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The growth of populations of protocells

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Abstract: the growth of protocells is discussed under different hypotheses (one or more replicators, linear and nonlinear kinetics) using a class of abstract models (Surface Reaction Models). A method to analyze the dynamics of successive protocell generations is presented, and it is applied to the problem of determining whether the duplication times of the protocell itself and of its genetic material eventually tend to a common value. The importance of the phenomenon of emergent synchronization for sustained protocell population growth and for evolvability is discussed.

1. Introduction

Protocells are lipid vesicles or micelles which are endowed with some rudimentary metabolism and contain "genetic" material, and which should be able to grow, reproduce and evolve. While viable protocells do not yet exist, their study is important in order to understand possible scenarios for the origin of life, as well as for creating new "protolife" forms which are able to adapt and evolve [Rasmussen et al, 2004b]. This endeavour has an obvious theoretical interest, but it might also lead to an entirely new "living technology", definitely different from conventional biotechnology.

Theoretical models can be extremely useful to devise possible protocells and to forecast their behaviour. In this paper we address an important issue in protocell research. The protogenetic material in a protocell is composed by a set of molecules which, collectively, are able to replicate themselves. At the same time, the whole protocell undergoes a growth process (its metabolism) followed by a breakup into two daughter cells. This breakup is a physical phenomenon which is frequently observed in lipid vesicles, and it has nothing to do with life, although it superficially resembles the division of a cell. In order for evolution to be possible, some genetic molecules should affect the rate of duplication of the whole container. Mechanisms have been proposed whereby this can be achieved (see below).

But then a new problem arises: the genetic material duplicates at a certain rate, while the lipid container grows, in general, at another rate. When the container splits into two, it may be that the genetic material has not yet doubled: in this case its density would be lower in the daughter protocells. Through generations, this density might eventually vanish. On the other hand, if the genetic material were faster than the container, it would accumulate in successive generations.

So, in order for a viable population of evolving protocells to form, it is necessary that the rhythms of the two processes are synchronized. In some models (like the Chemoton [Ganti, 2003]) this is imposed a priori in the kinetic equations, but it is unlikely that such a set of exactly coupled reactions spring up spontaneously. It is therefore interesting to consider the possibility that such synchronization be an emergent phenomenon, without imposing it a priori.

In the following we will consider this possibility by analyzing an abstract version of the so-called "Los Alamos bug", a model of protocells where the genetic material is composed by strands of PNA

[Rasmussen, 2003, 2004a]. These resemble the better-known nucleic acids DNA and RNA, but have a peptide backbone and it is believed that they might be found in the lipid phase of the protocell. According to this hypothesis, different PNA's may influence the growth rate of their "container" by catalyzing the formation of amphiphiles (which form the protocell membrane) from precursors. The detailed mechanisms whereby this might happen can be found in [Rasmussen, 2003, 2004a].

Inspired by the Los Alamos bug, we developed a more abstract class of models (which can describe also different specific models) which are called Surface Reaction Models [Serra et al., 2007a]. The simplest case (where the genetic material is composed by a single type of self-replicating molecule) will be described in section 2. This model couples the growth of the genetic material and that of the container, and a mathematical technique can be introduced to study how the quantity of the former varies in successive generations. This is described in section 3, where it is also shown that synchronization is indeed an emergent property, both in the case of linear and nonlinear kinetics. Note that the term "linear" refers to the rate equation of the replicator only: the overall model, with its coupling to the container growth and breakup, is definitely nonlinear.

Since there may be different kinds of replicators, with different rates, the case of two coexisting replicators (linear and nonlinear) is discussed in section 4. Section 5 is then devoted to the case where replicators directly interact: a comprehensive analytical theory can be developed for the linear case, while nonlinear kinetics is approached through simulations. A major consequence of synchronization is that the competition among protocells is darwinian, even if that of the replicators is not [Munteanu et al, 2006]. This aspect is discussed in the final section.

This paper aims at presenting a unified view of the major results concerning synchronization, while for detailed calculations and demonstrations the reader is referred to [Serra et al., 2007a, 2007b, 2007c, Filisetti, 2007], where further references to the scientific literature can also be found.

2. Surface reaction models

Let us first consider the case where there is a single replicator in the protocell lipid phase, and let its quantity (mass) be denoted by X . Let also C be the total quantity of "container" (e.g. lipid membrane in vesicles or bulk of the micelle). We suppose that the lipid density is constant, so the volume V of the lipid phase is proportional to C .

We assume, according to the Labug hypothesis, that the replicator favours the formation of amphiphiles and that, since precursors are found outside the protocell, only the fraction of X which is near the external surface is effective. We assume that also the replication of X takes place near the external surface. Let us further assume that

- spontaneous amphiphile formation is negligible
- the precursors (both of amphiphiles and of genetic molecules) are buffered
- the surface area S is proportional to V^β , and therefore also to C^β (β ranging between $2/3$ for a micelle and 1 for a very thin vesicle)
- diffusion is very fast within the protocell, so concentrations are constant everywhere in the lipid phase
- the protocell breaks into two identical daughter units when it reaches a certain volume ($C=\theta$)
- the rate limiting step which may appear in the replicator kinetic equations does not play a significant role when the protocell is smaller than the division threshold
- the contribution of X to the growth of C is linear
- the rate of replication of X in the bulk ($d[X]/dt$) would be proportional to $[X]^v$ (square brackets indicate concentrations)

Under these hypotheses, as shown in [Serra et al, 2007a] one obtains the following approximate equation which describes the growth of a protocell between two successive divisions:

$$\begin{cases} \frac{dC}{dt} = \alpha C^{\beta-1} X \\ \frac{dX}{dt} = \eta C^{\beta-1} X \end{cases} \quad [2.1]$$

When C reaches a critical value θ , the cell breaks into two equal daughter protocells; then, until the next duplication, the system is again ruled by Eq. 2.1. At the beginning of a new generation, both the initial value of X and that of C equal one half of the value which they have attained at the end of the previous generation, i.e. at the time of cell division.

Note that, under the above assumptions, the doubling time at generation i is determined by the initial value of X . Synchronization implies constant division times, so it is achieved if one observes the same initial value of X in two successive generations. Synchronization can of course also be detected by the fact that doubling times become equal in successive generations.

3. One type of replicator per cell

Let us first consider the linear case, i.e. let $\nu=1$ in Eq. 2.1. It is then immediate to observe that the quantity

$$Q = \eta C - \alpha X \quad [3.1]$$

is conserved during the continuous growth phase, so its value at the end of the growth is the same as it was at beginning. But since the protocell splits into two equal daughter cells, the initial value of Q , at the next generation, will be exactly one half of the previous value. As generations grow (i.e. as $t \rightarrow \infty$), then $Q \rightarrow 0$ and therefore the initial value of X approaches a constant value:

$$X_{\infty} = \frac{\eta \theta}{2\alpha} \quad [3.2]$$

It can also be proven that the doubling time asymptotically approaches the value $\ln 2 / \eta$. Therefore synchronization is achieved in the case where the replicator follows a linear (i.e. first order) kinetics.

The mathematical technique quickly described above can be applied to more general cases [Serra et al, 2007a, 2007b]. The key ingredient is that of finding a first integral of the equations which describe the continuous growth phase, and to obtain a recursion map for the initial values of X at successive generations, on the basis of the halving hypothesis. It can then be proven that the above result holds also for equations which are more general than the one considered above, and also for realistic protocell geometries. What is even more important, by renormalizing time it can be proven that the asymptotic behaviour is not affected by the value of β , so it suffices to consider the simpler $\beta=1$ case.

In particular, in the nonlinear case of Eq. 2.1 the conserved quantity is

$$Q = C(t)^{2-\nu} - \frac{\alpha}{\eta} X(t)^{2-\nu} \quad [3.3]$$

and synchronization can be proven using the same methods as those described above.

4. Coexisting replicators

There may be different replicators in a protocell: this would certainly be the case if they were nucleic acids, which can undergo random mutations, but the remark may hold also for more general hypotheses concerning their chemical nature.

Let us then suppose that in the same cell there are two self-replicators X and Y. The generalization of Eq. 2.1 is then

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

In this case one finds two first integrals of the continuous Eqs. 4.1, and one can then prove synchronization with the methods of section 3.

It is interesting to consider what happens when a the fastest replicator gives a smaller contribution to the growth of the whole container than the other one, e.g. to consider the case $\alpha' > \alpha''$ and $\eta' < \eta''$ [Serra et al., 2007a].

In the linear case ($\nu=1$) one finds that the fastest replicator displaces the other one, whose quantity per protocell eventually vanishes. The "altruist" get extinct in the long run. On the other hand, if $\nu < 1$ the two can co-exist, and tend asymptotically to a situation where their relative ratio is proportional to that of their kinetic coefficients η' and η'' .

5. Interacting replicators

In the case considered in section 4 there were different replicators in the same container, but they did not directly affect each other's synthesis. Let us now consider the case where replicators interact in a linear way. The model equations for the continuous growth between two successive divisions are then

$$\begin{cases} \frac{d\vec{X}}{dt} = C^{\beta-1} M \vec{X} \\ \frac{dC}{dt} = C^{\beta-1} \alpha \cdot \vec{X} \end{cases} \quad [5.1]$$

where the matrix element M_{ij} describes the effect of molecule of type j on the growth rate of molecule of type i.

By considering the case $\beta=1$ and using the techniques of section 3 one finds [Serra et al, 2007c] the following conditions for the asymptotic value of the quantity of X at the beginning of each replication cycle \mathbf{X}_∞ :

$$M \vec{X}_\infty = \lambda \vec{X}_\infty$$

$$\lambda = \frac{\ln 2}{\Delta T_\infty} \quad [5.2]$$

therefore \mathbf{X}_∞ must be an eigenvector of the matrix M belonging to the eigenvalue λ . It can be also proven that

$$\vec{X}(T_k) = e^{M(T_k - T_0)} \frac{\vec{X}_0}{2^{k-1}}$$

[5.3]

From Eq. 5.3, by considering the limit of very large times, one finds that the eigenvalue which must be considered in Eq.5.2 is the one with the largest real part, let us call it λ_1 .

Physical interpretation of these results requires that λ_1 (which is proportional to duplication time) be real and positive, and that \mathbf{X}_∞ be real and non negative (some components may vanish in the long time limit) . If the matrix M is non negative and non null (i.e. if every $M_{ij} \geq 0$ and there is at least one $M_{ij} \neq 0$) both conditions guaranteed by the Perron-Frobenius theorem, and in this case it can be proven that synchronization is always achieved. Numerical simulations [Filisetti, 2007] show that this is also the case whenever λ_1 is real and admits a nonnegative eigenvector.

When these conditions are not fulfilled, one often finds that some species get extinct, and that the above conditions apply to the remaining reduced system of equations. However, when the eigenvalues with the largest real part does not admit a non negative eigenvector, cases where synchronization does not take place may be observed. So the analytical theory is able to describe all those cases where the eigenvector corresponding to λ_1 is nonnegative¹, while simulations are required when this condition is not satisfied

When the replicators interact in a nonlinear way, although analytical theory may provide useful results, simulation is the main tool to explore the system behaviour. Preliminary experiments with some models of this kind show that, while synchronization is the most frequent outcome, interesting dynamical phenomena can also be observed, where the system approaches synchronization, and looks almost synchronized for fairly long times, but this stable situation abruptly changes. It may then be recovered after a turbulent transient. Nonlinear replication kinetics needs further exploration.

6. Conclusions

We have seen in section 4 that two replicators which are found in the same protocell, and which grow in a parabolic way (i.e. with sublinear kinetics, $v < 1$) can coexist. This phenomenon is typically observed also in population dynamics (i.e. without containers): sublinear kinetics leads to

¹ and also the trivial cases where there is no eigenvector with a nonnegative real part

asymptotic coexistence of several species [Maynard-Smith and Szathmary, 1997], a phenomenon which has been called "the survival of anybody".

On the other hand, selection pressure is much more effective in the darwinian case: the survival of only the fittest is guaranteed in population dynamics if the leading term in the kinetic equations is linear. Note that this corresponds to exponential growth, i.e. constant doubling time. But synchronization guarantees that this is exactly the case for protocells: even if the replicators interact in a parabolic way, the containers undergo exponential growth. Therefore, if different types of protocells exist, we can expect darwinian dynamics among them.

While we have proven this for the case of surface reaction model, the same phenomenon has also been observed in different models [Munteanu et al, 2006].

Therefore selection pressure might be much more effective at the protocell level than at the molecular level. While synchronization is an interesting phenomenon per se, this remark shows that it may have profound effects on the evolvability of protocells populations.

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References

- Filisetti, A. (2007): M.Sc thesis, Dept. of Social, Cognitive and Quantitative Sciences, Modena and Reggio-Emilia University
- Ganti, T. (2003): *Chemoton Theory* (Vol. I. Theory of Fluid Machineries; Vol. II: Theory of Living Systems). New York, KluwerAcademic/Plenum Publishers
- Maynard-Smith, J., & Szathmary, E. (1997): *Major transitions in evolution*. New York: Oxford University Press
- Munteanu, A., Attolini, C.S., Rasmussen, S., Ziock, H., & Solé, R.V. (2006): *Generic Darwinian selection in protocell assemblies*. DOI: SFI-WP 06-09-032, SFI Working Papers, Santa Fe Institute
- 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
- Rasmussen, S., Chen, L., Nilsson, M., & Abe, S. (2003): *Bridging nonliving and living matter*. *Artificial Life* **9**, 269-316
- Rasmussen, S., Chen, L., Stadler, B., & Stadler, P.F. (2004a): *Proto-organism kinetics*. *Origins Life and Evolution of the Biosphere* **34**, 171-180
- Rasmussen, S., Chen, L., Deamer, D., Krakauer, D.C., Packard, N.H., Stadler, P.F. & Bedeau, M.A. (2004b): *Transitions from non living to living matter*. *Science* **303**, 963-965
- Serra, R., Carletti, T. & Poli, I. (2007a): Synchronization phenomena in surface reaction models of protocells. *Artificial Life* **13**, 1-16
- Serra, R., Carletti, T. & Poli, I. (2007b): *Surface reaction models of protocells*. BIOMAT Proceedings, in press
- Serra, R., Carletti, T., Poli, I., Villani, M. & Filisetti, A. (2007c): *Conditions for emergent synchronization in protocells*. Submitted to ECCS-07: European Conference on Complex Systems

