Robust Stability of Sets For Uncertain Impulsive Gene Regulatory Networks

G. Stamov and M. Kostadinova - Gocheva

***Abstract*—This article extends methods of stability analysis for discontinuous impulsive gene regulatory networks (IGRNs). Main results: for the model, uniform global robust exponential stability and uniform robust global asymptotic stability are related to sets. The main methods of investigation are the comparison principle and Lyapunov-like impulsive functions.**

***Keywords*— Gene Regulatory Networks, Impulses, Robust stability of Sets**

I. INTRODUCTION

Gene regulatory networks, also known as genetic regulatory networks (GRNs), are specialized biological networks used to represent the interactions and exchanges between messenger RNA (mRNA) and protein molecules. Modern modeling methodologies that have assured the study of genetic regulatory systems' features have been made possible by the contributions of several specialists in the domains of biology, neurology, applied mathematics, biology, control science, and cybernetics. The use of systems of ordinary differential equations is among the most often used strategies [1], [11], [17].

Researchers have also employed impulsive differential equations to explain the development of discontinuous models since short-term (impulsive) disturbances are frequently seen in the behavior of GRNs [7], [16]. Models that are suggested are IGRNs [3], [8], [10], [13], [14].

The most researched aspects of many GRN models are their qualitative attributes. The stability behavior of them all drew the most attention from researchers [3], [4], [5], [6], [8], [10], [11], [12], [14], [17]. Molecular and cellular comprehension of the live organism depends heavily on the stability behavior of genetic networks [10]. But the stability of the GRN model's individual states was the focus of the majority of the research that had already been done. The concept of stability of sets is a fundamental aspect of extended stability. This concept covers various specific cases, such as the stability of a state, stability of invariant sets, and stability of moving manifolds [2], [9], [15]. The task involves conducting study on the stability characteristics of a specific region. This approach looks very suitable for studying the stability behavior of mRNA and proteins across different locations, particularly in the context of gene regulatory networks (GRNs). Moreover, the concept of extended stability is particularly interesting because of the fact that certain gene regulatory networks (GRNs) have the ability to reach several stable states. This research attempts to apply the concept of stability of sets to an impulsive control GRN model. An analysis will be conducted on the system's stable behavior in relation to a wide variety of conditions using the Lyapunov's function technique.

II. PRELIMINARY NOTES

We will use the next notations: $\mathbb{R}^n$ denotes the $n-$dimensional Euclidean space, the norm of a vector $x = (x_1, x_2, \ldots, x_n)^T \in \mathbb{R}^n$ is defined by

$||x|| = \sqrt{\sum_{i=1}^{n} x_i^2}$, $\mathbb{R}_+ = [0, \infty)$ and

$\mathbb{R}_+^n = \mathbb{R}_+ \times \ldots \times \mathbb{R}_+$.

We introduce the following IGRN model given by

$$\begin{cases} \dot{m_i} = -a_i m_i(t) + \sum_{j=1}^{n} w_{ij}(t) f_j\left(p_j(t)\right) + B_i(t), t \neq t_k, \\ \dot{p_i}(t) = -c_i p_i(t) + d_i(t) m_i(t), t \neq t_k, \\ \Delta m_i(t_k) = \propto_{ik} m_i(t_k) + \upsilon_{ik}, \\ \Delta p_i(t_k) = \gamma_{ik} p_i(t_k) + x_{ik}, \end{cases} \quad (1)$$

that regulates the concentrations of mRNA $m_i(t)$ and protein $p_i(t)$ at time t, where:

i/ $i, i = 1,2, \ldots, n$ is the number of nodes, the positive constants a_i, c_i represent the dilution rates, using the dimensionless transcriptional bounded rate $q_{ij}(t)$ at time t of transcription factor j to i, $w_{ij}(t)$ are defined as

$$w_{ij}(t) = \begin{cases} q_{ij}(t), & \text{when } j \text{ is an activator of gene } i, \\ -q_{ij}(t), & \text{when } j \text{ is a repressor of gene } i, \\ 0, & \text{when there is no link from the node } j \text{ to gene } i \end{cases}$$

$d_i(t) \in \mathbb{R}$ denotes the translation rate, f_j represents the regulatory (activation) of the protein function and is in the form

$$f_i(p_i) = \frac{(p_j/\beta_j)^{H_j}}{1+(p_j/\beta_j)^{H_j}},$$

where H_i denotes the Hill coefficient and β_j are positive scalars. $q_i(t)$ is defined as $q_i(t) = \sum j \in I_i q_{ij}(t)$, where I_i is the set of all repressors of gene i.

ii/ the moments $t_k \in \mathbb{R}_+, k = 1,2, \ldots$ are such that $t_1 < t_2 < \cdots < t_k < \cdots$ and $\lim_{k\to\infty} t_k = \infty$.

The scalars $m_i(t_k) = m_i(t_k^-)$ and $p_i(t_k) = p_i(t_k^-)$ represent the concentration of mRNA $m_i(t)$ and protein

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$p_i(t)$ before an impulsive perturbation at time t_k, respectively, $m_i(t_k^+)$ and $p_i(t_k^+)$ are the levels in the concentration of mRNA $m_i(t)$ and protein $p_i(t)$ after an impulsive perturbation at the moment t_k, respectively, the constant sequences $\{\alpha_{ik}\}, \{\gamma_{ik}\}, \in \mathbb{R}$ and the sequences $\{\nu_{ik}\}, \{\chi_{ik}\}, \in \mathbb{R}$ describe the intensity of abrupt changes of $m_i(t)$ and $p_i(t)$ at the impulsive moments t_k and can be applied as controls. We have:

$$\Delta m_{i(t_k)} = m_i(t_k^+) - m_i(t_k) = \alpha_{ik} m_i(t_k) + \nu_{ik}$$

$$\Delta p_{i(t_k)} = p_i(t_k^+) - p_i(t_k) = \gamma_{ik} p_i(t_k) + \chi_{ik},$$

$i = 1, 2, \ldots, n$ and $k = 1, 2, \ldots$

It is well known from the theory of discontinuous impulsive systems [7], [16] as well as from the results on IGRNs [3], [8], [10], [13], [14], that any solution of model (1)

$(m(t), p(t))^T, p(t, t_0, u_0) = (m(t, t_0, m_0), p(t, t_0, p_0))^T,$

where

$m(t; t_0, m_0) = (m_1(t; t_0, m_{01}), m_2(t; t_0, m_{02}), \ldots, m_n(t; t_0, m_{0n}))^T,$

$p(t; t_0, p_0) = (p_1(t; t_0, p_{01}), p_2(t; t_0, p_{02}), \ldots, p_n(t; t_0, p_{0n}))^T$

with intial values

$(m_0, p_0)^T = (m_{01}, \ldots, m_{0n}, p_{01}, \ldots, p_{0n})^T, m_{oi}, p_{oi} \in \mathbb{R}$

at some initial time $t_0 \in \mathbb{R}$.

This is a piecewise continuous function that has discontinuities at the moments t_k, $k = 1,2, \ldots$ and

$$m_i(t_k^+) = (1 + \alpha_{ik}) m_i(t_k) + \nu_{ik}$$

$$p_i(t_k^+) = (1 + \gamma_{ik}) p_i(t_k) + \chi_{ik}$$

for $i = 1,2, \ldots n$, $k = 1,2, \ldots$

For simplicity, we will use the next notation:

$$u(t) = (m(t), p(t))^T,$$

$$u(t, t_0, u_0) = (m(t; t_0, m_0), p(t; t_0, p_0))^T,$$

$$u_o = (m_0, p_0)^T$$

Let $t_0 \in [0, t_1)$. Consider the general set $M\ [t_0, \infty) \times \mathbb{R}_+^{2n}$ and introduce the next notations:

$$M(t) = \{u \in R_+^{2n}: (t, u) \in M, t \in \mathbb{R}_+\};$$

$$d(u, M(t)) \inf_{v \in M(t)} ||u - v||$$

is the distance between $u \in R_+^{2n}$ and $M(t)$;

$$M(t)(\varepsilon) = \{u \in R_+^{2n}: d(u, M(t)) < \varepsilon\} (\varepsilon > 0);$$

$$\overline{M}(t)(\varepsilon) = \{u \in R_+^{2n}: d(u, M(t)) \leq \varepsilon\}.$$

We will assume that for any $t \in \mathbb{R}_+$ the set $M(t)$ is not empty, and adopt the following boundedness and stability of sets definitions [2], [9], [15] with respect to the system (1).

Definition 1. The solutions of model (1) are:

(a) equi-M-bounded, if for any positive constant $\eta > 0$ there exists a constant $\beta = \beta(\eta) > 0$ such that $u_0 \in M(t_0^+)(\eta)$ imply $u(t; t_0, u_0) \in M(t)(\beta), t \geq 0$;

(b) uniformly M-bounded, if the number β in (a) does not depend from η.

Definition 2. The set M is said to be:

(a) uniformly stable with respect to system (1), if for any positive constants $\eta > 0$ and $\varepsilon > 0$ there exists a constant $\delta = \delta(\eta, \varepsilon) > 0$ such that and $u_0 \in M(t_0^+)(\delta)$ imply $u(t; t_0, u_0) \in M(t)(\varepsilon), t \geq 0$;

(b) uniformly globally attractive with respect to system (1), if for any positive constants $\eta > 0$, $\varepsilon > 0$ there exists a constant $\sigma = \sigma(\eta, \varepsilon) > 0$ such that $u_0 \in \overline{M}(t_0^+)(\eta)$ imply $u(t; t_0, u_0) \in M(t)(\varepsilon), t \geq \sigma$;

(c) uniformly globally asymptotically stable with respect to system (1), if M is a uniformly stable and uniformly globally attractive set of system (1), and if the solutions of system (1) are uniformly M-bounded;

(d) uniformly globally exponentially stable with respect to system (1), if there exist strictly positive constants k and κ such that

$$d(u(t; t_0, u_0), M(t)) \leq k d(u_0, M(t)) e^{\{-\kappa t\}}, t \geq 0.$$

The main results will be proven using Lyapunov's like piecewise functions from the class V_0. For this reason we need the sets and notations:

$$\mathcal{G}_k = \{(t, u): t \in (t_{k-1}, t_k), u \in R_+^{2n}\},$$

$$k = 1,2, \ldots, t_0 = 0, \qquad \mathcal{G} = \bigcup_{k=1}^{\infty} \mathcal{G}_k.$$

Definition 3. A function $V: [0, \infty) \times \mathbb{R}_+^{2n} \to \mathbb{R}_+$, belongs to the class V_0 if the following conditions are fulfilled:

1. $V(t, u)$ is continuous in G, locally Lipschitz continuous with respect to its second argument on each of the sets $\mathcal{G}_k$, and $V(t, u(t)) = 0$ for $(t, u) \in M, t \geq 0$ and $V(t, u(t)) > 0$ for $(t, u) \in \{\mathbb{R}_+ \times \mathbb{R}_+^{2n}\} \backslash M$;
2. For each $k = 1, 2, \ldots$ and $u \in \mathbb{R}_+^{2n}$, there exist the finite limits

$$V(t_k, u) = V(t_k^-, u) = \lim_{\substack{t \to t_k \\ t < t_k}} V(t, u),$$

$$V(t_k^+, u) = \lim_{\substack{t \to t_k \\ t < t_k}} V(t, u).$$

For $t \in [0, \infty), t \neq t_k, k = 1, 2, \ldots$, we define the following derivative of $V \in V_0$ with respect to the system (1)

$$D^+ V(t, u((t))) = \lim_{\xi \to 0^+} \sup \frac{1}{\xi} [V(t + \xi, u(t) + \xi F(t, u(t)) - V(t, u(t))].$$

The following comparison lemma from [16] will also be applied in our stability analysis.

III. ROBUST STABILITY OF SETS RESULTS

Throughout this paper, we assume that the following conditions are satisfied:

C1. The functions $w_{ij}(t)$ and $d_i(t)$ are bounded, i.e there exist positive constants $K_{ij}^{(1)}$, and $K_i^{(2)}$, such that

$$|w_{ij}(t)| \leq K_{ij}^{(1)}, \qquad |d_i(t)| \leq K_i^{(2)}$$

for $i = 1,2,\dots,n,\quad j = 1,2,\dots,n$ and $t \in \mathbb{R}_+$.

C2. The activation functions f_j, $j = 1,2,\dots,n$, are continuous and there exist positive constants l_j with

$$0 \leq \frac{f_{j(\xi_1)} - f_{j(\xi_2)}}{\xi_1 - \xi_2} \leq l_j$$

for $\xi_1, \xi_2 \in \mathbb{R}$, $\xi_1 \neq \xi_2$.

C3. $0 < t_1 < t_2 < \cdots < t_k < t_{k+1} < \cdots$, and $\lim_{k\to\infty} t_k = \infty$.

In our main theorems we will use the Hahn class of functions $\mathcal{K} = \{h \in C[\mathbb{R}_+, \mathbb{R}_+]$: h is strictly increasing and $h(0) = 0\}$.

Lemma 1. [18]
Assume that:
1. Conditions C1–C3 hold;
2. There exists a function $V \in V_0$ such that the inequalities

$$h_1(d(u, M(t))) \leq V(t,u) \leq h_2(d(u, M(t))),$$

hold, where $h_1(s) \to \infty$ as $s \to \infty$, $t \in \mathbb{R}_+$, $u \in \mathbb{R}_+^{2n}$, $h_1, h_2 \in \mathcal{K}$;

3. For $t \in \mathbb{R}_+$, $u \in \mathbb{R}_+^{2n}$,

$$V(t^+, u + I_k(u)) \leq V(t,u), t = t_k,$$

and the inequality

$$D^+V(t,u) \leq -h_3\left(d(u, M(t))\right), t \neq t_k, k = 1,2,\dots,$$

is valid, where $h_{3(s)} > 0$ for $s > 0$.

Then the set M is uniformly globally asymptotically stable with respect to system (1).

Lemma 2. [18]
Assume that, in *Lemma 2*, $h_i = c_i d^r(u, M(t))$ for $t \in \mathbb{R}_+, i = 1,2$, and $h_3 = c_3 d^r(u_0, M(t)))$ for $t \neq t_k$, where $c_i > 0$ are constants $i = 1,2,3, r \geq 1$, then the set M is uniformly globally exponentially stable with respect to system (1).

Lemma 3. [18]
Assume that:
1. Conditions C1–C3 hold;
2. The following condition met

$$\min\{\min_{1\leq i\leq n} a_i, \min_{1\leq i\leq n} c_i\} -$$

$$\frac{1}{2}\left(\sum_{i=1}^n K_i^{(2)} + \max_{1\leq i\leq n} \sum_{j=1}^n l_j K_{ij}^{(1)}\right) > 0$$

3. The constants α_{ik} and γ_{ik} are such that

$$-1 \leq \alpha_{ik} \leq 0, \ -1 \leq \gamma_{ik} \leq 0,$$

$i = 1,2,\dots,n, k = 1,2,\dots$

Then the set

$$M = \{\mathbb{R}_+ \times \mathbb{R}_+^{2n} : \underline{m}_i^* \leq u_i \leq \overline{m}_i^*, \underline{p}_i^* \leq u_i\, \overline{p}_i^*,$$
$$i = 1,2,\dots,n\}$$

is uniformly globally exponentially stable with respect to system (1).

In this section, a robust stability of sets result for the (IGRNs) model (1) will be presented. To this end we will extend the model (1) to incorporate uncertain terms.

Consider the following uncertain (IGRNs) model corresponding to the system (1):

$$\begin{cases} \dot{m}_i(t) = -(a_i + \tilde{a}_i)\, m_i(t) + \sum_{j=1}^n (w_{ij} + \tilde{w}_{ij}(t))(f_j\left(p_j(t)\right) \\ + \left(\tilde{f}_j\left(p_j(t)\right)\right) + B_i(t) + \tilde{B}_i(t), t \neq t_k \\ \dot{p}_i(t) = -(c_i + \tilde{c}_i)p_i(t) + (d_i(t) + \tilde{d}_i(t))m_i(t), t \neq t_k, \\ \Delta m_i(t_k) = (\alpha_{ik} + \tilde{\alpha}_{ik})m_i(t_k) + v_{ik} + \tilde{v}_{ik}, \\ \Delta p_i(t_k) = (\gamma_{ik} + \tilde{\gamma}_{ik})p_i(t_k) + x_{ik} + \tilde{x}_{ik}, \end{cases} \quad (2)$$

where the constants $\tilde{a}_i, \tilde{c}_i, \tilde{\alpha}_{ik}, \tilde{\gamma}_{ik}$ and the continuous functions $\tilde{w}_{ij}$, $\tilde{f}_j$, $\tilde{B}_i$, $\tilde{d}_i$, represent the uncertain terms in the system (2)[18]. Note that, if all of these constants and functions are zeros, then we will recover the ”nominal system” (1)[18].

In numerous applications, the activation function of a neural network model may involve uncertain terms. Uncertain parameters also appeared in the connection coefficients as well as in the external inputs, due to uncertainty in the environment, data measurement, etc. Thus, it is essential to study the effect of uncertain terms on the stability behavior of (IGRNs).

With the next definition we introduce the notion of robust exponential stability of a set with respect to system (2).

Definition 4. The set M is said to be robustly uniformly globally exponentially stable with respect to system (1) if for any constants $\tilde{a}_i, \tilde{c}_i, \tilde{\alpha}_{ik}, \tilde{\gamma}_{ik}$ and functions $\tilde{w}_{ij}$, $\tilde{f}_j$, $\tilde{B}_i$, $\tilde{d}_i$, the set M is uniformly globally exponentially stable with respect to system (2).

Here we need the next conditions:

C4. For $\tilde{a}_i^+ = \sup_{\chi\in\mathbb{R}} \tilde{a}_i(\chi), i = 1,2,\dots,m$, we have

$$\min_{1\leq i\leq n} a_i - a_i \leq \max_{1\leq i\leq n} \tilde{a}_i^+ \leq \max_{1\leq i\leq n} a_i - a_i,$$

$$\min_{1\leq i\leq n} c_i - c_i \leq \max_{1\leq i\leq n} \tilde{c}_i^+ \leq \max_{1\leq i\leq n} c_i - c_i,$$

C5. The functions $\tilde{c}_{ij}, \tilde{I}_i, \tilde{w}_{ij}, i, j = 1,2,3\dots,m$, are continuous on their domains, and

$$\sup_{t\in\mathbb{R}} \tilde{c}_{ij}(t) = \tilde{c}_{ij}^+, \ \sup_{t\in\mathbb{R}} \tilde{w}_{ij}(t) = \tilde{w}_{ij}^+.$$

C6. There exist positive constants $\tilde{L}_i, i = 1,2,\dots,n$, with

$$|\tilde{f}_j(\chi_1) - \tilde{f}_j(\chi_2)| \leq \tilde{L}_i|\chi_1 - \chi_2|,$$

for all $\chi_1, \chi_2 \in \mathbb{R}$, $\chi_1 \neq \chi_2$ and $\tilde{f}_j(0) = 0$.

C7. The unknown constants $\tilde{\gamma}_{ik}, \tilde{\chi}_{ik}$ are bounded and $\tilde{\gamma}_{ik} \in [-1-\gamma_{ik}, -\gamma_{ik}]$, $\tilde{\chi}_{ik} \in [-1-\chi_{ik}, -\chi_{ik}]$, $i = 1,2,\dots,n$.

Theorem 1.
1. Conditions *Lemma 2* hold.
2. The inequality

$$
\min_{1 \le i \le m} \Big\lfloor 2\left(\widetilde{d}_i + \underline{a_i} B_i\right)
- \overline{a_i} \sum_{j=1}^{m} ((L_j + \tilde{L}_j)(c_{ij}^{+} + \tilde{c}_{ij}^{+})
+ (M_j + \widetilde{M}_j)(w_{ij}^{+} + \widetilde{w}_{ij}^{+}) + (L_I + \tilde{L}_I)(c_{ji}^{+} + c_{ji}^{+}) \Big\rfloor
> \max_{1 \le i \le m} ((M_i + \widetilde{M}_i) \sum_{j=1}^{m} \overline{a_j} (w_{ji}^{+}) > 0
$$

is satisfied.

Then the set $M = [-\tau, \infty) \times \Omega \times \{\mathbb{R}^m : \underline{u_i^*} \le u_i \le \overline{u_i^*}, i = 1, 2, \dots, m\}$ is robustly uniformly globally exponentially stable with respect to the impulsive reaction-diffusion CGNN (2).

Proof. The proof of the uniform global exponential stability of the set M with respect to system (2) for any values of the uncertain terms can be conducted similarly to the proof of *Lemma 3* and *Lemma 4* using the assumptions C1–C7. Hence, it follows by Definition 2, that the set $M = [-\tau, \infty) \times \Omega \times \{\mathbb{R}^m : \underline{u_i^*} \le u_i \le \overline{u_i^*}, i = 1, 2, \dots, m\}$ is robustly uniformly globally exponentially stable with respect to the uncertain IGRN (2).

IV. Conclusion

The stability of set concept is introduced to an IGRN model for the first time. Using the Lyapunov function technique some efficient criteria are established. Examining delays is an interesting subject for future research. Fractional-order extensions of the proposed model and results will also be developed. The introduced stability notion can also be studied for other neural network biological models that possess several equilibrium states.

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