

PHYSICAL REVIEW E **94**, 032408 (2016)

## Modeling delayed processes in biological systems

Jingchen Feng,<sup>1</sup> Stuart A. Sevier,<sup>2</sup> Bin Huang,<sup>3</sup> Dongya Jia,<sup>4</sup> and Herbert Levine<sup>1,\*</sup><sup>1</sup>*Department of Bioengineering and Center for Theoretical Biological Physics, Rice University, Houston, Texas 77251-1892, USA*<sup>2</sup>*Department of Physics and Center for Theoretical Biological Physics, Rice University, Houston, Texas 77251-1892, USA*<sup>3</sup>*Department of Chemistry and Center for Theoretical Biological Physics, Rice University, Houston, Texas 77251-1892, USA*<sup>4</sup>*Graduate Program in Systems, Synthetic and Physical Biology and Center for Theoretical Biological Physics, Rice University, Houston, Texas 77251-1892, USA*

(Received 26 May 2016; published 21 September 2016)

Delayed processes are ubiquitous in biological systems and are often characterized by delay differential equations (DDEs) and their extension to include stochastic effects. DDEs do not explicitly incorporate intermediate states associated with a delayed process but instead use an estimated average delay time. In an effort to examine the validity of this approach, we study systems with significant delays by explicitly incorporating intermediate steps. We show that such explicit models often yield significantly different equilibrium distributions and transition times as compared to DDEs with deterministic delay values. Additionally, different explicit models with qualitatively different dynamics can give rise to the same DDEs revealing important ambiguities. We also show that DDE-based predictions of oscillatory behavior may fail for the corresponding explicit model.

DOI: [10.1103/PhysRevE.94.032408](https://doi.org/10.1103/PhysRevE.94.032408)

### I. INTRODUCTION

Delayed reactions are present in many biological systems. Most notably, the central dogma of biology describes how functional protein production results from a sequence of numerous processes covering transcription, translation, and post-translational modifications. The sequential nature of protein production causes delay from the point that RNA polymerase binds to promoter DNA to the appearance of fully functional proteins [1–3]. Moreover, the degradation of proteins can also require multiple steps [4]. In addition to delay created through reaction chains, the transportation of molecules within a cell is a highly stochastic diffusion process which itself can often generate significant delays within a system. For example, in a eukaryotic cell mRNA is first produced in the nucleus and then transported to the cytoplasm for further translation. Transportation can be viewed as a reaction chain if molecules at different spatial points are treated as intermediate products. However, the intermediate steps in the transportation process are reversible (i.e., molecules are free to move back and forth); in contrast, many reactions in protein production proceed in an irreversible manner. In this paper, we focus on the latter case and leave the former case for future study.

To date, delay in biological systems has been most extensively studied through delay differential equations (DDEs) and their extension to include stochasticity. DDEs omit intermediate steps associated with a delayed process and instead estimate the average delay time for those steps. Typically fixed delay values are considered [5–11], though DDEs with a distribution of delay values have been studied [12,13]. Several studies employ DDEs to illustrate that delay can induce oscillation in otherwise stable systems [1,7,11,14–18]. Intuitively, if we increase the delay from zero to a value comparable to the residence time [19] of the system, oscillations may appear because of a phase lag in regulation. Additionally, a recent study employing DDEs presented a less intuitive observation

that a relatively small transcriptional delay can stabilize bistable gene networks [5]. These studies demonstrate that a delay can greatly influence the dynamics and equilibrium properties of biological systems.

An obvious check on the validity of DDEs is to compare them to more complete models that explicitly incorporate intermediate steps into the system. We refer to such models as explicit models. In this study we compare the predictions of fixed delay systems and explicit models. Instead of applying delay differential equations [11,18], we simulate reactions as delayed stochastic systems (DSSs) using a Gillespie algorithm first proposed by Bratsun *et al.* [14]. We show by a series of paradigmatic examples that DSSs with fixed delay often mischaracterize system behavior. Our results should inject a needed note of caution into this common practice.

It is worth noting there has been an early study on DDEs with discrete delay and distributed delay [20]. The authors discuss the influence of the delay distribution on the systems by analyzing deterministic DDEs. However, the cases they study are mostly linear equations to allow analytical solutions. In this study we are motivated to study more practical problems, where DDEs could include nonlinear terms. Moreover, our discrete simulation allows us to study nonlinear behaviors caused by stochasticity, which is beyond the prediction of deterministic equations (see Sec. V).

The organization of the paper is as follows. In Sec. II, we discuss a self-activation circuit that has two stable states, first studied as a delayed stochastic system by Gupta *et al.* [5]. We construct two distinct explicit models for the same DSS and demonstrate that one model produces results consistent with the DSS while the other produces markedly different results. In Sec. III, we discuss how the original DSS can sometimes emerge as the limit of an explicit model with many intermediate steps of equal mean duration. In Sec. IV, we examine a toggle switch circuit, another common bistable system. In this case, we examine an explicit model that again exhibits quantitatively different behavior as compared to the parent DSS. In Sec. V, we discuss a simple linear system where a DSS with deterministic delay generates oscillations

---

\*Corresponding author: [herbert.levine@rice.edu](mailto:herbert.levine@rice.edu)

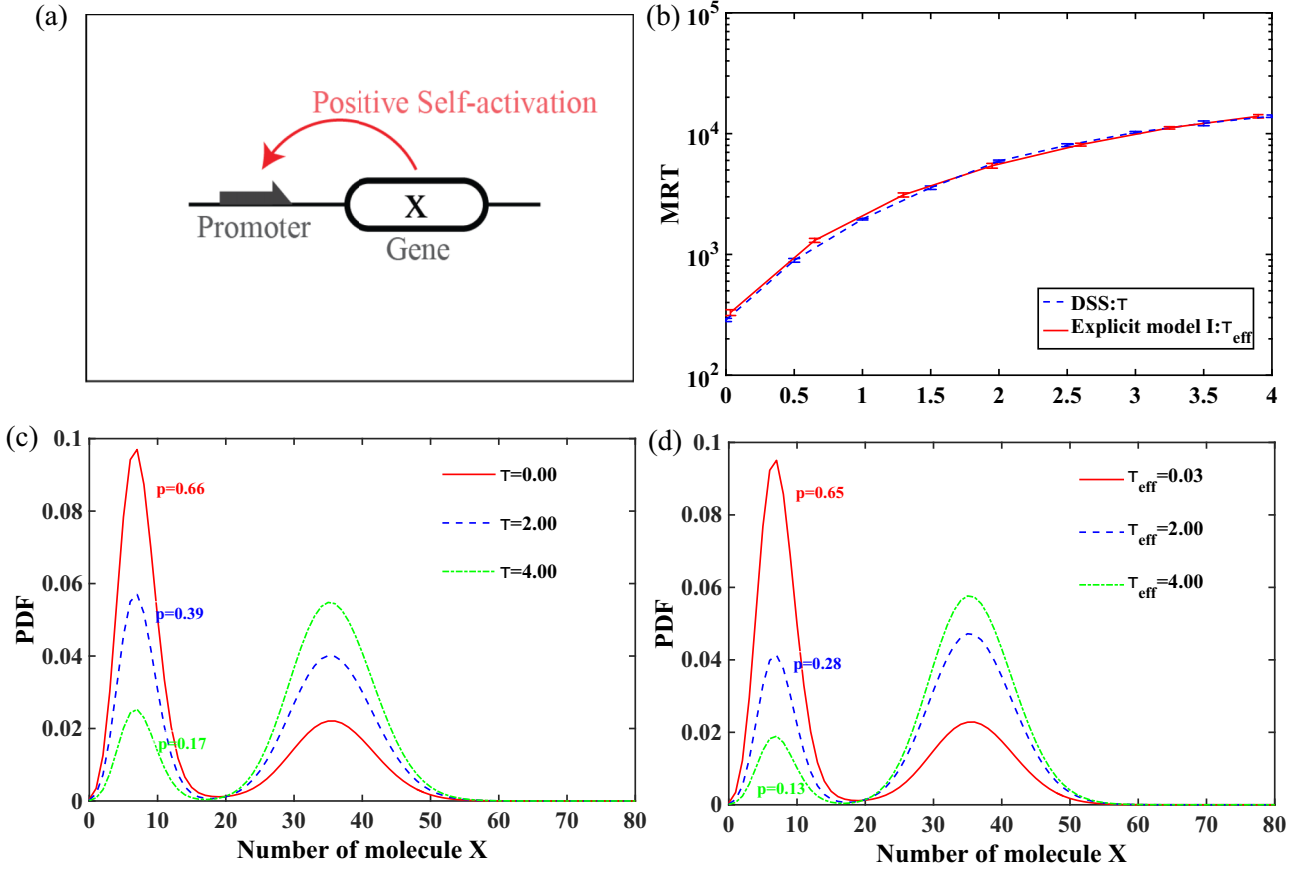


FIG. 1. (a) A schematic diagram of the self-activation circuit. (b) Mean residence time calculated with DSS and explicit model I. (c) Equilibrium distribution calculated with DSS. (d) Equilibrium distribution calculated by explicit model I.  $p$  is the proportion occupied by the low number state. For all plots parameter values  $\alpha = 5$ ,  $c = 19$ ,  $\gamma = \ln(2)$ , and  $b = 10$  are used. MRT and PDF stand for mean residence time and probability density function, respectively.

when explicit models do not. In Sec. VI, we summarize our work and its implications for constructing biological models.

## II. SELF-ACTIVATION CIRCUIT

### A. Delay differential equations

Consider the single-gene delayed positive feedback loop shown in Fig. 1(a). The dynamic behavior of the average number of molecule  $X$  is denoted by  $x$  and is determined by the following DDE:

$$\dot{x} = \alpha + \beta \frac{x(t - \tau)^b}{c^b + x(t - \tau)^b} - \gamma x(t), \quad (1)$$

where  $\alpha$  is the basal transcription rate due to leakiness of the promoter,  $\beta$  the increase in transcription rate due to protein binding to the promoter,  $b$  the Hill coefficient,  $c$  the concentration of  $x$  needed for half-maximal induction,  $\gamma$  the degradation rate coefficient of the protein, and  $\tau$  the transcriptional delay time. With the parameter values used in [5], the self-activation circuit is bistable.

We are interested in the stochastic version of this type of delayed system. Here, the right-hand side of Eq. (1) is reinterpreted as the rate for a reaction that produces an additional  $X$ . We employ the modified Gillespie algorithm

first proposed by Bratsun *et al.* [14] to carry out stochastic simulations. Here are the formal steps:

- (1) Set initial states  $\mathbf{X} = (X_1, \dots, X_N)$ ; set time  $t = 0$  and reaction counter  $i = 1$ .
- (2) Calculate the rates of each reaction  $a_\mu$ ,  $\mu = 1, \dots, M$ .
- (3) Generate two uniform random numbers  $u_1, u_2 \in [0, 1]$ .
- (4) Compute  $\Delta t_i = -\ln(u_1) / \sum_\mu a_\mu$ . The next reaction is scheduled at  $t + \Delta t_i$ .
- (5) If there are delayed reactions scheduled within the time interval  $[t, t + \Delta t_i]$ , then steps 2–4 are ignored. Update  $t$  to the next scheduled delay reaction time  $t_d$ .  $\mathbf{X}$  states are updated according to the delayed reaction channel, and update  $i = i + 1$ . Go to step 2. Otherwise, proceed to step 6.
- (6) Find the channel of the next reaction  $\mu$ , namely, take  $\mu$  to be an integer for which  $\sum_{j=1}^{\mu-1} a_j < u_2 a_t \leq \sum_{j=1}^\mu a_j$ , where  $a_t = \sum_{j=1}^M a_j$  is the total rate. Update  $t = t + \Delta t_i$ .
- (7) If the selected reaction  $\mu$  is not delayed, update  $\mathbf{X}$  according to the reaction channel; update  $i = i + 1$ . If the selected reaction is delayed, update is put off until  $t_d = t + \tau$ . Go to step 2.

Results for the self-activation circuit from stochastic DDEs are shown in Figs. 1(b) and 1(c). (We have validated our results by employing a different delay stochastic simulation method [21,22].) When the system has instant feedback (zero delay), the equilibrium distribution favors the low number state

[Fig. 1(c)] while for increasing delay the high number state becomes more occupied. In addition, the mean residence time (MRT), sometimes called the average first passage or transition time, of the low number state grows rapidly with increasing delay.

### B. Explicit model I

Suppose the delay in Eq. (1) originates from the existence of a precursor  $Y$ . We consider the following reaction scheme:

	Change of $x$	Change of $y$	Rate
$Y \rightarrow X$	+1	-1	$qy$
$\emptyset \rightarrow Y$	0	+1	$\alpha + \beta \frac{x^b}{c^b + x^b}$
$X \rightarrow \emptyset$	-1	0	$\gamma x$

Molecule  $Y$  is transformed into molecule  $X$ , which activates the production of  $Y$ . At the mean field level, we can write down the corresponding ordinary differential equations (ODEs) to match parameter values so as to obtain the same average value of molecules  $X$  and  $Y$  given by  $x$  and  $y$ , respectively, as

$$\dot{x} = qy - \gamma x, \quad (2)$$

$$\dot{y} = \alpha + \beta \frac{x^b}{c^b + x^b} - qy. \quad (3)$$

The transformation rate  $q$  sets the delay time of the system and Eqs. (2) and (3) have the same steady states in  $x$  as in Eq. (1) for all  $q$  with all shared parameter values staying constant.

To understand the relationship between  $q$  and  $\tau$  we conduct stochastic simulations of both the original DSS and the explicit process. We can tune the delay that arises from the existence of precursor by varying  $q$  and adjust its value based on our simulation results. As expected, we find the delay of the system should be proportional to  $1/q$ . When the effective delay is set as  $\tau_{\text{eff}} = \frac{2}{3} \frac{1}{q}$ , the MRT versus  $\tau_{\text{eff}}$  curve almost perfectly collapses with the MRT versus  $\tau$  calculated from the DSS [Fig. 1(b)]. We further calculated equilibrium configurations of the system with  $\tau_{\text{eff}} = 0.03, 2.00$ , and  $4.00$ . The stationary distribution for the explicit model is again reasonably consistent with those

calculated with DSS [Figs. 1(c) and 1(d)], there being only a modest difference at  $\tau_{\text{eff}} = 2.00$ .

### C. Explicit model II

If we regard  $X$  as a type of protein and  $Y$  as its mRNA instead of a precursor, we can obtain a different explicit model for the same DDEs [Eq. (1)]. Consider the following reactions:

	Change of $x$	Change of $y$	Rate
$\emptyset \rightarrow X$	+1	0	$qy$
$\emptyset \rightarrow Y$	0	+1	$\alpha + \beta \frac{x^b}{c^b + x^b}$
$X \rightarrow \emptyset$	-1	0	$\gamma x$
$Y \rightarrow \emptyset$	0	-1	$qy$

This case is different from the precursor transformation previously considered in that  $Y$  participates in the translation of protein  $X$  but has an independent decay process. In contrast to transformation, the translation process does not consume  $X$ . We have set the decay rate of  $Y$  equal to  $q$  so that the corresponding ODEs are also identical to Eqs. (2) and (3). Despite obeying the same ODEs, there are profound differences in the MRT versus delay  $\tau_{\text{eff}}$  curve and equilibrium distribution obtained by explicit stochastic simulation. Note that we have used here the same definition for  $\tau_{\text{eff}} = \frac{2}{3} \frac{1}{q}$  as in explicit model I, but the difference in the curves cannot be accommodated by just shifting this relationship. The MRT becomes notably smaller and, even in the small delay limit ( $\tau_{\text{eff}} \rightarrow 0$ ), the MRT does not equal to the case  $\tau = 0$  in the DSS [Fig. 2(a)]. Moreover, the equilibrium distribution of explicit model II is quantitatively different from its counterpart in explicit model I [Fig. 2(b)].

It is straightforward to understand the qualitative difference between explicit models I and II. Suppose at some time point  $t$ , the number of molecules  $Y$  happens to be higher than the number in the steady state, due to a fluctuation. In explicit model I, such an abundant  $Y$  will quickly be transformed into  $X$ . In contrast, the production of  $X$  does not consume  $Y$  in explicit model II. Consequently, those abundant  $Y$ 's produce a burst of  $X$  before they undergo independent decay. The

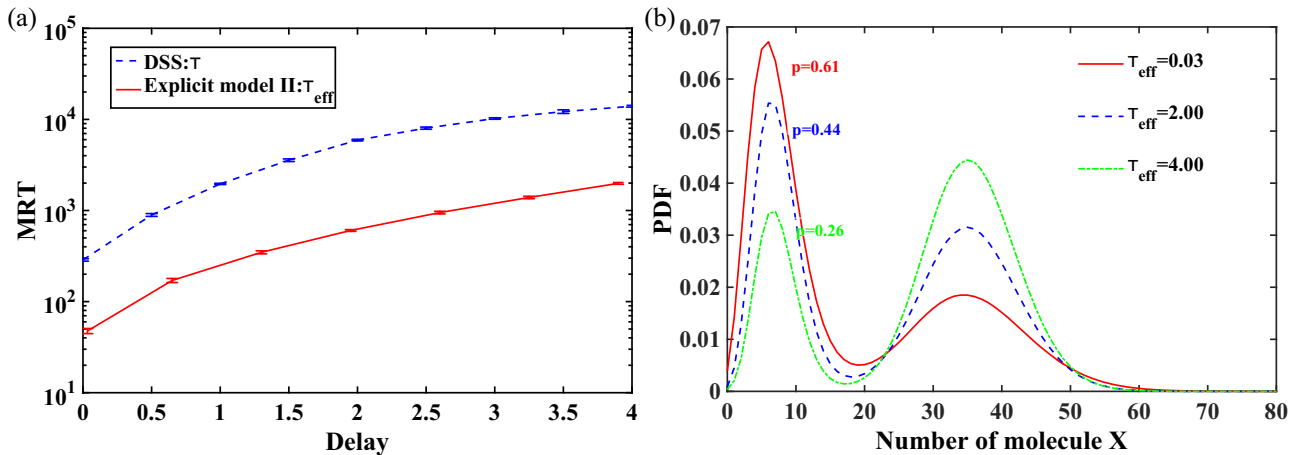


FIG. 2. (a) Mean residence time calculated by the DSS and by explicit model II. (b) Equilibrium distribution calculated by explicit model II.  $p$  is the proportion occupied by a low number state. All parameters are the same as in Fig. 1.

strengthened noise in explicit model II results in the greatly reduced mean residence time. This dichotomy points out an important ambiguity in the formulation of the delay equation. In the DDE (no fluctuation) limit, these models give rise to exactly the same steady states, and there is no obvious way to choose which explicit model is better without postulating the actual delay process being modeled. Once we include stochasticity, our DSS algorithm effectively assumes that a particle placed in the queue will be transformed to  $X$  after a fixed delay (and at that time point increase  $X$  to  $X + 1$ ) while disappearing. This clearly is analogous to the process described by the first explicit model, which therefore agrees much more quantitatively with the original DSS.

### III. FIXED VERSUS STOCHASTIC DELAY TIME

Given the reasonable agreement between explicit model I and the original DSS, we investigate in more detail the relationship between these two formulations. Let us first start with the deterministic limit given by the respective ODE systems. Starting from Eq. (3) and given  $x(t)$ , the solution of  $y(t)$  is determined as

$$y(t) = e^{-qt} y(0) + \int_0^t ds \left[ e^{-q(t-s)} \left( \alpha + \beta \frac{x(s)^b}{c^b + x(s)^b} \right) \right].$$

By integrating from the infinite past the initial condition becomes negligible and we rewrite the equation above as

$$y(t) = \alpha/q + \int_{-\infty}^t ds \left[ e^{-q(t-s)} \beta \frac{x(s)^b}{c^b + x(s)^b} \right].$$

Plugging back into Eq. (1) yields

$$\dot{x} = \alpha + \int_{-\infty}^t ds \left[ q e^{-q(t-s)} \beta \frac{x(s)^b}{c^b + x(s)^b} \right] - \gamma x.$$

From the equation above, it is clear that the delay caused by the additional variable  $y$  follows an exponential distribution with average value  $1/q$ . When  $q \rightarrow \infty$ , the peak of this distribution approaches infinity and the width of the peak approaches zero. Of course, by substituting it with a delta function distribution, we recover Eq. (1). The difference between the two models is that in the DDE the delay is fixed but in the explicit model the delay is exponentially distributed.

It is critical to realize that this observation regarding the difference between the two models also holds for the stochastic version. As already mentioned, one can think of the delayed reaction in the DSS algorithm as putting a produced particle into a queue and only at a fixed later time allowing it to be counted as an increase in  $X$ . The stochastic version of the explicit model creates a  $Y$  particle which then obeys a single exponential decay process to produce  $X$ ; everything is the same except that the delay is now stochastic. The fact that the mean equations and the actual stochastic processes have the same relationship to each other is ultimately due to the linearity of the reaction scheme governing the production and decay of  $X$  in the explicit model.

We can now extend our notion of an explicit model to allow for more than one precursor step. For example, let us imagine that there are two precursors. The ODEs for the explicit models

with two intermediate steps are

$$\dot{x} = qz - \gamma x, \quad (4)$$

$$\dot{y} = \alpha + \beta \frac{x^b}{c^b + x^b} - qy, \quad (5)$$

$$\dot{z} = qy - qz. \quad (6)$$

Here the molecules  $Y$  and  $Z$  are intermediate products. Assuming we know  $x(t)$ , then from Eq. (5)

$$y(t) = \int_{-\infty}^t ds \left[ e^{-q(t-s)} \left( \alpha + \beta \frac{x(s)^b}{c^b + x(s)^b} \right) \right].$$

Plugging it into Eq. (6),

$$z(t) = \int_{-\infty}^t dr e^{-q(t-r)} q \int_{-\infty}^r ds e^{-q(r-s)} \left( \alpha + \beta \frac{x(s)^b}{c^b + x(s)^b} \right).$$

Finally, Eq. (4) becomes

$$\dot{x} = \int_{-\infty}^t dr \int_{-\infty}^r ds \left[ q^2 e^{-q(t-s)} \left( \alpha + \beta \frac{x(s)^b}{c^b + x(s)^b} \right) \right] - \gamma x.$$

Integrating over  $r$  first, this becomes

$$\dot{x} = \int_{-\infty}^t ds \left[ (t-s) q^2 e^{-q(t-s)} \left( \alpha + \beta \frac{x(s)^b}{c^b + x(s)^b} \right) \right] - \gamma x.$$

After some rearrangement we obtain

$$\dot{x} = \alpha + \int_0^{\infty} ds' \left[ s' q^2 e^{-qs'} \beta \frac{x(t-s')^b}{c^b + x(t-s')^b} \right] - \gamma x.$$

So, the exponential distribution has been replaced by the  $\gamma$  distribution  $p_2 = tq^2 e^{-qt}$ . Again this holds also for the single particle stochastic dynamics where this distribution is now interpreted as the time it takes for a particle to be transformed from  $Y \rightarrow Z \rightarrow X$ , where each of the reactions is irreversible and occurs at the same rate  $p$ . A simple extension of the above shows that

$$p_n(t) = \frac{n^n t^{n-1}}{\tau^n (n-1)!} e^{-\frac{n}{\tau} t},$$

where now we have defined  $\tau = n/q$ . This can be proven by induction, using  $p_n(t) = \int_0^t p_{n-1}(t') p_1(t-t') dt' = \frac{q^n t^{n-1}}{(n-1)!} e^{-qt}$ . When  $t^* = \frac{n-1}{n} \tau$ ,  $p_n(t)$  reaches a maximum. As we vary the number of intermediate steps,  $n$ , and keep the mean value of delay  $\langle t \rangle = \tau$  the same, the distribution becomes increasingly sharp. A plot of  $p_n(t)$  is shown in Fig. 3.

Hence, the limiting process of making  $n$  large leads to a precise fixed value of the delay and asymptotically approaches the DSS. It then becomes a quantitative issue as to whether the actual process has intermediate states and to what extent they occur at roughly equal rates, as opposed to having one step dominate (being rate limiting), and whether the fixed delay version is a good enough approximation for that actual situation. For the simple self-activation case, we have shown that even with only one precursor the DSS is a reasonably accurate approach.

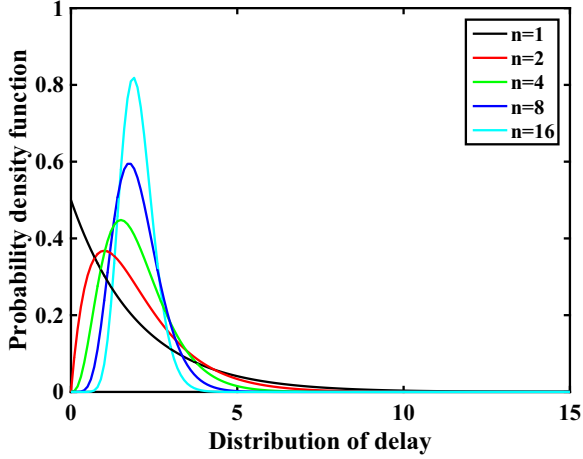


FIG. 3. Probability density function (PDF)  $p_n$ . Here the mean delay is fixed to be 2.

#### IV. THE TOGGLE SWITCH

We now extend our discussion to a more complex circuit, the toggle switch shown schematically in Fig. 4(a). If the average number of molecules  $X$  and molecule  $Y$  are represented by  $x$  and  $y$ , then the time evolution of  $x$  and  $y$  is

determined by the following DDEs (to simplify the problem, we have assumed that the delay exists only in the repressive regulation from  $Y$  to  $X$ ):

$$\dot{x} = \beta \frac{1}{1 + y(t - \tau)^2 / K^2} - \gamma x(t), \quad (7)$$

$$\dot{y} = \beta \frac{1}{1 + x(t)^2 / K^2} - \gamma y(t), \quad (8)$$

where  $\beta$  is the decrease in transcription rate due to protein binding to the promoter,  $K$  the concentration of  $X$  and  $Y$  needed for half-maximal reduction,  $\gamma$  the degradation rate coefficient of the protein, and  $\tau$  the transcriptional delay time. This DDE is again extended to a DSS by using the rates on the right-hand side of the above equations. We have chosen to use the same parameters as in Ref. [5], which puts the system in a bistable regime. Similar to the result for the self-activation circuit, the mean residence time of the  $X < Y$  state grows rapidly as delay increases [Fig. 4(b)]. The equilibrium distribution does not change significantly with varying delay and the probabilities of finding molecule levels in the attractive basin of each stable state are approximately equal [Fig. 4(c)].

We now construct the related explicit model, assuming that the delay in Eq. (7) originates from the existence of a precursor  $Z$ . We consider the following reactions:

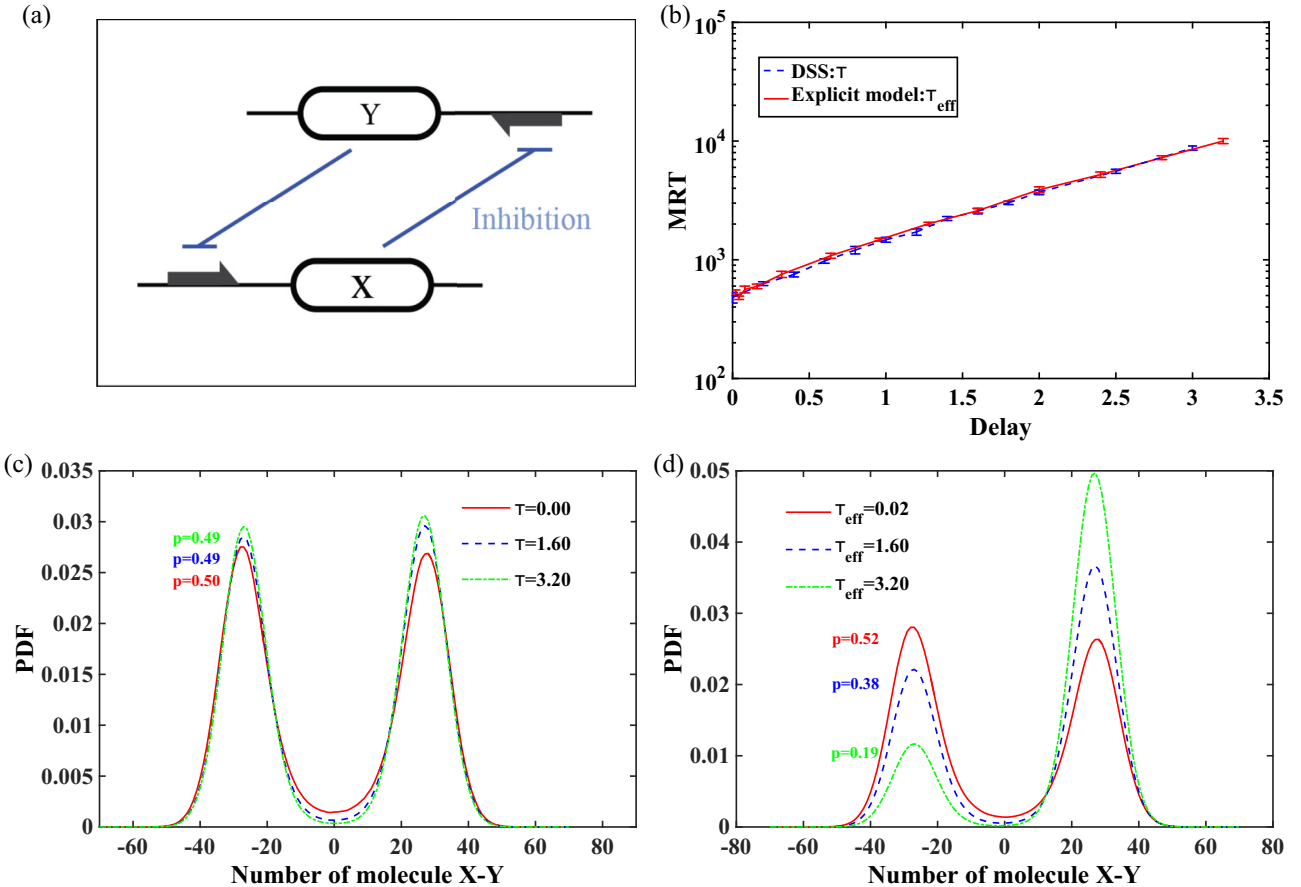


FIG. 4. (a) A schematic diagram of a toggle-switch circuit. (b) Mean residence time of  $X < Y$  state calculated by DSSs and the explicit model. (c) Equilibrium distribution calculated by DSSs. (d) Equilibrium distribution calculated by the explicit model.  $p$  is the proportion occupied by the  $X < Y$  number state;  $\beta = 21.9$ ,  $k = 6.8$ , and  $\gamma = \ln(2)$ .

	Change of $x$	Change of $y$	Change of $z$	Rate
$Z \rightarrow X$	+1	0	-1	$qz$
$\emptyset \rightarrow Y$	0	+1	0	$\beta \frac{1}{1+x^2/k^2}$
$\emptyset \rightarrow Z$	0	0	+1	$\beta \frac{1}{1+y^2/k^2}$
$X \rightarrow \emptyset$	-1	0	0	$\gamma x$
$Y \rightarrow \emptyset$	0	-1	0	$\gamma y$

Molecule  $Z$  is transformed into molecule  $X$ , which is a repressor of  $Y$ . Molecule  $Y$  further inhibits the production of  $Z$ . The corresponding ODEs are

$$\dot{x} = qz - \gamma x, \tag{9}$$

$$\dot{y} = \beta \frac{1}{1+x^2/k} - \gamma y, \tag{10}$$

$$\dot{z} = \beta \frac{1}{1+y^2/k} - qz. \tag{11}$$

By construction, Eqs. (9)–(11) have the same steady states of  $x$  as in Eqs. (7) and (8).

We can tune the delay that arises from the existence of a precursor by varying the  $q$  value. The delay of the system is proportional to  $1/q$  in the same manner as we have seen in the self-activation circuit. When the effective delay is defined as  $\tau_{\text{eff}} = 0.80 \frac{1}{q}$ , we find that the MRT of the  $X < Y$  state versus  $\tau_{\text{eff}}$  curve almost perfectly collapses with MRT versus  $\tau$  calculated from DSSs [Fig. 4(b)]. However, the equilibrium distribution in this explicit model is strongly influenced by the value of the delay, which suggests that the MRT of the  $X > Y$  state versus  $\tau_{\text{eff}}$  curve does not agree with its counterpart in the DSS. Alternatively, one could get a better match to the decay of the  $X > Y$  state and fail to match this one (data not shown). This is in stark contrast to the delay-independent equilibrium distribution in the DSS [Figs. 4(c) and 4(d)], which shows no such change.

As discussed above, the DSS results should be approached asymptotically if the number of intermediate states is increased. We test the rapidity of this convergence in Fig. 5. As we increase the number of intermediate reactions,  $n$ , the difference in the height of two peaks becomes smaller, as

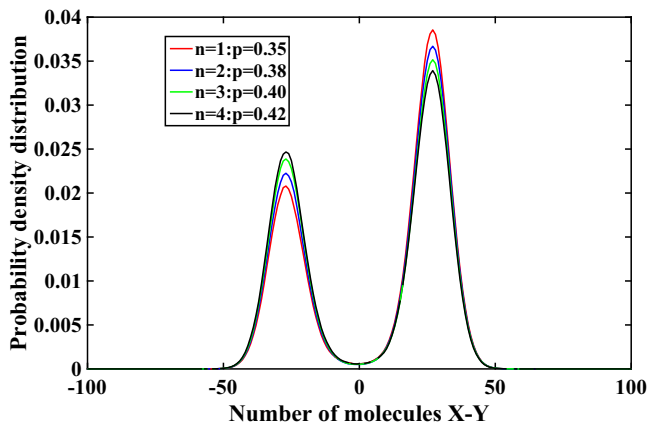


FIG. 5. Equilibrium distribution of toggle-switch circuit for  $\tau = 2$ .  $p$  shows the probability of  $X < Y$ . Recall that in the DSS,  $P(X < Y) \sim 0.5$ .

expected. Yet the difference is not negligible even for the relatively large number of intermediate reactions,  $n = 4$ . The width of the delay time distribution is still fairly significant at  $n = 4$  (Fig. 3). Apparently, the extra nonlinearity in the toggle-switch circuit makes the system more sensitive to having such a nontrivial distribution.

### V. DELAY-INDUCED OSCILLATION

Previous studies have argued that the introduction of delay in otherwise stable systems can induce oscillations [1,7,11,14–18,23]. Here we focus on the case of delayed protein decay, which has been shown to undergo oscillations in a DSS formulation [14]. Furthermore, it has been posited that this oscillation can be partially understood by writing down the DDE system for average number of protein  $X$ , represented by  $x$ , as

$$\frac{dx}{dt} = A - Bx(t) - Cx(t - \tau), \tag{12}$$

where  $A$  is the rate of protein production, and  $B$  and  $C$  are the rates of nondelayed and delayed degradation, respectively. Here we show that both of these statements need to be carefully reconsidered.

First, it is necessary to note that there is an inherent ambiguity in how to define the DSS for this case. We need to specify in particular whether a particle slated for a delayed decay can undergo regular decay while waiting in the queue. A master equation formulation of the stochastic version of Eq. (12) seems to allow this to occur (see Ref. [14]), but for the parameter set reported in that work the characteristic direct decay time  $1/B$  is much smaller than the delay  $\tau$  and therefore nearly all molecules  $X$  involved in delayed decay (i.e., placed in the queue waiting to decay) cannot finish this process and undergo direct decay instead. As a consequence, the last term on the right-hand side of Eq. (12) would not play any role in a stochastic simulation.

Consequently, in our simulation we prohibit molecules undergoing delayed decay from participating in direct decay. With the same parameter set used in Ref. [14],  $x$  oscillates [Fig. 6(a)]. The power spectrum calculated from time series of  $x$  [Fig. 6(c)] reveals oscillatory behavior by the location of the peaks. As expected these are separated by  $1/\tau$ . But, it is clear that the system is not accurately described by the above equation, even in an average sense. The simplest way to see this is to note that the mean value of  $X$  depends on the delay, whereas the steady-state solution of the equation does not. The fact that this equation can have oscillatory modes cannot be relevant for whether or not the stochastic system oscillates.

We now construct an explicit model analog of our DSS. Protein degradation often occurs through a sequence of events that are mediated by a complex proteolytic pathway [4]. It is thus reasonable to assume in the delayed degradation reaction that protein  $X$  will first be transformed into an intermediate product  $Y$ , which has an independent decay process. The existence of the intermediate product  $Y$  causes the delay in the degradation of  $X$  [4]. Here are the reactions involved:

	Change of $x$	Change of $y$	Rate
$\emptyset \rightarrow X$	+1	0	$A$
$X \rightarrow Y$	-1	+1	$Cx$
$X \rightarrow \emptyset$	-1	0	$Bx$
$Y \rightarrow \emptyset$	0	-1	$Dy$

The corresponding ODEs in the deterministic limit are

$$\frac{dx}{dt} = A - Bx - Cx, \quad (13)$$

$$\frac{dy}{dt} = Cx - Dy. \quad (14)$$

The average value of the delay is  $1/D$ . Therefore, we set  $D = 1/\tau$  in our explicit model to match the DSS. Note that, unlike the previous deterministic equation, the steady-state value of the total number of particles ( $x + y$ ) does depend on  $D$ ; it equals  $\frac{A}{B+C}(1 + C\tau)$  which scales linearly for long time delay and agrees with the data in Fig. 6(a).

For the case of linear reactions there can be no oscillations at the deterministic level. Since the system is linear, oscillations must mean imaginary eigenvalues of the Jacobian matrix

$$\mathbf{J} = \begin{pmatrix} -B - C & 0 \\ C & -D \end{pmatrix}.$$

A simple calculation shows, however, that the eigenvalues are  $-B - C$  and  $-D$ , yielding simple exponential relaxation.

In fact it is trivial to extend this result to the case of an arbitrary number of intermediates each of which is produced and decays via unimolecular reactions. In other words, the exact solution of any explicit model predicts no oscillatory behavior in the mean field limit. Any oscillations must be due to stochasticity.

In Fig. 6(b) we show a simulated time series for the total particle number in one intermediate explicit model, and its power spectrum is presented in Fig. 6(d). The time series of  $X$  generated by the DSS versus the explicit model look superficially similar [Figs. 6(a) and 6(b)]; however, the power spectrum of DSS and the explicit model are markedly different. In contrast to the equally spaced peaks in the power spectrum [Fig. 6(c)], there is no obvious peak in the explicit model [Fig. 6(d)]. Thus, the exponential distribution of delay values will wash out the oscillation. We have extended this calculation to the case of  $n = 4$  (Fig. 7) which has a somewhat peaked delay distribution. Even here, though, spectral peaks cannot be detected as the distribution is still wide enough to eliminate the peaks related to the fixed delay.

The results here and in the previous section on the toggle switch address the importance of delay distributions. Our results show that even when the number of intermediate reactions is increased up to four, there can still be non-negligible differences between DSSs and explicit models. Modeling of biological systems may require constructing explicit systems if one wants to obtain quantitatively accurate predictions.

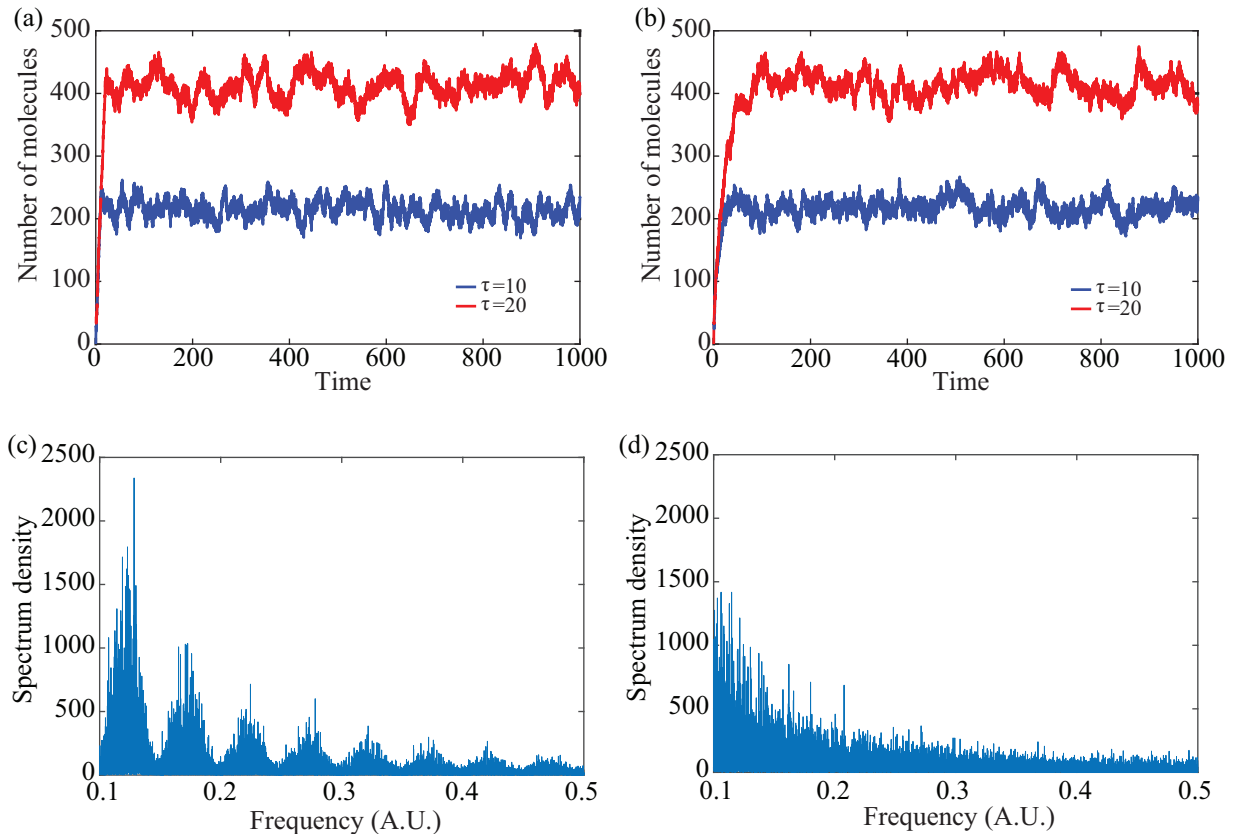


FIG. 6. (a) Time series of total number of molecules in DSS. (b) Time series of total number of molecules in explicit model. (c) Corresponding periodogram in DSS, where  $\tau = 10$ . (d) Corresponding periodogram in explicit model. Here  $A = 100$ ,  $B = 4.1$ ,  $C = 1.0$ , and  $D = 1/\tau = 0.1$ .

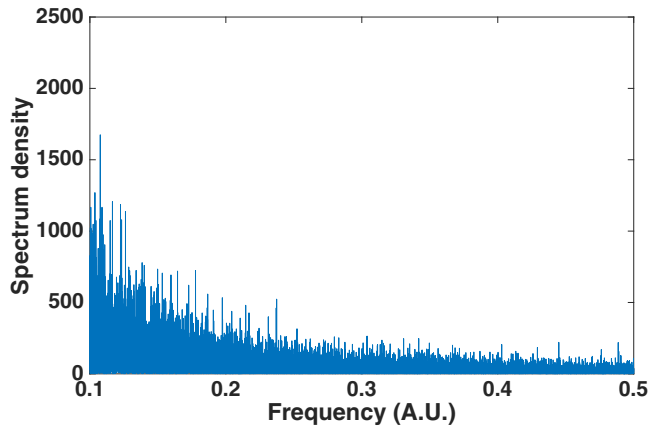


FIG. 7. Time series of the total number of molecules in the explicit model with  $n = 4$ . Parameters are the same as in Fig. 6.

## VI. DISCUSSION

Stochastic delayed differential systems have been very popular in biological physics due to their relative simplicity as compared to models that include a large number of intermediate steps that are anyway not being monitored in the experimental data. The cost of such simplicity is the conversion from Markovian explicit models to non-Markovian DSSs. In most cases, the non-Markovian property makes analytical studies challenging [20,24–26]. When the delay is much larger than the transition time between stable states, it can be assumed either that the delay does not affect the dynamics within each attractive basin or the joint probability  $P(X(t), X(t - \tau))$  can be decoupled as  $P(X(t))P(X(t - \tau))$ . Approximate analytical solutions can be derived with such assumptions [14,23]. In the small delay case, it is sometimes possible to derive approximate solutions for simple cases [27]. As for moderate delay problems, to the best of our knowledge,

there is no good way to derive analytical solutions, even approximately.

Because of the difficulty in solving DSSs analytically, two different but consistent stochastic simulation methods have been proposed to study these systems numerically [14,21,22]. Since the reaction rate depends on both  $X(t)$  and  $X(t - \tau)$ , both methods require the storage of system dynamics from  $t$  to  $t - \tau$ . Therefore, stochastic simulation methods become computationally inefficient for large  $\tau$ . As we have seen in our examples the rates of intermediate reactions in explicit models are proportional to  $1/\tau$ , so that long delays correspond to slow reactions. However, slow reactions do not increase the computational cost of a stochastic simulation. Thus for systems with long delays explicit models may be computationally preferable.

Beyond the issue of computational ease is the question of quantitative reliability. In this paper, we have demonstrated that DDEs often yield inaccurate transition times and equilibrium distributions. Additionally, there can exist multiple explicit models with fundamentally different dynamics that give rise to the same DDEs; some of these have stochastic extensions which correspond better than others to a given DSS; sometimes nonuniqueness exists when we attempt to formulate stochastic simulation directly to DDEs, as we have seen in the delay-induced oscillation case. Consequently results that depend strongly on having a fixed delay may be nonrobust when the cause of the delay is handled explicitly. In the end, we argue that more attention needs to be paid to the limitation of the DSS approach; blind use of this approach may cause significant mischaracterization of important biological systems.

## ACKNOWLEDGMENT

This work was supported by the U.S. National Science Foundation Physics Frontier Center program Grant No. PHY-1427654.

- 
- [1] W. Mather, M. R. Bennett, J. Hasty, and L. S. Tsimring, Delay-Induced Degrade-and-Fire Oscillations in Small Genetic Circuits, *Phys. Rev. Lett.* **102**, 068105 (2009).
  - [2] K. Josić, J. Manuel López, W. Ott, L. J. Shiao, and M. R. Bennett, Stochastic delay accelerates signaling in gene networks, *PLoS Comput. Biol.* **7**, e1002264 (2011).
  - [3] H. H. McAdams and L. Shapiro, Circuit simulation of genetic networks, *Science* **269**, 650 (1995).
  - [4] I. Levchenko, M. Seidel, R. T. Sauer, and T. A. Baker, A specificity-enhancing factor for the ClpXP degradation machine, *Science* **289**, 2354 (2000).
  - [5] C. Gupta, J. M. López, W. Ott, K. Josić, and M. R. Bennett, Transcriptional Delay Stabilizes Bistable Gene Networks, *Phys. Rev. Lett.* **111**, 058104 (2013).
  - [6] D. S. Glass, X. Jin, and I. H. Riedel-Kruse, Signaling Delays Preclude Defects in Lateral Inhibition Patterning, *Phys. Rev. Lett.* **116**, 128102 (2016).
  - [7] M. Barrio, K. Burrage, A. Leier, and T. Tian, Oscillatory regulation of Hes1: discrete stochastic delay modelling and simulation, *PLoS Comput. Biol.* **2**, e117 (2006).
  - [8] H. Momiji and N. A. M. Monk, Oscillatory notch-pathway activity in a delay model of neuronal differentiation, *Phys. Rev. E* **80**, 021930 (2009).
  - [9] S. R. Veflingstad, E. Plahte, and N. A. M. Monk, Effect of time delay on pattern formation: Competition between homogenisation and patterning, *Phys. D (Amsterdam, Neth.)* **207**, 254 (2005).
  - [10] L. G. Morelli, S. Ares, L. Herrgen, C. Schröter, F. Jülicher, and A. C. Oates, Delayed coupling theory of vertebrate segmentation, *HFSP J.* **3**, 55 (2009).
  - [11] J. Lewis, Autoinhibition with transcriptional delay: A simple mechanism for the zebrafish somitogenesis oscillator, *Curr. Biol.* **13**, 1398 (2003).
  - [12] V. Volterra, Remarques sur la note de m. régnier et mlle. lambin (étude d'un cas d'antagonisme microbien), *C. R. Acad. Sci.* **199**, 1684 (1934).
  - [13] V. A. Kostitzin, Sur les équations intégrodifférentielles de la théorie de l'action toxique du milieu, *C. R. Acad. Sci.* **208**, 1545 (1939).
  - [14] D. Bratsun, D. Volfson, L. S. Tsimring, and J. Hasty, Delay-induced stochastic oscillations in gene regulation, *Proc. Natl. Acad. Sci. USA* **102**, 14593 (2005).



- [15] K. Parmar, K. B. Blyuss, Y. N. Kyrychko, and S. J. Hogan, Time-delayed models of gene regulatory networks, *Comput. Math. Methods Med.*, **2015**, 347273 (2015).
- [16] M. Villasana and A. Radunskaya, A delay differential equation model for tumor growth, *J. Math. Biol.* **47**, 270 (2003).
- [17] M. K. Grammatikopoulos, E. A. Grove, and G. Ladas, Oscillations of first-order neutral delay differential equations, *J. Math. Anal. Appl.* **120**, 510 (1986).
- [18] M. H. Jensen, K. Sneppen, and G. Tian, Sustained oscillations and time delays in gene expression of protein Hes1, *FEBS Lett.* **541**, 176 (2003).
- [19] Residence time is defined as the time duration the system stays in the attractive basin of a stable state. It is also called first passage time or transition time.
- [20] K. L. Cooke and Z. Grossman, Discrete delay, distributed delay and stability switches, *J. Math. Anal. Appl.* **86**, 592 (1982).
- [21] X. Cai, Exact stochastic simulation of coupled chemical reactions with delays, *J. Chem. Phys.* **126**, 124108 (2007).
- [22] R. Barbuti, G. Caravagna, A. Maggiolo-Schettini, and P. Milazzo, Delay stochastic simulation of biological systems: A purely delayed approach, in *Transactions on Computational Systems Biology XIII* (Springer, New York, 2011), pp. 61–84.
- [23] L. S. Tsimring and A. Pikovsky, Noise-Induced Dynamics in Bistable Systems with Delay, *Phys. Rev. Lett.* **87**, 250602 (2001).
- [24] J. M. Mahaffy, K. M. Joiner, and P. J. Zak, A geometric analysis of stability regions for a linear differential equation with two delays, *Int. J. Bifurcation Chaos* **05**, 779 (1995).
- [25] U. an der Heiden, A. Longtin, M. C. Mackey, J. G. Milton, and R. Scholl, Oscillatory modes in a nonlinear second-order differential equation with delay, *J. Dyn. Differ. Equations* **2**, 423 (1990).
- [26] J. Bélair and S. A. Campbell, Stability and bifurcations of equilibria in a multiple-delayed differential equation, *SIAM J. Appl. Math.* **54**, 1402 (1994).
- [27] S. Guillouzic, I. L'Heureux, and A. Longtin, Small delay approximation of stochastic delay differential equations, *Phys. Rev. E* **59**, 3970 (1999).