ON THE IMPULSIVE GENE REGULATORY NETWORKS

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Abstract: *This paper presents an analysis of research on Impulsive Genetic Regulatory Neural Networks (IGRNs). These networks represent a specialized type of biological regulatory systems, which are subject to disruptions in their activity or sudden changes in their dynamics.*
Various mathematical models are being considered and detailed techniques are used to analyze the impact of impulsivity on gene expression models. The analysis of these networks, examines how impulsive genetic regulatory networks change the dynamics of gene expression and what their impact is on regulatory processes in cells.
The overview ends with summary of the obtained findings and conclusions, emphasizing the importance of impulsive genetic regulatory networks for interpreting complex mechanisms of gene regulation. This lays the foundation for future research and development in the field of gene regulation and cellular biology.

Keywords: *gene regulatory networks, impulses, gene expression, mathematical model*

1. INTRODUCTION

The study of genomic regulatory networks (GRNs) has been a significant topic of study in biology and neurobiology over the past few decades. How to build gene regulatory networks (GRNs) using gene expression data on the one hand, and what the dynamic properties of GRNs are on the other. In this paper, stability - one of the crucial dynamic properties of GRNs is analyzed [1].

Gene expression is a complex process regulated at multiple stages in protein synthesis. In addition to DNA transcriptional regulation, the best-studied form of regulation, gene expression can be controlled during RNA processing and transport (in eukaryotes), RNA translation, and post-translational modification of proteins. Protein degradation and turnover of intermediate RNA products can also be regulated within the cell. Proteins performing these regulatory functions are produced by other genes. This gives rise to genetic regulatory systems structured by networks of regulatory interactions between DNA, RNA, proteins, and small molecules [2].

Regulation of gene expression (or gene regulation) refers to the processes that cells use to create functional gene products (RNA, proteins) from the information stored in genes (DNA). These processes range from DNA-RNA transcription to post-translational modification of proteins. Gene regulation is crucial for life as it enhances the flexibility and adaptability of an organism by allowing it to express a protein when needed.

There are two main models for genetic networks:

1) Boolean or logical model;
2) Differential equations or dynamical system model.

A gene's state is determined by a Boolean function based on the states of other associated genes. In the Boolean model, each gene exhibits activity in either one of two states: ON or OFF. The concentrations of gene products, such as RNA and proteins, are described as continuous values in differential equations or the dynamic system model. This approach provides a more accurate representation and enables a comprehensive understanding of the nonlinear dynamic behavior exhibited by biological systems. However, compared to the Boolean model, simulations using this continuous model often require significantly more calculation time. Hybrid models that combine discrete and continuous system models have been developed to illustrate both switch-like and smooth fluctuations in genetic networks [3].

In 2002, Chen [3] introduced the DDE model for GRNs:

$$\begin{cases} \dot{m}(t) = -K_m m(t) + c(p(t,\tau_p)) \\ \dot{p}(t) = -K_p m(t) + d(p(t,\tau_m)) \end{cases} \quad (1)$$

where $\mathbb{R}^n$ denotes the n-dimensional Euclidean space $m = (m_1, \dots, m_n) \in \mathbb{R}^n$ и $p = (p_1, \dots, p_n) \in R^n$ represent the concentrations of mRNAs and proteins, respectively. $К_m = diag(K_{m1}, \dots, K_{mn}) \in \mathbb{R}^{n\times n}$ and $К_p = diag(K_{п1}, \dots, K_{пn}) \in \mathbb{R}^{n\times n}$ are positive real diagonal matrices that represent the degradation rates for mRNAs and proteins, respectively. $\tau_m = (\tau_{m1}, \dots, \tau_{mn}) \in \mathbb{R}^n$ and $\tau_p = (\tau_{p1}, \dots, \tau_{pn}) \in \mathbb{R}^n$ are positive real vectors indicating the time delays for mRNAs and proteins respectively, and $m(\tau, \tau_m) = (m_1(\tau - \tau_{m1}), \dots, m_n(\tau - \tau_{mn}))$ and $p(\tau, \tau_p) = (p_1(\tau - \tau_{p1}), \dots, p_n(\tau - \tau_{pn}))$, $c(p) = (c_1(p), \dots, c_n(p)) \in \mathbb{R}^n$ and $d(p) = (d_1(p), \dots, d_n(p)) \in \mathbb{R}^n$ are generally nonlinear.

This dynamic system model for time-delayed genetic regulatory networks using functional differential equations and analyzes the nonlinear properties of the model in terms of local stability and transitions from one steady state to another.

The quantities of proteins and mRNA are represented nonlinearly in an ordinary differential equation (ODE) model for genetic regulatory networks, which also accounts for the time delays in transcription and translation. It then analyzes local stability and bifurcation to provide complex information for understanding gene expression patterns and regulatory pathways. The proposed model transforms the original interacting network into a few simple transcendental equations, which greatly reduces the complexity of the model and facilitates robustness and bifurcation analysis when analyzing nonlinear robustness properties, even for large systems. [4]

To test the theory, a repressor model was used as a numerical example. The stability of the equilibrium state of the network with time delays is specifically analyzed. However, to understand the oscillatory behavior, it is necessary to study the nonlinear properties of periodic or chaotic solutions both analytically and numerically. [5]

2. MATHEMATICAL MODEL

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

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

We introduce the following (IGRNs) model given by:

$$\begin{cases} \dot{m}_\iota = -a_i m_i(t) + \sum_{j=1}^n w_{ij}(t) f_j\left(p_j(t)\right) + B_i(t), \ t \neq t_k, \\ \dot{p_\iota}(t) = -c_i p_i(t) + d_i(t) m_i(t), \ t \neq t_k, \\ \Delta m_i(t_k) = \propto_{ik} m_i(t_k) + \upsilon_{ik}, \\ \Delta p_i(t_k) = \gamma_{ik} p_i(t_k) + x_{ik}, \end{cases} \quad (2)$$

that regulates the concentrations of mRNA$m_i(t)$ and protein $p_i(t)$ at time t, where:
$i = 1,2, \dots, n$ e is the number of the node, the positive constantsa_i, c_i represent the dilution rates, using the dimensionless transcriptional bounded rate $q_{ij}(t)$ at time t of transcription factor j до i, $w_{ij}(t)$ are defined as

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

$d_i(t) \in \mathbb{R}$ denotes the translation rate, f_i 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 coefficients and β_j are positive scalars, $q_i(t)$ is defined as $q_i(t) = \sum \mu \in I_i\, q_{ij}(t)$, where I_i is the set of all repressors of gene *i*;
the moments $t_k \in \mathbb{R}_+$ $k = 1,2,...,$ are such that $t_1 < t_2 < \cdots < t_k < \cdots$ and $\lim_{k\to\infty} t_k = \infty$, the scalars $m_i(t_k) = m_i(t_k^-)$ и $p_i(t_k) = p_i(t_k^-)$ represent the concentration of mRNA $m_i(t)$ and protein $p_i(t)$ before an impulsive perturbation at time t_k, respectively, $m_i\left(t_k^+\right)$ and $p_i\left(t_k^+\right)$ 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$\{v_{ik}\}, \{\chi_{ik}\}, \in \mathbb{R}$ describe the intensity of abrupt changes of $m_i(t)$ и $p_i(t)$ at the impulsive moments t_k and can be applied as controls. We have:

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

and

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

where $i = 1,2,\ldots,n, k = 1,2,\ldots.$

It is well know from the theory of discontinuous impulsive models, as well as from the results on impulsive GRNs, that any solution of model (2)

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

where

$$m(t; t_0, m_0) = \left(m_1(t; t_0, m_{01}), m_2(t; t_0, m_{02}), \ldots, m_n(t; t_0, m_{0n})\right),$$
$$p(t; t_0, p_0) = \left(p_1(t; t_0, p_{01}), p_2(t; t_0, p_{02}), \ldots, p_n(t; t_0, p_{0n})\right),$$

with initial values$(m_0, p_0)^T = (m_{01}, \ldots, m_{0n,} p_{01}, \ldots, p_{0n})^T$, $m_{0i}, p_{0i} \epsilon \mathbb{R}$ at some initial time $t_0 \epsilon \mathbb{R}$, is a piecewise continuous function that has discontinuities at the moments $t_{k,}$ $k = 1,2,...$ and

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

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

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

Let, for simplicity we use the next notation:

$$u(t) = (m(t), p(t))^T,\ u\left(t, t_{0,}, u_0\right) = \left(m\left(t, t_{0,}, m_0\right), p\left(t, t_{0,}, p_0\right)\right)^T, \quad (3)$$

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

3. MAIN RESULTS

According to [6], the model used is of the form:

$$\begin{cases} \frac{\partial x(t,z)}{\partial t} = \sum_{k=1}^{m} \frac{\partial}{\partial z_k}(B_k \frac{\partial x(t,z)}{\partial z_k} - Ax(t,z) + Wf\big(y(t-\sigma(t),z)\big), \\ \frac{\partial y(t,z)}{\partial t} = \sum_{k=1}^{m} \frac{\partial}{\partial z_k}(G_k \frac{\partial y(t,z)}{\partial z_k} - Cy(t,z) + Dx(y(t-\tau(t),z)), \\ x(s,z) = \varphi(s,z) \quad y(s,z) = \varphi(s,z), \ \forall s \in [-\omega, 0], \end{cases} \tag{4}$$

where $z = (z_1, z_2, \dots, z_m)^T \in \Omega \subset R^m, \Omega = \{z| \ |z_k| \leq l_k, k = 1,2, \dots, m\}$ is the diffusion range of mRNAs and proteins, l_k is a constant.

$B_k = diag(b_{1k}, b_{2k}, \dots, b_{nk}) > 0$ and $G_k = diag(b_{1k}, b_{2k}, \dots, b_{nk}) > 0$ denote the transmission diffusion rate matrices of mRNA and protein, respectively. $x(t,z) = col\{x_1(t,z), x_2(t,z), \dots, x_n(t,z)\} \in R^n$, $y(t,z) = col\{y_1(t,z), y_2(t,z), \dots, y_n(t,z)\} \in R^n$.

The initial functions $\varphi(s,z), \varphi(s,z) \in C^1([-\omega, 0] \times \Omega, R^n), \omega = max\{\tau_2, \sigma_2\}$.

In this model, the finite-time stability analysis for the GRN unbounded Dirichlet conditions are given in Theorem 3.1 of [4].

This result focuses on the finite-time stability issues for GRNs, without considering exogenous inputs or network outputs. The feasibility of the proposed methods is elucidated through a numerical simulation example. Future research will build upon achieving improved stability conditions with fewer variables and investigating the state estimation problem or control problem for GRNs.

According to [7], the model used is of the form:

$$\begin{cases} \dot{x}(t) = -K_m x(t) + E\tilde{g}\big(y(t-\tau_p(t)\big), & t \neq t_k, \\ \dot{y}(t) = -K_p x(t) + Dx(y(t-\tau_m(t)), & t \neq t_k, \\ \Delta x(t) = J_k\big(x(t_k^-)\big), & t = t_{k,} \\ \Delta y(t) = H_k\big(y(t_k^-)\big), & t = t_{k,} \end{cases} \tag{5}$$

where $x(t) = \big[x_1(t), x_2(t), \dots, x_n(t)\big)^T$, $y(t) = \big[y_1(t), y_2(t), \dots, y_n(t)\big)^T$,

$K_m = diag(k_{m1}, k_{m2}, \dots, k_{mn})$, $K_p = diag\big(k_{p1}, k_{p2}, \dots, k_{pn}\big)$, $E = \sum_{j=1}^{n} f_{ij}, \dots, \sum_{j=1}^{n} f_{nj})$,

$\tilde{g}(.) = [\tilde{g}_1(.), \tilde{g}_2(.), \dots, \tilde{g}_n(.)]^T$, the time sequence t_k satisfies $0 < t_0 < t_1 < t_2 < \cdots < t_к < t_{k+1} < \cdots$, and $\lim_{k\to\infty} t_k = \infty, J_k, H_k \in R^n$. These sequences J_k and H_k are the effect of sudden change in the state of system. Assume that $\Delta x = x\big(t_k^+\big) + x(t_k^-)$ at fixed points sequence t_k, where $x\big(t_k^+\big) = \lim_{h\to 0} x(\tau_k + h)$ and $x\big(t_k^-\big) = \lim_{h\to 0} x(\tau_k - h)$.

The quadratic from$||x(t)||_Q^2$ is definite as $||x(t)||_Q^2 = x^T(t)Q(t)x(t)$ for any state vector x(t), и $Q(t)$ is the non-negative definite matrix.

The initial value for system (4) e $x(t_0) = \varphi(t), \ y(t_0) = \psi(t)$.

By considering the finite-time stability problem for GRNs with impulsive effects in (5), it is observed that sufficient conditions are established for the system to be stable for a finite time based on the functional method using Lyapunov-based techniques. A numerical example is presented to illustrate the numerical results obtained. In future analizyles, the finite- time stability will be further explored for genetic regulation with noise perturbations and the dynamics of stochastic GRNs with mixed time delays.

According to [8], the model used is of the form:

$$\begin{cases} \frac{\partial \tilde{m}_i(t,x)}{\partial \tau} = \sum_{k=1}^{l} \frac{\partial}{\partial x_k}\left(D_{ik} \frac{\partial \tilde{m}_i(t,x)}{\partial x_k}\right) \\ -a_i \tilde{m}_i(t,x) + \sum_{j=1}^{n} w_{ij}\, g_j\left(\tilde{p}_j(\tau - \sigma(t), x)\right) + q_i, \\ \frac{\partial \tilde{p}_i(t,x)}{\partial \tau} = \sum_{k=1}^{l} \frac{\partial}{\partial x_k}\left(D^*{}_{ik} \frac{\partial \tilde{p}_i(t,x)}{\partial x_k}\right) \\ -c_i \tilde{p}_i(t,x) + b_i \tilde{m}_i(\tau - \tau(t), x), \quad i = 1,2,\ldots,n, \end{cases} \tag{6}$$

where $x(t) = (x_1, x_2, \ldots, x_n)^T \in R^1$, $\Omega = \{x \mid |x_k| \le L_k\}$, L_k is constant, k = 1,2, … , l; $D_{ik}(t,x) > 0$ and $D_{ik}(t,x) > 0$ denote the transmission diffusion operator along the ith gene of mRNA and protein, respectively.
The initial conditions are given by

$$\tilde{m}_i(s,x) = \varphi_i(s,x)\,, s \in (-\infty, 0], \qquad i = 1,2,\ldots,n,$$
$$\tilde{p}_i(s,x) = \varphi_i^*(s,x)\,, s \in (-\infty, 0], \qquad i = 1,2,\ldots,n,$$

where $\varphi_i(s,x)$ и $\varphi_i^*(s,x)$ are bounded and continuous on$(-\infty, 0] \times \Omega$.

This study analyses the stability problem for delay genetic regulatory networks (DGRNs) with reaction-diffusion conditions (RDTs). DGRNs are mathematical models used to study regulatory processes in organisms genomes. They represent complex systems of genetic components, such as genes and proteins, that interact with each other and regulate gene expression.

The temporal dependence of gene regulation is considered in DGRNs. This means that the regulation of gene expression can be activated or deactivated after a certain period of time following a specific event or stimulus. In that case, the model can represent the dynamics of regulatory processes as the reason for the time delay in the flow of information in the genetic network.

The work is on the type of different boundary conditions, delay-dependent criteria with respect to LMI are obtained. Numerical examples of the effectiveness of the results proposed in this paper are presented.

According to [9], the model used is of the form:

$$\begin{cases} \frac{\partial \tilde{m}(t,x)}{\partial \tau} = \sum_{k=1}^{l} \frac{\partial}{\partial x_k}\left(D_k \frac{\partial \tilde{m}_i(t,x)}{\partial x_k}\right) - \tilde{A}_m(t,x) + Wf(\tilde{p}\big(t - \sigma(t)\big), x)), \\ \frac{\partial \tilde{p}(t,x)}{\partial \tau} = \sum_{k=1}^{l} \frac{\partial}{\partial x_k}\left(D_k^* \frac{\partial \tilde{p}(t,x)}{\partial x_k}\right) - \tilde{C}_m(t,x) + B\tilde{m}\big(t - \sigma(t)\big), x) \end{cases} \tag{7}$$

where
$A = diag(\mathrm{a}_1, \mathrm{a}_2, \ldots, \mathrm{a}_n)$, $B = diag(b_1, b_2, \ldots, b_n)$, $C = diag(c_1, c_2, \ldots, c_n)$,
$D_k = diag(D_{1k}, D_{2k}, \ldots, D_{nk})$, $D_K^* = diag(D_{1k}^*, D_{2k}^*, \ldots, D_{nk}^*)$,
$\tilde{m}(t,x) = col\big(\tilde{m}_1(t,x), \tilde{m}_2(t,x), \ldots, \tilde{m}_n(t,x)\big)$, $\tilde{p}(t,x) = col\big(\tilde{p}_1(t,x), \tilde{p}_2(t,x), \ldots, \tilde{p}_n(t,x)\big)$,
$f\,(\tilde{p}(t - \sigma(t), x)) = col(\,f_1(\tilde{p}_1(t - \sigma\,(t), x)), \ldots, (\,f_n(\tilde{p}_n(t - \sigma\,(t), x))$
$f_i\,\big(\tilde{p}_i(t - \sigma(t), x)\big) = g_i(\tilde{p}_i(t - \sigma\,(t), x) + p_i^*) - g_i(p_i^*) \quad i \in \{n\}$

The work focuses on the state estimation problem of DGRNs with RDT. A state observer is designed to estimate the concentrations of mRNA and proteins based on available network outputs, ensuring that the system error is asymptotically stable. A pair of numerical examples is presented to validate the theoretical results. It is believed that extending the results to H∞ is feasible but not applicable to other conditions.

4. CONCLUSION

Based on the achieved results in the field of differential equations, the following conclusion can be drawn: the condition for investigating the stability of sets has been satisfied.

The conclusion of this scientific work, based on the provided information, focuses on various aspects of stability and state estimation for delayed genetic regulatory networks (DGRNs) with reaction-diffusion conditions (RDTs). The following aspects have been examined:

1. Time stability for GRNs: The focus is on the finite-time stability issues for GRNs without considering exogenous inputs or network outputs. Functional Lyapunov-based methods and numerical simulations have been used to clarify the feasibility of the proposed stability methods.
2. Reaction-diffusion conditions in DGRNs: The focus is on the stability problems for DGRNs with RDTs. These are mathematical models used to investigate the regulatory processes in the genomes of organisms, taking into account the temporal dependence of gene regulation. Various boundary conditions and numerical examples have been considered to evaluate the effectiveness of the proposed results.
3. State estimation of DGRNs with RDTs: The focus is on the problem of state estimation for DGRNs with RDTs. A state observer has been designed to estimate the concentrations of mRNA and proteins based on network outputs. This observer ensures asymptotic stability of the system error.

   Numerical examples have been presented to validate the theoretical results.

In the future, it is expected that this work will be expanded to investigate additional aspects of stability, such as stochastic dynamics and noise disturbances in GRNs with RDTs. Furthermore, the problem of control for GRNs will be examined, aiming to achieve better stability conditions with fewer variables.

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