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Engineered internal noise stochastic resonator in gene network: A model study

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Abstract

Based on a genetic bistable switch model coupled with a gene oscillator model, we have constructed a mesoscopic stochastic model for the coupled synthetic gene network, and studied how internal noise would influence the oscillation of such a system. We found that the state-to-state transitions can occur if the internal noise is taken into account, and the performance of resulting oscillation can reach a maximum in a certain internal noise level, which indicates the occurrence of internal noise stochastic resonance (SR) and makes the coupled gene network work as a stochastic resonator. The potential role of such an effect on gene expression systems is also discussed.

Keywords: Synthetic gene network; Stochastic resonance; Internal noise; Bistable switch; State-to-state transition

1. Introduction

Recently, the effects of internal noise in complex biological systems have drawn ever-growing attention and a variety of important results were reported. In life systems, specially, the study of internal noise in gene expression is of great interest [1–10]. As pointed out by McAdams et al., gene expression process is a "noisy business" [1]. This "noise" has internal source due to the inherent molecular fluctuations as a result of stochastic reaction events in transcription and translation processes, as well as environmental external source. Currently, most studies in this field focus on where the internal noise comes from, how to characterize it and what its effect is, through both experimental and theoretical studies [3–5]. For instance, it was reported that the internal noise in the gene expression in prokaryotes mainly comes from the translation process [8]; while for eukaryotes, transcription process contributes a great level to the noise in the clonal population [9]. Moreover, since the circadian clock system is mainly regulated by gene expression process in molecular level, the internal noise effect on circadian oscillation is also remarkable [11]. For example, it was found that the circadian oscillation would become highly irregular characterized by rapid vanishing of autocorrelations when the maximum numbers of mRNA and protein molecules are relatively small [12]. To resist the destructive effects of internal noise, the circadian system may show robustness to internal noise by feedback loops or redundancy [13]. However, in some studies, internal noise may induce oscillations which are not present in the deterministic model, making the internal noise effect more complex [14,15].

Very recently, the study of engineered gene networks has gain much interest. Engineered gene networks have provided insights into how the network architecture influence its function, which makes the first step towards the understanding of the function of real gene regulatory networks [16]. For example, a bistable genetic toggle switch has been designed from two mutually repressing genes [17–21], and two oscillatory circuits in *E. coli* were constructed, one called the 'repressillator' consisting of three transcriptional repressors, and the other consisting of an activator and a repressor. However, the main concern of the study of engineered gene networks is how to design a circuit which is robust against the fluctuations in gene expression, which is unavoidable in the cell environment. But numerous studies have shown that nonlinear systems can often exploit noise to perform constructive functions, for instance, to enhance the detection and transportation of feeble signal, to induce transitions between two stable states, or to induce

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oscillation thus make oscillatory dynamics easier to happen. Therefore, our question is, is that possible to design a gene circuit which can "exploit" the gene noise?

Based on above considerations, we take a model study of a gene circuit consisting of a toggle switch coupled with an oscillator. The output of the gene oscillator acts as a signal input for the switch through the coupling. Intrinsic gene noise is accounted for by using chemical Langevin equations. Due to the existence of gene noise, random transitions between the two states of the switch could happen. Our target is to find out if such transitions could show some resonant behavior with the signal input from the oscillator, a phenomenon called stochastic resonance (SR), which has been widely studied in a variety of science community. Consequently, SR is found in reasonable parameter ranges and internal noise strength, indicating that the coupled circuit can function as a stochastic resonator, which might be a useful module for signal transmission and amplification in real gene regulatory networks.

2. Model description

The basic scheme of our design is plotted in Fig. 1. We couple a synthetic genetic bistable switch model [22] with an oscillator model [23], both models were proposed by Collins et al. The oscillator is a genetic circuit of ë phage consisting of two plasmids with the same promoter. On plasmid 1, the promoter controls the *cI* gene and thus regulates the expression of the CI protein. On plasmid 2, the promoter controls the *lac* gene, and thus regulates the production of the Lac protein. Interesting dynamics in the numbers of CI and Lac proteins arises due to the influence of two of the binding configurations on the transcriptional rate: (i) when a CI dimer is bound to OR2 and OR3* is vacant, the promoter is turned "on", i.e., its gene is transcribed at an amplified rate, and (ii) when a Lac tetramer is bound to OR3, the promoter is turned "off ", that means its gene is not transcribed. The deterministic dynamics of the oscillator is described by the equations:

$$\begin{aligned}\frac{dx_1}{dt} &= k_t \cdot M_1 \cdot \frac{1+x_1^2+\alpha'\sigma' x_1^4}{(1+x_1^2+\sigma' x_1^4)(1+y_1^4)} - k_x \cdot x_1 = b_1 - b_2 \\ \frac{dy_1}{dt} &= k_t \cdot M_2 \cdot \frac{1+x_1^2+\alpha'\sigma' x_1^4}{(1+x_1^2+\sigma' x_1^4)(1+y_1^4)} - k_y \cdot y_1 = c_1 - c_2\end{aligned} \quad (1)$$

Here b_1, b_2, c_1 and c_2 represent the production rate and decay rate of CI protein and Lac protein, respectively. x_1 and y_1 denote the concentrations of CI protein and Lac protein involved in the oscillator, and *kt*, *kx* and *ky* are rate constants of the processes of protein formation, degradation of CI protein and Lac protein, respectively. M_1 and M_2 represent the copy numbers of *cI* and *lac* gene, respectively. α' is the degree to which the transcription rate is increased when a CI dimer is bound to OR2 relative to binding at OR1, and σ' is the relative affinities for the dimer binding to OR1 versus that of binding to OR2.

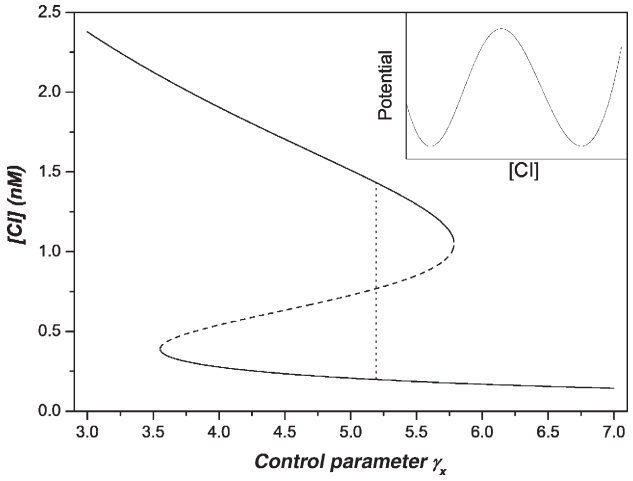

Fig. 2. Bifurcation plots for the steady–state concentration of CI protein on the control parameter γx for the gene switch. The plots in the dash line represent unstable steady–states of Eq. (2). The potential profile in the top right corner is a sketch of $\gamma x = 5.215$. Parameter values that remain unchanged during simulation: $m = 1.0$, $\alpha = 11.0$, $\sigma_1 = 2.0$, $\sigma_2 = 0.08$.

Then we introduce the genetic switch model [22], which is a simple kinetic model of λ phage for examining the bistability in a single-gene network. It has the same promoter and protein with plasmid 1 of the above model. The basic dynamical properties of this network are as follows. The gene *cI* expresses repressor (CI), which in turn dimerizes and binds to the DNA as a transcription factor (TF). This binding can take place at one of the three binding sites sequentially: the dimmer first binds to the OR1 site, the OR2, and last OR3. Positive feedback arises due to the fact that downstream transcription is enhanced by binding at OR2, while binding at OR3 represses transcription, effectively turning off production and thereby constituting a

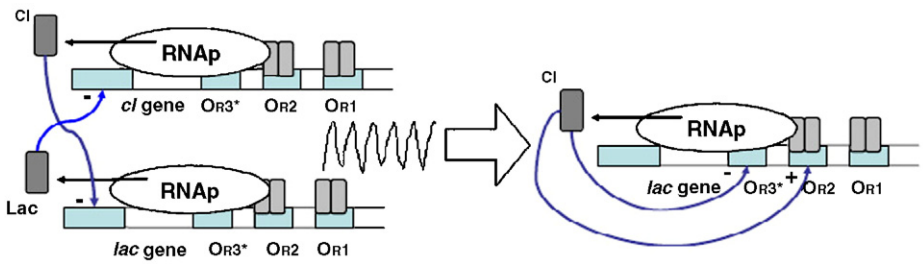

Fig. 1. Scheme for the model design of this work. The *cI* genes produce CI proteins, which show negative feedback on *lac* genes and repress the production of Lac proteins, and vice versa. Such a cross negative feedback loop generates sustained oscillation. The generated oscillation regulates the genetic bistable switch, which has the same plasmid as the plasmid 1 of the oscillator.

negative feedback loop. The deterministic dynamics of the system is described by the following equation:

$$\frac{dx}{dt} = \frac{m(1+x^2+\alpha\sigma_1 x^4)}{1+x^2+\sigma_1 x^4+\sigma_1\sigma_2 x^6} - \gamma_x x = a_1 - a_2 \quad (2)$$

Here x is the concentration of CI protein in the cell involved in the bistable switch dynamics, and σi denotes the relative affinities for the dimer binding to OR1 versus that of binding to OR2 (σ_1) and OR3 (σ_2). α represents the degree to which the transcription rate is increased then a CI dimer is bound to OR2 relative to binding at OR1. γx is the normalized degradation rate of CI protein. m is the copy number concentration of the plasmid.

In a common cell, the quantity of *cI* genes is much more than that of *lac* genes. Consequently, in some regions where *lac* genes exist, *cI* and *lac* genes form oscillatory circuits through the mechanism of Eq. (1); while in other regions the products of *cI* genes regulate their owns to constitute bistable switches (Eq. (2)). The bistable switches would not change the concentration of the CI protein in certain parameters' set, while the oscillatory circuits make the concentration of the CI protein oscillates with certain frequency and amplitude. Intuitively, this concentration change by the oscillator would influence the dynamic behavior of the bistable switch. We set the degradation rate of CI protein γx as the control parameter, and by assuming that the relative deviation of the concentration of CI protein from its average level affects the control parameter, we couple the two models with the equation:

$$\frac{dx}{dt} = \frac{m(1+x^2+\alpha\sigma_1 x^4)}{1+x^2+\sigma_1 x^4+\sigma_1\sigma_2 x^6} - \gamma_x \cdot (1 + K(x_1 - \bar{x_1})) \cdot x \quad (3)$$

Here $\bar{x}_1$ is the average value x_1 generated by Eq. (1). K represents the couple strength.

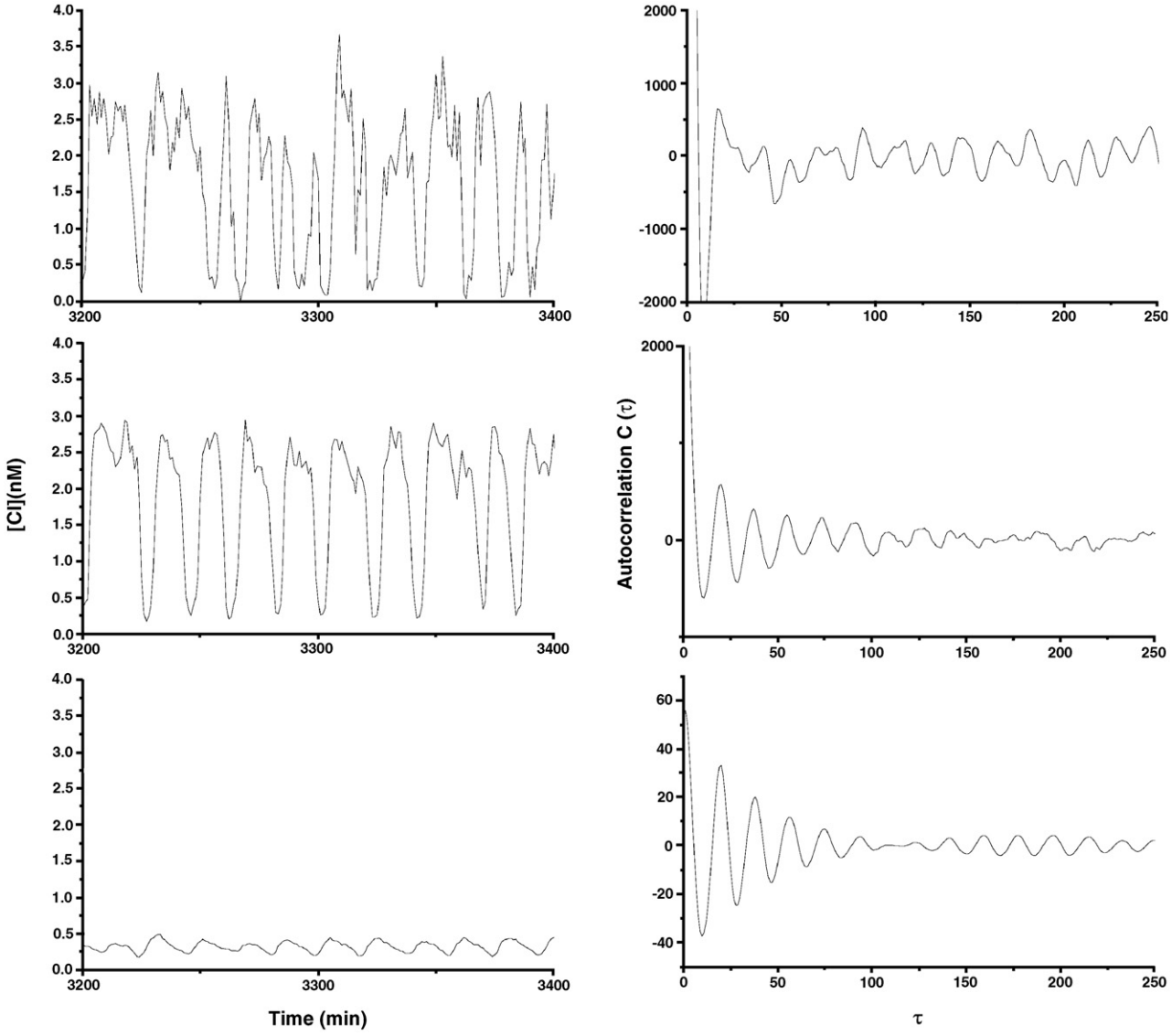

Fig. 3. The time series and corresponding autocorrelations of Eq. (4) at different system sizes. The corresponding sizes are 10^4, 100 and 10 from bottom to top. The initial value of x is fixed at 0.0 and the control parameter γ_x=5.215. Parameter values that remain unchanged during simulation: k_x=2.625, k_y=0.088, M_1=50, M_2=1, α'=11, σ'=2, K=4.924.

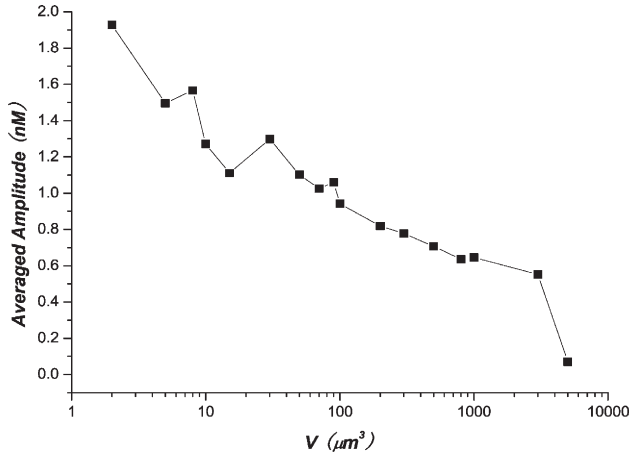

Fig. 4. The dependence of average amplitude on different system sizes. The results are obtained by the CLE (Eq. (4)). Solid lines are drawn to guide the eye.

Eq. (3) is still a deterministic equation without accounting for the internal noise for the bistable switch model. However, due to the finiteness of system size, the internal noise must be taken into account. Therefore, such a deterministic description is no longer valid. Intuitionally, one can describe such a reaction system as a birth–death stochastic process governed by a chemical master equation. Generally, there is no practical procedure to solve chemical master equation analytically, but one may adopt a widely used simulation algorithm, exact stochastic simulation (ESS) method proposed by Gillespie in 1977 [24]. However, ESS method is too time-consuming when the system size is not very small. Recently, an alternative method to study the internal noise, chemical Langevin (CL) method was proposed by Gillespie [25]. It was proved that the chemical Langevin equation (CLE) is a rather good approximation if a "macro-infinitesimal" time scale exists in the system. For the present model, the CLE of Eq. (3) reads:

$$\frac{dx}{dt} = a_1 - \gamma_x \cdot (1 + K(x_1 - \bar{x}_1)) \cdot x + \frac{1}{\sqrt{V}}\left(\sqrt{a_1}\cdot\xi_1(t) - \sqrt{a_2 \cdot (1 + K(x_1 - \bar{x}_1))}\cdot\xi_2(t)\right) \quad (4)$$

Here ξ_1 and ξ_2 are Gaussian white noise with zero mean $\langle\xi_i(t)\rangle = 0$ and correlation of $\langle\xi_i(t)\cdot\xi_j(t')\rangle = \delta_{ij}\cdot\delta(t-t')$. From the form of CLE one can easily see that the internal noise is related to the system size and the parameter values, as well as the state variables that evolves with time scale. Without the second terms in the brackets at the right side, the CLE Eq. (4) is equivalent with the deterministic Eq. (3). Therefore, these terms actually denote the internal noise.

3. Results and discussion

Before we study the dynamic behavior of the bistable switch coupling to a gene oscillator, we should figure out the bistable property of the deterministic equation Eq. (2) first. Since the degradation rate constant γx is easy to control externally, we choose it as the control parameter. Using parameters in Eq. (2) as $m = 1.0$, $\alpha = 11.0$, $\sigma_1 = 2.0$, $\sigma_2 = 0.08$, we obtain the bistable diagram

Fig. 2. From Fig. 2 one can see a bistable regime occurs as a result of the nonlinearity of the steady–state concentration of CI protein in Eq. (2). The bistability arises as a consequence of the competition between the production of x along with dimerization and its degradation. For those parameter values in the bistable region, the final concentration is determined by the initial concentration. The plots on the dash line in Fig. 2 represent unstable steady–states of Eq. (2). One can see that the unstable plots' values are not always the average of two stable steady–states' values. Here we choose $\gamma x = 5.215$, which is a relatively symmetrical value, as the potential profile shows (inserted figure in Fig. 2).

We then consider the switch coupling to the oscillator (Eq. (3)). We first fit $kx = 2.625$, $ky = 0.088$, $M_1 = 50$, $M_2 = 1$, $\alpha = 11$ and $\sigma^0 = 2$, which guarantee x_1 lie in the oscillatory region, and then perform numerical calculation of Eq. (3) using explicit Euler method with time step 0.001 min with different values of coupling strength K. We find that the average value of x depends on the initial concentration and the oscillation amplitude is relatively small when K is small. Specially, if the initial concentration is 0, the average value of the oscillation is about 0.5 (low branch); while if the initial value is 1, the average value of the oscillation is about 1.5 (high branch). It shows the system still has bistable property. When we enlarge K gradually, the amplitude increase gradually until K reaches a threshold value of about 4.93. When $K = 4.924$, the resulting oscillation has an amplitude is less than 0.6, however, the oscillation has amplitude over 1.5 and average value 1.0 when $K = 4.93$, which indicate the state-to-state transition (from high branch to low branch) occurs. We choose $K = 4.924$ in following study, where the system still have bistable property.

We then account for the internal noise with the parameter values of $\gamma x = 5.215$ and $K = 4.924$. From Fig. 3 one can see the time series of CLE (Eq. (4)) with three different system sizes. When the system size is comparatively large ($V = 10^4$), if we choose initial concentration at 0.0, the system oscillates near the lower branch (Fig. 3 left bottom). When the system size

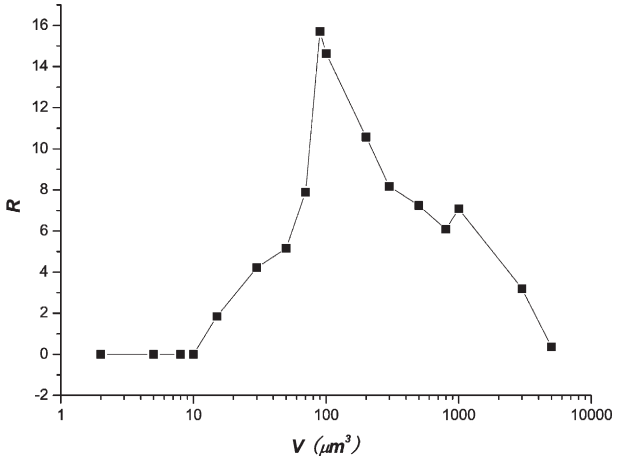

Fig. 5. The dependence of the order parameter R on system sizes. Solid line is drawn to guide the eye.

becomes smaller ($V=100$), the internal noise becomes larger, and the state-to-state transitions become more regular (Fig. 3 left middle). And when the system size becomes very small ($V=10$), the internal noise is too large, the transition becomes highly irregular (Fig. 3 left top), although its amplitude is relatively large.

It is well known that the amplitude of a biological oscillation is very important. From Fig. 3 one can see intuitively that the average amplitude of the time series of $V=10$ and $V=100$ is larger than that of $V=10^4$. We calculate the average amplitudes of different system sizes and show results in Fig. 4. One can see that the amplitudes decrease gradually with the increment of the system size.

From Fig. 4 one can see that the average amplitude of $V=10$ is a little larger than that of $V=100$, but in Fig. 3, the time series of $V=10$ is more irregular than that of $V=100$. We need to import another quantity to depict the regularity. Here we introduce the autocorrelation function $C(\tau)$. For a given time series, one can calculate the autocorrelation spectrum (Fig. 3 right), from which one can obtain the value of autocorrelation time τ. The autocorrelation functions of different system sizes are plotted in Fig. 3 right. One can see that the autocorrelation time τ is very short for $V=10$, while are quite long for $V=100$ and $V=10^4$. To consider the amplitude and autocorrelation time of different system size simultaneously, we use an order parameter $R=A^2\cdot\tau$. The dependencies of R on different system sizes are plotted in Fig. 5. From Fig. 5 one can see that with the increment of system size, R reaches a maximum at about $V=100$, which shows some resonance effect. Since the effect is caused by internal noise, it can also be regarded as an internal noise stochastic resonance (INSR) effect. Through the mechanism of INSR, we make the coupled networks work as an engineered stochastic resonator.

Cells are intrinsically noisy biochemical reactors: low reactant numbers can lead to significant static fluctuations in molecule numbers and reaction rates. The internal noise may lead to abundant stochastic behavior of gene expression process, which takes place within a single cell. Our study may suggest that the cellular internal noise, mainly coming from chemical circuit nature of gene network, would influence the cell's behavior to some content. Previous studies on genetic regulatory networks often view noise as a nuisance, so the regulatory mechanisms need to show robustness or resistance to random noise. However, in this work, by the mechanism of SR, the internal noise can induce oscillation with an amplified amplitude and regularity, as a result of the state-to-state transitions of the bistable switch. Our results may approve a view that environmental stimulus and internal noises couple together and may determine the behavior of a genetic system.

The second term of the CLE, the system size and reaction rates, corporately determine the magnitude of the internal noise. Therefore the internal noise SR is also some kind of system size resonance. From Fig. 5 one can see the performance of the state-to-state transition oscillation is optimal in $V\sim10^2$. Since the optimal system size exists in the present model, the biological organism may learn to adjust the kinetic parameters to make it work at an optimal size. Since the genetic regulation is a topic of central importance in biology, the internal noise SR and optimal system size effect are also remarkable. The next question is how biological organisms use this advantage to play functional roles in gene expression and other cellular processes. In addition, there are many genes in cell, not only two. Simple switch or oscillator cannot capture the main dynamic characteristics of all genes. One may resort to some new approaches such as complex networks or neural networks. What complex behaviors could be discovered through considering all genes? Further experimental and theoretical work will be of great help to answer these questions.

4. Conclusion

In the present letters, we have constructed a mesoscopic stochastic model for the coupled synthetic gene network, and studied how internal noise would influence the oscillation of such a system. We found that the state-to-state transitions can occur if the internal noise is taken into account, and the performance of resulting oscillation can reach a maximum in a certain internal noise level, which indicates the occurrence of internal noise stochastic resonance (SR) and makes the coupled gene network work as a stochastic resonator.

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