Frequency Domain Analysis of a Stochastic Biological Network Motif with Delay

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Abstract. In this paper, a set of delay stochastic differential equations, which involves the mechanisms of intrinsic and extrinsic noises, time delays and negative feedback, is proposed to describe the nonlinear dynamics within a general biological network motif. Frequency domain analysis method is exploited to study the interplays among such mechanisms.

Keywords: Intrinsic and extrinsic sources, negative feedback, transcriptional and translational time delay, frequency domain analysis.

1 Introduction

Intensive experimental studies have proved that noise plays an important role in gene regulation [1]. The firstly provided direct experimental evidence of the biochemical origin of phenotypic noise [2] has demonstrated that the level of phenotypic variation in an isogenic population can be regulated by genetic parameters. The outcome of Elowitz et al. (2002) [3] reveals that both intrinsic noise and extrinsic noise contribute substantially to overall variation. Transcription rate, regulatory dynamics, and genetic factors control the amplitude of noise. Blake et al. (2003) [4] demonstrate experimentally that, in eukaryotic gene expression, increased noise in the transcription of a regulatory protein leads to increased cell-cell variability in the target gene output, resulting in the prolonged bistable expression states. Through studying gene regulation at the single-cell level, Rosenfeld et al. (2005) [5] find that protein production rates fluctuate over a time scale of about one cell cycle, while intrinsic noise decays rapidly. In the same year, the result of Pedraza and Oudenaarden [6] has shown that noise in a gene is determined by its intrinsic fluctuations, transmitted noise from upstream genes, and global noise affecting all genes. Newman and co-workers [7] showed that classes of genes regulated by the same proteins have similar noise levels and that essential genes are often less noisy than inessential ones. Very recently,

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Zhu and Salahub [8] find that the most dominant noise source comes from promoter fluctuations. All the experimental works mentioned above highlight the importance of including stochastic effects in regulatory networks.

Noise arises in one of the two ways. Internal noise is inherent in the biochemical reactions. Its magnitude is proportional to the inverse of the system size, and its origin is often thermal. On the other hand, external noise originates in the random variation of one or more of the externally set control parameters. [9] Paulsson (2004)[10] reviewed these two kinds of noise from both mathematical and biological perspectives.

Systems with time delays are quite ubiquitous in nature. The experimental evidences [11,12] have shown that the role of time delays has come to light because the delays in the corresponding reactions are particularly long in comparison with other characteristic times of the system. For example, binding reactions and phosphorylation cost little waiting time for the next reaction, while transcription and translation involve so many sophisticated processes that the time lag should not be neglected. Hirata et al.(2002)[11] have shown that Hes1 protein oscillation is delayed by about 15 min relative to the Hes1 mRNA oscillation. This time delay may reflect the time required for protein degradation. Monk (2003)[12] notes that there is an average delay of around 10-20 min between the action of a transcription factor on the promoter of a gene and the appearance of the corresponding mature mRNA in the cytoplasm.

A model based on stochastic delay differential equations has the advantages of not only considering the intrinsic noise and extrinsic noise, but also not having to specify all the processes explicitly and their effect can be substituted for a time delay. Barrio et al.(2006)[13] compare previous continuous delay models with discrete stochastic delay models to explain oscillations in the numbers of Hes1 mRNA and Hes1 protein in mouse. They agree with the statement that discrete delay approach seems to give greater insight into the underlying cellular dynamics in terms of the system parameters. Tian et al.(2007)[14] have developed the delay chemical master equation for describing biological reactions. They find that for an oscillating system generated by time delays, noise can increase the robustness properties of the system to maintain the oscillating expression pattern.

Even numerous studies have been carried out as mentioned above, however, the delayed feedback control system combined with both intrinsic and extrinsic noise receives less attention and still remains further consistent study. The aim of this paper is to incorporate the effects of time delays and feedback into a general biological network motif. We study the interplays among such exponents by deriving the correlation function and power spectrum of the input and output signal. Numerical simulation is exploited for comparison with the analytical results.

This paper is organized as follows: In Sec.2,we propose a common biological network motif, which are quantified by a set of delay stochastic differential equations. In Sec.3, we analyze our model on frequency domain through analytical derivation. In Sec.4, we use numerical simulation to show the effect of delay, feedback and cross correlation. Last, summary and some physical discussions are presented in Sec.5.

2 A Stochastic Biological Network Motif with Delay

In recent years, the network motifs, which are the basic building blocks of networks, have been used to study complicated networks [15,16,17]. Shen-Orr and his coworkers find that much of the network is composed of repeated appearances of several highly significant motifs. Each network motif has a specific function in determining gene expression, such as generating temporal expression programs and governing the responses to fluctuating external signals [15].

We begin with a most common biological network motif, which is relative simple yet maintains a high degree of biological relevance [15,18]. Time delay is taken into account as a key point in protein degradation process, which represents essential time for gene transcription and translation. Meanwhile, stochastic behavior from both intrinsic and extrinsic sources is considered.

Our model is described by a set of chemical Langevin Equations,

$$\frac{d\mathcal{X}(t)}{dt} = A\mathcal{S}(t-\tau_1) - B\mathcal{X}(t) - C\mathcal{X}(t-\tau_2) + \eta_1(t), \tag{1}$$

$$\frac{d\mathcal{S}(t)}{dt} = k_{-1} - k_{-1}\mathcal{S}(t) - k_1\mathcal{S}(t)\mathcal{X}(t) + \eta_2(t) \tag{2}$$

where $\mathcal{S}$ represents an input signal, while $\mathcal{X}$ stands for the output. An example of this dynamics is the protein degradation [19]. B is non-delayed rates of the protein degradation, while A and C is the rate of the delayed production and degradation reaction separately. Here notes that $\mathcal{X}$ is regulated by the input signal $\mathcal{S}$ after time τ_1, and by itself with a time delay of τ_2. Moreover, the signal itself undergoes a negative feedback by the protein $\mathcal{X}$.

In Eqs. (1)-(2), $\eta_1(t)$ stands for intrinsic noise, which is related to low gene copy numbers; while $\eta_2(t)$ presents the extrinsic noise, which is attributable to a noisy cellular environment. Both of the intrinsic and extrinsic noise are Gaussian white noise,

$$< \eta_i(t) >= 0, < \eta_i(t)\eta_j(t') >=< \eta_i\eta_j > \delta(t-t'), \{i,j=1,2\}. \tag{3}$$

3 Frequency Domain Analysis

In biochemical networks, the noise in the output signal depends upon the noise in the biochemical reactions that constitute the network, the so-called intrinsic noise, and on the noise in the input signal, called extrinsic noise [3,10,20]. Zon et al. note that the noise properties of biochemical networks are most clearly elucidated via the power spectra of the time traces of the copy numbers of the components [21]. For complex networks with multiple noise sources and signal processing elements, direct analysis through the time domain solution becomes difficult or even obscures the intuitive connection between the calculated noise behavior and network elements. However, the power spectrum provided us an easy way for analyzing the noise in complex networks.

In order to analyze our model on the frequency domain, we first replace the $\mathcal{X}(t)$ and $\mathcal{S}(t)$ in Eqs. (1)-(2) by

$$\mathcal{X}(t) = \mathcal{X}^* + x(t), \mathcal{S}(t) = \mathcal{S}^* + s(t) \tag{4}$$

where $\mathcal{X}^*$ and $\mathcal{S}^*$ represent the stationary solution of the determinate equations of Eqs. (1)-(2) with $\tau_1 = \tau_2 = 0$, which can be expressed as

$$\mathcal{X}^* = \frac{\sqrt{1 + 4\epsilon A/B'} - 1}{2\epsilon}, \quad \mathcal{S}^* = \frac{B + C}{A}\mathcal{X}^* = \frac{1}{1 + \epsilon\mathcal{X}^*} \tag{5}$$

where $\epsilon = k_1/k_{-1}$ represents the strength of negative feedback mechanism. Then Eqs. (1)-(2) can be rewritten as

$$\frac{dx(t)}{dt} = As(t - \tau_1) - Bx(t) - Cx(t - \tau_2) + \eta_1(t) \tag{6}$$

$$\frac{ds(t)}{dt} = -Es(t) - Fx(t) - k_1 s(t)x(t) + \eta_2(t) \tag{7}$$

where $E = k_{-1} + k_1\mathcal{X}^*$ and $F = k_1\mathcal{S}^*$.

The Fourier transformations of Eqs. (1)-(2) take the form

$$i\omega x(\omega) = Ae^{-i\omega\tau_1}s(\omega) - Bx(\omega) - Ce^{-i\omega\tau_2}x(\omega) + \eta_1(\omega), \tag{8}$$

$$i\omega s(\omega) = -Es(\omega) - Fx(\omega) - \frac{k_1}{\sqrt{2\pi}}\int_{-\infty}^{\infty} s(\omega - \omega_0)x(\omega_0)d\omega_0 + \eta_2(\omega). \tag{9}$$

Since Eq. (9) is an integration equation, Eqs. (8)-(9) can be solved by interpolation method and truncated at a specific order. Under the approximations of weak noises and weak negative feedback mechanism, in this paper, the solutions of both $x(\omega)$ and $s(\omega)$ are retained up to the second order of $\eta_1(\omega)$ and $\eta_2(\omega)$. The validation of such approximations will be discussed further with our numerical simulation in Sec. 4. By defining the intermediate variables:

$$\begin{aligned}
&f_1(\omega) = i\omega + B + Ce^{-i\omega\tau_2}, \quad f_2(\omega) = Ae^{-i\omega\tau_1}, \quad f_3(\omega) = i\omega + E + F\frac{f_2(\omega)}{f_1(\omega)},\\
&g_1(\omega) = -\frac{F}{f_1(\omega)f_3(\omega)}, \quad g_2(\omega) = \frac{1}{f_3(\omega)}, \quad g_3(\omega) = -\frac{k_1}{\sqrt{2\pi}f_3(\omega)},\\
&J_1(\omega, \omega_0) = (\frac{Ff_2(\omega_0)}{f_1(\omega_0)f_3(\omega_0)} - 1)\frac{F}{f_1(\omega_0)f_1(\omega - \omega_0)f_3(\omega - \omega_0)},\\
&J_2(\omega, \omega_0) = -\frac{Ff_2(\omega_0)}{f_1(\omega_0)f_3(\omega_0)f_1(\omega - \omega_0)f_3(\omega - \omega_0)},\\
&J_3(\omega, \omega_0) = -(\frac{Ff_2(\omega_0)}{f_1(\omega_0)f_3(\omega_0)} - 1)\frac{1}{f_1(\omega_0)f_3(\omega - \omega_0)},\\
&J_4(\omega, \omega_0) = \frac{f_2(\omega_0)}{f_1(\omega_0)f_3(\omega_0)f_3(\omega - \omega_0)},\\
&I_k = \int_0^{\infty} J_k(0, \omega_0)d\omega_0, \quad \{k, m, n = 1, 2, 3, 4\},
\end{aligned} \tag{10}$$

$$I_{m,n}(\omega) = \int_{-\infty}^{\infty} J_m(\omega,\omega_0)J_n^*(\omega,\omega_0)d\omega_0,$$
$$L_{m,n}(\omega) = \int_{-\infty}^{\infty} J_m(\omega,\omega_0)J_n^*(\omega-\omega_0,\omega_0)d\omega_0.$$

The correlation functions of $x(\omega)$ and $s(\omega)$ can be obtained from Eqs. (8)-(9) and expressed as

$$\begin{aligned} S_s(\omega) =& < s(\omega)s^*(\omega') > \\ &= \alpha_1 < \eta_1^2 > +\alpha_2 < \eta_1\eta_2 > +\alpha_3 < \eta_2^2 > \\ &+\alpha_4(< \eta_1^2 >)^2 + \alpha_5(< \eta_2^2 >)^2 + \alpha_6(< \eta_1\eta_2 >)^2 \\ &+\alpha_7 < \eta_1^2 >< \eta_1\eta_2 > +\alpha_8 < \eta_1\eta_2 >< \eta_2^2 > \end{aligned} \tag{11}$$

$$\begin{aligned} S_x(\omega) =& < x(\omega)x^*(\omega') > \\ &= \beta_1 < \eta_1^2 > +\beta_2 < \eta_1\eta_2 > +\beta_3 < \eta_2^2 > \\ &+\beta_4(< \eta_1^2 >)^2 + \beta_5(< \eta_2^2 >)^2 + \beta_6(< \eta_1\eta_2 >)^2 \\ &+\beta_7 < \eta_1^2 >< \eta_1\eta_2 > +\beta_8 < \eta_1\eta_2 >< \eta_2^2 > . \end{aligned} \tag{12}$$

The parameters $\alpha_1, \beta_1, \alpha_2, \beta_2, \cdots, \alpha_8, \beta_8$ represent the contributions of $< \eta_1^2 >$, $< \eta_1\eta_2 >, \cdots, < \eta_1\eta_2 >< \eta_2^2 >$ to the correlation functions $S_s(\omega)$ and $S_x(\omega)$, respectively. With the aid of the intermediate variables defined in Eq. (11) and from Eqs. (8)-(9), those parameters can be expressed as

$$\alpha_1(\omega) = |g_1(\omega)|^2, \quad \alpha_2(\omega) = 2Re\left[g_1(\omega)g_2^*(\omega)\right], \quad \alpha_3(\omega) = |g_2(\omega)|^2,$$
$$\alpha_4(\omega) = 4\left|g_3(0)\right|^2 (I_1)^2\delta(\omega) + \left|g_3(\omega)\right|^2 (I_{1,1}(\omega) + L_{1,1}(\omega)),$$
$$\alpha_5(\omega) = 4\left|g_3(0)\right|^2 (I_4)^2\delta(\omega) + \left|g_3(\omega)\right|^2 (I_{4,4}(\omega) + L_{4,4}(\omega)),$$
$$\begin{aligned} \alpha_6(\omega) =& 4\left|g_3(0)\right|^2 \left[(I_2)^2 + (I_3)^2 + 2(I_1I_4 + I_2I_3)\right]\delta(\omega) \\ &+ \left|g_3(\omega)\right|^2 (I_{1,4}(\omega) + I_{4,1}(\omega) + I_{2,3}(\omega) + I_{3,2}(\omega) + I_{2,2}(\omega) + I_{3,3}(\omega) \\ &+L_{1,4}(\omega) + L_{4,1}(\omega) + L_{2,3}(\omega) + L_{3,2}(\omega) + L_{2,2}(\omega) + L_{3,3}(\omega)), \end{aligned}$$
$$\begin{aligned} \alpha_7(\omega) =& 8\left|g_3(0)\right|^2 (I_1I_2 + I_1I_3)\delta(\omega) + \left|g_3(\omega)\right|^2 (I_{1,2}(\omega) + I_{2,1}(\omega) + I_{1,3}(\omega) + I_{3,1}(\omega) \\ &+L_{1,2}(\omega) + L_{2,1}(\omega) + L_{1,3}(\omega) + L_{3,1}(\omega)), \end{aligned}$$
$$\begin{aligned} \alpha_8(\omega) =& 8\left|g_3(0)\right|^2 (I_2I_4 + I_3I_4)\delta(\omega) + \left|g_3(\omega)\right|^2 (I_{2,4}(\omega) + I_{4,2}(\omega) + I_{3,4}(\omega) + I_{4,3}(\omega) \\ &+L_{2,4}(\omega) + L_{4,2}(\omega) + L_{3,4}(\omega) + L_{4,3}(\omega)), \end{aligned}$$
$$\beta_1(\omega) = \left|\frac{f_2(\omega)}{f_1(\omega)}\right|^2 \alpha_1(\omega) + \frac{2Re[f_2(\omega)g_1(\omega)] + 1}{|f_1(\omega)|^2},$$
$$\beta_2(\omega) = \left|\frac{f_2(\omega)}{f_1(\omega)}\right|^2 \alpha_2(\omega) + \frac{2Re[f_2(\omega)g_2(\omega)]}{|f_1(\omega)|^2},$$
$$\beta_3(\omega) = \left|\frac{f_2(\omega)}{f_1(\omega)}\right|^2 \alpha_3(\omega), \quad \beta_4(\omega) = \left|\frac{f_2(\omega)}{f_1(\omega)}\right|^2 \alpha_4(\omega),$$

$$\beta_5(\omega) = \left|\frac{f_2(\omega)}{f_1(\omega)}\right|^2 \alpha_5(\omega), \quad \beta_6(\omega) = \left|\frac{f_2(\omega)}{f_1(\omega)}\right|^2 \alpha_6(\omega),$$
$$\beta_7(\omega) = \left|\frac{f_2(\omega)}{f_1(\omega)}\right|^2 \alpha_7(\omega), \quad \beta_8(\omega) = \left|\frac{f_2(\omega)}{f_1(\omega)}\right|^2 \alpha_8(\omega).$$

It is worthwhile to mention that a module, which consists of one component $\mathcal{X}$ and an input signal $\mathcal{S}$, has recently been discussed by Nicola and co-workers [20]. They explicitly described the detection of the signal by studying a set of coupled Langevin equations for the interacting species $\mathcal{S}$ and $\mathcal{X}$. It is very interesting that in absence of delays and feedback, which means $\tau_1 = \tau_2 = 0, \epsilon = 0$ in our model, the analytical results in Eqs. (11)-(12) can be reduced as

$$S_s(\omega) = \frac{F^2 < \eta_1^2 > -2F(B+C) < \eta_1\eta_2 > +((B+C)^2+\omega^2) < \eta_2^2 >}{(AF+E(B+C))^2 + (E^2 - 2AF + (B+C)^2)^2\omega^2 + \omega^4} \quad (13)$$
$$S_x(\omega) = \frac{(E^2+\omega^2) < \eta_1^2 > +2AE < \eta_1\eta_2 > +A^2 < \eta_2^2 >}{(AF+E(B+C))^2 + (E^2 - 2AF + (B+C)^2)^2\omega^2 + \omega^4} \quad (14)$$

which is consistent with the results presented in [20].

Another characteristic feature of the analytical results in Eqs. (11)-(12) is that when $< \eta_1\eta_2 >$ is assumed to be zero, which means that η_1 and η_2 are uncorrelated, both $S_s(\omega)$ and $S_s(\omega)$ can be written as a sum of intrinsic and extrinsic contributions which is the so called *the spectral addition rule* as derived in [10]. Even in this case, the coefficients in our results still include the effects coming from the time delays and negative feedback mechanism.

4 Numerical Calculations

In our numerical calculation, we use the second order stochastic Runge-Kutta method for integrating the chemical Langevin equations (1) and (2), and Gaussian integration method to calculate the integrations in(11). Parameters incorporated in Eqs. (1) and (2) are chosen as $A = 1$, $B = 2$, $C = 1$, $k_{-1} = 1$, $\epsilon = 1$, respectively. The strength of noises are $< \eta_1^2 >=< \eta_2^2 >=< \eta_1\eta_2 >= 0.01$. In this case, the system does not posses bifurcations and is always stable with a single stationary solution.

The numerical results have shown that the correlation functions $S_s(\omega)$ and $S_x(\omega)$ of $s(t)$ and $x(t)$ are precisely consistent between the ones with chemical Langevin equations (1)-(2) and the ones with (11)-(12), which verifies our truncation method in Eqs. (8)-(9).

4.1 Effect of Time Delay

It has been well recognized that time delay plays a very significant role in the dynamics of biological networks. Thus, we first pay our attentions to the roles of time delays in the general biological network motif discussed in this paper.

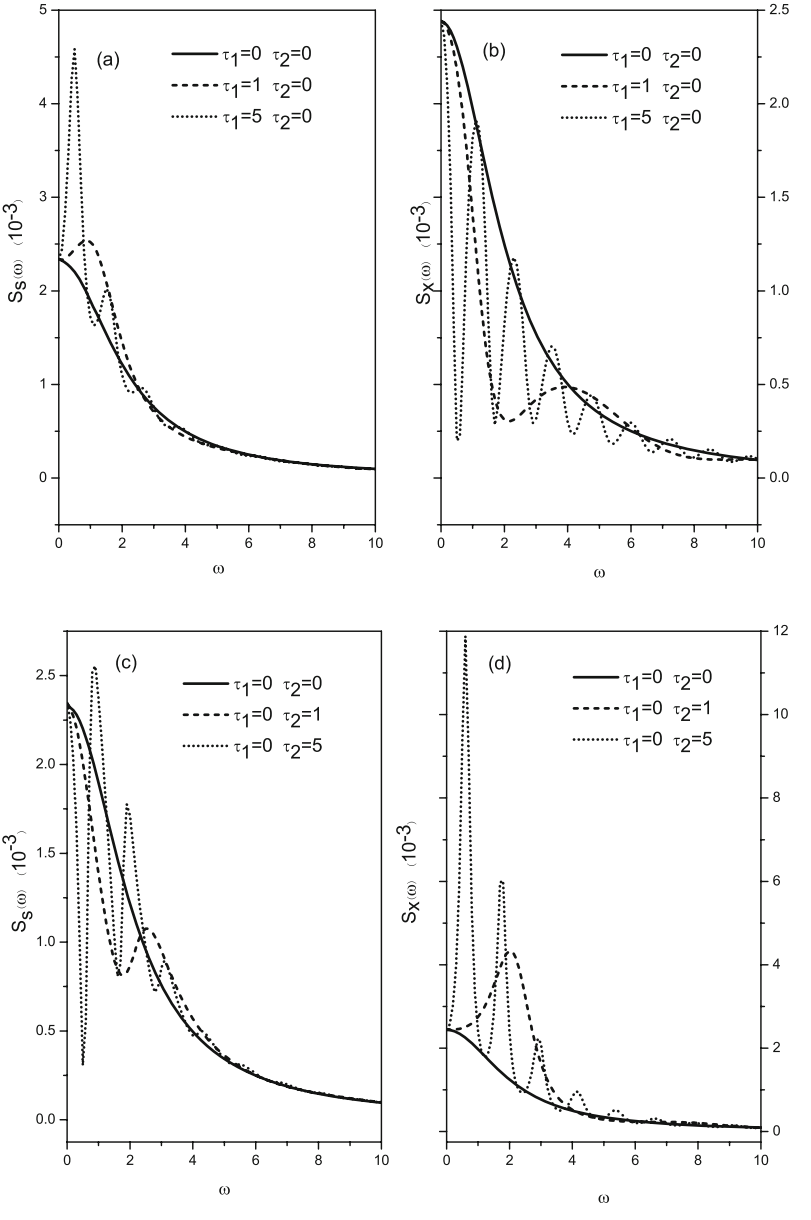

Fig. 1. Power spectrum of input $\mathcal{S}$ and output $\mathcal{X}$ related to the effect of time delays. Parameters incorporated in Eqs. (1) and (2) are chosen as $A = 1$, $B = 2$, $C = 1$, $k_{-1} = 1$, $\epsilon = 1$, respectively.

Figures 1(a-d) show the power spectrum of input $\mathcal{S}$ and output $\mathcal{X}$ related to the effect of time delays. It obviously shows that only the low frequency part of the power spectrum is sensitive to the variation of τ_1 when $\tau_2 = 0$. For

input signal $\mathcal{S}$, as τ_1 increases, both the magnitude of the main peak and the number of the peaks would increase, meanwhile, for output $\mathcal{X}$, the number of the peaks would increase while the magnitude of the main peak do not change with increasing τ_1.

When we turn to examine the effect of τ_2 when $\tau_1 = 0$, we could find that the output $\mathcal{X}$ shows much more complicated behavior than the input $\mathcal{S}$. On low frequency part of the power spectrum, not only the magnitude of the oscillation, but also the number would increase with the increasing τ_2 for both $S_s(\omega)$ and $S_x(\omega)$ of $s(t)$ and $x(t)$.

4.2 Effect of Feedback Negative Feedback Mechanism

Now we are at the position to study the effect of negative feedback mechanism which is also a very important dynamical component of the common network motif in biological and other systems [15,16,17]. Figures 2(a-d) show $S_s(\omega)$ and $S_x(\omega)$ with various values of ϵ that represents the effect of negative feedback mechanism. Here it should be noted that the term of negative feedback mechanism appearing in Eq. (2) is a nonlinear one, which is different from the linear one as discussed in [20].

From the numerical results, one may conclude that when the system undergoes no time delays, the strong negative feedback contributes to low frequency part of the power spectrum for both $\mathcal{X}$ and $\mathcal{S}$. This may reflect the fact that negative feedback makes biological network more robust against biochemical noise.

Together with the effect of the time delay, negative feedback does not only reduce the variance of the noise, but also shifts this noise to higher frequencies. The low frequency part of the power spectrum shows no simple relationship with the increasing strength of negative feedback. This may reveal that negative feedback may enhance the effect of time delay, while their quantitative relation is rather complicated and very difficult to work out analytically.

4.3 Effect of Correlation between Intrinsic and Extrinsic Noises

It has been shown by our numerical results that coefficients $\alpha_4 - \alpha_8$ and $\beta_4 - \beta_8$ are higher order small quantities than others. This consequence supports our method to retain the interpolation to the second order of $\eta_1(\omega)$ and $\eta_2(\omega)$ in Eqs. (8)-(9). The second order terms of $<\eta_1^2>$, $<\eta_1\eta_2>$ and $<\eta_2^2>$ make the dominant contributions to $S_s(\omega)$ and $S_x(\omega)$.

As an example, Fig. 3 shows the coefficients α_1, α_2, α_3, β_1, β_2 and β_3 for the case of $\tau_1 = 0$, $\tau_2 = 5$. From this figure, one may conclude that: (I) α_2, which corresponds to the contribution from correlation between intrinsic and extrinsic noises, is always negative. So we see that the contribution from correlation between intrinsic and extrinsic noises reduces the correlation $S_x(\omega)$, especially in the low frequency regime; (II) contrarily, β_2 is always positive and thus the contribution from correlation between intrinsic and extrinsic noises enhances the correlation $S_s(\omega)$.

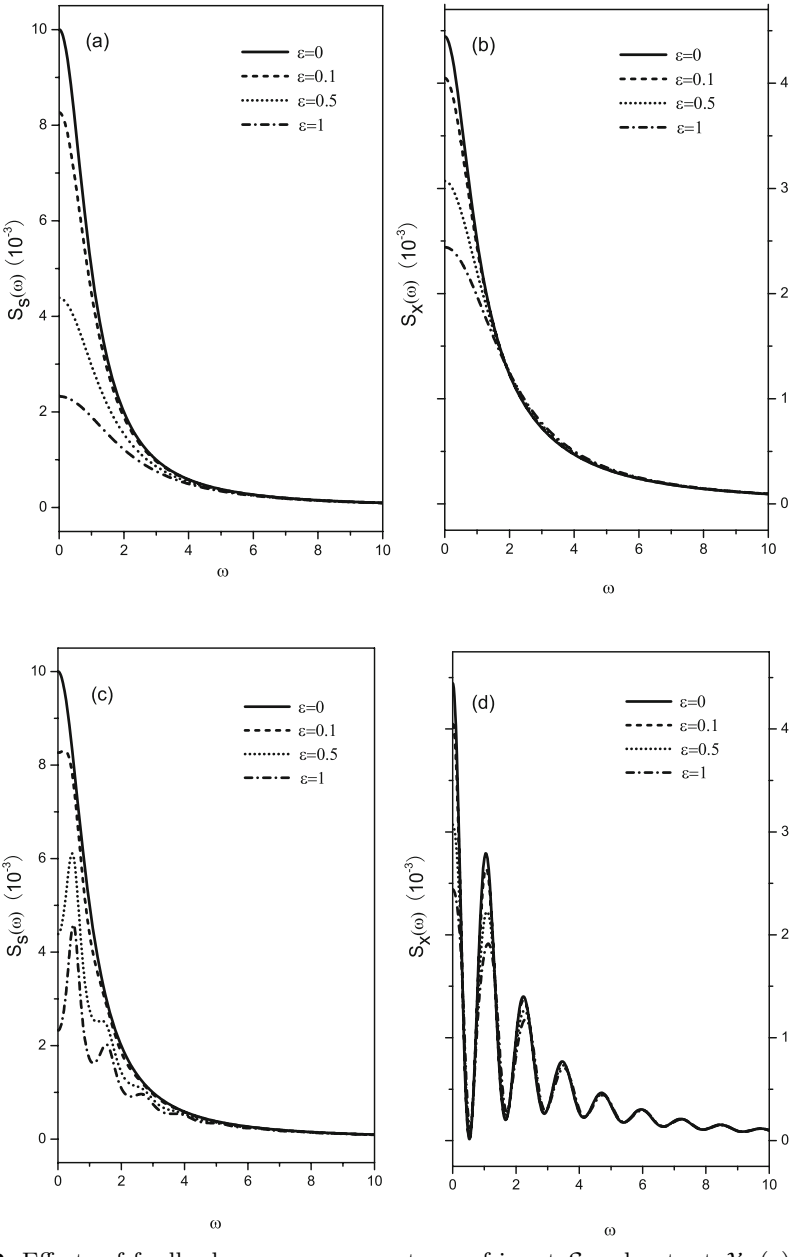

Fig. 2. Effects of feedback ϵ on power spectrum of input $\mathcal{S}$ and output $\mathcal{X}$. (a) $S_s(\omega)$ for $\tau_1 = \tau_2 = 0$; (b) $S_x(\omega)$ for $\tau_1 = \tau_2 = 0$; (c) $S_s(\omega)$ for $\tau_1 = 5, \tau_2 = 0$; (d) $S_x(\omega)$ for $\tau_1 = 5, \tau_2 = 0$. Other parameters are the same as in Fig. 1.

The coefficients α_1, α_2, α_3, β_1, β_2 and β_3 have the frequency selectivity and consist of several Gaussian distributions on frequency. This would be highly useful, because it would allow a modular description of noise propagation.

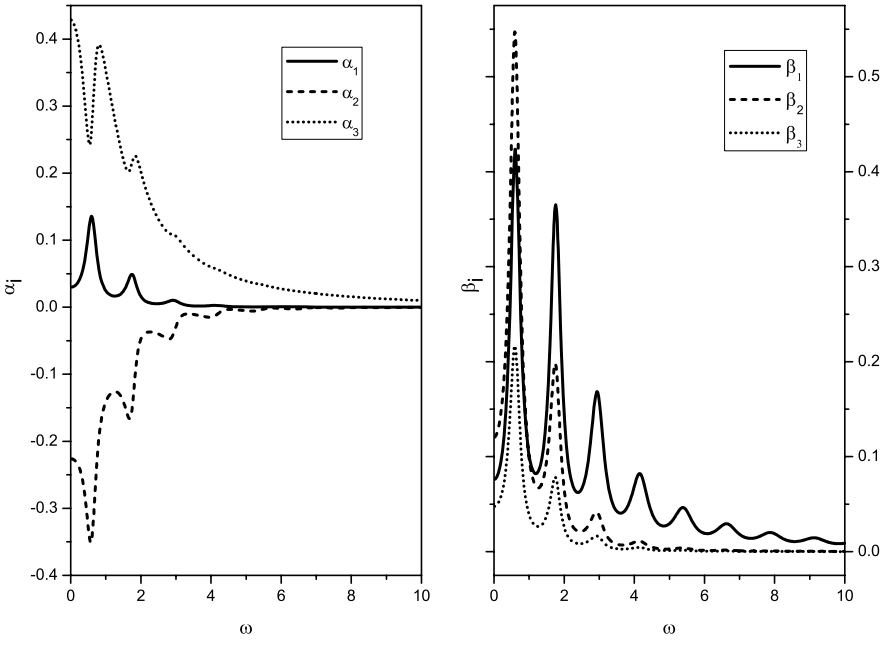

Fig. 3. Coefficients α_1, α_2, α_3, β_1, β_2 and β_3 for the case of $\tau_1 = 0$, $\tau_2 = 5$. Other parameters are the same as in Fig. 1. Note that the distance between two neighboring peaks is very close to $2\pi/\tau_2$.

5 Summary and Discussions

Stochasticity in biological networks has attracted intensive attention from both experimental and theoretical researchers in the last decade. With the aid of new experimental techniques, people could follow the gene expression in single cell over time. Stochasticity has been found to be very significant because of low gene copy number and fluctuating cellular environment. Time delay, which is found to be ubiquitous in nature, has now been considered as a key component in gene regulation.

In this paper, we first present a most common delayed biological network motif with intrinsic and extrinsic noises. Two time delays are introduced to reveal compound multistage reactions involving the sequential assembly of long molecules, meanwhile, negative feedback mechanism is presented to take into account the effects of internal degrees of freedom in the motif. We have derived the autocorrelation function and power spectrum analytically to show the effects of time delays and negative feedback mechanism, and carried out the frequency domain analysis.

From the numerical simulation, we have seen that different time delay corresponds to different shapes of spectrum, and only the low frequency part of the power spectrum is sensitive to the value changes of time delays. For input signal $\mathcal{S}$, as τ_1 increases, both the magnitude of the main peak and the number of the

peaks would increase. However, for output $\mathcal{X}$, the number of the peaks would increase while the magnitude of the main peak do not with increasing τ_1. As τ_2 increases, the output $\mathcal{X}$ shows much more complicated behavior than the input $\mathcal{S}$. On low frequency part of the power spectrum, not only the magnitude, but also the number of the oscillation would increase for both input $\mathcal{S}$ and output $\mathcal{X}$.

Here notes that τ_1 is the delay of signal transmission, and τ_2 is the delay of transcription and translation processes. And the non-Markovian effect, which means multi-peak behavior in the power spectrum, is due to the time delays. If we could measure these delays experimentally, noise of specific peak frequency would be filtered during noise propagation.

Negative feedback and the cross correlation between intrinsic and extrinsic noises may reduce the variance of the noise, and so as to make biological network more robust against biochemical noise.

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