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Chemical Physics Letters 401 (2005) 307–311
CHEMICAL PHYSICS LETTERS
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Internal noise stochastic resonance of synthetic gene network

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Received 28 October 2004; in final form 11 November 2004
Available online 8 December 2004

Abstract

We have constructed a mesoscopic stochastic model for a synthetic gene network, and studied how the internal noise would influence the genetic oscillations of such a system. We find that the internal noise can play rather constructive roles via a mechanism of internal noise stochastic resonance, i.e., the stochastic genetic oscillations can show best performance at an optimal internal noise level. Since the magnitude of the internal noise is determined by the system size, this phenomenon also demonstrates a kind of system size resonance.

1. Introduction

It is well known that many regulatory molecules act at rather low concentration in the processes of gene expression, leading to large random fluctuations on the reaction rates of the processes [1,2]. Since Arkin and co-workers [3] realized that the reactions underlying gene expression occur in abrupt stochastic bursts rather than successive deterministic manner, it has been realized that in various systems the intrinsic noise of gene expression is inherent and should be paid considerable attention [4]. Experimentally, the phenotypic noise in a single gene was differentially measured, which was the first direct experimental evidence of the biochemical origin of phenotypic noise [5]. Furthermore, the intrinsic noise of an autoregulatory genetic module was predicted and measured using an integrated approach [6]. Especially, experiments on eukaryotic gene expression showed that increased noise in the transcription of a regulatory protein leads to increased cell–cell variability in the target gene output, and the noise from transcription can be modulated at the translational level, highlighting a key difference between eukaryotic and prokaryotic source of noise [7]. Theoretically, the effects of molecular fluctuations were shown to be prominent and can not be ignored in models of transcriptional regulation [8,9], circadian rhythm [10,11] and signal cascades [12]. It was also found that the fluctuations in the concentrations of regulatory proteins can propagate through a genetic cascade [13], which can be used to facilitate the prediction of noise characteristics in networks of arbitrary connectivity. Meanwhile, the intrinsic and extrinsic contribution to noise in gene expression was investigated using a theoretical model, which enable us to study these two types of noise respectively [14].

Up to now, most of the studies accounting for the intrinsic noise in gene expression focus on how to measure, characterize and explain the intrinsic noise experimentally or theoretically, and how the system shows robustness to intrinsic noise by feedback loops or redundancy on viewing the noise as a nuisance. However, some recent studies have explored the roles of noise in the dynamics of gene expression, i.e., intrinsic noise may induce oscillations which are not present in the deterministic model [15], or induce bifurcations which have no counterpart in the deterministic description [16]. More importantly, in some reverse engineering approaches, some regulatory mechanisms may exploit

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doi:10.1016/j.cplett.2004.11.064

intrinsic noise to randomize outcomes, where variability is advantageous [2]. In this way, the intrinsic noise can be used to control a toggle switch [17–19], or a repressilator, in which three gene products inhibit the transcription of each other in a cyclic way [20].

Especially, among the studies where the intrinsic noise systematically facilitates the system properties, it was found that in a cellular control system intrinsic noise may enhance the sensitivity of intracellular regulation by stochastic focusing (SF) [12], and that in a genetic control circuit the fluctuations in repressor or corepressor numbers can improve the control of gene expression [21]. In addition, it was found that optimal internal noise effect exists in some sub-cellular system. Shuai and Jung [22,23] demonstrated that optimal intracellular calcium signaling appears at a certain size or distribution of the ion channel clusters. In previous studies, we have also found the constructive roles of internal noise or optimal system size effects in circadian clock system [24] and calcium signaling system [25]. Very recently, constructive effects of molecular fluctuations in a circadian rhythm system have also been studied [26]. Therefore, a straightforward question is: Is there any constructive roles of internal noise or optimal system size in mesoscopic gene expression process?

In the present Letter, we investigate the effect of internal noise on a synthetic gene network model [27], which is at the basic level of life system [28]. Dissected from naturally occurring networks to implement particular functions, synthetic gene networks reduce the complexity within naturally occurring networks, such that theoretical studies are possible to help exploring the evolutionary design principles of their native biological settings [29,30]. The validity of synthetic gene networks has been further supported by recent experimental progress [17–20,31]. In this work, we first construct a mesoscopic stochastic model for a synthetic gene network, and then demonstrate that internal noise is advantageous to the system performance in that the stochastic genetic oscillations can show best performance at an optimal internal noise level by a mechanism of internal noise stochastic resonance (INSR). Finally we show that such an INSR indicates some kind of system size resonance.

2. Model description

The genetic oscillator model proposed by Hasty et al. on 2002 [27] consists 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 when OR3* is vacant, the promoter is turned 'on', that is, 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. See [27] for more details.

The detailed list of reaction processes can be found in [27]. If quasi-steady-state assumption is taken into account, there are eight main reaction processes as listed in Table 1. Here, x and y denote the concentrations of CI protein and Lac protein, while X and Y represent the total numbers of CI protein and Lac protein, respectively. M_1 and M_2 represent the copy numbers of cI and lac gene, respectively. D^i denotes the promoter region of plasmid type i, where $i = 1, 2$. k_t, k_x and k_y are rate constants of the processes of protein formation, degradation of CI protein and Lac protein, respectively. α represents the degree to which transcription rate is increased when a CI dimer is bound to OR2, and σ is the affinity for a CI dimer binding to OR2 relative to binding at OR1. We choose the degradation rate constant of Lac protein k_y as control parameter.

If internal noise is not taken into account, the dynamics of the system is described by the following deterministic equation as in [27]

$$\begin{aligned}\frac{\mathrm{d}x}{\mathrm{d}t} &= k_t \cdot M_1 \cdot \frac{1 + x^2 + \alpha\sigma x^4}{(1 + x^2 + \sigma x^4)(1 + y^4)} - k_x \cdot x \\ &= a_1 + a_2 + a_3 - a_4, \\ \frac{\mathrm{d}y}{\mathrm{d}t} &= k_t \cdot M_2 \cdot \frac{1 + x^2 + \alpha\sigma x^4}{(1 + x^2 + \sigma x^4)(1 + y^4)} - k_y \cdot y \\ &= a_5 + a_6 + a_7 - a_8.\end{aligned} \tag{1}$$

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 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 it still provides the basis for numerical simulation. One of the widely used simulation algorithm is exact stochastic simulation method introduced by Gillespie in 1977 [32], which stochastically determines what is the next reaction step and when it will happen according to the transition probability of each reaction event. This simulation method exactly accounts for the internal noise. For the present model, the eight reaction steps and corresponding transition rates are listed in Table 1; one should note that the transition rates are proportional to the system size V. Although the exact stochastic simulation method has been widely used to study the effects of internal noise in many systems, it is too time-consuming when the system size is large. Recently, Gillespie developed the τ-leap method [33] that randomly deter-

Table 1
Reaction steps and corresponding transition rates involved in the model

Reaction steps	Description	Transition rates
$D^1 \rightarrow D^1 + X$	Generation of CI protein from *cI* gene	$W_1 = a_1 \cdot V = k_t \cdot M_1 \cdot \frac{1}{(1+x^2+\sigma x^4)(1+y^4)} \cdot V$
$D^1X_2 \rightarrow D^1X_2 + X$		$W_2 = a_2 \cdot V = k_t \cdot M_1 \cdot \frac{x^2}{(1+x^2+\sigma x^4)(1+y^4)} \cdot V$
$D^1X_2X_2 \rightarrow D^1X_2X_2 + X$		$W_3 = a_3 \cdot V = k_t \cdot M_1 \cdot \frac{\alpha\sigma x^4}{(1+x^2+\sigma x^4)(1+y^4)} \cdot V$
$X \rightarrow$	Degradation of CI protein	$W_4 = a_4 \cdot V = k_x \cdot x \cdot V = k_x \cdot X$
$D^1 \rightarrow D^1 + Y$	Generation of Lac protein from *lac* gene	$W_5 = a_5 \cdot V = k_t \cdot M_2 \cdot \frac{1}{(1+x^2+\sigma x^4)(1+y^4)} \cdot V$
$D^1X_2 \rightarrow D^1X_2 + Y$		$W_6 = a_6 \cdot V = k_t \cdot M_2 \cdot \frac{x^2}{(1+x^2+\sigma x^4)(1+y^4)} \cdot V$
$D^1X_2X_2 \rightarrow D^1X_2X_2 + Y$		$W_7 = a_7 \cdot V = k_t \cdot M_2 \cdot \frac{\alpha\sigma x^4}{(1+x^2+\sigma x^4)(1+y^4)} \cdot V$
$Y \rightarrow$	Degradation of Lac protein	$W_8 = a_8 \cdot V = k_y \cdot y \cdot V = k_y \cdot Y$

Parameter values that remain unchanged during simulation: $k_x = 2.625$, $M_1 = 50$, $M_2 = 1$, $\alpha = 11$, $\sigma = 2$.

mines how many steps will take place for each reaction channel in the next 'macro-infinitesimal' time interval τ. It has been proved that the τ-leap method is a rather good approximation of the exact method when the system size is large. Therefore, it is advisable for us to use the exact stochastic simulation method when the system size is small enough and employ the τ-leap method when the system size is too large for the exact stochastic simulation method.

In addition, a further alternative method to study the internal noise is chemical Langevin (CL) method, which was also proposed by Gillespie [34]. It was proved that the chemical Langevin equation (CLE) is a rather good approximation if a 'macro-infinitesimal' time scale exists in the system. 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 evolve with time scale. To further facilitate the simulation and show robustness of our results, we have also performed studies based on the CLE. For the present model, the CLE reads

$$\begin{aligned}\frac{dx}{dt} &= a_1 + a_2 + a_3 - a_4 + \frac{1}{\sqrt{V}}(\sqrt{a_1}\cdot\xi_1(t) + \sqrt{a_2}\cdot\xi_2(t) \\ &\quad + \sqrt{a_3}\cdot\xi_3(t) - \sqrt{a_4}\cdot\xi_4(t)), \\ \frac{dy}{dt} &= a_5 + a_6 + a_7 - a_8 + \frac{1}{\sqrt{V}}(\sqrt{a_5}\cdot\xi_5(t) + \sqrt{a_6}\cdot\xi_6(t) \\ &\quad + \sqrt{a_7}\cdot\xi_7(t) - \sqrt{a_8}\cdot\xi_8(t)).\end{aligned} \tag{2}$$

Here, a_1–a_8 are the transition rates per volume listed in Table 1, and ξ_1–ξ_8 is Gaussian white noise with zero mean $\langle\xi_i(t)\rangle = 0$ and correlation of $\langle\xi_i(t)\cdot\xi_j(t')\rangle = \delta_{ij}\cdot\delta(t-t')$. Without the second terms in the brackets at the right side, the CLE (2) is equivalent with the deterministic Eq. (1). Therefore, these terms actually denote the internal noise. It is quite clear that the magnitude of the internal noise is proportional to $1/\sqrt{V}$, and they depend not only on the control parameter but also on the concentrations of CI and Lac protein.

3. Results and discussion

It is already well known that noise often plays constructive roles near the bifurcation points. We perform numerical calculation of Eq. (1) using explicit Euler method with time step 0.001 min and parameters as listed in Table 1 and find that there exist a supercritical Hopf bifurcation points at about $k_y = 0.087$ and a subcritical one at about $k_y = 0.177$ in this model. Our numerical simulation will be exerted near the subcritical Hopf bifurcation point at about $k_y = 0.177$.

In the present work, we focus on the effect of internal noise when k_y is tuned very close to the Hopf bifurcation point but still inside the steady-state region. If the system stays inside the steady-state region and we do not account for the internal noise, the system would not oscillate. But if the internal noise is taken into account, simulation results via the exact stochastic simulation method, the τ-leap method or the CLE, all show stochastic oscillations as displayed in Fig. 1(a). Such stochastic oscillations do not solely contain random noisy information, for there are clear peaks in their power spectrums (Fig. 1(b)).

The stochastic oscillation due to internal noise implies some kind of resonance effect. There is no oscillation in the steady-state region when the internal noise is not taken into account. On the contrary, if the system size is too small, the internal noise becomes so large that sustained oscillation would be overwhelmed by random noise. Therefore, for some intermediate system size and corresponding internal noise level, the stochastic oscillation due to internal noise would be most pronounced. In Fig. 1(b), one can see the power spectrums for the stochastic oscillation of CI protein concentration of three different system sizes. The control parameter is $k_y = 0.178$, which is slightly larger than the right Hopf bifurcation point. The smoothed curves are obtained by nearest averaging over 50 points from the original ones. The time series used to calculate the power spectrum contains 16,384 data points with an average time interval 0.5 min. A Welch window function is used

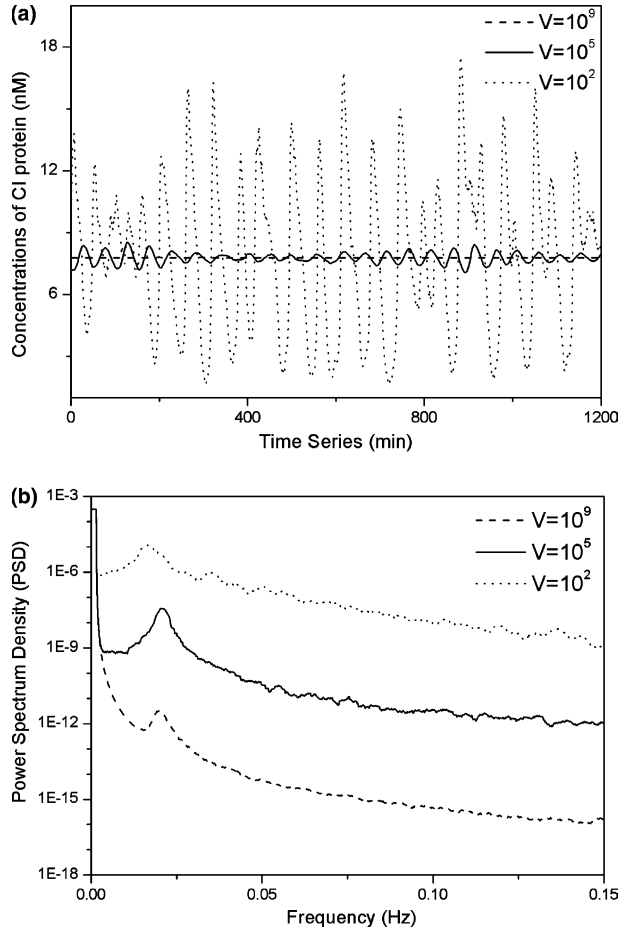

Fig. 1. (a) The stochastic oscillation of CI concentration for three different system sizes $V = 10^2$, 10^5 and 10^9, respectively. The control parameter is$k_y = 0.178$. The curve for $V = 100$ are obtained from exact stochastic simulation method, while the other two are obtained by τ-leap method. (b) Corresponding smoothed power spectrums for the time series in (a), respectively.

during the estimation of the power spectrum. One can see clear peaks in the power spectrum, which means that the time series contains periodic information. It is clear that when the system size increases from 100 to 10^9, both the signal level and noise background decrease at the peak. For an intermediate system size 10^5, the peak is the most pronounced among them.

To measure the relative performance of the stochastic oscillations quantitatively, we define an effective signal-to-noise ratio (SNR) β. See [24] for details about the definition and algorithm. The dependence of β on system size V for $k_y = 0.178$ is plotted in Fig. 2. One can see a clear peak is present for system size $V \sim 10^4$, which demonstrate the existence of a resonance effect. Since the resonance effect is caused by the difference of internal noise, we call it internal noise stochastic resonance (INSR) [35].

From Fig. 2 one can see good qualitative agreement among the chemical Langevin method, the exact stochastic simulation method and the τ-leap method, either in the agreement on the SNR values or the frequency at

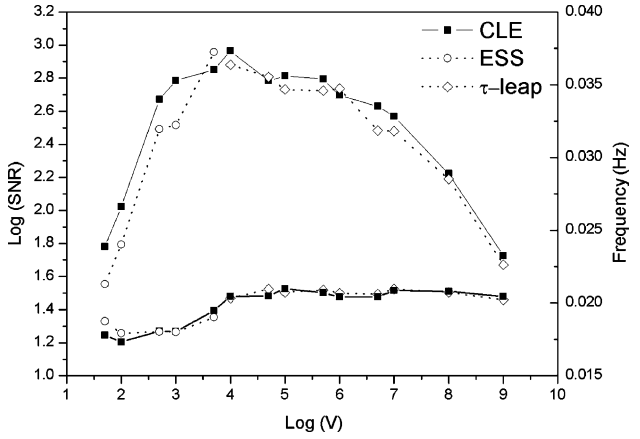

Fig. 2. The dependency of SNR and frequency of the peak in PSD on system size V for $k_y = 0.178$, the above curves are SNR values. Open circles: data obtained by exact stochastic simulation method for $V < 10^4$, open diamond: results from t-leap method for $V \geqslant 10^4$, solid square: data from CL method.

which the peak appears. Such agreements imply that it is convenient to use the CLE to study the qualitative effects of internal noise in a systematic way. Using the CL method, we have also studied how the SR behavior depends on the value of the control parameter. The results are shown in Fig. 3. When the control parameter becomes closer to the Hopf bifurcation point, the SR curve becomes higher. One can see the optimal system sizes are always about 10^4. It is shown that for those k_y slightly larger than the Hopf bifurcation point, the internal noise can play constructive role at a moderate system size. For k_y slightly smaller than the Hopf bifurcation point, the peak disappears and the SNR increases monotonically with the increment of system size. In this case, the internal noise due to small system size always plays destructive roles.

Our simulation is exerted near the subcritical Hopf bifurcation point of the system, where the system only

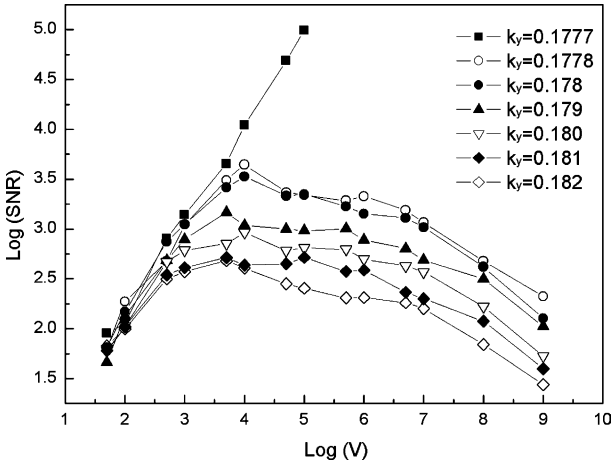

Fig. 3. The dependence of SNR on system size for different choices of the control parameter. The results are obtained by CL method.

shows a stable steady state when internal noise is not accounted for. However, once the internal noise is taken into account, periodic oscillation may be stimulated, so the sustained oscillation can be observed and it contains not only random signals of internal noise but also the inherently system signal. Furthermore, the performance of such sustained oscillation undergoes a maximum with the increment of internal noise, which implies the occurrence of INSR. 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, we show here that noise can play constructive roles via INSR such that the regulatory mechanism may exploit the advantage of internal noise. It was well known that many biological systems can take advantage of the benefits of noise for nonlinear transmission and amplification of feeble information, and here we have expanded such advantageous roles to the basic level of life system. In addition, from our results one can see the performance of sustained oscillation is optimal in $V \sim 10^3$–10^4. 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 process of gene expression is of ubiquitous importance in circadian clock control and metabolism, the INSR 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 or other cellular process, further experimental and theoretical work will be of great help to answer this question.

4. Conclusion

In conclusion, we have constructed a mesoscopic stochastic model for a synthetic gene network, and studied the effect of internal noise on the genetic oscillations of such a system. We find that the internal noise can play rather constructive roles via a mechanism of internal noise stochastic resonance, i.e., the stochastic genetic oscillations can show best performance at an optimal internal noise level. Since the magnitude of the internal noise is determined by the system size, this phenomenon also indicates a kind of system size resonance.

Acknowledgements

The authors are indebted to J. Hasty et al. for using their model. This work is supported by the National Science Foundation of China (20173052, 20203017, 20433050), and the Foundation for the Author of National Excellent Doctoral Dissertation of PR China (FANEDD).

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