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Single-variable reaction systems: Deterministic and stochastic models

M.N. Steijaert [a], A.M.L. Liekens [b], D. Bošnački [a], P.A.J. Hilbers [a], H.M.M. ten Eikelder [a,*]

[a] Department of Biomedical Engineering, Eindhoven University of Technology, P.O. Box 513, 5600 MB Eindhoven, The Netherlands
[b] VIB Department of Molecular Genetics, University of Antwerp, Universiteitsplein 1, B-2610 Wilrijk, Belgium

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ABSTRACT

Biochemical reaction networks are often described by deterministic models based on macroscopic rate equations. However, for small numbers of molecules, intrinsic noise can play a significant role and stochastic methods may thus be required. In this work, we analyze the differences and similarities between a class of macroscopic deterministic models and corresponding mesoscopic stochastic models. We derive expressions that provide a clear and intuitive view upon the behavior of the stochastic model. In particular, these expressions show the dependence of both the dynamics and the stationary distribution of the stochastic model on the number of molecules in the system. As expected, most properties of the stochastic model correspond well with those in the deterministic model if the number of molecules is large enough. However, for some properties, both models are inconsistent, even if the number of molecules in the stochastic model tends to infinity. Throughout this paper, we use a bistable autophosphorylation cycle as a running example. For such a bistable system, we give an explicit proof that the rate of convergence to the stationary distribution (or the second eigenvalue of the transition matrix) depends exponentially on the number of molecules.

1. Introduction

In the past decades, new biochemical techniques have led to a large increase in knowledge about biology at the molecular level. Simultaneously, a growing awareness has emerged that reductionism alone is insufficient for unraveling the complex interactions within biochemical networks. This awareness has led to the rise of the holistic field of systems biology, in which wet-lab experiments are combined with (multiscale) computational modeling. Traditionally, most of the systems investigated in this field are described by deterministic models based on ordinary differential equations (ODEs). In addition, there is a growing interest in stochastic modeling techniques [1,2]. The advantage of those stochastic techniques is that they explicitly take into account the intrinsic noise that is present in real-life biochemical networks.

In this paper, we focus on the relations between stochastic and deterministic models for a certain class of biochemical systems. More specifically, we consider systems consisting of a number of similar molecules that can each be in two 'configurations'. Suppose that the reversible interconversion between those configurations is defined by a macroscopic deterministic model based on kinetic rate laws. In principle, such a deterministic model describes the behavior of a reaction system for very large numbers of molecules. For a finite number of molecules, we can also introduce a mesoscopic[1] stochastic Markov model. The parameters for such a model can be derived from the deterministic model. It is generally assumed and for some elementary cases even proven that the expected behavior of the stochastic model corresponds with the dynamics of the deterministic model if the number of molecules in the described volume is large enough [3]. For many smaller systems, a deterministic model also yields a reasonable approximation, which can be analyzed more efficiently than the full stochastic system [4]. However, there are also systems that display significantly different behavior if the number of molecules is relatively small [5].

For some systems it is not trivial to explain how the expected behavior of the stochastic model relates to that of the deterministic model. This paper studies the relation between the stochastic and deterministic models for a specific class of reaction systems. As a running example, we study a bistable reaction system. More precisely, we use both a deterministic and a stochastic model to describe a highly idealized reaction module consisting of a phosphorylation reaction, a de-phosphorylation reaction and a *trans*-autophosphorylation reaction. This running example, further referred to as 'autophosphorylation cycle', illustrates the paradoxical combination of bistability and stochasticity. After all, the long-term behavior of a stochastic model of a chemical reaction system

* Corresponding author. Tel.: +31 40 247 5153.
E-mail address: h.m.m.t.eikelder@tue.nl (H.M.M. ten Eikelder).

[1] Following [10], we use the term *mesoscopic* to refer to the stochastic description of a system in terms of macroscopic variables.

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is in general independent of its initial state, which intuitively conflicts with the required bistability.

In Section 3, we derive a potential function that provides a framework for the analysis of the stochastic model for both small and larger numbers of molecules. This function is used to describe the stationary distribution of the stochastic model and the expected transition times (see Section 4). The expected times of transitions between individual states are also related to the rate at which the probability distribution converges to the stationary distribution. This convergence clearly depends on the eigenvalues of the transition matrix of the stochastic model. We prove in Section 5 that under certain conditions, the transition matrix has an eigenvalue which converges to zero exponentially fast with an increasing number of molecules. In each of Sections 2–5, we first introduce the generic theory and subsequently exemplify this using the autophosphorylation cycle introduced in Section 2. A discussion of both the generic theory and the autophosphorylation cycle follows in Section 6. In this section, we also discuss the resemblances and differences between our work and some classic and more recent research papers in the field of statistical physics.

2. Two models

2.1. Model definitions

In this paper, we focus on systems in which each molecule can be in two 'configurations'. This type of system occurs in many different biological processes. For instance, many signaling proteins can be modified by reversible post-translational modifications such as phosphorylation or methylation [6]. Other examples include molecules that can switch between different conformations or localizations within a cell.

The generic system consists of a total of N molecules, which can be in either of the configurations X_0 and X_1, and the overall reactions

$$X_0 \rightleftarrows X_1$$

To allow a comparison between systems with various values of N, we define the proportion x of the molecules that is in the X_1 configuration. This proportion can be derived from the number of molecules (denoted with #) or from the concentrations (in square brackets):

$$x = \frac{\#X_1}{\#X_0 + \#X_1} = \frac{\#X_1}{N} = \frac{[X_1]}{[X_0] + [X_1]}.$$

As mentioned before, we will compare two representations of this generic system.

The first representation of this system is the 'deterministic model'. In this representation, we use a system of ODEs to describe the time evolution of x. The rate at which x changes due to the reaction $X_1 \to X_0$ is given by a real, smooth, non-negative function $a(x)$; the rate of the opposite reaction is defined by a real, smooth, non-negative function $b(x)$. We further assume $a(x) > 0$ for all $0 \leqslant x < 1$, $a(1) = 0$, $b(x) > 0$ for all $0 < x \leqslant 1$ and $b(0) = 0$. The dynamics of the deterministic model are given by

$$\frac{dx}{dt} = a(x) - b(x). \tag{1}$$

The second representation of the system described above is the 'stochastic model'. In this representation, we consider all possible 'microstates' (further 'states'), each of which corresponds with an integer number of molecules in configuration X_1. Hence, a model with N molecules has $N+1$ possible states, which are numbered according to the number of X_1 molecules (see Fig. 1). We allow only one reaction to occur at a time; hence, from each state only direct

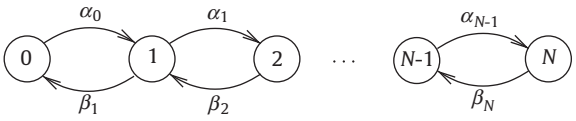

Fig. 1. The $N+1$ states of the stochastic model.

neighbor states can be reached in one reaction step. Due to this 'one-step-at-a-time property' and the Markovian properties of the model, the model is in fact a birth-and-death process [7] in which the forward and backward propensities α_k and β_k, have the role of birth and death rate, respectively.

One of the obvious differences between both models is that N is a parameter of the stochastic model but not an explicit part of the deterministic model. Consequently, the expected behavior of the stochastic model changes with growing N, while the deterministic model is independent of N. To allow a useful comparison, the stochastic models with different values of N must all have the same total concentration as is used in the deterministic model. This means that the volumes of the stochastic models scale linearly with N.

The propensities of state change α_k and β_k in the stochastic model can be related to the deterministic production rates $a(x)$ and $b(x)$ as follows:

$$\alpha_k = Na\left(\frac{k}{N}\right), \tag{2}$$

$$\beta_k = Nb\left(\frac{k}{N}\right). \tag{3}$$

Using those expressions, we ensure that both models act on the same time scale. The relations in (2) and (3) can be used for all unimolecular and pseudo-unimolecular reactions (i.e., reactions in which the total number of molecules does not change). In this way, assumptions about the deterministic model are transferred to the stochastic model. As a result, elementary steps that are hidden in the deterministic model remain hidden in the stochastic model. For the Michaelis–Menten reaction, this is discussed in [8].

Let $\mathbf{z}(t)$ be the probability distribution vector, which contains the probabilities $z_k(t)$ that the system is in a state $k \in \{0,\ldots,N\}$ at a time t. The dynamics of the state probabilities in the stochastic model are described by the Chemical Master Equation [9]:

$$\frac{d\mathbf{z}}{dt} = \mathbf{M} \cdot \mathbf{z}, \tag{4}$$

where the tridiagonal matrix $\mathbf{M} = (m_{ij})$ (with $i,j = 0,1,\ldots,N$), is given by

$$m_{ij} = \begin{cases} \alpha_j & \text{if } j = i-1, \\ \beta_j & \text{if } j = i+1, \\ -\alpha_i - \beta_i & \text{if } j = i, \\ 0 & \text{otherwise.} \end{cases}$$

The stationary distribution for such a birth-and-death process follows directly from its (stochastic) detailed balance property [10] and is given by:

$$Z_k = \frac{\prod_{i=0}^{k-1} \frac{\alpha_i}{\beta_{i+1}}}{\sum_{j=0}^{N}\left(\prod_{i=0}^{j-1} \frac{\alpha_i}{\beta_{i+1}}\right)}. \tag{5}$$

2.2. Trans-autophosphorylation

Throughout this paper we exemplify our methods with the bistable reaction system given by the following reactions:

$$X + S \overset{k_1,\kappa}{\to} X_P + S, \tag{6}$$

$$X + X_P \overset{k_2,\kappa}{\to} 2X_P, \tag{7}$$

$$X_P + U \overset{k_3,\kappa}{\to} X + U. \tag{8}$$