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2009 Chin. J. Chem. Phys. 22 359

(http://iopscience.iop.org/1674-0068/22/4/04)

ARTICLE

Fluctuation Resonance of Feed Forward Loops in Gene Regulatory Networks

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(Dated: Received on April 1, 2009; Accepted on April 19, 2009)

The feed forward loop (FFL), wherein a gene X can regulate target gene Z alone or cooperatively with gene Y, is one of the most important motifs in gene regulatory networks. Gene expression often involves a small number of reactant molecules and thus internal molecular fluctuation is considerable. Here we studied how an FFL responds to small external signal inputs at gene X, with particular attention paid to the fluctuation resonance (FR) phenomenon of gene Z. We found that for all coherent FFLs, where the sign of the direct regulation path from X to Z is the same as the overall sign of the indirect path via Y, the FR shows a regular single peak, while for incoherent FFLs, the FR exhibits distinct bimodal shapes. The results indicate that one could use small external signals to help identify the regulatory structure of an unknown FFL in complex gene networks.

Key words: Gene regulatory network, Fluctuation resonance, Feed-forward-loop

I. INTRODUCTION

Gene networks constitute one of the most important types of biological networks [1]. The nodes represent individual genes, which provide the blueprint for the synthesis of proteins through the key steps of transcription and translation. The proteins and their complexes act as regulatory molecules through binding to appropriate regions of the DNA and control initiation of gene transcription. The directed link from regulating gene to regulated gene is either activating or repressing in nature. The major topological features of the gene networks can be learned from the databases of some simple organisms like *E. coli* and *S. cerevisiae* [2,3]. For instance, the gene networks are "ultra-small", *i.e.*, the average path length between nodes is proportional to $\lg(\lg N)$, where N is the number of nodes in the network [4]. Another important feature is dissortativity: many real biological networks contain significantly recurring wiring patterns termed "network motifs" [2,5,6], and the component within one motif does not connect to that of other one directly. One of the most well-known and important motifs appearing in gene networks is the feed forward loop (FFL) [7,8], which contains three genes X, Y, and Z (Fig.1). Protein-X synthesized from gene-X regulates the expression of gene-Y and gene-Z, and protein-X and protein-Y also jointly regulate the expression of gene-Z. Each of the three transcriptional regulatory interactions in an FFL has either positive sign (activation) or negative sign (repression), and thus the motif can be in eight possible configurations which are of two types: coherent and incoherent. In a coherent (incoherent) FFL, the sign of the direct regulation path from x to z is the same as (different from) the overall sign of the indirect regulation path via y. As shown in Fig.1, one may also use an inducer, whose concentration can be periodically modulated, to control the expression of X, which provides a reasonable way to input an external signal into the FFL.

In recent years, the study of inherent or external noise in gene expression process has gained great interest [9–17]. For recent reviews, please see Ref.[9]. As pointed out by McAdams *et al.*, the gene expression process is a "noisy business" [10]. This "noise" has an internal source due to the inherent molecular fluctuations as a result of stochastic reaction events in transcription and translation processes, as well as environmental external source [11,12]. Currently, most studies in this field focus on where the internal noise comes from, how to characterize it and what its effect is, through both experimental and theoretical studies. For instance, it was reported that the internal noise in the gene expression in prokaryotes mainly comes from the translation process [13]; while for eukaryotes, transcription process

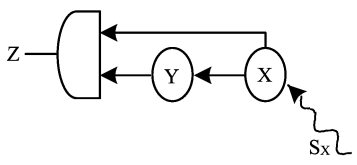

FIG. 1 FFL. Transcription factor X regulates transcription factor Y, and both jointly regulate Z. Sx is the inducer of X, whose concentration can be periodically modulated.

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contributes a great level to the noise in the clonal population [14]. Particularly, the properties of intrinsic noise in complex gene networks [15] have been studied theoretically using stochastic chemical kinetics, and a generalized summing rule was proposed by Paulsson [16,17] that successfully accounts for the propagation of noise in gene regulatory networks [18]. Moreover, since the circadian clock system is mainly regulated by gene expression processes at the molecular level, the internal noise effect on circadian oscillation is also remarkable [19]. For example, it was found that the circadian oscillation would become highly irregular, characterized by rapid vanishing of autocorrelations, when the maximum numbers of mRNA and protein molecules are relatively small [20]. To resist the destructive effects of internal noise, the circadian system may show robustness to internal noise by feedback loops or redundancy [21]. It is also worthy to mention that internal noise may also play constructive roles via inducing oscillations which are not present in the deterministic model [22–24].

Recently, Lipan and Wong presented a theory by which the structure of a genetic network can be uncovered by studying its response to external stimuli [25]. The use of an oscillatory signal is proved to be more advantageous than a step or impulse signal. The scheme was based on a new phenomenon, called fluctuation resonance (FR). For a single gene expression process, the fluctuation of the protein number would be also periodic in time if the transcription is subject to external periodic signal. FR reveals that the deviation from Poisson process would reach a clear-cut maximum when the frequency of the external signal is at an intermediate value. In the present work, we consider a stochastic genetic FFL, with an oscillatory signal stimulating the gene X, with particular attention paid to the FR behaviors of all the three genes. We find that for the first gene X, pure FR was observed at ω=2ω_0 with ω_0 as a natural frequency determined by the parameters of gene X, which is consistent with the theoretical prediction. For the second gene Y which is regulated by X, the main FR occurs at nearly 1.5ω_0, and when X is an activator, there is an additional small FR peak at about 0.3ω_0 which is absent if X negatively regulates Y. More interestingly, we find that the response of the gene Z clearly reflects the coherent properties of the system, with a single peak in coherent types of FFL and double peaks in incoherent FFLs, indicating that one could use a small external signal to help identify the regulatory structure of an unknown FFL in complex gene networks.

II. MODEL AND METHODS

A. Deterministic kinetics

Although we are mainly concerned with the fluctuation properties of the FFL, a deterministic description would be helpful to understand its regulatory dynamics. In the deterministic limit, the state of the FFL can be described by the concentrations of mRNA and protein of species X, Y, and Z. Generally, the kinetic equations are

$$\begin{aligned}
\frac{\mathrm{d}R_x}{\mathrm{d}t} &= \alpha_x + k_x f_x\left(P_x\right) - \gamma_{R,x}R_x + A\cos\left(\omega t\right)\\
\frac{\mathrm{d}P_x}{\mathrm{d}t} &= \beta_x R_x - \gamma_{P,x}P_x\\
\frac{\mathrm{d}R_y}{\mathrm{d}t} &= \alpha_y + k_y f_y\left(P_x\right) - \gamma_{R,y}R_y\\
\frac{\mathrm{d}P_y}{\mathrm{d}t} &= \beta_y R_y - \gamma_{P,y}P_y\\
\frac{\mathrm{d}R_z}{\mathrm{d}t} &= \alpha_z + k_z G\left(P_x, P_y\right) - \gamma_{R,z}R_z\\
\frac{\mathrm{d}P_y}{\mathrm{d}t} &= \beta_z R_z - \gamma_{P,z}P_z
\end{aligned} \tag{1}$$

Here, R_i and P_i (i=x, y, z) denote the concentrations of mRNA-i and protein-i, respectively; the (α, β, γ)-parameters denote the transcription, translation, and degradation rates of corresponding species, respectively, and the k_i denote the regulation strength on the transcription of gene-i. A and ω are respectively the amplitude and frequency of the external signal input into X. The function $f_x(P_x)$ describes the feedback-regulation of X-protein on the transcription of its own gene, which generally has the form of Hill-functions. For a positive feedback (activator),

$$f_x\left(P_x\right) = f_+\left(P_x\right) \equiv \frac{\left(P_x/K_x\right)^n}{1+\left(P_x/K_x\right)^n} \tag{2}$$

and for a negative regulation (repressor),

$$f_x\left(P_x\right) = f_-\left(P_x\right) \equiv \frac{1}{1+\left(P_x/K_x\right)^n} \tag{3}$$

where K_x is the dissociation constant that specifies the threshold protein concentration at which the regulation strength is at half its maximum value, and n is the Hill coefficient. Similarly, $f_y(P_x)$ denotes the regulation of X-protein on the transcription of gene Y, which can be f_+ or f_- depending on the sign of the regulation. The gate function $G(P_x, P_y)$ describes the regulation of X and Y protein on the transcription of gene Z, and is formulated as

$$G\left(P_x, P_y\right) = g_x\left(P_x; P_y\right) + g_y\left(P_y; P_x\right) \tag{4}$$

$$\begin{aligned}
g_i\left(P_i; P_j\right) &= g_+\left(P_i; P_j\right)\\
&\equiv \frac{\left(P_i/K_i\right)^n}{1+\left(P_i/K_i\right)^n+\left(P_j/K_j\right)^n}
\end{aligned} \tag{5}$$

for an activator and

$$\begin{aligned}
g_i\left(P_i; P_j\right) &= g_-\left(P_i; P_j\right)\\
&\equiv \frac{1}{1+\left(P_i/K_i\right)^n+\left(P_j/K_j\right)^n}
\end{aligned} \tag{6}$$

DOI:10.1088/1674-0068/22/04/359-365

for a repressor with K_i and K_j the corresponding dissociation constants. For a suitable choice of parameters and in the absence of the external signal, *i.e.* A=0, we assume Eq.(1) admits a steady state solution $\mathbf{u}$=$\mathbf{u}^*$ with d$\mathbf{u}^*$/dt=0, where

$$\mathbf{u} = (R_x, P_x, R_y, P_y, R_z, P_z)^T \tag{7}$$

denotes the state vector.

B. Master equation

As stated in the introduction, molecular fluctuations are considerable for gene regulatory networks. To begin, we first consider the case where the external signal is absent. Due to the presence of noise, the species concentrations will now fluctuate around the steady state $\mathbf{u}^*$. Generally, one can use linear noise approximation (LNA) [15,26] to investigate the noise properties. By performing Taylor expansions of the regulation functions f_x, f_y, and G at $\mathbf{u}^*$ and keeping only to the linear terms, one can obtain a linear differential equation governing the time evolution of species numbers $\mathbf{n}$=$\mathbf{u}V$ (V is the system volume) written in a vector-matrix form,

$$\frac{\mathrm{d}\mathbf{n}}{\mathrm{d}t} = (\mathbf{W} - \mathbf{\Gamma})\,\mathbf{n} + \mathbf{c} \tag{8}$$

where $\mathbf{W}$ denotes the regulation matrix whose entry W_{ij} denotes the regulation coefficient of species j on species i, $\mathbf{\Gamma}$ is a diagonal matrix with Γ_{ij}=$\delta_{ij}\gamma_i$ where γ_i is the degradation constant of species i, and $\mathbf{c}$ is a vector consisting of the constant parts in Eq.(1) after the Taylor expansion. (From now on, we will use bold-capital letters for matrix and bold-lowercase ones for vectors). Note that the entries of $\mathbf{W}$ can be positive or negative depending on the sign of the regulation. Such a linear approximation corresponds to a linear birth-death reaction network as follows,

$$n_i \;\rightarrow\; n_i + 1 \quad (\text{with rate } \sum_j W_{ij} n_j + c_i) \tag{9}$$

$$n_i \;\rightarrow\; n_i - 1 \quad (\text{with rate } \gamma_i n_i) \tag{10}$$

for i=1, ..., 6. These processes are discrete, random and Markovian, and can be described by the following master equation governing the time evolution of the joint probability distribution function $P(n_1, ..., n_6; t)$≡$P(\{n_i\}; t)$

$$\begin{aligned}\frac{\partial P(\{n_i\};t)}{\partial t} \;=\; & \sum_i \Big\{ (\Re_i^{-1} - 1)\Big[\Big(\sum_j W_{ij} n_j + c_i\Big)\cdot \\ & P(\{n_i;t\})\Big] + (\Re_i^{+1} - 1)\cdot \\ & [\gamma_i n_i P(\{n_i;t\})]\Big\}\end{aligned} \tag{11}$$

where the operator $\Re_i$ is defined as

$$\Re_i^{\pm 1} f(\{n_i\};t) = f(n_1, ..., n_i \pm 1, ..., n_6; t) \tag{12}$$

C. Fluctuation equations

Usually, the fluctuation of n_i is characterized by its variance σ_i=$\langle n_i^2\rangle$-$\langle n_i\rangle^2$ where $\langle\cdot\rangle$ means expectation. For gene expression problems, one often use the so-called Fano factor, defined as φ_i=$\sigma_i/\langle n_i\rangle$, that characterizes the deviation of the stochastic process from a Poisson one for which φ_i=1. To calculate σ_i, it is convenient to use the method of generating functions as shown in Ref.[26]. We will not go into details, but outline the main idea here.

We can define a generating function as

$$F(\{s_i\};t) = \sum_{\{n_i\}} \left(\prod_i {s_i}^{n_i}\right) P(\{n_i\};t) \tag{13}$$

which, according to Eq.(11), satisfies

$$\begin{aligned}\frac{\partial F(\{s_i\};t)}{\partial t} \;=\; & \sum_i (1 - s_i)\Big[\gamma_i(\partial_i F) - \\ & \sum_j W_{ij} s_j (\partial_j F) - c_i G\Big]\end{aligned} \tag{14}$$

wherein we have used ∂_j to represent the partial derivative of the variable s_j. Notice that $F|_1$= 1,

$$\partial_i F|_1 \;=\; \langle n_i\rangle \tag{15}$$

$$\partial_{ii} F|_1 \;=\; \langle {n_i}^2\rangle - \langle n_i\rangle \tag{16}$$

$$\partial_{ij} F|_1 \;=\; \langle n_i n_j\rangle \tag{17}$$

where $|_1$ means evaluating the expression at (s_i=1,$\forall i$). By calculating first derivative of s_i on both sides of Eq.(14) and evaluating at 1, one can reach the equation for the expectation values $\langle n_i\rangle$,

$$\frac{\mathrm{d}\langle n_i\rangle}{\mathrm{d}t} = \sum_j W_{ij}\langle n_j\rangle - \gamma_i\langle n_i\rangle + c_i \tag{18}$$

and in the matrix-vector form,

$$\frac{\mathrm{d}\langle \mathbf{n}\rangle}{\mathrm{d}t} = (\mathbf{W} - \mathbf{\Gamma})\langle \mathbf{n}\rangle + \mathbf{c} \tag{19}$$

Note that Eq.(19) is the same as Eq.(8). By taking the second derivative, we can obtain the evolution equation of the matrix $\mathbf{B}$=$\{B_{ij}$=$\partial_{ij}F|_1\}$ as

$$\begin{aligned}\frac{\mathrm{d}\mathbf{B}}{\mathrm{d}t} \;=\; & (\mathbf{W} - \mathbf{\Gamma})\times\mathbf{B} + \mathbf{B}\times \\ & (\mathbf{W} - \mathbf{\Gamma})^T + \big(\mathbf{L} + \mathbf{L}^T\big)\end{aligned} \tag{20}$$

where $$L_{ij} \;=\; (W_{ij} + c_i)\langle n_j\rangle \tag{21}$$

The variance and Fano factor read

$$\sigma_i \;=\; B_{ii} - \langle n_i\rangle^2 + \langle n_i\rangle \tag{22}$$

$$\varphi_i \;=\; 1 + \frac{B_{ii} - \langle n_i\rangle^2}{n_i} \tag{23}$$

DOI:10.1088/1674-0068/22/04/359-365

In the absence of external signal, Eqs.(19) and (20) admit steady state solutions,

$$\langle \mathbf{n} \rangle^* = -\frac{\mathbf{c}}{\mathbf{W}-\mathbf{\Gamma}} \quad (24)$$

$$\mathbf{B}^* = \mathrm{Lyap}\left(\mathbf{W}-\mathbf{\Gamma}, \mathbf{L}+\mathbf{L}^T\right) \quad (25)$$

where $\mathrm{Lyap}(\mathbf{M},\mathbf{N})$ denotes the solution of Lyapunov matrix equation

$$\mathbf{M}\times\mathbf{X}+\mathbf{X}\times\mathbf{M}^T+\mathbf{N}=0 \quad (26)$$

We now consider that a small external signal with $0<A\ll 1$ is input into X. In this case, both the expectation values and variances are periodic functions. For a single gene expression process, it is still possible to analytically obtain the equation of the periodic fluctuations as done in Ref.[25]. For the FFL considered here, however, such a purely analytical treatment is not possible. Nevertheless, thanks to the fact that A is fairly small, one may still perform linear noise approximation as shown above. It is reasonable to assume that $n_i(t)$ will oscillate with a small amplitude around ${n_i}^*$, and to the lowest order of approximation, one can still obtain Eqs.(19) and (20), given that the vector $\mathbf{c}$ is now replaced by

$$\mathbf{c}(t)=\{c_i(t)=c_{i,0}+\delta_{i1}\cdot A\cos(\omega t)\} \quad (27)$$

We can thus perform numerical simulations of Eqs.(19), (20), and (27) to investigate the fluctuation properties under the stimulus of a small input signal.

III. RESULTS

In Ref.[25], the authors have shown that a single gene expression process with negative self-regulation and subject to periodic external signal can show FR behavior. In the case of a single gene, one mainly accounts for the fluctuation properties of the protein P. As stated above, the expectation value $\langle P\rangle$ and variance σ_P of the protein number are both periodic functions of time with the same frequency as that of the signal. One can use

$$\delta_P(t)=\sigma_P(t)-\langle P(t)\rangle \quad (28)$$

to represent the deviation from a Poisson process, and it is also a periodic function. We may write

$$\langle P(t)\rangle = P_0+X_p\cos(\omega t) \quad (29)$$

$$\sigma_P(t) = \sigma_0+X_{PP}\cos(\omega t) \quad (30)$$

then FR tells that the factor

$$\eta_p=\frac{|X_{pp}|}{|X_p|} \quad (31)$$

shows a clear resonance effect with the signal frequency, *i.e.*, η_p reaches a maximum when $\omega=2\omega_0$ with the characteristic frequency

$$\omega_0=\sqrt{k_1k_p+\gamma_R\gamma_P} \quad (32)$$

where k_p is the translation coefficient, γ_R and γ_P are respectively the degradation constants of the mRNA and protein, and $k_1>0$ is the negative regulation coefficient of the gene itself.

In the present work, the dynamics of gene X is not affected by those of gene Y and Z. Therefore, X should show the same FR behavior as above. We note that the resonance condition $\omega=2\omega_0$ was obtained analytically in [25], and we thus can use it to test the validity of Eqs.(19), (20), and (27). In our notation, we can write

$$\langle n_i(t)\rangle = n_{i,0}+X_i\cos(\omega t) \quad (33)$$

$$\delta_i(t) = \delta_{i,0}+X_{ii}\cos(\omega t) \quad (34)$$

for i=1,...,6, and the characteristic frequency should be

$$\omega_0=\sqrt{\gamma_1\gamma_2-W_{12}W_{21}} \quad (35)$$

in the case of negative self-regulation on gene X, $W_{12}<0$. The numerical results are shown in Fig.2, where

$$\eta_2=\frac{|X_{22}|}{|X_2|} \quad (36)$$

here the subscript '2' refers to the second component of the state vector, *i.e.*, P_x. Eq.(32) shows a clear peak exactly at $2\omega_0$, which demonstrates that validity of Eqs.(19), (20), and (27).

We now consider the fluctuation properties of the Y-mRNA and protein. Note that protein X can act as an activator or repressor for the transcription of gene Y. The results are shown in Fig.3 for typical parameters, where η_4 for protein Y is depicted for X to be an activator (a) and a repressor (b). FR is still observed in both cases; however, the resonance peak now appears

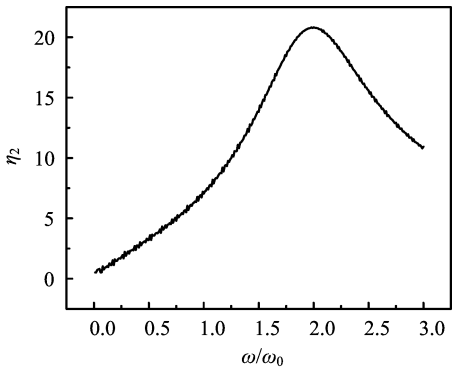

FIG. 2 Fluctuation resonance of gene X in the FFL. The factor η_2 for the protein X is depicted as a function of ω/ω_0. The matrix or vector elements are transcription rate c_1=0.01 s^{-1}, translation rate $W_{21}=5.8\times10^{-3}$ s^{-1}, degradation constants for X-mRNA $\gamma_1=0.2\times10^{-3}$ s^{-1} and X-protein $\gamma_2=0.1\times10^{-3}$ s^{-1}, the negative regulation constant $W_{12}=-0.5\times10^{-4}$ s^{-1}, and $W_{11}=W_{22}=c_2=0$. The characteristic frequency is ω_0, as shown in Eq.(35) from now on. The signal amplitude is A=0.05.

DOI:10.1088/1674-0068/22/04/359-365

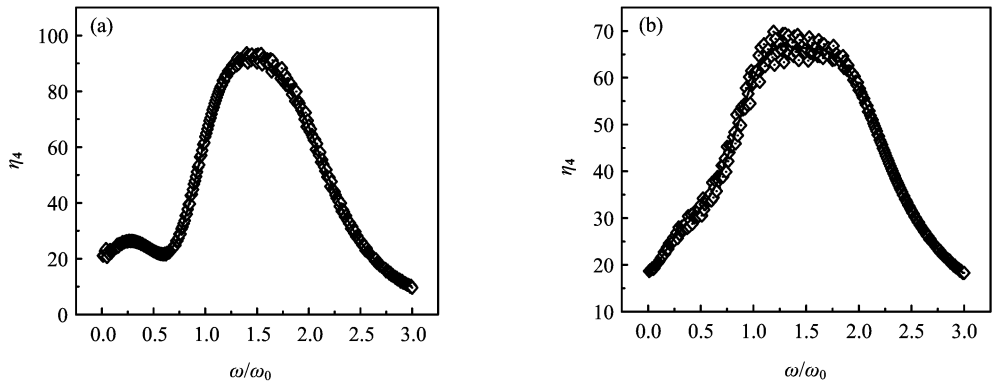

FIG. 3 Fluctuation resonance of gene Y in the FFL. The factor η_4 for the protein Y is depicted as a function of external frequency ω/ω_0. (a) X is an activator. (b) X is a repressor. The parameters for gene Y are the same as those for X, *i.e.*, c_3=0.01 s^{-1}, W_{32}=5.8×10^{-3} s^{-1}, γ_3=0.2×10^{-3} s^{-1}, γ_4=0.1×10^{-3} s^{-1} and W_{33}=W_{44}=c_4=0. The regulation constant is W_{34}=±0.5×10^{-4} s^{-1} depending on the sign of regulation. A=0.05. The lines are drawn to guide the eyes.

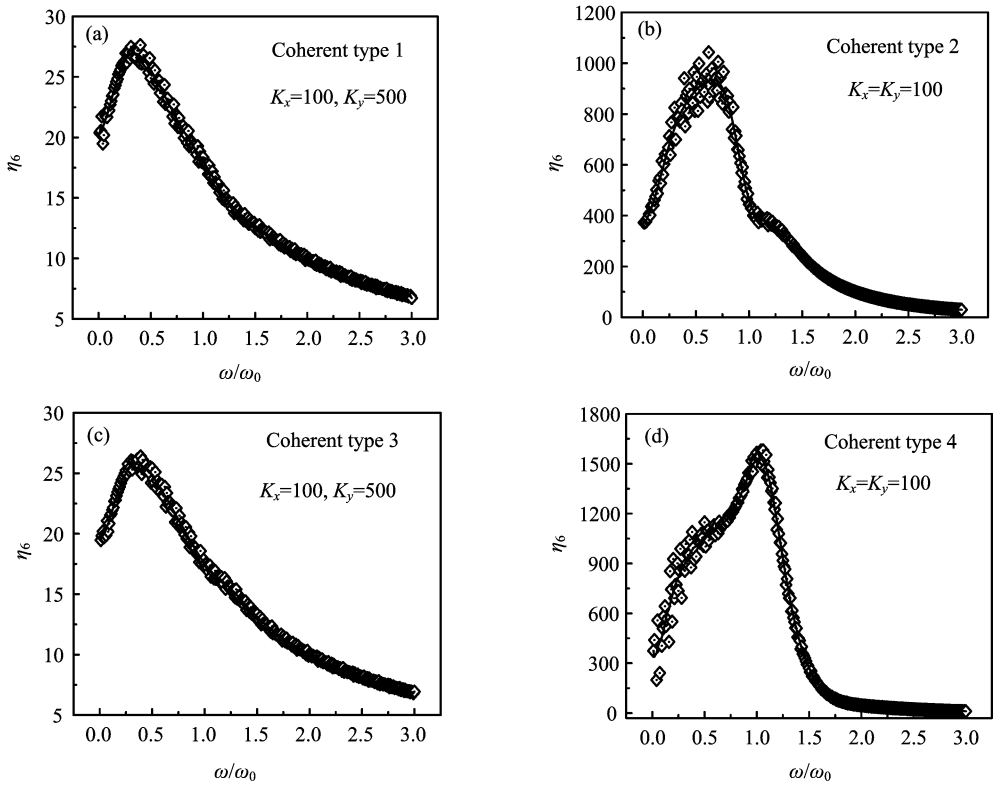

FIG. 4 Fluctuation resonance of gene Z for four coherent types of FFL. The parameters for gene X and Y are the same as in Figs. 2 and 3. The translation and degradation rates for Z are also the same as those for X and Y, *i.e.*, W_{65}=5.8×10^{-3} s^{-1}, γ_5=0.2×10^{-3} s^{-1}, γ_6=0.1×10^{-3} s^{-1}. The parameters associated with the regulations are: regulation strength k_z=0.5×10^{-4} s^{-1}, hill coefficient n=2, c_5=0.01 s^{-1}, W_{55}=W_{66}=c_6=0. The lines are drawn to guide the eyes.

near ω=1.5ω_0. In addition, for X to be an activator, the main peak is accompanied by a much smaller one at ω≈0.3ω_0. Since an analytical expression for η_4 is not available, the locations of the peaks cannot be exactly identified. For other choice of parameters, the observed phenomena are qualitatively similar.

The situation for gene Z is much more complicated because it is regulated by both gene X and Y. Our main finding is that the overall FR behavior of protein Z depends on whether the FFL is coherent or not. We may use the three regulation signs ($S_{X\to Z}, S_{X\to Y}, S_{Y\to Z}$) to characterize the FFL type, where S is +(−) for a positive (negative) regulation. Figure 4 and 5 show the FR behaviors for protein Z for all the eight types of FFLs. The four coherent FFLs are then denoted by (+++), (−−+), (+−−), and (−+−), respectively, and

DOI:10.1088/1674-0068/22/04/359-365

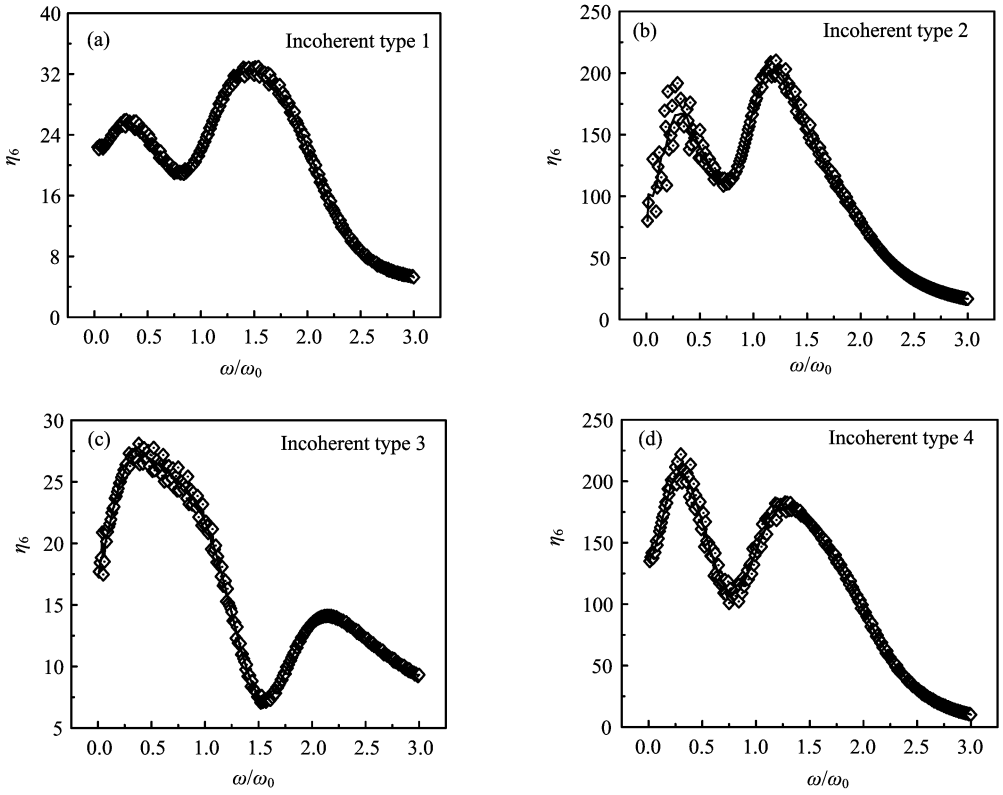

FIG. 5 Fluctuation resonance of gene Z for four incoherent types of FFL. The parameters are the same as in Fig.4. The lines are drawn to guide the eyes.

those four incoherent types are $(++-)$, $(---)$, $(-++)$, and $(+-+)$, respectively. The regulation constant W_{56} is obtained from Taylor expansion of the Hill function $G(P_x, P_y)$ around the steady state. Interestingly, for all coherent FFLs, the η_6 factor for protein Z shows a single remarkable peak at an intermediate frequency, however, for all incoherent FFLs, the η_6 exhibits a clear-cut bimodal shape. In addition, types 2 and 4 (either coherent or incoherent) show much larger η-factors than those of types 1 and 3, which remains an open question to us. Such observations are robust to parameter choices, given that a steady state can be achieved in the absence of the external signal. Therefore, the FR behavior of the Z protein provides a useful way to deduce the coherent structure of the FFL, which might be of practical interest in the reverse engineering of real gene regulatory networks.

IV. CONCLUSION

In summary, we studied the fluctuation properties of a feed forward loop (FFL) motif subject to small external signal, by using a chemical master equation and linear noise approximation. In an FFL, a gene X can regulate the target gene Z alone or cooperatively with gene Y, and it can be coherent or incoherent depending on the signs of the regulations. Particular attention is paid to the so-called fluctuation resonance (FR) behaviors, which describe to what extent the fluctuation of the protein number deviates from that of a Poisson process, of the three proteins involved in the FFL. Most interestingly, we find that FRs of the target gene Z show regular bell-shapes for coherent FFLs, while they show distinct bimodal shape for incoherent FFLs. Such a finding indicates that one might use a small external signal to identify the coherent structures of an FFL which could be of practical interest in reverse engineering gene regulatory networks.

V. ACKNOWLEDGMENT

This work was supported by the National Natural Science Foundation of China (No.20673106).

[1] H. Jeong, S. P. Mason, A. L. Barabasi, and Z. N. Oltvai, Nature **411**, 41 (2001).
[2] S. Shen-Orr, R. Milo, S. Mangan, and U. Alon, Nat. Genet. **31**, 64 (2002).
[3] D. Thieffry, A. M. Huerta, E. Perez-Rueda, and J. Collado-Vides, Bioessays **20**, 433 (1998).

DOI:10.1088/1674-0068/22/04/359-365

[4] A. L. Barabási and Z. N. Oltvai, Nat. Genet. **36**, 101 (2004).
[5] R. Milo, S. Shen-Orr, S. Itzkovitz, N. Kashtan, D. Chklovskii, and U. Alon, Science **298**, 824 (2002).
[6] T. I. Lee, N. J. Rinaldi, F. Robert, D. T. Odom, Z. Bar-Joseph, G. K. Gerber, N. M. Hannett, C. T. Harbison, C. M. Thompson, I. Simon, J. Zeitlinger, E. G. Jennings, H. L. Murray, D. B. Gordon, B. Ren, J. J. Wyrick, J. Tagne, T. L. Volkert, E. Fraenkel, D. K. Gifford, and R. A. Young, Science **298**, 799 (2002).
[7] S. Mangan and U. Alon, Proc. Natl. Acad. Sci. USA **100**, 11908 (2003).
[8] I. Bose, B. Ghosh, and R. Karmakar, Phys. A **346**, 49 (2005).
[9] (a) C. V. Rao, D. M. Wolf, and A. Arkin, Nature **420**, 231 (2002);
(b) M. Karn, T. C. Elston, W. J. Blake, and J. J. Collins, Nature Review Genetics **6**, 451 (2005).
[10] H. H. McAdams and A. Arkin, Trend. Genetics **15**, 65 (1999).
[11] M. B. Elowitz, A. L. Levine, E. D. Siggia, and P. S. Swain, Science **297**, 1183 (2002).
[12] P. S. Swain, M. B. Elowitz, and E. D. Siggia, Proc. Natl. Acad. Sci. USA **99**, 12795 (2002).
[13] J. Hasty and J. J. Collins, Nature Genetics **31**, 13 (2002).
[14] W. J. Blake, M. Kærn, C. R. Cantor, and J. J. Collins, Nature **422**, 633 (2003).
[15] M. Thattai and A. V. Oudenaarden, Proc. Natl. Acad. Sci. USA **98**, 8614 (2001).
[16] J. Paulsson, Nature **427**, 415 (2004).
[17] J. M. Pedraza and J. Paulsson, Science **319**, 339 (2008).
[18] J. M. Pedraza and A. van Oudenaarden, Science **307**, 1965 (2005).
[19] J. C. Dunlap, Cell **96**, 271 (1999).
[20] D. Gonze, J. Halloy, and A. Goldbeter, Proc. Natl. Acad. Sci. USA **99**, 673(2002).
[21] N. Barkai and S. Leibler, Nature **403**, 267 (2000).
[22] J.M.G. Vilar, H. Y. Kueh, N. Barkai, and S. Leibler, Proc. Natl. Acad. Sci. USA **99**, 5988 (2002).
[23] Z. H. Hou and H. W. Xin, J. Chem. Phys. **119**, 12508 (2003).
[24] T. J. Xiao, J. Ma, Z. H. Hou, and H. W. Xin, New. J. Phys. **9**, 403 (2007).
[25] O. Lipan and W. H. Wong, Proc. Natl. Acad. Sci. USA **102**, 7063 (2005).
[26] C. W. Gardiner, *Handbook of Stochastic Methods for Physics, Chemistry and the Natural Sciences*, Heidelberg: Springer, (1983).

DOI:10.1088/1674-0068/22/04/359-365