2019 IEEE 58th Conference on Decision and Control (CDC)
Palais des Congrès et des Expositions Nice Acropolis
Nice, France, December 11-13, 2019

Proportional and derivative controllers for buffering noisy gene expression

Saurabh Modi, Supravat Dey and Abhyudai Singh [1]

Abstract— **Inside individual cells, protein population counts are subject to molecular noise due to low copy numbers and the inherent probabilistic nature of biochemical processes. Such random fluctuations in the level of a protein critically impact functioning of intracellular biological networks, and not surprisingly, cells encode diverse regulatory mechanisms to buffer noise. We investigate the effectiveness of proportional and derivative-based feedback controllers to suppress protein count fluctuations originating from two noise sources: bursty expression of the protein, and external disturbance in protein synthesis. Designs of biochemical reactions that function as proportional and derivative controllers are discussed, and the corresponding closed-loop system is analyzed for stochastic controller realizations. Our results show that proportional controllers are effective in buffering protein copy number fluctuations from both noise sources, but this noise suppression comes at the cost of reduced static sensitivity of the output to the input signal. Next, we discuss the design of a coupled feedforward-feedback biochemical circuit that approximately functions as a derivate controller. Analysis reveals that this derivative controller effectively buffers output fluctuations from bursty stochastic expression, while maintaining the static input-output sensitivity of the open-loop system. As expected, the derivative controller performs poorly in terms of rejecting external disturbances. In summary, this study provides a systematic stochastic analysis of biochemical controllers, and paves the way for their synthetic design and implementation to minimize deleterious fluctuations in gene product levels.**

I. Introduction

Advances in single-cell technologies over the last decade have revealed striking differences between individual cells of the same population. For example, the level of a given protein can vary considerably across cells within a population, in spite of the fact that cells are identical clones of each other and are exposed to the same environment [1]–[3]. Such intercellular stochastic differences in gene expression patterns have tremendous consequences for biology and medicine [4]–[6], including stochastic cell-fate assignment [7]–[10], microbial bet hedging [11], [12], bacterial and cancer drug-resistance [13], [14].

Stochastic variations in the level of protein primarily arise from two main sources:

- Low-copy number fluctuations in underlying biomolecular components (genes, mRNA, proteins). Moreover, this shot noise is amplified by the fact that transcription of genes is not a continuous process but happens in sporadic bursts [15]–[17].
- External disturbances in the protein synthesis rate due to fluctuations in expression-related machinery (RNA polymerases, Ribosomes, etc.) or intercellular differences in cell-cycle stage/cell size [18], [19].

Given these noise sources, cells encode diverse regulatory mechanisms to suppress stochasticity in the level of a protein around a set point. Perhaps the simplest example of this is a negative feedback loop, where the protein directly or indirectly inhibits its own synthesis [20]–[27]. Furthermore, design of in-vitro/in-silico synthetic feedback system based on linear PID or nonlinear controllers is an intense area of current research [28]–[36]. In this contribution, we investigate design of biochemical circuits that function as *approximate* proportional and derivative-based controllers, and systematically investigate their effectiveness in buffering protein noise levels.

In Section II, we introduce an open-loop model of stochastic gene expression where the protein is expressed in random bursts, and its expression is impacted by an upstream noisy input (Fig. 1). We provide exact analytical formulas for the protein mean and noise levels in open loop. Section II also introduces the mathematical tools to be used throughout the paper for the analysis of stochastic dynamical systems. In Section III and IV, we discuss designs of nonlinear biochemical circuits that function as approximate proportional and derivate controllers, respectively. Given the nonlinearities introduced by feedback loops, we use the Linear Noise Approximation method [37], [38] to derive closed-form expressions for the noise levels and investigate the noise suppression properties of feedback controllers.

Symbols and Notation: Throughout the paper we denote chemical species by capital letters, and use corresponding small letters for molecular counts. For example, if Y denotes a protein species, then $y(t)$ is the number of molecules of Y at time t inside the cell. We use angular brackets to denote the expected value of random variables and stochastic processes. Given a scalar random process $y(t) \in \{0,1,2,\ldots\}$ that takes non-negative integer values, then

$$\langle y(t)^m \rangle := \sum_{i=0}^{\infty} i^m \mathbb{P}(y(t)=i), \quad m \in \{1,2,\ldots\} \tag{1}$$

represent its m^{th} order uncentered moment and $\mathbb{P}(y(t)=i)$ is the probability of having i molecules. Steady-state statistical moments are denoted by

$$\overline{\langle y^m \rangle} := \lim_{t\to\infty} \langle y(t)^m \rangle. \tag{2}$$

Finally, noise in the level of protein species is quantified by the steady-state coefficient of variation squared (variance

[1]Abhyudai Singh, Saurabh Modi, Supravat Dey are with the Departments of Electrical and Computer Engineering, Biomedical Engineering at the University of Delaware, Newark, DE 19716, USA. absingh@udel.edu, saurmodi@udel.edu, sdey@udel.edu

divided by mean squared) that is defined as

$$CV_Y^2 := \frac{\overline{\langle y^2\rangle} - \overline{\langle y\rangle}^2}{\overline{\langle y\rangle}^2}. \tag{3}$$

II. Systems modeling of gene expression

We start by introducing simple models of the gene expression process with a particular focus on incorporating noise mechanisms that drive fluctuations in the level of a protein.

A. Incorporating bursty dynamics

Transcription of individual genes inside single cells has been shown to occur in bursts of activity, followed by periods of silence [39]–[42]. Motivated by these experimental findings, we phenomenologically model protein copy-number fluctuations via a *bursty birth-death process* [43]–[45]. More specifically, bursts arrive at a constant Poisson rate k_y that corresponds to the frequency with which the gene becomes active. Each bursts arrival event, results in the synthesis of $B_y \in \{1,2,\ldots\}$ protein molecules, where the burst size B_y is an independent and identically distributed random variable that is drawn from an arbitrary positively-valued probability distribution.

Let $y(t)$ denote the intracellular copy number of protein Y at time t. Then, based on the above model description, the probability of a burst event of size $B_y = j$ molecules occurring in the next infinitesimal time interval $(t, t+dt]$ is

$$\mathbb{P}(y(t+dt) = y(t) + j | y(t)) = k_y \mathbb{P}(B_y = j) dt. \tag{4}$$

Assuming each protein molecule decays with a constant rate γ_y, defines the probability for the protein death event occurring in the time interval $(t, t+dt]$ as

$$\mathbb{P}(y(t+dt) = y(t) - 1 | y(t)) = \gamma_y y dt. \tag{5}$$

Having defined an integer-valued continuous-time Markov process $y(t)$ via the probabilities (4)-(5), we now focus our attention on its statistical moments. We refer the reader to [46] for a thorough analysis of moment dynamics for stochastic systems of the form (4)-(5), and only provide the main result here – the time evolution of the expected value of $y(t)^m$ is given by

$$\frac{d\langle y(t)^m\rangle}{dt} = \langle G(y)\rangle, \quad m \in \{1,2,\ldots\} \tag{6}$$

where the infinitesimal generator G takes the form

$$G(y) := \sum_{j=0}^{\infty} k_y \mathbb{P}(B_y = j)[(y+j)^m - y^m] + \gamma_y y[(y-1)^m - y^m]. \tag{7}$$

Intuitively, the right-hand-side of (7) is simply the product of the change in y^m when an event occurs and the probabilistic rate at which it occurs, summed across all possible events. Substituting the appropriate value of m in (6) yields the following moment dynamics

$$\frac{d\langle y\rangle}{dt} = k_y \langle B_y\rangle - \gamma_y \langle y\rangle \tag{8a}$$

$$\frac{d\langle y^2\rangle}{dt} = \gamma_y(\langle y\rangle - 2\langle y^2\rangle) + k_y\langle B_y^2\rangle + 2k_y\langle y\rangle\langle B_y\rangle \tag{8b}$$

where $\langle B_y\rangle$ is the mean protein burst size, and $\langle B_y^2\rangle$ is its second-order moment. Subsequent steady-analysis of (8) reveals the protein mean and noise levels to be

$$\overline{\langle y\rangle} = \frac{k_y\langle B_y\rangle}{\gamma_y}, \quad CV_Y^2 = \frac{\langle B_y\rangle + \langle B_y^2\rangle}{2\langle B_y\rangle\overline{\langle y\rangle}}, \tag{9}$$

respectively. $B_y = 1$ with probability one leads to Poissonian fluctuations in Y copy numbers with $CV_Y^2 = 1/\overline{\langle y\rangle}$. If the burst size B_y is assumed to be a geometrically-distributed random variable with mean burst size $\langle B_y\rangle$ (as shown experimentally for an *E. coli* gene [47]), then $\langle B_y^2\rangle = 2\langle B_y\rangle^2 - \langle B_y\rangle$, and the above noise levels reduce to

$$CV_Y^2 = \frac{\langle B_y\rangle}{\overline{\langle y\rangle}} = \frac{\gamma_y}{k_y}. \tag{10}$$

A key point worth mentioning is that the product $CV_Y^2 \times \overline{\langle y\rangle}$ is independent of the burst frequency k_y, while CV_Y^2 in (10) is independent of the mean burst size $\langle B_y\rangle$. Thus, simultaneous measurements of both the mean and protein noise levels allows for discerning whether a change in $\overline{\langle y\rangle}$ is a result of alterations in k_y or $\langle B_y\rangle$.

B. Incorporating external disturbance

Next, we introduce another important source of stochasticity that arises from external disturbances in the protein synthesis rate. These disturbances correspond to fluctuations in the abundance of enzymes, such as, transcription factors, RNA polymerases, etc. We lump these factors into a single species X and model its stochastic dynamics via a bursty birth-death process analogous to (4)-(5):

$$\mathbb{P}(x(t+dt) = x(t) + j | x(t)) = k_x \mathbb{P}(B_x = j) dt, \tag{11a}$$

$$\mathbb{P}(x(t+dt) = x(t) - 1 | x(t)) = \gamma_x x dt. \tag{11b}$$

Here k_x is the arrival rate of bursts in X, B_x is the burst size, and γ_x is the decay rate of X. Then, as per (9)

$$\overline{\langle x\rangle} = \frac{k_x\langle B_x\rangle}{\gamma_x}, \quad CV_X^2 = \frac{\langle B_x\rangle + \langle B_x^2\rangle}{2\langle B_x\rangle\overline{\langle x\rangle}}. \tag{12}$$

The disturbance is connected to the synthesis of Y by assuming that the frequency of protein Y bursts is proportional to $x(t)$, and is given by $k_y x(t)/\overline{\langle x\rangle}$. The division by $\overline{\langle x\rangle}$ ensures that the average burst arrival rate is k_y. This leads to a system of coupled bursty birth-death processes given by (11) and

$$\mathbb{P}(y(t+dt) = y(t) + j | y(t), x(t)) = \frac{k_y x}{\overline{\langle x\rangle}} \mathbb{P}(B_y = j) dt \tag{13a}$$

$$\mathbb{P}(y(t+dt) = y(t) - 1 | y(t), x(t)) = \gamma_y y dt. \tag{13b}$$

The statistical moments of this joint process evolve as per

$$\frac{d\langle y(t)^{m_1} x(t)^{m_2}\rangle}{dt} = \langle G(y,x)\rangle, \quad m_1, m_2 \in \{0,1,2,\ldots\}$$

$$G(y,x) := \sum_{j=0}^{\infty} \frac{k_y x}{\overline{\langle x\rangle}} \mathbb{P}(B_y = j)[(y+j)^{m_1}x^{m_2} - y^{m_1}x^{m_2}]$$

$$+ \sum_{j=0}^{\infty} k_x \mathbb{P}(B_x = j)[y^{m_1}(x+j)^{m_2} - y^{m_1}x^{m_2}]$$

$$+ \gamma_x x[y^{m_1}(x-1)^{m_2} - y^{m_1}x^{m_2}] + \gamma_y y[(y-1)^{m_1}x^{m_2} - y^{m_1}x^{m_2}] \tag{14}$$

[46]. To write moment dynamics in a compact form we define a vector

$$\mu = [\langle x\rangle, \langle y\rangle, \langle xy\rangle, \langle x^2\rangle, \langle y^2\rangle]^T \tag{15}$$

that consists of all the first and second order moments of $x(t)$ and $y(t)$. Then, its time evolution is given by a system of linear differential equations

$$\dot{\mu} = \hat{a} + A\mu, \tag{16}$$

where vector $\hat{a}$ and matrix A are obtained via (15) by choosing appropriate values of m_1, m_2. Steady-state analysis of (16) results in the same mean Y level as (9), and the following noise level

$$CV_Y^2 = \overbrace{CV_{int}^2}^{\text{Intrinsic noise}} + \overbrace{\frac{\gamma_y}{(\gamma_y+\gamma_x)}CV_X^2}^{\text{External disturbance}}, \quad CV_{int}^2 = \frac{\langle B_y\rangle + \langle B_y^2\rangle}{2\langle B_y\rangle\overline{\langle y\rangle}}, \tag{17}$$

that can be decomposed into two components. The first component CV_{int}^2 is the noise contribution from stochastic bursts computed earlier in (9), and has been referred to in literature as the *intrinsic noise* in Y [48]–[51]. The second component is the noise contribution of the external disturbance, and has been referred to as the *extrinsic noise* in Y. Note that the ratio $\gamma_y/(\gamma_y+\gamma_x)$ quantifies the time-averaging of upstream fluctuation in X by Y. For example, fast fluctuations in X are efficiently averaged out by Y, and this ratio approaches zero for $\gamma_x \to \infty$. In contrast, slow fluctuations in X lead to inefficient time-averaging that increases Y noise levels to

$$CV_Y^2 = CV_{int}^2 + CV_X^2, \quad \gamma_x \ll \gamma_y. \tag{18}$$

Next, we investigate how negative feedback regulation suppresses different noise components in (17) to minimize fluctuations in Y copy numbers around it mean $\overline{\langle y\rangle}$.

III. Noise suppression using proportional controller

To implement a negative feedback loop we first introduce a new protein species Z that functions as a noisy sensor of Y. Protein Z is also assumed to be synthesized in bursts of size B_z, and senses Y via its burst frequency $k_z y(t)$ that responds linearly to any changes in Y levels. This leads to the following bursty birth-death process for $z(t)$

$$\mathbb{P}(z(t+dt) = z(t)+j | y(t), z(t)) = k_z y \mathbb{P}(B_z = j)dt, \tag{19a}$$

$$\mathbb{P}(z(t+dt) = z(t)-1 | y(t), z(t)) = \gamma_z z dt, \tag{19b}$$

where γ_z is the decay rate of protein Z. Recall from Section II-B that the frequency of bursts in the Y protein was $k_y x(t)/\overline{\langle x\rangle}$ in the open-loop system. To close the feedback loop, we now modify this burst frequency to $k_y g(z) x(t)/\overline{\langle x\rangle}$, where $g(z)$ is a positively-valued monotonically decreasing function of $z(t)$. Typically, g takes the form of a Hill function that mechanistically arises from the fast binding-unbinding of the protein to the gene's promoter region to regulate transcriptional activity. Within this feedback there are three noise mechanisms at play: external disturbance X impacting synthesis of Y, expression of Y in stochastic bursts, and a noisy sensor Z that measures Y and inhibits it (Fig. 1). The overall stochastic system is given by (11), (19) and

$$\mathbb{P}(y(t+dt) = y(t)+j | y(t), x(t), z(t)) = \frac{k_y g(z) x}{\overline{\langle x\rangle}} \mathbb{P}(B_y = j)dt \tag{20a}$$

$$\mathbb{P}(y(t+dt) = y(t)-1 | y(t), x(t), z(t)) = \gamma_y y dt. \tag{20b}$$

A. Analysis of Mean levels

At equilibrium, the mean levels of the random processes $x(t)$, $y(t)$ and $z(t)$ satisfy

$$\overline{\langle x\rangle} = \frac{k_x\langle B_x\rangle}{\gamma_x}, \quad \overline{\langle z\rangle} = \frac{k_z\langle B_z\rangle\overline{\langle y\rangle}}{\gamma_z}, \quad \frac{k_y\overline{\langle g(z)x\rangle}\langle B_y\rangle}{\overline{\langle x\rangle}} = \gamma_y\overline{\langle y\rangle}. \tag{21}$$

Assuming copy-number fluctuations are tightly regulated by the feedback system, and that they are small,

$$\frac{\overline{\langle g(z)x\rangle}}{\overline{\langle x\rangle}} \approx \frac{g(\overline{\langle z\rangle})\overline{\langle x\rangle}}{\overline{\langle x\rangle}} = g(\overline{\langle z\rangle}). \tag{22}$$

Given that $g(z)$ is a positively-valued monotonically decreasing function, using (21) and (22), the steady-state mean level of Y is the unique solution to the equation

$$k_y g\left(\frac{k_z\langle B_z\rangle\overline{\langle y\rangle}}{\gamma_z}\right)\langle B_y\rangle = \gamma_y\overline{\langle y\rangle}. \tag{23}$$

Having solved for the means, the burst frequency of Y can now be approximated using Taylor series as

$$k_y g(z)x/\overline{\langle x\rangle} \approx k_y g(\overline{\langle z\rangle})\left(\frac{x}{\overline{\langle x\rangle}} - f_p\frac{z-\overline{\langle z\rangle}}{\overline{\langle z\rangle}}\right) \tag{24}$$

where

$$f_p := -\frac{\overline{\langle z\rangle}}{g(\overline{\langle z\rangle})}\frac{dg(z)}{dz}\bigg|_{z=\overline{\langle z\rangle}} > 0 \tag{25}$$

is the log sensitivity of the function g evaluated at steady state. Note that if the sensor dynamic is very fast compared to the measurand Y (i.e., $\gamma_z \gg \gamma_y$), then $z(t) \propto y(t)$, and the burst frequency in (24) will be proportional to the error $y - \overline{\langle y\rangle}$. Hence, this circuit architecture can be interpreted as an approximate proportional controller with feedback gain f_p. Finally, if we consider the parameter k_y in Y's burst frequency as an environmental input, then one can define a static sensitivity of $\overline{\langle y\rangle}$ to k_y

$$S_{k_y}^{\overline{\langle y\rangle}} := \frac{k_y}{\overline{\langle y\rangle}}\frac{d\overline{\langle y\rangle}}{dk_y} \tag{26}$$

which using (21) and (25) is given by

$$S_{k_y}^{\overline{\langle y\rangle}} = \frac{1}{1+f_p} \tag{27}$$

and monotonically decreases with increasing gain. Note for the open-loop system $f_p = 0$ and $S_{k_y}^{\overline{\langle y\rangle}} = 1$ as mean $\overline{\langle y\rangle}$ is simply proportional to k_y from (9).

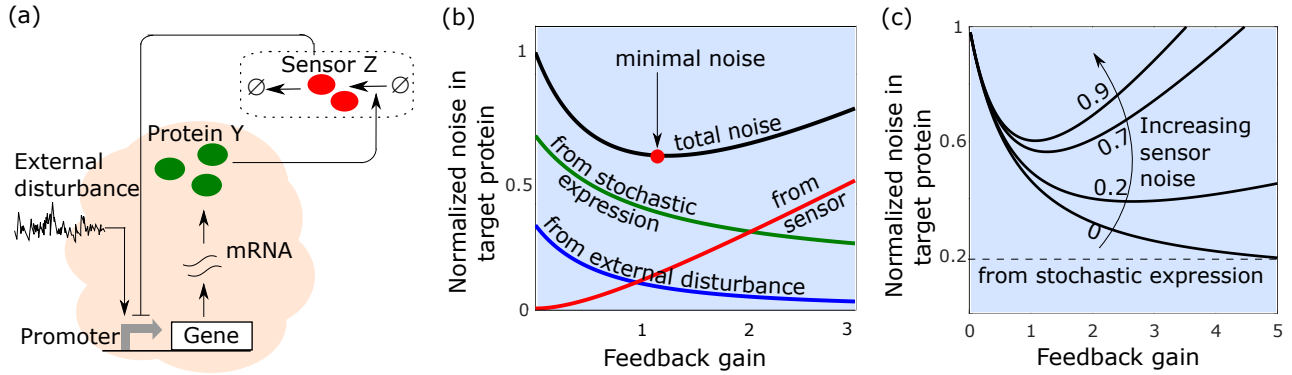

Fig. 1. **Implementation and noise decomposition for a proportional feedback controller.** (a) Schematic of a proportional controller where the protein Y is sensed by a noisy sensor Z that inhibits the synthesis of Y. (b) Different components in the noise levels of protein Y from (28) plotted as a function of the feedback gain f_p. While feedback selectively attenuates noise due to external disturbance and stochastic expression of Y, it amplifies the sensor noise, leading to a non-monotonic profile for the total noise. The noise contribution from the external disturbance decreases rapidly as a function of f_p and approaches zero for $f_p \to \infty$. In contrast, the intrinsic noise decreases slowly and asymptotically approaches a non-zero limit. In this plot, noise levels are normalized to the open-loop noise ($f_p = 0$), with other parameters chosen as $CV_Z^2 = 0.4$, $CV_{int}^2 = CV_{ext}^2 = 0.2$. $\gamma_z = 5\gamma_y = 15\gamma_x$. (c) The normalized total noise in Y from (28) with respect to the feedback gain f_p for different levels of sensor noise. The total noise CV_Y^2 is minimized at an optimal feedback gain, which critically depends on the extent of sensor noise CV_Z^2.

B. Analysis of Noise levels

Next, we focus on computing the noise levels in Y for the overall feedback system. As before, we define a vector μ that consists of all the first and second order moments of $x(t)$, $y(t)$ and $z(t)$. The time evolution of μ can be obtained by expanding (15) to the three-species system, where Y's nonlinear burst frequency is replaced by its linear approximation (24). Having linear probabilistic rates for all birth-death events results in a linear dynamical system (16) that can be solved analytically to obtain steady-state moments. This analysis yields the following noise level for protein Y

$$CV_Y^2 = \overbrace{\frac{(\gamma_y + f_p\gamma_y + \gamma_z)}{(f_p+1)(\gamma_y+\gamma_z)}CV_{int}^2}^{\text{Intrinsic noise}} + \overbrace{\frac{\gamma_y((\gamma_z+\gamma_y)(\gamma_x+\gamma_z)+\gamma_x\gamma_y f_p)}{(1+f_p)(\gamma_y+\gamma_z)((\gamma_x+\gamma_y)(\gamma_x+\gamma_z)+\gamma_y\gamma_z f_p)}CV_X^2}^{\text{External disturbance}} + \overbrace{\frac{f_p^2\gamma_y}{(f_p+1)(\gamma_y+\gamma_z)}CV_Z^2}^{\text{Sensor noise}}. \quad (28)$$

which can be decomposed into three components. The first component is the intrinsic noise in Y due to its bursty expression, and it decreases with increasing feedback gain f_p approaching a non-zero lower bound $\gamma_y CV_{int}^2/(\gamma_y+\gamma_z)$ as $f_p \to \infty$. This lower bound represents a fundamental limit to which intrinsic noise can be decreased, and this limit is determined by how fast the sensor dynamics is compared to Y's decay rate. The second component is the noise contribution from the external disturbance that monotonically decreases to zero as $f_p \to \infty$. The third component arises from the fact that the sensor Z is itself noisy, where

$$CV_Z^2 = \frac{\langle B_z\rangle + \langle B_z^2\rangle}{2\langle B_z\rangle\overline{\langle z\rangle}} \quad (29)$$

is the noise in Z due to its own expression occurring in random bursts. This third component is amplified with increasing feedback gain, and as a consequence, the total noise CV_Y^2 is a non-monotonic function of f_p with noise being minimal at an optimal feedback strength (Fig. 1). When $f_p = 0$, (28) reduces to the open-loop noise (17).

To further simplify the formula we assume that sensor dynamics is sufficiently fast ($\gamma_z \gg \gamma_y$), and the time-scale of disturbance fluctuations are slow ($\gamma_x \ll \gamma_y$). In this case, the sensor noise contribution becomes minimal, and (28) simplifies to

$$CV_Y^2 = \overbrace{\frac{1}{1+f_p}CV_{int}^2}^{\text{Intrinsic noise}} + \overbrace{\frac{1}{(1+f_p)^2}CV_X^2}^{\text{External disturbance}}. \quad (30)$$

Note that the contribution from external disturbance decreases as $1/f_p^2$ compared to $1/f_p$ for the intrinsic noise. Hence, proportional feedback is much more effective in buffering stochasticity from external inputs rather than the intrinsic noise. This point relates to the static sensitivity $S_{k_y}^{\overline{\langle y\rangle}} = 1/(1+f_p)$ defined in (26), where increasing feedback gain suppresses noise, but it comes at the loss of adapting Y levels to changes in the environmental input.

IV. Noise Suppression using Derivative Controller

Having completed the analysis for a proportional controller we next turn our attention to a derivative controller. Given the space constraints, we refer the read to [52] for details on the derivative-controller design and its subsequent mathematical analysis. The basic design is shown in Fig. 2, where the protein activates the sensor Z as per (19), and then Z activates the burst frequency of Y, and Y inhibits it own burst frequency. Consider the burst frequency of Y to be $k_y(x/\overline{\langle x\rangle})(z/y)^h$. Then, the stochastic dynamics of Y is

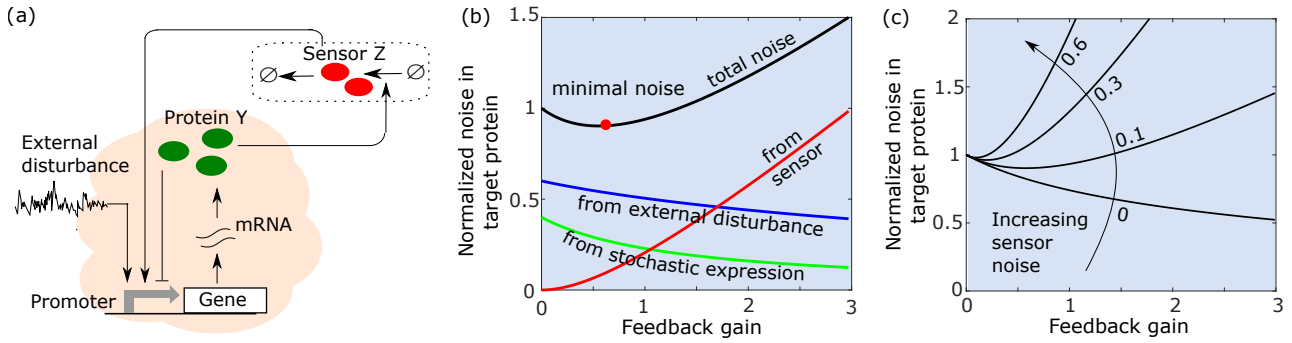

Fig. 2. **Implementation and noise decomposition for a derivative-based controller** (a) Schematic of the derivative controller where Y activates the sensor Z, Z activates the burst frequency of Y, while Y represses its own burst frequency (b) Different noise components in (32) are plotted as a function of the derivative feedback gain f_d. Noise levels are normalized by the open-loop noise (17) and other parameters are chosen as $CV^2_{int} = 0.25$, $CV^2_Z = 0.1$, $CV^2_X = 0.45$, $\gamma_x = \frac{1}{5}\gamma_y$, $\gamma_z = 3\gamma_y$. While both the intrinsic noise, and the noise contribution from the external disturbance decrease with increasing f_d, the noise contribution from the sensor increases. In contrast to the proportional feedback, the intrinsic noise decreases faster than the disturbance contribution. (c) The noise in Y as a function of the derivative feedback gain f_d emphasizes the nonmonotonic noise profile for different levels of sensor noise CV^2_Z.

described by

$$\begin{aligned}\mathbb{P}(y(t+dt) &= y(t)+j|y(t),x(t),z(t)) \\ &= k_y \frac{x}{\langle x\rangle}\left(\frac{z}{y}\right)^h \mathbb{P}(B_y = j)dt \qquad (31a)\\ \mathbb{P}(y(t+dt) &= y(t)-1|y(t),x(t),z(t)) = \gamma_y y dt. \qquad (31b)\end{aligned}$$

As before, the external disturbance is described by (11). Then Linear Noise Approximation yields the following noise in protein Y

$$\begin{aligned}CV^2_Y = &\overbrace{\frac{(\gamma_y+\gamma_z)}{\gamma_y+\gamma_z f_d+\gamma_z}CV^2_{int}}^{\text{Intrinsic noise}} \\ &+\overbrace{\frac{\gamma_y(\gamma_y(\gamma_x+\gamma_z)+\gamma_z(\gamma_x+\gamma_z+\gamma_z f_d))}{(\gamma_y+\gamma_z f_d+\gamma_z)(\gamma_y(\gamma_x+\gamma_z)+\gamma_x(\gamma_x+\gamma_z f_d+\gamma_z))}CV^2_X}^{\text{External disturbance}} \\ &+\overbrace{\frac{f_d^2\gamma_z^2}{\gamma_y(\gamma_y+\gamma_z f_d+\gamma_z)}CV^2_Z}^{\text{Sensor noise}}. \qquad (32)\end{aligned}$$

where $f_d := h\gamma_y/\gamma_z > 0$ is the derivative feedback gain [52]. Analysis of the resulting noise components reveals that both the intrinsic noise, and the noise contribution from the external disturbance, decrease with increasing gain f_d, with the former showing a much faster decay (Fig. 2). The noise contribution from the sensor amplifies with increasing feedback gain resulting in the total noise CV^2_Y being minimized at an intermediate gain (Fig. 2). Interestingly, noise reduction occurs in spite of the fact that the mean protein level for Y is proportional to k_y and the sensitivity $S^{\langle y\rangle}_{k_y} = 1$ as in the open-loop system [52].

V. Conclusion

While PID controllers have become quite standard in industry, designing biochemical circuits that perform analogous functions inside cells is a highly nontrivial problem. Here we present simple circuits that function as *approximate* proportional and derivative controllers assuming fluctuations in molecular counts are small around their respective means. Our analysis of biochemically-implemented proportional feedback reveals the following properties:

- Proportional feedback is more efficient in suppressing stochasticity arising from noisy input signals, compared to noise arising from protein expression occurring in random bursts (Fig. 1).
- Any form of measurement noise (for example, due to stochastic expression of the sensor protein), leads to an optimal feedback gain for minimizing total protein noise, reminiscent of traditional feedback controllers.
- Noise suppression comes at the cost of reduced static input-output sensitivity, i.e., the protein levels are precisely regulated for a given environment, but do not respond to new environments.

We further provide design of a biochemical circuit for derivate-based control. In essence, the derivative of a signal is sensed by taking the difference of a delayed-signal (the sensor output) and the original signal. Intriguingly, our analysis shows that this controller suppresses intrinsic noise in the protein while preserving the open-loop static input-output sensitivity (Fig. 2). As part of future work, we will investigate biochemical networks for integral feedback control, and constructing biological PID controllers for a given static input-output sensitivity, noise in the target protein, and transient response.

References

[1] A. Bar-Even, J. Paulsson, N. Maheshri, M. Carmi, E. O'Shea, Y. Pilpel, and N. Barkai, "Noise in protein expression scales with natural protein abundance," *Nature Genetics*, vol. 38, pp. 636–643, 2006.

[2] W. J. Blake, G. Balazsi, M. A. Kohanski, F. J. Isaacs, K. F. Murphy, Y. Kuang, C. R. Cantor, D. R. Walt, and J. J. Collins, "Phenotypic consequences of promoter-mediated transcriptional noise," *Molecular Cell*, vol. 24, pp. 853–865, 2006.

[3] J. R. S. Newman, S. Ghaemmaghami, J. Ihmels, D. K. Breslow, M. Noble, J. L. DeRisi, and J. S. Weissman, "Single-cell proteomic analysis of S. cerevisiae reveals the architecture of biological noise," *Nature Genetics*, vol. 441, pp. 840–846, 2006.

[4] A. Eldar and M. B. Elowitz, "Functional roles for noise in genetic circuits," *Nature*, vol. 467, pp. 167–173, 2010.

[5] T. Wang and M. J. Dunlop, "Controlling and exploiting cell-to-cell variation in metabolic engineering," *Current Opinion in Biotechnology*, vol. 57, pp. 10–16, 2019.

[6] A. H. K. Roeder, "Use it or average it: stochasticity in plant development," *Current Opinion in Plant Biology*, vol. 41, pp. 8–15, 2018.

[7] A. Singh and L. S. Weinberger, "Stochastic gene expression as a molecular switch for viral latency," *Current Opinion in Microbiology*, vol. 12, pp. 460–466, 2009.

[8] T. M. Norman, N. D. Lord, J. Paulsson, and R. Losick, "Memory and modularity in cell-fate decision making," *Nature*, vol. 503, pp. 481–486.

[9] H. Maamar, A. Raj, and D. Dubnau, "Noise in gene expression determines cell fate in bacillus subtilis," *Science*, vol. 317, pp. 526–529, 2007.

[10] H. H. Chang, M. Hemberg, M. Barahona, D. E. Ingber, and S. Huang, "Transcriptome-wide noise controls lineage choice in mammalian progenitor cells," *Nature*, vol. 453, pp. 544–547, 2008.

[11] J.-W. Veening, W. K. Smits, and O. P. Kuipers, "Bistability, epigenetics, and bet-hedging in bacteria," *Annual Review of Microbiology*, vol. 62, pp. 193–210, 2008.

[12] T. M. Norman, N. D. Lord, J. Paulsson, and R. Losick, "Stochastic switching of cell fate in microbes," *Annual Review of Microbiology*, vol. 69, pp. 381–403, 2015.

[13] S. M. Shaffer, M. C. Dunagin, S. R. Torborg, E. A. Torre, B. Emert, C. Krepler, M. Beqiri, K. Sproesser, P. A. Brafford, M. Xiao, E. Eggan, I. N. Anastopoulos, C. A. Vargas-Garcia, A. Singh, K. L. Nathanson, M. Herlyn, and A. Raj, "Rare cell variability and drug-induced reprogramming as a mode of cancer drug resistance," *Nature*, vol. 546, pp. 431–435, 2017.

[14] N. Balaban, J. Merrin, R. Chait, L. Kowalik, and S. Leibler, "Bacterial persistence as a phenotypic switch," *Science*, vol. 305, pp. 1622–1625, 2004.

[15] D. Nicolas, B. Zoller, D. M. Suter, and F. Naef, "Modulation of transcriptional burst frequency by histone acetylation," *Proceedings of the National Academy of Sciences*, vol. 115, pp. 7153–7158, 2018.

[16] A. Raj, C. Peskin, D. Tranchina, D. Vargas, and S. Tyagi, "Stochastic mRNA synthesis in mammalian cells," *PLOS Biology*, vol. 4, p. e309, 2006.

[17] S. Chong, C. Chen, H. Ge, and X. S. Xie, "Mechanism of Transcriptional Bursting in Bacteria," *Cell*, vol. 158, pp. 314–326, 2014.

[18] C. A. Vargas-Garcia, K. R. Ghusinga, and A. Singh, "Cell size control and gene expression homeostasis in single-cells," *Current opinion in systems biology*, vol. 9, pp. 109–116, 2018.

[19] A. Mena, D. Medina, J. García-Martínez, V. Begley, A. Singh, S. Chávez, M. Muñoz-Centeno, and J. Pérez-Ortín, "Asymmetric cell division requires specific mechanisms for adjusting global transcription." *Nucleic acids research*, p. gkx974, 2017.

[20] A. Becskei and L. Serrano, "Engineering stability in gene networks by autoregulation," *Nature*, vol. 405, pp. 590–593, 2000.

[21] Y. Dublanche, K. Michalodimitrakis, N. Kummerer, M. Foglierini, and L. Serrano, "Noise in transcription negative feedback loops: simulation and experimental analysis," *Molecular Systems Biology*, vol. 2, p. 41, 2006.

[22] A. Singh and J. P. Hespanha, "Optimal feedback strength for noise suppression in autoregulatory gene networks," *Biophysical Journal*, vol. 96, pp. 4013–4023, 2009.

[23] D. Orrell and H. Bolouri, "Control of internal and external noise in genetic regulatory networks," *Journal of Theoretical Biology*, vol. 230, pp. 301–312, 2004.

[24] S. Kumar and A. J. Lopez, "Negative feedback regulation among sr splicing factors encoded by rbp1 and rbp1-like in drosophila," *The EMBO Journal*, vol. 24, pp. 2646–2655, 2005.

[25] A. Singh and J. P. Hespanha, "Evolution of autoregulation in the presence of noise," *IET Systems Biology*, vol. 3, pp. 368–378, 2009.

[26] D. J. Stekel and D. J. Jenkins, "Strong negative self regulation of prokaryotic transcription factors increases the intrinsic noise of protein expression," *BMC Systems Biology*, vol. 2, p. 6, 2008.

[27] H. El-Samad and M. Khammash, "Regulated degradation is a mechanism for suppressing stochastic fluctuations in gene regulatory networks," *Biophysical Journal*, vol. 90, pp. 3749–3761, 2006.

[28] R. Sawlekar, F. Montefusco, V. V. Kulkarni, and D. G. Bates, "Implementing nonlinear feedback controllers using dna strand displacement reactions," *IEEE Transactions*, vol. 15, p. 443, 2016.

[29] A. Milias-Argeitis, S. Summers, J. Stewart-Ornstein, I. Zuleta, D. Pincus, H. El-Samad, M. Khammash, and J. Lygeros, "In silico feedback for in vivo regulation of a gene expression circuit," *Nature Biotechnology*, vol. 29, 2011.

[30] E. Klavins, "Proportional-integral control of stochastic gene regulatory networks," *IEEE conference on Decision and Control*, 2010.

[31] G. Buzi and M. Khammash, "Implementation considerations, not topological differences, are the main determinants of noise suppression properties in feedback and incoherent feedforward circuits," *PLoS Computational Biology*, vol. 12, p. e1004958, 2016.

[32] J. Uhlendorf, A. Miermont, T. Delaveau, G. Charvin, F. Fages, S. Bottani, G. Batt, and P. Hersen, "Long-term model predictive control of gene expression at the population and single-cell levels," *Proceedings of the National Academy of Sciences*, vol. 109, pp. 14 271–14 276, 2012.

[33] C. Briat, C. Zechner, and M. Khammash, "Design of a synthetic integral feedback circuit: Dynamic analysis and dna implementation," *ACS Synthetic Biology*, vol. 5, pp. 1108–1116, 2016.

[34] C. Briat, A. Gupta, and M. Khammash, "Antithetic integral feedback ensures robust perfect adaptation in noisy biomolecular networks," *Cell Systems*, vol. 2, pp. 15–26, 2016.

[35] Y. Qian and D. D. Vecchio, "Realizing 'integral control' in living cells: how to overcome leaky integration due to dilution?" *Journal of The Royal Society Interface*, vol. 15, 2018.

[36] M. E. Wall, W. S. Hlavacek, and M. A. Savageau, "Design principles for regulator gene expression in a repressible gene circuit," *Journal of Molecular Biology*, vol. 332, pp. 861–876, 2003.

[37] N. Van Kampen, *Stochastic Processes in Physics and Chemistry*. Elsevier, 2011.

[38] S. Modi, M. Soltani, and A. Singh, "Linear noise approximation for a class of piecewise deterministic markov processes," *American Control Conference (ACC)*, 2018.

[39] K. B. Halpern, S. Tanami, S. Landen, M. Chapal, L. Szlak, A. Hutzler, A. Nizhberg, and S. Itzkovitz, "Bursty gene expression in the intact mammalian liver," *Molecular Cell*, vol. 58, pp. 147–156, 2015.

[40] A. M. Corrigan, E. Tunnacliffe, D. Cannon, and J. R. Chubb, "A continuum model of transcriptional bursting," *eLife*, vol. 5, p. e13051, 2016.

[41] T. Fukaya, B. Lim, and M. Levine, "Enhancer control of transcriptional bursting," *Cell*, vol. 166, pp. 358–368, 2015.

[42] A. Singh, B. Razooky, C. D. Cox, M. L. Simpson, and L. S. Weinberger, "Transcriptional bursting from the HIV-1 promoter is a significant source of stochastic noise in HIV-1 gene expression," *Biophysical Journal*, vol. 98, pp. L32–L34, 2010.

[43] N. Kumar, A. Singh, and R. V. Kulkarni, "Transcriptional bursting in gene expression: Analytical results for genera stochastic models," *PLOS Computational Biology*, vol. 11, p. e1004292, 2015.

[44] N. Friedman, L. Cai, and X. S. Xie, "Linking stochastic dynamics to population distribution: an analytical framework of gene expression," *Physical Review Letters*, vol. 97, no. 16, p. 168302, 2006.

[45] V. Shahrezaei and P. S. Swain, "Analytical distributions for stochastic gene expression," *Proceedings of the National Academy of Sciences*, vol. 105, pp. 17 256–17 261, 2008.

[46] A. Singh and J. P. Hespanha, "Approximate moment dynamics for chemically reacting systems," *IEEE Transactions on Automatic Control*, vol. 56, pp. 414–418, 2011.

[47] J. Yu, J. Xiao, X. Ren, K. Lao, and X. S. Xie, "Probing gene expression in live cells, one protein molecule at a time," *Science*, vol. 311, pp. 1600–1603, 2006.

[48] A. Singh and M. Soltani, "Quantifying intrinsic and extrinsic variability in stochastic gene expression models," *PLOS ONE*, vol. 8, p. e84301, 2013.

[49] J. Paulsson, "Model of stochastic gene expression," *Physics of Life Reviews*, vol. 2, pp. 157–175, 2005.

[50] A. Hilfinger and J. Paulsson, "Separating intrinsic from extrinsic fluctuations in dynamic biological systems," *Proceedings of the National Academy of Sciences*, vol. 108, pp. 12 167–12 172, 2011.

[51] P. S. Swain, M. B. Elowitz, and E. D. Siggia, "Intrinsic and extrinsic contributions to stochasticity in gene expression," *Proceedings of the National Academy of Sciences*, vol. 99, pp. 12 795–12 800, 2002.

[52] S. Modi, S. Dey, and A. Singh, "An approximate derivate-based controller for regulating gene expression," *bioRxiv*, 2019. [Online]. Available: https://www.biorxiv.org/content/early/2019/03/16/579615