Available online at www.sciencedirect.com
ScienceDirect
Journal of Theoretical Biology 243 (2006) 214–221
Journal of Theoretical Biology
www.elsevier.com/locate/yjtbi

External noise and feedback regulation: Steady-state statistics of auto-regulatory genetic network

Bing-Liang Xu[a], Yi Tao[b,*]

[a]College of Grassland Sciences, Gansu Agriculture University, Lanzhou, PR China
[b]Key Laboratory of Animal Ecology and Conservation Biology, Institute of Zoology, Chinese Academy of Sciences, Beijing, PR China

Received 26 November 2005; received in revised form 1 June 2006; accepted 2 June 2006
Available online 12 June 2006

Abstract

The steady-state statistics of a single gene auto-regulatory genetic network with the additive external Gaussian white noises is investigated. The main result shows that the negative feedback will result in that the mRNA noise has a positive contribution to the protein noise, but the positive feedback will result in that the mRNA noise has a negative contribution to the protein noise. If there is no feed back, then the contribution of mRNA noise to protein noise is always positive. On the other hand, the analysis and numerical simulations of linear and nonlinear feedback show that it is possible that the negative feedback increases, but the positive feedback decreases, the protein noise.

Keywords: External Noise; Gene expression; Auto-regulatory genetic network; Feedback regulation

1. Introduction

Auto-regulation is a ubiquitous motif in biochemical pathway, essential in the management of protein and chemical concentrations through feedback, i.e. the expression level of a gene is regulated negatively or positively by its own production (Keller, 1995; Smolen et al., 1998; Becskei and Serrano, 2000; Becskei et al., 2001; Cinquin and Demongeot, 2002; Hasty et al., 2000; Thattai and van Oudenaarden, 2001; Isaacs et al., 2003; Simpson et al., 2003). The fundamental importance of stochastic noise in gene expression has been realized by many authors (Hasty et al., 2000; Thattai and van Oudenaarden, 2001, 2002; Isaacs et al., 2003; Simpson et al., 2003; MacAdams and Arkin, 1997; Arkin et al., 1998; Paulsson et al., 2000; Paulsson and Ehrenberg, 2000; Berg et al., 2000; Kepler and Elston, 2001; Hasty and Collings, 2002; Ozbudak et al., 2002; Swain et al., 2002; Sasai and Wolynes, 2003; Paulsson, 2004). In general, the stochastic noise arises in gene expression in one of two ways. The internal noise is inherent in the biochemical reactions, i.e. it is determined by the structure, reaction rates, and species concentrations of the underlying biochemical networks (Hasty et al., 2000; Thattai and van Oudenaarden, 2001; MacAdams and Arkin, 1997). Its magnitude is proportional to the inverse of the system size, and its origin is often thermal. A more precise illustration is that internal noise is due to the fact that system itself consists of discrete particles. It is inherent in the very mechanism by which the state of the system evolves and cannot be divorced from its equations of motion Van Kampen (1992). Paulsson (2004) pointed out that random fluctuations in genetic networks are inevitable as chemical reactions are probabilistic and many genes, RNAs and proteins are present in low numbers per cell, and presented a simple equation that unifies and extends both the mathematical and biological perspectives. Raser and O'Shea (2005) summarized the origins, consequences and control of noise in gene expression. Arias and Hayward (2005) considered the implication of transcriptional noise for development and suggested the existence of molecular devices that are dedicated to filtering noise.

The external noise originates in the random variation of one or more of the externally set control parameters (Hasty

*Corresponding author. Tel.: +86 514 938 9604.
E-mail address: snowdiey@yahoo.com (Y. Tao).

0022-5193/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.jtbi.2006.06.003

et al., 2000), i.e. the external noise denotes fluctuation created in an otherwise deterministic system by the application of a random force, whose stochastic properties are supposed to be known (Van Kampen, 1992). Hasty et al. (2000) and Isaacs et al. (2003) investigated a single gene auto-regulatory network and demonstrated how external noise can be used to control the network in the concentration of protein. Their results suggested that an external noise source could be used as a switch and/or amplifier for gene expression. Recently, Becskei et al. (2005) developed a noise amplifier that detects fluctuations in the level of low-abundance mRNAs in yeast, and found that the observed fluctuations are not due to the low number of molecules expressed from a gene per se but originate in the random, rare events of gene activation. The frequency of these events and the correlation between stochastic expressions of genes in a single cell depend on the positioning of the genes along the chromosomes. These results imply that external noise turned out to be the dominant noise source in eukaryotic gene regulation at the promoter level. Paulsson (2005) pointed out that study of Becskei et al. shows how noise propagate through gene expression in yeast and shows that chromosomal position has a more central role than previously thought.

In this paper, a single gene auto-regulatory genetic network is investigated. Our main goal is to show that when the Gaussian noise sources are introduced into this system, how the feedback regulation influences the effect of the white noise, i.e. how the feedback regulation influences the statistical properties of the system. This paper is organized as follows. In Section 2.1 we present the general form of the auto-regulatory system, Section 2.2 shows the asymptotical stability and stationary-state statistics, the external noise analysis is given in Section 2.3, in Section 2.4 we discuss the linear and nonlinear feedback regulations, and the numerical simulations are presented in Section 2.5. The conclusions are given in Section 3.

2. Model and analysis

2.1. Network model

Consider a single gene auto-regulatory genetic network. Let $r(t)$ and $p(t)$ be the concentrations of mRNA and protein at time t, respectively. The rate equation of $r(t)$ and $p(t)$ originates as a first approximation. It describes the evolution of the averages of concentrations of mRNA and protein:

$$\frac{\mathrm{d}r}{\mathrm{d}t} = -\gamma r + f(p),$$

$$\frac{\mathrm{d}p}{\mathrm{d}t} = k'r + \gamma' p, \tag{1}$$

where the parameters γ and γ' are the decay rates of mRNA and protein, respectively, k' is the translation rate, and the function $f(p)$ represents the feedback regulation of the protein on the transcription with $f(p)>0$ for all possible values of p where $f(0)>0$ is called the fundamental transcription rate (Thattai and van Oudenaarden, 2001; Simpson et al., 2003; Cherry and Adler, 2000). For convenience, we assume that the feedback regulation function $f(p)$ is monotonic, i.e. $\mathrm{d}f(p)/\mathrm{d}p>0$ (or $\mathrm{d}f(p)/\mathrm{d}p<0$). The feedback is positive if $\mathrm{d}f(p)/\mathrm{d}p>0$, conversely, it is negative if $\mathrm{d}f(p)/\mathrm{d}p<0$.

In order to investigate how the feedback regulation acts on the external noise, the Gaussian white noise sources are incorporated:

$$\frac{\mathrm{d}r}{\mathrm{d}t} = -\gamma r + f(p) + \omega(t),$$

$$\frac{\mathrm{d}p}{\mathrm{d}t} = k'r - \gamma' p + \xi(t), \tag{2}$$

where both $\omega(t)$ and $\xi(t)$ are the white noises with $\langle\omega(t)\rangle = \langle\xi(t)\rangle = 0$, $\langle\omega(t)\omega(s)\rangle = 2D_\omega\delta(t-s)$, $\langle\xi(t)\xi(s)\rangle = 2D_\xi\delta(t-s)$, $\langle\omega(t)\xi(s)\rangle = 0$ (i.e. we assume that $\omega(t)$ and $\xi(t)$ are independent of each other), where $\delta()$ is the Dirac function. In general, this stochastic differential equation is called the Langevin equation.

2.2. Steady-state statistics of Eq. (2)

Let us first consider the stability of the deterministic dynamics Eq. (1). Let (r^*,p^*) be the equilibrium of Eq. (1), i.e. it is the solution of equation

$$-\gamma r + f(p) = 0,$$

$$k'r - \gamma' p = 0.$$

From the differential equation theory, the equilibrium (r^*,p^*) is locally asymptotically stable if the term $\gamma\gamma' - k'f'(p^*)$ is positive where $f'(p^*) = \mathrm{d}f(p)/\mathrm{d}p|_{p=p^*}$ (proof is in Appendix A). Obviously, if the feedback is negative, then (r^*,p^*) must be asymptotically stable. On the other hand, for the positive feedback, (r^*,p^*) is asymptotically stable if and only if $\gamma\gamma' - k'f'(p^*)>0$. In this paper, we always assume that (r^*,p^*) is asymptotically stable.

For Eq. (2), we consider only its steady-state statistics, i.e. the statistics of Eq. (2) when the system state $(r(t),p(t))$ is near the stable equilibrium (r^*,p^*) (Thattai and van Oudenaarden, 2001; Van Kampen, 1992; Tao et al., 2005). Let $\phi(r,p;t)$ be the joint probability density function of mRNA and protein. The Fokker–Planck equation of $\phi(r,p;t)$ (Van Kampen, 1992; Soong, 1973) is

$$\frac{\partial\phi(r,p;t)}{\partial t} = -\frac{\partial}{\partial r}(-\gamma r + f(p))\phi - \frac{\partial}{\partial p}(k'r - \gamma' p)\phi + D_\omega\frac{\partial^2\phi}{\partial r^2} + D_\xi\frac{\partial^2\phi}{\partial p^2}. \tag{3}$$

Thus, for the steady-state statistics, this Fokker–Planck equation implies that when the system state is near the stable equilibrium (r^*,p^*), for large time t, the expectations

of mRNA and protein concentrations are

$$\langle r\rangle = \lim_{t\to\infty}\langle r(t)\rangle = r^*,$$

$$\langle p\rangle = \lim_{t\to\infty}\langle <p(t)\rangle = p^*, \tag{4}$$

the variances of mRNA and protein concentrations, denoted by $\sigma_r^2(t)$ and $\sigma_p^2(t)$, are

$$\sigma_r^2 = \lim_{t\to\infty}\sigma_r^2(t) = \frac{\gamma'(\gamma+\gamma')D_\omega + f'(p^*)^2 D_\xi - k'f'(p^*)D_\omega}{(\gamma+\gamma')(\gamma\gamma' - k'f'(p^*)}$$
$$= \frac{1}{\gamma\gamma' - k'f'(p^*)}\left(\gamma' D_\omega + \frac{f'(p^*)^2 D_\xi - k'f'(p^*)D_\omega}{\gamma+\gamma'}\right),$$

$$\sigma_p^2 = \lim_{t\to\infty}\sigma_p^2(t) = \frac{\gamma(\gamma+\gamma')D_\xi + k'^2 D_\omega - k'f'(p^*)D_\xi}{(\gamma+\gamma')(\gamma\gamma' - k'f'(p^*))}$$
$$= \frac{1}{\gamma\gamma' - k'f'(p^*)}\left(\gamma D_\xi + \frac{k'^2 D_\omega - k'f'(p^*)D_\xi}{\gamma+\gamma'}\right), \tag{5}$$

and the covariance of $r(t)$ and $p(t)$, denoted by $Cov(r(t),p(t))$, is

$$Cov(r,p) = \lim_{t\to\infty} Cov(r(t),p(t)) = \frac{\gamma' k' D_\omega + \gamma f'(p^*)D_\xi}{(\gamma+\gamma')(\gamma\gamma' - k'f'(p^*))} \tag{6}$$

(proof is in Appendix B).

2.3. External noise in gene expression

Similarly to Paulsson (2004), in general Eq. (2) can be expressed as

$$\frac{dr}{dt} = R_r^+(r,p) - R_r^-(r,p) + \omega(t),$$
$$\frac{dp}{dt} = R_p^+(r,p) - R_p^-(r,p) + \xi(t), \tag{7}$$

where $R_r^+(r,p) = f(p)$, $R_r^-(r,p) = \gamma r$, $R_p^+(r,p) = k'r$ and $R_p^-(r,p) = \gamma' p$. Use $H_{r,r} = \partial\ln(R_r^-/R_r^+)/\partial\ln(r)$ to measure how the balance between production and elimination of mRNA is affected by itself (Paulsson, 2004). Similarly, we have also $H_{r,p}$, $H_{p,r}$ and $H_{p,p}$. Thus, the variances σ_r^2 and σ_p^2 around the stable equilibrium (r^*,p^*) can be also expressed as

$$\sigma_r^2 = \frac{1}{H_{r,r}H_{p,p} - H_{r,p}H_{p,p}} \times\left(D_\omega\tau_1 H_{p,p} + \frac{\langle r\rangle^2\tau_2 H_{r,p}((D_\xi/\langle p\rangle^2)\cdot(H_{r,p}/\tau_1) - (D_\omega/\langle r\rangle^2)\cdot(H_{p,r}/\tau_2))}{H_{r,r}/\tau_1 + H_{p,p}/\tau_2}\right),$$

$$\sigma_p^2 = \frac{1}{H_{r,r}H_{p,p} - H_{r,p}H_{p,p}} \times\left(D_\xi\tau_2 H_{r,r} + \frac{\langle p\rangle^2\tau_1 H_{p,r}((D_\omega/\langle r\rangle^2)\cdot(H_{p,r}/\tau_2) - (D_\xi/\langle p\rangle^2)\cdot(H_{r,p}/\tau_1))}{H_{r,r}/\tau_1 + H_{p,p}/\tau_2}\right) \tag{8}$$

with $H_{r,r}H_{p,p} - H_{r,p}H_{p,r} > 0$ that is equivalent to the asymptotical stability conditions of the equilibrium (r^*,p^*), where $\tau_1 = 1/\gamma$ and $\tau_2 = 1/\gamma'$ are average lifetimes of mRNA and protein molecules, respectively. Eq. (8) implies also that if $H_{r,p}\neq 0$, i.e. there is positive or negative feedback, then the variance of protein concentration, σ_p^2, can be rewritten as

$$\sigma_p^2 = \frac{D_\xi\tau_2 H_{r,r} + D_\omega b^2\tau_2(H_{p,r}H_{p,p}/H_{r,p})}{H_{r,r}H_{p,p} - H_{r,p}H_{p,r}} - \langle p\rangle^2\frac{\sigma_r^2}{\langle r\rangle^2}\cdot\frac{\tau_1}{\tau_2}\cdot\frac{H_{p,r}}{H_{r,p}}, \tag{9}$$

where $b = k'/\gamma$ is the average number of proteins produced per transcript (Thattai and van Oudenaarden, 2001). Similarly, if $H_{r,p} = 0$, i.e. there is no feedback, then σ_p^2 is

$$\sigma_p^2 = \frac{D_\xi}{H_{p,p}/\tau_2} + \langle p\rangle^2\frac{\sigma_r^2}{\langle r\rangle^2}\cdot\frac{H_{p,r}^2}{H_{p,p}^2}\cdot\frac{H_{p,p}/\tau_2}{H_{r,r}/\tau_1 + H_{p,p}/\tau_2}, \tag{10}$$

where the variance of mRNA is $\sigma_r^2 = \frac{D_\xi}{H_{r,r}/\tau_1}$.

From Paulsson (2004), we here use also the ratios $\sigma_r^2/\langle r\rangle^2$ and $\sigma_p^2/\langle p\rangle^2$ to measure the external noise in gene expression. Thus, the protein noise is

$$\frac{\sigma_p^2}{\langle p\rangle^2} = \frac{D_\xi\tau_2 H_{r,r} + D_\omega b^2\tau_2(H_{p,r}H_{p,p}/H_{r,p})}{(H_{r,r}H_{p,p} - H_{r,p}H_{p,r})\langle p\rangle^2} - \frac{\sigma_r^2}{\langle r\rangle^2}\cdot\frac{\tau_1}{\tau_2}\cdot\frac{H_{p,r}}{H_{r,p}} \tag{11}$$

if $H_{r,p}\neq 0$, and

$$\frac{\sigma_p^2}{\langle p\rangle^2} = \frac{D_\xi}{H_{p,p}/\tau_2}\langle p\rangle^{-2} + \frac{\sigma_r^2}{\langle r\rangle^2}\cdot\frac{H_{p,r}^2}{H_{p,p}^2}\cdot\frac{H_{p,p}/\tau_2}{H_{r,r}/\tau_1 + H_{p,p}/\tau_2} \tag{12}$$

if $H_{r,p} = 0$. Obviously, Eq. (11) reveals an important property: if the feedback is positive, then the effect of mRNA noise on the protein noise is negative; conversely, if the feedback is negative, then the effect of mRNA noise on the protein noise is positive. Eq. (12) is very similar to Paulsson's analysis for intrinsic and extrinsic noises in gene expression (Paulsson, 2004), i.e. if there is no feedback, the effect of mRNA noise on the protein noise is always positive, and the term $(D_\xi/H_{p,p}/\tau_2)\langle p\rangle^{-2}$ should represent the noise due to the births and deaths of protein molecules because of the white noise $\xi(t)$, and the term $\sigma_r^2/\langle r\rangle^2\cdot H_{p,r}^2/H_{p,p}^2\cdot(H_{p,p}/\tau_2)/(H_{r,r}/\tau_1 + H_{p,p}/\tau_2)$ the noise due to the fluctuations in reaction rates (Paulsson, 2004).

2.4. Linear and nonlinear auto-regulatory network

Case I: *Linear auto-regulatory network*. In this case, the feedback regulation $f(p)$ is assumed to be a linear function defined as $f(p)=kp+K$ where $k=0$, <0 and >0 correspond to the no feedback, negative feedback and positive feedback, respectively, and the parameter K is the fundamental transcriptional rate. The stable equilibrium point is $(r^*,p^*)=(K\gamma',Kk')/(\gamma\gamma'-kk')$ with $\gamma\gamma'-kk'>0$, and the expectations are $\langle r\rangle=r^*$ and $\langle p\rangle=p^*$ around (r^*,p^*). From Eq. (5), the protein noise is given by

$$\frac{\sigma_p^2}{\langle p\rangle^2}=\frac{\langle p\rangle^{-1}}{Kk'}\left(\gamma D_\xi+k'\,\frac{k'D_\omega+kD_\xi}{\gamma+\gamma'}\right). \tag{13}$$

Notice that $\partial(\sigma_p^2/\langle p\rangle^2)/\partial k<0$ for all $-\infty<k<\gamma\gamma'/k'$. Thus, for the linear feedback regulation $f(p)=kp+K$, if the fundamental transcriptional rate is fixed, then we must have that the positive feedback decreases, but negative feedback increases, the protein noise, i.e.

$$\left.\frac{\sigma_p^2}{\langle p\rangle^2}\right|_{k>0}<\left.\frac{\sigma_p^2}{\langle p\rangle^2}\right|_{k=0}<\left.\frac{\sigma_p^2}{\langle p\rangle^2}\right|_{k<0}. \tag{14}$$

In the above analysis, if $D_\xi=0$, i.e. the protein noise is only due to the random fluctuations of mRNA, or mRNA provides the randomly fluctuating environment for protein, as mRNA fluctuations randomize protein synthesis (Paulsson, 2004), then the noise of protein can be rewritten as

$$\frac{\sigma_p^2}{\langle p\rangle^2}=\frac{k'D_\omega}{K(\gamma+\gamma')\langle p\rangle}=\frac{\gamma\gamma'-kk'}{\gamma+\gamma'}\cdot\frac{D_\omega}{K^2}, \tag{15}$$

i.e. if protein noise come entirely from few transcripts, it should decrease with the rate of transcription (increasing mRNA numbers) but not with the rate of translation (increasing only protein numbers) (Paulsson, 2005).

Case II. *Nonlinear auto-regulatory network*. In this case, for convenience both the positive and negative feedback are taken as the Hill-type functions (Cherry and Adler, 2000; Kaern, 2003). The feedback is defined as $f(p)=p^\alpha/(\beta+p^\alpha)+\theta$ for positive, and $f(p)=\beta/(\beta+p^\alpha)$ for negative, with $\alpha>0$, $\beta>0$ and $\theta>0$, where θ is the fundamental transcription rate for positive feedback. From Eq. (5), the protein noise around a stable equilibrium (r^*,p^*) is given by

$$\frac{\sigma_p^2}{\langle p\rangle^2}=\frac{\gamma D_\xi+\gamma'k'D_\omega/f'(p^*)}{\gamma\gamma'-k'f'(p^*)}\langle p\rangle^{-2}-\frac{\gamma'^2}{k'f'(p^*)}\cdot\frac{\sigma_r^2}{\langle r\rangle^2}, \tag{16}$$

where

$$f'(p^*)=\left.\frac{\mathrm{d}f(p)}{\mathrm{d}p}\right|_{p=p^*}=\left.\frac{\alpha\beta p^{\alpha-1}}{(\beta+p^\alpha)^2}\right|_{p=p^*}>0$$

for positive feedback and

$$f'(p^*)=\left.\frac{\mathrm{d}f(p)}{\mathrm{d}p}\right|_{p=p^*}=\left.-\frac{\alpha\beta p^{\alpha-1}}{(\beta+p^\alpha)^2}\right|_{p=p^*}<0$$

for negative feedback. This result can be explained using Eq. (13), i.e. the negative feedback will lead that the mRNA noise has a positive contribution to the protein noise, and the positive feedback will lead that the mRNA noise has a negative contribution to the protein noise.

2.5. Numerical simulation

For the numerical simulation, without loss of generality, we consider only a stochastic difference equation that corresponds to Eq. (2):

$$\begin{aligned}r_{t+1}&=(1-\gamma)r_t+f(p_t)+\omega_t,\\ p_{t+1}&=k'r_t+(1-\gamma')p_t+\xi_t,\end{aligned} \tag{17}$$

where both ω_t and ξ_t are random variables with $\omega_t\sim N(0,\sigma_\omega^2)$ and $\xi_t\sim N(0,\sigma_\xi^2)$ for $t=1,2,\ldots,\langle\omega_t\omega_s\rangle=0$ and $\langle\xi_t\xi_s\rangle=0$ if $t\neq s$, and $\langle\omega_t\xi_s\rangle=0$ for all possible t and s. Similarly to the analysis in above, both the linear and nonlinear feedback regulations will be simulated.

The linear feedback $f(p_t)$ is given by $f(p_t)=kp_t+K$ where, similarly to above analysis about the linear auto-regulatory network, the parameter $k=0$, <0 and >0 correspond to the no feedback, negative feedback and positive feedback, respectively, and the parameter K is a constant for all three possible situations. It is easy to know that the equilibrium point of the deterministic difference dynamics

$$\begin{aligned}r_{t+1}&=(1-\gamma)r_t+kp_t+K,\\ p_{t+1}&=k'r_t+(1-\gamma')p_t\end{aligned}$$

is $(r^*,p^*)=(K\gamma',Kk')/(\gamma\gamma'-kk')$ with $\gamma\gamma'-kk'>0$. The simulation is completed using MATLAB where the parameters are taken as $\gamma=0.9$, $\gamma'=0.1$, $\alpha=10$, $k'=0.1$, $\sigma_\omega^2=\sigma_\xi^2=1$, and $k=-0.8,-0.7,\ldots,-0.1,0,0.1,\ldots,0.7,0.8$. The statistics of the simulation results for different k values are plotted in Figs. 1 and 2, where the statistics of mRNA concentration is plotted in Fig. 1, and the statistics of protein concentration is plotted in Fig. 2. These simulation results support strongly the theoretical analysis.

For the nonlinear feedback simulation, the positive feedback is $f(p_t)=p_t^\alpha/(\beta+p_t^\alpha)+\theta$, and the negative feedback $f(p_t)=\beta/(\beta+p_t^\alpha)$ (Hill-type functions). For both the positive and negative feedback, i.e.

$$\begin{aligned}r_{t+1}&=(1-\gamma)r_t+\frac{p_t^\alpha}{\beta+p_t^\alpha}+\theta+\omega_t,\\ p_{t+1}&=k'r_t+(1-\gamma')p_t+\xi_t\end{aligned}$$

and

$$\begin{aligned}r_{t+1}&=(1-\gamma)r_t+\frac{\beta}{\beta+p_t^\alpha}+\omega_t,\\ p_{t+1}&=k'r_t+(1-\gamma')p_t+\xi_t,\end{aligned}$$

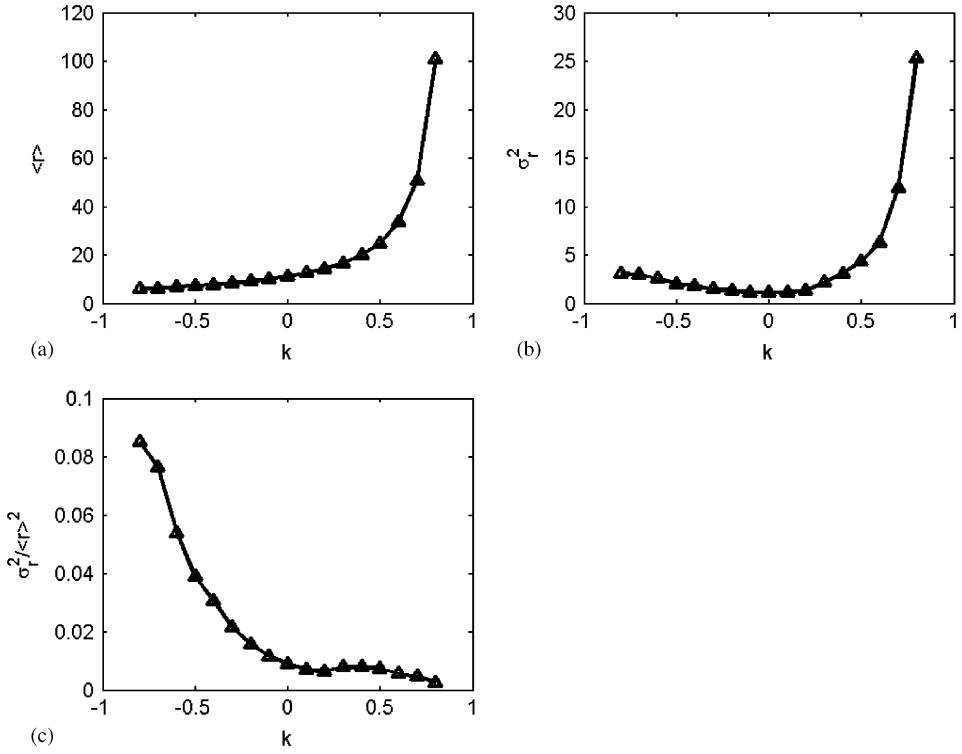

Fig. 1. For the linear feedback, the statistics of mRNA concentration for different k values are plotted: (a) expectation $\langle r\rangle$; (b) variance σ_r^2; (c) mRNA noise $\sigma_r^2/\langle r\rangle^2$.

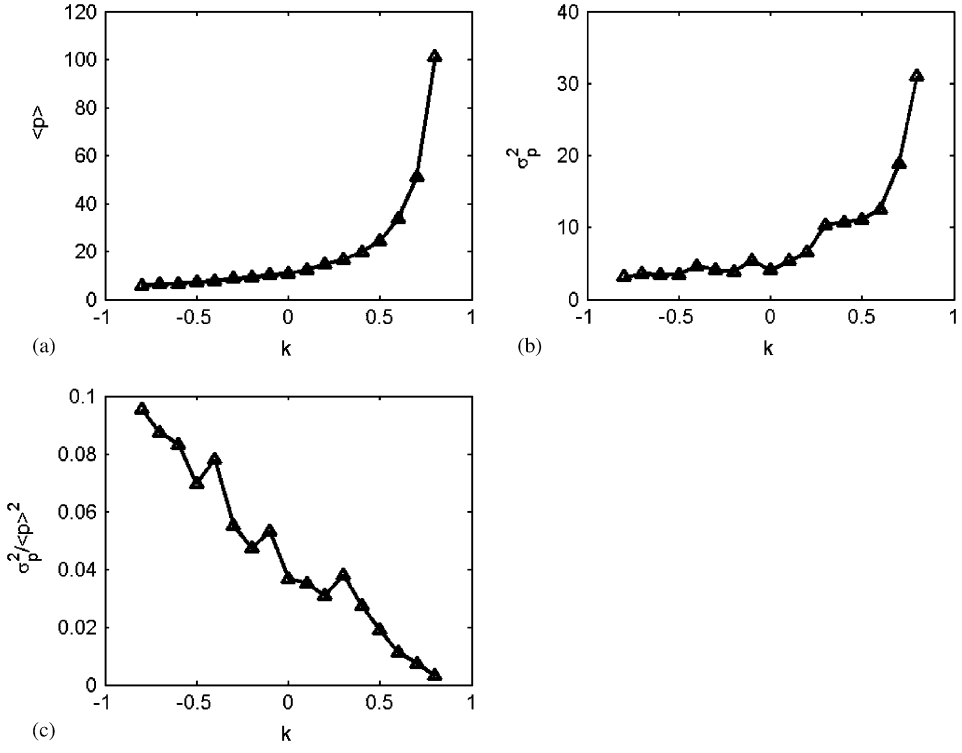

Fig. 2. For the linear feedback, the statistics of protein concentration for different k values are plotted: (a) expectation $\langle p\rangle$; (b) variance σ_p^2; (c) protein noise $\sigma_p^2/\langle p\rangle^2$ that decreases with increasing of k values.

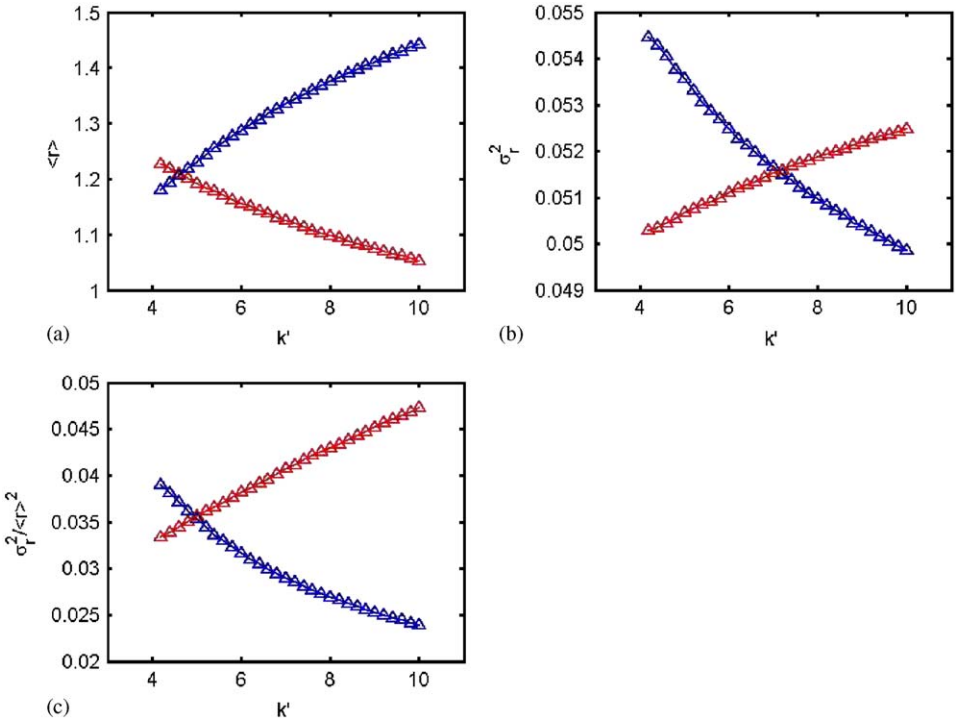

Fig. 3. For the nonlinear feedback, the statistics of mRNA concentration for different k' values are plotted where blue line corresponds the positive feedback, and red line the negative feedback: (a) expectation $\langle r\rangle$; (b) variance σ_r^2; (c) mRNA noise $\sigma_r^2/\langle r\rangle^2$.

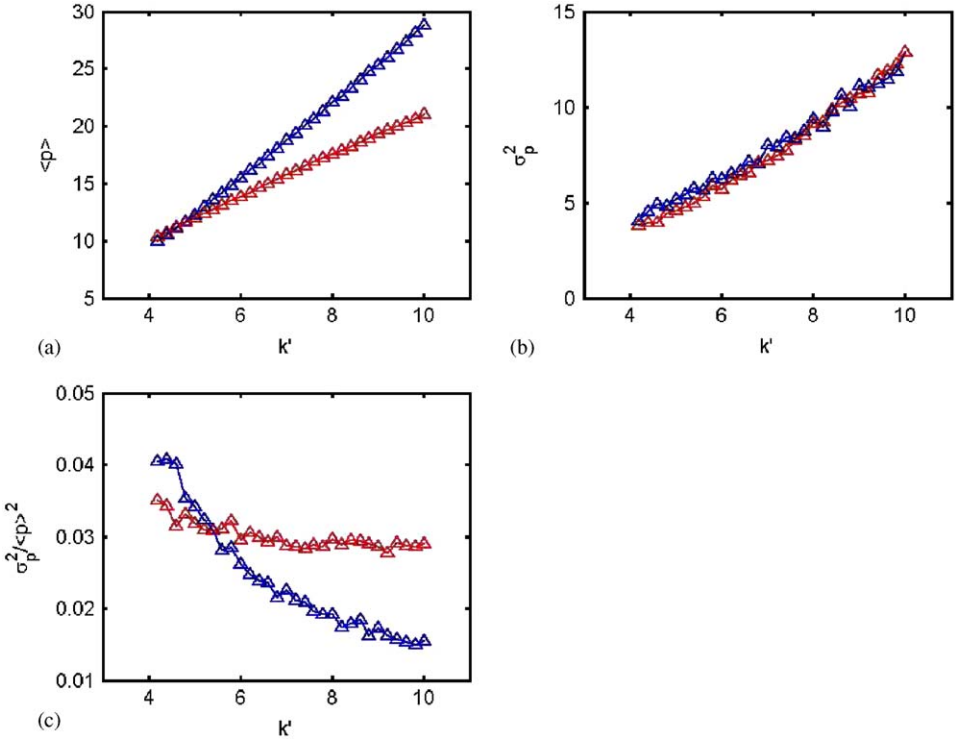

Fig. 4. For the nonlinear feedback, the statistics of protein concentration for different k' values are plotted where blue line corresponds to the positive feedback, and red line the negative feedback: (a) expectation $\langle p\rangle$; (b) variance σ_p^2; (c) protein noise $\sigma_p^2/\langle p\rangle^2$ that shows also that for the nonlinear feedback, it is still possible that the negative feedback increases, but the positive feedback reduces, the protein noise.

we take the parameters $\alpha = 0.5$, $\beta = 5$, $\gamma = \gamma' = 0.5$, $\theta = 0.2$, and $k' = 4 + 0.2 \times i$ for $i = 1, 2, \ldots, 30$, and for simplicity we let $\sigma_\omega^2 = 0$ and $\sigma_\xi^2 = 1$. The simulation results for different k' values are plotted in Figs. 3 and 4, where the statistics of mRNA concentration is plotted in Fig. 3, and the statistics of protein concentration is plotted in Fig. 4.

3. Conclusion

In this paper, the steady-state statistics of a single gene auto-regulatory genetic network with the additive external Gaussian white noises is investigated. We here accept Paulsson's (2004) suggestion using square of standard deviation to measure the mRNA and protein noises. Similar to Paulsson (2004), the protein noise can be also decomposed into two parts: the central finding is that the negative feedback will result in that mRNA noise has a positive contribution to the protein noise, but the positive feedback will result in that the mRNA noise has a negative contribution to the protein noise. It is necessary to point out that if there is no feedback, the mRNA noise has always a positive contribution to the protein noise. The analysis of linear and nonlinear feedback and the results of numerical simulations show also that it is possible that the negative feedback increases, but the positive feedback decreases, the protein noise. However, it is important to note that the negative (or positive) feedback makes an mRNA-independent contribution to the total noise (see Eq. (16)). This result provides an important theoretical intuition for understanding the stochastic fluctuation in gene expression and gene regulation in the real living system.

Appendix A

The Jacobian matrix of Eq. (1) at the equilibrium (r^*, p^*) is

$$\mathbf{J} = \begin{pmatrix} -\gamma & f'(p^*) \\ k' & -\gamma' \end{pmatrix},$$

where $f(p^*) = \mathrm{d}f(p^*)/\mathrm{d}p$, and the eigenvalues of $\mathbf{J}$ are

$$\lambda_{1,2} = \frac{(\gamma + \gamma') \pm \sqrt{(\gamma + \gamma')^2 - 4(\gamma\gamma' - k'f'(p^*))}}{2}.$$

Thus, the equilibrium (r^*, p^*) is locally asymptotically stable if and only is the term $\gamma\gamma' - k'f'(p^*)$ is positive, i.e. the real parts of the eigenvalues λ_1 and λ_2 are negative.

Appendix B

In order to obtain the steady-state statistics of Eq. (2), let $x = r - r^*$ and $y = p - p^*$, substitute these in Eq. (3), expand the coefficients in x and y and retain only the lowest non-zero terms:

$$\frac{\partial\phi(x,y;t)}{\partial t} = -\frac{\partial}{\partial x}(-\gamma x + f'(p^*)y)\phi - \frac{\partial}{\partial y}(k'x - \gamma' y) + D_\omega \frac{\partial^2\phi}{\partial x^2} + D_\xi \frac{\partial^2\phi}{\partial y^2}. \tag{18}$$

Using boundary conditions $\lim_{x\to\pm\infty}\phi(x,y;t) = 0$, $\lim_{y\to\pm\infty}\phi(x,y;t) = 0$, $\lim_{x\to\pm\infty}\partial\phi(x,y;t)/\partial x = 0$ and $\lim_{y\to\infty}\partial\phi(x,y;t)/\partial y = 0$, we have

$$\frac{\mathrm{d}\langle x(t)\rangle}{\mathrm{d}t} = \int_{-\infty}^{\infty}\int_{-\infty}^{\infty} x\frac{\partial\phi}{\partial t}\,\mathrm{d}x\,\mathrm{d}y = -\gamma\langle x(t)\rangle + f'(p^*)\langle y(t)\rangle,$$

$$\frac{\mathrm{d}\langle y(t)\rangle}{\mathrm{d}t} = \int_{-\infty}^{\infty}\int_{-\infty}^{\infty} y\frac{\partial\phi}{\partial t}\,\mathrm{d}x\,\mathrm{d}y = k'\langle x(t)\rangle - \gamma'\langle y(t)\rangle, \tag{19}$$

and

$$\frac{\mathrm{d}\langle x(t)^2\rangle}{\mathrm{d}t} = \int_{-\infty}^{\infty}\int_{-\infty}^{\infty} x^2\frac{\partial\phi}{\partial t}\,\mathrm{d}x\,\mathrm{d}y = -2\gamma\langle x(t)^2\rangle + 2f'(p^*)\langle x(t)y(t)\rangle + 2D_\omega,$$

$$\frac{\mathrm{d}\langle x(t)y(y)\rangle}{\mathrm{d}t} = \int_{-\infty}^{\infty}\int_{-\infty}^{\infty} xy\frac{\partial\phi}{\partial t}\,\mathrm{d}x\,\mathrm{d}y = k'\langle x(t)^2\rangle - (\gamma + \gamma')\langle x(t)y(t)\rangle + f'(p^*)\langle y(t)^2\rangle,$$

$$\frac{\mathrm{d}\langle y(t)^2\rangle}{\mathrm{d}t} = \int_{-\infty}^{\infty}\int_{-\infty}^{\infty} y^2\frac{\partial\phi}{\partial t}\,\mathrm{d}x\,\mathrm{d}y = 2k'\langle x(t)y(t)\rangle - 2\gamma'\langle y(t)^2\rangle + 2D_\xi. \tag{20}$$

For Eq. (19), it is easy to see that the origin $(0,0)$ is its globally asymptotically stable equilibrium, that corresponds to

$$\frac{\mathrm{d}}{\mathrm{d}t}\begin{pmatrix}\langle x(t)\rangle \\ \langle y(t)\rangle\end{pmatrix} = 0,$$

since the stability of Eq. (19) is identical with the stability of Eq. (1). This shows that the expectations of the mRNA and protein concentrations are $\langle r\rangle = \lim_{t\to\infty} = r^*$ and $\langle p\rangle = \lim_{t\to\infty} = p^*$, respectively.

Similarly, for Eq. (20), its asymptotically stable equilibrium is

$$\langle x^2\rangle = \lim_{t\to\infty}\langle x(t)^2\rangle = \frac{\gamma'(\gamma + \gamma')D_\omega + k^2 D_\xi - k'f'(p^*)D_\omega}{(\gamma + \gamma')(\gamma\gamma' - k'f'(p^*))},$$

$$\langle xy\rangle = \lim_{t\to\infty}\langle x(t)y(t)\rangle = \frac{\gamma' k' D_\omega + \gamma f'(p^*)D_\xi}{(\gamma + \gamma')(\gamma\gamma' - k'f'(p^*))},$$

$$\langle y^2\rangle = \lim_{t\to\infty}\langle y(t)^2\rangle = \frac{\gamma(\gamma+\gamma')D_\xi + k'^2 D_\omega - k'f'(p^*)D_\xi}{(\gamma+\gamma')(\gamma\gamma' - k'f'(p^*))}, \quad (21)$$

that corresponds to

$$\frac{\mathrm{d}}{\mathrm{d}t}\begin{pmatrix}\langle x(t)^2\rangle\\ \langle x(t)y(t)\rangle\\ \langle y(t)^2\rangle\end{pmatrix} = 0,$$

since the Jacobian matrix of Eq. (20) at the equilibrium is

$$\begin{pmatrix}-2\gamma & 2f'(p^*) & 0\\ k' & -(\gamma+\gamma') & f'(p^*)\\ 0 & 2k' & -2\gamma'\end{pmatrix},$$

and the eigenvalues of the Jacobian matrix are

$$\lambda_1 = -(\gamma+\gamma'),$$

$$\lambda_{1,2} = -(\gamma+\gamma') \pm \sqrt{(\gamma+\gamma')^2 - 4(\gamma\gamma' - k'f'(p^*))}.$$

This means that if the origin $(0,0)$ of Eq. (19) is globally asymptotically stable, then the equilibrium of Eq. (20) given by Eq. (21) must be also asymptotically stable. Notice that $x = r - r^*$ and $y = p - p^*$. Thus, for large time t, we must have $\sigma_r^2 = \langle x^2\rangle$, $\sigma_p^2 = \langle y^2\rangle$ and $Cov(r,p) = \langle xy\rangle$.

References

Arias, A.M., Hayward, P., 2005. Nature Rev. Genetics 7, 34–44.
Arkin, A., Ross, J., McAdams, H.H., 1998. Genetics 149, 1633–1648.
Becskei, A., Serrano, L., 2000. Nature 405, 590–593.
Becskei, A., Seraphin, B., Serrano, L., 2001. EMBO J. 20, 2528–2535.
Becskei, A., Kaufmann, B.B., van Oudenaarden, A., 2005. Natural Genetics 37, 973–1044.
Berg, O.G., Paulsson, J., Ehrenberg, M., 2000. Biophys. J. 79, 2944–2953.
Cherry, J.L., Adler, F.R., 2000. J. Theor. Biol. 203, 117–133.
Cinquin, O., Demongeot, J., 2002. J. Theor. Biol. 216, 229–241.
Hasty, J., Collings, J.J., 2002. Nature Genetics 31, 13–14.
Hasty, J., Pradines, J., Dolink, M., Collins, J.J., 2000. Proc. Natl Acad. Sci. 97, 2075–2080.
Isaacs, F.J., Hasty, J., Cantor, C.R., Collins, J.J., 2003. Proc. Natl Acad. Sci. 100, 7714–7719.
Kaern, M., 2003. Regulatory dynamics in engineered gene networks—the physico-chemical foundation of transcriptional regulation with application to systems biology, ICBS 2003, Fourth International Conference on Systems Biology.
Keller, A.D., 1995. J. Theor. Biol. 172, 169–185.
Kepler, T.B., Elston, T.C., 2001. Biophys. J. 81, 3116–3136.
MacAdams, H.H., Arkin, A., 1997. Proc. Natl Acad. Sci. 94, 814–819.
Ozbudak, E.M., Thattai, M., Kurtser, I., Grossman, A.D., van Oudenaarden, A., 2002. Nature Genetics 31, 69–73.
Paulsson, J., 2004. Nature 427, 415–418.
Paulsson, J., 2005. Natural Genetics 37, 923–926.
Paulsson, J., Ehrenberg, M., 2000. Phys. Rev. Lett. 84, 5447–5450.
Paulsson, J., Berg, O.G., Ehrenberg, M., 2000. Proc. Natl Acad. Sci. 97, 7148–7153.
Raser, J.M., O'Shea, E.K., 2005. Science 309, 2010–2013.
Sasai, M., Wolynes, P.G., 2003. Proc. Natl Acad. Sci. 100, 2374–2379.
Simpson, M.L., Cox, C.D., Sayler, G.S., 2003. Proc. Natl Acad. Sci. 100, 4551–4556.
Smolen, P., Baxter, D.A., Byrne, J.H., 1998. Am. J. Cell Physiol. 274, 531–542.
Soong, T.T., 1973. Random Differential Equations in Science and Engineering. Academic Press, New York and London.
Swain, P.S., Elowitz, M.B., Siggia, E.D., 2002. Proc. Natl Acad. Sci. 99, 12795–12800.
Tao, Y., Jia, Y.T., Dewey, T.G., 2005. J. Chem. Phys. 122, 124108.
Thattai, M., van Oudenaarden, A., 2001. Proc. Natl Acad. Sci. 98, 8614–8619.
Thattai, M., van Oudenaarden, A., 2002. Biophys. J. 82, 2943–2950.
Van Kampen, N.G., 1992. Stochastic Process Theory in Physics and Chemistry. North-Holland, Amsterdam.