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ON THE STABILITY OF CONTINUOUS-TIME SYSTEMS WITH STOCHASTIC DELAY: APPLICATIONS TO GENE REGULATORY CIRCUITS

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ABSTRACT

In this paper the dynamics and stability of a linear system with stochastic delay are investigated. We assume that the delay may take finitely many different values and its dynamics are modeled by a continuous-time Markov chain. Semi-discretization is used to derive the dynamics of the second moment which leads to necessary and sufficient stability conditions for the trivial solution. We apply these results to investigate the stability of the steady state of an auto-regulatory gene-protein network. We demonstrate that stochastic delay may stabilize the system when the corresponding deterministic system with average delay is unstable.

INTRODUCTION

The presence of vast amounts of biological data along with the increase of computational capabilities raises hope for being able to develop quantitative models for complex biological processes in living cells and analyze their behavior. In particular, the process of protein production inside living cells has generated a lot of interests in systems biology. The two major processes involved in protein production are transcription and translation. During transcription the information contained in a gene (a segment of DNA) is copied into messenger RNA (mRNA). Then, through translation, protein is produced from mRNA. Some proteins (called transcription factors) can bind to a particular site of a gene (called the promoter region) and effect transcription ei-

ther repressing or activating the gene. An arising network of interactions among genes and proteins is called a gene regulatory network (GRN).

Modeling and analysis of GRNs have attracted a lot of attention among researchers in systems biology [1–4]. Earlier models used ordinary differential equations (ODEs) to describe the dynamics of GRNs [5–7], that can be used to characterize stability of equilibria and find periodic solutions emerging through bifurcations. However, transcription and translation processes comprise of many steps that take significant time to be completed, and thus, their products become active after some delay time. Consequently, a more accurate way to describe the dynamics of GRNs is to introduce delays in the describing equations [8–11]. For instance, it has been shown that delay may lead to oscillations in models with negative feedback [6, 11–13]. Also, experimental data shows robust oscillations in synthetic networks as a result of transcriptional delay [14, 15]. When delay is incorporated, the dynamics can be described by delay differential equations that can be analyzed with existing analytical and numerical tools [16–18].

Another key feature of biochemical reactions taking place in cells is their highly stochastic nature [19]. Providing a quantitative description of these processes in macroscopic scale, while considering delays and stochasticity is a challenging task. One way to attack this problem is to incorporate delays in stochastic simulations at the molecular level where delays were typically considered to be constant [20–22]. However, some effects of stochastic delay variations were taken into account [13]. A

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difficulty of using molecular-level stochastic description of gene expression is that it becomes unfeasible for large numbers of molecules and species. On one hand, the analytical framework becomes very involved due to the large number of partial differential equations required to describe the time evolution of probability distribution functions. On the other hand, numerical methods become computationally very expensive [22]. Additionally, important concepts, such as stability and robustness, are difficult to characterize using this approach.

The effects of time delay on stochastic gene expression were investigated in [23] by adding noise to a deterministic delayed dynamical system. The resulting stochastic delay differential equations (SDDEs) may provide a tractable description to evaluate stability. However, there is no work in the literature that considers stochasticity in the delays in the framework of delay differential equations, so we target this challenging problem here. Our description can be used to capture the macroscopic behavior of gene regulatory networks while still representing essential stochastic effects in the delay originated at the molecular level. In particular, this framework allows us to derive necessary and sufficient conditions for stability of equilibria.

Linear delay differential equations with a random delay were investigated in [24, 25] where the delay was modeled by a continuous-time Markov chain. Lyapunov stability theorems were used to obtain sufficient conditions of stability and this approach was extended to nonlinear systems in [26]. The Lyapunov approach has also been applied to discrete-time systems in [27–29] where, again, it leads to sufficient conditions for stability that are typically very conservative. For discrete-time linear systems with random delays the mean-square dynamics were analyzed in [30–32]. For example, in [31] the delay was assumed to be independent and identically distributed (i.i.d.) at each time step and necessary and sufficient conditions were derived for the stability of the trivial solution.

In this paper, we consider a linear continuous-time system described by a delay differential equation where the stochasticity in the delay is modeled as a continuous-time Markov chain. This system has two sources of randomness: jump probabilities between delay values and randomness in the duration of the times the delay is held at a value. We use semi-discretization and find an approximating discrete-time system. Then we conclude about the stability of this discrete map by looking at the asymptotic behavior of the first and second moments of the state. This allows us to derive necessary and sufficient stability conditions. We apply our results to a linearized model of an auto-regulatory GRN with transcriptional negative feedback, called self-repressor. We draw a stability chart in the plane of system parameters and emphasize on the difference between the stochastic system and its deterministic counterpart.

MODELING AND DISCRETIZATION

In order to investigate the effects of stochastic delay variations, we consider the following linear dynamical system

$$\dot{x}(t) = ax(t) + bx(t - \tau), \tag{1}$$

where $x \in \mathbb{R}$ and the delay τ is considered to be a continuous-time Markov chain such that it takes values from the finite set $\{\tau_1, \tau_2, ..., \tau_N\}$. The probability transition matrix which governs the jumps between these delay values is given by

$$Q = \begin{bmatrix} q_{11} & q_{21} & \cdots & q_{N1} \\ q_{12} & q_{22} & \cdots & q_{N2} \\ \vdots & \vdots & \ddots & \vdots \\ q_{1N} & q_{2N} & \cdots & q_{NN} \end{bmatrix}, \tag{2}$$

where the probability of jumping from $\tau = \tau_i$ to $\tau = \tau_j$ is denoted by q_{ij}. Note that, for each column, the sum of the elements is 1 and also $q_{ii} = 0$ for $i = 1, \ldots, N$, because at the time of jump the delay must jump to another value. We assume that the matrix Q is fixed over time.

The delay remains constant before jumping to another value and the corresponding holding time is a random variable with exponential distribution due to the properties of a continuous-time Markov chain, namely, being memoryless and having time-homogeneity. We denote these holding times by $T_k = t_k - t_{k-1}$ where t_k is the time right before the delay jumps for the kth time (i.e., $k = 1, 2, 3, \ldots$ counts the number of jumps.) Fig. 1(a) depicts a sample realization of the time evolution of the delay. Here we suppose that at time $t = 0$ the delay is $\tau = \tau_{m_1}$, $m_1 \in \{1, \ldots, N\}$. Then we generate a random real number T_1 from an exponential distribution and the delay is kept constant along the time interval $0 \le t < T_1 = t_1$. Then it jumps to a new value $\tau = \tau_{m_2}$, $m_2 \in \{1, \ldots, N\}$, $m_2 \ne m_1$, based on the transition probabilities $q_{m_1 j}, j = 1, \ldots, N$, cf. Eq. (2). Now another random number T_2 is generated based on the same exponential distribution independently of T_1. The delay is held at the new value during $T_1 \le t < T_1 + T_2 = t_2$ and so forth. We remark that the randomness in the delay makes the state $x(t)$ in Eq. (1) to be a stochastic variable.

Our aim is to analyze the stability of the trivial solution $x(t) \equiv 0$ of system (1). To this end, first we discretize the system using semi-discretization [17]. As mentioned above, the delay is fixed for a random amount of time T_k (holding time) and then it jumps to another value. First, we discretize time by dividing it into small intervals of length h and approximate the holding times by multiples of h, i.e., $T_k \approx \ell(k)h$ where $\ell(k)$ is a random integer. Here we denote the time right before the delay jumps for the kth time by t'_k, that is, $t'_k - t'_{k-1} = \ell(k)h$; see Fig. 1(a). That is, the delay is kept constant at $\tau = \tau_{m_1}$ along the

time interval $0 \le t < \ell(1)h = t'_1$ and $\tau = \tau_{m_2}$ along the interval $\ell(1)h \le t < (\ell(1)+\ell(2))h = t'_2$ and so on. For a continuous-time Markov chain the holding times are independent, exponentially-distributed random variables. Since the geometric distribution may be regarded as a discrete version of the exponential distribution, we assume that the $\ell(k)$-s are geometrically distributed:

$$\mathrm{P}\big(\ell(k)=\ell\big) = \delta(1-\delta)^{\ell-1}, \quad \ell = 1,2,3,\dots \qquad (3)$$

where P stands for the probability and the parameter $0 \le \delta \le 1$ is assumed to be fixed over time and does not depend on the value of the delay. Figure 1(b) depicts a possible realization of the approximated delay process.

To complete the description, we apply semi-discretization where we approximate the delayed term as a constant along each time interval of length h. This assumption results in an ordinary differential equation with a piece-wise constant term on the right hand side, that is, the approximation of (1) can be written as

$$\dot{x}(t) = ax(t) + bx(t_{i-r_m}), \quad t \in [ih,(i+1)h), \qquad (4)$$

where $t_{i-r_m} = (i-r_m)h$, $r_m = \lfloor \frac{\tau_m}{h} \rfloor$, and τ_m is the delay in the time interval $[ih,(i+1)h)$ and $m \in \{1,2,...,N\}$. Assuming a constant delayed term is equivalent to saying that the delay increases linearly from $r_m h$ to $(r_m+1)h$ in the time interval $t \in [ih,(i+1)h)$; see [17]. Figure 1(c) illustrates this approximation by zooming in a part of Fig. 1(b).

To build up a discrete map for time evolution of system (4), we first introduce the notation $x(t_i) = x(i)$ and $x(t_{i-r_m}) = x(i-r_m)$. Applying the variation of constants method we can solve (4) along the time interval $[ih,(i+1)h)$ which yields

$$x(i+1) = \alpha x(i) + \beta x(i-r_m), \qquad (5)$$

where $\alpha = \mathrm{e}^{ah}$ and $\beta = -\frac{b}{a}(1-\mathrm{e}^{ah})$. This equation updates the state based on its current and past values. Using an augmented state vector $z(i) = [x(i) \quad x(i-1) \cdots x(i-R-1)]^{\mathrm{T}} \in \mathbb{R}^R$, where $R = \max_m \{r_m\}+1$, we can construct the discrete map

$$z(i+1) = G_{s(k)}z(i), \qquad (6)$$

where $G_{s(k)} \in \{G_m, m = 1,\dots,N\}$ and $G_m \in \mathbb{R}^{R\times R}$ such that

$$G_m = \begin{bmatrix} \alpha & 0 & \cdots \beta \cdots & 0 \\ 1 & 0 & \cdots & 0 & 0 \\ 0 & 1 & \ddots & \vdots & \vdots \\ \vdots & & \ddots & 0 & 0 \\ 0 & \cdots & 0 & 1 & 0 \end{bmatrix}. \qquad (7)$$
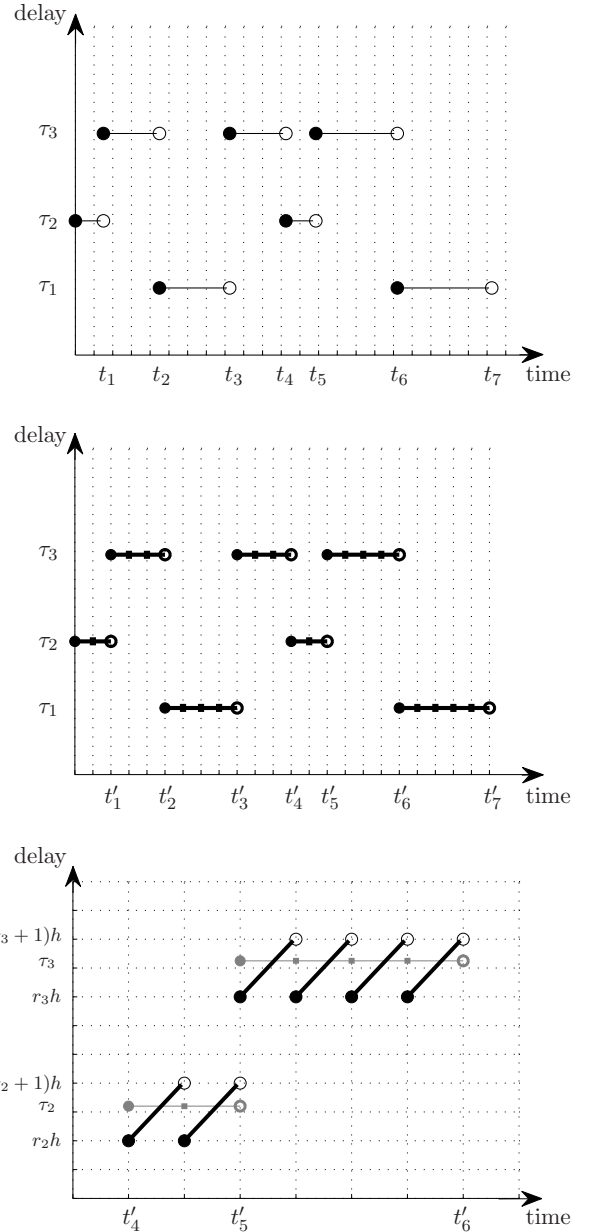

FIGURE 1. (a) A sample realization of the time evolution of the delay τ with $N = 3$ possible values; (b) A sample realization of the approximated process of delay evolution; (c) Delay variation after applying semi-discretization technique.

The matrices $\{G_m, m = 1,2,\dots,N\}$ correspond to the N different delay values such that β lies in the first row and in the $(r_m+1)^{th}$ column. At each delay jump a different matrix $G_{s(k)}$ is chosen and it is kept constant for $\ell(k)$ time steps (the discrete analogy of the holding time). Hence, if we consider the state vectors at the ends of the holding times $X(k+1) =$

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$z(\ell(1) + \cdots + \ell(k)) \in \mathbb{R}^R$, we can write

$$X(k+1) = (G_{s(k)})^{\ell(k)} X(k). \tag{8}$$

Indeed, $s(k)$ is a finite state Markov chain with support $\{1, 2, \ldots, N\}$ and transition probabilities described by matrix Q in (2), because the jumps in the delay τ in (1) corresponds to jumps in $s(k)$ in (8). In the following section, we derive equations for the first and second moments of system (8).

DYNAMICS AND STABILITY

In this section, we establish conditions for the stability of the trivial solution of the stochastic dynamical system (8). First we derive equations for the time evolution of the mean. Then the dynamics of the second moment are derived that result in necessary and sufficient stability conditions.

Behavior of the mean

First we characterize the dynamics of the mean of system (8), i.e., $\mathbb{E}[X(k)]$, where $\mathbb{E}$ stands for the expected value of a random variable. If the mean is unstable then the system will be unstable, that is, stability of the mean provides a necessary condition for the stability of the stochastic system.

From (8) we can derive

$$\mathbb{E}[X(k+1)|s(k+1) = j] = \mathbb{E}\left[(G_{s(k)})^{\ell(k)} X(k)|s(k+1) = j\right]$$
$$= \sum_{i=1}^{N} \mathbb{E}\left[(G_{s(k)})^{\ell(k)} X(k)|s(k+1) = j, s(k) = i\right]$$
$$\times \mathrm{P}\left(s(k) = i|s(k+1) = j\right), \tag{9}$$

We exploit the independence of $\ell(k)$ and $X(k)$ along with Bayes' rule to write (9) as follows

$$\mathbb{E}[X(k+1)|s(k+1) = j]$$
$$= \sum_{i=1}^{N} \mathbb{E}\left[(G_i)^{\ell(k)}|s(k+1) = j, s(k) = i\right] \mathbb{E}[X(k)|s(k+1) = j, s(k) = i]$$
$$\times \frac{\mathrm{P}\left(s(k+1) = j|s(k) = i\right) \mathrm{P}\left(s(k) = i\right)}{\mathrm{P}\left(s(k+1) = j\right)}. \tag{10}$$

Now, we note that $\ell(k)$-s are independent, identically distributed (*i.i.d.*), and they are also independent of all $s(k)$-s which yields $\mathbb{E}\left[(G_i)^{\ell(k)}|s(k+1) = j, s(k) = i\right] = \mathbb{E}\left[(G_i)^{\ell(k)}\right]$. We further note that based on Eq. (8), $X(k)$ depends on $s(k-1)$. Moreover, since the jump occurs from $s(k-1)$ to $s(k)$, information

about $s(k)$ gives information about $s(k-1)$. However, due to the Markov property of the jump process, information about $s(k+1)$ gives no extra information about $s(k-1)$, given that $s(k)$ is already known, that is, $\mathbb{E}[X(k)|s(k+1) = j, s(k) = i] = \mathbb{E}[X(k)|s(k) = i]$. Thus, (10) simplifies to

$$\mathbb{E}[X(k+1)|s(k+1) = j]$$
$$= \sum_{i=1}^{N} \mathbb{E}\left[(G_i)^{\ell(k)}\right] \mathbb{E}[X(k)|s(k) = i] \frac{q_{ij} \mathrm{P}(s(k) = i)}{\mathrm{P}(s(k+1) = j)}, \tag{11}$$

where we used the substitution $q_{ij} = \mathrm{P}\left(s(k+1) = j|s(k) = i\right)$, cf. (2).

Defining

$$f(G_i) := \mathbb{E}\left[(G_i)^{\ell(k)}\right] = \sum_{\ell=1}^{\infty} (G_i)^{\ell} \mathrm{P}\left(\ell(k) = \ell\right), \tag{12}$$

and rearranging Eq. (11) we obtain

$$\mathbb{E}[X(k+1)|s(k+1) = j] \mathrm{P}(s(k+1) = j)$$
$$= \sum_{i=1}^{N} f(G_i) q_{ij} \mathbb{E}[X(k)|s(k) = i] \mathrm{P}(s(k) = i). \tag{13}$$

Let $m_j(k) := \mathbb{E}[X(k)|s(k) = j] \mathrm{P}(s(k) = j) \in \mathbb{R}^R$. Then Eq. (13) can be written as

$$m_j(k+1) = \sum_{i=1}^{N} q_{ij} f(G_i) m_i(k). \tag{14}$$

Now defining $\hat{m}(k) := \begin{bmatrix} m_1(k)^\mathrm{T} & \cdots & m_N(k)^\mathrm{T} \end{bmatrix}^\mathrm{T} \in \mathbb{R}^{NR}$, we can write

$$\hat{m}(k+1) = \mathbf{M}\hat{m}(k), \tag{15}$$

where $\mathbf{M} \in \mathbb{R}^{NR \times NR}$ is given by

$$\mathbf{M} = \begin{bmatrix} q_{11}f(G_1) & q_{21}f(G_2) & \cdots & q_{N1}f(G_N) \\ q_{12}f(G_1) & q_{22}f(G_2) & \cdots & q_{N2}f(G_N) \\ \vdots & \vdots & & \vdots \\ q_{1N}f(G_1) & q_{2N}f(G_2) & \cdots & q_{NN}f(G_N) \end{bmatrix}$$
$$= (Q \otimes I_R) \mathrm{diag}(f(G_i)). \tag{16}$$

Here $\otimes$ denotes the Kronecker product, I_R is the $R \times R$ identity matrix, and $\mathrm{diag}(f(G_i))$ is a block diagonal matrix with $f(G_1), \cdots, f(G_N)$ as diagonal elements.

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Let

$$m(k) := \mathbb{E}[X(k)] = \sum_{j=1}^{N} \mathbb{E}[X(k)|s(k) = j] \, \mathrm{P}(s(k) = j) = \sum_{j=1}^{N} m_j(k).$$
(17)

If the spectral radius $\rho(\mathbf{M})$ of matrix $\mathbf{M}$ is less than 1, then system (15) is stable (i.e., $\hat{m}(k) \to 0$ as $k \to \infty$), which implies $m(k) \to 0$ as $k \to \infty$. (The spectral radius is defined by $\rho(\mathbf{M}) = \max_i\{|\lambda_i|\}$ where λ_i, $i = 1, \ldots, NR$, are the eigenvalues of $\mathbf{M}$.) Of course, to ensure stability, the series in (12) must also converge. We summarize these results in the following theorem.

Theorem 1 Consider system (8) where $s(k)$ is a Markov chain with transition matrix (2) and domain $\{1, \ldots, N\}$, $G_{s(k)}$ are $R \times R$ matrices, and $\ell(k)$ are independent, identically distributed (*i.i.d.*) random variables. Assume that $\ell(k)$ is independent of $s(k)$ and $X(k)$. Then $m(k) = \mathbb{E}[X(k)] \to 0$ as $k \to \infty$ (i.e., the mean is stable), if

$$(a) \quad f(G_i) \text{ exists for } i = 1, \ldots, N,$$
$$(b) \quad \rho(\mathbf{M}) < 1,$$
(18)

where $f(G_i)$ is defined by (12) and $\mathbf{M}$ is defined by (16).
Proof. The proof is given by the arguments shown before the theorem.

Condition (a) in (18) can be further refined, since $\ell(k)$-s are geometrically distributed. One can substitute Eq. (3) into Eq. (12) and write

$$f(G_i) = \sum_{\ell=1}^{\infty} (G_i)^{\ell} \mathrm{P}(\ell(k) = \ell) = \sum_{\ell=1}^{\infty} (G_i)^{\ell} \delta(1-\delta)^{\ell-1}$$
$$= \delta G_i \sum_{\ell=0}^{\infty} [(1-\delta)G_i]^{\ell} = \delta G_i [I - (1-\delta)G_i]^{-1}. \quad (19)$$

The summation in Eq. (19) is convergent if $\rho((1-\delta)G_i) < 1$. Thus we can state the following theorem.

Theorem 2 Consider system (8) with the same assumptions stated in Theorem 1. Further assume that $\ell(k)$ obey the geometric distribution (3). Then $m(k) = \mathbb{E}[X(k)] \to 0$ as $k \to \infty$, if

$$(a) \quad (1-\delta)\rho(G_i) < 1, \quad i = 1, \ldots, N,$$
$$(b) \quad \rho(\mathbf{M}) < 1,$$
(20)

where $\mathbf{M}$ is defined by (16).
Proof. The proof is given by the arguments shown before the theorem.

Behavior of the second moment

Theorems 1 and 2 give conditions for the stability of the mean of the stochastic system (8). Since our main quest is to find necessary and sufficient criteria for the stability of (8), we use the definition of the mean-square stochastic stability [33]. Equation (8) is mean square stable if for any initial distributions on $X(1)$ and $s(1)$ we have

$$(a) \quad \|\mathbb{E}[X(k)]\| \to 0 \quad \text{as } k \to \infty,$$
$$(b) \quad \|\mathbb{E}[X(k)X(k)^{\mathrm{T}}]\| \to 0 \quad \text{as } k \to \infty. \quad (21)$$

where $\mathbb{E}[X(k)X(k)^{\mathrm{T}}]$ is the second moment matrix of system (8). To ensure part (b) of (21), we seek a necessary and sufficient condition for the stability of the second moment. We proceed as follows

$$\mathbb{E}[X(k+1)X(k+1)^{\mathrm{T}}|s(k+1) = j]$$
$$= \mathbb{E}\left[(G_{s(k)})^{\ell(k)}X(k)X(k)^{\mathrm{T}}\left((G_{s(k)})^{\ell(k)}\right)^{\mathrm{T}}|s(k+1) = j\right]$$
$$= \sum_{i=1}^{N} \mathbb{E}\left[(G_{s(k)})^{\ell(k)}X(k)X(k)^{\mathrm{T}}\left((G_{s(k)})^{\ell(k)}\right)^{\mathrm{T}}|s(k+1) = j, s(k) = i\right]$$
$$\times \mathrm{P}(s(k) = i|s(k+1) = j). \quad (22)$$

Now we use the law of total probability along with the Bayes' rule to write (22) as

$$\mathbb{E}[X(k+1)X(k+1)^{\mathrm{T}}|s(k+1) = j]$$
$$= \sum_{i=1}^{N} \sum_{\ell=1}^{\infty} \mathbb{E}\left[(G_i)^{\ell(k)}X(k)X(k)^{\mathrm{T}}\left((G_i)^{\ell(k)}\right)^{\mathrm{T}}\Big|s(k+1) = j,\right.$$
$$\left. s(k) = i, \ell(k) = \ell\right] \mathrm{P}(\ell(k) = \ell|s(k+1) = j, s(k) = i)\frac{q_{ij}\mathrm{P}(s(k) = i)}{\mathrm{P}(s(k+1) = j)}. \quad (23)$$

Similar to the derivation of (11), noticing the fact that $\ell(k)$ is independent of $X(k)$ and $s(k)$, and that the statistical properties of $X(k)$ given $s(k)$ do not change by further knowing $s(k+1)$, Eq. (23) simplifies to

$$\mathbb{E}[X(k+1)X(k+1)^{\mathrm{T}}|s(k+1) = j]$$
$$= \sum_{i=1}^{N} \sum_{\ell=1}^{\infty} (G_i)^{\ell} \mathbb{E}[X(k)X(k)^{\mathrm{T}}|s(k) = i]\left((G_i)^{\ell}\right)^{\mathrm{T}}\mathrm{P}(\ell(k) = \ell)$$
$$\times \frac{q_{ij}\mathrm{P}(s(k) = i)}{\mathrm{P}(s(k+1) = j)}. \quad (24)$$

Defining $S_j(k) := \mathbb{E}\left[X(k)X(k)^{\mathrm{T}}|s(k)=j\right]\mathrm{P}(s(k)=j) \in \mathbb{R}^{R\times R}$ and rearranging Eq. (24), we obtain

$$S_j(k+1) = \sum_{i=1}^{N}\sum_{\ell=1}^{\infty} q_{ij}(G_i)^{\ell}S_i(k)\left((G_i)^{\ell}\right)^{\mathrm{T}}\mathrm{P}(\ell(k)=\ell). \quad (25)$$

Notice that

$$\begin{aligned}S(k) &:= \mathbb{E}\left[X(k)X(k)^{\mathrm{T}}\right]\\ &= \sum_{j=1}^{N}\mathbb{E}\left[X(k)X(k)^{\mathrm{T}}|s(k)=j\right]\mathrm{P}(s(k)=j) = \sum_{j=1}^{N}S_j(k),\end{aligned}$$
$$(26)$$

that is, summing (25) for all j-s we obtain the dynamics of the second moment. However, the second moment is a matrix-valued quantity and further transformations are needed in order to characterize its stability. Let $H = [h_1 \cdots h_R]$ be an $R \times R$ matrix with h_i being its ith column and define the operator $vec(H) := [h_1^{\mathrm{T}} \cdots h_R^{\mathrm{T}}]^{\mathrm{T}} \in \mathbb{R}^{R^2}$ that puts the columns of the matrix below each other. Then we define the NR^2-dimensional vector

$$\hat{v}(k) = \left[\left(vec\big(S_1(k)\big)\right)^{\mathrm{T}} \cdots \left(vec\big(S_N(k)\big)\right)^{\mathrm{T}}\right]^{\mathrm{T}}, \quad (27)$$

and use this definition to reformulate Eq. (25):

$$\hat{v}(k+1) = \mathbf{D}\,\hat{v}(k), \quad (28)$$

where the matrix $\mathbf{D} \in \mathbb{R}^{NR^2 \times NR^2}$ is given by

$$\mathbf{D} = (Q\otimes I_{R^2})\left[\sum_{\ell=1}^{\infty}\mathrm{diag}\big((G_i)^{\ell}\otimes(G_i)^{\ell}\big)\mathrm{P}(\ell(k)=\ell)\right]. \quad (29)$$

This matrix can be further simplified by using definition (12) and noting that $\big(G_i^{\ell}\otimes G_i^{\ell}\big) = (G_i\otimes G_i)^{\ell}$:

$$\mathbf{D} = (Q\otimes I_{R^2})\,\mathrm{diag}\big(f(G_i\otimes G_i)\big). \quad (30)$$

For the second moment of system (8) to be stable, $f(G_i\otimes G_i)$ must exist for $i=1,\ldots,N$, which means the series inside brackets in Eq. (29) must converge. Also, if $\rho(\mathbf{D}) < 1$, system (28) is stable meaning that $\hat{v}(k) \to 0$ as $k \to \infty$, which implies $S(k) \to 0$ as $k \to \infty$. The reverse is also true: if $S(k) \to 0$ for any initial condition $S(1)$, then $f(G_i\otimes G_i)$ exists and $\rho(\mathbf{D}) < 1$.

The first part is obvious, because otherwise the second moment would not be well-defined. To prove the second part we note that in Eq. (26) all S_j-s are positive semi-definite and symmetric. Thus,

$$0 \le S_j(k) \le S(k) \to 0 \quad \text{as} \quad k \to \infty \quad \text{for} \quad j=1,\ldots,N, \quad (31)$$

which shows $S_j(k) \to 0$ as $k \to \infty$ for $j=1,\ldots,N$. Hence, definition (27) implies that $\hat{v}(k) \to 0$ as $k \to \infty$ for any initial $\hat{v}(1)$. Consequently, the spectral radius of $\mathbf{D}$ must be less than 1, i.e., $\rho(\mathbf{D}) < 1$, since $\hat{v}(k+1) = \mathbf{D}^k\hat{v}(1)$. We state these results in the following theorem.

Theorem 3 Consider system (8) where $s(k)$ is a Markov chain with transition matrix (2) and domain $\{1,\ldots,N\}$, $G_{s(k)}$ are $R \times R$ matrices, and $\ell(k)$ are independent, identically distributed ($i.i.d.$) random variables. Assume that $\ell(k)$ is independent of $s(k)$ and $X(k)$. Then $S(k) = \mathbb{E}\left[X(k)X(k)^{\mathrm{T}}\right] \to 0$ as $k \to \infty$ for any initial condition $S(1)$, if and only if

$$\begin{aligned}(a) \quad &f(G_i\otimes G_i)\text{ exist for } i=1,\ldots,N,\\ (b) \quad &\rho(\mathbf{D}) < 1,\end{aligned} \quad (32)$$

when $f(.)$ is defined in (12) and $\mathbf{D}$ is defined in (30).

Proof. The proof is given by the arguments shown before the theorem.

Conditions (32) can be refined considering that $\ell(k)$ are geometrically distributed. Similar to our result from Eq. (19), we know that $f(G_i\otimes G_i)$ exists if $\rho\big((1-\delta)(G_i\otimes G_i)\big) < 1$. This would require that

$$(1-\delta)\rho(G_i\otimes G_i) < 1 \;\Leftrightarrow\; (1-\delta)\big(\rho(G_i)\big)^2 < 1. \quad (33)$$

Thus we can state the following theorem.

Theorem 4 Consider system (8) with the same assumptions stated in Theorem 3. Further assume that $\ell(k)$ obey the geometric distribution (3). Then $S(k) = \mathbb{E}\left[X(k)X(k)^{\mathrm{T}}\right] \to 0$ as $k \to \infty$ for any initial condition $S(1)$, if and only if

$$\begin{aligned}(a) \quad &(1-\delta)(\rho(G_i))^2 < 1, \quad i=1,\ldots,N,\\ (b) \quad &\rho(\mathbf{D}) < 1.\end{aligned} \quad (34)$$

Proof. The proof is given by the arguments shown before the theorem.

Note that stability of the second moment (converging to zero) implies the stability of the first moment. In other words,

part (b) in (21) implies part (a) in (21). This can be seen noting that convergence in r^{th} order implies convergence in s^{th} order if $s \leq r$; see [33]. In particular, $\|\mathbb{E}\left[X(k)X(k)^T\right]\| \to 0$ implies $\mathbb{E}\left[|X(k)|^2\right] \to 0$ which implies $\mathbb{E}\left[|X(k)|\right] \to 0$ or $\mathbb{E}\left[X(k)\right] \to 0$. Therefore, if conditions (34) hold the stochastic system (8) will be mean-square stable according to definition (21).

CASE STUDY: ANALYSIS OF SELF-REPRESSOR

The self-repressor is a single-gene regulatory network in which the protein produced by a gene binds to the promoter region of the same gene and represses its own production. The production of the protein is performed through several biological processes as shown by the sketch in Fig. 2.

A simplified mathematical model is given in [34]:

$$\dot{p}(t) = -\gamma p(t) + \frac{\sigma}{1 + p^2(t - \tau)} + \sigma_0, \qquad (35)$$

where $p(t)$ stands for the concentration of protein molecules (measured in units of the number of proteins required to half-maximally repress the gene) and γ is the ratio of the protein degradation rate and mRNA degradation rate. In this model a Hill function is used to represent how proteins repress the production. In the presence of a saturating number of repressor proteins, the promoter strength (number of mRNA transcripts produced per unit time) is σ_0 (due to "leakiness" of the promoter), and when there is no repressor around, it is $\sigma + \sigma_0$. Also, τ is an aggregated delay caused by all non-instantaneous biological reactions measured in units of mRNA lifetime. Here we will use the parameters given in [35]: $\gamma = 0.2069$, $\sigma = 44.59$, and $\sigma_0 = 0.0446$.
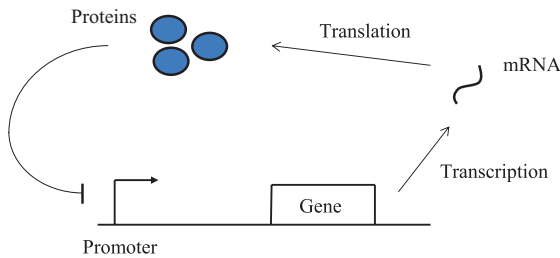
FIGURE 2. A negative feedback auto-regulatory network, also called a self-repressor. Proteins produced after transcription and translation processes bind to the promoter of the same gene and repress it.

System (35) has an equilibrium point at $p = p^*$ which is the solution of the equation $\gamma p^* - \sigma_0 = \sigma/(1 + p^{*2})$. To study the

stability of this fixed point we linearize (35) about the equilibrium and obtain the following equation

$$\dot{\tilde{p}}(t) = a\tilde{p}(t) + b\tilde{p}(t - \tau), \qquad (36)$$

where $\tilde{p} = p - p^*$ and for the parameters above, $a = -\gamma = -0.2069$ and $b = -2\sigma p^*/(1 + p^{*2})^2 = -0.3882$, cf. (1).

Let's suppose the delay τ in Eq. (36) is stochastic taking values in the set $\{2, 10, 13\}$ with transition probability matrix

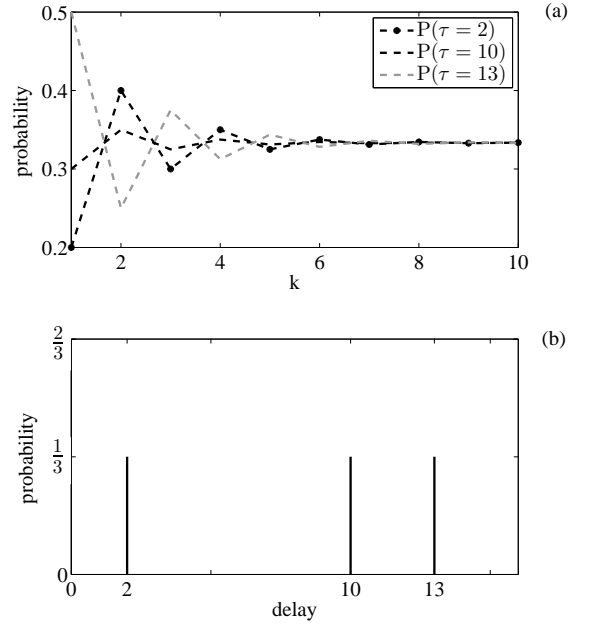$$Q = \begin{bmatrix} 0 & 0.5 & 0.5 \\ 0.5 & 0 & 0.5 \\ 0.5 & 0.5 & 0 \end{bmatrix}. \qquad (37)$$

FIGURE 3. (a) Time evolution of the probability of being at delays τ_1, τ_2, and τ_3 versus jump number k given the initial distribution $\pi(1) = [0.2 \ 0.3 \ 0.5]^T$. (b) Probability distribution of delays for $k \to \infty$.

From the finite-state Markov chain theory [36], we know that given the initial probability distribution over delays, it can be obtained using the update formula

$$\pi(k+1) = Q\pi(k), \qquad (38)$$

where $\pi(k) \in \mathbb{R}^N$ is the probability distribution over delays in k^{th} jump. Equation (38) implies that the probability distribution of the delays approaches a stationary distribution as time goes to infinity if all eigenvalues of Q are inside the unit circle in the complex plane. (Note that Q always has an eigenvalue at 1 that is related to the constant column's sum feature implied by the normalization of the transition probabilities.) For the probability transition matrix (37), the probability of the delays approach a uniform distribution for any initial probability distribution. This is demonstrated in Fig. 3 using the initial distribution $\pi(1) = [0.2 \ 0.3 \ 0.5]^T$.

Performing linear stability analysis for (36) with fixed delay (deterministic system), it can be shown that for the parameters above, the fixed point is stable for $\tau \lesssim 6.5$ and unstable for $\tau \gtrsim 6.5$. Note that we use $\tau_1 = 2 < 6.5$, $\tau_2 = 10 > 6.5$, and $\tau_3 = 13 > 6.5$. Let $h = 0.4$ and $\ell_{avg} = 7$, i.e., the average holding time for the delay is $\ell_{avg} h = 2.8$. Since Eq. (3) implies $\ell_{avg} = \mathbb{E}(\ell) = 1/\delta$, we have $\delta = 0.143$. For the stochastic system, we have $\rho(\mathbf{D}) = 0.9452 < 1$, which means the system is stable. In this example, even though two of the three possible values for the delay are destabilizing, the resultant system is still stable. This means that the stability results for the stochastic system cannot be concluded by analyzing the behavior of the corresponding deterministic system.
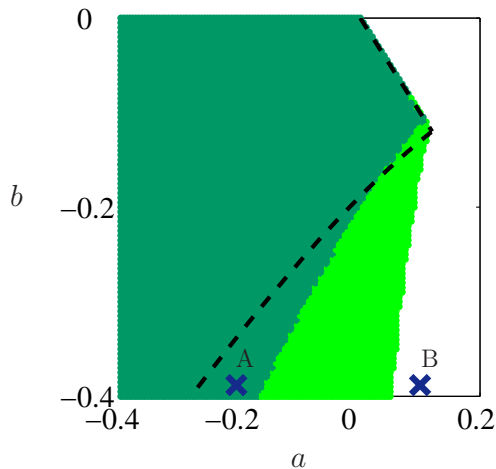
To further elaborate on this, we vary the parameters a and b in (36) and evaluate the stability. Figure (4) shows the stability region in the (a, b)-plane. The dark shaded area shows the region in which the stochastic system (36) is mean-square stable. Light shaded area indicates the region in which the first moment (mean) is stable, but the second moment is not. The black dashed curve shows the boundary of the stable region for the deterministic system with a fixed delay $\tau_{avg} \approx 8.33$ that is equal to the average of all possible delays. In Fig. 5, we demonstrate the time evolution of the system by using the parameters of the points marked A and B in Fig. 4. The 300 sample trajectories are plotted as thin gray curves while the mean and the standard deviation are indicated by thick black and thick red curves, respectively. Indeed, the system is stable in case A and unstable in case B.
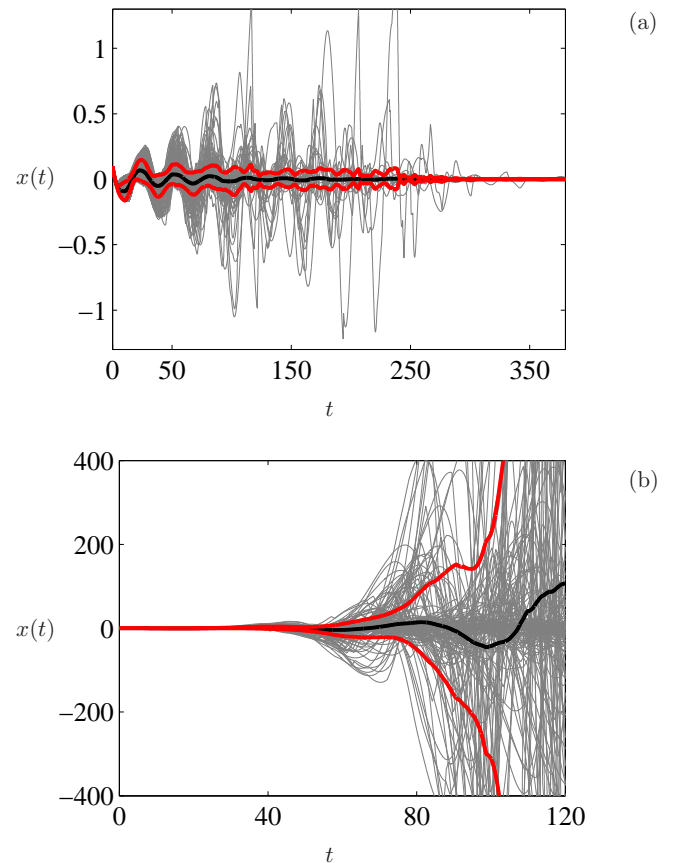

FIGURE 4. Stability chart in the plane of parameters a and b. Dark shaded area is the region of stability; i.e., the second moment (and the mean) are stable. Light shaded area shows the region in which only first moment (but not the second moment) is stable. The black dashed curve shows the boundary of stability region of a deterministic system with a fixed average delay $\tau_{avg} \approx 8.33$. Simulations for points A and B are displayed in Fig. 5(a) and 5(b), respectively.

FIGURE 5. (a) Simulation results for the system (36) using the parameters at point A in Fig. 4. (b) Simulation results using the parameters at point B in Fig. 4. The black curve shows the mean and the red curves show the mean plus and minus the standard deviation based on the gray sample trajectories.

8

DISCUSSION

We investigated the dynamics of a continuous-time linear system with stochastic delay. We assumed that the delay is a continuous-time Markov chain and approximated the holding times of the delay by a discrete geometric distribution. Then we discretized the system using semi-discretization technique to be able to construct a map which describes the stochastic evolution of the state. We used the definition of the mean-square stability and found necessary and sufficient stability conditions. We applied the results to analyze the stability of the steady state of a simple genetic network. Our results show that the stability of a stochastically delayed system cannot be simply speculated from the behavior of the deterministic system. For instance, conservative ideas like only considering the most critical delay or rough conjectures such as taking the average of delays could be far from the stochastic case.

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