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Stochastic Modeling and Analysis of Genetic Networks

Mustafa Khammash and Hana El Samad

Abstract— **Much of the mathematical modeling of genetic networks represents gene expression and regulation as deterministic processes. There is now, however, considerable experimental evidence indicating that significant stochastic fluctuations are present in these processes. Stochasticity is an inherent feature of biological dynamics, and as such, should be the subject of in-depth analysis. The investigation of stochastic properties in genetic systems involves the formulation of a correct representation of molecular noise, followed by the formulation of mathematically sound approximations for these representations. It also involves devising efficient computational algorithms capable of tackling the complexity of the dynamics involved. In this paper we review a number of these techniques and provide compelling examples that illustrate the richness of phenomena that can result from the interaction of dynamics and noise in genetic networks.**

I. Introduction

Internal regulation of biochemical reactions is an essential task that cells should accurately accomplish for growth and survival. It has become increasingly apparent that the accurate modeling of this regulation yields valuable insight into regulatory biological systems, and holds the promise of uncovering the principles behind their operation in health and disease. The traditional mathematical description of the time evolution of well-stirred biochemical reactions is a set of coupled, ordinary differential equations. These equations model the evolution of the molecular populations as a continuous, deterministic process, with variables representing population concentrations. However, within the cell, the chemically reacting system of molecules in general and the genetic networks they implement actually possess neither of those attributes: Molecular populations are whole numbers and change by discrete, integer amounts. Furthermore, the occurrence of a chemical reaction is by itself a random process subject to thermal fluctuations, and hence is stochastic in nature. When the molecular populations of some reactant species are very small, or if the dynamic structure of the system makes it susceptible to noise amplification as is often the case in cellular systems, discreteness and stochasticity play an important role. Whenever that happens, the ordinary differential equations approach does not accurately describe the true behavior of the system. This is further corroborated by physical evidence pointing to purely stochastic phenomena in a number of genetic networks [1], [2], [3]. In this paper, we extract the essence of these phenomena through a sequence of motivating simple examples. We then review some old and more recent mathematical methods commonly used for modeling of stochastic cellular dynamics. We end our exposition with some examples that illustrate the principles of noise attenuation through feedback and noise exploitation in cellular networks, all analyzed using the methods presented.

M. Khammash and H. El Samad are with the Department of Mechanical Engineering, University of California at Santa Barbara, Santa Barbara, CA 93106, USA khammash@engr.ucsb.eduand helsamad@engr.ucsb.edu

II. Deterministic versus Stochastic Modeling

As in chemical kinetics, biochemical reactions in biological networks can be described using the laws of mass-action, yielding a set of differential equations that give the succession of concentration of species adopted by the network over time. Consider for example the reaction $A+B\xrightarrow{k}C$. The deterministic formulation of chemical kinetics would yield the following description $\frac{d[C]}{dt}=k[A]\cdot[B]$ where $[\cdot]$ denotes the concentration. In contrast, the discrete stochastic formulation of the above reaction is concerned with the *probability* that at a given time, t, the number of molecules of species A and B take certain values. Thus, populations of various reactants are treated as random variables, and reactions take place randomly according to certain probabilities determined by several factors. For example, given a certain population of A and B, say n_a and n_b, at time t, the probability that one of the above reactions takes place within the interval $[t,t+dt)$ is given by $\frac{k\cdot n_a\cdot n_b}{V}dt$, where V is the volume of the space containing the reactants. The stochastic approach to chemical kinetics is discussed in more detail later in this paper. In the meantime, the reader should keep in mind that in the mesoscopic stochastic formulation of chemical kinetics, molecular species are characterized by their probability density function (*pdf*). This *pdf* quantifies the amount of fluctuations around a certain mean value that molecular populations can assume. In the limit of an infinite number of molecules, fluctuations become negligible, and the mesoscopic description generates the macroscopic description. In intermediate regimes, however, fluctuations need to be accounted for as they can generate distinct phenomena that make a deterministic description erroneous. This is illustrated in the following examples.

A. Deterministic equilibrium versus the mean of the distribution

Although the macroscopic deterministic description is often assumed to be an acceptable approximation of the behavior of the mean value of a process, it sometimes fail to capture this mean value. Such an effect has been recently described in a simple example, and the phenomenon it implements termed "stochastic focusing" [4]. More specifically, the example describes sensitivity amplification that results from the use of noisy signals and that goes beyond what noise-free signals can achieve. The molecular interactions described in the example include a protein I,

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produced constitutively at rate $k = 10^4$ and degraded or converted to P molecules at rates $k_a S$ ($k_a = 9.9 \times 10^3$) and $k_p = 10^4$, respectively. P molecules are in turn degraded with normalized rate constant 1. S is a signalling molecule degraded at a rate $k_d = 10^3$ and produced at a constant rate $k_s = 10k_d$, and therefore assumes Poisson statistics. These interactions are given by

$$\phi \underset{k_a S}{\overset{k}{\rightleftharpoons}} I \xrightarrow{k_p} P \xrightarrow{1} \phi \qquad\qquad \phi \underset{k_d}{\overset{k_s}{\rightleftharpoons}} S \tag{1}$$

With this choice of parameters, the scheme in (1) can be approximated by $\phi \underset{1}{\overset{kq}{\rightleftharpoons}} P$, where $q = \frac{1}{1+S/K}$, with $K = k_p/k_a$. Signalling to this system through S can for example be implemented by halving its concentration through a one-half decrease in the synthesis rate k_s. If S were a noiseless signal, this two-fold decrease can never result in more than a two-fold increase in the average number of product P due to the intrinsic limitation of the hyperbolic inhibition q (see Figure 1). However, when signal noise is accounted for, a two-fold decrease in the average signal concentration results in about a 3-fold increase in P, therefore indicating that the deterministic description grossly under-estimated the mean of the distribution. This effect is a natural consequence of the fact that the average of a nonlinear function (q in this case) is generally not the same as the function of the average.

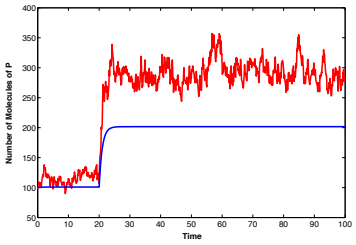


Fig. 1. Stochastic (red) and deterministic (blue) simulation of the system in (1).

B. Noise Induced Switching in Multistable Systems

The effect of fluctuations in multistable systems can be substantial as noise can influence the convergence to equilibria or even cause switching from one equilibrium to another. One of the best studied examples of multistability in genetic systems is the bacteriophage λ system [5]. A simplified model for the bacteriophage λ was proposed in [6]. In their model, the gene cI expresses the λ repressor CI which dimerizes and binds to DNA as a transcription factor at either of two binding sites, $OR1$ or $OR2$. Binding of this transcription factor to $OR1$ enhances transcription of CI (positive feedback), while binding to $OR2$ represses transcription of CI (negative feedback). The molecular

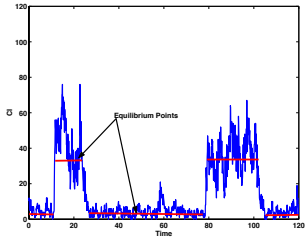


Fig. 2. Stochastic time trajectory of CI. Noise causes switching between the two equilibrium points of the system.

reactions in this system proceed as follows

$$\begin{aligned} 2CI &\overset{K_1}{\rightleftharpoons} CI_2 \quad ; \quad CI_2 + D \overset{K_2}{\rightleftharpoons} DCI_2 \\ CI_2 + D &\overset{K_3}{\rightleftharpoons} DCI_2^*; \quad DCI_2 + CI_2 \overset{K_4}{\rightleftharpoons} DCI_2CI_2 \\ DCI_2 + P &\xrightarrow{k_t} DCI_2 + P + nCI \quad ; \quad CI \xrightarrow{k_d} \phi \end{aligned}$$

where the DCI_2 and DCI_2^* complexes denote the binding to OR_1 and OR_2 respectively, and DCI_2CI_2 denotes binding to both sites. K_i are forward equilibrium constants, k_t is protein synthesis rate, and k_d is degradation rate. P is the concentration of the RNA polymerase assumed here to be constant, and n is the number of proteins per mRNA transcript, taken here to be 2. Production of CI from the naked DNA is also assumed to occur, but at a very slow rate r. Ordinary differential equations that describe these chemical reactions implement a bistable system. In the deterministic setting, the system's trajectories converge to one or the other of the equilibria and stay there for all future times for any given set of initial conditions. However, as we incorporate the effect of molecular noise in this description, we notice that switching between the two stable equilibria is possible if the noise amplitude is sufficient to drive the trajectories occasionally out of the basin of attraction of one equilibrium into the basin of attraction of the other equilibrium as shown in Figure 2.

III. Stochastic Models of Gene Expression and Regulation

Here, we introduce the stochastic formulation of chemical kinetics using the Chemical Master Equation (CME)

A. Stochastic Formulation of Chemical Kinetics and the Master Equation

The CME describes the time evolution of the *pdf*, as opposed to deterministic rate equation descriptions of the concentration of molecules [7]. In the CME, reaction rates are transformed into probability transition rates. The CME can be derived based on the Markov property of chemical reactions. Using this Markov property, one can write the Chapman-Kolmogorov equation, an identity that must be obeyed by the transition probability of any Markov process. Using stationarity and taking the limit for infinitesimally vanishing time intervals, one obtains the CME, as the differential form of the Chapman-Kolmogorov equation [7].

Here, we only give the expression for the CME and refer the reader to [7] or [8] for a more detailed account.

In a chemically reacting system involving N molecular species $S_1,....S_N$ reacting through M reaction channels $R_1....R_M$, we define the state vector $X(t) = [X_1(t)....X_N(t)]^T$, where $X_i(t)$, $i = 1,2..,N$ is a random number that defines the number of molecules of species S_i in the system at time t. We assume that the system is well stirred and in thermal equilibrium. Under these circumstances, each reaction channel R_k is characterized by a *propensity function* w_k and an N-dimensional *state change vector* $s_k = [s_{1k}....s_{Nk}]^T$. The vector s_k represents the stoichiometric change of the molecular species by an R_k reaction, while $w_k(x)dt$ is the probability that one R_k reaction will occur in state $X(t) = x$ during the next infinitesimal time interval dt. We let $W(\cdot) = [w_1(\cdot),...,w_M(\cdot)]^T$ be the vector of propensity functions and $S = \{s_k\}_{k=1..M}$ be the stoichiometry matrix. The CME for this system is then given by

$$\begin{aligned}\frac{\partial P(x,t|x_0,t_0)}{\partial t} &= \sum_{k=1}^{M}[w_k(x-s_k)P(x-s_k,t|x_0,t_0) \\ &- w_k(x)P(x,t|x_0,t_0)] \end{aligned} \quad (2)$$

where $P(x,t|x_0,t_0)$ should be interpreted as the probability that at time t, $X(t) = x$ given that $X(t_0) = x_0$ (x and x_0 are integers). For clarity, we give a simple example. Consider a protein existing in two states A or B. This protein can transform from A to B with a transition rate k_1 and from B to A at a rate k_2, i.e. $A \underset{k_2}{\overset{k_1}{\rightleftharpoons}} B$. For this system,

$$S = \begin{bmatrix} -1 & 1 \\ 1 & -1 \end{bmatrix}, W = \begin{bmatrix} k_1 n_a \\ k_2 n_b \end{bmatrix}$$

where n_a and n_b are the numbers of A and B respectively. The Master Equation for this system can be written as

$$\begin{aligned}&\frac{dP(n_a,n_b;t|n_a(t_0),n_b(t_0);t_0)}{dt} = \\ &k_1(n_a+1)P(n_a+1,n_b-1;t|n_a(t_0),n_b(t_0);t_0) \\ &+k_2(n_b+1)P(n_a-1,n_b+1;t|n_a(t_0),n_b(t_0);t_0) \\ &-(k_1n_a+k_2n_b)P(n_a,n_b;t|n_a(t_0),n_b(t_0);t_0)\end{aligned} \quad (3)$$

In general, the CME is not analytically or numerically solvable in any but the simplest cases. Therefore, one has to resort to Monte Carlo type simulations that produce a random walk through the possible states of the system under study. We briefly describe the Gillespie Stochastic Simulation Algorithm (SSA) as the most commonly used representative of these stochastic simulation methods [9].

B. Numerical Methods

1) Exact Monte Carlo Simulations: The SSA involves the computation of the probability and time of occurrence of elementary reactions. More specifically, starting at time t, the time τ to the next occurring reaction is the exponentially distributed random variable with mean $\frac{1}{w_0(x)}$. Furthermore, the next reaction R_k to occur is the one whose index k is the integer random variable with probability $\frac{w_k(x)}{w_0(x)}$, where $w_0(x)$ is given by $w_0(x) = \sum_{k=1}^{M} w_j(x)$. To generate these random variables, one can draw two random number r_1 and r_2 from the uniform distribution in the unit interval, and then take $\tau = \frac{1}{w_0(x)} ln \frac{1}{r_1}$ and k to be the smallest integer satisfying $\sum_{j'=1}^{k} w_{j'}(x) > r_2 w_0(x)$. Based on τ and R_k one can then advance the simulation time by τ, and update the state of the system and repeat until final time or state. The trajectory obtained in this fashion is a stochastic realization based on the description of the Master Equation. The Gillespie stochastic algorithm tracks exactly all the reactions that occur in the system and the species they affect. This often represents a large computational load which makes these simulations rather prohibitive if the system has species with large numbers of molecules or reactions that evolve at fast time scales. There are many attempts to make the SSA more computationally efficient such as improved computational and data storage capabilities [10], the incorporation of quasi-steady-state approximations [12], and "leaping" procedures for stiff systems whereby the algorithm leaps over a number of reactions using preselected τ values [13].

C. Approximation Methods

1) Linear Noise Approximations: A less computationally demanding, yet approximate, approach is the simplification of the master equation in a Linear Noise Approximation (LNA). Roughly speaking, the LNA involves the expansion of the master equation in Taylor series near macroscopic system trajectories or stationary points. Terms of first order in the expansion are then identified with the macroscopic rate equations, while terms of second order describe the approximate noise acting on the system. More specifically, approximate explicit expressions for the covariance matrix C of the fluctuations in the components of the system is obtained as the solution of an Algebraic Lyapunov equation $AC + CA^T + D = 0$, where A is a Jacobian matrix of the deterministic evolution equations evaluated at the steady state, while D is a diffusion matrix that embodies the contribution of every chemical reaction to the overall fluctuations. We present next the multivariable LNA of the CME [14].

Using the master equation in (2), we compute expressions for the first two moments of the process X. For the first moment of any X_i, we multiply (2) by X_i and take summation over all variables $X_1,...X_N$. For the second order moment, say $E[X_iX_j]$, we multiply by (2) X_iX_j and again take summations. This results in the following set of equations

$$\frac{dE[X_i]}{dt} = \sum_{k=1}^{M} s_{ik} E[w_k(X)] \quad (4)$$

$$\begin{aligned}\frac{dE[X_iX_j]}{dt} &= \sum_{k=1}^{M}(s_{ik}E[X_j w_k(X)] + E[X_i w_k(X)]s_{jk} \\ &+ s_{ik}s_{jk}E[w_k(X)])\end{aligned} \quad (5)$$

where $(i,j = 1,...N)$. The symbol E denotes expectation on

the pdf $P(x;t)$. Let $\Gamma(X)$ be defined as

$$\begin{bmatrix} E[X_1w_1(X)] & E[X_2w_1(X)] & . & . & E[X_Nw_1(X)] \\ E[X_1w_2(X)] & E[X_2w_2(X)] & . & . & E[X_Nw_2(X)] \\ . & . & . & . & . \\ . & . & . & . & . \\ E[X_1w_M(X)] & E[X_2w_M(X)] & . & . & E(X_Nw_M(X)) \end{bmatrix}$$

and let $E[W(X)]$ denote the vector of expected values $E[w_i(X)]$ and

$$D(X) = S\{diagE[W(X)]\}S^T$$

where $\{diagE[W(X)]\}$ is a matrix having $E[w_i(X)], i = 1,..,N$ on the diagonal and zero elsewhere. In this matrix notation, the relations in (4) translate to

$$\frac{dE[X]}{dt} = SE[W(X)] \quad (6)$$

$$\frac{d\Sigma_X}{dt} = S\Gamma(X) + \Gamma(X)^T S^T + D(X) \quad (7)$$

where Σ_X is the second moment matrix, i.e. $C = \Sigma_X - E[X]E[X]^T$.

a) The Linear Propensity Case: Suppose that the propensities functions appearing in the CME are linear functions of the state variables, i.e. $w_k(X) = \alpha_k X_j$ (for some j) when $k \in \{1,...,h\}$. In this case $S\Gamma = S[\frac{\partial W}{\partial_X}]\Sigma_X$ and $SE[W(X)] = S^h[\frac{\partial W}{\partial_X}]E[X]$, where $[\frac{\partial W}{\partial_X}]$ is the jacobian of W . Therefore, equations (6) and (7) become

$$\frac{dE[X]}{dt} = S[\frac{\partial W}{\partial_X}]E[X]$$

$$\frac{d\Sigma_X}{dt} = S[\frac{\partial W}{\partial_X}]\Sigma_X + \Sigma_X(S[\frac{\partial W}{\partial_X}])^T + D(X) \quad (8)$$

It is easy to show that in this case, the mean $E[X]$ follows exactly the evolution of the deterministic rate equations, which we denoted by ϕ. That is $\frac{d\phi}{dt} = S\frac{\partial W}{\partial \phi}\phi$.

To get an equation for C, we add and subtract $S[\frac{\partial W}{\partial_X}]E[X]E[X]^T$ and $E[X]^T E[X](S[\frac{\partial W}{\partial_X}])^T$ from (8) to get

$$\begin{aligned} \frac{d\Sigma_X}{dt} &= S[\frac{\partial W}{\partial_X}]C + C(S[\frac{\partial W}{\partial_X}])^T + S[\frac{\partial W}{\partial_X}]E[X]E[X]^T \\ &+ E[X]^T E[X](S[\frac{\partial W}{\partial_X}])^T + D(X) \end{aligned} \quad (9)$$

Here, notice that $S[\frac{\partial W}{\partial_X}]E[X]E[X]^T = \frac{dE[X]}{dt}E[X]^T$

Hence, equation (9) becomes

$$\begin{aligned} \frac{d\Sigma}{dt} &= S[\frac{\partial W}{\partial_X}]C + C(S[\frac{\partial W}{\partial_X}])^T + \frac{dE[X]}{dt}E[X]^T \\ &+ E[X]\frac{dE[X]}{dt}^T + D(X) \end{aligned} \quad (10)$$

Therefore, the stationary covariance of X, computed from (10) is given by the solution of the Lyapunov equation

$$S[\frac{\partial W}{\partial X}]C + C(S[\frac{\partial W}{\partial_X}])^T + D(X) = 0$$

evaluated at $E[X] \simeq \phi_s$, where ϕ_s is the steady-state solution of the deterministic rate equations. The matrix D can always be written as BB^T where $B = S\sqrt{diag(W(\phi_s))}$ with $\sqrt{diag(W(\phi_s)}$ being a diagonal matrix with $\sqrt{diag(w_k(\phi_s))}$ on the diagonal. Hence, the effect of intrinsic stochasticity can be thought of as Gaussian noise added through the matrix B to a system having state matrix $S^h[\frac{\partial W}{\partial_X}]$.

b) The Nonlinear Propensity Case: The procedure above does not generalize to nonlinear propensity functions since the matrix Γ will involve higher order moments. However, an approximation is possible. Assume that the pdf $P(X;t)$ is tightly distributed about the $X = \phi(t)$ with $\phi(t)$ being the deterministic solution. Specifically $\frac{d\phi}{dt} = SW(\phi)$. Let $X(t) = \phi(t) + \xi(t)$, where ξ is a stochastic term denoting the deviation from the deterministic term $\phi(t)$. Expanding in Taylor series around $\phi(t)$ and replacing in the rate equation

$$\begin{aligned} \frac{dE[X]}{dt} &= \frac{d\phi}{dt} + \frac{dE[\xi]}{dt} \\ &= SW(\phi) + S\frac{\partial W(z)}{\partial z}|_{z=\phi}E[\xi] + o(|\xi|^2) \end{aligned}$$

The assumption on the pdf implies that terms of order $o(|\xi|^2)$ can be neglected, therefore recovering the equation $\frac{d\phi}{dt} = SW(\phi)$ for the mean of X. In addition, we get

$$\frac{dE[\xi]}{dt} = S\frac{\partial W(z)}{\partial z}|_{z=\phi}E[\xi]$$

At the same time,

$$\begin{aligned} E[X_iw_j(X)] &= \phi_i w_j(\phi) + E[\xi_i]w_j(\phi) \\ +\phi_i\frac{\partial w_j(z)}{\partial z}|_{z=\phi}E[\xi] &+ \frac{\partial w_j(z)}{\partial z}|_{z=\phi}E[\xi_i\xi] + o(|\xi|^2) \end{aligned}$$

Therefore,

$$\begin{aligned} \Gamma(X) &\simeq \Gamma(\phi) + W(\phi)E[\xi]^T + \frac{\partial W(z)}{\partial z}|_{z=\phi}E[\xi]\phi^T \\ &+ S\frac{\partial W(z)}{\partial z}|_{z=\phi}\Sigma_\xi \end{aligned}$$

where Σ_ξ is the covariance matrix of ξ. Furthermore,

$$\begin{aligned} D(X) &= D(\phi + \xi) \simeq S\{diagE[W(\phi) + \frac{\partial W(z)}{\partial z}|_{z=\phi}\xi]\}S^T \\ &= S\{diagW(\phi)\}S^T + S\{diag\frac{\partial w_i(z)}{\partial z}|_{z=\phi}E[\xi]\}S^T \end{aligned}$$

We summarize the resulting equations

$$\begin{aligned} \frac{dE[\xi]}{dt} &= A\ E[\xi] \\ \frac{d\Sigma_\xi}{dt} &= S\Gamma(\phi) + \Gamma(\phi)^T S^T + SW(\phi)E[\xi]^T \\ &+ E[\xi]W(\phi)^T S^T + AE[\xi]\phi^T \\ &+ \phi E[\xi]^T A^T + A\Sigma_\xi + \Sigma_\xi A^T \\ &+ S\{diagW(\phi)\}S^T + S\{diag\frac{\partial w_i(z)}{\partial z}|_{z=\phi}E[\xi]\}S^T \end{aligned}$$

where $A = S\frac{\partial W(z)}{\partial z}|_{z=\phi}$. If the matrix A is Hurwitz, $E[\xi]$ tends to zero as $t \to \infty$. Let ϕ_s be deterministic the steady

state solution. Since at steady state $SW(\phi_s) = 0$, $\Gamma(\phi_s) = SW(\phi_s)\phi_s^T = 0$. The steady-state covariance for ξ is then given by the solution of the algebraic Lyapunov equation

$$A_s\Sigma_\xi + \Sigma_\xi A_s^T + D_s = 0 \tag{11}$$

where $A_s = S\frac{\partial W(z)}{\partial z}|_{z=\phi_s}$ and $D_s = S[diagW(\phi_s)]S^T$. One can perform an appropriate change of variables whereby the number of molecules for all the species in a system will be scaled up or down. For example, one can define $\psi(t) = N\phi(t)$. N is commonly called the system size. Since $\Sigma_{\xi_\psi} = N\Sigma_{\xi_\phi}$, the steady-state of ϕ (hence the mean of X) grows linearly with N while its associated noise strength grows as the square root of N. This in agreement with the intuition that as the number of molecules in a system increases, the noise strength affecting it, normalized by the mean, decreases.

2) The Finite State Projection (FSP) Approach: The Finite State Projection (FSP) method is concerned with getting approximate solutions to the CME directly. We briefly outline the key idea of this approach.

Given N possible molecular species of interest, the set of all possible states is $\mathbb{N}^N$. One can *apriori* fix a sequence $x_1, x_2, \ldots$ of elements in $\mathbb{N}^N$ and define $\mathbf{X} := [x_1, x_2, \ldots \quad]^T$. The particular sequence $x_1, x_2, \ldots$ may be chosen to visit every element of the entire space $\mathbb{N}^N$. In this case, the choice of $\mathbf{X}$ corresponds to a particular enumeration of the space $\mathbb{N}^N$. Once $\mathbf{X}$ is selected, the CME can be written as a single linear expression:

$$\dot{\mathbf{P}}(\mathbf{X};t) = \mathbf{A}\cdot\mathbf{P}(\mathbf{X};t), \tag{12}$$

where $\mathbf{P}(\mathbf{X};t) := [P(x_1,t), p(x_2,t), \ldots \quad]^T$, is the complete probability density state vector at time t, and $\mathbf{A}$ is the *state reaction matrix*. The columns and rows of $\mathbf{A}$ are uniquely defined by the system's stoichiometry and the choice of $\mathbf{X}$. Beginning at any state, $\mathbf{x}_i$, there can be a maximum of $\mathbf{M}$ possible reactions; each reaction leads to a different state: $\mathbf{x}_j = \mathbf{x}_i + s$, where s is the state change vector.

The state reaction matrix contains information regarding every reaction, each weighted by the corresponding propensity function. $\mathbf{A}$ has the properties that it is independent of t; all of its diagonal elements are non-positive; all its off-diagonal elements are non-negative; and all its columns sum to exactly zero. The solution to the linear ODE beginning at $t = 0$ and ending at $t = t_f$ in Eqn 12 is the expression:

$$\mathbf{P}(\mathbf{X};t_f) = \Phi(0,t_f)\cdot\mathbf{P}(\mathbf{X};0). \tag{13}$$

In the case where there are only a finite number of reachable states, the operator, $\Phi(0,t_f)$, is simply the exponential of $\mathbf{A}t_f$, and one can easily compute the solution. In the more realistic situation when $\mathbf{A}$ is infinite dimensional or extremely large, the exact analytic solution is unclear or vastly difficult to compute. In these cases, one can devise a systematic means of approximating the full system using finite dimensional sub-systems. This systematic truncation approach is the essence of the FSP method [11].

The FSP method utilizes approximations based on projecting the infinite dimensional state space onto a finite dimensional one, while providing a bound for the error. One such projections is given by the following theorem:

Theorem 1 ([11]): Consider any Markov process in which the probability density state vector evolves according to the ODE (12), where $\mathbf{A}$ has no negative off-diagonal entries. Let $\mathbf{A}_J$ be a principle sub-matrix of $\mathbf{A}$ specified by the indexing set J, and let $\mathbf{P}(\mathbf{X}_J;t)$ be a vector of the corresponding elements of $\mathbf{P}(\mathbf{X};0)$. If for $\varepsilon > 0$, and $t_f \geq 0$

$$\mathbf{1}^T\exp(\mathbf{A}_J t_f)\mathbf{P}(\mathbf{X}_J;0) \geq 1-\varepsilon, \tag{14}$$

then

$$\exp(\mathbf{A}_J t_f)\mathbf{P}(\mathbf{X}_J;0) \leq \mathbf{P}(\mathbf{X}_J;t_f) \leq \exp(\mathbf{A}_J t_f)\mathbf{P}(\mathbf{X}_J;0) + \varepsilon\mathbf{1}.$$

This result is the basis for an algorithm that truncates the infinite state, computes the error between the probability density given by the full system and the truncated one, and then either stops or considers a new finite truncation, depending on whether the error is within prescribed tolerances. Preliminary experience with this method shows that, for several realistic problems of interest, it is superior to the SSA both in accuracy and speed.

IV. Examples

A. Noise Attenuation Through Feedback

It has been suggested that the robust operation of genetic networks in the presence of noise is in part the outcome of feedback regulatory loops [15]. Here, we present a simplified example illustrating the essence of noise rejection by feedback. A thorough treatment in the setting of the heat shock response of bacteria was given in [16]. The example we present corresponds to a protein x_1 produced from a constant pool of substrate. x_1 promotes the production of another protein x_2, which is then degraded with first order kinetics at a rate λ_2. We consider two scenarios for the degradation of protein x_1. In the first scenario, x_1 is degraded at a constitutive rate λ_0. In the second scenario, the end product of the cascade, protein x_2 regulates the degradation of x_1 in a closed loop fashion. The degradation of x_1 is therefore a function of x_2, $f(x_2)$ multiplied by the concentration of x_1. We choose a linear function f of x_2, i.e. $f(x_2) = \lambda_r x_2$. We now use the LNA to compares the properties of these two schemes. The steady-state jacobian for constitutive degradation system, denoted here by A^{cs}, is given by

$$A^{cs} = \begin{bmatrix} -\lambda_0 & 0 \\ k & -\lambda_2 \end{bmatrix} \doteq \begin{bmatrix} -\alpha^{cs} & 0 \\ \lambda^{cs} & -\nu^{cs} \end{bmatrix}$$

while the stationary jacobian of regulated degradation system, denoted by A^s, is given by

$$A^s = \begin{bmatrix} -\lambda_r x_2^s & -\lambda_r x_1^s \\ k & -\lambda_2 \end{bmatrix} \doteq \begin{bmatrix} -\alpha^s & -\theta^s \\ \lambda^s & -\nu^s \end{bmatrix}$$

We ensure internal consistency between the two models by requiring that steady-state values in the two models be

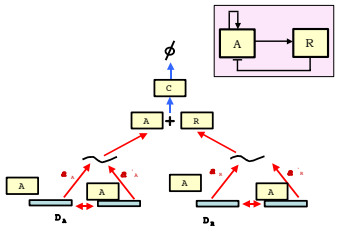
the same. We ensure this by setting $\lambda_0 = \lambda_r x_2^s$ for constitutive degradation. Hence, $\alpha^s = \alpha^{cs}$, $\lambda^s = \lambda^{cs}$, and $\nu^s = \nu^{cs}$. The two systems possess diagonal diffusion matrices D that are identical in this case, with d_{11} and d_{22} denoting the non-zero terms. Solving the Lyapunov equation, we extract the difference between constitutive degradation variance $C_{x_2}^{cs}$ for x_2 and that of regulated degradation $C_{x_2}^{s}$

$$C_{x_2}^{cs} - C_{x_2}^{s} = \Omega \frac{\lambda^{cs}\theta^s(\alpha^{cs^2}d_{22} + \lambda^{cs^2}d_{11})}{2\alpha^{cs}\nu^{cs}(\alpha^{cs}+\nu^{cs})(\alpha^{cs}\nu^{cs}+\theta^s\lambda^{cs})} > 0$$

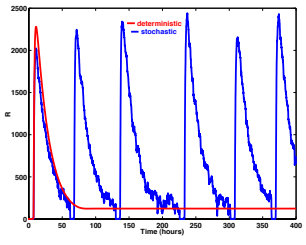
This is always a positive and is a monotonically increasing function of the feedback gain θ^s, hence the advantage of feedback in noise attenuation. This result is mirrored closely by exact stochastic simulations using SSA.

B. Noise Exploitation and Coherence Resonance

To adapt the alternation of day and night, most living organisms have developed the capability of generating oscillating expressions of proteins in their cells with a period close to 24 hours, known as the circadian rhythm. The Vilar-Kueh-Barkai-Leibler (VKBL in short) description of the circadian oscillator incorporates an abstraction of a minimal set of essential, experimentally determined mechanisms in the system [17]. More specifically, the VKBL model involves two genes, an activator A and a repressor R, which are transcribed into *mRNA* and subsequently translated into proteins. The activator A binds to the A and R promoters and increases their expression rate. Therefore, A implements a positive loop acting on its own transcription. At the same time, R sequesters A to form a complex C, therefore inhibiting it from binding to the gene promoter and acting as a negative feedback loop. These interactions are depicted in Figure 3 For the parameter values given in [17], a



(a)



(b)

Fig. 3. (a) The molecular components of the VKBL model of the circadian oscillator (b) Noise induced oscillations.

differential equations model for the dynamics of Figure 3 exhibits autonomous oscillations with an approximate period of 24 hours. These oscillations, however, disappear from the deterministic model as the degradation rate of the repressor δ_R is decreased to the quarter of its value, as the system undergoes a supercritical Hopf Bifurcation in the neighborhood of this value. The unique deterministic equilibrium of the system becomes stable (see Figure 3 (b)). However, as the effects of molecular noise are accounted for, it is observed that oscillations in the stochastic system pertain (see Figure 3(b)). In fact, the regularity of these noise-induced oscillations, in an otherwise stable deterministic system, can be manipulated by tuning the level of noise in the network. This can be done, for example, by changing the number of molecules or speed of molecular reactions [18]. This phenomenon is a manifestation of *coherence resonance*, and illustrates the crucial interplay between noise and dynamics.

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