

MOMENT ANALYSIS OF LINEAR TIME-VARYING DYNAMICAL SYSTEMS WITH RENEWAL TRANSITIONS*

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Abstract. Stochastic dynamics of several systems can be modeled via piecewise-deterministic time evolution of the state, interspersed by random discrete events. Within this general class of systems, we consider time-triggered stochastic hybrid systems (TTSHS), where the state evolves continuously according to a linear time-varying dynamical system. Discrete events occur based on an underlying renewal process (timer), and the intervals between successive events follow an arbitrary continuous probability density function. Moreover, whenever the event occurs, the state is reset based on a linear affine transformation that allows for the inclusion of state-dependent and independent noise terms. Our key contribution is derivation of necessary and sufficient conditions for the stability of statistical moments, along with exact analytical expressions for the steady-state moments. These results are illustrated in an example from cell biology, where deterministic synthesis and decay of a gene product (RNA or protein) is coupled to random timing of cell-division events. As experimentally observed, cell-division events occur based on an internal timer that measures the time elapsed since the start of cell cycle (i.e., last event). Upon division, the gene product level is halved, together with a state-dependent noise term that arises due to randomness in the partitioning of molecules between two daughter cells. We show that the TTSHS framework is conveniently suited to capture the time evolution of gene product levels, and we derive unique formulas connecting its mean and variance to underlying model parameters and noise mechanisms. Systematic analysis of the formulas reveal counterintuitive insights, such as if the partitioning noise is large, then making the timing of cell division more random reduces noise in gene product levels. In summary, the theory developed here provides novel tools for characterizing moments in an important class of stochastic dynamical systems that arises naturally in diverse application areas.

Key words. impulsive renewal systems, stochastic hybrid systems, piecewise-deterministic Markov processes, cell-to-cell variability in gene products, gene expression, cell-cycle time

AMS subject classifications. 60K05, 60K15, 93E03, 93E15

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1. Introduction. We study a class of stochastic systems that couple continuous linear dynamics with random discrete events that occur based on an underlying renewal process. Such systems have been referred to in the literature as time-triggered stochastic hybrid systems (TTSHS) [17, 12, 18, 13] and are an important subclass of piecewise-deterministic Markov processes [25, 24, 14, 19] with applications in different disciplines. For example, TTSHS have been shown to arise ubiquitously in networked control systems, where a dynamical system is controlled over a noisy communication network, and signals are received at discrete random times [3, 33, 4, 30, 32, 6, 84, 2, 41, 35]. Other TTSHS applications include modeling disturbances in nanosensors [83], capturing stochastic effects in cellular biochemical processes [5, 86, 82, 15, 85], and neuroscience [71].

Previously, we studied a subclass of TTSHS where the continuous dynamics was modeled by a linear time-invariant system, and the time intervals between successive

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discrete events was restricted to follow a phase-type distribution (i.e., mixture and/or sum of exponential random variables) [83]. Further, the states of the system after each reset are random. For such systems, statistical moments of the state space can be computed exactly by numerically solving a system of differential equations [83]. Building on this prior work, here we generalize the results in several new directions:

- Time intervals between events follow an arbitrary positively valued and continuous probability density functions (pdf).
- We provide an explicit condition for the existence and convergence of statistical moments, together with their exact closed-form formulas.
- We use TTSHS to study the fundamental process of gene expression inside cells, where production/decay of a protein is coupled to random cell-division events.
- We allow continuous dynamics to be a time-varying linear system.

The main contribution of this paper is the inclusion of time-varying dynamics in TTSHS and allowing the states after each reset to be random. We start by introducing the notation used throughout the paper, followed by a mathematical description of TTSHS. Before presenting the results on TTSHS with time-varying dynamics, we first consider the simpler case of linear time-invariant systems.

Notation. The set of real number is denoted by $\mathbb{R}$. Constant vectors are indicated by a hat, e.g., $\hat{a}$, and matrices are denoted by capital letters. Further, the transpose of a matrix A is given by $A^\top$ and the n -dimensional identity matrix is denoted by I_n . We show zero vectors and matrices with the same notation, e.g., $A = \hat{a} = 0$. Random variables are indicated by bold letters. The expected value of a random variable $\mathbf{x}$ at time t ($\mathbf{x}(t)$) is denoted by $\langle \mathbf{x} \rangle$, where we drop t for simplicity. The expected value in steady-state is denoted by $\langle \mathbf{x} \rangle \equiv \lim_{t \rightarrow \infty} \langle \mathbf{x} \rangle$.

2. Linear time-invariant TTSHS. The state of the system $\mathbf{x} \in \mathbb{R}^{n \times 1}$ evolves as per the following ordinary differential equation:

$$(1) \quad \frac{d\mathbf{x}}{dt} = \hat{a} + A\mathbf{x}(t)$$

for a given constant vector $\hat{a} \in \mathbb{R}^{n \times 1}$ and matrix $A \in \mathbb{R}^{n \times n}$. Random events are assumed to occur at times $\mathbf{t}_s$, $s \in \{1, 2, \dots\}$, and the time interval between events

$$(2) \quad \tau_s \equiv \mathbf{t}_s - \mathbf{t}_{s-1}$$

is an independent and identically distributed (iid) random variable that follows a continuous positively valued pdf f . Throughout the paper we assume a finite mean time interval $\langle \tau_s \rangle < \infty$, but higher-order moments of τ_s can be infinite, allowing for heavy-tailed timing distributions.

Whenever the events occur the state is reset as

$$(3) \quad \mathbf{x}(\mathbf{t}_s^-) \mapsto \mathbf{x}(\mathbf{t}_s^+),$$

where $\mathbf{x}(\mathbf{t}_s^-)$ and $\mathbf{x}(\mathbf{t}_s^+)$ denote the state of the TTSHS just before and after the event, respectively. We assume $\mathbf{x}(\mathbf{t}_s^+)$ to be a random variable, whose average value is related to its value just before the event by a linear affine map

$$(4) \quad \langle \mathbf{x}(\mathbf{t}_s^+) \rangle = J\mathbf{x}(\mathbf{t}_s^-) + \hat{r},$$

where $J \in \mathbb{R}^{n \times n}$ and $\hat{r} \in \mathbb{R}^{n \times 1}$ are a constant matrix and vector, receptively. Furthermore, the covariance matrix of $\mathbf{x}(\mathbf{t}_s^+)$ is defined by

$$(5) \quad \begin{aligned} & \langle \mathbf{x}(\mathbf{t}_s^+) \mathbf{x}^\top(\mathbf{t}_s^+) \rangle - \langle \mathbf{x}(\mathbf{t}_s^+) \rangle \langle \mathbf{x}(\mathbf{t}_s^+) \rangle^\top \\ &= Q\mathbf{x}(\mathbf{t}_s^-) \mathbf{x}^\top(\mathbf{t}_s^-) Q^\top + B\mathbf{x}(\mathbf{t}_s^-) \hat{c}^\top + \hat{c} \mathbf{x}^\top(\mathbf{t}_s^-) B^\top + D. \end{aligned}$$

Here $Q \in \mathbb{R}^{n \times n}$ and $B \in \mathbb{R}^{n \times n}$ are constant matrices, and $\hat{c} \in \mathbb{R}^{n \times 1}$ is a constant vector. Moreover $D \in \mathbb{R}^{n \times n}$ is a constant symmetric positive semidefinite matrix. Intuitively, (5) formalizes the noise added to the state during the reset (event), with $Q = B = D = \hat{c} = 0$ implying that $\mathbf{x}(t_s^+)$ is simply a deterministic linear function of $\mathbf{x}(t_s^-)$. A constant state-independent noise can be incorporated through a nonzero matrix D with $Q = B = \hat{c} = 0$. The generality of (5) allows for state-dependent noise terms that can potentially be quadratic (nonzero Q) or linear (nonzero B and $\hat{c}$) functions of the state, and we will see an example of it later in the manuscript.

3. Statistical analysis of linear time-invariant TTSHS. A convenient approach to implement the TTSHS represented by (1)–(5) is via a timer τ that measures the time elapsed since the last event (Figure 1). The timer increases between events and resets to zero whenever the events occur. Let the probability that an event occurs in the next infinitesimal time $(t, t + dt]$ be $h(\tau)dt$, where

$$(6) \quad h(\tau) \equiv \frac{f(\tau)}{1 - \int_{y=0}^{\tau} f(y)dy}$$

is the event arrival rate (hazard rate). Then, τ_s follows the continuous positively valued pdf

$$(7) \quad \tau_s \sim f(\tau) = h(\tau)e^{-\int_0^{\tau} h(y)dy}$$

[65, 26, 23], and the timer follows the continuous positively valued pdf

$$(8) \quad \tau \sim p(\tau) = \frac{1}{\langle \tau_s \rangle} e^{-\int_0^{\tau} h(y)dy}$$

[94]. Note that $f(\tau)$ and $p(\tau)$ are connected but are not always equal. As a simple example, a constant (timer-independent) hazard rate $h(\tau) = 1/\langle \tau_s \rangle$ leads to exponentially distributed τ_s and τ . Similarly, a monomial function

$$(9) \quad h(\tau) = \frac{k}{\lambda} \left(\frac{\tau}{\lambda} \right)^{k-1}$$

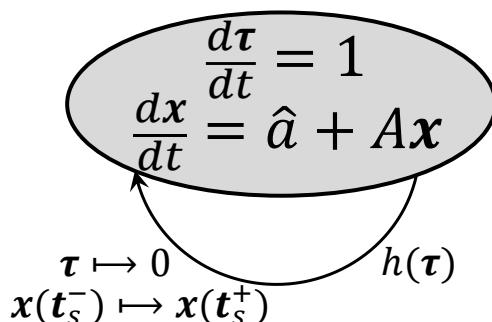


FIG. 1. Schematic of TTSHS with continuous dynamics described by a linear time-invariant system. As the state evolves according to a linear system, events occur at discrete times that change the state of the system according to (3). The timing of events is controlled by renewal transitions defined through a timer τ that linearly increases over time between events and is reset to zero each time an event occurs. Choosing the event arrival rate $h(\tau)$ based on (6) ensures that the time interval between events is iid with probability distribution f .

with positive constants k and λ results in a Weibull distribution for τ_s with pdf

$$(10) \quad f(\tau) = \frac{k}{\lambda} \left(\frac{\tau}{\lambda} \right)^{k-1} e^{-(\tau/\lambda)^k}$$

and mean $\langle \tau_s \rangle = \lambda \Gamma(1 + 1/k)$, where Γ is the gamma function. In this case the timer follows the following distribution:

$$(11) \quad p(\tau) = \frac{1}{\lambda \Gamma(1 + 1/k)} e^{-(\tau/\lambda)^k}.$$

Having defined the probability distributions of τ_s and τ , we next summarize our main results in theorems/corollaries, and we refer the reader to the appendix for proofs.

3.1. Mean of vector $\mathbf{x}$. In general, the expected value of $\mathbf{x}$ depends on the entire distribution of τ_s , as shown below.

THEOREM 3.1. *For the TTSHS (1)–(5) the steady-state mean of $\mathbf{x}$ is given by*

$$(12) \quad \overline{\langle \mathbf{x} \rangle} = \langle e^{A\tau} \rangle (I_n - J \langle e^{A\tau_s} \rangle)^{-1} \left(J \left\langle e^{A\tau_s} \int_0^{\tau_s} e^{-Al} \hat{a} dl \right\rangle + \hat{r} \right) + \left\langle e^{A\tau} \int_0^{\tau} e^{-Al} \hat{a} dl \right\rangle$$

if and only if the expected value

$$(13) \quad \langle e^{A\tau_s} \rangle = \int_0^\infty f(\tau) e^{A\tau} d\tau$$

exists and all the eigenvalues of the matrix $J \langle e^{A\tau_s} \rangle$ are inside the unit circle.

Please see Appendix A for a detailed proof. In this theorem, the vector

$$(14) \quad \left\langle e^{A\tau_s} \int_0^{\tau_s} e^{-Al} \hat{a} dl \right\rangle = \int_0^\infty f(\tau) \left(e^{A\tau} \int_0^{\tau} e^{-Al} \hat{a} dl \right) d\tau$$

is obtained by taking the expected value with respect to τ_s , and

$$(15) \quad \langle e^{A\tau} \rangle = \int_0^\infty p(\tau) e^{A\tau} d\tau, \quad \left\langle e^{A\tau} \int_0^{\tau} e^{-Al} \hat{a} dl \right\rangle = \int_0^\infty p(\tau) \left(e^{A\tau} \int_0^{\tau} e^{-Al} \hat{a} dl \right) d\tau$$

is obtained by taking the expected value with respect to τ . While Theorem 3.1 represents the most general result, we consider simplifications of (12) in special cases.

COROLLARY 3.2. *If the TTSHS (1)–(5) satisfies stability condition of Theorem 3.1 and the matrix A is invertible, then*

$$(16) \quad \overline{\langle \mathbf{x} \rangle} = \frac{1}{\langle \tau_s \rangle} (I_n - \langle e^{A\tau_s} \rangle) A^{-1} (I_n - J \langle e^{A\tau_s} \rangle)^{-1} (J (I_n - \langle e^{A\tau_s} \rangle) A^{-1} \hat{a} + \hat{r}) \\ - \frac{1}{\langle \tau_s \rangle} (I_n - \langle e^{A\tau_s} \rangle) A^{-2} \hat{a} - A^{-1} \hat{a}.$$

Thus, for an invertible matrix A , the steady-state expected value can directly be computed from the moment generating function $\langle e^{A\tau_s} \rangle$ (see Appendix B). Interestingly, there are some scenarios where knowing a few lower-order moments of τ_s are sufficient to determine $\langle \mathbf{x} \rangle$ (see Appendix C).

COROLLARY 3.3. Consider the TTSHS (1)–(5) with $A = 0$, and all eigenvalues of the matrix J are inside the unit circle; then

$$(17) \quad \overline{\langle \mathbf{x} \rangle} = (I_n - J)^{-1} (J \langle \boldsymbol{\tau}_s \rangle \hat{a} + \hat{r}) + \frac{\langle \boldsymbol{\tau}_s^2 \rangle}{2 \langle \boldsymbol{\tau}_s \rangle} \hat{a}$$

only depends on the first- and the second-order moments of $\boldsymbol{\tau}_s$.

We will revisit this corollary later on, as it is pertinent to the example of gene expression.

Note that Theorem 3.1 by itself is not guaranteeing divergence of the states of system. To illustrate this point, consider a simple scalar system

$$(18) \quad \frac{d\mathbf{x}}{dt} = a\mathbf{x}(t),$$

where $a > 0$ is a constant parameter. Any time that a reset occurs, the state of the system exactly halves ($J = 1/2$, $\hat{r} = 0$), and there is no added noise to the states of the system ($Q = B = D = \hat{c} = 0$)

$$(19) \quad \langle \mathbf{x}(t_s^+) \rangle = \frac{\mathbf{x}(t_s^-)}{2}, \quad \langle \mathbf{x}^2(t_s^+) \rangle - \langle \mathbf{x}(t_s^+) \rangle^2 = 0.$$

Now assume that events happen in exponentially distributed time intervals, so based on Theorem 3.1 the steady-state mean of $\mathbf{x}$ is zero if

$$(20) \quad J \langle e^{A\boldsymbol{\tau}_s} \rangle = \frac{1}{2} \langle e^{a\boldsymbol{\tau}_s} \rangle = \frac{1}{2} \frac{1}{1 - a \langle \boldsymbol{\tau}_s \rangle} < 1 \Rightarrow \langle \boldsymbol{\tau}_s \rangle < \frac{1}{2a}.$$

Further, for linear systems with exponentially distributed discrete events there exist well-established methods to derive moment dynamics [72, 34, 73]. We can write the second-order moment dynamics as

$$(21) \quad \frac{d\langle \mathbf{x}^2 \rangle}{dt} = 2a \langle \mathbf{x}^2 \rangle - \frac{3}{4 \langle \boldsymbol{\tau}_s \rangle} \langle \mathbf{x}^2 \rangle.$$

For having a zero steady-state second-order moment we need to have $\langle \boldsymbol{\tau}_s \rangle < \frac{3}{8a}$. These two different conditions mean that depending on the period of events, we can have different scenarios:

$$(22) \quad \text{Exponentially distributed } \boldsymbol{\tau}_s : \begin{cases} \langle \boldsymbol{\tau}_s \rangle < \frac{3}{8a} & \text{Zero mean and variance,} \\ \frac{3}{8a} < \langle \boldsymbol{\tau}_s \rangle < \frac{1}{2a} & \text{Zero mean, infinite variance,} \\ \frac{1}{2a} < \langle \boldsymbol{\tau}_s \rangle & \text{Infinite mean and variance.} \end{cases}$$

Hence, it is possible to have a system where the steady-state mean is almost zero but sample paths diverge with probability one (infinite variance). In order to obtain meaningful information about a system we need to study the second-order moments as well.

3.2. Second-order moments of TTSHS. In order to calculate the second-order moments, we start by deriving the dynamics of $\mathbf{x}\mathbf{x}^\top$ between two successive events,

$$(23) \quad \frac{d(\mathbf{x}\mathbf{x}^\top)}{dt} = \frac{d\mathbf{x}}{dt} \mathbf{x}^\top + \mathbf{x} \frac{d\mathbf{x}^\top}{dt} = A\mathbf{x}\mathbf{x}^\top + \mathbf{x}\mathbf{x}^\top A^\top + \hat{a}\mathbf{x}^\top + \mathbf{x}\hat{a}^\top.$$

To proceed further, we introduce a new transformation called “vectorization,” i.e., a linear transformation that converts a matrix into a column vector. For instance,

$$(24) \quad A = \begin{bmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{bmatrix} \Rightarrow \text{vec}(A) = \begin{bmatrix} a_{11} & a_{21} & a_{12} & a_{22} \end{bmatrix}^\top,$$

where $\text{vec}()$ stands for the vectorization of a matrix. By putting all the columns of the matrix $\mathbf{x}\mathbf{x}^\top$ into one vector $\text{vec}(\mathbf{x}\mathbf{x}^\top) \in \mathbb{R}^{n^2 \times 1}$, (23) can be transformed as

$$(25) \quad \frac{d\text{vec}(\mathbf{x}\mathbf{x}^\top)}{dt} = (I_n \otimes A + A \otimes I_n)\text{vec}(\mathbf{x}\mathbf{x}^\top) + (I_n \otimes \hat{a} + \hat{a} \otimes I_n)\mathbf{x},$$

where $\otimes$ denotes the Kronecker product. Note that in transforming (23) to (25) we used the fact that for three matrices M_1 , M_2 , and M_3 ,

$$(26) \quad \begin{aligned} \text{vec}(M_1 M_2 M_3) &= (M_3^\top \otimes M_1)\text{vec}(M_2) \\ \Rightarrow \begin{cases} \text{vec}(A\mathbf{x}\mathbf{x}^\top) = \text{vec}(A\mathbf{x}\mathbf{x}^\top I_n) = (I_n \otimes A)\text{vec}(\mathbf{x}\mathbf{x}^\top), \\ \text{vec}(\mathbf{x}\mathbf{x}^\top A^\top) = \text{vec}(I_n \mathbf{x}\mathbf{x}^\top A^\top) = (A \otimes I_n)\text{vec}(\mathbf{x}\mathbf{x}^\top), \\ \text{vec}(\hat{a}\mathbf{x}^\top) = \text{vec}(\hat{a}\mathbf{x}^\top I_n) = (I_n \otimes \hat{a})\mathbf{x}, \\ \text{vec}(\mathbf{x}\hat{a}^\top) = \text{vec}(I_n \mathbf{x}\hat{a}^\top) = (\hat{a} \otimes I_n)\mathbf{x} \end{cases} \end{aligned}$$

[48]. It turns out that if we define a vector $\boldsymbol{\mu} \equiv [\mathbf{x}^\top \text{vec}(\mathbf{x}\mathbf{x}^\top)^\top]^\top \in \mathbb{R}^{(n+n^2) \times 1}$, its time evolution can also be represented by a TTSHS, albeit a more complex one. More specifically,

$$(27) \quad \frac{d\boldsymbol{\mu}}{dt} = \hat{a}_\mu + A_\mu \boldsymbol{\mu},$$

between two successive events, where

$$(28) \quad A_\mu \equiv \left[\begin{array}{c|c} A & 0 \\ \hline I_n \otimes \hat{a} + \hat{a} \otimes I_n & I_n \otimes A + A \otimes I_n \end{array} \right], \hat{a}_\mu \equiv \left[\begin{array}{c} \hat{a} \\ 0 \end{array} \right].$$

Furthermore, whenever an event occurs, $\boldsymbol{\mu}$ is reset as

$$(29) \quad \boldsymbol{\mu}(t_s^-) \mapsto \boldsymbol{\mu}(t_s^+),$$

where the expected value of $\boldsymbol{\mu}(t_s^+)$ is given by (see Appendix D.1)

$$(30a) \quad \langle \boldsymbol{\mu}(t_s^+) \rangle = J_\mu \boldsymbol{\mu}(t_s^-) + \hat{r}_\mu,$$

$$(30b) \quad J_\mu \equiv \left[\begin{array}{c|c} J & 0 \\ \hline \begin{array}{c} B \otimes \hat{c} + J \otimes \hat{r} \\ + \hat{c} \otimes B + \hat{r} \otimes J \end{array} & J \otimes J + Q \otimes Q \end{array} \right], \hat{r}_\mu \equiv \left[\begin{array}{c} \hat{r} \\ \text{vec}(D + \hat{r}\hat{r}^\top) \end{array} \right].$$

In summary, we have recast the stochastic dynamic of $\boldsymbol{\mu}$ as a TTSHS (27)–(30), and a similar analysis as in Theorem 3.1 leads to the following result (see Appendix D.2).

THEOREM 3.4. *Assuming the original TTSHS given by (1)–(5) satisfies Theorem 3.1, then*

$$(31) \quad \begin{aligned} \overline{\langle \boldsymbol{\mu} \rangle} &= \left\langle e^{A_\mu \tau} \int_0^\tau e^{-A_\mu l} \hat{a}_\mu dl \right\rangle \\ &+ \langle e^{A_\mu \tau} \rangle (I_{n^2+n} - J_\mu \langle e^{A_\mu \tau_s} \rangle)^{-1} \left(J_\mu \left\langle e^{A_\mu \tau_s} \int_0^{\tau_s} e^{-A_\mu l} \hat{a}_\mu dl \right\rangle + \hat{r}_\mu \right) \end{aligned}$$

if and only if all the eigenvalues of the matrix $(J \otimes J + Q \otimes Q) \langle e^{A\tau_s} \otimes e^{A\tau_s} \rangle$ are inside the unit circle.

Theorems 3.1 and 3.4 provide sufficient conditions for the existence of the first two moments of $\mathbf{x}$.

Remark 1. If A is a symmetric Hurwitz matrix, J is a diagonal positive definite matrix, and all of its eigenvalues are inside the unit circle, then the steady-state mean of $\mathbf{x}$ exists. Moreover, if Q is diagonal, $J \otimes J + Q \otimes Q$ is positive definite, and all of its eigenvalues are inside the unit circle, then the second-order moments of $\mathbf{x}$ also exist (see Appendix E). Note that in these cases the first two moments of $\mathbf{x}$ remain bounded even though higher-order moments of $\boldsymbol{\tau}_s$ may be unbounded.

The different corollaries of Theorem 3.1 that consider special cases can also be generalized to Theorem 3.4. For instance, if A_μ is invertible, then similar to Corollary 3.2, the steady-state mean of vector $\boldsymbol{\mu}$ takes the form

$$(32) \quad \begin{aligned} \overline{\langle \boldsymbol{\mu} \rangle} &= \frac{1}{\langle \boldsymbol{\tau}_s \rangle} (I_{n^2+n} - \langle e^{A_\mu \boldsymbol{\tau}_s} \rangle) A_\mu^{-1} (I_{n^2+n} - J_\mu \langle e^{A_\mu \boldsymbol{\tau}_s} \rangle)^{-1} \\ &\quad \times (J_\mu (I_{n^2+n} - \langle e^{A_\mu \boldsymbol{\tau}_s} \rangle) A_\mu^{-1} \hat{\mathbf{a}} + \hat{\mathbf{r}}_\mu) - \frac{1}{\langle \boldsymbol{\tau}_s \rangle} (I_{n^2+n} - \langle e^{A_\mu \boldsymbol{\tau}_s} \rangle) A_\mu^{-2} \hat{\mathbf{a}}_\mu - A_\mu^{-1} \hat{\mathbf{a}}_\mu. \end{aligned}$$

Moreover, as an extension of Corollary 3.3, we show in Appendix F that when $A = 0$, $\overline{\langle \mathbf{x} \mathbf{x}^\top \rangle}$ only depends on the first three moments of $\boldsymbol{\tau}_s$.

Finally, we apply Theorem 3.4 to a subclass of TTSHS where matrix A is Hurwitz and $Q = \hat{\mathbf{r}} = 0$, $J = I_n$ in (4)–(5), which corresponds to $\langle \mathbf{x}(\mathbf{t}_s^+) \rangle = \mathbf{x}(\mathbf{t}_s^-)$ and

$$(33) \quad \langle \mathbf{x}(\mathbf{t}_s^+) \mathbf{x}^\top(\mathbf{t}_s^+) \rangle - \langle \mathbf{x}(\mathbf{t}_s^+) \rangle \langle \mathbf{x}(\mathbf{t}_s^+) \rangle^\top = B \mathbf{x}(\mathbf{t}_s^-) \hat{\mathbf{c}}^\top + \hat{\mathbf{c}} \mathbf{x}^\top(\mathbf{t}_s^-) B^\top + D.$$

Here discrete events do not affect the mean behavior of the system but function to impart noise at random times. We have previously studied these systems in the context of nanosensors, where gas molecules impinging on the sensor strike at random times and change the sensor velocity by adding a zero-mean noise term [83]. Using Corollary 3.2 and Theorem 3.4 for this subclass results in $\overline{\langle \mathbf{x} \rangle} = -A^{-1} \hat{\mathbf{a}}$ and

$$(34) \quad \begin{aligned} \text{vec}(\overline{\langle \mathbf{x} \mathbf{x}^\top \rangle}) &= -(I_n \otimes A + A \otimes I_n)^{-1} \\ &\quad \times \left(\left(\frac{1}{\langle \boldsymbol{\tau}_s \rangle} B \otimes \hat{\mathbf{c}} + \frac{1}{\langle \boldsymbol{\tau}_s \rangle} \hat{\mathbf{c}} \otimes B + I_n \otimes \hat{\mathbf{a}} + \hat{\mathbf{a}} \otimes I_n \right) \overline{\langle \mathbf{x} \rangle} + \frac{1}{\langle \boldsymbol{\tau}_s \rangle} \text{vec}(D) \right). \end{aligned}$$

As expected, the steady-state mean is independent of $\boldsymbol{\tau}_s$. Counterintuitively, the second-order moment only depends on the mean arrival times $\langle \boldsymbol{\tau}_s \rangle$, and making the timing of events more stochastic for fixed $\langle \boldsymbol{\tau}_s \rangle$ will not have any effect on the magnitude of random fluctuations in $\mathbf{x}$. We next illustrate the theory developed for TTSHS with the biological example of gene expression.

4. Quantifying noise in gene expression via TTSHS. The process of gene expression by which information encoded in DNA is used to synthesize gene products (RNA and proteins) is fundamental to life. Measurements of gene product levels inside individual cells reveal a striking heterogeneity: the level of a gene product can vary considerably among cells of the same population, in spite of the fact that cells are genetically identical and are exposed to the same extracellular environment [22, 9, 62]. Such cell-to-cell variation or expression noise critically impacts functioning of intracellular circuits [21, 61], drives seemingly identical cells to different fates [47, 1, 97, 55], and is implicated in emerging medical problems, such as HIV latency [77, 70, 63], cancer drug resistance [69], and bacterial persistence [7, 49, 42]. Thus, uncovering noise

mechanisms that lead to cell-to-cell expression variation has tremendous implications for both biology and medicine.

Considerable theoretical and experimental research over the last decade has primarily focused on characterizing stochasticity inherent in the different steps of gene expression [76, 80, 75, 11, 58, 16, 60]. Here we focus on a different mechanism: noise in the timing of the cell cycle, or time taken by a newborn cell to complete its cell cycle and divide into two daughter cells. While much work coupling gene expression with the cell cycle considers deterministic timing of division [40, 38], data across organisms point to cell-cycle times following a nonexponential distribution that is often approximated by a lognormal or gamma distribution [45, 91, 89]. We have previously studied the contribution of noisy cell-cycle times in driving stochastic variations of a stable protein, i.e., protein with no active degradation [86], or have ignored randomness in the partitioning of molecules between the two daughters at the time of division [5]. Exploiting the TTSHS framework, we present a novel unified theory of how noisy cell-cycle times combine with randomness in the molecular partitioning process to shape variations in the level of gene product with an arbitrary decay rate.

4.1. Average gene product level for random cell-cycle times. Consider a gene product synthesized at a constant rate $k_x > 0$ and degrading via first-order kinetics with rate $\gamma_x > 0$. Then, its level $\mathbf{x}(t)$ within the cell at time t evolves as

$$(35) \quad \frac{d\mathbf{x}}{dt} = k_x - \gamma_x \mathbf{x}(t).$$

Cell-division events occur at times $\mathbf{t}_s$, $s \in \{1, 2, \dots\}$ with cell-cycle times $\boldsymbol{\tau}_s \equiv \mathbf{t}_s - \mathbf{t}_{s-1}$ being iid random variables. Assuming perfect partitioning of molecules between two daughters for now, the level is exactly halved at the time of division,

$$(36) \quad \mathbf{x}(\mathbf{t}_s^+) = \frac{\mathbf{x}(\mathbf{t}_s^-)}{2} \quad \text{with probability one.}$$

In the context of the original TTSHS (1)–(5) this corresponds to $A = -\gamma_x$, $\hat{a} = k_x$, $J = 1/2$, and $\hat{r} = Q = B = \hat{c} = D = 0$.

Since $A = -\gamma_x < 0$ and $J < 1$, then as per Remark 1 the mean of $\mathbf{x}$ exists, and using Corollary 3.2

$$(37) \quad \overline{\langle \mathbf{x} \rangle} = \frac{k_x}{\gamma_x} - \frac{k_x}{2\gamma_x^2 \langle \boldsymbol{\tau}_s \rangle} \frac{1 - \langle e^{-\gamma_x \boldsymbol{\tau}_s} \rangle}{1 - \frac{1}{2} \langle e^{-\gamma_x \boldsymbol{\tau}_s} \rangle}.$$

If the gene product happens to be a protein whose half-life is much longer than the average cell-cycle time ($1/\gamma_x \gg \langle \boldsymbol{\tau}_s \rangle$), then taking the limit $\gamma_x \rightarrow 0$ in (37) yields

$$(38) \quad \overline{\langle \mathbf{x} \rangle} = \frac{k_x \langle \boldsymbol{\tau}_s \rangle (3 + CV_{\boldsymbol{\tau}_s}^2)}{2}, \quad CV_{\boldsymbol{\tau}_s}^2 \equiv \frac{\langle \boldsymbol{\tau}_s^2 \rangle - \langle \boldsymbol{\tau}_s \rangle^2}{\langle \boldsymbol{\tau}_s \rangle^2},$$

where $CV_{\boldsymbol{\tau}_s}^2$ represents the noise in cell-cycle times as quantified by its coefficient of variation squared. Note that (38) could also have been derived directly from Corollary 3.3. These results exemplify the earlier point that while in general, the average gene product level depends on the entire distribution of the cell-cycle time, in some limiting cases it is completely characterized by just the first two moments of $\boldsymbol{\tau}_s$. Moreover, in proving Corollary 3.3 we showed that

$$(39) \quad \langle \boldsymbol{\tau}^i \rangle = \frac{\langle \boldsymbol{\tau}_s^{i+1} \rangle}{(i+1) \langle \boldsymbol{\tau}_s \rangle}.$$

Hence, $\langle \tau \rangle = \frac{1}{2} \langle \tau_s \rangle (CV_{\tau_s}^2 + 1)$, and the mean of a gene product in a cell in (38) can be represented as

$$(40) \quad \overline{\langle \mathbf{x} \rangle} = k_x \langle \tau_s \rangle + k_x \langle \tau \rangle,$$

where the first term in the right-hand side shows the products inherited from the mother cell and the latter is the products synthesized in the cell.

4.2. Stochasticity in gene product levels for random cell-cycle times.

In order to calculate the second-order moments, we define a new vector $\boldsymbol{\mu} = [\mathbf{x} \ \mathbf{x}^2]^T$, whose time evolution can also be described by a TTSHS. From (27) it follows that

$$(41) \quad \frac{d\boldsymbol{\mu}}{dt} = \hat{a}_\mu + A_\mu \boldsymbol{\mu}, \quad A_\mu = \begin{bmatrix} -\gamma_x & 0 \\ 2k_x & -2\gamma_x \end{bmatrix}, \quad \hat{a}_\mu = \begin{bmatrix} k_x \\ 0 \end{bmatrix},$$

and at the time of division

$$(42) \quad \langle \boldsymbol{\mu}(t_s^+) \rangle = J_\mu \boldsymbol{\mu}(t_s^-) + \hat{r}_\mu, \quad J_\mu = \begin{bmatrix} 1/2 & 0 \\ 0 & 1/4 \end{bmatrix}, \quad \hat{r}_\mu = 0.$$

Since $A = -\gamma_x < 0$, $J = 1/2$, $Q = 0$, and $J \otimes J + Q \otimes Q = 1/4 < 1$, then $(J \otimes J + Q \otimes Q) \langle e^{A\tau_s} \otimes e^{A\tau_s} \rangle = 1/4 \langle e^{-2\gamma\tau_s} \rangle$. Hence, based on Theorem 3.4 the steady-state second-order moment of $\mathbf{x}$ exists, and (see Appendix G)

$$(43) \quad \overline{\langle \mathbf{x}^2 \rangle} = \frac{k_x^2}{\gamma_x^2} + \frac{k_x^2}{16\gamma_x^3 \langle \tau_s \rangle} \frac{-14 + 17 \langle e^{-\gamma_x \tau_s} \rangle + \langle e^{-2\gamma_x \tau_s} \rangle (2 - 5 \langle e^{-\gamma_x \tau_s} \rangle)}{(1 - \frac{1}{4} \langle e^{-2\gamma_x \tau_s} \rangle) (1 - \frac{1}{2} \langle e^{-\gamma_x \tau_s} \rangle)}.$$

Using the coefficient of variation squared to quantify the noise in $\mathbf{x}$,

$$(44) \quad CV_{\text{cell cycle}}^2 \equiv \frac{\overline{\langle \mathbf{x}^2 \rangle} - \overline{\langle \mathbf{x} \rangle}^2}{\overline{\langle \mathbf{x} \rangle}^2} \\ = \frac{-8 (1 - \frac{1}{4} \langle e^{-2\gamma_x \tau_s} \rangle) (1 - \langle e^{-\gamma_x \tau_s} \rangle)^2 + 4\gamma_x \langle \tau_s \rangle (1 - \frac{1}{4} \langle e^{-\gamma_x \tau_s} \rangle^2) (1 - \langle e^{-2\gamma_x \tau_s} \rangle)}{8 (1 - \frac{1}{4} \langle e^{-2\gamma_x \tau_s} \rangle) (-1 + \langle e^{-\gamma_x \tau_s} \rangle + 2\gamma_x \langle \tau_s \rangle (1 - \frac{1}{2} \langle e^{-\gamma_x \tau_s} \rangle))^2},$$

where $CV_{\text{cell cycle}}^2$ denotes the noise in the gene product level due to randomness in cell-cycle times. Before analyzing this formula further, we next consider another physiologically relevant noise source that arises from molecular partitioning errors.

4.3. Inclusion of randomness in the molecular partitioning process.

In reality, biomolecules in the mother cell are probabilistically partitioned between the two daughters at the time of division. For a discrete number of molecules, this process is well characterized via a binomial distribution [29, 64]. Recent work has also reported several scenarios (such as protein multimerization) that lead to higher noise than expected from simple binomial partitioning [37, 38]. Randomness in the partitioning process can be incorporated in the TTSHS framework with each division event resetting $\mathbf{x}(t_s^-) \mapsto \mathbf{x}(t_s^+)$, where

$$(45) \quad \langle \mathbf{x}(t_s^+) \rangle = \frac{\mathbf{x}(t_s^-)}{2}, \quad \langle \mathbf{x}^2(t_s^+) \rangle - \langle \mathbf{x}(t_s^+) \rangle^2 = b \mathbf{x}(t_s^-).$$

Intuitively, (45) implies that on average, each daughter inherits half the number of molecules in the mother cell, with the variance in $\mathbf{x}(t_s^+)$ scaling linearly with $\mathbf{x}(t_s^-)$. The motivation for this linear variance scaling comes from the binomial distribution and phenomenologically captures the notion that lower number of molecules $\mathbf{x}(t_s^-)$ will

lead to much higher noise in $\mathbf{x}(\mathbf{t}_s^+)$, i.e., higher coefficient of variation. The positive parameter b can be interpreted as the magnitude of stochasticity in the partitioning process.

With the above modification we have a TTSHS where $A = -\gamma_x$, $\hat{a} = k_x$, $J = 1/2$, $B = b$, $\hat{c} = 1/2$, and $\hat{r} = Q = D = 0$. While the steady-state mean of gene product level is still the same as (37), inclusion of the nontrivial noise term in (45) leads to (from Theorem 3.4)

$$(46) \quad \overline{\langle \mathbf{x}^2 \rangle} = \frac{bk_x}{2\gamma_x^2 \langle \tau_s \rangle} \frac{1 - \langle e^{-2\gamma_x \tau_s} \rangle}{1 - \frac{1}{4} \langle e^{-2\gamma_x \tau_s} \rangle} \frac{1 - \langle e^{-\gamma_x \tau_s} \rangle}{1 - \frac{1}{2} \langle e^{-\gamma_x \tau_s} \rangle} + \frac{k_x^2}{\gamma_x^2} + \frac{k_x^2}{16\gamma_x^3 \langle \tau_s \rangle} \frac{-14 + 17\langle e^{-\gamma_x \tau_s} \rangle + \langle e^{-2\gamma_x \tau_s} \rangle (2 - 5\langle e^{-\gamma_x \tau_s} \rangle)}{(1 - \frac{1}{4} \langle e^{-2\gamma_x \tau_s} \rangle) (1 - \frac{1}{2} \langle e^{-\gamma_x \tau_s} \rangle)},$$

which yields the following elegant decomposition for gene product noise levels:

$$(47) \quad \text{Total Noise} = \frac{\overline{\langle \mathbf{x}^2 \rangle} - \langle \mathbf{x} \rangle^2}{\langle \mathbf{x} \rangle} = CV_{\text{cell cycle}}^2 + CV_{\text{partitioning}}^2,$$

$$CV_{\text{partitioning}}^2 = b \frac{1 - \langle e^{-2\gamma_x \tau_s} \rangle}{1 - \frac{1}{4} \langle e^{-2\gamma_x \tau_s} \rangle} \frac{1 - \langle e^{-\gamma_x \tau_s} \rangle}{-1 + \langle e^{-\gamma_x \tau_s} \rangle + 2\gamma_x \langle \tau_s \rangle (1 - \frac{1}{2} \langle e^{-\gamma_x \tau_s} \rangle)} \frac{1}{\langle \mathbf{x} \rangle}.$$

Here $CV_{\text{cell cycle}}^2$ is the noise contribution for random cell-cycle times as determined earlier, and the new term $CV_{\text{partitioning}}^2$ quantifies the contribution from partitioning noise. Note that unlike $CV_{\text{cell cycle}}^2$, $CV_{\text{partitioning}}^2$ is inversely related to the mean $\langle \mathbf{x} \rangle$ and would become the dominating noise term at low molecular levels.

Both noise contributions $CV_{\text{cell cycle}}^2$ and $CV_{\text{partitioning}}^2$ monotonically decrease to zero with increasing degradation rate γ_x for a fixed mean $\langle \mathbf{x} \rangle$ (Figure 2). This makes intuitive sense, as rapid turnover rates allow for faster convergence to mean levels after

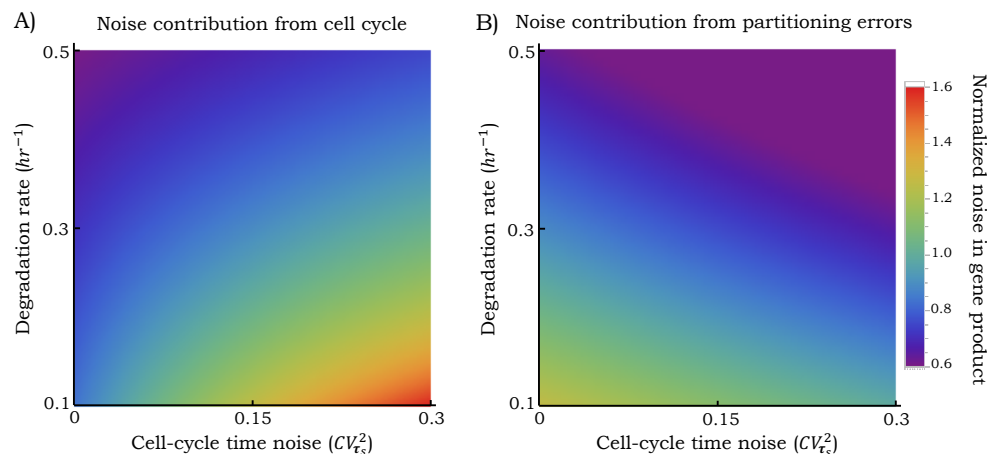


FIG. 2. The noise contributions show similar behavior with respect to decay rate, but contrasting behavior with respect to noise in cell-cycle times. A two-dimensional color plot of the two noise contributions in (47) as a function of the gene product decay rate and the noise in cell-cycle times. Increasing $CV_{\tau_s}^2$ increases the noise contribution from random cell-cycle times but decreases the contribution from random partitioning. Both noise contributions decrease monotonically with increasing decay rate. Noise levels are normalized to their value when $CV_{\tau_s}^2 = 0$ and $\gamma_x = 0.1 \text{ hr}^{-1}$. We used gamma distributed τ_s with a fixed mean cell-cycle time of $\langle \tau_s \rangle = 2 \text{ hrs}$. The mean of $\mathbf{x}$ is fixed at 100 molecules by simultaneously changing k_x .

random perturbations. In the limit of fast decay rate ($\gamma_x \rightarrow \infty$), we have $e^{-\gamma_x \tau} \rightarrow 0$ and $e^{-2\gamma_x \tau} \rightarrow 0$ for any given value of $\tau > 0$. Hence, $\langle e^{-\gamma_x \tau_s} \rangle \rightarrow 0$ and $\langle e^{-2\gamma_x \tau_s} \rangle \rightarrow 0$ for any continuous distribution of τ_s and we obtain the asymptotes

$$(48) \quad CV_{\text{cell cycle}}^2 \approx \frac{1}{8\gamma_x \langle \tau_s \rangle}, \quad CV_{\text{partitioning}}^2 \approx \frac{1}{2\gamma_x \langle \tau_s \rangle} \frac{b}{\langle x \rangle},$$

which only depend on the mean cell-cycle times and show very similar scaling that differs by a factor of $4b$ over mean. Interestingly, noise contributions show contrasting behavior to increasing noise in cell-cycle times—increasing $CV_{\tau_s}^2$ for fixed τ_s increases $CV_{\text{cell cycle}}^2$ but decreases $CV_{\text{partitioning}}^2$ (Figure 2(b)). This implies that depending on the degree of randomness in partitioning (parameter b), the total noise may decrease, increase, or remain somewhat invariant of $CV_{\tau_s}^2$ (Figure 3). Finally, taking the limit $\gamma_x \rightarrow 0$ in (47), we recover our prior result for stable gene products [86]

$$(49) \quad \text{Total noise} = \frac{1}{27} + \frac{\overbrace{4 \left(9 \frac{\langle \tau_s^3 \rangle}{\langle \tau_s \rangle^3} - 9 - 6CV_{\tau_s}^2 - 7CV_{\tau_s}^4 \right)}^{CV_{\text{cell cycle}}^2}}{27(3 + CV_{\tau_s}^2)^2} + \frac{\overbrace{16b}{CV_{\text{partitioning}}^2}}{3(3 + CV_{\tau_s}^2)} \frac{1}{\langle x \rangle},$$

explicitly showing $CV_{\text{partitioning}}^2$ to be a decreasing function of $CV_{\tau_s}^2$ and the dependence of gene product noise levels on just the first three moments of τ_s .

5. Linear timer-dependent TTSHS. While our analysis has been restricted to continuous dynamics modeled as a linear time-invariant system, we now generalize

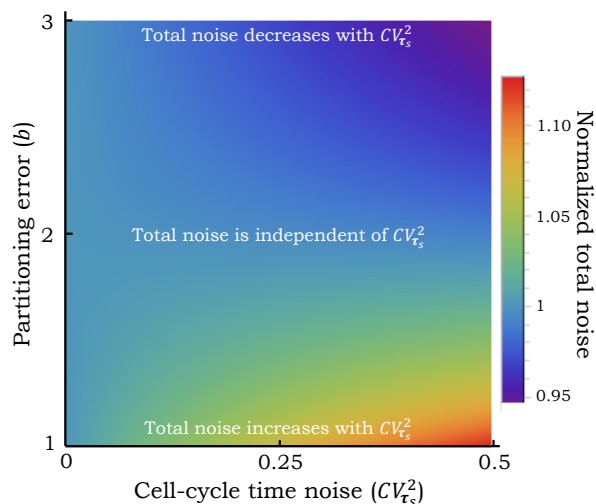


FIG. 3. Gene product noise levels can either increase or decrease with increasing noise in cell-cycle times. The total noise in (47) is plotted as a function of parameter b in the partitioning process and noise in cell-cycle times. While for small (large) values of b the noise levels increase (decrease) with increasing $CV_{\tau_s}^2$, intermediate values of b can make the total noise approximately invariant of $CV_{\tau_s}^2$. Noise levels are normalized to their value when $CV_{\tau_s}^2 = 0$, the mean of x is fixed at 20 molecules by simultaneously changing k_x , and $\gamma_x = 0.1 \text{ hr}^{-1}$. The rest of parameters are chosen equal to their value in Figure 2.

these results to time-varying systems. It is important to point out that by time varying we imply

$$(50) \quad \frac{d\mathbf{x}}{dt} = \hat{a}(\boldsymbol{\tau}) + A(\boldsymbol{\tau})\mathbf{x}(t),$$

where the vector $\hat{a}(\boldsymbol{\tau})$ and the matrix $A(\boldsymbol{\tau})$ vary arbitrarily with the timer state. This extension is particularly relevant to the gene expression example discussed previously. As a newborn cell progresses through its cell cycle, it increases in size, and the number of copies of a given gene has to double before cell division. These changes in cell size and gene dosage within the cell cycle critically influence the production rates of RNA and proteins [81, 66, 59, 52, 101, 54, 39, 78] and correspond to k_x in (35) being timer-dependent. Such a timer-dependent production rate is also needed for analyzing genes that are expressed at specific instants or durations within the cell cycle [67, 66, 8]. Thus, (50) captures expression dynamics of a wide class of genes, and looking beyond biology, it aids in the analysis of physical, ecological, and engineering systems with time-varying dynamics. In addition to (50), we also generalize the reset value $\mathbf{x}(t_s^+)$ by allowing $J(\boldsymbol{\tau})$, $\hat{r}(\boldsymbol{\tau})$ in (4), and $Q(\boldsymbol{\tau})$, $B(\boldsymbol{\tau})$, $\hat{c}(\boldsymbol{\tau})$, $D(\boldsymbol{\tau})$ in (5) to be timer dependent.

5.1. The steady-state moments of linear timer-dependent TTSHS. Suppose that the states of the system after the s th reset are given by $\mathbf{x}(t_s^+)$; then the states of the system for any $\boldsymbol{\tau}$ before the $s + 1$ th event are

$$(51) \quad \mathbf{x}(t_s + \boldsymbol{\tau}) = \Phi(\boldsymbol{\tau}, 0)\mathbf{x}(t_s^+) + \int_0^{\boldsymbol{\tau}} \Phi(\boldsymbol{\tau}, l)\hat{a}(l)dl, \quad \Phi(\boldsymbol{\tau}, l) = \Psi(\boldsymbol{\tau})\Psi^{-1}(l)$$

[90]. Here $\Psi(\boldsymbol{\tau})$ is called the fundamental matrix and satisfies the following:

$$(52) \quad \frac{d\Psi}{d\boldsymbol{\tau}} = A(\boldsymbol{\tau})\Psi(\boldsymbol{\tau}), \quad |\Psi(\boldsymbol{\tau})| \neq 0,$$

where $|\cdot|$ denotes determinant of a matrix. Building upon this introduction, the following theorem gives the steady-state mean of $\mathbf{x}$.

THEOREM 5.1. *The steady-state mean of the states of the timer-dependent TTSHS given by (50) and (3) is*

$$(53) \quad \overline{\langle \mathbf{x} \rangle} = \langle \Phi(\boldsymbol{\tau}, 0) \rangle (I_n - \langle J(\boldsymbol{\tau}_s)\Phi(\boldsymbol{\tau}_s, 0) \rangle)^{-1} \\ \times \left(\left\langle J(\boldsymbol{\tau}_s) \int_0^{\boldsymbol{\tau}_s} \Phi(\boldsymbol{\tau}_s, l)\hat{a}(l)dl \right\rangle + \langle \hat{r}(\boldsymbol{\tau}_s) \rangle \right) + \left\langle \int_0^{\boldsymbol{\tau}} \Phi(\boldsymbol{\tau}, l)\hat{a}(l)dl \right\rangle$$

if and only if $\langle \Phi(\boldsymbol{\tau}_s, 0) \rangle$ exist and all the eigenvalues of $\langle J(\boldsymbol{\tau}_s)\Phi(\boldsymbol{\tau}_s, 0) \rangle$ are inside the unit circle.

Please see Appendix H for the proof. Here we use the notation $\boldsymbol{\tau}_s$ when we take expected value with respect to $\boldsymbol{\tau}_s$ (e.g., $\langle \Phi(\boldsymbol{\tau}_s, 0) \rangle$) and we use $\boldsymbol{\tau}$ when we take expected value with respect to $\boldsymbol{\tau}$ (e.g., $\langle \Phi(\boldsymbol{\tau}, 0) \rangle$). Note that for a general $A(\boldsymbol{\tau})$, one needs to calculate Φ for obtaining mean of $\mathbf{x}$. However, except in a few cases, the closed form of Φ does not exist [90]. One of these few cases is $A(\boldsymbol{\tau}) = 0$, where Φ in (53) is simply I_n . In this case

$$(54) \quad \overline{\langle \mathbf{x} \rangle} = (I_n - \langle J(\boldsymbol{\tau}_s) \rangle)^{-1} \left(\left\langle J(\boldsymbol{\tau}_s) \int_0^{\boldsymbol{\tau}_s} \hat{a}(l)dl \right\rangle + \langle \hat{r}(\boldsymbol{\tau}_s) \rangle \right) + \left\langle \int_0^{\boldsymbol{\tau}} \hat{a}(l)dl \right\rangle.$$

This equation simplifies to (17) for time-invariant J , $\hat{r}$, and $\hat{a}$. Another limit in which the matrix Φ can be derived easily is when $A(\tau)$ and $e^{\int_0^\tau A(y)dy}$ can commute, in this case

$$(55) \quad \Phi(\tau, 0) = e^{\int_0^\tau A(y)dy}, \quad \int_0^\tau \Phi(\tau, l) \hat{a}(l) dl = e^{\int_0^\tau A(y)dy} \int_0^\tau e^{-\int_0^l A(y)dy} \hat{a}(l) dl,$$

and as a result (53) simplifies to

$$(56) \quad \begin{aligned} \overline{\langle \mathbf{x} \rangle} &= \left\langle e^{\int_0^\tau A(y)dy} \right\rangle \left(I_n - \left\langle J(\tau_s) e^{\int_0^{\tau_s} A(y)dy} \right\rangle \right)^{-1} \\ &\times \left(\left\langle J(\tau_s) e^{\int_0^{\tau_s} A(y)dy} \int_0^{\tau_s} e^{-\int_0^l A(y)dy} \hat{a}(l) dl \right\rangle + \langle \hat{r}(\tau_s) \rangle \right) \\ &+ \left\langle e^{\int_0^\tau A(y)dy} \int_0^\tau e^{-\int_0^l A(y)dy} \hat{a}(l) dl \right\rangle. \end{aligned}$$

Examples of this case include $A(\tau)$ being diagonal (dynamics of each state depends only on itself), and if $A(\tau) = Ak(\tau)$, where A is a constant matrix and $k(\tau)$ is a scalar time-varying function.

Moreover, similar to section 3.2, we can define the vector $\boldsymbol{\mu} \equiv [\mathbf{x}^\top \text{vec}(\mathbf{x}\mathbf{x}^\top)^\top]^\top$, where its dynamics between the events is given by

$$(57) \quad \frac{d\boldsymbol{\mu}}{dt} = \hat{a}_\mu(\tau) + A_\mu(\tau)\boldsymbol{\mu}.$$

Here $\hat{a}_\mu(\tau)$ and $A_\mu(\tau)$ are similar to (28) for time-varying $\hat{a}(\tau)$ and $A(\tau)$. This system is in the form of (50) and hence its solution between the events is similar to (51) for appropriate Φ_μ . Further, during an event, the states of vector $\boldsymbol{\mu}$ change as (29), where the mean of $\boldsymbol{\mu}(t_s^+)$ is related to $\boldsymbol{\mu}(t_s^-)$ as

$$(58) \quad \langle \boldsymbol{\mu}(t_s^+) \rangle = J_\mu(\tau) \boldsymbol{\mu}(t_s^-) + \hat{r}_\mu(\tau).$$

In this equation $J_\mu(\tau)$ and $\hat{r}_\mu(\tau)$ are time-varying counterparts of J_μ and $\hat{r}_\mu$ in (30).

Given this reformulation, similar to Theorem 3.4, we can derive the second-order moments of $\mathbf{x}$ through the vector $\boldsymbol{\mu}$. The steady-state mean of $\boldsymbol{\mu}$ is

$$(59) \quad \begin{aligned} \overline{\langle \boldsymbol{\mu} \rangle} &= \langle \Phi_\mu(\tau, 0) \rangle (I_n - \langle J_\mu(\tau_s) \Phi_\mu(\tau_s, 0) \rangle)^{-1} \\ &\times \left(\left\langle J_\mu(\tau_s) \int_0^{\tau_s} \Phi_\mu(\tau_s, l) \hat{a}_\mu(l) dl \right\rangle + \langle \hat{r}_\mu(\tau_s) \rangle \right) + \left\langle \int_0^\tau \Phi_\mu(\tau, l) \hat{a}_\mu(l) dl \right\rangle \end{aligned}$$

if and only if all the eigenvalues of the matrix $\langle (J(\tau_s) \otimes J(\tau_s) + Q(\tau_s) \otimes Q(\tau_s)) (\Phi(\tau_s, 0) \otimes \Phi(\tau_s, 0)) \rangle$ are inside the unit circle. Furthermore, it is straightforward to see that (55) can be extended to vector $\boldsymbol{\mu}$, i.e., if $A_\mu(\tau)$ and $e^{\int_0^\tau A_\mu(y)dy}$ can commute, then

$$(60) \quad \Phi_\mu(\tau, 0) = e^{\int_0^\tau A_\mu(y)dy}, \quad \int_0^\tau \Phi_\mu(\tau, l) \hat{a}_\mu(l) dl = e^{\int_0^\tau A_\mu(y)dy} \int_0^\tau e^{-\int_0^l A_\mu(y)dy} \hat{a}_\mu(l) dl.$$

Finally, Remark 1 also can be generalized to the timer-dependent case if (1) $A(\tau)$ is a symmetric negative definite matrix for all the values of τ , and (2) the matrices $J(\tau)$ and $J(\tau) \otimes J(\tau) + Q(\tau) \otimes Q(\tau)$ are diagonal positive definite and all of their eigenvalues are inside the unit circle. Then the first- and second-order moments of $\mathbf{x}$ exist irrespective of distribution of τ_s . In the next part, we use our results to study the time-varying synthesis rate.

5.2. Timer-dependent gene expression dynamics. Revisiting the gene expression example, (35) is now modified as

$$(61) \quad \frac{d\mathbf{x}}{dt} = k_x(\boldsymbol{\tau}) - \gamma_x \mathbf{x}(t),$$

where $k_x(\boldsymbol{\tau})$ represents a generalized timer-dependent production rate. Assuming the same structure of resets as in (45), Theorem 5.1 yields

$$(62) \quad \overline{\langle \mathbf{x} \rangle} = \frac{\langle e^{-\gamma_x \boldsymbol{\tau}_s} \rangle}{\gamma_x \langle \boldsymbol{\tau}_s \rangle} \frac{1 - \langle e^{-\gamma_x \boldsymbol{\tau}_s} \rangle}{2 - \langle e^{-\gamma_x \boldsymbol{\tau}_s} \rangle} \left\langle \int_0^{\boldsymbol{\tau}_s} e^{\gamma_x l} k_x(l) dl \right\rangle + \left\langle e^{-\gamma_x \boldsymbol{\tau}} \int_0^{\boldsymbol{\tau}} e^{\gamma_x l} k_x(l) dl \right\rangle.$$

In the limit of constant synthesis rate $k_x(\boldsymbol{\tau}) = k_x$

$$(63a) \quad \left\langle \int_0^{\boldsymbol{\tau}_s} e^{\gamma_x l} k_x(l) dl \right\rangle = k_x \left\langle \int_0^{\boldsymbol{\tau}_s} e^{\gamma_x l} dl \right\rangle = \frac{k_x}{\gamma_x} \langle e^{\gamma_x \boldsymbol{\tau}_s} \rangle,$$

$$(63b) \quad \left\langle e^{-\gamma_x \boldsymbol{\tau}} \int_0^{\boldsymbol{\tau}} e^{\gamma_x l} k_x(l) dl \right\rangle = k_x \left\langle e^{-\gamma_x \boldsymbol{\tau}} \int_0^{\boldsymbol{\tau}} e^{\gamma_x l} dl \right\rangle = \frac{k_x}{\gamma_x}.$$

By putting (63) back in (62), the mean of $\mathbf{x}$ simplifies to (65) for constant synthesis rate. Moreover, by taking the limit $\gamma_x \rightarrow 0$ in (62), we obtain the mean of stable gene products

$$(64) \quad \overline{\langle \mathbf{x} \rangle} = \left\langle \int_0^{\boldsymbol{\tau}_s} k_x(l) dl \right\rangle + \left\langle \int_0^{\boldsymbol{\tau}} k_x(l) dl \right\rangle.$$

Interestingly, from (64) it follows that for a given constant mean level of $\mathbf{x}$, high values of $k_x(\boldsymbol{\tau})$ when $\boldsymbol{\tau}$ is small (beginning of cell cycle) result in lower $\langle k_x(\boldsymbol{\tau}) \rangle$. This means that production at the beginning of the cell cycle needs fewer production events and fewer resources to keep a given mean of $\mathbf{x}$. Finally, suppose that $k_x(\boldsymbol{\tau}) = k_x$; then

$$(65) \quad \overline{\langle \mathbf{x} \rangle} = \left\langle \int_0^{\boldsymbol{\tau}_s} k_x(l) dl \right\rangle + \left\langle \int_0^{\boldsymbol{\tau}} k_x(l) dl \right\rangle = k_x (\langle \boldsymbol{\tau}_s \rangle + \langle \boldsymbol{\tau} \rangle),$$

which is equal to (40).

For a general $k_x(\boldsymbol{\tau})$ providing the analytic formulas for noise of an unstable gene product is convoluted. On the other hand, for a stable product ($\gamma_x \approx 0$) the noise contribution from cell-cycle time variations and partitioning errors is

$$(66a) \quad CV_{\text{cell cycle}}^2 = \frac{2 \langle \int_0^{\boldsymbol{\tau}_s} (k_x(\tau) \int_0^{\tau} k_x(l) dl) d\tau \rangle - \langle \int_0^{\boldsymbol{\tau}_s} k_x(l) dl \rangle^2}{3 (\langle \int_0^{\boldsymbol{\tau}_s} k_x(l) dl \rangle + \langle \int_0^{\boldsymbol{\tau}} k_x(l) dl \rangle)^2} + \frac{2 \langle \int_0^{\boldsymbol{\tau}} (k_x(\tau) \int_0^{\tau} k_x(l) dl) d\tau \rangle - \langle \int_0^{\boldsymbol{\tau}} k_x(l) dl \rangle^2}{(\langle \int_0^{\boldsymbol{\tau}_s} k_x(l) dl \rangle + \langle \int_0^{\boldsymbol{\tau}} k_x(l) dl \rangle)^2},$$

$$(66b) \quad CV_{\text{partitioning}}^2 = \frac{8b}{3} \frac{\langle \int_0^{\boldsymbol{\tau}_s} k_x(l) dl \rangle}{\langle \int_0^{\boldsymbol{\tau}_s} k_x(l) dl \rangle + \langle \int_0^{\boldsymbol{\tau}} k_x(l) dl \rangle} \frac{1}{\overline{\langle \mathbf{x} \rangle}}.$$

These results simplify to (49) for a constant synthesis rate.

As an example, we study protein count and noise in a mammalian cell. The volume of mammalian cells is highly variable within a population [92, 10]. However, a key necessity for maintaining cellular functions is to keep concentration of different proteins constant. This means that the number of proteins should scale with the volume of a cell [50, 100, 51]. To cover this case, consistent with measurements, we assume that the synthesis rate scales with the cell volume which is an exponential function

of the cell cycle [93]. Thus, we assume that synthesis rate $k_x(\tau)$ is exponentially increasing throughout the cell cycle and eventually doubles at the end of cell cycle [95]; the synthesis rate is

$$(67) \quad k_x(\tau) = k_x e^{\frac{\ln(2)\tau}{\langle\tau_s\rangle}},$$

where k_x is a nonnegative constant. Since a large number of proteins in mammalian cells are stable [68], we do not need to consider the degradation of $\mathbf{x}$. Hence we can replace (67) in (64) to derive the mean

$$(68) \quad \overline{\langle\mathbf{x}\rangle} = \frac{k_x \langle\tau_s\rangle \left((1 + \ln(2)) \left\langle 2^{\frac{\tau_s}{\langle\tau_s\rangle}} \right\rangle - 1 - 2\ln(2) \right)}{\ln^2(2)}, \quad \left\langle 2^{\frac{\tau_s}{\langle\tau_s\rangle}} \right\rangle = \int_0^\infty f(\tau) 2^{\frac{\tau}{\langle\tau_s\rangle}} d\tau.$$

While for a constant synthesis rate, the mean of a stable gene product just depends on the mean and noise of cell-cycle times, for an exponentially increasing production rate the mean of $\mathbf{x}$ depends on the entire distribution of cell-cycle times.

In the next step, we calculate the noise contribution from cell-cycle time variations and partitioning errors by replacing (67) in (66),

$$(69a) \quad CV_{\text{cell cycle}}^2 = \frac{\ln(2) \left(\left\langle 4^{\frac{\tau_s}{\langle\tau_s\rangle}} \right\rangle - 1 \right) - 2 \left(\left\langle 2^{\frac{\tau_s}{\langle\tau_s\rangle}} \right\rangle - 1 \right)^2}{2 \left((1 + \ln(2)) \left\langle 2^{\frac{\tau_s}{\langle\tau_s\rangle}} \right\rangle - 1 - 2\ln(2) \right)^2},$$

$$(69b) \quad CV_{\text{partitioning}}^2 = \frac{8b \ln(2) \left(\left\langle 2^{\frac{\tau_s}{\langle\tau_s\rangle}} \right\rangle - 1 \right)}{3 \left((1 + \ln(2)) \left\langle 2^{\frac{\tau_s}{\langle\tau_s\rangle}} \right\rangle - 1 - 2\ln(2) \right)} \frac{1}{\overline{\langle\mathbf{x}\rangle}}.$$

Our analysis shows that these noise terms are more affected by statistical characteristics of cell-cycle time than the case of constant synthesis rate (Figure 4). This

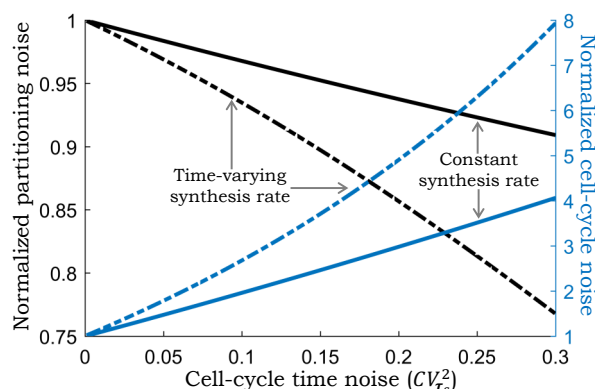


FIG. 4. The noise in a gene product is more sensitive to cell-cycle time variations when the synthesis rate is not constant. For a time-varying synthesis rate, the noise contribution from partitioning errors and cell-cycle time is affected more by $CV_{\tau_s}^2$ when $k_x(\tau)$ is timer-dependent. Noise levels are normalized to their value when $CV_{\tau_s}^2 = 0$. The mean cell-cycle time is $\tau_s = 20$ min (fast growing bacteria) and the rest of parameters are chosen equal to their value in Figure 2.

means that keeping concentration constant will make cells more vulnerable to cell-cycle noise. However, in the limit of large b , a cell can exploit this dependency to reduce the contribution of noisy cell-cycle times (Figure 4). Moreover, in the limit of deterministic cell-cycle times, noise values in (69) are slightly higher than those of constant synthesis rate in (49). This implies that keeping the concentration constant also may come with the price of having higher noise levels in the count level.

In addition to mammalian cells, measurements show that in fast growing bacteria the synthesis rate is continuously increasing [95]. In these cells multiple gene replication occurs throughout the cell cycle and the amount of other components required for expression (e.g., RNA polymerases and ribosomes) is limited. Hence, maybe considering a linearly increasing instead of exponentially increasing synthesis rate is more physiological. Our analysis reveals that in this case the noise behavior is similar to Figure 4 qualitatively.

Finally, our analytical results provide a unique method for inferring partitioning noise in a gene product. Current experiments are able to quantify distribution of cell-cycle time [96]. By measuring noise in a gene product we can use (69a) to calculate the contribution of cell-cycle time variations to total noise. The subtraction of total noise from (69a) provides the noise contribution from partitioning and hence it can be used to infer the partitioning scenario of a specific protein (parameter b).

6. Conclusion. Moment analysis of stochastic hybrid systems often relies on deriving a set of differential equations for the time evolution of moments [34, 73]. For linear stochastic systems, moments can be obtained exactly by solving these sets of differential equations. However, nonlinearities within stochastic hybrid systems, such as the hazard rate (6), lead to unclosed dynamics in the sense that time evolution of lower-order moments depends on higher-order moments. In such cases, moment computations are performed by employing either approximate closure schemes [53, 98, 44, 43, 79, 31, 74, 87, 27, 20] or constraints imposed by positive semidefiniteness of moment matrices [28, 46].

Instead of relying on moment dynamics, here we used an alternative approach to derive exact analytical expressions for the first two steady-state moments of TTSHS. Our main results (Theorems 3.1, 3.4, and 5.1) connect these moments to the system dynamics and the distribution of event arrival times. While knowledge of the entire distribution of τ_s is generally needed to compute the moments, if $A = 0$, then the mean of $\mathbf{x}$ just depends on the first two moments of τ_s , and the second-order moments of $\mathbf{x}$ depend on the first three moments of τ_s (Corollary 3.3 and Appendix F). Interestingly, if A is Hurwitz, and the resets only add a zero-mean noise term that can be state-dependent, then the extent of random fluctuations in $\mathbf{x}$ is affected only by the average frequency of events $1/\langle\tau_s\rangle$ (equation (34)). Analogous results were derived for time-varying TTSHS where $\hat{a}$ and A vary with the timer between events. Finally, applying the theory of TTSHS to the biological example of gene expression resulted in novel formulas for the mean and variance at the level of a gene product and how these levels are impacted by stochasticity in cell-cycle times and the molecular partitioning process.

Recent works has provided stability results for multimode TTSHS (systems that allow for stochastic switching between systems) when the states of the system do not change after resets [56, 57]. Future works will extend our method to consider multimode TTSHS where values of the states after each reset are random. Further, recent work has shown that for some nonlinear stochastic systems moment dynamics become automatically closed at some higher-order moments, and hence moments can

be computed exactly in spite of unclosed moment dynamics of lower-order moments [88]. It will be interesting to explore classes of TTSHS with nonlinear continuous dynamics, or state-dependent event arrival rates for which moments can be computed exactly.

Appendix A. Proof of Theorem 3.1. Using (1), the states of TTSHS right before the s th event $\mathbf{x}(t_s^-)$ are related to the states of TTSHS right after the $s-1$ th event $\mathbf{x}(t_{s-1}^+)$ as

$$(70) \quad \mathbf{x}(t_s^-) = e^{A\tau_s} \int_0^{\tau_s} e^{-Al} \hat{a} dl + e^{A\tau_s} \mathbf{x}(t_{s-1}^+).$$

Thus, by using (4), the mean of the states after the s th event is

$$(71) \quad \langle \mathbf{x}(t_s^+) \rangle = J \left\langle e^{A\tau_s} \int_0^{\tau_s} e^{-Al} \hat{a} dl \right\rangle + J \langle e^{A\tau_s} \rangle \langle \mathbf{x}(t_{s-1}^+) \rangle + \hat{r}.$$

Note that in order to obtain (71) we took expectation with respect to τ_s and hence similar to (4) the right-hand side of the above equation is deterministic. In order to have a finite $\langle \mathbf{x}(t_s^+) \rangle$ in (71), $\langle e^{A\tau_s} \int_0^{\tau_s} e^{-Al} \hat{a} dl \rangle$ and $\langle e^{A\tau_s} \rangle$ should be finite. If these matrices are not finite, then concluding (71) from (70) is not possible because the expected values can be indeterminate. This proves the only-if part of Theorem 3.1. In the following, we show that $\langle e^{A\tau_s} \rangle$ being finite means that $\langle e^{A\tau_s} \int_0^{\tau_s} e^{-Al} \hat{a} dl \rangle$ is also finite.

The fact that a matrix exponential $e^{A\tau}$ can be written as

$$(72) \quad e^{A\tau} = \sum_{i=0}^{\infty} A^i \frac{\tau^i}{i!}$$

means that A and $e^{A\tau}$ can commute. Thus

$$(73) \quad \begin{aligned} A \left\langle e^{A\tau_s} \int_0^{\tau_s} e^{-Al} \hat{a} dl \right\rangle &= A \int_0^{\infty} f(\tau) e^{A\tau} \int_0^{\tau} e^{-Al} \hat{a} dl d\tau \\ &= \int_0^{\infty} f(\tau) e^{A\tau} \int_0^{\tau} e^{-Al} A \hat{a} dl d\tau \\ &= \int_0^{\infty} f(\tau) e^{A\tau} (I_n - e^{-A\tau}) \hat{a} d\tau \\ &= -(I_n - \langle e^{A\tau_s} \rangle) \hat{a}, \end{aligned}$$

and existence of $\langle e^{A\tau_s} \rangle$ means that all the terms in (71) are finite so $\langle \mathbf{x}(t_s^+) \rangle$ is finite if and only if $\langle e^{A\tau_s} \rangle$ is finite.

Moreover, from (71) the mean of the states right after an event in steady-state ($s \rightarrow \infty$) exists if and only if eigenvalues of $J \langle e^{A\tau_s} \rangle$ are inside the unit circle. In this limit the steady-state mean of the states ($s \rightarrow \infty$) right after an event can be written as

$$(74) \quad \lim_{s \rightarrow \infty} \langle \mathbf{x}(t_s^+) \rangle = (I_n - J \langle e^{A\tau_s} \rangle)^{-1} \left(J \left\langle e^{A\tau_s} \int_0^{\tau_s} e^{-Al} \hat{a} dl \right\rangle + \hat{r} \right).$$

By using (1) and (74), the steady-state mean of the states between events for any values of τ is

$$(75) \quad \begin{aligned} \lim_{s \rightarrow \infty} \langle \mathbf{x}(t_s + \tau) \rangle &= e^{A\tau} (I_n - J \langle e^{A\tau_s} \rangle)^{-1} \left(J \left\langle e^{A\tau_s} \int_0^{\tau_s} e^{-Al} \hat{a} dl \right\rangle + \hat{r} \right) \\ &\quad + e^{A\tau} \int_0^{\tau} e^{-Al} \hat{a} dl. \end{aligned}$$

The mean of the states can be obtained by taking the expected value of $\langle \mathbf{x}(t_s + \boldsymbol{\tau}) \rangle$ in (75) with respect to all the values of $\boldsymbol{\tau}$ by using (8). However, to have a finite $\langle \mathbf{x} \rangle$ we need to show that $\langle e^{A\boldsymbol{\tau}} \rangle$ and $\langle e^{A\boldsymbol{\tau}} \int_0^{\boldsymbol{\tau}} e^{-Al} \hat{a} dl \rangle$ are also finite.

In the following we show that when all the elements of $\langle e^{A\boldsymbol{\tau}_s} \rangle$ are bounded then $\langle e^{A\boldsymbol{\tau}} \rangle$ exists and is finite. To do so we first expand $\langle e^{A\boldsymbol{\tau}_s} \rangle$,

$$(76) \quad \langle e^{A\boldsymbol{\tau}_s} \rangle = \int_0^\infty h(\tau) e^{-\int_0^\tau h(y) dy} e^{A\tau} d\tau.$$

Then we aim to apply the integral by parts,

$$(77) \quad \int_0^\infty u dv = (uv)_0^\infty - \int_0^\infty v du,$$

by assuming that $u = e^{A\tau}$ and $dv = h(\tau) e^{-\int_0^\tau h(y) dy}$. Note that

$$(78) \quad \frac{d}{d\tau} e^{-\int_0^\tau h(y) dy} = -h(\tau) e^{-\int_0^\tau h(y) dy},$$

hence

$$(79) \quad \int_0^\infty h(\tau) e^{-\int_0^\tau h(y) dy} e^{A\tau} d\tau = \left(-e^{-\int_0^\tau h(y) dy} e^{A\tau} \right)_0^\infty + \int_0^\infty e^{-\int_0^\tau h(y) dy} e^{A\tau} A d\tau.$$

Finally

$$(80) \quad \langle e^{A\boldsymbol{\tau}_s} \rangle = \left(-e^{-\int_0^\tau h(y) dy} e^{A\tau} \right)_0^\infty + \int_0^\infty e^{-\int_0^\tau h(y) dy} e^{A\tau} A d\tau = I_n + \langle \boldsymbol{\tau}_s \rangle \langle e^{A\boldsymbol{\tau}} \rangle A,$$

where we used the fact that $\lim_{\tau \rightarrow \infty} e^{-\int_0^\tau h(y) dy} e^{A\tau} = 0$. For the sake of simplicity of mathematical notation we proof this for the scalar case of $A = a$. From (8) it follows that

$$(81) \quad \int_0^\infty p(\tau) d\tau = 1 \Rightarrow \int_0^\infty e^{-\int_0^\tau h(y) dy} d\tau = \langle \boldsymbol{\tau}_s \rangle < \infty \Rightarrow \lim_{\tau \rightarrow \infty} e^{-\int_0^\tau h(y) dy} = 0.$$

In the following, assume that $\lim_{\tau \rightarrow \infty} e^{a\tau}$ is infinite, hence

$$(82) \quad \lim_{\tau \rightarrow \infty} e^{-\int_0^\tau h(y) dy} e^{a\tau} = 0 \times \infty.$$

We use l'Hôpital's rule

$$(83) \quad \lim_{\tau \rightarrow \infty} e^{-\int_0^\tau h(y) dy} e^{a\tau} = -\frac{1}{a} \lim_{\tau \rightarrow \infty} h(\tau) e^{-\int_0^\tau h(y) dy} e^{a\tau}.$$

Note that we assumed a moment generating function exists, hence

$$(84) \quad \langle e^{a\boldsymbol{\tau}_s} \rangle < \infty \Rightarrow \lim_{\tau \rightarrow \infty} h(\tau) e^{-\int_0^\tau h(y) dy} e^{a\tau} = 0.$$

Moreover, similar to (73) we have

$$(85) \quad A \left\langle e^{A\boldsymbol{\tau}} \int_0^{\boldsymbol{\tau}} e^{-Al} \hat{a} dl \right\rangle = -(I_n - \langle e^{A\boldsymbol{\tau}} \rangle) \hat{a}.$$

Hence, existence of $\langle e^{A\tau_s} \rangle$ means that all the matrices in (12) exist and this completes our proof. On a final note, we consider the random initial condition for all the systems presented in this paper.

Appendix B. Proof of Corollary 3.2. Taking integral by parts, $\langle e^{A\tau} \rangle$ can be written as

$$(86) \quad \begin{aligned} \langle e^{A\tau} \rangle &= \frac{1}{\langle \tau_s \rangle} \int_0^\infty e^{-\int_0^\tau h(y)dy} e^{A\tau} d\tau = \frac{1}{\langle \tau_s \rangle} \left(e^{-\int_0^\tau h(y)dy} e^{A\tau} A^{-1} \right)_0^\infty \\ &\quad + \frac{1}{\langle \tau_s \rangle} \int_0^\infty h(\tau) e^{-\int_0^\tau h(y)dy} e^{A\tau} A^{-1} d\tau = \frac{-1}{\langle \tau_s \rangle} (I_n - \langle e^{A\tau_s} \rangle) A^{-1}. \end{aligned}$$

Moreover

$$(87) \quad \left\langle e^{A\tau_s} \int_0^{\tau_s} e^{-Al} \hat{a} dl \right\rangle = \langle e^{A\tau_s} (I_n - e^{-A\tau_s}) A^{-1} \hat{a} \rangle = -(I_n - \langle e^{A\tau_s} \rangle) A^{-1} \hat{a}.$$

Finally, the last integral in (12) can be written as

$$(88) \quad \begin{aligned} \int_0^\infty e^{-\int_0^\tau h(y)dy} e^{A\tau} \int_0^\tau e^{-As} \hat{a} dl d\tau &= \int_0^\infty e^{-\int_0^\tau h(y)dy} e^{A\tau} (I_n - e^{-A\tau}) A^{-1} \hat{a} d\tau \\ &= -(I_n - \langle e^{A\tau_s} \rangle) A^{-2} \hat{a} - \langle \tau_s \rangle A^{-1} \hat{a}. \end{aligned}$$

Appendix C. Proof of Corollary 3.3. When $A = 0$ we have the following:

$$(89) \quad e^{A\tau} = I_n, \quad e^{A\tau} \int_0^\tau e^{-Al} \hat{a} dl = \tau \hat{a}.$$

Further

$$(90) \quad \frac{1}{\langle \tau_s \rangle} \left(\int_0^\infty e^{-\int_0^\tau h(y)dy} d\tau \right) = \int_0^\infty p(\tau) d\tau = 1.$$

Hence (12) simplifies to

$$(91) \quad \overline{\langle \mathbf{x} \rangle} = J(I_n - J)^{-1} \langle \tau_s \rangle \hat{a} + (I_n - J)^{-1} \hat{r} + \frac{1}{\langle \tau_s \rangle} \int_0^\infty \tau e^{-\int_0^\tau h(y)dy} d\tau \hat{a}.$$

Moreover, from (6) we can calculate the second-order moment $\langle \tau_s^{i+1} \rangle$ as

$$(92) \quad \langle \tau_s^{i+1} \rangle = \int_0^\infty \tau^{i+1} h(\tau) e^{-\int_0^\tau h(y)dy} d\tau,$$

in which integrating by parts results in

$$(93) \quad \langle \tau_s^{i+1} \rangle = (i+1) \int_0^\infty \tau^i e^{-\int_0^\tau h(y)dy} d\tau.$$

Hence from (8) we have

$$(94) \quad \langle \tau^i \rangle = \frac{1}{\langle \tau_s \rangle} \int_0^\infty \tau^i e^{-\int_0^\tau h(y)dy} d\tau = \frac{\langle \tau_s^{i+1} \rangle}{(i+1) \langle \tau_s \rangle},$$

and by picking $i = 1$, (91) simplifies to (17).

Appendix D. Proof of Theorem 3.4.

D.1. Statistical moments of μ after an event. Based on (5)

$$(95) \quad \begin{aligned} \langle \mathbf{x}(t_s^+) \mathbf{x}^\top(t_s^+) \rangle &= \langle \mathbf{x}(t_s^+) \rangle \langle \mathbf{x}(t_s^+) \rangle^\top + Q \mathbf{x}(t_s^-) \mathbf{x}^\top(t_s^-) Q^\top \\ &\quad + B \mathbf{x}(t_s^-) \hat{\mathbf{c}}^\top + \hat{\mathbf{c}} \mathbf{x}^\top(t_s^-) B^\top + D. \end{aligned}$$

Further from (4), $\langle \mathbf{x}(t_s^+) \rangle \langle \mathbf{x}(t_s^+) \rangle^\top$ can be written as

$$(96) \quad \begin{aligned} \langle \mathbf{x}(t_s^+) \rangle \langle \mathbf{x}(t_s^+) \rangle^\top &= J \mathbf{x}(t_s^-) \mathbf{x}^\top(t_s^-) J^\top \\ &\quad + J \mathbf{x}(t_s^-) \hat{\mathbf{r}}^\top + \hat{\mathbf{r}} \mathbf{x}^\top(t_s^-) J^\top + \hat{\mathbf{r}} \hat{\mathbf{r}}^\top. \end{aligned}$$

Combining these two equations and using (26) results in (30).

D.2. Necessary and sufficient condition on existence of μ . Let us define

$$(97) \quad \mathbf{u} \equiv e^{A\tau_s} \int_0^{\tau_s} e^{-Al} \hat{\mathbf{a}} dl.$$

Using (70), the $\mathbf{x} \mathbf{x}^\top$ right before the s th event ($\mathbf{x}(t_s^-) \mathbf{x}^\top(t_s^-)$) is related to $\mathbf{x}(t_{s-1}^+)$ as

$$(98) \quad \begin{aligned} \mathbf{x}(t_s^-) \mathbf{x}^\top(t_s^-) &= \mathbf{u} \mathbf{u}^\top + \mathbf{u} (e^{A\tau_s} \mathbf{x}(t_{s-1}^+))^\top + (e^{A\tau_s} \mathbf{x}(t_{s-1}^+)) \mathbf{u}^\top \\ &\quad + (e^{A\tau_s} \mathbf{x}(t_{s-1}^+)) (e^{A\tau_s} \mathbf{x}(t_{s-1}^+))^\top. \end{aligned}$$

Thus the mean of the second-order moment of the states after the s th event is

$$(99) \quad \begin{aligned} \langle \mathbf{x}(t_s^+) \mathbf{x}^\top(t_s^+) \rangle &= Q \langle \mathbf{u} \mathbf{u}^\top \rangle Q^\top + J \langle \mathbf{u} \mathbf{u}^\top \rangle J^\top \\ &\quad + Q \left(\left\langle \mathbf{u} \mathbf{x}(t_{s-1}^+)^\top e^{A^\top \tau_s} \right\rangle + \left\langle \mathbf{u} \mathbf{x}(t_{s-1}^+)^\top e^{A^\top \tau_s} \right\rangle^\top \right) Q^\top \\ &\quad + J \left(\left\langle \mathbf{u} \mathbf{x}(t_{s-1}^+)^\top e^{A^\top \tau_s} \right\rangle + \left\langle \mathbf{u} \mathbf{x}(t_{s-1}^+)^\top e^{A^\top \tau_s} \right\rangle^\top \right) J^\top \\ &\quad + Q \left\langle e^{A\tau_s} \mathbf{x}(t_{s-1}^+) \mathbf{x}^\top(t_{s-1}^+) e^{A^\top \tau_s} \right\rangle Q^\top \\ &\quad + J \left\langle e^{A\tau_s} \mathbf{x}(t_{s-1}^+) \mathbf{x}^\top(t_{s-1}^+) e^{A^\top \tau_s} \right\rangle J^\top + B \langle \mathbf{u} \rangle \hat{\mathbf{c}}^\top \\ &\quad + B \langle e^{A\tau_s} \mathbf{x}(t_{s-1}^+) \rangle \hat{\mathbf{c}}^\top + J \langle \mathbf{u} \rangle \hat{\mathbf{r}}^\top + J \langle e^{A\tau_s} \mathbf{x}(t_{s-1}^+) \rangle \hat{\mathbf{r}}^\top \\ &\quad + \hat{\mathbf{c}} \langle \mathbf{u}^\top \rangle B^\top + \hat{\mathbf{c}} \langle \mathbf{x}^\top(t_{s-1}^+) e^{A^\top \tau_s} \rangle B^\top \\ &\quad + \hat{\mathbf{r}} \langle \mathbf{u}^\top \rangle J^\top + \hat{\mathbf{r}} \langle \mathbf{x}^\top(t_{s-1}^+) e^{A^\top \tau_s} \rangle J^\top + D + \hat{\mathbf{r}} \hat{\mathbf{r}}^\top. \end{aligned}$$

By using vectorization, we have

$$(100) \quad \begin{aligned} \text{vec}(\langle \mathbf{x}(t_s^+) \mathbf{x}^\top(t_s^+) \rangle) &= (J \otimes J + Q \otimes Q) \langle e^{A\tau_s} \otimes e^{A\tau_s} \rangle \text{vec}(\langle \mathbf{x}(t_{s-1}^+) \mathbf{x}^\top(t_{s-1}^+) \rangle) \\ &\quad + (J \otimes J + Q \otimes Q) (\langle e^{A\tau_s} \otimes \mathbf{u} \rangle + \langle \mathbf{u} \otimes e^{A\tau_s} \rangle) \langle \mathbf{x}(t_{s-1}^+) \rangle \\ &\quad + ((B \otimes \hat{\mathbf{c}} + J \otimes \hat{\mathbf{r}}) \langle I_n \otimes e^{A\tau_s} \rangle + (\hat{\mathbf{c}} \otimes B + \hat{\mathbf{r}} \otimes J) \langle e^{A\tau_s} \otimes I_n \rangle) \langle \mathbf{x}(t_{s-1}^+) \rangle \\ &\quad + \text{vec}(Q \langle \mathbf{u} \mathbf{u}^\top \rangle Q^\top + J \langle \mathbf{u} \mathbf{u}^\top \rangle J^\top + B \langle \mathbf{u} \rangle \hat{\mathbf{c}}^\top + J \langle \mathbf{u} \rangle \hat{\mathbf{r}}^\top \\ &\quad + \hat{\mathbf{c}} \langle \mathbf{u}^\top \rangle B^\top + \hat{\mathbf{r}} \langle \mathbf{u}^\top \rangle J^\top + D + \hat{\mathbf{r}} \hat{\mathbf{r}}^\top). \end{aligned}$$

Hence, the steady-state moments of vector μ right after an event exists if and only if all the eigenvalues of $(J \otimes J + Q \otimes Q)\langle e^{A\tau_s} \otimes e^{A\tau_s} \rangle$ are inside the unit circle. The rest of the proof is similar to Appendix A.

Appendix E. Proof of Remark 1. Based on Corollary 11 of [99], for a negative definite symmetric matrix M_1 and a positive semidefinite matrix M_2 we have

$$(101) \quad \lambda_{\min}(M_1 M_2) \geq \lambda_{\min}(M_1) \lambda_{\max}(M_2),$$

where $\lambda_{\min}$ and $\lambda_{\max}$ denote the smallest and the largest eigenvalue of a matrix, respectively. Based on the fact that the exponential of a symmetric matrix is positive definite and $-J$ is symmetric negative definite (J is diagonal positive definite) we have

$$(102) \quad \lambda_{\min}(-J \langle e^{A\tau_s} \rangle) \geq \lambda_{\min}(-J) \lambda_{\max}(e^{A\tau_s}).$$

Given the fact that $\lambda_{\min}(-J) = -\lambda_{\max}(J)$ and $\lambda_{\min}(-J \langle e^{A\tau_s} \rangle) = -\lambda_{\max}(J \langle e^{A\tau_s} \rangle)$, we have

$$(103) \quad \lambda_{\max}(J \langle e^{A\tau_s} \rangle) \leq \lambda_{\max}(J) \lambda_{\max}(e^{A\tau_s}).$$

The proof of the second part of this remark is from the fact that the eigenvalues of the Kronecker product of two matrices are the multiplication of their eigenvalues [36].

Appendix F. Extension of Corollary 3.3. In the limit of $A = 0$, $\langle e^{A\mu\tau_s} \rangle$ in (31) simplifies to

$$(104) \quad A_\mu = \left[\begin{array}{c|c} 0 & 0 \\ \hline I_n \otimes \hat{a} + \hat{a} \otimes I_n & 0 \end{array} \right], \Rightarrow \langle e^{A_\mu\tau_s} \rangle = \left[\begin{array}{c|c} I & 0 \\ \hline (I_n \otimes \hat{a} + \hat{a} \otimes I_n) \langle \tau_s \rangle & I \end{array} \right].$$

Moreover

$$(105) \quad \left\langle e^{A_\mu\tau_s} \int_0^{\tau_s} e^{-A_\mu l} \hat{a}_\mu dl \right\rangle = \left[\begin{array}{c} \hat{a} \langle \tau_s \rangle \\ \hline \frac{1}{2} (I_n \otimes \hat{a} + \hat{a} \otimes I_n) \hat{a} \langle \tau_s^2 \rangle \end{array} \right].$$

Similarly

$$(106) \quad \begin{aligned} \langle e^{A_\mu\tau_s} \rangle &= \left[\begin{array}{c|c} I & 0 \\ \hline (I_n \otimes \hat{a} + \hat{a} \otimes I_n) \langle \tau \rangle & I \end{array} \right], \\ \left\langle e^{A_\mu\tau_s} \int_0^{\tau_s} e^{-A_\mu l} \hat{a}_\mu dl \right\rangle &= \left[\begin{array}{c} \hat{a} \langle \tau \rangle \\ \hline \frac{1}{2} (I_n \otimes \hat{a} + \hat{a} \otimes I_n) \hat{a} \langle \tau^2 \rangle \end{array} \right]. \end{aligned}$$

By using (94) we see that all the terms in (31) only depend on the first three moments of τ_s .

Appendix G. Matrices needed to calculate $\overline{\langle \mu \rangle}$ for a gene product.

$$(107) \quad \begin{aligned} \langle e^{A_\mu\tau_s} \rangle &= \left[\begin{array}{c|c} \langle e^{-\gamma_x\tau_s} \rangle & 0 \\ \hline 2 \frac{k_x}{\gamma_x} (\langle e^{-\gamma_x\tau_s} \rangle + \langle e^{-2\gamma_x\tau_s} \rangle) & \langle e^{-2\gamma_x\tau_s} \rangle \end{array} \right], \\ \left\langle e^{A_\mu\tau_s} \int_0^{\tau_s} e^{-A_\mu l} \hat{a}_\mu dl \right\rangle &= \left[\begin{array}{c} \frac{k_x}{\gamma_x} (1 - \langle e^{-\gamma_x\tau_s} \rangle) \\ \hline \frac{k_x^2}{\gamma_x^2} (\langle e^{-2\gamma_x\tau_s} \rangle - 2 \langle e^{-\gamma_x\tau_s} \rangle + 1) \end{array} \right], \end{aligned}$$

and

$$(108) \quad \begin{aligned} \langle e^{A_\mu\tau} \rangle &= \left[\begin{array}{c|c} \langle e^{-\gamma_x\tau} \rangle & 0 \\ \hline 2 \frac{k_x}{\gamma_x} (\langle e^{-\gamma_x\tau} \rangle + \langle e^{-2\gamma_x\tau} \rangle) & \langle e^{-2\gamma_x\tau} \rangle \end{array} \right], \\ \left\langle e^{A_\mu\tau} \int_0^{\tau} e^{-A_\mu l} \hat{a}_\mu dl \right\rangle &= \left[\begin{array}{c} \frac{k_x}{\gamma_x} (1 - \langle e^{-\gamma_x\tau} \rangle) \\ \hline \frac{k_x^2}{\gamma_x^2} (\langle e^{-2\gamma_x\tau} \rangle - 2 \langle e^{-\gamma_x\tau} \rangle + 1) \end{array} \right]. \end{aligned}$$

Using the fact that

$$(109) \quad \langle e^{-\gamma_x \tau} \rangle = \frac{1}{\langle \tau_s \rangle} \frac{1}{\gamma_x} (1 - \langle e^{-\gamma_x \tau_s} \rangle), \quad \langle e^{-2\gamma_x \tau} \rangle = \frac{1}{\langle \tau_s \rangle} \frac{1}{2\gamma_x} (1 - \langle e^{-2\gamma_x \tau_s} \rangle)$$

(see Appendix C), (108) can be changed to just contain expected values with respect to τ_s . Putting these matrices and vectors back in Theorem 3.4 we derive $\langle \mathbf{x} \rangle$ as in (43).

Appendix H. Proof of Theorem 5.1. Using (50), the states of TTSHS right before the s th event are

$$(110) \quad \mathbf{x}(t_s^-) = \int_0^{\tau_s} \Phi(\tau_s, l) \hat{a}(l) dl + \Phi(\tau_s, 0) \mathbf{x}(t_{s-1}^+).$$

Thus, the mean of the states after the s th event is

$$(111) \quad \langle \mathbf{x}(t_s^+) \rangle = \left\langle J(\tau_s) \int_0^{\tau_s} \Phi(\tau_s, l) \hat{a}(l) dl \right\rangle + \langle J(\tau_s) \Phi(\tau_s, 0) \rangle \langle \mathbf{x}(t_{s-1}^+) \rangle + \langle \hat{r}(\tau_s) \rangle.$$

Hence, for the steady-state mean of states to not blow up, eigenvalues of $\langle J(\tau_s) \Phi(\tau_s, 0) \rangle$ should be inside the unit circle. In this limit the mean of the states just after an event in steady-state ($s \rightarrow \infty$) is

$$(112) \quad \lim_{s \rightarrow \infty} \langle \mathbf{x}(t_s^+) \rangle = (I_n - \langle J(\tau_s) \Phi(\tau_s, 0) \rangle)^{-1} \left(\left\langle J(\tau_s) \int_0^{\tau_s} \Phi(\tau_s, l) \hat{a}(l) dl \right\rangle + \langle \hat{r}(\tau_s) \rangle \right).$$

By using (112), the steady-state mean of the states between events for any τ is

$$(113) \quad \lim_{s \rightarrow \infty} \langle \mathbf{x}(t_s + \tau) \rangle = \Phi(\tau, 0) (I_n - \langle J(\tau_s) \Phi(\tau_s, 0) \rangle)^{-1} \\ \times \left(\left\langle J(\tau_s) \int_0^{\tau_s} \Phi(\tau_s, l) \hat{a}(l) dl \right\rangle + \langle \hat{r}(\tau_s) \rangle \right) + \int_0^{\tau} \Phi(\tau, l) \hat{a}(l) dl.$$

Thus, taking the expected value of $\langle \mathbf{x}(t_s + \tau) \rangle$ with respect to τ results in the mean of the states as in (53). The rest of proof is similar to that of Theorem 3.1.

REFERENCES

- [1] E. ABRANCHES, A. M. V. GUEDES, M. MORAVEC, H. MAAMAR, P. SVOBODA, A. RAJ, AND D. HENRIQUE, *Stochastic NANOG fluctuations allow mouse embryonic stem cells to explore pluripotency*, Development, 141 (2014), pp. 2770–2779.
- [2] A. ANTA AND P. TABUADA, *To sample or not to sample: Self-triggered control for nonlinear systems*, IEEE Trans. Automat. Control, 55 (2010), pp. 2030–2042.
- [3] D. ANTUNES, J. HESPAÑA, AND C. SILVESTRE, *Volterra integral approach to impulsive renewal systems: Application to networked control*, IEEE Trans. Automat. Control, 57 (2012), pp. 607–619.
- [4] D. ANTUNES, J. HESPAÑA, AND C. SILVESTRE, *Stability of networked control systems with asynchronous renewal links: An impulsive systems approach*, Automatica, 49 (2013), pp. 402–413.
- [5] D. ANTUNES AND A. SINGH, *Quantifying gene expression variability arising from randomness in cell division times*, J. Math. Biol., 71 (2015), pp. 437–463.
- [6] D. J. ANTUNES AND B. A. KHASHOOEI, *Consistent event-triggered methods for linear quadratic control*, in Proceedings of the IEEE 55th Conference on Decision and Control, 2016, pp. 1358–1363.

- [7] N. BALABAN, J. MERRIN, R. CHAIT, L. KOWALIK, AND S. LEIBLER, *Bacterial persistence as a phenotypic switch*, Science, 305 (2004), pp. 1622–1625.
- [8] M. BILLMAN, D. RUEDA, AND C. BANGHAM, *Single-cell heterogeneity and cell-cycle-related viral gene bursts in the human leukaemia virus HTLV-1*, Wellcome Open Research, 2 (2017).
- [9] W. J. BLAKE, M. KAERN, C. R. CANTOR, AND J. J. COLLINS, *Noise in eukaryotic gene expression*, Nature, 422 (2003), pp. 633–637.
- [10] A. K. BRYAN, A. GORANOV, A. AMON, AND S. R. MANALIS, *Measurement of mass, density, and volume during the cell cycle of yeast*, Proc. Nat. Acad. Sci. USA, 107 (2010), pp. 999–1004.
- [11] L. CAI, N. FRIEDMAN, AND X. S. XIE, *Stochastic protein expression in individual cells at the single molecule level*, Nature, 440 (2006), pp. 358–362.
- [12] O. L. V. COSTA, *Stationary distributions for piecewise-deterministic markov processes*, J. Appl. Probab., 27 (1990), pp. 60–73.
- [13] O. L. V. COSTA AND F. DUFOUR, *Stability and ergodicity of piecewise deterministic Markov processes*, SIAM J. Control Optim., 47 (2008), pp. 1053–1077.
- [14] O. L. V. COSTA, M. D. FRAGOSO, AND R. P. MARQUES, *Discrete-Time Markov Jump Linear Systems*, Springer, New York, 2008.
- [15] B. DAIGLE, M. SOLTANI, L. PETZOLD, AND A. SINGH, *Inferring single-cell gene expression mechanisms using stochastic simulation*, Bioinform., 31 (2015), pp. 1428–1435.
- [16] R. D. DAR, B. S. RAZOOKY, A. SINGH, T. V. TRIMELONI, J. M. MCCOLLUM, C. D. COX, M. L. SIMPSON, AND L. S. WEINBERGER, *Transcriptional burst frequency and burst size are equally modulated across the human genome*, Proc. Nat. Acad. Sci. USA, 109 (2012), pp. 17454–17459.
- [17] M. H. A. DAVIS, *Piecewise-deterministic markov processes: A general class of non-diffusion stochastic models*, J. R. Stat. Soc. Ser. B Methodol., 46 (1984), pp. 353–388.
- [18] M. H. A. DAVIS, *Markov Models and Optimization*, Chapman and Hall, London, 1993.
- [19] B. DE SAPORTA, F. DUFOUR, AND H. ZHANG, *Numerical Methods for Simulation and Optimization of Piecewise Deterministic Markov Processes*, Wiley, New York, 2015.
- [20] L. DEVILLE, S. DHOPLE, A. D. DOMÍNGUEZ-GARCÍA, AND J. ZHANG, *Moment closure and finite-time blowup for piecewise deterministic markov processes*, SIAM J. Appl. Dyn. Syst., 15 (2016), pp. 526–556.
- [21] A. ELGAR AND M. B. ELOWITZ, *Functional roles for noise in genetic circuits*, Nature, 467 (2010), pp. 167–173.
- [22] M. B. ELOWITZ, A. J. LEVINE, E. D. SIGGIA, AND P. S. SWAIN, *Stochastic gene expression in a single cell*, Science, 297 (2002), pp. 1183–1186.
- [23] M. EVANS, N. HASTINGS, AND B. PEACOCK, *Statistical Distributions*, 3rd ed., Wiley, New York, 2000.
- [24] D. P. D. FARIAS, J. C. GEROMEL, J. B. R. D. VAL, AND O. L. V. COSTA, *Output feedback control of Markov jump linear systems in continuous-time*, IEEE Trans. Automat. Control, 45 (2000), pp. 944–949.
- [25] X. FENG, K. A. LOPARO, Y. JI, AND H. J. CHIZECK, *Stochastic stability properties of jump linear systems*, IEEE Tran. Automat. Control, 37 (1992), pp. 38–53.
- [26] M. FINKELSTEIN, *Failure rate and mean remaining lifetime*, in Failure Rate Modelling for Reliability and Risk, Springer Ser. Reliab. Eng., Springer, New York, 2008, pp. 9–44.
- [27] K. R. GHUSINGA, M. SOLTANI, A. LAMPERSKI, S. V. DHOPLE, AND A. SINGH, *Approximate moment dynamics for polynomial and trigonometric stochastic systems*, in Proceedings of the IEEE 56th Conference on Decision and Control, 2017, pp. 1864–1869.
- [28] K. R. GHUSINGA, C. A. VARGAS-GARCIA, A. LAMPERSKI, AND A. SINGH, *Exact lower and upper bounds on stationary moments in stochastic biochemical systems*, Phys. Biol., 14 (2017), 04LT01.
- [29] I. GOLDING, J. PAULSSON, S. ZAWILSKI, AND E. COX, *Real-time kinetics of gene activity in individual bacteria*, Cell, 123 (2005), pp. 1025–1036.
- [30] T. GOMMANS, D. ANTUNES, T. DONKERS, P. TABUADA, AND M. HEEMELS, *Self-triggered linear quadratic control*, Automatica, 50 (2014), pp. 1279–1287.
- [31] R. GRIMA, *A study of the accuracy of moment-closure approximations for stochastic chemical kinetics*, J. Chem. Phys., 136 (2012), 154105.
- [32] W. P. M. H. HEEMELS, K. H. JOHANSSON, AND P. TABUADA, *An introduction to event-triggered and self-triggered control*, in Proceedings of the IEEE 51st Conference on Decision and Control, 2012, pp. 3270–3285.
- [33] J. P. HESPANHA, *Modeling and analysis of networked control systems using stochastic hybrid systems*, Ann. Rev. Control, 38 (2014), pp. 155–170.

- [34] J. P. HESPAÑA AND A. SINGH, *Stochastic models for chemically reacting systems using polynomial stochastic hybrid systems*, Internat. J. Robust Nonlinear Control, 15 (2005), pp. 669–689.
- [35] J. P. HESPAÑA AND A. R. TEEL, *Stochastic impulsive systems driven by renewal processes*, in Proceedings of the International Symposium on Mathematical Theory of Networks and Systems, 2005, pp. 606–618.
- [36] R. A. HORN AND C. R. JOHNSON, *Topics in Matrix Analysis*, Cambridge University Press, Cambridge, UK, 1991.
- [37] D. HUH AND J. PAULSSON, *Non-genetic heterogeneity from stochastic partitioning at cell division*, Nature Genetics, 43 (2011), pp. 95–100.
- [38] D. HUH AND J. PAULSSON, *Random partitioning of molecules at cell division*, Proc. Nat. Acad. Sci. USA, 108 (2011), pp. 15004–15009.
- [39] H. KEMPE, A. SCHWABE, F. CRÉMAZY, P. J. VERSCHURE, AND F. J. BRUGGEMAN, *The volumes and transcript counts of single cells reveal concentration homeostasis and capture biological noise*, Molecular Biol. Cell, 26 (2015), pp. 797–804.
- [40] L. KEREN, D. VAN DIJK, S. WEINGARTEN-GABBAY, D. DAVIDI, G. JONA, A. WEINBERGER, R. MILO, AND E. SEGAL, *Noise in gene expression is coupled to growth rate*, Genome Res., 25 (2015), pp. 1893–1902.
- [41] B. A. KHASHOEEI, D. J. ANTUNES, AND W. P. M. H. HEEMELS, *Output-based event-triggered control with performance guarantees*, IEEE Trans. Automat. Control, 62 (2017), pp. 3646–3652.
- [42] R. S. KOH AND M. J. DUNLOP, *Modeling suggests that gene circuit architecture controls phenotypic variability in a bacterial persistence network*, BMC Systems Biol., 6 (2012), p. 47.
- [43] Z. KONKOLI, *Modeling reaction noise with a desired accuracy by using the X level approach reaction noise estimator (XARNES) method*, J. Theoret. Biol., 305 (2012), pp. 1–14.
- [44] I. KRISHNARAJAH, A. COOK, G. MARION, AND G. GIBSON, *Novel moment closure approximations in stochastic epidemics*, Bull. Math. Biol., 67 (2005), pp. 855–873.
- [45] G. LAMBERT AND E. KUSSELL, *Quantifying selective pressures driving bacterial evolution using lineage analysis*, Phys. Rev. X, 5 (2015), 011016.
- [46] A. LAMPERSKI, K. R. GHUSINGA, AND A. SINGH, *Analysis and control of stochastic systems using semidefinite programming over moments*, IEEE Trans. Automat. Control, 64 (2019), pp. 1726–1731.
- [47] R. LOSICK AND C. DESPLAN, *Stochasticity and cell fate*, Science, 320 (2008), pp. 65–68.
- [48] H. D. MACEDO AND J. N. OLIVEIRA, *Typing linear algebra: A biproduct-oriented approach*, Sci. Computer Program., 78 (2013), pp. 2160–2191.
- [49] E. MAISONNEUVE, M. CASTRO-CAMARGO, AND K. GERDES, *(p)ppGpp controls bacterial persistence by stochastic induction of toxin-antitoxin activity*, Cell, 154 (2013), pp. 1140–1150.
- [50] S. MARGUERAT AND J. BÄHLER, *Coordinating genome expression with cell size*, Trends in Genetics, 28 (2012), pp. 560–565.
- [51] S. MARGUERAT, A. SCHMIDT, S. CODLIN, W. CHEN, R. AEBERSOLD, AND J. BÄHLER, *Quantitative analysis of fission yeast transcriptomes and proteomes in proliferating and quiescent cells*, Cell, 151 (2012), pp. 671–683.
- [52] A. MENA, D. A. MEDINA, J. GARCÍA-MARTÍNEZ, V. BEGLEY, A. SINGH, S. CHÁVEZ, M. C. MUÑOZ-CENTENO, AND J. E. PÉREZ-ORTÍN, *Asymmetric cell division requires specific mechanisms for adjusting global transcription*, Nucleic Acids Res., 45 (2017), pp. 12401–12412.
- [53] S. MODI, M. SOLTANI, AND A. SINGH, *Linear noise approximation for a class of piecewise deterministic markov processes*, in Proceedings of the American Control Conference, 2018, pp. 1993–1998.
- [54] J. NARULA, A. KUCHINA, D.-Y. D. LEE, M. FUJITA, G. M. SÜEL, AND O. A. IGOSHIN, *Chromosomal arrangement of phosphorelay genes couples sporulation and DNA replication*, Cell, 162 (2015), pp. 328–337.
- [55] T. M. NORMAN, N. D. LORD, J. PAULSSON, AND R. LOSICK, *Stochastic switching of cell fate in microbes*, Ann. Rev. Microbiol., 69 (2015), pp. 381–403.
- [56] M. OGURA AND C. F. MARTIN, *Stability analysis of linear systems subject to regenerative switchings*, Systems Control Lett., 75 (2015), pp. 94–100.
- [57] M. OGURA AND V. M. PRECIADO, *Stability of markov regenerative switched linear systems*, Automatica, 69 (2016), pp. 169–175.
- [58] E. M. OZBUDAK, M. THATTAL, I. KURTSEER, A. D. GROSSMAN, AND A. VAN OUDENAARDE, *Regulation of noise in the expression of a single gene*, Nature Genetics, 31 (2002),

- pp. 69–73.
- [59] O. PADOVAN-MERHAR, G. P. NAIR, A. G. BIAESCH, A. MAYER, S. SCARFONE, S. W. FOLEY, A. R. WU, L. S. CHURCHMAN, A. SINGH, AND A. RAJ, *Single mammalian cells compensate for differences in cellular volume and DNA copy number through independent global transcriptional mechanisms*, *Molecular Cell*, 58 (2015), pp. 339–352.
 - [60] A. RAJ, C. PESKIN, D. TRANCHINA, D. VARGAS, AND S. TYAGI, *Stochastic mRNA synthesis in mammalian cells*, *PLOS Biology*, 4 (2006), p. e309.
 - [61] A. RAJ AND A. VAN OUDENAARDEN, *Nature, nurture, or chance: stochastic gene expression and its consequences*, *Cell*, 135 (2008), pp. 216–226.
 - [62] J. M. RASER AND E. K. O'SHEA, *Noise in gene expression: Origins, consequences, and control*, *Science*, 309 (2005), pp. 2010–2013.
 - [63] B. S. RAZOOKY, A. PAI, K. AULL, I. M. ROUZINE, AND L. S. WEINBERGER, *A hardwired HIV latency program*, *Cell*, 160 (2015), pp. 990–1001.
 - [64] D. R. RIGNEY, *Stochastic model of constitutive protein levels in growing and dividing bacterial cells*, *J. Theoret. Biol.*, 76 (1979), pp. 453–480.
 - [65] S. M. ROSS, *Reliability theory*, in *Introduction to Probability Models*, 10th ed., Academic Press, New York, 2010, pp. 579–629.
 - [66] K. M. SCHMOLLER AND J. M. SKOTHEIM, *The biosynthetic basis of cell size control*, *Trends in Cell Biology*, 25 (2015), pp. 793–802.
 - [67] K. M. SCHMOLLER, J. J. TURNER, M. KOIVOMAGI, AND J. M. SKOTHEIM, *Dilution of the cell cycle inhibitor Whi5 controls budding-yeast cell size*, *Nature*, 526 (2015), pp. 268–272.
 - [68] B. SCHWANHAUSSER, D. BUSSE, N. LI, G. DITTMAR, J. SCHUCHHARDT, J. WOLF, W. CHEN, AND M. SELBACH, *Global quantification of mammalian gene expression control*, *Nature*, 473 (2011), pp. 337–342.
 - [69] S. M. SHAFFER ET AL., *Rare cell variability and drug-induced reprogramming as a mode of cancer drug resistance*, *Nature*, 546 (2017), pp. 431–435.
 - [70] A. SINGH, *Stochastic analysis of genetic feedback circuit controlling HIV cell-fate decision*, in *Proceedings of the IEEE 51st Conference on Decision and Control*, 2012, pp. 4918–4923.
 - [71] A. SINGH, *Modeling Noise Mechanisms in Neuronal Synaptic Transmission*, *bioRxiv:10.1101/119537*, 2017.
 - [72] A. SINGH AND J. P. HESPANHA, *Models for multi-specie chemical reactions using polynomial stochastic hybrid systems*, in *Proceedings of the IEEE 44th Conference on Decision and Control*, 2005, pp. 2969–2974.
 - [73] A. SINGH AND J. P. HESPANHA, *Stochastic hybrid systems for studying biochemical processes*, *Philos. Trans. A*, 368 (2010), pp. 4995–5011.
 - [74] A. SINGH AND J. P. HESPANHA, *Approximate moment dynamics for chemically reacting systems*, *IEEE Trans. Automat. Control*, 56 (2011), pp. 414–418.
 - [75] A. SINGH, B. S. RAZOOKY, R. D. DAR, AND L. S. WEINBERGER, *Dynamics of protein noise can distinguish between alternate sources of gene-expression variability*, *Molecular Systems Biology*, 8 (2012), p. 607.
 - [76] A. SINGH AND M. SOLTANI, *Quantifying intrinsic and extrinsic variability in stochastic gene expression models*, *PLOS ONE*, 8 (2013), e84301.
 - [77] A. SINGH AND L. S. WEINBERGER, *Stochastic gene expression as a molecular switch for viral latency*, *Current Opinion in Microbiology*, 12 (2009), pp. 460–466.
 - [78] S. O. SKINNER, H. XU, S. NAGARKAR-JAISWAL, P. R. FREIRE, T. P. ZWAKA, AND I. GOLDING, *Single-cell analysis of transcription kinetics across the cell cycle*, *eLife*, 5 (2016), p. e12175.
 - [79] P. SMADBECK AND Y. N. KAZNESSIS, *A closure scheme for chemical master equations*, *Proc. Nat. Acad. Sci. USA*, 110 (2013), pp. 14261–14265.
 - [80] M. SOLTANI, P. BOKES, Z. FOX, AND A. SINGH, *Nonspecific transcription factor binding can reduce noise in the expression of downstream proteins*, *Phys. Biol.*, 12 (2015), p. 055002.
 - [81] M. SOLTANI AND A. SINGH, *Effects of cell-cycle-dependent expression on random fluctuations in protein levels*, *Roy. Soc. Open Sci.*, 3 (2016), 160578.
 - [82] M. SOLTANI AND A. SINGH, *Moment dynamics for linear time-triggered stochastic hybrid systems*, in *Proceedings of the IEEE 55th Conference on Decision and Control*, 2016, pp. 3702–3707.
 - [83] M. SOLTANI AND A. SINGH, *Moment-based analysis of stochastic hybrid systems with renewal transitions*, *Automatica*, 84 (2017), pp. 62–69.
 - [84] M. SOLTANI AND A. SINGH, *Control design and analysis of a stochastic event-driven system*, in *Proceedings of the IEEE Conference on Decision and Control*, 2018, pp. 5789–5794.
 - [85] M. SOLTANI AND A. SINGH, *Linear piecewise-deterministic markov processes with families of random discrete events*, in *Proceedings of the European Control Conference*, 2018,

- pp. 447–452.
- [86] M. SOLTANI, C. A. VARGAS-GARCIA, D. ANTUNES, AND A. SINGH, *Intercellular variability in protein levels from stochastic expression and noisy cell cycle processes*, PLOS Comput. Biol., (2016), e1004972.
 - [87] M. SOLTANI, C. A. VARGAS-GARCIA, AND A. SINGH, *Conditional moment closure schemes for studying stochastic dynamics of genetic circuits*, IEEE Trans. Biomed. Systems Circuits, 9 (2015), pp. 518–526.
 - [88] E. SONTAG AND A. SINGH, *Exact moment dynamics for feedforward nonlinear chemical reaction networks*, IEEE Life Sciences Lett., 1 (2015), pp. 26–29.
 - [89] E. B. STUKALIN, I. AIFUWA, J. S. KIM, D. WIRTZ, AND S. SUN, *Age-dependent stochastic models for understanding population fluctuations in continuously cultured cells*, J. Roy. Soc. Interface, 10 (2013), 20130325.
 - [90] K. S. TSAKALIS AND P. A. IOANNOU, *Linear Time-varying Systems: Control and Adaptation*, Prentice-Hall, Englewood Cliffs, NJ, 1993.
 - [91] R. TSUKANOV, G. RESHES, G. CARMON, E. FISCHER-FRIEDRICH, N. S. GOV, I. FISHOV, AND M. FEINGOLD, *Timing of z-ring localization in escherichia coli*, Phys. Biol., 8 (2011), 066003.
 - [92] A. TZUR, R. KAFRI, V. S. LEBLEU, G. LAHAV, AND M. W. KIRSCHNER, *Cell growth and size homeostasis in proliferating animal cells*, Science, 325 (2009), pp. 167–171.
 - [93] 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, 8 (2018), pp. 109–116.
 - [94] C. A. VARGAS-GARCÍA, M. SOLTANI, AND A. SINGH, *Conditions for cell size homeostasis: A stochastic hybrid systems approach*, IEEE Life Sciences Lett., 2 (2016), pp. 47–50.
 - [95] N. WALKER, P. NGHE, AND S. J. TANS, *Generation and filtering of gene expression noise by the bacterial cell cycle*, BMC Biol., 14 (2016), pp. 1–10.
 - [96] P. WANG, L. ROBERT, J. PELLETIER, W. L. DANG, F. TADDEI, A. WRIGHT, AND S. JUN, *Robust growth of escherichia coli*, Current Biol., 20 (2010), pp. 1099–1103.
 - [97] L. S. WEINBERGER, R. D. DAR, AND M. L. SIMPSON, *Transient-mediated fate determination in a transcriptional circuit of HIV*, Nature Genetics, 40 (2008), pp. 466–470.
 - [98] P. WHITTLE, *On the use of the normal approximation in the treatment of stochastic processes*, J. R. Stat. Soc. Ser. B Methods., 19 (1957), pp. 268–281.
 - [99] F. ZHANG AND Q. ZHANG, *Eigenvalue inequalities for matrix product*, IEEE Trans. Automatic Control, 51 (2006), pp. 1506–1509.
 - [100] J. ZHURINSKY, K. LEONHARD, S. WATT, S. MARGUERAT, J. BÄHLER, AND P. NURSE, *A coordinated global control over cellular transcription*, Current Biol., 20 (2010), pp. 2010–2015.
 - [101] C. J. ZOPF, K. QUINN, J. ZEIDMAN, AND N. MAHESHRI, *Cell-cycle dependence of transcription dominates noise in gene expression*, PLOS Comput. Biol., 9 (2013), e1003161.