Mutation in Autocatalytic Reaction Networks

An Analysis based on Perturbation Theory

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Abstract

A class of kinetic equations describing catalyzed and template induced replication, and mutation is introduced. This ODE in its most general form is split into two vector fields, a replication and a mutation field. The mutation field is considered as a perturbation of the replicator equation. The perturbation expansion is a Taylor series in a mutation parameter λ. First second and higher order contributions are computed by means of the conventional Raleigh-Schrödiger approach. Qualitative shifts in the positions of rest points and limit cycles on the boundary of the physically meaningful part of concentration space are predicted from flow topologies. The results of the topological analysis are summarized in two theorems which turned out to be useful in applications: the restpoint migration theorem (RPM) and the limit cycle migration theorem (LCM). Quantitative expressions for the shifts of rest points are computed directly from the perturbation expansion. The concept is applied to a collection of selected examples from biophysical chemistry and biology.

1. Autocatalytic reaction networks

An *autocatalytic reaction network* consists of elements $\mathbf{I}_k$ which are produced by a copying mechanism. All elements are thus capable of template induced (self-) reproduction. The elements are predominantly viewed as polynucleotide molecules – RNA or DNA – but they may be equally well virions, cells or even organisms. The notion of a *replicator* – originally invented by Richard Dawkins [1] and now used in biology for "*an entity that passes on its structure largely intact in successive replications*" [2] – is a useful characterization of the relevant property of the elements considered here.

Forgetting about mutation in the first place the act of replication can be expressed by a formal reaction equation of the type

$$(\mathbf{A}) + \mathbf{I}_k \xrightarrow{\mathcal{F}_k} 2\,\mathbf{I}_k \; ; \quad k = 1, 2, \ldots, n \; .$$

The collection of materials from which the replicators $\mathbf{I}$ are built is denoted symbolically by $\mathbf{A}$. We are dealing here exclusively with conditions under which the available amount of $\mathbf{A}$ is constant at every instant and hence it does not enter as a variable into the kinetic differential equations. Accordingly we write $\mathbf{A}$ in parentheses.

The replication efficiency of a particular replicator $\mathbf{I}_k$ is generally expressed as a function of concentrations $c_k = [\mathbf{I}_k]$: $\mathcal{F}_k(\mathbf{c})$ with $\mathbf{c} = (c_1, c_2, \ldots, c_n)$. Particle numbers expressed by $N_k = c_k \cdot V$ may be used equally well – V being the volume of the system. The replication functions $\mathcal{F}_k(\mathbf{c})$ are understood as generalized reaction rate parameters since they comprise a whole series of uncatalyzed and catalyzed replication processes. Application of mass action kinetics yields a polynomial expansion:

$$\mathcal{F}_k(\mathbf{c}) \; = \; F_k + \sum_{j=1}^{n} F_{kj} c_j \, + \sum_{i=1}^{n} \sum_{j=1}^{n} F_{kji} c_j c_i \; \ldots \, , \;\; k = 1, 2, \ldots, n \; . \qquad (1)$$

The dimensions of the expansion coefficients are $[t^{-1} \cdot m^{-\nu}]$ with $\nu = 0, 1, \ldots$, reciprocal time and reciprocal concentration units just to compensate for the dimension of the polynomial in concentrations. We are dealing with a quasi-linear replication network if only the constant terms of the expansions are considered. Then $\mathcal{F}_k$ does not depend on replicator concentrations and the individual replicators $\mathbf{I}_k$ replicate independently. Replication may be considered as a simple copying mechanism with $\mathbf{I}_k$ acting as template.

Truncation of the expansion after the linear terms in the functions $\mathcal{F}_k(\mathbf{c})$ yields the simplest essentially nonlinear replication networks. These systems will be characterized as second order autocatalytic reaction networks since the individual catalytic processes involve two replicators which fulfil different tasks: $\mathbf{I}_k$ acts as template – as it does in the first order process – and $\mathbf{I}_j$ acts as catalyst.

The expansion coefficients of $\mathcal{F}_k(\mathbf{c})$ can be understood also as rate constants of the net-growth in the concentration of $\mathbf{I}_k$. Then they may be decomposed into replication and degradation terms:

$$F_k \;=\; A_k - D_k \;, \qquad F_{kj} \;=\; A_{kj} - D_{kj} \;, \;\ldots\; . \tag{1a}$$

In case polynucleotides are considered the replication term – as represented by the rate constants $A_{k,\ldots}$ – refers to the synthesis of new macromolecules induced by the template $\mathbf{I}_k$. Degradation means cleavage of polymers. In replication, the constant term (A_k) in the expansion series refers to template induced copying without catalytic help by any other replicator. This does not necessarily mean uncatalysed replication. In contrary, the only *in vitro* RNA replication essay which has been studied extensively by kinetic techniques [3]1983 uses a protein catalyst, the enzyme Qβ replicase. The first order degradation terms (D_k) describe cleavage of $\mathbf{I}_k$ which is independent of all other replicators present. It may be either simple hydrolysis or degradation catalysed by non-RNA molecules.

The discovery of catalytic action of RNA molecules by Thomas Cech [4]1986 and others provides the basis for a molecular interpretation of the linear terms in the expansion series (1). RNA catalysed synthesis of complementary-strand RNA as reported recently [5]1989 is the basis of RNA catalysed RNA replication. The second order terms in degradation, D_{kj}, are of particular interest too: they describe specific cleavage of a substrate $\mathbf{I}_k$ which is catalysed by an other RNA molecule $\mathbf{I}_j$. Examples of this class are well known in M-RNA splicing. Even fairly small RNA molecules like the *hammerhead* ribozymes [6]1987 can catalyse degradation specificly.

If only terms of the same order in the expansion (1a) – first, second, third ... – are considered, the dynamics of the reaction network is – as shown in previous studies [7]1978 – independent of the total concentration $c = \sum_{k=1}^{n} c_k$ up to a transformation of the time-axis. Thus we can use normalized or relative concentrations x_k as variables without loosing generality. They are easily expressed in terms of conventional concentrations c_k or particle numbers N_k:

$$x_k \;=\; c_k \Big/ \sum_{i=1}^{n} c_i \;=\; N_k \Big/ \sum_{i=1}^{n} N_i \qquad \text{and} \qquad \sum_{k=1}^{n} x_k \;=\; 1 \;. \tag{2}$$

Concentrations are non-negative quantities by definition and so are the normalized concentrations. Therefore any distribution of n species in a population is described by an n-dimensional state vectors $\mathbf{x} = (x_1, x_2, \ldots, x_n)$ restricted to the unit simplex

$$S_n \doteq \left\{ \mathbf{x} \in \mathbb{R}^n \;\middle|\; x_k \geq 0 \wedge \sum_{k=1}^{n} x_k = 1 \right\} .$$

S_n is a compact $(n-1)$-dimensional subset of $\mathbb{R}^n$. In the language of physics the reduction in degrees of freedom is tantamount to the restriction by the normalization.

In normalized concentrations the replication function has the same analytical form as in equation (1) except the variables $\mathbf{c}$ are replaced by $\mathbf{x}$. There is a minor but nevertheless important difference: relative concentrations are numbers and hence all rate constants A_k, A_{kj}, ... , have the dimension of a reciprocal time, $[t^{-1}]$. Needless to say, there are also differences in the numerical values.

2. Mutation and selection constraints

In order to distinguish error-free replication and mutation we introduce a mutation matrix Q whose elements determine the frequencies of mutation: $Q_{k\ell}$ represents the fraction of replications with $\mathbf{I}_\ell$ as template which yield $\mathbf{I}_k$ as error copy. Since replication has to be necessarily either correct or erroneous, Q is a column-stochastic matrix:

$$\sum_{k=1}^{n} Q_{k\ell} = 1 \quad \forall \quad k = 1, 2, \ldots, n . \tag{3}$$

Error-free copying and mutations are understood as parallel reactions:

$$(\mathbf{A}) + \mathbf{I}_k \xrightarrow{Q_{kk}\mathcal{F}_\ell} 2\,\mathbf{I}_k ; \qquad k = 1, 2, \ldots, n \tag{4a}$$

$$(\mathbf{A}) + \mathbf{I}_\ell \xrightarrow{Q_{k\ell}\mathcal{F}_k} \mathbf{I}_k + \mathbf{I}_\ell ; \quad k, \ell = 1, 2, \ldots, n . \tag{4b}$$

It is important to realize that no rules of mutation have been laid down yet. Depending on whether we restrict errors to point mutations or whether we include also insertions and deletions the details in the structure of the mutation matrix Q are entirely different.

The use of model assumptions for mutation, however, will be inevitable in all specific applications because otherwise the large number of mutation parameters represented by the $n\times(n-1)$ independent entries of the mutation matrix Q is prohibitive. In case of the *uniform error rate model* [8]1989 we have for example

$$Q_{k\ell} \;=\; q^{\nu}\left(\frac{1-q}{q}\right)^{d_{k\ell}} \tag{5}$$

Only two parameters, the error rate per digit (q) and the Hamming distance ($d_{k\ell}$) between the two sequences of chain length ν, $\mathbf{I}_k$ and $\mathbf{I}_\ell$, are required to derive all mutation rates $Q_{k\ell}$.

In addition to the network of autocatalytic processes the details of the experimental setup or the environmental conditions have to be known in order to be able to formulate the kinetic differential equations. The setup, in essence, has to fulfil two criteria: it has to provide an open system in order to keep the processes away from thermodynamic equilibrium and it should introduce a selection constraint which makes the mathematical analysis sufficiently simple. Here we model a constraint which meets the experimental conditions in an *evolution reactor* [9]1979. An unspecific dilution flow $\Phi(t)$ controls the total concentration of replicating molecules, $c(t)=\sum_{i=1}^n c_i(t)=c_0=const$:

$$\Phi(t) \;=\; \sum_{i=1}^{n} \mathcal{F}_i(\mathbf{x})\,x_i\ . \tag{6}$$

Unspecific means here that the probability to be diluted out of the reactor within the next time interval is the same for each molecule. Thus the loss in normalized concentration of a given replicator $\mathbf{I}_k$ is $x_k\cdot\Phi(t)$ per time unit. Other conditions, for example those of a continuously stirred tank reactor (CSTR), are suitable for an analytical approach as well [10]1985.

The flux $\Phi(t)$ is easily recognized as the mean rate of reproduction in the ensemble and thus equation (6) has a straight forward interpretation when we consider momentary population dynamics [11]1971: every element which replicates faster than the average will increase in frequency and the concentration of every element which is less efficient than the average will decrease. This principle of differential selection holds no matter how complex the replication process is in detail.

The kinetic differential equations account for production by correct replication and mutation as well as for loss by the dilution flow:

$$\frac{\mathrm{d}x_k}{\mathrm{dt}} \;=\; \sum_{\ell=1}^{n} Q_{k\ell}\mathcal{F}_\ell(\mathbf{x})\,x_\ell \;-\; x_k\Phi(t) \;=\; \sum_{\ell=1}^{n}\big(Q_{k\ell}-x_k\big)\,\mathcal{F}_\ell(\mathbf{x})\,x_\ell\ ;\quad k=1,2,\ldots,n\ . \tag{7}$$

The term *replication-mutation equation* seems appropriate for the general class of differential equations (7). Needless to say, that care is needed when $\mathcal{F}_k(\mathbf{x})$ comprises both replication and degradation: then degradation terms have to be separated before the introduction of mutation.

The mutation matrix Q becomes an $(n \times n)$-dimensional unit matrix in the limit of vanishing replication errors: $Q \to \Im\mathrm{d}$. Then the kinetic differential equation reduces to:

$$\frac{\mathrm{d}x_k}{\mathrm{dt}} \;=\; x_k \left(\mathcal{F}_k(\mathbf{x}) \;-\; \sum_{j=1}^{n} \mathcal{F}_j(\mathbf{x})\, x_j \right) \;=\; \mathcal{R}_k(\mathbf{x}) \;; \quad k = 1, 2, \ldots, n \;. \tag{8}$$

A new term, *replicator equation* was coined for these class of differential equations because of its widespread use. Indeed the same class of equations was found to be important in very different applications ranging from the theory of molecular evolution to dynamic models of games in sociobiology [12]1983.

Introducing the vector field $\vec{\mathcal{R}}(\mathbf{x}) = \{\mathcal{R}_k(\mathbf{x});\, k = 1, \ldots, n\}$ which we call a *replicator field* equation (8) may be written as $\frac{\mathrm{d}\mathbf{x}}{\mathrm{dt}} = \vec{\mathcal{R}}(\mathbf{x})$. We note a useful general property: equation (8) is invariant to the addition of an arbitrary function $\psi(\mathbf{x})$ to the replication functions: $\mathcal{F}_i(\mathbf{x}) \Longrightarrow \mathcal{F}_i(\mathbf{x}) + \psi(\mathbf{x})\ \forall\, i$. This invariance may be used, for example, to eliminate degradation in case all degradation rate constants are the same, $D_1 = D_2 = \ldots = D_n = D$, by setting $\psi = D$.

It is important to stress that the notion of a *replicator equation* refers to the mathematical structure of a kinetic differential equation. The individual functions $\mathcal{F}_k(\mathbf{x})$ may comprise contributions which are of entirely different physical nature – like degradation – but which do not change the structure of the mathematical expressions.

3. Some definitions and properties of replicator equations

For C^1 vector fields on Ω we shall use the standard norm ‡: let $h \in C^1(\Omega)$, let . be an arbitrary operator norm and ∂h the Jacobian of h, then

$$h^{\ddagger} \;=\; \sup_{x \in \Omega} \big\{ |h(x)|, \partial h(x) \big\} \;. \tag{9}$$

A set $W \subset C^1(\Omega)$ is called a neighbourhood of $f \subset C^1(\Omega)$ iff there is a $\delta > 0$ such that

$$\big\{ g \in C^1(\Omega) \;\big|\; f - g^{\ddagger} < \delta \big\} \;\subset\; W \;.$$

We shall need the condition $\vec{\mathcal{R}} \in C^1(\Omega)$ which is clearly fulfilled if the replication functions are given by (1).

3.1. The environment of the simplex S_n

In order to be able to discuss extrapolations from the physical state space into its environment in $\mathbb{R}^n$ we define the set

$$\Sigma_n \doteq \left\{ \mathbf{x} \in \mathbb{R}^n \;\middle|\; \sum_{k=1}^{n} x_k = 1 \right\} .$$

The set Σ thus is the hyperplane in which the simplex S_n is embedded. We shall use a subset $\Omega_n \subset \Sigma_n$ with the two properties

(I) $S_n \subset \Omega_n,\ \exists\, \delta > 0 :\ \mathrm{dist}\,(\mathrm{bd}\, S_n, \mathrm{bd}\, \Omega_n) > \delta$ and

(II) Ω_n is open and bounded.

By dist (A, B) we mean the distance between two arbitarily chosen points of the two sets A and B. The environment of S_n is thus represented by the set $\Omega_n \backslash S_n$.

3.2. Boundary sets and subsimplices

The simplex S_n is partitioned into interior and boundary. The interior, int S_n, is the set of state vectors whose coordinates are strictly positive – no species vanishes. The boundary bd S_n consists of subsimplices on which at least one species $\mathbf{I}_k$ is non-existing. The subsimplices are invariant sets since the relation

$$x_k = 0 \quad \Longrightarrow \quad \dot{x}_k = 0 \quad \Longrightarrow \quad \ddot{x}_k = 0 \quad \ldots$$

holds for any replicator field – as follows straightway from equation (8).

Two boundary subsets are useful in the forthcoming derivations:

$$F_K \doteq \left\{ \mathbf{x} \in S_n \;\middle|\; k \in K \iff x_k = 0 \right\} \qquad \text{and}$$

$$\bar{F}_K \doteq \left\{ \mathbf{x} \in S_n \;\middle|\; k \in K \implies x_k = 0 \right\} .$$

The index K comprises all possible combinations of vanishing concentrations:

$$K \in I \qquad \text{with} \qquad I \doteq \mathcal{P}(\mathcal{N}) \setminus \{\emptyset, \mathcal{N}\}$$

wherein $\mathcal{P}(\mathcal{N})$ is the power set of $\mathcal{N} = \{1, 2, \ldots, n\}$. The boundary sets $\bar{F}_K$ themselves are simplices: $\bar{F}_K = S_m(\mathcal{N}\backslash K)$, where $m = \#(\mathcal{N}\backslash K) = n - \#K$ the number of non-vanishing variables. The set F_K is then simply the interior of this (sub)simplex S_m. Note, that K refers to the vanishing relative concentrations and thus we have, for example, $\bar{F}_{12} \doteq \{0 \le x_3 \le 1\,;\ x_4 = 1 - x_3\}$.

In complete analogy to F_K and $\bar{F}_K$ we define two sets in Ω_n:

$$\Phi_K \doteq \Big\{ \mathbf{x} \in \Omega_n \;\Big|\; k \in K \iff x_k = 0 \Big\} \qquad \text{and}$$

$$\bar{\Phi}_K \doteq \Big\{ \mathbf{x} \in \Omega_n \;\Big|\; k \in K \implies x_k = 0 \Big\} .$$

Relations between the different types of boundary sets are illustrated in figure 1.

3.3. Reduction Lemma

Let us define a hyperplane through the origin of an n-dimensional Cartesian space which is parallel to the simplex S_n:

$$\Sigma'_n \doteq \Big\{ \mathbf{x} \in \mathbb{R}^n \;\Big|\; \sum_{k=1}^{n} x_k = 0 \Big\} .$$

The replicator field $\vec{\mathcal{R}}(\mathbf{x})$ is seen as a mapping $\Omega_n \to \Sigma'_n$ since by equation (8),

$$\vec{\mathcal{R}}: \quad \mathbf{x} \to \Big[\mathcal{R}_k(\mathbf{x}) = x_k \Big(\mathcal{F}_k(\mathbf{x}) - \textstyle\sum_{j=1}^{n} \mathcal{F}_j(\mathbf{x})\, x_j \Big) \Big]_{k \in \mathcal{N}} ,$$

we have $\sum_{k=1}^{n} \mathcal{R}_k(\mathbf{x}) = 0$. For any replicator field $\vec{\mathcal{R}}$ the relation $\vec{\mathcal{R}}(\Omega_n) \subseteq \Sigma'_m$ holds: the replicator equation leaves the simplex S_n invariant.

Reduction Lemma. Let $K \subset \mathcal{N}$ and $m = \#K$. For any replicator equation $\dot{\mathbf{x}} = \vec{\mathcal{R}}(\mathbf{x})$, $\vec{\mathcal{R}} : S_n \to \Sigma'_n$ there exists – up to a permutation of indices – exactly one replicator equation $\dot{\mathbf{y}} = \widetilde{\mathcal{R}}(\mathbf{y})$, $\widetilde{\mathcal{R}} : S_m \to \Sigma'_m$ and $\mathbf{y} \in \mathbb{R}^m$, such that the restriction of $\vec{\mathcal{R}}$ to $\bar{F}_K$ and $\widetilde{\mathcal{R}}$ generate the same flow.

A proof of the Lemma is found in [13].

Every restriction leads to a uniquely defined replicator equation which is derived straightway. Consider, for example, a second order replicator equation which is characterized by linear replication functions: $\mathcal{F}_k \doteq (F \cdot \mathbf{x})_k$ with an arbitrary matrix $F \in \mathbb{R}^{n \times n}$; $F \doteq \{F_{kj};\, k, j \in \mathcal{N}\}$.

Corollary. Let $\dot{\mathbf{x}} = \vec{\mathcal{R}}$ be a second order replicator equation. Then we get the restricted replicator equation on a subsimplex S_m with $m = \#(\mathcal{N} \backslash K)$ by the following procedure: omit all rows and comlumns with indices $k_j \in K$ and renumber the remaining elements from 1 to m.

Fig. 1: The simplex S_3 embedded in $\mathbb{R}^3$. The boundary $\mathrm{bd}\, S_3$ is partitioned into six subsets: $F_{(1)}, F_{(2)}, F_{(3)}, F_{(1,2)}, F_{(1,3)}$ and $F_{(2,3)}$. Note that the indices define the variables which have zero values. $F_{(1,2)}$, for example, is the corner $\mathbf{e}_3 = (x_1, x_2, x_3) = (0, 0, 1)$. In addition we show the environment of S_3 in Σ_3 as defined by the set $\Omega_3 \backslash S_3$ and its partitioning.

3.4. Transversal eigenvectors and eigenvalues

Consider the linearized replicator field in the neighbourhood of equilibrium points $\overline{\mathbf{x}}$ which is determined by the Jacobian

$$\partial\vec{\mathcal{R}}(\mathbf{x}) \;=\; J(\mathbf{x}) \;\doteq\; \left\{\frac{\partial\vec{\mathcal{R}}_k}{\partial x_j};\, j,k \in \mathcal{N}\right\} .$$

Lateron we shall assume that the conditions for the applicability of the Hartman-Grobman linearization theorem [14] are fulfilled. Then $\partial\vec{\mathcal{R}}$ is hyperbolic and has n eigenvectors. As a consequence of the conservation law $\sum_{k=1}^{n} x_k = 1$ only $n-1$ eigenvectors are required to describe the dynamics on the simplex S_n. They lie in Σ_n' and thus are paralell to Σ_n. Indeed, the n-th eigenvector, $\xi_0(\overline{\mathbf{x}})$ points out of the hyperplane Σ_n and is therefore called the *external* eigenvector.

At points on the boundary of S_n the remaining eigenspace (E) is partitioned again: $\mathrm{bd}\, S_n$ is invariant and hence we have exactly $n-1-\#K$ eigenvectors spanning the subsimplex $S_m(\mathcal{N}\backslash K)$ if $\overline{\mathbf{x}} \in F_K$. Finally we have $\#K$ eigenvectors which point into $\mathrm{int}\, S_n$. We shall call them *transversal eigenvectors*; they constitute a *transversal eigenspace* (E_T). For short we shall use also the notions of *external* and *transversal eigenvalues* for the corresponding eigenvalues. Transversal components of vector fields and the components in the boundary sets will also be indicated by $\perp$ and $\|$, respectively.

According to [7] the external eigenvalue is simply given by

$$\omega_0 \;=\; -\sum_{j=1}^{n} \mathcal{F}_j(\overline{\mathbf{x}})\, \overline{x}_j \;=\; -\overline{\mathcal{F}}(\overline{\mathbf{x}}) \;.$$

No trajectory can intersect the $\mathrm{bd}\, S_n$ and hence there are no complex transversal eigenvalues. Hofbauer and Sigmund [15] showed that the transversal eigenvalues are given by

$$\omega_k \;=\; \mathcal{F}_k(\overline{\mathbf{x}}) \;-\; \overline{\mathcal{F}}(\overline{\mathbf{x}}) \;.$$

Hofbauer also defined a fixed point $\overline{\mathbf{x}}$ as **saturated** if and only if all its transversal eigenvalues are non-positive. We shall call the transversal eigenspace $E_T(\overline{\mathbf{x}})$ **stable** if and only if all transversal eigenvalues are negative. The notion of *saturation* of an equilibrium point may be interpreted such that the vector field in its surrounding does not *"call for missing variables"*.

Theorem 3.4.1. Let $K \in I$ and $\widehat{\mathbf{x}} \in F_K$ be a regular equilibrium of $\vec{\mathcal{R}}$. Then the following statements are equivalent:

(I) The transversal eigenspace $E_T(\widehat{\mathbf{x}})$ is stable.

(II) The fixed point $\widehat{\mathbf{x}}$ is saturated.

(III) There is a neighbourhood $\mathcal{U}(\widehat{\mathbf{x}}) \subset \Omega$ such that for all $\mathbf{x} \in \mathcal{U}(\widehat{\mathbf{x}})\backslash \bar{F}_K$ and for all $k \in K$ the following holds $\mathcal{R}_k(\mathbf{x}) < 0 \iff x_k > 0$ and vice versa.

The proof is given in [14]. This result may be generalized partly to non-regular restpoints as stated in the following theorem.

Theorem 3.4.2. Let $\overline{\mathbf{x}} \in F_K$ be a – not necessarily regular – fixed point of $\vec{\mathcal{R}}$. Let at least one of the transversal eigenvalues be positive. Then there is at least one $\ell \in K$ and a neighbourhood $\mathcal{U}(\overline{\mathbf{x}})$ such that for all $\mathbf{x} \in \mathcal{U}(\overline{\mathbf{x}})\backslash \bar{F}_K$ it holds that $\mathcal{R}_k(\mathbf{x}) > 0$ iff $x_\ell > 0$ and vice versa.

3.5. Robustness, permanence and persistence

The notion of **robustness** plays an important role in the classification of replicator equations and hence needs to be defined precisely. Let $W \subseteq C^1(\Omega)$ and let R_W be the set of all replicator fields $\vec{\mathcal{R}}$ built from functions in W. A replicator field $\vec{\mathcal{R}} = f$ is called **robust** with respect to W if there is an $\epsilon > 0$ such that for all $g \in R_W$ with $f - g^{\ddagger} < \epsilon$ holds that f and g are topologically equivalent. The notion of robustness is a generalization of structural stability: any structurally stable replicator field is robust.

A replicator equation is said to be **permanent** if the following stability criterion is fufilled [15]:

$$\exists\, \delta > 0 : \quad \liminf_{t\to+\infty} x_k(t) > \delta \;\forall\, k = 1,\ldots,n \text{ if } x_k(0) > 0 \ .$$

No type $\mathbf{I}_k$ which was present at time $t = 0$ vanishes in a permanent replicator equation.

There are two less stringent conditions than permanence: **strong persistence** which is obtained from the permanence condition by putting $\delta = 0$, and **persistence** which requires

$$\limsup_{t\to+\infty} x_k(t) > 0$$

for all orbits in the interior of the state space.

In contradiction to the criterion of permanence we say a network leeds to **exclusion** if at least one type $\mathbf{I}_k$ dies out in the limit $t \to \infty$.

4. The perturbation approach

The basic assumption of our approach is the partitioning of the replication-mutation equation (7) into a replication and a mutation field:

$$\frac{d\mathbf{x}}{dt} = \vec{\mathcal{R}}(\mathbf{x}) + \vec{\mathcal{M}}(\mathbf{x},\lambda) = \vec{\mathcal{L}}(\mathbf{x},\lambda) \ . \tag{10}$$

The replication field is defined in equation (8). There is no obvious normal form for a mutation field $\vec{\mathcal{M}}(\mathbf{x},\lambda) = \{\mathcal{M}_k(\mathbf{x},\lambda);\ k = 1,\dots,n\}$ but several necessary conditions have to be fulfilled in order to render the mutation model physically acceptable. For example, mutation frequencies are non-negative quantities and have to meet the conservation law (3). Other conditions are motivated by mathematical needs and plausibility arguments. We assume a single characteristic parameter λ which controls all mutation frequencies. For example, all mutation frequencies vanish asymptotically as $\lambda \to 0$. For technical reasons we postulate that the mutation field $\vec{\mathcal{M}}$ is sufficiently smooth.

The approach used here is related to the *method of small parameters* of Karlin and McGregor [16,17]19721972 who applied it in less elaborate form to difference equations in population biology.

4.1. The mutation field

A mutation field $\vec{\mathcal{M}}$ is suitable for the perturbation approach if it has the following properties:

(I) For all $K \in I$ and all $k \in K$ holds: $\mathbf{x} \in F_K$ implies that
$\mathcal{M}_k(\mathbf{x},\lambda) \geq 0$ for all $\lambda > 0$ and sufficiently small.

(II) For all $K \in I$ and all $\mathbf{x} \in F_K$ $\exists\, k \in K$ such that
$\mathcal{M}_k(\mathbf{x},\lambda) > 0$ for all $\lambda > 0$ and sufficiently small.

(III) $\vec{\mathcal{M}}(\mathbf{x},0) = 0\,\forall\,\mathbf{x} \in \Omega$.

(IV) $\vec{\mathcal{M}}(.,\lambda) \in C^1(\Omega)$ and $\vec{\mathcal{M}}(\mathbf{x},\lambda)$ is bounded on any compact subset of Ω at least for sufficiently small values of λ.

(V) $\vec{\mathcal{M}}(\mathbf{x},\lambda)$ is analytic in λ for all $\mathbf{x} \in \Omega$ at least in a sufficiently small neighbourhood of $\lambda = 0$.

It is useful to illustrate the meaning of these five properties. Conditions (I) and (II) concern the direction of the vector field at the boundary of the simplex S_n.

Relative concentrations are restricted to the range $0 \leq x_k \leq 1 \, \forall \, k \in \mathcal{N}$ and hence no trajectory of the replication-mutation equation (7) can cross the boundary $\mathrm{bd}\, S_n$ in outward direction. Since the replication field is invariant on $\mathrm{bd}\, S_n$ the mutation field cannot point outwards at the boundary. Mutation, nevertheless, is able to create non-existing species and therefore at least one component of the mutation field has to point into the $\mathrm{int}\, S_n$.

Condition (iii) expresses the already mentioned requirement of asymptotic convergence towards the replicator equation in the limit $\lambda \to 0$. Conditions (iv) and (v) are technical requirements which allow for Taylor series expansion with respect to the mutation parameter λ and for calculation of the Jacobian matrix.

4.2. Perturbation of equilibria

Equilibrium points may retain all or some of their qualitative properties when they are subjected to small perturbations in parameter space. In order to study this issue we recall some continuity properties of maps and dynamical systems. Continuity follows from a few results on C^1 maps (f), their Jacobians at given points $\mathbf{x}_0$ $(\partial f(\mathbf{x}_0))$, general real-valued matrices and equilibrium points which are briefly repeated here – details and proofs are given in many textbooks, e.g.in [18] :

Lemma 4.2.1. Let the map $f : W \to E$ be continuously differentiable and choose $\mathbf{x}_0 \in W$ such that the linear operator $\partial f(\mathbf{x}_0)$ is invertible. Then there is a neighbourhood $\mathcal{N}(f)$ and an open set $\mathcal{U} \subseteq W$ with $\mathbf{x}_0 \in \mathcal{U}$ such that for all $g \in \mathcal{N}(f)$ holds:

(i) $g \,|\, \mathcal{U}$ is one-to-one and (ii) $f(\mathbf{x}_0) \in g(\mathcal{U})$.

Lemma 4.2.2. Let A be a real-valued $m \times m$ matrix, $A \in \mathbb{R}^{m \times m}$, with $n(A)$ eigenvalues with negative real parts and $p(A)$ eigenvalues with positive real parts and $m \geq n + p$. Then there is a positive ε such that for all matrices $B \in \mathbb{R}^{m \times m}$ with $A - B_\infty < \varepsilon$:

- B has at least $n(A)$ eigenvalues with negative real parts and at least $p(A)$ eigenvalues with positive real parts.

In lemma 4.2.2 it was not assumed that A is invertible. For hyperbolic matrices A and B we have: $n(A) = n(B)$, $p(A) = p(B)$ and $n(A) + p(A) = m$. From the lemma follows also that for any upper bound $\delta > 0$ on the difference in the eigenvalues of A and B there exists a bound $\varepsilon > 0$ for the difference of the two matrices.

The two lemmas can be extended straightway to equilibrium points. Thereby one finds:

Lemma 4.2.3. Let E be a vector space with a norm, let $f : W \to E$ be a continuously differentiable map and let $\widehat{\mathbf{x}}_0 \in W$ be a regular equilibrium of the differential equation $\dot{\mathbf{x}} = f(\mathbf{x})$. Then there is a neighbourhood $\mathcal{N}(f)$ for all $\varepsilon > 0$ such that for all $g \in \mathcal{N}(f)$ it holds that there exists a unique $\widehat{\mathbf{x}}$ which fulfils:

(I) $g(\widehat{\mathbf{x}}) = 0$ and (II) $\widehat{\mathbf{x}} - \widehat{\mathbf{x}}_0 < \varepsilon$.

Corollary. Let $f \in C^1(W)$ and $f(\mathbf{x};\lambda)$ be continuous in λ and let $\widehat{\mathbf{x}}(\lambda_0)$ be a regular equilibrium of $\dot{\mathbf{x}} = f(\mathbf{x};\lambda_0)$. Then for any neighlourhood $\mathcal{U}\big(\widehat{\mathbf{x}}(\lambda_0)\big)$ there exists a neighbourhood $\mathcal{V}(\lambda_0)$ such that for all $\lambda \in \mathcal{V}(\lambda_0)$ there is a uniquely defined fixed point $\widehat{\mathbf{x}}(\lambda) \in \mathcal{U}\big(\widehat{\mathbf{x}}(\lambda_0)\big)$ of $\dot{\mathbf{x}} = f(\mathbf{x};\lambda)$ which is regular.

The analogue of lemma 4.2.2 for equilibrium points takes the following form:

Lemma 4.2.4. Let $\overline{\mathbf{x}}_0$ be a fixed point of $\dot{\mathbf{x}} = f(\mathbf{x})$ whose Jacobian has $p(f)$ positive and $n(f)$ negative eigenvalues and let $\mathcal{U}_\varepsilon(\overline{\mathbf{x}}_0)$ be an arbitrarily small neighbourhood of this fixed point. If $g \in \mathcal{N}(f)$ – $\mathcal{N}(f)$ being a sufficiently small neighbourhood of f – admits a fixed point in $\mathcal{U}_\varepsilon(\overline{\mathbf{x}}_0)$, then the Jacobian of this – not necessarily unique – fixed point fulfils: $n(g) \geq n(f)$ and $p(g) \geq p(f)$.

Corollary. Let the fixed point $\widehat{\mathbf{x}}_0$ be regular in lemma 4.2.4. Then $\widehat{\mathbf{x}}$ is unique and regular for sufficiently small ε. Let $\widehat{\mathbf{x}}_0$ be hyperbolic. Then $\widehat{\mathbf{x}}$ is hyperbolic as well for sufficiently small ε, and $n(g) = n(f)$ and $p(g) = p(f)$ hold.

4.3. The restpoint migration theorem

Addition of a mutation field $\vec{\mathcal{M}}$ to the replicator equation $\dot{\mathbf{x}} = \vec{\mathcal{R}}(\mathbf{x})$ destroys the invariance of surface subsets F_K. Hence all fixed points of the replicator equation which were situated on the boundary of the simplex $\mathrm{bd}\, S_n$ have to migrate either into the interior $\mathrm{int}\, S_n$ or into the surrounding set $\Omega_n \backslash S_n$. Application of the previously described continuity properties to the replication-mutation equation (10) allows one to derive a general theorem which predicts the qualitative, mutation induced shifts in the positions of fixed points of the replicator field. The theorem represents the basis of forthcoming systematic investigations.

Restpoint migration theorem. Let $\overline{\mathbf{x}}_0$ be a rest point of the replicator equation $\dot{\mathbf{x}} = \vec{\mathcal{R}}(\mathbf{x})$ which lies on $\mathrm{bd}\, S_n$, say $\overline{\mathbf{x}}_0 \in F_K$, and let $\vec{\mathcal{M}}$ be a mutation field for

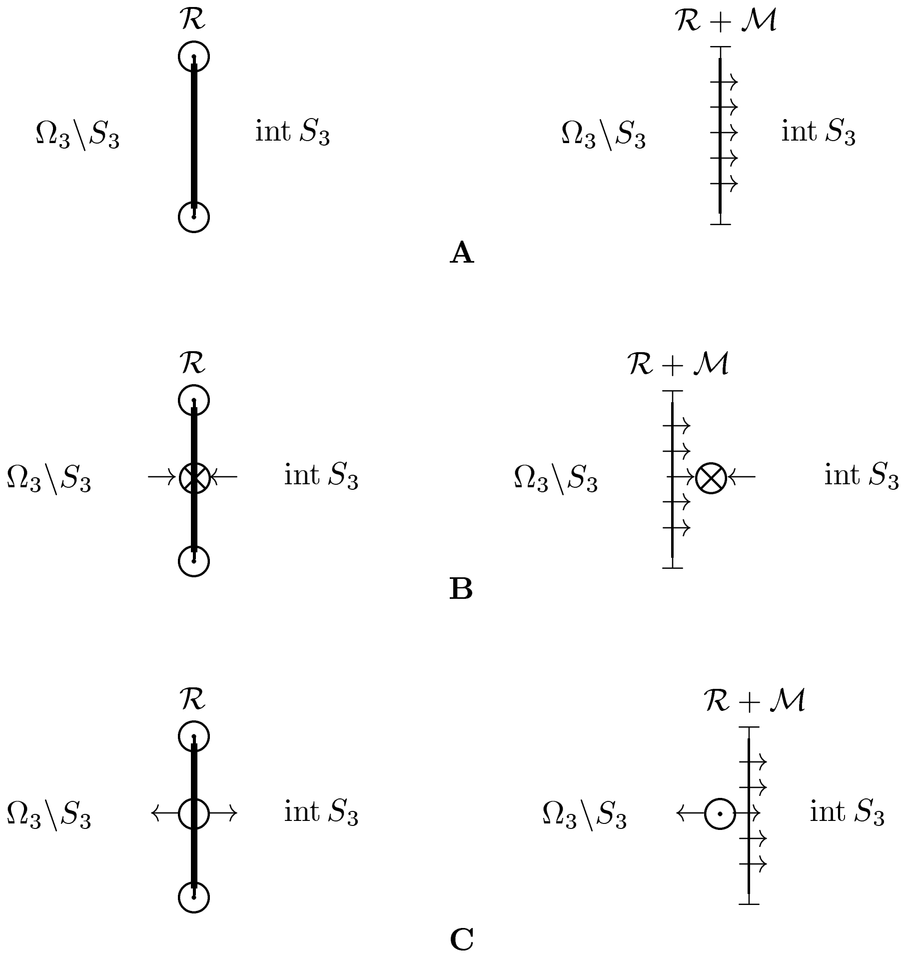

Fig. 2: An illustration of the restpoint migration theorem. We show three qualitatively different scenarios (**A**, **B** and **C**) on an edge of the simplex S_3. The invariant boundary subset of the replicator equation $\dot{\mathbf{x}} = \vec{\mathcal{R}}(\mathbf{x})$ is destroyed by the mutation field $\vec{\mathcal{M}}$ which introduces a vectorial flow into the interior int S_3. Three cases are shown:

A: no fixed point is situated on the edge,

B: a hyperbolic fixed point with a stable transversal eigenspace ($\bigotimes$) migrates into int S_3 and

C: a hyperbolic fixed point with one – or more – positive transversal eigenvalue ($\bigodot$) leaves the simplex and migrates into the environment $\Omega_3 \backslash S_3$.

which $\mathcal{M}_k(\overline{\mathbf{x}}_0, \lambda) > 0$ holds for all $k \in K$. Then the following statements are true for sufficiently small values of the perturbation parameter $\lambda > 0$:

(I) If the restpoint $\widehat{\mathbf{x}}_0$ is regular then
$$\widehat{\mathbf{x}}(\lambda) \in \operatorname{int} S_n \quad \Longleftrightarrow \quad \text{the transversal eigenspace } E_T(\widehat{\mathbf{x}}_0) \text{ is } \textbf{stable}.$$

(II) If the transversal eigenspace $E_T(\overline{\mathbf{x}})$ has at least one positive eigenvalue, $\omega_\ell > 0$, then all fixed points $\overline{\mathbf{x}}_j$ derived from $\overline{\mathbf{x}}_0$ at small positive λ-values lie outside the simplex S_n,
$$\overline{\mathbf{x}}_j(\lambda) \in \Omega_n \backslash S_n \; ; \; j = 1, \ldots$$

The proof is given in two parts corresponding to I and II.

Proof. Part I: We choose a small neighbourhood of the regular fixed point $\mathcal{U}_\varepsilon(\widehat{\mathbf{x}}_0)$ which has the following properties:

(I) $\mathcal{U}_\varepsilon \subseteq \Omega$,

(II) $\vec{\mathcal{M}}(\mathbf{x}, \lambda) > 0$ for all $\mathbf{x} \in \mathcal{U}_\varepsilon(\widehat{\mathbf{x}}_0)$ and all $k \in K$,

(III) $x_\ell > 0$ for all $x \in \mathcal{U}_\epsilon(\widehat{\mathbf{x}}_0)$ and all $\ell \in \mathcal{N} \backslash K$,

(IV) $\mathcal{R}_k(\mathbf{x}) < 0 \Longleftrightarrow x_k > 0$ and $\mathcal{R}_k(\mathbf{x}) > 0 \Longleftrightarrow x_k < 0$ for all $k \in K$ and all $\mathbf{x} \in \mathcal{U}_\varepsilon(\widehat{\mathbf{x}}_0)$.

Condition (IV) is equivalent to stability of $E_T(\widehat{\mathbf{x}}_0)$ by theorem 3.4.1. The remaining three conditions are also fulfilled if ε is chosen sufficiently small. The replication-mutation field $\vec{\mathcal{L}}(\mathbf{x}, \lambda)$ fulfils $\mathcal{L}_k(\mathbf{x}, \lambda) > 0$ on $\mathcal{U}_\varepsilon(\widehat{\mathbf{x}}_0) \cap F_K$ for all $k \in K$ and for sufficiently small $\lambda > 0$ because $\vec{\mathcal{R}}_{\parallel}(\mathbf{x})$ vanishes on this set.
We know from the corollary to lemma 4.2.4 that there is exactly one fixed point in $\mathcal{U}_\varepsilon(\widehat{\mathbf{x}}_0)$ for $\lambda > 0$ and sufficiently small and we have shown that it cannot be in $\mathcal{U}_\varepsilon(\widehat{\mathbf{x}}_0) \cap F_K$. We consider now a point $\mathbf{y}$ in the set $\mathcal{U}_\varepsilon(\widehat{\mathbf{x}}_0) \backslash S_n$: here we have $y_k < 0$ for at least one $k \in K$. By condition (IV) we have $\mathcal{R}_k(\mathbf{y}) > 0$ for this k and therefore $\mathcal{L}_k(\mathbf{y}, \lambda) > 0$ is true as well. Thus there is no fixed point in $\mathcal{U}_\varepsilon(\widehat{\mathbf{x}}_0) \backslash S_n$ and consequently the fixed point must lie in the interior $\operatorname{int} S_n$.
If the transversal eigenspace $E_T(\widehat{\mathbf{x}}_0)$ is not stable then we have at least one $j \in K$ such that $\mathcal{R}_j(\mathbf{x}) > 0$ for an $\mathbf{x} \in \mathcal{U}_\varepsilon(\widehat{\mathbf{x}}_0)$ with $x_j > 0$. By the same argument as above we cannot have a fixed point in $\mathcal{U}_\varepsilon(\widehat{\mathbf{x}}_0) \cap S_n$ and therefore it must lie outside the simplex, in $\Omega_n \backslash S_n$.

Part II: The proof for regular fixed points is extended to general fixed points. By definition of $\vec{\mathcal{M}}$ there is no fixed point on $\operatorname{bd} S_n$ for $\lambda > 0$. The transversal eigenspace $E_T(\overline{\mathbf{x}}_0)$ has at least one positive eigenvalue and hence we have $\mathcal{R}_\ell(\mathbf{x}) >$

0 for at least one $\ell \in K$ in $\mathcal{U}_\varepsilon(\overline{\mathbf{x}}_0) \cap \operatorname{int} S_n$. By the same argument as above we conclude that there exists no rest point in the interior of the simplex, int S_n, which lies close to $\overline{\mathbf{x}}_0$.

The meaning of the restpoint migration theorem is illustrated in figure 2 by means of a simple example. We consider the mutation field $\vec{\mathcal{M}}(\lambda)$ in the limit of weak mutation – expressed by small values of the mutation parameter λ. Then the vector field $\vec{\mathcal{L}} = \vec{\mathcal{R}} + \vec{\mathcal{M}}$ in the neighbourhood of a restpoint has to match to the vector field on the boundary of S_n which has to have at least one non-zero transversal component pointing towards the interior (int S_n). Regular restpoints – and evidently hyperbolic restpoints as well – migrate into the interior of the simplex if and only if their transversal eigenspace is stable. In case the fixed point has one positive transversal eigenvalue it is shifted into the environment: $\Omega_n \backslash S_n$.

It is worth pointing at the fact that in the proof of the restpoint migration theorem we used nowhere the restriction of the ODE onto the simplex S_n. The theorem is equally valid therefore on boundary surfaces of Lotka-Volterra systems with mutation provided F_K is replaced by the corresponding boundary surface of the positive orthant and the neighbourhood of this orthant is substituted for Ω_n. The same is true for the limit cycle migration theorem to be proved in the next section 4.4.

4.4. The limit cycle migration theorem

The notion of *saturation* is generalized from rest points to arbitrary orbits in the ω-limit set of a replicator equation of type (8). The results obtained in this section are more general: they hold for Lotka-Volterra type equations too.

Definition: Let ψ be an orbit in the ω-limit set of the replicator equation on the boundary of S_n, $\psi \in F_K$. Then we define the following time average for any arbitrary $x \in \psi$

$$\bar{\lambda}_k \;=\; \lim_{T\to\infty} \frac{1}{T} \int_0^T \Big[\mathcal{F}_k\big(\mathbf{x}(\tau)\big) \;-\; \overline{\mathcal{F}}\big(\mathbf{x}(\tau)\big)\Big]\, d\tau \quad \text{for} \quad k \in K \;. \tag{11}$$

We note that $\bar{\lambda}_k$ depends on the orbit ψ but does not depend on the choice of initial condition $\mathbf{x}(0)$. An orbit ψ is **saturated** if $\bar{\lambda}_k \leq 0$ holds for all $k \in K$.

Lemma 4.4.1. Let $\chi \in F_K$ be a periodic orbit of equation (8). Then χ is hyperbolic if and only if the following two conditions are fulfilled:

(I) χ is hyperbolic in the restriction of the replicator equation onto $\bar{F}_K$, and

(II) $\bar{\lambda}_k \neq 0$ for all $k \in K$.

Proof. The linearization of (8) along the orbit χ can be factorized in the following way:

$$\partial\vec{\mathcal{R}}\big(\mathbf{x}(t)\big) \quad = \quad \begin{pmatrix} J\big(\mathbf{x}(t)\big) & Q\big(\mathbf{x}(t)\big) \\ 0 & \Lambda\big(\mathbf{x}(t)\big) \end{pmatrix}$$

where $J\big(\mathbf{x}(t)\big)$ is the restriction of the linearization of (8) onto $\bar{F}_K$, which can be achieved always by a change in coordinates, and

$$\Lambda\big(\mathbf{x}(t)\big) \quad = \quad \operatorname{diag}\Big\{\mathcal{F}_k\big(\mathbf{x}(t)\big) \; - \; \overline{\mathcal{F}}\big(\mathbf{x}(t)\big)\Big\}_{k\in K}$$

is the linearization in the transversal eigenspace which is already in diagonal form – see section 3.4 and [15]. For diagonal matrices we use the notation: $\operatorname{diag} A = \big\{a_{ij} \doteq a_{ii} \cdot \delta_{ij}\big\}$.
Let Ξ be an arbitrary Poincaré section and T be the period of χ. The Poincaré map of the linearized ODE is then given by the solution of

$$\begin{aligned} \dot{\mathbf{X}}_L(t) &= J\big(\mathbf{x}(t)\big) \cdot \mathbf{X}_L(t) \quad \text{on} \quad F_K \\ \dot{\xi}_k(t) &= \Big\{\mathcal{F}_k\big(\mathbf{x}(t)\big) \; - \; \overline{\mathcal{F}}\big(\mathbf{x}(t)\big)\Big\}\, \xi_k(t) \quad \text{for all} \quad k \in K \end{aligned}$$

at times 0, T, $2T$, etc. The first equation is the linearization of the replicator equation in F_K around the periodic orbit; $\mathbf{X}_L$ represents coordinates $\ell \in \{\mathcal{N}\backslash K\}$. Since the solutions of the differential equation in $\mathbf{X}_L$ do not enter the stability discussion we shall not consider them any further.
The linear ODEs in the transversal space are solved readily:

$$\begin{aligned} \xi_k(t) &= \xi_k(0)\,\exp\Big\{\int_0^t \Big[\mathcal{F}_k\big(\mathbf{x}(\tau)\big) \; - \; \overline{\mathcal{F}}\big(\mathbf{x}(\tau)\big)\Big]\,d\tau\Big\} \\ &= \xi_k(0)\,p(t)\,\exp\Big\{\frac{t}{T}\int_0^T \Big[\mathcal{F}_k\big(\mathbf{x}(\tau)\big) \; - \; \overline{\mathcal{F}}\big(\mathbf{x}(\tau)\big)\Big]\,d\tau\Big\} \\ &= \xi_k(0)\,p(t)\,\exp\big(t\,\bar{\lambda}_k\big)\ , \end{aligned}$$

where $p(t)$ is some periodic function in t. Accordingly

$$\mu_k \;=\; \exp\big(\bar{\lambda}_k\big) \quad \text{for all} \quad k \in K$$

are the Floquet multiplier for the transversal directions.

Limit cycle migration theorem. Let $\chi \in F_K$ be a hyperbolic periodic orbit of the replicator equation (8), and let $\vec{\mathcal{M}}(\mathbf{x}, \lambda)$ be a mutation field with the same properties as in the perturbation of equilibria (section 4.2). Then there is a neighbourhood $\mathcal{W}(\chi)$ such that the following four statements hold for small perturbations $\vec{\mathcal{M}}(\mathbf{x}, \lambda)$:

(I) there is a unique periodic orbit $\tilde{\chi}(\lambda)$ which lies entirely in $\mathcal{W}(\chi)$,

(II) $\tilde{\chi}(\lambda)$ does not intersect the boundary of S_n,

(III) $\tilde{\chi}(\lambda)$ is hyperbolic, and

(IV) $\tilde{\chi}(\lambda) \in \operatorname{int} S_n \iff \tilde{\chi}$ is **saturated**.

Proof. Proofs for items I and III are found in the monograph by Hirsch and Smale [18]. Item II follows from the fact that the flow of the perturbed system points into $\operatorname{int} S_n$ everywhere on $\operatorname{bd} S_n$.
Item IV: Suppose the S_n is not saturated. Then there is at least one tranversal direction ℓ such that $\lambda_\ell > 0$. Let ψ be an orbit which lies entirely in $\mathcal{W}(\chi)$ and contains a point in $\operatorname{int} S_n$. Then the coordinate x_ℓ is positive for $t > t_0$. Since $x_\ell(T + t_0) > x_\ell(t_0)$ holds for the unperturbed system and $\mathcal{M}_\ell(\mathbf{x}, \lambda) > \delta$ holds for all x_k with $k \in F_K$, there is a $\tilde{\delta} > 0$ such that $x_\ell(T + t_0) > x_\ell(t_0) + \tilde{\delta}$. Thus ψ cannot be entirely contained in $\mathcal{W}(\chi)$ for arbitrarily long times and there is no periodic orbit in $\mathcal{W}(\chi) \cap S_n$.
If, on the other hand, $\tilde{\chi}$ lies in $\mathcal{W}(\chi) \cap S_n$, then

$$\int_0^{\tilde{T}} \mathcal{R}_k\Big(y(t)\Big)\, dt \; + \; \int_0^{\tilde{T}} \mathcal{M}_k\Big(y(t)\Big)\, dt \quad = \quad 0$$

must hold for $y \in \tilde{\chi}$ with $\tilde{T}$ being the period of the perturbed closed orbit $\tilde{\chi}$. Since the contribution of mutation, $\mathcal{M}_k$, is always positive, the first integral must be negative. Both, χ and $\tilde{\chi}$, are hyperbolic the chracteristic exponents have to be negative in all transversal directions: $\bar{\lambda}_k < 0$ for all $k \in K$.

We end this section by summarizing some results on second order replicator equations derived by Hofbauer and Sigmund [15] and extending them to perturbed orbits:

Lemma 4.4.2. Let $\psi \in F_K$ be an orbit in the ω-limit set of a second order replicator equation. Then there is a rest point in F_K and the characteristic exponents $\bar{\lambda}_k$ are given by the transversal eigenvalues of this rest point.

Corollary. Let $\chi \in F_K$ be a periodic orbit of a second order replicator equation. The the two statements are true:

(I) The periodic orbit χ is hyperbolic if and only if χ is also hyperbolic on the restriction of the second order replicator equation onto F_K and the transversal eigenvalues of the interior rest point on the subsimplex $\bar{F}_K$ are all non-zero.

(II) If the periodic orbit $\chi \in F_K$ is hyperbolic, then the periodic orbit $\tilde{\chi} \in \mathcal{W}(\chi)$ of the perturbed system lies in $\operatorname{int} S_n$ if and only if the interior rest point of the subsimplex $\bar{F}_K$ is saturated.

4.5. The perturbation expansion

In order to be able to calculate the positions of fixed points as functions of the mutation parameter λ the perturbation expansion has to be considered in explicit form. Let $\mathbf{x}_0$ be some point of the unperturbed replicator field $\vec{\mathcal{L}}(\mathbf{x},0) = \vec{\mathcal{R}}(\mathbf{x})$ and, let $\mathbf{x}(\lambda)$ be its position in the vector field $\vec{\mathcal{L}}(\mathbf{x},\lambda)$ which is supposed to be sufficiently smooth according to the criteria given in section 4.1. Then the shift vector is given by

$$\vec{\xi}(\lambda) \;=\; \mathbf{x}(\lambda) \;-\; \mathbf{x}_0\;. \tag{12}$$

In order to formulate an expansion of the vector field around the point $\mathbf{x}_0$ we shall use the following notation for the various partial derivatives:

$$\mathbf{L}_{\alpha\beta\ldots\mu} \;=\; \frac{\partial^m \vec{\mathcal{L}}(\mathbf{x},\lambda)}{\partial x_\alpha \partial x_\beta \ldots \partial x_\mu}\Bigg|_{\mathbf{x}=\mathbf{x}_0} \tag{13 a}$$

$$\mathbf{L}^{(k)} \;=\; \frac{\partial^k \vec{\mathcal{L}}(\mathbf{x},\lambda)}{\partial \lambda^k}\Bigg|_{\lambda=0} \tag{13 b}$$

$$\mathbf{L}^{(k)}_{\alpha\beta\ldots\mu} \;=\; \frac{\partial^{(k+m)} \vec{\mathcal{L}}(\mathbf{x},\lambda)}{\partial \lambda^k \partial x_\alpha \partial x_\beta \ldots \partial x_\mu}\Bigg|_{\mathbf{x}=\mathbf{x}_0,\lambda=0} \tag{13 c}$$

Herein m is the total number of indices referring to partial differentials in relative concentrations – repetitions of indices, of course, are allowed. It is important to remember that the various derivatives of the vector field $\vec{\mathcal{L}}$ are all n-dimensional vectors.

Expansion of the vector field $\vec{\mathcal{L}}$ into a Taylor series around the point $\mathbf{x}_0$ yields

$$\vec{\mathcal{L}}(\mathbf{x},0) \;-\; \vec{\mathcal{L}}(\mathbf{x}_0,0) \;=\; \sum_{i=1}^{n} \mathbf{L}_i \xi_i \;+\; \tfrac{1}{2} \sum_{i=1}^{n}\sum_{j=1}^{n} \mathbf{L}_{ij}\xi_i\xi_j \;+\; \ldots\;.$$

The expansion coefficients of the Taylor expansion and the shift vector $\vec{\xi}$ are now subjected to the conventional Rayleigh-Schrödinger perturbation expansion series:

$$\mathbf{L}_{..}(\lambda) \;=\; \mathbf{L}_{..} \,+\, \lambda\,\mathbf{L}_{..}^{(1)} \,+\, \lambda^2\,\mathbf{L}_{..}^{(2)} \,+\, \dots \quad \text{and} \tag{14}$$

$$\vec{\xi}(\lambda) \;=\; \lambda\,\mathbf{d}^{(1)} \,+\, \lambda^2\,\mathbf{d}^{(2)}\;. \tag{15}$$

Insertion of the perturbation series into the Taylor expansion yields the following terms up to second order:

$$\begin{aligned}\vec{\mathcal{L}}(\mathbf{x},\lambda) - \vec{\mathcal{L}}(\mathbf{x}_0,0) \;=\;& \lambda\,\mathbf{L}^{(1)} &&+ \lambda^2\,\mathbf{L}^{(2)} &&+\dots\\ +\;& \lambda\sum_{i=1}^{n}\mathbf{L}_i d_i^{(1)} &&+ \lambda^2\sum_{i=1}^{n}\mathbf{L}_i d_i^{(2)} &&+\dots\\ & &&+ \lambda^2\sum_{i=1}^{n}\mathbf{L}_i^{(1)} d_i^{(1)} &&+\dots\\ & &&+ \lambda^2\sum_{i=1}^{n}\sum_{j=1}^{n}\mathbf{L}_{ij} d_i^{(1)} d_j^{(1)} &&+\dots\end{aligned} \tag{16}$$

Primarily we are interested here in the positions of fixed points. Let us choose therefore $\mathbf{x}_0$ to be an equilibrium of $\vec{\mathcal{L}}(\mathbf{x},0)$, $\overline{\mathbf{x}}_0$, and $\mathbf{x}(\lambda)$ to be an equilibrium of $\vec{\mathcal{L}}(\mathbf{x},\lambda)$, $\overline{\mathbf{x}}(\lambda)$. Within the frame of the perturbation approach the postition of such a fixed point is given by equation (15):

$$\overline{\mathbf{x}}(\lambda) \;=\; \overline{\mathbf{x}}_0 \,+\, \lambda\,\mathbf{d}^{(1)} \,+\, \lambda^2\,\mathbf{d}^{(2)}\;\dots\;.$$

Then the two equations $\vec{\mathcal{L}}(\overline{\mathbf{x}}_0,0) = 0$ and $\vec{\mathcal{L}}(\overline{\mathbf{x}},\lambda) = 0$ are fulfilled. The latter condition has to hold for all values of $\lambda \geq 0$ and sufficiently small to guarantee convergence of the perturbation series. As a consequence the coefficients of λ^n have to vanish for each order $n = 1, 2, \dots$ independently. Let $J = (\mathbf{L}_i,\; i = 1,\dots,n)$ be the Jacobian of $\vec{\mathcal{L}}$ at the position $\overline{\mathbf{x}}_0$. Now we obtain

$$\begin{aligned} J\cdot\mathbf{d}^{(1)} &= -\,\mathbf{L}^{(1)}\\ J\cdot\mathbf{d}^{(2)} &= -\,\mathbf{L}^{(2)} - \sum_{i=1}^{n}\mathbf{L}_i^{(1)} d_i^{(1)} - \sum_{i=1}^{n}\sum_{j=1}^{n}\mathbf{L}_{ij} d_i^{(1)} d_j^{(1)}\end{aligned}$$

In applying the perturbation formalism to replication-mutation fields we recall that $\vec{\mathcal{L}}(\mathbf{x}_0,0) = \vec{\mathcal{R}}(\mathbf{x}_0)$ and $\vec{\mathcal{L}}(\mathbf{x},\lambda) - \vec{\mathcal{L}}(\mathbf{x}_0,0) = \vec{\mathcal{M}}(\mathbf{x},\lambda)$. Making use of the same notation as shown in (13) to the mutation field $\vec{\mathcal{M}}$ we find:

$$\mathbf{d}^{(1)} \;=\; -\,J^{-1}\cdot\mathbf{M}^{(1)} \;=\; -\,J^{-1}\cdot\left.\frac{\partial\vec{\mathcal{M}}(\mathbf{x},\lambda)}{\partial\lambda}\right|_{\mathbf{x}=\overline{\mathbf{x}}_0,\lambda=0}\;. \tag{17}$$

Accordingly we are in the position to compute the – linearized – initial shifts of regular rest points straightaway by inverting the Jacobian. If necessary, the results might well be improved by adding the second order terms whose computation, however, is somewhat more involved:

$$\mathbf{d}^{(2)} \;=\; -\,J^{-1} \cdot \left(\mathbf{M}^{(2)} + \sum_{i=1}^{n} \mathbf{M}_i^{(1)} d_i^{(1)} + \sum_{i=1}^{n}\sum_{j=1}^{n} \mathbf{M}_{ij} d_i^{(1)} d_j^{(1)}\right) . \tag{18}$$

Expression derived from the perturbation expansion are given here up to second order only. It is not difficult to compute them for the higher orders by recursion. The corresponding formulas, however, are rather clumsy and the are hardly used in the actual computations. We dispense therefore from showing them here.

4.6. Perturbation by other vector fields

The perturbation approach as outlined in the last section 4.5 is not restricted mutation fields. Other vector fields – provided they are sufficiently smooth in order to meet conditions analogous to those given in section 4.1 – may be used in the expansion equally well. As an example we consider a replicator field with an adjustable, continuously changing parameter λ:

$$\mathcal{R}_k(\mathbf{x},\lambda) = x_k \left(\mathcal{F}_k(\mathbf{x},\lambda) \;-\; \sum_{j=1}^{n} \mathcal{F}_j(\mathbf{x},\lambda)\, x_j\right);\;\; k = 1,2,\ldots,n\ .$$

It is straightforward then to derive the following theorem [13]:

Theorem 4.6.1. Let $\widehat{\mathbf{x}}_0 \in F_K$ be a regular rest point of $\vec{\mathcal{R}}(\mathbf{x},\lambda_0)$. Then there exists a neighbourhood $\mathcal{V}(\lambda_0)$ for each neighbourhood $\mathcal{U}(\widehat{\mathbf{x}}_0)$ such that for any $\lambda \in \mathcal{V}(\lambda_0)$ the following two conditions hold:

(I) $\widehat{\mathbf{x}}(\lambda)$ is a uniquely determined fixed point of the replicator equation $\dot{\mathbf{x}} = \vec{\mathcal{R}}(\mathbf{x},\lambda)$ with $\widehat{\mathbf{x}}(\lambda) \in \mathcal{U}(\widehat{\mathbf{x}}_0)$, and

(II) $\widehat{\mathbf{x}}(\lambda) \in F_K$.

An immediate consequence of this theorem is that all corners $\mathbf{e}_k$ $(k = 1,2,\ldots,n)$ of the simplex S_n are fixed points for all replicator equations – a result which is not hard to derive directly from equation (8).

5. Applications

In this section we shall provide a collection of examples which will show that the perturbation approach might be widely used in analytical investigations of replication-mutation systems. The examples fall in two major groups: the quasi-species model is an example of first order replication, the weak selection case, the Schloegl model, the hypercycle, recombination and the chaotic attractor discussed at the end of this section represent special cases of the second order replication-mutation system.

5.1. Weak selection

A second order replication-mutation equation (7) with $\mathcal{F}_k = \sum_{j=1}^{n} A_{kj}x_j$ is considered. We assume that the degradation rate constants are the same for all types $\mathbf{I}_k$: $D_k = D$. Hence this term can be absorbed in the flux term $\Phi(t)$. A mean replication rate constant α is defined and the actually used constants are counted as deviations from this mean:

$$\alpha \;=\; \frac{1}{n^2}\sum_{i=1}^{n}\sum_{j=1}^{n} A_{ij} \quad \text{and} \quad \widetilde{A} \;\doteq\; \big\{a_{ij} = A_{ij} - \alpha\big\} \ .$$

In the weak selection scenario differences in replication rate constants are small:

$$\beta \;=\; \max\big\{a_{ij}\big\} \quad \text{and} \quad \frac{\beta}{\alpha} \ll 1 \ .$$

Then the dynamics of the replication-mutation equation is determined by the mutation terms. It is suggestive therefore to use the conventional mutation equation (see for example ref.[15], p.250):

$$\frac{\mathrm{d}\mathbf{x}}{\mathrm{dt}} \;=\; \vec{\mathcal{B}}(\mathbf{x},Q) \quad \text{with} \quad \vec{\mathcal{B}}(\mathbf{x},Q) \;=\; (Q - \Im\mathrm{d})\,\mathbf{x} \ , \tag{19}$$

or in components $\mathcal{B}_k(\mathbf{x},Q) = \sum_{j=1}^{n} Q_{kj}x_j \,-\, x_k$, as an appropriate reference system. The replication-mutation equation may now be written as

$$\frac{\mathrm{d}\mathbf{x}}{\mathrm{dt}} \;=\; \vec{\mathcal{L}}(\mathbf{x},A,Q) \;=\; \alpha\cdot\vec{\mathcal{B}}(\mathbf{x},Q) \,+\, \vec{\mathcal{S}}(\mathbf{x},\widetilde{A},Q)$$

with $\vec{\mathcal{S}}(\mathbf{x},\widetilde{A},Q) = \vec{\mathcal{R}}(\mathbf{x},\widetilde{A}) + \vec{\mathcal{M}}(\mathbf{x},\widetilde{A},Q)$. We may rescale the time axis by the factor α and find for the weak selection case:

$$\frac{\mathrm{d}\mathbf{x}}{\mathrm{dt}} \;=\; \vec{\mathcal{B}}(\mathbf{x},Q) \,+\, \frac{1}{\alpha}\,\vec{\mathcal{S}}(\mathbf{x},\widetilde{A},Q) \ . \tag{20}$$

Theorem 5.1.1. Let $\vec{\mathcal{M}}$ be a mutation field in the sense of section 4.1. Then the selection-mutation equation $\dot{\mathbf{x}} = \vec{\mathcal{L}}(\mathbf{x}, \widetilde{A}, Q)$ has a unique, hyperbolic and globally stable equilibrium in int S_n, if β/α is sufficiently small.

Proof. The matrix Q has a simple eigenvalue $\omega_1 = 1$ as follows from the theorem on stochastic matrices by Perron and Frobenius. Thus $Q - \Im\mathrm{d}$ is not invertible in $\mathbb{R}^n$. Let $\widehat{\mathbf{x}}$ be the strictly positive eigenvector to the eigenvalue $\omega_1 = 1$. Without loosing generality we may assume that it is nomalized such that $\sum_{j=1}^n \hat{x}_j = 1$. Hence $\widehat{\mathbf{x}}$ is the unique solution of $(Q - \Im\mathrm{d})\,\widehat{\mathbf{x}} = \vec{0}$ on Σ_n' – that means it is the unique restpoint of the mutation equation.

It is easy to check that $(Q - \Im\mathrm{d})$ leaves Σ_n' invariant. Thus $\mathbb{R}^n$ may be written as the direct sum $\mathbb{R}^n = \mathrm{Ker}\,(Q - \Im\mathrm{d}) \oplus \Sigma_n'$. The operator $(Q - \Im\mathrm{d})$ is invertible on Σ_n' and furthermore its restriction to this subspace is hyperbolic since all eigenvalues of Q except ω_1 have real parts strictly smaller than one by the theorem of Perron and Frobenius. Lemma 4.2.3 and lemma 4.2.4 complete the proof.

Note that the equation

$$(Q - \Im\mathrm{d}) \cdot \mathbf{d}^{(1)} \;=\; -\vec{\mathcal{S}}(\widehat{\mathbf{x}})$$

has a unique solution $\mathbf{d} \in \Sigma_n'$ since $\vec{\mathcal{S}}(\widehat{\mathbf{x}}) \in \Sigma_n'$.

5.2. Perturbation expansion and uniform error rates

The general replication-mutation equation (7) has to be partitioned into a replication and a mutation field. The replication field is given by equation (8). Making use of (3) – which expresses that the mutation matrix Q is a stochastic matrix – we derive for the mutation field:

$$\begin{aligned}\mathcal{M}_k(\mathbf{x}, \lambda) \;&=\; \sum_{\ell=1}^{n} Q_{k\ell}(\lambda)\mathcal{F}_\ell(\mathbf{x})\,x_\ell \;-\; \mathcal{F}_k(\mathbf{x})\,x_k \;= \\ &=\; \sum_{\ell=1}^{n} \Big(Q_{k\ell}(\lambda)\mathcal{F}_\ell(\mathbf{x})\,x_\ell \;-\; Q_{\ell k}(\lambda)\mathcal{F}_k(\mathbf{x})\,x_k \Big)\;. \end{aligned} \tag{21}$$

A perturbation parameter which is adequate to the problem to be solved has yet to be found. We start with a formal expansion of the elements of the mutation matrix Q:

$$Q_{k\ell}(\lambda) \;=\; \sum_{j=1}^{\infty} \frac{1}{j|} \frac{\partial^j Q_{k\ell}(\lambda)}{\partial \lambda^j}\bigg|_{\lambda=0} \cdot \lambda^j \;=\; \sum_{j=1}^{\infty} Q_{k\ell}^{(j)} \cdot \lambda^j\;. \tag{22}$$

This expansion can be written in terms of equation (14) whereby we make use of the fact that $\vec{\mathcal{M}}(\mathbf{x},0)=0$:

$$\vec{\mathcal{M}}(\mathbf{x},\lambda) \;=\; \sum_{j=1}^{\infty} \mathbf{M}^{(j)}\,\lambda^j \quad \text{with} \quad M_k^{(j)} \;=\; \sum_{\ell=1}^{n} Q_{k\ell}^{(j)}\mathcal{F}_\ell(\mathbf{x})\,x_\ell \;-\; Q_{\ell k}^{(j)}\mathcal{F}_k(\mathbf{x})\,x_k \;. \tag{21a}$$

From normalization of mutation frequencies, equation (3), follows that the coeffients of the Taylor expansion fulfil:

$$\sum_{k=1}^{n} Q_{k\ell}^{(j)} \;=\; 0\;. \tag{23}$$

Equation (21) shows that the contributions of the diagonal elements $Q_{kk}^{(j)}$ cancel.

One way to relate the expansion more closely to the biophysical background of mutation is to introduce a mean – first order – mutation rate as perturbation parameter

$$\varrho \;=\; \lambda\cdot\frac{1}{n(n-1)}\sum_{k=1}^{n-1}\sum_{\ell>k}^{n} Q_{k\ell}^{(1)} \tag{24}$$

which replaces λ. This change is tantamount to a rescaling of the perturbation expansion

$$\mathcal{M}_k(\mathbf{x},\lambda) \;=\; \sum_{j=1}^{\infty}\left\{\sum_{\ell=1}^{n} \mathcal{Q}_{k\ell}^{(j)}\mathcal{F}_\ell(\mathbf{x})\,x_\ell \;-\; \mathcal{Q}_{\ell k}^{(j)}\mathcal{F}_k(\mathbf{x})\,x_k\right\}\varrho^j\;. \tag{24a}$$

The elements of this expansion are simply the rescaled matrix elements of the mutation matrix at different orders j in the perturbation parameter:

$$\mathcal{Q}_{k\ell}^{(j)} \;=\; \left(\frac{\varrho}{\lambda}\right)^j Q_{k\ell}^{(j)}\;. \tag{24b}$$

This scaled expansion may act as a standard form for replication-mutation systems which facilitates comparison of different models.

Rescaling of the mutation parameter does not dispense from the need to assign a physical quantity to λ or ϱ. This requires a model of the mutation process and we give here one example: point mutations within the uniform error rate model [8]. No deletions and insertions are considered and the chain length ν of the sequences is conserved. Since we use the model here as an illustrative example and do not aim at a precise description of real polynucleotide sequences we shall assume that the number of symbol classes is $\kappa=2$ [8] which means that we are dealing with binary (**0**,**1**) instead of natural four-letter (**G**,**A**,**C**,**U**) sequences. An extension of the results to $\kappa=4$, or arbitrary κ is not difficult. As mentioned in section 2, mutations are assumed to occur with constant frequencies $(1-q)$ per site and generation. Mutation frequencies are independent of the position in the sequence. Then the elements of the mutation matrix Q are given by equation (5). Instead of the suggestive error rate $(1-q)$ we shall use a modified mutation rate constant [19]1987:

$$\varepsilon \quad = \quad \frac{1-q}{q} \; . \tag{25}$$

The off-diagonal elements of the mutation matrix Q are scaled by the corresponding diagonal terms and thus have a very simple form:

$$\widetilde{Q}_{k\ell} \;=\; \frac{Q_{k\ell}}{Q_{kk}} \;=\; \varepsilon^{d_{k\ell}} \;; \quad k,\ell=1,2,\ldots,n\,;\; k\neq\ell\;. \tag{25a}$$

As in equation (5) we denote the Hamming distance of the two sequences in question, $\mathbf{I}_k$ and $\mathbf{I}_\ell$, by $d_{k\ell}$. In order to fulfil the two criteria given by equations (3) and (23) we shall modify the diagonal elements of matrix $\widetilde{Q}$. This change in the diagonal terms is well justified since they cancel according to equation (21) and thus do not contribute to the mutation field. The elements of the mutation matrix built according to these criteria read:

$$\widetilde{Q}_{k\ell}(\varepsilon) \;=\; \begin{cases} 2 \;-\; \sum_{k=1}^{n}\,\varepsilon^{d_{k\ell}}\;, & \text{if } k=\ell \\ \varepsilon^{d_{k\ell}}\;, & \text{if } k\neq\ell\;. \end{cases} \tag{25b}$$

Choosing ε as perturbation parameter one obtains by simple calculus:

$$\widetilde{Q}^{(j)}_{k\ell}(\varepsilon) \;=\; \frac{1}{j|}\,\frac{\partial^j\widetilde{Q}_{k\ell}}{\partial\varepsilon^j} \;=\; \begin{cases} -\sum_{k=1}^{n}\binom{d_{k,\ell}}{j}\,\varepsilon^{d_{k\ell}-j}\;, & \text{if } k=\ell \\ \binom{d_{k,\ell}}{j}\,\varepsilon^{d_{k\ell}-j}\;, & \text{if } k\neq\ell\;. \end{cases} \tag{25c}$$

Denoting - for the sake of completeness – the original mutation matrix $\widetilde{Q}(\varepsilon)$ at $\varepsilon=0$ by $\widetilde{Q}^{(0)}$, we find for the matrices in the expansion series $(j>0)$:

$$\begin{aligned} \widetilde{Q}^{(0)}_{k\ell} \;&=\; \delta_{k\ell} \\ \widetilde{Q}^{(j)}_{k\ell} \;&=\; \begin{cases} -\binom{\nu}{j}\,, & \text{if } k=\ell \text{ and } j>0 \\ 1\,, & \text{if } k\neq\ell,\; d_{k\ell}=j \text{ and } j>0 \\ 0\,, & \text{if } k\neq\ell,\; d_{k\ell}\neq j \text{ and } j>0 \end{cases} \end{aligned} \tag{25d}$$

As expected $\widetilde{Q}^{(0)}$ is the unit matrix. The matrices $\widetilde{Q}^{(j)}$ with $j>0$ have a very simple structure too. They contain – apart from the diagonal elements which

$$\begin{pmatrix} 1-\varepsilon(2+\varepsilon) & \varepsilon & \varepsilon & \varepsilon^2 \\ \varepsilon & 1-\varepsilon(2+\varepsilon) & \varepsilon^2 & \varepsilon \\ \varepsilon & \varepsilon^2 & 1-\varepsilon(2+\varepsilon) & \varepsilon \\ \varepsilon^2 & \varepsilon & \varepsilon & 1-\varepsilon(2+\varepsilon) \end{pmatrix}$$

$$\widetilde{Q}$$

$$\begin{pmatrix} -2(1+\varepsilon) & 1 & 1 & 2\varepsilon \\ 1 & -2(1+\varepsilon) & 2\varepsilon & 1 \\ 1 & 2\varepsilon & -2(1+\varepsilon) & 1 \\ 2\varepsilon & 1 & 1 & -2(1+\varepsilon) \end{pmatrix} \qquad \begin{pmatrix} -2 & 0 & 0 & 2 \\ 0 & -2 & 2 & 0 \\ 0 & 2 & -2 & 0 \\ 2 & 0 & 0 & -2 \end{pmatrix}$$

$$\frac{\partial \widetilde{Q}}{\partial \varepsilon} \qquad \frac{\partial^2 \widetilde{Q}}{\partial \varepsilon^2}$$

$$\begin{pmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix} \qquad \begin{pmatrix} -2 & 1 & 1 & 0 \\ 1 & -2 & 0 & 1 \\ 1 & 0 & -2 & 1 \\ 0 & 1 & 1 & -2 \end{pmatrix} \qquad \begin{pmatrix} -1 & 0 & 0 & 1 \\ 0 & -1 & 1 & 0 \\ 0 & 1 & -1 & 0 \\ 1 & 0 & 0 & -1 \end{pmatrix}$$

$$\widetilde{Q}^{(0)} \qquad \widetilde{Q}^{(1)} \qquad \widetilde{Q}^{(2)}$$

Fig. 3: The mutation matrix $\widetilde{Q}(\varepsilon)$, its first two derivatives with respect to the mutation parameter ε and the matrices $\widetilde{Q}^{(j)}$ of the perturbation expansion (21). The mutation matrix refers to the four binary sequences on length $\nu=2$: **00**, **01**, **10** and **11**, respectively.

were chosen such that equation (23) is fulfilled – the entries $\widetilde{Q}^{(j)}_{k\ell}=1$ where the Hamming distance matches the order of the expansion: $d_{k\ell}=j$. They have zero entries everywhere else. For the purpose of illustration a simple example, the mutation matrices of binary sequences of chain length $\nu=2$, is shown in figure 3. A different, but not unrelated approach was used recently to calculate the matrix of Hamming distances from the mutation matrix Q by differentiation with respect to the single digit accuracy q [20]1989.

The perturbation expansion introduced here has always a finite number of terms only. The largest distance in the sequence space of strings with length ν is simply

ν. Hence the elements of highest order in ε are ε^ν and the $(\nu+1)$-th derivative of the Q matrix is identical zero therefore.

5.3. The molecular quasi-species

The concept of *quasi-species* was introduced in order to be able to handle frequent mutation in asexual replication[21]1977 (The problem was studied first without using the particular notion of quasi-species by Eigen [11]. For a recent, comprehensive and updated presentation see [8]). The quasi-species is the stationary mutant distribution of a first order replication-mutation equation. It is commonly centered around a master sequence, $\mathbf{I}_m$ and can be visualized as a localized population in sequence space. Quasi-species and error thresholds were discussed extensively in the past [8,11,21-23]19821988. We apply here our perturbation concept to this problem and compare the results with those derived previously.

Asexual replication implies that the replication rate functions are restricted to the constant terms, $\mathcal{F}_k = A_k$. Degradation rate constants are assumed to be equal as in section 5.1. Conditions which have to be imposed on the replication rate constants A_k and on the matrix Q in order to guarantee that $\vec{\mathcal{M}}(\mathbf{x},\lambda)$ is an acceptable mutation field in the sense of section 4.1 are: $A_k > 0$ for all $k = 1,\ldots,n$ and irreducibility of Q. Since this problem is more pertinent to second order vector fields we postpone the proof to the forthcoming section 5.4. We start with the error free case. The Jacobian is easily computed and its matrix elements have the following general form:

$$J_{ij} \;=\; \begin{cases} A_i(1-x_i) \;-\; \bar{A}, & \text{if } i=j \\ -A_j\,x_i, & \text{if } i \neq j\ . \end{cases}$$

The corners of the simplex S_n, given as unit vectors $\mathbf{e}_k$, are regular fixed points and they are the only fixed points of the replicator field. Clearly we have $\bar{A}=A_k$ at the corner $\mathbf{e}_k$. The rest point at $\mathbf{e}_m$ which corresponds to the most efficiently replicating type, the master sequence $\mathbf{I}_m$, $A_m = \max\{A_k;\ k=1,\ldots,n\}$, is asymptotically stable. All other fixed points are saddles, one is a source. Without loosing generality we reorder the types $\mathbf{I}_k$ according to decreasing replication rate constants: $A_1 > A_2 \geq A_3 \geq \ldots \geq A_n$. We do not consider cases with degenerate master sequences which were treated for example in [23].

The transversal eigenspace at the corners is $(n$–$1)$-dimensional and hence comprises all eigenvectors except the external eigenvector. The external eigenvalue is $\omega_0 = -\bar{A}$ and the transversal eigenvalues at $\mathbf{e}_k$ are given by

$$\omega_\ell \;=\; A_\ell - \bar{A}\,;\ \ell=1,\ldots,n,\ \ell\neq k.$$

Accordingly only the fixed point $\mathbf{e}_1$ is saturated. Application of RPM theorem yields that it migrates into the interior of the simplex S_n and represents the quasi-species. All other $n-1$ fixed points are shifted into the environment, $\Omega_n \backslash S_n$. The same result was obtained previously by simple algebraic techniques [20].

The shift vectors are readily obtained from equation (17):

$$d_k^{(1)}(\mathbf{e}_\ell) \;=\; \begin{cases} -\sum_{j=1, j\neq\ell}^{n} \frac{A_\ell}{A_\ell - A_j}\, Q_{j\ell}^{(1)}, & \text{if } k=\ell \\ \frac{A_\ell}{A_\ell - A_k}\, Q_{k\ell}^{(1)}, & \text{if } k\neq\ell\;. \end{cases}$$

We are now in a position to compute the first order shifts for all fixed points. Higher orders may be added on desire.

In order to compare the perturbation expansion of the mutation field with previous results we consider the error threshold. It should be mentioned that the approach presented here is based on an analysis of the positions of rest points an therefore pursues a philosophy which is different from previous derivations although the results obtained will be essentially the same. The existence of error thresholds in replication prone to errors was first analysed by Eigen [11]. At small error rates a stationary mutant distribution is formed which is dominated by the master sequence and its most frequent mutations. The frequency of a given mutant is determined by its replication rate and its Hamming distance to the master sequence. There is a critical value ot the error rate ($\varepsilon^{(cr)}$) at which the structure of the stationary mutant distribution changes radically. Above the error threshold differences in replication rates have little and eventually no influence on the mutant distribution which in many cases approaches the uniform distribution. Because of the enormously large number of possible sequences (2^ν, or more if more symbol classes are admitted) the concentrations are extremely small in such distributions. Then realistic, that means finite populations cannot approach any stationary state. Instead they drift randomly through sequence space [24-26]198519841989.

The conventional way to derive the error threshold starts out form the first order replication-mutation equation which we write for convenience in vector form (again equal degradation rate constants are assumed which are compensated by the flux term):

$$\frac{d\mathbf{x}}{dt} \;=\; (Q\,A \,-\, \bar{A}\cdot\Im\mathrm{d})\,\mathbf{x} \;=\; (W \,-\, \bar{A}\cdot\Im\mathrm{d})\,\mathbf{x} \tag{26}$$

Q is the mutation matrix and A is a diagonal matrix: $A = \mathrm{diag}\,\{A_k\}$. The dynamics of equation (26) is readily expressed in terms of the eigenvectors $\mathbf{w}_k$ of the value matrix $W = Q\,A$. In particular the quasi-species is represented by the dominant eigenvector of this matrix, $\mathbf{w}_1$. Around the critical error rate $\varepsilon^{(cr)}$ the eigenvector $\mathbf{w}_1(\varepsilon)$ changes abruptly from an organized distribution – commonly centered around a single master sequence $\mathbf{I}_1$ – into an ensemble which is characteristic for the limit of the population at high error rates [26]. As shown below, this ensemble is the uniform distibution in case of the uniform error rate model. The origin of this abrupt change is an avoided crossing of the two largest eigenvalues $\omega_1(\varepsilon)$ and $\omega_2(\varepsilon)$ around $\varepsilon^{(cr)}$. The eigenvectors $\mathbf{w}_2(\varepsilon)$ at values $\varepsilon < \varepsilon^{(cr)}$ and $\mathbf{w}_1(\varepsilon)$ at values $\varepsilon > \varepsilon^{(cr)}$, both resemble closely the high error rate limit of the mutant distribution. The longer the chain length ν, the narrower becomes the critical range and the sharper becomes the transition from the organized quasi-species to the uniform distribution. This behaviour reminds one very much of a cooperative transition as observed with biopolymers, or of a higher order phase transition in spin systems [27,28]19871987. In reality we are always dealing with chain lengths of a least a few tens. The normalized concentrations of all sequences $\mathbf{I}_k$ – including the master sequence become very small above the error thershold ($\bar{x}_k \approx 1/2^\nu$ for binary sequences).

The eigenvectors of the value matrix W may be computed from a conventional perturbation expansion

$$W \;=\; \mathrm{diag}\,\{W_{kk}\} \,+\, \lambda\, W' \quad \text{with} \quad W' \doteq \{W'_{k\ell} = W_{k\ell}\,(1-\delta_{k\ell})\}$$

by choosing $\lambda = 1$ as expansion parameter [22]. Eigen derived his expression for the error threshold [11],

$$Q_{11}^{(cr)} = \sigma_1^{-1} \text{ with } \sigma_1 = A_1 \,/\, \bar{A}_{-1} \text{ and } \bar{A}_{-1} = \sum_{j=2}^{n} A_j \bar{x}_j \,/\, \sum_{j=2}^{n} \bar{x}_j ,$$

form the diagonal element of the value matrix W_{ii} and the condition $\bar{x}_1 = 0$.

Let us first prove the conjecture that the dominant eigenvector $\mathbf{w}_1$ of any value matrix derived from the uniform error rate model approaches the uniform distribution at high error rates.

Consider the limiting case $q = \frac{1}{2}$ and hence $\varepsilon = 1$. All elements of the matrix Q are equal

$$Q_{k\ell} \;=\; q^\nu \varepsilon^{d_{k\ell}} \;=\; \frac{1}{2^\nu} \;=\; \frac{1}{n} \;=\; Q \;.$$

Insertion into equation (26) yields the ODE

$$\frac{\mathrm{d}x_k}{\mathrm{d}t} \;=\; \bar{A}\,(Q \,-\, x_k)\,;\; k = 1, 2, \ldots, n \;,$$

which has a unique, asymptotically stable restpoint in the center of the simplex S_n, $\mathbf{C} = \left(\frac{1}{n}, \frac{1}{n}, \ldots, \frac{1}{n}\right)$, which corresponds to a shift vector $\mathbf{d} = \left(-\frac{(n-1)}{n}, \frac{1}{n}, \ldots, \frac{1}{n}\right)$.

By our first order perturbation theory we compute now the error rate at which the asymptotically stable restpoint at the corner $\mathbf{e}_1$ migrates to the point determined by the dominant eigenvector of the Q matrix.

$$d_1^{(1)}(\mathbf{e}_1)\cdot\lambda \;=\; -1+\frac{1}{n} \;=\; -\Big(\sum_{j=2,d_{j1}=1}^{n}\frac{A_1}{A_1-A_j}\,Q_{j1}^{(1)}\Big)\,\lambda \;=$$
$$=\;-\Big(\sum_{j=2,d_{j1}=1}^{n}\frac{A_1}{A_1-A_j}\Big)\,\varepsilon\;.$$

We introduce a mean first order shift $\bar\delta^{(1)}$ which is the average shift of the single error mutants [29],

$$\bar\delta^{(1)} \;=\; \frac{1}{\nu}\sum_{j=2,d_{j1}=1}^{n}\frac{A_1}{A_1-A_j}\;,$$

and find:

$$\varepsilon\cdot\nu\cdot\bar\delta^{(1)} \;=\; 1-\frac{1}{n}\;. \tag{27}$$

Next we make use of two approximations:

(1) $n\gg\nu>1$ for sufficiently large n and hence $\frac{1}{n}$ can be neglected on the r.h.s. of (27) – this approximation is tantamount to the assumption that the concentration of the master sequence vanishes at the error threshold [11] – and,

(2) $\varepsilon\approx(1-q)$ which is certainly fulfilled for sufficiently long sequences where the error threshold occurs at values of $q^{(cr)}$ very close to $q=1$ – see also below.

With these approximations we obtain a simple relation between the mean first order shift $\bar\delta^{(1)}$, the single digit accuracy q and the diagonal element of the mutation matrix Q_{11}:

$$q\;=\;1-\frac{1}{\nu\bar\delta^{(1)}}\quad\text{and}\quad Q_{11}=q^{\nu}\approx 1-\nu(1-q)=\frac{\bar\delta^{(1)}-1}{\bar\delta^{(1)}}\;.$$

Without the second approximation we would have obtained $q=(1+1/\nu\bar\delta^{(1)})^{-1}$ which agrees in first order of $(\nu\bar\delta^{(1)})^{-1}$ with the expression given above; $\nu\bar\delta^{(1)}$ is large for long chains since $\bar\delta^{(1)}>1$.

Making use of Eigen's error threshold, $Q_{11}^{(cr)}=\sigma_1^{-1}$ we find

$$\sigma_1 \;=\; \bar\delta^{(1)}\;/\;(\bar\delta^{(1)}-1)\;.$$

This expression can be related to the conventional formula for the superiority by inserting the definition of the mean first order shift and after some algebraic manipulations one finds (all summations run over single error mutants exclusively: $j = 2, \ldots, n$ and $d_{j1} = 1$):

$$\sigma_1 = \frac{\sum_j \frac{A_1}{A_1 - A_j}}{\sum_j \frac{A_j}{A_1 - A_j}} = A_1 \frac{\sum_j d_j^{(1)}(\mathbf{e}_1) \cdot \varepsilon}{\sum_j A_j \, d_j^{(1)}(\mathbf{e}_1) \cdot \varepsilon} = \frac{A_1}{\bar{A}_{-1}^{(1)}} ,$$

where $d_j^{(1)}(\mathbf{e}_1) \cdot \varepsilon = \bar{x}_j^{(1)}$, the first order approximation to the relative concentration of $\mathbf{I}_j$ and $\bar{A}_{-1}^{(1)} = \sum_j A_j \bar{x}_j \;/\; \sum_j \bar{x}_j$ is the mean replication rate of all single error mutants. The formal expression obtained is precisely the same as in the original derivation. The two perturbation expansions are consistent.

It is important, however, to realize the implicit difference in the two expressions for the error threshold. Our perturbation expansion is restricted in first order to single error mutations, whereas all mutants are included in the perturbation treatment based on the value matrix W. Whether or not truncation of the summation yields a substantially different result is a matter of the replication rate landscape.

5.4. Second order replication-mutation equations

The homogeneous second order replicator equation is obtained from (7) by insertion of $\mathcal{F}_k = \sum_{j=1}^{n} A_{kj} x_j$. We call the matrix $A \doteq \{A_{ij};\, i,j = 1, \ldots, n\}$ a replication matrix and we shall assume all entries of A to be nonnegative. Again we assume equal degradation rate constants which can be absorbed in the flux term. We start here with general properties and continue with a presentation of special cases.

The question of applicability of the perturbation approach is somewhat more subtle than with first order replication-mutation systems since A is a matrix rather than a vector. Hence we have to search for the conditions which have to be fulfilled by the matrices A and Q in order to render $\vec{\mathcal{M}}$ an acceptable mutation field in the sense of section 4.1. We start with three lemmas.

Lemma 5.4.1. Let $\vec{\mathcal{M}}(\mathbf{x}, \lambda)$ be in the form of equation 21. If $\vec{\mathcal{M}}$ is a proper mutation field in the sense of section 4.1 then the relation $A_{kk} > 0$ holds for all k.

Proof. On the corner $\mathbf{e}_k$ of S_n we have $\mathcal{M}_\ell(\mathbf{x}, \lambda) = Q_{\ell k}$ for all $\ell \neq k$. In order to guarantee positive components of $\vec{\mathcal{M}}$ $A_{kk} > 0$ has to be fulfilled.

Lemma 5.4.2. Let $K \in I$ and $L = \mathcal{N} \backslash K$. Furthermore we assume $A_{jj} > 0$ for all j and $\mathbf{x} \in F_K$. Then $\sum_{j \in L} A_{ij} x_j > 0$ holds for all $i \in L$.

Proof. Since $j \in L$ we have $x_j > 0$. Thus we have $\sum_{j \in L} A_{ij} x_j \geq A_{ii} x_i > 0$ for all $i \in L$.

Lemma 5.4.3. Let us define two sets in anlogy to section 3.2:

$$\begin{aligned}\Psi_K &= \{\vec{\xi} \in \mathbb{R}^n_+ | k \in K \iff \xi_k = 0\} \\ \overline{\Psi}_K &= \{\vec{\xi} \in \mathbb{R}^n_+ | k \in K \implies \xi_k = 0\}\end{aligned}$$

and let Q be a nonegative matrix. Then the following three statements are equivalent:

(I) Q does **not** leave $\overline{\Psi}_K$ invariant,

(II) there is a $k \in K$ such that $\exists \vec{\xi} \in \Psi_K$ such that $(Q\vec{\xi})_k > 0$, and

(III) there is a $k \in K$ such that for all $\mathbf{x} \in F_K$ holds $\mathcal{M}_k(\mathbf{x}, \lambda) > 0$ for $\lambda > 0$.

The proof of this lemma follows directly from the properties of irreducible matrices [30].

On the basis of the three lemmas it is rather simple to prove the prerequisites of an acceptable vector field $\vec{\mathcal{M}}$.

Theorem 5.4.1. The vector field $\vec{\mathcal{M}}$ defined in this section 5.4 is a mutation field in the sense of section 4.1 if and only if all diagonal elements of the replication matrix A are strictly positive and the mutation matrix $Q(\lambda)$ is irreducible for $\lambda > 0$.

Proof. Irreducibility of Q implies by application of lemma 5.4.3 that condition I listed in section 4.1 is fulfilled. Lemma 5.4.2 guarantees that condition II is satisfied and the remaining conditions III to V are fulfilled by the definitions of the perturbation expansion in section 5.2.

Irreducibility of the mutation matrix Q is the minimal physical requirement. It can be interpreted best by means of an associated directed graph which is constructed from the matrix by assigning a directed edge $k \to \ell$ to every strictly positive matrix element $Q_{\ell k} > 0$. If Q is irreducible the associated graph is strongly connected

[30]. This means that we find a directed arc from every species $\mathbf{I}_i$ to every species $\mathbf{I}_j$ with $i,j = 1,\dots,n$. In other words there has to be a path from every species to every species by a series of consecutive mutations.

5.5. Restpoint shifts in second order replication-mutation equations

The Jacobian of a second order replicator field $\vec{\mathcal{R}}(\mathbf{x})$ at an arbitrary point $\mathbf{x}$ in $\operatorname{int} S_n$ is readily computed:

$$\begin{aligned} J_{km}(\mathbf{x}) &= \alpha_{km}(\mathbf{x})\cdot x_k \ + \psi_k(\mathbf{x})\cdot\delta_{km} \ , \qquad (28)\\ \text{with}\quad \alpha_{km}(\mathbf{x}) &= \left(A_{km} - \sum_{i=1}^{n}(A_{im}+A_{mi})x_i\right)\\ \text{and}\quad \psi_k(\mathbf{x}) &= \sum_{j=1}^{n} A_{kj}\,x_j \ - \sum_{i=1}^{n}\sum_{j=1}^{n} A_{ij}\,x_i\,x_j \ . \end{aligned}$$

Let us now consider a fixed point in some subset of S_n: $\overline{\mathbf{x}}\in F_K$. We include here the interior by allowing $\operatorname{int} S_n \equiv F_0$. Since $x_k = 0$ for $k\in K$ and $\psi_k(\overline{\mathbf{x}}) = 0$ for $k\in\mathcal{N}\backslash K$, equation (28) simplifies to:

$$J_{km} \ = \ \begin{cases} \psi_k(\overline{\mathbf{x}})\cdot\delta_{km} & \text{for } k\in K \ , \\ \alpha_{km}(\overline{\mathbf{x}})\cdot x_k & \text{for } k\in\mathcal{N}\backslash K \ . \end{cases}$$

The expressions $\psi_k(\overline{\mathbf{x}})$ are just the transversal eigenvalues of $J(\overline{\mathbf{x}})$ as defined in section 3.4 .

The fixed points at the corners of the simplex S_n represent the most simple cases. For the corner $\mathbf{e}_\ell$ we find:

$$\psi_k(\mathbf{e}_\ell) \ = \ A_{k\ell} - A_{\ell\ell} \quad \text{and} \quad J_{km}(\mathbf{e}_\ell) \ = \ \begin{cases} \left(A_{k\ell} - A_{\ell\ell}\right)\delta_{km}\ , & \text{for } k\neq\ell, \\ \alpha_{km}\ , & \text{for } k=\ell\,. \end{cases}$$

It is easily verified that from equations (22) and (23) follows

$$\vec{\mathcal{M}}_k(\mathbf{e}_\ell,\lambda) \ = \ \sum_{j=1}^{\infty} Q_{k\ell}^{(j)}\,A_{\ell\ell}\cdot\lambda^j \ .$$

Making use of the fact that the sum over all components of the first order shift $\mathbf{d}^{(1)}(\mathbf{e}_\ell)$ vanishes we find:

$$d_k^{(1)}(\mathbf{e}_\ell) \ = \ \begin{cases} \sum_{j=1,j\neq\ell}^{n} \frac{A_{\ell\ell}}{A_{j\ell}-A_{\ell\ell}}\,Q_{j\ell}^{(1)}\ , & \text{if } k=\ell \\ -\frac{A_{\ell\ell}}{A_{k\ell}-A_{\ell\ell}}\,Q_{k\ell}^{(1)}\ , & \text{if } k\neq\ell \ . \end{cases}$$

The shift vector $\mathbf{d}^{(1)}(\mathbf{e}_\ell)$ is thus well defined if and only if all components of $\vec{\psi}$ representing eigenvalues of the Jacobian fulfil $\psi_k(\mathbf{e}_\ell) = A_{k\ell} - A_{\ell\ell} \neq 0$ or, in other words, if the fixed point at $\mathbf{e}_\ell$ is regular.

Fixed points on edges – $\overline{\mathbf{x}} \in F_K$ with $\mathcal{N}\backslash K = \{\ell, m\}$, denoted by $\mathbf{f}_{\ell m}$ – are much harder to study but the expressions derived by the analogous procedure are still useful for further analytical work. We make use of the following abbreviations:

$$\Delta_{ij} = A_{ii}A_{jj} - A_{ij}A_{ji}, \;\; \Sigma_{ij} = A_{ij} + A_{ji} - A_{ii} - A_{jj} \;\; \text{and} \;\; \Pi_{ij}^{(k)} = A_{ki}\big(A_{ij} - A_{jj}\big) \; .$$

As follows from section 3.4 the Jacobian is diagonal in the transversal eigenspace: $J_{kj}(\mathbf{f}_{m\ell}) = \gamma_k(\mathbf{f}_{\ell m}) \cdot \delta_{kj}$. Now we are in a position to express the coordinates and the transversal eigenvalues $\gamma_k(\mathbf{f}_{\ell m})$ in compact form (Ref.[16], p.185):

$$(\mathbf{f}_{\ell m})_k \;=\; \begin{cases} \frac{A_{\ell m} - A_{mm}}{\Sigma_{\ell m}} \;, & \text{if } k = \ell \;, \\ \frac{A_{m\ell} - A_{\ell\ell}}{\Sigma_{\ell m}} \;, & \text{if } k = m \;, \\ 0 \;, & \text{if } k \neq \ell, m \;. \end{cases}$$

$$\gamma_k(\mathbf{f}_{\ell m}) \;=\; \frac{\Pi_{\ell m}^{(k)} + \Pi_{m\ell}^{(k)} + \Delta_{\ell m}}{\Sigma_{\ell m}} \;, \quad k \neq \ell \neq m \;.$$

A straight computation yields the first order contributions to the mutation field:

$$M_k^{(1)}(\mathbf{f}_{\ell m}) \;=\; \frac{\Delta_{\ell m}}{\Sigma_{\ell m}^2} \cdot \Big(Q_{k\ell}(A_{\ell m} - A_{mm}) \;+\; Q_{km}(A_{m\ell} - A_{\ell\ell}) \Big) \;.$$

After some rather tedious algebraic manipulations we find eventually for $\mathbf{d}^{(1)}(\mathbf{f}_{\ell m})$:

$$d_k^{(1)}(\mathbf{f}_{\ell m}) \;=\; \begin{cases} -\frac{1}{\gamma_k(\mathbf{f}_{\ell m})} \cdot M_k^{(1)}(\mathbf{f}_{\ell m}) \,, & \text{if } k \neq \ell, m \,, \\ -\frac{M_\ell^{(1)}(\mathbf{f}_{\ell m})}{(\mathbf{f}_{\ell m})_\ell \, (\alpha_{\ell\ell} - \alpha_{\ell m})} \;-\; \sum\limits_{\substack{j=1 \\ j \neq \ell, m}}^{n} \frac{\alpha_{\ell j} - \alpha_{\ell m}}{\alpha_{\ell\ell} - \alpha_{\ell m}} \cdot d_j^{(1)}(\mathbf{f}_{\ell m}) \,, & \text{if } k = \ell \,, \\ -\frac{M_m^{(1)}(\mathbf{f}_{\ell m})}{(\mathbf{f}_{\ell m})_m \, (\alpha_{mm} - \alpha_{m\ell})} \;-\; \sum\limits_{\substack{j=1 \\ j \neq \ell, m}}^{n} \frac{\alpha_{mj} - \alpha_{m\ell}}{\alpha_{mm} - \alpha_{m\ell}} \cdot d_j^{(1)}(\mathbf{f}_{\ell m}) \,, & \text{if } k = m \,. \end{cases}$$

Again we made use of the fact that the sum of all components of the first order shift has to vanish.

We end this presentation of calculations on first order shifts of fixed points by adding an expicit formula from which the shift of an interior restpoint $\overline{\mathbf{x}}$ can be computed. We define

$$B \;\doteq\; \{b_{k\ell} = \alpha_{k\ell};\, k, \ell = 1, \ldots, n\} \quad \text{and} \quad \mathbf{m} \;\doteq\; \{m_k = \frac{M_k^{(1)}(\overline{\mathbf{x}})}{\bar{x}_k};\, k = 1, \ldots, n\} \;.$$

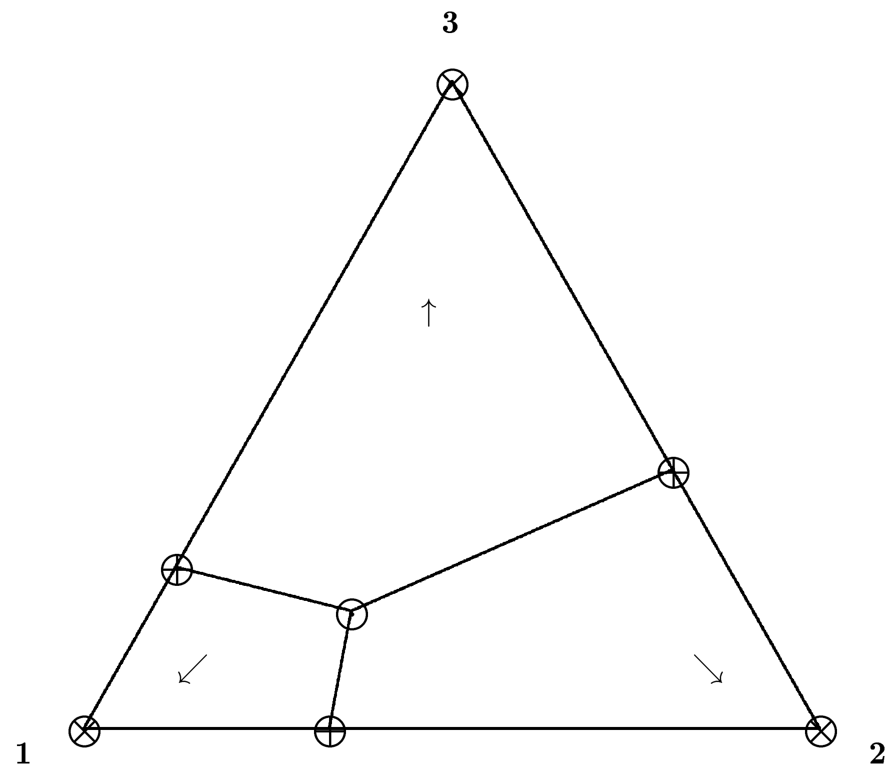

Fig. 4: Fixed point diagram of the Schlögl model with three species. All fixed points are regular. The source is denoted by $\odot$, the three saddle points by $\oplus$ and the three sinks at the corners by $\otimes$. The following parameters were chosen: $A_{11}=1$, $A_{22}=2$ and $A_{33}=3$. Note that all fixed points have stable transversal eigenspaces E_T and hence will move into the interior $\operatorname{int} S_n$ at finite mutation rates $\lambda > 0$.

Then the perturbation equation is of the form:

$$B \cdot \mathbf{d}^{(1)} = -\mathbf{m} .$$

This matrix equation is certainly hard to evaluate analytically. It may serve, however, as a useful tool in numerical computation.

It is worth mentioning that the formulas derived here can be applied also to fixed points occuring in Lotka-Volterra equations [13]. The basis for this applicability is a diffeomorphism relating the solution curves of a given second order replicator equation to those of a Lotka-Volterra equation [31]1981.

In the multi-dimensional Schlögl model [32]1986 the replication matrix is diagonal, $A_{k\ell} = A_{kk} \cdot \delta_{k\ell}$. It represents the simplest possible case of a second order replicator equation. We have $2^n - 1$ regular fixed points $\widehat{\mathbf{x}}_K$, in particular there is exactly one fixed point in F_K for all $K \in I$. The n restpoints at the corners are sinks, the one in F_0 is a source, and all other fixed points are saddle points. The fixed point diagram of the three-dimensional Schlögl model is sketched in figure 4 as an illustrative example. The transversal eigenspace $E_T(\widehat{\mathbf{x}}_K)$ is stable for all $2^n - 1$ equilibrium points. According to the RPM theorem all fixed points migrate into $\mathrm{int}\, S_n$ and for small values of λ we have one source, $2^n - (n+1)$ saddles and n sinks there. The dynamics of the Schlögl model at larger mutations rates has been studied analytically for cases up to $n \leq 4$ [33].

5.6. The elementary hypercycle

Elementary hypercycles were invented as the most simple autocatalytic reaction networks which allow for the suppression of selection or competition among replicating elements [7]. They were studied extensively in the past. We mention only some of the earlier publications on this subject [34-37]1978198019791981. Elementary hypercycles represent a special class or second order replicator equations whose replication functions are given by: $\mathcal{F}_k = \delta_{k,k-1} \cdot x_{k-1}$; $k = 1, \ldots, n$ and k, k–1 are mod n. We choose a slightly different reaction matrix in order to guarantee that $\vec{\mathcal{M}}$ is an acceptable mutation field (see section 5.4):

$$A = \{A_{kj} = \delta_{k,j-1} + a;\ (k, j\text{–}1) \bmod n\} = \begin{pmatrix} a & a & \ldots & a & a+1 \\ 1+a & a & \ldots & a & a \\ a & 1+a & \ldots & a & a \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ a & a & \ldots & 1+a & a \end{pmatrix}$$

which leads to the same replicator dynamics since the differential equation (9) is invariant to additive constants to columns of the replication matrix A.

The differential equation of the elementary hypercycle leeds to a peculiar distribution of fixed points [34]. There is one fixed point in $\mathrm{int}\, S_n$ and all corners of S_N are fixed points. In addition there are one-, two-, three- and higer dimensional manifolds of fixed points. We start by listing some topological features of the mutation free model. For proofs see [7,13,15,34,37]:

Lemma 5.6.1. Let $\overline{\mathbf{x}} \in F_K$ be a fixed point of the elementary hypercycle equation. Then all points $\mathbf{x} \in \bar{F}_K$ are fixed points.

Lemma 5.6.2. An edge connecting $\mathbf{e}_\ell$ and $\mathbf{e}_m$, $\overline{\mathbf{e}_\ell\mathbf{e}_m} = F_{\mathcal{N}\setminus\{\ell,m\}}$ of the simplex S_n consists of fixed points if and only if $|\ell - m| > 1$. We call such a set of fixed point an *fixed point edge*.

Lemma 5.6.3. A subsimplex $S_{\{L\}} = F_{\mathcal{N}\setminus L}$ has interior fixed points $\overline{\mathbf{x}} \in S_{\{L\}}$ if all edges $\overline{\mathbf{e}_r\mathbf{e}_s}$ with $r, s \in L$ fixed point edges.

The three lemmas can be summarized in one corollary:

Corollary. The face $\bar{F}_K$ of the simplex S_n consists of fixed points if and only if $|r - s| > 1$ holds for all pairs $r, s \in \mathcal{N}\setminus K$.

In order to find out under which conditions such subsets consisting of fixed point exist we define

$$\ell_{max} \ = \ \begin{cases} \frac{n}{2} & \text{if } n \text{ even}, \\ \frac{n-1}{2} & \text{if } n \text{ odd}, \end{cases} \qquad \text{and} \qquad \nu \ = \ \begin{cases} n-1 & \text{if } n \text{ even}, \\ n-2 & \text{if } n \text{ odd}. \end{cases}$$

Let $L = \{1, 3, \ldots, \nu\}$. Clearly $\#L = \ell_{max}$ and L fulfils the condition of the corollary. On the other hand, it is obvious that we cannot choose a set L with more than ℓ_{max} elements and still fulfil the above mentioned conditions:

Lemma 5.6.4. For any $\ell \leq \ell_{max}$ there exists at least one subset $L \subset \mathcal{N}$ such that $\ell = \#L$ and $S_{\{L\}}$ consists entirely of fixed points. There exists no such subset $L' \subseteq \mathcal{N}$ such that $S_{\{L'\}}$ consists entirely of fixed points and $\#L > \ell_{max}$.

Let us now consider the transversal eigenvalues at the fixed points of elementary hypercycles. Let $\overline{\mathbf{x}}$ be some fixed point of the hypercycle equation with $\overline{\mathbf{x}} \in F_K$. Then the transversal eigenvalues are given by

$$\omega_k \ = \ \bar{x}_{k-1} \ : \ (k-1) \bmod n \quad \text{for all } k \in K \ ,$$

and we derive the following lemma.

Lemma 5.6.5. Let $\overline{\mathbf{x}} \in F_K$ be a restpoint. Then the transversal eigenspace at $\overline{\mathbf{x}}$ has at least one eigenvalue which fulfils $\omega_1 \geq 1/m$ with $m = n - \#K$.

Proof. Let $L = \mathcal{N} \backslash K = \{i_1, \ldots, i_m\}$ with $m = n - \#K$. The existence of a fixed point $\overline{\mathbf{x}}$ on F_K implies $|i_r - i_s| \neq 1$ for all $r, s \in \{1, \ldots, m\}$. Thus we have $j = (i_r + 1) \in K$ and the corresponding eigenvalue is given by $\omega_j = \bar{x}_{j-1} = \bar{x}_{i_r}$. From $\sum_{i=1}^{m} \bar{x}_{i_r} = 1$ we conclude that $\max_r \bar{x}_{i_r} \geq 1/m$.

The existence of at least one positive transversal eigenvalue for all fixed points $\overline{\mathbf{x}}$ of the elementary hypecycle equation with $\overline{\mathbf{x}} \in \mathrm{bd}\, S_n$ implies that all fixed points on the boundary leave the simplex at arbitrarily small mutation rates according to RPM theorem.

Since the interior fixed point of the elementary hypercycle equation is regular [34] we obtain the following final result:

Theorem 5.6.1. The replication mutation equation of the elementary hypercycle contains a unique fixed point in $\mathrm{int}\, S_n$ for sufficiently small mutation rates $\lambda > 0$.

This result can be generalized to arbitrary replicator fields:

Theorem 5.6.2. Let $\dot{\mathbf{x}} = \vec{\mathcal{R}}(\mathbf{x})$ be robustly persistent. Then S_n contains a unique equilibrium for sufficiently small values $\lambda > 0$.

Proof. If the vector field is robustly persistent, then there is no saturated equilibrium on $\mathrm{bd}\, S_n$ and the unique interior fixed point is regular (for a proof of this statement see [15], p.186). Since S_n is compact there exist a positive constant c such that $\omega = \max_i \Big(\mathcal{F}_i(\overline{\mathbf{x}}) - \overline{\mathcal{F}}(\overline{\mathbf{x}})\Big) \geq c > 0$. If $\overline{\mathbf{x}}$ is a fixed point on the boundary we have $\bar{x}_i = 0$ and thus ω is a transversal eigenvalue. According to RPM theorem the fixed point leaves the simplex S_n at small values of the perturbation parameter.

5.7. Replication and mutation in the three species model

The enormous variety of different cases is prohibitive for a comprehensive classification of second order replicator equations with more than three species. Even the system with $n = 3$ several attempts [35,38-40]198119831990 were necessary before the – after elimination of cases related to each other by symmetry or time reversal – 47 essentially different phase protraits were fully characterized [39]. We are now in a position to study the influence of mutation on these dynamical systems.

For second order replicator fields the definition of robustness as given in section 3.5 can be easily casted in matrix form: a second order replicator field with a replication matrix A is **robust** if there exists an $\epsilon > 0$ for all matrices $B \in \mathbb{R}^{n \times n}$ such that the phase portrait of

$$\frac{\mathrm{d}x_k}{\mathrm{dt}} = \Big(\big[A\mathbf{x}\big]_k - \mathbf{x}^t A\mathbf{x} \Big) \; ; \; k = 1, \ldots, n \tag{29}$$

can be transformed by means of a homeomorphism ϑ_ϵ into the phase portrait of

$$\frac{\mathrm{d}x_k}{\mathrm{dt}} = \Big(\big[(A + \epsilon B)\mathbf{x}\big]_k - \mathbf{x}^t (A + \epsilon B)\mathbf{x} \Big) \; .$$

From Peixoto's theorem [41] 1962 and the nonexistence of isolated periodic orbits in three species replicator equations [42] follows a straight condition for structural stability. A second order replicator field $\vec{\mathcal{R}}$ with $n = 3$ is structurally stable on a compact neighbourhood $\mathcal{V}(S_3)$ if and only if the following two conditions are fulfilled:

(I) all fixed points are hyperbolic, and

(II) there are no saddle connections.

The majority of second order replicator fields is thus not structurally stable since there are saddle-connections along the boundary $\mathrm{bd}\, S_3$. From the classification of possible phase potraits of replicator fields on S_3 with exclusively hyberbolic fixed points given in [39] follows that there is no saddle connection which is not entirely contained in an edge of the simplex. This leaves only two possibilities:

(I) two saddles at corners which are connected by the edge between them, and

(II) a saddle point in the interior of an edge which is connected to a corner saddle.

Both types of connections are robust since edges are invariant and the restriction of the flow onto the edge is structurally stable. The saddle connections cannot be broken by arbitrary small perturbation of replicator type. The results can be summarized in:

Theorem 5.7.1. A second order replicator field $\vec{\mathcal{R}}$ is robust on S_3 if and only if all its fixed points are hyperbolic. Robustness is a generic property of these replicator fields.

Let us define a set $\mathcal{A}$ of replication matrices A whose replicator fields are characterized by having at least one nonhyperbolic restpoint: $\mathcal{A} \in \mathbb{R}^{3\times 3}$ and $A \in \mathcal{A}$. The condition expressed in terms of replication rate constants $A_{k\ell}$ yields somewhat unhandy equations [13,40]. From these conditions one derives easily that the set

$\mathcal{A}$ is compact and nowhere dense in $\mathbb{R}^{3\times 3}$ and hence the set of all robust second order replicator fields is open dense.

The criterion of robustness reduces the number of different phase portraits on S_3 from 47 to 19. It should be emphasized here that there is no analogon of theorem 5.7.1 in replicator fields for more than three species.

For the application of perturbation theory we have to release from the invariance with respect to time reversal. Instead of 19 there are now exactly 35 different robust phase portraits of the replicator field with three species [40]. Addition of the mutation field and application of the RPM theorem to the phase portraits yields only seven different fixed point diagrams for the replication mutation system. Figure 5 shows these patterns together with the 35 phase portraits of the replicator fields from which they were derived. In one case (**6A** , **6B**) we expect two different structurally stable phase portraits for the same pattern and hence we are eventually dealing with eight structurally stable phase portraits for the three species in the weak mutation case. The properties of the phase portraits are listed in table 1. Interesting enough two phase portraits contain stable closed orbits. We are thus confronted with the following theorem which we prove by giving one example:

Theorem 5.7.2. The second order replication mutation equation admits stable limit cycles for arbitrarily small values of the mutation parameter λ.

Proof. We consider the replication matrix

$$A = \begin{pmatrix} 3 & 1 & 4 \\ 4 & 3 & 1 \\ 1 & 4 & 3 \end{pmatrix}$$

whose replicator field does not belong to the non-robust set, $A \notin \mathcal{A}$. All fixed points of the replicator equation are hyperbolic. The phase portrait belongs to the last class (**7**) shown in figure 5 and it contains three saddle points in the corners and an unstable interior fixed point in the center of S_3. By RPM theorem the three saddles are shifted into the surrounding set $\Omega_3 \backslash S_3$ and thus the phase portrait of the perturbed replicator equation contains as source at the center as its unique fixed point. From the direction of the replication mutation vector field $\vec{\mathcal{L}}$ follows that the simplex S_3 is forward invariant and therfore it must contain an attractor. The simplex on the other hand is two-dimensional and the theorem of Poincaré and Bendixon applies: there must be at least one limit cycle in $\operatorname{int} S_n$.

Numerical computation suggest that the limit cycle is unique.

Fig. 5: Eight structurally stable phase portraits of the replication mutation equation for three species obtained from the corresponding replicator fields by apllication of the RPM theorem. We show the eigth phase portraits (**1**,…,**6A**,**6B**,**7**) together with the 35 diagrams (r.h.s.) from which they are derived.

Table 1: Classification and characterization of structurally stable phase portraits of the second order replication mutation equation for three species in the limit of small mutation rates. The diagrams are obtained by application of the RPM theorem to the 35 robust phase portraits of the error free systems [40].

	Number of			Existence of
No. †	sources	saddles	sinks	limit cycles
1	0	0	1	no
2	0	1	2	no
4	0	2	3	no
7	1	0	0	yes
6A	1	1	1	no
6B	1	1	1	yes
5	1	2	2	no
3	1	3	3	no

† The numbers refer to figure 5 where the individual phase portraits are shown together with those of the replicator equations from which they were derived.

The eight structurally stable phase portraits are related among each other by eleven generic bifurcations which falls into three classes:

(I) saddle-node bifurcations of the simple type (IA) and saddle-node bifurcations on a loop (IB),

(II) saddle-loop bifurcations, and

(III) supercritical Hopf bifurcations.

Figure 6 shows the eight phase portraits together with the eleven bifurcations between them. In the – mutation free – replicator equation the corresponding generic bifurcations are degenerate: we observe only degenerate Hopf bifurcations and all other bifurcations are transcritical. Mutation breaks these degeneracies in a certain sense. A transcritical bifurcation is split into two saddle node bifurcations and a degenerate Hopf bifurcation yields supercritical Hopf bifurcations.

Fig. 6: The eight structurally stable phase portraits of the replication mutation equation for three species at small mutation rates and the eleven generic bifurcations between them. The phase portraits at the bifurcations points are marked by **H** for Hopf, by **S** for saddle-node and by **L** for saddle-loop bifurcations.

5.8. Deterministic chaos and mutation

The last example is chosen from a replication mutation equation with $n=4$ whose replicator part shows deterministic chaos at some parameter values [43,44]1987. The chaotic regime was studied systematically in a two-dimensional parameter

Fig. 7: The chaotic attractor in the replicator equation for four species with $\mu = \nu = 0$. **A** shows a trajectory of the chaotic attractor and ten fixed points on the boundary $\mathrm{bd}\, S_4$. In **B** we sketch a periodic trajectory within the chaotic regime which illustrates the role of the saddle focus in the $\overline{123}$-plane.

space. The replication matrix is expressed in terms of two parameters μ and ν:

$$A(\mu,\nu) = \begin{pmatrix} 0 & 0.5 - 0.437 & -0.1 + 0.1\nu & 0.1 + 0.337\nu \\ 1.1 - 0.563\nu & 0 & -0.6 + 0.564\nu & -0.001\nu \\ -0.5 - 0.035\nu & 1 - 0.62\nu & 0 & 0.655\nu \\ 1.7 + \mu - 1.164\nu & -1 - \mu + 0.968\nu & -0.2 + 0.196\nu & 0 \end{pmatrix}$$

Chaos is observed in a subset of the range $-1.5 \leq \mu \leq 0.2$ and $-0.7 \leq \nu \leq 1.1$. A typical example of a chaotic trajectory is shown in figure 7. The deterministic chaos arises by a Šilnikov type mechanims (see [44] and [14], pp.318-325). Here we choose $\nu = 0$ which limits the appearence of the strange attractor to $-0.105 \leq \mu \leq 0.209$. This chaotic regime is interrupted by several periodic windows (for further details see [44]). In order to be able to handle mutation straightway we assume equal error rates between any pair of the four species. This assumption is a special case of the *house of cards* model frequently applied in theoretical population genetics [45].

In the sense of equation 24 we are dealing with a mutation matrix of the form

$$\mathcal{Q} = \begin{pmatrix} 1-3\varrho & \varrho & \varrho & \varrho \\ \varrho & 1-3\varrho & \varrho & \varrho \\ \varrho & \varrho & 1-3\varrho & \varrho \\ \varrho & \varrho & \varrho & 1-3\varrho \end{pmatrix} .$$

In order to render the problem accesible to our method we had to add a constant to all elements of the replication matrix – as we did in the hypercycle model (section 5.6): $A_{ij} \to A_{ij} + a$ with $a = 8$. As mentioned before such an additive constant is compensated by the flux term and does not change the dynamics of the ODE.

Influence of mutation on the positions of the fixed points is expressed in terms of first order shift vectors: $\overline{\mathbf{x}}_{\{L\}}(\varrho) - \overline{\mathbf{x}}_{\{L\}}(0) = \mathbf{d}^{(1)}_{\{L\}} \cdot \varrho$ with $L = \mathcal{N} \setminus K$. The replicator system sustains ten fixed points at the boundary $\mathrm{bd}\, S_4$ with $L = \{1\}, \{2\}, \{3\}, \{4\}, \{12\}, \{13\}, \{14\}, \{123\}, \{124\}$ and $\{134\}$, respectively. All fixed points except $\overline{\mathbf{x}}_4$ are hyperbolic; two of them are sinks, $\overline{\mathbf{x}}_3$ and $\overline{\mathbf{x}}_{14}$, $\overline{\mathbf{x}}_4$ is a source and all remaining equilibria are saddles. We can apply our RPM theorem to all restpoints except $\overline{\mathbf{x}}_4$ which turns out to be of little importance anyway. All shifts are given in [44]; we present here only the data for the four most relevant fixed points in table 2. The two stable restpoints move into $\mathrm{int}\, S_n$ whereas the fixed point $\overline{\mathbf{x}}_{123}$ leaves the simplex. This has an important consequence for the strange attractor whose appearence is caused by a Šilnikov type mechanism: the fixed point $\overline{\mathbf{x}}_{123}$ has its stable manifold in the $\overline{123}$-plane and plays the role of the critical saddle focus into which the trajectories spiral before they are driven out by

Table 2: Examples of first order shift vectors for some fixed points of a replicator field with chaotic dynamics ($\nu = 0$). The mutation rates are assumed to be equal, $Q_{ij} = \varrho$. The complete list of shift vectors is given in [44].

$L^{\dagger}$	Fixed point $\overline{\mathbf{x}}_{\{L\}}$	Shift vector $\mathbf{d}^{(1)}_{\{L\}}$
1	$\begin{pmatrix} 1 \\ 0 \\ 0 \\ 0 \end{pmatrix}$	$\frac{16}{11(10\mu+17)} \cdot \begin{pmatrix} -(60\mu+47) \\ -5(10\mu+17) \\ 11(10\mu+17) \\ -55 \end{pmatrix}$
3	$\begin{pmatrix} 0 \\ 0 \\ 1 \\ 0 \end{pmatrix}$	$\frac{40}{3} \cdot \begin{pmatrix} 6 \\ 1 \\ -10 \\ 3 \end{pmatrix}$
14	$\frac{1}{2(5\mu+9)} \begin{pmatrix} 1 \\ 0 \\ 0 \\ 10\mu+17 \end{pmatrix}$	$\frac{810\mu+1457}{2(5\mu+3)(5\mu+9)(5\mu+11)(10\mu+17)} \cdot \begin{pmatrix} (5\mu+11)(100\mu^2+265\mu+167) \\ (5\mu+9)(5\mu+11)(10\mu+17) \\ (5\mu+3)(5\mu+9)(10\mu+17) \\ -1000\mu^3-4875\mu^2-7730\mu-3979 \end{pmatrix}$
123	$\frac{1}{32} \begin{pmatrix} 10 \\ 7 \\ 15 \\ 0 \end{pmatrix}$	$\frac{43}{112(3\mu+5)} \cdot \begin{pmatrix} -6(9\mu-13) \\ 87\mu+61 \\ -33\mu+553 \\ -672 \end{pmatrix}$

† The fixed points are denoted by indicating the nonvanishing variables: $L = \mathcal{N} \setminus K$.

the unstable manifold (see for example figure 7 B). It is to be expected therefore that mutation even at small error rates destroys the chaotic attractor since the saddle focus moves into the space outside S_4 which is not accessible to physically meaningful trajectories. At some mutation rate $\varrho^{(cr)}$ the trajectories can no longer come sufficiently close to the saddle focus and the Šilnikov mechanism breaks down. Furthermore the stable fixed point $\overline{\mathbf{x}}_{14}$ moves into $\mathrm{int}\, S_4$ and thus the limit crisis occurs earlier.

In order to verify this conjecture on the fate of the chaotic attractor at finite mutation rates we studied the attractor in the two-dimensional parameter space (μ, ϱ) by integration of the corresponding ODE. Figure 8 summarizes the changes

Fig. 8: Extension of the chaotic regime into the range of small mutation rates. The dynamics of the strange attractor shown in figure 7 with $\nu = 0$ and $-0.25 < \mu < 0.5$ and an error rate of $0 \leq \varrho \leq 10^{-4}$ is shown. Typical shapes of the attractor in the vertically hatched region converge to a stable point on the edge $\overline{14}$. Periodic attractors are characterized by period mulipicities ($\mathbf{1} \equiv$ simple limit cycle). Chaotic dynamics is observed in the aerea with slanted hatching. Note that a Feigenbaum-sequence-like path with successive period doublings ($\mathbf{1}\rightarrow\mathbf{2}\rightarrow\mathbf{4}\rightarrow\mathbf{8}\rightarrow \ldots$) appears in the approach towards chaos from high to low mutation rates ϱ.

in the shape of the attractor due to mutation. Error rates as small as 2×10^{-5} are sufficient to wipe out the strange attractor. At error rates ϱ larger than some 10^{-3} the attractor is transformed into an asymptotically stable restpoint. Proceeeding in opposite direction from high to low error rates we find for some μ values a series of period doublings which ends up in deterministic chaos and which is very similar to the well known Feigenbaum sequence. A higly complex bifurcation pattern arises when mutation is introduced near the limit crisis of the unperturbed attractor [44]. At the present available resolution in is not decidable yet whether the bifurcation set forms a fractal or not.

6. Conclusions

Perturbation theory provides a useful tools to analyse the changes in the phase portraits of replicator fields which are induced by mutation. Qualitative shifts of restpoints and limit cycles are predicted by application of two theorems: the restpoint migration (RPM) theorem and the limit cycle migration (LCM) theorem. Quantitative shifts are calculated from a perturbation expansion. The perturbation parameter is chosen according to the mutation model applied. In case only point mutations are considered and the uniform error rate model is used, the series expansion has a finite number of terms and the mutation matrices contain nonvanishing entries only when the Hamming distance of the mutation coincides with the order of the term in the expansion. The quantitative approach was applied here to a quasi-linear replicator field in order to show how well the conventional results are reproduced by the perturbation expansion. The important feature of the approach presented here, however, is that it can be applied equally well to various nonlinear systems for which results are hard to get by other techniques. The collection of examples presented in the last section should illustrate the widespread applicability of our approach.

The technique to include mutation into replicator equations which was developed and used in this paper is rather versatile and may be applied to investigate very different problems. Apart from the examples given here applications to models of gene duplication, genetic recombination and coevolution are currently studied. We would like to stress that vector fields of other than mutational origin can be introduced into replicator fields by the same method provided they fulfil the flux and smoothness requirements listed.

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