Discussion of synchronization problems during cell cycle in artificial cell modeling

Eugenia Schneider[1], Michael Mangold[1]

[1]Max-Planck-Institute for Dynamics of Complex Technical Systems, 39106 Magdeburg, Germany
eschneider@mpi-magdeburg.mpg.de
mangold@mpi-magdeburg.mpg.de

Extended abstract

In the last decades, progresses were made in the insight of microbiological processes. The mathematical description of biological processes by system biological models has been widely accepted as useful for a deepened understanding of existing biological systems. This development paves the way towards a systematic construction of artificial biological systems with tailored properties, which is the topic of synthetic biology.

Our aim is to evolve an artificial cell model consisting of functional biological devices like genome, transcriptome, proteome and metabolome. Although various mathematical models have been proposed to describe an artificial cell (Gánti, 2003; Novák and Tyson, 2008), there is a need for further theoretical analysis and mathematical modeling for a proper understanding of interactions between the functional devices.

Most of the artificial cell models may be structured into three functional devices representing a container forming the boundary of the cell, a metabolism generating the building blocks of the cell, and a programming part containing genetic information and regulating the processes inside the cell (Rasmussen et al., 2003). Self-replication of an artificial cell requires a synchronization of those three functional devices in such a way that at the end of the cell cycle the material in each of the devices has at least doubled. A key problem, which is addressed in this work, seems to be how to find a structure that guarantees this synchronization in a robust way, i.e. more or less independent of the kinetic parameter values. The need for the biological robustness is justified by the aim to be able to deal with perturbations.

As a starting point, we consider the Chemoton model described by T. Gánti (Gánti, 2003). The Chemoton consists of three self-reproducing functional devices: the autocatalytic chemical cycle representing the metabolism, the template polymerization subsystem serving as an information carrier and the membrane representing a container which grows proportional to the polymerization process. Although the Chemoton model is able to show self-sustained oscillations, these oscillations are not necessarily synchronized with cell

growth. To achieve this, a careful tuning of the kinetic parameters is required. The question is, if there is a model structure related to the Chemoton approach that possesses an inherent mechanism guaranteeing the synchronization of metabolism, program and container for a wide range of kinetic parameter values.

As a first step towards such a model structure, we combine the devices of the Chemoton model with the less complex structure of minimal cascade model for the mitotic oscillator described by Goldbeter (1991). The schematic representation of our artificial cell model is shown in Figure 1.
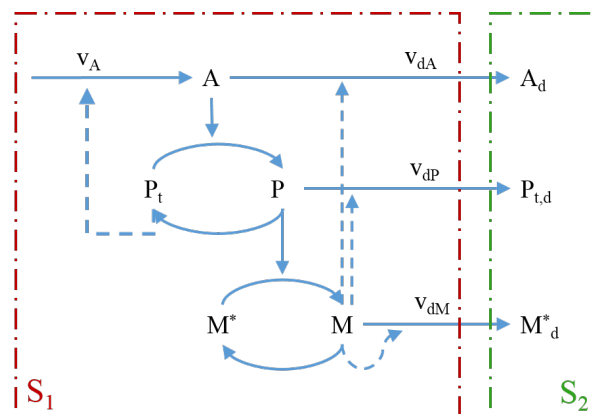

Figure 1: Artificial cell model based on Goldbeter's minimal cascade including the functional devices of Chemoton. System S_1 represents the mother cell and contains the metabolism A, the polymer template P_t, the new growing polymer P, catalytically inactive membrane building blocks M^* and catalytically active membrane building blocks M. The blue solid arrows display catalysis and the dashed arrows show induction. S_2 represent the daughter cell with metabolism component A_d, the polymer template $P_{t,d}$ and the membrane initially composed of inactive membrane building blocks M_d^*.

The mother cell consists of three main devices: the metabolism (A), the polymerization subsystem and the

membrane. We assume that the total quantity of the polymer template P_t and the growing polymer P is $P_t + P = 2$. The membrane is assumed to consist of catalytically inactive building blocks M^* and catalytically active building blocks M whose total concentration amounts to $M^* + M = 2$. The activity of metabolism A is induced by the polymer template $P_t = (2 - P)$ with a constant rate v_A and hence slows down towards the end of the polymer replication when there is hardly P_t in the cell. The polymer replication is catalyzed by A and terminates when P_t is consumed. During the polymerization the growing polymer P catalyzes the conversion of catalytically inactive membrane building blocks M^* into the active state M. After the terminated replication the double-stranded polymer splits into the polymer template P_t and the new polymer $P_{t,d}$ of the daughter cell induced by M with a constant rate v_{dP}. Furthermore, M triggers the transformation of A and M to daughter cell components A_d and M_d^* with constant degradation rates v_{dA}, v_{dM}. The conversion into the daughter cell devices initiates the cell division in our model. Obviously the proposed structure establishes a close interaction between the activation of the metabolism and the replication of the polymer. This interaction forces a synchronization between metabolism and polymerization. For the sake of simplicity volume changes of the mother cell are neglected in a first step. The mass balances of the components A, P, M, A_d, $P_{t,d}$ and M_d^* result in the following set of differential equations:

$$\frac{dA}{dt} = v_A(2 - P) - \frac{v_{dA}MA}{K_{mdA} + A}$$

$$\frac{dP}{dt} = \frac{k_1 A(2 - P)}{K_{m1} + (2 - P)} - \frac{k_2 P}{K_{m2} + P} - v_{dP}MP$$

$$\frac{dM}{dt} = \frac{k_3 P(2 - M)}{K_{m3} + (2 - M)} - \frac{k_4 M}{K_{m4} + M} - v_{dm}M^2$$

$$\frac{dA_d}{dt} = \frac{v_{dA}MA}{K_{mdA} + A}$$

$$\frac{dP_{t,d}}{dt} = v_{dP}MP$$

$$\frac{dM_d^*}{dt} = v_{dm}M^2$$

The model shows an oscillatory behavior with a stable limit cycle based on the model structure (Figure 2 a, b). When the activity of metabolism A increases, the replicating polymer P increases as well and only then the concentration of the catalytically active building blocks M increases. At high concentrations of M the concentrations of A and P begin to decrease caused by conversion into daughter cell components. As soon as the replicated polymer is split induced by M the metabolism A becomes active again. It is assumed that the cell division occurs at a time point t_{div}, when the concentration of M decreases caused by inactivation of M during the separation of the daughter cell. The concentrations A_d, $P_{t,d}$ and M_d^* at the time point t_{div} are

chosen to determine new initial conditions of the daughter cell: $A_d(t_0) = A_d(t_{div})$, $P_d(t_0) = 2 - P_{t,d}(t_{div})$, $M_d(t_0) = 2 - M_d^*(t_{div})$. The dynamic behavior simulation of the daughter cell is repeated with the new initial conditions. As shown in Figure 2 c, the daughter cell converges on a periodic cycle as well.
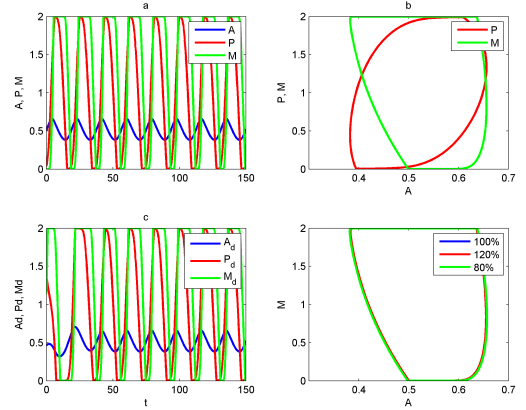

Figure 2: Simulation results of the artificial cell model: dynamic behavior of mother cell components A, P, M (a) and stable limit cycles (b); dynamic behavior of daughter cell's metabolism A_d, growing polymer P_d, catalytically active membrane building blocks M_d (c); limit cycles for different parameter sets of mother cell components (d).

The self-reproducing property of the model could be verified by consideration of daughter cell components. The quantities of conversed materials are sufficient to initiate a new cell cycle of the daughter cell after a certain phase of adaptation (Figure 2 c). Thus the model offers a robust self-replicating state. Furthermore, the system shows the same periodicity for parameter changes of $\pm 20\%$ (Figure 2 d) and is therefore robust in respect of parameter uncertainties. Further interesting aspects, which we want to consider, are how could we modify the structure of Chemoton model to achieve the same qualitative behavior as the system described here.

References

Gánti, T. (2003). *Chemoton theory*, volume 1: Theoretical foundations of fluid machineries, pages 144–159. Kluwer Academic/Plenum Publishers.

Goldbeter, A. (1991). A minimal cascade model for the mitotic oscillator involving cyclin and cdc2 kinase. *Proceedings of the National Academy of Sciences*, 88(20):9107–9111.

Novák, B. and Tyson, J. J. (2008). Design principles of biochemical oscillators. *Nature Reviews Molecular Cell Biology*, 9(12):981–991.

Rasmussen, S., Chen, L., Nilsson, M., and Abe, S. (2003). Bridging nonliving and living matter. *Artificial Life*, 9(3):269–316.