

RESEARCH OUTPUTS / RÉSULTATS DE RECHERCHE

Synchronization phenomena in surface-reaction models of protocells

Serra, Roberto; Carletti, Timoteo; Poli, Irene

Published in:
Artificial Life

Publication date:
2007

Document Version
Early version, also known as pre-print

[Link to publication](#)

Citation for pulished version (HARVARD):

Serra, R, Carletti, T & Poli, I 2007, 'Synchronization phenomena in surface-reaction models of protocells', *Artificial Life*, vol. 13, no. 2, pp. 123-138.

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal ?

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Synchronization phenomena in surface-reaction models of protocells

Roberto Serra^{*o\$}, *Timoteo Carletti*^{#o}, *Irene Poli*^o

^o Dipartimento di Statistica, Università Ca' Foscari, San Giobbe - Cannaregio 873, 30121 Venezia, Italy;

^{*} Dipartimento di Scienze Sociali, Cognitive e Quantitative, Università di Modena e Reggio Emilia, via Allegri 9, 42100 Reggio Emilia, Italy

[#] Département de mathématique, Université Notre Dame de la Paix Namur, Rempart de la Vierge 8, B 5000 Namur, Belgium

^{\$} corresponding author ; e-mail rserra@unimore.it

Abstract

A class of generic models of protocells is introduced, which are inspired by the “Los Alamos bug” hypothesis but which, due to their abstraction level, can be applied to a wider set of detailed protocell hypotheses. These models describe the coupled growth of the lipid container and of the self-replicating molecules.

A technique to analyze the dynamics of populations of such protocells is described, which couples a continuous-time formalism for the growth between two successive cell divisions, and a discrete map which relates the quantity of self-replicating molecules in successive generations. This technique allows one to derive several properties in an analytical way.

It is shown that, under fairly general assumptions, the two growth rates synchronize, so that the lipid container doubles its size when the quantity of self-replicating molecules has also doubled – thus giving rise to exponential growth of the population of protocells. Such synchronization had been postulated a priori in previous models of protocells, while it is here an emergent property.

We also compare the rate of duplication of two populations generated by two different protocells with different kinds of self-replicating molecules, considering the interesting case where the rate of self-replication of one kind is higher than that of the other, but its contribution to the container growth rate is smaller. It is shown that in this case the population of offsprings of the protocell with the faster replicating molecule will eventually grow faster than the other.

The case where two different types of self-replicating monomers are present in the same protocell is also analyzed, and it is shown that, if the replication follows a first order kinetic equation, then the faster replicator eventually displaces the slower one, while if the growth is sublinear the two coexist.

It is also proven by an appropriate rescaling of time that the results which concern the system asymptotic dynamics hold both for micelles and vesicles.

Keywords: protocell, self-replication, dynamical model, synchronization

1. Introduction

While present day cells are endowed with highly sophisticated mechanisms, which represent the outcome of almost four billion-years of evolution, it is generally believed that the first life-forms were much simpler. Such protocells [11, 14] should have had an embodiment structure (micelle or vesicle), a simplified metabolism and a way to give rise to new protocells. Moreover, there should have been a rudimentary genetics, so that the offspring of a cell was “similar” to its parent.

Besides their interest for the origin of life problem, protocells may be of much practical interest [11]: it is possible to envisage populations of such entities which grow and reproduce, specialized for useful tasks like e.g. drug synthesis.

While protocells have not yet been built, it is extremely interesting to understand under which conditions these systems can actually evolve. Models are required to address this issue and, due to the uncertainties about the details, high-level abstract models are particularly relevant.

We present here a protocell model loosely inspired by the so-called “Los Alamos bug” (briefly Labug in the following) hypothesis [9, 10]; however it abstracts from many details and can therefore be compatible also with other specific protocell models. This choice has been motivated by the quest for a model to describe how an initial population of protocells might evolve, rather than to present a detailed account of the working of a single exemplar.

The level of detail can somehow be compared to that of a model by Kaneko [5], who however considered the interaction of two molecular types, which catalyze each other’s formation, having in mind a relationship similar to that of nucleic acids and proteins. In the Labug hypothesis, on the

contrary, one deals with a single kind of self-replicating molecule¹ - briefly SRM in the following - and a lipid container, which can be either a micelle or a vesicle. On the one hand, the presence of the SRM affects the growth rate of the container, e.g. by favoring the formation of amphiphiles from precursors, which exist in the neighborhood of the protocell outer surface (amphiphiles are supposed to be quickly incorporated in the lipid membrane). On the other hand, the very existence of the lipid container is a necessary condition for the working of the protocell, as it is assumed that SRMs are preferentially found in the lipid phase.

So SRM catalytic activity favors the growth of the lipid container, which provides in turn the physical conditions appropriate for the replication of SRMs, without being however a catalyst. The relationship between containers and SRMs is different from the one considered by Kaneko and therefore requires the use of different equations. As we will show in the next sections, one of the main features of our models is that all the reactions occur close to the surface of the protocell, that's why we called them "surface reaction models".

In section 2 we will introduce the basic features of a model with only one kind of SRM involved and we consider some slightly different versions depending on the growth rate for the SRM: a linear one and a sublinear one as suggested by the LA bug papers [9,10] and others [7, 13]. The model is continuous in time, and the dynamics is smooth during the growth of a protocell, but it is assumed that once the membrane size reaches a threshold, the protocell splits into two daughters units, as in the Chemoton model [4].

We will then consider the evolution of a population of protocells, ignoring for the time being mutations in the SRM. In particular, it must be appreciated that the concentration of SRMs affects the growth rate of the protocell itself, and therefore the doubling time of the population. Starting

¹ Actually, the self-replicating molecules in the Labug hypothesis are PNA; here however we will not make any specific hypothesis, and we will only suppose that the self-replicating molecules can be found in the lipid phase

from the first protocell, which is born with a certain amount of SRMs, the rate of replication of SRMs will in general be different from that of the growth of the container. A consequence is that the amount of SRMs at the protocell division time may be different from twice its initial value, so each daughter protocell could start with a quantity of SRMs different from that of the parent protocell. Therefore the duplication time of the second generation will also be different from that of the first one. A natural question is how will these two quantities change in time, under the combined action of continuous growth and sudden division. Our main result is that, under very general assumptions, the initial quantity of SRMs in successive generations tends to a fixed point, and therefore the doubling time of the SRMs and that of the lipid container converge to the same value.

Note that the problem of assuring consistency between the replication rates of the different protocell components is present in every Chemoton-like model, where protocell division is assumed to take place at a certain critical size. In the original Chemoton model [2, 4] the issue is handled by assuming a priori a stoichiometric coupling between the different processes, while here synchronization of protocell and SRM duplication times is an emergent property of the model, derived without assuming ad hoc stoichiometric ratios.

In order to prove this result we introduce a mathematical technique which is well suited for this kind of problems: the continuous growth between two successive divisions allows conserved quantities, which are used to derive an iteration map for the value of the SRM quantity in successive generations. The map tends to a fixed point (thus proving synchronization) and provides quantitative information about the kinetics of protocell replication.

We also compare the rate of duplication of two populations generated by two different protocells. Assume that the lipid container is made of the same molecules for both protocells, and that the two parent protocells differ only for the kind of SRM - let us call them type X and type Y. It is obvious

that, if both the rate of self-replication and the increase in container growth rate due to X are higher than Y, then the population of offsprings of the X-containing protocells will grow faster than that of the Y-containing ones. A more interesting case is the one where the rate of self-replication of X is higher than that of Y, but its contribution to the container growth rate is smaller than that of Y. It will be shown that in this case the population of offsprings of the protocell with the faster replicating molecule will eventually grow faster than the other.

In section 3 we address another important issue, namely the effects of the presence of different kinds of SRMs in a single protocell. They may be for example the outcome of random mutations from an initial single molecule, or may have a different origin. We will analyze the case where the two different types, X and Y, are present in the same protocell, supposing that there are no direct interactions between them, although of course the two are coupled by their co-inhabiting the same protocell. It will be shown that, if the replication kinetics is linear, the faster replicator eventually displaces the slower one. Also the extreme case of parasitic self-replicating molecules, which do not contribute at all to the growth of the protocell, will be analyzed.

In section 4 we introduce a model where the replication of the two SRMs in the same protocell is non-linear, a hypothesis which is supported by detailed studies on template replication [1, 13]. Then the questions of the previous sections will be again analyzed with this new model and, as we will see, some different answers will appear due to non-linearity, in particular it will be shown that different species of SRMs can coexist. While this is the usual behavior with parabolic growth laws [6], the coupling with the growth of the container makes a precise analysis necessary in the case of protocells.

In the final section, we will summarize the main results and discuss possible further improvements of our models.

2. A basic model

Let C be the total quantity of “container” (e.g. lipid membrane in vesicles or bulk of the micelle) and V its volume, which is equal to C/ρ (where ρ is the density, which will be assumed constant). S will denote the surface area, which is a function of V : typically, S is approximately proportional to V for a large vesicle with a very thin surface (a condition which will be referred to as the “thin vesicle case”), and to $V^{2/3}$ for a micelle. Let X denote the total quantity (mass) of genetic material in the protocell lipid phase. Note that the model presented below is invariant with respect to the choice of the way in which either C or X is measured; for example, if they were measured as number of molecules the equations would retain exactly the same form (of course, the units of the kinetic constants would be different).

We assume, according to the Labug hypothesis, that only the fraction of the total X , which is near the external surface, is effective in catalyzing amphiphiles formation. That is because precursors are found outside the protocell. For the same reason this applies also to the replication of X itself, here the precursors are nucleotides. Let us denote volume concentrations with square brackets. The total fraction of active X is proportional to $\delta S[X]_s$, where $[X]_s$ is the volume concentration of X in a layer of width δ below the external surface.

Let $[P]$ be the concentration of precursors of amphiphiles in the external solution near the protocell surface; assuming it to be buffered, then it is just a constant. If the growth of the lipid membrane and the replication of SRM both take place near the surface, we have:

$$\begin{cases} \frac{dC}{dt} = \alpha' S[X]_S [P] + \chi S[P] - \gamma \varphi(C) \\ \frac{dX}{dt} = \eta' S[X]_S^\nu - \lambda \psi(X) \end{cases}, \quad [2.1]$$

for some positive constants, denoted by Greek letters.

The first term of the first equation is the growth due to the transformation of precursors into amphiphiles, $P \rightarrow A$, catalyzed by the X-SRM, assuming the amphiphile A to be quickly incorporated in the membrane once produced. The second term is a spontaneous growth, due to spontaneous formation of amphiphiles, while the third term accounts for possible release of amphiphiles previously incorporated in the membrane (note that the exact form for the decay term has not been specified).

The second equation describes autocatalytic growth of the X-SRM (with a possible non first order kinetics described by the exponent $\nu > 0$). Possible degradation is taken into account by the last term $\lambda \psi(X)$.

We now neglect the term of spontaneous amphiphile formation, which is assumed to be smaller than the catalyzed term. We assume $[P] = \text{constant}$ and we suppose that S is proportional to V^β , and therefore also to C^β (β ranging between $2/3$ and 1). In this section and the following we will also assume $\nu=1$ (linear self-replication kinetics), an assumption which will be released in section 2.3 and in the whole section 4. By slightly redefining the constants we obtain:

$$\begin{cases} \frac{dC}{dt} = \alpha'' C^\beta [X]_S - \gamma \varphi(C) \\ \frac{dX}{dt} = \eta'' C^\beta [X]_S - \lambda \psi(X) \end{cases}. \quad [2.2]$$

But $[X]_s$ is proportional to the concentration of X in the whole lipid phase, which is² $X/V = \rho X/C$.

Therefore, again incorporating constant terms in the rate constants:

$$\begin{cases} \frac{dC}{dt} = \alpha X C^{\beta-1} - \gamma \varphi(C) \\ \frac{dX}{dt} = \eta X C^{\beta-1} - \lambda \psi(X) \end{cases} \quad [2.3]$$

To get a feeling for the behavior of equations [2.3], let us consider the growth of a vesicle container with a very thin membrane ($\beta \cong 1$) in the case where X is constant and $\varphi(C) = C$. Then the first equation becomes:

$$\frac{dC}{dt} = k - \gamma C \quad [2.4]$$

where $k = \eta X_0$ is a constant, X_0 being the initial concentration of SRMs. Eq. 2.4 describes the growth of the lipid container up to its asymptotic value k/γ (provided that the initial value C_0 is smaller than k/γ).

We will assume that the protocell breaks into two identical daughters units when it reaches a certain threshold θ . Moreover, we will assume that the growth is essentially exponential, i.e. that the rate limiting steps in Eq. [2.3] above do not play a significant role when $C < \theta$. Therefore the growth of a protocell up to its critical size is approximately ruled by the following equations (coming back to a generic container and non constant X):

$$\begin{cases} \frac{dC}{dt} = \alpha C^{\beta-1} X \\ \frac{dX}{dt} = \eta C^{\beta-1} X \end{cases} \quad [2.5]$$

This system of equations [2.5] will be the starting point for further analysis.

²We assume here that transport in the lipid phase is extremely fast, leading to homogeneous concentrations of SRM in the whole vesicle membrane or micelle.

2.1 Analysis of the model

Starting with an initial quantity of container C at time T_0 equal to $\theta/2$, we assume that once C reaches critical value θ it will divide into two equal protocells of size $\theta/2$. Let ΔT_0 be the time interval needed to double C from this initial condition, and let $T_1 = T_0 + \Delta T_0$ be the time when the critical mass θ is reached. Since the initial value for C is fixed, ΔT_0 is a function of the initial quantity of SRMs, X_0 . The final value of X , just before the division is then $X(T_1)$. Because we assume perfect halving at the division, each offspring will start with an initial concentration of SRM equal to $X_1 = X(T_1)/2$. The successive doubling time will be denoted by $T_2 = T_1 + \Delta T_1$, and the third generation will start with an initial value $X_2 = X(T_2)/2$, a.s.o.

We generalize the preceding discussion with the following equations, which refer to the k^{th} cell division cycle that starts at time T_k and ends at time T_{k+1} :

$$\frac{\theta}{2} = \int_{T_k}^{T_{k+1}} \dot{C}(t) dt, \quad \text{and} \quad X_{k+1} = \frac{1}{2} X(T_{k+1}) \quad [2.6]$$

Note that in general $X(T_{k+1}) \neq 2X(T_k)$, although we will prove that this condition is asymptotically approached. Note also that the time needed to double the value of C is not constant between two successive generations, although we will also prove that constancy is also asymptotically approached.

³If the protocell which had been produced first had a different size, the initial C of each of its daughter cells would be exactly $\theta/2$, so we would take one of these daughters as our initial point.

We observe that the function $Q(t) = \eta C(t) - \alpha X(t)$ is a first integral for system [2.5], namely it is a constant quantity during each division cycle. Hence evaluating it at the beginning and at the end of the k -th generation we get:

$$\eta C(T_{k+1}) - \alpha X(T_{k+1}) = \eta C(T_k) - \alpha X(T_k).$$

Using the halving hypothesis and the doubling size threshold to divide as in Eq. 2.6 we obtain:

$$2\alpha X_{k+1} - \alpha X_k = \eta \frac{\theta}{2}.$$

This relation can be solved with respect to X_{k+1} , leading to:

$$X_{k+1} = \frac{X_k + D}{2}$$

where $D \equiv \theta\eta/2\alpha$. This can be iterated leading to

$$X_{k+1} = \left(\frac{1}{2}\right)^{k+1} X_0 + \frac{D}{2} \sum_{m=0}^k \left(\frac{1}{2}\right)^m = \left(\frac{1}{2}\right)^{k+1} X_0 + \left(1 - \frac{1}{2^{k+1}}\right) D. \quad [2.7]$$

The interesting result is that, in the limit of large k , the initial quantity of SRMs converges to a fixed value:

$$X_k \rightarrow D, \quad [2.8]$$

no matter how large the initial value of X_0 was and independently of the type of the protocell container: micelle or vesicle, i.e. $\beta=2/3$ or $\beta=1$.

This result tells us also that, after sufficiently many generations, the division period converges to a fixed value, therefore leading to exponential growth of the protocell population. In the thin vesicle case the doubling time can be computed explicitly using the second relation of system [2.5] for $\beta=1$.

In fact in this case we can solve the equation for X to get at the k -th generation:

$$X(t) = X_k e^{\eta t} ,$$

which at the end of the division cycle gives:

$$2X_{k+1} = X_k e^{\eta \Delta T_k} .$$

Thus in the limit of large k , recalling [2.8], we get:

$$\Delta T_k \rightarrow \frac{1}{\eta} \ln 2 . \quad [2.9]$$

No matter what the initial value of X is, the population tends to a condition where the doubling time is ruled by η only.

In order to treat more general cases, for instance with $\beta=2/3$, we observe that [2.5] becomes:

$$\begin{cases} \frac{dC}{dt} = \alpha C^{-1/3} X \\ \frac{dX}{dt} = \eta C^{-1/3} X \end{cases} . \quad [2.10]$$

Using once again the first integral Q to eliminate the dependence on X , we get:

$$\frac{dC}{dt} = (\eta C - Q) C^{-1/3} = \eta C^{2/3} - Q C^{-1/3}$$

which could be explicitly solved, providing however a cumbersome relationship $f(C)=t$, which would be very hard to invert in order to get an explicit expression for ΔT_∞ . On the other hand, we can find a good estimate for the limit of the division period for arbitrary $\beta < 1$ because during each division cycle we have $\theta/2 \leq C(t) \leq \theta$. From the second equation of [2.10] we then get, for the k -th division cycle:

$$X_k e^{\eta \Delta T_k / \theta^{1-\beta}} \leq 2X_{k+1} \leq X_k e^{2^{1-\beta} \eta \Delta T_k / \theta^{1-\beta}} ,$$

thus in the limit of large k and recalling that $X_k \rightarrow D$, we obtain the bound for T_∞ :

$$2^{\beta-1} \frac{\theta^{1-\beta}}{\eta} \ln 2 \leq T_{\infty} \leq \frac{\theta^{1-\beta}}{\eta} \ln 2.$$

Note that also in this case the doubling time bounds estimates are based on η only. The fact that the behavior of the protocell is qualitatively the same for the vesicle case or the micelle case, is a general result of our model that we will prove in the next section.

To conclude this first analysis let us indeed compare two different initial protocells, which may have different parameter values. It is intuitive (and could be proven) that if both α and η are greater for one protocell than the other, that one will replicate faster. But what happens if we compare two different protocells, one better at replicating nucleic acid, the other more efficient in generating new membrane material? For the $\beta=1$ case the answer is clear from the above equations [2.8] and [2.9]: the doubling time depends upon the rate of replication of the SRM only, and the population with the higher η will become the fastest growing one. Numerical simulations confirm that the same holds also for the $\beta=2/3$ case.

Finally, it is important to remark that the results given above also hold in cases which are far more general than [2.5]. To derive them we have used only the constancy of the quantity Q , which can be straightforwardly proven for all the systems of the form

$$\begin{cases} \frac{dC}{dt} = \alpha f(C, X) \\ \frac{dX}{dt} = \eta f(C, X) \end{cases} \quad [2.11]$$

for arbitrary functions $f(C, X)$.

2.2 Micelle or vesicle doesn't matter.

We will now show that our model can give a unified qualitative description for both the micelle (i.e. $\beta=2/3$) and “thin vesicle” (i.e. $\beta=1$) cases. Once having done this, we will work only directly with the $\beta=1$ case as it is computationally simpler. By the arguments given in this section, the conclusions thus obtained can then be straightforwardly applied also to the asymptotic behavior of micelles, as well as to vesicles of intermediate size, where $1 > \beta > 2/3$.

Let us observe that $C(t)$ is positive for any finite t , so one can define a new time:

$$\tau = \tau_0 + \int_0^t C(s)^{\beta-1} ds, \quad [2.12]$$

note that $d\tau/dt = C(t)^{\beta-1}$. Now let $\omega(t)$ be a quantity which satisfies a differential equation of the form

$$\frac{d\omega(t)}{dt} = C(t)^{\beta-1} F(\omega(t)), \quad [2.13]$$

for an arbitrary function F . Define $\psi(\tau) \equiv \omega(t(\tau))$, i.e. the same quantity ω but read in the new time variable, then its evolution is given by:

$$\frac{d\psi(\tau)}{d\tau} = \frac{dt}{d\tau} \frac{d\omega(t)}{dt} = F(\psi(\tau)). \quad [2.14]$$

Let us now apply this idea to equation [2.5]

$$\left\{ \begin{array}{l} \frac{dC}{dt} = \alpha C^{\beta-1} X \\ \frac{dX}{dt} = \eta C^{\beta-1} X \end{array} \right\},$$

and define $c(\tau) = C(t(\tau))$, $x(\tau) = X(t(\tau))$. In terms of the new variables, using [2.14], the above equations become:

$$\begin{cases} \frac{dc}{d\tau} = \alpha x \\ \frac{dx}{d\tau} = \eta x \end{cases},$$

which have exactly the form of the model in the thin vesicle case. Therefore the analysis of the general case can be reduced to that of the $\beta=1$ case (taking into due account the fact that the new time τ is a function of t , the real time). Thus the asymptotic qualitative behavior is the same irrespective of the choice of the exponent, $\beta-1$. This implies that the evolution of a population of micelles or vesicles will be qualitatively the same: both will converge to a fixed point, but with different time scales.

2.3 A non-linear model

The methods used to study the linear model in section 2.1 can be easily adapted to the case where the SRMs follow a non-linear growth law, as suggested for the Labug model [9,10]. Starting from equation [2.1] and recalling that $[X]_s$ is proportional to X/C and S is proportional to C^β , we get:

$$\begin{cases} \frac{dC}{dt} = \alpha X C^{\beta-1} \\ \frac{dX}{dt} = \eta X^\nu C^{\beta-\nu} \end{cases},$$

where $0 < \nu < 1$, and once again all constant terms have been incorporated in the rate constants. We could perform the analysis in the general case, but thanks to our previous remark, it will be enough to consider only the case $\beta = 1$, which simplifies the system to:

$$\begin{cases} \frac{dC}{dt} = \alpha X \\ \frac{dX}{dt} = \eta X^\nu C^{1-\nu} \end{cases}. \quad [2.15]$$

It can be directly verified that the following quantity is conserved during each division cycle:

$$Q = C(t)^{2-\nu} - \frac{\alpha}{\eta} X(t)^{2-\nu} .$$

Evaluating Q at the beginning and at the end of the k-th period one gets (recalling the earlier results that follow from Eq. 2.6, namely that C doubles from $\theta/2$ to θ at each division cycle and that $X_{k+1} = X(T_{k+1})/2$) the following relation involving X_{k+1} and X_k :

$$X_{k+1}^{2-\nu} = \frac{\eta\theta^{2-\nu}}{\alpha 2^{2-\nu}} \left(1 - \left(\frac{1}{2} \right)^{2-\nu} \right) + \left(\frac{1}{2} \right)^{2-\nu} X_k^{2-\nu} , \quad [2.16]$$

which can be rewritten as follows:

$$\zeta_{k+1} = H + p\zeta_k , \quad [2.17]$$

once we define the auxiliary quantities:

$$\begin{aligned} p &\equiv \left(\frac{1}{2} \right)^{2-\nu} \\ H &\equiv \frac{\eta}{\alpha} p(1-p)\theta^{2-\nu} . \\ \zeta_k &\equiv X_k^{2-\nu} \end{aligned} \quad [2.18]$$

The relation [2.17] for ζ_k can be explicitly solved to give:

$$\zeta_{k+1} = p^{k+1} \zeta_0 + H \sum_{m=0}^k p^m = p^{k+1} \zeta_0 + H \frac{1-p^{k+1}}{1-p} . \quad [2.19]$$

In the limit of large k, since $p < 1$, we get:

$$\zeta_k \rightarrow \zeta_\infty = \frac{H}{1-p} . \quad [2.20]$$

thus ζ_k , and therefore X_k , tends to a constant asymptotic value and in this limit the division time becomes in this limit constant as well. Once again we have exponential growth of the population size even though the replication rate of SRMs is parabolic (see also [7, 12])

3. More SRMs in the same protocell

Let us now introduce a second model where two different, non-interacting SRMs are present in the same protocell. This model of course generalises the previous one and moreover will allow us to consider new kinds of problems, for instance the coexistence of SRMs (section 4) or the presence of parasites (§ 3.1).

Starting again by considering a linear replication law for SRMs, the model can be described with equations analogous to [2.5], namely:

$$\left\{ \begin{array}{l} \frac{dC}{dt} = \alpha' C^{\beta-1} X + \alpha'' C^{\beta-1} Y \\ \frac{dX}{dt} = \eta' C^{\beta-1} X \\ \frac{dY}{dt} = \eta'' C^{\beta-1} Y \end{array} \right. . \quad [3.1]$$

It is easy to guess that, if one of the two SRM outperforms the other both in replication rate and in contributing to the growth of the lipid container, it will be present in a higher proportion than the other in successive generations. So let us consider the more interesting case where X is better than Y to catalyze lipid production, while replication of Y is faster than that of X:

$$\alpha' > \alpha'' \text{ and } \eta'' > \eta' .$$

As previously discussed we will only analyze the thin vesicle case, $\beta=1$. Hence we study the system:

$$\begin{cases} \frac{dC}{dt} = \alpha' X + \alpha'' Y \\ \frac{dX}{dt} = \eta' X \\ \frac{dY}{dt} = \eta'' Y \end{cases} \quad [3.2]$$

There are two first integrals:

$$Q_1(t) = C(t) - \frac{\alpha'}{\eta'} X(t) - \frac{\alpha''}{\eta''} Y(t) \quad \text{and} \quad Q_2(t) = \frac{(X(t))^{\eta''}}{(Y(t))^{\eta'}} \quad [3.3]$$

as a direct computation easily shows. Imposing the constancy of these two functions over one duplication cycle we get two relations involving X_k and Y_k , that can be analyzed to fully describe the dynamics of the model.

Recalling the halving hypothesis for both SRMs, the constancy of Q_2 at the k -th division cycle gives us:

$$\frac{(X_{k+1})^{\eta''}}{(Y_{k+1})^{\eta'}} = \left(\frac{1}{2}\right)^{-(\eta'' - \eta')} \frac{(X_k)^{\eta''}}{(Y_k)^{\eta'}},$$

which allows us to relate the relative quantities of X and Y for the k^{th} division cycle with the same ratio at the initial time:

$$\frac{(X_k)^{\eta''}}{(Y_k)^{\eta'}} = \left(\frac{1}{2}\right)^{-(k+1)(\eta'' - \eta')} \frac{(X_0)^{\eta''}}{(Y_0)^{\eta'}}. \quad [3.4]$$

Since we assume that $\eta'' > \eta'$, we get from [3.4], in the limit of large k :

$$\frac{(X_k)^{\eta''}}{(Y_k)^{\eta'}} \rightarrow 0. \quad [3.5]$$

Therefore the relative proportion of X-type molecules with respect to those of Y-type vanishes through successive generations.

The constancy of Q_1 at the k -th division cycle determines a second relation between X_k and Y_k :

$$\frac{1}{D'}(2X_{k+1} - X_k) + \frac{1}{D''}(2Y_{k+1} - Y_k) = 1, \quad [3.6]$$

where

$$D' = \frac{\theta\eta'}{2\alpha'} \quad \text{and} \quad D'' = \frac{\theta\eta''}{2\alpha''}$$

There are four possible different options compatible with [3.6] namely:

- (1) X_k tends to 0 while Y_k tends to a finite non-zero limit Y_∞ ;
- (2) Y_k tends to infinity while X_k stays bounded;
- (3) both X_k and Y_k diverge in a way compatible with [3.4];
- (4) both X_k and Y_k vanish in a way compatible with [3.4];

However, only the first one is also compatible with the relation [3.5], thus in this case we have:

$$X_k \rightarrow 0 \quad \text{and} \quad Y_k \rightarrow Y_\infty = D''. \quad [3.7]$$

Hence the division time reaches a constant value that can be determined as follows. By [3.2c] we get:

$$2Y_{k+1} = Y_k e^{\eta'' \Delta T_k}$$

then in the limit of large k we have, $\Delta T_k \rightarrow \Delta T_\infty = \ln 2 / \eta''$, exactly as in the case of section 2, equations [2.8] and [2.9].

All the other possibilities must be rejected because the relation [3.6] cannot be satisfied when at least one between X and Y is unbounded or when both are equal to zero.

We are therefore led to the following result: if two different SRMs are present, the one with slowest replication rate asymptotically disappears in the future generations, in the case of linear replication.

3.1 Fast replicating parasite

Let us now consider the case of a parasitic fast replicating SRM, say Y, which gives no contribution to the growth of the lipid container, $\alpha''=0$ and $\eta'' > \eta'$. Then system [3.2] still admits Q_2 as a first integral, so that, reasoning as before, we get:

$$\frac{(X_k)^{\eta''}}{(Y_k)^{\eta'}} \rightarrow 0, \quad [3.8]$$

and again four possibilities as before have to be discussed. There is a second first integral that now reads $Q_1(t) = C(t) - \frac{\alpha'}{\eta'} X(t)$, from which we get a new relation for X at the beginning and at the end of any division cycle:

$$\frac{\theta}{2} = \frac{\alpha'}{\eta'} (2X_{k+1} - X_k). \quad [3.9]$$

This equation cannot be verified if $X_k \rightarrow 0$ or $X_k \rightarrow \infty$, thus the only case left is $X_k \rightarrow X_\infty$, with X_∞ finite positive value which must be equal to $D' \equiv \theta\eta'/2\alpha$ to satisfy [3.9]. The constancy of X_∞ implies the constancy of the division time which approaches the asymptotic value $\Delta T_\infty = \ln 2/\eta'$. Then [3.8] can hold if and only if $Y_k \rightarrow \infty$. Perhaps this pathological behavior is fragile with respect to a small change in the system of equations. Indeed it disappears in the non-linear model considered in section 4.1.

We observe that thanks to our remark of section 2.2, these results also hold in the case of a micelle container, except that we cannot derive an explicit formula for the asymptotic doubling time, but again we can obtain upper and lower bounds following the same lines that we showed at the end of section 2.1 (detailed calculations are omitted here).

4. Non-linear SRM kinetics

We will now consider a model where the replication kinetics of the two SRMs replication is non-linear in their concentrations, while that for the growth of the lipids is still linear. Assume moreover that the two SRMs are non-interacting. The starting model, in the case $\beta=1$ as usual, is:

$$\begin{cases} \frac{dC}{dt} = \alpha' X + \alpha'' Y \\ \frac{dX}{dt} = \eta' X^\nu C^{1-\nu} \\ \frac{dY}{dt} = \eta'' Y^\nu C^{1-\nu} \end{cases}, \quad [4.1]$$

where the exponent is the same for both X and Y, but the kinetic coefficients differ. There are now two conserved quantities:

$$\begin{aligned} Q_1 &= C(t)^{2-\nu} - \frac{\alpha'}{\eta'} X(t)^{2-\nu} - \frac{\alpha''}{\eta''} Y(t)^{2-\nu} \\ Q_2 &= \frac{X(t)^{1-\nu}}{\eta'} - \frac{Y(t)^{1-\nu}}{\eta''} \end{aligned}; \quad [4.2]$$

the conservation of Q_1 implies, between two consecutive divisions:

$$\theta^{2-\nu} \left(1 - \left(\frac{1}{2} \right)^{2-\nu} \right) = \frac{\alpha'}{\eta'} \left((2X_{k+1})^{2-\nu} - X_k^{2-\nu} \right) + \frac{\alpha''}{\eta''} \left((2Y_{k+1})^{2-\nu} - Y_k^{2-\nu} \right), \quad [4.3]$$

while the conservation of Q_2 implies :

$$\frac{1}{\eta'} \left((2X_{k+1})^{1-\nu} - X_k^{1-\nu} \right) = \frac{1}{\eta''} \left((2Y_{k+1})^{1-\nu} - Y_k^{1-\nu} \right). \quad [4.4]$$

From [4.3] it turns out that X and Y cannot both vanish, or both become unbounded. However from [4.4] one can infer that the vanishing (or diverging) of X implies that of Y and vice versa. Therefore neither X nor Y tends to 0 or diverges. Thus both X_n and Y_n tend to finite values X_∞ and Y_∞ .

From [4.4] it then turns out that:

$$Y_\infty^{1-\nu} = \frac{\eta''}{\eta'} X_\infty^{1-\nu}, \quad [4.5]$$

which when inserted into [4.3] determines the value of X_∞ .

Thus both SRMs will reach a finite asymptotic value and the same is true for the duplication time, namely there is synchronization of both SRMs and container growth, with coexistence of two kinds of SRM.

4.1 Non-linear fast replicating parasite

In section 3.1 we already studied the case of a fast replicating SRM parasite in the case of the linear model. Let us now analyze the non-linear model, where the SRM growth follows a non-linear law. Let Y be the fast, $\eta'' > \eta'$, parasite, which doesn't contribute to the growth of the container, so the model to study is given by:

$$\begin{cases} \frac{dC}{dt} = \alpha' X \\ \frac{dX}{dt} = \eta' X^\nu C^{1-\nu} \\ \frac{dY}{dt} = \eta'' Y^\nu C^{1-\nu} \end{cases} \quad [4.6]$$

There are still two conserved quantities (cfr. [4.2] with $\alpha''=0$):

$$\begin{aligned} Q_1 &= C(t)^{2-\nu} - \frac{\alpha'}{\eta'} X(t)^{2-\nu} \\ Q_2 &= \frac{X(t)^{1-\nu}}{\eta'} - \frac{Y(t)^{1-\nu}}{\eta''} \end{aligned} \quad [4.7]$$

As in the single-SRM case, conservation of Q_1 during a division period, leads to:

$$X_{k+1}^{2-\nu} = \frac{\eta' \theta^{2-\nu}}{\alpha' 2^{2-\nu}} \left(1 - \left(\frac{1}{2} \right)^{2-\nu} \right) + \left(\frac{1}{2} \right)^{2-\nu} X_k^{2-\nu},$$

which can be solved as we did in § 2.3, to give:

$$X_\infty = \left(\frac{H}{1-p} \right)^{\frac{1}{2-\nu}}, \quad [4.8]$$

while conservation of Q_2 leads to (cfr [4.5]):

$$Y_\infty = \left(\frac{\eta''}{\eta'} \right)^{\frac{1}{1-\nu}} X_\infty.$$

Thus in this case, both SRMs, the useful SRM and the parasite one, will survive, reaching an asymptotic constant value. Also in this case there is synchronization with the division cycle.

5. Conclusions

In this paper we have introduced a class of abstract models of protocells, called surface reaction models because the growth of the lipid container and that of the self-replicating molecules take place near the cell surface. Although the inspiration was drawn from the Los Alamos bug hypothesis, the high abstraction level of our models may allow their application to a broader set of detailed models. Moreover, while our methods have been devised for models where growth and replication take place at the protocell outer surface, it may be worthwhile to explore their application to different approaches, like those where replication is supposed to take place in the inner compartment (see e.g. [8]).

We also introduced a powerful analytical technique to study the behavior of this class of protocell models, which combines continuum methods, used to describe the growth between two successive protocell duplications, and discrete maps which relate the initial value of the relevant quantities of two successive generations. This technique also allows us to draw conclusions on the asymptotic properties of a micelle or a thick vesicle, by analyzing the “thin vesicle” case only, i.e. $\beta=1$.

It has been shown that, under very general conditions, the replication rate becomes constant in the long time limit, which in turn implies exponential growth of the population of protocells, unless there are other limitations to growth. Synchronization of container and SRM duplication is here an emergent property, while in earlier models, like the Chemoton, it was imposed a priori through a stoichiometric coupling.

We recently became aware of the fact that a similar synchronization has been demonstrated by Rasmussen and co-workers in another protocell model, using a different approach [12]. This

suggests that such synchronization phenomena may be “generic”, i.e. common to several protocell models

In the case where the growth of the self-replicating molecules is linear, it has been shown here that the doubling time depends only upon the rate constant for self-replication (so if there are two kinds of protocells, one with higher α and lower η than the other, the former will eventually be outperformed by the latter) and that, if there are two different SRMs in the same protocell, the one which is slower in replicating itself vanishes in the long time limit, even if it can provide a faster growth rate for the container. In the case of fast parasites these will dominate and lead to halting the growth.

However, in the case where the growth of the self-replicating molecules is sublinear, it has been shown that two different SRMs coexist, reaching fixed ratios. While this could be expected in parabolic growth laws [6], the peculiar features of this protocell model, which couples self-replication with container growth, require a precise analysis.

This coexistence of different self-replicating molecules opens the interesting possibility of the existence of “optimal” mixtures of different SRM (with different kinetic parameters) able to lead to a high growth rate for the population of protocells.

The models we studied are quite general and they can be applied to describe several specific systems. Some possible future directions of research include the following ones. Our models are fully deterministic and we can introduce and discuss the effects of random fluctuations in the division threshold and halving property. In our description each protocell “doesn’t feel” the other ones because it produces all what it needs by itself, thus it could be interesting to consider interactions between different protocells, as for instance exchange of genetic material. Finally, as

already mentioned, we neglected the inner dynamics, assumed to be fast and in equilibrium; therefore one could improve the model by introducing a more realistic kinetics which, for instance, takes into account finite diffusion rates and limitations to the supply of building blocks or more detailed information about the protocell growth process (see e.g. [3]).

Acknowledgments

Support from the EU FET- PACE project within the 6th Framework Program under contract FP6-002035 (Programmable Artificial Cell Evolution) is gratefully acknowledged. We had stimulating and useful discussions with Norman Packard and Marco Villani during the warm hospitality at the European Center for Living Technology. We also thank the participants to the PACE workshop on “Evolution and Self-assembly” held at the European Center for Living Technology on march 16-18, 2006, and in particular Steen Rasmussen for helpful comments.

References

- [1] Bag B.G., & Von Kiedrowski, G. (1996): *Template autocatalysis and molecular replicator*. Pure and Applied Chemistry **68**, 2145-2152
- [2] Carletti, T. (2006): *Stability, mutation and evolution in a population of Chemotons*, submitted
- [3] Chen, I.A., & Szostak, J.W. (2004): *A kinetic study of the growth of fatty acid vesicles*. Biophysical Journal **87**, 988-998
- [4] Ganti, T. (2003): *Chemoton Theory* (Vol. I. Theory of Fluid Machineries; Vol. II: Theory of Living Systems). New York, KluwerAcademic/Plenum Publishers
- [5] Kaneko, K. (2005): *On Recursive Production and Evolvability of Cells: Catalytic Reaction Network Approach*. Advances in Chemical Physics **130B**, 543-598

- [6] Maynard-Smith, J., & Szathmary, E. (1997): *Major transitions in evolution*. New York: Oxford University Press
- [7] Munteanu, A., Attolini, C.S., Rasmussen, S., Ziock, H., & Solé, R.V. (2006): *Generic Darwinian selection in protocell assemblies*, submitted
- [8] Oberholzer, T., Wick, R., Luisi, P.L., & Biebricher, C.K. (1995): *Enzymatic RNA replication in self-reproducing vesicles: an approach to a minimal cell*. *Biochemical and Biophysical Research Communications* **207**, 250-257
- [9] Rasmussen, S., Chen, L., Nilsson, M., & Abe, S. (2003): *Bridging nonliving and living matter*. *Artificial Life* **9**, 269-316
- [10] Rasmussen, S., Chen, L., Stadler, B., & Stadler, P.F. (2004): *Proto-organism kinetics*. *Origins Life and Evolution of the Biosphere* **34**, 171-180
- [11] Rasmussen, S., Chen, L., Deamer, D., Krakauer, D.C., Packard, N.H., Stadler, P.F. & Bedeau, M.A. (2004): *Transitions from non living to living matter*. *Science* **303**, 963-965
- [12] Rochelau, T., Rasmussen, S., Nielsen, P.E., Jacobi, M.N. & Ziock, H. (2006): *Emergence of protocellular growth laws*, submitted
- [13] Stadler, B.M.R. , & Stadler, P.F. (2003): *Molecular replicator Dynamics*. *Advances in Complex Systems* **6**, 47-77
- [14] Szostak, D., Bartel, P.B., & Luisi, P.L. (2001): *Synthesizing life*. *Nature* **409**, 387-390