Noise transmission and delay-induced stochastic oscillations in biochemical network motifs*

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With the aid of stochastic delayed-feedback differential equations, we derive an analytic expression for the power spectra of reacting molecules included in a generic biological network motif that is incorporated with a feedback mechanism and time delays in gene regulation. We systematically analyse the effects of time delays, the feedback mechanism, and biological stochasticity on the power spectra. It has been clarified that the time delays together with the feedback mechanism can induce stochastic oscillations at the molecular level and invalidate the noise addition rule for a modular description of the noise propagator. Delay-induced stochastic resonance can be expected, which is related to the stability loss of the reaction systems and Hopf bifurcation occurring for solutions of the corresponding deterministic reaction equations. Through the analysis of the power spectrum, a new approach is proposed to estimate the oscillation period.

Keywords: biological stochasticity, time delay, oscillation and resonance, network motif

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1. Introduction

The structure and function of cellular networks are bridged by dynamical processes occurring from micro- to macro-scales. However, the biological networks involve enormous elemental molecules interacting with each other in a very complex manner. Such complexity makes it difficult to describe the features of biological networks and interaction mechanisms between molecules in a dynamical way.[1] To simplify these complex biological systems, an effective method is to decompose them into several simpler, functionally independent modules,[2,3] such as pathways in metabolism and motifs in genetic regulatory networks. Reference [4] reviewed a set of recurring regulation patterns in microorganism transcription networks with an emphasis on experimental studies.

When one studies dynamical mechanisms of biochemical reactions occurring in network motifs, their bulk aspects of reactions may be described by a set of differential equations for the concentrations of component species involved. Since biological processes are fundamentally stochastic and stochasticity may play an important role in gene expression, the interactions among these molecules are supposed to occur randomly. The origin of stochasticity in biological network motifs comes from two sources of noise, which have given rise to intensive study[5−13] within the last decade. One is the intrinsic noise which comes from the random reaction type and reaction time due to the small molecular populations of some species, and the other is the extrinsic noise generated by the interaction with other stochastic systems in the environment.

Another very important factor in studying the dynamical mechanisms of the biochemical reactions is time delays which are inevitable in many real systems and reflect the transmission time needed for the transport of matter, energy and information through the systems.[14−18] The basic idea behind delayed reactions is to reduce a multi-step process (involving the sequential assembly of long molecules) to a single delayed process.[19,20] The underlying approach is that fast reactions (such as dimerization, protein-

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DNA binding/unbinding) in the multi-step process are eliminated and slow reactions (such as transcription, translation, degradation) remain with a certain characteristic delay time. This delayed modeling technique has been shown to be very useful in studying genetic dynamics at the molecular level.[16,20−26] In order to understand the complete dynamics occurring in network motifs, it is imperative to consider the effects of time delay.

It is also worth mentioning that developmental transcription network motifs often use intricate feedback loops that are composed of several transcription factors regulated to each other.[4,27] Such feedback mechanisms also may occur in some multiple coupled signaling motifs[22] and are activated by detecting incoming noise.[2] As a consequence, each factor does not perform its function independently of the others. Interactions among factors and their coordinates are crucial for carrying out all the complex functions of network motifs.

Considering the above-mentioned phenomena, a set of basic equations to describe the dynamical processes of the biochemical reactions should be a set of stochastic delayed-feedback differential equations. Here it should be noted that the influence of time delay and noise on the dynamics of system is different for various systems with different feedback mechanisms. With this conclusion in mind, we can turn our attention to model biochemical reaction systems and, in another sense, to describe noise propagation through biochemical networks which has been revealed to be an important issue in the understanding of cell functions.[2,12,13,28] Many works on various subjects have been carried out, such as to what degree a certain biological system can be decomposed into functionally independent modules. Or, in other words, to what degree it can be modularly designed[29] How can we eliminate fast reactions from the reaction networks and what is the role of substrate reactions (multistage and time delay)? When the message molecule is detected, how do feedback and correlations affect the signal transduction? Finally, how reliably can biochemical networks transmit information in the presence of noise?

Recent experimental[30] and theoretical[31] have shown that noise in biomolecular systems may induce a bistable oscillatory (dynamical switching) behaviour that is both quantitatively and qualitatively different from what is predicted or possible deterministically. It has also been clarified[12,13,28] that when the intrinsic and extrinsic noises are uncorrelated, and when an input signal has a single exponential relaxation time, a noise addition rule (NAR) can be justified and a cascade description of noise transmission can be used to describe the signal transduction processes occurring in the whole large-scale network. This clarification would be very meaningful for a modular description of noise propagation.[29] However, the feedback mechanisms and correlation interactions among the network motifs cannot be generally ignored and a single exponential relaxation property is not always reasonably justified. Reference [2] introduced three elementary detection motifs to analyse the effects of noise, and showed that the correlation between the intrinsic and extrinsic noise precludes a quantitative description of noise propagation for large-scale biochemical networks. In this case, the NAR derived by Refs. [12] and [13] does not hold, and then the propagation of noise is only accurately quantified when the correlated subnetworks are regrouped into independent modules.

On the other hand, time delay was not taken into account in the above studies although it can be crucial for determining individual properties of biochemical networks (for example, see Ref. [21]) and describing transient processes,[20] such as gene regulation, transcription, translation, among others. Previous works[20,22] have shown that when the time delay is incorporated in the differential equations, it will characteristically change the nature of the solutions of such equations,[22], which show very significant statistical features.[20]

Theoretical approaches for studying the effects of delay and feedback mechanisms have been discussed in Ref. [20] where generating function techniques have been used for studying master equations of delayed systems, and computing power spectra which are in good agreement with simulations. However, in our understanding, reference [20] did not treat the extrinsic and intrinsic noise separately. The method used in Ref. [20] is also based on some strong assumptions. It is therefore logical and very interesting to systematically study the effects of time delays on the dynamics of biochemical reactions. Such a study should provide us with many valuable phenomena and physical insights.

For this purpose, in this paper, we will in Section 2 present a generic biological motif which includes the main dynamical mechanisms and elements

such as the intrinsic and extrinsic noise, the feedback mechanism, and the time delay in genetic regulation networks. With the virtue of the stochastic delayed-feedback differential equations and Fourier transformation method, we will systematically analyse the effects of time delays on the frequency domain and compare our results with those of Refs. [2] and [20]. In order to make our discussions more transparent, we apply our delayed motif to two realistic biological systems: gene transcription and translation in Section 3 and the post-translational modification process in Section 4. Finally, we will summarize our discussions in Section 5.

2. A generic biological motif with delays

We consider a generic biological motif that consists of two slow reacting molecules S and X. We assume that there exists a domain of a macroscopically infinitesimal time interval because the other fast multistage reactions will be represented by the delay times. A chemical Langevin equation[32,33] can thus be used to describe the dynamics of molecular population. We further assume that the system is in its steady state, fluctuations of S and X are around their stationary values, i.e., $\mathcal{S} = S - \langle S\rangle$ and $\mathcal{X} = X - \langle X\rangle$ are small, and one may apply the linear-noise approximation[34] to linearize the chemical Langevin equation. Therefore, the following set of Langevin equations is used to describe the motif:

$$\frac{\mathrm{d}\mathcal{S}(t)}{\mathrm{d}t} = -A\mathcal{S}(t) + F\mathcal{X}(t-\tau_2) + \xi(t), \tag{1a}$$

$$\frac{\mathrm{d}\mathcal{X}(t)}{\mathrm{d}t} = H\mathcal{S}(t-\tau_1) - E\mathcal{X}(t) + \eta(t). \tag{1b}$$

Where A, E, F, and H denote reaction constants, $\xi(t)$ is a random factor for molecule S, and $\eta(t)$ for X, which originate mainly from their fluctuation and take small values. When we regard S as an input variable, $\eta(t)$ can be considered as an intrinsic noise, and $\xi(t)$ as an extrinsic noise for X, since $\xi(t)$ contains environmental fluctuations. Following Refs. [2], [12], [13], [28], and [32]–[34], both $\xi(t)$ and $\eta(t)$ are assumed to be Gaussian white noise satisfying the following relations:

$$\langle\xi(t)\rangle = \langle\eta(t)\rangle = 0, \tag{2a}$$

$$\langle\xi(t)\xi(t')\rangle = \langle\xi^2\rangle\,\delta(t-t'), \tag{2b}$$

$$\langle\eta(t)\eta(t')\rangle = \langle\eta^2\rangle\,\delta(t-t'), \tag{2c}$$

$$\langle\xi(t)\eta(t')\rangle = \langle\eta(t)\xi(t')\rangle = \lambda\,\langle\xi\eta\rangle\,\delta(t-t'). \tag{2d}$$

Here λ denotes a strength parameter of correlation between $\xi(t)$ and $\eta(t)$. In order to justify the approximation of $\xi(t)$ and $\eta(t)$ by Gaussian white noise, we have simulated the reactions of gene transcription and translation (Eqs. (8) in the following) by means of a delay stochastic simulation algorithm (DSSA).[32,33] It has been shown that the results obtained with the DSSA method are consistent with those obtained with a set of chemical Langevin equations (Eq. (16)) where $\xi(t)$ and $\eta(t)$ are approximated by Gaussian white noise. Thus, Gaussian white noise can be considered as a reasonable approximation to $\xi(t)$ and $\eta(t)$ for the subjects considered in this paper. Note also that Gaussian white noise is widely used in the literature.[12,13]

A discussion on an implication of Eq. (1) can be found elsewhere.[2] Here, it should be emphasized that the most essential difference of Eq. (1) from a corresponding equation in the literature[2] rests on the fact that the former takes account of two kinds of time delay τ_1 and τ_2 whereas the latter does not. For simplicity, we assume that both τ_1 and τ_2 are constants. However, variable delay times drawn from, e.g., some probability distribution, can also be considered.[35] Here it should be noted that a model with the above setup has previously been discussed and studied with an alternative approach in Ref. [20].

A characteristic feature of time delays is to induce stochastic oscillations into an otherwise simple, stable dynamical system. This property has been supported by recent studies on gene regulation networks.[16,21,22]

Following Refs. [2] and [36], we apply the Fourier transformation method to Eq. (1), and obtain the power spectra for S and X as

$$S_s(\omega) = \frac{(E^2+\omega^2)\left\langle\xi^2\right\rangle + 2\lambda F\left[E\cos\omega\tau_2 - \omega\sin\omega\tau_2\right]\langle\xi\eta\rangle + F^2\left\langle\eta^2\right\rangle}{\left[-\omega^2 + AE - FH\cos\omega\left(\tau_1+\tau_2\right)\right]^2 + \left[(A+E)\omega + FH\sin\omega\left(\tau_1+\tau_2\right)\right]^2}, \tag{3a}$$

$$S_x(\omega) = \frac{H^2\left\langle\xi^2\right\rangle + 2\lambda H\left[A\cos\omega\tau_1 - \omega\sin\omega\tau_1\right]\langle\xi\eta\rangle + (A^2+\omega^2)\left\langle\eta^2\right\rangle}{\left[-\omega^2 + AE - FH\cos\omega\left(\tau_1+\tau_2\right)\right]^2 + \left[(A+E)\omega + FH\sin\omega\left(\tau_1+\tau_2\right)\right]^2}. \tag{3b}$$

In Eq. (3), $\langle\eta^2\rangle$, $\langle\xi^2\rangle$, and $\langle\xi\eta\rangle$ terms represent the contributions from intrinsic and extrinsic noise, and the correlation between them, respectively. All these terms are modulated by the time delays of multistage biological processes.

From Eqs. (1) and (3), it can be seen that the correlation between the molecule $\mathcal{S}(t)$ and the intrinsic noise $\eta(t)$ comes from two distinct origins: the feedback mechanism F and the correlation $\langle\xi\eta\rangle$. In the case of small correlations, i.e., $F \approx 0$ and $\langle\xi\eta\rangle \approx 0$, equation (3) changes to

$$S_s^0(\omega) = \frac{\langle\xi^2\rangle}{\omega^2 + A^2}, \tag{4a}$$

$$S_x^0(\omega) = \frac{H^2\langle\xi^2\rangle}{(\omega^2 + A^2)(\omega^2 + E^2)} + \frac{\langle\eta^2\rangle}{\omega^2 + E^2}. \tag{4b}$$

Combining those two equations, one obtains the output power spectrum X as

$$S_x^0(\omega) = \frac{1}{\omega^2 + E^2}\left[H^2 S_s^0(\omega) + \langle\eta^2\rangle\right]. \tag{5}$$

This result verifies that NAR[12,13] is justified when there are no correlations between the input signal $\mathcal{S}(t)$ and the intrinsic noise $\eta(t)$. In this case, the intrinsic and extrinsic noise contribute to the spectrum of the output X separately.

From the above discussions, we may understand the following phenomena:

(i) When NAR is verified, the high frequency part is filtered by the network motifs. This is a direct consequence of no correlation. When the correlation plays a role in the reaction process, part of the noise is transferred to the high frequency region of the power spectrum $S_x(\omega)$. We will discuss this mechanism in more detail in the following sections.

(ii) Since the correlation between $\mathcal{S}(t)$ and the intrinsic noise $\eta(t)$ is ignored in obtaining NAR, $\mathcal{S}(t)$ only has a single exponential relaxation time determined by Eq. (1a) and its spectrum is expressed by a typical pure noise spectrum like the Lorentzian form given in Eq. (4a). In this case, the time delay τ_1 will not have a significant effect on the dynamics.

(iii) Equation (5) provides us with a variant of the fluctuation–dissipation theorem in nonequilibrium statistical mechanisms. This means that the nonequilibrium and dissipation nature might be a cause of the reaction process.

Now let us turn to the general case where the correlation between the intrinsic and extrinsic noise plays a role. When $\tau_1 = 0$, $\tau_2 = 0$, and $\lambda = 1$, one obtains,

$$S_s^1(\omega) = \frac{(\omega^2 + E^2)\langle\xi^2\rangle + 2EF\langle\xi\eta\rangle + F^2\langle\eta^2\rangle}{\left[-\omega^2 + AE - FH\right]^2 + (A+E)^2\omega^2}, \tag{6a}$$

$$S_x^1(\omega) = \frac{H^2\langle\xi^2\rangle + 2AH\langle\xi\eta\rangle + (\omega^2 + A^2)\langle\eta^2\rangle}{\left[-\omega^2 + AE - FH\right]^2 + (A+E)^2\omega^2}. \tag{6b}$$

The denominator on the right-hand side of Eq. (6) is always greater than zero, which ensures finiteness of $S_s^1(\omega)$ and $S_x^1(\omega)$. These analytical results in Eq. (6) are consistent with the ones presented by Ref. [2]. It is obvious that the correlations (originating from $F \neq 0$ and $\langle\xi\eta\rangle \neq 0$) break down NAR and impede a modular description of biological motifs. In this case, the biological motifs can only be quantified accurately if the correlated subnetworks are regrouped into independent modules. Note that in general, NAR overestimates the contribution of noise. Violation of NAR means that the effects of delay and a negative feedback mechanism may significantly reduce the effect of noise and make biochemical network motifs more robust against biochemical noise.

Finally, we can examine the effects coming from time delays. It has been shown in Ref. [20] that time delays may cause non-Markovian effects statistically and induce stochastic oscillation in the spectra. It is very interesting to note that, when $\tau_1 \neq 0$ and $\tau_2 \neq 0$, the denominators on the right-hand side of Eq. (3) become periodic functions of $\tau = \tau_1 + \tau_2$ and both $S_s(\omega)$ and $S_x(\omega)$ will show oscillation against ω, quite different from $(S_s^0(\omega), S_x^0(\omega))$, and $(S_s^1(\omega), S_x^1(\omega))$.

It is worthwhile mentioning that the denominators on the right-hand side of Eq. (3) are not always greater than zero, and for some specific values of τ satisfying the relations:

$$-\omega^2 + AE - FH\cos(\omega\tau) = 0, \tag{7a}$$

$$\omega(A+E) + FH\sin(\omega\tau) = 0, \tag{7b}$$

the denominators take a null value. It is clear from Appendix A that equation (7) holds at $\tau = \tau_c$, i.e., at the critical bifurcation point. In this case, both $S_s(\omega)$ and $S_x(\omega)$ tend to infinity, which may indicate coherence between $\mathcal{S}(t)$ and $\mathcal{X}(t)$. This phenomenon is called delay-induced stochastic resonance, which is related to the occurrence of Hopf bifurcation in the solutions of the corresponding deterministic equations (1). It should be emphasized that, as shown in Eq. (3) and discussed in Appendix A, the presence of the feedback mechanisms denoted by F and H is needed for occurrence of the delay-induced resonance. When either F and H does not play any role, the delay-induced resonance will not be expected.

Generally speaking, the appearance of stochastic resonance depends on the fact that there exists a resonant amplitude of noise, at which the output performance of the considered systems has a stochastic resonance peak against noise magnitude. In various

systems, the approaches to determine such resonant amplitude might use different mechanisms.[37−39] As an example, in the system size stochastic resonance, the resonant amplitude can be found by adjusting the system size,[40] which nonlinearly changes the relative strength of noise in comparison with the deterministic terms.

The resonant phenomenon discussed in this paper is similar to that of the Brusselator model of Ref. [41]. In our model, we use delay as a source of the oscillatory dynamics, incorporated with noise $\eta(t)$ and $\xi(t)$. When there is no delay ($\tau = 0$), the power spectra are typical pure noise spectra. When delay increases, the peaks appear and when delay reaches critical values, large peaks appear with almost infinite heights. It is very interesting to note that, when delay increases further (larger than the critical value), the height decreases. These phenomena convince us that there exists indeed a strong coherent motion stimulated by delay effects incorporated with noise.

From the viewpoint of nonlinear dynamics, one may understand this phenomenon in that the delay makes the deterministic terms (effective potential) change into an oscillatory one which is close to transition into the limit cycle domain. With this characteristic property, it may be termed as stochastic resonance with delayed dynamics or, equivalently, a resonance with delay and noise. This is what we believe to be new. We will analytically discuss this phenomenon in more detail in the following sections.

To summarize this section, we conclude the above discussions and found new phenomena in Table 1.

Table 1. Summary of discussions in Section 2.

No correlation between $\mathcal{S}(t)$ and $\eta(t)$	No delay	General case
$F \approx 0$ and $\langle \xi\eta \rangle \approx 0$	$\tau_1 = 0, \tau_2 = 0$	$F \neq 0, H \neq 0, \langle \xi\eta \rangle \neq 0,$ $\tau_1 \neq 0, \tau_2 \neq 0$
1) Power spectra for S and X are given in Eq. (4). 2) The NAR (5) is justified. 3) The $\mathcal{S}(t)$ only has a single exponential relaxation time determined by Eq. (1a) and its spectrum is expressed by a typical pure noise spectrum like the Lorentzian form given in Eq. (4a).	1) Power spectra for S and X are given in Eq. (6). 2) The NAR (5) is broken down and a modular description of biological motifs is impeded. 3) Biological motifs can be quantified accurately if the correlated subnetworks are regrouped into independent modules.	1) Power spectra for S and X are given in Eq. (3). 2) Critical bifurcation points τ_c exist (determined by Eq. (7) and discussed in Appendix A) and Hopf bifurcation can be expected. 3) Delay-induced stochastic resonance appears at τ_c.

In order to make the above discussions more transparent, in the following sections, we will exploit the above analytical results of the power spectra to two realistic biological networks in gene regulation, in which time delay plays an important role.

3. Gene transcription and translation

The reactions of gene transcription and translation are very complex, and are essentially stochastic processes. Transcription combines the process of RNA guided by DNA, and contains three main steps: transcription initiation, elongation, and termination of transcription.[42−44] Transcription initiation is the main step,[44] where the cell regulates what kinds of proteins and what amounts of them should be produced. An introduction of time delay into transcription is needed to take account of the initiation and elongation. Translation occurs in the ribosome which is composed of rRNA and several kinds of proteins, and connects all kinds of RNA in the cells and some dozens of protein factors. Then the hereditary message stored in the DNA is translated into the protein through the mRNA.[42] The accuracy of translation requires a time delay whenever a new amino acid is added to a growing polypeptide chain.[44] This time delay is more obviously compared with the other reaction time, and it should be taken into account in modeling the process.

The direct autorepression of a gene by its own product is able to generate oscillation, whose period is determined by the delays of gene transcription and translation. To clearly analyse the delay effects on the stochasticity of gene transcription and translation, let us consider the widely studied model of cell-autonomous oscillations in the zebrafish gener-

ated by *her1* and/or *her7*, which was first proposed by Lewis:[23,45]

$$P(t) \xrightarrow{E} \phi(t), \tag{8a}$$
$$M(t) \xrightarrow{A} \phi(t), \tag{8b}$$
$$\phi(t) \xrightarrow{f(P(t))} M(t+\tau_M), \tag{8c}$$
$$M(t) \xrightarrow{H} P(t+\tau_P). \tag{8d}$$

Here $M(t)$ represents the number of mRNA molecules in the cell over time, and $P(t)$ represents the corresponding protein molecule number. In reactions (8), $P(t) \xrightarrow{E} \phi(t)$ is a decay channel for the intermediate protein, $M(t) \xrightarrow{A} \phi(t)$ is for the degradation of mRNA, while the other two reactions represent the interreaction between the protein and mRNA with a certain time delay. H denotes a production rate of new protein molecules, E and A denote the decay rates of the protein and mRNA, respectively, τ_M represents the time between the initiation of transcription and the arrival of the mature mRNA molecule in the cytoplasm, τ_P stands for the time between the initiation of translation and the emergence of a bioactive protein molecule,[23] $f(P)$ is a Hill-type function[23,46] as

$$f(P) = \frac{k}{1+(P/P_0)^N}, \tag{9}$$

where k represents a strength of function $f(P)$ and corresponds to a number of mRNA molecules per diploid cell per minute. P_0 corresponds to a threshold number of the protein molecules and N is a Hill coefficient which determines the steepness of $f(P)$.

When the biochemical reactions occur in a well-stirred system, spatial information about individual molecules may be ignored.[47] Under this approximation, one may use the stochastic delayed differential equations to quantitatively study the stochastic processes in Eq. (8) in gene transcription and translation. A set of chemical Langevin equations is presented as follows:

$$\frac{\mathrm{d}M(t)}{\mathrm{d}t} = f(P(t-\tau_M)) - AM(t) + \xi(t), \tag{10a}$$
$$\frac{\mathrm{d}P(t)}{\mathrm{d}t} = HM(t-\tau_P) - EP(t) + \eta(t). \tag{10b}$$

Following Ref. [32], the stochastic terms $\xi(t)$ and $\eta(t)$ are expressed as

$$\eta(t) = -(EP(t))^{1/2}\Gamma_E(t) + (HM(t))^{1/2}\Gamma_H(t), \tag{11a}$$
$$\xi(t) = -(AM(t))^{1/2}\Gamma_A(t) + (f(P(t)))^{1/2}\Gamma_f(t), \tag{11b}$$

where $\Gamma_E(t)$, $\Gamma_H(t)$, $\Gamma_A(t)$, and $\Gamma_f(t)$ are altogether standard Gaussian white noise, and are independent of each other, i.e.,

$$\langle \Gamma_i(t)\Gamma_j(t')\rangle = \delta_{ij}, \quad \{i,j = E,H,A,f\}. \tag{12}$$

Therefore $\xi(t), \eta(t)$ are also Gaussian white noise, which have zero means and their correlations are

$$\left\langle \eta^2 \right\rangle = E\left\langle P\right\rangle + H\left\langle M\right\rangle, \tag{13a}$$
$$\left\langle \xi^2 \right\rangle = A\left\langle M\right\rangle + f(\langle P\rangle), \tag{13b}$$
$$\langle \eta\xi\rangle = 0. \tag{13c}$$

Here $\langle P\rangle$ and $\langle M\rangle$ are stationary solutions of Eq. (10) with $\tau_P = \tau_M = 0$, which satisfy the relations

$$\langle M\rangle = \frac{E}{H}\langle P\rangle, \quad \langle P\rangle = \frac{H}{AE} f(\langle P\rangle).$$

Thus the strength of fluctuations is determined by the chemical reactions. Note that $\eta(t)$ and $\xi(t)$ are all intrinsic noise in a case that the protein and mRNA are treated as one system. When one regards only the protein as the interested system, $\eta(t)$ is the intrinsic noise while $\xi(t)$ is treated as the extrinsic noise, since it brings the external fluctuations to the system of interest.

Let $p(t) = P(t) - \langle P\rangle$ and $m(t) = M(t) - \langle M\rangle$. With the aid of Taylor expansion, equation (10) can be written as

$$\frac{\mathrm{d}m(t)}{\mathrm{d}t} = -Am(t) + f'p(t-\tau_M) + \frac{f''}{2}p^2(t-\tau_M) + \cdots + \xi(t), \tag{14a}$$
$$\frac{\mathrm{d}p(t)}{\mathrm{d}t} = Hm(t-\tau_P) - Ep(t) + \eta(t), \tag{14b}$$

where

$$f' = \frac{\mathrm{d}f(P)}{\mathrm{d}P}\Big|_{P=\langle P\rangle} = -\frac{NkP_0^N(\langle P\rangle)^{N-1}}{(P_0^N + (\langle P\rangle)^N)^2}, \tag{15a}$$
$$f'' = \frac{\mathrm{d}^2 f(P)}{\mathrm{d}P^2}\Big|_{P=\langle P\rangle} = \frac{NkP_0^N((N+1)(\langle P\rangle)^N - (N-1)P_0^N)}{(P_0^N + (\langle P\rangle)^N)^3}. \tag{15b}$$

By virtue of the first-order approximation, where $p(t-\tau)$ in Eq. (14a) is kept up to first order, equation (14) is reduced to

$$\frac{\mathrm{d}m(t)}{\mathrm{d}t} = f'p(t-\tau_M) - Am(t) + \xi(t), \quad (16a)$$

$$\frac{\mathrm{d}p(t)}{\mathrm{d}t} = Hm(t-\tau_P) - Ep(t) + \eta(t), \quad (16b)$$

which have the same form as those in Eq. (1) discussed in Section 2. Exploiting Eq. (3), one may easily and conveniently discuss the spectrum of $S_p(\omega)$ and $S_m(\omega)$.

According to our previous paper,[22] the basic properties of $p(t)$ and $m(t)$ satisfying the chemical Langevin equation (16), such as local stability of the stationary solution and nature of bifurcation, are known to be mainly determined by the linear part. The nonlinear terms play the role of determining the direction and stability of bifurcated periodic solutions. Since we are mainly interested in the properties of $p(t)$ and $m(t)$, in this paper, the first-order approximation is a reasonable one.

To study the influence of noise, we begin by investigating a corresponding deterministic system. For this aim, let us first write down a set of such deterministic equations which correspond to Eq. (10), and examine a characteristic property of their solutions,

$$\frac{\mathrm{d}M(t)}{\mathrm{d}t} = f(P(t-\tau_M)) - AM(t), \quad (17a)$$

$$\frac{\mathrm{d}P(t)}{\mathrm{d}t} = HM(t-\tau_P) - EP(t). \quad (17b)$$

Coupled differential equations in Eqs. (17) are numerically solved with the fourth-order Rugge–Kutta method. Following Ref. [23], we choose parameters as $H = 4.5$, $E = A = 0.23$. Those in the Hill-type function $f(P)$ are $k = 33$, $P_0 = 40$, and $N = 2$. The transcriptional and translational delay times are set to be $\tau_M = 12$ min and $\tau_P = 2.8$ min, respectively.

Figure 1 shows time evolutions of concentrations for mRNA and protein obtained from Eq. (17), respectively. When there are no time delays, the concentrations of mRNA and protein molecules tend to converge to their steady value in a short time (around several minutes). However, the time delays in transcription and translation can induce sustained oscillations for mRNA and protein molecule concentrations (delay-induced oscillations). Based on linear stability analysis discussed in Appendix A, there occurs a Hope bifurcation when one sets $\tau = \tau_M + \tau_P$ as a bifurcation parameter. With the aid of Eq. (A9), one may obtain the first three critical values of τ as $\tau_{c1} = 7.54$, $\tau_{c2} = 36.6$, and $\tau_{c3} = 65.6$. When τ is shorter than the critical value (τ_{c1}), the mRNA and protein concentrations tend to converge toward their steady value. Once τ starts to change, and becomes larger than τ_{c1}, a Hopf bifurcation will occur and the concentrations will oscillate in a limit cycle. Using the centre manifold theorem and the normal form theory as described in our previous paper,[22] it is easily shown that oscillations of the concentrations are locally stable.

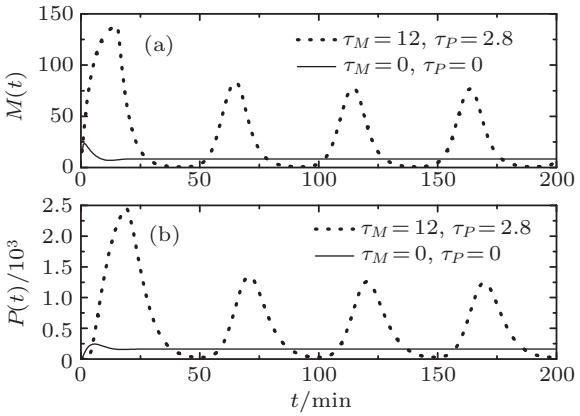


Fig. 1. Time evolution of concentrations for mRNA and protein obtained with deterministic equations (17). Parameters are chosen as $H = 4.5$, $E = 0.23$, $A = 0.23$, $k = 33$, $P_0 = 40$, $N = 2$, $\tau_M = 12$ min, and $\tau_P = 2.8$ min. The abscissa t is in units of minutes.

Here it should be noted that, as discussed in Section 2, the correlation between $m(t)$ and $\eta(t)$ results from two distinct origins. One is the feedback mechanism and the other the correlation $\langle \xi\eta \rangle$. Since the reactions of gene transcription and translation under discussion are characterized by Eq. (8) with condition (13c), one may analyse the pure feedback mechanism of the effects coming from time delay on the reaction. Note that the feedback mechanism discussed here is negative, because the relation $f' < 0$ holds, as shown in Eq. (15a).

When we consider a number of mRNA molecules as an input signal in the reaction described by Eq. (8), as discussed in Section 2, NAR is justified, provided that there are no correlations between $m(t)$ and the noise $\eta(t)$ (i.e., $k = 0$). The spectral functions $S_m(\omega)$ and $S_p(\omega)$ in terms of $\langle \eta^2 \rangle$ and $\langle \xi^2 \rangle$ are given in Eq. (4), and their spectra are centred at $\omega = 0$ and distributed in the low-frequency region. Setting those values of $S_m(\omega)$ and $S_p(\omega)$ as noise background, we show $S_m(\omega)$ and $S_p(\omega)$ for various strengths k of $f(P)$

in Fig. 2.

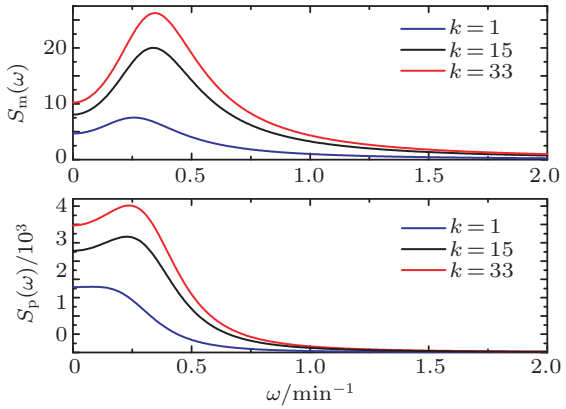


Fig. 2. (colour online) Effect of the feedback mechanism on power spectra $S_m(\omega)$ and $S_p(\omega)$ calculated with Eq. (3) for $k = 1$, 15, 33. Delay times τ_P and τ_M are set as zero. The other parameters are the same as those in Fig. 1. The abscissa ω is in units of minutes^{-1}.

As is easily seen from Fig. 2, the negative feedback mechanism strongly enhances the spectra $S_m(\omega)$ and $S_p(\omega)$ especially in their high-frequency region, and moves their peaks toward higher frequency. It is also understood from Fig. 2 that, for each curve, there are three points satisfying $\mathrm{d}S_m(\omega)/\mathrm{d}\omega = 0$ or $\mathrm{d}S_p(\omega)/\mathrm{d}\omega = 0$, that is, $\omega = 0$, $\omega = \omega_p(\omega_m)$, and $\omega \to \infty$. Within these three points, $\omega = 0$ and $\omega \to \infty$ are normal for a stochastic spectrum. The peak at $\omega = \omega_p$ (ω_m) represents the effect of the feedback mechanism. When $k \to 0$, this peak will tend to $\omega \to 0$ and finally coincide with the peak at $\omega = 0$. When k increases, the height of the peak increases and its centre moves toward higher-frequency region. This could be advantageous, because high-frequency fluctuations are usually filtered more effectively by the network downstream.[2]

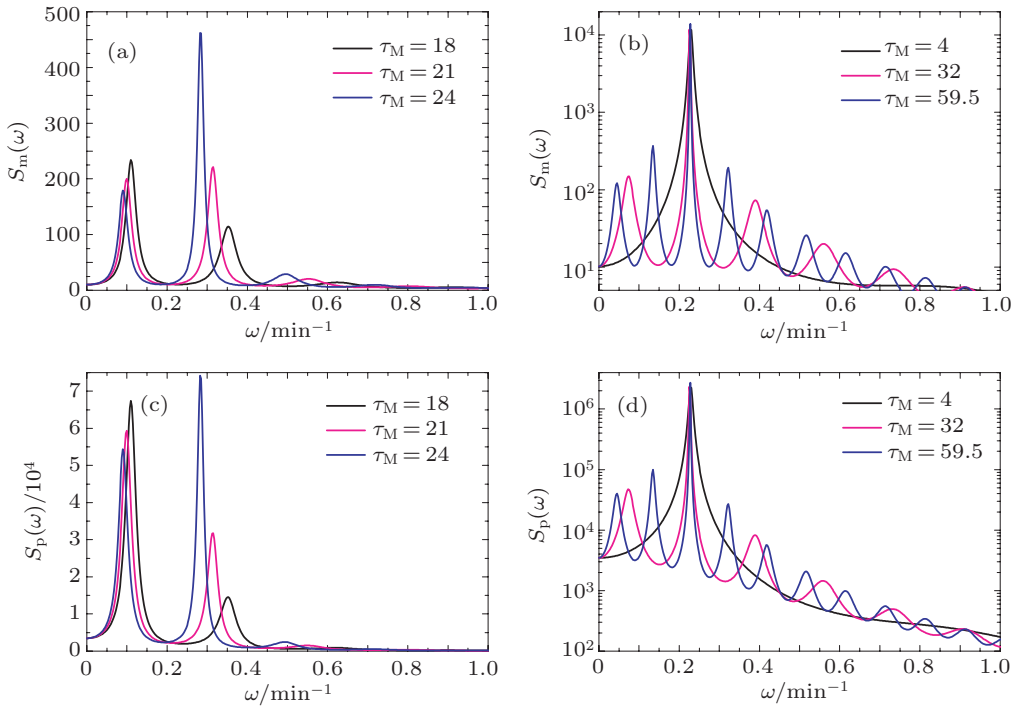


Fig. 3. (colour on line) Power spectra of mRNA and protein calculated with Eq. (3) for various τ. The delay time causes oscillation on the frequency domain. Panels (a) and (c) show the time delay effects between τ_{c1} and τ_{c2}. Panels (b) and (d) show the time delay effects near τ_{c1}, τ_{c2}, and τ_{c3}. Parameters are the same as those in Fig. 1.

Let us discuss the effects of time delays on the spectra $S_m(\omega)$ and $S_p(\omega)$ which are shown in Fig. 3. Correspondingly, several sample trajectories of concentration for mRNA obtained from Eq. (16) are shown in Fig. 4. As is discussed in Appendix A, only the sum of τ_P and τ_M affects the nature of the stationary solutions of Eq. (7). Thus, for the sake of simplicity and without loss of generality, we fix the time delay τ_P as 2.8 min and focus on τ_M. From Figs. 3(b) and 3(d), one may see that there is only a single high and wide peak both for $S_m(\omega)$ and $S_p(\omega)$ in the case with $\tau < \tau_{c1}$, (say, $\tau_M = 4$ min, $\tau = 6.8$ min). As τ reaches τ_{c1}, the peak becomes higher and narrower. When τ takes much larger values satisfying $\tau > \tau_{c1}$, there appear two large peaks accompanied with several small peaks as shown in Figs. 3(a) and 3(c). As

τ increases, the first peak tends to move toward the low-frequency region, and becomes shorter and narrower (hereafter, the peaks are numbered from lower to higher frequency). Meanwhile, the second peak goes toward the higher-frequency region, and becomes higher and narrower. As τ takes much larger values, the third, the fourth, and so on, will become the highest peak.

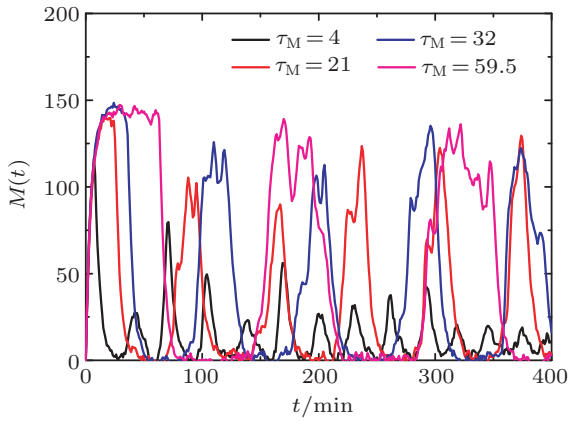


Fig. 4. (colour online) Samples of time evolution of concentration for mRNA obtained from Eq. (16). Parameters are the same as those in Fig. 1.

Figure 5 shows the frequency of the first three peaks in the spectrum $S_m(\omega)$. All of these move toward the lower-frequency region as τ increases. When the total delay time reaches the critical value, i.e., τ_{c1}, τ_{c2}, and τ_{c3}, the spectrum takes infinity at the critical frequency (ω_c). This phenomenon indicates coherent correlation between $m(t)$ and $p(t)$. Namely, the noise propagates transparently through the network. It is very interesting to note that the centre of the highest peak for the cases of $\tau \approx \tau_{c1}$, $\tau \approx \tau_{c2}$, and $\tau \approx \tau_{c3}$ is located in almost the same frequency region. This coincidence occurs, because ω_c corresponding to τ_{c1}, τ_{c2}, and τ_{c3} satisfies the same condition as those given by Eqs. (A6) and (A7).

From the above discussion, one may conclude that (a) the correlation between $m(t)$ and $\eta(t)$ violates NAR; (b) the delay in gene transcription and translation produces multiple peaks in the power spectrum; when the delay time τ_M becomes longer, the more peaks appear; (c) accompanied by intrinsic and extrinsic noise, the delay induces stochastic resonance, which is related to the loss of stability in the nonlinear dynamical system (8), and to the occurrence of Hopf bifurcation in the solutions of the corresponding deterministic equations (17).

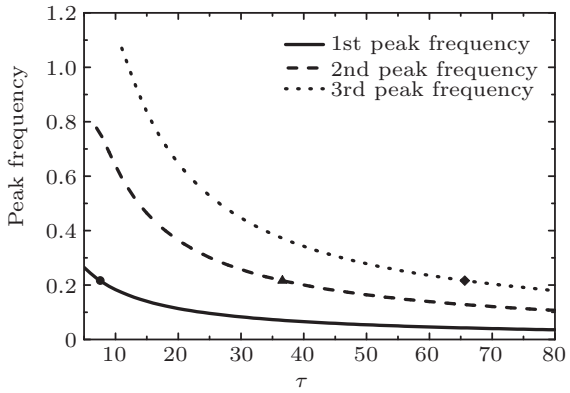


Fig. 5. Peak frequencies in $S_M(\omega)$ with increasing $\tau = \tau_M + \tau_P$. The solid line represents the frequency of the first peak, the dashed line that of the second peak, and the dotted line that of the third peak. Peaks are numbered from lower to higher frequencies as shown in Fig. 3. The circle stands for $\tau_{c1} = 7.54$, triangle for $\tau_{c2} = 36.6$, and diamond for $\tau_{c3} = 65.6$. These critical delay time corresponds to the same critical frequency ($\omega_c = 0.216$), at which the spectra become infinity. Parameters are chosen as the same as those in Fig. 1.

Generally speaking, the power spectrum gives us important information on frequency, and provides us with a new approach to estimate the oscillation period of the concentration. The oscillation period obtained in the previous work[48] was based on an expansion near the Hopf bifurcation, and it becomes invalid in a region far from the bifurcation point. In our understanding, the oscillation period should be determined by the time delay in a course of transcription and translation, and correspond to the lowest-frequency peak, which is depicted in Fig. 3. With the aid of an analysis on the power spectrum, one may obtain the frequency $\omega_1(\tau)$ of the lowest-frequency peak, and calculate the corresponding oscillation period $T_1(\tau)$ by $T_1(\tau) = 2\pi/\omega_1(\tau)$. The resultant period as a function of time delay τ is shown by a solid line in Fig. 6. It is clearly seen that the oscillation period is a linear function of τ.

In order to confirm the above results, we also numerically solve the deterministic equations (17) with the fourth-order Rugge–Kutta method and obtain a corresponding oscillation period $T_2(\tau)$ of $M(t)$ and $P(t)$ for various τ, which are shown by a dotted line in Fig. 6. From this figure, it is seen that the resultant period approximately shows a linear relation with respect to τ except in a small τ region. It is very interesting to mention that these two lines come together at a point which is defined through $T_c(\tau_{c1}) = 2\pi/\omega_c$, where ω_c means a critical frequency of Hopf bifurcation determined by Eq. (A7). At this point, it should

be noted that $T_c(\tau_{c1})$ is consistent with the result obtained by Ref. [48].

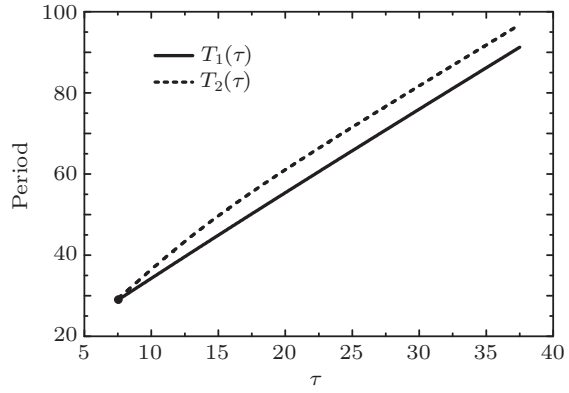


Fig. 6. Oscillation periods of mRNA and protein against time delay τ. The circle represents the Hopf bifurcation point ($\tau_c = 7.54$). The dashed line is obtained from numerical solutions of deterministic equations (17). The solid line is calculated via $2\pi/\omega_1$, where ω_1 is a frequency of the first peak in $S_m(\omega)$. Parameters are chosen as $H = 4.5$, $E = 0.23$, $A = 0.23$, $k = 33$, $\tau_M = 12$, $\tau_P = 2.8$.

We are now at a position to consider the effects of cross-correlation between the intrinsic and extrinsic noise on the power spectra of mRNA and protein, which are shown in Figs. 7(a) and 7(b). Here it should be noted that strictly, according to Gillespie's chemical Langevin method,[32,33] the stochastic terms $\xi(t)$ and $\eta(t)$ are described by Eqs. (11)–(13). However, in order to examine the effects of noise on the power spectrum, we formally define $\langle\xi^2\rangle = D_1^2, \langle\eta^2\rangle = D_2^2, \langle\xi\eta\rangle = \lambda D_1 D_2$ instead of definition in Eq. (13). The D_1, D_2 are strengths of the intrinsic and extrinsic noise, respectively. λ is the correlation intensity. Note that the weak noise approximation is applied in this case. The numerical results

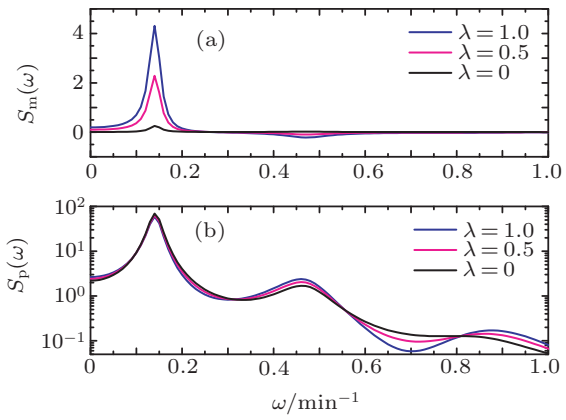


Fig. 7. (colour online) Power spectra of (a) mRNA and (b) protein. Parameters are chosen as $H = 4.5$, $E = 0.23$, $A = 0.23$, $k = 33$, $\tau_M = 12$, $\tau_P = 2.8$, $D_1 = 0.1$, $D_2 = 0.05$.

in Fig. 7 show that the correlations between the intrinsic and extrinsic noise enhance the oscillations of spectrum of mRNA $S_m(\omega)$ as is shown in Fig. 7(a). Namely, it changes the height of the peak, but does not influence the peak frequency. Meanwhile, it dampens the oscillation of the spectrum of the protein $S_p(\omega)$ in Fig. 7(b), especially at the frequency of the main peak.

4. The post-translational modification

A post-translational modification process has been known to be necessary for making functional protein molecules,[2,36,47,49] and to be generally an important final stage in producing active species.[50] Typical examples[36,49,51] include acetylation, glycosylation, and phosphorylation of amino acid residues. Modification reactions are encountered both in eukaryotes and prokaryotes.[36]

Normally, the post-translational modification of matured protein consists of three steps: folding, cyclization, and oxidation.[47] Let us consider the following model of post-translational modification[2,36,47] given by

$$\phi(t) \xrightarrow{B} nS(t), \tag{18a}$$

$$S(t) \xrightarrow{A} \phi(t), \tag{18b}$$

$$S(t) \xrightarrow{C} X(t+\tau), \tag{18c}$$

$$X(t) \xrightarrow{E} \phi(t). \tag{18d}$$

Here A, B, C, and E are reaction constants, and S represents an initial protein. A decay channel $S(t) \xrightarrow{A} \phi(t)$ for an intermediate protein is retained to take account (for instance) of dilution effects coming from cell growth. The $\phi(t) \xrightarrow{B} nS(t)$ is the production reaction of S, where n represents the protein number being produced instantaneously. Through the modification reaction $S(t) \xrightarrow{C} X(t+\tau)$, one obtains the final product protein X. This happens because the modification reaction introduces a time delay before each protein is converted into the active species. The $X(t) \xrightarrow{E} \phi(t)$ is the degradation reaction of X. Based on the same considerations as those used in modeling the reaction of gene transcription and translation in Section 3, one may describe the post-translational modification processes in Eq. (18) by introducing a set of chemical Langevin equations given as follows:[47]

$$\frac{\mathrm{d}S(t)}{\mathrm{d}t} = -(C+A)S(t) + nB + \xi(t), \tag{19a}$$

$$\frac{\mathrm{d}X(t)}{\mathrm{d}t} = CS(t-\tau) - EX(t) + \eta(t). \quad (19b)$$

Similar to Eq. (11) and following Ref. [32], we express the intrinsic noise $\xi(t)$ and extrinsic noise $\eta(t)$ as

$$\xi(t) = n\sqrt{B}\Gamma_B(t) - \sqrt{CS}\Gamma_C(t) - \sqrt{AS}\Gamma_A(t), \quad (20a)$$
$$\eta(t) = \sqrt{CS}\Gamma_C(t) - \sqrt{EX}\Gamma_E(t), \quad (20b)$$

where $\Gamma_A(t)$, $\Gamma_B(t)$, $\Gamma_C(t)$, $\Gamma_E(t)$ are independent standard Gaussian white noise. Thus, $\xi(t)$, $\eta(t)$ are also expressed by Gaussian white noise, and their correlations are given by

$$\langle \xi^2 \rangle = (C+A)\langle S \rangle + n^2 B, \quad (21a)$$
$$\langle \eta^2 \rangle = E\langle X \rangle + C\langle S \rangle, \quad (21b)$$
$$\langle \xi\eta \rangle = -C\langle S \rangle. \quad (21c)$$

Here $\langle S \rangle$ and $\langle X \rangle$ are stationary solutions of such deterministic equations which correspond to Eqs. (19), and are given as follows:

$$\langle S \rangle = nB/(C+A), \quad \langle X \rangle = C/E\langle S \rangle.$$

In the same way as we discussed in Section 3, let us first examine a set of deterministic equations given by

$$\frac{\mathrm{d}S(t)}{\mathrm{d}t} = -(C+A)S(t) + nB, \quad (22a)$$
$$\frac{\mathrm{d}X(t)}{\mathrm{d}t} = CS(t-\tau) - EX(t), \quad (22b)$$

which correspond to Eqs. (19). Equations (22) are analytically solved as,

$$S(t) = (S(0) - \frac{nB}{A+C})\,\mathrm{e}^{-(A+C)t} + \frac{nB}{A+C}, \quad (23a)$$
$$X(t) = (X(0) - \frac{K_1}{E-(A+C)} - \frac{K_2}{E})\,\mathrm{e}^{-Et} + \frac{K_1}{E-(A+C)}\,\mathrm{e}^{-(A+C)t} + \frac{K_2}{E}, \quad (23b)$$

where

$$K_1 = C\left(S(0) - \frac{nB}{A+C}\right)\mathrm{e}^{(A+C)\tau}, \quad K_2 = \frac{nBC}{A+C},$$

and $S(0)$ and $X(0)$ are initial values of $S(t)$ and $X(t)$.

It can be seen from Eqs. (23) that the following relations hold:

$$S(t \to +\infty) \to \frac{nB}{A+C} = \langle S \rangle,$$
$$X(t \to +\infty) \to \frac{K_2}{E} = \langle X \rangle.$$

A system organized by the deterministic equations in Eqs. (22) always tends to reach toward a stable state independent of the choice of parameters, and is not expected to show the Hopf bifurcation.

Introducing $s(t) = S(t) - \langle S \rangle$ and $x(t) = X(t) - \langle X \rangle$, from Eqs. (19), one obtains

$$\frac{\mathrm{d}s(t)}{\mathrm{d}t} = -(C+A)s(t) + \xi(t), \quad (24a)$$
$$\frac{\mathrm{d}x(t)}{\mathrm{d}t} = Cs(t-\tau) - Ex(t) + \eta(t). \quad (24b)$$

With the aid of Eqs. (24), the power spectra of $s(t)$ and $x(t)$ are expressed as

$$S_s(\omega) = \frac{\langle \xi^2 \rangle}{(A+C)^2 + \omega^2}, \quad (25a)$$
$$S_x(\omega) = \frac{C^2\langle \xi^2 \rangle + \left((C+A)^2 + \omega^2\right)\langle \eta^2 \rangle}{\left(E(C+A) + \omega^2\right)^2 + \omega^2\left(C+A+E\right)^2} + \frac{2\left((C+A)C\cos(\omega\tau) - C\omega\sin(\omega\tau)\right)\langle \xi\eta \rangle}{\left(E(C+A) + \omega^2\right)^2 + \omega^2\left(C+A+E\right)^2}. \quad (25b)$$

In marked contrast to the case with the gene transcription and translation processes in Eq. (8), a feedback process does not contribute to protein S in Eq. (19a) for the case with post-translational modification process in Eqs. (18), although there exists the correlation $\langle \xi\eta \rangle \neq 0$ in Eq. (21c). Therefore, the power spectrum $S_s(\omega)$ in Eq. (25a) shows a typical noise spectrum. The above discussion indicates that the effects of time delay are clearly studied by exploring the second term on the right-hand of Eq. (25b) with $\langle \xi\eta \rangle \neq 0$.

Now let us study a property of the solutions of the set of stochastic equations in Eqs. (19). As mentioned in Section 2 and discussed in Appendix A, the presence of the feedback mechanisms is a necessary condition for an occurrence of delay-induced resonance, because it appears at the critical time delay value where Hopf bifurcation occurs. Therefore, in the model of post-translational modification, Eqs. (18), the delay-induced resonance is not expected.

Since the system has only one stable state defined by $\langle S \rangle$ and $\langle X \rangle$, the Wiener–Khintchine Theorem might be applied. In this case, one may apply the second-order stochastic Rugge–Kutta method[52] to solve Eqs. (24) numerically and obtain the power spectrum through Fourier transformation of the autocorrelation functions given by

$$K_s(T) = \langle s(t)s(t+T) \rangle, \quad (26a)$$
$$K_x(T) = \langle x(t)x(t+T) \rangle, \quad (26b)$$

where $\langle s(t)\rangle = \langle x(t)\rangle = 0$ has been used. Our numerical results show that the power spectra obtained by the present method are in good agreement with those obtained by Eqs. (25), as shown in Figs. 8 and 9.

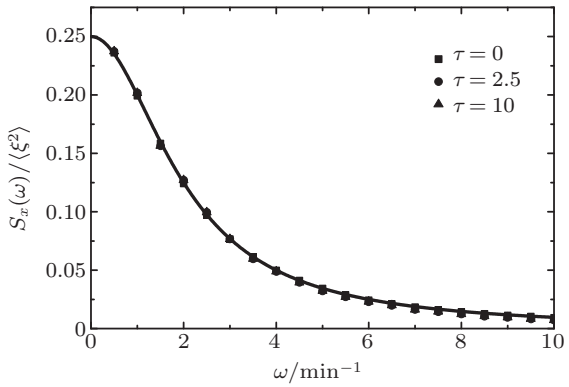


Fig. 8. Power spectrum of the input signal S scaled by $\langle\xi^2\rangle$. The solid line represents analytical results obtained with Eqs. (25). Square, circle, and triangle marks are the Fourier transformation of the auto-correlation functions obtained with Eqs. (24) for $\tau = 0, \tau = 2.5$, and $\tau = 10$, respectively. Parameters are chosen as $A = 1$, $C = 1$, $E = 4$, $n = 1$.[47,49]

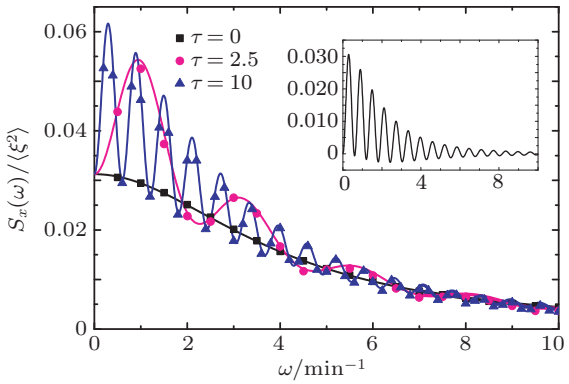


Fig. 9. (colour online) Power spectra of the output signal X scaled by $\langle\xi^2\rangle$. The solid line represents analytical results obtained with Eqs. (25). Square, circle, and triangle marks are the Fourier transformation of the auto-correlation function obtained with Eqs. (25) for $\tau = 0$, $\tau = 2.5$, and $\tau = 10$, respectively. The inner figure depicts $S_x(\omega)\,|_{\tau=10} - S_x(\omega)|_{\tau=0}$. Parameters are the same as those in Fig. 8.

Comparing Figs. 8 and 9, one may clearly see that the delay in the post-translation modification reaction induces an oscillation property in $S_x(\omega)$, whereas it will not cause any change in $S_s(\omega)$. From Fig. 9, one may understand not only that an oscillation period of $S_x(\omega)$ depends on the delay time τ, but also that a number of peaks increase and their widths become narrower, as the time delay increases. It is also recognized that the frequencies of the peaks move towards the lower-frequency direction as a whole, when the time delay increases. As shown in Figs. 8 and 9, the critical phenomenon and stochastic resonance are not observed in either $S_x(\omega)$ or $S_s(\omega)$, which is different from the gene transcription and translation cases. In order to show that the delay time dependence of $S_x(\omega)$, $S_x(\omega)\,|_{\tau=10} - S_x(\omega)|_{\tau=0}$ is depicted in the inner figure of Fig. 9, which indicates the property of damped oscillation.

Figure 10 shows the effects of cross-correlation $\langle\xi\eta\rangle$ on the power spectrum $S_x(\omega)$, which helps us to understand the origins of the oscillation of the power spectrum of active protein molecules. It is obvious that if either the correlation $\langle\xi\eta\rangle$ or the delay time τ is equal to zero, there will be no oscillation in the power spectrum $S_x(\omega)$. Therefore, one may understand that the delay time together with the correlation between the intrinsic and extrinsic noise are the reasons for the generation of such oscillations in the spectrum $S_x(\omega)$.

The inset of Fig. 10 shows the quantity

$$S_x(\omega)\,\big|_{\langle\xi\eta\rangle=-C\langle S\rangle,\tau=10} - S_x(\omega)\big|_{\langle\xi\eta\rangle=0,\tau=10}\,.$$

It is very interesting to note that this quantity behaves like a damped oscillation. The origin of this damping phenomenon in Figs. 9 and 10 is the denominator of the second term in Eq. (25b), i.e., the deterministic part of Eqs. (19) is responsible for damping the oscillation of the spectrum. The post-translation modification connects a series of reactions, and the cross-correlation takes an important role during noise transduction from one step to another. For example, in the cycling course of the matured protein, the decay of the doubled protein will influence the formation of the circled protein. And in the oxidation course, the decay of the circled protein will influence the formation of the matured protein.[53]

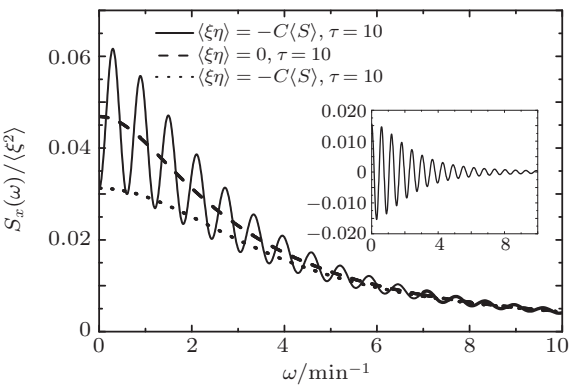


Fig. 10. Effects of cross correlation on $S_x(\omega)$. The inset depicts $S_x(\omega)\,\big|_{\langle\xi\eta\rangle=-C\langle S\rangle,\tau=10} - S_x(\omega)\big|_{\langle\xi\eta\rangle=0,\tau=10}$. Parameters are the same as those in Fig. 8.

From the above discussions, one can obtain the following conclusions:

(I) Even though the deterministic model only yields a steady state (no Hopf bifurcation), stochastic oscillation can occur when noise is considered. A similar situation is expected in intracellular calcium oscillation in a cell system.[54] Stochastic models can show spatial and temporal structures even with parameters that provide a non-oscillatory or non-excitable region for the corresponding deterministic system.

(II) Delay and noise can induce the oscillation of the active protein molecule X, whereas the upstream signal molecule S remains in a non-oscillatory stochastic state. This might be meaningful in a description of network motifs. When the feedback from the active protein molecules to the upstream signal molecule is absent, special care should be taken with regard to the active protein molecule and its effect on the downstream molecule.

(III) From an experimental point of view, clarification of the damping mechanism responsible for spectrum oscillation is particularly important, because in general lower frequency is much more significant than higher frequency in biological systems.

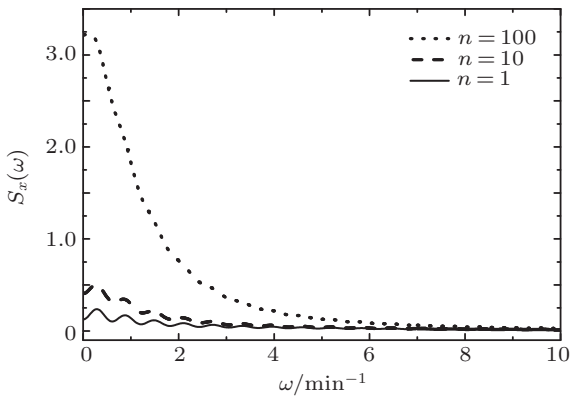


Fig. 11. Effect of n on $S_x(\omega)$. Large n conceals the oscillation in the power spectrum. Parameters are chosen as $A = 1$, $B = 5$, $C = 1$, $E = 4$, $\tau = 10$.

At the end of this section, we examine the influence of the production reaction in Eq. (18a) of S denoted by n on the features of the power spectrum, which is shown in Fig. 11. The protein is produced by translation of the mRNA, which is expressed as S in this model. When n is small, the oscillation of the power spectrum is obvious, and it disappears for very large n. This is caused by the fact that the oscillation in the spectrum comes from the cross-correlation. When n becomes large enough, the contribution of intrinsic noise becomes the dominant part of $S_x(\omega)$, and the contribution of the cross-correlation in comparison with the intrinsic part becomes trivial. In the case of very large n, the effects of time delay can be ignored. Thus the system is sensitive to the variation in the production rate n.

5. Summary

In this paper, we provide an analytical framework for systematically analysing the correlation between delay and noise through a generic feedback biological motif with time delays. Although the model is relatively simple, it maintains a high degree of relevance on biochemical systems and noise transmission processes.

We applied the analytical results on generic motifs into two well-studied realistic biological networks in gene regulation: gene transcription and translation, and post-translation modification of protein. Power spectra are discussed to illustrate the effects of intrinsic and extrinsic noise and time delays. It is shown that time delay can have a significant impact on dynamic behaviour of the system, and produce very rich physical phenomena in the dynamical solutions of the model equations.

We have clarified that the correlation between the intrinsic and extrinsic noise violates NAR and impedes a modular description of biological motifs. It should be noted that in general, NAR overestimates the contribution of noises. Violation of NAR means that the effect of delay and a negative feedback mechanism can significantly reduce the effect of noise and make biochemical network motifs more robust against biochemical noise.

We have also clarified, which we believe to be new, that there exists a resonant motion stimulated by delay incorporated with noise. This has very great biological significance from an experimental point of view, because stochastic oscillation is a very common phenomenon in biological systems.

This study may provide us with some general understanding on delay-induced stochastic oscillations in biochemical network motifs and ought to be applicable to more wide range of real biological systems where the negative and/or positive feedback dynamics, as well as the time delay, have the characteristic physical and biological background.

Appendix A: Linear stability analysis of Eq. (1)

The corresponding deterministic equations of Eq. (1) are

$$\frac{\mathrm{d}\mathcal{S}(t)}{\mathrm{d}t} = -A\mathcal{S}(t) + F\mathcal{X}(t-\tau_2),$$
$$\frac{\mathrm{d}\mathcal{X}(t)}{\mathrm{d}t} = H\mathcal{S}(t-\tau_1) - E\mathcal{X}(t), \tag{A1}$$

whose characteristic equation reads

$$\lambda^2 + (A+E)\lambda + AE - FHe^{-\lambda\tau} = 0, \tag{A2}$$

where $\tau = \tau_1 + \tau_2$. When $\tau = 0$, the solutions of Eq. (A2) can be expressed as,

$$\lambda_{1,2} = \frac{-(A+E) \pm \sqrt{(A+E)^2 - 4(AE-FH)}}{2}. \tag{A3}$$

It is obvious that $\lambda_{1,2}$ are real and negative when

$$0 \le 4(AE - FH) \le (A+E)^2. \tag{A4}$$

In this case, the solutions of Eq. (A1) are locally asymptotically stable. However, when $\tau > 0$, the nature of the stationary solutions of Eq. (A1) will become complex because the characteristic equation (A2) is a transcendental equation. The complex solution of λ, i.e., $\lambda = \mu + \mathrm{i}\,\omega$, should also be discussed.

Here we choose τ as the bifurcation parameter. After replacing λ with $\lambda = \mu + \mathrm{i}\,\omega$ in Eq. (A2) and separating its real and image parts, we can obtain

$$\mu^2 - \omega^2 + (A+E)\mu + AE - FH\,\mathrm{e}^{-\mu\tau}\cos\omega\tau = 0, \tag{A5a}$$

$$2\mu\omega + (A+E)\omega - FH\,\mathrm{e}^{-\mu\tau}\sin\omega\tau = 0. \tag{A5b}$$

In the critical bifurcation point, $\tau = \tau_\mathrm{c}$, $\mu = 0$, and $\lambda = \mathrm{i}\,\omega_\mathrm{c}$. Equation (A5) becomes

$$-\omega_\mathrm{c}^2 + AE - FH\cos(\omega_\mathrm{c}\tau_\mathrm{c}) = 0, \tag{A6a}$$

$$\omega_\mathrm{c}(A+E) + FH\sin(\omega_\mathrm{c}\tau_\mathrm{c}) = 0. \tag{A6b}$$

And the solution of ω_c reads

$$\omega_\mathrm{c} = \sqrt{\frac{-(A^2+E^2) + \sqrt{(A^2+E^2)^2 - S_\mathrm{cr}}}{2}}, \tag{A7}$$

where

$$S_\mathrm{cr} = 4(A^2E^2 - F^2H^2) < 0 \tag{A8}$$

is the condition of real solution of ω_c. Then τ_c can be obtained with Eq. (A6). In this case, when τ passes through τ_c, a Hopf bifurcation occurs at the stationary solution of Eq. (A1).

Case 1 Gene transcription and translation

When we assume $A^2E^2 - F^2H^2 < 0$ and consider the fact that

$$\sin(\omega_\mathrm{c}\tau_\mathrm{c}) = \frac{-\omega_\mathrm{c}(A+E)}{FH} > 0,$$
$$\cos(\omega_\mathrm{c}\tau_\mathrm{c}) = \frac{-\omega_\mathrm{c}^2 + AE}{FH} < 0,$$

we have

$$\tau_{\mathrm{c},k} = \frac{1}{\omega_\mathrm{c}}\left\{(2k-1)\pi - \arcsin\left(\frac{-\omega_\mathrm{c}(A+E)}{FH}\right)\right\}, \tag{A9}$$

where $k = 1, 2, 3, \ldots$. Thus Hopf bifurcation can occur in this case.

Case 2 Post-translational modification

Since $F = 0$ in this motif, equation (A2) is reduced to

$$\lambda^2 + (A+E)\lambda + AE = 0. \tag{A10}$$

The two solutions of eigenvalue λ are $\lambda_1 = -A$ and $\lambda_2 = -E$. Because both λ_1 and λ_2 are negative, the system is thus always stable for all ranges of parameters. The time delay will not change the stability of the system and Hopf bifurcation cannot be expected in this case.

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