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Reducing noise through translational control in an auto-regulatory gene network

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Abstract— **Auto-regulatory transcriptional feedback, where the protein expressed from a gene inhibits its own transcription, is known to reduce stochastic fluctuations in protein numbers. Recent work has demonstrated the existence of negative feedback loops not only at the transcriptional level but also at the translational level. We investigate the noise suppression abilities of feedback loops at the translational level and compare them with transcriptional feedback. In particular, we consider two feedbacks at the translational level: translation blocking feedback, where the protein inhibits the translation of its mRNA, and degradation enhancing feedback, where the protein increases the degradation rate of its mRNA.**

We derive analytical formulas for the protein noise level corresponding to different feedback mechanisms. These noise levels are then compared with each other for fixed steady-state average number of protein and mRNA molecules. We show that translation blocking feedback always yields smaller levels of protein noise than transcriptional feedback. We further show that the difference between the protein noise levels with translation blocking and transcriptional feedback critically depends on how fast the protein dynamics is compared to the mRNA dynamics. In particular, this difference increases as we make the protein dynamics faster than the mRNA dynamics, while making it slower has an opposite effect.

Finally, we show that degradation enhancing feedback provides the same noise level as transcriptional feedback. This result shows that regulation at the translational level may not always be better than regulation at the transcriptional level in terms of reducing noise in the protein population.

I. INTRODUCTION

The probabilistic nature of gene expression and low copy numbers of RNAs and proteins within cells, lead to large statistical fluctuations in protein levels [1], [2], [3]. Various negative feedback mechanisms exists within gene networks that help reduce stochastic fluctuations in protein levels. One such common and well characterized mechanism is an auto-regulatory transcriptional feedback, where the protein expressed from a gene inhibits its own transcription [4], [5]. Both theoretical and experimental studies have shown that such negative feedback at the transcriptional level reduces noise in protein numbers [6], [7], [8], [9], [10]. Recent work has provided evidence of negative feedback loops at the translational level, where the protein can inhibit the translation rate and/or enhance the degradation rate of its mRNA [11], [12]. We investigate if such feedbacks at the translational level are more effective in reducing protein noise level than transcriptional feedback.

As shown in Figure 1, we consider a simple model for gene expression where the mRNA is transcribed at a rate T_x, the protein is translated from the mRNA at a rate L_x, and both the mRNA and the protein degrade at rates a_x and d_x, respectively. We denote by $\mathbf{m}(t)$ and $\mathbf{x}(t)$ the number of molecules of mRNA and protein, respectively, at time t (see Table I for a summary of notation used in this paper). In the stochastic formulation of this gene expression model, the molecular counts $\mathbf{m}(t)$ and $\mathbf{x}(t)$ are both stochastic processes. We quantify the protein noise level by the coefficient of variation

$$\sqrt{\frac{\mathbf{E}^*[\mathbf{x}^2]-\mathbf{x}^{*2}}{\mathbf{x}^{*2}}}, \tag{1}$$

where $\mathbf{x}^*$ is the steady-state average number of protein molecules and $\mathbf{E}^*[\mathbf{x}^2]$ is the steady-state value of the moment $\mathbf{E}[\mathbf{x}^2]$ [13]. In section II, we start by quantifying the noise

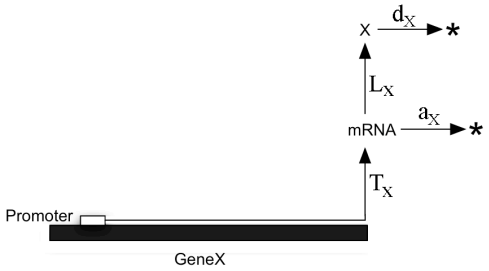

Fig. 1. A simple model for gene expression.

level in the protein population when there is no feedback mechanism present (as in Figure 1). In section III, we introduce a transcriptional negative feedback by assuming that the transcription rate of the gene is a monotonically decreasing function $g_1(\mathbf{x})$ of the protein count $\mathbf{x}$. Assuming that the fluctuations in protein/mRNA counts about their mean levels are sufficiently small, we derive an explicit formula for the protein noise level using the linear noise approximation. In this approximation, the protein noise level with transcriptional feedback is always smaller than the noise level with no feedback. It is important to point out that this comparison is made keeping the steady-state average production rate for both the protein and the mRNA fixed. This ensures that the steady-state average number of mRNA and protein molecules, with and without negative feedback, are the same. Such a form of comparison is also referred to

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in literature as a *mathematically controlled comparison* [14], [15].

TABLE I

A SUMMARY OF THE NOTATION USED IN THIS PAPER.

$\mathbf{m}(t)$	Number of mRNA molecules at time t
$\mathbf{x}(t)$	Number of protein molecules at time t
$\mathbf{m}^*$	Steady-state average number of mRNA molecules
$\mathbf{x}^*$	Steady-state average number of protein molecules
T_x	Transcriptional rate of the gene with no feedback
L_x	Translation rate of the gene with no feedback
a_x	mRNA degradation rate with no feedback
d_x	Protein degradation rate
N_x	Burst size of the gene given by L_x/a_x
e_x	Ratio of the protein degradation rate d_x and the mRNA degradation rate a_x
$g_1(\mathbf{x})$	Transcription rate of the gene with transcriptional feedback
$g_2(\mathbf{x})$	Translation rate of the mRNA with translation blocking feedback
$g_3(\mathbf{x})$	Degradation rate of the mRNA with degradation enhancing feedback
κ	Feedback gain defined as $\left\lvert \frac{d\log(g_i(\mathbf{x}))}{d\log(\mathbf{x})}\vert_{\mathbf{x}=\mathbf{x}^*} \right\rvert$. Assumed same for all feedback mechanisms

We next investigate the noise suppression abilities of feedback loops at the translational level. In particular, we focus on translation blocking feedback, where the protein inhibits the translation of its own mRNA (see Figure 2). This feedback is incorporated in the gene expression model by assuming that the mRNA translation rate is a function of the protein count $\mathbf{x}$. Table II summarizes our conclusions on the protein noise levels for the different feedback mechanisms.

Comparing these noise levels for a fixed average number of protein molecules $\mathbf{x}^*$, we conclude that translation blocking feedback is always more effective in attenuating protein noise than transcriptional feedback. We further show that the difference in the protein noise level with translation blocking and transcriptional feedback critically depends on $e_x = d_x/a_x$, which is a measure of how fast the protein dynamics is compared to the mRNA dynamics. In particular, making the protein dynamics much faster than the mRNA dynamics (i.e., increasing e_x), increases this difference, and enhances the noise suppression ability of the translation blocking feedback compared to the transcriptional feedback. On the other hand, making the mRNA dynamics much faster than the protein dynamics (i.e., decreasing e_x), decreases this difference, and diminishes the advantage of using translation blocking feedback over transcriptional feedback for noise reduction.

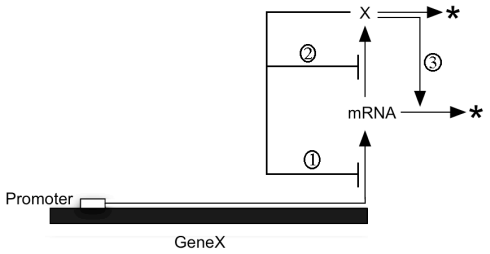

Fig. 2. An auto-regulatory gene network with three different mechanisms of auto-regulation. Mechanisms 1, 2 and 3 correspond transcriptional feedback, translation blocking feedback and degradation enhancing feedback, respectively.

TABLE II

PROTEIN NOISE LEVELS OBTAINED USING THE LINEAR NOISE APPROXIMATION FOR DIFFERENT NEGATIVE FEEDBACK MECHANISMS

Feedback mechanism	Steady-state protein noise level
No feedback	$\sqrt{\frac{1+N_x+e_x}{\mathbf{x}^*(1+e_x)}}$
Transcriptional feedback	$\sqrt{\frac{1+N_x+e_x+\kappa e_x}{\mathbf{x}^*(1+e_x)(1+\kappa)}}$
Translation blocking feedback	$\sqrt{\frac{1+N_x+e_x+\kappa e_x}{\mathbf{x}^*(1+\kappa)(1+(1+\kappa)e_x)}}$
Degradation enhancing feedback	$\sqrt{\frac{1+N_x+e_x+\kappa e_x}{\mathbf{x}^*(1+e_x)(1+\kappa)}}$

We also consider another feedback mechanism at the translational level: degradation enhancing feedback, where the protein increases the degradation rate of its mRNA. This feedback mechanism has also been previously considered in [16] in the context of regulated protein degradation. Consistent with the prediction of [16], the linear noise approximation gives the same protein noise level for degradation enhancing feedback and transcriptional feedback (see Table II). This emphasizes an important point that feedback at the translational level is not always more effective than feedback at the transcriptional level in terms of reducing noise in the protein population, which contradicts what had been previously conjectured in [22].

II. GENE EXPRESSION MODEL WITH NO REGULATION

We consider a model of gene expression which takes into account both the mRNA and protein dynamics. As shown in Figure 1, the protein production is decomposed into two steps: transcription and translation. We assume that the mRNA is transcribed from the gene *GeneX* at a constant rate T_x and the protein X is translated from the mRNA at a constant rate L_x. Both mRNA and the protein decay at rates a_x and d_x respectively. As the average lifetime of a mRNA is $1/a_x$ and proteins are made from it at a rate L_x, $N_x = L_x/a_x$ denotes the average number of proteins produced per mRNA, which is referred to as the *burst size* of the gene *GeneX*. We

denote by $\mathbf{m}$ and $\mathbf{x}$, the number of molecules of the mRNA and protein X, respectively. As a continuous deterministic model based on chemical rate equations does not provide information about the stochastic fluctuation in the protein, we consider a stochastic formulation that treats births and deaths of the mRNA and the protein as probabilistic events. Given that $\mathbf{x}(t) = x$ and $\mathbf{m}(t) = m$, the probabilities of the four reactions corresponding to births and deaths of the mRNA and the protein happening in the infinitesimal time interval $(t, t+dt]$ are given by

$$\Pr\{\mathbf{x}(t+dt) = x, \mathbf{m}(t+dt) = m+1\} = T_x dt \tag{2a}$$
$$\Pr\{\mathbf{x}(t+dt) = x, \mathbf{m}(t+dt) = m-1\} = a_x m dt \tag{2b}$$
$$\Pr\{\mathbf{x}(t+dt) = x+1, \mathbf{m}(t+dt) = m\} = L_x m dt \tag{2c}$$
$$\Pr\{\mathbf{x}(t+dt) = x-1, \mathbf{m}(t+dt) = m\} = d_x x dt \tag{2d}$$

[17], [18]. We model the time evolution of the number of molecules $\mathbf{x}$ and $\mathbf{m}$ through a Stochastic Hybrid System (SHS), the state of which is $\mathbf{y} = [\mathbf{m}, \mathbf{x}]^T$. This SHS is characterized by trivial continuous dynamics

$$\dot{\mathbf{y}} = 0 \tag{3}$$

and four reset maps $\phi_i(\mathbf{y})$

$$\mathbf{y} \mapsto \phi_1(\mathbf{y}) = \begin{bmatrix} \mathbf{m}+1 \\ \mathbf{x} \end{bmatrix}, \quad \mathbf{y} \mapsto \phi_2(\mathbf{y}) = \begin{bmatrix} \mathbf{m}-1 \\ \mathbf{x} \end{bmatrix} \tag{4a}$$
$$\mathbf{y} \mapsto \phi_3(\mathbf{y}) = \begin{bmatrix} \mathbf{m} \\ \mathbf{x}+1 \end{bmatrix}, \quad \mathbf{y} \mapsto \phi_4(\mathbf{y}) = \begin{bmatrix} \mathbf{m} \\ \mathbf{x}-1 \end{bmatrix} \tag{4b}$$

with transition intensities

$$\lambda_1(\mathbf{y}) = T_x, \ \lambda_2(\mathbf{y}) = a_x \mathbf{m}, \ \lambda_3(\mathbf{y}) = L_x \mathbf{m}, \ \lambda_4(\mathbf{y}) = d_x \mathbf{x} \tag{5}$$

corresponding to the transcription, translation, mRNA and protein degradation rates in (2) (see [19]). We now determine the time evolution of the first and second order moments of $\mathbf{y}$, i.e., the expected values $\mathbf{E}[\mathbf{m}]$, $\mathbf{E}[\mathbf{x}]$, $\mathbf{E}[\mathbf{x}^2]$, $\mathbf{E}[\mathbf{m}^2]$ and $\mathbf{E}[\mathbf{mx}]$. This moment dynamics can be obtained using the Dynkin's equation for the above SHS, according to which we have that

$$\frac{d\mathbf{E}[\psi(\mathbf{y})]}{dt} = \mathbf{E}\left[\sum_{i=1}^{4} \left(\psi(\phi_i(\mathbf{y})) - \psi(\mathbf{y})\right) \lambda_i(\mathbf{y})\right] \tag{6}$$

[20], [21]. Using (6) with appropriate choices for $\psi(\mathbf{y})$ we conclude that

$$\frac{d\mathbf{E}[\mathbf{m}]}{dt} = T_x - a_x \mathbf{E}[\mathbf{m}] \tag{7a}$$
$$\frac{d\mathbf{E}[\mathbf{x}]}{dt} = L_x \mathbf{E}[\mathbf{m}] - d_x \mathbf{E}[\mathbf{x}] \tag{7b}$$
$$\frac{d\mathbf{E}[\mathbf{m}^2]}{dt} = T_x + a_x \mathbf{E}[\mathbf{m}] + 2T_x \mathbf{E}[\mathbf{m}] - 2a_x \mathbf{E}[\mathbf{m}^2] \tag{7c}$$
$$\frac{d\mathbf{E}[\mathbf{x}^2]}{dt} = L_x \mathbf{E}[\mathbf{m}] + d_x \mathbf{E}[\mathbf{x}] + 2L_x \mathbf{E}[\mathbf{mx}] - 2d_x \mathbf{E}[\mathbf{x}^2] \tag{7d}$$
$$\frac{d\mathbf{E}[\mathbf{mx}]}{dt} = L_x \mathbf{E}[\mathbf{m}^2] + T_x \mathbf{E}[\mathbf{x}] - d_x \mathbf{E}[\mathbf{mx}] - a_x \mathbf{E}[\mathbf{mx}]. \tag{7e}$$

By setting to zero the right-hand sides of (7), we obtain the following steady-state moments:

$$\mathbf{m}^* = \frac{T_x}{a_x}, \quad \mathbf{x}^* = \frac{L_x T_x}{d_x a_x} \tag{8a}$$
$$\mathbf{E}^*[\mathbf{m}^2] = \frac{a_x T_x + T_x^2}{a_x^2} \tag{8b}$$
$$\mathbf{E}^*[\mathbf{x}^2] = \frac{L_x T_x}{d_x a_x} + \frac{L_x(d_x a_x L_x T_x + d_x L_x T_x^2 + a_x L_x T_x^2)}{d_x^2 a_x^2 (d_x + a_x)} \tag{8c}$$
$$\mathbf{E}^*[\mathbf{mx}] = \frac{d_x a_x L_x T_x + d_x L_x T_x^2 + a_x L_x T_x^2}{d_x a_x^2 (d_x + a_x)} \tag{8d}$$

where $\mathbf{m}^*$ and $\mathbf{x}^*$ represent the steady-state average number of molecules of the mRNA and the protein, respectively, and $\mathbf{E}^*$ denotes the steady-state value of the respective moment. Substituting the steady-states from (8) in (1) we obtain the following coefficient of variation of $\mathbf{x}$

$$CV_{no-regulation} = \sqrt{\frac{1 + N_x + e_x}{\mathbf{x}^*(1+e_x)}} \tag{9}$$

where $e_x = d_x/a_x$ is the ratio of the protein and the mRNA degradation rate, and $CV_{no-regulation}$ represents the protein noise level when there is no feedback mechanism present.

III. Transcriptional regulation in gene expression

We now put a negative feedback in the gene expression model introduced in the previous section. In particular, this feedback is at the transcriptional level where any increase (decrease) in protein numbers, decreases (increases) the transcription rate of the gene. We assume that the transcription rate of the gene is given by $g_1(\mathbf{x})$ where g_1 is a monotonically decreasing function of the protein count $\mathbf{x}$. Such an auto-regulatory gene network with transcriptional feedback can be modeled by the SHS (3)-(5), except that now

$$\lambda_1(\mathbf{y}) = g_1(\mathbf{x}). \tag{10}$$

In order to write the moment dynamics we linearize the function $g_1(\mathbf{x})$ about the steady-state average number of protein molecules $\mathbf{x}^*$. This approximation is valid as long as the stochastic fluctuations are small in the sense that the protein count does not leave the region in which $g_1(\mathbf{x})$ is approximately linear. Towards this end, we assume

$$\lambda_1(\mathbf{y}) = g_1(\mathbf{x}) \approx g_1(\mathbf{x}^*)\left[1 - \kappa\left(\frac{\mathbf{x} - \mathbf{x}^*}{\mathbf{x}^*}\right)\right] \tag{11}$$

where the dimensionless constant

$$\kappa = -\frac{\mathbf{x}^*}{g_1(\mathbf{x}^*)} \frac{dg_1(\mathbf{x})}{d\mathbf{x}}|_{\mathbf{x}=\mathbf{x}^*} > 0 \tag{12}$$

can be though of as the feedback gain and $g_1(\mathbf{x}^*)$ is the average transcription rate. For comparison purposes we choose $g_1(\mathbf{x}^*)$ such that the steady-state average counts of the mRNA and the protein are equal to their corresponding values in the previous section, where there was no regulation. This is done by taking the average transcription rate $g_1(\mathbf{x}^*) = T_x$, which is

the transcription rate of the gene when there is no negative feedback (see Figure 1).

Using Dynkin's equation with the linearized transition intensity (11) we have the following moment dynamics

$$\frac{d\mathbf{E}[\mathbf{m}]}{dt} = T_x - \kappa T_x \frac{\mathbf{E}[\mathbf{x}]-\mathbf{x}^*}{\mathbf{x}^*} - a_x\mathbf{E}[\mathbf{m}] \tag{13a}$$

$$\frac{d\mathbf{E}[\mathbf{x}]}{dt} = L_x\mathbf{E}[\mathbf{m}] - d_x\mathbf{E}[\mathbf{x}] \tag{13b}$$

$$\frac{d\mathbf{E}[\mathbf{m}^2]}{dt} = T_x(1+\kappa) + a_x\mathbf{E}[\mathbf{m}] + 2T_x\mathbf{E}[\mathbf{m}] + 2\kappa T_x\mathbf{E}[\mathbf{m}] - 2a_x\mathbf{E}[\mathbf{m}^2] - \kappa T_x\frac{\mathbf{E}[\mathbf{x}]}{\mathbf{x}^*} - 2\kappa T_x\frac{\mathbf{E}[\mathbf{mx}]}{\mathbf{x}^*} \tag{13c}$$

$$\frac{d\mathbf{E}[\mathbf{x}^2]}{dt} = L_x\mathbf{E}[\mathbf{m}] + d_x\mathbf{E}[\mathbf{x}] + 2L_x\mathbf{E}[\mathbf{mx}] - 2d_x\mathbf{E}[\mathbf{x}^2] \tag{13d}$$

$$\frac{d\mathbf{E}[\mathbf{mx}]}{dt} = L_x\mathbf{E}[\mathbf{m}^2] + T_x\mathbf{E}[\mathbf{x}] + \kappa T_x\mathbf{E}[\mathbf{x}] - d_x\mathbf{E}[\mathbf{mx}] - a_x\mathbf{E}[\mathbf{mx}] - \kappa T_x\frac{\mathbf{E}[\mathbf{x}^2]}{\mathbf{x}^*}. \tag{13e}$$

From (13a) and (13b) the steady-state means are given by

$$\mathbf{m}^* = \frac{T_x}{a_x}, \quad \mathbf{x}^* = \frac{L_xT_x}{d_xa_x} \tag{14}$$

which, by construction, are the same as those obtained in Section II with no feedback [see (8)]. A steady-state analysis of the remaining equations yields the following steady-state coefficient of variation of $\mathbf{x}$

$$CV_{transcription-regulation} = \sqrt{\frac{1+N_x+e_x+\kappa e_x}{\mathbf{x}^*(1+e_x)(1+\kappa)}}. \tag{15}$$

Comparing (15) with the noise level (9) when there is no feedback, we see that

$$\frac{CV_{transcription-regulation}}{CV_{no-regulation}} = \sqrt{\frac{1+N_x+e_x+\kappa e_x}{(1+\kappa)(1+N_x+e_x)}}. \tag{16}$$

As expected, when $\kappa = 0$, the right-hand-side of (16) is equal to one. When $\kappa > 0$, this quantity is always smaller than one, which shows that for fixed $\mathbf{m}^*$ and $\mathbf{x}^*$, the protein noise level with transcriptional negative feedback is always smaller than the noise level with no feedback.

IV. Translational regulation in gene expression

We now consider more sophisticated forms of negative feedback where regulation occurs at the translational level. In particular, we consider two such forms of feedback: translation blocking feedback and degradation enhancing feedback.

A. Translation blocking feedback

We first consider a negative feedback mechanism where the protein inhibits the translation of its own mRNA and refer to it as the *translation blocking feedback*. The simplest biological mechanism by which such a feedback is implemented is when a protein binds to its own mRNA and prevents ribosomes from accessing the mRNA and carry out translation. We model this translation blocking feedback by assuming that the translation rate of the mRNA is given by $g_2(\mathbf{x})$, where g_2 is a monotonically decreasing function of the protein count $\mathbf{x}$.

The SHS corresponding to this feedback mechanism is given by (3)-(5), but now with

$$\lambda_3(\mathbf{y}) = g_2(\mathbf{x})\mathbf{m}. \tag{17}$$

As before, we assume that the stochastic fluctuations in $\mathbf{x}$ and $\mathbf{m}$ around their respective means $\mathbf{x}^*$ and $\mathbf{m}^*$ are sufficiently small and approximate the above transition intensity as

$$\lambda_3(\mathbf{y}) = g_2(\mathbf{x})\mathbf{m} \approx g_2(\mathbf{x}^*)\left[\mathbf{m} - \kappa\ \mathbf{m}^*\left(\frac{\mathbf{x}-\mathbf{x}^*}{\mathbf{x}^*}\right)\right], \tag{18}$$

ignoring quadratic and higher order terms in $\mathbf{x}-\mathbf{x}^*$ and $\mathbf{m}-\mathbf{m}^*$. In equation (18), the dimensionless constant

$$\kappa = -\frac{\mathbf{x}^*}{g_2(\mathbf{x}^*)}\frac{dg_2(\mathbf{x})}{d\mathbf{x}}|_{\mathbf{x}=\mathbf{x}^*} > 0 \tag{19}$$

is the feedback gain of the translation blocking feedback and $g_2(\mathbf{x}^*)$ is the average translation rate of the mRNA. We take $g_2(\mathbf{x}^*) = L_x$, which is the translation rate of the mRNA when there is no negative feedback (see Figure 1). As we will shortly see, this choice ensures that the steady-state means $\mathbf{x}^*$ and $\mathbf{m}^*$ are equal to their corresponding values when there is no feedback.

Using (18) and the Dynkin's equation, the time evolution of all the first and second order moments of $\mathbf{x}$ and $\mathbf{m}$ are now given by

$$\frac{d\mathbf{E}[\mathbf{m}]}{dt} = T_x - a_x\mathbf{E}[\mathbf{m}] \tag{20a}$$

$$\frac{d\mathbf{E}[\mathbf{x}]}{dt} = L_x\mathbf{E}[\mathbf{m}] - \kappa L_x\frac{\mathbf{m}^*(\mathbf{E}[\mathbf{x}]-\mathbf{x}^*)}{\mathbf{x}^*} - d_x\mathbf{E}[\mathbf{x}] \tag{20b}$$

$$\frac{d\mathbf{E}[\mathbf{m}^2]}{dt} = T_x + a_x\mathbf{E}[\mathbf{m}] + 2T_x\mathbf{E}[\mathbf{m}] - 2a_x\mathbf{E}[\mathbf{x}^2] \tag{20c}$$

$$\frac{d\mathbf{E}[\mathbf{x}^2]}{dt} = L_x\mathbf{E}[\mathbf{m}] + \kappa L_x\mathbf{m}^* + d_x\mathbf{E}[\mathbf{x}] + 2L_x\mathbf{E}[\mathbf{mx}] + 2\kappa L_x\mathbf{m}^*\mathbf{E}[\mathbf{x}] - 2d_x\mathbf{E}[\mathbf{x}^2] - \frac{\kappa L_x\mathbf{m}^*\mathbf{E}[\mathbf{x}]}{\mathbf{x}^*} - \frac{2\kappa L_x\mathbf{m}^*\mathbf{E}[\mathbf{x}^2]}{\mathbf{x}^*} \tag{20d}$$

$$\frac{d\mathbf{E}[\mathbf{mx}]}{dt} = L_x\mathbf{E}[\mathbf{m}^2] + \kappa L_x\mathbf{E}[\mathbf{m}]\mathbf{m}^* + T_x\mathbf{E}[\mathbf{x}] - d_x\mathbf{E}[\mathbf{mx}] - a_x\mathbf{E}[\mathbf{mx}] - \kappa T_x\frac{\mathbf{m}^*\mathbf{E}[\mathbf{mx}]}{\mathbf{x}^*}. \tag{20e}$$

A steady-state analysis of the above equations yields

$$\mathbf{m}^* = \frac{T_x}{a_x}, \quad \mathbf{x}^* = \frac{L_xT_x}{d_xa_x} \tag{21a}$$

$$CV_{translation-blocking} = \sqrt{\frac{1+N_x+e_x+\kappa e_x}{\mathbf{x}^*(1+\kappa)(1+(1+\kappa)e_x)}}. \tag{21b}$$

Comparing the above noise level (21b) with the noise level (9) we have that

$$\frac{CV_{translation-blocking}}{CV_{no-regulation}} = \sqrt{\frac{(1+N_x+e_x+\kappa e_x)(1+e_x)}{(1+N_x+e_x)(1+(1+\kappa)e_x)(1+\kappa)}} < 1, \quad \kappa > 0, \tag{22}$$

which implies that like transcriptional feedback, for fixed $\mathbf{m}^*$ and $\mathbf{x}^*$, translation blocking feedback also results in smaller protein noise level than the noise level when there is no feedback. We next compare the noise suppression abilities of transcriptional and translation blocking feedback. Towards that end, we compute that

$$\frac{CV_{translation-blocking}}{CV_{transcription-regulation}} = \sqrt{\frac{1}{1+\kappa\frac{e_x}{1+e_x}}} < 1 \tag{23}$$

which shows that translation blocking feedback is always better than transcriptional feedback in terms of reducing noise in the protein population. Note from (23) that, for a fixed feedback gain κ, the above ratio monotonically decreases with increasing e_x and

$$\lim_{e_x\to 0} \frac{CV_{translation-blocking}}{CV_{transcription-regulation}} = 1 \tag{24a}$$

$$\lim_{e_x\to \infty} \frac{CV_{translation-blocking}}{CV_{transcription-regulation}} = \sqrt{\frac{1}{1+\kappa}}. \tag{24b}$$

We recall that $e_x = d_x/a_x$ is a measure of how fast the protein dynamics is compared to the mRNA dynamics. The above result shows that when e_x is large, i.e., the protein dynamics is much faster than the mRNA dynamics, the noise suppression ability of the translation blocking feedback is far superior to that of transcriptional feedback. However, when e_x is small, i.e., the protein dynamics is much slower than the mRNA dynamics, the difference in the noise suppression abilities of the two feedback mechanisms is small.

B. Degradation enhancing feedback

We next consider another negative feedback mechanism at the translational level where the protein enhances the degradation rate of its own mRNA. We refer to this mechanism as the *degradation enhancing feedback*. Such a feedback mechanism arises when the protein activates enzymes involved in the degradation of the mRNA. We model the degradation enhancing feedback by assuming that the degradation rate of the mRNA is given by $g_3(\mathbf{x})$ where g_3 is a monotonically increasing function of $\mathbf{x}$.

The SHS corresponding to this feedback mechanism is given by (3)-(5) but now with

$$\lambda_2(\mathbf{y}) = g_3(\mathbf{x})\mathbf{m}. \tag{25}$$

Linearizing this transition intensity we have

$$\lambda_2(\mathbf{y}) = g_3(\mathbf{x})\mathbf{m} \approx g_2(\mathbf{x}^*)\left[\mathbf{m} + \kappa\ \mathbf{m}^*\left(\frac{\mathbf{x}-\mathbf{x}^*}{\mathbf{x}^*}\right)\right] \tag{26}$$

where

$$\kappa = \frac{\mathbf{x}^*}{g_3(\mathbf{x}^*)}\frac{dg_3(\mathbf{x})}{d\mathbf{x}}|_{\mathbf{x}=\mathbf{x}^*} > 0 \tag{27}$$

is the feedback gain of the degradation enhancing feedback. Taking $g_3(\mathbf{x}^*) = a_x$, which is the degradation rate of the mRNA when there is no negative feedback (see Figure 1), we have the following moment dynamics

$$\frac{d\mathbf{E}[\mathbf{m}]}{dt} = T_x - a_x\mathbf{E}[\mathbf{m}] - \kappa a_x\frac{\mathbf{m}^*(\mathbf{E}[\mathbf{x}]-\mathbf{x}^*)}{\mathbf{x}^*} \tag{28a}$$

$$\frac{d\mathbf{E}[\mathbf{x}]}{dt} = L_x\mathbf{E}[\mathbf{m}] - d_x\mathbf{E}[\mathbf{x}] \tag{28b}$$

$$\frac{d\mathbf{E}[\mathbf{m}^2]}{dt} = T_x + a_x\mathbf{E}[\mathbf{m}] + 2T_x\mathbf{E}[\mathbf{m}] - 2a_x\mathbf{E}[\mathbf{x}^2] - a_x\kappa\mathbf{m}^* + 2a_x\kappa\mathbf{E}[\mathbf{m}]\mathbf{m}^* + a_x\kappa\frac{\mathbf{m}^*\mathbf{E}[\mathbf{x}]}{\mathbf{x}^*} - 2a_x\kappa\frac{\mathbf{m}^*\mathbf{E}[\mathbf{x}\mathbf{m}]}{\mathbf{x}^*} \tag{28c}$$

$$\frac{d\mathbf{E}[\mathbf{x}^2]}{dt} = L_x\mathbf{E}[\mathbf{m}] + d_x\mathbf{E}[\mathbf{x}] + 2L_x\mathbf{E}[\mathbf{m}\mathbf{x}] - 2d_x\mathbf{E}[\mathbf{x}^2] \tag{28d}$$

$$\frac{d\mathbf{E}[\mathbf{m}\mathbf{x}]}{dt} = L_x\mathbf{E}[\mathbf{m}^2] + \kappa a_x\mathbf{E}[\mathbf{x}]\mathbf{m}^* + T_x\mathbf{E}[\mathbf{x}] - d_x\mathbf{E}[\mathbf{m}\mathbf{x}] - a_x\mathbf{E}[\mathbf{m}\mathbf{x}] - \kappa a_x\frac{\mathbf{m}^*\mathbf{E}[\mathbf{x}^2]}{\mathbf{x}^*}. \tag{28e}$$

A steady-state analysis of the above equations yields

$$\mathbf{m}^* = \frac{T_x}{a_x}, \quad \mathbf{x}^* = \frac{L_xT_x}{d_xa_x} \tag{29a}$$

$$CV_{degradation-enhancing} = \sqrt{\frac{1+N_x+e_x+\kappa e_x}{\mathbf{x}^*(1+e_x)(1+\kappa)}}. \tag{29b}$$

Comparing (29b) with (15), we conclude that the protein noise level with degradation enhancing feedback is identical to the noise level with transcriptional feedback. This result shows that regulation at the translational level is not always better than regulation at the transcriptional level in terms of reducing stochastic fluctuations in protein numbers.

V. Discussion and Future work

We analyzed the noise suppression properties of three different auto-regulatory negative feedback loops. 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 three feedback mechanisms. Comparing these formulas for fixed steady-state average number of molecules and fixed feedback gain κ we concluded that

$$CV_{translation-blocking} < CV_{transcription-regulation} \tag{30a}$$

$$CV_{degradation-enhancing} = CV_{transcription-regulation} \tag{30b}$$

$$CV_{transcription-regulation} < CV_{no-regulation}. \tag{30c}$$

These results show that transcriptional feedback and degradation enhancing feedback, which directly control the production and degradation of the mRNA, and hence indirectly control the production of the protein, provide the same protein noise level. On the other hand, translation blocking feedback which directly controls the production of the protein always provides smaller noise in protein numbers. In summary, the mechanism by which regulation at the translational level can provide better noise suppression than regulation at transcriptional level is through translation blocking feedback where the translation rate of the mRNA decreases with increasing protein count.

Our results support and explain the observation made in [22] that regulation at the translational level always provides better noise suppression than transcriptional regulation. This observation was based on an auto-regulatory negative feedback mechanism where the protein binds to its mRNA and changes both the translation and degradation rate of the mRNA. This feedback loop corresponds to a mixture of translation blocking and degradation enhancing feedback. Our analysis shows that it is the translation blocking component of the feedback that causes this mixed feedback to provide better noise suppression than transcriptional feedback. Without the translation blocking feedback component, we predict that this feedback at the translational level would provide the same noise suppression as the transcriptional feedback.

We investigated the noise suppression properties of both translation blocking and transcriptional feedback when the protein dynamics is much faster/slower than the mRNA dynamics. In particular, we showed that in the limit when the protein dynamics is much slower than the mRNA dynamics, we have

$$\lim_{e_x \to 0} (CV_{transcription-regulation} - CV_{translation-blocking}) = 0, \tag{31}$$

and both feedback mechanisms provide the same level of noise suppression. However, as we increase e_x from zero, i.e., as we make the protein dynamics much faster than the mRNA dynamics, this difference increases and translation blocking feedback becomes increasingly more effective in reducing protein noise than transcriptional feedback.

One direction for future work is to determine if translation blocking feedback indeed occurs more often when e_x is not small. Another direction of future work is to analyze other auto-regulatory mechanisms that are possible in our gene expression model. Figure 3 plots eight different auto-regulatory mechanisms out of which six are negative feedback loops and two are negative feedforward loops. Our goal would be analyze and compare the noise suppression abilities of all these feedback and feedforward loops.

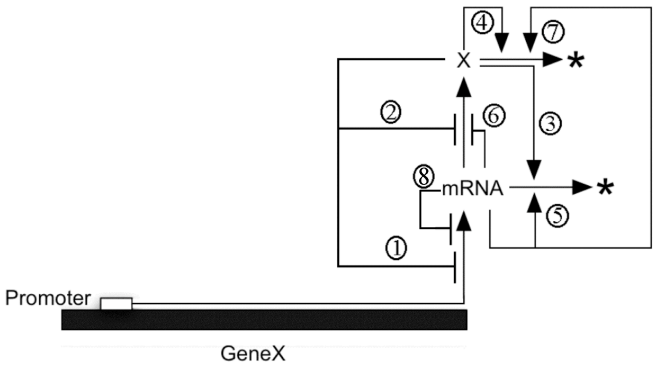

Fig. 3. An auto-regulatory gene network with eight different mechanisms of auto-regulation. Auto-regulation mechanisms 1, 2, 3, 4, 5, 8 are negative feedback loops while mechanisms 6 and 7 are negative feedforward loops.

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