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Multistability and sustained oscillations in a model for protein complex formation

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HIGHLIGHTS

- We study a generic model for the formation of protein complexes.
- Association and dissociation rates are independent parameters.
- At least four elementary protein species are necessary for bistability or oscillations.

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ABSTRACT

We investigate a model for the formation of protein complexes where each protein can occur at most once in a complex. The reaction rates for association and dissociation of proteins can be chosen independently for each reaction, without imposing detailed balance conditions. We show that this simple model can display multistability and periodic oscillations when it contains at least four different protein species. We prove that a system with three elementary species cannot be multistable.

1. Introduction

Most processes in biological cells are carried out by proteins that assemble into complexes ranging from homo- and heterodimers [1–3] to large structures composed of many different polypeptides [4–6]. Essential tasks such as DNA replication, cell cycle control, or DNA damage repair are carried out by such protein complexes. While some protein complexes are stable and permanent, others assemble in response to internal and external cellular signals [7].

The assembly and disintegration of protein complexes is a part of the larger chemical reaction network in biological cells, which is far from thermodynamic equilibrium and therefore displays complex dynamical phenomena, such as the oscillation of glycolysis [8] and the decision on cycle progression via cellular switching [9,10]. Feedback loops are the most important design elements that enable these phenomena [11–14]. Positive feedback loops are required for multiple steady states [11,15], and unlimited multistability can already be obtained in the small subnetwork of multisite phosphorylation [16]. Negative feedback loops are required for periodic oscillations [12]. In fact, chemical kinetics is so versatile that any type of calculation can be performed with it, i.e., it is Turing universal [17]. This universality can also be displayed by subsystems based on DNA strand displacement reactions [18]. The reactions occurring in such systems are nonlinear [19,20], using Michaelis Menten kinetics or Hill functions.

Theoretical investigations of the dynamics of protein complex formation [1,21,22] often use models that satisfy detailed balance relations in equilibrium. This means that in equilibrium all association/dissociation reactions occur with the same

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rate in both directions. Such equilibria are global attractors of the dynamics of the system [23]. However, since the association of transient complexes is triggered in response to internal and external cellular signals, binding and dissociation reactions may be catalyzed. This means that they involve energy-supplying interactions, such as phosphorylation, and therefore detailed balance need not be satisfied at equilibria (which are also called steady states or fixed points).

In this paper, we will investigate under which conditions multistability and periodic oscillations can occur in networks for protein complex formation. These networks are much simpler than the global network since they consist exclusively of association and dissociation reactions and do not allow for the transformation of biomolecules into other molecules. This means that simple positive feedback loops of the form $A+B \to 2A$ are not possible; molecules A and B can only undergo the association and dissociation reactions $A+B \rightleftharpoons AB$. However, positive feedback loops are very important when the system shall move to a different steady state after a transient triggering signal that changes for instance the rates for association or dissociation or the concentration of a protein in its active form. We will confine ourselves to heterocomplexes where each type of protein occurs only once and will prove that complex formation with only three proteins cannot show bistability. Explicitly excluding complexes with multiple identical proteins still allows homomers if these occur as impartible species during the formation of the complex.

For systems with four protein species, we will demonstrate explicitly bistability by giving several examples. Similarly, we will argue that periodic oscillations are not possible with only three protein species and give several examples for periodically oscillating systems with four species.

In the next section, we will describe in more detail the model used for our investigation. In Section 3.1 of the results we discuss the conditions required for bistability and show several examples. Section 3.2 of the results presents a similar study for periodic oscillations. In the discussion section we summarize and discuss our findings. The mathematical framework of chemical reaction network theory [24–27,23,28–30] required for proving that multistability cannot occur with three protein species, and the associated proof, are presented in the Appendix.

2. Materials and methods

Our model for the formation of protein complexes has the following building blocks:

(i) There are m different elementary protein species A, B, C, etc. In this paper, we will only discuss the cases $m = 3$ and $m = 4$.

(ii) Protein complexes are composed of several proteins and are denoted as AB, ABC, etc. Every protein can appear at most once in a complex. Protein complexes consisting of the same combination of elementary species are considered as indistinguishable, independently of their order of assembly. This means that there are altogether $N = 2^m - 1 - m$ complexes consisting of 2 or more proteins.

(iii) The system is closed, and the total amount of each elementary protein is conserved.

(iv) The only chemical reactions that are allowed in the network are the assembly of two reactants to a protein complex and the dissociation of a protein complex into two reactants:

$$A + B \rightleftharpoons AB, \qquad AB + C \rightleftharpoons ABC, \ldots. \tag{1}$$

We allow for reaction constants being zero, which means that a reaction may occur only in one direction or not at all.

For $m = 3$, the complete set of possible reactions is

$$A + B \rightleftharpoons AB, \tag{2}$$

$$A + C \rightleftharpoons AC, \tag{3}$$

$$B + C \rightleftharpoons BC, \tag{4}$$

$$ABC \rightleftharpoons \begin{cases} AB + C, \\ AC + B, \\ BC + A. \end{cases} \tag{5}$$

While it is clear that a system with $m = 2$ elementary species, which has only the reaction $A + B \rightleftharpoons AB$, always settles into a unique and stable steady state, this is not obvious for the network (2)–(5) or for systems with even more elementary species.

3. Results and discussion

3.1. Multistability

Thomas' conjecture [31] states that a positive feedback loop is a necessary (but not sufficient) condition for multiple fixed points in a dynamical system. Christophe Soulé [15] proved that the conjecture holds for differential mappings within an open finite dimensional real vector space, thus validating it for systems of chemical reactions with non-zero concentrations. A positive feedback loop in this context means that there must exist a set of parameters for which one of the concentrations