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Genetic negative feedback circuits for filtering stochasticity in gene expression

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Abstract— **The inherent stochastic nature of biochemical reactions coupled with low copy numbers of many mRNA species can create large stochastic fluctuations in protein levels over time. These fluctuations in protein molecular counts are referred to as gene-expression noise and are known to profoundly effect biological function and phenotype. Cells often encode negative feedback circuits to suppress or filter gene-expression noise and reduce intercellular variability in protein levels. We here compare and contrast the noise suppression ability of different negative feedback architectures. Using stochastic models of gene-expression we derive analytical formulas that quantify the extent of stochastic fluctuations in protein levels corresponding to different negative feedback circuits. These formulas reveal that some feedback architectures are inherently better at noise suppression, while the performance of others is dependent on the parameters of gene-expression. More specifically, our results show that among different negative feedback architectures, negative feedback through the mRNA provides the best filtering of gene-expression noise in a mathematically controlled comparison. Finally, we discuss potential ways these negative feedback circuits can be implemented within the process of gene-expression.**

I. Introduction

Gene-expression is the process by which protein molecules are synthesized from individual genes through transcription and translation (Figure 1). Random timing of individual biochemical reactions associated with the different steps of gene-expression can create considerable stochastic fluctuations in protein levels inside living cells over time [1], [2]. Cell-to-cell variation in protein levels generated by these stochastic fluctuations are often referred to as gene-expression noise. Increasing evidence suggests that gene-expression noise can be detrimental for the functioning of essential proteins whose levels have to be tightly maintained within certain bounds for optimal performance [3], [4]. Moreover, many diseased states have been attributed to an increase in expression noise in particular genes [5], [6], [7]. Given that stochasticity in protein levels can have significant effects on biological function and phenotype, cells actively use different regulatory mechanisms to minimize expression noise.

Negative feedback loops are key regulatory motifs within cells that help reduce stochasticity in protein levels. A common and well characterized negative feedback mechanism is protein mediated transcriptional regulation where the protein expressed from a gene inhibits its own transcription [8], [9]. For example, it is estimated that over 40% of Escherichia coli transcription factors regulate their own expression through this feedback mechanism [10]. Both theoretical and experimental studies have shown that such a negative feedback at the transcriptional level reduces noise in protein numbers [11], [12], [13]. Recent work has provided evidence of more sophisticated negative feedback loops where the protein inhibits the translation of its own mRNA [14] or mRNA inhibits the transcription of its gene [15]. We here compare and contrast the noise suppression ability of these different feedback mechanisms in gene expression.

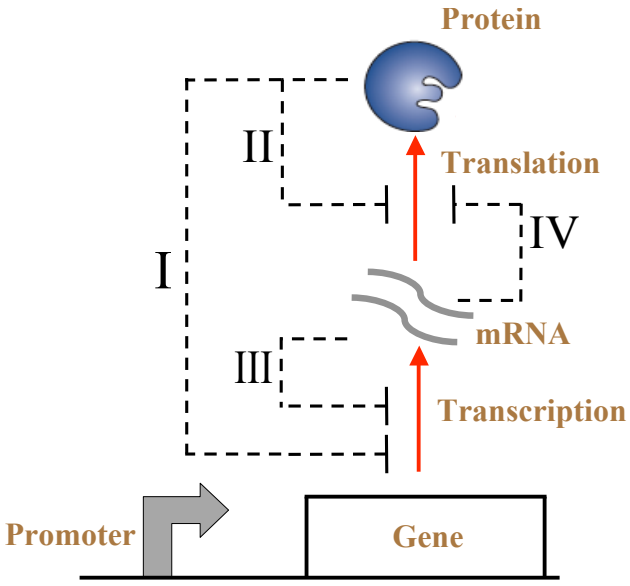

Fig. 1. The process of gene-expression where mRNAs are transcribed from the gene and proteins are translated from individual mRNAs (red arrows). Different feedback mechanisms in gene-expression where the rate of transcription or translation is a monotonically deceasing function of either the mRNA or protein population count (dashed lines).

Gene expression is typically modeled by assuming that mRNA transcription and protein translation from individual mRNAs occurs at fixed constant rates. Feedback mechanisms can be incorporated in this model by assuming that the transcriptional rate or translation rate is a monotonically decreasing function of either the protein or the mRNA population count. This procedure results in four different negative feedback circuits, which are illustrated in Figure 1. For example, feedback circuit I corresponds to protein mediated transcriptional regulation where the transcription rate is a decreasing function of the protein count. Similarly, feedback circuit IV corresponds to a scenario where the protein translation rate per mRNA is a decreasing function of the mRNA count.

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TABLE I

FREQUENCY AND RESET MAPS FOR DIFFERENT STOCHASTIC EVENTS IN THE GENE-EXPRESSION MODEL

Event	Reset in population count	Probability event will occur in $(t, t+dt]$
Transcription	$m(t) \to m(t)+B$	$k_m dt$
mRNA degradation	$m(t) \to m(t)-1$	$\gamma_m m(t) dt$
protein translation	$p(t) \to p(t)+1$	$k_p m(t) dt$
protein degradation	$p(t) \to p(t)-1$	$\gamma_p p(t) dt$

We derive analytical expressions for the protein noise levels for each of these different feedback circuits. Using these expressions we determine which feedback provides the best noise suppression, and how does its performance depend on gene-expression parameters such as mRNA and protein half-life. It is important to point out that comparisons between different feedback circuits are done keeping the mean protein and mRNA population count fixed. Furthermore, we assume that different feedbacks also have the same feedback strength, which is measured by the sensitivity of the transcription/translation rate to the mRNA/protein count. Such a form of comparison is called a *mathematically controlled comparison*.

II. GENE-EXPRESSION NOISE WITHOUT FEEDBACK REGULATION

We begin by first quantifying the extent of stochasticity in protein levels in a gene-expression model with no feedback regulation. Consider a model where transcriptional events take place at rate k_m with each event creating a burst of B mRNA molecules, where B is an arbitrary discrete random variable with probability distribution

$$\text{Probability}\{B = z\} = \alpha_z,\ z = \{1, 2, 3, \ldots\}. \tag{1}$$

Typically $B = 1$ with probability one. However, many genes encode promoters that allow for transcriptional bursting where $B > 1$ and many mRNAs can be made per transcriptional event [16], [17], [18]. Protein molecules are translated from each single mRNA at rate k_p. We assume that mRNAs and proteins degrade at constant rates γ_m and γ_p, respectively. In the stochastic formulation of this model, transcription, translation and degradation are probabilistic events that occur at exponentially distributed time intervals [19]. Moreover, whenever a particular event occurs, the mRNA and protein population count is reset accordingly. Let $m(t)$ and $p(t)$ denote the number of molecules of the mRNA and protein at time t, respectively. Then, the reset in $m(t)$ and $p(t)$ for different gene-expression and degradation events is shown in the second column of Table I. The frequency with which different events occur is determined by the third column of Table I, which lists the probability that a particular event will occur in the next infinitesimal time interval $(t, t+dt]$.

To quantify noise in protein levels we first write the differential equations that describe the time evolution of the different statistical moments of the mRNA and protein count. The moment dynamics can be obtained using the following result: For the above gene-expression model, the time-derivative of the expected value of any differentiable function $\varphi(m, p)$ is given by equation (2) shown on the top of next page [20], [21]. Here, and in the sequel we use the symbol $\langle . \rangle$ to denote the expected value. Using (2) with appropriate choices for $\varphi(m, p)$ we obtain the following moment dynamics:

$$\frac{d\langle m \rangle}{dt} = k_m \langle B \rangle - \gamma_m \langle m \rangle, \quad \frac{d\langle p \rangle}{dt} = k_p \langle m \rangle - \gamma_p \langle p \rangle \tag{3a}$$

$$\frac{d\langle m^2 \rangle}{dt} = k_m \langle B^2 \rangle + \gamma_m \langle m \rangle + 2k_m \langle B \rangle \langle m \rangle - 2\gamma_m \langle m^2 \rangle \tag{3b}$$

$$\frac{d\langle p^2 \rangle}{dt} = k_p \langle m \rangle + \gamma_p \langle p \rangle + 2k_p \langle mp \rangle - 2\gamma_p \langle p^2 \rangle \tag{3c}$$

$$\frac{d\langle mp \rangle}{dt} = k_p \langle m^2 \rangle + k_m \langle B \rangle \langle p \rangle - \gamma_p \langle mp \rangle - \gamma_m \langle mp \rangle. \tag{3d}$$

As done in many studies we quantify noise in protein levels through the coefficient of variation squared defined as

$$CV^2 = \bar{\sigma}^2 / \langle \bar{p} \rangle^2, \tag{4}$$

where $\bar{\sigma}^2$ is the steady-state variance in protein levels and $\langle \bar{p} \rangle$ denotes the steady-state mean protein count. Quantifying the steady-state moments from (3) and substituting in (4) we obtain

$$CV^2 = \frac{(\langle B^2 \rangle + \langle B \rangle)\gamma_p}{2\langle B \rangle (\gamma_p + \gamma_m) \langle \bar{m} \rangle} + \frac{1}{\langle \bar{p} \rangle} \tag{5}$$

where

$$\langle \bar{p} \rangle = \frac{\langle B \rangle k_m}{\gamma_p \gamma_m},\ \langle \bar{m} \rangle = \frac{\langle B \rangle k_m}{\gamma_m} \tag{6}$$

denote the steady-state mean mRNA and protein count, respectively. The first term on the right-hand-side of (5) corresponds to noise in protein levels that arises from stochastic production and degradation of mRNA molecules, and is inversely proportional to the mean mRNA count $\langle \bar{m} \rangle$. The second term in (5) represents Poissonian noise arising from random birth-death of individual protein molecules. Given that mRNA population counts are typically orders of magnitude smaller than protein population counts $\big(\langle \bar{m} \rangle / \langle \bar{p} \rangle \approx 10^{-3}$ from [22]$\big)$, we ignore the second term in

$$\frac{d\langle\varphi(m,p)\rangle}{dt}=\left\langle\sum_{z=1}^{\infty}k_m\alpha_z[\varphi(m+z,p)-\varphi(m,p)]+\gamma_m m[\varphi(m-1,p)-\varphi(m,p)]+k_p m[\varphi(m,p+1)-\varphi(m,p)]\right\rangle$$
$$+\left\langle\gamma_p p[\varphi(m,p-1)-\varphi(m,p)]\right\rangle. \tag{2}$$

(5) and approximate CV^2 as

$$CV^2\approx\frac{(\langle B^2\rangle+\langle B\rangle)\gamma_p}{2\langle B\rangle(\gamma_p+\gamma_m)\langle\bar{m}\rangle}. \tag{7}$$

This approximation implies that gene-expression noise primarily arises from fluctuations in mRNA counts that are transmitted downstream to the protein level. In summary, (7) represents the steady-state noise in protein level when there is no feedback in gene-expression.

III. Gene-expression noise with negative feedback regulation

In this section we compare and contrast the magnitude of gene-expression noise for different negative feedback circuits shown in Figure 1. To do this, we derive approximate analytical expressions for the coefficient of variation squared of $p(t)$ corresponding to feedback architectures I to IV.

A. Feedback regulation at the transcriptional level

We first consider protein mediated transcriptional regulation which corresponds to feedback circuit I in Figure 1. Transcriptional regulation is incorporated in the above gene-expression model by assuming that the transcription rate is dependent on the protein levels. More specifically, transcriptional events occur at rate $k_m(p)$, which is a monotonically decreasing function of the protein population count $p(t)$. This corresponds to a negative feedback mechanism where any increase (decrease) in protein numbers is compensated by a decrease (increase) in the transcription rate. To quantify the protein noise levels we use the *linear noise approximation* [23], which involves linearizing the transcription rate $k_m(p)$ about the steady-state average number of protein molecules $\langle\bar{p}\rangle$. This approximation is valid as long as the stochastic fluctuations in protein counts are small, which is likely to be true for tightly regulated essential proteins. Towards this end, we assume

$$k_m(p)\approx k_m(\langle\bar{p}\rangle)\left[1-\kappa\left(\frac{p(t)-\langle\bar{p}\rangle}{\langle\bar{p}\rangle}\right)\right] \tag{8}$$

where $k_m(\langle\bar{p}\rangle)$ is the average transcription rate. The dimensionless constant

$$\kappa=-\frac{\langle\bar{p}\rangle}{k_m(\langle\bar{p}\rangle)}\frac{dk_m(p)}{dp}|_{p=\langle\bar{p}\rangle}>0 \tag{9}$$

determines the sensitivity of the transcription rate to the protein count and can be interpreted as the strength of the negative feedback. The dimensionless constant κ determines the sensitivity of the transcription rate to the protein count and can be interpreted as the strength of the negative feedback.

To obtain the time evolution of the statistical moments we use (2), with k_m now replaced by (8). This results in the following moment dynamics:

$$\frac{d\langle m\rangle}{dt}=\langle k_m(p)\rangle\langle B\rangle-\gamma_m\langle m\rangle,\ \frac{d\langle p\rangle}{dt}=k_p\langle m\rangle-\gamma_p\langle p\rangle \tag{10a}$$
$$\frac{d\langle m^2\rangle}{dt}=\langle k_m(p)\rangle\langle B^2\rangle+\gamma_m\langle m\rangle+2\langle k_m(p)m\rangle\langle B\rangle-2\gamma_m\langle m^2\rangle \tag{10b}$$
$$\frac{d\langle p^2\rangle}{dt}=k_p\langle m\rangle+\gamma_p\langle p\rangle+2k_p\langle mp\rangle-2\gamma_p\langle p^2\rangle \tag{10c}$$
$$\frac{d\langle mp\rangle}{dt}=k_p\langle m^2\rangle+\langle k_m(p)p\rangle\langle B\rangle-\gamma_p\langle mp\rangle-\gamma_m\langle mp\rangle. \tag{10d}$$

Quantifying the steady-state moments from (10) and substituting in (4) gives the following protein noise level for feedback circuit I:

$$CV_{\mathrm{I}}^2=\frac{\gamma_p(\langle B\rangle+\langle B^2\rangle)}{2\langle B\rangle(\gamma_p+\gamma_m)(1+\kappa)\langle\bar{m}\rangle}, \tag{11}$$

where the steady-state mean protein count is the unique solution to the equation

$$\frac{\langle B\rangle k_p k_m(\langle\bar{p}\rangle)}{\gamma_m\gamma_p}=\langle\bar{p}\rangle \tag{12}$$

and the steady-state mean mRNA count is given by

$$\langle\bar{m}\rangle=\frac{\langle\bar{p}\rangle\gamma_p}{k_p}. \tag{13}$$

As done in the previous section, to obtain the noise level (11) we assumed that the protein population count is much larger than the mRNA population count, and hence ignored expression noise arising from random birth and death of individual protein molecules. Throughout the paper we use $CV_{\mathrm{X}}^2,\ \mathrm{X}\in\{\mathrm{I},\mathrm{II},\mathrm{III},\mathrm{IV}\}$ to denote the steady-state protein noise level corresponding to feedback circuit X.

For negative feedback circuit III, the frequency of transcription events $k_m(m)$ is a decreasing function of the mRNA copy number $m(t)$. Assuming fluctuations in $m(t)$ are sufficiently small, $k_m(m)$ can be linearized as

$$k_m(m)\approx k_m(\langle\bar{m}\rangle)\left[1-\kappa\left(\frac{m(t)-\langle\bar{m}\rangle}{\langle\bar{m}\rangle}\right)\right] \tag{14}$$

where

$$\kappa=-\frac{\langle\bar{m}\rangle}{k_m(\langle\bar{m}\rangle)}\frac{dk_m(m)}{dm}|_{m=\langle\bar{m}\rangle}>0 \tag{15}$$

is interpreted as the strength of the negative feedback circuit III. Replace the right-hand-side of (14) with k_m in equation

(2) results in the following moment dynamics

$$\frac{d\langle m\rangle}{dt} = \langle k_m(m)\rangle\langle B\rangle - \gamma_m\langle m\rangle, \frac{d\langle p\rangle}{dt} = k_p\langle m\rangle - \gamma_p\langle p\rangle \quad (16a)$$

$$\frac{d\langle m^2\rangle}{dt} = \langle k_m(m)\rangle\langle B^2\rangle + \gamma_m\langle m\rangle + 2\langle k_m(m)m\rangle\langle B\rangle - 2\gamma_m\langle m^2\rangle \quad (16b)$$

$$\frac{d\langle p^2\rangle}{dt} = k_p\langle m\rangle + \gamma_p\langle p\rangle + 2k_p\langle mp\rangle - 2\gamma_p\langle p^2\rangle \quad (16c)$$

$$\frac{d\langle mp\rangle}{dt} = k_p\langle m^2\rangle + \langle k_m(m)p\rangle\langle B\rangle - \gamma_p\langle mp\rangle - \gamma_m\langle mp\rangle. \quad (16d)$$

Steady-state analysis of the above moment equation results in the following protein noise level for negative feedback architecture III

$$CV^2_{\rm III} = \frac{\gamma_p(\langle B\rangle + \langle B^2\rangle)}{2\langle B\rangle(\gamma_p + \gamma_m(1+\kappa))(1+\kappa)\langle\bar{m}\rangle}. \quad (17)$$

B. Feedback regulation at the translational level

We next consider feedback circuit II, where the protein translation rate per mRNA is a monotonically decreasing function $k_p(p)$ of the protein count $p(t)$. Thus, the total protein production rate $z(t) = k_p(p)m$ is now dependent on both the mRNA and protein population count. As before, we assume that the stochastic fluctuations in $p(t)$ and $m(t)$ around their respective means $\langle\bar{p}\rangle$ and $\langle\bar{m}\rangle$ are sufficiently small and approximate the total protein production rate $z(t)$ as

$$z(t) = k_p(p)m \approx k_p(\langle\bar{p}\rangle)\left[m(t) - \kappa\ \langle\bar{m}\rangle\left(\frac{p(t)-\langle\bar{p}\rangle}{\langle\bar{p}\rangle}\right)\right], \quad (18)$$

where $k_p(\langle\bar{p}\rangle)$ is the average protein translation rate per mRNA and the dimensionless constant

$$\kappa = -\frac{\langle\bar{p}\rangle}{k_p(\langle\bar{p}\rangle)}\frac{dk_p(p)}{dp}|_{p=\langle\bar{p}\rangle} > 0 \quad (19)$$

is the strength of the negative feedback circuit II. The moment dynamics corresponding to this feedback can be obtained from (2) with $k_p m$ replaced by (18). This results in the following moment dynamics

$$\frac{d\langle m\rangle}{dt} = k_m\langle B\rangle - \gamma_m\langle m\rangle, \quad \frac{d\langle p\rangle}{dt} = \langle z\rangle - \gamma_p\langle p\rangle \quad (20a)$$

$$\frac{d\langle m^2\rangle}{dt} = k_m\langle B^2\rangle + \gamma_m\langle m\rangle + 2\langle k_m m\rangle\langle B\rangle - 2\gamma_m\langle m^2\rangle \quad (20b)$$

$$\frac{d\langle p^2\rangle}{dt} = \langle z\rangle + \gamma_p\langle p\rangle + 2\langle zp\rangle - 2\gamma_p\langle p^2\rangle \quad (20c)$$

$$\frac{d\langle mp\rangle}{dt} = \langle zm\rangle + k_m\langle p\rangle\langle B\rangle - \gamma_p\langle mp\rangle - \gamma_m\langle mp\rangle. \quad (20d)$$

Substituting (19) in (20) and performing a steady-state analysis of the resulting moment equations yields:

$$CV^2_{\rm II} = \frac{\gamma_p(\langle B\rangle + \langle B^2\rangle)}{2\langle B\rangle(\gamma_m + \gamma_p(1+\kappa))(1+\kappa)\langle\bar{m}\rangle}. \quad (21)$$

Finally, we consider feedback circuits IV where the protein translation rate per mRNA is a monotonically decreasing function $k_p(m)$ of the protein count $m(t)$. The procedure for quantifying protein noise levels for IV is very similar to that used for feedback circuits II except that the total protein production given by equation (18) is now modified as

$$z(t) = k_p(m)m \approx k_p(\langle\bar{m}\rangle)\left[m(t) - \kappa\left(m(t) - \langle\bar{m}\rangle\right)\right] \quad (22)$$

where

$$\kappa = -\frac{\langle\bar{m}\rangle}{k_p(\langle\bar{m}\rangle)}\frac{dk_p(m)}{dm}|_{m=\langle\bar{m}\rangle} > 0 \quad (23)$$

is the strength of the negative feedback circuit IV. Note that in this case $\kappa < 1$ since total protein production $z(t)$ is always an increasing function of the mRNA population count $m(t)$. Moment dynamics corresponding to feedback circuit IV is obtained by replacing (22) in equation (20). A steady-state analysis of the resulting moment equations gives

$$CV^2_{\rm IV} = \frac{\gamma_p(\langle B\rangle + \langle B^2\rangle)(1-\kappa)^2}{2\langle B\rangle(\gamma_m + \gamma_p)\langle\bar{m}\rangle}. \quad (24)$$

C. Comparison of gene-expression noise across negative feedback circuits

To assess the noise suppression abilities of different feedback circuits we perform a mathematically controlled comparison where all circuits are assumed to have the same feedback strength and steady-state mean mRNA count. Analytical expressions for the protein noise levels derived in the previous section (i.e., equations (11), (17), (21) and (24)) show the following relationship: When the mRNA half life is much longer then the protein half-life ($\gamma_m < \gamma_p$) then

$$CV^2_{IV} < CV^2_{II} < CV^2_{III} < CV^2_{I}. \quad (25)$$

On the other hand when the mRNA half-life is shorter than the protein half-life ($\gamma_m > \gamma_p$) then we have

$$CV^2_{IV} < CV^2_{III} < CV^2_{II} < CV^2_{I}. \quad (26)$$

Based on these result the main findings of this paper can be summarized as follows:

1) Assuming all feedback topologies have the same negative strength, feedback circuit IV provides the best noise suppression irrespective of the parameters of gene-expression.
2) Among different feedback architectures, negative feedback circuit I is the least effective in reducing gene-expression noise.
3) Depending on the mRNA and protein half-life, feedback circuit II or III will provide the second best suppression of gene-expression noise.

IV. Conclusions

What regulatory mechanisms control stochasticity in protein levels such that cellular process can occur with sufficient high fidelity is a fundamental question in biology. We here analyzed the noise suppression properties of four different negative feedback loops within gene-expression (Figure 1). Assuming that stochastic fluctuations in the populations of the protein and the mRNA are sufficiently small, we derived

explicit analytical formulas for the protein noise level for each of the four feedback mechanisms. These formulas reveal that some negative feedback architectures are inherently better at noise suppression.

Our results indicate that in a mathematically controlled comparison, feedback circuit IV provides the best suppression of gene-expression noise. More specifically, for a fixed feedback strength, a feedback mechanism where the protein translation rate per mRNA is a monotonically decreasing function of the mRNA count provides the least amount of statistical fluctuations in the protein count. Such feedback circuits can potentially be implement using microRNAs that are derived from introns within pre-mRNAs. For example, an intron-derived microRNA that inhibits translation of its own mRNA will create a scenario where the protein translation rate per mRNA is inversely proportional to the mRNA population count. Finally, our results have also shown that in between all the feedback architectures, feedback topology I is the least effective in buffering gene-expression noise. In summary, we have developed results that connect stochasticity in protein levels to the negative feedback architecture in gene expression. These results will not only be helpful in analyzing naturally occurring negative feedback circuits but also be useful for designing synthetic feedback circuits to reduce random fluctuations in protein copy numbers.

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