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Conditions for emergent synchronization in protocells

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Summary. In this paper we study general protocell models, called *Surface Reactions Models* [10], aiming to understand the synchronization of genetic material and container productions, a necessary condition to assure sustainable growth in protocell. Synchronization has been proved to be an emergent property in many relevant protocell models [10], assuming both linear and nonlinear law for the replications rates; in this paper, contrarily with those previous studies, we improve the model by allowing linear interaction between replicators: catalysis and/or inhibition. Extending some techniques introduced in [10], we are able to give a quite general analytical answer about the synchronization phenomenon in this more general context. We also report some numerical results to investigate cases which are not yet amenable to analytical calculations.

1 Introduction: the problem of synchronization

Several attempts are currently under way to obtain protocells capable of growth and duplication, endowed with some limited form of genetics [7, 9, 12], either to understand which are the minimal requirements for a life form to exist and evolve, or by the search for indications about the way in which primitive life might have developed on earth.

In order to study how protocells can evolve, given that they do not yet exist, it is necessary to consider simplified models able to capture universal behaviors without carefully adding complicating details [3]. A protocell should comprise at least one kind of “container” molecule (typically a lipid or amphiphile) and one kind of replicator molecule (loosely speaking, “genetic material”). There are therefore two kinds of reactions which are crucial for the working of the protocell, which will be called here “key” reactions: those which synthesize the container molecules and those which synthesize the replicators.

The two key reactions may take place at different rates. However, to achieve sustained growth of a population of protocells it is necessary that

the two are proceed at equal pace, i.e. that the genetic material has doubled when the protocell splits into two (a condition referred to as “synchronization”). See [10] for a detailed discussion of the importance of this aspect. Note that synchronization has a further important property, namely that, even in the case where the kinetic equations for the replicators are sublinear, it leads to exponential growth of the population of protocells (a straightforward consequence of constant doubling time) and therefore to strictly Darwinian selection among protocells.

In this paper we will concentrate on a class of protocell architectures which have been called “Surface Reaction Models” [10, 11] since both kinds of key reactions take place on the surface of the cell membrane. A well-known specific model of this kind is the so-called “Los Alamos bug” (briefly, Labug, described in detail in [8, 9]), where replicators are PNAs which can be found in the membrane, either in its interior or on its surface. In order to address the problems related to synchronization several abstract models have been considered [10, 11] and synchronization has always been proved to be an emergent property, in the sense that, through successive generations of protocells, the doubling times of container and replicators tend asymptotically to the same value even if in the beginning they were different. This was contrasted to earlier models, like the well-known Chemoton [1], where synchronization was achieved by ad hoc hypotheses concerning the form of the kinetic equations.

In our previous works we had considered separately both cases of a single self-replicating molecule and more replicators but without direct interaction among them. The most striking result has been that synchronization was always achieved, under a variety of conditions, including linear and non-linear kinetics.

The fact that several different hypotheses lead asymptotically to synchronization raises the question whether this is a general property of the surface reaction models. In the present paper we therefore explore a wider class of models, taking into account direct interaction among the replicators. We consider the case of linear replication kinetics, finding sufficient conditions to guarantee synchronization: note however that, since protocell division is taken into account, the overall model is non-linear, so its analysis is far from trivial. The treatment of the subject is mostly analytical, but there are some cases where computer simulations are necessary to compute the asymptotic behaviours. Major results of the present work include i) the determination of conditions for synchronization and ii) the evidence of cases where such synchronization is not achieved.

2 Surface reaction models of protocells

Let us start by introducing the model under study; for the lack of space some details will be omitted, nevertheless because of some similarities with previous models, we refer to [10] for a more complete introduction.

Let $\mathbf{X} = (X_1, X_2, \dots, X_N)$, denote the total quantity (mass) of N different types of replicating molecules in the protocell lipid phase and let C be the total quantity of “container” (e.g. lipid membrane in vesicles or bulk of the micelle).

As previously stated we assume that only the fraction which is near the external surface of the replicators X_i , favors the formation of amphiphiles and also that their replications take place near the external surface. Following the assumptions discussed in detail in [10, 11] one obtains [10, 11] the following approximate equation which describes the growth of a protocell between two successive divisions:

$$\frac{d\mathbf{X}}{dt} = C^{\beta-1} M \mathbf{X} \quad \text{and} \quad \frac{dC}{dt} = C^{\beta-1} \boldsymbol{\alpha} \cdot \mathbf{X} = C^{\beta-1} (\alpha_1 X_1 + \dots + \alpha_N X_N), \quad (1)$$

where $\boldsymbol{\alpha} = (\alpha_1, \dots, \alpha_N)$ denotes the coupling term between the container and each replicator, while the (constant and real) matrix element M_{ij} represents the contribution of X_j to the growth of X_i .

An important simplification can now be considered: as it was demonstrated in [10], in order to determine whether there is synchronization in the asymptotic time limit, one can limit himself to consider the $\beta = 1$ case (the final result does not depend on β , while of course this parameter affects the speed with which it is approached). With this simplification, the basic equations (which are valid between two successive divisions) are then

$$\frac{d\mathbf{X}}{dt} = M \mathbf{X} \quad \text{and} \quad \frac{dC}{dt} = \boldsymbol{\alpha} \cdot \mathbf{X}. \quad (2)$$

Moreover we assume that protocell division takes place when the mass (or equivalently the volume) of the protocell reaches a certain critical size, here named θ . Without loss of generality we may then assume that the initial protocell size is one half of the final value, otherwise this condition will be satisfied from the second generation on.

So, starting with an initial quantity of container C at time T_0 equal to $\theta/2$, we assume that once C reaches the 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. The final value of \mathbf{X} just before the division, denoted by $\mathbf{X}(T_1)$, satisfies the relation, because of our assumption of perfect halving at the division, $\mathbf{X}_1 = \mathbf{X}(T_1)/2$. This procedure can be iterated to each division, resulting in a map which relates the amount of \mathbf{X} and the end of the k -th division, to the same quantity at the beginning of the cycle:

$$\frac{\theta}{2} = \int_{T_k}^{T_{k+1}} \frac{dC}{dt} dt \quad \text{and} \quad \mathbf{X}_{k+1} = \frac{1}{2} \mathbf{X}(T_{k+1}). \quad (3)$$

3 Synchronization in linear surface–reaction models

Synchronization will be achieved if after sufficiently many cell divisions, the initial quantity of all inner chemicals between successive duplications approaches a constant value, $\mathbf{X}(T_k) \rightarrow \mathbf{X}_\infty$, for some finite positive value \mathbf{X}_∞ . As observed above, this implies that, as k grows, also the division time approaches a constant finite value, $\Delta T_k \rightarrow \Delta T_\infty$.

To determine the occurrence of synchronization we study the behavior of the system in the continuous growth phase between two successive generation, ruled by Eq. 2, hence the required map, at the k -th division cycle, is:

$$\mathbf{X}(T_{k+1}) = e^{M\Delta T_k} \mathbf{X}_k \quad \text{and} \quad \mathbf{X}_{k+1} = \frac{1}{2} e^{M\Delta T_k} \mathbf{X}_k, \quad (4)$$

from which a necessary and sufficient condition to ensure synchronization is easily obtained $\mathbf{X}_\infty = \frac{1}{2} e^{M\Delta T_\infty} \mathbf{X}_\infty$, which is equivalent to require:

$$M\mathbf{X}_\infty = \lambda\mathbf{X}_\infty \quad \text{and} \quad \lambda = \frac{\log 2}{\Delta T_\infty}. \quad (5)$$

Let us observe that since eigenvectors are determined up to a multiplicative constant, Eqs. 5 do not suffice to determine the asymptotic state of the system, but that the matrix M can be assumed to be invertible¹, thus from Eqs. 2 we get $\frac{d\mathbf{C}}{dt} = \boldsymbol{\alpha} \cdot M^{-1} \frac{d\mathbf{X}}{dt}$, hence the quantity $Q(t) = C(t) - \boldsymbol{\alpha} \cdot M^{-1} \mathbf{X}(t)$, is a first integral. Evaluating $Q(t)$ at the beginning and at the end of the k -th division and using the hypotheses of exact division and halving materials, we obtain in the limit of large k :

$$\frac{\theta}{2} = \boldsymbol{\alpha} \cdot M^{-1} \mathbf{X}_\infty, \quad (6)$$

which together with Eqs. 5 gives us:

$$\Delta T_\infty = \frac{\theta \log 2}{2\boldsymbol{\alpha} \cdot \mathbf{X}_\infty}, \quad (7)$$

which is the required relationship. The general approach is now clear: from the matrix of the coefficients M one computes the eigenvalues, λ , which in turn determine the asymptotic interval between two successive divisions ΔT_∞ (Eq. 5b). The components of the eigenvector \mathbf{X}_∞ are determined except for a constant, which can be determined from Eq. 6.

Let us now consider the conditions under which the matrix M has the required properties. Remember that the X_i 's are the quantities of the different replicators, therefore they must be real and non-negative, so in order for synchronization to take place in a linear system the (real) matrix M must have a real positive eigenvalue λ with such a real, non-negative eigenvector.

This condition is surely satisfied (applying the Perron-Frobenius theorem [4, 5]) once the matrix M is *non-negative* and *non-null*; physically this assumption implies that there is *no negative interference* between different replicators i and j , the only possible alternatives being that either i favors (e.g. catalyzes) the formation of j or that it does not influence it in any way. Moreover, we must also require that at least one of the entries M_{ij} does not vanish, since otherwise there would be no replication at all.

One can prove that synchronization arises under weaker conditions, in particular the matrix M can have negative entries, but then the *autocatalytic contributions*, i.e. $M_{ii} > 0$, must be *large enough* with respect to the possible inhibitory terms. More precisely using the *Gershgorin circle theorem* [2] and

¹ In fact without loss of generality we will consider the case where $\det M \neq 0$; if this were not the case, some of the differential equations for the X_i 's would be redundant (i.e. their values at time t could be expressed as a function of the values of the other variables at t) and they could therefore be removed from the set of differential equations under consideration.

the assumption that M is a strictly diagonally dominant matrix, i.e. for all i , $|M_{ii}| > \sum_{j \neq i} |M_{ij}|$, then once again one has synchronization provided the off diagonal terms are small enough.

We observed that for generic matrices, i.e. M_{ij} can have both positive and negative signs, and there are no particular relations between their values, synchronization is not always reached, even if there are positive eigenvalues. These situations are surely interesting but for the lack of space and because they deserve future investigations, we here limit ourselves to consider the case where the matrix M is still diagonalizable with the largest eigenvalue real and positive, but the associate eigenvector has not a definite sign.

A possible ansatz could be to extend the previous theory to this case by assuming that, whenever one of X_i 's becomes negative, it has to be interpreted as being actually equal to zero (the non-physical negative value indicating some limitation of the model used). The value of X_i may become positive again at a later time if it is produced by reactions involving other replicators. To test this hypothesis we performed dedicated numerical simulations which show that it often happens that some components get permanently extinguished. If we drop from the matrix M those components which the simulation shows go to extinction, we obtain a reduced matrix M' such that, if it is positive and non-null, the previous analytical theory applies and correctly predicts asymptotic duplication time and quantities of replicators (see left panel of Fig. 1). It may however happen that this latter condition is not satisfied and numerical simulations show that in some cases the synchronization is achieved, while in other cases different behaviors are found, the duplication time does not reach a constant value but seems to oscillate periodically in time (see right panel of Fig. 1).

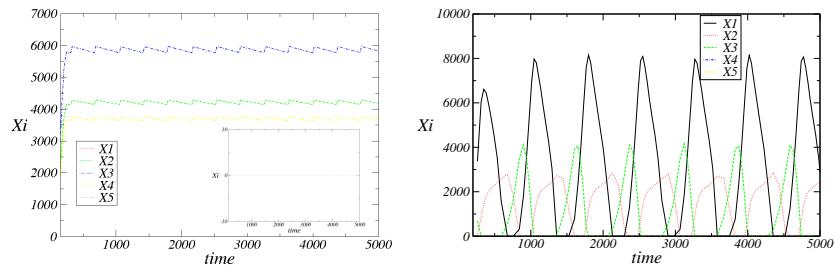


Fig. 1. General cases. On the left an example with 5 replicators such that the interaction matrix possesses a real eigenvalue whose unique eigenvector has negative entries, the “surviving” replicators are those which might have been predicted by inspection of the eigenvector, i.e. X_2 , X_3 and X_4 , in the inset we show X_1 and X_5 that goes to extinction. Right panel an example with 5 replicators such that the interaction matrix possesses a real eigenvalue whose unique eigenvector has negative entries but synchronization is not achieved.

4 Conclusions

In the present paper we address some relevant questions about the synchronization phenomenon for systems where the kinetic equations are linear, while of course non-linear terms may play a key role. While the analysis of non-linear kinetics lies beyond the scope of the present work, let us briefly mention that there are indeed some cases where unbounded growth of the replicator can be observed, as it may happen (depending upon the values of some parameters) when there are two replicators X and Y whose growth rate is proportional to XY . We have also considered models where the growth of each replicator is proportional to its quantity times a sigmoid function which depends upon the presence of other replicators, playing the role of some activating function. We observed that in several cases synchronization is achieved but, depending upon this non-linear term a more intriguing phenomenon can sometimes be observed: the system seems to approach synchronization, but at a certain point there is a sudden drop of one replicator, with a dramatic increase of the replications time. This is followed by a recovery, which may be followed by a further “crisis”, a.s.o. Contrary to what has been observed in some systems with linear kinetics, the crises do not seem to be periodic in time. Further studies are necessary to give a comprehensive account of the behavior of these non-linear systems.

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