A Stochastic Simulation Algorithm For Biochemical Reactions With Delays

Pei Wang
Sch. Math. Inf. Sci.
Henan University
Kaifeng 475004, China
Email: wp0307@126.com

Jinhu Lü
Acad. Math. Syst. Sci.
Chinese Academy of Sciences
Beijing 100190, China
Email: jhlu@iss.ac.cn

Li Wan
Sch. Math. Comput. Sci.
Wuhan Textile University
Wuhan 430073, China
Email:wanlinju@yahoo.com.cn

Yao Chen
Sch. Elect. Inf. Eng.
Beijing Jiaotong Univ.
Beijing 100044, China
Email: chenyao07@gmail.com

***Abstract*—Biochemical systems can be described by biochemical reactions. Biochemical reactions can be investigated through mathematical modeling and stochastic simulations. Deterministic and stochastic models are two basic categories of models for biochemical reactions. Due to transmembrane transportation of biochemical species and delayed degradation, time delays are ubiquitous in coupled biochemical systems. Therefore, models for biochemical reactions can be further classified into delayed and un-delayed ones. For biochemical systems without delays, researchers have established the connections between deterministic models and stochastic models directly from the deterministic ones. For delayed biochemical systems, researchers have proposed some stochastic simulation methods to cope with biochemical reactions with time delays. However, the existing delayed stochastic simulation algorithms (SSA) are all incapable of realizing the comparison between highly nonlinear deterministic delayed models and stochastic models directly from the the deterministic ones. In this paper, we proposed a delayed SSA, which can realize the comparison between deterministic models and its stochastic counterparts. Furthermore, one can also use the algorithm to investigate intrinsic noise-induced behaviors, and the effect of system volumes. Several numerical examples show the effectiveness and correctness of our algorithm.**

I. Introduction

Biochemical systems can be theoretically analyzed through mathematical models [1]-[22]. Generally speaking, there are two classes of models: stochastic models and deterministic models. The chemical master equation (CME) is a stochastic model, and it can exactly describe the biochemical systems. Deterministic models include ordinary differential equation (ODE) models, delayed differential equation (DDE) models, partial differential equation (PDE) models and so on. Deterministic models are simple models, which are obtained based on some ideal hypotheses. And many factors are ignored in the deterministic models, such as intrinsic noise in the biochemical systems and system volume.

Though the CME can exactly reflect the biochemical systems, it is always too complex for biochemical systems, especially for systems with several species and very high molecular numbers. Researchers have proposed some exact SSAs to numerically simulate the CME. The well-known algorithm is proposed by Gillespie in the year 1977 [4]. And after then, some accelerated algorithms, such as the τ-leap method [6], the hybrid method [7] have been proposed. Time delays are ubiquitous in biochemical systems [8]-[14], to stochastically simulate biochemical systems with time delays, researchers have proposed some delayed stochastic simulation algorithms [8], [9], [10], [11], such as the exact direct method [10], the rejection method [9], [10]. Since before we give our main results, we will have to have an overview on related works as preliminaries in Section II, we will not discuss these algorithms in detail here.

In the year 2002, Gonze and coauthors [17] investigated the relationships between deterministic models and stochastic models for circadian rhythms. Where they established an ODE model for the circadian rhythm system from detailed biochemical reactions, and they called the detailed biochemical reactions as developed stochastic model, and the developed model can be simulated by the classical Gillespie algorithm. Moreover, they rewrite the ODE system as birth-death processes, where the gain terms in the right hand of a differential equation are treated as birth precesses,and the lose terms are treated as death processes. These terms are transformed into propensity functions by scaling with system volume Ω. They call the birth-death stochastic models as undeveloped stochastic models, and the undeveloped stochastic model can also be simulated by the Gillespie algorithm. Gonze and coauthors found that the undeveloped stochastic model can well reflect the dynamics as the developed ones,and obviously, the undeveloped stochastic model is much simpler and more time-saving.

However, when there are time delays in the deterministic models, can we rewrite the deterministic models into undeveloped stochastic models? Since the existing delayed SSAs proposed in Ref.[8], [9], [10], [11] were only known to be used to treat developed stochastic models, how can we simulate the highly nonlinear undeveloped delayed stochastic models? Motivated by the above mentioned problems, in this paper, we will propose an undeveloped delayed SSA and discuss the comparison between highly nonlinear deterministic modes and its stochastic counterparts.

The left paper is organized as follows: Section II briefly overviews the Gillespie algorithm and the rejection algorithm for developed delayed stochastic models. Our algorithm for the undeveloped delayed stochastic models will be proposed in Section III. In Section IV, we will give some numerical examples to illustrate the effectiveness and correctness of our algorithm. Conclusions and some discussions will be in the last Section V.

2013 The 7th International Conference on Systems Biology (ISB)
978-1-4799-1389-3/13/$31.00 ©2013 IEEE

II. Overviews and Preliminaries

Before we introduce the new stochastic simulation algorithm, we have a brief overview on stochastic simulation algorithms for biochemical reactions, and take them as our preliminaries.

In the year 1977, Gillespie proposed the direct Gillespie algorithm [4] to simulate biochemical reactions. Suppose the fixed volume Ω contains a spatially uniform mixture of N chemical species, which can interact through M specified chemical reaction channels. The N chemical species are denoted by $S_i, i = 1, 2, ..., N$, and X_i denotes molecular number of S_i. The $\mu' th$ reaction channel is denoted as R_μ, and $a_\mu, (\mu = 1, 2, ..., M)$ denotes the propensity of the reaction channel R_μ. State-change vector $\nu_j = (\nu_{1j}, \nu_{2j}, ..., \nu_{Nj})^T$ denotes the dynamics of the reaction channel R_j, where ν_{ij} represents the changes of species S_i in the R_j reaction channel. t denotes the time, and t_{stop} denotes the maximum time considered of the reaction systems. There are two key points in the direct Gillespie algorithm, namely, which is the next reaction and when the next reaction to happen. Based on the idea of the Monte Carlo simulation, Gillespie has resolved the two key points and given the following exact simulation algorithm. Steps for the algorithm are as follows:

The Direct Gillespie Algorithm:

Step 1. Input values for initial state $X(0) = (X_1(0), ..., X_N(0))^T$ for N species, set time $t = 0$ and reaction counter $i = 1$.

Step 2. When time $t < t_{stop}$, compute the propensities for M reaction channels $a_\mu, \mu = 1, ..., M$ and compute the total propensity $a_0 = \Sigma_\mu a_\mu$, if $a_0 = 0$, stop, else go to step 3-6.

Step 3. Generate uniform random numbers $u_1, u_2 \in [0, 1]$.

Step 4. Compute the time interval until the next reaction $\Delta t_i = -lnu_1/\Sigma_\mu a_\mu$.

Step 5. Find the channel of the next reaction j, namely take j to be the integer for which $\Sigma_{v=1}^{j-1} a_v < u_2 a_0 \leq \Sigma_{v=1}^{j} a_v$.

Step 6. Update X as $X + \nu_j$ according to the $j' th$ reaction channel, update time $t = t + \Delta t_i$ and increase counter $i = i + 1$, go to step 2.

The direct Gillespie algorithm is very time-consuming, and it is almost not feasible even with several species. Therefore, based on the direct Gillespie algorithm, there have been some accelerated algorithms. Such as the τ-leap method [5], [6], the next reaction method, the accurate hybrid stochastic simulation method proposed in Ref.[7].

To cope with chemical reactions with time delays, Bratsun and coauthors[8], Barrio and coauthors[9],Cai [10] and Chen et al. [11] have proposed some stochastic simulation algorithms to deal with chemical reactions with time delays. Among these algorithms, the direct exact stochastic simulation algorithm for chemical reactions with delays [10] was proved to be equivalent to the rejection method proposed by [9]. For simplicity, we mainly overview the rejection method.

Suppose some of the reaction channels or all the reaction channels incur a time delay, and we use $\mathcal{R}_D$ to denote reaction channels with time delays. A reaction $R_i \in \mathcal{R}_D$ will finish with a delay of τ_i after it is initiated. Consequently, the product of reaction R_i will be available after a delay of τ_i, and thus the population of the product will change after a time delay of τ_i. The delayed reactions can further be classified into nonconsuming reactions and consuming reactions, where for nonconsuming reactions, the reactants of an unfinished reaction can participate in a new reaction, and when the nonconsuming reaction occurs, the population of the reactants does not change. While for consuming ones, the reactants of an unfinished reaction cannot participate in a new reaction, and when a consuming reaction occurs, the population of the reactants changes immediately. Following the notations in [10], denote the set of nonconsuming reactions as R_{D1} and the set of consuming reactions as R_{D2}. The rejection algorithm is described as follows [9], [10]:

The Rejection Algorithm:

Step 1. Input values for initial state $X(0) = (X_1(0), ..., X_N(0))^T$ for N species, set time $t = 0$ and reaction counter $COUNT = 1$.

Step 2. When time $t < t_{stop}$, compute propensities for the M reaction channels $a_\mu(\mu = 1, ..., M)$ and compute the total propensity $a_0 = \Sigma_\mu a_\mu$, if $a_0 = 0$, stop, else go to step 3-4.

Step 3. Generate an uniform random number $u_1 \in [0, 1]$. Based on u_1, generate $\Delta t_i = -lnu_1/\Sigma_\mu a_\mu$.

Step 4. If there are delayed reaction(s) to finish in the interval $[t, t + \Delta t_i)$, discard Δt_i, update time t by t_d, where t_d is the time when the first delayed reaction finishes, update state vector X, update $COUNT$ by $COUNT + 1$ and repeat step 2-4. If there is no delayed reaction in the interval $[t, t + \Delta t_i)$, proceed to step 5-7.

Step 5. Generate an uniform random number $u_2 \in [0, 1]$. And find the channel of the next reaction j, namely take j to be the integer for which $\Sigma_{v=1}^{j-1} a_v < u_2 a_0 \leq \Sigma_{v=1}^{j} a_v$.

Step 6. If $R_j \notin \mathcal{R}_D$, update X according to the $j' th$ reaction channel, update $COUNT$ by $COUNT + 1$. If $R_j \in \mathcal{R}_{D2}$, update X by $X + \widetilde{\nu_j}$, where $\widetilde{\nu_j} = (\widetilde{\nu_{1j}}, \widetilde{\nu_{2j}}, ..., \widetilde{\nu_{Nj}})^T$, $\widetilde{\nu_{ij}} = \nu_{ij}$ if $\nu_{ij} \leq 0$, and $\widetilde{\nu_{ij}} = 0$ if $\nu_{ij} > 0$. update $COUNT$ by $COUNT + 1$. If $R_j \in \mathcal{R}_{D1}$, marking the reaction as $\mathcal{R}_{D1}$, change the state vector at $t = t + \Delta t_i + \tau_j$.

Step 7. Set $t = t + \Delta t_i$, go to step 2.

The above algorithm is effective for developed delayed chemical reactions, but it is invalid for undeveloped delayed chemical reactions. In the following section, based on the notations in this section, we propose our stochastic simulation algorithm to cope with undeveloped chemical reactions with time delays.

III. The Undeveloped Delayed Stochastic Simulation Algorithm

In this section, we propose a stochastic simulation algorithm to cope with undeveloped chemical reactions with time delays, for simplicity, we call this algorithm as undeveloped delayed stochastic simulation algorithm (UDSSA). The UDSSA is also based on the direct Gillespie algorithm. Suppose we have established the following delayed differential equation model for a biochemical system:

$$\begin{aligned} \dot{x_i} = \; & f_i(t; x_1(t), x_2(t), ..., x_N(t); \\ & x_1(t - \tau_1), x_2(t - \tau_2), ..., x_N(t - \tau_N); \lambda_i) \\ & - g_i(t; x_1(t), x_2(t), ..., x_N(t); \\ & x_1(t - \tau_1), x_2(t - \tau_2), ..., x_N(t - \tau_N); \theta_i). \\ & i = 1, 2, ..., N. \end{aligned} \quad (1)$$

Where $x_i (i = 1, 2, ..., N)$ denotes the concentration of the

978-1-4799-1389-3/13/$31.00 ©2013 IEEE

$i'th$ species. τ_i denotes the time delay for the $i'th$ species. λ_i and θ_i are two sets of parameter vectors for the $i'th$ equation of system (1). $f_i(t; x_1(t), x_2(t), ..., x_N(t); x_1(t-\tau_1), x_2(t-\tau_2), ..., x_N(t-\tau_N); \lambda_i)$ and $g_i(t; x_1(t), x_2(t), ..., x_N(t); x_1(t-\tau_1), x_2(t-\tau_2), ..., x_N(t-\tau_N); \theta_i)$ are non-negative functions of $t, x_1(t), x_2(t), ..., x_N(t), x_1(t-\tau_1), x_2(t-\tau_2), ..., x_N(t-\tau_N)$, which represent the comprehensive generation rate and consumption rate, respectively.

For systems without time delays, Gonze and Goldbeter and coauthors [17] have proved that the deterministic ODE models for biochemical systems can be rewritten as birth-death biochemical reactions. And the birth-death biochemical reactions were called as undeveloped stochastic models, the stochastic models can be simulated by Gillespie's direct method. They have shown the effectiveness of the stochastic models in investigating the dynamics of the circadian system.

Following the method of Gonze et al., we rewrite system (1) as stochastic birth-death reactions, which are listed in Tab.1.

TABLE I. UNDEVELOPED STOCHASTIC MODEL DIRECTLY FROM SYSTEM (1).

Reaction	Propensity function	Increment of molecular numbers
$\emptyset \xrightarrow{a_i} X_i$	a_i	$(0, 0, ..., 0, \underbrace{1}_{i'th}, 0, ...0, 0)^T$
$X_i \xrightarrow{b_i} \emptyset$	b_i	$(0, 0, ..., 0, \underbrace{-1}_{i'th}, 0, ...0, 0)^T$

Where

$$\begin{aligned} a_i &= \Omega f_i(t; X_1(t)/\Omega, ..., X_N(t)/\Omega; \\ &\quad X_1(t-\tau_1)/\Omega, ..., X_N(t-\tau_N)/\Omega; \lambda_i); \\ b_i &= \Omega g_i(t; X_1(t)/\Omega, ..., X_N(t)/\Omega; \\ &\quad X_1(t-\tau_1)/\Omega, ..., X_N(t-\tau_N)/\Omega; \theta_i); \\ &\quad i = 1, 2, ..., N. \end{aligned} \tag{2}$$

Ω denotes system volume. $X_i(t)$ represents the molecular number for the $i'th$ species at time t. It is noted that, if $f_i(.)$ and $g_i(.)$ were the sum of serval separate terms, then the reactions in (2) should be divided into several separate birth and death reactions for species X_i.

Let's give our stochastic simulation algorithm for biochemical reactions as presented in Tab.1 and Eq.(2). Most parts of the stochastic simulation processes are similar to the direct Gillespie algorithm, except that when one computes the propensity functions with time delays. The main idea of treating the delayed propensity functions is that, when we compute the propensity functions with time delays at time t, we use the history values of X_i at time $t-\tau_i$ to replace the terms $X_i(t-\tau_i)(i = 1, 2, ..., N)$. We note that, since the reaction time steps are randomly generated, therefore, the values of $X_i(t-\tau_i)(i = 1, 2, ..., N)$ can not be always exactly derived, one can only guarantee to call the closest history values at time points t_d, where $|t_d - (t-\tau_i)|$ has the minimum value. Detailed procedures of the UDSSA algorithm are as follows:

The UDSSA:

Step 1. Input values for initial history state $X(t_0) = (X_1(t_0), ..., X_N(t_0))^T$ for the N species, where $t_0 \leq 0$. Input time delays $\tau_1, ..., \tau_N$. Input the stop time t_{stop} and set time $t = 0$ and reaction counter $COUNT = 1$.

Step 2. When time $t < t_{stop}$, compute propensities $a_\mu, b_\mu, \mu = 1, ..., N$ for the $2N$ reaction channels, where the closest history values of $X_i(t-\tau_i)$ is used to compute a_μ, b_μ. Then compute the total propensity $a_0 = \Sigma_\mu(a_\mu + b_\mu)$, if $a_0 = 0$, stop, else go to step 3-6.

Step 3. Generate uniform random numbers $u_1, u_2 \in [0, 1]$.

Step 4. Compute the time interval until the next reaction $\Delta t_i = -lnu_1/\Sigma_\mu a_\mu$.

Step 5. Find the channel of the next reaction j, namely take j to be the integer for which $\Sigma_{v=1}^{j-1} a_v < u_2 a_0 \leq \Sigma_{v=1}^{j} a_v$.

Step 6. Update X according to the $j'th$ reaction channel, update time $t = t + \Delta t_i$, and increase counter $COUNT = COUNT + 1$, go to step 2.

Obviously, this method is not an exact algorithm, however, we can numerically prove the powerful of the UDSSA to simulate stochastic models directly from deterministic delayed models.

IV. NUMERICAL EXAMPLES

A. Example 1: The single gene auto-repression

First of all, we consider a simple example, where there is a single gene X, a protein molecule is produced by this gene with a delay after the transcription process is initiated. And the protein molecular further form dimer and act as a repressor, which inhibit the expression of gene X. We denote the time delay as τ, D represents free promoter binding site for gene X, for simplicity, we also use X, X_2 to denote the protein number and the dimer number. By the law of mass action and the conservation law $[D]+[DX_2] = constant$, we can deduce the mathematical model for this system as:

TABLE II. CHEMICAL REACTIONS IN THE SINGLE GENE AUTO-REPRESSION SYSTEM.

Fast reactions	Dissociation const.	Slow reactions	React. rates
$X + X \rightleftharpoons X_2$	K_1	$D \rightarrow D + X$	r_1
$D + X_2 \rightleftharpoons DX_2$	K_2	$X \rightarrow \phi$	r_2

$$\dot{x} = \frac{\alpha}{1 + x^2(t-\tau)} - \beta x. \tag{3}$$

Where α, β represent the maximal dimensionless transcriptional rate and the degradation rate, respectively. One sets $\alpha = 2, \beta = 0.5, \tau = 10$ in system (3). We can transform system (3) into birth-death processes. The birth process is: $\phi \rightarrow X$, with the propensity function

$$a_1 = \frac{\Omega^3 \alpha}{\Omega^2 + X^2(t-\tau)}.$$

The death process is $X \rightarrow \phi$, with the propensity function

$$b_1 = \beta X.$$

Deterministic simulation result of system (3) by using DDE23 in Matlab, and stochastic simulation results for the birth-death processes based on the UDSSA are shown in Fig.1. In our stochastic simulations, we have set $\tau = 10, \Omega = 10$ and $\Omega = 50$. From the simulation results, we see that the stochastic algorithm can well reflect the dynamics of the system. With the increasing of system volumes, the stochastic evolution curves

978-1-4799-1389-3/13/$31.00 ©2013 IEEE

of molecular numbers can well approximate the deterministic one [19]. Fig.2 shows the case with $\tau = 2, \Omega = 10$, where the system can only converge to its single stable steady state, since the delay is too weak to induce oscillations.

B. Example 2: The toggle switch genetic circuits

Next, we consider the two-component toggle switch system [22], where there are two genes X, Y in the circuit. The product of one gene represses the expression of the other gene. And the two genes consist a positive feedback loop. We use D_x, D_y to denote free promoter binding sites for gene X and Y. For simplicity, we also use X, Y to denote proteins that produced by gene X, Y. X_2, Y_2 represent dimers, which can combine with promoter sites and regulate the expression of the other gene. We further suppose the total concentration of promoter binding sites for the two genes are constants,and denoted by $[D_xT], [D_yT]$,respectively. Basic biochemical reactions are listed in Tab.III.

TABLE III. CHEMICAL REACTIONS IN THE GENETIC TOGGLE SWITCH SYSTEM.

Fast reactions	Dissociation constant
$X + X \rightleftharpoons X_2$	K_1
$Y + Y \rightleftharpoons Y_2$	K_2
$D_y + X_2 \rightleftharpoons D_yX_2$	K_3
$D_x + Y_2 \rightleftharpoons D_xY_2$	K_4
Slow reactions	**Reaction rates**
$D_x \to D_x + X$	r_1
$D_y \to D_y + Y$	r_2
$X \to \phi$	r_3
$Y \to \phi$	r_4
Conservation laws	
$[D_x] + [D_xY_2] = [D_xT]$	$[D_y] + [D_yX_2] = [D_yT]$

Similar to the case of the single gene circuit, one can deduce delayed differential equation model for the toggle switch system as follows:

$$\begin{cases} \dot{x} = \frac{\alpha_1}{1+y^2(t-\tau_2)} - \beta_1 x, \\ \dot{y} = \frac{\alpha_2}{1+x^2(t-\tau_1)} - \beta_2 y, \end{cases} \tag{4}$$

Where τ_1, τ_2 are time delays. α_i and β_i are dimensionless maximal transcriptional rates and degradation rates, respectively. The corresponding undeveloped stochastic models are shown in Tab.IV.

TABLE IV. UNDEVELOPED STOCHASTIC MODEL DIRECTLY FROM SYSTEM (4).

Reaction	Propensity function	Increment of molecular numbers
$\emptyset \xrightarrow{a_1} X$	$a_1 = \frac{\Omega^3 \alpha_1}{\Omega^2 + Y^2(t-\tau_2)}$	$(1, 0)^T$
$X \xrightarrow{b_1} \emptyset$	$b_1 = \beta_1 X$	$(-1, 0)^T$
$\emptyset \xrightarrow{a_1} Y$	$a_2 = \frac{\Omega^3 \alpha_2}{\Omega^2 + X^2(t-\tau_1)}$	$(0, 1)^T$
$Y \xrightarrow{b_1} \emptyset$	$b_2 = \beta_2 Y$	$(0, -1)^T$

First of all, we take $\alpha_1 = 4, \alpha_2 = 5, \beta_1 = 0.25, \beta_2 = 0.5, \tau_1 = 5, \tau_2 = 8$. In stochastic simulations, we also set system volume $\Omega = 10$. From deterministic simulation results of panel (a) in Fig.3, we see that the system has two stable steady states, since under two sets of arbitrarily chosen initial conditions, the system converges to two sets of different steady states. Panel (b) of Fig.2 shows the stochastic simulation

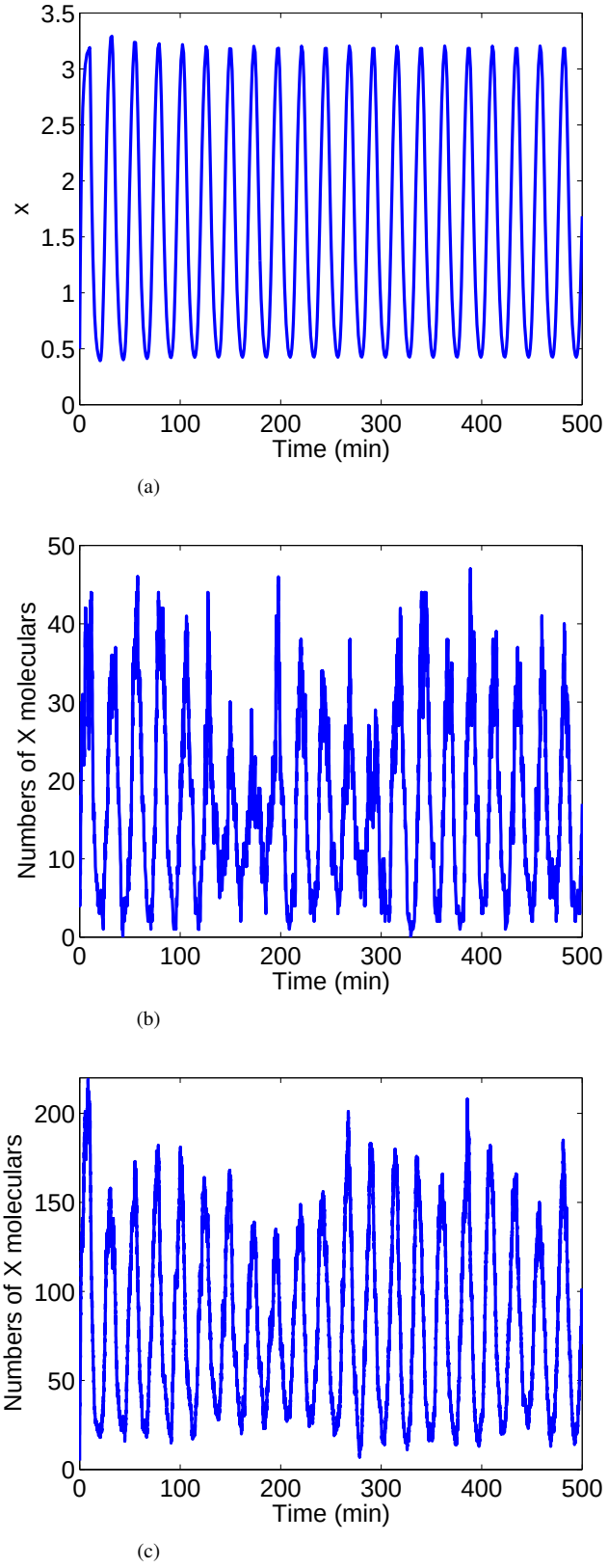

Fig. 1. Deterministic and stochastic simulation results for the single gene auto-repression system. Here, $\tau = 10$. Panel (b) shows the stochastic simulation result with $\Omega = 10$. Panel (c) shows the result with $\Omega = 50$.

978-1-4799-1389-3/13/$31.00 ©2013 IEEE

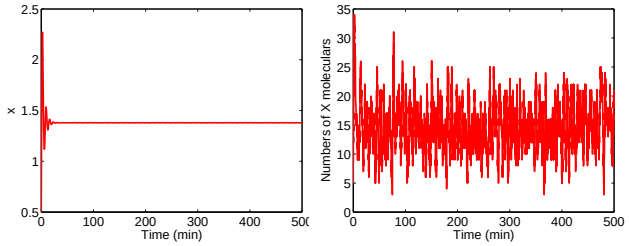

Fig. 2. Deterministic and stochastic simulation results for the single gene auto-repression system. Where $\tau = 2, \Omega = 10$.

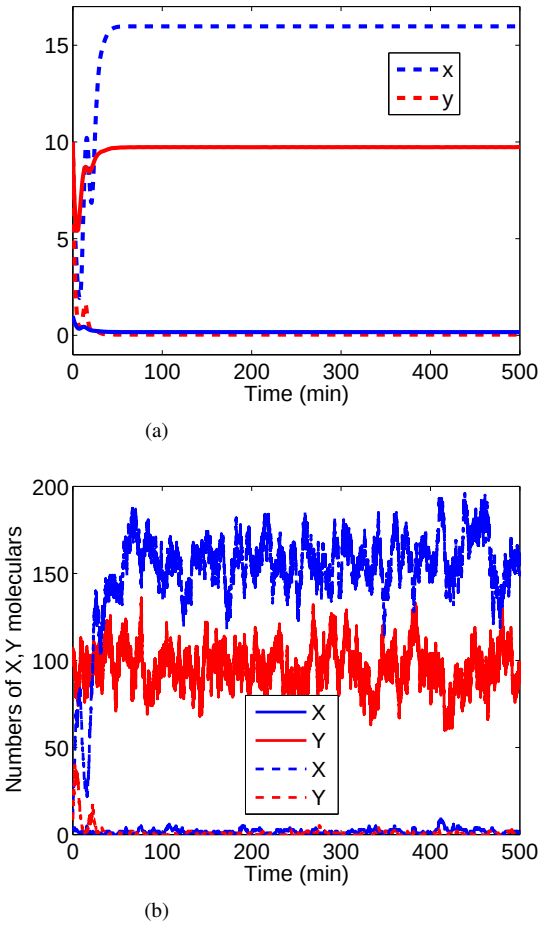

Fig. 3. (a) Deterministic and (b) stochastic simulation results for the undeveloped delayed toggle switch system. Where $\tau_1 = 5, \tau_2 = 8, \Omega = 10$ for panel (b).

results by using the proposed UDSSA. From the results of the UDSSA, one can also derive two sets of steady states under different sets of initial molecular numbers, and the molecular numbers are just about 10 fold of the deterministic ones. Which demonstrates the effectiveness of the UDSSA to reflect system dynamics.

Intrinsic noise in the toggle switch system can induce bistable behaviors [19]. For the cases in Fig.3, although the system can display bistable behavior, there are no bistable switch in the stochastic simulations. To verify whether the UDSSA can simulate bistable switch behaviors, we randomly

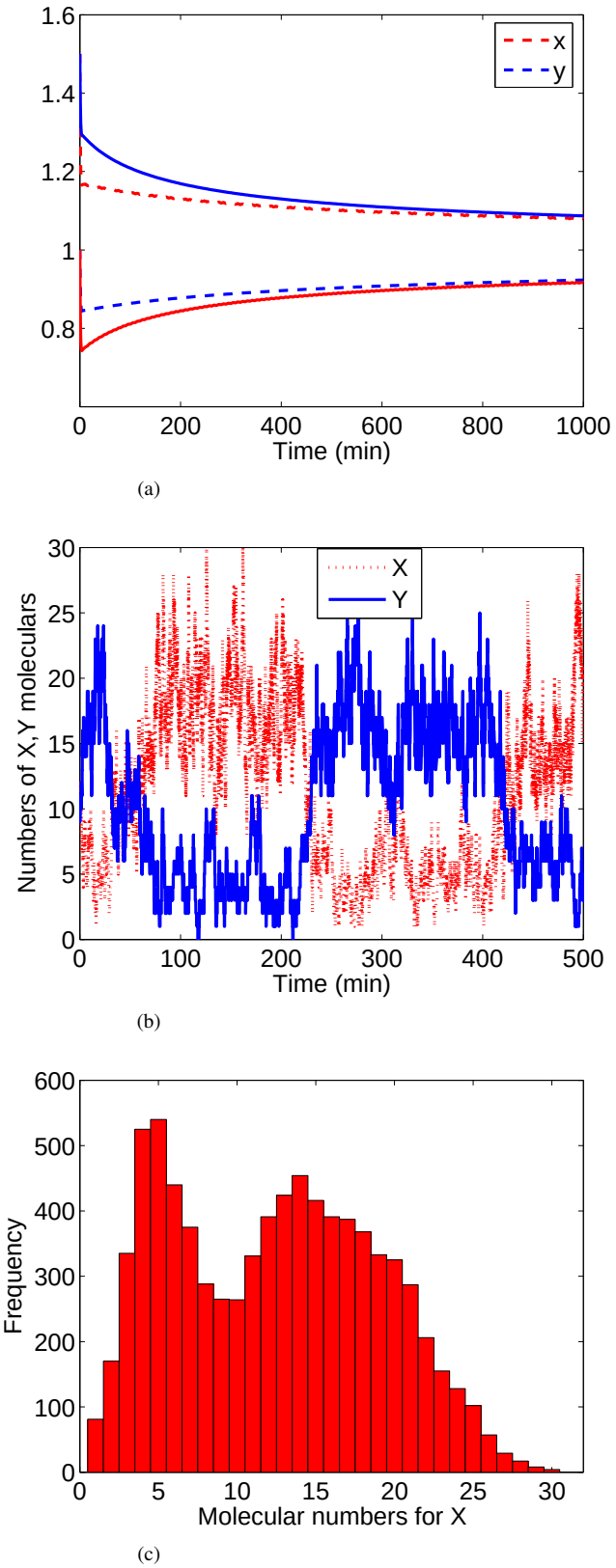

Fig. 4. Deterministic (a) and stochastic simulation (b) results for the toggle switch system. Panel (c) shows the distribution of molecular numbers for X. Here, we have set $\alpha_1 = 1, \beta_1 = 0.5, \alpha_2 = 0.5, \beta_2 = 0.25, \tau_1 = 1, \tau_2 = 2, \Omega = 10$.

978-1-4799-1389-3/13/$31.00 ©2013 IEEE

choose another set of parameters, that is $\alpha_1 = 1, \beta_1 = 0.5, \alpha_2 = 0.5, \beta_2 = 0.25, \tau_1 = 1, \tau_2 = 2, \Omega = 10$. Then, the system is also bistable, and stochastic simulation results show that intrinsic noise can induce bistable switch behavior, and molecular numbers distribution for X shows bimodal distribution, which is a typical feature of bistability. Therefore, the example of the two genes system demonstrates the effectiveness of the UDSSA in investigating intrinsic noise-induced behaviors.

V. Conclusion

In this paper, we have proposed a SSA for biochemical reactions with delays, called UDSSA. This algorithm can realize the comparison between deterministic delay models for biochemical systems and its stochastic counterparts. A main difference of the UDSSA from the other algorithms is that, the UDSSA can cope with the cases that the propensity functions are highly nonlinear and contain time delays. The main idea of the UDSSA is that, if there were time delays in the propensity functions, history values for molecular numbers are used to compute the propensity functions. Since time steps of the SSA are randomly generated, therefore, in the UDSSA, we can only guarantee that the closest history molecular values are used. Thus, the UDSSA is not an exact algorithm.

However, the UDSSA can exactly reflect the stochastic dynamics in biochemical systems rewritten from the deterministic models. From two examples, we find that the simulation results by the UDSSA are well consist with the deterministic ones, and the stochastic results can reflect the effect of intrinsic noise and system sizes. Moreover, when time delays are zeros, the UDSSA degenerates into the direct Gillespie algorithm.

Acknowledgment

This work was supported by Science Foundation of Henan University under Grants 2012YBZR007, Science and Technology Research Projects of Hubei Provincial Department of Education under Grants: D20131602. and also partly supported by the National Natural Science Foundation of China under Grants 60804039, 60974081, 11271295 and 60821091.

References

[1] U. Alon, *An introduction to systems biology: Design principles of biological circuits,* Chapman & Hall/CRC, 2007.

[2] H. Song, P. Smolen, E. Av-Ron, D.A. Baxter and J.H. Byrne, Dynamics of a minial model of interlocked positive and negative feedback loops of transcriptional regulation by cAMP-response element binding proteins, *Biophys. J.,* vol. 92, pp. 3407-3424, May 2007.

[3] W. Wischert, A. Wunderlin, A. Pelster, M.Olivier and J. Groslambert, Delay-induced instabilities in nonlinear feedback systems. *Phys. Rev. E,* vol.49, pp.203-219, Jan. 1994.

[4] D. Gillespie, Exact stochastic simulation of coupled chemical reactions. *J. Phys. Chem.,* vol. 81, no.25, pp. 2340-2361, 1977.

[5] D. Gillespie, The chemical langevin equation. *J. Chem. Phys.* 113: 297-306, 2000.

[6] D. Gillespie, Approximate accelerated stochastic simulation of chemically reacting systems. *J. Chem. Phys.,* vol. 115, no.4, pp.1716-1733, July 2001.

[7] H. Salis and Y. Kaznessis, Accurate hybrid simulation of a system of coupled chemical or biochemical reactions. *J. Chem. Phys.,* vol.122, art.no. 054103, Feb. 2005.

[8] D. Bratsun, D. Volfson, L.S.Tsimring and J.Hasty, Delay-induced stochastic oscillations in gene regulation. *Proc. Natl. Acad. Sci. USA,* vol. 102, no.41, pp.14593-14598, Oct. 2005.

[9] M. Barrio, K. Burrage, A. Leier and T. Tian, Oscillatory regulation of Hes1: discrete stochastic delay modelling and simulation. *PLOS Comput. Biol.,* vol. 2, no.9, art,no. e117, Sep. 2006.

[10] X. Cai, Exact stochastic simulation of coupled chemical reactions with delays. *J. Chem. Phys.,* vol. 126, art.no. 124108, Mar. 2007.

[11] L. Chen, R. Wang, T. Zhou and K. Aihara, Noise-induced cooperative behavior in a multi-cell system. *Bioinformatics,* Vol.21, pp.2722-2729, 2005.

[12] P. Wang, J. Lü, Y. Zhang and M. J. Ogorzalek, Intrinsic noise induced state transition in coupled positive and negative feedback genetic circuit. *IEEE Int. Conf. Syst. Biol.(ISB),* Zhuhai, China, pp.356-361, Sep.2-4, 2011.

[13] L. Wan, Q. Zhou, Z. Zhou and P. Wang, Dynamical behaviors of stochastic Hopfield neural networks with mixed time-delays. *Abst. Appl. Anal.,* Vol. 2013, Art. ID 384981, 2013.

[14] L. Wan, Q. Zhou and P. Wang, Ultimate boundedness and attractor for stochastic Hopfield neural networks with time-varying delays. *Nonlinear Analysis: RWA,* vol. 13, pp.953-958, 2012.

[15] A. Goldbeter, A model for circadian oscillation in the Drosophila period protein(PER). *Proc. R. Soc. Lond. B* vol. 261, pp. 319-324,1995.

[16] A. Goldbeter, Biochemical oscillations and cellular rhythms. the molecular bases of periodic and chaotic behaviour. Cambridge Univ. Press, Cambridge, UK, 1996.

[17] D.Gonze, J.Halloy and A.Goldbeter, Determinnstic versus stochastic models for circadian rhythms, *J.Biol. Phys.,* vol. 28, no.4, pp.637-653, 2002.

[18] D.Gonze and A. Goldbeter, Circadian rhythms and molecular noise. *Chaos,* vol. 16, art.no. 026110, 2006.

[19] P. Wang, J. Lü and M. J. Ogorzalek, Synchronized switching induced by colored noise in the genetic toggle switch systems coupled by quorum sensing mechanism. *Proc. of the 30th Chinese Contr. Confer.(CCC2011),* Yantai, China, pp.6605-6609, July 22-24, 2011.

[20] P. Wang, J. Lü and M. J. Ogorzalek, Global relative parameter sensitivities of the feed-forward loops in genetic networks. *Neurocomput.,* vol. 78, pp. 155-165, Feb. 2012.

[21] G.M.Süel, J. Garcia-Ojalvo, L.M.Liberman and M.B. Elowitz, An excitable gene regulatory circuit induces transient cellular differentiation. *Nature,* vol.440, pp.545-550, Mar. 2006.

[22] T. Gardner, C. Cantor and J. Cantor, Construction of a genetic toggle switch in Escherichia coli. *Nature,* vol. 403, pp. 339-342, 2000.

978-1-4799-1389-3/13/$31.00 ©2013 IEEE