Critical condition for the occurrence of a noise-reduction effect

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Based on a copy number control model of bacterial plasmid, the internal noise near a given steady state is investigated by using the linear noise approximation. All the parameters are restricted to a certain region so that the time spent near the steady state is long enough and the absorbing state can be neglected. For the noise in the plasmid molecules, a transition occurs with increasing the noise in the signal molecules under certain conditions. A noise-reduction mechanism, noise suppression by noise, is found. More importantly, the critical condition for the occurrence of the noise-reduction effect is given in our theoretical treatment.

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Living systems are inherently noisy [1–3]. Biochemical systems involve many kinds of molecules, but each kind is usually composed of just a small number of molecules, which can lead to significant statistical fluctuations in molecule numbers and reaction rates. These fluctuations are known as intrinsic noise [4,5]. The origins of intrinsic noise have been investigated theoretically and experimentally [6,7].

It is important to emphasize that organisms have evolved networks to function in the extremely noisy cellular environment. These networks may be resistant to or could even be taking advantage of the cellular noise to perform their functions. Thus, exploring methods for controlling and attenuating the noises are important if one wants to understand the networks that operate with high stability and reliability. It has been suggested that this robust operation is the result of intricate noise attenuation and exploitation mechanisms, such as feedback regulatory loops [6,8] and availability through multimerization and sequestration [9,10]. Coupled with other mechanisms, feedback loops have been shown to yield dynamics that exhibit sophisticated behavior, including phenomena of noise suppression by noise [11–13].

Paulsson *et al.* [12,13] showed that intrinsic noise in cellular control systems can be exploited to increase sensitivity amplification. It is demonstrated that random signal fluctuations can reduce fluctuations in a controlled process. An obvious and relevant question concerns the conditions under which such a noise-reduction effect occurs in the stochastic system. The related theoretical investigation is very important, however, to our knowledge, there is little in the literature devoted to the topic. Thus, it would be very interesting to investigate the critical condition. We try to address a biological problem: how one biological network regulates itself appropriately so that all the related physiological parameters can meet the critical condition and the noise-reduction mechanism is in operation.

In this report, based on a copy number control (CNC) model of bacterial plasmid, the internal noise in the negative feedback system near a stable steady state is investigated by using the linear noise approximation method. One focus of ours is to provide a detailed theoretical analysis for the noise-reduction effect, presented in Ref. [13]. The stationary covariance matrix for the fluctuations is derived by using linear noise approximation. More importantly, the critical condition for the occurrence of the noise-reduction effect is also derived. The molecular numbers in the given equilibrium state are moderate and some parameter values are restricted to a particular region so that the absorbing state in the stochastic process can be neglected approximately and the generic master equation can still be used. Therefore, for simplicity, the extinctions will not be dealt with more explicitly.

A minimal regulatory network consists of two molecular species including the plasmid molecule and the signal molecule, that regulate each other's synthesis [13,14]. This is an unique CNC system, because its kinetic mechanisms constitute simple intracellular standards, but also because it is virtually identical to models of CNC of bacterial plasmid. The macroscopic equations describing the negative feedback system are

$$\frac{dx}{dt} = \frac{kx}{1+\frac{s}{K}} - x, \tag{1}$$

$$\frac{ds}{dt} = k_s x - k_d s, \tag{2}$$

where x and s are continuous concentration variables for the plasmids and inhibitors. The rate equations of x and s describes the dynamics of the system in the macroscopic limit. The plasmid production rate per plasmid $\frac{k}{1+\frac{s}{K}}$ (response frequency) is a function of the inhibitor concentration. Plasmids are also continuously diluted as all intracellular components in a growing host. The rate constant for exponential host cell growth has been put equal to 1. Inhibitors are constitutively synthesized and the rate constant k_s per plasmid is degraded and diluted according to first order kinetics with total rate constant k_d. A parameter Ω is defined as the system size. The numbers of the regulated component molecules and signal molecules can be expressed as $\bar{x}=x\Omega$ and $\bar{s}=s\Omega$. If $k>1$, a steady state exists in the system. A detailed description of the model can be found in Ref. [14].

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Equations (1) and (2) have an attracting fixed point $(x_0,s_0)=(0,0)$ and an unstable fixed point $(x_0,s_0)'=\left(\frac{(k-1)Kk_d}{k_s},(k-1)K\right)$. However, the underlying stochastic process behaves quite differently. A large enough fluctuation ultimately depletes the plasmid population. The state with no plasmids is an absorbing state, which is actually stable.

In order to investigate the effect of stochastic noise on the CNC system near a given stable equilibrium, the linear noise approximation (LNA) is used in our theoretical treatment. The LNA was known in the early literature as the van Kampen's system size expansion [15] and was recently rederived for multivariate CMEs [16,17]. The LNA offers an elegant analytic method to probe the effects of molecular noise on small-scale chemical reaction pathways, and is used extensively [16–19]. The stationary covariance matrix C^0 contains the variances and covariances of the fluctuations in the components of the system. Approximate explicit expressions for C^0 is obtained as the solution of an algebraic Lyapunov equation [16]

$$A^0C^0+C^0(A^0)^T+\Omega B^0=0. \tag{3}$$

A^0 is the stationary Jacobian matrix of the deterministic equations. B^0 is the stationary diffusion matrix.

Intrinsic noise arises from the fact that the system consists of discrete particles. Let $P(\bar{x},\bar{s},t)$ be the joint probability distribution that the numbers of plasmid and signal molecules equal exactly $\bar{x}$ and $\bar{s}$ at time t. We investigate the transient behavior of the sample paths.

Therefore, a generic master equation of $P(\bar{x},\bar{s},t)$ ($\bar{x}\geq 1,\bar{s}\geq 1$) can be written in terms of the step-operator in the following form:

$$\frac{dP(\bar{x},\bar{s},t)}{dt}=\left[\frac{k}{1+\frac{\bar{s}}{K\Omega}}(E_x^{-1}-1)\bar{x}+(E_x^1-1)\bar{x}+k_s(E_s^{-1}-1)\bar{x}+k_d(E_s^1-1)\bar{s}\right]P(\bar{x},\bar{s},t), \tag{4}$$

where the symbol E represents a step operator, which is defined as $E_i^1f(N_i)=f(N_i+1)$, $E_i^{-1}f(N_i)=f(N_i-1)$. It should be pointed out that if two conditions are satisfied, (i) the numbers of plasmid and signal molecules for the given steady state are moderate or larger and (ii) some parameter values are restricted to certain a range and chosen appropriately, then the mean time it takes this stochastic process to reach the absorbing state is relatively long. For this reason, in this report we can assume that the plasmid does not go extinct. Thus, the above generic master Eq. (4) is approximately equivalent to the renormalized master equation provided in Ref. [13], and we only investigate the noise character during the transient state of the sample trajectories in the stochastic process.

Equation (4) can rarely be solved analytically. A less computationally demanding, yet approximate, approach is the simplification of the master equation in the LNA, which depends upon two simplifications. First, the total concentration of the ith species ($i=1,2$) is given by $\bar{x}=x\Omega+\Omega^{1/2}\xi(t)$, $\bar{s}=s\Omega+\Omega^{1/2}\delta(t)$, where x and s are the solutions of Eqs. (1) and (2), ξ and δ are two new variables associated with number fluctuations, and Ω is the system size. Second, the action of the step operator is well described by the Taylor series. Furthermore, we introduce the probability density for the fluctuations $\Pi(\xi,\delta,t)$. Inserting the above step operators into Eq. (4), we can easily write the continuous chemical master equation of $\Pi(\xi,\delta,t)$, which is used to expand the equation in inverse powers of Ω. An approximate evolution equation for $\Pi(\xi,\delta)$ is obtained by collecting terms with first order in $\frac{1}{\Omega^{1/2}}$. The coefficient matrices A^0 and B^0 in the stable equilibrium is derived from the evolution equation (not shown).

We now use the LNA to compute the steady-state covariance matrix C^0. In order to solve the Lyapunov Eq. (3), A^0 and B^0 should be inserted into Eq. (3). The explicit expressions for C^0 is given by

$$\begin{pmatrix} C_{xx}^0 & C_{xs}^0 \\ C_{sx}^0 & C_{ss}^0 \end{pmatrix}=\begin{pmatrix} \bar{x}\frac{k}{k-1}+\frac{\bar{x}}{k_s}\frac{k-1}{k}+\frac{\bar{s}}{k_s} & \frac{\bar{s}k}{k-1} \\ \frac{\bar{s}k}{k-1} & \bar{s}+\frac{\bar{s}^2}{\bar{x}}\cdot\frac{k}{k-1} \end{pmatrix}. \tag{5}$$

We can write C_{ss}^0 and C_{xx}^0 in the steady state as

$$C_{ss}^0=\bar{s}^0+\frac{\bar{s}^{0^2}}{\bar{x}^0}\frac{k}{k-1}, \tag{6}$$

$$C_{xx}^0=\bar{x}^0\frac{k}{k-1}+\frac{\bar{x}^0}{k_s}\frac{k-1}{k}+\frac{\bar{s}^0}{k_s}. \tag{7}$$

From Eqs. (6) and (7), the noise strength, defined by the Fano factor [6], is expressed as

$$F_x=\frac{C_{xx}^0}{\bar{x}^0}=\frac{k}{k-1}+\frac{k-1}{kk_s}+\frac{1}{k_s}, \tag{8}$$

$$F_s=\frac{C_{ss}^0}{\bar{s}^0}=1+\frac{\bar{s}^0}{\bar{x}^0}\frac{k}{k-1}. \tag{9}$$

It is noticed that F_x in Eq. (8) does not depend on $\bar{x}^0$ and $\bar{s}^0$. F_x is the same if $\bar{s}^0=\bar{x}^0$ in Eq. (9).

For a given steady state $\bar{s}^0=\bar{x}^0=100$, the numbers of the plasmid and signal molecules are moderate. The internal noise is investigated quantitatively. The analytical results are plotted in Fig. 1 (see the solid curves). From top to bottom, three cases are shown, respectively. The noise strength of the plasmid molecules F_x as a function of k is plotted in Figs. 1(a), 1(c), and 1(e). F_x with increasing F_s is shown in Figs. 1(b), 1(d), and 1(f), respectively. Some important results are summarized as below. (i) As shown in the left column, it is found that with the increase of k, F_x finally reaches a plateau under different k_s. Before the plateau, F_x goes through a valley with increasing k for $k_s=0.2$ and $k_s=0.3$, however, F_x almost decreases monotonously for $k_s=0.8$. In addition, k_s is smaller, the region where F_x is an increasing function of k is larger. (ii) As observed in the right column, for F_x, a transition point [denoted with the arrows in (b) and (d)] exists with increasing F_s, while it nearly disappears in (f). It is shown that the noise-reduction effect occurs before the transition

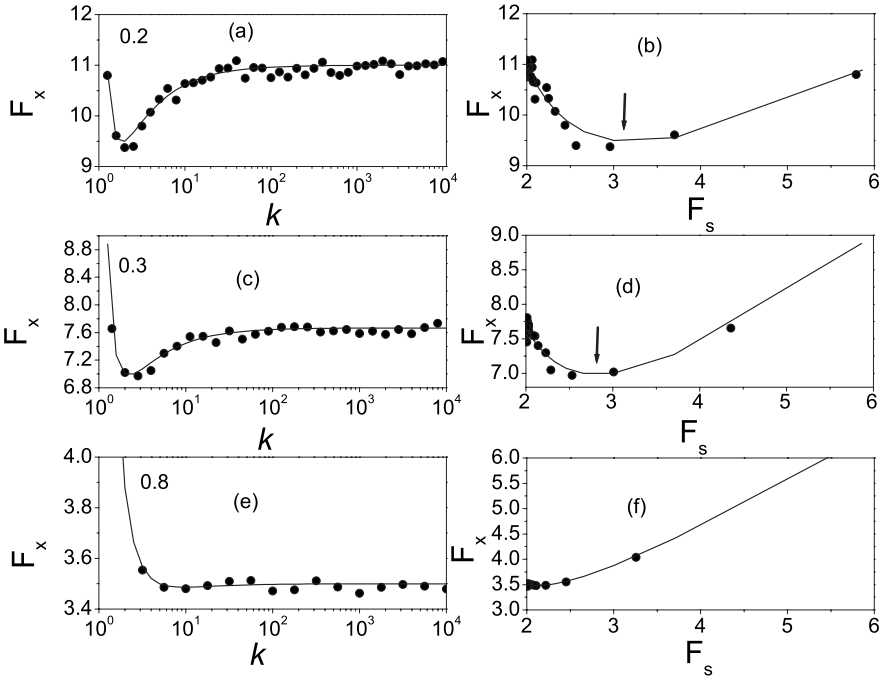

FIG. 1. F_x as a function of k (in the left column) and F_x vs F_s (in the right column) for different k_s. From top to bottom, $k_s=0.2$, 0.3, and 0.8, respectively. For F_x, the transition point [denoted with arrows in (b) and (d)] exists clearly with increasing F_s, while it nearly disappears in (f). The numerical results obtained from the CLEs are shown with the filled circles.

point. Initially, with the enhancement of the signal noise F_s, the fluctuation in the plasmid molecules F_x decreases, which is a remarkable phenomenon (i.e., noise-reduction effect). The increase of internal noise in the signal molecules results in lower variances of the regulated plasmid molecules, which enhances robustness against stochastic fluctuations and cellular noise. Such a noise-reduction mechanism implies noise suppression by noise. After passing through a minimal value (i.e., the transition point), the noise-reduction phenomenon disappears. Furthermore, it is found that the region exhibiting a noise-reduction effect becomes smaller with increasing k_s, until it disappears for $k_s \geq 1$.

Furthermore, the chemical Langevin equation (CLE) method proposed by Gillespie in 2000 [20] is adopted to simulate the internal noise. The numerical results are also plotted in Fig. 1. It is shown the analytical results obtained from the LNA are in good agreement with the numerical results from CLEs. This implies that our results from the LNA are not due to the approximation.

In order to find the condition under which such a noise-reduction effect occurs, we settle the problem by a simple mathematical analysis using Eqs. (8) and (9). To provide a clear observation, we define

$$Q = \frac{k}{k-1}. \tag{10}$$

Therefore, Eqs. (8) and (9) have the new forms

$$F_x = Q + \frac{1}{Qk_s} + \frac{1}{k_s}, \tag{11}$$

$$F_s = 1 + \frac{\bar{s}^0}{\bar{x}^0} Q. \tag{12}$$

Because the variance of the signal molecules F_s is an increasing function of Q, then if the variance of the plasmid molecules F_x is a decreasing function of Q, the increase of F_s can result in a decrease of F_x. Obviously, the critical condition for the occurrence of the noise-reduction effect is

$$\frac{dF_x}{dQ} = 1 - \frac{1}{k_s Q^2} = 0. \tag{13}$$

A reduction expression of the critical condition is obtained by inserting Eq. (10) into Eq. (13)

$$k_s \frac{k^2}{(k-1)^2} = 1. \tag{14}$$

Some discussion is in order regarding the above critical condition. (i) If $k_s \frac{k^2}{(k-1)^2} < 1$ (i.e., $k_s < 1$), it is implied that F_x is a decreasing function of Q, i.e., an increasing function of k. When k decreases, Q will increase, therefore F_s will increase but F_x will decrease, which shows the occurrence of the noise-reduction phenomenon (see the curves shown in Fig. 1 before the transition point). (ii) If $k_s \frac{k^2}{(k-1)^2} > 1$, an opposite result is obtained. After passing through the transition point, the noise-reduction phenomenon disappears for large k.

The main results show the following. (i) Whether the noise-deduction effect occurs is determined only by two parameters, i.e., k and k_s. (ii) If $k_s \geq 1$, the inequality $k_s \frac{k^2}{(k-1)^2} < 1$ is not satisfied for any k. (iii) When k_s is very small, there exists a certain parameter region of k to meet the inequality. If k_s is smaller, the region is wider. (iv) For $\frac{dF_x}{dQ} = 0$, the minimal variance of the plasmid molecules is obtained, which is $\frac{2\bar{x}^0}{\sqrt{k_s}} + \frac{\bar{s}^0}{k_s}$.

In Fig. 2, we display the region where the noise-reduction effect can occur in the k_s-k-parameter plane. It is shown that the region of k corresponding to the occurrence of the noise-reduction effect becomes smaller with increasing k_s, until it disappears. The result can also be observed directly from the

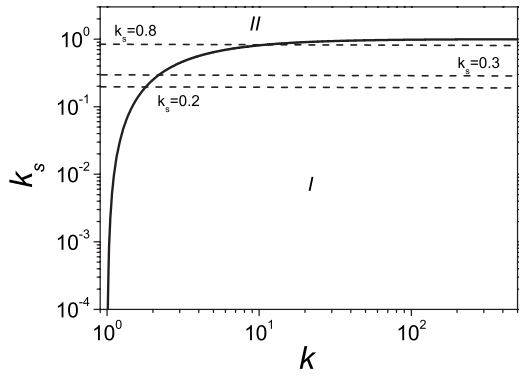

FIG. 2. The region I corresponding to the occurrence of the noise-reduction effect in the k_s-k-parameter plane. The critical condition, i.e., Eq. (14), is plotted with the solid line. Three dashed lines correspond to the three cases $k_s=0.2$, $k_s=0.3$, and $k_s=0.8$ shown in Fig. 1.

three dashed lines shown in Fig. 2. The range of dashed line in the region I becomes smaller with the enhancement of k_s, which implies that the region exhibiting a noise-reduction effect becomes smaller with increasing k_s, until it nearly disappears for $k_s=0.8$. This result is consistent with the discussion about the three cases in Fig. 1.

Based on a CNC model of bacterial plasmid, the internal noise-reduction effect is investigated by using the linear noise approximation. Through a simple theoretical analysis, an interesting noise-reduction mechanism is found. For the noise in the plasmid molecules, a transition point exists when the noise is increased in the signal molecules under certain a condition (i.e., $k_s<1$). This implies that the noise in the plasmid molecules can be reduced by increasing the noise in signal molecules before the transition point, which requires that a certain condition is satisfied. The critical condition is given clearly. Our results show that whether the noise-reduction effect occurs only depends on two parameters for any given steady state.

It is noted that the noise strength in the plasmid molecule in the LNA treatment is larger when the noise is included in signal molecule as compared to the case where signal molecule is approximated by its steady state value. Therefore, it is not the stochastic focusing (i.e., SF) phenomena that we observe after the LNA treatment. It is just that signal molecule and plasmid molecule depend differently on k.

In this report, the molecular numbers in the given steady state (i.e., $\bar{s}^0=\bar{x}^0=100$) are moderate and one parameter k_s is restricted to a particular region around $k_s>0.14$, so that the expected times for the system to be absorbed in (0,0) along the observed sample trajectories of the stochastic process are relatively long. Therefore, we can assume that the plasmid does not go extinct and only investigate the noise character of the transient state of the sample paths by using a generic master equation. However, for lower molecular numbers and other parameter values, the time taken by the stochastic process to reach the absorbing state is very short, the extinctions should be dealt with more explicitly, and the renormalized master equation is required. A challenging question is how to solve the renormalized master equations by LNA, which will motivate our further work.

Noise control and attenuation is a topic of central importance in biology. Our results not only confirm the noise reduction of the regulated component by signal noise found in Ref. [13], but also provide a critical condition for the occurrence of the noise-reduction effect. We expect that the CNC network regulates itself appropriately so that all the related physiological parameters can meet the critical condition. Our result should still be tested or verified by the theoretical and experimental work in the future.

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