Distributions of the First Passage Time in a Bistable Biological System

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It has been shown that a biological system with interlinked positive and negative feedback loops has the potential to generate rich dynamical behaviors such as monostability, bistability, oscillation, and excitability. Here, we demonstrate that tuning different feedback strengths can lead to the system generating bistability of two different types: two stable steady states, or both a stable steady state and a stable limit cycle. In particular, computing the distribution of the first passage time (FPT) between the two attractors for each type using the stochastic simulation algorithm based on the master equation, we find that the FPT obeys a single-peak distribution if the stochastic trajectories cross the separatrix of the saddle point, and a multi-peak distribution if they across the separatrix of the unstable limit cycle. Such a remarkable difference indicates that the FPT is an effective index for identifying the type of bistability.

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I. INTRODUCTION

In biology, cell differentiation, biological memory, etc., are closely related to bistability. Traditionally, bistability means that a system has two distinct stable steady states (such bistability is called Type-I for convenience). The relevant biological examples include the λ phage lysis-lysogeny switch [1, 2], several mitogen-activated protein kinase cascades in animal cells [3–5], and cell cycle regulatory CI circuits in Xenopus and Saccharomyces cerevisiae [6, 7]. Aside from Type-I bistability, there is another kind of bistability, i.e., a stable steady state and a stable limit cycle (SLC) coexisting (such bistability is called Type-II bistability for distinction). Type-II bistability has been found in biological systems [8–10] and even in chemical systems [11–13]. These two types of bistability have also been observed in different biological systems with different topological interlinks. A natural question is whether a biological system can simultaneously generate the two types of bistability. Furthermore, what are the biophysical mechanisms of generating them, and how can we distinguish them?

On the other hand, a gene regulatory network is composed of a set of biochemical reactions, thus inevitably involving stochastic fluctuations (molecular noise) that can be viewed as a kind of energy for this system. For a bistable system, noise can induce

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transient transitions between two different attractors, e.g., noise-induced coherent switching [14] or synchronous switching [15]. However, previous related studies focused more on stochastically switching phenomena occurring in Type-I bistable systems, but less on the first passage time (FPT), an important characteristic of quantifying a stochastic switch. The main interest of this paper is in showing common characteristics in the distribution of the FPT for both Type-I and Type-II bistable systems. For this, we consider a gene regulatory circuit at the transcription level, which is composed of interlinked positive and negative feedback loops. In spite of the simplicity in the network structure, this circuit can exhibit complex dynamics including monostability, bistability, oscillation, and excitability [16, 17]. We first simply describe the mechanism of generating these phenomena by analyzing the global bifurcation of this system, then demonstrate that the system can generate two different types of bistability: two stable steady states, and both a stable steady state and a SLC, by plotting the phase diagram of the trajectories, and finally we compute the distribution of the FPT for each type of bistability based on the master equation describing the microscopic motion of molecules. Interestingly, we find whether the distribution of the FPT is single-peak or multi-peak depends on the stochastic trajectories crossing the separatrix of the saddle point or the unstable limit cycle (ULC) between two basins of attraction.

II. MATHEMATICAL MODEL

The circuit, which is composed of coupled positive and negative feedback loops and will be investigated in this paper, is a common building block of many signaling systems [8, 16–18]. In this circuit, the master regulator X positively regulates its own expression, forming a positive feedback. Meanwhile, it also promotes the expression of the repressor Y that in turn induces the degradation of X, yielding a negative feedback. Under some conditions, e.g., if some biological processes such as transcription, translation, the binding of transcription factor to the promoter, etc., is integrated into a single step, the standard quasi steady-state equilibrium assumption is made, and both the activator and repressor are assumed to be under the control of the same promoter, the deterministic model for this circuit can be governed by the following set of differential equations [18]

\[
\begin{align*}
\frac{dX}{dt} &= a_1 + b_1 \frac{[X]/K}{1 + ([X]/K)^n} - c[X][Y] - d_1[X], \\
\frac{dY}{dt} &= a_2 + b_2 \frac{([X]/K)^n}{1 + ([X]/K)^n} - d_2[Y],
\end{align*}
\]

where \([X]\) and \([Y]\) denote the concentrations of the proteins X and Y, respectively. Suppose that the basal synthesis rate of X is a constant \(a_1\), and the basal synthesis rate of Y is \(a_2\). Parameters \(b_1\) and \(b_2\) are the maximum rates of the expression of the regulated proteins X and Y, respectively. The parameters \(K\) and \(n\) are the Michaelis constant and Hill coefficient, respectively. The interaction of the regulators X and Y leads to the degradation of X with the rate \(c\). Parameters \(d_1\) and \(d_2\) are degradation rates of the proteins X and Y, respectively. Note that all the parameters are dimensionless.

For the above model, we point out that the parameter \(b_1\) can represent positive feedback strength whereas the parameter \(b_2\) can represent negative feedback strength in
the case that \( c \) is fixed. Since our interest is in investigating the effects of feedback, we change only the values of \( b_1 \) and \( b_2 \) while keeping the other parameters fixed, e.g., \( a_1 = 0.02, a_2 = 0.3, d_1 = 0.02, d_2 = 0.1, K = 1.732, c = 0.1, \) and \( n = 2 \), most of which are estimated according to the published parameter values for fundamental processes in gene expression [18, 19].

<table>
<thead>
<tr>
<th>Reactions</th>
<th>Reaction rate functions</th>
</tr>
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<tbody>
<tr>
<td>( \phi P_1 \rightarrow X )</td>
<td>( P_1 = a_1 \Omega )</td>
</tr>
<tr>
<td>( X \rightarrow \phi P_2 )</td>
<td>( P_2 = d_1 N_X )</td>
</tr>
<tr>
<td>( \phi P_3 \rightarrow X )</td>
<td>( P_3 = b_1 \Omega \frac{N_X^2}{1+K^2/(K+Q^2)} )</td>
</tr>
<tr>
<td>( X + Y \rightarrow \phi P_4 )</td>
<td>( P_4 = cN_X N_Y / \Omega^2 )</td>
</tr>
<tr>
<td>( \phi \rightarrow Y P_5 )</td>
<td>( P_5 = a_2 \Omega )</td>
</tr>
<tr>
<td>( Y \rightarrow \phi P_6 )</td>
<td>( P_6 = d_2 N_Y )</td>
</tr>
<tr>
<td>( \phi \rightarrow X P_7 )</td>
<td>( P_7 = b_2 \Omega \frac{N_Y^2}{1+K^2/(K+Q^2)} )</td>
</tr>
</tbody>
</table>

For the convenience of subsequently investigating effects of the stochastic fluctuations (or molecular noise) on the system’s dynamical behaviors, we list some key reactions, referring to Table I, where the representative reactions (the left column) and their rate functions (the right column) are given. In this table, \( N_X \) and \( N_Y \) represent the number of species molecules of \( X \) and \( Y \), respectively, and \( \Omega \) denotes the volume of the entire culture. Note that two species molecules in this table are modeled as a birth-death process for simplification. To show the effect of molecular noise, we use the famous Gillespie stochastic algorithm [20] to generate a time series of random variables directly from the biochemical reactions in Table I.

III. RESULTS

We give first the global bifurcation diagram in the \((b_1, b_2)\) phase plane, which shows the dynamical regions respectively for monostability, bistability, oscillation, and excitability, then two phase diagrams respectively for the trajectories of the Type-I and Type-II bistable systems, and finally the distributions of the first passage times for both bistable systems.

III-1. Global bifurcation diagram and bistability

In order to have a complete view for the effect of feedback on the bistability of different types in system (1), we first plot a bifurcation diagram in the \((b_1, b_2)\) parameter plane using the AUTO software, referring to Fig. 1. The entire dynamical region is approximately divided into five sub-regions, denoted respectively by I–V. In regions I and II, only a single steady state exists, but the concentrations of \( X \) and \( Y \) in region I are respectively higher
than those in region II, mainly due to a stronger positive feedback strength $b_1$ and a weaker negative feedback strength $b_2$ in the former region. Region III is bounded by three curves: the one consisting of the limit points (LP) and the other two consisting of the subcritical Hopf bifurcation (Sub-H) points and saddle-node-on-the-invariant-circle (SNIC) bifurcation points, the system has three steady states, but only the lowest steady state in the $([X],[Y])$ phase plane is stable. Region IV is also bounded by three curves: two consisting of subcritical Hopf (Sub-H) points, and the other consisting of SNIC bifurcation points. Moreover, the system in this region has a SLC, which surrounds an unstable steady state. Region V is bounded by two curves, i.e., the LP and homoclinic (HC) curves, the system has two stable steady states and an unstable steady state. A similar bistable region is also found in the region marked by B (see the inset of Fig. 1, a locally enlarged region). The boundary of which consists of three curves: HC, LP, and Sub-H. In the region B the system has two stable steady states and an unstable steady state, but the higher stable steady state is surrounded by ULC in the $([X],[Y])$ phase plane. We also find a bistable region A, where the system exhibits the Type-II bistability. Note that region B is very narrow, so is region A, which consists of two parts (see the inset of Fig. 1 or the right-top corner).

Next, we show that the deterministic system (1) can generate a Type-I bistability,
which can further be divided into two cases with different dynamical characters, depending on the feedback strengths. More precisely, for \( b_1 = 3.55 \) and \( b_2 = 1.4 \) (called case I for convenience, in region V of Fig. 1), the system has two stationary states: \( SS_1([X] \approx 0.094, [Y] \approx 3.041) \) and \( SS_2([X] \approx 1.772, [Y] \approx 10.158) \). Both are stable focuses and are separated by the saddle point \( SP([X] \approx 0.210, [Y] \approx 3.203) \), see Fig. 2(a). Moreover, the attracting basin of the stable focus \( SS_1(BASS_1) \) and the attracting basin of the stable focus \( SS_2(BASS_2) \) are separated not only by two separatrices going into the saddle point, denoted by \( S_1 \) and \( S_2 \) (see the solid arrow lines in Fig. 2(a)), but also by other two separatrices outgoing from the saddle points, respectively denoted by \( S_3 \) and \( S_4 \) (see the dashed arrow line in Fig. 2(a)). However, if \( b_1 = 3.48 \) and \( b_2 = 1.5 \) (called case II, in region B of Fig. 1), then the system also has three similar steady states: two stable focuses \( SS_1([X] \approx 0.092, [Y] \approx 3.042) \) and \( SS_2([X] \approx 1.608, [Y] \approx 9.943) \), and a saddle point \( SP([X] \approx 0.224, [Y] \approx 3.246) \), which separates the former, and 4 similar separatrices (see the solid and dashed arrow lines in Fig. 2(b)), where the separatrices are outgoing from the saddle points, \( S_3 \) and \( S_4 \) converge to the stable focus \( SS_1 \), and the separatrix outgoing from ULC and going into the saddle points \( SP, S_1 \), is invisible because ULC and \( S_1 \) are very close, see Fig. 2(b).

Finally, we show that the deterministic system (1) can generate a Type-II bistability. If \( b_1 = 5.021 \) and \( b_2 = 2.4 \) (in region IV of Fig. 1), then the system has only a stable focus point \( SS([X] \approx 1.647, [Y] \approx 14.398) \), which is surrounded by a ULC (see the dashed-line circle in Fig. 3) and a SLC (see the solid-line circle in Fig. 3). The two attractors are separated by the ULC. Moreover, the interior of the ULC forms the basin of attraction of the stable focus \( SS(BASS) \), but the exterior forms the basin of attraction of the stable limit (BASL).
For each type of bistability, whether the deterministic trajectories evolve asymptotically to which one of the two stable attractors depends on the initial values of the system’s variables.

III-2. Distribution of first passage time

From the above analysis in Subsection III-1, we have seen that the deterministic system (1) can generate bistability of two different types, which depends on the feedback strengths (refer to regions V, A, and B marked in Fig. 1). In this subsection, we consider the effects of stochastic fluctuations on the trajectories, focusing on the distribution of the first passage time. For this, we use the famous Gillespie algorithm to generate a time series for random variables from the biochemical reaction (see Table I), and consider the transition of the stochastic trajectories through the ULC or the separatrix of the saddle point between the two attracting basins. Since stochastic trajectories through the separatrix from one attracting basin to another attracting basin are a stochastic process, FPT is a stochastic variable, which should obey a probability distribution in principle, denoted by $P(t)$. In order to compute the distribution of FPT for each type of bistability, we first need to reasonably define FPT.

First, we consider the Type-I bistability. For case I with $\Omega = 200$, Figure 4(a) shows stochastic switching between two basins of attraction, where the stochastic trajectory can cross the separatrix ($S_1$ or $S_2$) of the saddle point and visit one or the other basins of attraction in an irregular way. Figure 4(c) illustrates the time series of the number of $X$ molecules, which clearly demonstrates stochastic switching between two stable focuses. To ensure that the stochastic trajectories cross the separatrix $S_1$ from $BASS_2$ to $BASS_1$ for the first time, we select only those trajectories that cross a line segment $N_X = 50, 1000 \leq N_Y \leq 1800$. Such a selection is reasonable since, on the one hand, we find that the first time of trajectories crossing the separatrix is almost the same as that of trajectories crossing the line segment, and on the other hand, this selection can ensure that the stochastic trajectories...
FIG. 4: Characteristics of Type-I bistability. (a), (c), and (e) Case I with $\Omega = 200$, (b), (d), and (f) Case II with $\Omega = 1000$. The other parameters are the same as in Figs. 2(a) and 2(b), respectively. (a) and (b) show the phase diagram for stochastic trajectories, where the meaning of the nullclines and symbols are similar to that of the nullclines and symbols in Fig. 2; (c) and (d) show the time series of the number of $X$ molecules, (e) and (f) show histogram diagrams of the distribution of FPT from the attracting basin of the stable focus $SS_2(BASS_2)$ to the attracting basin of the stable focus $SS_1(BASS_1)$, where the solid curve is the fitting result.

For case II with $\Omega = 1000$, the definition of FPT is different, since the system exhibits some different dynamics in contrast to case I. Figure 4(b) shows the phase diagram for the stochastic trajectories. To ensure that the stochastic trajectories cross the ULC from $BASS_2$ to $BASS_1$ for the first time, we define FPT as the time that the stochastic trajectories can cross the separatrix $S_1$, for example, those which return to $BASS_2$ cross the separatrix (note: We can not consider those trajectories that cross the separatrix for the first time, referring to Fig. 4(a)). Therefore, we obtain a histogram diagram of $P(t)$, which exhibits a single peak, where the solid curve is the fitting result, referring to Fig. 4(e).
trajectories cross the line segment \(N_X = 800, 7850 \leq N_Y \leq 10000\), since the first time of the stochastic trajectories crossing the ULC is almost the same as that of the stochastic trajectories crossing this line segment. Figure 4(f) shows the histogram diagram for the probability distribution of the FPT, which exhibits multi-peaks, where the solid curve is the fitting result. However, there exist some differences between cases I and II. The first difference is that \(P(t)\) for the latter seems to have several local extremes (we observe that at least 4 extremes are visible from Fig. 4(f)). The existence of multi-peaks would imply that there is a specific region in the phase plane where stochastic trajectories favor crossing the ULC. The second difference is that the appearance of secondary peaks would indicate that the stochastic trajectories have a chance to form some circulations around the ULC before outgoing from the ULC. The third difference is that the time series of the number of X molecules has the same characters in two cases (see Figs. 4(c) and 4(d), but the corresponding distribution function of the FPT from \(BASS_2\) to \(BASS_1\) is different (see Figs. 4(e) and 4(f)).

Next, we consider stochastic switching occurring in the system with Type-II bistability. Figure 5(a) shows the phase diagram for the stochastic trajectory with \(\Omega = 1000\). From this figure, we observe two attracting basins: \(BASS\) and \(BASLC\), which are separated by a ULC. When considering the transitions from \(BASS\) to \(BASLC\), or vice versa, we clearly see that the shape of the two attracting basins has an important effect on the stochastic trajectories that circulate in BASLC. The distance between SLC and ULC is smaller in case of high \(N_Y\) values than in the case of small \(N_Y\) values, so the stochastic trajectories can passage a certain area close to the cycles but still remain in BASLC, implying that they have fewer chances to cross the ULC when they locate in the lower part of the SLC. Moreover, the stochastic trajectories can easily cross the ULC when they locate in the high part of the SLC, since the SLC and ULC are very close. Figure 5(b) illustrates the time series of the number of X molecules, which clearly demonstrates stochastic switching between the SLC and the stable focus.

Figures 5(c) and 5(d) altogether describe the distributions of the FPT of the stochastic trajectories crossing the ULC between two different attractors, where Figure 5(c) shows the transitions from \(BASLC\) to \(BASS\). To ensure that the stochastic trajectories remain in \(BASS\) after leaving the \(BASLC\), we select only those trajectories that cross the line segment \(N_X = 1647, 11000 \leq N_Y \leq 14500\). Thus, we define the FPT as the time that the trajectories cross this line segment, and obtain the histogram diagram of \(P(t)\), which exhibits a multi-peak distribution, referring to Fig. 5(c), where the solid curve is the fitting result, and the inset shows the longer-time tendency for the change of the FPT with time. Moreover, the distance between subsequent peaks is approximately equal to the period of oscillations of the SLC, but the distribution becomes wider and wider or flatter and flatter over the evolution of time, mainly due to the diffusion of phases during the circulation of the stochastic trajectory along the SLC. This result is in accord with the previous ones [12, 13]. Figure 5(d) shows the distribution of the FPT from \(BASS\) to \(BASLC\). In order to ensure such a passage, we consider only those stochastic trajectories that cross the line segment \(0 < N_X \leq 60, N_Y = 8000\) for the first time. Consequently, \(P(t)\) also exhibits multi-peaks. This result is in accord with Fig. 4(f).
FIG. 5: Characteristics of the system with Type-II bistability for $b_1 = 5.021$, $b_2 = 2.4$, and $\Omega = 1000$. (a) shows the phase diagram for the stochastic trajectories, where the meaning of the nullclines is similar to that of the nullclines in Fig. 2. (b) shows the time series of the number of X molecules. (c) and (d) show histogram diagrams for the distribution of the FPT of the stochastic trajectories crossing the ULC between two different attractors, where the solid curve is the fitting result. In (c), the transitions occur from BASLC to the attracting basin of the stable focus ($BASS_1$), and the inset shows the longer-time tendency for the change of the FPT with time, and in (d), the transitions occur from $BASS_2$ to BASLC.

Note that there exist some common characteristics between Figs. 5(c) and 5(d). First, both distributions exhibit multi-peaks. Second, the appearance of secondary peaks would indicate that the stochastic trajectories have a chance to form some circulations inside or outside the ULC before crossing the ULC.

IV. CONCLUSIONS

Feedback, as one of the most common regulation mechanisms, exists widely in gene regulatory networks [18, 21, 22]. We have investigated a simple two-component regulatory system, which is composed of coupled positive and negative feedback loops, by focusing on the effect of feedback strengths, and have shown rich dynamical behavior, such as monostability, bistability (Type-I bistability and Type-II bistability), oscillation, and excitability. For bistability of each type, we have found that molecular noise can induce stochastic switching between two attractors.

Nowakowski and Kawczyński have investigated the distributions of the FPT from $BASS_1$ to $BASS_2$ (refer to Fig. 4(b)) and from BASLC to $BASS$ (refer to Fig. 5(a)) in a
model of thermochemical systems, and showed that the distribution of the FPT can exhibit multi-peaks [12, 13]. Here, we have further considered the distributions of the FPT from $BASS_2$ to $BASS_1$ (see Figs. 4(a) and 4(b)) or from $BASS$ to BASLC (see Fig. 5(a)). However, we have shown that whether the distribution of the FPT is single-peak or multi-peak depends on the stochastic trajectories crossing the separatrix of the saddle point or ULC between two basins of attraction. This indicates that the FPT is a useful index for identifying the type of bistability.

From the viewpoint of network structure, a circuit consisting of coupled positive and negative loops can have other network topologies, which involve network topology equivalence (by topological equivalence, we mean that two circuits have the same path signs or loop gains, where one gain is defined as the product of all regulatory signs in the path or loop with one positive/negative sign standing for activating/repressive regulation). For example, an alternative circuit for the network studied in this paper is the one where $X$ that is taken as an auto-activator represses $Y$ that in turn activates $X$. These two circuits are topologically equivalent, but a natural issue is whether the alternative circuit can also exhibit similar dynamical characteristics. Thus, our next interest is to investigate differences in dynamics between two topologically equivalent circuits. Such an investigation should be significant from the viewpoint of biological evolution.

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