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Hofbauer, J.

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Josef Hofbauer

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INTERNATIONAL INSTITUTE FOR APPLIED SYSTEMS ANALYSIS
A-2361 Laxenburg, Austria

PREFACE

Fisher's Fundamental Theorem of Natural Selection is extended to the selection mutation model with mutation rates $\varepsilon_{ij} = \varepsilon_i$, i.e. depending only on the target gene, by constructing a simple Lyapunov function. For other mutation rates stable limit cycles are possible. A basic tool is the description of some of the dynamical models as gradients with respect to a non-Riemann metric.

A. Kurzhanski
Chairman
System and Decision
Sciences Program

THE SELECTION MUTATION EQUATION

Josef Hofbauer
Institut für Mathematik, Universität Wien, Austria

The classical selection model in population genetics, due to Fisher, Wright and Haldane, is in principle well understood. The basic result is Fisher's "Fundamental Theorem of Natural Selection" saying that the mean fitness of the population is steadily increasing, which is true for both the discrete time and continuous time model (see e.g. [4,5,6,11,13]. From this one can conclude that the state of the population tends to equilibrium [12].

For more general selection models, taking into account e.g. recombination, mutation or different fertilities, the state of knowledge is less satisfying. The basic problem would be to extend the "fundamental theorem" to these more general models, i.e. to prove that mean fitness, or some suitable generalization of it, is a Lyapunov function. Then the dynamic behaviour would again be reduced to a study of fixed points. The main success in this direction, and essentially the only one (besides Theorem 1 below), was Ewens' generalization to multi-locus systems with additive fitness scheme [5]. In contrast to this Akin [1,2] proved a very general theorem (Theorem 5 below) implying that most of the extensions of the classical selection equation, in particular those allowing recombination or mutation, exhibit a more complicated dynamical behaviour: oscillations (periodic orbits, stable limit cycles) are possible. Hence the usual fixed point analysis cannot provide a complete and adequate picture of the evolution of the population. In particular the search for maximizing principles (= Lyapunov functions) is a hopeless task. (See [9] for a recent survey on this question).

This paper is devoted to a study of combined action of selection and mutation. We will show that, despite Akin's general result, for a special class of mutational effects, namely when mutation rates i→ j depend only on the resulting allele j, a simple generalization of the Fundamental Theorem holds (§ 2). This result was motivated by Hadeler's paper [7] who proved maintenance of stability properties of a polymorphism when equal mutation rates are allowed. In § 3 we show that these equations are even gradients with respect to a certain Riemannian metric, introduced by Shahshahani [15]. § 4 contains a discussion of Akin's result on cycling together with a concrete example of a stable limit cycle in a 3-allelic system. We conclude with some results for the discrete time model (§ 5).

My special thanks are due to Prof.K. Sigmund. It was his paper [16] and his lectures on Shahshahani gradients which led me to find the Lyapunov function (2.6).

1. The Model

The standard selection + mutation model for separated generations is as follows (cf. Crow-Kimura [4]). Consider one gene locus with n alleles $A_1,\dots,A_n$ and let $x_1,\dots,x_n$ be their relative frequences in the gene pool of the population at time of mating. Assuming random mating, the relative number of gametes of (ordered) genotype A_iA_j will be x_ix_j. Due to natural selection only a proportion of $w_{ij}x_ix_j$ will survive into procreative age, where $w_{ij} = w_{ji} \geq 0$ are the fitness parameters. So the number of newly produced genes A_j is proportional to $\Sigma_k\, w_{jk}x_jx_k = x_j(Wx)_j$. Now let ϵ_{ij} be the mutation rate from A_j to A_i (for $i \neq j$), then

$$\epsilon_{ij} \geq 0 \quad \text{and} \quad \sum_{i=1}^{n} \epsilon_{ij} = 1 \quad \text{for all} \quad j = 1,\dots,n \tag{1.1}$$

for suitably defined ϵ_{ii}. Then the frequency x_i' of genes A_i in the gene pool of the new generation is proportional to $\Sigma_j\, \epsilon_{ij}x_j(Wx)_j$. More precisely, it is given by

$$x_i' = \sum_{j=1}^{n} \epsilon_{ij} x_j (Wx)_j / W(x) \tag{1.2}$$

with $W(x) = x.Wx = \Sigma_{r,s=1}^{n} w_{rs} x_r x_s$ the <u>mean fitness</u> of the population as the usual normalization factor. This is the <u>discrete time selection mutation equation</u>. Since differential equations are easier to handle mathematically we replace the difference $x_i' - x_i$ by $\dot{x}_i = dx_i/dt$ in order to obtain the continuous time selection mutation equation

$$\dot{x}_i = W(x)^{-1} \cdot \sum_{j,k} \epsilon_{ij} x_j w_{jk} x_k - x_i \tag{1.3}$$

This is the equation studied by Hadeler [7]. Usually, e.g. in the classical selection equation which corresponds to the special case $\epsilon_{ii} = 1$ and $\epsilon_{ij} = 0$ for $i \neq j$, the vectorfield (1.3) is multiplied by the positive factor $W(x)$, which is equivalent to a change of velocity. For our purpose this is not useful, however.

Crow and Kimura [4], p. 265 and Akin [1] consider a different model for overlapping generations: selection acts in the usual way with Malthusian fitness values m_{ij}; mutation effects, being small in general, change the gene frequencies linearly. Arguing that simultaneous action of selectional and mutational forces in a small time interval Δt is of smaller order $(\Delta t)^2$, they arrive at a continuous time model with separate selection and mutation terms:

$$\dot{x}_i = x_i \left(\sum_{j=1}^{n} m_{ij} x_j - x.Mx \right) + \sum_{j=1}^{n} (\epsilon_{ij} x_j - \epsilon_{ji} x_i) \tag{1.4}$$

The three equations (1.2)-(1.4) describe dynamical system on the probability simplex

$$S_n = \{ x = (x_1, \ldots, x_n) \in \mathbb{R}^n : x_i \geq 0 \text{ and } \sum_{i=1}^{n} x_i = 1 \}.$$

Rather than going into a discussion of which of the models (1.3) and (1.4) is the "correct" or at least "better" one, it seems to be more useful to observe the following connection between them:

Rewrite (1.3) as

$$W(x)\dot{x}_i = x_i[(Wx)_i - W(x)] + \sum_{j\neq i} [\varepsilon_{ij}x_j(Wx)_j - \varepsilon_{ji}x_i(Wx)_i]$$

and replace

$$\varepsilon_{ij} \to \delta\varepsilon_{ij} \quad (\text{for } i\neq j) \quad \text{and} \quad w_{ij} \to 1+\delta m_{ij} \tag{1.5}$$

to obtain

$$\dot{x}_i = \delta x_i[(Mx)_i - x.Mx] + \delta \sum_{j\neq i} (\varepsilon_{ij}x_j - \varepsilon_{ji}x_i) + O(\delta^2).$$

Thus after a rescaling of time, $t \to t/\delta$, Hadeler's equation (1.3) with (1.5) yields Akin's uncoupled version (1.4) in the limit $\delta \to 0$. So for small selection differences and small mutation rates both models are essentially equivalent.

2. Special Mutation Rates

In this section we restrict ourselves to the case of special mutation rates satisfying

$$\varepsilon_{ij} = \varepsilon_i \quad \text{for} \quad i \neq j \tag{2.1}$$

i.e. mutation rates depending only on the resulting alleles. It will become clear in § 3 (see especially Theorem 4) that this case deserves a separate analysis. (1.1) implies here

$$\varepsilon_{ii} = 1+\varepsilon_i - \varepsilon \quad \text{with} \quad \varepsilon = \sum_{j=1}^{n} \varepsilon_j, \tag{2.2}$$

and (1.3) simplifies to

$$\begin{aligned} W(x)\dot{x}_i &= x_i[(Wx)_i - W(x)] + \varepsilon_i W(x) - \varepsilon x_i(Wx)_i \\ &= x_i[(1-\varepsilon)(Wx)_i - W(x)] + \varepsilon_i W(x) \end{aligned} \tag{2.3}$$

Hadeler [7] considered the case of equal mutation rates $\varepsilon_i = \varepsilon/n$. He posed the problem of finding a Lyapunov function in this case, in order to globalize his stability results. This will now be done. We write (2.3) as a <u>replicator equation</u> [11,16]

$$\dot{x}_i = x_i[f_i(x) - \bar{f}(x)] \tag{2.4}$$

with

$$f_i(x) = (1-\varepsilon)\frac{(Wx)_i}{W(x)} + \frac{\varepsilon_i}{x_i} \quad \text{and} \quad \bar{f}(x) = \sum_{i=1}^{n} x_i f_i(x) = 1. \tag{2.5}$$

Obviously the functions $f_i(x)$ fulfill the integrability conditions $\partial f_i/\partial x_j = \partial f_j/\partial x_i$. This implies the existence of an integral $V(x)$, with $f_i(x) = \partial V/\partial x_i$, which is easily computed to

$$V(x) = \frac{1-\varepsilon}{2} \log W(x) + \sum_{i=1}^{n} \varepsilon_i \log x_i. \tag{2.6}$$

Then

$$\dot{V}(x) = \sum_{i=1}^{n} \frac{\partial V}{\partial x_i}\dot{x}_i = \Sigma\, x_i f_i[f_i - \bar{f}] = \Sigma\, x_i (f_i - \bar{f})^2 \geq 0 \tag{2.7}$$

This proves

<u>Theorem 1</u>: $V(x)$ is a global Lyapunov function for the continuous time selection mutation equation (1.3) with special mutation rates (2.1).

Exponentiating $V(x)$ we obtain the more suggestive Lyapunov function

$$\bar{V}(x) = W(x)^{1-\varepsilon} \prod_{i=1}^{n} x_i^{2\varepsilon_i}. \tag{2.8}$$

For $\varepsilon = 0$, i.e. no mutation, $\bar{V}(x)$ reduces to the mean fitness function $W(x)$. So (2.7) is a surprisingly simple and straightforward generalization of Fisher's Fundamental Theorem of Natural Selection:

The change of the modified mean fitness function $\bar{V}(x)$ is proportional to the variance of the selection + mutation terms $f_i(x)$. The precise mathematical meaning of (2.7) (in terms of Shahshahani gradients) will be discussed in § 3. There we will also see that this result cannot be extended to mutation matrices which do not satisfy (2.1). When dealing with only $n=2$ alleles however, (2.1) is no restriction. This case is analyzed in a nice way in Roughgarden [13] p. 117ff, also using the Lyapunov function (2.8).

Recalling (1.5) the same result carries over to Akin's equation (1.4). Since $\log(1+\delta m)/\delta \to m$ as $\delta \to 0$, the above Lyapunov function for Hadeler's equations is replaced by

$$V(x) = \frac{1}{2}x.Mx + \sum_{i=1}^{n} \epsilon_i \log x_i \qquad (2.9)$$

and the fundamental relation (2.7) holds again, if we set

$$f_i(x) = (Mx)_i + \frac{\epsilon_i}{x_i} \quad \text{and} \quad \bar{f}(x) = x.Mx + \epsilon .$$

(Compare also [2, p. 57f]).

As a consequence of (2.7) we obtain

Corollary: All orbits of the continuous time selection mutation equations (1.3) and (1.4) converge to the set of fixed points. These are given by the solutions of the equations $f_i(x) = \text{const}$.

The simple form of the Lyapunov function (2.6) allows us to globalize Hadeler's result [7].

Theorem 2: Suppose the model without mutation (i.e. $\epsilon_{ij} = 0$ for $i \neq j$) admits a stable polymorphism (= interior equilibrium). Then for every choice of mutation rates satisfying (2.1) with $\epsilon = \Sigma\, \epsilon_j \leq 1$, the equations (1.2), (1.3) and (1.4) have exactly one stationary solution in S_n. This solution is globally stable for the differential equations and at least locally stable for the difference equation.

Proof. Let $p \in \operatorname{int} S_n$ be the (exponentially) stable polymorphism assumed to exist for the selection equation. Then p is a (strict) global maximum of mean fitness $W(x) = x.Wx$: $W(x) \leq W(p)$ for all $x \in S_n$. Since $p.Wx = x.Wp = p.Wp$, we obtain $(x-p).W(x-p) \leq 0$ or

$$\xi.W\xi \leq 0 \quad \text{for all} \quad \xi \in R^n_0 = \{\xi \in R^n : \Sigma\, \xi_i = 0\} \tag{2.10}$$

(with equality only for $\xi = 0$). Together with this well-known stability condition the parallelogram rule for the quadratic form W(x) implies

$$W\left(\frac{x+y}{2}\right) - \frac{1}{2}[W(x) + W(y)] = -W\left(\frac{x-y}{2}\right) \geq 0.$$

Hence mean fitness W(x) is a (strictly) concave function on S_n and so is log W(x). The same holds for the log x_i, and so the Lyapunov functions V(x) in (2.6) and (2.9) are strictly concave on S_n. But then V(x) can have only one critical point which is a global maximum. Corollary 1 then implies the global convergence. The proof of the discrete time case is deferred to § 5.

Remark. Although this result looks very plausible and coincides with intuition it is not true for more general mutation rates that do not satisfy (2.1), as we will see in § 4. Also if selection alone produces a globally stable stationary state on the boundary of S_n, the conclusion does not hold. Even for n = 2 alleles mutation terms may produce an additional stable fixed point on the opposite side of the simplex. This somewhat unexpected effect was observed by Bürger [3].

3. Shahshahani Gradients

In this section I want to explain why it is possible to find such a simple generalization of the Fundamental Theorem for special mutation rates. The main point in the proof of Theorem 1 was, after writing the differential equation in "replicator" form

$$\dot{x}_i = \hat{f}_i(x) = x_i[f_i(x) - \bar{f}(x)], \quad \bar{f}(x) = \Sigma\, x_i f_i(x) \qquad (3.1)$$

that the $f_i(x)$ have a common integral V. Thus the trick will work whenever the related system $\dot{x}_i = f_i(x)$ on $\mathbb{R}^n$ is the gradient of some potential V(x). In this case (2.7) holds and V(x) is also a Lyapunov function for the corresponding replicator equation (3.1). For the classical selection equation the $f_i(x)$ are linear functions: $f_i(x) = \Sigma\, w_{ij} x_j$ and the symmetry $w_{ij} = w_{ji}$ ensures the existence of the potential $V(x) = x.Wx$.

The question arises whether there is more behind this analogy. In fact Kimura's Maximum Principle claims that for the selection model the change of gene frequencies occurs in such a way that the increase in mean fitness is maximal (see Crow and Kimura [4], p. 230). A precise mathematical interpretation of this statement could only mean that the selection equation is a gradient with mean fitness as potential. But this is obviously not true. The situation was cleared up by Shahshahani [15] and analyzed further in great detail by Akin [1] and Sigmund [16]. That a differential equation is a gradient means essentially that the vector field is orthogonal to the contour lines of its potential function. So gradient systems depend in an essential way on the notion of orthogonality, or angle, or inner product. And in fact Crow and Kimura replace the usual distance by a certain variance in their proof of the maximum principle [4], p. 230ff. So, following Shahshahani, let us define a new inner product $\langle X,Y\rangle_p$ for vectors X,Y in the tangent space $T_p S_n = \mathbb{R}^n_o$ at every point $p \in \operatorname{int} S_n$ by

$$\langle X,Y\rangle_p = \sum_{i=1}^{n} p_i^{-1}\, X_i Y_i \qquad (3.1)$$

This is a Riemannian metric for int S_n. It is easy to check that this Riemannian manifold is essentially isometric to the part of the (n-1) dimensional sphere lying in the positive orthant (with the usual Euclidean metric), by the simple change of coordinates $\sqrt{x_i} = y_i$ (see [1], p. 39,55 for details).

For a differentiable function V on S_n, the Shahshahani gradient $\mathrm{Grad}_p V$ is then the unique vector $\in T_pS_n$ with

$$\langle \mathrm{Grad}_p V, Y\rangle_p = D_pV(Y) \quad \text{for all} \quad Y \in T_pS_n, \tag{3.2}$$

where $D_pV: T_pS_n \to \mathbb{R}$ is the derivative of V at p.

Gradients $f = \mathrm{grad}\, V$ with respect to the Euclidean metric are easy to recognize: Here the integrability conditions $\partial f_i/\partial x_j = \partial f_j/\partial x_i$, or equivalently the symmetry of the Jacobian matrix of f are necessary and sufficient conditions. It would be useful to have a similar characterization for vectorfields on S_n, which are given in form (3.1), to be Shahshahani gradients. If the vectorfield $\hat{f}$ in (3.1) is defined in a whole neighbourhood of int S_n we may compute

$$\frac{\partial \hat{f}_i}{\partial x_j} = \delta_{ij}(f_i - \bar{f}) + x_i\left(\frac{\partial f_i}{\partial x_j} - \frac{\partial \bar{f}}{\partial x_j}\right) \tag{3.3}$$

But since we are interested only in S_n itself, only the action on vectors in $T_pS_n = \mathbb{R}^n_0$ is of relevance. So, following Akin [1], p. 173, we consider the bilinear form

$$H_p\hat{f}(Y,Z) = \langle Y, (D_p\hat{f})(Z)\rangle_p \quad \text{for} \quad Y,Z \in T_pS_n = \mathbb{R}^n_0. \tag{3.4}$$

Concrete evaluation gives

$$\begin{aligned} H_p\hat{f}(Y,Z) &= \sum_{i,j} \frac{1}{p_i} \frac{\partial \hat{f}_i}{\partial x_j}\Big|_{x=p} Y_iZ_j \\ &= \sum_i p_i^{-1}(f_i - \bar{f})Y_iZ_j + \sum_{i,j} f_{i,j}(p)Y_iZ_j \end{aligned} \tag{3.5}$$

with $f_{i,j} = \partial f_i/\partial x_j$ for short. Since at interior equilibria the first sum disappears this leads to a considerable simplification of the original formula (3.3). Now we can state

Theorem 3: For a vectorfield $\hat{f}_i(x) = x_i[f_i(x) - \bar{f}(x)]$, as in (3.1) defined in a neighbourhood U of int S_n, the following conditions are equivalent:

(a) $\hat{f}_i$ is a Shahshahani gradient on int S_n.

(b) There exist functions $V, \psi : U \to \mathbb{R}$ such that $f_i(x) = \frac{\partial V}{\partial x_i} + \psi(x)$ holds on int S_n.

(c) The Jacobian bilinear form $H_p\hat{f}$ is symmetric at every $p \in$ int S_n.

(d) $f_{i,j} + f_{j,k} + f_{k,i} = f_{i,k} + f_{k,j} + f_{j,i}$ holds on int S_n for all i,j,k.

Proof. (a) ⇒ (b). If $\hat{f} = \operatorname{Grad} V$, then (3.2) implies

$$\langle \hat{f}(x), Y \rangle_x = \sum_i \partial V/\partial x_i . Y_i$$

for all $Y \in \mathbb{R}^n_0$ and all $x \in$ int S_n. Choosing $Y_i = Z_i - x_i(\Sigma Z_j)$ for arbitrary $Z \in \mathbb{R}^n$, we obtain by equating coefficients

$$\hat{f}_i(x) = x_i\left[\frac{\partial V}{\partial x_i} - \sum_j x_j \frac{\partial V}{\partial x_j}\right] \text{ on } S_n.$$

Comparing with (3.1) we conclude that (b) holds.

(b) ⇒ (c). Since the f_i are of the form

$$f_i(x) = \partial V/\partial x_i + \psi(x) + (\Sigma x_j - 1)\varphi_i(x) \quad \text{for} \quad x \in U,$$

the φ_i being arbitrary functions, the partials are given by

$$\frac{\partial f_i}{\partial x_j} = \frac{\partial^2 V}{\partial x_i \, \partial x_j} + \frac{\partial \psi}{\partial x_j} + \varphi_i(x) \quad \text{for} \quad x \in \text{int } S_n.$$

Inserting this into (3.5), the terms with ψ, φ_i disappear by $\Sigma\, Y_i = \Sigma\, Z_j = 0$. What remains is a symmetric bilinear form.

(c) ⇒ (d). The symmetry of $H_p\hat{f}(Y,Z)$ implies $\Sigma(f_{i,j} - f_{j,i}) Y_i Z_j \equiv 0$ for all $Y, Z \in \mathbb{R}^n_o$. With $Y = e_i - e_k$ and $Z = e_j - e_k$ (e_j being the unit vectors in $\mathbb{R}^n$) we obtain (d).

(d) ⇒ (b). Define for $x_1 + \ldots + x_{n-1} < 1$, $x_i > 0$

$$g_i(x_1, \ldots, x_{n-1}) = f_i(x_1, \ldots, x_{n-1}, 1 - x_1 - \ldots - x_{n-1}) \qquad (3.6)$$

Then g_i coincide with f_i on S_n and $g_{i,j} = f_{i,j} - f_{i,n}$ by the chain rule. So (d) implies (with $k = n$):

$$g_{i,j} - g_{n,j} = g_{j,i} - g_{n,i}$$

These are just the integrability conditions for $g_i - g_n$ $(1 \le i \le n-1)$ on $\mathbb{R}^{n-1}$. Thus we find an integral $V = V(x_1, \ldots, x_{n-1})$ with

$$g_i - g_n = \frac{\partial V}{\partial x_i} \qquad i = 1, \ldots, n-1$$

Recalling (3.6) this implies (b) with $\psi = g_n$.

(b) ⇒ (a). From $\Sigma\, Y_i = 0$ we compute

$$\langle \hat{f}(x), Y \rangle_x = \Sigma \frac{1}{x_i} x_i \left[\frac{\partial V}{\partial x_i} + \psi(x) - \bar{f}\right] Y_i =$$

$$= \Sigma \frac{\partial V}{\partial x_i} Y_i = (D_x V)(Y)$$

Thus (3.1) is established.

Remark. (a) ⇔ (b) is taken from Sigmund [16]. Condition (c) is due to Akin [1], p. 175. The explicit integrability condition (d) which is the most useful in applications was motivated by the corresponding cycle condition for linear f_i's discovered by Sigmund [16].

In particular, conditions (b)-(d) are obviously satisfied if $f_{i,j} = f_{j,i}$. This explains the analogy pointed out in the beginning of this section and implies

Corollary: The selection mutation equations (1.3) and (1.4) with special mutation rates (2.1) are Shahshahani gradients with potential V given by (2.6) and (2.9) respectively.

That this is not true for more general mutation rates is a consequence of the following theorem, which corrects the slight mistake in [1], p. 181 that made this paper possible (see also [2], p. 57).

Theorem 4: The mutation equation

$$\dot{x}_i = \sum_{j=1}^{n} \epsilon_{ij} x_j - x_i \tag{3.7}$$

is a Shahshahani gradient if and only if the mutation rates satisfy (2.1).

Proof. Writing (3.7) in replicator form (3.1), we have $f_i(x) = \Sigma_j \epsilon_{ij} x_j / x_i$ and hence for $i \neq j$, $f_{i,j} = \epsilon_{ij}/x_i$. The integrability condition (d) then says (for i,j,k pairwise different)

$$\frac{\epsilon_{ij}}{x_i} + \frac{\epsilon_{jk}}{x_j} + \frac{\epsilon_{ki}}{x_k} = \frac{\epsilon_{ik}}{x_i} + \frac{\epsilon_{kj}}{x_k} + \frac{\epsilon_{jk}}{x_j} \quad \text{for all} \quad x \in \text{int } S_n.$$

This implies, by taking the limit $x_i \to 0$, that $\epsilon_{ij} = \epsilon_{ik}$ for all $j \neq k$, and hence $\epsilon_{ij} = \epsilon_i$ $(i \neq j)$. Therefore (ϵ_{ij}) is of the special form (2.1).

Of course this theorem does not mean that the general mutation equation (3.7) behaves less nicely from the purely qualitative point of view. (3.7) is a linear equation and if $\epsilon_{ij} > 0$ holds for sufficiently many $i \neq j$, the Perron-Frobenius theorem implies the existence, uniqueness and global stability of a polymorphic equilibrium (see Akin [1], p. 160ff). So the Shahshahani metric is just not the right tool to study mutation. But Theorem 5 below shows that it is still relevant for the combined action of selection and mutation.

4. Limit Cycles

This section deals with more general mutation rates than (2.1). Our emphasis is to demonstrate that the Corollary of Theorem 1 is no longer true in this case: The dynamic behaviour is in general not gradient-like. The following simple example shows that stable limit cycles may occur.

In order to make computations tractable we take the simplest nontrivial case: We assume that all homozygotes A_iA_i have the same fitness and also all heterozygotes A_iA_j $(i \neq j)$. When working with the simpler equation (1.4) this means $m_{ij} = s\delta_{ij}$, where s measures the selective advantage of the homozygotes. Motivated by the successful treatment of the hypercycle and similar systems in Schuster et al. [14], we assume mutation rates to be cyclic symmetric, i.e. $\epsilon_{ij} = \epsilon_{j-i}$. Then $\Sigma_{i=0}^{n-1} \epsilon_i = 1$, where the index i of ϵ_i is now considered as a residue modulo n. Then (1.4) reads

$$\dot{x}_i = sx_i(x_i - Q(x)) + \sum_{j=1}^{n} \epsilon_{j-i} x_j - x_i \tag{4.1}$$

with $Q(x) = \Sigma_{i=1}^{n} x_i^2$. Obviously the barycenter $\underline{m} = (\frac{1}{n}, \ldots, \frac{1}{n})$ of the simplex is a stationary solution of (4.1). We compute the Jacobian of (4.1):

$$D_{ij}(x) = \partial\dot{x}_i/\partial x_j = s\delta_{ij}(x_i - Q(x)) + s\, x_i(\delta_{ij} - 2x_j) + \epsilon_{j-i} - \delta_{ij} \tag{4.2}$$

The divergence of the vector field is the trace of the Jacobian

$$\begin{aligned} \mathrm{div} = \Sigma\, D_{ii}(x) &= s\, \Sigma(x_i - Q(x)) + s(\Sigma\, x_i - 2\Sigma\, x_i^2) + n\epsilon_0 - n = \\ &= s(2-(n+2)Q(x)) + n(\epsilon_0 - 1). \end{aligned}$$

Since the flow is restricted to S_n we have to subtract the eigenvalue transversal to S_n, given by $-\bar{f}(x) = -sQ(x)$, to obtain the divergence div_0 within S_n:

$$\mathrm{div}_0 = s(2-(n+1)Q(x)) + n(\epsilon_0 - 1). \tag{4.3}$$

Since $Q(x) = \Sigma\, x_i^2 \geq \frac{1}{n}(\Sigma x_i)^2 = \frac{1}{n}$, we have for positive s

$$\mathrm{div}_0 \leq s(1-\frac{1}{n}) + n(\epsilon_0 - 1). \qquad (4.4)$$

So the divergence is negative on $S_n \backslash \{\underline{m}\}$ whenever

$$s \leq \frac{n^2}{n-1}(\epsilon_0 - 1). \qquad (4.5)$$

Now we specialize to $n = 3$ alleles. Then the eigenvalues $\lambda, \bar{\lambda}$ at $\underline{m}$ within S_3 are easily computed as

$$\lambda = s/3 - 1 + \epsilon_0 + \epsilon_1 \omega + \epsilon_2 \bar{\omega}$$

with $\omega = \exp(2\pi i/3)$. They are complex if $\epsilon_1 \neq \epsilon_2$ and their real part is

$$\mathrm{Re}\, \lambda = \frac{s}{3} - \frac{3}{2}(\epsilon_1 + \epsilon_2).$$

For $s = \frac{9}{2}(\epsilon_1 + \epsilon_2)$ the eigenvalues are purely imaginary and a Hopf bifurcation occurs, taking s as parameter. Since for all $s \leq \frac{9}{2}(\epsilon_1 + \epsilon_2)$ $\mathrm{div}_0 < 0$ holds on $S_3 \backslash \{\underline{m}\}$ by (4.4) and (4.5), Bendixson's negative criterion implies that there are no periodic orbits in this case, i.e. as long as $\underline{m}$ is stable (see Fig. 1a). Hence the bifurcation is supercritical and <u>stable</u> limit cycles appear if s is slightly larger than $\frac{9}{2}(\epsilon_1 + \epsilon_2)$, i.e. when $\underline{m}$ becomes an unstable focus. (Fig. 1b). If s increases further, 3 pairs of fixed points are created simultaneously and the limit cycle, whose period tends to infinity, disappears in a triangle of heteroclinic orbits. (This is sometimes called a "blue sky bifurcation", see Fig. 1c,d).

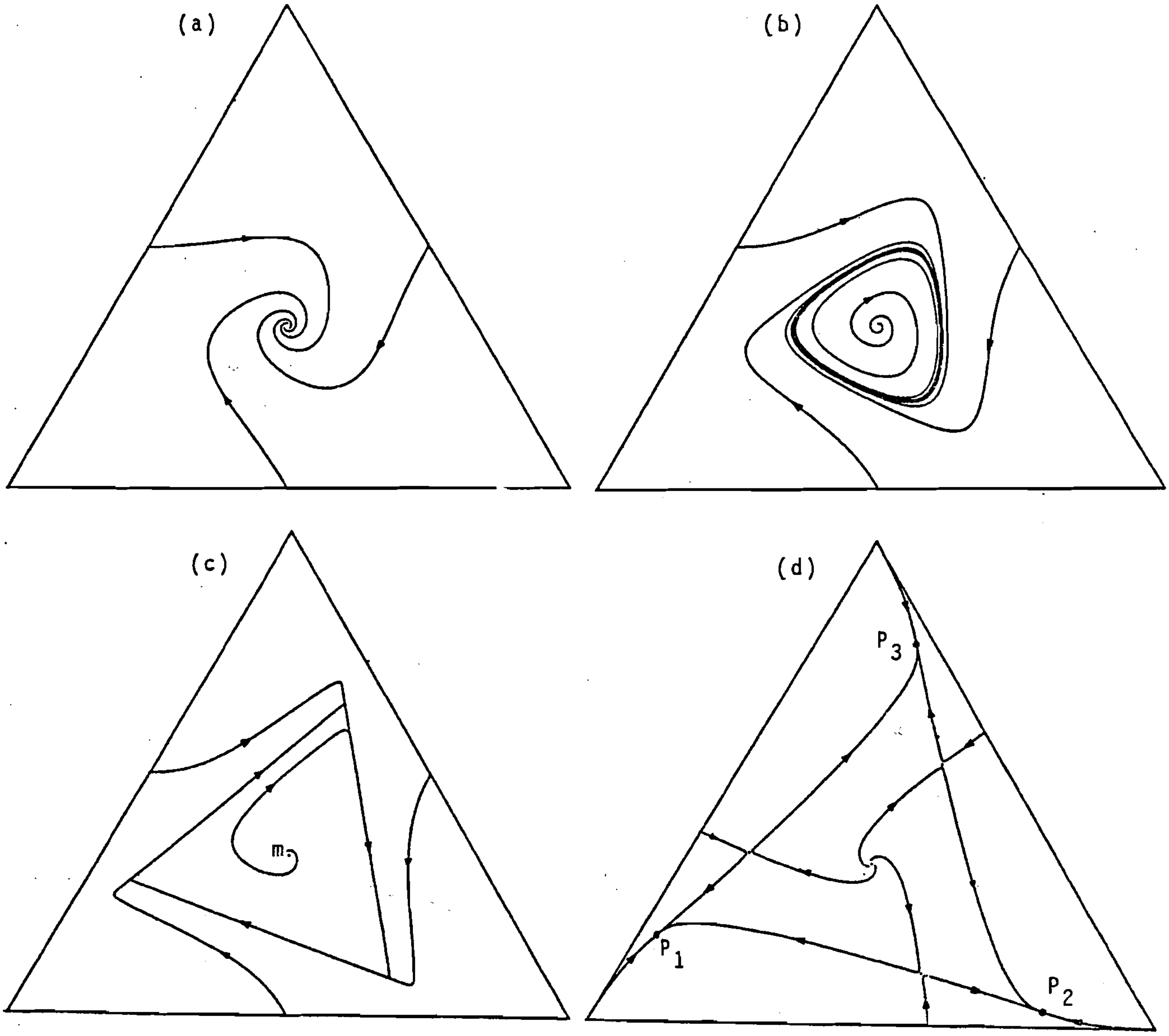

Figure 1: Phase portraits of the three-allelic selection mutation equation (4.1) with $s=1$, $\epsilon_1=\epsilon$, $\epsilon_2=0$.

(a) $\epsilon=0.28$. Strong mutation ($\epsilon/s \geq 2/9$) leads to gradient-like behaviour with $\underline{m}$ as globally stable focus.

(b) $\epsilon=0.2$. For moderate mutation rates ($1/6<\epsilon/s<2/9$) there exists a stable limit cycle.

(c) $\epsilon=1/6$. At this critical value three fixed points, cyclically joined by heteroclinic orbits, are created.

(d) $\epsilon=0.14$. Gradient-like behaviour for weak mutation ($\epsilon/s<1/6$). The three stable fixed points P_1, P_2, P_3 correspond to the well-known selection-mutation balance.

I am indebted to Dr.F. Kemler for producing the computer plots.

So we see that the interaction of mutation and selection may lead to stable limit cycles. Maybe this is not too surprising for the above example since the fixed point for the mutation field ($s = 0$) is already a focus which is then destabilized by the selection part. But one can also construct examples of Hopf bifurcations when the selection field has a stable polymorphism (compare the remark in § 2). Moreover the same bifurcation behaviour appears for any mutation rates that are not of the special form (2.1). This is a consequence of the following basic theorem of Akin [1], p. 186:

Theorem 5: Let $\hat{f}(x)$ be a vectorfield on S_n which is not a Shahshahani gradient (e.g. any mutation field (3.7) with mutation rates not of the form (2.1)). Then there exists a family of selection matrices $(m^\lambda_{ij}) = M^\lambda$, such that the combined field

$$\dot{x}_i = \hat{f}_i(x) + x_i((M^\lambda x)_i - x.M^\lambda x)$$

(this is then (1.4)) undergoes a Hopf bifurcation and periodic orbits occur.

In this general form, however, Akin's theorem does not say anything on the stability of the periodic orbits. It could happen that the Hopf bifurcations are always subcritical or critical. The periodic orbits would then be of less biological relevance since they would not be observable. But the above example just shows that stable limit cycles are indeed possible.

By the approximation argument (1.5) the same result holds for Hadeler's version (1.3), at least after the mutation rates ε_{ij} are rescaled to $\delta\varepsilon_{ij}$ by some small factor $\delta > 0$. With the rescaling $W \to 1 + \delta W$ the difference equation (1.2) turns out to behave essentially like Euler's discretization of the differential equation (1.3), with $\delta W/(1 + \delta W)$ as step length. Thus Akin's Hopf bifurcation result also carries over to the discrete time model, and stable limit cycles (= attracting invariant curves) also occur in (1.2) for nonspecial mutation rates. (For a precise treatment of this idea see [10]).

Akin also applied his theorem to other equations, in particular to multilocus systems. He proved that the vector field on S_n that models the effects of recombination between two loci is never a gradient with respect to Shahshahani's metric. Thus Hopf bifurcations occur. The actual computations proving that even stable limit cycles are possible are more difficult in this case, however; see Akin's memoir [2]. It is tempting to conjecture that even more complicated dynamic behaviour, i.e. chaotic motion, is possible for these two extensions of the selection model, allowing either mutations or recombination.

We conclude with a critical remark. It is not quite clear how relevant this cycling result is for real biological populations. Indeed mutation rates are usually much smaller than selection rates. The selection + mutation field can then be treated as a perturbation of the selection equation. Since the latter is structurally stable in general, small mutations will not change the situation very much: Only the boundary equilibria will move inwards the simplex S_n, if they are stable, and some of the unstable ones will move outwards. It would be useful to find concrete estimates of how large the mutation rates may be (compared e.g. with the variance of the w_{ij}) in order to retain a gradient-like behaviour.

5. The Difference Equation

In this last section I want to collect a few results on the difference equation (1.2). It would be desirable to show that our function V from (2.6) serves as a Lyapunov function for the discrete time model too, if mutation rates are special. But this seems to be a much harder problem which I haven't yet managed to solve. So I confine myself to some partial results which indicate that the difference equation behaves similarly to the differential equation.

In order to generalize Hadeler's theorem [7] to the difference equation we have to exclude overshooting effects. This is done by means of the following lemma, which is essentially contained in Losert and Akin [12].

Lemma: All eigenvalues of the derivative of the discrete time selection equation at any point $p \in S_n$ (which need not be an equilibrium point) are nonnegative. For interior p all eigenvalues corresponding to directions within S_n are even strictly positive (if all $w_{ii} > 0$).

Proof. The derivative is given by

$$D_{ij} = \delta_{ij} \frac{(Wp)_i}{p . Wp} + \frac{p_i \, w_{ij}}{p.Wp} - 2 \, \frac{p_i (Wp)_i (Wp)_j}{(p.Wp)^2} \tag{5.1}$$

Since the selection equation is a Shahshahani gradient, Theorem 3(c) applies and D is selfadjoint with respect to the Shahshahani inner product. Thus it is sufficient to consider the quadratic form

$$\langle x,Dx \rangle_p = \sum_{i=1}^{n} \frac{(Wp)_i}{p.Wp} \frac{x_i^2}{p_i} + \frac{x.Wx}{p.Wp} - 2\left(\frac{x.Wp}{p.Wp}\right)^2 . \tag{5.2}$$

Now $Dp = 0$ and so the eigenvalue corresponding to the (irrelevant) direction orthogonal to S_n is zero. Substituting $y = x-(x.Wp/p.Wp)p$ the corresponding one-dimensional degeneracy of the quadratic form (5.2) can be eliminated:

$$\begin{aligned} \langle x,Dx \rangle_p &= \sum_{i=1}^{n} \frac{(Wp)_i}{p.Wp} \frac{y_i^2}{p_i} + \frac{y.Wy}{p.Wp} = \\ &= \frac{1}{2p.Wp} \sum_{i,j=1}^{n} w_{ij} \left[\left(\frac{p_j}{p_i}\right)^{1/2} y_i + \left(\frac{p_i}{p_j}\right)^{1/2} y_j \right]^2 \geq 0, \end{aligned} \tag{5.3}$$

with equality only for $y=0$ (since $w_{ii}>0$). Therefore (5.2) is a positive definite quadratic form on $\mathbb{R}_0^n$ and so all eigenvalues of D are positive. For boundary p the additional eigenvalues pointing into the interior of S_n are given by $(Wp)_i/p.Wp$ and are obviously nonnegative.

Proof of Theorem 2 for discrete time.
(1.2) reduces for special mutation rates (2.1) to

$$x_i' = (1-\epsilon)\ x_i(Wx)_i/x.Wx + \epsilon_i \qquad (5.4)$$

We know already from Theorem 2 that there is a unique equilibrium $p \in S_n$ which is stable for the differential equation (2.3). Now the derivatives of (1.2) and of (1.3) differ only by the identity matrix. This implies that all eigenvalues of (5.4) have real part less than 1. Since the derivative of (5.4) differs from that of the pure selection equation only by the factor $1-\epsilon \geq 0$, its eigenvalues are real and nonnegative, according to the lemma. Thus they are all located within the unit circle and p is stable for the dynamics (5.4).

For general mutation rates we can view the difference equation (1.2) as the composition of the selection map $T: x_i \rightarrow x_i(Wx)_i/x.Wx$ and the linear stochastic map $x \rightarrow Px$, $(Px)_i = \Sigma_j\ \epsilon_{ij}\ x_j$. Now the inversion theorem of Losert and Akin [12] says that (whenever $w_{ij}>0$ for all i, j) the selection map T is a diffeomorphism of S_n, i.e. a bijective smooth map $S_n \rightarrow S_n$ whose inverse function is also smooth. (The local invertibility corresponds to that part of the lemma claiming that 0 is not an eigenvalue of the derivative). As long as mutation rates are not too large we have det $P>0$. Then mutation maps S_n onto a smaller simplex $P(S_n)$ inside S_n. Thus the combined map (1.2) is a diffeomorphism from S_n onto $P(S_n)$, whenever all $w_{ij}>0$ and det $P>0$. This result suggests that (1.2) will not behave much worse than the differential equation (1.3). In particular it completely settles the $n=2$ allelic case, as no overshooting effects are possible as long as det $P=1-\epsilon_1-\epsilon_2>0$ and so orbits converge monotonically towards the equilibrium states.

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