SPATIAL DYNAMICS AND THE EVOLUTION OF ENZYME PRODUCTION

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Abstract. We re-examine the problem of the evolution of protein synthesis or enzyme production using a stochastic cellular automaton model, where the replicators are fixed in the sites of a two-dimensional square lattice. In contrast with the classical chemical kinetics or mean-field predictions, we show that a small colony of mutant, protein-mediated (enzymatic) replicators has an appreciable probability to take over a resident population of simpler, direct-template replicators. In addition, we argue that the threshold phenomenon corresponding to the onset of invasion can be described quantitatively within the physics framework of nonequilibrium phase transitions. We study also the invasion of a resident population of enzymatic replicators by more efficient replicators of the same kind, and show that although slightly more efficient mutants cannot invade, invasion is a likely event if the productivity advantage of the mutants is large. In this sense, the establishment of a population of enzymatic replicators is not a 'once-forever' evolutionary decision.

Keywords: prebiotic evolution, replicator dynamics, spatial dynamics, cellular automaton, protein synthesis, nonequilibrium phase-transitions

1. Introduction

Common wisdom says that long-term evolution is the result of invasions of mutant traits and that the success of invasion attempts is determined by the fitness of the mutant. Exceptions to this pattern lead inevitably to paradoxes. The purpose of this article is to re-examine one such paradox which has played a major role in the theoretical development of pre-biotic evolution, namely, the evolution of enzyme production or protein synthesis (Eigen, 1971; Michod, 1983; Szathmáry and Maynard Smith, 1997; Alves *et al*., 2001). Underlying this issue is, of course, the current paradigm about the nature of the first functioning bio-molecules, the so-called RNA-world, which asserts that early nucleic acids (or related precursor molecules) replicated directly via some template mechanism and the protein synthesis was subsequently 'invented' by those replicators (Orgel, 1986, 1992; Joyce, 2002). Although nucleic acids are ideally suited for replication, large molecules can replicate accurately only if assisted by specialized protein catalysts (enzymes), whose synthesis, in turn, is impossible without a blueprint provided by the replicating nucleic acids. In the absence of evidences about pre-biotic biochemical

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events, the appeal of the various solutions of this chicken-and-egg riddle (see e.g., Dyson, 1985; Shapiro, 1987; Maynard Smith and Szathmáry, 1995) is necessarily subjective. From the theoretical viewpoint, the nucleic-acids-first assumption is more appealing because the notion of replication can easily be transcribed to mathematical terms and the consequences of the model fully calculated.

Since in the pre-biotic or chemical evolution context natural selection may be viewed as the dynamics of replicators (Szathmáry and Maynard Smith, 1997) most of the studies on this subject have focused on the competition between replicators. Following Michod (1983), in this contribution we consider two types of replicators, namely nonenzymatic or Malthusian replicators which use a direct template mechanism to replicate, and enzymatic or hypercyclic replicators which have developed a protein-mediated mechanism of replication. Much of our knowledge on the dynamics of replicators stems from analyses carried out in the chemical kinetics or mean-field framework, in which the replicators are perfectly mixed, i.e., each replicator can interact with all the others in the system (Eigen, 1971). Of particular importance is the finding that, in a homogeneous population, a mutant replicator of the hypercyclic kind cannot invade a resident population of more primitive Malthusian replicators. A possible solution to this problem of evolution of protein synthesis is provided by the structured deme formulation of group selection (Wilson, 1980), where it is assumed that the replicators are localized in natural compartments, such as rock crevices, clay particles, or water droplets, so that the benefits of enzymatic replication are enhanced in favor of the mutant replicators (Michod, 1983). In that formulation the notion of group or deme is somewhat blurred as there is a stage in the life cycle of the replicators when they leave their demes to effectively interact with each other. Although it is not hard to envision such a scenario in the context of viral selection dynamics (Szathmáry, 1992, 1993), where the burst of the infected cells releases free viruses in the blood stream which then compete to infect new cells, it requires some stretch of imagination to apply Wilson's formulation to pre-biotic evolution. In particular, one needs to assume that the replicators are regularly released from their compartments and then confined again through, say, the action of tides or winds.

Another hindrance to understanding evolution of protein synthesis in the mean-field framework is the finding that the fixation of a population of hypercyclic replicators is a 'once-forever' decision, in the sense that it cannot be invaded by a mutant replicator of similar type, no matter what the superiority of the mutant is (Eigen and Schuster, 1978). Such a situation corresponds to an evolutionary cul-de-sac, making it impossible to explain, for example, the evolution of the sophisticated mechanism of replication of DNA from simpler ancestral enzymatic replicators. However, in this case we are not aware of any solution proposed in the literature.

In this contribution we show that in the extremely incomplete mixing regime, where the replicators are fixed in their positions in a lattice so that only nearest-neighbor interactions are allowed, many of the results derived in the mean-field limit lose their validity. In particular, by evaluating numerically the probability Π

that a small colony of mutant replicators takes over a population of replicators of a different kind, we find that the evolution of enzyme production occurs quite naturally, in the sense that the above-mentioned difficulties are absent in such a spatial framework.

This paper is organized as follows. In Section 2 we define the replication mechanisms of both Malthusian and hypercyclic replicators and present a brief analysis of the mean-field limit in order to illustrate the impossibility of invasion of any resident population by a colony of hypercyclic mutants. Following the cellular automaton implementation proposed by Boerlijst and Hogeweg (1991), we also present the set of rules that govern the dynamics of the replicators in a two-dimensional square lattice in the position-fixed or contact process limit. In Section 3 we describe the physics framework to study nonequilibrium phase transitions (Grassberger and De La Torre, 1979) and apply that formalism to a somewhat more fundamental problem, namely the stability of small colonies of spontaneously generated self-replicating molecules against the vaccum. In section 4 we present the results concerning the invasion of a resident population of either Malthusian or hypercyclic replicators by mutant hypercyclic replicators. Finally, in Section 5 we discuss the limitations of our model and present some concluding remarks.

2. The Model

The replication mechanism that defines a Malthusian replicator corresponds to the simplest reproduction process, namely the binary fission of a parent replicator, and is modeled by the chemical reaction

$$A + E \quad \xrightarrow{s} \quad 2A\,, \tag{1}$$

where A is the Malthusian replicator and E is the source material (mononucleotide resources). It is well-known that the concentration of A grows exponentially with the rate constant s, provided that the concentration of E is kept constant, hence the name Malthusian replicator. This explosive growth can be avoided by imposing a constraint on the total concentration of replicators which in practice can be implemented by a dilution flux (Eigen, 1971). Alternatively, one can allow the replicators to be degraded by hydrolysis into its mononucleotide components E according to the reaction

$$A \quad \xrightarrow{\gamma} \quad E\,, \tag{2}$$

which seems a more natural approach to limit the growth of a population of replicators.

The definition of enzymatic replication is more involved. First we assume that, given the appropriate resources E' (e.g., amino-acids), the hypercyclic replicators B produce a protein P via the reaction

$$B + E' \quad \longrightarrow \quad P \ , \tag{3}$$

which, in turn, catalyses the replication of B,

$$B + P + E \quad \longrightarrow 2B + P \ . \tag{4}$$

In addition, we assume that the reactions involving the production of P and its decay into the resources E' are much faster than Reaction (4), so that the concentration of P is always at its equilibrium value, i.e., $[P] \propto [B]$. Hence, for the purpose of mathematical modeling, enzymatic replication can be described by the simpler reaction scheme

$$2B + E \quad \stackrel{c}{\longrightarrow} 3B \ , \tag{5}$$

which leads to a hyperbolic growth of the concentration of the hypercyclic replicator B (Eigen and Schuster, 1978; Szathmáry and Maynard Smith, 1997). We note that this reaction scheme describes an one-membered hypercycle. Here the rate c is a measure of the efficiency of the enzyme production mechanism as well as of the efficiency of the protein-mediated replication. Throughout this paper we will make the (admittedly unrealistic) assumption that the enzyme P is already specific for the replicator that produced it. A more plausible approach would be to consider the primordial enzymes as some kind of general catalysts, which would facilitate the replication of a wide spectrum of replicators (Michod, 1983; Alves *et al.*, 2001). Furthermore, we assume for simplicity that the degradations of A and B are governed by the same decay rate γ and, more importantly, that the mononucleotide components E are the same for both types of replicators. This setting is clearly well suited to study the dynamics of replicators competing for a limited supply of mononucleotide resources. We note that the reaction scheme (5) also describes sexual reproduction, where two replicators are needed to produce a third one.

2.1. THE MEAN-FIELD LIMIT

We re-derive now the classic mean-field results concerning the invasion of a resident population by a colony of mutant replicators (Michod, 1983) using a model suitable for comparison with the Boerlijst-Hogeweg cellular automaton (Boerlijst and Hogeweg, 1991). We consider two types of replicators, residents and invaders, whose concentrations at time t are denoted by $x_1(t)$ and $x_2(t)$, respectively. In addition, the abundance of the mononucleotide source materials required to assemble a new replicator is denoted by $e(t)$. A replicator has a probability γ of decaying

into its components, and the tendency of these components to remain in their unorganized state is modeled by a stiffness parameter k. In a homogeneous medium, replicator dynamics may be described by the nonlinear difference equations

$$\begin{aligned} e(t+1) &= \tfrac{k}{Z} e(t) + \gamma [x_1(t) + x_2(t)] \\ x_i(t+1) &= x_i(t)[\tfrac{s_i + c_i x_i(t)}{Z} e(t) + 1 - \gamma] \,, \end{aligned} \tag{6}$$

for $i = 1, 2$ and where

$$Z = k + \sum_{i=1}^{2} x_i(t)[s_i + c_i x_i(t)] \,, \tag{7}$$

ensures that $e + x_1 + x_2 = 1$ for all time t. Here s_i and c_i are the productivities of the nonenzymatic and enzymatic replication processes, respectively. According to the basic Reactions (1) and (5), Malthusian replicators are characterized by $s_i > 0$ and $c_i = 0$, and hypercyclic replicators by $s_i = 0$ and $c_i > 0$. Next we will show how to derive the condition on the productivity parameters of invaders and residents which must be satisfied in order to guarantee the success of the invasion, without resorting to the full stability analysis of the difference equations. Let us consider the stationary state in the case where only the resident replicators are present in the lattice, so that the steady-state concentrations are obtained by setting $x_1(t+1) = x_1(t) = x_1^*$, $x_2(t) = 0$ and $e(t+1) = e(t) = e^*$ in Equation (6). In particular, we can eliminate e^* in favor of x_1^* using

$$e^* = \frac{\gamma x_1^*}{(1 - k/Z)} \tag{8}$$

where Z is given by Equation (7). To verify whether this steady state is stable against invasion by a small colony of mutant replicators we rewrite the equation for $x_2(t)$ keeping only terms of first order in the concentration of invaders. This yields

$$x_2(t+1) - x_2(t) = \gamma x_2(t) \left(\frac{s_2}{s_1 + c_1 x_1^*} - 1 \right) \,, \tag{9}$$

where we have used Equation (8) to eliminate e^*. Invasion is successful provided that the initially small concentration of invaders increases, i.e., provided that the condition

$$\frac{s_2}{s_1 + c_1 x_1^*} > 1 \,, \tag{10}$$

is satisfied. We recall that x_1^* is the non-zero equilibrium solution of Equations (6) for $x_2 = 0$, i.e., the steady-state concentration of the unperturbed resident population of replicators. It is then clear from Equation (10) that a protein-assisted or

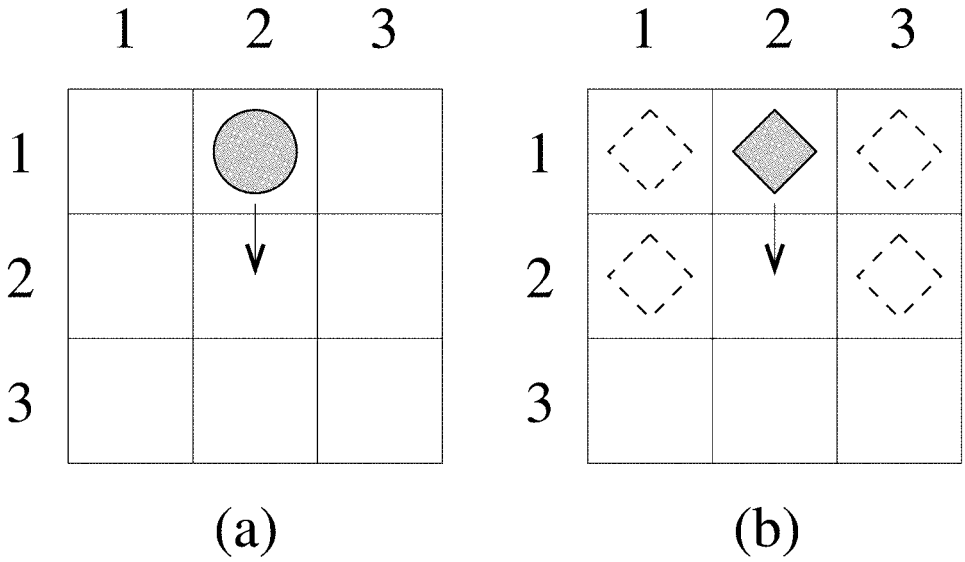

Figure 1. Illustration of the cellular automaton rules for the update of the empty cell at position (2,2) in the case of (a) a Malthusian replicator located at (1,2) and (b) a hypercyclic replicator located at (1,2). In case (b), replication can take place provided that at least one of the cells at positions (1,1), (1,3), (2,1), (2,3) is occupied by other hypercyclic replicator.

hypercyclic invader ($s_2 = 0$) can never take over or even establish a colony in a resident population of replicators, regardless of their type. Moreover, a mutant Malthusian replicator ($c_2 = 0$) can invade a resident population of Malthusian replicators if $s_2 > s_1$. Explicit knowledge of x_1^* is required only in the case of Malthusian replicators invading a resident population of hypercyclic replicators. However, since this situation is not directly related to the onset of protein synthesis, it will not be considered further in the present contribution. Actually, henceforth we will focus on the case of hypercyclic invaders only. We note that in the mean-field framework there is no stable steady-state solution corresponding to the coexistence between invading and resident replicators.

2.2. THE POSITION-FIXED LIMIT

We now turn to the study of the replicator dynamics in an explicitly spatial framework. Following the suggestion that chemical evolution started with surface-bonded autocatalytic chemical networks that take advantage of the enormous thermodynamic and kinetic gains of surface binding reactions (Wächtershäuser, 1988, 1997), we consider a two-dimensional space consisting of $L \times L$ cells in a square toroidal lattice. Each cell is either empty or occupied by a single replicator and it is assumed that an empty cell contains all source materials required to assemble a new replicator. As before, a replicator has a probability γ of decaying; after decay the cell becomes empty and an empty cell has a probability proportional to k to

remain so. The replication mechanism depends on the nature as well as on the local neighborhood of the replicators, according to the following local rules which are applied simultaneously to all cells in the lattice (Boerlijst and Hogeweg, 1991):

(1) a Malthusian replicator in one of the four nearest neighbor cells (Von Neumann neighborhood) of an empty cell can replicate into that cell with probability proportional to the productivity parameter s (see Figure 1a).
(2) a hypercyclic replicator in the von Neumann neighborhood of an empty cell can replicate into that cell if there are other replicators of its kind in the intersection of the Moore neighborhoods of both cells. The probability of this type of replication is proportional to c for each pair of replicators. We recall that the Moore neighborhood of a cell consists of its nearest and next-nearest neighbors, and in the square lattice it corresponds to the eight cells surrounding the central cell in Figure 1.

For example, an empty cell surrounded by two Malthusian resident replicators at positions (1,2) and (2,3) and three invading hypercyclic replicators at positions (2,1), (3,1) and (3,2) can be occupied by the invaders with probability $4c_2/(k + 2s_1 + 4c_2)$. The main advantage of this formulation is that the probability of occupancy of an empty cell is always well-defined, regardless of the (positive) values of the replication parameters. We note, in addition, that the stiffness parameter k gives the scale of the productivity parameters s_i and c_i only, and so henceforth we set $k = 1$ without loss of generality. As a result, the productivity parameters are now dimensionless quantities. Furthermore, we will fix the value of the decay constant at $\gamma = 0.05$ and the lattice size at $L = 200$, as we have verified that changing the values of these parameters does not affect the characterization of the onset of invasion.

Before embarking on the quantitative study of the probability of invasion of a resident population by hypercyclic mutants, we would like to point out the altruistic nature of the hypercyclic replication mechanism (Maynard Smith, 1979). In fact, consider in Figure 1b the behavior of the replicator at (1,1) that gives catalytic support to the hypercyclic replicator at (1,2) to occupy the central cell. In doing so, it substantially decreases its own chance of occupying cell (1,2) when it becomes vacant, because of the presence of a new replicator at position (2,2).

3. Spreading Analysis

The first step of our analysis is the establishment of a resident population of replicators in a stationary state. Since this problem may also be viewed as the invasion of an empty lattice (the vacuum) by a small colony of spontaneously created replicators (Ferreira and Fontanari, 2002), we take advantage of its simplicity to introduce the tools and concepts that we will need in the study of the competition between

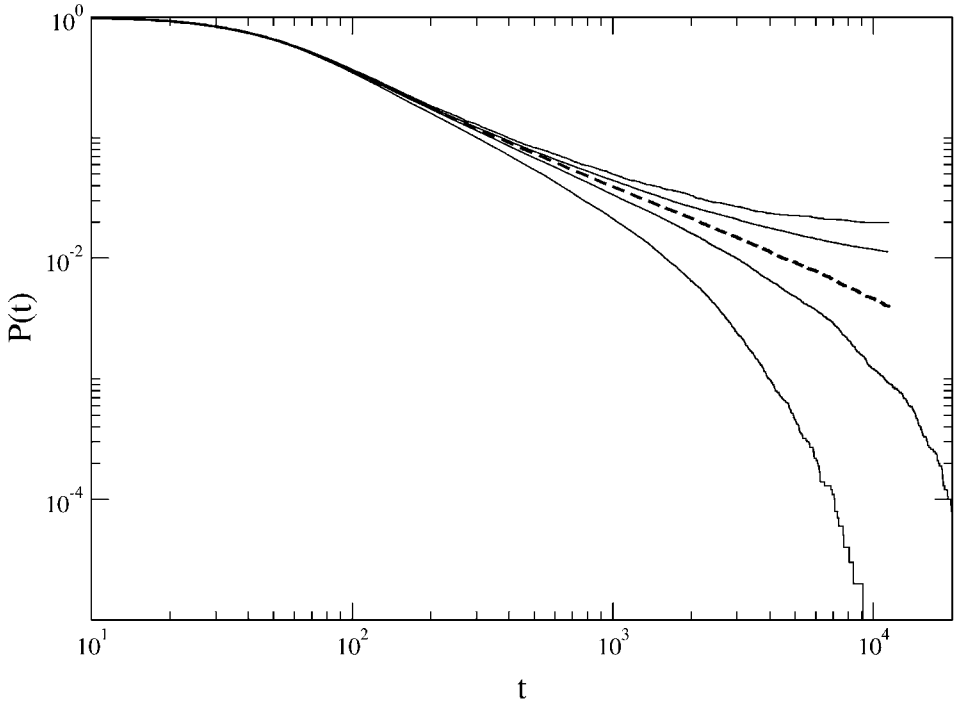

Figure 2. The log-log plot of $P(t)$ as a function of t for (top to bottom) $c_1 = 0.0196$, 0.0195, 0.0193 (dashed line), 0.0192 and 0.0190. The dashed straight line corresponds to our estimate of the critical rate c_1^c for the onset of the invasion.

distinct replicators. Here we consider in detail the case of hypercyclic replicators only.

The initial colony is composed of four replicators located in the von Neumann neighborhood of the central empty cell of an otherwise empty lattice of infinite size. Finite size effects are absent because the lattice size is taken large enough so that during the time we follow the evolution of the colony the replicators can never reach the lattice boundaries. This of course sets an upper limit to the number of generations we can follow the colony and so, in particular, we let the population evolve up to typically $t = 10^4$ for $L = 200$. We concentrate on the time dependence of the survival probability of the colony, $P(t)$. For each time t we carried out 10^5 independent runs, all starting with the same initial colony so that $P(t)$ is estimated as the fraction of runs for which there is at least one replicator in the lattice at time t. In Figure 2 we present a log-log plot of $P(t)$ as function of t in the vicinity of the critical rate c_1^c corresponding to the onset of the invasion. In fact, close to this transition point, i.e., for $\Delta \equiv (c_1 - c_1^c) \approx 0$, we expect that the survival probability obeys the scaling hypothesis

$$P(t) \cong t^{-\delta} \varphi(\Delta^{\nu} t) \,, \tag{11}$$

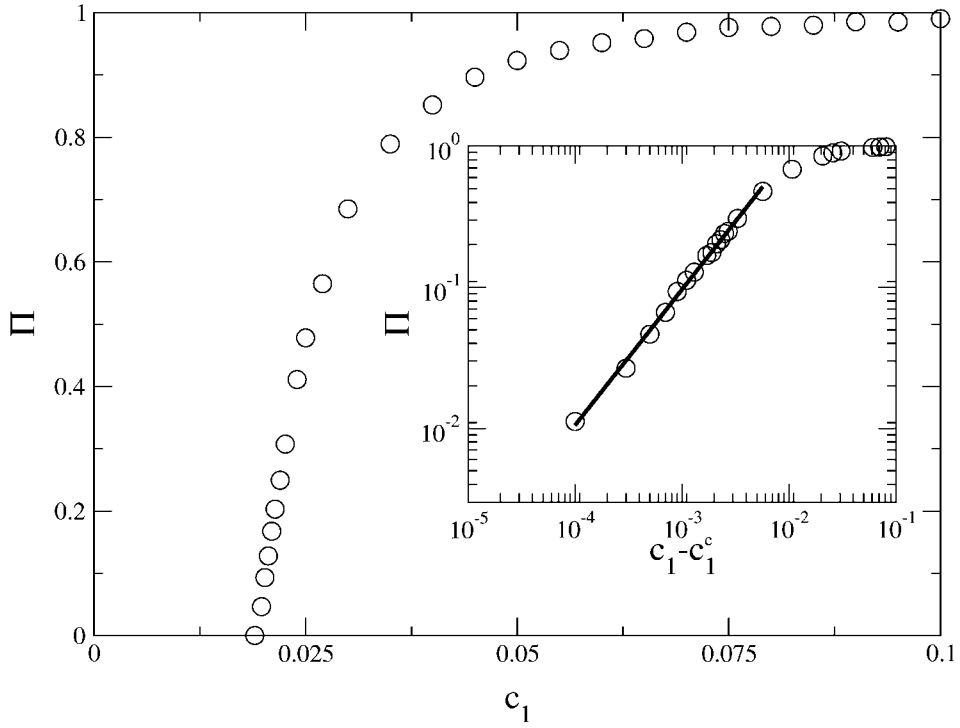

Figure 3. Probability that a small colony of hypercyclic replicators of productivity c_1 establishes a resident population in an empty lattice. The inset shows the fitting (Equation (11)) with $c_1^c = 0.0193$ and $\beta = 0.97$.

where δ and ν are critical exponents, and φ is a universal scaling function (Grassberger and De La Torre, 1979). The asymptotic straight line shown in Figure 2 is the signature of the critical point ($\Delta = 0$), while upward and downward deviations indicate supercritical and subcritical behaviors, respectively. From the data of that figure we find $c_1^c = 0.0193 \pm 0.0001$ and $\delta = 0.92 \pm 0.01$. This technique, known as spreading analysis, yields very precise estimates of the critical values of the parameters at which the onset of the invasion occurs.

As mentioned before, our main interest is in the evaluation of the probability of invasion, defined by

$$\Pi = \lim_{t\to\infty} P(t) \,, \tag{12}$$

so that $\Pi = 0$ in the subcritical ($c_1 < c_1^c$) regime and $\Pi > 0$ in the supercritical ($c_1 > c_1^c$) regime. The existence of these two regimes is illustrated in Figure 3 where the probability of invasion is shown as a function of the rate c_1.

The physicists' compulsion for quantitativeness can be partly satisfied by looking at the behavior of Π close to the critical point c_1^c. Explicitly, we assume that

$$\Pi \cong \Delta^{\beta} \,, \tag{13}$$

so that by using the previous estimate of c_1^c and a simple log-log plot of Π as function of the distance Δ (see the inset of Figure 3) we can easily evaluate the critical exponent β. It yields $\beta = 0.97 \pm 0.03$. There are many (good) reasons for our fondness of critical exponents. The values of these exponents are, in general, insensitive to variations in the details of the model. For instance, changes in the number of replicators forming the initial colony, in the value of the decay constant γ, or in the geometry of the lattice, affect the invasion threshold c_1^c but not the critical exponents. In this sense, models characterized by the same set of critical exponents are said to belong to the same universality class. Understanding what features determine the universality class of a nonequilibrium phase transition (such as the one described in this section) is a major open problem in statistical physics. Surprisingly, the critical exponents δ, ν and β are not all independent, and in the following we will derive the scaling relation between them.

Since the supercritical regime is characterized by a non-vanishing invasion probability $\Pi > 0$, the explicit time dependence in Equation (11) must be balanced by the scaling function φ. We can see this by rewriting that equation as

$$P(t) \cong \Delta^{\nu\delta} \psi(\Delta^{\nu} t) \tag{14}$$

where $\psi(x) = x^{-\delta}\varphi(x)$ with $\lim_{x\to\infty} \psi(x) > 0$. Hence $\Pi \cong \Delta^{\nu\delta}$ and so

$$\beta = \nu\delta \ . \tag{15}$$

Since we have already estimated the exponent δ, we now consider the evaluation of ν. In the subcritical regime the time correlations are short-ranged so that one expects $P(t)$ to decay exponentially, i.e.,

$$P(t) \cong \Delta^{\nu\delta} \exp\left(-|\Delta|^{\nu} t\right) \ , \tag{16}$$

which corresponds to the scaling function $\varphi(x) = x^{\delta} \exp(-|x|)$ in the limit of x large. Figure 4 not only illustrates the adequacy of this assumption but also permits the evaluation of the decay constant

$$\lambda = |\Delta|^{\nu} \ , \tag{17}$$

from the asymptotic slopes of the curves ln P vs t. The results presented in the inset of Figure 4, showing the dependence of λ on the distance $\left|c_1 - c_1^c\right|$ from the critical point, allow the calculation of the exponent ν as the slope of the straight line, yielding $\nu = 1.07 \pm 0.01$. Once this exponent is known we can use the scaling relation (Equation (15)) to obtain an independent estimate of β. We find $\beta = 0.98 \pm 0.02$, verifying then the quality of our numerical estimates.

Next we address the problem of establishing a resident population of Malthusian replicators. In this case the initial colony consists of a single replicator located at the center of an empty lattice. Applying the procedure described above we found

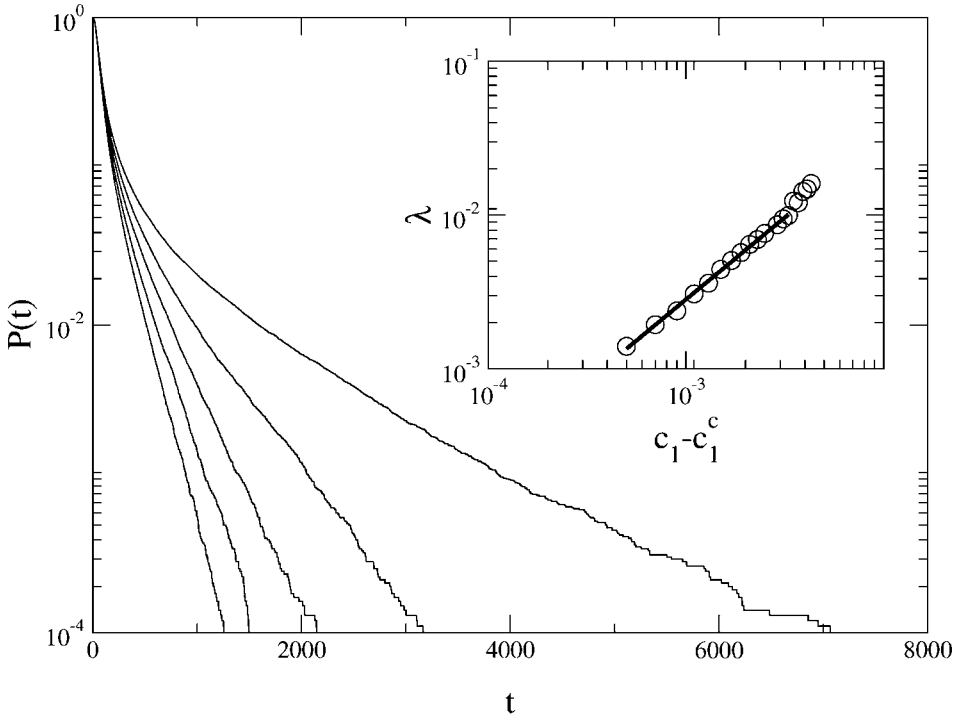

Figure 4. The log-linear plot of $P(t)$ against t for several values of the rate c_1 in the subcritical regime (left to right) c_1 = 0.0174, 0.0176, 0.0182, 0.0186 and 0.0190. The inset shows the log-log plot of the time decay constant λ against $\left|c_1 - c_1^c\right|$. The slope of the straight line yields $\nu = 1.07 \pm 0.01$.

that the threshold for the onset of invasion is $s_1^c = 0.020 \pm 0.001$ and that the transition is characterized by the exponents $\delta = 0.45 \pm 0.01$, $\nu = 1.31 \pm 0.01$ and $\beta = 0.59 \pm 0.02$ (Ferreira and Fontanari, 2002). These results indicate that the phase-transition is in the celebrated universality class of the directed percolation, which comprises as diverse problems as the Reggeon field theory of particle physics (Grassberger and De La Torre, 1979), the forest-fire propagation biased by external wind (Grassberger, 1989) and the stochastic versions of the 'Game of Life' (Monetti and Albano, 1997), to mention only a few.

We must note that since the vacuum is an absorbing state, i.e., a configuration from which the system cannot escape, the principle of detailed balance is broken and so the stationary state is in fact in nonequilibrium. In this sense, if the population is left to evolve for arbitrarily large times, it will ultimately return to its initial state, the vacuum.

In practice, we say that the population reached the stationary regime when the number of replicators starts to fluctuate around some well-defined mean value.

4. Results

We now proceed with the analysis of the invasion of a resident population by a colony of hypercyclic mutant replicators. Once the resident population reaches stationarity, the invasion process is implemented as follows. An empty cell is chosen randomly and the resident replicators located in its Von Neumann neighborhood are then transformed into hypercyclic replicators of productivity c_2. In this sense the invaders can be viewed as mutant resident replicators. Invasion can fail already at the outset if there are fewer than two replicators surrounding the empty cell. The perturbed system is then left to evolve according to the cellular automaton rules. The entire procedure, which includes the generation of the initial stationary resident population, is repeated 10^6 times and $P(t)$ is estimated as the fraction of runs for which there is at least one mutant replicator in the lattice. We have verified that after a transient regime of about 5×10^5 lattice updates only one type of replicator persists, in agreement with the mean-field prediction. From the nature of the surviving replicators one can tell whether the invasion was successful or not. The probability of invasion Π can then be estimated simply as the fraction of successful invasions.

We first consider a resident population of Malthusian replicators of productivity s_1. The invasion probability Π is shown in Figure 5 for different values of s_1. Clearly, the larger the replication efficiency of the resident replicators, the lower the probability of invasion. However, as illustrated in the inset, when the productivity of the invaders is measured in units of s_1 the dependence on the parameters of the resident population disappears near the transition point. However, an explicit dependence on s_1, as well as on the decay parameter γ, reappears for very large values of this ratio, when the success of the invasion is determined solely by the probability that the initial mutants spread to the neighboring cells before their decay.

The numerical machinery of the last section was set to work on the data of Figure 5 yielding $c_2^c/s_1 = 0.60 \pm 0.01$ for the critical productivities ratio at the onset of invasion. The critical exponents are $\delta = 2.45 \pm 0.01$, $\nu = 0.63 \pm 0.04$, and $\beta = 1.5 \pm 0.1$, thus indicating that this transition belongs to a universality class distinct from the previous ones. We note that the larger the value of β, the slower the increase of the invasion probability as the distance from the critical point increases. In that sense, invading a lattice already inhabited by Malthusian replicators is slightly less likely than invading an empty lattice, as expected. Of course, the remarkable finding here is that, contrary to the celebrated mean-field prediction, protein-mediated replicators do have a considerable probability to take over a resident population of direct template replicators.

The results for the case where the resident population is composed of hypercyclic replicators of productivity c_1 are presented in Figure 6. As before, near the invasion point the dependence on c_1 enters only through the ratio c_2/c_1. Our attempt to fit these data using the framework of Section 3 results in unusually

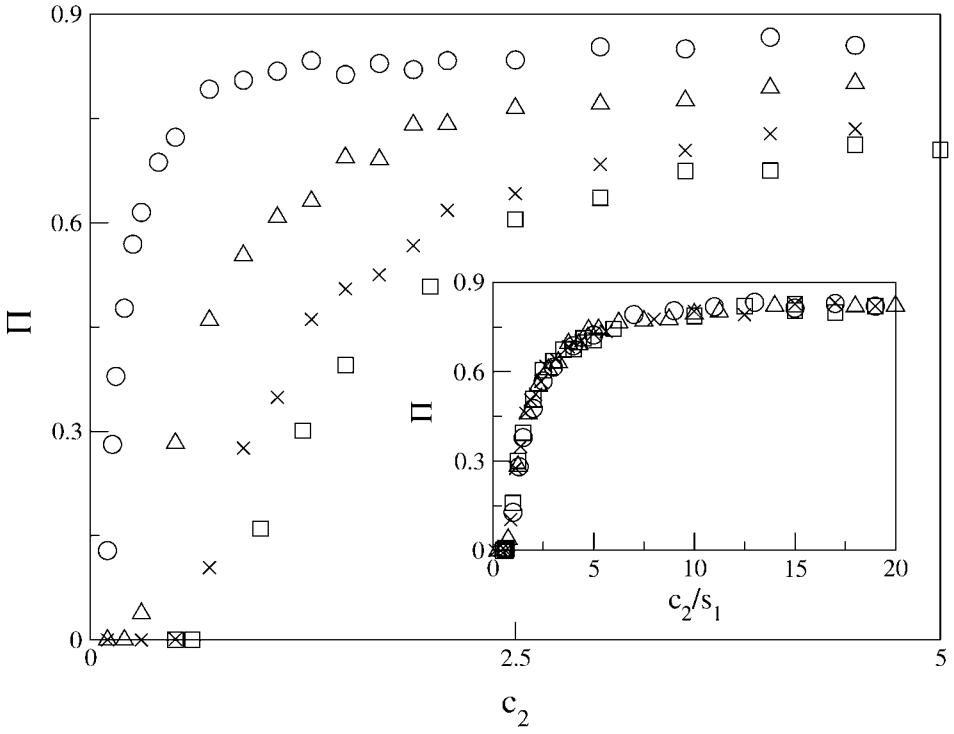

Figure 5. Probability that mutant hypercyclic replicators of productivity c_2 invade a population of Malthusian replicators of productivity $s_1 = 0.1$ (○), 0.4 (△), 0.8 (×), and 1.0 (□). The inset illustrates the collapse of the curves when Π is plotted against the ratio c_2/s_1.

large exponents, e.g., $\beta \approx 10$, and very poor fitting qualities. We recall that the larger the value of the exponent β, the flatter the invasion probability Π at the critical point, $\Delta = 0$. (In order not to unduly multiply notation we will denote the distance to the critical point $c_2 - c_2^c$ by the same symbol Δ). It seems then that the critical behavior here is somewhat pathological, in that it does not fit in the standard physics framework of nonequilibrium phase transitions. In particular, we find that the data in Figure 6 is fitted very well by the flat function

$$\Pi \approx \exp\left[-C\left(\frac{\Delta}{c_1}\right)^{-\alpha}\right], \tag{18}$$

where the fitting parameters are $C = 4.26 \pm 0.05$, $c_2^c/c_1 = 1.00 \pm 0.01$ and $\alpha = 0.66 \pm 0.01$. The flatness of Π in the vicinity of the critical point (i.e., all derivatives of Π with respect to Δ vanish at the critical point) reflects the enormous difficulty of slightly more efficient mutants to take over a population of enzymatic replicators. In other words, if the mutants have only a small advantage over the residents, then the invasion is deemed to failure, in agreement with the mean-field

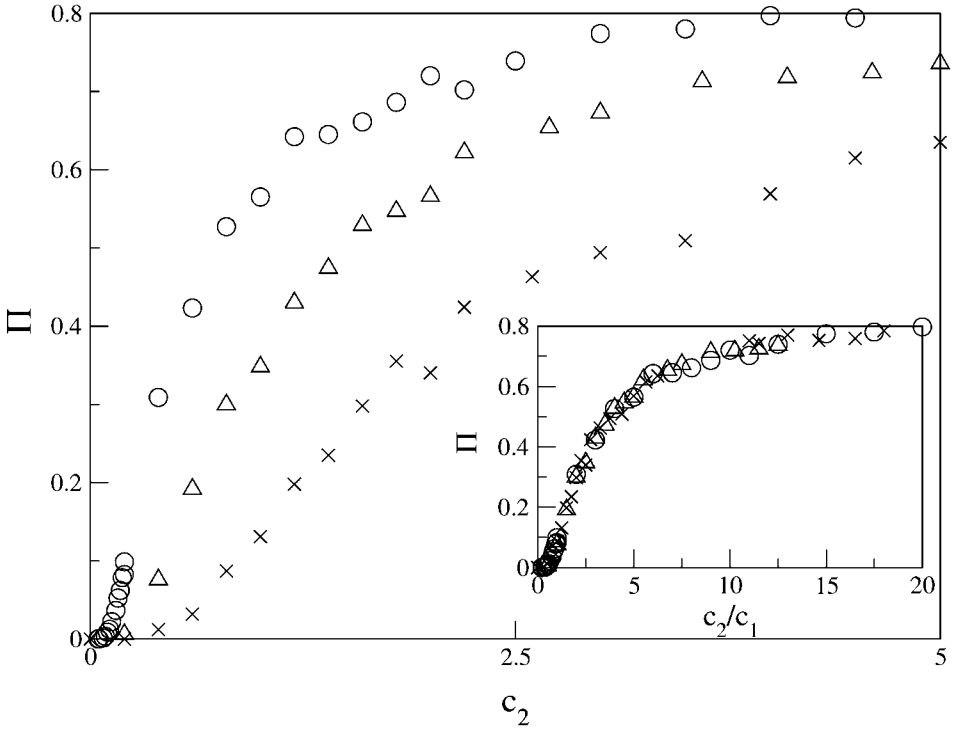

Figure 6. Probability that mutant hypercyclic replicators of productivity c_2 invade a resident population of hypercyclic replicators of productivity $c_1 = 0.2$ (○), 0.4 (△) and 0.8 (×). The inset shows the collapse of the curves when Π is plotted against the ratio c_2/c_1.

predictions. However, if that advantage is large (i.e., c_2 is much greater than c_1) then invasion *does* occur with high probability, showing thus that the establishment of a population of protein-mediated replicators is not a 'once-forever' evolutionary decision, and that such populations can evolve under the guidance of natural selection.

5. Conclusion

Although the model considered in this paper builds heavily on the by now classical elementary hypercycle proposed by Eigen and Schuster (1977, 1978) and its lattice version formulated by Boerlijst and Hogeweg (1991), in this concluding section we point out the limitations of the model and discuss its relevance to the study of the evolution of enzyme production.

We begin by addressing the delicate question of why the reaction Scheme (5) or, equivalently, the presence of the quadratic term cx^2 in the growth Equation (6) can be used to describe the promotion of replication through an enzyme translated from

the replicator. (Clearly, that setting describes the reproduction scheme of obligatory auto-mutualistic replicators, in which a replicator cannot be replicated without the presence of another copy of its own type.) The underlying assumption here is that the concentration of the enzyme is directly proportional to the concentration of the enzyme-producing replicator x, yielding a probability per unit of time proportional to x^2 for the interaction between replicators and proteins, in the case of a *homogeneous* population of reactants (Michod, 1983). Actually, this assumption seems to have a certain tradition in the field of pre-biotic evolution. For instance, in the original formulation of the elementary hypercycle there are two very distinct types of molecules: the information carriers (replicators) B_k and the enzymes P_k (Eigen and Schuster, 1977). The former exhibit two kinds of instruction, one for their own reproduction and the other for the translation into enzyme P_k which, in turn, provides catalytic help for the replication of the subsequent replicator B_{k+1}. However, the standard hypercycle growth equation for the concentration $x_k = [B_k]$ involves only the concentrations of the replicator members, which appear in the quadratic form $x_k x_{k-1}$, from where one concludes that the enzyme concentration $\left[P_{k-1}\right]$ was replaced by the concentration x_{k-1} of the replicator that codes for that enzyme (Eigen and Schuster, 1978). There is, of course, no fundamental difficulty of explicitly taking into account the time evolution of the enzyme concentrations (i.e., to consider Reactions (3) and (4) directly). The reason this is usually not done is that it complicates unnecessarily the analysis without bringing any qualitative feature which is not already present in the simpler reaction scheme involving only the concentrations of the replicators. Specifically, in the case of the one-membered hypercycle both schemes predict a hyperbolic growth for the replicator concentration. For this same reason the cellular automaton version of the hypercycle put forward by Boerlijst and Hogeweg (1991) is based on the set of reactions that involve the replicators only. Although these precedents lend support to our claim that the obligatory auto-mutualism reproduction Scheme (5) exhibits all the essential features of the problem of the evolution of enzyme production, a definitive assessment must necessarily rely on the study of cellular automaton models that explicitly take into account the presence of the enzyme in the lattice cells (Rosas and Fontanari, in prep.).

By virtue of the obligatory auto-mutualism of the hypercyclic replicators their success in the establishment of a colony or in the invasion of a resident population depends critically on the initial pattern of the invaders. In our setup the invasion was initiated by assuming that all resident replicators in the von Neumann neighborhood of a randomly chosen empty cell become hypercyclic mutants. The invasion success depends then on the unlikely event that at least two and at most four neighboring replicators mutate at the same time. This situation is somewhat reminiscent of the Allee effect (Allee, 1931) in population dynamics in which, contrary to predictions based on arguments of competition between individuals for a limited resource, the reproductive output of an individual increases as the population size increases. In general, this effect is caused by the increased cost of

mate finding experienced by biparentally reproducing organisms at low densities. However, we can dispense with the assumption of simultaneous mutation events by admitting, as in Michod (1983), that the hypercyclic replicators also possess some potential for nonenzymatic template-directed replication, though with a productivity much lower than that of the 'pure' Malthusian replicators, so that invasion is still impossible in the mean-field framework. The invasion is then initiated as soon as the (single) hypercyclic mutant generates an offspring, thus turning on the mechanism of enzymatic replication. To make things even we should also assume that the Malthusian replicators can benefit from the enzyme produced by the hypercyclic replicators, thus removing the unrealistic assumption of enzyme specificity. We plan to report on the simulations of this more general model in a forthcoming contribution.

A plausible scenario for the origin of life is one of diffusion-controlled chemical reactions taking place on adsorbing surfaces (probably pyrite) where each reactant can move randomly on the surface (Wächtershäuser, 1988, 1997; Maynard Smith and Szathmáry, 1995). Since the diffusion process of reactants complicates considerably the analysis, in this contribution we have focused on two rather extreme regimes, namely the infinite diffusion or mean-field limit and the position-fixed limit. Assuming, however, that the invasion probability is a continuous function of the chemicals' diffusion rates, the value of Π in such a setting should lie between the fixed position estimate and the mean-field lower bound $\Pi = 0$. Of course, this is a rather conservative statement which may prove wrong if a threshold phenomenon happens to take place as the diffusion rates increase. We cannot discard this possibility as, despite the local nature of diffusion, its main effect is to disperse the couples of hypercyclic replicators apart, thus precluding the formation of the clumps that are so essential to their survival. Nonetheless, since the diffusion rates are determined mainly by the physical properties of the adsorbing surface on which the reactions take place, one can simply assume that the surface binding is strong enough to prevent those rates from reaching the threshold above which the formation of clumps of hypercyclic replicators would be impossible.

For a more complete treatment of the dynamics of replicators, our basic reaction Schemes (1) and (5) should also include the effects of mutation. For instance, replicator A might produce, via erroneous replication, another replicator A' characterized by a different, usually smaller, productivity parameter s. This situation can be modeled using Eigen's equations but, qualitatively, taking into account mutations should simply transform our results for the competition of replicators (viewed as species) into statements about the competition of quasispecies, i.e., the cloud of mutants that accompany the wild-type replicator (Eigen, 1971). In fact, the evolution of the internal structure in the population, in particular, the famous error catastrophe which occurs at a high mutation rate, can easily be accounted for in the cellular automaton framework, provided that one avoids the explosive proliferation of mutant replicators by grouping all of them into a single class, the so-called error tail (see, e.g., Campos *et al*., 2000). In that setting, the productivity

parameters of the wild-type replicators must be multiplied by the probability of perfect replication, yielding thus the effective efficiency of replication. On the other side, if one neglects back-mutations, then replicators in the error tail will always produce, though less efficiently, offspring in that same class. It is not clear to us, however, whether the spatial dynamics will have any effect on the value of the error threshold, beyond which the heritable genetic information is irreversibly lost (Eigen, 1971). In this context, we should mention that the production of enzymes may be viewed as a major transition in the evolution of life because it has made possible for the first time the decoupling of function (phenotype) from the information that codes for the function (genotype). This decoupling opened the possibility for derived products (e.g., enzymes) of the genotype to promote its growth (Michod, 1983) . Such a promotion could well take place through a substantial increase of the replication fidelity of the nucleotide sequence via the action of replicases or more sophisticated proof-reading mechanisms.

In contrast with the group selection approach to the evolution of protein synthesis (Michod, 1983; Szathmáry and Maynard Smith, 1997; Alves *et al*., 2001), the assumptions involved in the makeup of our scenario are rather natural, requiring no far-fetched surmises such as, say, the periodical washing of rock crevices or condensation of water droplets. However, explicitly taking into account the local spatial correlations makes the problem just too difficult to treat analytically and, therefore, less attractive to more quantitatively attuned researchers, who do not content themselves with semi-quantitative results of plain simulations. To satisfy those readers we have discussed at some length the physics framework of nonequilibrium phase transitions and argued that many threshold phenomena in the dynamics of replicators can be quantitatively studied using concepts and tools from statistical mechanics. Conversely, as physicists we were delighted to learn that some of those phenomena simply do not fit into our framework.

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