Negative feedback through mRNA provides the best control of gene-expression noise

Abhyudai Singh Member, IEEE

Abstract—Genetically identical cell populations exposed to the same environment can exhibit considerable cell-to-cell variation in the levels of specific proteins. This variation or expression noise arises from the inherent stochastic nature of biochemical reactions that constitute gene-expression. Negative feedback loops are common motifs in gene networks that reduce expression noise and intercellular variability in protein levels. Using stochastic models of gene expression we here compare different feedback architectures in their ability to reduce stochasticity in protein levels. A mathematically controlled comparison shows that in physiologically relevant parameter regimes, feedback regulation through the mRNA provides the best suppression of expression noise. Consistent with our theoretical results we find negative feedback loops through the mRNA in essential eukaryotic genes, where feedback is mediated via intron-derived microRNAs. Finally, we find that contrary to previous results, protein mediated translational regulation may not always provide significantly better noise suppression than protein mediated transcriptional regulation.

Index Terms—Gene-expression noise, negative feedback, noise suppression, microRNAs, linear noise approximation

1 INTRODUCTION

The inherent probabilistic nature of biochemical reactions that constitute gene-expression together with low copy numbers of mRNAs can lead to large stochastic fluctuations in protein levels [1], [2], [3]. Intercellular variability in protein levels generated by these stochastic fluctuations is often referred to as gene-expression noise. Increasing evidence suggests that gene-expression noise can be detrimental for the functioning of essential and housekeeping proteins whose levels have to be tightly maintained within certain bounds for optimal performance [4], [5], [6]. Moreover, many diseased states have been attributed to an increase in expression noise in particular genes [7], [8], [9]. 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 [10], [11], [12], [13], [14], [15], [16].

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 [17], [18], [19], [20]. For example, it is estimated that over 40% of Escherichia coli transcription factors regulate their own expression through this feedback mechanism [21]. Both theoretical and experimental studies have shown that such a negative feedback at the transcriptional level reduces noise in protein numbers [22], [23], [24], [25], [26], [27], [28]. Recent work has provided evidence of more sophisticated negative feedback loops where the protein inhibits the translation of its own mRNA [29], [30] or mRNA inhibits the transcription of its gene [31], [32]. We here compare and contrast the noise suppression ability of these different feedback mechanisms in gene-expression.

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 count or the mRNA count. This procedure results in four different negative feedback architectures, which are illustrated in Figure 1. For example, feedback architecture I corresponds to protein...
mediated transcriptional regulation where the transcription rate is a decreasing function of the protein count. Similarly, feedback architecture IV corresponds to a scenario where the protein translation rate per mRNA is a decreasing function of the mRNA count.

We derive analytical expressions for the protein noise levels for each of these different feedback architectures. 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 architectures are done keeping the mean protein and mRNA 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 also referred to in literature as a mathematically controlled comparison [33].

The paper is organized as follows: In Section 2 we quantify the extent of stochasticity in protein levels in a gene-expression model with no negative feedback. Protein noise levels for feedback architectures I – IV are computed in Section 3. In Section 4 we compare the noise suppression abilities of the different feedback architectures. Finally, a discussion of our results is provided in Section 5.

2 Gene Expression Model with No Regulation

We consider a gene-expression 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, \quad z = \{1, 2, 3, \ldots\).
\]

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 [34], [35], [36]. Protein molecules are translated from each single mRNA at rate \( k_p \). We assume that mRNAs and proteins degrade at constant rates \( \gamma_m \) and \( \gamma_p \), respectively. In the stochastic formulation of this model, transcription, translation and degradation are probabilistic events that occur at exponentially distributed time intervals. 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 1. The frequency with which different events occur is determined by the third column of Table 1, 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 \( \Phi(m,p) \) is given by equation (2) [37], [38]. Here, and in the sequel we use the symbol \( \langle \cdot \rangle \) to denote the expected value. Using (2) with appropriate choices for \( \Phi(m,p) \) we obtain the following moment dynamics:

\[
\frac{d\langle m \rangle}{dt} = k_m \langle B \rangle - \gamma_m \langle m \rangle, \quad \frac{d\langle p \rangle}{dt} = k_p \langle m \rangle - \gamma_p \langle p \rangle \quad (3a)
\]

\[
\frac{d\langle m^2 \rangle}{dt} = k_m \langle B^2 \rangle + \gamma_m \langle m \rangle + 2k_m \langle B \rangle \langle m \rangle - 2\gamma_m \langle m^2 \rangle \quad (3b)
\]

\[
\frac{d\langle p^2 \rangle}{dt} = k_p \langle m \rangle + \gamma_p \langle p \rangle + 2k_p \langle mp \rangle - 2\gamma_p \langle p^2 \rangle \quad (3c)
\]

\[
\frac{d\langle mp \rangle}{dt} = k_p \langle m^2 \rangle + k_m \langle B \rangle \langle p \rangle - \gamma_p \langle mp \rangle - \gamma_m \langle mp \rangle. \quad (3d)
\]

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

\[
CV^2 = \frac{\sigma^2}{\langle p \rangle^2},
\]

where \( \sigma^2 \) is the steady-state variance in protein levels and \( \langle p \rangle \) denotes the steady-state mean protein count [39], [40]. Quantifying the steady-state moments from (3) and substituting in (4) we obtain

\[
CV^2 = \frac{\langle (B^2) \rangle + \langle B \rangle \gamma_p}{2\langle B \rangle (\gamma_p + \gamma_m) \langle m \rangle} + \frac{1}{\langle p \rangle} \quad (5)
\]

where

\[
\langle \tilde{m} \rangle = \frac{\langle B \rangle k_m}{\gamma_m}, \quad \langle \tilde{p} \rangle = \frac{\langle \tilde{m} \rangle k_p}{\gamma_p} \quad (6)
\]
\[
\frac{d\langle m, p \rangle}{dt} = \left\langle \sum_{z=1}^{m} k_m \alpha_z [\phi(m+z,p) - \phi(m,p)] + \gamma_m \phi(m-1,p) - \phi(m,p)] + k_p \phi(m,p+1) - \phi(m,p) \right\rangle + \langle \gamma_p p[m(p-1) - \phi(m,p)] \rangle .
\]

(2)

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 of magnitude smaller than protein population counts \( \langle \bar{m} \rangle / \langle \bar{p} \rangle \approx 10^{-3} \) from [2], we ignore the second term in (5) and approximate \( CV^2 \) as

\[
CV^2 \approx \frac{\langle (B^2) \rangle + \langle B \rangle \gamma_p}{2 \langle B \rangle (\gamma_p + \gamma_m) \langle m \rangle}.
\]

(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. Next, we quantify protein noise levels for different feedback mechanisms.

3 INTRODUCING REGULATORY MECHANISMS IN GENE-EXPRESSION

We first consider protein mediated transcriptional regulation which corresponds to feedback architecture I in Figure 1.

3.1 Protein mediated transcriptional regulation

Transcriptional regulation is incorporated in the 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 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 [41], 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

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

(8)

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

\[
\kappa = -\frac{\langle \bar{p} \rangle}{k_m(\langle \bar{p} \rangle)} \frac{dk_m(p)}{dp} \bigg|_{p=\langle \bar{p} \rangle} > 0
\]

(9)
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:

\[
\begin{align*}
\frac{dm}{dt} &= k_m(p)(B) - \gamma_m \langle m \rangle \\
\frac{dp}{dt} &= k_p \langle m \rangle - \gamma_p \langle p \rangle \\
\frac{dm^2}{dt} &= k_m(p) \langle B \rangle + \gamma_m \langle m \rangle + 2k_m(p)m \langle B \rangle - 2 \gamma_m \langle m^2 \rangle \\
\frac{dp^2}{dt} &= k_p \langle m \rangle + \gamma_p \langle p \rangle + 2k_p(mp) - 2 \gamma_p \langle p^2 \rangle \\
\frac{d(mp)}{dt} &= k_p \langle m \rangle + k_m(p)p \langle B \rangle - \gamma_p \langle mp \rangle - \gamma_m \langle mp \rangle.
\end{align*}
\]

(10a)

(10b)

(10c)

(10d)

(10e)

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

\[
CV^2_I = \frac{\gamma_p \langle (B) + (B^2) \rangle}{2 \langle B \rangle (\gamma_p + \gamma_m)(1 + \kappa) \langle m \rangle},
\]

(11)

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

\[
\frac{\langle B \rangle k_p k_m(\langle \bar{p} \rangle)}{\gamma_m \gamma_p} = \langle \bar{p} \rangle
\]

(12)

and the steady-state mean mRNA count is given by

\[
\langle \bar{m} \rangle = \frac{\langle \bar{p} \rangle \gamma_p}{k_p}.
\]

(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 \( CV^2_X \), \( X \in \{I, II, III, IV \} \) to denote the steady-state protein noise level corresponding to feedback architecture X. Moreover, \( CV^2 \), given by equation (7) represents the noise level when there is no feedback. Comparing the analytical expressions in (7) and (11) one can see that for \( \kappa > 0 \), the noise level with protein mediated transcriptional regulation is always smaller than the noise level with no feedback. As expected, when \( \kappa = 0 \) (i.e., the transcription rate is independent of the protein count and there is no feedback), \( CV^2_I = CV^2 \).
Feedback type | Description | Expression noise \((CV^2)\) | Ref.
--- | --- | --- | ---
| | Fixed transcription and translation rates | No feedback, feedback strength \(\kappa = 0\) | |
| | | \(CV^2 = \frac{\gamma_p(\langle B \rangle + \langle B^2 \rangle)}{2\langle B \rangle (\gamma_p + \gamma_m)(m)}\) | |
| | Transcription rate decreasing function of protein count | Feedback architecture I, feedback strength \(\kappa > 0\) | [19,20]
| | | \(CV^2_I = \frac{\gamma_p(\langle B \rangle + \langle B^2 \rangle)}{2\langle B \rangle (\gamma_p(1 + \kappa) + \gamma_m)(1 + \kappa)(m)}\) | |
| | Translation rate decreasing function of protein count | Feedback architecture II, feedback strength \(\kappa > 0\) | [29,30]
| | | \(CV^2_{II} = \frac{\gamma_p(\langle B \rangle + \langle B^2 \rangle)}{2\langle B \rangle (\gamma_p + \gamma_m)(m)}\) | |
| | Translation rate decreasing function of mRNA count | Feedback architecture III, feedback strength \(\kappa > 0\) | [31,32]
| | | \(CV^2_{III} = \frac{\gamma_p(1 - \kappa^2)(\langle B \rangle + \langle B^2 \rangle)}{2\langle B \rangle (\gamma_p + \gamma_m)(m)}\) | [45,46]
| | Translation rate decreasing function of mRNA count | Feedback architecture IV, feedback strength \(0 < \kappa < 1\) | |

Fig. 2. Gene expression noise measured by the coefficient of variation squared \((CV^2)\) of the protein count corresponding to different feedback circuits. Here the random variable \(B\) denotes the transcriptional burst size, \(\langle m \rangle\) denotes the steady-state mean mRNA count, \(\gamma_p\) and \(\gamma_m\) represent the protein and mRNA degradation rate, respectively. The dimensionless constant \(\kappa\) represents the strength of the negative feedback. The last column provides references of genes that encode the corresponding feedback architecture.

### 3.2 Protein mediated translational regulation

We now consider a more sophisticated form of negative feedback where proteins regulate gene-expression at the translational level (feedback architecture II in Figure 1). We model protein mediated translational regulation by assuming that 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 \(k_p(p)m\) is 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 \(\langle \tilde{p} \rangle\) and \(\langle \tilde{m} \rangle\) are sufficiently small and approximate the total protein production rate as

\[
k_p(p)m \approx k_p(\langle \tilde{p} \rangle) \left[ m(t) - \kappa \langle \tilde{m} \rangle \left( \frac{p(t) - \langle \tilde{p} \rangle}{\langle \tilde{p} \rangle} \right) \right],
\]

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

\[
\kappa = -\frac{\langle \tilde{p} \rangle}{k_p(\langle \tilde{p} \rangle)} \left. \frac{dk_p(p)}{dp} \right|_{p=\langle \tilde{p} \rangle} > 0\]

is the strength of the negative feedback architecture II. The moment dynamics corresponding to this feedback can again be obtained from (2), with \(k_p m\) replaced by the right-hand-side of (14). Following steps similar to those in the previous section, we obtain the following protein noise level for feedback architecture II:

\[
CV^2_{II} = \frac{\gamma_p(\langle B \rangle + \langle B^2 \rangle)}{2\langle B \rangle (\gamma_p(1 + \kappa) + \gamma_m)(1 + \kappa)(m)}.
\]  

Finally, we consider feedback architectures III and IV. The procedure for quantifying protein noise levels for III and IV is very similar to that used for feedback architectures I and II, except that the transcription and translation rates are now monotonically decreasing functions of the mRNA count rather than the protein count. Due to space considerations we only present the final result in Figure 2, which lists the protein noise levels for different feedback architectures.

### 4 Comparisons between different gene regulatory architectures

Analytical expressions in Figure 2 show two general trends across different feedback architectures. Firstly, the protein noise levels are inversely proportional to the steady-state mean mRNA count. Secondly, increasing the feedback strength \(\kappa\), i.e., making the transcriptional/translational
rates more sensitive to the protein/mRNA count, results in lower protein noise levels. To assess the noise suppression abilities of different feedback architectures we perform a mathematically controlled comparison where all circuits are assumed to have the same feedback strength and steady-state mean mRNA count.

We first compare the noise suppression abilities of protein mediated transcriptional and translational regulation (i.e., feedback architectures I and II). Towards that end, we compute the ratio

$$\frac{CV_{I}^2}{CV_{II}^2} = \frac{\gamma_p + \gamma_m}{\gamma_m + \gamma_p(1 + \kappa)} < 1, \quad (17)$$

which shows that feedback architecture II always provides better noise suppression than I. For a fixed feedback gain $\kappa$, the above ratio monotonically decreases with increasing $\gamma_p/\gamma_m$ and

$$\lim_{\gamma_p/\gamma_m \to 0} \frac{CV_{I}^2}{CV_{II}^2} = 1, \quad \lim_{\gamma_p/\gamma_m \to \infty} \frac{CV_{I}^2}{CV_{II}^2} = \frac{1}{1 + \kappa} < 1. \quad (18a)$$

Thus, when the protein half-life is much smaller than the mRNA half-life ($\gamma_p/\gamma_m \gg 1$) then the noise suppression ability of feedback architecture II is far superior to that of I. However, when the mRNA half-life is much smaller than the protein half-life ($\gamma_p/\gamma_m \ll 1$), the difference in the noise suppression abilities of the two feedback mechanisms is small.

Comparing the noise suppression abilities of protein mediated translation regulation and mRNA mediated transcriptional regulation (i.e., feedback architectures II and III) we find

$$\frac{CV_{II}^2}{CV_{I}^2} = \frac{\gamma_m(1 + \kappa) + \gamma_p}{\gamma_m + \gamma_p(1 + \kappa)}. \quad (19)$$

The above ratio shows that in genetic circuits where protein molecules are more stable than the mRNA ($\gamma_p < \gamma_m$), mRNA mediated transcriptional regulation provides better noise suppression than protein mediated translation regulation. On the other hand, if a gene encodes a very unstable protein such that $\gamma_p > \gamma_m$, then protein mediated translation regulation outperforms mRNA mediated transcriptional regulation.

Finally, our results indicate that feedback architecture IV provides the best noise suppression, irrespective of the mRNA and protein degradation rates. This is illustrated in Figure 3 which plots $CV_{X}^2$, $X \in \{I, II, III, IV\}$ as a function of the negative feedback strength $\kappa$. As can be seen from the figure, feedback architecture IV provides the best noise suppression while feedback architecture I is the least effective in reducing gene-expression noise. Moreover, depending on the mRNA and protein half-life, feedback architecture II or III will provide the second best suppression of expression noise.

5 Discussion

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 feedback architectures are inherently better at noise suppression, while the performance of others is dependent on the parameters of gene-expression.

5.1 Which feedback provides the best noise suppression?

Our results indicate that in a mathematically controlled comparison, feedback architecture 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. This result raises an interesting question of how this feedback architecture is implemented within genes.

In recent years microRNAs, which represent a class of short non-coding RNAs, have been recognized as key regulators of gene expression [42]. These microRNAs typically regulate gene-expression at the translational level by directly binding to a mRNA transcript and inhibiting protein translation [43]. In eukaryotes, genes contain non-coding segments called introns, which are removed from the transcribed mRNA transcripts through splicing. Removal of introns is a necessary step before mRNAs can start translating proteins and microRNAs can be derived from the excised introns [44], [42]. Recent studies have shown that many microRNAs are contained within the intronic regions of the same gene, whose translational activity is regulated by that microRNA [45], [46]. In other words, both the microRNA and its target mRNA originate from the same gene, and hence, are coexpressed. This structural relationship between them creates a negative feedback circuit, where any random increase in mRNA counts automatically increases microRNA levels, which in turn reduces the mRNA translation rate. Given that disruption of these microRNA mediated feedback loops have been associated with cancer progression and neurodegenerative diseases [45], feedback IV type architectures play a critical role in these genes to minimize protein level fluctuations about desired set points.

5.2 Feedback architecture II versus III

A mathematically controlled comparison between protein mediated translation regulation (feedback architecture II) and mRNA mediated transcriptional regulation (feedback architecture III) showed that their relative noise suppression abilities is dependent on the protein and mRNA half-life (Figure 3). Reference [47] does a survey of about 2000 genes in budding yeast and shows that for most genes the ratio $\gamma_p/\gamma_m$ is much smaller than one, i.e., genes encode short-lived mRNAs but long-lived proteins. In this physiologically relevant parameter regime, feedback architecture
Gene expression noise with increasing negative feedback strength ($\kappa$) for different circuit architectures when mRNA half-life is smaller than protein half-life (right) and when mRNA half-life is larger than protein half-life (left). The y-axis is normalized by the gene-expression noise when there is no feedback. These plots correspond to a 5-hour protein half-life with a 1-hour (right) and 10-hour (left) mRNA half-life.

III is predicted to provide better noise suppression than architecture II, and second best noise suppression among all the different feedback architectures.

In addition to inhibiting translation, increasing evidence suggests that microRNAs can also modulate the transcriptional activity of genes [48]. Thus, like IV, feedback architecture III can also be implemented using intron-derived microRNAs. An example of feedback architecture III is present in the endothelial nitric-oxide synthase (eNOS) gene. This gene encodes an essential protein required for generating nitric oxide and its levels need to be tightly regulated as its over-expression and under-expression have been related to diseased states [32]. Data suggests that small RNAs derived from introns within the eNOS gene repress the transcriptional activity of the eNOS gene [31], [32]. Thus, any increase in eNOS mRNA transcripts would inhibit further transcriptional events from the gene creating an effective negative feedback circuit for eNOS homeostasis.

5.3 Protein mediated feedback circuits

Above analysis suggests that in physiologically relevant parameter regime, mRNA mediated feedback circuits (feedback architecture III & IV) provide better noise suppression than protein mediated feedback circuits (feedback architecture I & II). However, these comparisons where done at a fixed feedback strength. Typically, protein molecules do not function as monomers but bind together to form dimers, tetramers, etc. Such protein multimerization can induce cooperativity in a feedback circuit that makes transcription/translation rates ultra sensitive to protein levels, and hence, substantially increase the negative feedback strength [26], [27]. Thus protein mediated feedback loops can also provide effective noise suppression by operating at much higher values of $\kappa$ compared to mRNA mediated feedback loops.

Consistent with the observations of [16], we find that feedback architecture II always provides better noise suppression than architecture I. However, the difference in the protein noise level with feedback architectures I and II critically depends on $\gamma_p/\gamma_m$, i.e., increasing $\gamma_p/\gamma_m$, i.e., making the protein half-life much shorter than the mRNA half-life, increases this difference, and enhances the noise suppression ability of feedback architecture II compared to I. On the other hand, decreasing $\gamma_p/\gamma_m$, i.e., making the protein half-life much longer than the mRNA half-life, decreases this difference, and diminishes the advantage of using feedback architecture II over I for noise reduction.

In physiologically relevant parameter regime where $\gamma_p/\gamma_m$ is much smaller than one [47], our analysis predicts that protein mediated translational regulation may not provide significantly better noise suppression than protein mediated transcriptional regulation.

In summary, we have developed analytical formulas that connect stochasticity in protein levels to the negative feedback architecture. These formulas reveal that mRNA mediated feedback circuits are superior to protein mediated feedback circuits for noise reduction under physiologically relevant parameter regimes. Consistent with this prediction we find many essential genes encoding mRNA dependent feedback circuit through intro-derived microRNAs. Our analysis not only make experimentally testable predictions but also will be helpful in designing precise synthetic gene networks with minimal fluctuations in protein levels.

ACKNOWLEDGMENTS

The author would like to thank Joao Hespanha, Mustafa Khammash, Leor Weinberger and members of the Weinberger lab for many discussion on this topic.