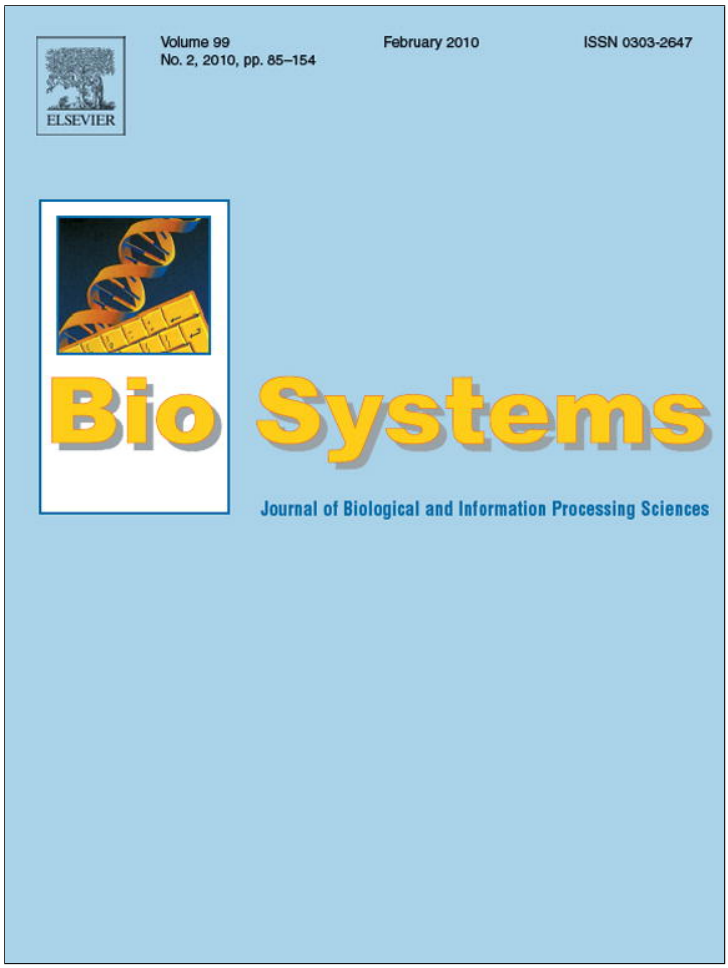

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Selection advantage of metabolic over non-metabolic replicators: A kinetic analysis

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ABSTRACT

A kinetic analysis and simulation of the replication reactions of two competing replicators—one non-metabolic (thermodynamic), the other metabolic, are presented. Our analysis indicates that in a rich resource environment the non-metabolic replicator is likely to be kinetically selected for over the metabolic replicator. However, in the more typical resource-poor environment it will be the metabolic replicator that is the kinetically more stable entity, and the one that will be kinetically selected for. Accordingly, a causal relationship between the emergence of a simple replicator and the emergence of a metabolic system is indicated. The results lend further support for the "replication first" school of thought in the origin of life problem by providing a mechanistic basis for the emergence of a metabolism, once a simple non-metabolic replicating system has itself been established. The study reaffirms our view that the roots of Darwinian theory may be found within standard chemical kinetic theory.

1. Introduction

One of the major questions regarding the origin of life problem concerns the emergence of a metabolic capability. Even so-called simple living systems, such as a bacterial cell, possess a highly complex metabolic system whose role is to provide the bacterial cell with the necessary energy to provide for life's complex, energy demanding processes. Two general schools of thought regarding the emergence of metabolism appear to have established themselves: one, that life began through the emergence of some replicating entity, possibly RNA-like, which then complexified and acquired a metabolic capability, and two, that an autocatalytic metabolic cycle spontaneously emerged, which then evolved by Darwinian selection into simple life forms (Orgel, 2008; Shapiro, 2006). Given the difficulties that have been raised regarding the likelihood of the second possibility, we wish to explore the feasibility of the first option, namely, that life on earth was initiated by the emergence of some relatively simple replicating entity, which subsequently complexified and acquired a metabolic capability. But how and why would some replicating entity have incorporated a metabolic capability? The question here is not so much the historic one—i.e., what was the actual historic pathway taken by a simple prebiotic replicator on the long road from inanimate to animate, but a more fundamental one, namely, what physicochemical principles could explain the transformation of a simple replicating entity into a more complex metabolic one, one able to exploit an external energy source in order to facilitate and further its replicative agenda.

It would seem that the role of metabolism in governing life's processes is central to understanding the nature of living systems. In recent papers, one of us has argued that life's teleonomic character – the undeniable empirical observation that living systems act on their own behalf – may be understood in terms of their metabolic character (Pross, 2008). Specifically, it was argued that the incorporation of a metabolic capability into some non-metabolic replicator would have transformed that replicator from being non-teleonomic into becoming teleonomic, or expressed in physicochemical terms, from being a thermodynamically driven replicator into a kinetically driven one. If that is indeed the case, then the view that the incorporation of a metabolic capability into a simple replicator would have been a crucial step linking inanimate to animate, becomes further strengthened (Maynard-Smith and Szathmary, 1995). But how did the transformation of a non-metabolic (thermodynamic) replicator into a metabolic (kinetic) replicator come about? While the actual historic pathway that was taken on the long road to life may never be known, we can consider the kinetic and thermodynamic implications of such a transformation in order to explore whether such a transformation was feasible and likely to take place.

Accordingly, in this paper we present a kinetic analysis of the competition between two competing replicators, one metabolic, one non-metabolic, in order to assess the likely evolutionary outcome when a mixed population of the two replicator kinds is

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obtained, through, for example, the chance mutation of a non-metabolic replicator into a metabolic one.

2. Materials and Methods

We consider a population composed of two kinds of replicators, denoted R_1 and R_2. Both replicators require a resource, $\tilde{N}$, in order to replicate. $\tilde{N}$ may be regarded as a bundle of "energized" nucleotides or amino acids that provide the replicators both with the raw materials and stored energy necessary to drive the replication process.

The replicators R_1 and R_2 are almost identical except in one respect: while R_1 is only capable of replicating in the presence of the energized resource $\tilde{N}$, R_2 is capable of "energizing" the unenergized equivalent of $\tilde{N}$, which we denote by N. In this sense, it may be argued that R_2 has a primitive energy-gathering, or metabolic, capability, while R_1 does not.

In the simplest scenario, we assume that the replicators are immersed in an environment that is maintained at fixed concentrations of $\tilde{N}$ and N, which are denoted by $c_{\tilde{N}}$ and c_N, respectively. The replication of R_1 and R_2 is assumed to occur via the following reaction steps:

$$\begin{aligned}
&(a) R_1 + \tilde{N} \rightarrow R_1\tilde{N} \text{ (second-order rate constant } \tilde{k}_{11})\\
&(b) R_1\tilde{N} \rightarrow R_1 + \tilde{N} \text{ (first-order rate constant } \tilde{k}_{12})\\
&(c) R_1 + N \rightarrow R_1N \text{ (second-order rate constant } k_{11})\\
&(d) R_1N \rightarrow R_1 + N \text{ (first-order rate constant } k_{12})\\
&(e) R_1\tilde{N} \rightarrow R_1 + R_1 \text{ (first-order rate constant } k'_1)\\
&(f) R_2 + \tilde{N} \rightarrow R_2\tilde{N} \text{ (second-order rate constant } \tilde{k}_{21})\\
&(g) R_2\tilde{N} \rightarrow R_2 + \tilde{N} \text{ (first-order rate constant } \tilde{k}_{22})\\
&(h) R_2 + N \rightarrow R_2N \text{ (second-order rate constant } k_{21})\\
&(i) R_2N \rightarrow R_2 + N \text{ (first-order rate constant } k_{22})\\
&(j) R_2N \rightarrow R_2\tilde{N} \text{ (first-order rate constant } \tilde{k})\\
&(k) R_2\tilde{N} \rightarrow R_2 + R_2 \text{ (first-order rate constant } k'_2)
\end{aligned} \tag{1}$$

Defining $n_{R_1}, n_{R_2}, n_{R_1\tilde{N}}, n_{R_1N}, n_{R_2\tilde{N}}, n_{R_2N}$ respectively, then the chemical reaction dynamics of the replicators is governed by the following system of differential equations:

$$\begin{aligned}
&(a)\frac{dn_{R_1}}{dt} = -\tilde{k}_{11}c_{\tilde{N}}n_{R_1} - k_{11}c_Nn_{R_1} + \tilde{k}_{12}n_{R_1\tilde{N}} + k_{12}n_{R_1N} + 2k'_1n_{R_1\tilde{N}}\\
&(b)\frac{dn_{R_1\tilde{N}}}{dt} = \tilde{k}_{11}c_{\tilde{N}}n_{R_1} - \tilde{k}_{12}n_{R_1\tilde{N}} - k'_1n_{R_1\tilde{N}}\\
&(c)\frac{dn_{R_1N}}{dt} = k_{11}c_Nn_{R_1} - k_{12}n_{R_1N}\\
&(d)\frac{dn_{R_2}}{dt} = -\tilde{k}_{21}c_{\tilde{N}}n_{R_2} - k_{21}c_Nn_{R_2} + \tilde{k}_{22}n_{R_2\tilde{N}} + k_{22}n_{R_2N} + 2k'_2n_{R_2\tilde{N}}\\
&(e)\frac{dn_{R_2\tilde{N}}}{dt} = \tilde{k}_{21}c_{\tilde{N}}n_{R_2} - \tilde{k}_{22}n_{R_2\tilde{N}} + \tilde{k}n_{R_2N} - k'_2n_{R_2\tilde{N}}\\
&(f)\frac{dn_{R_2N}}{dt} = k_{21}c_Nn_{R_2} - k_{22}n_{R_2N} - \tilde{k}n_{R_2N}
\end{aligned} \tag{2}$$

We will present the results of numerical simulations of the above system of equations in the following section. However, in certain parameter regimes, we can make a number of simplifying assumptions that will allow us to obtain an analytical solution to the dynamics.

To begin, we may assume that the rate constants $\tilde{k}_{11}, k_{11}, \tilde{k}_{12}, k_{12}$ are sufficiently large that the resource binding and dissociation reactions for R_1 are at equilibrium. We also assume that $\tilde{k}$ is so large that the amount of R_2N in the system is negligible.

We define the equilibrium constants $\tilde{K}_1 = \tilde{k}_{11}/\tilde{k}_{12}$ and $K_1 = k_{11}/k_{12}$, so that

$$\begin{aligned}
&(a) n_{R_1\tilde{N}} = \tilde{K}_1c_{\tilde{N}}n_{R_1}\\
&(b) n_{R_1N} = K_1c_Nn_{R_1}
\end{aligned} \tag{3}$$

We can then define $n_{R_1,tot} = n_{R_1} + n_{R_1\tilde{N}} + n_{R_1N}$ to be the total amount of R_1 in the system. We then have

$$n_{R_1} = \frac{n_{R_1,tot}}{1 + \tilde{K}_1c_{\tilde{N}} + K_1c_N} \tag{4}$$

so that

$$\frac{dn_{R_1,tot}}{dt} = k'_1\frac{\tilde{K}_1c_{\tilde{N}}}{1 + \tilde{K}_1c_{\tilde{N}} + K_1c_N}n_{R_1,tot} \tag{5}$$

For R_2, we may assume a quasi-steady-state for $R_2\tilde{N}$, so that

$$\begin{aligned}
&0 = \tilde{k}_{21}c_{\tilde{N}}n_{R_2} - \tilde{k}_{22}n_{R_2\tilde{N}} + k_{21}c_Nn_{R_2} - k'_2n_{R_2\tilde{N}}\\
&\Rightarrow n_{R_2\tilde{N}} = \frac{\tilde{k}_{21}c_{\tilde{N}} + k_{21}c_N}{\tilde{k}_{22} + k'_2}n_{R_2}
\end{aligned} \tag{6}$$

Now, to simplify this further, we will assume that all of the second-order resource binding constants are equal, and that all of the resource dissociation constants are equal. This implies that $K \equiv K_1 = \tilde{K}_1$. If we also assume that k'_2 is small compared to the binding and dissociation rate constants, then we obtain:

$$n_{R_2\tilde{N}} = K(c_{\tilde{N}} + c_N)n_{R_2} \tag{7}$$

Defining $n_{R_2,tot} = n_{R_2} + n_{R_2\tilde{N}}$ to be the total amount of R_2 in the system, we have

$$\frac{dn_{R_2,tot}}{dt} = k'_2\frac{K(c_{\tilde{N}} + c_N)}{1 + K(c_{\tilde{N}} + c_N)}n_{R_2,tot} \tag{8}$$

Our final system of equations is then

$$\begin{aligned}
\frac{dn_{R_1,tot}}{dt} &= k'_1\frac{Kc_{\tilde{N}}}{1 + K(c_{\tilde{N}} + c_N)}n_{R_1,tot}\\
\frac{dn_{R_2,tot}}{dt} &= k'_2\frac{K(c_{\tilde{N}} + c_N)}{1 + K(c_{\tilde{N}} + c_N)}n_{R_2,tot}
\end{aligned} \tag{9}$$

We now make one more simplifying assumption, namely that $c_{\tilde{N}}, c_N$ may be taken to be small. In this case, we are in the resource-limited growth regime, and we obtain:

$$\begin{aligned}
\frac{dn_{R_1,tot}}{dt} &= k'_1Kc_{tot}x_{\tilde{N}}n_{R_1,tot}\\
\frac{dn_{R_2,tot}}{dt} &= k'_2Kc_{tot}n_{R_2,tot}
\end{aligned} \tag{10}$$

where $x_{\tilde{N}}$ denotes the fraction of resource that is of type $\tilde{N}$, while c_{tot} is the total concentration of both energized and unenergized resource.

From this system of equations, we see that the metabolizers will drive the non-metabolizers to extinction whenever $k'_2 > k'_1x_{\tilde{N}}$, or equivalently, when $x_{\tilde{N}} < k'_2/k'_1$. In general, we will assume that $k'_2 < k'_1$, since the metabolizer can both energize the resource N as well as replicate. Since this replicator can multi-task, we assume it is less efficient than the non-metabolizing replicator at any given corresponding task.

Therefore, once the fraction of energized resource drops below a certain value, the metabolizers will take over the population. It is useful to note that this phenomenon is related to the error catastrophe of quasispecies theory (Tannenbaum and Shakhnovich, 2005).

The above scenario, although the simplest one for illustrating the selection for one type of replicator over another in a given environment, is difficult to realize experimentally. A more implementable scenario is one where the replicators are placed in a chemostat and fed by a continual supply of energized and non-energized resource, held at a fixed ratio. The chemostat is held at a fixed volume V, with a volumetric flow rate into and out of the chemostat given by F. The feed into the chemostat only contains energized and unenergized resource at concentrations $c_{\tilde{N},0}$ and $c_{N,0}$ respectively, while the feed out of the chemostat contains a mixture of all the species. Here, the populations cannot grow indefinitely, but rather reach a maximal size that is sustainable by the flow of resource into the chemostat. Nevertheless, selection does occur in a chemostat, which, in the absence of mutation, usually leads to the presence of only one type of replicator at steady-state.

Taking into account flows into and out of the chemostat, we obtain that the replicator dynamics inside the chemostat is characterized by the following system of ordinary differential equations:

$$\begin{aligned}
&(a)\frac{dn_{R_1}}{dt} = -\tilde{k}_{11}c_{\tilde{N}}n_{R_1} - k_{11}c_Nn_{R_1} + \tilde{k}_{12}n_{R_1\tilde{N}} + k_{12}n_{R_1N} + 2k'_1n_{R_1\tilde{N}} - \left(\frac{F}{V}\right)n_{R_1}\\
&(b)\frac{dn_{R_1\tilde{N}}}{dt} = \tilde{k}_{11}c_{\tilde{N}}n_{R_1} - \tilde{k}_{12}n_{R_1\tilde{N}} - k'_1n_{R_1\tilde{N}} - \left(\frac{F}{V}\right)n_{R_1\tilde{N}}\\
&(c)\frac{dn_{R_1N}}{dt} = k_{11}c_Nn_{R_1} - k_{12}n_{R_1N} - \left(\frac{F}{V}\right)n_{R_1N}\\
&(d)\frac{dn_{R_2}}{dt} = -\tilde{k}_{21}c_{\tilde{N}}n_{R_2} - k_{21}c_Nn_{R_2} + \tilde{k}_{22}n_{R_2\tilde{N}} + k_{22}n_{R_2N} + 2k'_2n_{R_2\tilde{N}} - \left(\frac{F}{V}\right)n_{R_2}\\
&(e)\frac{dn_{R_2\tilde{N}}}{dt} = \tilde{k}_{21}c_{\tilde{N}}n_{R_2} - \tilde{k}_{22}n_{R_2\tilde{N}} + \tilde{k}n_{R_2N} - k'_2n_{R_2\tilde{N}} - \left(\frac{F}{V}\right)n_{R_2\tilde{N}}\\
&(f)\frac{dn_{R_2N}}{dt} = k_{21}c_Nn_{R_2} - k_{22}n_{R_2N} - \tilde{k}n_{R_2N} - \left(\frac{F}{V}\right)n_{R_2N}\\
&(g)\frac{dc_N}{dt} = \left(\frac{F}{V}\right)(c_{N,0} - c_N) - \left(\frac{k_{11}}{V}\right)n_{R_1}c_N + \left(\frac{k_{12}}{V}\right)n_{R_1N} - \left(\frac{k_{21}}{V}\right)n_{R_2}c_N + \left(\frac{k_{22}}{V}\right)n_{R_2N}\\
&(h)\frac{dc_{\tilde{N}}}{dt} = \left(\frac{F}{V}\right)(c_{\tilde{N},0} - c_{\tilde{N}}) - \left(\frac{\tilde{k}_{11}}{V}\right)n_{R_1}c_{\tilde{N}} + \left(\frac{\tilde{k}_{12}}{V}\right)n_{R_1\tilde{N}} - \left(\frac{\tilde{k}_{21}}{V}\right)n_{R_2}c_{\tilde{N}} + \left(\frac{\tilde{k}_{22}}{V}\right)n_{R_2\tilde{N}}
\end{aligned} \tag{11}$$

3. Results and Discussion

We may simulate the full system of equations (Eqs. (2) and (11)) numerically to demonstrate regimes where the metabolizers and non-metabolizers are respectively dominant. Simulation results using the basic model of Eq. (2) are given in Figs. 1–3, while

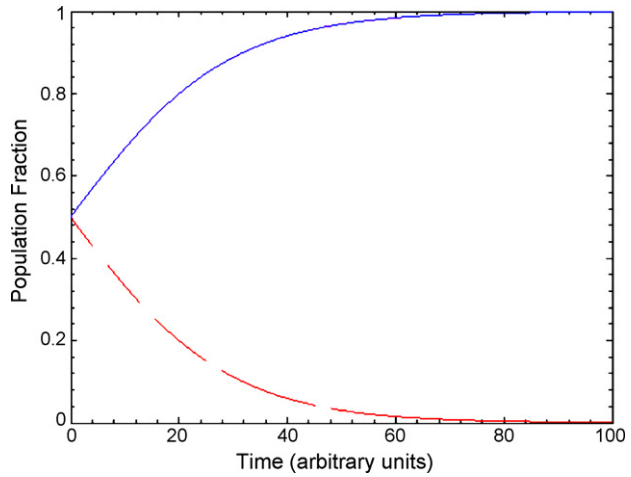

Fig. 1. A plot of the population fraction of the metabolizers (dashed red line) and non-metabolizers (solid blue line) as a function of time. Parameters chosen are $\tilde{k}_{ij} = k_{ij} = 10$, $k'_1 = 1$, $k'_2 = 0.5$, $\tilde{k} = 10$, $c_{\tilde{N}} = c_N = 1$, so as to simulate a high resource environment. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

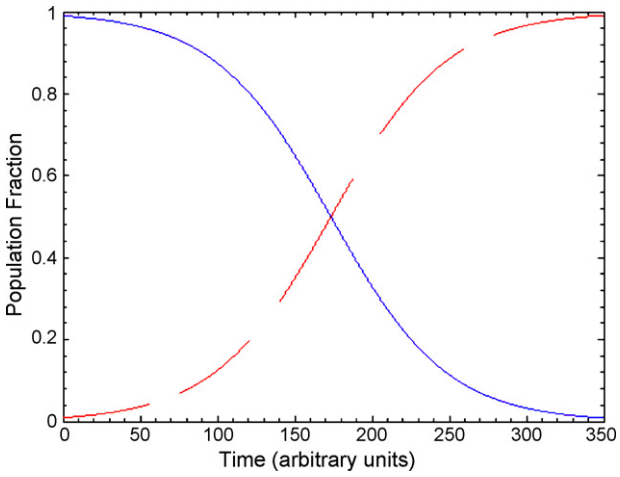

Fig. 3. A plot of the population fraction of the metabolizers (dashed red line) and non-metabolizers (solid blue line) as a function of time. Parameters chosen are $\tilde{k}_{ij} = k_{ij} = 10$, $k'_1 = 1$, $k'_2 = 0.5$, $\tilde{k} = 10$, $c_{\tilde{N}} = 0.4$, $c_N = 1$. In contrast to Fig. 2, the initial concentration of metabolizer is 100 times less than the initial concentration of non-metabolizer. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

simulation results using the chemostat model of Eq. (11) are given in Fig. 4.

The first point that emerges from the simulation results is that, a priori, the result of the competition between metabolic and non-metabolic replicators is not predetermined, but is dependent on the reaction conditions. Two general situations can be identified—one where the competitive reaction proceeds with a high concentration of energized resource, $\tilde{N}$, the other with a low concentration of that energized resource.

First, if the concentration of energized resource is relatively high, then the analysis indicates that the non-metabolizers will prevail over the metabolizers (as shown in Fig. 1). This outcome is not unexpected. Recall, we have assumed that the simple non-metabolic replicator is an intrinsically faster replicator than the more complex metabolic one. Metabolic complexification is predicted to reduce the rate of the direct replication pathway (Eq. (1)a and e vs Eq. (1)f and k). Furthermore, in the presence of a high concentration of energized resource, then an inherently strong thermodynamic driving force for replication would be anticipated enabling simple replicators to replicate efficiently. Accordingly, it comes as no surprise that in the resource-rich environment the non-metabolic replicator prevails. Indeed, in his classic replication experiments on the Q_β virus conducted in the late 1960s, Spiegelman (1967) found that an initially extended RNA sequence mutated into a much shorter RNA sequence, one that showed higher replicating efficacy than the initial longer sequence. In that case, the high replicative efficacy of the shorter sequence resulted directly from the resource-rich environment that had been artificially provided.

However, the analysis also indicates that if the concentration of energized resource is relatively low (see Fig. 2), then it would be the metabolizers – those replicators that would have the capability to gather energy from an external source – that would prevail over the non-metabolizers. The metabolizers prevail even though we have assumed the metabolizers are intrinsically slower replicators than the non-metabolizers ($k'_2 < k'_1$). Simply, having an additional pathway by which the activated complex $R_2\tilde{N}$ may be obtained (Eq. (1)h and j) results in the metabolizer being the kinetically more sta-

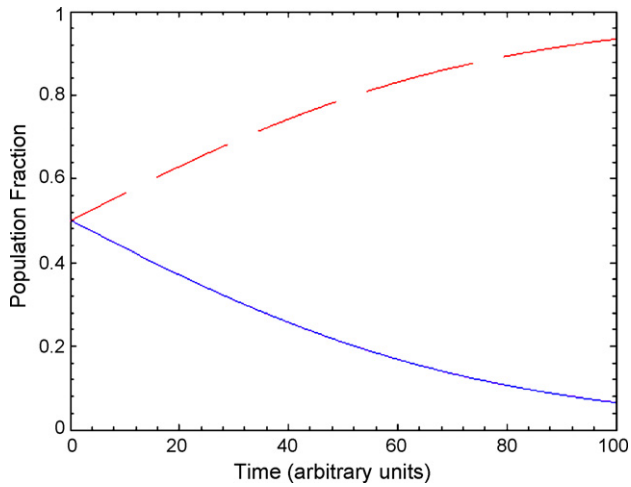

Fig. 2. A plot of the population fraction of the metabolizers (dashed red line) and non-metabolizers (solid blue line) as a function of time. Parameters chosen are $\tilde{k}_{ij} = k_{ij} = 10$, $k'_1 = 1$, $k'_2 = 0.5$, $\tilde{k} = 10$, $c_{\tilde{N}} = 0.4$, $c_N = 1$, so as to simulate a low resource environment. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

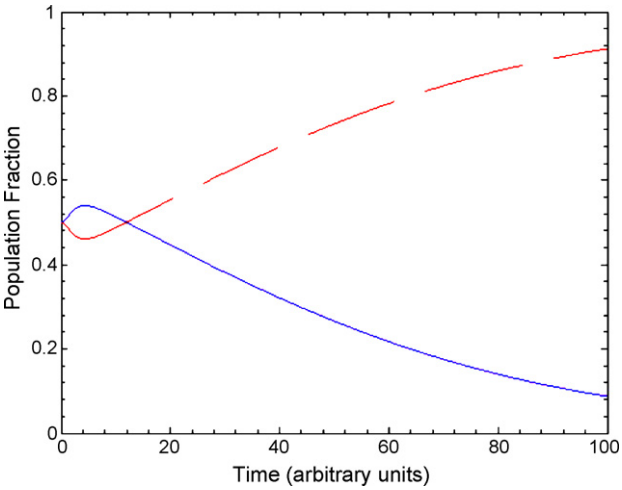

Fig. 4. A plot of the population fraction of the metabolizers (dashed red line) and non-metabolizers (solid blue line) as a function of time in a chemostat. Parameters chosen are the same as for Fig. 2, and where $F = V = 1$. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

ble replicator, and therefore the one that is kinetically selected for. A simple topological analogy might help clarify the point: if the road that all cars need to traverse were downhill, then cars would not need to have an engine. However, for a typical ground topology, with both uphill and downhill sections, then clearly those cars with an engine would perform more effectively than those without! Significantly, even when the non-metabolizer starts off at a concentration 100 times that of the metabolizer, the same qualitative result is observed, as shown in Fig. 3. Thus, as a function of time the concentration of non-metabolizer, initially high, drops off toward zero, while the concentration of metabolizer exhibits the opposite behavior, starting from its initial low concentration, before finally dominating the reaction mixture. Therefore, as seen in Fig. 3, the metabolizer and non-metabolizer concentration curves cross-over.

The significance of this result is apparent: if a non-metabolic replicator were to undergo some mutation into one with metabolic capabilities, that metabolic replicator, even though initially present in low concentration, would, through its metabolic capability, likely end up driving the non-metabolic replicator into extinction, leading to its domination of the reaction system. In other words, in the real world where the availability of energized resource is likely to be limited, metabolizers would be expected to be kinetically selected for over the non-metabolizers. Specifically, we find that once the fraction of unenergized resource would pass through some critical value, the relative kinetic stability of metabolizers and non-metabolizers would invert.

Finally it is of interest to explore the metabolizer–non-metabolizer competition under chemostat conditions, that is, with specified input and output flows, rather than under the more simple fixed resource concentration assumed in the previous simulations. The result of such a simulation is illustrated in Fig. 4 and reveals an interesting pattern. Initially when the resource concentration is relatively high the non-metabolizer is the one that appears to be winning the competitive reaction, in analogy to what was observed in Fig. 1. But this is short-lived—under chemostat conditions where the resource concentration varies with time, as the concentration of energized resource is used up, the metabolizer "catches-up" and begins to out-replicate the non-metabolizer, so that the steady-state outcome is one in which the metabolizer ends up dominating the reaction mixture. Thus the important general conclusion from the entire simulation study is that under both fixed resource concentration conditions (if energized resource concentration is not excessive) as well as chemostat flow conditions, metabolizers are likely to be kinetically selected for.

The significance of the above analysis to the origin of life issue can now be mentioned. Given the empirical observation that living systems are both replicative and metabolic, and given the controversy regarding the question whether the emergence of life began with some replicating entity which then became metabolic, or the emergence of some entity that was both metabolic and replicative (or was initially metabolic and subsequently became replicative) (Orgel, 2008; Shapiro, 2006), our analysis provides additional support for the former possibility, namely that some prebiotic non-metabolic replicator emerged and became metabolic through a process of kinetic selection. Recall, there is clear empirical evidence for the existence of simple non-metabolic replicating entities (Spiegelman, 1967; Eigen, 1971; Joyce, 1994; Orgel, 1992; Sievers and von Kiedrowski, 1994; Rebek, 1994). This study now provides theoretical support for the idea that such an entity could enhance its kinetic stability through the incorporation of a metabolic capability, thereby becoming both replicative and metabolic. In other words, our analysis supports the idea that metabolism and replication are related in a Darwinian sense, suggesting that replication would have necessarily preceded metabolism. Contrariwise, and as has been previously noted (Orgel, 2008), there is no empirical support and questionable theoretical support for the idea that a system that is both metabolic and replicative could have emerged spontaneously, or, alternatively, that a metabolic system emerged spontaneously and then would have taken on a replicative capability.

Thus, in seeking to create a coherent physicochemical framework that would bridge between inanimate and animate, we find yet additional support for the concept of dynamic kinetic stability as a unifying concept, that on the one hand is strictly chemical in its essence, yet incorporates within it the central Darwinian theme of selection (Pross and Khodorkovsky, 2004; Pross, 2009).

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