

Adaptive Dynamics of Parabolic Replicators

G. MESZÉNA^{1,3*} and E. SZATHMÁRY^{2,3}

¹Department of Biological Physics, Eötvös University, Budapest, Hungary,

²Department of Plant Taxonomy and Ecology, Eötvös University, Budapest, Hungary,

³Collegium Budapest (Institute for Advanced Study), Budapest, Hungary

(Received: 14 June 2001,

Accepted:)

Dátum?

The growth of many artificial replicators is approximately parabolic (sub-exponential) in solution, due to the self-inhibition through duplex formation by the association of single-stranded molecules. This type of growth implies “survival of everybody” under a selection constraint. Parabolic growth requires high enough concentration so that the single strands can find one another. The selective outcome is more complicated when spontaneous decay of molecules is also taken into account. When double strands decompose at a slower rate than single strands, coexistence or survival of the fittest becomes a quantitative issue. Here we investigate the evolution of parabolic replicators by the methods of adaptive dynamics. Directional selection for higher replication rate in general results in a “parabolic quasi-species”, due to the fact that the fittest template is followed by a moving shadow of inferior templates that owe their presence to parabolic growth. Under the assumption of cross-hybridisation between non-identical templates molecular coexistence disappears when such pairing is sufficiently non-selective, because replicators do not inhibit themselves more than they limit the others. At intermediate specificity of pairing adaptive branching of the population becomes feasible, due to the fact that distant enough sequences are able to escape from cross-limitation by other sub-populations.

Keywords: Parabolic replicators, dynamical coexistence, adaptive dynamics, origin of life

“... the Struggle for Existence amongst all organic beings throughout the world ... inevitably follows from their high geometrical powers of increase ...”
(Darwin: *Origin of Species*..., 1859)

1. Introduction: the world of parabolic replicators

The idea of natural selection is intrinsically tied to a basic exponential growth tendency of populations of evolutionary units, defined by:

$$\frac{dN_i}{dt} = k_i N_i^p \quad (1)$$

where N_i is the population density (in population dynamics) or the concentration (in chemistry) of

species i , and $p = 1$. If this type of growth prevails, only the species with the highest growth rate constant k_{\max} survives under a selection constraint, such as (cf. Eigen, 1971):

$$\frac{dN_i}{dt} = k_i N_i^p - N_i \sum_j k_j N_j^p \quad (2)$$

which sets up the system so that the total density is kept unity (without loss of generality). There are other types of selection constraint, but the conclusion remains valid. Obviously, exponential growth cannot go on forever, one obvious constraint being resource limitation, which acts as an extrinsic constraint.

* Corresponding author: Géza Meszéna, Collegium Budapest, Department of Biological Physics, Eötvös University, Pázmány Péter sétány 1A, H-1117 Budapest, Hungary, E-mail: geza.meszena@elte.hu.

There are, however, intrinsic deviations from growth with $p = 1$. In this paper we consider the case of $p < 1$, i.e. sub-exponential (Szathmáry and Gladkih, 1989) or, especially, parabolic ($p = 1/2$, Von Kiedrowski, 1993) growth. Such type of growth was first observed by Von Kiedrowski (1986) in case of a non-enzymatically replicating oligonucleotide analogue. Since then a whole zoo of such replicators was synthesized and tested (see Von Kiedrowski, 1999). The selection consequences of this type of growth were later realized (Szathmáry and Gladkih, 1989) to result in ‘survival of everybody’ (Szathmáry, 1991) instead of ‘survival of the fittest’.

The reason for parabolic growth in such systems is that template and copy associate easily, although reversibly. The associated double-stranded form is replicationally inert: another round of templated synthesis can follow only after dissociation (Von Kiedrowski, 1986). Association hence results in self-inhibition of the replicator. The lower the concentration N , the faster the growth, hence the ‘protected polymorphism’, to use a term from population genetics. Indeed, a globally stable equilibrium of coexisting replicators could be proven for the purely parabolic system (Varga and Szathmáry, 1997)

Complications abound, however, as realized by Szathmáry and Gladkih (1989), parabolic growth (and survival of everybody) prevails only if the density (concentration) of replicators is high enough, because if this condition is not met, single strands do not find each other and there is no strong enough self-inhibition (see Wills et al., 1998 on this point). Another departure from the case of ‘survival of everybody’ arises when decay (decomposition) rates are also taken into account, as observed by Lifson and Lifson (1999). In particular, one can introduce (exponential) spontaneous decay attacking the different molecular species. The Lifsons argued that when this is done, the possibility for coexistence vanishes. However, as realized by Von Kiedrowski and Szathmáry (2000), and confirmed by Scheuring and Szathmáry (2001), coexistence is nevertheless possible if not only single strands but also double strands decompose. A chemically feasible analogue has been suggested in the chromatographized replicator model (Von Kiedrowski and Szathmáry, 2000), where selection for higher replication rate is possi-

ble. In that model it is assumed that replicators of the parabolic type grow and move in a chromatography column, and that the double strands bind better than the single stands. Consequently, the single strands are washed out more readily, resulting in a higher apparent decay rate for single than for double strands. Hence the decay rates of single strands and double strands are analogous to the corresponding desorption rates from the chromatography column.

Undoubtedly, binding to mineral surfaces is likely to have crucially contributed to the selection dynamics of replicators (e.g. Czárán and Szathmáry, 2000). The above-mentioned chromatographized replicator model indicates the validity of this insight for parabolic replicators, too. A more explicit treatment is being presently worked out.

True, sustained, exponential growth of a real population is not realistic. In ecology population growth is often approximated by the logistic curve. It is clear, however, that true population dynamics can be arbitrarily complicated and can vary according to the species and to the circumstances. Analysing the evolutionary consequences of all of the growth laws separately would be cumbersome. More importantly, if Darwinian selection would be restricted to, and dependent on, specific assumptions on population dynamics, it could not be considered as a general phenomenon of biology.

Fortunately, there is a tautological, but useful, way of considering any kind of population growth as “instantaneously” exponential. Population dynamics of any population can be written into the form

$$\frac{dN}{dt} = r(E) \cdot N, \quad (3)$$

where the “environment” E denotes all factors affecting the demographic parameters of an individual, including the rest of the population. $r(E)$ is the instantaneous rate of population growth. If, in a thought experiment, E were kept constant, then the population grew exponentially according to this rate. In reality, the environment of the individual is always affected by the population growth, i.e. E depends on N .

The instantaneous rate of increase determines the course of selection at the given moment. In competition between two populations, the ratio of population sizes (N_1 and N_2) changes according to

the difference between the growth rates (r_1 and r_2) in the given environment:

$$\frac{d}{dt} \frac{N_1}{N_2} = (r_1(E) - r_2(E)) \frac{N_1}{N_2}. \quad (4)$$

In this sense, the instantaneous growth rate is the genuine measure of the fitness in the situation characterised by E (cf. Metz et al., 1992). In case of parabolic growth ($p = 1/2$), $r^{\text{par}}(E) = \alpha / \sqrt{N}$. That is, reproduction is enhanced by lower population size. At higher density, the replication capability of an individual is limited by product inhibition.

The following distinction is of crucial importance. If the competing parabolic replicators are affected by their own population sizes ($r_i^{\text{par}} = \alpha_i / \sqrt{N_i}$, where $i = 1, 2$ distinguishes between the competitors), then the rare type has an extra advantage over the other due to its rarity. In contrast, if they are affected by the total population size ($r_i^{\text{par}} = \alpha_i / \sqrt{N_1 + N_2}$) then $r_1 / r_2 = \alpha_1 / \alpha_2$ and rarity causes no relative advantage. Individuals of both populations receive the same amount of product inhibition from the rest of the population. In this case, while the exponential growth rates are not fixed, their ratio is. The fitter outcompetes the less fit.

In this paper we consider the limits to selection of parabolic replicators when both single and double strands are allowed to decay. We consider competition of such replicators in Section 2, and evolution of them in Section 3. Section 3.1 introduces the concept of a ‘‘parabolic quasi-species’’, the cloud of variants existing due to the partly non-Darwinian character of selection. Section 3.2 presents results on parabolic replicators with significant cross-hybridisation between strands that differ in sequence. Finally, we discuss the interpretation and the significance of these findings (Section 4).

2. Competition between parabolic replicators

In this section we investigate competition among several parabolic replicator species. As we will see, the behaviour depends strongly on the ability of the two types of strands to form a mixed pair (hybridisation). First, in Section 2.1, we consider

the special case of no hybridisation, then, in Section 2.2, the general case.

2.1. Replicators with no hybridisation

Let A_i and B_i denote the concentrations of the single strands and the double strands of the species i , respectively. ($i = 1, \dots, n$, n is the number of species.) Their respective decay rates are d_i and δ_i . In presence of the monomers, a single strand of type i is transformed into a double strand by template copying at the rate $k_i R$, where R is the monomer (resource) concentration and k_i is the replication rate constant. The monomers are generated continuously at rate ρ and are consumed during replication. Two single strands can spontaneously pair up into a double strand with rate a . A double strand can dissociate into two single strands with rate b . These processes are summarised by the differential equations (see Von Kiedrowski and Szathmary, 2000; Scheuring and Szathmary, 2001):

$$\frac{dR}{dt} = \rho - R \sum_{i=1}^n k_i A_i \quad (5)$$

$$\frac{dA_i}{dt} = 2(b_i B_i - a_i A_i^2) - A_i(k_i R + d_i) \quad (6)$$

$$\frac{dB_i}{dt} = a_i A_i^2 - b_i B_i + k_i R A_i - \delta_i B_i. \quad (7)$$

The model can be interpreted for complementary pairing on the following way. The total population of $2n$ sequences is split into two sets of n fully complementary sequences. The i^{th} molecule of set 1 is complementary to the i^{th} molecule of set 2.

We will use the total concentrations

$$M_i = A_i + 2B_i \quad (8)$$

for the replicators satisfying the equation

$$\frac{dM_i}{dt} = A_i(k_i R - d_i) - 2\delta_i B_i. \quad (9)$$

It will be often convenient to consider the ‘‘fast pairing’’ limit, in which pairing and dissociation are fast compared to replication and decay. Then, these processes equilibrates and

$$bB_i = aA_i^2. \quad (10)$$

In the fast pairing limit and at high concentration, which are good assumptions for a typical experimental situation, $M_i \approx 2 \cdot B_i$ and $A_i \propto M_i^{1/2}$. Then, for $\delta = 0$ and for constant R , the dynamics eq. (9) assumes the shape (1) with $p = 1/2$, justifying to consider these replicators as “parabolic”.

We set $n = 2$ and investigate whether species 2, while rare, can grow in the equilibrium population of species 1, without assuming fast pairing. The equilibrium condition for species 1 reads as

$$A_1(k_1 R - d_1) - 2\delta_1 B_1 = 0, \quad (11)$$

leading to the equilibrium resource density

$$R_1 = \frac{1}{k_1} \left[d_1 + 2\delta_1 \frac{B_1^e}{A_1^e} \right]. \quad (12)$$

(A_1^e , and B_1^e are the equilibrium values of A_1 and B_1 .) Initial growth of the second species is given by

$$\frac{dM_2}{dt} = A_2(k_2 R - d_2), \quad (13)$$

because B_2 is negligible compared to A_2 when replicator 2 is rare. This growth is positive in the equilibrium (12) if and only if

$$R_1 > \frac{d_2}{k_2}. \quad (14)$$

that is, when

$$k_2 > k_2^{\min} = k_1 \frac{d_2}{d_1 + 2\delta_1 \frac{B_1^e}{A_1^e}}. \quad (15)$$

If $d_1 = d_2 = d \neq 0$ and $\delta_1 = \delta_2 = \delta$ then the invasion criterion becomes

$$k_2 > k_2^{\min} = k_1 \frac{1}{1 + 2 \frac{\delta}{d} \frac{B_1^e}{A_1^e}} \quad (16)$$

(Fig. 1). Observe that $k_2^{\min} \leq k_1$, the equality holds only at $\delta = 0$.

The rare species can always grow if its replication rate is higher than that of the resident. If $\delta = 0$ then $k_2^{\min} = k_1$ and, by symmetry,

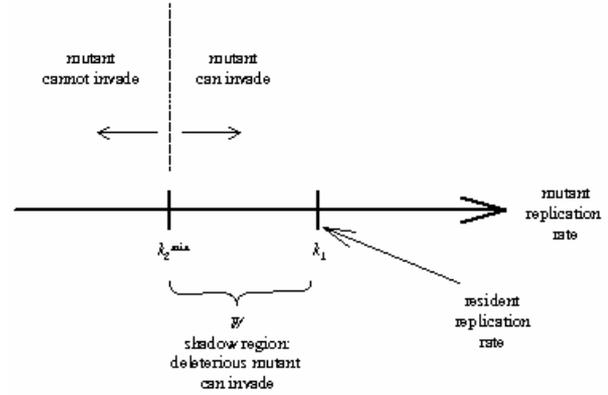


Fig. 1. Range of invasion. Resident strategy k_1 can be invaded by any strategy above k_2^{\min} . There is a “shadow” region between the two, in which the rate strategy is disadvantageous, but able to invade

$k_1^{\min} = k_2$. This is the (only) case of undisturbed Darwinism: The species with the higher replication rate outcompetes the one with the lower one, and vice versa. No species coexistence is possible with different replication rates. On the other hand, if $\delta > 0$, $k_2^{\min} < k_1$, so even a species with lower replication rate than that of the resident can grow if its disadvantage is not too high. If $k_2^{\min} < k_2 < k_1$, sequences with replication rates k_1 and k_2 can mutually invade each other. That is, they are able to coexist. This calculation confirms those of Scheuring and Szathmáry (2001). One can take steps further, however.

In particular, behind the resident k , there is a “shadow” region in which any strategy can invade and coexist. The width

$$W = k_1 - k_2^{\min} = 2 \cdot \frac{\delta}{d} \cdot \frac{B_1^e}{A_1^e} \cdot k_2^{\min} \quad (17)$$

of the “shadow” is small if $\delta \ll d$ and/or if $B_1^e \ll A_1^e$. In the fast pairing limit,

$$W = 2 \cdot \frac{a\delta}{bd} \cdot A_i^e \cdot k_2^{\min}. \quad (18)$$

That is, the shadow becomes narrow for low concentrations, when pairing is rare.

We can conclude that the disadvantage of the more abundant type, relative to the rare one, comes from the decay of the double strands. The shadow disappears if the double strands are either rare or does not decay. The notion of *lifetime reproductive*

ratio, which is defined as the expected number of offspring of a single strand during its entire lifespan, is useful to interpret this result. A population increases/decreases, or is in equilibrium, if its lifetime reproductive ratio is higher/lower than, or equals to, 1 (cf. Mylius and Diekmann, 1995; Pásztor et al., 1996). At low concentration, when all of the strands are unpaired, their lifetime reproductive ratio is k/d , as the expected lifetime is $1/d$. At higher concentration, the strands spend a fraction of their lifetime in the inactive, paired, form. If $\delta = 0$, they are immune to decay during this period, so their expected total time until decay spent in the unpaired form remains $1/d$. Consequently, pairing delays replication but does not affect the lifetime reproductive ratio. Increasing concentration slows down population growth but cannot stop it. The situation is different when $\delta > 0$. As decay occurs during the paired state, the expected time spent unpaired is decreased by pairing. Higher concentrations lead to lower lifetime reproductive ratio. When it decreases to 1, the population stops growing. Then another, non-hybridising, strand with lower replication rate can invade if its lower concentration compensates for its lower replication rate. [These arguments do not directly apply when both the single and the double strands are immortal, as the lifetime reproductive ratio has no meaning in this case. Note, however, that the dilution term in eq. (2) is equivalent of subscribing equal decay rates for the single and for the double strands.]

2.2 Replicators with cross-hybridisation

Here we allow pairing between similar, but different, sequences. For notational convenience, we will distinguish between the double strands of types (ij) and (ji) for $i \neq j$. As an arbitrary choice, we divide the double strands containing a strand of type i and a strand of type j evenly between these two classes. B_{ij} denotes the concentration of the type (ij) . By definition, $B_{ij} = B_{ji}$. a_{ij} , b_{ij} and δ_{ij} denote the pair-forming rate, the de-pairing rate and the decay rate of the type (ij) , respectively. All of these parameters are symmetrical in the exchange of the indices.

The dynamical equations are

$$\frac{dR}{dt} = \rho - R \sum_{i=1}^n k_i A_i \quad (19)$$

$$\frac{dA_i}{dt} = \sum_j [b_{ij} B_{ij} + b_{ji} B_{ji} - (a_{ij} + a_{ji}) A_i A_j] - A_i (k_i R + d_i) \quad (20)$$

$$\frac{dB_{ij}}{dt} = a_{ij} A_i A_j - b_{ij} B_{ij} + l_{ij} k_i A_i R - \delta_{ij} B_{ij} \quad (21)$$

where

$$l_{ij} = \begin{cases} 1, & \text{for } i = j \\ 0, & \text{for } i \neq j \end{cases} \quad (22)$$

The total concentration is

$$M_i = A_i + \sum_j (B_{ij} + B_{ji}), \quad (23)$$

obeying the dynamics

$$\frac{dM_i}{dt} = A_i (k_i R - d_i) - \sum_j (\delta_{ij} B_{ij} + \delta_{ji} B_{ji}). \quad (24)$$

In the fast pairing limit, when

$$B_{ij} = \frac{a_{ij}}{b_{ij}} \cdot A_i \cdot A_j, \quad (25)$$

the dynamics becomes

$$\begin{aligned} M_i &= A_i + \sum_j (B_{ij} + B_{ji}) = \\ &= A_i \cdot \left[1 + \sum_j \left(\frac{a_{ij}}{b_{ij}} + \frac{a_{ji}}{b_{ji}} \right) A_j \right]. \end{aligned} \quad (26)$$

Let us repeat the invasion analysis for this case. The equilibrium state of a single resident of type 1 is:

$$R_1 = \frac{1}{k_1} \left[d_1 + 2\delta_{11} \frac{B_{11}^e}{A_1^e} \right] \quad (27)$$

as there is no other type of sequence to pair. The growth rate of the rare type 2:

$$\begin{aligned} \frac{dM_2}{dt} &= A_2 \frac{k_2}{k_1} \left(d_1 + 2\delta_{11} \frac{B_{11}^e}{A_1^e} \right) - \\ &- d_2 A_2 - \delta_{12} B_{12} - \delta_{21} B_{21}. \end{aligned} \quad (28)$$

Here the concentration of the (2,2) pairs was neglected due to the rarity of the species 2. If $d_1 = d_2 = d \neq 0$ and $\delta_{11} = \delta_{12} = \delta_{21} = \delta$ then the invasion criterion becomes

$$k_2 > k_2^{\min} = k_1 \cdot \frac{1 + \frac{\delta}{d} \cdot \frac{B_{12} + B_{21}}{A_2}}{1 + 2 \frac{\delta}{d} \cdot \frac{B_{11}^e}{A_1^e}}. \quad (29)$$

At random pairing, $a_{12} = a_{11}$ and $b_{11} = b_{12}$, so the pairing equilibrium reads as

$$\frac{B_{12}}{A_2} = \frac{B_{21}}{A_2} = \frac{B_{11}}{A_1}. \quad (30)$$

According to eq. (29), $k_2^{\min} = k_1$ for random pairing. The higher k outcompetes the lower one.

Suppose now, that different strands are less able to form a duplex, than the identical ones, manifested in higher de-pairing rate for the heteroduplexes: $b_{12} > b_{11}$. We suppose no difference in the pairing rates ($a_{12} = a_{11}$), as they are dominated by the pair formation entropy, which is independent of the sequences. Then,

$$\frac{B_{12}}{A_2} < \frac{B_{11}}{A_1} \quad (31)$$

and, consequently, $k_2^{\min} < k_1$.

These results resemble to the behaviour of the Lotka–Volterra competition model: Decreasing product inhibition, just like the decreasing competition in the LV case, facilitate coexistence of different phenotypes. The analogy becomes quantitative, when the concentrations are low such that paired strands are very rare and thus $M_i \approx A_i$. Then eq. (26) can be rewritten into the form of Lotka–Volterra type population dynamics:

$$\frac{dA_i}{dt} = r_i^0 \left(1 - \frac{\sum_j \alpha_{ij} A_j}{K_i} \right) A_i, \quad (32)$$

where the carrying capacity is

$$K_i = k_i R - d_i, \quad (33)$$

the initial growth rate is

$$r_i^0 = A_i (k_i R - d_i), \quad (34)$$

and the competition coefficient is

$$\alpha_{ij} = \frac{a_{ij} \delta_{ij}}{b_{ij}} + \frac{a_{ji} \delta_{ji}}{b_{ji}}. \quad (35)$$

Note that both r_i^0 and K_i depend on the resource concentration R . This means that approximation of the model by Lotka–Volterra dynamics, strictly speaking, supposes also to keep the resource level constant. Still, the coexistence caused by self-inhibition is properly represented by the Lotka–Volterra approximation.

3. Evolution of parabolic replicators

How does parabolic coexistence alter the course of Darwinian evolution via small mutational steps? To study this question, we trivialise the relation between the sequence and the phenotype. We suppose a one-dimensional phenotype parameter and assume that similar sequences have similar phenotypes. Consequently, we suppose that the possibil-

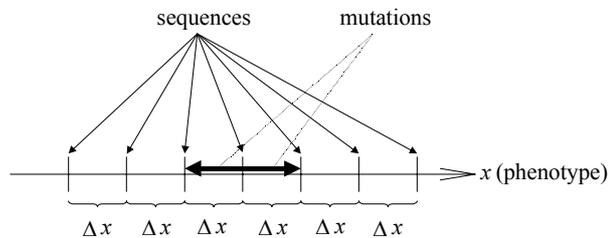


FIG. 2 The phenotype space of replicators. The phenotype values realised by specific sequences are spaced uniformly with distances Δx between them. It is supposed that similar sequences have similar phenotypes, so a mutation produces an adjacent phenotype

ity of hybridisation decreases with the phenotype difference between the strands. Discrete points, spaced by the uniform distances Δx along the phenotype space, represent the phenotypes corresponding to individual sequences. Mutation of a phenotype leads to one of the two neighbouring phenotypes (Fig. 2).

The evolutionary simulations proceed as follows (Metz et al., 1996; Geritz et al., 1997, 1998). The combined population dynamics of several competing phenotypes is followed according to the

differential eqs (5–7) or (19–21). If the density of a species decreases below a threshold, it is removed from the simulation. At random instances, new phenotypes, with low densities, are introduced as mutants of the phenotypes already present (the mutation rate is defined on a per individual basis). A mutant phenotype is chosen randomly from the two neighbours (on the linear phenotype scale) of the ancestral phenotype.

As a representation of the Darwinian idea of evolution by small steps, it is usual to assume in evolutionary simulations that mutation step size is small as compared to the relevant distances in the phenotype space. For the parabolic replicators, this assumption would mean that the distance Δx between the neighbouring phenotypes should be small as compared to the “recognition distance” within which two strands can form a pair. Obviously, it is violated in case when only the identical sequences can form a pair. Consequently, we have to deal with two, entirely different regimes. The “no cross-hybridisation” case will be studied in Section 3.1 while the recognition distance will be chosen larger than Δx in Section 3.2.

Note the discrepancy between the random creation of the mutants and the deterministic way of following their fate. This kind of simulation neglects the fact that even an advantageous mutant can go extinct because of the demographic stochasticity at low density, affecting the speed of evolution. The qualitative picture is affected only when the relative speeds (of different species and/or of different directions) matter, which is not the case in our investigations.

3.1. The parabolic quasi-species

In this subsection we study the evolutionary version of the competition model of Section 2.1: the population dynamics is determined by the eqs (5–7).

For the first go, we identify the phenotype of interest with the replication rate k . Figure 3a shows the course of evolution for $\delta = d$. After a short transitional period, a relatively constant distribution of strategies emerges and moves towards the direction of increasing replication rate. In the “shadow” of the species with the highest k (the k^{\max}), there is a tail of coexisting species with

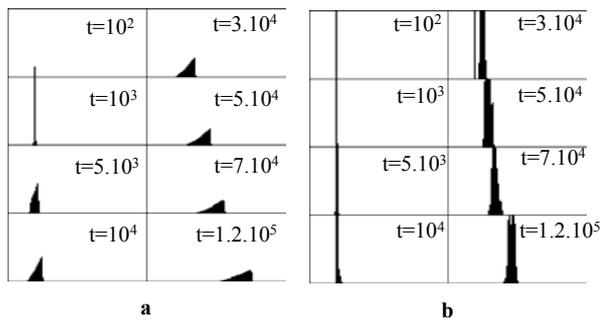


FIG. 3. Directional evolution of the parabolic quasi-species with $\delta = d = 0.01$ (a) and the non-parabolic case $\delta = 0$. Horizontal axes: $k \in [0, 0.1]$, vertical axes: total density $M \in [0, 0.5]$. The other parameters: $\rho = 0.1$, $a = b = 0.03$, $\Delta k = 0.02$, mutation rate: 0.01, initial density of a mutant: 0.01, extinction threshold: 0.009. The initial replication rate is 0.0

lower replication rates. Understandably, the densities of the species are decreasing with the decreasing replication rate. Lower replication rate should be compensated by the advantage of the lower population size. When a new mutant arrives with replication rate higher than k^{\max} (that is, with replication rate $k^{\max} + \Delta k$, where Δk is the distance between the adjacent phenotypes), it invades and the whole population shifts into the direction of higher k .

We will refer to this moving distribution as “parabolic quasi-species”. The term “quasi-species” was introduced by Eigen and Schuster (1977) as a description of the cloud of mutants around the most abundant type (the master sequence), in mutation-selection balance. In our case, instead of mutation-selection balance, it is parabolic coexistence that shapes the quasi-species distribution.

In comparison, in Figure 3b, one can observe the evolution of the same system, but without double-strand decay. Instead of the characteristic shape of the parabolic quasi-species, one can observe the classical one, the cloud of mutants.

In order to determine the shape of the parabolic quasi-species analytically, we suppose that the mutation events are so rare that, when a new mutant arrives, the species, which are present already, have equilibrated. Moreover, we will suppose that pairing is fast.

Let k^{\max} denote the rate of replication of the best sequence present at a given time. In line with the analysis of the previous Section, the sequences

with $k \in (k^{\min}, k^{\max})$ can coexist with the best one, where k^{\min} is defined by the relation

$$\frac{k^{\max} - k^{\min}}{k^{\min}} = 2 \cdot \frac{\delta}{d} \cdot \frac{B^{\max}}{A^{\max}} = \frac{2\delta a}{b} \cdot A^{\max}. \quad (36)$$

Here, A^{\max} and B^{\max} denote the equilibrium concentration of the single-stranded and the double-stranded form of the best sequence, respectively.

The equilibrium equation

$$R = \frac{1}{k_i} \left[d + 2\delta \frac{B_i}{A_i} \right] \quad (37)$$

should hold for each species, distinguished by the index i . By rearranging and taking into account the fast pairing equilibrium (10) one obtains

$$A_i = \frac{b}{2a\delta} (R \cdot k_i - d) \quad (38)$$

for the single-strand densities, which changes linearly with the replication rate. The corresponding M_i values can be calculated from (8) and (10) to obtain the quadratic shape of the quasi-species

$$M_i = \frac{2a}{b} A_i^2 + A_i, \quad (39)$$

visible in Figure 3a.

It is important to note that the width of the parabolic quasi-species goes to zero in the continuous limit $\Delta k \rightarrow 0$. According to eq. (36), the $k^{\max} - k^{\min}$ is proportional to the density of the best species. However, the *per-species* density should go to zero, when more and more species load the resource in the $\Delta k \rightarrow 0$ limit (see Appendix for the detailed calculations).

A slightly different model with optimising, instead of directional, selection is simulated in Figure 4 as a warming-up for model versions of the next Section. The replication rate is a quadratic function of the phenotype x , as

$$k = k_0(1 - x^2), \quad (40)$$

while the other parameters are constant. Otherwise, the model is identical to the previous one. Phenotype x can represent any molecular-level continuous parameter, which has a non-monotonous impact on the replication rate, like a shape param-

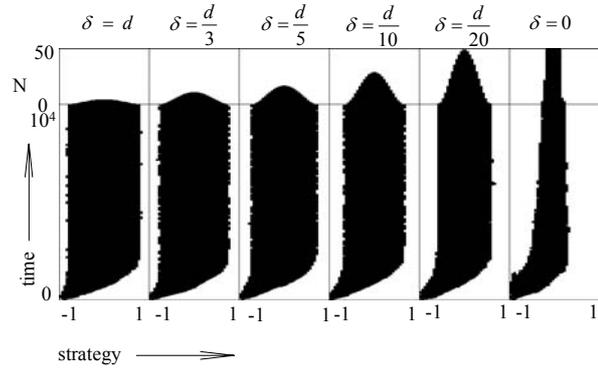


FIG. 4. Optimising evolution of parabolic replicators for different δ/d values. It leads to equilibrium parabolic quasi-species with tails on both sides. Lower plots: the evolutionary process. Each point represents a strategy, which is present at the given time. Upper plots: density distribution at the final time. Decreasing double-strand decay rate decreases the width of the quasi-species and moves the behaviour closer to the Darwinian one. Parameters: $k_0 = 0.00125$, $\Delta x = 0.05$, initial strategy: $x = -0.9$, $\rho = 1$, the others are identical to the values used at Fig. 3

ter, a binding constant, a pK value, or the temperature the replicator is optimised to.

The behaviour of the system is very similar to the previous one, except for the fact that the parabolic quasi-species stops at the optimum and assumes a symmetric shape with decreasing densities at both sides. The analytic calculation of the shape would be similar to the previous case.

3.2. Branching evolution in case of cross-hybridisation

We re-investigate the problem of optimising evolution described at the end of the previous Section, allowing for cross-hybridisation.

We suppose that ability of pair formation decreases with increasing phenotype differences between the strands. (Obviously, the assumption, that the same continuous parameter scales the pair formation and determines the replication rate, is, again, a trivialisation of the genotype-phenotype mapping.) More precisely, the dissociation rate b_{ij} between the phenotypes x_i and x_j increases with the phenotype difference $x_i - x_j$ according to

$$\frac{1}{b_{ij}} = \left(\frac{1}{b_{\min}} - \frac{1}{b_{\max}} \right) e^{-\frac{(x_i - x_j)^2}{2\sigma^2}} + \frac{1}{b_{\max}}. \quad (41)$$

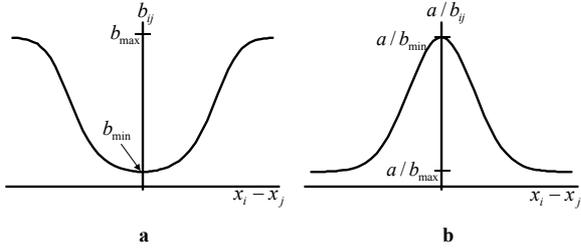


FIG. 5. Change of de-pairing rate (a) and the equilibrium constant of the pair formation (b) as a function of phenotype difference

(See Fig. 5a. The second term, which puts an upper limit for the dissociation, was introduced by technical reasons, to avoid the numerical difficulties that the introduction of exponentially large rates would cause.) Parameter σ is the “recognition width”: sequences with strategy difference much higher than σ cannot form a persistent pair with each other. As before, pair-formation rates are supposed to be independent from the phenotype difference:

$$a_{ij} = a. \quad (42)$$

The replication rates are defined by eq. (40) again. All of the other parameters are constant.

Then the pairing equilibrium is characterised by

$$\begin{aligned} \frac{B_{ij}}{A_i \cdot A_j} &= \frac{a}{b_{ij}} = \\ &= a \left(\frac{1}{b_{\min}} - \frac{1}{b_{\max}} \right) e^{-\frac{(x_i - x_j)^2}{2\sigma^2}} + \frac{a}{b_{\max}} \end{aligned} \quad (43)$$

(Fig. 5b), corresponding to a maximum in the binding free energy when the sequences are identical. The approximating Lotka–Volterra model has the competition coefficient

$$\alpha_{ij} = 2a\delta \left[\left(\frac{1}{b_{\min}} - \frac{1}{b_{\max}} \right) e^{-\frac{(x_i - x_j)^2}{2\sigma^2}} + \frac{1}{b_{\max}} \right]. \quad (44)$$

Figure 6a shows the simulation results for different pairing widths. The dominant feature of the plot is the (often repeated) branching of the evolutionary process.

There are two kinds of selection pressure in the model. First, there is an element of optimising selection as the central strategy $x = 0$ has the highest replication rate. Second, it is advantageous to

be different from the rest of the population because of the decreased product inhibition. To understand the σ -dependence of the interplay between these forces and the parabolicity, one has to compare the recognition width with two relevant distances in the phenotype space: the discreteness Δx and the scale on which the replication rate changes.

When $\sigma \gg \Delta x$, a mutant sequence and its ancestor can pair with each other, so the advantage of rarity is of $O((\Delta x / \sigma)^2)$ small between them. So, for $x \neq 0$, nothing stops a mutant with higher k to outcompete its less advantageous ancestor completely. The step-by-step process of such substitutions proceeds until the fitness gradient vanishes at the phenotype $x = 0$ maximising the replication rate.

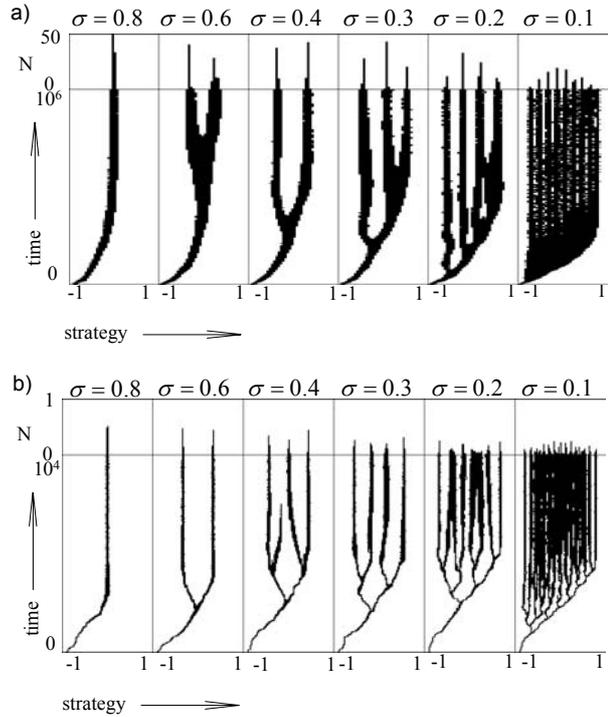


FIG. 6. Branching adaptive dynamics. Comparison between parabolic replicators with cross-hybridisation (a) and the Lotka–Volterra competition model (b). Lower plots: the evolutionary process. Each point represents a strategy, which is present at the given time. Upper plots: density distribution at the final time. The control parameter σ is the hybridisation width and the competition width in the two cases, respectively. While the details are incomparable, behaviour of the two models are remarkably similar. Decreasing σ increases the number of emerging branches. For low σ , there is no branching, at all. $b_{\min} = 0.03$, $b_{\max} = 1.0$, $K_0 = 1.0$. The mutation rate is 0.001 and 0.1 on (a) and (b), respectively. The other parameters are the same as in Fig. 4. On (b), the, in principle, continuous phenotype space was divided into 80

At the “singular” phenotype $x = 0$, both kinds of the selection pressure are of $O(\Delta x^2)$, so the outcome depends on the balance between them. If the replication rate decreases sharply on the scale of recognition width, as on the leftmost plot in Figure 6a with a relatively large σ , advantage of being different from the established population of the singular phenotype cannot overcome the disadvantage of having a smaller replication rate than of the singular phenotype. Then, the singular phenotype is a local ESS, as no other phenotype can invade it. This is the classical, Darwinian, optimisation. As every strategy is product-inhibited (almost) uniformly by the whole population, no strategy acquires advantage, or disadvantage, from product-inhibition.

In contrast, if the decrease of the replication rate is moderate, or small, on the scale of recognition width, a rare mutant, with a phenotype slightly different from the singular one, gains an advantage from being different and invades. The disruptive selection emerging in this situation splits the population and the sub-populations evolve away from each other. The diverging evolution ceases when the distance between the branches reaches the order of σ and the phenotypes feel no longer the inhibitory effects of each other. The branching process may repeat itself several times for smaller σ s.

This behaviour is remarkably similar to the adaptive dynamics of the Lotka–Volterra competition model (Metz et al., 1996), which is recapitulated in Figure 6b with the carrying capacity function

$$K = K_0(1 - x^2), \quad (45)$$

imitating the shape of the replication rate function (40), and with the competition kernel

$$\alpha_{ij} = \left(\frac{1}{b_{\min}} - \frac{1}{b_{\max}} \right) e^{-\frac{(x_i - x_j)^2}{2\sigma^2}} + \frac{1}{b_{\max}}, \quad (46)$$

mimicking the shape of (44).

Note that the simulation parameters for the parabolic replicators was *not* chosen to satisfy the Lotka–Volterra limit described in Section 2.2. Most of the strands are paired at the given circumstances. Moreover, the carrying capacity curve (45) does not reflect the dependence on the resource

concentration expressed in eq. (33). Still, the LV competition picture captures the essence of the evolutionary consequences of cross-hybridisation. The non-constant initial growth rate (eq. (34)), which is missing from this simulation also, does not have an evolutionary significance.

On the rightmost plot of Figure 6a ($\sigma = 0.1$, $\Delta x = 0.05$) the condition $\sigma \gg \Delta x$ starts to be violated. The dense branching pattern becomes very similar to the comparable simulation without cross-hybridisation (leftmost panel of Fig. 4), when a parabolic quasi-species evolves to the optimum and settles down there. Even at $\sigma = 0.2$ one can observe a departure from the “ideal” behaviour described above: the first branching occurs before reaching the maximal k .

4. Discussion

Clearly, the world of artificial replicators and their dynamical behaviour is constantly expanding (Von Kiedrowski, 1999). We see our work as a step forward in the analysis of the underlying dynamics. The coupling of a field in evolutionary biology (namely, adaptive dynamics) and one in chemistry (namely, replicator synthesis and analysis) is exciting, is likely to yield to useful results and pose further questions. In this section we discuss some connections to ecological theory and adaptive dynamics and some directions in which the present work could be developed further.

4.1. Connections to the theory of coexistence and branching

If the environment can be fully characterised by a finite number of “limiting factors”, the number of coexisting strategies cannot be larger than the number of limiting factors for the generic existence of the equilibrium (MacArthur and Levins, 1964; Levin, 1970). In this context, environment includes all factors affecting the lifetime reproductive ratio of an individual. This concept of limiting factors, useful in ecology, becomes tautological for non-hybridising parabolic replicators: each replicator is a limiting factor for itself. At random pairing, no independent limitation exists for the different species. Instead, all of them are limited by the total

population size via product inhibition. Accordingly, we cannot observe parabolic coexistence in case of unrestricted hybridisation. (Together with the resource, there are two limiting factors in this case. This situation allows at most two types to coexist. However, this coexistence would require difference between the double-strand decay rates and is not discussed in this paper.)

The intermediate case, when the equilibrium constant (43) decreases with the increasing phenotype difference between the strands, is analogous to the Lotka–Volterra competition model of MacArthur and Levins (1967), Metz et al. (1996). Even though the number of limiting factors is infinite, similar phenotypes cannot coexist. (Roughgarden, 1979, provided an example of coexistence of continuously many species in this model, but this example turned out to be structurally unstable, Sasaki and Ellner, 1995; Gyllenberg and Meszéna, *in prep.*) This *limiting similarity* principle is model-independent: the more similar the phenotypes are (either in their dependence on the limiting factors, or in their effects on them), the narrower interval of the parameter(s) allow them to coexist (Meszéna and Metz, *in press*). From this point of view, the non-hybridising parabolic replicators should not be regarded as similar, even if the difference between their parameters is small. A specific strand of phenotype A is inhibited by the population A, but not by the population B, and vice versa. They are distinctly different *sequences*, even if their phenotypes are similar. In contrast, cross-hybridising replicators follows the limiting similarity principle and coexists robustly only when their difference is comparable, at least, with the recognition width.

When limiting similarity applies, a mutant, which is similar to its ancestor, cannot coexist with the ancestor. If the mutant is able to grow initially, then it will outcompete the resident (Jacobs et al., *in prep.*; Geritz et al., *in press*). The exception is the vicinity of a “singular” phenotype, where the fitness landscape is flat. Evolution via small mutation steps is directional, until such a singular point is reached. Then, it may, or may not branch, depending on whether the advantage of being different from the rest of the population outweighs the disadvantage of departure from the singular strategy (Metz et al., 1996, Geritz et al., 1997, 1998). There are several possible biological reasons for

advantage of being different: resource heterogeneity, habitat heterogeneity, asymmetric competition, etc. Among others, Meszéna et al. (1997), Geritz et al. (1999), Kisdi (1999), Kisdi and Geritz (1999), Doebeli and Dieckmann (2000), Mathias et al. (2001), Mathias and Kisdi (*in press*) contain examples of evolutionary branching in such situations. We demonstrated that decreasing product inhibition with increasing phenotype difference is one of the possible mechanisms behind branching.

4.2. Future directions

The effect of increased chain length. One consequence of this is that, under the assumptions of our model, the possible values for replication rate constants come closer to each other (Δk decreases). This decreases the concentration per sequence, which, in turn, would result in a shorter shadow of inferior competitors (or, put differently, in a narrower width of the “parabolic quasi-species”). There is a counter-effect, however: longer templates associate more strongly, which by itself would lead to a stronger prevalence of parabolic growth, hence a longer shadow. But, of course, very long templates do not dissociate at all from their copies; hence growth as such ceases. Clearly, this needs an extended analysis.

The speed of adaptation. Imagine the case of directional selection for larger k in a population of replicators. The parabolic quasi-species attains, as we have shown, a certain quasi-stationary width. Under selection for larger k there is an irreversible effect: the whole distribution moves in one direction and, barring large fluctuations, there is no way back. This is a ratchet-like mechanism. How fast does the ratchet click? We do not know. If the process is limited by variation, i.e. the supply of mutants, then the answer is an extension of the results of Dieckmann and Law (1996). But if mutations are frequent enough (as it is likely for rudimentary replication mechanisms; cf. Eigen, 1971), the speed is determined by mutation, selection and the dynamics of growth; including, importantly, stochastic effects. How is one to incorporate chance, affecting single and double strands? Investigations in this direction are underway.

Selection for an optimum strategy. What is strategy, in realistic chemical terms, going beyond

the rate of ligation (k) itself? Note that, for example, ionic strength affects template polymerisation processes. Under given environmental conditions adaptation to this environment will be caused by directional, then stabilizing, and then (depending on the nature of cross-pairing between different sequences) disruptive selection.

Genotype–phenotype mapping. We have used a simplistic approach to this mapping problem: similar sequences have similar phenotypes. Moreover, persistence of the duplexes is determined by the very same continuous phenotypic parameter as the replication rate. What if more than one sequence can show the same phenotype? Or, when pair persistence is unrelated to the replication rate? Furthermore, one may wonder about the possibility of a rugged fitness landscape, such as can be caused by RNA structures (Fontana and Schuster, 1998). Yet this is unlikely to apply for the majority of parabolic replicators: they are short, quasi-linear oligomers. Longer molecules tend to have more interesting phenotypes, but they do not seem to be capable of replication in solution, because of the too strong binding of template and copy. They need a different replication mechanism, not considered in this paper.

Towards exponential dynamics. Wang and Sutherland (1997) presented evidence for replication process with $p = 0.8$. Clearly, departure from $p = 1/2$, as valid for most non-enzymatic replicators, is one of the most exciting research directions on the road to exponential growth ($p = 1$), implying survival of the fittest. The adaptive dynamics of replication rate exponents is virgin territory, waiting for exploration. One wonders about the possible trade-offs among parameters of association–dissociation, ligation, etc. How are the trade-offs allocated in sequence space? Experiments, accompanied by theory, should be carried out.

Acknowledgements

We thank Günter Von Kiedrowski, István Scheuring and Éva Kisdi for valuable discussions and an anonymous referee for correcting a mistake. This work was financed from the grants OTKA T033097, FKFP 0187/1999 and NWO-OTKA N 34028.

References

- CZÁRÁN, T. and SZATHMÁRY, E. (2000): Coexistence of replicators in prebiotic evolution. In DIECKMANN, U., LAW, R. and METZ, J. A. J. (eds): *The Geometry of Ecological Interactions: Simplifying Spatial Complexity*. IIASA and Cambridge University Press, pp. 116–134.
- DARWIN, CH. (1859): *On the Origin of Species by Means of Natural Selection, or The Preservation of Favoured Races in the Struggle for Life*. First Edition. Harvard University Press.
- DIECKMANN U. and LAW, R. (1996): The dynamical theory of coevolution: a derivation from stochastic ecological processes. *J. Math. Biol.* **34**:579–612.
- DOEBELI, M. and DIECKMANN, U. (2000): Evolutionary branching and sympatric speciation caused by different types of ecological interactions. *Am. Nat.* **156**:S77.
- EIGEN, M. (1971): Molecular selforganization and the early stages of evolution. *Quart. Rev. Biophys.* **4**:149–212.
- EIGEN, M. and SCHUSTER, P. (1977): The hypercycle: A principle of natural self-organization. Part A: emergence of the hypercycle. *Naturwiss.* **64**:541–565.
- FONTANA, W. and SCHUSTER, P. (1998): Shaping space: The possible and the attainable in RNA genotype-phenotype mapping. *J. Theor. Biol.* **194**:491–515.
- GERITZ, S. A. H., GYLLENBERG, M., JACOBS, F. J. A. and PARVINEN, K. (in press): Invasion dynamics and attractor inheritance. *J. Math. Biol.*
- GERITZ S. A. H., METZ, J. A. J., KISDI, É. and MESZÉNA, G. (1997): Dynamics of adaptation and evolutionary branching. *Phys. Rev. Letters* **78**:2024–2027.
- GERITZ S. A. H., KISDI, É., MESZÉNA and METZ, J. A. J. (1998): Evolutionarily singular strategies and the adaptive growth and branching of the evolutionary tree. *Evol. Ecol.* **12**:35–57.
- GERITZ, S. A. H., VAN DER MEIJDEN, E. and METZ, J. A. J. (1999): Evolutionary dynamics of seed size and seedling competitive ability. *Theor. Popul. Biol.* **55**:324–343.
- JACOBS, F. J. A., METZ, J. A. J., GERITZ, S. A. H. and MESZÉNA, G. (in prep.): Invasion implies fixation.
- KISDI, É. (1999): Evolutionary branching under asymmetric competition. *J. Theor. Biol.* **197**:149–162.
- KISDI, É. and GERITZ, S. A. H. (1999): Adaptive dynamics in allele space: evolution of genetic polymorphism by small mutations in a heterogeneous environment. *Evolution* **53**:993–1008.
- LEVIN, S. M. (1970): Community equilibria and stability, and an extension of the competitive exclusion principle. *Amer. Nat.* **104**:413–423.
- LIFSON, S. and LIFSON, H. (1999): Models of prebiotic replication: Survival of the fittest versus extinction of the unfit. *J. Theor. Biol.* **199**:425–433.
- MACARTHUR, R. and LEVINS, R. (1964): Competition, habitat selection and character displacement in a patchy environment. *Proc. Natl. Acad. Sci. USA* **51**:1207–1210.
- MACARTHUR, R. and LEVINS, R. (1967): The limiting similarity, convergence, and divergence of coexisting species. *Amer. Nat.* **101**(921):377–385.

- MATHIAS, A., KISDI, É. and OLIVIERI, I. (2001): Divergent evolution of dispersal in a heterogeneous landscape. *Evolution*, **55**:246–259.
- MATHIAS, A. and KISDI, É. (in press): Evolutionary branching and coexistence of germination strategies. In DIECKMANN, U. and METZ, J. A. J. (eds): *Elements of Adaptive Dynamics*. Cambridge University Press.
- MESZÉNA G., CZIBULA, I. and GERITZ, S. A. H. (1997): Adaptive dynamics in a 2-patch environment: A toy model for allopatric and parapatric speciation. *J. Biol. Syst.* **5**:265–284.
- MESZÉNA, G. and METZ, J. A. J. (in press): The role of effective environmental dimensionality. In: METZ, J. A. J. and DIECKMANN, U. (eds): *Elements of Adaptive Dynamics*. Cambridge University Press.
- METZ, J. A. J., NISBET, R. M. and GERITZ, S. A. H. (1992): How should we define ‘fitness’ for general ecological scenarios? *Trends Ecol. Evol.* **7**:198–202.
- METZ, J. A. J., GERITZ, S. A. H., MESZÉNA, G., JACOBS, F. J. A. and VAN HEERWAARDEN, J. S. (1996): Adaptive dynamics, a geometrical study of the consequences of nearly faithful reproduction. In STRIEN, S. J. VAN and VERDUYN LUNEL, S. M. (eds): *Stochastic and Spatial Structures of Dynamical Systems*. North Holland, Amsterdam, pp. 183–231.
- MYLIUS, S. D. and DIEKMANN, O. (1995): On evolutionarily stable life histories, optimization and the need to be specific about density dependence. *Oikos* **74**:218–224.
- PÁSZTOR, E., MESZÉNA, G. and KISDI, É. (1996): R_0 or r : a matter of taste? *J. Evol. Biol.* **9**:511–518.
- ROUGHGARDEN, J. A. (1979): *Theory of Population Genetics and Evolutionary Ecology: An introduction*. Macmillan, New York.
- SASAKI, A. and ELLNER, S. (1995): The evolutionary stable phenotype distribution in a random environment. *Evolution* **49**(2):337–350.
- SCHEURING, I. and SZATHMÁRY, E. (2001): Survival of replicators with parabolic growth tendency and exponential decay. *J. Theor. Biol.* **212**:99–105.
- SZATHMÁRY, E. (1991): Simple growth laws and selection consequences. *Trends Ecol. Evol.* **6**:366–370.
- SZATHMÁRY, E. and GLADKIH, I. (1989): Sub-exponential growth and coexistence of non-enzymatically replicating templates. *J. Theor. Biol.* **138**:55–58.
- VARGA, Z. and SZATHMÁRY, E. (1997): An extremum principle for parabolic competition. *Bull. Math. Biol.* **59**:1145–1154.
- VON KIEDROWSKI, G. (1986): A self-replicating hexadeoxy nucleotide. *Angew. Chem. Int. Ed. Engl.* **25**:932–935.
- VON KIEDROWSKI, G. (1993): Minimal replicator theory I: Parabolic versus exponential growth. *Bioorg. Chem. Frontiers* **3**:113–146.
- VON KIEDROWSKI, G. (1999): Molekulare Prinzipien der artifizuellen Selbstreplikation. In GANTEN, D. (ed.): *Gene, Nerone, Qubits & Co. Unsere Welten der Information*. S. Hirzel Verlag, Stuttgart, pp. 123–145.
- VON KIEDROWSKI, G. and SZATHMÁRY, E. (2000): Selection versus coexistence of parabolic replicators spreading on surfaces. *Selection* **1**:173–179.
- WANG, B. and SUTHERLAND, I. O. (1997): Self-replication in a Diels-Alder reaction. *Chem. Commun* **16**:1495–1496.
- WILLS, P. R., KAUFFMAN, S. A., STADLER, B. M. R. and STADLER, P. F. (1998): Selection dynamics in autocatalytic systems: Templates replicating through binary ligation. *Bull. Math. Biol.* **160**:1073–1098.

APPENDIX

Here we develop the more detailed formulas for the width

$$W = k_{\max} - k_{\min} \quad (\text{A1})$$

of the parabolic quasi-species with special interest in the limit $\Delta k \rightarrow 0$. No cross-hybridisation is supposed. The equilibrium condition of the resource dynamics (3) can be written into the form

$$\frac{\rho}{R} = \sum_i k_i A_i = \frac{b}{2a\delta} \sum_i (Rk_i - d)k_i. \quad (\text{A2})$$

Using eq. (38) for the shape of the quasi-species and its consequence, the expression

$$k_{\min} = \frac{d}{R} \quad (\text{A3})$$

for the lower edge of the quasi-species, one obtains the relation

$$\frac{\rho}{d} k_{\min} = \frac{bd}{2a\delta k_{\min}} \sum_i (k_i - k_{\min})k_i. \quad (\text{A4})$$

If the difference Δk between the adjacent k values is small enough, the summation can be approximated by the integral

$$\begin{aligned} \sum_i (k_i - k_{\min})k_i &\approx \frac{1}{\Delta k} \int_{k_{\min}}^{k_{\max}} (k - k_{\min})k dk = \\ &= \frac{1}{\Delta k} \left(\frac{W^3}{3} + k_{\min} \frac{W^2}{2} \right) \end{aligned} \quad (\text{A5})$$

which leads to the relation

$$\frac{W^3}{3} + k_{\min} \frac{W^2}{2} = \frac{2a\delta}{bd^2} \rho k_{\min}^2 \Delta k. \quad (\text{A6})$$

This result establishes a monotonously increasing relation between Δk and W . The width of the parabolic quasi-species diminishes in the limit $\Delta k \rightarrow 0$. For small Δk , that is, for small W , this relation can be written as

$$W = 2\sqrt{\frac{a\delta}{bd^2} \rho k_{\min} \Delta k}. \quad (\text{A7})$$