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Effect of feedback regulation on stochastic gene expression

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Abstract

Stochastic noise in gene expression arises as a result of species in small copy number undergoing transitions between discrete chemical states. Here the noise in a single gene network is investigated using the Ω-expansion techniques. We show that the linear noise approximation implies an invariant relationship between the normalized variances and normalized covariance in steady-state statistics. This invariant relationship provides an exactly statistical interpretation for why the stochastic noise in gene expression should be measured by the normalized variance. The nature of the normalized variance reveals the basic relationship between the stochasticity and system size in gene expression. The linear noise approximation implies also that for both mRNA and protein, the total noise can be decomposed into two basic components, one concerns the contribution of average number of molecules, and other the contribution of interactions between mRNA and protein. For the situation with linear feedback, our results clearly show that for two genes with the same average number of protein molecules, the gene with negative feedback will have a small protein noise, i.e., the negative feedback will reduce the protein noise. For the effect of the burst size on the protein noise, we show also that the protein intrinsic noise will decrease with the increase of the burst size, but the protein extrinsic noise is independent of the burst size.

Keywords: Gene expression; Feedback regulation; Linear noise approximation; Intrinsic and extrinsic noises

1. Introduction

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. In order to identify the sources of noise in gene expression, Ozbudark et al. (2002) incorporated a single fluorescent reporter gene, the green fluorescent protein gene (*gfp*), into the chromosome of *Bacillus subtilis*, varied independently the rates of transcription and translation of the reporter gene, and quantitatively measured the resulting changes in the phenotypic noise characteristics. Their result provides the first direct experimental evidence of the biochemical origin of phenotypic noise, demonstrating that the level of phenotypic variation in an isogenic population can be regulated by genetic parameters. This result is consistent with a long-standing hypothesis that protein fluctuations depend on the number of proteins made per mRNA transcript (Paulsson, 2004; Thattai and van Oudenaarden, 2001; McAdams and Arkin, 1997; Rigney and Schieve, 1977; Berg, 1978; Paulsson and Ehrenberg, 2000, 2001). Elowitz et al. (2002) instead inserted two types of *gfp* into the *Escherichia coli* chromosome and used correlation between them to infer where the fluctuations came from (Paulsson, 2004). Blake et al. (2003) investigated the stochastic gene expression in *Saccharomyces cerevisiae*. They showed that stochasticity arising from transcription contributes significantly to the level of heterogeneity within a eukaryotic clonal population, in contrast to observations in prokaryotes, (Ozbudark et al., 2002) and that such noise can be modulated at the translation level. They suggested that eukaryotes differ from prokaryotes because promoter fluctuations and transcriptional reinitiation produce a non-monotonous transcription noise (see also Paulsson, 2004).

An important issue for biological systems is how gene regulation is controlled given its stochastic nature. Becski

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and Serrano (2000) designed and constructed a simple genetic circuit consisting of a regulator and transcriptional repressor modules in *E. coli*, and demonstrated an increase in stability produced by negative feedback. Becski et al. (2001) used a positive feedback to construct a synthetic gene switch in *S. cerevisiae*. Thattai and van Oudenaarden developed a theoretical framework to investigate the stochastic noise in gene regulatory networks (Paulsson, 2004, see also Ozbudark et al., 2002; Thattai and van Oudenaarden, 2002; Tao, 2004; Tao et al., 2005) and they suggested that the noise can be measured by the Fano factor, which is defined as the ratio of variance to average, because the Fano factor of an arbitrary stochastic system reveals deviations from Poissonian behavior. A similar model was analyzed independently by Paulsson et al. (2000) (see also Paulsson and Ehrenberg, 2001; Berg et al., 2000). They calculated the stationary distribution for geometrically distributed translation bursts, and formulated the variance over squared average in terms of internal and time-averaged external fluctuations.

Recently, Paulsson (2004, 2005) interpreted the fluctuation–dissipation theorem (linear noise approximation) in gene expression. He suggested that the noise in gene expression should be measured by the variance over squared average rather than the Fano factor. Because of that, in statistics, the variance should be normalized by the squared average since the variance is a second order moment. On the other hand, he pointed out that the Fano factor only works well for univariate discrete random process, where the variance often is proportional to the average with a proportionality constant that reflects the overall nature of the process, and for multivariate random processes, the Poisson distribution holds no special position and using the Fano factor can be misleading. For the noise decomposition, Paulsson illustrated that all cell components display intrinsic noise due to random births and deaths of individual molecules, and extrinsic noise due to fluctuations in reaction rates, and that the terms "intrinsic" and "extrinsic" generically distinguish between the origin and propagation of noise, and their biological meaning is always defined in conjunction with a specified component or process. For the mRNA–protein and gene–mRNA–protein models, Paulsson (2004, 2005) showed that the intrinsic noise depends on the average number of molecules and how systematic adjustments quench spontaneous fluctuations.

In this paper, a single gene regulatory network is investigated. Our main goal is to show how the feedback regulation acts on the stochastic noise in gene expression. Actually, this model has been studied by some authors, but here we will focus our attention on why we should use the normalized variance (variance over squared average) to measure the noise rather than the Fano factor, on what the extrinsic noise means in statistics if the noise is measured by the normalized variance, and on how the linear and nonlinear feedback acts on the noise.

2. Theory

2.1. Single gene network

Consider a single gene regulatory network (i.e., mRNA–protein system), where the concentrations of mRNA and protein at time t are denoted by $r(t)$ and $p(t)$, respectively. The macroscopic rates equation is given by

$$\frac{\mathrm{d}r}{\mathrm{d}t} = s_r^+(p) - s_r^-(r),$$
$$\frac{\mathrm{d}p}{\mathrm{d}t} = s_p^+(r) - s_p^-(p), \tag{1}$$

where $s_r^\pm$ and $s_p^\pm$ are the macroscopic rates of mRNA and protein with $s_r^-(r) = r/\tau_r$ and $s_p^-(p) = p/\tau_p$ where τ_r and τ_p are the lifetimes of mRNA and protein molecules, respectively. The term $s_r^+(p)$ in Eq. (1) represents the feedback of protein on the transcription. For this system, we assume that there is at least one asymptotically stable fixed point, denoted by $(r^\star, p^\star)$.

2.2. Linear noise approximation

Let Ω be the size parameter of the system (normally, this parameter is defined as the volume) (van Kampen, 1992). The numbers of mRNA and protein molecules can be expressed as $n_r = \Omega r$ and $n_p = \Omega p$. For the stochastic fluctuations in mRNA and protein numbers, the probabilities of having n_r mRNAs and n_p proteins are described by a birth-and-death Markov process with events

$$n_r \xrightarrow{s_r^\pm} n_r \pm 1,$$
$$n_p \xrightarrow{s_p^\pm} n_p \pm 1,$$

where $S_r^\pm = \Omega s_r^\pm$ and $S_p^\pm = \Omega s_p^\pm$ are the mesoscopic rates. According to Paulsson (2004), use $H_{r,r} = \partial \ln(S_r^-/S_r^+)/\partial \ln(n_r)$ to measure how the balance between production and elimination of mRNA is affected by itself. Similarly, we have also $H_{r,p}$, $H_{p,r}$, and $H_{p,p}$.

Let $\Phi(n_r, n_p; t)$ be the joint probability distribution that the number of mRNAs and proteins equal exactly n_r and n_p at time t. The master equation of $\Phi(n_r, n_p; t)$ is

$$\partial_t \Phi(n_r, n_p; t) = \Omega\Big[(E_r^+ - 1)s_r^-\Big(\frac{n_r}{\Omega}\Big)\Phi + (E_r^- - 1)s_r^+\Big(\frac{n_p}{\Omega}\Big)\Phi + (E_p^+ - 1)s_p^-\Big(\frac{n_p}{\Omega}\Big)\Phi + (E_p^- - 1)s_p^+\Big(\frac{n_r}{\Omega}\Big)\Phi\Big], \tag{2}$$

where the symbol E is the step operator, which is defined as $E^\pm g(n) = g(n \pm 1)$. From van Kampen (1992), the joint probability distribution $\Phi(n_r, n_p; t)$ can be anticipated to have a sharp maximum around the macroscopic values $n_r(t) = \Omega r(t)$ and $n_p(t) = \Omega p(t)$ determined by Eq. (1) with

the width of order $n_r^{1/2}, n_p^{1/2} \sim \Omega^{1/2}$. Let

$$n_r = \Omega r(t) + \Omega^{1/2}\xi_r,$$
$$n_p = \Omega p(t) + \Omega^{1/2}\xi_p, \tag{3}$$

where $r(t)$ and $p(t)$ are the solutions of Eq. (1), and ξ_r and ξ_p are two new variables associated with number fluctuations. The joint probability distribution $\Phi(n_r, n_p; t)$ is now rewritten as the function of ξ_r and ξ_p, i.e., $\Phi(n_r, n_p; t) = \Psi(\xi_r, \xi_p; t)$. Using the Ω-expansion (van Kampen, 1992), we have

$$\begin{aligned}\frac{\partial \Psi}{\partial t} = & -\frac{\partial}{\partial \xi_r}\left(-\frac{\mathrm{d}s_r^-(r)}{\mathrm{d}r}\xi_r + \frac{\mathrm{d}s_r^+(p)}{\mathrm{d}p}\xi_p\right)\Psi \\ & + \frac{1}{2}(s_r^+(p) + s_r^-(r))\frac{\partial^2 \Psi}{\partial \xi_r^2} \\ & - \frac{\partial}{\partial \xi_p}\left(\frac{\mathrm{d}s_p^+(r)}{\mathrm{d}r}\xi_r - \frac{\mathrm{d}s_p^-(p)}{\mathrm{d}p}\xi_p\right)\Psi \\ & + \frac{1}{2}(s_p^+(r) + s_p^-(p))\frac{\partial^2 \Psi}{\partial \xi_p^2}\end{aligned} \tag{4}$$

(see Appendix). This equation is a linear Fokker–Planck equation, whose coefficients depend on time t through $r(t)$ and $p(t)$, and it is called the linear noise approximation (van Kampen, 1992) (also called the fluctuation–dissipation theorem in physics, Paulsson, 2004, 2005).

When the state of Eq. (1) is near the stable fixed point $(r^\star, p^\star)$, Eq. (4) can be approximated as

$$\begin{aligned}\frac{\partial \Psi}{\partial t} = & -\frac{\partial}{\partial \xi_r}(a_{11}\xi_r + a_{12}\xi_p)\Psi + D_r\frac{\partial^2 \Psi}{\partial \xi_r^2} \\ & - \frac{\partial}{\partial \xi_p}(a_{21}\xi_r + a_{22}\xi_p)\Psi + D_p\frac{\partial^2 \Psi}{\partial \xi_p^2}\end{aligned} \tag{5}$$

with boundary conditions

$$\lim_{\xi_r, \xi_p \to \pm\infty} \Psi = \lim_{\xi_r, \xi_p \to \pm\infty} \frac{\partial \Psi}{\partial \xi_r} = \lim_{\xi_r, \xi_p \to \pm\infty} \frac{\partial \Psi}{\partial \xi_p} = 0,$$

where $D_r = r^\star/\tau_r$, $D_p = p^\star/\tau_p$, and

$$a_{11} = -\frac{\mathrm{d}s_r^-(r^\star)}{\mathrm{d}r} = -\frac{H_{r,r}}{\tau_r},$$
$$a_{12} = \frac{\mathrm{d}s_r^+(p^\star)}{\mathrm{d}p} = -\frac{r^\star}{p^\star}\cdot\frac{H_{r,p}}{\tau_r},$$
$$a_{21} = \frac{\mathrm{d}s_p^+(r^\star)}{\mathrm{d}r} = -\frac{p^\star}{r^\star}\cdot\frac{H_{p,r}}{\tau_p},$$
$$a_{22} = -\frac{\mathrm{d}s_p^-(p^\star)}{\mathrm{d}p} = -\frac{H_{p,p}}{\tau_p}.$$

Since the fixed point $(r^\star, p^\star)$ is asymptotically stable, the matrix $\mathbf{A} = (a_{ij})_{2\times 2}$ satisfies that $a_{11} + a_{22} < 0$ and $a_{11}a_{22} - a_{12}a_{21} > 0$. Notice that

$$\frac{\mathrm{d}\langle \xi_r \rangle}{\mathrm{d}t} = a_{11}\xi_r + a_{12}\xi_p,$$
$$\frac{\mathrm{d}\langle \xi_p \rangle}{\mathrm{d}t} = a_{21}\xi_r + a_{22}\xi_p \tag{6}$$

and

$$\frac{\mathrm{d}\mathbf{\Xi}}{\mathrm{d}t} = \mathbf{A}\mathbf{\Xi} + (\mathbf{A}\mathbf{\Xi})^{\mathrm{T}} + 2\mathbf{D}, \tag{7}$$

where $\mathbf{\Xi} = (\Xi_{ij})_{2\times 2}$ with $\Xi_{11} = \langle \xi_r^2 \rangle$, $\Xi_{12} = \Xi_{21} = \langle \xi_r \xi_p \rangle$ and $\Xi_{22} = \langle \xi_p^2 \rangle$, $\mathbf{A} = (a_{ij})_{2\times 2}$ and $\mathbf{D} = (d_{ij})_{2\times 2}$ with $d_{11} = D_r$, $d_{12} = d_{21} = 0$ and $d_{22} = D_p$ (see Appendix). Notice that the expectations and variances of n_r and n_p are $\langle n_r \rangle = \Omega r$, $\langle n_p \rangle = \Omega p$, $\sigma_r^2 = \Omega\langle \xi_r^2 \rangle$ and $\sigma_p^2 = \Omega\langle \xi_p^2 \rangle$, respectively, and the covariance of n_r and n_p is $Cov(n_r, n_p) = \Omega\langle \xi_r \xi_p \rangle$. Thus, the statistics around a stable fixed point $(r^\star, p^\star)$ can be determined by the stationary solutions of Eqs. (6) and (7).

3. Results

3.1. Steady-state statistics

From the stationary solutions of Eqs. (6) and (7), the steady-state statistics around a stable fixed point follow

$$\frac{\sigma_r^2}{\langle n_r \rangle^2}\cdot\frac{H_{p,r}}{\tau_p} + \frac{Cov(n_r, n_p)}{\langle n_r \rangle\langle n_p \rangle}\left(\frac{H_{r,r}}{\tau_r} + \frac{H_{p,p}}{\tau_p}\right) + \frac{\sigma_p^2}{\langle n_p \rangle^2}\cdot\frac{H_{r,p}}{\tau_r} = 0 \tag{8}$$

and

$$H_{r,r}H_{p,r}\left(\frac{\sigma_r^2}{\langle n_r \rangle^2} - \frac{1}{\langle n_r \rangle H_{r,r}}\right) = H_{r,p}H_{p,p}\left(\frac{\sigma_p^2}{\langle n_p \rangle^2} - \frac{1}{\langle n_p \rangle H_{p,p}}\right), \tag{9}$$

where for both mRNA and protein, the variance over squared average, i.e., $\sigma_r^2/\langle n_r \rangle^2$ and $\sigma_p^2/\langle n_p \rangle^2$, is called the normalized variance, and the term $Cov(n_r, n_p)/(\langle n_r \rangle\langle n_p \rangle)$ is called the normalized covariance, and where the variances, σ_r^2 and σ_p^2, and covariance, $Cov(n_r, n_p)$, are given by

$$\sigma_r^2 = \frac{\langle n_r \rangle(H_{r,r}H_{p,p} - H_{r,p}H_{p,r})/\tau_r + \langle n_r \rangle H_{p,p}^2/\tau_p + (\langle n_r \rangle^2/\langle n_p \rangle)H_{r,p}^2/\tau_r}{(H_{r,r}/\tau_r + H_{p,p}/\tau_p)(H_{r,r}H_{p,p} - H_{r,p}H_{p,r})},$$
$$\sigma_p^2 = \frac{\langle n_p \rangle(H_{r,r}H_{p,p} - H_{r,p}H_{p,r})/\tau_p + \langle n_p \rangle H_{r,r}^2/\tau_r + (\langle n_p \rangle^2/\langle n_r \rangle)H_{p,r}^2/\tau_p}{(H_{r,r}/\tau_r + H_{p,p}/\tau_p)(H_{r,r}H_{p,p} - H_{r,p}H_{p,r})} \tag{10}$$

and

$$Cov(n_r, n_p) = -\frac{\langle n_r \rangle H_{r,r}H_{r,p}/\tau_r + \langle n_p \rangle H_{p,r}H_{p,p}/\tau_p}{(H_{r,r}/\tau_r + H_{p,p}/\tau_p)(H_{r,r}H_{p,p} - H_{r,p}H_{p,r})}. \tag{11}$$

In the above equations, the terms $H_{r,r}/\tau_r + H_{p,p}/\tau_p$ and $H_{r,r}H_{p,p} - H_{r,p}H_{p,r}$ refer the locally asymptotical stability of Eq. (1), i.e., for the Jacobian matrix of Eq. (1) about the fixed point (r^*, p^*), the real parts of its eigenvalues are negative if both the terms $H_{r,r}/\tau_r + H_{p,p}/\tau_p$ and $H_{r,r}H_{p,p} - H_{r,p}H_{p,r}$ are positive.

For noise measure, Paulsson expounded that the variance over squared average is certainly a more suitable basis for experimental interpretations since (i) in most experimental studies so far the average number of proteins per cell is too high to contribute substantial spontaneous fluctuations; (ii) by plotting the variance over squared

average as a function of the inverse average, any univariate scaling behavior is easily identified without introducing scaling problems for any extrinsic noise; (iii) the relevance of a function typically depends on the normal size of the system (Paulsson, 2004, 2005). On the other hand, Paulsson also pointed out that in statistics the variance should be normalized by the squared average since the variance is a second order moment. Kaern et al. (2005) pointed out that it is sometimes advantageous to use the Fano factor, defined as the variance over average, as a different measure for the stochasticity in gene expression, where the Fano factor is called also the noise strength. They think of that the noise-strength measure has proved useful as a tool to interpret experimental data because of its ability to discriminate between the rate of transcription and translational efficiency.

For the single gene regulatory network, Eq. (8) provides a statistical interpretation for why we should use the normalized variance to measure the noise in gene expression, i.e., there is an invariant relationship between the normalized variances, $\sigma_r^2/\langle n_r\rangle^2$ and $\sigma_p^2/\langle n_p\rangle^2$, and the normalized covariance, $Cov(n_r,n_p)/(\langle n_r\rangle\langle n_p\rangle)$, that is independent of any possible feedback regulation mechanisms, and that of the average numbers of mRNA and protein molecules. In Eq. (8), the term $H_{p,r}/\tau_p$ represents a normalized effect, i.e., the effect of mRNA on the balance between the elimination and production of protein is normalized by the lifetime of protein. Similarly, we have the identical interpretations for the terms $H_{r,p}/\tau_r$, $H_{r,r}/\tau_r$ and $H_{p,p}/\tau_p$. For $\sigma_p^2/\langle n_p\rangle^2$, we have that

$$\frac{\partial}{\partial\langle n_p\rangle}\left(\frac{\sigma_p^2}{\langle n_p\rangle^2}\right) = -\frac{1}{\langle n_p\rangle^2}\cdot\frac{(H_{r,r}H_{p,p}-H_{r,p}H_{p,r})/\tau_p+H_{r,r}^2/\tau_r}{(H_{r,r}/\tau_r+H_{p,p}/\tau_p)(H_{r,r}H_{p,p}-H_{r,p}H_{p,r})} < 0, \tag{12}$$

i.e., (i) the normalized variance of protein will decrease with the increase of the average number of protein molecules; (ii) the change rate of $\sigma_p^2/\langle n_p\rangle^2$ due to the change of $\langle n_p\rangle$ is independent of the average number of mRNA molecules; and (iii) for large $\langle n_p\rangle$ the change of $\sigma_p^2/\langle n_p\rangle^2$ due to the change of $\langle n_p\rangle$ should be small. This nature of $\sigma_p^2/\langle n_p\rangle^2$ reveals the basic relationship between the stochasticity and system size in single gene network. On the other hand, if the Fano factor, i.e., the variance over average, is used to measure the noise (Paulsson, 2004), where the covariance should be normalized by $\sqrt{\langle n_r\rangle\langle n_p\rangle}$, we will see that in statistics there is no an invariant relationship between the Fano factors, $\sigma_r^2/\langle n_r\rangle$ and $\sigma_p^2/\langle n_p\rangle$, and $Cov(n_r,n_p)/\sqrt{\langle n_r\rangle\langle n_p\rangle}$ such that it is independent of the average numbers of mRNAs and proteins. Obviously, this is an explanation based on the viewpoint of statistics for why using Fano factor to measure the noise can be misleading. However, it is easy to see that the nature of the Fano factor is different from the normalized variance. For $\sigma_p^2/\langle n_p\rangle$, we have that

$$\frac{\partial}{\partial\langle n_p\rangle}\left(\frac{\sigma_p^2}{\langle n_p\rangle}\right) = \frac{1}{\langle n_r\rangle}\cdot\frac{H_{p,r}^2/\tau_p}{(H_{r,r}/\tau_r+H_{p,p}/\tau_p)(H_{r,r}H_{p,p}-H_{r,p}H_{p,r})} > 0, \tag{13}$$

i.e., (i) the Fano factor $\sigma_p^2/\langle n_p\rangle$ will increase with the increase of the average number of protein molecules; (ii) the change rate of $\sigma_p^2/\langle n_p\rangle$ due to the change of $\langle n_p\rangle$ depends on the average number of mRNA molecules, but it is independent of the average number of protein molecules; and (iii) the change of $\sigma_p^2/\langle n_p\rangle$ due to the change of $\langle n_p\rangle$ should be linear. Evidently, as a noise measure, the Fano factor might be sometimes convenient and useful for to interpret experimental data (Kaern et al., 2005), but it cannot characterize correctly the relationship between the stochasticity and system size since the stochastic noise in gene expression arise as a result of species in small copy number undergoing transitions between discrete chemical states (Paulsson, 2004).

3.2. Intrinsic and extrinsic noise

All cell components display intrinsic noise due to random births and deaths of individual molecules, and extrinsic noise due to fluctuations in reaction rates (Paulsson, 2004). As pointed out by Paulsson (2005), from a physical viewpoint, the terms "intrinsic" and "extrinsic" have no specific meaning other than "inside" and "outside", and thus always depend on the definition of system versus environment. For the single gene regulatory network Eq. (1), Eq. (7) implies that $\sigma_r^2/\langle n_r\rangle^2$ and $\sigma_p^2/\langle n_p\rangle^2$ can be expressed as

$$\frac{\sigma_r^2}{\langle n_r\rangle^2} = \frac{1}{\langle n_r\rangle H_{r,r}} - \frac{H_{r,p}}{H_{r,r}}\cdot\frac{Cov(n_r,n_p)}{\langle n_r\rangle\langle n_p\rangle},$$
$$\frac{\sigma_p^2}{\langle n_p\rangle^2} = \frac{1}{\langle n_p\rangle H_{p,p}} - \frac{H_{p,r}}{H_{p,p}}\cdot\frac{Cov(n_r,n_p)}{\langle n_r\rangle\langle n_p\rangle}, \tag{14}$$

i.e., from a statistical viewpoint, for both mRNA and protein the total noise can be decomposed into two basic components, one concerns the contribution of average number of molecules (system size), and other the contribution of interactions between mRNA and protein. According to Paulsson's interpretation (Paulsson, 2004), for the terms $1/(\langle n_r\rangle H_{r,r})$ and $1/(\langle n_p\rangle H_{p,p})$, $H_{r,r}$ and $H_{p,p}$ are interpreted as the statistical bias to return to the average rather than deviate further, and for the terms $-H_{r,p}/H_{r,r}\cdot Cov(n_r,n_p)/(\langle n_r\rangle\langle n_p\rangle)$ and $-H_{p,r}/H_{p,p}\cdot Cov(n_r,n_p)/(\langle n_r\rangle\langle n_p\rangle)$, the factors $H_{r,p}/H_{r,r}$ and $H_{p,r}/H_{p,p}$ are called the normalized susceptibility factors. On the other hand, notice

that $-Cov(n_r,n_p)/(\langle n_r\rangle\langle n_p\rangle)$ can be expressed as

$$-\frac{Cov(n_r,n_p)}{\langle n_r\rangle\langle n_p\rangle} = \frac{H_{r,r}H_{p,p}}{H_{r,r}H_{p,p}-H_{r,p}H_{p,r}}\left[\frac{1}{\langle n_p\rangle H_{p,p}}\cdot\frac{H_{r,p}}{H_{r,r}}\cdot\frac{H_{r,r}/\tau_r}{H_{r,r}/\tau_r+H_{p,p}/\tau_p} + \frac{1}{\langle n_r\rangle H_{r,r}}\cdot\frac{H_{p,r}}{H_{p,p}}\cdot\frac{H_{p,p}/\tau_p}{H_{r,r}/\tau_r+H_{p,p}/\tau_p}\right], \quad (15)$$

where the factor $H_{r,r}H_{p,p}/(H_{r,r}H_{p,p}-H_{r,p}H_{p,r})$ measures the relative importance of $H_{r,r}H_{p,p}$, i.e., if the feedback is positive, then it will be less than one, and conversely, if the feedback is negative, then it will be bigger than one, and $H_{r,r}/\tau_r/(H_{r,r}/\tau_r+H_{p,p}/\tau_p)$ and $H_{p,p}/\tau_p/(H_{r,r}/\tau_r+H_{p,p}/\tau_p)$ are the time-averages for mRNA and protein, respectively (Paulsson, 2004). Hence, in Eq. (15), the term $1/(\langle n_p\rangle H_{p,p})\cdot H_{r,p}/H_{r,r}\cdot H_{r,r}/\tau_r/(H_{r,r}/\tau_r+H_{p,p}/\tau_p)$ represents how the fluctuation in the number of protein molecules affects the interactions between mRNA and protein, and the term $1/(\langle n_r\rangle H_{r,r})\cdot H_{p,r}/H_{p,p}\cdot H_{p,p}/\tau_p/(H_{r,r}/\tau_r+H_{p,p}/\tau_p)$ how the fluctuation in the number of mRNA molecules affects the interactions between mRNA and protein. Notice also that the interactions between mRNA and protein in statistics mainly reflect how the fluctuations in the reaction rates are affected by the fluctuations in the numbers of mRNA and protein molecules. Thus, for the mRNA–protein system, we define that (i) the intrinsic noises of mRNA and protein are measured by $1/(\langle n_r\rangle H_{r,r})$ and $1/(\langle n_p\rangle H_{p,p})$, respectively; and (ii) the extrinsic noises of mRNA and protein are measured by $-H_{r,p}/H_{r,r}\cdot Cov(n_r,n_p)/(\langle n_r\rangle\langle n_p\rangle)$ and $-H_{p,r}/H_{p,p}\cdot Cov(n_r,n_p)/(\langle n_r\rangle\langle n_p\rangle)$, respectively. According to this definition, for both mRNA and protein, the extrinsic noise represents only how the total noise deviates from the intrinsic noise. It is necessary to point out that for the situation with no feedback regulation, i.e., $H_{r,p}=0$, the mRNA extrinsic noise is zero, and the protein extrinsic noise is

$$\frac{\sigma_p^2}{\langle n_p\rangle^2}-\frac{1}{\langle n_p\rangle H_{p,p}} = \frac{\sigma_r^2}{\langle n_r\rangle^2}\cdot\frac{H_{p,r}^2}{H_{p,p}^2}\cdot\frac{H_{p,p}/\tau_p}{H_{r,r}/\tau_r+H_{p,p}/\tau_p}, \quad (16)$$

that reflects how the stochastic fluctuation in number of mRNA molecules affects the protein noise. The situation with no feedback has been discussed by Paulsson (2004). Here, we mainly focus our attention on how the protein noise is affected by the feedback regulation.

3.3. Effect of feedback regulation

In order to show clearly how the feedback regulation acts on the noise, the macroscopic rate equation, Eq. (1), is rewritten as

$$\frac{dr}{dt}=-\gamma r+f(p),\qquad \frac{dp}{dt}=k'r-\gamma' p, \quad (17)$$

where γ and γ' are the degradation rates of mRNA and protein that are defined as $\gamma=\tau_r^{-1}$ and $\gamma'=\tau_p^{-1}$, k' is the translation rate of protein, and the function $f(p)$ represents the feedback regulation on the transcription. For this macroscopic rate equation, we still assume that there is at least one stable fixed point. Around the stable fixed point we have $H_{r,r}=H_{p,p}=1$, $H_{p,r}=-1$ and $H_{r,p}=-\langle b\rangle\tau_p f'(p^\star)$ where $f'(p^\star)=df(p^\star)/dp$, and $\langle b\rangle$ is the expected number of protein molecules produced per mRNA transcript, which is defined as $\langle b\rangle=k'/\gamma$ and called also the burst size (Paulsson, 2004; Thattai and van Oudenaarden, 2001; McAdams and Arkin, 1997). Thus, the total noise of protein can be expressed as

$$\frac{\sigma_p^2}{\langle n_p\rangle^2}=\frac{1}{\langle n_p\rangle}+\frac{1}{\langle b\rangle\tau_p f'(p^\star)}\left(\frac{\sigma_r^2}{\langle n_r\rangle^2}-\frac{1}{\langle n_r\rangle}\right) \quad (18)$$

with $f'(p^\star)\neq 0$.

For the situation with linear feedback, $f(p)$ is taken as a linear function,

$$f(p)=kp+K_0, \quad (19)$$

where the parameter K_0 is the fundamental transcription rate, $k>0$ and $k<0$ correspond to positive and negative feedback, respectively, and the stable fixed point is $(r^\star,p^\star)=(K_0\gamma',K_0k')/(\gamma\gamma'-kk')$ with $\gamma\gamma'-kk'>0$. The total noise of protein is given by

$$\frac{\sigma_p^2}{\langle n_p\rangle^2}=\frac{\gamma'}{\Omega K_0}\left(\frac{1}{\langle b\rangle}+\frac{\gamma-k}{\gamma+\gamma'}\right), \quad (20)$$

and the protein extrinsic noise is

$$\frac{\sigma_p^2}{\langle n_p\rangle^2}-\frac{1}{\langle n_p\rangle}=\frac{\gamma(\gamma'+k)}{\Omega K_0(\gamma+\gamma')}, \quad (21)$$

where

$$\frac{1}{\langle n_p\rangle}=\left(\frac{\Omega K_0}{\langle b\rangle^{-1}\gamma'-k}\right)^{-1} \quad (22)$$

with $\langle b\rangle^{-1}\gamma'-k>0$. Obviously, for given parameters γ, γ', k' and K_0, the protein intrinsic noise, $1/\langle n_p\rangle$, will increase with the decrease of k, but the protein extrinsic noise, $\sigma_p^2/\langle n_p\rangle^2-1/\langle n_p\rangle$, will decrease with the decrease of k. This implies that for given genetic parameters, the negative feedback will have two opposite effects on the protein noise, i.e., it will increase the protein intrinsic noise through decreasing the average number of protein molecules, and will reduce the protein extrinsic noise through damping the fluctuations in reaction rates. Hence, for two genes with the same parameters γ, γ', k' and K_0, the gene with negative feedback will have a large total noise in the number of protein molecules. But it may be more interested biologically to compare the effect of negative feedback for two genes with the same average number of protein molecules. In this context, if we assume that the average number of protein molecules is fixed, then the term ΩK_0 in Eq. (19) can be replaced by the term $\langle n_p\rangle(\langle b\rangle^{-1}\gamma'-k)$, i.e., Eq. (20)

can be rewritten as

$$\frac{\sigma_p^2}{\langle n_p\rangle^2}=\frac{1}{\langle n_p\rangle}\cdot\frac{\gamma'}{\gamma+\gamma'}\cdot\frac{(\gamma+\gamma')+(\gamma-k)\langle b\rangle}{\gamma'-\langle b\rangle k} \tag{23}$$

with

$$\frac{\partial}{\partial k}\left(\frac{\sigma_p^2}{\langle n_p\rangle^2}\right)=\frac{1}{\langle n_p\rangle}\cdot\frac{\gamma\gamma'}{\gamma+\gamma'}\cdot\frac{\langle b\rangle(1+\langle b\rangle)}{(\gamma'-\langle b\rangle k)^2}>0. \tag{24}$$

This means that for two genes with the same average number of protein molecules, $\langle n_p\rangle$, the gene with negative feedback will have a small total noise in the number of protein molecules. This conclusion provides a reasonable explanation in biology for the effect of negative feedback on the protein noise. On the other hand, for both the intrinsic noise and total noise, they will decrease with the increase of burst size $\langle b\rangle$, but the extrinsic noise is independent of $\langle b\rangle$. The above results show clearly how the linear feedback acts on the protein noise.

The Monte Carlo simulation results for the situation with linear feedback are plotted in Fig. 1a and b, where the time unit for the simulation is minute, the protein half-life is $\ln 2/\gamma' = 60$ min, and the mRNA half-life is $\ln 2/\gamma = 2$ min. In Fig. 1a, in order to show the effect of negative feedback on the protein noise, two cases are considered, i.e., (i) the fundamental transcriptional rate K_0 is fixed at $K_0 = 10$ for different k values, that corresponds to Eq. (20); and (ii) the average number of protein molecules $\langle n_p\rangle$ is fixed at $\langle n_p\rangle = 100$ for different k values where $K_0 = \langle n_p\rangle(\langle b\rangle^{-1}\gamma' - k)$, that corresponds to Eq. (23). In both cases, the bust size is taken as $\langle b\rangle = k'/\gamma = 10$, and the parameter k is varied from -1 to -0.1 in increments of 0.1. In Fig. 1b the burst size $\langle b\rangle$ is varied from 1 to 14 in increments of 1 where the parameter k is fixed at $k = -0.5$. The algorithm of the Monte Carlo simulation is from Gillespie (1977) (see Appendix). The main results of the Monte Carlo simulation show clearly that the theoretical analysis is correct, i.e., for two genes with the same average number of protein molecules, the gene with negative feedback will have a small protein noise, but for two genes with the same fundamental transcriptional rate, the gene with negative feedback will have a big protein noise; and the protein noise will decrease with the increase of burst size $\langle b\rangle$.

For the situation with nonlinear feedback, $f(p)$ is taken as the Hill type function,

$$f(p)=\frac{k_{max}}{1+(p/k_d)^{\beta}} \tag{25}$$

with $\mathrm{d}f(p)/\mathrm{d}p<0$ for all possible values of p, where k_{max} is the maximum of the transcription rate, k_d is the dissociation constant that specifies the threshold protein concentration at which the transcription rate is at half its maximum value, and the parameter β is the Hill coefficient and determines the steepness of the repression curve (Paulsson, 2004). For example, the *cI* repressor protein acts on the promoters P_R and P_{RM} of phage λ with a k_d about 50 and 1000 nm, respectively (Thattai and van Oudenaarden, 2001; Shea and Ackers, 1985). Typical biological values β range from 1 (hyperbolic control) to over 30 (sharp switching) (Thattai and van Oudenaarden, 2001). Around the stable fixed point, the total noise of protein is

$$\frac{\sigma_p^2}{\langle n_p\rangle^2}=\frac{\gamma'}{\langle n_p\rangle}\left(\frac{\gamma'}{\langle b\rangle}-f'(p^\star)\right)^{-1}\left(\frac{1}{\langle b\rangle}+\frac{\gamma-f'(p^\star)}{\gamma+\gamma'}\right), \tag{26}$$

and the protein extrinsic noise is

$$\frac{\sigma_p^2}{\langle n_p\rangle^2}-\frac{1}{\langle n_p\rangle}=\frac{\gamma(\gamma'+f'(p^\star))}{\langle n_p\rangle(\gamma+\gamma')}\left(\frac{\gamma'}{\langle b\rangle}-f'(p^\star)\right)^{-1}, \tag{27}$$

where

$$f'(p^\star)=-\frac{\gamma'\beta}{\langle b\rangle}\left(1-\frac{\gamma' p^\star}{k_{max}\langle b\rangle}\right)$$

that represents the strength of the negative feedback at the stable fixed point. It is easy to see that the contribution of the protein extrinsic noise to the total noise is negative if $\gamma'+f'(p^\star)<0$.

Similarly to the situation with linear feedback, the Monte Carlo simulation results for the nonlinear feedback are plotted in Fig. 2a and b, that show how the Hill coefficient β and the dissociation constant k_d act on the protein noise (see Appendix). The parameters γ and γ' are kept identical to Fig. 1, i.e., $\ln 2/\gamma = 2$ min and $\ln 2/\gamma' = 60$ min, the burst size and the maximum value of transcription rate are taken as $\langle b\rangle = 10$ and $k_{max} = 3$, respectively. In Fig. 2a the Hill coefficient β is varied from 1 to 10 in increments of 1 where the dissociation constant is fixed at $k_d = 800$, and in Fig. 2b the dissociation constant k_d is varied from 500 to 1400 in increments of 100 where the Hill coefficient is fixed at $\beta = 5$. The results show clearly that the total noise of protein will decrease with the increase of β, and it will increase with the increase of k_d. Obviously, the effects of the Hill coefficient and dissociation constant on the protein noise are completely different.

4. Conclusions

Gene expression is an inherently stochastic process. How to measure and decompose noise in gene expression are very important for identifying different sources of noise. In this paper, a single gene network is investigated using the Ω-expansion techniques (van Kampen, 1992). For the noise measure, we show that the linear noise approximation (it is called also the fluctuation–dissipation theorem in physics) implies an invariant relationship between the normalized variances, $\sigma_r^2/\langle n_r\rangle^2$ and $\sigma_p^2/\langle n_p\rangle^2$, and the normalized covariance, $Cov(n_r,n_p)/(\langle n_r\rangle\langle n_p\rangle)$, in steady-state statistics (see Eq. (8)). Notice that this invariant relationship is independent of any possible feedback regulation mechanisms and that of average numbers of mRNA and protein molecules. Thus, it provides an exactly statistical

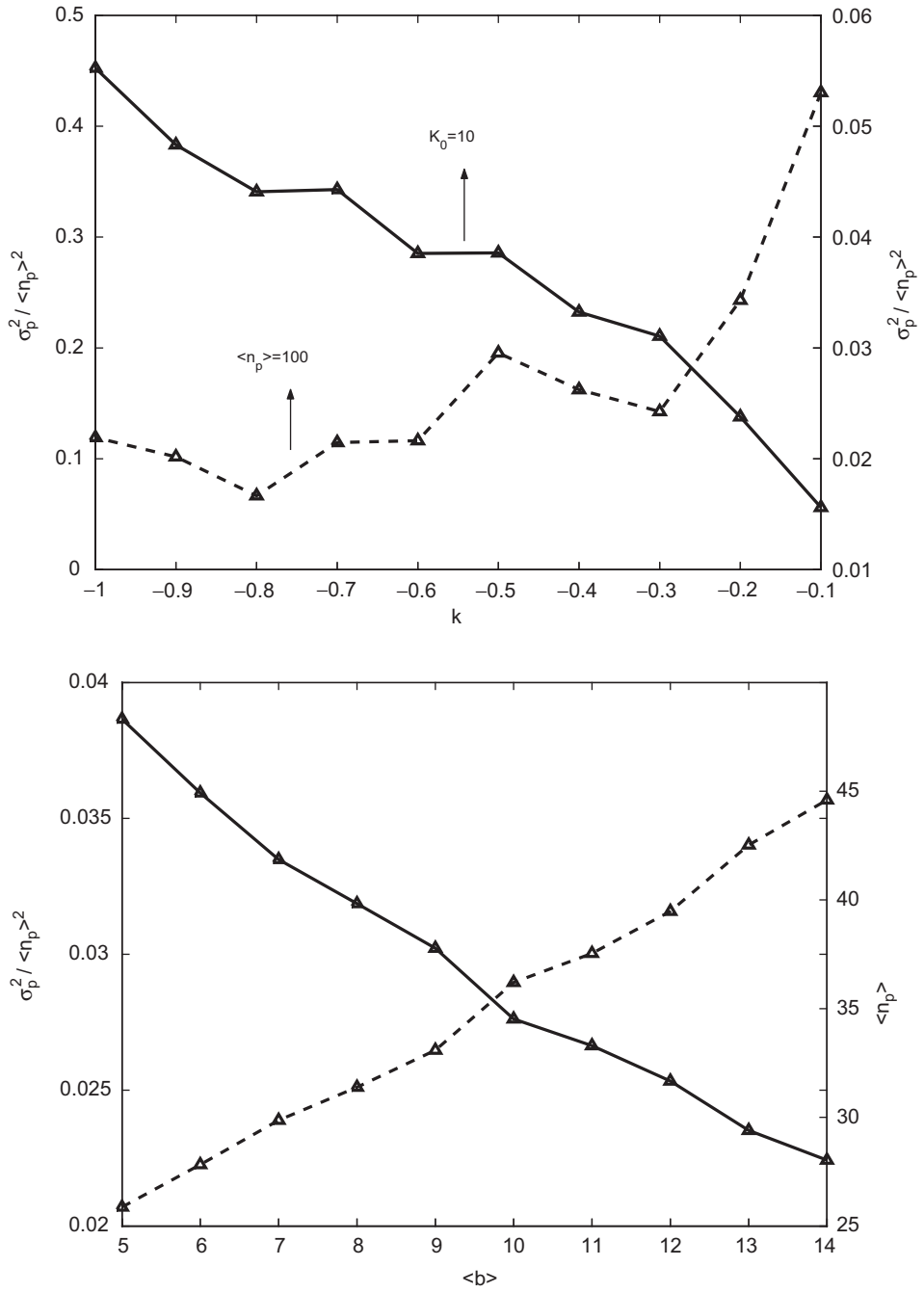

Fig. 1. (a) Noise control by the linear feedback. The total noise of protein is plotted versus the different values of the parameters k, where the case with fixed fundamental transcription rate at $K_0 = 10$ is scaled on the left axis (solid line), and the case with fixed average number of protein molecules at $\langle n_p \rangle = 100$ is scaled on the right axis (dash line). The illustrations are given in the main text. (b) Noise control by the linear feedback. The total noise of protein scaled on the left axis (solid line) and average number of proteins scaled on the right axis (dash line) are plotted versus the different values of burst size $\langle b \rangle$, respectively. The illustrations are given in the main text.

interpretation for why the stochastic noise in gene expression should be measured by the normalized variance. For the nature of protein noise, $\sigma_p^2/\langle n_p \rangle^2$, our analysis shows that (i) $\sigma_p^2/\langle n_p \rangle^2$ will decrease with the increase of $\langle n_p \rangle$; and (ii) the change rate of $\sigma_p^2/\langle n_p \rangle^2$ due to the change of $\langle n_p \rangle$ is independent of $\langle n_r \rangle$, and for large $\langle n_p \rangle$ the change of $\sigma_p^2/\langle n_p \rangle^2$ due to the change of $\langle n_p \rangle$ should be small. However, the nature of $\sigma_p^2/\langle n_p \rangle^2$ reveals the basic relationship between the stochasticity and system size. On the other hand, for the noise decomposition, the linear noise approximation implies also that for both mRNA and protein, the total noise can be decomposed into two basic components, one concerns the contribution of average number of molecules (system size), and other the contribution of interactions between mRNA and protein. According to Paulsson (2004, 2005), for the single gene network

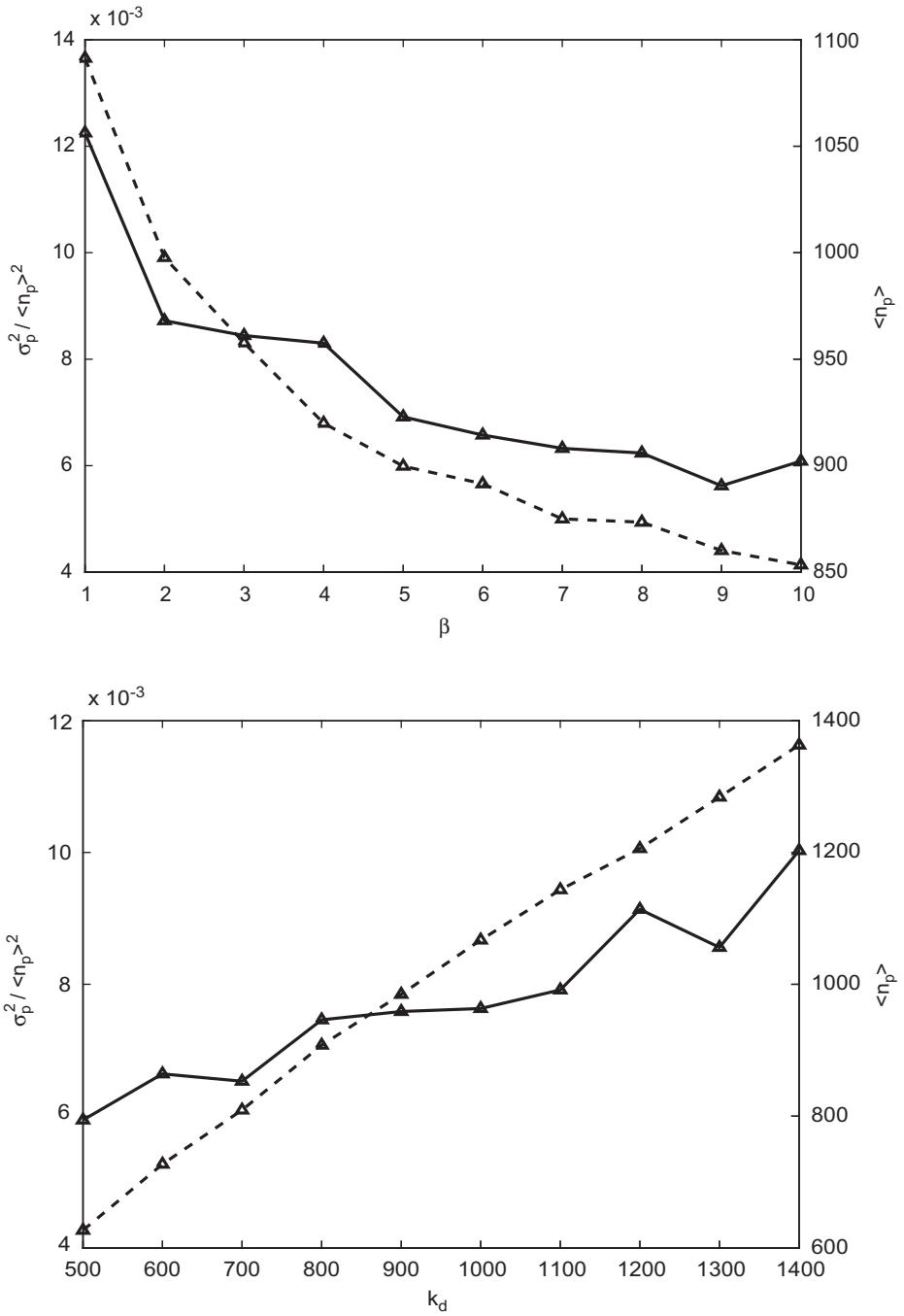

Fig. 2. (a) Noise control by the nonlinear feedback. The total noise of protein scaled on the left axis (solid line) and average number of proteins scaled on the right axis (dash line) are plotted versus the different values of Hill coefficient β. The illustrations are given in the main text. (b) Noise control by the nonlinear feedback. The total noise of protein scaled on the left axis (solid line) and average number of proteins scaled on the right axis (dash line) are plotted versus the different values of the dissociation constant k_d. The illustrations are given in the main text.

(mRNA–protein system), we define that the intrinsic noises of mRNA and protein are measured by $1/(\langle n_r\rangle H_{r,r})$ and $1/(\langle n_p\rangle H_{p,p})$, respectively, and the extrinsic noises of mRNA and protein are measured by $-H_{r,p}/H_{r,r}\cdot Cov(n_r,n_p)/(\langle n_r\rangle\langle n_p\rangle)$ and $-H_{p,r}/H_{p,p}\cdot Cov(n_r,n_p)/(\langle n_r\rangle\langle n_p\rangle)$, respectively, since the interactions between mRNA and protein in statistics mainly reflect the effect of fluctuations in numbers of mRNA and protein molecules on the biochemical reaction rates. For instance, if there is no feedback, the protein extrinsic noise only show that how the fluctuation in number of mRNA molecules acts the protein noise (see Eq. (16) and Paulsson, 2004).

For the situation with linear feedback, our results show that for the given parameters γ, γ', K_0, and k', then the negative feedback will have two opposite effects on the protein noise, i.e., it will increase the protein intrinsic through decreasing the average number of protein

molecules, but will reduce the protein extrinsic noise through damping the fluctuations in biochemical reaction rates. This implies that if two genes have the same genetic parameters γ, γ', K_0, and k', then the gene with negative feedback will have a large protein noise. But, for two genes with the same average number of protein molecules, the gene with negative feedback will have a small protein noise, i.e., the negative feedback will reduce the protein noise. This conclusion should be more important in biology (see Eqs. (23) and (24)). For the effect of the burst size $\langle b\rangle$ on the protein noise, it is also easy to see that the protein intrinsic noise will decrease with the increase of $\langle b\rangle$ but the protein extrinsic noise is independent of $\langle b\rangle$. The results of Monte Carlo simulation for the linear feedback show clearly that the theoretical analysis is correct (see Fig. 1a and b). These results should be useful for identifying noise sources from experimental data. For the situation with nonlinear feedback where the Hill type function is taken as the feedback function, we show that the effects of the Hill coefficient β and dissociation constant k_d on the protein noise are completely different, i.e., the total noise of protein will decrease with the increase of β (see Fig. 2a), and it will increase with the increase of k_d (see Fig. 2b).

Recently, for the future directions of stochastic gene expression, Kaern et al. (2005) pointed out that there is a clear need to address in great detail how gene expression responds to fluctuations in signal transduction, how gene-expression noise is transmitted through regulatory circuits and control loops, and how the architecture of regulatory networks allows cell to deal with or take advantage of unreliable, fluctuating signals. Similarly, Paulsson (2005) also pointed out that:

(i) There are no strong indications that genes, RNAs and proteins are the critical molecules that contribute small-number fluctuations.
(ii) Many enzyme and substrate concentrations are statistically correlated. Such correlations may even have evolved to suppress total protein fluctuations.
(iii) The discrete probabilistic events are assumed to be exponential, yet we know that gene activation, transcription and translation consist of numerous small steps. Does this qualitatively change the nature of the fluctuations in concentrations?

As an example for (ii), Paulsson assumed that a gene for a certain protein is transcribed by a certain sigma factor. He further assumed that the corresponding mRNA is degraded by an RNase that is transcribed by the same sigma factor. A random increase in the concentration of the sigma factor then increase both the synthesis and degradation rates of the mRNA, and the two effects could partially cancel out. In this example, we are very interested in the exact effect of the sigma factor on the stochastic fluctuations in gene expression. If we assume that the concentration of the sigma factor is a random variable, and that the decay and transcriptional rates of the mRNA are the functions of the RNase and sigma factor, respectively, then from the basic idea in Sections 2 and 3 we should be able to identify the contributions of the sigma factor and correlation between the sigma factor and RNase to the mRNA and protein noises.

Appendix

Derivation of Eq. (4). For Eqs. (2) and (3), and the joint probability distribution $\Phi(n_r,n_p;t)=\Psi(\xi_r,\xi_p;t)$, notice that $n_r\to n_r\pm1\Leftrightarrow\xi_r\to\xi_r\pm\Omega^{-1/2}$ and $n_p\to n_p\pm1\Leftrightarrow\xi_p\to\xi_p\pm\Omega^{-1/2}$, and that the Taylor expansions of the step operators $E_r^{\pm1}$ and $E_p^{\pm1}$ are

$$E_r^{\pm1}=1\pm\Omega^{-1/2}\frac{\partial}{\partial\xi_r}+\frac{1}{2}\Omega^{-1}\frac{\partial^2}{\partial\xi_r^2}\pm\cdots,$$
$$E_p^{\pm1}=1\pm\Omega^{-1/2}\frac{\partial}{\partial\xi_p}+\frac{1}{2}\Omega^{-1}\frac{\partial^2}{\partial\xi_p^2}\pm\cdots \tag{28}$$

(see van Kampen, 1992). The time derivative in Eq. (3) is taken with constants n_r and n_p, i.e., $\mathrm{d}\xi_r/\mathrm{d}t=-\Omega^{-1/2}\,\mathrm{d}r/\mathrm{d}t$ and $\mathrm{d}\xi_p/\mathrm{d}t=-\Omega^{-1/2}\,\mathrm{d}p/\mathrm{d}t$. Hence

$$\begin{aligned}\partial_t\Phi&=\frac{\partial\Psi}{\partial t}-\Omega^{-1/2}\frac{\mathrm{d}r}{\mathrm{d}t}\cdot\frac{\partial\Psi}{\partial\xi_r}-\Omega^{-1/2}\frac{\mathrm{d}p}{\mathrm{d}t}\cdot\frac{\partial\Psi}{\partial\xi_p}\\&=\Omega\Bigg[\left(\Omega^{-1/2}\frac{\partial}{\partial\xi_r}+\frac{1}{2}\Omega^{-1}\frac{\partial^2}{\partial\xi_r^2}+\cdots\right)\\&\quad\times s_r^-(r(t)+\Omega^{-1/2}\xi_r)\Psi\\&\quad+\left(-\Omega^{-1/2}\frac{\partial}{\partial\xi_r}+\frac{1}{2}\Omega^{-1}\frac{\partial^2}{\partial\xi_r^2}-\cdots\right)\\&\quad\times s_r^+(p(t)+\Omega^{-1/2}\xi_p)\Psi\\&\quad+\left(\Omega^{-1/2}\frac{\partial}{\partial\xi_p}+\frac{1}{2}\Omega^{-1}\frac{\partial^2}{\partial\xi_p^2}+\cdots\right)\\&\quad\times s_p^-(p(t)+\Omega^{-1/2}\xi_p)\Psi\\&\quad+\left(-\Omega^{-1/2}\frac{\partial}{\partial\xi_p}+\frac{1}{2}\Omega^{-1}\frac{\partial^2}{\partial\xi_p^2}+\cdots\right)\\&\quad\times s_p^+(r(t)+\Omega^{-1/2}\xi_r)\Psi\Bigg],\end{aligned} \tag{29}$$

where the terms $s_r^-(r(t)+\Omega^{-1}\xi_r)$, $s_r^+(p(t)+\Omega^{-1}\xi_p)$, $s_p^-(p(t)+\Omega^{-1}\xi_p)$ and $s_p^+(r(t)+\Omega^{-1}\xi_r)$ are taken their Taylor expansions about $\xi_r=0$ and $\xi_p=0$, i.e.,

$$s_r^-(r+\Omega^{-1/2}\xi_r)=s_r^-(r)+\Omega^{-1/2}\frac{\mathrm{d}s_r^-(r)}{\mathrm{d}r}\xi_r+\cdots,$$
$$s_r^+(p+\Omega^{-1/2}\xi_p)=s_r^+(p)+\Omega^{-1/2}\frac{\mathrm{d}s_r^+(p)}{\mathrm{d}p}\xi_p+\cdots,$$
$$s_p^-(p+\Omega^{-1/2}\xi_p)=s_p^-(p)+\Omega^{-1/2}\frac{\mathrm{d}s_p^-(p)}{\mathrm{d}p}\xi_p+\cdots,$$
$$s_p^+(r+\Omega^{-1/2}\xi_r)=s_p^+(r)+\Omega^{-1/2}\frac{\mathrm{d}s_p^+(r)}{\mathrm{d}r}\xi_r+\cdots.$$

Collecting the terms in Eq. (20) of order Ω^0, we have Eq. (4).

Derivation of Eqs. (6) *and* (7). From Eq. (5) and its boundary conditions, we have

$$\begin{aligned}\frac{\mathrm{d}\langle\xi_r\rangle}{\mathrm{d}t} &= \int_{-\infty}^{\infty}\int_{-\infty}^{\infty}\xi_r\frac{\partial\Psi}{\partial t}\,\mathrm{d}\xi_r\,\mathrm{d}\xi_p\\ &= a_{11}\langle\xi_r\rangle + a_{12}\langle\xi_p\rangle,\\ \frac{\mathrm{d}\langle\xi_p\rangle}{\mathrm{d}t} &= \int_{-\infty}^{\infty}\int_{-\infty}^{\infty}\xi_p\frac{\partial\Psi}{\partial t}\,\mathrm{d}\xi_r\,\mathrm{d}\xi_p\\ &= a_{21}\langle\xi_r\rangle + a_{22}\langle\xi_p\rangle,\end{aligned} \tag{30}$$

and

$$\begin{aligned}\frac{\mathrm{d}\langle\xi_r^2\rangle}{\mathrm{d}t} &= \int_{-\infty}^{\infty}\int_{-\infty}^{\infty}\xi_r^2\frac{\partial\Psi}{\partial t}\,\mathrm{d}\xi_r\,\mathrm{d}\xi_p\\ &= 2a_{11}\langle\xi_r^2\rangle + 2a_{12}\langle\xi_r\xi_p\rangle + 2D_r,\\ \frac{\mathrm{d}\langle\xi_r\xi_p\rangle}{\mathrm{d}t} &= \int_{-\infty}^{\infty}\int_{-\infty}^{\infty}\xi_r\xi_p\frac{\partial\Psi}{\partial t}\,\mathrm{d}\xi_r\,\mathrm{d}\xi_p\\ &= a_{21}\langle\xi_r^2\rangle + (a_{11}+a_{22})\langle\xi_r\xi_p\rangle + a_{12}\langle\xi_p^2\rangle,\\ \frac{\mathrm{d}\langle\xi_p^2\rangle}{\mathrm{d}t} &= \int_{-\infty}^{\infty}\int_{-\infty}^{\infty}\xi_p^2\frac{\partial\Psi}{\partial t}\,\mathrm{d}\xi_r\,\mathrm{d}\xi_p\\ &= 2a_{21}\langle\xi_r\xi_p\rangle + 2a_{22}\langle\xi_p^2\rangle + 2D_p.\end{aligned} \tag{31}$$

Obviously, Eq. (31) can be equivalently expressed as Eq. (7).

Monte Carlo simulations. The algorithm of Monte Carlo simulations is from Gillespie (1977) for stochastic coupled chemical reactions. In order to do the simulations, a mesoscopic rate equation, that corresponds to Eq. (11), is considered, i.e.,

$$\begin{aligned}\frac{\mathrm{d}n_r}{\mathrm{d}t} &= -\gamma n_r + f(n_p),\\ \frac{\mathrm{d}n_p}{\mathrm{d}t} &= k'n_r - \gamma' n_p.\end{aligned} \tag{32}$$

The stochastic fluctuations in n_r and n_p are described by a birth-and-death process with events

$$n_r \xrightarrow{\gamma n_r} n_r - 1,$$

$$n_r \xrightarrow{f(n_p)} n_r + 1,$$

$$n_p \xrightarrow{\gamma' n_p} n_p - 1,$$

$$n_p \xrightarrow{k' n_r} n_p + 1,$$

where $f(n_p) = kn_p + K_0$ for linear feedback, and $f(n_p) = k_{max}(1 + (n_p/k_d)^{\beta})^{-1}$ for nonlinear feedback.

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