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Mathematical analysis of a generalised p53-Mdm2 protein gene expression model

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ABSTRACT

We propose the generalisation of the p53-Mdm2 protein gene expression model introduced by Monk (2003). We investigate the stability of a unique positive steady state and formulate conditions which guarantee the occurrence of the Hopf bifurcation. We show that oscillatory behaviour can be caused not only by time lag in protein transcription process, but also can be present in the model without time delay. Moreover, we investigate the stability of new born periodic solutions. Theoretical results are illustrated by numerical simulations and interpreted from the biological point of view.

1. Introduction

The p53 protein was discovered in 1979 and its name is connected with its molecular weight determined by the analysis of SDS-PAGE (which in fact has been incorrectly calculated). The p53 protein is involved in many biological processes including cell cycle regulation, cell differentiation and apoptosis. As a tumour suppressor it is one of the subjects of interests of scientists working on the designing and improvement of cancer therapies. It also plays an important role in the treatment of neurodegenerative diseases such as cerebral ischemia, traumatic brain injury, epilepsy and Alzheimer's disease. In [1,2] it is demonstrated that an inhibition of p53 prevents cell death in different models of neurodegenerative disorders.

For the first few years it was thought that p53 is an oncogene, that is a gene that may cause the growth of cancer cells. Only later it turned out that its role is rather reverse and it is a tumour-suppressor that is protein which is necessary to keep the cell division under control. Just like a car brakes regulate its speed, the tumour-suppressor gene acts as brakes to the cell cycle, the DNA replication and the division of cells. If these proteins do not act properly, the uncontrolled growth defining the feature of cancer cells can appear. It is so in the case of p53 protein which was found to not act correctly in the most of human cancers, for more details see e.g., [3].

In 1992, Lane [4] called the p53 protein "guardian of the genome" because of its ability to guard the cells from the malignant transformations. When DNA is damaged (e.g., by ionizing radiation or chemicals), the appropriate p53-mediated pathways are activated. This yields the arrest of the cell in the cycle, which prevents the proliferation of the cell containing

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damaged DNA. Next, the biochemical processes involved in DNA repair are triggered. If they are successful, the cell resumes its progression and the cell division can take place. If the repair is unsuccessful due to excessive damage, the p53-mediated apoptotic pathway becomes functional, leading to apoptosis, i.e., the process of programmed cell death.

To understand the action of the p53 protein it is crucial to take into account the interaction between p53 and Mdm2 proteins, see [5–10]. That interaction is the main negative regulator of the p53 protein in the cell because in the normal cells the p53 pathway is switched off, that is p53 activity is kept low, such that the cell cycle progression is not disrupted by a negative feedback loop consisting of the p53 and Mdm2 genes. Additionally the p53 protein acts as a transcription factor and regulates the expression of several target genes including Mdm2 gene. On the other hand, the Mdm2 protein inhibits the p53 activity, forming a negative feedback loop and this ability of Mdm2 to keep p53 under control is essential for the normal cell function. The repression of Mdm2 operates via three main mechanisms:

(i) Mdm2 binds p53 at its DNA binding domain in such a way that the latter can not function as a transcription factor;
(ii) p53 with binding Mdm2 is labelled for degradation;
(iii) Mdm2 is responsible for an export of p53 from the nucleus to the cytoplasm changing its transcriptional activity.

In the mammalian cells DNA damaged activates of a protein called ATM kinase [11,12] and phosphorylation of the p53 protein at a specific site, preventing the binding of the Mdm2 protein to p53. In the absence of Mdm2 mediated degradation of p53, quantity of p53 proteins stabilizes at a higher level than under the presence of Mdm2. In fact, the interactions between the feedback loops in p53 gene expression system are much more complex, see e.g., [13]. One of the first models of the p53 gene expression system was proposed by Bar-Or et al. in [3], where it is numerically shown how the oscillatory behaviour of both p53 and Mdm2 protein may vary depending on the system parameters. Later, experimental results showed that p53-Mdm2 interactions proposed in [3] lead, under particular experimental conditions, to undamped oscillations in the concentrations of the considered proteins [14–17].

More recently, Gordon et al. [18] and Sturrock et al. [19] studied models postulating that the p53-Mdm2 oscillations have their source in a nuclear transport of the proteins between the cytoplasm and cell nucleus. In that models transport was modelled by a passive diffusion and the impact of the diffusion rates on the behaviour of the concentration of the p53 protein was investigated. Many models that include the stochastic effect were also considered, see e.g., [15,20–23]. For example in [15], the negative and positive feedback loops with some random noise added into protein's production terms were studied.

On the other hand, models taking into account a transcriptional time delay were considered by a number of the research groups [24–26], but none of these examples includes the mathematical analysis. The exception is the article [26] in which the existence and the direction of the Hopf bifurcation for simple p53-Mdm2 system with time delay is investigated.

It is worth pointing out that some much more complex models of the p53 gene regulatory network were also proposed. For example in [24] the feedback loop involving five components was considered. Some models consisting of several ODEs that include both negative and positive feedback loops were considered, [27–29]. Also large models that consist of more than ten differential equations [30] were studied. Clearly, in reality the dynamics of the p53 signalling pathway is more complex, and it involves some additional, experimentally confirmed, feedback loops (both positive and negative), see [13,31], which were neglected in the considered model. As a consequence in this model it is not possible to have a second positive steady state as in [31], where the positive feedback through PTEN is taken into account. Thus, the dynamics of the studied system clearly differs from that more complex models. However, we wish to point out that in this paper we consider p53 system right after the DNA damage when the longer positive feedback is not activated. The advantage of such complex models is that they describe the studied phenomenon more precisely, but their main disadvantage is that the mathematical analysis of theirs properties (even only quantitative) is hardly possible. Moreover, such large complex models contains a large number of parameters and estimation of them usually is a very challenging task. However, all these models include the p53-Mdm2 complex which consists of three main components: the p53 and Mdm2 proteins and Mdm2 mRNA. Thus, following [14] we consider a generalised mathematical model of p53-Mdm2 with two Hill functions, which describe the influence of Mdm2 protein concentration on the rate of degradation of p53 and the influence of p53 protein concentration on the rate of transcription of Mdm2 mRNA, respectively.

The paper is organized as follows. In Section 1.1 we formulate a generalisation of the p53-Mdm2 model proposed by Monk. In Section 2 we prove analytically the existence of positive steady state and provide the conditions guaranteeing the occurrence of the Hopf bifurcation. Moreover, we investigate the stability of new born periodic solutions. We also analyse the direction of the Hopf bifurcation for the p53-Mdm2 system without time delay by computing the first Lyapunov coeffcient. Finally, in Section 3 we present the numerical simulations illustrating our analytical results and discuss our findings.

1.1. Model presentation

In the presented paper we consider a generalisation of p53-Mdm2 model, which original version was proposed by Monk in [14]. We assume that: the p53 protein is produced with a constant rate α_p and it is degraded with the rate μ_{p_1}, the p53 degradation rate is increased by the Mdm2 presence and it is described by the term with function f_p with the maximal Mdm2-induced degradation rate μ_{p_2}. The Mdm2 mRNA production is upregulated by p53 and in the considered system it is described by the term $\alpha_{m_1} f_r(p(s-\tilde{\tau}))$ assuming the maximal initiation rate at the level of α_{m_1} and taking into account the delay of the transcript elongation, splicing and processing, as well as the protein transport time between the cytoplasm