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Bifurcation analysis of a mathematical model for genetic regulatory network with time delays

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ABSTRACT

In this paper, we aim to investigate the dynamics of a gene regulatory network which is a time-delayed version of the model proposed by Elowitz and Leibler *[Nature 403 (2000) 335–338]*. Based on the normal form theory and center-manifold reduction, Hopf bifurcations including the bifurcation direction and stability of the bifurcated periodic orbits are investigated. We also discuss effects of transcriptional rate and time delay on the amplitude and period of the oscillation of the network. It shows that variations of time delay or transcriptional rate can change the period and amplitude of the oscillation. More precisely, (i) the amplitude increases with small time delay, while the change of amplitude is not sensitive to relatively large time delay. However, the robustness of amplitudes is not true any more for the case of using the transcriptional rate as parameter, where amplitude always increases quickly and linearly with the transcriptional rate; (ii) the period of oscillation increases as the time delay increases, but it grows up initially as the transcriptional rate increases and then keeps unchanged to certain constant value, which implies that the robustness of period to the transcriptional rate variations occurs. Our numerical simulations also support the theoretical conclusions, namely both suggest that time delay and transcriptional rate can be used as control parameters in genetic regulatory networks.

1. Introduction

Gene regulation is one of the greatest mysteries in modern science. Since there is great difficulty in finding the mechanisms that relate multiple biochemical processes inside a cell, the study of how protein within a cell regulates its own products or the products of other proteins is necessary and important. Unfortunately, most cellular processes involve many different molecules interconnected. Thus the metabolism of a cell consists of many interlinked reactions, in which products of one reaction affect the next. These reactions form a metabolic network where interlinked molecules have cross-talk and affect different signalling cascades [2,26,45].

A set of genes and gene products, together with their regulatory interactions, constitutes a genetic regulatory network. A model of such a network describes interactions between DNAs, RNAs, proteins and small molecules in an organism, through which gene expression is controlled [30,42]. Gene regulatory network can be used to model many biological phenomena that describe feedback processes such as heart beat, breathing, temperature and even our sleeping habits. There are many biological

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phenomena that are very helpful for our lives and need us to find answers such as how cells respond to DNA damage. It is also a very interesting topic in cancer biology. One of the main tasks that many mathematical biologists are currently working on is the development of mathematical models. For example, the model for p53, which is a tumor suppressor protein also known as tumor protein 53, gene network, which is used to investigate the dynamics of p53 protein. As we know, the p53 protein is one of the main guardians that protect us against damages in our DNA [46,51].

Besides what mentioned above, computational models of regulatory networks are also expected to benefit several other fields; for example, in medicine, mechanisms of diseases that are characterised by dysfunction of regulatory processes can be elucidated. Development of predictive model is very beneficial to biotechnological projects by saving time and costs of conducting some costly or unreasonable lab experiments. So gene regulatory networks (GRNs) have become an emerging area of research in biological and biomedical science. Mathematical study on GRNs is an important attempt toward solving challenging problems.

In both development of mathematical models and conducting experiments, it is important to understand the interactions between genes and their protein products. Recently, experiments [1,14,23,37] and theoretical techniques [15,28,35,47,48] have been developed to understand the dynamics of gene regulatory networks. Theoretically, the gene network structure as an abstraction of the system of chemical dynamics includes how protein products affect the expression of other genes and their associated proteins. Thus, mathematical models of gene regulatory networks can greatly help us to discover higher order structure of an organism and to gain deep insights into both static and dynamic behaviours of gene networks through the information of parameters obtained from either experimental or observation data.

Several mathematical models of gene regulatory networks have been proposed over the last couple of decades, for example [30,38] and the references in. And the most common modeling techniques include graphs, Boolean networks, Bayesian networks, Petri nets, reverse engineering methods, and coupled differential equations, [3,7,10,13,21,31,40,43,47,55] to name but a few. It is getting clearer and clearer that simple mathematical models, such as the ones governed by ordinary differential equations alone are not good enough to capture the rich phenomena observed in experiments.

That the fact of time delay comes naturally due to the slow biochemical reactions in transcription and translation, or degradation and other cellular processes within a cell makes introducing time delays into the models an important attempt to improve model performance. It has become one of the important areas in mathematical biology and is attracting more applications, such as in infectious disease dynamics, ecology, circadian rhythms, epidemiology, tumor growth and neural networks [5,11,12,39,44,50]. In modeling of the gene expression, time delays can be of the same order of the time scale of system, and thus taking them into account can potentially change the system dynamics [47]. Therefore, in this paper, we are going to study the dynamic of a such model where time delays play an important role.

As in all physical systems, stability is a key characteristic for gene regulatory networks. In past years, quite a few work have been done on the stability and bifurcation analysis of gene regulatory networks with or without time delay; please see [4,49] for example. Based on Lyapunov stability theory and method of linear matrix inequality, authors of [27,34] discussed the robust stability of gene regulatory networks with distributed delay or time-varying delays and polytropic parameter uncertainties. In [53], exponential stability was considered for a class of stochastic gene network. To characterise the transient and steady state behavior of the transcriptional regulation, based on a mean field approximation method, Goutsias and Kim [22] studied stochastic transcriptional regulatory systems with time delays. In [62], utilizing Ito's differential formula and Lyapunov–Krasovskii function, delay-range-dependent and rate-dependent stability criteria are proposed for a class of delayed gene regulatory networks with stochastic disturbances.

Bifurcation, which involves emergence of oscillatory behaviours, can help us to understand parameter sensitivity observed in genetic regulatory networks and provides us information benefiting the networks [36,47,48,52,51]. Therefore, the investigation of bifurcation of GRNs is significant. Furthermore, Hopf bifurcation can tell us how the biological system exhibits periodic response due to the delay; more precisely the first Hopf bifurcation induced by time delay can lead us to interesting results such as the dependence of delay on the amplitude of oscillation. As we know, many methods for analysing Hopf bifurcation have been reported in literature, such as integral averaging technique, the Fredholm alternative, the implicit function theorem, method of multiple time scales, center manifold reduction and normal form theory [9,18–21,25,26,30,35,62–65,54].

Authors of reference [56] considered

$$\begin{aligned} \dot{M} &= \alpha_m f(P(t-T_m)) - \mu_m M(t), \\ \dot{P} &= \alpha_p M(t-T_p) - \mu_p P(t), \end{aligned} \tag{1.1}$$

where α_m is the transcription rate and α_p is the translation rate; μ_m and μ_p are degradation rates of the mRNA and the protein, respectively; τ_m and τ_p are transcriptional and translational time delays of the protein, respectively. By performing center manifold reduction, stability and periodic solutions generated by Hopf bifurcation were investigated [56], where the total delay $\tau = T_m + T_p$ was treated as bifurcation parameter. For the same system, reference [47], by the Lindstedt's method, provided approximations of the amplitude and frequency of the resulting limit cycle. Please notice that the authors of [47] studied only a special case of (1.1):

$$\mu_m = \mu_p = \mu, f(P(t-T_m) = \frac{1}{1+\left(\frac{P(t-T)}{P_0}\right)^n}, T_p = 0.$$