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Modelling and simulating reaction–diffusion systems using coloured Petri nets

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ABSTRACT

Reaction–diffusion systems often play an important role in systems biology when developmental processes are involved. Traditional methods of modelling and simulating such systems require substantial prior knowledge of mathematics and/or simulation algorithms. Such skills may impose a challenge for biologists, when they are not equally well-trained in mathematics and computer science. Coloured Petri nets as a high-level and graphical language offer an attractive alternative, which is easily approachable. In this paper, we investigate a coloured Petri net framework integrating deterministic, stochastic and hybrid modelling formalisms and corresponding simulation algorithms for the modelling and simulation of reaction–diffusion processes that may be closely coupled with signalling pathways, metabolic reactions and/or gene expression. Such systems often manifest multiscaleness in time, space and/or concentration. We introduce our approach by means of some basic diffusion scenarios, and test it against an established case study, the Brusselator model.

1. Introduction

Reaction–diffusion systems often play an important role in systems biology, such as for the modelling of developmental processes [1,2]. Cellular or subcellular biological processes with fast diffusion of species can be seen as homogeneous, and thus spatial effects can be ignored. However, if the diffusion is slow, the spatial distribution of species is not uniform and has to be taken into account.

A traditional and widely used approach to represent such reaction–diffusion processes deploys deterministic partial differential equations (PDEs) [3], which describe the time evolution of spatially dependent concentrations. Although this formalism is attractive and mathematically well understood, it becomes inaccurate or even inapplicable when there are relatively few numbers of chemical species or stochastic fluctuations play an important role in a biological process.

Consequently, stochastic modelling of reaction–diffusion systems, using, e.g., chemical master equations [4], is increasingly gaining attention. It deals with discrete numbers of molecules of the chemical species involved and provides more accurate results than deterministic PDEs. A couple of stochastic simulation algorithms have been proposed, see, e.g., [2] for a review. For example, Brownian dynamics is a particle-based approach with continuous time and space, in which molecules evolve in terms of the Langevin equation. Cellular automata work on a lattice with a finite number of states in discrete time, in which diffusion is realized by the transition of molecules from some sites to neighbouring sites. Recently, Gillespie's stochastic simulation algorithm (SSA) [5] has been extended for spatial simulation by dividing a system into a number of well-mixed subvolumes or compartments, in which diffusion is treated as a random jump between neighbouring subvolumes or compartments [6,7].

Biological systems including reaction–diffusion processes usually comprise a variety of chemical and physical processes, e.g., molecular binding, enzymatic reactions and complex protein interactions. Some species can be present in small numbers of molecules, and other species in large numbers of molecules; some reactions may be slow, but others fast. For such highly heterogeneous reaction–diffusion systems, a single modelling and simulation method is usually not sufficient. It is necessary to combine different stochastic and deterministic methods to build a hybrid simulator addressing different aspects of a system [2], e.g., using SSA for small numbers of molecules and numerical integration of ordinary differential equations (ODEs) for large numbers of molecules, which are considered as concentrations.

Recently, we have explored different scenarios for the modelling and analysis of (multiscale) biological systems using coloured

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Petri nets. For example, in [8,9] we discussed spatial modelling and the colouring of space (discretisation), and in [10,11] the modelling of membrane systems and coupled Ca^{2+} channels, respectively.

In this paper, we will describe in detail how to model and simulate reaction–diffusion systems using a coloured Petri net framework that contains coloured stochastic Petri nets ($\mathcal{SPN}^{\mathcal{C}}$), coloured continuous Petri nets ($\mathcal{CPN}^{\mathcal{C}}$), and coloured generalised hybrid Petri nets ($\mathcal{GHPN}^{\mathcal{C}}$). We will show how standard high-level formalisms, which are typical for and well established in computer science, can be conveniently applied to deal with important biological problems, e.g., the reaction–diffusion problem. Compared with our previous work, this paper will address some specific issues associated with the modelling of reaction–diffusion systems. We present a systematic and step-wise approach to modelling them using coloured Petri nets and discuss in detail the colouring of space and the flexible representation of diffusion rates.

We are motivated by a couple of reasons. Firstly, coloured Petri nets are graphical and intuitive means, which are easy to construct and comprehend. Colours can be used to represent the locality of species, and thus diffusion can be treated as recolouring of species. Secondly, coloured Petri nets permit a parameterised modelling style. They allow us to easily change the size (resolution) of the space by changing the number of colours, or to adapt the notion of space by adapting the colour definitions. Thirdly, coloured Petri nets are promising to provide a unifying framework integrating deterministic, stochastic and hybrid formalisms to model and simulate different types of reaction–diffusion systems. Coloured Petri nets offer a large variety of analysis techniques, enable a wide range of analysis tasks (e.g., simulation with varying diffusion rates or different initial concentrations), and are supported by powerful tools like Snoopy [12,13]. Therefore, we are pioneering to apply coloured Petri nets, as we do believe that biologists are ready to use such convenient methods to cope with reaction–diffusion systems.

The main contributions of this paper are as follows. We present a new coloured Petri net approach with special emphasis on systems biology to model and simulate reaction–diffusion systems. Distinguished features of our approach are a method for representing spatial attributes of reaction–diffusion systems using easily exchangeable colour definitions, and a method for a flexible representation of state- and/or space-dependent diffusion rates.

In the remainder of this paper, we first briefly recall reaction–diffusion systems in Section 2 and coloured Petri nets in Section 3. We then introduce how to model reaction–diffusion systems using coloured Petri nets in Section 4 and give a case study, the Brusselator, in Section 5, followed by related work, reproducibility and the conclusions in Sections 6, 7 and 8, respectively.

2. Reaction–diffusion systems

When there is an abundance of species, a reaction–diffusion process can be modelled as a system of deterministic differential equations. For example, a biological deterministic reaction–diffusion system and its evolution over time τ can be given by a system of PDEs [14]

$$\frac{\partial S}{\partial \tau} = f(S) + D\nabla^2 S \tag{1}$$

where S is a vector of concentrations of chemical species, f denotes the production and degradation of species, D is a diagonal matrix of diffusion coefficients, and ∇ is the Laplacian operator.

However, small abundance of species causes deterministic models to become inaccurate or even inappropriate, thus stochastic approaches have been used to simulate stochastic fluctuations. In this case, a reaction–diffusion system can be formulated as a master equation and thus stochastic simulation algorithms like the Gillespie stochastic simulation algorithm (SSA) have to be applied. A common approach [6,15] is to divide the whole system volume Ω into N well-mixed subvolumes (compartments), each of which has a size of h. Therefore, diffusion is treated as a Markov jump process between neighbouring subvolumes with a rate constant $k = D_c/h^2$, where D_c is the diffusion constant.

For example, consider a species, S, diffusing in one-dimensional space, see Fig. 1. For this, the whole space is divided into N subvolumes. We denote the number of molecules of S in the ith subvolume by S_i, $i = 1, 2, \ldots, N$. Assume k_1 and k_2 are two rate constants of the two diffusion directions, the one from left to right and the other from right to left, respectively. Then the diffusion process can be described as a set of chemical reactions

$$S_j \underset{k_2}{\overset{k_1}{\rightleftharpoons}} S_{j+1}, \quad j = 1, 2, \ldots, N-1, \tag{2}$$

each governed by mass action kinetics parameterised with the rate constants k_1 and k_2.

Let $p(\mathbf{n}, \tau)$ be the joint probability at time τ such that $S_i = n_i$, $i = 1, 2, \ldots, N$, with $\mathbf{n} = (n_1, n_2, \ldots, n_N)$, denoting the number of molecules of species S in each of the N subvolumes. Let $L2R_i, R2L_i : \mathbb{N}^N \to \mathbb{N}^N$ be two functions [15] defined by

$$\begin{aligned} L2R_i : (n_1 \ldots, n_{i-1}, n_i, \ldots, n_N) \\ \to (n_1 \ldots, n_{i-1} - 1, n_i + 1, \ldots, n_N), \end{aligned} \tag{3}$$

with $i = 2, \ldots, N$, and

$$\begin{aligned} R2L_i : (n_1 \ldots, n_i, n_{i+1}, \ldots, n_N) \\ \to (n_1 \ldots, n_i + 1, n_{i+1} - 1, \ldots, n_N), \end{aligned} \tag{4}$$

with $i = 1, \ldots, N-1$.

$L2R_i$ ($R2L_i$) describes the change of the number of molecules in subvolume i, caused by its left (right) neighbouring subvolume $i-1$($i+1$).

Then, the master equation that corresponds to the system of chemical reactions given by Eq. (2) can be written as

$$\begin{aligned} \frac{\partial p(\mathbf{n}, \tau)}{\partial \tau} = k_1 \sum_{i=2}^{N} \{(n_i + 1) p(L2R_i \mathbf{n}, \tau) - n_i p(\mathbf{n}, \tau)\} \\ + k_2 \sum_{i=1}^{N-1} \{(n_i + 1) p(R2L_i \mathbf{n}, \tau) - n_i p(\mathbf{n}, \tau)\}, \end{aligned} \tag{5}$$

where the first (second) term on the right hand side corresponds to diffusion jumps from left (right) neighbours [15]. This equation can be seen as a discretisation in space of the diffusion item (the second item) of Eq. (1).

3. Coloured Petri nets

3.1. Petri nets

Petri nets [16] are weighted, directed, bipartite graphs, consisting of places, transitions and arcs that connect them. Places usually represent passive system components like atoms, molecules, genes, mRNAs, proteins, cells, or entire populations. Transitions represent active system components like different kinds of chemical reactions, e.g., association, dissociation, translation, transcription or diffusion. A place may contain one or more tokens,

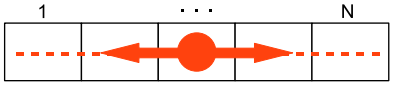

Fig. 1. Diffusion in one-dimensional space. Each non-boundary subvolume has two neighbours, the immediately left and right neighbours.