition between the two kinds of quasispecies to be remarkably sharp, in contrast to the continuous 'classical' error threshold. The underlying nature of these two thresholds is clarified by the above bifurcation analysis.

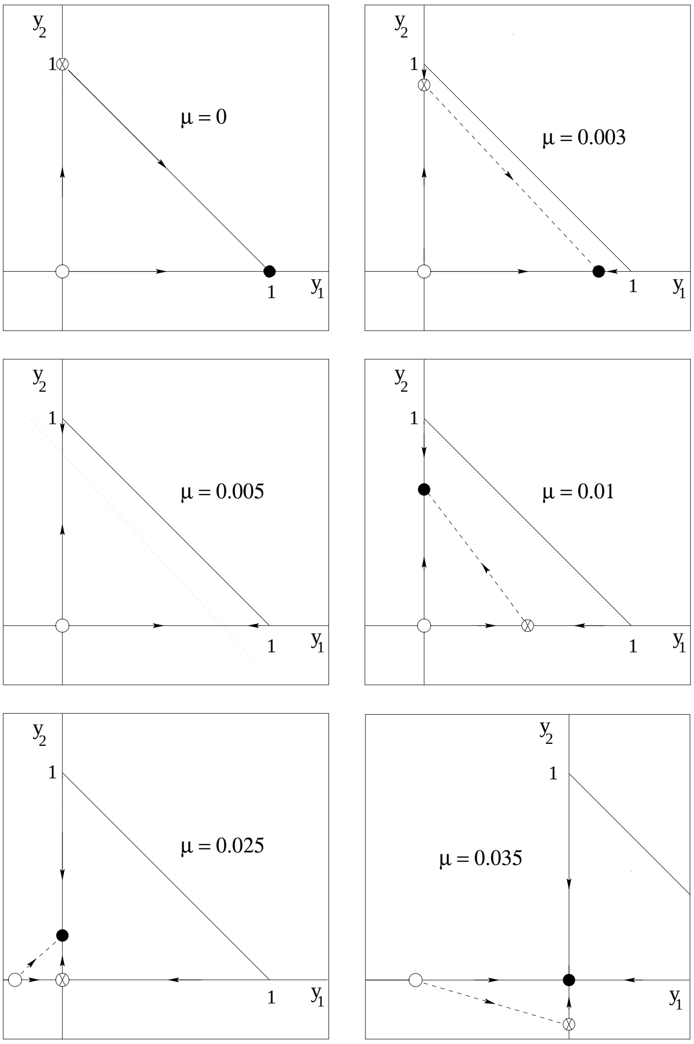

Figure 2: Equilibria of the haploid three-class model, eq. (13), for various values of μ. Other parameters: $r_1 = 1, r_2 = 9/10, \kappa_1 = 50, \kappa_2 = 30$. Bullets: stable equilibria; open circles: unstable equilibra; crossed circles: saddle points. Dashed: saddle node connection joining the equilibria (B) and (C). Dotted: line of equilibria (D). Arrows indicate the direction of the flow. For $0 < \mu < \mu_0$, the stable equilibrium is (C) but exchanges stability with (B) when μ passes through μ_0. Increasing μ further leads to loss of (C) from S_2 at $\mu = \mu_1$, and of (B) at $\mu = \mu_2$, after which the origin is the only equilibrium in S_2, and is stable.

5 Diploid populations and limit cycles

We now turn to diploid three-class models, i.e.

$$\dot{y}_i = f_i(y) = y_i \, g_i(y), \quad i = 1, 2, \tag{16}$$

where (cf. eq. (11))

$$g_i(y) = r_i + (\Phi y)_i - (r, y) - (y, \Phi y) - \kappa_i \mu \tag{17}$$

with $\Phi \neq 0$. As long as $\kappa_1 = \kappa_2$, the mutation rates of the system in barycentric coordinates have the form $m_{ij} = m_i$ for $i \neq j$, with $m_1 = m_2 = 0, m_3 = \kappa\mu$. It has been shown by Hofbauer (1985) that, in this special case, the differential equation is a gradient with respect to the Shahshahani metric, as long as it is confined to $\mathring{S}_2$, the interior of S_2. This guarantees that all solutions converge to the set of equilibria, and the eigenvalues of the linearization at these equilibria are real. In particular, periodic orbits are excluded. However, we have shown previously (Baake & Wiehe, 1996) that Hopf bifurcations do take place *outside* of S_2. For $\kappa_1 \neq \kappa_2$, these may be displaced into the interior of S_2, giving rise to Hopf bifurcations. The latter are predicted by Akin's theorem for all mutation vectorfields which are not Shahshahani gradients (Akin, 1979, Ch. IV). Our previous analysis relied on the local properties of the equilibria which are not on the coordinate axes. We will complement this view here by looking at the complete picture including boundary equilibria, and see how limit cycles may emerge from the nontrivial equilibria which wander into the interior of S_2.

The equilibria of (16) are of types (A)–(D) like in the haploid case, that is, they occur on the y_1- or y_2-axis, or when $g_1(y) = g_2(y) = 0$. The latter, however, occurs generically now in contrast to the haploid case. All equilibria may be calculated explicitly, but this yields unwieldy expressions in the case (D). For $\mu = 0$, there are, generically, two solutions of (D): one is on the straight line through $(1,0)^t$ and $(0,1)^t$ (we will call it the $B_1 B_2$-equilibrium in the following); the other one is, in general, on none of the straight lines that contain the edges of S_2 (we will therefore call it the 'nontrivial' equilibrium).

Obviously, the flow on every axis corresponds to a two-class situation as dealt with in detail in Section 3. It has a similar bifurcation structure with transcritical and saddle-node bifurcations, which may give rise to multiple stability and multiple error thresholds. What makes the picture more complicated is the fate of the equilibria (D).

Let us, for definiteness, turn to a numerical example (see Fig. 3). The fitness landscape chosen is quite inconspicuous; it has a global maximum, with the homozygote B_1 the fittest genotype. Thus, without mutation, both equilibria (D) are outside S_2. With increasing μ, however, they wander into $\mathring{S}_2$, via exchange of stability with the equilibria (B) and (C) on the y_1- and y_2-axes. Then, a homoclinic orbit forms from the stable and unstable manifolds of the (former) B_1B_2-equilibrium, with the nontrivial equilibrium inside as the spiral source, which gives rise to a stable limit cycle. Increasing μ further makes the limit cycle shrink and disappear in a 'backward' Hopf bifurcation, and finally, the (D) equilibria dematerialize in a saddle-node bifurcation.

6 Discussion

We have tackled examples of decoupled sequence space selection-mutation models with two and three fitness classes. They turn out to allow a characterization of error thresholds and similar transition phenomena as bifurcations. In the simplest example, the well-known error threshold of the haploid single-peaked landscape emerges as a transcritical bifurcation. The diploid single-peaked landscape has both a transcritical and a saddle-node bifurcation, providing for the bistability observed before (Bürger, 1983; Wiehe *et al.*, 1995). As a consequence, one finds two error thresholds in such models, associated with a 'static' and 'dynamic' aspect of evolution, respectively. Establishing a favourable mutant may be much more sensitive to mutation than is maintenance of genetic information. In the extreme case of complete recessivity, it may never succeed, even in a single-peaked fitness landscape. These equilibrium considerations are further corroborated by studies of convergence times. For a favourable but recessive allele, fixation times are greatly prolonged as compared with an intermediate fitness scheme; so is the dangerous initial phase, during which the new rare mutant is easily lost due to mutation pressure. This might shed new light on the old question of evolution of dominance. The observation that the wild type is often dominant sollicited the classical controversy between Fisher and Wright in the twenties and thirties, Fisher explaining dominance as the result of the action of some modifier locus (e.g. Fisher, 1928), Wright (1934) insisting on dominance as a physiological property of the gene product. The question has remained a matter of debate ever since (the referees of the present paper disagreed, too). Its present status is surveyed by Wagner & Bürger (1985), Orr (1991), and Mayo & Bürger (1996). The cautious conclusion may be drawn that many cases of dominance stem from physiological reasons, as is suggested by experiments with 'artificial diploids' from the normally haploid *Chlamodomonas reinhardtii*; there are, however, definite examples of dominance modification of heterozygotes, like the evolution of industrial melanism. Nevertheless, our analysis allows to speculate about a third possibility. Certain recessive mutants might not have been established in the population because this would have taken too long; they were eliminated by

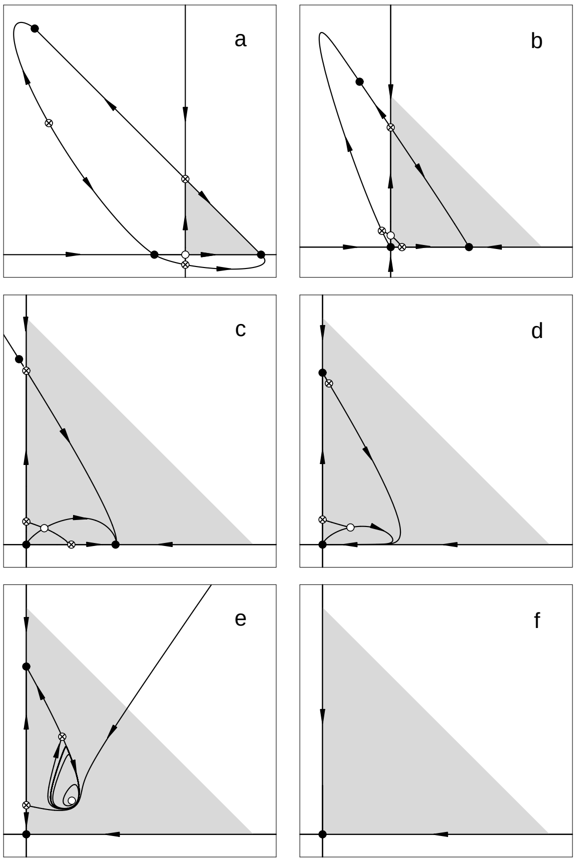

Figure 3: Equilibria and selected trajectories of the diploid three-class model (16) for various values of μ. Sequence lengths: $\kappa_1 = 30$, $\kappa_2 = 10$. Fitness parameters: $w_{11} = 8.653$, $w_{12} = 5.772$, $w_{13} = 0.621$, $w_{22} = 3.855$, $w_{23} = -1.127$, $w_{33} = -1.706$. Horizontal axes: y_1; vertical axes: y_2. Bullets: stable equilibria; open circles: unstable equilibra; crossed circles: saddle points. The unit simplex is shaded. (a) $\mu = 0$. (b) $\mu = 0.085$; two equilibria on the axes have entered S_2 via a transcritical bifurcations with the equilibrium at the origin. (c) $\mu = 0.093$; the nontrivial equilibrium has entered S_2 via a transcritical bifurcation with an equilibrium on the y_1 axis. (d) $\mu = 0.095$; two equilibria on the y_1 axis have vanished in a saddle node, and the B_1B_2-equilibrium has entered S_2 in a transcritical bifurcation with an equilibrium on the y_2 axis. (e) $\mu = 0.1$; a homoclinic orbit has formed from the stable and unstable manifolds of the former B_1B_2-equilibrium, with the nontrivial equilibrium inside as a spiral source that ejects a stable limit cycle. (f) $\mu = 0.15$; the limit cycle has collapsed onto the nontrivial equilibrium ('backward' Hopf bifurcation); both equilibria in the interior have vanished through a saddle node; so have two equilibria on the y_2 axis; the origin is left as the only equilibrium, and is stable.

mutation pressure before selection managed to establish them in the population.

The haploid three-class model exhibits a global bifurcation which explains the behaviour of the 'quasi-degenerate quasispecies' observed before numerically and with the help of approximations (Schuster & Swetina, 1988).

The diploid three-class model exhibits stable limit cycles, even for very simple fitness landscapes. This complements the results of Hofbauer (1985) who found limit cycles in selection-mutation models with *cyclic* mutation (which is, however, hard to interpret in molecular terms). In our case, the periodic orbit emerges from equilibria that wander from the outside into the interior of the simplex when the mutation rate increases. It is not clear whether such cycles are observable in real populations. But they demonstrate that, even in seemingly simple situations, mutation-selection balance need not be a simple matter.

Finally, a word is in order concerning the relevance of the fitness landscapes considered in this paper. We are well aware of the fact that there is no obvious biological justification for landscapes with one (or two) isolated peaks (Charlesworth, 1990); after all, they rely on a fittest allele that is so rare in sequence space that it may never have been found. Numerical investigations have, however, demonstrated the error threshold phenomenon in more realistic, rugged landscapes (see, e.g., Tarazona, 1992). Our idealized examples should thus be understood as case studies that are tractable analytically and provide some ideas for the mathematical structure that may underly more complicated cases. Analytical results for more plausible fitness landscapes have been presented elsewhere (Baake *et al.*,1997).

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