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Stability and Flipping Dynamics of Delayed Genetic Toggle Switch

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A detailed analysis of the stability and flipping dynamics of a delayed exclusive toggle switch is performed. We use forward flux sampling method combined with delayed stochastic simulation algorithm to get the stationary distribution function, the switching rate, and pathways, as well as the transition state ensemble. Interestingly, under the influence of time delay, the stationary distribution corresponding to the stable states become narrower and the population in the transition region is significantly enhanced. In addition, the flipping rate increases monotonically with delay. Such findings demonstrate that time delay could reduce the stability of the bistable genetic switch dramatically. Furthermore, the transition pathways, characterized by the difference in the protein numbers and the state of operator, show larger discrepancy between the forward and backward switching process with increasing delay, indicating that transcriptional and translational delay can remarkably affect the flipping dynamics. Specifically, for the transition state, the difference in the probability of finding the operator site bound by the two different protein dimers is enlarged by delay, which further illustrates the crucial role of time delay on the stability and switching dynamics of genetic toggle switches.

Key words: Toggle switch, Delay forward, Flux sampling

I. INTRODUCTION

In vivo, genes, proteins and metabolites are connected by biochemical reactions and intermolecular interactions. These reactions and interactions generate most of the central functions of a living cell [1] and together form the gene regulatory networks. Various gene regulatory networks have been characterized experimentally or theoretically up to now [2–8]. Multistability is one common property in many of these gene regulatory networks, which plays an important role in the dynamics of living cells and organisms [9–13], contributing to cellular memory, robustness against molecule fluctuation, and population diversity for cells. Multistability can typically be achieved by switches, which are the basic building modules for complex molecular networks. One common way to construct a switch is through a pair of genes that mutually repress each other. One classical example is the lysogenic state of λ-phage in *Escherichia* coli which has been studied thoroughly [14–17]. In this switch CI and Cro repress the synthesis of each other by binding to the promoter sites. Another example is the toggle switch constructed by Gardner *et al.*, which is composed of two repressors and two promoters [4]. Each promoter is inhibited by the repressor that is transcribed by the opposing promoter. This switch can exhibit robust bistability. So far, significant attention has been paid to the stability of genetic switches and lots of theoretical studies have been carried out [18–25]. For instance, the stability of genetic switches is studied by mean-field analysis and it is found that the stability grows exponentially with the mean number of transcription factor molecules involved in the switching [18]. Such stability can also be enhanced by spatially arranging the operons so that competing regulatory molecules mutually exclude each other at the operator regions [19].

Moreover, it is demonstrated that the study on the switching dynamics is the key to get an insight to the underlying mechanism of the stability of biochemical switches and therefore, the multistability of gene regulatory networks. To this end, the switching pathways have to be analyzed. However, switching in genetic switches is rare event and brute-force simulation is prohibitively expensive. To solve this problem, special simulation method has to be employed. Recently, the dynamics of the switching paths in a bistable genetic switch has been studied using a newly developed forward flux sampling (FFS) method [20]. Interestingly, though the model is symmetric, it is shown that the two kinds of protein dimers bind to the operator site

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with different probability on the transition state ensemble and the switching paths for forward and backward transition do not coincide. Besides, FFS method has also been used to study the effect of elementary reaction rate on the stability of both exclusive and general toggle switch. The mechanism of the variation in stability is well elucidated by analyzing the switching process [25].

Gene regulation processes usually involve large timescale separations. Fast reactions such as the binding or release of a transcription factor to an operator site or the dimerization of some proteins occur on timescales of seconds, while the transcription or translation of a gene may take minutes or even hours. Generally, transcriptional and translational processes are not only slow but also involve numbers of elementary reactions. These multi-step processes could be treated as delayed reactions, in which the initiating events are separated from the appearance of products by certain interval of time delay. When delays in biochemical reactions are not as significant as the other character time scales of the genetic system, they shall not affect the quasiequilibrium behavior of gene regulatory networks and therefore negligible. However, when the delay time is large enough, its effect on biochemical system can not be ignored. Recent studies indicate that delay could be pivotal in inducing oscillations in gene regulation [26–30]. However, how the delay affect the stability and flipping dynamics of biochemical switches remains unsolved.

In this work, we have used forward flux sampling method together with committor probability to study the effect of delay in an exclusive genetic toggle switch model. We find that time delay can alter the stationary distribution significantly and increase the transition rate of flipping between stable states. The influence of delay on the flipping dynamics is also studied. The results show that delay can affect the switching pathways, vary the total copy numbers of the transcription factors and the state of the operator site during the switching process. Since delay is ubiquitous in gene regulatory networks, the comprehensive understanding on how delay affects the stability and switching behavior in biochemical systems is important.

II. MODEL AND METHODS

A. Toggle switch model

In this work, we consider the model thoroughly studied by Warren [18], which consists of two genes A and B that mutually repress each other. The model is given by the elementary reactions as follows,

$$\mathrm{A}+\mathrm{A}\underset{k_f}{\overset{k_b}{\rightleftharpoons}}\mathrm{A}_2, \qquad \mathrm{B}+\mathrm{B}\underset{k_b}{\overset{k_f}{\rightleftharpoons}}\mathrm{B}_2 \tag{2}$$

$$\mathrm{O}+\mathrm{A}_2\underset{k_{\mathrm{off}}}{\overset{k_{\mathrm{on}}}{\rightleftharpoons}}\mathrm{OA}_2, \quad \mathrm{O}+\mathrm{B}_2\underset{k_{\mathrm{off}}}{\overset{k_{\mathrm{on}}}{\rightleftharpoons}}\mathrm{OB}_2 \tag{3}$$

$$\mathrm{O}\overset{k_{\mathrm{prod}}}{\Rightarrow}\mathrm{O}+\mathrm{A}, \qquad \mathrm{O}\overset{k_{\mathrm{prod}}}{\Rightarrow}\mathrm{O}+\mathrm{B} \tag{4}$$

$$\mathrm{OA}_2\overset{k_{\mathrm{prod}}}{\Rightarrow}\mathrm{OA}_2+\mathrm{A}, \quad \mathrm{OB}_2\overset{k_{\mathrm{prod}}}{\Rightarrow}\mathrm{OB}_2+\mathrm{B} \tag{5}$$

$$\mathrm{A}\xrightarrow{\mu}\emptyset, \qquad \mathrm{B}\xrightarrow{\mu}\emptyset \tag{6}$$

herein, A and B are two kinds of transcription factors (TFs). They each can form homodimers which regulate the transcriptional process by binding to the regulatory region of the DNA. Such regulatory region is represented by an operator site O. When dimer A_2 is bound to O, the production of B is blocked and *vice versa*.

In this work, the exclusive model is adopted, which means the operator can not be bound by both A_2 and B_2 dimers at the same time. When the operator site is unbound, A and B can be produced with the same rate. The proteins can also degrade or dilute, as indicated in Eq.(6). For most simulations with this bistable switch model, a standard set of parameter values was used as follows: k_f=$5k_{\mathrm{prod}}V$, k_b=$5k_{\mathrm{prod}}$, k_{on}=$5k_{\mathrm{prod}}V$, k_{off}=k_{prod}, and μ=$0.3k_{\mathrm{prod}}$ [25]. Herein, k_{prod}^{-1} is used as a unit of time for our simulation and the cell volume V is used, as the unit of volume.

On gene regulatory networks, it has been noted that the transcription and translation processes are so complex that time delays should be included [26, 31–34]. In this work, the synthesis of protein A and B are simulated as delayed reactions. The wide arrows in Eqs. (4) and (5) indicate that if the reactions are initiated, the proteins are produced after a delay time τ. Such delay could be induced by the accumulative steps of transcription, translation, or some other events. For simplicity and without loss of generality, we use the same delay time τ for all the four reactions.

B. Delayed stochastic simulation algorithm

The gene regulation processes are intrinsic noisy [35, 36] and internal noise should be included. To this end, we resort to the exact stochastic simulation algorithm (SSA) proposed by Gillespie [37]. At each time step, it stochastically determines the reaction event and the reaction time for the next reaction according to the probability which is associated with the rate of each reaction. The molecule numbers of different reacting species as well as the probability are updated at each time step. When the delay reactions are taken into account, such algorithm has to be modified. Algorithm for delayed reactions was developed lately and has found its applications in many biochemical systems [26, 31, 34, 38]. Recently, Roussel *et al.* extended such algorithm and found that many experiment phenomena were well reproduced by simulation [34]. A brief procedure to the delayed stochastic simulation algorithm (DSSA) is as follows: To begin, a waiting list is generated to store the delayed output events. At each time step the next reaction event R^* and the corresponding

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reaction time is determined by standard SSA algorithm. If R^* is delayed and the next reaction time is t^*, R^* is placed in the list and will occur at time $t^*+\tau$. On the other hand, if R^* is non-delayed, the time of the next reaction t^* is compared with the times in the list of scheduled delayed reactions. If there is a delayed reaction which will occur sooner than t^*, this delayed reaction will be carried out instead of R^* and the time is updated to t_d, which is the completion time for the delayed event. If no delayed reaction takes place in t^*, the molecule numbers of all reacting species are updated according to R^* and the time is advanced to t^*. Then new R^* and t^* are generated and the above process repeats. One could also resort to Ref.[26] for more details about DSSA. In this work, about 10^3 time steps are processed during one delayed reaction.

C. Forward flux sampling method and committor function

It is noted that though the system could flip between alternative states due to the random fluctuation, it spends most of its time in stable states. Therefore, the switching is a rare event and a proper method is needed for computer simulation. In this work, we adopt a recently developed FFS method to analyze the flipping process in a exclusive toggle switch model.

The FFS method has been used to simulate rare events in both equilibrium and nonequilibrium systems [20, 22, 23, 39, 40]. In FFS method, a series of interfaces are introduced between the initial and final states, which is noted as A and B, respectively. The system is forced to evolve from A to B in a ratchet-like manner. The interfaces are defined by an order parameter $\lambda(x)$, herein, x represents the phase-space coordinates. State A is defined as $\lambda(x)<\lambda(0)$ and state B is defined as $\lambda(x)>\lambda(n)$. The remaining nonintersecting interfaces which lie between states A and B are defined by intermediate values of λ_i ($0<i<n$). For all i, $\lambda_{i+1}>\lambda_i$, and any path from A to B must cross each interface in turn. The transition rate R from A to B is calculated as

$$\begin{aligned} R &= \bar{\Phi}_{\mathrm{A},0} P\left(\lambda_n|\lambda_0\right) \\ &= \bar{\Phi}_{\mathrm{A},0} \prod_{i=0}^{n-1} P\left(\lambda_{i+1}|\lambda_i\right) \end{aligned} \tag{7}$$

herein, $\bar{\Phi}_{\mathrm{A},0}$ is the average flux of trajectories crossing in the direction of B.

$$P(\lambda_n|\lambda_0) = \prod_{i=0}^{n-1} P\left(\lambda_{i+1}|\lambda_i\right) \tag{8}$$

$P(\lambda_n|\lambda_0)$ is the probability that a trajectory crossing λ_0 in the direction of B will eventually reach B before returning to A, and $P\left(\lambda_{i+1}|\lambda_i\right)$ is the probability that a trajectory which reaches λ_i, having come from A, will reach λ_{i+1} before returning to A. With FFS method, one can obtain not only the transition rate, but also the stationary distribution function and the transition path ensemble. For more information about FFS, please refer to Ref.[40].

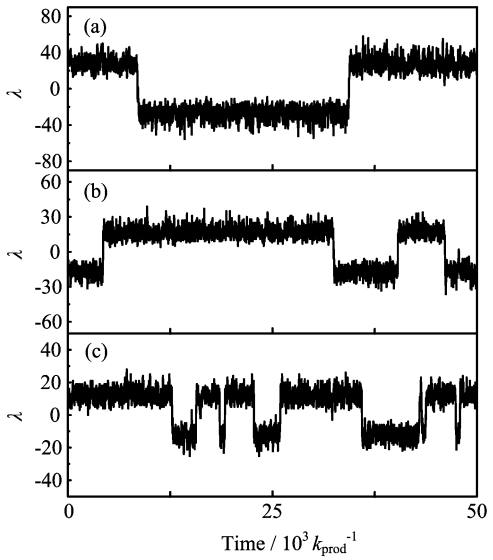

FIG. 1 The λ difference between the numbers of protein A and B as a function of time (in unit of k_{prod}^{-1}). From top to down, the delay time τ=0 (a), τ=0.3 (b), and τ=0.6 (c), respectively.

In this work, the order parameter for FFS simulation is chosen as the difference between the total copy numbers of the two proteins, which is given by

$$\lambda = N_{\mathrm{A}} - N_{\mathrm{B}} \tag{9}$$

$$N_{\mathrm{A}} = n_{\mathrm{A}} + 2n_{\mathrm{A}_2} + 2n_{\mathrm{OA}_2} \tag{10}$$

$$N_{\mathrm{B}} = n_{\mathrm{B}} + 2n_{\mathrm{B}_2} + 2n_{\mathrm{OB}_2} \tag{11}$$

Using DSSA, we obtain the time series of λ as shown in Fig.1. From Fig.1 (a) to (c), the delay time is τ=0, τ=0.3, and τ=0.6, respectively. It is observed that λ shows typical bistable behavior, indicating the system flips from state rich in A proteins to state rich in B proteins under the influence of internal noise. At large τ, the switching becomes more frequent and the range of flipping gets smaller.

To study the effect of delay on the stability of toggle switch, we need to elucidate the switching process by analyzing the transition paths. To do this, an order parameter that reflects the true reaction process is needed. Therefore, we resort to the committor function $P_{\mathrm{B}}(x)$. The committer function is defined as the probability that a trajectory initiated from configuration x will reach the final state B before the initial state A [41, 42]. Since $P_{\mathrm{B}}(x)$ is correlated with the progress of the transition, it has been used to analyze the transition pathways in biochemical switches [20, 25]. For every configuration along the transition paths derived from FFS method, the P_{B} can be readily obtained by firing several trial trajectories from this configuration

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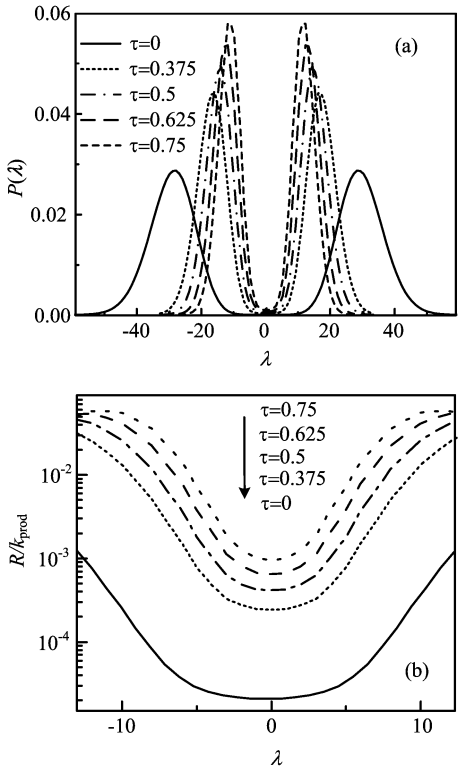

FIG. 2 (a) Probability distributions $P(\lambda)$ are plotted for different delay times. (b) The distributions around λ=0.

and record the times that these trajectories end up in state B. The collection of configurations with $P_{\rm B}$=0.5 is known as the "transition state ensemble" (TSE). The configurations on TSE provide insight into the transition mechanism and are thus of particularly importance for analyzing the transition process.

III. RESULTS AND DISCUSSION

In the present work, we mainly focus on how delay would affect the stability and the switching pathway in biochemical switches. We study the stationary distribution function under different delay time. The stationary distribution function $P(q)$ is obtained by summing up the probability that system stays in the vicinity of order parameter q during all the trial runs on every interface and combining the contribution from both forward and backward transitions [23]. In this work, q is selected as q=λ.

For the FFS simulation, we select the interfaces in the same way as in Ref.[23]. The values for λ_0 and λ_n is 27 and -27, respectively. During the sampling, at least 5000 configurations are stored in order to investigate the statistical properties of the ensemble of switching pathways. We get the stationary distribution function for different delay time τ in Fig.2. $P(\lambda)$ represents the probability of finding system at certain value of λ. It is

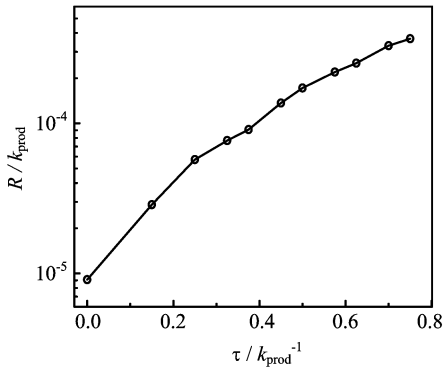

FIG. 3 Switching rate R as a function of delay time τ.

shown in Fig.2 that the stationary distribution exhibits two peaks at $\lambda\approx\pm27$ when delay is absent, which corresponds to the stable states of the system. At large delay, however, the shape of distribution changes significantly. With the increment of delay time τ, the gap between the two peaks shrinks greatly, but the bistable behavior remains even if the delay is large. Such findings together with the phenomena in Fig.1 illustrate that delay in protein synthetic process may alter the stable states for switching and thus affect the stability of genetic switches.

Figure 2(b) gives the distribution around λ=0. It is noted that at relative large τ, the probability of finding system in the diving surface λ=0 is much larger than that with smaller delay, which means the potential barrier between the stable states gets lower and the flipping becomes easier. Since the minimum of $P(\lambda)$ shows the unstable state of the system, which is located at λ=0 in this case, it provides us the implication that the switching pathways in the phase-space may have been varied by delay.

In Fig.3, transition rate R of the flipping between the two stable states is plotted as a function of delay time τ. The initial and final states for FFS simulations are selected according to the stationary distribution shown in Fig.2(a) and R is obtained by Eq.(7). It can be observed that the transition rate increases monotonically with the delay time τ, indicating that delay evidently reduces the stability of toggle switch.

In order to get an insight to the mechanism of how delay affects the transition process, we perform an analysis to the switching paths using committer function $P_{\rm B}$. Through FFS simulation, an ensemble of transition trajectories from A to B is obtained. For every configuration in this ensemble, we fire 100 trial trajectories and note the times that the trial trajectories reach B, from which the committor probability is calculated. The configurations with the same $P_{\rm B}$ are selected to form the $P_{\rm B}$ ensemble. By calculating the average $N_{\rm A}$ and $N_{\rm B}$ in the $P_{\rm B}$ ensemble, we get the average switching pathways which are shown in Fig.4. Herein, $\langle N_{\rm A}\rangle_{P_{\rm B}}$ and $\langle N_{\rm B}\rangle_{P_{\rm B}}$ represent the average $N_{\rm A}$ and $N_{\rm B}$ with the

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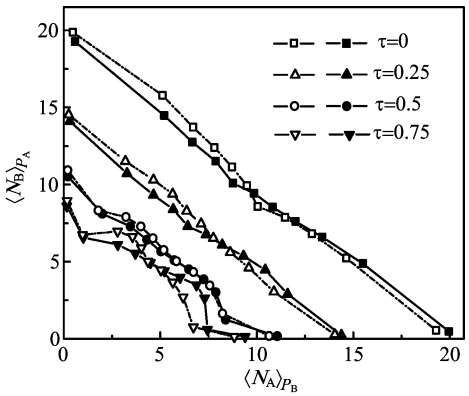

FIG. 4 Average switching pathways projected onto the N_A, N_B surface for different values of τ. $\langle N_A \rangle_{P_B}$ and $\langle N_B \rangle_{P_B}$ denote the average N_A and N_B with the same P_B, respectively. Solid symbols are transition paths from A to B, open symbols are transition paths from B to A.

same P_B, respectively. The average paths for A to B transition are present with the solid symbols while the B to A paths are given by the open symbols. As show in Fig.4, the average numbers for A and B proteins decrease with increasing delay. This may be due to the fact that time delay hinders the synthesis of both species. We see that the A to B paths and B to A paths don't differ from each other so significantly when the delay is absent or the delay time is small. If the delay is large, however, the backward trajectory deviates from the forward trajectory, as the path of τ=0.75 indicates. Since the genetic switch is a non-equilibrium system, it does not obey the detailed balance and therefore exhibits asymmetry for forward and backward transition, as mentioned in Ref.[20]. It seems that such asymmetry is enhanced by large delay. In addition, at small delay time τ=0.25 for instance, the average switching paths on the N_A, N_B surface are approximately straight lines, which are parallel to the non-delayed paths. For large τ, the paths become twisted, which means that the average number of the two proteins undergoes larger fluctuation during the switching process. Such findings imply that transcriptional and translational delay can remarkably affect switching pathways and thus, the stability of biochemical switches.

It is noted that during the switching process, the state of operator site O plays an important role in the switching mechanism, as shown in Ref.[25]. The state of the operator affects the production of A and B proteins and may decide the total copy numbers of each protein. Therefore, we also investigate the state of the operator O with the progress of the transition. In Fig.5, we plot the probability that the operator is in three different states OA_2, OB_2, and O as functions of P_B. $\langle N_{OX} \rangle_{P_B}$ represents the probability that the operator is in the given state OX. The transition paths from A to B are presented with the solid lines while the paths for B to A transition are given by the dash-dotted lines. For the A to B transition, the probability that O is bound by A_2 in delayed switches is larger when P_B is smaller than 0.2. At larger P_B, however, $\langle N_{OA_2} \rangle_{P_B}$ decreases with τ. On the other hand, the probability that operator is in state OB_2 decreases with delay time τ when P_B is small. For large P_B, $\langle N_{OB_2} \rangle_{P_B}$ shows no significant change with τ. For the probability that the operator is unbound, it is relatively large at small P_B. The probabilities for B to A transition are also shown, it is obvious that the A to B and B to A trajectories do not coincide with each other, which again emphasizes the fact that such switch system lacks detailed balance. For the same P_B, as τ increases, the difference in $\langle N_{OX} \rangle_{P_B}$ between the forward and backward transition becomes larger, indicating that delay makes the switching pathways more asymmetric. It is worth mentioning that such difference is larger for the medial P_B, specially for P_B around 0.5, which corresponds to the transition state. Besides these, the overall probability of O unbound increases with the delay time while the probability of O binding to A_2 and B_2 decreases with delay. The above analysis on the operator state again demonstrates that delay could dramatically affect the switching process.

The enhancement of asymmetry in transition paths due to the time delay is also illustrated in Fig.6 where the distribution of $P(\lambda)$ in the TSE of A to B flipping is plotted for different operator states. From Fig.6 (a) to (d), the delay time τ is 0, 0.25, 0.5, and 0.75, respectively. The distribution of $P(\lambda)$ is divided into three histograms. The area of each histogram gives the probability of the operator site in such state. Figure 6 shows that as τ increases, the probability of O bound by A_2 decreases while the probability that O remains unbound increases monotonically. The probability of finding operator bound by B_2, however, shows no obvious change. Therefore, with the increment of delay, the difference in the area under OA_2 and OB_2 histograms is further increased. Such phenomenon indicates that under the influence of delay the operator spends even less time in state of OA_2 than that in state OB_2 for the configurations which have equal probability to go to A or B.

IV. CONCLUSION

Delay induced by the complexity of transcriptional and translational processes has been found to be the dominant source of large deterministic variability which is usually recognized as bifurcation. However, the effect of such delay on the flipping dynamics of gene switches has not yet been studied for the switching between two stable states, which is a rare event and is thus computatively expensive. In this work, we have employed the FFS method to study the stability and switching dynamics of an exclusive toggle switch in which the delay of protein synthetic process is considered. It is found that the system shows bistability even at large

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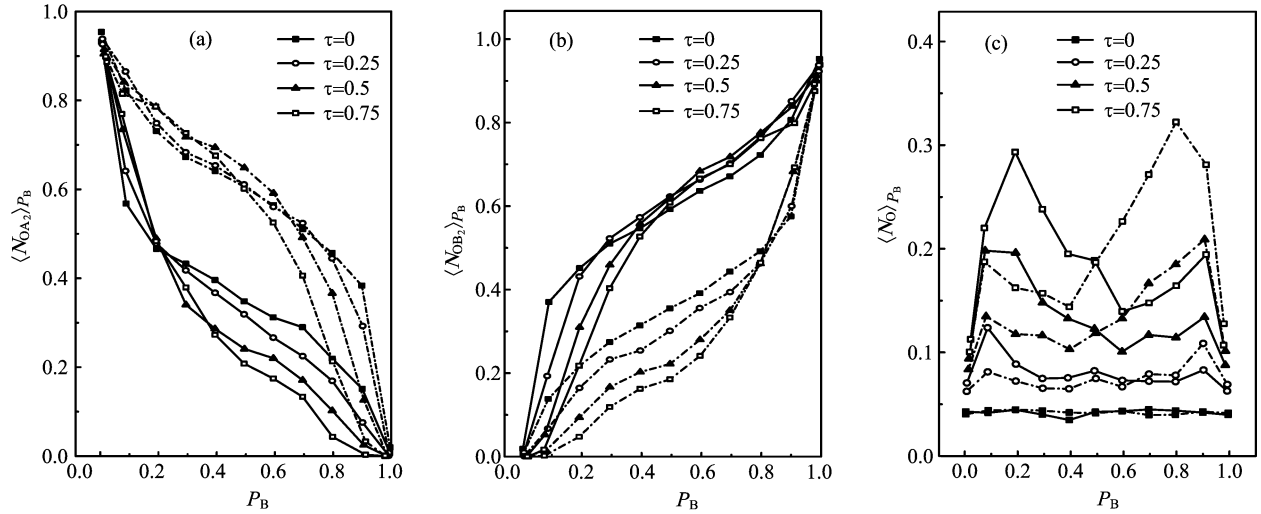

FIG. 5 The probability $\langle N_{OX}\rangle_{P_B}$ that the operator is in state OX as functions of P_B for OA_2 (a), OB_2 (b), and O (c), respectively. Solid lines are transition paths from A to B, dash dotted lines are transition paths from B to A.

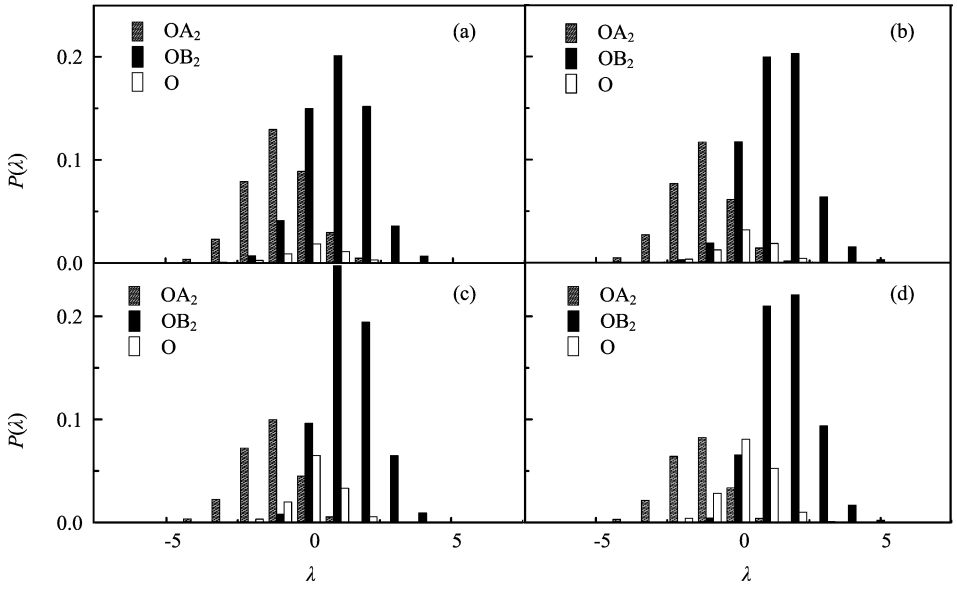

FIG. 6 The probability distribution $P(\lambda)$ on the transition state ensemble for the transition from A to B. The state of the operator site. From (a) to (d), the delay time is τ=0, τ=0.25, τ=0.5, and τ=0.75, respectively.

delay time, but the stationary distributions are significantly affected. The flipping rate between the two stable states increases monotonically with delay, showing the negative effect of delay on the stability of the toggle switch. We have also investigated how delay influences the switching pathways, where both the total copy numbers of the transcription factors and the state of operator site during the switching process show clear variations. Since transcriptional and translational delay is of ubiquitous importance in gene regulatory networks, the present work may provide us new insights into the underlying mechanism on how the dynamics of real biochemical switches are influenced by time delay. We also hope that such findings may find applications in synthetic system biology to help design delay-dependent gene circuits with multistability [43].

V. ACKNOWLEDGEMENT

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