Switch dynamics for stochastic model of genetic toggle switch

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HIGHLIGThS

• In this paper, we found that the relationship between the MFPT and noise intensity is negative correlation.
• This paper showed that noise in degradation rates can indeed induce switching in the genetic toggle switch.
• This paper proposed a method how to control the biological switch.

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ABSTRACT

Recently, more and more biological experiments have indicated that noise plays an important role in bistable systems, such as the case of the bimodal population distribution in the genetic toggle switch. In this paper, we further verify that noise in degradation rates can indeed induce switching in the genetic toggle switch. Meanwhile, we apply the theory of mean first passage time (MFPT) in high dimensional system to the above stochastic model. According to our assumption, the high order finite difference method is used to compute the MFPT (that the average time switching from one steady state to the other) and we find that the relationship between the MFPT and noise intensity is negative correlation. The result is also verified through another numerical simulation method.

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Introduction

Bistability arises within a wide range of biological systems from the λ phage switch in bacteria to cellular signal transduction pathways in mammalian cells [1]. A system is termed bistable if it can switch from one steady state to the other under a set of external stimuli [2]. We know that regulatory mechanism plays a very important role in realizing switching of bistable systems. There are a lot of regulatory mechanisms in bistable biological systems. For instance, positive feedback [3–5], positive and negative feedback and double-negative feedback [6,7]. It is well known that quantitative mathematical model is a very useful tool for studying regulatory mechanisms in complex biological systems. Bistability, a typical behavior of biological systems, has been studied extensively through deterministic modeling and stochastic modeling. In the context of deterministic modeling, most research has focused on analyzing bistability properties of biological systems from regulatory mechanisms and kinetic parameters [5–11]. Recently some studies have indicated that noise can induce stochastic switching from one state to another in the bistable systems of gene regulations though stochastic modeling [1,2,12–15].
Zhou et al. [2], through introducing multiplicative noises to a typical genetic toggle switch [16] interfaced by a quorum-sensing signaling pathway, showed that noise can induce switching between two alternative states. However, so far few studies have taken into account how the mean first passage time (MFPT) [17] which gives the average time switching from one state to another is affected by stochastic fluctuations in the genetic toggle switch [2].

It is well known that bistable biological systems have two distinct steady states corresponding to high and low (on/off) concentration states [18]. The mean first passage time (MFPT) has been widely used for quantifying the average time from high to low concentration [19,20] and vice versa. Unfortunately, most research in bistable biological systems only focus on the switching time from one dimensional systems [14,21,22] or from statistical simulation in terms of numerical simulation methods [23].

Herein we address the issue on how stochastic fluctuations in degradation rates for the genetic toggle switch influence the MFPT. To this end, first, we introduce a general MFPT theory for high dimensional [24]. Then, based on the improved genetic toggle switch [2], we demonstrate bimodal population distributions in the genetic toggle switch and find noise can indeed induce switching between two alternative states. Finally, we use high-order accurate finite difference methods [25] to estimate the MFPT of the system from one stable state to another. We find that the MFPT tends to decreases when noise strength increases. For the sake of comparison, we use as well statistical simulation to further verify the above result.

1. Mean first passage time for homogeneous processes

In this section, we wish to treat the multidimensional first passage time problem and introduce the classical stochastic method [16,17] in this paragraph. To compute the earliest time at which a particle whose position is described by a Fokker–Planck equation, initially inside a region $R$ with boundary $S$, leaves that region, we consider the problem of solving the backward Fokker–Planck equation with an absorbing boundary condition on $S$ [18], namely,

$$P(x', t| x, 0) = 0 \quad (x \in S). \quad (1)$$

As is noted in Ref. [18], the probability that at time $t$ the particle is still in $R$ is

$$G(x, t) = \int_R dx' P(x', t|x, 0). \quad (2)$$

Let the time that the particle leaves $R$ be $T$. Then we can rewrite (2) as

$$\text{Prob}(T \geq t) = \int_R dx' P(x', t|x, 0). \quad (3)$$

Which means that $G(x, t)$ is the same as $\text{Prob}(T \geq t)$. Since the process is homogeneous, we can write $P(x', t|x, 0) = P(x', 0|x, -t)$, and the backward Fokker–Planck equation can be written

$$\partial_t P(x', t|x, 0) = \sum_i A_i(x) \partial_i P(x', t|x, 0) + \frac{1}{2} \sum_{ij} B_{ij}(x) \partial_i \partial_j P(x', t|x, 0). \quad (4)$$

Then we substitute (2) into (4) and we find $G(x, t)$ obeys the following equation

$$\partial_t G(x, t) = \sum_i A_i(x) \partial_i G(x, t) + \frac{1}{2} \sum_{ij} B_{ij}(x) \partial_i \partial_j G(x, t). \quad (5)$$

The initial conditions on (5) will arise as follows:

(a) $P(x', 0|x, 0) = \delta(x - x')$ So that

$$G(x, 0) = \begin{cases} 1 & x \in R \\ 0 & x \in \text{elsewhere} \end{cases}$$

(b) the boundary condition (1) requires

$$G(x, t) = 0 \quad (x \in S).$$

Since $G(x, t) = 0$ is the probability that $T \geq t$, So the mean first passage time $T(x) = \langle T \rangle$ is given by $T(x) = - \int_0^\infty t \partial_t G(x, t) dt$, after integrating by parts, we can gain the following equation

$$T(x) = \int_0^\infty G(x, t) dt. \quad (6)$$

2. Model description

Well known a synthetic bistable gene-regulatory network that is called a genetic toggle switch in Escherichia coli [6]. The genetic toggle switch is composed of two genes, lacI and $\lambda cl$, and two constitutive promoters, promoter 1 and promoter 2. lacI and $\lambda cl$ encode the transcriptional regulator proteins LacI and $\lambda Cl$, respectively. Meanwhile, promoter 1, that transcribes the lacI gene, is inhibited by $\lambda Cl$. Promoter 2, that transcribes the $\lambda cl$ gene, is inhibited by LacI. This design has two stable
states: one in which the $\lambda Cl$ is high state corresponding to the expression of the $laci$ is low, and one in which the $Laci$ is high corresponding to the expression of the $\lambda cl$ is low. Soon afterwards, Kobayashi et al. [26], through designing an engineered genetic circuit that respond to biological signals, demonstrated that transitions from one stable state to the other can be induced by a signal that temporarily brings the system out of the region of bistability. Fig. 1 illustrates the schematic diagram of the functional architecture and dynamics of the switch [26].

As is illustrated in Fig. 1, when $\lambda Cl$ level is decreased, $laci$ expression is derepressed and $Laci$ level increases. This represses $\lambda cl$ expression, which decreases $\lambda Cl$ level and further increases $Laci$ level. The same result can be achieved by increasing the level of $Laci$.

We know that the genetic toggle switch [16] is a robust bistable system. Although the noise-induced transitions between the steady states are rare [26], noise has significant impact on the dynamic behavior of the bistable systems in transitions [12,15]. Recently, considering stochastic fluctuations that are multiplicative noises (for the difference between multiplicative noise and additive noise, we can refer to Ref. [15]) in degradation rates of repressors, an improved genetic toggle switch system is described by the following stochastic model [2]:

$$
\begin{align*}
\frac{dx_1}{dt} &= \frac{a_1}{1 + (x_2)^{n_1}} - (d_1 + \xi_1(t))x_1 + b_1 \\
\frac{dx_2}{dt} &= \frac{a_2}{1 + (x_1)^{n_2}} - (d_2 + \xi_2(t))x_2 + b_2,
\end{align*}
$$

where $x_1$ and $x_2$ are the concentrations of $Laci$ and $\lambda Cl$ that are encoded by genes $laci$ and $cl$, respectively. The parameters $a_i$ and $n_i$ ($i = 1, 2$) are the dimensionless transcription rates in absence of repressor and the hill coefficients, respectively. $d_i$ and $b_i$ ($i = 1, 2$) are the degradation rates and the basal synthesis rates, respectively. $\xi_1$ and $\xi_2$ are mutually independent random variables and are assumed as Gaussian noises with zero mean and delta-correlated: $\langle \xi(t)\xi'(t') \rangle = D \delta(t - t')$. Here $D$ is noise strength.

Here we fix parameters as follows: $a_1 = 2.5$, $a_2 = 5$, $d_1 = d_2 = 1$, $b_1 = b_2 = 0.5$, $n_1 = n_2 = 4$. Although the above chosen parameter values [2] are enough to maintain bistability of the genetic toggle switch in the absence of noise, the noise-induced bimodal population distribution is not observed in the deterministic system corresponding to (7). In order to demonstrate noise can induce bimodal distribution, we first transform the stochastic model (7) into the corresponding Fokker–Planck equation according to the formula between Fokker–Planck equation and stochastic differential equation [24]. The result is

$$
\partial_t P = -\sum_i \partial_i [A_i(x)P] + \frac{1}{2} \sum_{ij} \partial_i \partial_j [B_{ij}(x)P]
$$

the coefficient matrices associated with the Fokker–Planck equation (8) are given by

$$
A = \begin{pmatrix}
\frac{a_1}{1 + (x_2)^{n_1}} & -d_1x_1 + b_1 \\
\frac{a_2}{1 + (x_1)^{n_2}} & -d_2x_2 + b_2
\end{pmatrix}
$$

$$
B = \begin{pmatrix}
(Dx_1)^2 & 0 \\
0 & (Dx_2)^2
\end{pmatrix}
$$

Fig. 1. Transition in the genetic toggle switch.
Fig. 2. The bimodal distribution for noise strength $D = 0.02$.

where $x = (x_1, x_2)'$, $P = P(x, t|x_0, 0)$ is conditional probability density which represents the system, initially at $x_0$ at time $t = 0$, is in state $x$ at time $t$. Eq. (8) is subjected to initial condition $P(x, 0|x_0, 0) = \delta(x - x_0)$ and the normalization condition $\int_{R^2} P(x, t|x_0) = 1$. Then we use high order finite difference method to simulate Eq. (8) for noise amplitude $D = 0.02$. Fig. 2 gives the joint probability density function for $t = 150$ s. It is not difficult to find that the bimodal distribution is shown in Fig. 2, which indicates that noise indeed plays a very important role in the bimodal distribution for bistable system.

3. Results

3.1. Noise-induced switching from one state to the other

To clarify how multiplicative noises induce switching from one state to another, we then perform stochastic simulations for the system (7). First, we obtain the two stable states for the deterministic system corresponding to (7): one is $(x_1, x_2) = (2.8514, 0.6308)$, the other is $(x_1, x_2) = (0.5299, 5.2234)$. Starting from the same starting point at $x_1 = 2.8514, x_2 = 0.6308$ (the initial state is also applied in the following all simulations), namely, the protein LacI concentration is initially in high state corresponding to the state that the protein $\lambda CI$ is low state, run 10,000 times simulations such that we can obtain a good sampling of the protein $\lambda CI$ probability density. In Fig. 3 we plot the protein $\lambda CI$ probability density for different noise intensities at a moderate time $t$. It shows that the peak at the low steady state is much higher when the noise intensity $D$ is small, indicating that the $\lambda CI$ concentration concentrates on the low concentration state. Increasing the noise strength in a finite interval, the peak at the high state becomes higher while the peak of low state tend to lower. Until certain noise amplitude, the high concentration state of the protein $\lambda CI$ becomes more populated, which means the transition from one steady state to another.

3.2. The mean first passage time (MFPT)

First passage problems play a significant role in the quantitative understanding of biological observations and experiments [27]. For example, David Frigola and colleagues [14] found that state-dependent intrinsic noise in autoactivation dynamics drive an asymmetric switching by observing the relationship between switching rates as the inverse of the MFPT and energy barrier. The result is in agreement with the asymmetric stochastic switching system as the galactose signaling network in yeast [28]. Therefore, the MFPT analysis for the genetic toggle switch can help us to extensively understand the switching dynamics that are observed in the experiment. Here we are interested in evaluating the effect of multiplicative noises on transitions between the stable steady states by the mean first passage time. By simulating the stochastic differential equation (7), Fig. 4 illustrates the time courses of protein LacI and $\lambda CI$ concentrations for different noise intensity. It is shown that noise cannot only induce switching, more interestingly, the greater the noise intensity, the shorter the MFPT.

As is shown in Fig. 4, the fluctuations in the initial protein concentration display small deviations when the switching from one steady state to another does not occur. Under this condition, we set a moderate region $R$ in which the small fluctuations in initial steady state are included. As long as the fluctuation leaves the region $R$, we think that the transition between two stable steady states occurs, which means the first passage happens. In order to quantitatively describe how noises in degradation rates modifies the MFPT, we use the MFPT theory in Section 2 and perform simulations. According to the steps in Section 2, Eq. (8) is converted into the type of Eq. (5). Where the involved $x, A$ and $B$ had been mentioned in Section 3. We know that it is very difficult to get the analytical solutions of Eq. (5), therefore, we resort to high order finite difference method to simulate Eq. (5). It is noted that our simulation result is based on the above assumption. Fig. 5(a) shows the relationship between the MFPT and noise intensity. We find that the MFPT gradually decrease when noise amplitude increases in a finite interval. Besides, we note that slope is very steep when noise intensity is very small, in particular for noise intensity $D = 0$. Since the deterministic genetic toggle system cannot spontaneously switching from one stable state to the other, in other words,
Fig. 3. The multiplicative noise introduced into the degradation rate can induce switching between two stable steady states for different noise intensities.

Fig. 4. The dependence relationship of the repressor protein concentrations, LacI and λCI, on the noise intensity $D$.

the MFPT is infinite. To further verify the rationality of the above assumption, we use as well the statistical method [23] to compute the MFPT for the genetic toggle switch. We find that the tendency in Fig. 5(b) is consistent with that of Fig. 5(a).

4. Conclusion

Herein we have introduced stochastic approaches to study the effect of multiplicative noises in degradation rates on the dynamics of the single genetic toggle switch. First, we have further verified that noise can indeed induce switching between two stable states based on the single genetic toggle switch. Then we applied the high dimensional MFPT theory for homogeneous processes in the stochastic model, by computing MFPT which obeys the backward Fokker–Planck equation using high
order finite difference method, we find that the relationship between the MFPT and noise intensity is negative correlation. In fact, the simulation result is based on the above prescribed assumption. While the rationality of the assumption has been verified by using statistic method [23] to compute the MFPT.

Although we only consider the MFPT in a two dimensional bistable biological system, the numerical simulation method based on the above prescribed assumption can be extended to three dimensional or higher dimension bistable biological systems. In addition, the analysis result reported in this work for MFPT only consider absorbing boundary condition. However, for reflecting boundary condition or the combination of reflection and absorbing boundary conditions, we need to make greater efforts in the future work.

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