Stability Analysis of Hybrid Stochastic Gene Regulatory Networks

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Abstract

Gene regulatory networks (GRNs) represent complex nonlinear coupled dynamical systems that models gene functions and regulations at the system level. Previous research has described GRNs as coupled nonlinear systems under parametric perturbations without considering the important aspect of stochasticity. However, a realistic model of a GRN is that of a hybrid stochastic retarded system that represents a complex nonlinear dynamical system including time-delays and Markovian jumping as well as noise fluctuations. In this paper, we interpret GRNs as hybrid stochastic retarded systems and prove their asymptotical stability. The theoretical results are elucidated in an illustrative example and thus shown how they can be applied to reverse engineering design.

Key words: Genetic regulatory network, retarded systems, Markov chain, stochastic systems, p-th moment stability

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1 Introduction

Gene regulatory combining a coupled dynamics of fast and slow states constitute an important class of biological networks [1]. Synthetic design of such networks is very sensitive to parameter perturbations. Errors in parameters such as external perturbations and modeling errors are caused by data inaccuracies or computation errors. These perturbations can lead to location errors of equilibria, to instabilities, and even to spurious states. Therefore, a rigorous understanding of the qualitative robustness properties of gene regulatory networks with respect to parameter variations on both a fast or slow time scale and under consideration of a transcriptional time delay [4] became imperative. In [2], the gene regulatory networks are formulated as coupled nonlinear differential systems operating at different time-scales under vanishing perturbations and time delays. In [3], gene regulatory networks are described as either two-time scale systems without delay [3] or as unperturbed systems [5].

It is well-known that molecules and reaction rates are subject to significant statistical fluctuations and especially gene regulation is an intrinsically noisy process due to intracellular and extracellular noise perturbations and environmental fluctuations. Additionally, the transition from one state to the next is based on certain transition probabilities forming a homogeneous Markov chain with finite state space. This aspect motivates the formulation of a stochastic model with Markovian switches to describe the dynamics of gene regulation. Previous work investigated genetic regulatory networks with parameter uncertainties and noise perturbations [7] or of Markov-type with delays and uncertain mode transition rates [8]. It is naturally to propose a more detailed model with delays that combines Markovian jumping and noise perturbations and analyze its dynamic behavior. In this paper, we analyze the robustness properties of gene regulatory networks, modeled by a system of competitive differential equations, from a rigorous analytic standpoint [6]. The network under study models the delayed nonlinear dynamics under consideration of Markovian jumping and noise perturbations.

2 Problem Statement

Gene regulatory networks represent circuits of genes that interact and regulate the expression of other genes by proteins. The change in expression of a gene is regulated by protein synthesis in transcriptional, translational and post-translational processes. Taking into account a transcriptional time delay [4] and the fact that mRNA typically decays much faster than the protein, we considered in a previous work [2] the gene regulatory network described by the following equation

$$\begin{aligned}\dot{M}_i(t) &= -a_i M_i(t) + \sum_{j=1}^{n} \tilde{w}_{ij}\tilde{g}_j(P_j(t-\rho)) + B_i \\ \dot{P}(t) &= -c_i P_i(t) + d_i M_i(t)\end{aligned} \tag{1a}$$

where $M_i(t), P_i(t) \in R$ are the concentrations of mRNA and protein of the ith node, respectively. The parameters a_i and c_i are the decay rates of mRNA and protein, respectively; d_i is the translation rate, $\tilde{g_j}(x) = \frac{\left(\frac{x}{\beta_j}\right)^{H_j}}{\left(1+\left(\frac{x}{\beta_j}\right)^{H_j}\right)}$, $B_i = \sum_{j\in I_i} b_{ij}$ and I_i is the set of all the j which is a repressor of gene i, $\tilde{W} = (\tilde{w_{ij}}) \in R^{n\times n}$ is defined as follows

$$\tilde{w}_{ij} = \begin{cases} b_{ij}, & : \text{ if transcription factor j is an activator of gene i} \\ 0, & : \text{ if there is no link from node j to i} \\ -b_{ij} & : \text{ if transcription factor j is a repressor of gene i} \end{cases} \tag{2}$$

Let $(M^{*^T}, P^{*^T})^T$ be an equilibrium point of the system (1a). By shifting the equilibrium of the system to the origin, we obtain a general formulation of the GRN as a nonlinear coupled system with both time-varying delays for feedback regulation $\rho_i(t)$ and translation $\sigma_i(t)$:

$$\begin{aligned}\dot{M}_i(t) &= -a_i M_i(t) + f_j(P_1(t-\rho_1(t)), \cdots, P_n(t-\rho_n(t))) \\ \dot{P}(t) &= -c_i P_i(t) + d_i M_i(t-\sigma_i(t))\end{aligned} \tag{3a}$$

We thus obtain $g_i(p_i(t)) = \tilde{g}_i(P_i(t)+P_i^*) - \tilde{g}_i(P_i^*)$. Because $\tilde{g}_i$ is a monotonically increasing function with saturation, $g_i(\cdot)$ satisfies the sector condition $0 \leq \frac{g_i(x)}{x} \leq k_i$.

In terms of Hill function we obtain

$$\begin{aligned}\dot{M}_i(t) &= -a_i M_i(t) + \sum_{j=1}^{n} \tilde{w}_{ij} g_j(P_j(t-\rho_j(t))) \\ \dot{P}(t) &= -c_i P_i(t) + d_i M_i(t-\sigma_i(t))\end{aligned} \tag{4a}$$

Further for simplicity, we will assume that all feedback regulation and translational delays are equal $\rho_1 = \cdots, \rho_n = \rho$ and $\sigma_1 = \cdots, \sigma_n = \sigma$. The above model can be formulated as a n-dimensional GRN

$$\begin{aligned} \dot{\mathbf{M}}(t) &= \mathbf{AM}(t) + \mathbf{Wg}(\mathbf{p}(t - \rho(t))) \\ \dot{\mathbf{P}}(t) &= -\mathbf{CP}(t) + \mathbf{DM}(t - \sigma(t)) \end{aligned} \tag{5a}$$

with $A = \mathrm{diag}\{a_1, a_2, \cdots, a_n\}$, $C = \mathrm{diag}\{c_1, c_2, \cdots, c_n\}$ and $D = \mathrm{diag}\{d_1, d_2, \cdots, d_n\}$.

3 Theoretical Concepts of Hybrid Stochastic Retarded Systems

In the following, we will introduce some notations and theoretical concepts from stochastic functional differential equation theory we will be using throughout this paper.

Notations:

$(\Sigma, \mathcal{F}, \{\mathcal{F}_t\}_{t\geq 0}, P)$: complete probability space with a filtration $\{\mathcal{F}\}_{t\geq 0}$ that is right-continuous and $\mathcal{F}_0$ contains the P-null sets.

$B(t) = (B_1(t), \cdots, B_m(t))^T$: m-dimensional Brownian motion defined on the probability space.

$|\cdot|$ is the Euclidean norm in R^n.

$\mathcal{C}([-\tau, 0]; R^n)$ with $\tau \geq 0$ denotes the family of all continuous R^n-valued functions ψ on $[-\tau, 0]$ with the norm $||\psi|| = \sup\{|\psi(\theta)| : -\tau \leq \theta \leq 0\}$.

$\mathcal{C}^b_{\mathcal{F}_0}([-\tau, 0]; R^n)$ is the family of all $\mathcal{F}_0$-measurable bounded $\mathcal{C}([-\tau, 0]; R^n)$-valued random variables $\zeta = \{\zeta(\theta) : -\tau \leq \theta \leq 0\}$.

Let $r(t), t \geq 0$, be a right-continuous Markov chain on the probability space taking values in a finite space $S = \{1, 2, \cdots, N\}$ with generator $\Gamma = (\gamma_{ij})_{N\times N}$ given by

$$P\{r(t+\Delta) = j : r(t) = i\} = \begin{cases} \gamma_{ij}\Delta + o(\Delta), & : \quad \text{if} \quad i \neq j, \\ 1 + \gamma_{ij}\Delta + o(\Delta) & : \quad \text{if} \quad i = j, \end{cases} \tag{6}$$

where $\Delta > 0$ and $\gamma_{ij} \geq 0$ is the transition rate from i to j if $i \neq j$ while $\gamma_{ij} = -\sum_{i\neq} \gamma_{ij}$.

We also assume that the Markov chain $r(\cdot)$ is independent of the Brownian motion $B(\cdot)$. The sample pathes of $r(t)$ are right-continuous step functions with a finite number of simple jumps in any finite subinterval of $R_+ := [0, \infty)$.

In the following we describe a hybrid stochastic retarded system (HRRS) driven by continuous-time Markovian chains [6] used in stochastic modeling. Let such a n-dimensional HRRS be given as

$$dx(t) = f(x_t, t, r(t))dt + g(x_t, t, r(t))dB(t) \tag{7}$$

on $t \geq 0$ with initial data $x_0 = \{x(\theta) : -r \leq \theta \leq 0\} = \theta \in \mathcal{C}^b_{\mathcal{F}_0}([\tau, 0]; R^n)$ and with

$$\begin{cases} f & : \quad \mathcal{C}([-\tau, 0]; R^n) \times R_+ \times S \to R^n \\ g & : \quad \mathcal{C}([-\tau, 0]; R^n) \times R_+ \times S \to R^{n\times m} \end{cases}$$

with measurable functions with $f(0, t, i) = 0$ and $g(0, t, i) = 0$ for all $t \geq 0$. Thus, (7) has a trivial solution $x(t; 0) = 0$. $x_t = \{x(t + \theta) : -r \leq \theta \leq 0\}$ represents a $\mathcal{C}([-r, 0]; R^n)$-valued stochastic process. We also assume that g, h are smooth functions such that (7) has only continuous solutions $x(t; \zeta)$ on $t \geq 0$.

Further $C^{2,1}(R^n \times R_+ \times S)$ is the family of all nonnegative functions $V(x, t, i)$ on $R^n \times R_+ \times S$ being twice continuously differentiable in x and once in t. With $V \in \mathcal{C}^{2,1}(R^n \times R_+ \times S; R_+)$, we define an operator $\mathcal{C}$, from $\mathcal{C}([-\tau, 0]; R^n) \times R_+ \times S \to R$ by

$$\begin{aligned} \mathcal{L}V(x_t, t, i) = {} & V_t(x, t, i) + V_x(x, t, i)f(x_t, t, i) && (8)\\ & + \frac{1}{2}\mathrm{trace}[g^T(x_t, t, i)V_{xx}(x, t, i)g(x_t, t, i)] && (9)\\ & + \sum_{j=1}^{N} \gamma_{ij}V(x, t, j) && (10) \end{aligned}$$

where

$$\begin{cases} V_t(x,t,i) & : & = \frac{\partial V(x,t,i)}{\partial t} \\ V_x(x,t,i) & : & = \left(\frac{\partial V(x,t,i)}{\partial x_1}, \cdots, \frac{\partial V(x,t,i)}{\partial x_n}\right) \\ V_{xx}(x,t,i) & : & = \left(\frac{\partial^2 V(x,t,i)}{\partial x_i \partial x_j}\right)_{n\times n} \end{cases}$$

We give a useful definition regarding the stability of HRRS.

Definition The trivial solution of (7) is

a.) pth ($p > 0$) moment stable if, for every $\epsilon > 0$, there exists $\delta = \delta(\epsilon) > 0$ such that

$$E|x(t;\zeta)|^p \leq \epsilon, \quad \forall t \geq 0$$

whenever $||\zeta||^p < \delta_0$;

b.) globally pth moment asymptotically stable if it is pth moment stable and, moreover, for all $\zeta \in \mathcal{C}^b_{\mathcal{F}_0}([-\tau, 0]; R^n)$,

$$\lim_{t\to\infty} E|x(t;\zeta)|^p = 0 \tag{11}$$

As shown in [6], we immediately see that (global) pth moment (asymptotic) stability implies (global) stochastic (asymptotic) stability.

4 Asymptotic Stability Analysis of Hybrid Stochastic Retarded GRNs

The objective of this study is to discuss the stability properties of the hybrid stochastic retarded GRN. The analysis is based on a mathematical model and a rigorous analytic standpoint.

Based on the above model described by equation (4), we will now introduce noise perturbations and Markovian jumping parameters. As previously discussed, the parameters of the GRN may change randomly at discrete time instances or in other words, the GRN has finite modes and it can switch from one to another at different times determined by a Markov chain. Since the switching probabilities are not a priori known, the GRN can be modeled by a hybrid system. The system of the GRN has both continuous and discrete states which are described by a Markovian jumping system. We can rewrite the GRN from equation (5a) as a hybrid stochastic retarded system

$$dX(t) = F(X(t), t, r(t))dt + G(X(t), X(t-\rho(t)), X(t-\sigma(t)), t, r(t))dB(t) \tag{12}$$

with $X(t) = [M(t), P(t)], Y(t-\rho(t)) = X(t-\rho(t)) = [0, \cdots, 0, P(t-\rho(t))]$ and $Z(t-\sigma(t)) = X(t-\sigma(t)) = [M(t-\sigma(t)), 0, \cdots, 0]$. X, Y and Z are $2n \times 1$ vectors. $G(X(t), X(t-\rho(t)), X(t-\sigma(t)), t, r(t))$ is the noise intensity function. The Markov chain $r(\cdot)$ is given as in (6) and $B(\cdot)$ is the Brownian motion.

We will make the following assumptions for computational simplicity without loss of generality.

Assumptions:

(A1) Let us assume that $\sum_{j=1}^{N} \gamma_{ij} = 1$.

(A2) The trace can be approximated as trace$[G^T(x, y, z, t, i) \cdot G(x, y, z, t, i)] \leq \rho_1|x(t)|^2 + \rho_2|y(t)|^2 + \rho_3|z(t)|^2$.

(A3) For the nonlinear term, we assume $F(x, y, z, t, i) \leq -\rho_4|x(t)|^2 + \rho_5|y(t)|^2 + \rho_6|z(t)|^2$.

Theorem: Let $p > 0$, $c_2 \geq c_1 > 0$ and $\lambda_{oi} \geq 0, \lambda_{1i} \geq 0, \lambda_{2i} \geq 0$ such that $\lambda_{0i} \geq \lambda_{1i} + \lambda_{2i}$ for all $1 \leq i \leq N$. Let $\lambda : R \times S \rightarrow R$ be a continuous nondecreasing function with respect to $s \in R$ for all $s \geq 0$ and $1 \leq i \leq N$. Moreover $\lambda(s, i)/s > 0$ for all $s > 0$ and $1 \leq i \leq N$. Assume that there exists a function $V \in C^{2,1}(R^n \times R_+ \times S; R^+)$ such that the following inequality [10,9]

$$c_1|X|^p \leq V(X, t, i) \leq c_2|X|^p, \quad \forall (X, t) \in R^n \times [-\tau, \infty) \tag{13}$$

is satisfied and, moreover, for all $1 \leq i \leq N$, let

$$E\mathcal{L}V(X, Y, Z, t, i) \leq -\frac{1}{2}E\lambda(c_1|X|^p,) \tag{14}$$

for all $t \geq 0$. For all $X, Y, Z \in R^n, t \geq 0$ and $1 \leq k \leq N$, we assume

$$\begin{aligned}
\mathcal{L}V(X, Y, Z, t, i) \leq & -\lambda_{oi} \max_{1 \leq k \leq N} V(X, t, k) && (15)\\
& + \lambda_{1i} \min_{1 \leq k \leq N} V(Y, t-\rho(t), k) && (16)\\
& + \lambda_{2i} \min_{1 \leq k \leq N} V(Z, t-\sigma(t), k) && \\
& - \lambda(\max_{1 \leq k \leq N} V(X, t, k), i) && (17)
\end{aligned}$$

then under the assumptions A1 to A3 the trivial solution of is globally pth moment asymptotically stable.

Proof:

In [6] was shown that the following inequalities are valid

$$\min_{1\leq i\leq N} EV(Y, t-\rho(t), i) \leq \max_{1\leq i\leq N} EV(X, t, i) + \frac{1}{2(1+\lambda_{1i})} E\lambda(\max_{1\leq i\leq N} V(X, t, i) \tag{18}$$

and

$$\min_{1\leq i\leq N} EV(Z, t-\sigma(t), i) \leq \max_{1\leq i\leq N} EV(X, t, i) + \frac{1}{2(1+\lambda_{2i})} E\lambda(\max_{1\leq i\leq N} V(X, t, i) \tag{19}$$

Based on the above assumptions A1 to A3 and the above inequalities (13) to (19), we obtain

$$\begin{aligned} E\mathcal{L}V(X, Y, Z, t, i) \leq & -\lambda_{oi} \max_{1\leq k\leq N} EV(X, t, k) \qquad (20) \\ & + \lambda_{1i} \min_{1\leq k\leq N} EV(Y, t-\rho(t), k) \\ & + \lambda_{2i} \min_{1\leq k\leq N} EV(Z, t-\sigma(t), k) \\ & - \lambda(\max_{1\leq k\leq N} EV(X, t, k), i) \\ \leq & -\frac{1}{2} E\lambda(c_1|X|^p, i) \qquad (21) \end{aligned}$$

for all $1 \leq k \leq N$. Since $\lambda(s, i)/s > 0$ for all $s > 0$ and $1 \leq k \leq N$, we can show that $E\lambda(c_1|X|^p, i) > 0$ if $E|X|^p > 0$ and this completes the proof.

Remark 1: By choosing as a Lyapunov function $V : R \times R_+ \times S \to R_+$ as $V(X, t, i) = X^2, \forall i$, we obtain as a consequence of the stability conditions based on the assumptions (A1) to (A3):

$$\begin{aligned} \rho_5 + \rho_6 &> 2\rho_4 - \rho_1 \qquad (22a) \\ \rho_1 - 2\rho_4 &> \rho_2 + \rho_3 \end{aligned}$$

The derived conditions (22a) can be used in reversed engineering design.

Remark 2: The above Theorem was adapted from [6]. The derived theoretical concepts are illustrated in an example.

Example 1: Let us consider a two-gene Markovian model (5a) with $A = \text{diag}(1.4 \quad 1.52), C = \text{diag}(1.4 \quad 1.32)$ and $D = \text{diag}(1 \quad 1)$ and $W = \begin{bmatrix} 1.2 & 1 \\ 1.2 & -1.3 \end{bmatrix}$

and $\zeta(t)$ being the Gaussian noise. Let $r(t)$ be a right-continuous Markov chain taking values in $S = 1, 2$ with $\Gamma = (\gamma_{ij})_{2\times 2} = \begin{bmatrix} -1.68 & 1.68 \\ 1.49 & -1.49 \end{bmatrix}$. Let us assume that we want to determine the parameters ρ_1, ρ_2 and ρ_3. Based on the conditions (22a) and the Theorem, we can derive the inequalities $\rho_1 > 0.74$ and $\rho_1 - 3.04 > \rho_2 + \rho_3$ to be fullfilled in order to ensure the stability of system (5a).

In summary, we have shown that the most detailed model of GRN known yet and described by a hybrid stochastic retarded system is asymptotically stable.

5 Conclusion

We analyzed the dynamical behavior of genetic regulatory networks subject to noise perturbations and time-delays, and with both continuous and discrete states described by Markovian jumping systems based on the theory of hybrid stochastic retarded systems. The proposed model represents the most complex GRN model known so far in the literature. We assumed that the nonlinear nominal system and the noise intensity are bounded and that the Markov chain is independent of the Brownian motion. Specifically, we applied these theoretical concepts to study asymptotic stability properties of gene regulatory networks. In this sense we established stability results for the perturbed genetic regulatory network and determined the conditions that ensure the existence of globally pth moment asymptotically stable equilibria of the perturbed system. A sufficient condition for the nonlinear part and the noise intensity function are derived. The established results have potential application for reverse engineering and robust biosynthetic gene regulatory network design.

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