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Analysis of the Most Probable Exit Path in the synthetic gene network with genetic toggle

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Abstract

In the process of the development of biotechnology, the research on the manipulation and regulation of biochemical molecules such as genes and proteins has become a hot direction. In particular, the synthetic gene network with genetic toggle has attracted the attention of many scholars due to its great creative space and strong operability. However, the current research on synthetic gene network with genetic toggle mainly focuses on the influence of noise on the stability of the system and stochastic resonance. Little research has been done on exploring the switching process of the system with genetic toggle under noise excitation. In this paper, the most probable exit path (MPEP) is proposed to understand the switching of genetic toggle in the system. Firstly, we studied the MPEP of protein concentration switching in a bistable synthetic gene network with genetic toggle in E.coli organism when noise intensity is very small. Large deviation theory is used to explore the MPEP of protein concentration switching from a new perspective. Secondly, OM action functional is introduced to get the MPEP of the system under Gaussian white noise excitation. It is revealed that two independent noises have opposite effects on protein concentration switching. Finally, the MPEP is shown by energy landscape, and it is found that the reduction of noise intensity is not conducive to protein concentration switching.

Keywords: The synthetic gene network, Most probable exit path, Large deviation theory, Action functional, Energy landscape
1 Introduction

The complex stochastic dynamic behavior of the nonlinear system excited by noise is quite different from that of the original deterministic system. A system is termed bistable if it can switch between two distinct stable steady states but cannot rest in intermediate states under the excitation of external stimuli. Biological examples of bistable systems include the λ phage lysis-lysogeny switch \([1] \), several mitogen-activated protein kinase cascades in animal cells \([2–4] \), and cell cycle regulatory CI circuits in Xenopus and Saccharomyces cerevisiae \([5, 6] \).

Noise excitation has an important effect on the long-term behavior of dynamic system. For a nonlinear dynamic system interfered by small-noise, it has the possibility of transferring from one initial steady state to another steady state in a finite time, and this stochastic dynamic phenomenon is called dissociation behavior. Due to the ubiquitous noise effect in nature, various fields such as chemistry, physics, engineering and biology will inevitably encounter dissociation problems, such as gene regulation system \([7, 8] \), chemical reaction system \([9, 10] \), cancer cell proliferation in pathology and epidemiology system \([11, 12] \), etc. Therefore, it is of great practical significance to study exit problems.

The first complete results of the exit problem were given by Freidlin and Wentzell using large deviation theory \([13, 14] \). The large deviation theory studies the behavior of large deviation generated by stochastic dynamic system. Its core idea is that when a small probability event occurs, it will choose the most likely one from many “almost impossible” ways with a great probability. Freidlin and Wentzell \([13] \) describe the difficulty of generating sample trajectories of each small probability event by introducing action functional. The extremum of the action functional describes the most probable way of occurrence of the small probability event, which is named the most probable exit path (MPEP). The study of the MPEP can be applied to various fields. Franovic et al. \([15] \) studied the most probable activation path of the FHN neural system, and the corresponding random trajectory around the most probable path is clustered. Han et al. \([40] \) investigated the most probable trajectory of stochastic tumor-immune system and it is found that the disturbance caused by noise in tumor immune system is beneficial to patients under known initial conditions and known boundary conditions. Xu et al. \([18] \) proposed the maximum likelihood state to study the probabilistic behavior of a simplified random thermohaline cycle system. The results show that the system changes along the trajectory of the maximum likelihood state. Mao et al. \([16] \) studied the exit problem of stochastic SIR model with limited medical resource and determined its most probable exit path. Zheng \([17] \) established a probabilistic framework based on the nonlocal Fokker-Planck equation to investigate the maximum likelihood climate change for an energy balance system under the influence of greenhouse effect and Lévy fluctuations. Liu \([19] \) explored noise-induced escape from the domain of attraction of a stable state in a fast-slow insect outbreak system. A complete investigation on the structural change of the MPEP in a fast-slow insect outbreak system under different noise ratios was given.

In the process of development of biotechnology, the research on the operation and regulation of biochemical molecules, such as gene fragments and proteins, which carry the code of life, has gradually become a hot direction. Synthetic biology, which is
based on gene regulation network, contains huge creative space and strong operability, so it can produce a lot of practical application value and attracts more and more scholars’ attention. Synthetic gene network is a gene network module decomposed from natural network, which can reduce the complexity of natural gene network and facilitate the simple and effective research of scientific theory and artificial experiment. The synthetic gene network with genetic toggle can well show the natural gene network with the switching property, and can be designed, synthesized and regulated according to any requirement of the actual situation. Therefore, scholars have conducted a large number of studies on the synthetic gene networks with genetic toggle.

In 2000, Gardner et al. constructed a bistable synthetic gene network with genetic toggle in E.coli for the first time. The dynamic stability, switching and oscillatory changes of the synthetic gene network with genetic toggle induced by random excitation were revealed. By means of average field analysis, Warren et al. theoretically studied the average field model of synthetic gene network with genetic toggle in random noise environment and the stability of its dynamic response. And they revealed the influence rule of random noise on the stability of the model and toggle switching between stable states. Li et al. studied the oscillation caused by random noise in synthetic gene network, used stochastic dynamics method to describe the response of synthetic gene network to environmental disturbance, and found that external random environmental disturbance can stimulate the oscillation behavior. Chen et al. explored the cooperative behavior of synthetic gene network caused by random noise and found that random noise could cause the dynamic behavior of multiple protein concentrations in synthetic gene network. Shi et al. revealed the vibration resonance of synthetic gene network under high and low frequency signals. It is found that the system response shows a tendency of nonlinear change under signal modulation. Liu studied the effect of synthetic gene networks under random noise and periodic signals. Xu et al. revealed the switching problem of synthetic gene networks with genetic toggle under two multiplicative Gaussian noises without the effect of periodic signal. Garcia-Ojalvo et al. investigated the reconfigurable logic operation in synthetic gene networks with genetic toggle, analyzed the logic gate operation of synthetic gene networks, and found that the gene circuits of synthetic gene networks with genetic toggle could switch between different logical operation modes by changing the input signals.

Most of the existing researches at home and abroad mainly focus on the basic research of stability, switching and oscillation under the action of noise. In this paper, we provided a new perspective of “the most probable exit path (MPEP)” to study the stochastic dynamic behavior of bistable synthetic gene network with genetic toggle under random perturbation. The proposal of the MPEP provides another angle for the study of the exit problem, and provides the path as an intuitive tool to understand the specific behavior of exit.

In this paper, we first introduced the basic properties of deterministic and random system about the bistable synthetic gene network with genetic toggle. Secondly, the FW action functional proposed by the large deviation theory was used to obtain the MPEP when the protein concentration of the system was switched. Then, considering the influence of noise intensity, OM action functional was adopted to solve the
MPEP of switching protein concentration, and the influence of different noise intensity was analyzed. Finally, the energy landscape was introduced, and the quasi-potential proposed in the large deviation theory was combined to show the MPEP from the perspective of energy.

2 Model analysis

The synthetic gene network with genetic toggle in E.coli organism is known as a bistable synthetic gene regulatory network\[21, 23, 29\]. It is composed of *LacI* protein and *λcI* protein transcribed by *LacI* gene and *λcI* gene. The synthesis of these two mutually inhibitory proteins is regulated and expressed by the mutually inhibitory *LacI* gene and *λcI* gene. There are two possible states for these two proteins. *LacI* gene expression is on when *λcI* gene expression is off, or *LacI* gene expression is off when *λcI* gene expression is on. The relationship of mutual inhibition is shown in Fig.1[21, 22].

![Fig. 1: Schematic diagram of a model with genetic toggle.](image)

The protein dynamics is described by the following equations[6]

\[
\begin{align*}
\frac{dx_1}{dt} &= \frac{\alpha_1}{1 + x_2^{m_1}} - d_1 x_1 + g_1, \\
\frac{dx_2}{dt} &= \frac{\alpha_2}{1 + x_1^{m_2}} - d_2 x_2 + g_2,
\end{align*}
\]

(1)

where \(x_1\) and \(x_2\) are the concentrations of *LacI* and *λcI*, respectively. \(\alpha_1\) and \(\alpha_2\) are the dimensionless transcription rates in the absence of repressor, \(d_i\) and \(g_i\) (\(i = 1,2\))
are the degradation rates and the basal synthesis rates, and $m_1$ and $m_2$ are the Hill coefficients, respectively. In this paper, parameters were fixed as follows: $\alpha_1 = \alpha_2 = 3.5, d_1 = d_2 = 1.0, g_1 = g_2 = 0.5, m_1 = m_2 = 4.0$.

Fig. 2: Vector field diagram of deterministic system, red line is $x_1$-nulline, green line is $x_2$-nulline.

Fig. 2 showed the vector field of the system, where the red line represented the $x_1$-nulline and the blue line represented the $x_2$-nulline. It can be seen from Fig. 2 that the system has three equilibrium points, among which two stable equilibrium points are $S_1 = (0.5173, 3.7661)$ and $S_2 = (3.7661, 0.5173)$, representing the steady-state protein concentration in the system, and one unstable equilibrium point is $S_u = (1.3361, 1.3661)$.

Biological experiments and studies have shown that noise due to the intrinsically random nature of the biochemical reactions involved or due to environmental fluctuations is widespread in biological systems with a small number of molecules. In the synthetic gene network of E.coli, noise is caused by various random fluctuations, transient chemical induction, interaction between proteins and random interference stimulation in the process of translation, transcription and polymerization of gene proteins in a series of biochemical reactions [30–35].

Considering the excitation of Gaussian white noise, the dynamic equations of the two proteins are as follows

$$\frac{dx_1}{dt} = \frac{\alpha_1}{1 + x_2^{m_1}} - d_1 x_1 + g_1 + \xi_1(t),$$

$$\frac{dx_2}{dt} = \frac{\alpha_2}{1 + x_1^{m_2}} - d_2 x_2 + g_2 + \xi_2(t),$$

(2)
where label $f_1(x_1, x_2) = \frac{\alpha_1}{1 + x_1^2} - d_1 x_1 + g_1, f_2 = \frac{\alpha_2}{1 + x_1^2} - d_2 x_2 + g_2, f(x) = (f_1(x_1, x_2), f_2(x_1, x_2))$.

Gaussian white noises $\xi_1(t), \xi_2(t)$ are independent of each other, and meet the statistical properties

$$<\xi_1(t)> = <\xi_2(t)> = 0,$$
$$<\xi_i(t)\xi_j(t)> = D_i \delta_{ij} \ (i = 1, 2; j = 1, 2),$$

where $D_i (i = 1, 2)$ represent noise intensity, which are the small quantities.

![Fig. 3: Time history diagram under noise excitation, noise intensity $D_1 = D_2 = 0.1$.](image)

The time history diagram of system (2) under noise excitation was shown in Fig. 3 (set noise intensity $D_1 = D_2 = 0.1$). Red represents $LacI$ protein concentration, blue represents $\lambda cI$ protein concentration. As can be seen from the Fig. 3, the expressions of the two types of genes are mutually inhibited, that is, when the expression of $LacI$ gene is on, the expression of $\lambda cI$ gene is off. At this time, the concentration of $LacI$ protein is high, while the concentration of $\lambda cI$ protein is low, and the system is in $S_1$ state; conversely, the system is in $S_2$ state. In addition, with the increase of time, the protein concentration of the system changes. In other words, the system exits and transfers from one stable state to another stable state under the influence of noise. Therefore, the most probable exit path (MPEP) obtained in this paper is used to display the path with the highest probability when the random system occurs exit.
3 FW action functional

In 1998, Freidlin and Wentzell\[13\] obtained the difficulty of sample trajectory $X_t^\varepsilon$ passing near a given trajectory $\varphi_t$ by introducing the action functional, and its probability estimation is as follows

$$P_x \left\{ \sup_{0 \leq t \leq T} |X_t^\varepsilon - \varphi_t| < \delta \right\} \sim \exp\{-D^{-1} S_{OT}(\varphi)\},$$

(3)

where $S_{OT}(\varphi)$ is called FW action functional, and $L$ is the Lagrange of the system.

When the noise intensity tends to 0, that is, $D \rightarrow 0$, according to Eq.(3), only those trajectories that minimize the action functional have overwhelming probability, while the probability of other trajectories will be weakened exponentially.

In order to describe the minimum value of the action functional in Eq.(3), Freidlin and Wentzell\[13\] defined the concept of quasi-potential. For a time interval $[0, T]$, quasi-potential has the following form

$$\Psi(x_1, x_2) = \inf_{T > 0} \inf_{\varphi \in C^{1+\frac{3}{2}}_{x_1, x_2}(0, T)} \{S_{OT}(\varphi)\}.$$  

(4)

That is, the quasi-potential is the minimum action functional of all absolutely continuous sample tracks between the initial position $x_1$ and the final position $x_2$, and requires a lower bound on both path and time. In this section, noise intensity was fixed as $D = D_1 = D_2$.

The Fokker-Planck equation corresponding to Eq.(2) is

$$\frac{\partial P(x_1, x_2, t)}{\partial t} = -\frac{\partial}{\partial x_1} \left[ f_1(x_1, x_2) P \right] - \frac{\partial}{\partial x_2} \left[ f_2(x_1, x_2) P \right] + \frac{D}{2} \left[ \frac{\partial^2 P}{\partial x_1^2} + \frac{\partial^2 P}{\partial x_2^2} \right].$$

(5)

Under the influence of small noise, the WKB approximation can be adopted as follows\[36, 37\]

$$P(x) = c(x) \exp\left\{-\frac{\Psi(x)}{D}\right\},$$

(6)

where, $c(x)$ is the pre-factor function and $\Psi(x)$ is the quasi-potential.

Substituting Eq.(6) into Eq.(5), the Hamilton-Jacobi equation is obtained

$$H(x, p) = f(x)p + \frac{1}{2} p^T \sigma p,$$

(7)

where, $p$ stands for momentum and $\Psi$ for quasi-potential.
Using the Roy method, the auxiliary Hamilton equation of the system is obtained

\[
\begin{align*}
\dot{x}_1 &= \frac{\partial H}{\partial p_1} = \frac{\alpha_1}{1 + x_2^m} - d_1 x_1 + g_1 + p_1, \\
\dot{x}_2 &= \frac{\partial H}{\partial p_2} = \frac{\alpha_2}{1 + x_1^m} - d_2 x_2 + g_2 + p_2, \\
\dot{p}_1 &= -\frac{\partial H}{\partial x_1} = d_1 p_1 + \frac{\alpha_2 m_2 x_1^m - 1}{(1 + x_1^m)^2} p_2, \\
\dot{p}_2 &= -\frac{\partial H}{\partial x_2} = \frac{\alpha_1 m_1 x_2^m - 1}{(1 + x_2^m)^2} p_1 + d_2 p_2,
\end{align*}
\]

where

\[
p_1 = \frac{\partial \Psi}{\partial x_1}, \quad p_2 = \frac{\partial \Psi}{\partial x_2}.
\]

The equation of quasi potential evolution along the characteristic line is

\[
\dot{\Psi} = \dot{x}_1 \cdot p_1 + \dot{x}_2 \cdot p_2 = \frac{1}{2}(p_1^2 + p_2^2).
\]

Geometric minimum action method (gMAM)\textsuperscript{[38]} was used to get the most probable exit path (MPEP) of the system. The result was presented in Fig.4.

The MPEP obtained using the gMAM method is visually presented in Fig.4, where the red line shows the MPEP from \( S_1 \) to \( S_2 \), the blue line shows the MPEP from \( S_2 \) to \( S_1 \). As shown by the solid red line in Fig.4a, the system is at a stable point \( S_1 \) at first. When the momentum \( p \) increases, the system exits along the MPEP and reaches the saddle point \( S_u \). Due to the attraction of the other stable point \( S_2 \), the system will eventually relax to another stable point \( S_2 \). The path from the saddle point \( S_u \) to the other attractor \( S_2 \) is tangent to the boundary of its vector field, indicating that the system will eventually relax to another stable state and does not need momentum support. The solid blue line in Fig.4a revealed a similar situation and did not be repeated here.

At the beginning, the synthetic gene network system is in a state of low \( \text{LacI} \) protein concentration and high \( \text{\lambda cI} \) protein concentration, which is \( S_1 \). Under the continuous influence of small noises such as biological environment, biochemical reaction and cell concentration, the system exited, \( \text{LacI} \) protein concentration increased, \( \text{\lambda cI} \) protein concentration decreased. Finally it followed the MPEP reaching a state of high \( \text{LacI} \) protein concentration and low \( \text{\lambda cI} \) protein concentration, which is \( S_2 \). The MPEP intuitively presents the exit behavior of the system. It provides a theoretical basis for controlling the switching of the protein concentration of the system, and provides certain help for controlling the transcription, expression, differentiation and other behaviors of cells at the cellular level.
Fig. 4: The MPEP of the system obtained using the gMAM method: (a) solid red line displays the MPEP from $S_1$ to $S_2$, (b) solid blue line displays the MPEP from $S_2$ to $S_1$.

4 OM action functional

In Section 3, the most probable exit path (MPEP) of the system was obtained by means of the FW action functional in large deviation theory. This process requires the system under the disturbance of small noise, that is, the noise limit tends to zero. However, in
practical application, although the noise intensity is very small, it cannot be ignored. Therefore, OM action functional\cite{39} proposed by Onsager and Machlup is adopted to get the MPEP, and analyze the influence of noise intensity on the MPEP\cite{40}.

Before exploring the MPEP of the system, the probability of a random trajectory passing through a path’s domain or pipeline needs to be studied. Consider a pipe around the reference path $\varphi(t)$, $t \in [0, t_f]$. If $\delta$ is small enough, the probability that the solution process $x(t)$ falls inside the pipe is

$$
P_x \left\{ \sup_{0 \leq t \leq t_f} |x(t) - \varphi(t)| < \delta \right\} \propto C(\delta) \exp\left\{ -\frac{1}{2} \int_0^{t_f} \text{OM}(\dot{\varphi}, \varphi) dt \right\},
$$

(11)

where, the integrand $\text{OM}(\dot{\varphi}, \varphi)$ is called OM function and $\int_0^{t_f} \text{OM}(\dot{\varphi}, \varphi) dt$ is called OM action functional.

Similar to Freidlin-Wentzell large deviation theory, the global minimum of OM action functional corresponds to the path with the highest probability, that is, the MPEP. Then, the calculation of probability is transformed into a variational problem, where the MPEP satisfies the equation

$$
\frac{d}{dt} \left( \frac{\partial \text{OM}(\dot{x}, x)}{\partial \dot{x}} \right) = \frac{\partial \text{OM}(\dot{x}, x)}{\partial x},
$$

(12)

satisfying the boundary conditions $x(0) = S_1, x(t_f) = S_2$. Specifically, in the two-dimensional system, $x = (x_1, x_2), \dot{x} = (\dot{x}_1, \dot{x}_2)$.

To facilitate the solution, Eq.(12) is transformed into an equivalent Hamiltonian system, which is derived as follows

$$
d\text{OM}(\dot{x}, x) = \left( \frac{\partial \text{OM}(\dot{x}, x)}{\partial \dot{x}} \right)^T \cdot dx + \left( \frac{\partial \text{OM}(\dot{x}, x)}{\partial x} \right)^T \cdot d\dot{x},
$$

(13)

and

$$
\left( \frac{\partial \text{OM}(\dot{x}, x)}{\partial \dot{x}} \right)^T \cdot d\dot{x} = d \left\{ \left( \frac{\partial \text{OM}(\dot{x}, x)}{\partial \dot{x}} \right)^T \cdot \dot{x} \right\} - \dot{x}^T \cdot d \left( \frac{\partial \text{OM}(\dot{x}, x)}{\partial x} \right).
$$

(14)

Label

$$
p = \frac{\partial \text{OM}(\dot{x}, x)}{\partial x}.
$$

(15)

By substituting Eq.(12), Eq.(14) and Eq.(15) into Eq.(13), we can get

$$
d \left( p^T \cdot \dot{x} - \text{OM}(\dot{x}, x) \right) = \dot{x}^T \cdot dp - \dot{p}^T \cdot dx,
$$

(16)

let the Hamiltonian function be

$$
H(x, p) = p^T \cdot \dot{x} - \text{OM}(\dot{x}, x).
$$

(17)
According to Eq.(16), it can be deduced that Hamiltonian system is
\[
\dot{x} = \frac{\partial H}{\partial p} , \quad \dot{p} = - \frac{\partial H}{\partial x} ,
\]
the boundary condition is
\[
x(0) = S_1 , \quad x(t_f) = S_2 .
\]

According to literature[41], the form of OM function under Gaussian noise is
\[
OM(\dot{x}, x) = (\dot{x} - b)^T (AA^T)^{-1} (\dot{x} - b) + \text{Tr} [A \nabla (A^{-1} b)] ,
\]
where, \( b \) and \( A \) represent drift coefficient and diffusion matrix respectively, and \( \text{Tr}[\bullet] \) represents the trace of matrix. The Hamiltonian can be obtained by Eq.(17)
\[
H(x, p) = \frac{1}{4} p^T AA^T p + b^T p - \text{Tr} [A \nabla (A^{-1} b)] .
\]

Finally, the Hamiltonian system for the synthetic gene network system is obtained
\[
\begin{align*}
\dot{x}_1 &= \frac{\partial H}{\partial p_1} = \frac{\alpha_1}{1 + x_2^{m_1}} - d_1 x_1 + g_1 + \frac{1}{2} D_1 p_1 , \\
\dot{x}_2 &= \frac{\partial H}{\partial p_2} = \frac{\alpha_2}{1 + x_2^{m_2}} - d_2 x_2 + g_2 + \frac{1}{2} D_2 p_2 , \\
\dot{p}_1 &= - \frac{\partial H}{\partial x_1} = d_1 p_1 + \frac{\alpha_2 m_2 x_2^{m_2-1}}{(1 + x_2^{m_2})^2} p_2 , \\
\dot{p}_2 &= - \frac{\partial H}{\partial x_2} = \frac{\alpha_1 m_1 x_2^{m_1-1}}{(1 + x_2^{m_1})^2} p_1 + d_2 p_2 ,
\end{align*}
\]

Eq.(22) is solved to obtain the MPEP of the system, and the influence of different final state time and noise intensity is analyzed, as displayed in Fig.5 and Fig.6.
Fig. 5: The MPEP of the system, noise intensity $D_1 = D_2 = 0.05$: (a) the MPEP of the system at different final times, (b) $x_1$ and $x_2$ paths over time.

In Fig. 5, the MPEP of the system from $S_1$ to $S_2$ under different final state times was displayed (fixed noise intensity $D_1 = D_2 = 0.05$). Under different final state times, the MPEP of the system from $S_1$ to $S_2$ can be obtained by solving Eq. 22, which was presented in Fig. 5a. The MPEP of two types of protein concentrations $x_1$ and $x_2$ under different final state times were respectively shown in Fig. 5b.

With the increase of the final state time $t_f$, the MPEP of the system is closer and closer to the saddle point $S_u$. This result is consistent with the above routing
conclusion obtained by using FW action functional. This indicates that the longer the final state time is, the better it is to accurately predict the MPEP of the system exit. In addition, the MPEP of the two types of protein concentrations $x_1$ and $x_2$ over time given in Fig.5b also verified the path trend shown in Fig.5a. Under the continuous influence of small noises such as biological environment, biochemical reaction and cell concentration, $LacI$ protein concentration increased, $\lambda cI$ protein concentration decreased, and finally the system reached the protein concentration of $S_2$ state.

Although the large deviation theory investigates the evolutionary behavior of the system at a long time scale, it is often necessary to set a final state time for researches in practical applications. So it has certain value for practical application research.

Under different noise intensities, the MPEP of the system from $S_1$ to $S_2$ was presented, as shown in Fig.6. In Fig.6a, the MPEP from $S_1$ to $S_2$ was given when noise intensity $D_1$ took different values, and noise intensity $D_2 = 0.05$ was fixed. On the contrary, Fig.6b showed the MPEP of the system from $S_1$ to $S_2$ under different noise intensity $D_2$, where fixed $D_1 = 0.05$.

It is observed that within a certain range, the MPEP of the system was closer to the saddle point $S_u$ as the noise intensity $D_1$ decreased. When $D_1 = 0.03$, the MPEP passed through the saddle point to $S_2$. This revealed that, within a certain range, the smaller the intensity of the first Gaussian white noise $\xi_1$, the more beneficial it is to accurately predict the MPEP for the system to exit. However, the opposite was observed in Fig.6b. As the noise intensity $D_2$ increased, the MPEP of the system was closer to the saddle point $S_u$. In particular, at $D_2 = 0.09$, the MPEP of the system passed completely through the saddle point. It is found that, within a certain range, the influence of the second white Gaussian noise $\xi_2$ on the MPEP of the system is completely opposite to that of the first noise $\xi_1$. That is, to a certain extent, the increase in the intensity of $\xi_2$ is conducive to more accurately obtaining the MPEP of the system exit.
In the practical application and research of biology, gene proteins are inevitably affected by random fluctuations, environmental stimuli and other noises in the process of many biochemical reactions. The research in this section mainly focuses on the influence of noise intensity on the MPEP of the system, so it has certain guiding significance for practical application. The MPEP of system exit can be obtained more accurately by controlling the intensity of two independent noises. This will provide some reference value for observing the behavior of gene transcription and expression in random environment.

Fig. 6: The MPEP of the system transformation under different noise intensity: (a) fixed $D_2 = 0.05$, (b) fixed $D_1 = 0.05$. 
5 Energy landscape

In this paper, the most probable exit path (MPEP) for a bistable system was explored when it transitioned between two stable states. The large deviation theory provides the theoretical mathematical basis. In order to demonstrate more intuitively, landscape was introduced to better quantify the random process.

Epigenetic landscape, first proposed by Waddington in 1957, is a metaphor for the cell development process[42, 43]. In Waddington’s theory, the developmental dynamics of multicellular organisms is a process that occurs in a multistable system, where each attractor state represents a cell type and the attractor transition corresponds to the cell differentiation pathway. This understanding can also be used to understand the concept of energy landscape. For multidimensional nonlinear gene regulatory network systems, transitions between attractor states correspond to changes in cell phenotypes during normal development and disease[44, 45].

5.1 Vector field decomposition theory

In a bistable system, energy needs to be obtained to overcome the height of the barrier in order to make the transition out, so the potential function is introduced to describe it. For any point $x$ in the system state space, the potential function $U(x)$ can tell us the probability and direction of transitions between attractor states in the stochastic system.

In one-dimensional systems, one often obtains the potential function by integrating

$$\frac{dx}{dt} = F(x) = -\nabla U. \quad (23)$$

Since high-dimensional non-equilibrium systems are generally not gradient systems, Eq.(23) is not valid, and we divide it into two parts

$$\frac{dx}{dt} = F(x) = -\nabla U + F_c, \quad (24)$$

where, the quasi-potential acts as the potential function of the system. So the finite and smooth non-gradient vector field $F(x)$ is decomposed into two parts: one is the gradient of the quasi-potential function $U$, and the other represents the remaining driving force of the dynamic system.

In the gene regulation network of non-gradient systems, we adopted the quasi-potential function based on the steady-state probability density function and derived the corresponding form to some extent[46].

According to Boltzmann law, the steady-state probability of each state $x$ is associated with the potential $U^{\text{prob}}$

$$U^{\text{prob}}(x, t) \sim \ln(P(x, t)). \quad (25)$$
Since \( \mathbf{F}(x) \neq -\nabla U^{\text{prob}} \), the driving force \( \mathbf{F}(x) \) requires an additional component. Under the constraint of Eq. (25), that is, the gradient force emitted by the probabilistic flux is taken as a component. Wang et al. deduced the following decomposition [46].

The time evolution of the probability density function \( P(x, t) \) is controlled by the Fokker-Planck equation

\[
\frac{\partial P(x, t)}{\partial t} = -\nabla \cdot (\mathbf{F}P) + D \cdot \nabla^2 P,
\]

where, the drift term is the driving force \( \mathbf{F}(x) \) of the system, and \( D \) represents the diffusion term. The time change in probability density can be written as probability flux \( J(x, t) \)

\[
\begin{aligned}
\frac{\partial P(x, t)}{\partial t} &= -\nabla \cdot J(x, t), \\
J(x, t) &= \mathbf{F}P - D \cdot \nabla P.
\end{aligned}
\]

When steady-state is considered, \( \frac{\partial P(x, t)}{\partial t} = 0 \), then the divergence of steady-state probability flux \( J_{ss} \) disappears, that is, \( \nabla \cdot J_{ss}(x, t) = 0 \), thus obtaining

\[
\mathbf{F} = \frac{J_{ss}}{P_{ss}} + D \cdot \frac{\nabla P_{ss}}{P_{ss}} = -\nabla (-\ln(P_{ss})) \cdot D + \frac{J_{ss}}{P_{ss}}
\]

\[
= -\nabla U^{\text{prob}} + \mathbf{F}_c.
\]

That is

\[
\begin{aligned}
-\nabla U^{\text{prob}} &= -\nabla (-\ln(P_{ss})) \cdot D, \\
\mathbf{F}_c &= \frac{J_{ss}}{P_{ss}}.
\end{aligned}
\]

According to the form of the probability density function of the system, the more stable state corresponds to the lower potential. Intuitively, the logarithm of the steady-state probability density function is proposed as the quasi-potential function of the system [45, 47, 48]. Meanwhile, the quasi-potential \( U \) presents the barrier of transformation between the steady state, and the remaining part of the driving force \( \mathbf{F}_c \), will not contribute to the effort required for transformation.

5.2 Energy landscape

According to the theory of subsection 5.1, the vector field decomposition form of the system was given. Therefore, the method of drawing energy landscape proposed in references [49–53] was applied to draw the energy landscape of the synthetic gene network, and the MPEP was shown in it.

The commonly used methods, such as Lyapunov exponent, only provide the method to judge the local stability of the system, while the energy landscape describes the stability of the system from the global perspective. It is helpful to observe the global stochastic dynamic behavior of the system. In the energy landscape, the highest local probability (lowest potential energy) is used to characterize the attraction
domain of the system and the height difference of the barrier is used to characterize the relative stability of the system. This provides a good tool for measuring the global stability of the system.

In this section, energy landscape was adopted to analyze the global dynamics of the synthetic gene network. The potential well of different attractors and the MPEP were get, as displayed in Fig.7. In addition, the influence of different noise intensity on the potential well was analyzed. In this section, \( D = D_1 = D_2 \) was set.

Fig.7 presented the energy landscape of the system at different noise intensities and plotted the MPEP of the system. The yellow line represented the MPEP of the system from \( S_1 \) to \( S_2 \), and the blue line represented the MPEP of the system from \( S_2 \) to \( S_1 \). It can be observed that under different noise intensities, there are always two potential wells in the energy landscape, which are represented by the numbers 1 and 2. They represent the two stable states of the system, \( S_1 \) and \( S_2 \), which correspond to the bistability of the system. Moreover, it visually shows the MPEP of the system from one attractor to another, where the yellow is the MPEP from \( S_1 \) to \( S_2 \) and the blue line is the MPEP from \( S_2 \) to \( S_1 \).

When the noise intensity is changed in a certain range, the number of potential wells does not change, but the depth and width of potential wells change. With the decrease of noise intensity, the barrier between the two attractors gradually deepens and the depth of the potential well increases, that is, the decrease of noise intensity is not conducive to the transition of the system. In addition, as the noise intensity decreases, the width of the potential well also decreases, indicating that the smaller the noise intensity is, the smaller the diffusion range of the system around the attractor is.

In other words, with the decrease of various random fluctuations, transient chemical induction and other noises interference, it becomes more and more difficult to switch protein concentration in the synthetic gene network system, and the system will be more concentrated in a stable state.
Fig. 7: The MPEP of the system exit under different noise intensity: (a) $D = 0.5$, (b) $D = 0.1$, (c) $D = 0.05$, (d) $D = 0.03$, (e) $D = 0.01$, (f) $D = 0.005$. 
6 Conclusion

In this paper, the most probable exit path (MPEP) of protein concentration switching in a bistable synthetic gene network with genetic toggle in E.coli was observed. Firstly, in the deterministic case, the system is bistable, that is, the system has two stable states, representing two different types of protein concentration states of the system. Under the excitation of noise, the system will exit, that is, the concentrations of two types of proteins will change under various random fluctuations such as biochemical reactions and transient chemical induction. In order to more directly analyze the transformation of protein concentration in the synthetic gene network with genetic toggle, the MPEP of the system is considered.

Secondly, based on the knowledge of large deviation theory, this paper obtained the MPEP by using gMAM method, and intuitively demonstrated the exit behavior of the system. In addition, the MPEP with different final state times and noise intensities was got by OM action functional. It is found that within a certain range, the first noise is not conducive to the accurate exit of the system, and the second noise, on the contrary, is conducive to the accurate exit of the system.

Finally, according to the vector field decomposition theory, the driving force of the system is divided into two parts, in which the quasi-potential acts as the potential function of the system. The energy landscape is introduced to display the MPEP of the system. It is observed that the noise intensity does not change the number of system attractors, but affect the depth and width of the potential well of the attractors. That is, with the decrease of noise intensity, the depth of the attractor potential well increases and the width decreases, indicating that the smaller the stimuli of various random fluctuations of biochemical reactions, transient chemical induction, interaction between proteins and random interference, the more unfavorable the switching of protein concentration in the system.

In short, we used action functional to obtain the MPEP, and conducted stochastic dynamic analysis of bistable synthetic gene network with genetic toggle from a new perspective. Through the MPEP, the mechanism of protein concentration switching in the system was intuitively understood. In addition, the concept of quasi-potential proposed in large deviation theory was introduced into the vector field decomposition, so that the dynamic analysis of the system was carried out by using the energy landscape. The MPEP of the system intuitively shows the exit behavior of the system, which is conducive to a good observation of the switching of protein concentration, so as to provide a theoretical basis for further study of cell transcription, expression, differentiation and other behaviors. In addition, in the aspect of biomedicine, this study hopes to provide certain help for disease prevention and tumor control at the genetic level.

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Data Availability Statements

The data that support the finding of this study are available from the corresponding author upon reasonable request.

Conflict of Interest Statements

The authors declare that they have no conflict of interest.

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