Application of Stochastic Petri Nets and Gillespie Algorithm to biological systems

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Current modeling, simulation and analysis of biological systems are mainly performed by continuous deterministic models. However, cellular behaviors are stochastic, the deterministic models cannot fully explain the biological systems, and the study of stochastic behaviors in the cell could help to understand the organization, design and evolution of the cell. Stochastic Petri Nets are ideal tools for stochastic modeling. In the present paper, we study the modeling and quantitative analysis of biological systems with Stochastic Petri Nets. After a brief description of Stochastic Petri Nets theory, we first construct Stochastic Petri Nets models for several typical biological systems: a cycle reaction system, a transcriptional regulation system and the actin filament elongation and branching system. Then, we simulate the evolution for the state of these biological Stochastic Petri Nets models with Gillespie algorithm.

**Key words:** Gillespie Algorithm, Stochastic Petri Nets, systems biology.

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**INTRODUCTION**

Petri Nets are mathematical descriptions of discrete subsequent systems. They have both rigorous mathematical formulation and intuitive graph representation, and thus have been widely applied to many research areas (Proth, 2006). They are also powerful tools for modeling and simulating biological systems, and have already been used to some types of biological systems, such as gene regulation (Remy et al., 2006; Chaouiya et al., 2008, 2011), signal transduction (Sackmann et al., 2006), metabolism (Voss et al., 2003; Koch et al., 2005; Ding & Li, 2009), etc. [the reader is urged to read two excellent review papers in this field: Chaouiya (2007) and Heiner et al. (2008)]. At present, the structure oriented qualitative analysis with standard Petri Nets is widely used in biological systems (Chaouiya, 2007; Heiner et al., 2008; Ding & Li, 2009). However, cellular behaviors (e.g. gene regulation) are stochastic (Shahrezaei & Swain, 2008; Sinsyn et al., 2009). The deterministic models with standard Petri Nets cannot accurately simulate the dynamics of the biological systems. As an important extension of standard Petri Nets, Stochastic Petri Nets allow us to quantitatively analyze the state of biological systems (Goss & Peccoud, 1998).

On the other hand, (Stochastic) Petri Nets are ideal tools for (stochastic) modeling of biological systems (Voss et al., 2003; Koch et al., 2005; Remy et al., 2006; Sackmann et al., 2006; Chaouiya, 2007; Chaouiya et al., 2008, 2011; Heiner et al., 2008; Ding & Li, 2009). First of all, Petri Nets are proposed to model and analyze system properties such as concurrency, communication and synchronization, and due to the high consistent structure (place – molecular species, transition – reaction, arc – stoichiometric coefficient, etc.), the behaviors of Petri Nets are similar to the ones of biological systems. Second, they have rigorous mathe-
mathematical formulation, which provides a solid theoretical framework to simulate the structure and dynamics. In addition, there are many Stochastic Petri Nets modeling software tools, so that we can easily draw, modify and analyze the models. At last, they support lots of qualitative and quantitative methods (Proth, 2006).

Thus, this article will use the theory of Stochastic Petri Nets to model biological systems. We first construct the Stochastic Petri Nets models for the following biological systems: a cycle reaction system (Székely et al., 2012), a transcriptional regulation system (Marquez-Lago & Burrage, 2007) and the actin filament elongation and branching system (Kawska et al., 2012). Then, we simulated the evolution for the state of these biological Stochastic Petri Nets models using the Gillespie Algorithm (Gillespie, 1976, 1977).

MATERIALS AND METHODS

Stochastic Petri Nets Conception

In general, the Petri Nets studies of biological systems are mainly performed with standard Petri Nets (i.e., place/transition Nets), the main elements of the network are place, transition and arcs (see Table 1 for the terminology). The formal definition of standard Petri Nets could be described by the four-tuple $\mathcal{N} = (P, T, Pre, Post)$, where: $P = \{p_1, ..., p_u\}(u > 0)$ denotes a finite set for places, $T = \{t_1, ..., t_v\}(v > 0)$ denotes a finite set for transitions, $Pre$ is a $v \times u$ matrix containing the weights of the arcs which go from places to transitions and $Post$ is a $v \times u$ matrix containing the weights of the arcs which go from transitions to places.

Experience has shown that the standard Petri Nets are particularly effective tools in modeling biological systems, and have already been applied to types of biological systems (e.g. gene regulation, signal transduction, metabolism) (Voss et al., 2003; Koch et al., 2005; Remy et al., 2006; Sackmann et al., 2006; Chaouiya, 2007; Chaouiya et al., 2008, 2011; Heiner et al., 2008; Ding & Li, 2009). However, the studies in this field mainly focus on qualitative analysis of biological systems while the application of high-level Petri Nets theory (especially Stochastic Petri Nets) is very limited (Goss & Peccoud, 1998; Chaouiya, 2007; Heiner et al., 2008).

Stochastic Petri Nets are important extensions to standard Petri Nets, which add two important elements: marking and weight function (Table 1). The formal definition of Stochastic Petri Nets could be described by the seven-tuple $\mathcal{N} = (P, T, Pre, Post, M, h, c)$, where: the new added vector $M$ is the initial state of the system, the vector $h$ is the reaction rate regulation, and the vector $c$ is the reaction rate constant (Goss & Peccoud, 1998). To construct Stochastic Petri Nets model of a biological system, molecular species are represented by places (circles in graphical representation), reactions are represented by transitions (rectangles in graphical representation), and stoichiometric coefficients are marked beside arcs (of course, we also need the $M$, $h$ and $c$). Using the graphical Petri Nets tool Snoopy (see http://www-dssz.informatik.tu-cottbus.de/software/snoopy.html for the current version) (Marwan et al., 2012), we give some simple examples in which Stochastic Petri Nets are used to model basic biochemical reactions (Fig. 1).

<table>
<thead>
<tr>
<th>Stochastic Petri Nets term</th>
<th>Graph representation</th>
<th>Biochemical analogy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Place</td>
<td>○</td>
<td>Molecular species (e.g., metabolite)</td>
</tr>
<tr>
<td>Transition</td>
<td>□</td>
<td>Reaction</td>
</tr>
<tr>
<td>Arc</td>
<td>→</td>
<td>Stoichiometric coefficient</td>
</tr>
<tr>
<td>Marking</td>
<td>●</td>
<td>Number of molecules</td>
</tr>
<tr>
<td>Weight function</td>
<td>NA</td>
<td>Reaction rate</td>
</tr>
</tbody>
</table>
Stochastic Petri Nets Construction

To demonstrate the construction of Stochastic Petri Nets, we take a simple cycle reaction system [Székely et al. (2012), see RESULTS AND DISCUSSION – Cycle Reaction System for the initial model and parameters]. According to the theory of Stochastic Petri Nets, we can create the graphic representation of Stochastic Petri Nets model for the cycle reaction system (Fig. 2).

The corresponding formal definition, i.e., the seven-tuple $N = (P, T, \text{Pre}, \text{Post}, M, h, c)$ could be constructed as below:

Step 1, define a vector $P$ containing all of the metabolite names (according to their appearance order in the reactions list above), i.e., $P = \{X_1, X_2, X_3, X_4, X_5\}$ here.

Step 2, define a vector $T$ containing all of the reaction names (according to their appearance order in the reactions list above), i.e., $T = \{\text{X}_2 \text{Anabolism}, \text{X}_3 \text{Anabolism}, \text{X}_4 \text{Anabolism}, \text{X}_5 \text{Anabolism}\}$ here.

Step 3, define a matrix $\text{Pre}$ containing the weights of the arcs which go from places to transitions (each row represents a reaction and each column represent a reactant in the reaction, according to their appearance order in $T$ and $P$), i.e.,

\[
\text{Pre} = \begin{bmatrix}
1 & 0 & 0 & 0 & 0 \\
0 & 1 & 0 & 0 & 0 \\
0 & 0 & 1 & 0 & 0 \\
0 & 0 & 0 & 1 & 0 \\
0 & 0 & 0 & 0 & 1
\end{bmatrix}
\]

Step 4, define a matrix $\text{Post}$ containing the weights of the arcs which go from transitions to places (each row represents a reaction and each column represent a resultant in the reaction, according to their appearance order in $T$ and $P$), i.e.,

\[
\text{Post} = \begin{bmatrix}
0 & 1 & 0 & 0 & 0 \\
0 & 0 & 1 & 0 & 0 \\
0 & 0 & 0 & 1 & 0 \\
0 & 0 & 0 & 0 & 1
\end{bmatrix}
\]

Step 5, define a vector $M$ containing the initial state of the system (according to their appearance order in $P$), i.e., $M = (200, 100, 100, 100, 100)^T$ here.

Step 6, define a vector $h$ containing the reaction rate regulation (according to their appearance order in $T$), i.e., $h(p, c) = (c_1 \times X_1, c_2 \times X_2, c_3 \times X_3, c_4 \times X_4, c_5 \times X_5)^T$ here.

Step 7, define a vector $c$ containing the reaction rate constant (according to their appearance order in $T$), i.e., $c = (0.5, 0.5, 0.5, 0.5, 0.5)^T$ here.

Gillespie Algorithm

Generally, in Stochastic Petri Nets models of biological systems, the new reaction rate regulation and rate constant are used to represent the stochastic changes in the system, that is, the state of the Stochastic Petri Nets will change according (in a random and dynamic way) to reaction rate regulation and rate constant, and the state transition probability is only dependent on the current status. Thus, the stochastic simulation methods (such as Gillespie Algorithm) could be used to simulate the evolution for the state of Stochastic Petri Nets.

Gillespie stochastic simulation algorithm is a standard algorithm for the current simulation in biochemical reaction systems. We engage R (R Core Team, 2013) and use the R package “smfsb” (see http://cran.r-project.org/web/packages/smfsb/index.html for the current version) for the simulation (Wilkinson, 2011). The basic analysis steps are summarized as follows:

Step 1, initialization, i.e., given the reaction rate constant vector $c = (c_1, c_2, \dots, c_v)$, as well as the initial molecule numbers of every substance $x = (x_1, x_2, \dots, x_u)$ in the system at the initial time $t = 0$.

Step 2, calculate all of reaction rate regulation in the system under the current state, i.e., $h_i(x, c_i)$ ($i = 1, 2, \ldots, v$), and $h(x, c) = h_1(x, c_1) + h_2(x, c_2) + \ldots + h_v(x, c_v)$.

Step 3, according to the random number $e^{h(x, c)\tau}$, to determine the next event occurred after a time interval $\tau$.

Step 4, according to the random number, $h_i(x, c_i)/h(x, c)$ ($i = 1, 2, \ldots, v$), to determine the changes of the molecule numbers of every substance in the system.
when the next event occurs, that is \( x' \).

Step 5, update time \( t = t + t' \), update the molecule numbers of every substance in the system \( x = x + x' \).

Step 6, if \( t < T_{\text{max}} \), then go to step 2.

### RESULTS AND DISCUSSION

#### Cycle Reaction System

We first use a simple cycle reaction system which is constructed by Székely et al. (2012) to perform the Stochastic Petri Nets modeling and Gillespie stochastic simulation experiment. This cycle reaction system contains five chemical reactions, as described below:

As a simple illustrative example, we assume that the values of \( c_1, c_2, c_3, c_4 \) and \( c_5 \) are all equal to 0.5. In addition, we assume that at the initial moment time \( t = 0 \), the initial quantity \( X_1 \) in the system is 200, the initial quantity of other substances are all 100. According to the theory of Stochastic Petri Nets (see MATERIALS AND METHODS – Stochastic Petri Nets Construction), we can create the corresponding Stochastic Petri Nets model for the cycle reaction system, as follows:

\[
N = (P, T, \text{Pre}, \text{Post}, M, h, c),
\]
\[
P = \{ X_1, X_2, X_3, X_4, X_5 \},
\]
\[
T = \{ X_2 \text{Anabolism}, X_3 \text{Anabolism}, X_4 \text{Anabolism}, X_5 \text{Anabolism}, X_1 \text{Anabolism} \},
\]
\[
\begin{bmatrix}
1 & 0 & 0 & 0 & 0 \\
0 & 1 & 0 & 0 & 0 \\
0 & 0 & 1 & 0 & 0 \\
0 & 0 & 0 & 1 & 0 \\
0 & 0 & 0 & 0 & 1
\end{bmatrix}
\]
\[
\begin{bmatrix}
0 & 1 & 0 & 0 & 0 \\
0 & 0 & 1 & 0 & 0 \\
0 & 0 & 0 & 1 & 0 \\
1 & 0 & 0 & 0 & 0
\end{bmatrix}
\]
\[
M = (200, 100, 100, 100, 100) \mathbb{T},
\]
\[
h(p, c) = (c_1 \times X_1, c_2 \times X_2, c_3 \times X_3, c_4 \times X_4, c_5 \times X_5) \mathbb{T},
\]
\[
c = (0.5, 0.5, 0.5, 0.5, 0.5) \mathbb{T}.
\]

Subsequently, we use the Gillespie stochastic simulation algorithm to simulate the evolution for the state of the Stochastic Petri Nets model of the cycle reaction system; the time evolution of the numbers of every substance in the system is shown in Figure 3.

#### Transcriptional Regulation System

Then, we used Marquez-Lago and Burrage transcriptional regulation system (Marquez-Lago & Burrage, 2007) to perform the Stochastic Petri Nets modeling and Gillespie stochastic simulation experiment. The chemical reactions involved in the transcriptional regulation system are described below:

First, according to the experimental data, we can obtain the values of \( c_1, c_2, c_3, \ldots, c_{12} \) (15, 15, 5 \times 10^{-4}, 2, 1 \times 10^{-3}, 6, 5, 5 \times 10^{-4}, 2, 1 \times 10^{-3}, 6 \) and 5, respectively). In addition, we assume that at the initial moment time \( t = 0 \), the initial quantity of \( E_A \) and \( E_B \) in the system are both 100, the initial quantity for other substances are all 10. Based on the theory of Stochastic Petri Nets, we can then construct the Stochastic Petri Nets model corresponding to the transcriptional regulation system, as follows:

\[
N = (P, T, \text{Pre}, \text{Post}, M, h, c),
\]
\[
P = \{ A, B, E_A, E_B, E_{AB}, E_{AB2}, E_{BA}, E_{BA2} \},
\]
\[
T = \{ A \text{ Production}, B \text{ Production}, E_{AB} \text{ Anabolism}, E_{AB} \text{ Catabolism}, E_{AB2} \text{ Anabolism}, E_{AB2} \text{ Catabolism}, E_{BA} \text{ Anabolism}, E_{BA} \text{ Catabolism}, B \text{ Degradation} \}.
\]
FIG. 3. Simulating the evolution of Stochastic Petri Nets model for the cycle reaction system.

FIG. 4. Simulating the evolution of Stochastic Petri Nets model for transcriptional regulation system.
\[ M = (10, 10, 100, 100, 10, 10, 10, 10) \] T, 
\[ h(p, c) = (c_1 \times E_A, c_2 \times E_B, c_3 \times E_A \times B, c_4 \times E_A B, c_5 \times \nabla A B \times B, c_6 \times E_A B^2, c_7 \times A, c_8 \times E_A B, c_9 \times \nabla A B, c_{10} \times \nabla A B^2, c_{11} \times E_A B^2, c_{12} \times B) \] T, 
\[ c = (15, 15, 5 \times 10^{-3}, 2, 1 \times 10^{-3}, 6, 5, 5 \times 10^{-4}, 2, 1 \times 10^{-3}, 6, 5) \] T. 

Subsequently, we use the Gillespie stochastic simulation algorithm to simulate the evolution for the state of the Stochastic Petri Nets model of the transcriptional regulation system; the time evolution of the numbers of every substance in the system is shown in Figure 4.

**Actin Filament Elongation and Branching System**

Actin filaments are one of the major three kinds of cytoskeletal filaments, which play a fundamental role in many biological processes, such as cell division, cell motility, endocytosis, and morphogenesis. At last, we use the actin filament elongation and branching system (Kawska et al., 2012) to further demonstrate the Stochastic Petri Nets modeling and Gillespie stochastic simulation experiment in biological systems. The reactions of this process are described below:

First, according to the experimental data (Kawska et al., 2012), we obtain the values for \( c_1, c_1r, c_2, c_2r, c_3, c_4 \) and \( c_{4r} \), we consequently initialize the rate constants vector \( c \) of the reaction systems to \((42.9, 25.6, 0.80, 0.74, 11.6, 3.0, 0.00155)\) T. Then, we used the best fit of experimental data to initialize the initial state of the system, that is, at the initial moment time \( t = 0 \), there are 50 Arp2/3, 25 filaments and 20 CP (nM), we assume that GAct and NPF are fit of Arp2/3, thus vector \( M \) is \((50, 50, 50, 0, 25, 0, 0, 20, 0) \) T.

According to the theory of Stochastic Petri Nets, we can then construct the corresponding Stochastic Petri Nets model for the system, which is described below:

**Stochastic Petri Nets**

\[ N = (P, T, Pre, Post, M, h, c), \]
\[ P = \{GAct, NPF, Arp2/3, G^*, Filament, B, Bp, CP, Bc\}, \]
\[ T = \{G^* Formation, G^* Degradation, Branching, Reverse Branching, Actin Polymerization, Capping, Reverse Capping\}, \]
\[ M = (10, 10, 100, 100, 10, 10, 10, 10) \] T,
\[ h(p, c) = (c_1 \times GAct \times NPF \times Arp2/3, c_1r \times G^*, c_2 \times G^* \times Filament, c_2r \times B, c_3 \times GAct \times B, c_4 \times CP \times Bp, c_{4r} \times B) \] T,
\[ c = (42.9, 25.6, 0.80, 0.74, 11.6, 3.0, 0.00155) \] T.

\[ \]
Subsequently, we applied the Gillespie stochastic simulation algorithm to simulate the evolution of the Stochastic Petri Nets model for actin filaments elongation and branching system; the time evolution of the number of substances in the system is shown in Figure 5.

To validate the efficiency of using Stochastic Petri Nets in modeling biological systems, we revisit the transcriptional regulation system above. With a more empirical initial state (Székely et al., 2012), we implemented the simulation $1 \times 10^6$ times. The simulation results are then compared to the results from Székely et al. (2012) (Table 2), and it is clear that the results are consistent between the two studies, which have shown that Stochastic Petri Nets are useful in stochastic modeling in biological systems.

### TABLE 2. A comparative study of the transcriptional regulation system to validate the efficiency of using Stochastic Petri Nets in modeling biological systems

<table>
<thead>
<tr>
<th>Molecular species</th>
<th>Initial molecular number</th>
<th>Final molecular number*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>State #1</td>
</tr>
<tr>
<td>A</td>
<td>20000</td>
<td>10421</td>
</tr>
<tr>
<td>B</td>
<td>15000</td>
<td>4884</td>
</tr>
<tr>
<td>$E_A$</td>
<td>9500</td>
<td>3595</td>
</tr>
<tr>
<td>$E_B$</td>
<td>9500</td>
<td>1528</td>
</tr>
<tr>
<td>$E_A B$</td>
<td>2000</td>
<td>4593</td>
</tr>
<tr>
<td>$E_A B_2$</td>
<td>500</td>
<td>3813</td>
</tr>
<tr>
<td>$E_B A$</td>
<td>2000</td>
<td>3854</td>
</tr>
<tr>
<td>$E_B A_2$</td>
<td>500</td>
<td>6618</td>
</tr>
</tbody>
</table>

*Final molecular numbers in state #1 are from Székely et al. (2012), while those in state #2 are obtained in our simulation.
With the three biological systems as examples, we have demonstrated that Stochastic Petri Nets models can be easily constructed and analyzed for biological systems. With the examples, it is clear that Stochastic Petri Nets have rigorous mathematical formulation, but it’s unlike traditional mathematical tools (e.g., Kolmogorov equations) which can only study small biological systems (Mosconi et al., 2008). Stochastic Petri Nets are easy scalable in its scale with detailed biochemical data of biological systems. Many existing software can be easily used to construct Stochastic Petri Nets models of biological systems, and as well as solve related questions in such models, which facilitate biologists to focus on the construction, analysis and understand of biological Stochastic Petri Nets models, rather than the implementation.

CONCLUSION

Since 1993, the Petri Nets are used to simulate the metabolic processes (Reddy et al., 1993) and many research groups tracking the topic [(see review papers of Chaouiya (2007) and Heiner et al. (2008)]. Typically, Petri Nets modeling analysis of biological systems is mainly performed with standard Petri Nets (i.e., Place/Transition Nets). However, these studies only focus on the application of standard Petri Nets to complete some qualitative analysis of biological systems, in defiance of the stochastic behaviors in these systems. In contrast, Stochastic Petri Nets could overcome the challenge (Goss & Peccoud, 1998).

Combined with the theory of Stochastic Petri Nets and Gillespie algorithm, this article performs the modeling and quantitative analysis of biological systems. With the three examples, the intuitionistic graphical representation, rigorous mathematical formulation, and many existing software made Stochastic Petri Nets are ideal tools for stochastic modeling in biological systems.

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