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Simulating bistable biochemical systems by means of reactive multiparticle collision dynamics

Jiang-Xing Chen [a], Jin-Xing Zhu [a], Ye-Hua Zhao [b,*], Wei-Gang Sun [b], Jiang-Rong Xu [a], He-ping Ying [c]

[a] Department of Physics, Hangzhou Dianzi University, Hangzhou 310018, China
[b] Department of Mathematics, Hangzhou Dianzi University, Hangzhou 310018, China
[c] Department of Physics, Zhejiang University, Hangzhou 310027, China

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ABSTRACT

Based on a reactive multiple particle collision method, we construct a mesoscopic dynamics model to simulate chemical system. The validity of the reactive multiple particle collision method under various conditions in a double-feedback bi-stable chemical system is studied. Then, we extend it to simulate diffusion-limited reactions with fast reaction rate in cellular environment. Using the improved method, we observe bi-stable behavior with randomly distributed reactants and spatial domain separation of opposite phases. The particle-based mesoscopic method is computationally efficient, although hydrodynamic interactions and fluctuation are both properly accounted for. Stochastic effects shown to play dominant roles in biochemical dynamics are also considered. The improved method could be used to explore a variety of reactions with disparate scale of reaction rates.

1. Introduction

The classical description of a reaction in solution is based on the mass-action law. This mean-field approximation assumes that (i) the number of molecules is very large so that molecular discreteness can be ignored by a continuous variable, the molar concentration; (ii) the reaction medium is perfectly-mixed so that homogeneous conditions prevail throughout. However, the environment in the living cell is very different from that usually encountered in laboratory studies of chemical reactions [1]. The first assumption is invalid due to small reaction volumes, the intrinsic molecular noise results from low copy number of molecules plays a important role in reaction kinetic. For example, internal noise was shown to induce bi-stability in a system which otherwise would have a unique steady state [2]. Diffusion and reaction are two of the most basic transport mechanisms that underlie the description of a wide range of chemical and biological processes. The second assumption also breaks down when the reaction, compared with diffusion, is very fast. It results from two reasons (i) the cell cytoplasm is a crowded environment, which make the diffusion very slow [3]; (ii) the reaction with big rate k itself is very fast. The diffusion-limited local reaction prevents the reactants to diffuse long distance, which leads to inhomogeneous distribution. In these cases, the usual deterministic differential equation may give misleading results. Consequently, a stochastic description, incorporating the essentially random nature of individual reaction events, is required.

If spatial degrees of freedom play no role when the system is well stirred, birth–death master equation approaches have been applied to describe such reacting systems [4,5]. The master equation can be simulated efficiently using Gillespies algorithm [6,7]. However, if spatial degrees of freedom must be taken into account, then the construction of algorithms is still a

* Corresponding author. Tel.: +86 571 85965662.
E-mail addresses: jxchen@hdu.edu.cn (J.-X. Chen), yhzhao@hdu.edu.cn (Y.-H. Zhao), wgsun@hdu.edu.cn (W.-G. Sun).

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matter of active research. Recently, Rohlf et al. [8] developed a efficient particle-based mesoscopic dynamics method for the simulation of spatially distributed chemically reacting systems under equilibrium and nonequilibrium conditions. This reactive multiple particle collision dynamics (RMPC) is governed by a Markov chain in the full phase space of the system, which reduces to mass action rate laws in the mean field limit. Its validity is perfectly demonstrated in a Selkov model in which diffusion of reactions are slow and their concentrations are high. This condition is similar to the case described by the mean-field approach. Further improvement of the RMPC can concern on two natural questions. One is that: could its validity be kept when the reactions are fast and the solution is dilute. Another is that: could it be applied to simulate the inhomogeneous distribution of reactants.

On the other hand, bi-stability may lead to the emergence of spatial coherence resonance where noise plays an important role [8]. For example, internal noise [9,10] and external noise [11,12] may lead to spatial coherence resonance in excitable media. Bi-stable chemical systems are the basic building blocks for intracellular memory and cell fate decision circuits [13]. These circuits are built from molecules presented at low copy numbers which may result in the intrinsic molecular noise. An example is gene transcription where only tens of free RNA polymerase molecules are involved in the process. Those molecules diffuse slowly in complex intracellular geometries. Inhomogeneous distribution of reactants may result from rapid reactions. In such condition, stochastic descriptions of the chemical reactions is necessary.

In this paper, we use a bi-stable chemical systems to exemplify the validity of RMPC in various conditions. The outline of this paper is as follows. In Section 2, we present a bi-stable biochemical system built on the double-negative feedback principle [13–15]. RMPC method is employed to construct a stochastic model to simulate the reaction and diffusion processes. In Section 3, we discuss the validity of RMPC in various conditions and extend it to simulate dilute and diffusion-limited reaction in cellular environment. In Section 4, we present the bi-stable behavior of the double-negative feedback systems. A conclusion is given in Section 5.

2. Simulation model

2.1. Reaction network based on double-negative feedback principle

We model a bi-stable biochemical system by the following reaction network [14,15]:

$$E_A \xrightarrow{k_1} E_A + A, \tag{1}$$

$$E_B \xrightarrow{k_1} E_B + B, \tag{2}$$

$$E_A + B \underset{k_d}{\overset{k_a}{\rightleftharpoons}} E_A B, \tag{3}$$

$$E_B + A \underset{k_d}{\overset{k_a}{\rightleftharpoons}} E_B A, \tag{4}$$

$$E_A B + B \underset{k_d}{\overset{k_a}{\rightleftharpoons}} E_A B_2, \tag{5}$$

$$E_B A + A \underset{k_d}{\overset{k_a}{\rightleftharpoons}} E_B A_2, \tag{6}$$

$$A \xrightarrow{k_4} \emptyset, \tag{7}$$

$$B \xrightarrow{k_4} \emptyset. \tag{8}$$

Here E_A and E_B are two kinds of enzymes. In the reaction (1) and (2), two different compounds A and B are synthesized by E_A and E_B with phenomenological rate constant $k_1 = 150\ s^{-1}$, respectively. The double-negative feedback principle is illustrated by the reactions (3)–(6) where the activity of E_A (E_B) will be inhibited by associating with B (A) when they encounter with phenomenological rate constants $k_a = 1.2 \times 10^8\ s^{-1}\ M^{-1}$ and $k_d = 10\ s^{-1}$. Free compounds A and B decay with $k_4 = 6\ s^{-1}$ in reactions (7) and (8).

2.2. Diffusion dynamics

The diffusion dynamics of reactive species and solvent molecules is described by multiparticle collision dynamics (MPC). This mesoscopic dynamics method preserves important general features of full molecular dynamics, such as the basic mass, momentum and energy conservation laws [16,17]. However, it is computationally efficient since there are no forces among the majority of the particles in the system. Because our dynamics preserves the basic conservation laws, hydrodynamic interactions and fluctuation, are properly accounted for and no additional assumptions about friction coefficients or random forces as that in Langevin equations need be made. Stochastic effects as discussed above were shown to play dominant roles in biochemical dynamics [18,19]. They may fully be considered in MPC. MPC dynamics has been used to study the dynamics of colloidal suspensions, polymer, protein, molecular machines in chemically active media [20], lipid bilayer [21], and