Controlling Temporal Precision in Protein Levels with Dynamic External Disturbances

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Abstract—Gene expression is inherently a stochastic process, leading to randomness in the timing of events. A problem of interest is to understand how cells achieve temporal precision. Previous work has shown that if a gene product (protein) is stable then a no feedback strategy provides minimum noise in timing. Here we investigate the form of optimal feedback strategy when the protein production rate is affected by an external dynamic disturbance (noise). We specifically consider a telegraph process (two state) for the external disturbance and show that the best strategy is still no feedback. Using this strategy, we provide an exact formula for the minimum achievable noise. Finally, we examine the effect of model parameters on the minimum noise.

I. INTRODUCTION

Each living cell continually monitors its micro-environment. The cellular response to changes in its micro-environment entails accumulation of appropriate regulatory proteins. Important cellular events and decisions are often coupled to corresponding regulatory proteins attaining their functional concentrations. Examples of such events include lysis of a bacterial cell by bacteriophage λ [1]–[3], decision to enter meiosis by diploid yeast cells [4], cell-cycle control in bacteria [5]–[7], etc. Recent single-cell experiments have shown that timing of cellular events is stochastic [1], [8], presumably because gene expression (the process by which proteins are made) is inherently stochastic [9]–[18]. This raises a fundamental question: how do cells regulate gene expression to control or minimize the noise in timing?

Recent works have investigated the question of precision in timing by setting up a first-passage time problem [19]–[25]. Although there are some variations in their model formulations, a common theme of these works is that they examined gene regulation strategies which minimize noise in timing as quantified by coefficient of variation squared. One important finding is that for a stable protein, a constant rate of protein production minimizes noise in timing around a fixed mean as opposed to a negative or a positive feedback [22]. For an unstable protein, however, a positive feedback that counters the protein degradation performs better than no feedback and negative feedback strategies [22]. Interestingly, the no feedback strategy is optimal even in presence of static extrinsic noise [22], [26]. However, whether this holds if the extrinsic noise is dynamic is yet to be investigated.

Here we incorporate dynamic extrinsic noise by considering an upstream switch that transitions between two states, ON and OFF (Fig. 1). The protein production rate depends upon the state of the switch in the sense that protein production only occurs when the switch is ON. The protein production rate is assumed to have a self-feedback. Our analysis shows that for a stable protein, the best feedback strategy to minimize noise in timing is still the no feedback strategy.

The remainder of this paper is organized as follows. In section II, we describe the model of protein production and compute the probability density function as well as moments of the first-passage time. In section III, we formulate the problem of finding best feedback strategy that would ensure precision in timing of a cellular event, around a given fixed mean time. Specifically, we consider a limiting case of stable protein and deterministic burst size and obtain exact analytical results for the optimal feedback strategy as well as the minimum achievable noise in timing.

Notation: We use $\mathbb{N}$ to denote the set of natural numbers including zero: $\{0, 1, \dots, \infty\}$. $\mathbb{P}$ denotes probability.

II. MODEL FORMULATION

In this section, we describe our model and compute probability density function (pdf) as well as moments of the event timing. The calculations largely follow our previous work [22].

Let $x(t)$ denote the protein level in a cell at time t . Our goal is to compute the pdf and moments of the first-passage time (FPT)

$$T := \inf\{t : x(t) \geq X\}. \quad (1)$$

Here X is the critical threshold for $x(t)$ to trigger a cellular event. For simplicity, we assume that $x(0) = 0$, although this assumption can be relaxed.

To characterize T , we require a description of $x(t)$. We consider a rather simple model of gene expression, consisting of production in bursts and degradation (Fig. 1). The production rate is taken to be a positive valued function of the protein level $x(t)$. Since we only care about values of $x(t)$ in the set $\Omega := \{0, 1, \dots, X - 1\}$, it is convenient to denote the production rate by k_i where $i \in \Omega$. Further, each protein molecule degrades with a constant rate γ . The burst size distribution is assumed to be general, but independent of protein level

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$$\mathbb{P}(B = j) = \beta_j \geq 0, \quad j \in \{0, 1, \dots\}, \quad \sum_{j=0}^{\infty} \beta_j = 1. \quad (2)$$

Fig. 1. Gene expression model with protein production, degradation, feedback and external disturbance $z(t)$. The external disturbance (extrinsic noise) switches between two states, OFF and ON. The transition from OFF to ON occurs with a rate u whereas the transition from ON to OFF occurs with a rate v . $z(t)$ affects the production rate of a protein, which is produced in bursts. The rate of protein production is also self-regulated. Each protein molecule degrades with rate γ .

Next, we incorporate external disturbance (or extrinsic noise) in this model. To this end, let $z(t)$ denote the level of a species that affects the protein production rate as $k_i z(t)$. Note that a static extrinsic noise is a special case of our formulation, where the dependence on time is dropped and z is drawn from a distribution. We assume that $z(t)$ is a switch that takes two states, ON ($z = 1$) and OFF ($z = 0$), and stochastically transitions between these states (Fig. 1). The rate of OFF to ON transition is u and ON to OFF transition is v . In future, we would consider more general processes, e.g., a (finite) state birth-death process or an Ornstein-Uhlenbeck (OU) process. With this setup, we now proceed to compute the pdf of FPT defined in (1).

A. Event Timing Distribution

Let us consider the joint state $[z(t) \ x(t)]^\top$, which lives on the state-space $\{0, 1\} \times \mathbb{N} = \{0, 1\} \times \Omega \cup \{0, 1\} \times \mathbb{N} \setminus \Omega$ with $\Omega = \{0, 1, \dots, X-1\}$. A convenient way to think about FPT is to think of the states $\{0, 1\} \times \mathbb{N} \setminus \Omega$ as absorbing states. This allows us to focus on the evolution of our states in $\{0, 1\} \times \Omega$ and account for the absorbing state space by probabilities of leaving $\{0, 1\} \times \Omega$. Let $p_{0,i}$ and $p_{1,i}$ respectively denote the probabilities that $[z(t) \ x(t)]^\top = [0 \ i]^\top$ and $[z(t) \ x(t)]^\top = [1 \ i]^\top$, where $i \in \Omega$. Then, we can write the probability density function, $f_T(t)$, of FPT

$$f_T(t) = \sum_{i=0}^{X-1} k_i \left(1 - \sum_{j=0}^{X-i-1} \beta_j \right) p_{1,i}(t). \quad (3)$$

To compute $p_{1,i}$ we write the master equation that governs time evolution of $p_{0,i}$ and $p_{1,i}$ over the state-space $\{0, 1\} \times \Omega$

$$\frac{dp_{0,i}}{dt} = -up_{0,i} + vp_{1,i}, \quad + (i+1)\gamma p_{0,i+1} - i\gamma p_{0,i}, \quad 0 \leq i \leq X-2, \quad (4a)$$

$$\frac{dp_{0,X-1}}{dt} = -up_{0,X-1} + vp_{1,X-1} - (X-1)\gamma p_{0,X-1}, \quad (4b)$$

$$\frac{dp_{1,i}}{dt} = up_{0,i} - vp_{1,i} + \sum_{l=0}^{i-1} k_l \beta_{i-l} p_{1,l} - k_i (1 - \beta_0) p_{1,i} + (i+1)\gamma p_{1,i+1} - i\gamma p_{1,i}, \quad 0 \leq i \leq X-2, \quad (4c)$$

$$\frac{dp_{1,X-1}}{dt} = up_{0,X-1} - vp_{1,X-1} + \sum_{l=0}^{X-2} k_l \beta_{X-1-l} p_{1,l} - k_{X-1} (1 - \beta_0) p_{1,X-1} - (X-1)\gamma p_{1,X-1}. \quad (4d)$$

It is convenient to express the master equation (4) in a compact form

$$\frac{d\mathbf{P}(t)}{dt} = \mathbf{A}\mathbf{P}(t). \quad (5a)$$

where $\mathbf{P}$ is the vector

$$\mathbf{P}(t) = [p_{0,0} \ \dots \ p_{0,X-1} \ p_{1,0} \ \dots \ p_{1,X-1}]^\top, \quad (5b)$$

and the matrix $\mathbf{A}$ is a block diagonal matrix

$$\mathbf{A} = \begin{bmatrix} \mathbf{A}_{00} & \mathbf{A}_{01} \\ \mathbf{A}_{10} & \mathbf{A}_{11} \end{bmatrix}. \quad (5c)$$

The (m, n) -th elements of these matrices are given by

$$(\mathbf{A}_{00})_{mn} = \begin{cases} (m-1)\gamma, & n = m+1 \\ -u - (m-1)\gamma, & n = m \\ 0, & \text{otherwise.} \end{cases} \quad (5d)$$

$$(\mathbf{A}_{01})_{mn} = \begin{cases} v, & n = m \\ 0, & \text{otherwise.} \end{cases} \quad (5e)$$

$$(\mathbf{A}_{10})_{mn} = \begin{cases} u, & n = m \\ 0, & \text{otherwise.} \end{cases} \quad (5f)$$

$$(\mathbf{A}_{11})_{mn} = \begin{cases} 0, & j > i+1 \\ (i-1)\gamma, & j = i+1 \\ -v - k_{m-1}(1 - \beta_0) - (i-1)\gamma, & n = m \\ k_{n-1}\beta_{n-m}, & n < m. \end{cases} \quad (5g)$$

where $m, n \in \{1, \dots, X\}$.

The system in (5) has the solution

$$\mathbf{P}(t) = \exp(\mathbf{A}t)\mathbf{P}(0), \quad (6)$$

where $\mathbf{P}(0)$ is the initial probability distribution of states. Upon substituting (6) in (3), we get

$$f_T(t) = \mathbf{U}^\top \mathbf{P}(t) = \mathbf{U}^\top \exp(\mathbf{A}t)\mathbf{P}(0). \quad (7a)$$

Here, $\mathbf{U}$ represents the following $2X$ -dimensional vector

$$\mathbf{U} = [0 \ \dots \ 0 \ k_0(1 - \sum_{j=1}^{X-1} \beta_j) \ \dots \ k_{X-1}]^\top. \quad (7b)$$

We take the initial condition as

$$\mathbf{P}(0) = [0 \quad \dots \quad 0 \quad 1 \quad 0 \dots \quad 0]^\top, \quad (7c)$$

which corresponds to $[z(0) \quad x(0)] = [1 \quad 0]$. We next use the pdf in (7) to compute the moments of T .

B. Moments of Event Timing

The m^{th} order moment of T is defined as

$$\langle T^m \rangle = \int_0^\infty t^m f_T(t) dt \quad (8a)$$

$$= \mathbf{U}^\top \left(\int_0^\infty \exp(\mathbf{A}t) dt \right) \mathbf{P}(0) \quad (8b)$$

$$= (-1)^{m+1} m! \mathbf{U}^\top (\mathbf{A}^{-1})^{m+1} \mathbf{P}(0). \quad (8c)$$

Here, we have used the fact that $\mathbf{A}$ has negative diagonal elements and for each column, the sum of the absolute values of non-diagonal elements is less than that of the diagonal element [27, pp 48–49]. In other words, $\mathbf{A}$ is full-rank and has eigenvalues with negative real parts.

One can write inverse of $\mathbf{A}$ in a standard form [28]

$$\mathbf{A}^{-1} = \begin{bmatrix} \mathbf{A}'_{00} & \mathbf{A}'_{01} \\ \mathbf{A}'_{10} & \mathbf{A}'_{11} \end{bmatrix}, \quad (9a)$$

where the matrices that make up $\mathbf{A}^{-1}$ can be computed in several ways, depending upon which one of those are invertible. In our case, we note that $\mathbf{A}_{00}$ is easily invertible. We use this to get the following [28]

$$\mathbf{A}'_{00} = \mathbf{A}_{00}^{-1} + \mathbf{A}_{00}^{-1} \mathbf{A}_{01} (\mathbf{A}_{11} - \mathbf{A}_{10} \mathbf{A}_{00}^{-1} \mathbf{A}_{01})^{-1} \mathbf{A}_{10} \mathbf{A}_{00}^{-1}, \quad (9b)$$

$$\mathbf{A}'_{01} = -\mathbf{A}_{00}^{-1} \mathbf{A}_{01} (\mathbf{A}_{11} - \mathbf{A}_{10} \mathbf{A}_{00}^{-1} \mathbf{A}_{01})^{-1}, \quad (9c)$$

$$\mathbf{A}'_{10} = -(\mathbf{A}_{11} - \mathbf{A}_{10} \mathbf{A}_{00}^{-1} \mathbf{A}_{01})^{-1} \mathbf{A}_{10} \mathbf{A}_{00}^{-1}, \quad (9d)$$

$$\mathbf{A}'_{11} = (\mathbf{A}_{11} - \mathbf{A}_{10} \mathbf{A}_{00}^{-1} \mathbf{A}_{01})^{-1}. \quad (9e)$$

We substitute these to (8a) to compute moments.

Thus far we have derived the pdf and a semi-analytical form for moments of T . We now use these to investigate the optimal feedback strategy as discussed in the next section.

III. OPTIMAL FEEDBACK STRATEGY

We begin by first stating the optimization problem, which is to find the feedback strategy that minimizes noise in timing (quantified by coefficient of variation squared) around a given mean time. Because assume a fixed mean time, an equivalent problem is

$$\min_{k_0, k_1, \dots, k_{X-1}} \langle T^2 \rangle, \quad (10a)$$

$$\text{subject to} \quad \langle T \rangle = c. \quad (10b)$$

It is important to note that solving this problem analytically is usually not possible, unless we reduce it to a much simpler problem. To this end, we make the following simplifications

- The protein is stable, i.e., $\gamma = 0$. This is motivated from the observation the formulas of moments of FPT greatly simplify for the model without extrinsic noise [22].

- The burst size distribution is $\mathbb{P}(B = 1) = 1$ with probability one, which implies that $\beta_1 = 1, \beta_i = 0 \forall i \neq 1$. Our prior work has shown that different burst size distributions have minor influence on the optimal feedback strategy [26].

With the aforementioned assumptions, we proceed towards computing the moments of FPT. To this end, we first compute $\mathbf{A}^{-1}$.

A. Computation of $\mathbf{A}^{-1}$

Upon simplification, it is easy to note that matrix $\mathbf{A}$ consists of three diagonal matrices

$$\mathbf{A}_{00} = \text{diag} [-u \quad -u \quad \dots \quad -u], \quad (11a)$$

$$\mathbf{A}_{01} = \text{diag} [v \quad v \quad \dots \quad v], \quad (11b)$$

$$\mathbf{A}_{10} = \text{diag} [u \quad u \quad \dots \quad u], \quad (11c)$$

and one bidiagonal matrix whose elements are given by

$$(\mathbf{A}_{11})_{mn} = \begin{cases} -v - k_{m-1}, & n = m \\ k_{n-1}, & n = m - 1 \\ 0, & \text{otherwise} \end{cases} \quad (11d)$$

Using these, we compute the elements of the block matrix $\mathbf{A}^{-1}$. We first compute $\mathbf{A}'_{11} = (\mathbf{A}_{11} - \mathbf{A}_{10} \mathbf{A}_{00}^{-1} \mathbf{A}_{01})^{-1}$. Because both $\mathbf{A}_{10}$ and $\mathbf{A}_{00}$ both are diagonal matrices, $-\mathbf{A}_{10} \mathbf{A}_{00}^{-1}$ is an identity matrix. Thus, $\mathbf{A}'_{11} = (\mathbf{A}_{11} + \mathbf{A}_{01})^{-1}$. Note that $\mathbf{A}_{01}$ is a diagonal matrix with all its elements being v . These could cancel out $-v$ terms from the diagonal of $\mathbf{A}_{11}$. As a result, we get the elements of $\mathbf{A}_{11} + \mathbf{A}_{01}$

$$(\mathbf{A}_{11} + \mathbf{A}_{01})_{mn} = \begin{cases} -k_{m-1}, & n = m \\ k_{n-1}, & n = m - 1 \\ 0, & \text{otherwise} \end{cases} \quad (12a)$$

A straightforward application of the result in [29] gives the following lower triangular matrix

$$\mathbf{A}'_{11} = - \begin{bmatrix} \frac{1}{k_0} & & & \\ \frac{1}{k_1} & \frac{1}{k_2} & & \\ \frac{1}{k_2} & \frac{1}{k_2} & \frac{1}{k_2} & \\ \vdots & \vdots & \vdots & \vdots \\ \frac{1}{k_{X-1}} & \frac{1}{k_{X-1}} & \frac{1}{k_{X-1}} & \frac{1}{k_{X-1}} \end{bmatrix}. \quad (12b)$$

We next compute $\mathbf{A}'_{10}$. Because $-\mathbf{A}_{10} \mathbf{A}_{00}^{-1}$ is an Identity matrix, we have

$$\mathbf{A}'_{10} = \mathbf{A}'_{11} \quad (12c)$$

To compute $\mathbf{A}'_{01}$, we note that $-\mathbf{A}_{00}^{-1} \mathbf{A}_{01}$ is an Identity matrix multiplied by v/u , resulting in

$$\mathbf{A}'_{01} = \frac{v}{u} \mathbf{A}'_{11} \quad (12d)$$

Proceeding in the same manner, we finally obtain

$$\mathbf{A}'_{00} = \text{diag} [-1/u \quad -1/u \quad \dots \quad -1/u] + \frac{v}{u} \mathbf{A}'_{11}. \quad (12e)$$

B. Computing FPT moments

Having determined $\mathbf{A}^{-1}$, we can now compute the moments of T , specifically the first two moments as they are required in the optimization problem (10). These are given by

$$\langle T \rangle = \mathbf{U}^\top \mathbf{A}^{-2} \mathbf{P}(0), \quad \langle T^2 \rangle = -2\mathbf{U}^\top \mathbf{A}^{-3} \mathbf{P}(0). \quad (13)$$

We note that $\mathbf{U}^\top \mathbf{A}^{-1}$ appears in both moments, so we compute this first. With the simplifying assumptions of stable protein and a deterministic burst size, we now have $\mathbf{U}^\top$ as a row vector of zeros, except for its last element which is k_{X-1} . Therefore, $\mathbf{U}^\top \mathbf{A}^{-1}$ is simply the last row of $\mathbf{A}^{-1}$ multiplied by k_{X-1} , which results in a row vector with each element equal to -1 .

Using $\mathbf{U}^\top \mathbf{A}^{-1}$, $\langle T \rangle$ simplifies to

$$- [1 \quad 1 \quad \dots \quad 1] \mathbf{A}^{-1} \mathbf{P}(0). \quad (14a)$$

Note that $\mathbf{P}(0)$ also has all its elements zero except for $(X+1)^{th}$ element. Thus, we get

$$\langle T \rangle = [1 \quad 1 \quad \dots \quad 1] \times \left[\frac{v}{u} \frac{1}{k_0} \quad \dots \quad \frac{v}{u} \frac{1}{k_{X-1}} \quad \frac{1}{k_0} \quad \dots \quad \frac{1}{k_{X-1}} \right]^\top, \quad (14b)$$

which results in

$$\langle T \rangle = \left(1 + \frac{v}{u}\right) \sum_{i=0}^{X-1} \frac{1}{k_i}. \quad (14c)$$

Now, we can compute $\langle T^2 \rangle$. From the calculations of $\langle T \rangle$, we already know $\mathbf{U}^\top \mathbf{A}^{-1}$ and $\mathbf{A}^{-1} \mathbf{P}(0)$. Utilizing $\mathbf{A}^{-1} \mathbf{P}(0)$, we first compute $\mathbf{A}^{-2} \mathbf{P}(0)$. To this end, let us use short-hand notation $\kappa = \left[\frac{1}{k_0} \quad \dots \quad \frac{1}{k_{X-1}} \right]^\top$, so that we have

$$\mathbf{A}^{-2} \mathbf{P}(0) = \begin{bmatrix} \mathbf{A}'_{00} & \mathbf{A}'_{01} \\ \mathbf{A}'_{10} & \mathbf{A}'_{11} \end{bmatrix} \begin{bmatrix} \frac{v}{u} \kappa \\ \kappa \end{bmatrix} \quad (15a)$$

$$= \begin{bmatrix} \frac{v}{u} \mathbf{A}'_{11} & \frac{v}{u} \mathbf{A}'_{11} \\ \mathbf{A}'_{11} & \mathbf{A}'_{11} \end{bmatrix} \begin{bmatrix} \frac{v}{u} \kappa \\ \kappa \end{bmatrix} - \begin{bmatrix} \frac{v}{u^2} \kappa \\ 0 \end{bmatrix} \quad (15b)$$

$$= \begin{bmatrix} \frac{v^2}{u^2} \mathbf{A}'_{11} \kappa + \frac{v}{u} \mathbf{A}'_{11} \kappa \\ \frac{v}{u} \mathbf{A}'_{11} \kappa + \mathbf{A}'_{11} \kappa \end{bmatrix} - \begin{bmatrix} \frac{v}{u^2} \kappa \\ 0 \end{bmatrix}. \quad (15c)$$

Therefore, we can write $\langle T^2 \rangle$ as

$$\langle T^2 \rangle = \frac{2v}{u^2} \sum_{i=0}^{X-1} k_i + 2 \left(1 + \frac{v}{u}\right)^2 e_0, \quad (15d)$$

where e_0 is the sum of all elements of the vector $-\mathbf{A}'_{11} \kappa$

$$e_0 = \sum_{i=0}^{X-1} \frac{1}{k_i} \left(\sum_{j=i}^{X-1} \frac{1}{k_j} \right). \quad (15e)$$

Before we compute the optimal feedback strategy using these expressions, we first show that the expressions of the first two moments obtained above simplify to previously

known expressions in limiting case $v \rightarrow 0$. In this limit, we obtain

$$\langle T \rangle = \sum_{i=0}^{X-1} \frac{1}{k_i}, \quad \langle T^2 \rangle = 2 \sum_{i=0}^{X-1} \frac{1}{k_i} \left(\sum_{j=i}^{X-1} \frac{1}{k_j} \right), \quad (16)$$

which are same as those obtained in [22].

C. Optimal feedback strategy

We can solve the optimization problem in (10) using method of Lagrange multiplier. Let λ be the Lagrange's multiplier, then we can rewrite the problem as

$$\min_{k_0, k_1, \dots, k_{X-1}} \langle T^2 \rangle + \lambda (\langle T \rangle - c). \quad (17)$$

We can determine the critical points of this objective function by taking derivatives with respect to the decision variables $k_0, k_1, \dots, k_{X-1}, \lambda$, which gives us the following system of equations to be solved

$$\frac{\partial \langle T^2 \rangle}{\partial k_i} + \lambda \frac{\partial \langle T \rangle}{\partial k_i} = 0, \quad 0 \leq i \leq X-1, \quad (18a)$$

$$\sum_{i=0}^{X-1} \frac{1}{k_i} - c = 0. \quad (18b)$$

The derivatives of $\langle T \rangle$ with respect to k_i 's are given by

$$\frac{\partial \langle T \rangle}{\partial k_i} = - \left(1 + \frac{v}{u}\right) \frac{1}{k_i^2}, \quad 0 \leq i \leq X-1. \quad (19)$$

Likewise, the derivative of $\langle T^2 \rangle$ with respect to $k_i, 0 \leq i \leq X-1$ are

$$\frac{\partial \langle T^2 \rangle}{\partial k_i} = - \frac{2v}{u^2} \frac{1}{k_i^2} - \left(1 + \frac{v}{u}\right)^2 \left(\frac{2}{k_i^3} + \frac{1}{k_i^2} \sum_{\substack{j=0 \\ j \neq i}}^{X-1} \frac{1}{k_j} \right). \quad (20)$$

Assuming $k_i \neq 0$ to avoid pathological cases and substituting these derivatives in (18), the system of equations to be solved becomes

$$\frac{2v}{u^2} + \left(1 + \frac{v}{u}\right)^2 \left(\frac{2}{k_i} + \sum_{\substack{j=0 \\ j \neq i}}^{X-1} \frac{1}{k_j} \right) + \lambda = 0, \quad (21a)$$

$$\sum_{i=0}^{X-1} \frac{1}{k_i} - c = 0, \quad (21b)$$

where $0 \leq i \leq X-1$. Solution to optimal k_i obtained by solving above system is

$$k_i = \left(1 + \frac{v}{u}\right) \frac{X}{c}. \quad (22)$$

Thus, the optimal strategy is a no feedback strategy, which corresponds to a constant rate of protein production. The optimal transcription rate increases with increase in X , meaning that a faster production rate is required to attain a higher threshold X in a given mean time $\langle T \rangle = c$. In the limit when $\frac{v}{u} \ll 1$ (i.e., when $z(t)$ primarily lives in the ON state), $k_i = X/c$, which is the optimal transcription rate when $z(t)$ is not considered in the model as obtained previously in [30].

Fig. 2. The minimum noise achieved by the optimal feedback strategy decreases with the ratio (u/v) of transition rates of the external disturbance. The noise is higher when the timescale of extrinsic noise (v) is smaller than the event timing $\langle T \rangle = c$.

D. Minimum achievable noise in FPT

Using the result on optimal feedback strategy in (22), we can find the minimum noise in timing. To this end, we first compute $\langle T^2 \rangle$ when $k_i = (1 + \frac{v}{u}) \frac{X}{c}$. Substituting this in (15), we obtain

$$\langle T^2 \rangle = \frac{X+1}{X} c^2 + 2c \frac{v}{u^2} \frac{1}{1 + \frac{v}{u}}. \quad (23)$$

Therefore the minimum value of the coefficient of variation squared is

$$\frac{\langle T^2 \rangle - c^2}{c^2} = \frac{1}{X} + \frac{v}{u} \frac{2}{(u+v)c}. \quad (24)$$

The first term $1/X$ in the above expression is the minimum achievable noise in absence of the extrinsic noise $z(t)$ [31]. The second term stems from the dynamics of $z(t)$ and it also depends on the fixed mean event time $\langle T \rangle = c$. In Fig. 2, we plot this minimum achievable noise for various ratios of the transition rates u/v and the timescale of fluctuations in $z(t)$, which is set by v in comparison with the average event timing. We find that the noise is higher when the switching is slow. Moreover, when $u/v \gg 1$, the minimum noise approaches the Poisson limit $1/X$.

IV. CONCLUSION

In this paper, we considered a model of gene expression consisting of production in bursts, degradation, feedback regulation, and dynamic extrinsic disturbance (noise). We derived semi-analytical forms of the first-passage time distribution and moments for this model. For a special case where burst is deterministically equal to one and the protein of interest is stable, we derived exact formulae for the first two moments and also obtained the optimal feedback strategy that would provide minimum noise in timing around a given fixed mean time. We found that the optimal feedback strategy is no feedback (constant production rate), which was earlier found to be optimal in absence of the extrinsic noise as well as in presence of static extrinsic noise [22]. We further showed that

the minimum achievable noise is a function of the ratio of transition rates of the extrinsic noise as well as the timescale of these transitions. In future, we will examine the effect of a general burst size distribution as well as protein degradation on the optimal feedback strategy and minimum achievable noise. Another extension would be to consider a more general process for the dynamic noise such as birth-death and OU process.

ACKNOWLEDGMENT

AS is supported by NIH 1R01GM124446-01.

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