

# Stochastic Stability and its Application to the Analysis of Gene Regulatory Networks

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**Abstract**— As gene regulatory network design and implementation becomes more common, understanding the stochastic stability properties of these networks is increasingly becoming more of a necessity. A study of such properties would uncover regimes of stable behavior under both cellular intrinsic biochemical noise, and extrinsic uncertainty resulting from fluctuating environments and noisy interconnections between individual networks. In this work, we revise and specialize common notions of stochastic stability to study two prototypical models of gene regulatory networks that have extensively been used in the biological literature.

## I. INTRODUCTION

Gene regulatory networks can be broadly defined as groups of genes that are activated by particular signals and stimuli, and once activated, orchestrate their operation to regulate certain biological functions, such as metabolism, development, and the cell cycle. The operation of gene regulatory networks takes place in the noisy environment of the cell. The inherent stochasticity in biochemical processes (such as binding, transcription, and translation) generates what is known as “intrinsic noise”. Furthermore, variations in the amounts or states of cellular components and species that affect those biochemical reactions, in addition to cross-talk between individual genes, generates fluctuations, termed “extrinsic noise”. Intrinsic and extrinsic noises endow genetic regulatory systems with dynamical features that should be thoroughly explored if one hopes to understand, reverse engineer, and manipulate cellular processes. As a matter of fact, as “designer gene circuits” [1] (i.e. genetic networks that are designed, then the designs built and inserted into the cell) become common practice, it becomes imperative to look at the perturbed behavior of these systems in the environment where they have been plugged. In view of the fact that these synthetic networks are usually built to test a hypothesis or make a prediction, one should check that potential noise sources do not shadow the correct answer, or even unexpectedly destabilize or change the dynamic behavior of the nominal design. These ideas are not novel in the design of control systems. Underlying this is the observation that noise, both in its multiplicative and additive form, can induce a wide, and sometime unexpected, range of dynamical behavior, especially when acting upon

This material is based upon work supported by the National Science Foundation under Grant NSF-ITR CCF-0326576 and the Institute for Collaborative Biotechnologies through grant DAAD19-03-D-0004 from the U.S. Army Research Office.

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a nonlinear system. In fact, the problem of large deviations of systems away from an equilibrium state, and transitions to a new state in response to noise has long attracted the close attention of researchers. In the last few years, substantial evidence has emerged in support of the idea that even weak noise can produce drastic qualitative changes in the properties of a system, such as transformation of a stable equilibrium into an unstable one (and vice versa)[2], the occurrence of multi-stability [3] or noise induced oscillations [4], the occurrence of stochastic resonance [5] and stochastic ratchets. Although these phenomena have been observed and studied mostly in engineering such as electronic circuits and mechanical oscillators, their presence is currently being uncovered in gene regulatory networks [6]. In this work, we report on some preliminary results concerning the stochastic stability properties of two gene regulatory networks that have been build and thoroughly analyzed in the biological literature. These two networks were adopted as a first illustration because they are simple prototypes of core cellular functionality.

This paper is organized as follows. We first provide a short mathematical background and define the notions of stochastic stability that we use. Thereafter, we provide standard theorems that characterize stochastic stability in terms of Lyapunov functions. We then specialize the theorems to provide stability conditions that can be easily checked for the type of examples we are concerned with. We finally tackle the special examples using the machinery exposed.

## II. MATHEMATICAL BACKGROUND

Let  $\Omega$  be a sample space with a  $\sigma$  algebra  $\mathcal{F}$  of subsets of  $\Omega$ . If a probability measure  $\mathbb{P}$  is defined on  $(\Omega, \mathcal{F})$ , then the triple  $(\Omega, \mathcal{F}, \mathbb{P})$  is called a probability space. On this probability space we consider an autonomous stochastic differential equation of the Itô type given by

$$\frac{dx}{dt} = F(x) + \sigma(x)\xi_t \quad (1)$$

where  $x(t_0) \in \mathbb{R}^n$ ,  $\xi_t$  is Gaussian-distributed white noise perturbation with zero mean and unit variance, and the maps  $F, \sigma : \mathbb{R}^n \rightarrow \mathbb{R}^n$  satisfy the usual Lipschitz and linear growth conditions which guarantee the existence and uniqueness for the solutions  $x$  [7]. In this case, we shall call a sample path  $x(t)$  of (1) an Itô diffusion.

*Definition 1:* Let  $x(t)$  be a time-homogeneous Itô diffusion in  $\mathbb{R}^n$ . The infinitesimal generator  $\mathcal{L}$  of  $x(t)$  is defined as

$$\mathcal{L}g(z) = \lim_{t \rightarrow 0} \frac{E[g(x(t))] - g(z)}{t}, \quad z \in \mathbb{R}^n$$

where  $g$  is any function such that the limit exists. If  $g \in \mathcal{C}^2$  and has compact support, one can use equation (1) and the Itô formula to compute the expression for  $E[g(x(t))]$ . Using this expression, the limit can then be calculated and one obtains the following expression for the generator of  $x(t)$

$$\begin{aligned}\mathcal{L}g(x) &= \sum_{i=1}^n F_i \frac{\partial g}{\partial x_i} + \frac{1}{2} \sum_{i,j=1}^n b_{ij} \frac{\partial^2 g}{\partial x_i \partial x_j} \\ &= F(x) \frac{\partial g}{\partial x} + \frac{1}{2} \text{trace}[\sigma(x)\sigma^T(x) \frac{\partial^2 g}{\partial x^2}]\end{aligned}$$

Let  $x^*$  be a fixed point of the unperturbed system  $\dot{x} = F(x)$ , i.e.  $F(x^*) = 0$ . Without loss of generality, we assume that  $x^* = 0$ .

#### A. Vanishing Stochastic Perturbations

When  $\sigma(x^*) = 0$ ,  $x^*$  is also a fixed point of the perturbed system (1). In this case, one can address the stability of the fixed point  $x^*$  using the stochastic counterpart of deterministic Lyapunov theory, a task that was started in the 1960's by Has'minskii and others [10], [11]. In this paper, we will only deal with the notion of stability in probability. Other closely related notions such as  $p$ -stability (e.g. 1-stability referring to stability in the mean, and 2-stability referring to stability in the second moment) are possible, and will be addressed elsewhere.

*Definition 2:* Let  $x(t; t_0, x_0)$  be a sample path of the diffusion process described by (1) issuing from the point  $x_0$  at time  $t_0$ . The equilibrium point  $x^*$  of (1) is

- stable in probability if

$$\lim_{x_0 \rightarrow x^*} \mathbb{P}\{\sup_{t \geq t_0} \|x(t; t_0, x_0) - x^*\| > \varepsilon\} = 0 \quad \forall \varepsilon > 0$$

- asymptotically stable if it is stable in probability and

$$\lim_{x_0 \rightarrow x^*} \mathbb{P}\{\lim_{t \rightarrow \infty} \|x(t; t_0, x_0) - x^*\| = 0\} = 1$$

- globally stable if it is stable in probability and

$$\mathbb{P}\{\lim_{t \rightarrow \infty} \|x(t; t_0, x_0) - x^*\| = 0\} = 1$$

Notice that this case is the stochastic counterpart of equilibrium stability analysis in the presence of vanishing deterministic perturbations.

#### B. Non-vanishing Stochastic Perturbations

In this case, the system is under the influence of a stochastic perturbation that does not vanish at the equilibrium point, i.e.  $\sigma(x^*) \neq 0$ . The study of stochastic stability in this setting could be conceived as the stochastic counterpart of studying stability in the presence of non-vanishing deterministic perturbations. In this situation, one can no longer study stability of the equilibrium point  $x^*$ , nor should one expect the solution of the unperturbed system to approach the equilibrium point at  $t \rightarrow \infty$ . Instead, in the deterministic setting, the notion of ultimate boundedness should be introduced, whereby it has to be checked that the trajectory  $x(t)$  will eventually reside in a bounded region around the equilibrium point. In a similar spirit, one has to

approach the stability problem by considering the density function of the process  $x(t)$ , and prove that it converges to a stationary density, which might not be exactly centered at the deterministic fixed point. A density is defined as the function  $u(t, x)$  which satisfies

$$\text{prob}\{x(t) \in C\} = \int_C u(t, z) dz$$

It is understood that  $u(t, x)$  is an  $L^1$  function, which is nonnegative and has an integral over its domain which is identically equal to 1. Let  $B = \{b_{ij}\}_{n \times n} = \sigma(x)\sigma^T(x)$ . It can be shown that if  $b_{ij}$  and  $F_i(x)$  and their derivatives are continuous, and  $B$  satisfies the uniform parabolicity condition

$$B > \varepsilon I \quad (2)$$

where  $I$  is the identity matrix, and  $\varepsilon > 0$ , then  $u(t, x)$  satisfies the Fokker-Planck (or Kolmogorov forward) equation

$$\frac{\partial u}{\partial t} = \frac{1}{2} \sum_{i,j=1}^n \frac{\partial^2}{\partial x_i \partial x_j} (b_{ij}u) - \sum_{i=1}^n \frac{\partial}{\partial x_i} (F_i u) \quad (3)$$

We are interested in studying the behavior of (3) for  $t > 0$  for some initial density  $u(0, x) = f(x)$

*Definition 3:* We say that the coefficients  $b_{ij}$  and  $F_i$  of equation (3) are regular for the Cauchy problem if they are  $\mathcal{C}^4$  functions satisfying the uniform parabolicity conditions (2) and the following growth conditions

$$\begin{aligned}|b_{ij}(x)| &\leq M \\ |\tilde{F}_i(x)| &\leq M(1 + \|x\|) \\ |\tilde{c}_x| &\leq M(1 + \|x\|^2)\end{aligned} \quad (4)$$

where

$$\begin{aligned}\tilde{F}_i(x) &= -F_i(x) + \sum_{j=1}^n \frac{\partial b_{ij}(x)}{\partial x_j} \\ \tilde{c}_x &= \frac{1}{2} \sum_{i,j=1}^n \frac{\partial^2 b_{ij}(x)}{\partial x_i \partial x_j} - \sum_{i=1}^n \frac{\partial F_i}{\partial x_i}\end{aligned}$$

*Definition 4:* A family of operators  $P_t : L^1(\mathbb{R}^n) \rightarrow L^1(\mathbb{R}^n), t \geq 0$ , is called a stochastic semigroup if it satisfies the following conditions

$$\begin{aligned}P_t(\lambda_1 f_1 + \lambda_2 f_2) &= \lambda_1 P_t f_1 + \lambda_2 P_t f_2 \\ &\quad \forall f_1, f_2 \in L^1(\mathbb{R}^n); \lambda_1, \lambda_2 \in \mathbb{R} \\ P_t f &\geq 0 \quad \forall f \geq 0, f \in L^1(\mathbb{R}^n) \\ \|P_t f\| &= \|f\|, \forall f \geq 0, f \in L^1(\mathbb{R}^n) \\ P_{t_1+t_2} f &= P_{t_1}(P_{t_2} f), \forall f \in L^1(\mathbb{R}^n)\end{aligned} \quad (5)$$

If  $b_{ij}$  and  $F_i$  are regular for the Cauchy problem and  $f$  is a continuous function satisfying  $|f(x)| \leq ce^{\alpha|x|^2}$  ( $c > 0, \alpha > 0$ ), then (3) has a unique solution which is given by

$$u(t, x) = \int_{\mathbb{R}^n} \Gamma(t, x, y) f(y) dy \quad (6)$$

where the kernel  $\Gamma$ , called the independent solution, is independent of the initial density function  $f$ . Having this

solution, we can define a family of operators  $\{P_t\}_{t \geq 0}$  by

$$\begin{aligned} P_0 f(x) &= f(x) \\ P_t f(x) &= \int_{\mathbb{R}^n} \Gamma(t, x, y) f(y) dy \end{aligned} \quad (7)$$

Using the properties of  $\Gamma$ , one can prove that  $\{P_t\}_{t \geq 0}$  is a stochastic semigroup. This semigroup describes the behavior of the system (1).

*Definition 5:* Let  $\mathcal{D}$  be a set of densities. A stochastic semigroup  $\{P_t\}_{t \geq 0}$  is called asymptotically stable if there exists a unique  $f^* \in \mathcal{D}$  such that  $P_t f^* = f^*, \forall t$  and  $\lim_{t \rightarrow \infty} P_t f = f^*, \forall f \in \mathcal{D}$ .

Other possible behaviors for the stochastic semigroup  $\{P_t\}_{t \geq 0}$  include asymptotic periodicity and sweeping.

### III. STABILITY IN PROBABILITY OF EQUILIBRIA IN THE CASE OF VANISHING STOCHASTIC PERTURBATIONS

In this section, we characterize stochastic stability in the presence of vanishing perturbations in terms of the existence of a Lyapunov function. We state the following theorem.

*Theorem 6:* ([10]) Let  $B_r = \{x : \|x - x^*\| < r\}$ . Suppose there exists a function  $V : B_r \rightarrow \mathbb{R}^+$  which is  $\mathcal{C}^2$  in  $B_r \setminus \{x^*\}$ , such that  $V(x^*) = 0$  and  $V(x) > 0, \forall x \in B_r \setminus \{x^*\}$  (called a Lyapunov function). Suppose that  $\mathcal{L}V \leq 0$  on  $B_r$ . Then  $x^*$  is stable in probability. If  $\mathcal{L}V < 0$  on  $B_r \setminus \{x^*\}$  then  $x^*$  is asymptotically stable.

A natural direction based on this theorem is to identify the classes of systems where stability of the unperturbed system would imply that of the perturbed system, through the use of the same Lyapunov function. An easy extension occurs in the case where the stability of the equilibrium in the unperturbed system is exponential. In this case, and under the assumption that  $[\frac{\partial F}{\partial x}]$  is bounded, a well known converse Lyapunov theorem (see [9]) insures the presence of a Lyapunov function that satisfies

$$\begin{aligned} c_1 \|x\|^2 &\leq V(x) \leq c_2 \|x\|^2 \\ \dot{V} &\leq -c_3 \|x\|^2 \\ \left\| \frac{\partial V}{\partial x} \right\| &\leq c_4 \|x\| \\ \left\| \frac{\partial^2 V}{\partial x^2} \right\| &\leq c_5 \end{aligned} \quad (8)$$

for all  $x \in B_r$  for some positive constants  $c_1, c_2, c_3, c_4, c_5$

*Lemma 7:* Suppose that  $x^*$  is an exponentially stable equilibrium point of the unperturbed system in the neighborhood  $B_r$ . Further, suppose that the jacobian  $[\frac{\partial F}{\partial x}]$  is bounded and let  $V$  be a Lyapunov function of the unperturbed system satisfying (8). Then  $x^*$  is stable in probability for all vanishing stochastic perturbations satisfying

$$\|\sigma(x)\| \leq \gamma \|x\|$$

where  $\gamma^2 < \frac{2c_3}{c_5}$ .

*Proof:* Let  $V(x)$  be as described in the statement of the lemma. Then

$$\begin{aligned} \mathcal{L}V &\leq -c_3 \|x\|^2 + \frac{1}{2} \text{trace}[\sigma(x)\sigma^T(x) \frac{\partial^2 V}{\partial x^2}] \\ &\leq -c_3 \|x\|^2 + \frac{1}{2} \sigma^T(x) \frac{\partial^2 V}{\partial x^2} \sigma(x) \\ &\leq -c_3 \|x\|^2 + \frac{1}{2} \|\sigma(x)\|^2 \left\| \frac{\partial^2 V}{\partial x^2} \right\| \\ &\leq -c_3 \|x\|^2 + \frac{1}{2} K \gamma^2 \|x\|^2 \end{aligned}$$

Now, if  $\gamma^2 < \frac{2c_3}{K}$  then  $\mathcal{L}V \leq 0$  and the conclusion follows from theorem (6). ■

One should keep in mind that the bounds given in these results might be conservative due to the worst-case analysis adopted. Therefore, physical intuition about the system and the structure of the noise term can possibly guide better estimates for the region of stability.

### IV. ASYMPTOTIC STABILITY OF SOLUTIONS OF THE FOKKER-PLANCK EQUATION IN THE CASE OF NON-VANISHING STOCHASTIC PERTURBATIONS

We first state a theorem and extend it using a lemma.

*Theorem 8:* ([8]) Assume that the coefficients  $b_{ij}$  and  $F_i$  are regular for the Cauchy problem and that there is a Lyapunov function  $V$  satisfying

$$\mathcal{L}V(x) \leq -\alpha V(x) + \beta \quad (9)$$

with positive constants  $\alpha$  and  $\beta$ . Then the stochastic semigroup  $\{P_t\}_{t \geq 0}$  is asymptotically stable.

The proof of this theorem requires the use of the properties of stochastic semigroups and (9) to prove the existence of the limiting density  $f^*$  of  $\{P_t\}_{t \geq 0}$ . We will omit the proof here, but refer the reader to [8] for more details.

*Lemma 9:* Assume that the coefficients  $b_{ij}$  and  $F_i$  are regular for the Cauchy problem and that the unperturbed system  $\dot{x} = F(x)$  has a Lyapunov function such that

$$\dot{V}(x) \leq -\alpha V(x) \quad (10)$$

$$\left\| \frac{\partial^2 V}{\partial x^2} \right\| \leq K \quad (11)$$

where  $\alpha$  and  $K$  are positive constants. Then the stochastic semigroup  $\{P_t\}_{t \geq 0}$  generated by the solution of the Fokker-Planck equation corresponding to (1) is asymptotically stable.

*Proof:* The infinitesimal generator applied to  $V$  gives

$$\begin{aligned} \mathcal{L}V &= \dot{V}(x) + \frac{1}{2} \text{trace}(\sigma(x)\sigma^T(x) \frac{\partial^2 V}{\partial x^2}) \\ &\leq -\alpha V(x) + \frac{1}{2} \sigma^T(x) \frac{\partial^2 V}{\partial x^2} \sigma(x) \\ &\leq -\alpha V(x) + \frac{1}{2} \|\sigma(x)\|^2 \left\| \frac{\partial^2 V}{\partial x^2} \right\| \\ &\leq -\alpha V(x) + \frac{1}{2} nMK \end{aligned} \quad (12)$$

Using theorem (8) the conclusion of the lemma follows. ■

## V. APPLICATIONS

In this section, we provide two examples of gene regulatory networks where stochastic stability can be investigated using the machinery detailed above. Initial analysis and experimental investigation of these examples was geared toward the assessment of noise rejection and stability properties. We identify the various conditions where such conclusions can be safely drawn.

### A. Linear Transcription/Translation Modules

In a recent paper, the dynamics of transcription/translation were investigated through a simple model for gene expression prokaryotes [12]. Transcription and translation processes constitute the core of the “central dogma” of biology. First, coding regions of *DNA* (genes) are “transcribed” to synthesize these *RNA* molecules. Thereafter, proteins are generated through the “translation” of these *RNA* molecules. These proteins, in turn, affect the production of other proteins (or even auto-regulate their own production), or catalyze and regulate reactions responsible for various cellular activities. In the model of [12], mRNA molecules (*R*) are transcribed constitutively off a *DNA* template strand and at a rate  $K_R$ . mRNA molecules are then translated at a rate  $K_P$  to yield proteins as the end product (*P*). The control scheme in this setup is implemented through the regulation of mRNA production by the end product *P*. This is in turn expressed as  $K_R = K_1 - K_2P$ . Finally, mRNA and proteins are degraded at rates  $\gamma_R$  and  $\gamma_P$  respectively. This simple model is shown in Figure 1. A gene circuit corresponding to this model was experimentally constructed in *B. subtilis* and used to test the hypothesis that feedback regulation is an efficient tool for intrinsic noise rejection in gene regulatory networks.

1) *Description of the model:* Using mass-action kinetics, the model of the setup in Figure 1 can be described by

$$\begin{bmatrix} \dot{R} \\ \dot{P} \end{bmatrix} = \begin{bmatrix} -\gamma_R & -K_2 \\ K_P & -\gamma_P \end{bmatrix} \begin{bmatrix} R \\ P \end{bmatrix} + K_1 \quad (13)$$

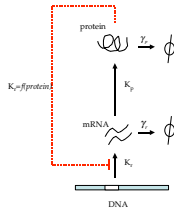


Fig. 1. Simple Transcription and Translation Gene Circuit

It can be easily verified that the unique positive fixed point of the system in (13) is  $(R^*, P^*) = (\frac{K_1 \gamma_P}{K_2 K_P + \gamma_R \gamma_P}, \frac{K_1 K_P}{K_2 K_P + \gamma_R \gamma_P})$ . We shift the equilibrium of the system to the origin by defining

$$x = \begin{bmatrix} x_1 \\ x_2 \end{bmatrix} = \begin{bmatrix} R - R^* \\ P - P^* \end{bmatrix}$$

Therefore, (13) becomes

$$\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \end{bmatrix} = \begin{bmatrix} -\gamma_R & -K_2 \\ K_P & -\gamma_P \end{bmatrix} \begin{bmatrix} x_1 \\ x_2 \end{bmatrix} \doteq Ax \quad (14)$$

2) *Additive noise:* We now consider the case of additive white noise disturbances. One can think of additive white noise as the result of extrinsic noise (due to environmental variations, for example). However, in this case, and due to the linearity of the system, it can be proved that the addition of white noise captures accurately the effect of intrinsic biochemical noise as described by the chemical master equation. We consider

$$\dot{x} = Ax + \sigma \xi \quad (15)$$

where  $\xi$  is white noise and  $\sigma$  is such that  $B = \sigma \sigma^T$  is nonsingular. Obviously, the uniform parabolicity requirement is automatically satisfied, and all the other conditions appearing in Theorem 8 and Lemma 9 are easy to verify in this example. It is also easy to check that  $A$  is Hurwitz. Therefore, for every positive definite matrix  $Q$ , there exists a unique positive definite matrix  $P$  that solves

$$PA + A^T P + Q = 0$$

Let  $V(x) = x^T P x$ . Then,

$$\begin{aligned} \dot{V}(x) &= \frac{\partial V}{\partial x} Ax = -x^T Q x \leq -\lambda_{\min}(Q) \|x\|_2^2 \\ &= -\frac{\lambda_{\min}(Q)}{\|P\|_2} \|x\|_2^2 \|P\|_2 \leq -\frac{\lambda_{\min}(Q)}{\lambda_{\max}(P)} V(x) \end{aligned}$$

Also,

$$\left\| \frac{\partial^2 V}{\partial x^2} \right\|_2 = \|2P\|_2 \leq 2\lambda_{\max}(P) \quad (16)$$

Therefore, by Lemma 9, we conclude that the stochastic semigroup generated by the Fokker-Planck equation corresponding to (15) is asymptotically stable. In fact, the limiting density is Gaussian and can be found by various methods, such as the method of undetermined coefficients by substituting  $u(t, x) = ce^{\sum_{i,j=1}^n \rho_{ij} x_i x_j}$  into the corresponding Fokker-Planck equation. This is a well known result in stochastic differential equations theory.

3) *Parametric noise:* We now consider the situation where the entries of the matrix  $A$  are corrupted by noise. Specifically, we consider the situation where

$$\begin{aligned} \gamma'_R &= \gamma_R + \delta_1 \xi \\ K'_2 &= K_2 + \delta_2 \xi \\ \gamma'_P &= \gamma_P + \delta_3 \xi \\ K'_P &= K_P + \delta_4 \xi \end{aligned}$$

In this case, we study the system

$$\dot{x} = Ax + \sigma x \xi \quad (17)$$

where

$$\sigma = \begin{bmatrix} -\delta_1 & -\delta_2 \\ \delta_3 & -\delta_4 \end{bmatrix}$$

Using the same Lyapunov function as in the previous case, we get that

$$\begin{aligned} \mathcal{L}V &\leq -\lambda_{\min}(Q)\|x\|_2^2 + \lambda_{\max}(P)\|\sigma x\|_2^2 \\ &\leq -\lambda_{\min}(Q)\|x\|_2^2 + \lambda_{\max}(P)\|\sigma\|_2^2\|x\|_2^2 \end{aligned} \quad (18)$$

Therefore,  $\mathcal{L}V \leq 0$  if  $\|\sigma\|_2^2 < \frac{\lambda_{\min}(Q)}{\lambda_{\max}(P)}$ . A choice for  $Q$  that maximizes this ratio can be checked to be  $Q = I$  where  $I$  is the identity matrix. Therefore, the equilibrium point  $(R^*, P^*)$  is stable in probability for all parametric noise of the form (17) such that  $\|\sigma\|_2^2 < \frac{1}{\lambda_{\max}(P)}$ . This estimate of the noise size is conservative. Indeed, in the case of linear systems, better bounds and conditions for stability can be found. We mention without proof one such result, and use it to find a destabilizing intensity for the parametric noise.

*Lemma 10:* ([13]) Consider the system in (1) with  $\sigma(x) = \sigma x$ . Then the equilibrium point 0 is stable in probability if and only if

$$\text{Re}\lambda(\mathcal{M}) < 0$$

where

$$\mathcal{M} = I_n \otimes A + A \otimes I_n + \sigma \otimes \sigma$$

with  $\otimes$  being the Kronecker product and  $I_n$  the identity matrix. This condition is equivalent to the existence of a symmetric positive definite matrix  $P$  as a solution to the equation  $AP + PA^T + B^T PB + Q = 0$  for any symmetric positive definite matrix  $Q$ .

We now borrow the model parameter values from [12], and use the previous lemma to find perturbations  $\sigma$  that destabilize the system. One such choice is shown in Figure 2 for a noisy perturbation affecting  $\gamma_r$ . The figure shows  $x_2$  which undergoes bursts of growing amplitudes.

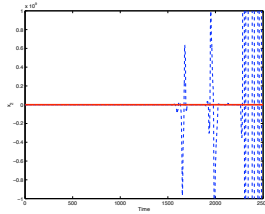


Fig. 2. transcription/translation module destabilized by noise. The system is stable for low levels of noise (solid line) and unstable for higher levels (dotted line)

### B. A Nonlinear Gene Regulation Model

Our second example is borrowed from [14] where a simple autoregulatory gene circuit was designed in the bacterium *E. coli* [14]. In their circuit, a repressor protein tetracyclin (*TetR*) was fused to green fluorescent protein, and placed down of a lambda promoter containing two tetracyclin operator. By binding to these operators, *TetR* can inhibit its own production, hence implementing a negative feedback loop. The experimental setup is shown in Figure 3.



Fig. 3. *TetR* regulatory network

1) *Description of the Model:* The method used to design and analyze this circuit is based on a transcriptional level, promoter control model that assumes statistical thermodynamic equilibrium between operator binding sites and regulatory proteins. The kinetic model for production of the repressor  $R$  is given by

$$\frac{dR}{dt} = \langle RNAP_{pr} \rangle K_{pr} A_R - \lambda_{deg} R \quad (19)$$

where  $K_{pr}$  is the rate of *RNAP* isomerization from closed to open complex,  $A_R$  is the number of protein ( $R$ ) molecules synthesized per complex formed,  $\lambda_{deg}$  is the protein degradation rate, and  $\langle RNAP_{pr} \rangle$  is the fractional saturation of the promoter by *RNA* polymerase taken to be the cumulative probability that *RNAP* is bound to promoter.  $\langle RNAP_{pr} \rangle$  can be computed based on standard thermodynamical, yielding the following differential equation for the concentration of the repressor

$$\dot{R} = nk_1 a \frac{k_p P}{1 + k_p P + k_r R} - k_{deg} R \quad (20)$$

where  $P$  is the concentration of the *RNA* polymerase,  $k_p$  and  $k_r$  are the binding constants of the polymerase and the repressor respectively,  $k_1$  is the promoter isomerization rate from closed to initiating complex,  $a$  the proportionality constant between mRNA and protein,  $k_{deg}$  is the degradation rate of the repressor, and  $n$  is the gene copy number. This system has two real equilibrium points located at

$$R_{1,2}^* = \frac{k_{deg}(1 + \gamma_1) \pm \sqrt{[k_{deg}(1 + \gamma_1)]^2 + 4\gamma_1\gamma_2 k_{deg} k_r}}{2k_{deg} k_r}$$

where we have defined  $\gamma_1 = nk_1 a$  and  $\gamma_2 = k_p P$ . Since we are considering chemical concentrations, which can only assume positive or zero values, we consider the unique positive equilibrium point that we subsequently denote by  $R^*$ . Note that the system described by (20) is positive in the sense that  $\mathbb{R}^+$  is forward invariant, i.e. if  $x(t_0) \in \mathbb{R}^+$ , then  $x(t, x(t_0)) \in \mathbb{R}^+, \forall t \in I$ , where  $I$  is the maximal forward interval of existence of the solution  $x(t, x(t_0))$ . To see that the system in (20) is positive, it suffices to check that  $F(0) = \frac{\gamma_1 \gamma_2}{1 + \gamma_2} > 0$ . We shall use this fact in what follows.

2) *Additive white noise:* We first consider the effect of additive white noise on the system in (20). As before, we shift the equilibrium point of the system to zero by defining  $x = R - R^*$ . The equation for the system is then given by

$$\dot{R} = \frac{\gamma_1 \gamma_2}{1 + \gamma_2 + k_r(x + R^*)} - k_{deg}(x + R^*) + \sigma \xi \quad (21)$$

We check that the growth conditions in (4) are satisfied.

$$\begin{aligned} |\tilde{F}(x)| &= \left| -\frac{\gamma_1 \gamma_2}{1 + \gamma_2 + k_r(x + R^*)} + k_{deg}(x + R^*) \right| \\ &\leq \gamma_1 \gamma_2 + k_{deg} R^* + k_{deg} |x| \leq \lambda(1 + |x|) \end{aligned}$$

where  $\lambda = \max\{\gamma_1 \gamma_2 + k_{deg} R^*, k_{deg}\}$ . Similarly,

$$\begin{aligned} |\tilde{c}(x)| &= \left| -\frac{\gamma_1 \gamma_2}{(1 + \gamma_2 + k_r(x + R^*))^2} + k_{deg} \right| \\ &\leq \gamma_1 \gamma_2 + k_{deg} \end{aligned}$$

Therefore, conditions (4) are satisfied with  $M = \max\{\sigma^2, \lambda, \gamma_1 \gamma_2 + k_{deg}\}$ . Of course, the uniform parabolicity condition (2) is still trivially satisfied. Now, consider the Lyapunov function  $V(x) = \frac{1}{2}x^2$ . Then

$$\begin{aligned} \dot{V} &= x \left[ \frac{\gamma_1 \gamma_2}{1 + \gamma_2 + k_r(x + R^*)} - k_{deg}(x + R^*) \right] \\ &= - \left[ \frac{\gamma_1 \gamma_2 k_r}{(1 + \gamma_2 + k_r(x + R^*))(1 + \gamma_2 + k_r R^*)} + k_{deg} \right] x^2 \end{aligned}$$

where we have used the fact that  $\frac{\gamma_1 \gamma_2}{1 + \gamma_2 + k_r R^*} - k_{deg} R^* = 0$ . Notice that  $1 + \gamma_2 + k_r(x + R^*) \geq 0$  since  $x + R^* = R \geq 0$ . Also,  $\frac{\partial^2 V}{\partial x^2} = 1$ . All the conditions of Lemma 9 are satisfied, and we can conclude the asymptotic stability of the stochastic semigroup generated by the Fokker-Planck equation corresponding to (20). It is implied here that this stability is for every initial distribution  $u(0, R)$  where  $R$  lies entirely in  $\mathbb{R}^+$ .

3) *Parametric Noise*: We now consider the situation where one of the parameters in (20) is corrupted by noise. Suppose, for example, that the promoter isomerization rate  $k_1$  fluctuates rapidly around its mean value, that is

$$k_1' = k_1 + \delta_1 \xi \quad (22)$$

with  $\xi$  corresponding to white noise. With this varying  $k_p$ , the dynamics of the system become

$$\begin{aligned} \dot{R} &= \frac{\gamma_1 \gamma_2}{1 + \gamma_2 + k_r(x + R^*)} - k_{deg}(x + R^*) \\ &+ \frac{\gamma_2 \delta_1 n a}{1 + \gamma_2 + k_r(x + R^*)} \xi \end{aligned} \quad (23)$$

As opposed to the previous case, noisy parameters result in what is referred to as multiplicative noise, i.e. noise that depends on the state of the system itself. As in the additive noise case, straightforward algebra shows that  $B = \left(\frac{\gamma_2 \delta_1 n a}{1 + \gamma_2 + k_r(x + R^*)}\right)^2$  satisfies the uniform parabolicity condition and that  $\tilde{F}(x)$  and  $\tilde{c}(x)$  satisfy the growth conditions. Therefore, using the same  $V(x) = \frac{1}{2}x^2$  and Lemma (9), we conclude that a stochastic parametric perturbation of any magnitude of the form (22) cannot possibly change the stability behavior of the system.

For the case of vanishing perturbations, it can also be readily shown again using theorem (6) and lemma (7) that the equilibrium point  $R^*$  preserves its stability for any perturbation  $\sigma(x)$  such that  $|\sigma(x)| \leq \gamma|x|$  where  $\gamma^2 < 2\gamma_1 \gamma_2 k_r$

## VI. CONCLUSIONS AND FUTURE WORK

In this work, we have illustrated the use of stochastic stability notions in the study of the behavior of gene regulatory networks. We have mostly inferred stochastic stability based on the type of deterministic stability that the system possesses. In some instances, this approach can yield conservative results as there are examples where noise can increase the region of stability of a system. In this case, and in order to prove stability, an approach based on the construction of a Lyapunov function that has a negative infinitesimal generator (but not necessarily a negative derivative) would be necessary. The use of algorithmic methods, such as SOSTOOLS [15] can be of great applicability in that respect. Furthermore, it is likely that exploiting the structure of the classes of systems that arise in the modeling of gene networks can possibly yield more accurate stochastic stability bounds. In addition, studying cascades of these systems (such as signal transduction pathways) would ultimately necessitate considering and extending notions of stochastic input-to-state stability [16]. Finally, for the analysis of stochastic stability in the presence of intrinsic biochemical noise, one needs to account for the special structure of the coupling between the noise and the system. We are actively pursuing all of these issues.

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