APOPTOSIS INDUCTION BY PINNING CONTROL BY MEANS OF P53 FOR OVEREXPRESSED MDM2

INDUCCIÓN DE APOPTOSIS POR CONTROL TIPO "PIN" POR MEDIO DE P53 PARA MDM2 SOBREEXPRESADO

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Abstract: This paper presents pinning control to regulate the activity of the p53-Mdm2 network. This network considers p53 degradation mediated by Mdm2 increased expression, which perturbs p53 normal stress response. Model considers three proteins: p53, Mdm2 and ARF. p53 is regulated through a feedback loop involving its transcriptional target gen Mdm2 and an indirect regulator ARF. Two scenarios are presented. For the first scenario, the network responds to Mdm2 overexpression and p53 downregulation without external input; afterwards, for the second scenario, apoptosis is induced by pinning control. The network dynamical behavior and effectiveness of the proposed controller are illustrated via simulations.

Keywords: Gene regulatory network, complex networks, pinning control, p53 and Mdm2.

Resumen: Este artículo presenta el control tipo "PIN" para regular la actividad de la red p53-Mdm2. Esta red considera la degradación de p53 mediada por el incremento de Mdm2, el cual perturba la respuesta de estrés normal de p53. El modelo considera tres proteínas: p53, Mdm2 y ARF. p53 es regulado a través de un ciclo de retroalimentación que involucra su gen objetivo Mdm2 y un regulador indirecto ARF. Se presentan dos escenarios. Para el primer escenario, la red responde a un incremento de Mdm2 y una baja regulación de p53 sin ninguna entrada externa; luego, en el segundo escenario apoptosis es inducido por el control tipo "PIN". El comportamiento dinámico de la red y la efectividad del controlador propuesto son ilustrados vía simulaciones.

Palabras Claves: Redes de regulación genética, redes complejas, control tipo PIN, p53 y Mdm2.

1. INTRODUCTION

Complex networks are currently an active area of scientific research. Real-world networks are complex, such as the internet, World Wide Web (WWW), social networks, communication networks, and biological systems, among others (Barabasi, 1999; Strogatz, 2001; Cohen, 2010; Liu, 2011). To understand the molecular mechanisms underlying important biological processes, a detailed description of gene regulatory networks is required. Interactions between the components of a process can be modelled as a complex network with nodes and edges. In this network, the nodes represent genes or proteins related to them, and their regulators. On the other hand, the edges represent physical interactions and/or regulatory relationships between nodes (Levine, 2005; Peter, 2015).

In order to model gene regulatory networks, different methods are available, which are roughly divided into four classes (De Jong, 2002; Schlitt, 2007; Angelin-Bonnet, 2018). The first one are logical models, which describes qualitatively regulatory networks, such as Boolean Networks (Lähdesmäki, 2003; Wang, 2012), Probabilistic Boolean and multivalued Networks (Shmulevich, 2002a, 2002b), and Bayesian networks (Perrin, 2003; Liu, 2016); the second one is described by continuous models as ordinary differential equations (Mestl, 1995; Cao, 2012) and S-system formalism (Kikuchi, 2003); the third one is the single molecule level models (Dulin, 2013) which account for interactions between individual molecules; and finally, the fourth one, hybrid models which combine different approaches like discrete and continuous aspects (Xu *et al.*, 2007).

On the other hand, in relation to control of complex networks, different control techniques have been applied as in (Yang, 2012; Yu, 2012; Wang, 2017; Wu, 2018). A simple yet effective control technique named as pinning control is presented in (Wang, 2002; Zhou, 2008; Chen, 2014), which applies local control actions to a small fraction of network nodes to achieve a desired goal.

In this work, the p53-Mdm2 regulatory network is represented by a continuous model of six ordinary differential equations. Deregulation of the negative activity of Mdm2 over p53 can lead to oncogenic events. Mdm2 overexpression has been reported for a group of human cancers (Momand *et al.*, 1998).

The p53-Mdm2 complex network is highly regulated (Kruse *et al.*, 2009). In order to improve our comprehension of the regulation patters and the system responses, we provide a mathematical model, which is perturbed by local control actions (pinning control) to accomplish a group of desired behaviors, such as the induction of p53-dependent cell death (apoptosis) for the scenario of Mdm2 overexpression.

The rest of the paper is organized as follows: Section 2, contains relevant information about network components and mathematical preliminaries for gene regulatory networks. In section 3, we illustrate the p53-Mdm2 network and the performance of the proposed control algorithm via simulations using Matlab/Simulink. Finally, conclusions are drawn in Section 4.

2. MATEMATICAL FUNDAMENTALS

One the most used approaches for gene regulatory networks models is the rate-equation approach, where the main variables are the concentrations of different components, i.e., RNAs, proteins, and other molecules within the cell, whereas the dynamical equations represent the concentration rates of production and decay (De Jong, 2002).

2.1 Gene regulatory network mathematical model

In this paper, a mathematical model for a gene regulatory network is represented by using the framework of complex networks (Barabasi, 1999). Consider a general network consisting of N non-identical nodes with nonlinear diffusive couplings, where each node is a scalar dynamical system, which represents the concentration of proteins, an mRNA, or a small molecule. The state equations of this network are given by

$$\dot{x_i} = f_i(x_i) + g_i(x_1, x_2, \cdots, x_N, t), \quad i = 1, 2, \cdots, N, \tag{1}$$

where $x_i \in \mathbb{R}$ is the state of node i for $i = 1, 2, \cdots, N$ $f_i = \mathbb{R} \mapsto \mathbb{R}$ represents the self-dynamics of node i related to individual processes as: the degradation process of RNA, proteins, and so on, and $g_i = \mathbb{R}^N \mapsto \mathbb{R}$ denotes the nonlinear coupling function between nodes, associated to changes of x_i due to transcription, translation, repression, activation or other interaction processes.

The degradation function is represented in the literature as a negative linear function $-\alpha_i x_i$ where $\alpha_i > 0$ is the degradation rate. Moreover, among the regulation functions found in the literature, one of the most used is control curve (De Jong, 2002):

$$h^{+}(x_j, D_j, m) = \frac{x_j^m}{x_j^m + D_j^m},$$

with $D_j > 0$ the threshold for the regulatory influence of x_j on a target gene, and $m > 0$ is the Hill coefficient. Note that in this function, the transcription factor j is the gene activator. To express the transcription factor j for a gene inhibitor, the regulation function is given by

$$h^{-}(x_j, D_j, m) = 1 - h^{+}(x_j, D_j, m).$$

2.2 Network control

In this paper, a control scheme is proposed to drive (1) to evolve in a desirable manner for treatment or intervention purposes, i.e., the control goal is to force equation (1) to track a reference trajectory given as

$$y = y_r(t).$$

The control objective mentioned above is achieved by applying local feedback controllers to a small fraction of the network nodes, according to the pinning control methodology (Li, 2004; Song, 2010; Su, 2013) as briefly explained in the following.

where $K_i > 0$ is a control feedback gain. The following assumptions are proposed, where

$$D_i = \{e_i : \|e_i\| < \delta\}, \quad \delta > 0, \; D = \cup_{i=1}^{N} D_i,$$

with $e_i = x_i - y_r(t)$.

Assumption 1: (Xiang and Chen, 2007) There is a continuously differentiable Lyapunov function $V : \mathcal{D} \subseteq \mathbb{R} \mapsto \mathbb{R}_+$ satisfying $V(x(0)) = 0$, such that for each node function $f_i(\cdot)$, there is a scalar θ_i guaranteeing

$$\frac{\partial V(x_i)}{\partial x_i}(f_i(x_i) + \theta_i x_i) < 0, \quad \forall x_i \in D_i, x_i \neq 0, \tag{4}$$

where θ_i represents the passivity degree.

Assumption 2: (Khalil, 1996) The function $g_i(\cdot)$, for each node in network (1) is Lipschitz continuous, i.e.,

$$\|g_i(x_1, \cdots, x_N, t) - g_i(y_1, \cdots, y_N, t)\| \leq L_c^f \|x - y\|, \tag{5}$$

where $L_c^f > 0$.

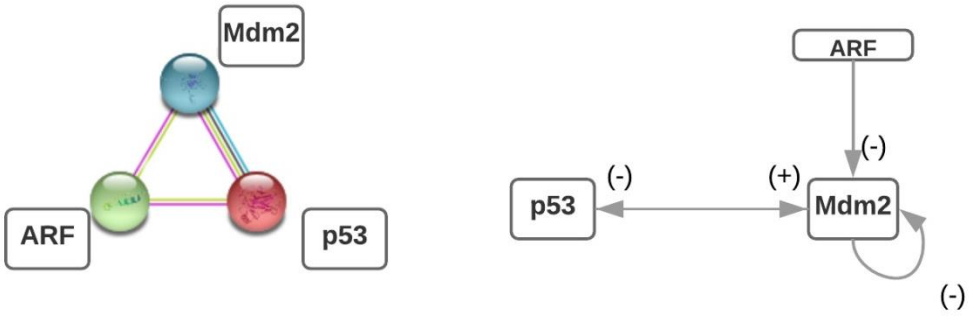


Fig. 1 Schematic model of p53 including Mdm2 sequestration by ARF.

Without loss of generality, let the first l nodes be selected to be pinned, where $1 \leq l \leq N$, and l can be as small as one. Thus, the controlled network can be written as

$$\dot{x_i} = f_i(x_i) + g_i(x_1, x_2, \cdots, x_N, t) + u_i, \quad i = 1, 2, \cdots, l.$$
$$\dot{x_i} = f_i(x_i) + g_i(x_1, x_2, \cdots, x_N, t), \quad i = l+1, l+2, \cdots, N. \tag{2}$$

For simplicity, a local linear negative feedback control law is used, given by:

$$u_i = -K_i(x_i - y_r(t)), \quad i = 1, 2, \cdots, l, \tag{3}$$

Under these assumptions, the control gain K_i can be selected, such that network (1) fulfills the desired goals. The formal analysis is being developed. In the following section, we provide an example of the proposed approach using a gene regulatory network (p53-Mdm2 regulatory network) derived from actual gene expression data.

3. P53-MDM2 NETWORK

3.1 p53-Mdm2 model

p53 is considered a key piece for regulation of cellular behaviors which allows the detection of damaged DNA as well as irreversible damage to the cell. For these reasons, p53 has been described as "the guardian of the genome" because of its role to ensuring genome stability by preventing mutation (Efeyan,2007; Ryan, 2011). Thus, studying its regulation in signaling networks is critical to characterize the stimuli that lead the cell to repair the damage or opt for self-destruction (apoptosis) through the activation of p53 target genes. Fig. 1 shows the interaction system of p53 and Mdm2 (Mouse double minute 2 homolog). It has been observed experimentally that p53 has a close relationship with its inhibitor Mdm2, and that modifications in their mutual interaction condition are related to different cell stressors, such as radiation-induced damage, alterations due to viral infections, among others (Kessis, 1993; Kruse, 2009; Hu, 2012). Mdm2 is a p53 interacting protein, which represses p53 transactivation activity (Schon, 2002; Shangary, 2008; Wang, 2017). Finally, ARF (Alternate Reading Frame) is an Mdm2 inhibitor, which in normal cell function is downregulated; conversely, in response to oncogenic signaling or oxidative stress, ARF is upregulated, leading to an inhibition of Mdm2, which in consequence eliminates a restrictive control of Mdm2 over p53, and eventually results in stable p53 promoting cell cycle arrest or apoptosis. Thus, the components of this network can form a feedback loop, which inhibits or promotes p53 activation (Haupt, 1997; Pant, 2013; Zhang, 2015). Modified from (Leenders and Tuszynski, 2013), using the principle of mass-action and the saturable transcription kinetics, the p53-Mdm2 system behavior is mathematically described as follows:

$$\begin{aligned}
\dot{x_1} &= k_p - k_1 x_1 x_2 - d_p x_1 \\
\dot{x_2} &= k_m + k_2 \frac{{x_1}^{1.8}}{{k_D}^{1.8} + {x_1}^{1.8}} - k_0 x_2 \\
\dot{x_3} &= k_0 x_2 - d_{rc} x_3 \\
\dot{x_4} &= k_T x_3 - k_i x_4 \\
\dot{x_5} &= k_i x_4 - d_{mn} {x_5}^2 - k_3 x_5 k_6 \\
\dot{x_6} &= k_a - d_a x_6 - k_3 x_5 k_6
\end{aligned} \tag{6}$$

where, $\dot{x_1}$, $\dot{x_2}$, $\dot{x_3}$, $\dot{x_4}$, $\dot{x_5}$ and $\dot{x_6}$ are p53, mRNA Mdm2 induction, mRNA Mdm2 cytoplasmic translocation, Mdm2 cytoplasmic RNA translation, Mdm2 nuclear degradation, and ARF respectively.

Table 1: Model Parameters.

Parameter	Description	Value
k_p	p53 production	0.5 proteins/s
k_1	Mdm2 dependent p53 degradation	$9.963x10^{-6}$/s
d_p	p53 Decay	$1.925x10^{-5}$/s
k_m	p53-Independent Mdm2 production	$1.5x10^{-3}$RNA/s
k_2	p53-Dependent Mdm2 production	$1.5x10^{-2}$/s
k_D	Dissociation constant in promoter region	740 proteins
k_0	RNA transport from nucleus to cytoplasm	$8.0x10^{-4}$/s
d_{rc}	Mdm2 mRNA decay in cytoplasm	$1.444x10^{-4}$/s
k_T	Transcription rate	$1.66\,x10^{-2}$ proteins/s
k_i	Protein transport from cytoplasm to nucleus	$9.0x10^{-4}$/s
d_{mn}	Mdm2 autoubiquitination	$1.66x10^{-7}$/s
k_a	ARF production	0.5 proteins/s
d_a	ARF decay	$3.209x10^{-5}$/s
k_3	Mdm2-ARF complex formation rate	$9.963x10^{-6}$/s

Parameters in (6) are as follows: k_p is the p53 production rate, k_1 the p53 ubiquitination by Mdm2, and d_p being the p53 degradation independent from Mdm2 ubiquitination of the first equation. This way, k_m is p53-independent Mdm2 mRNA production, k_2 is the maximum p53-dependent Mdm2 mRNA production, k_D is the p53 dissociation constant for Mdm2 promoter region, and k_0 is Mdm2 mRNA transport rate from nucleus to cytoplasm. Furthermore, d_{rc} represents Mdm2 mRNA decay rate in the cytoplasm, k_T is the Mdm2 mRNA translation rate, and k_i represents the protein transport Mdm2 from cytoplasm to nuclear localization. Mdm2 autoubiquitination is settled at rate d_{mn} and Mdm2 shows binding capacity to ARF at rate k_3. Finally, ARF is translated at the rate k_a and degraded at the rate d_a. The values used for these parameters are in Table 1.

3.2 p53-Mdm2 response without control

For normal conditions, p53 is downregulated and stays at very low levels thanks to the negative regulator Mdm2, which promotes p53 proteasomal degradation. Under stressors such as γ-radiation that induce DNA damage, p53 is activated and several cellular responses are triggered to repair this damage or mediate controlled cell death (apoptosis) The negative feedback loop between Mdm2 and p53 is responsible for the typical oscillatory pattern of p53 activation (Lahav, 2008). To obtain this behavior, the basic feedback loop must be active such that p53 induces Mdm2 production; the production of Mdm2 increases the degradation rate of p53, especially under DNA damage. This model also includes production/transportation time delays to model the nuclear concentrations of Mdm2, because it has to move between compartments from the nucleus to the cytoplasm and back to the nucleus; furthermore, requires a positive feedback for p53 which involves the activation of ARF, inhibiting Mdm2 (Leenders and Tuszynski, 2013).

Mdm2 regulates p53 through multiple mechanisms, including proteasomal mediated degradation, enhanced p53 cytoplasm exportation that leads to degradation, p53 inhibition of transcriptional activities, p53 translation inhibition, and so on. The overexpression of Mdm2 has been reported in a variety of tumors (including sarcoma, leukemia, breast carcinoma, melanoma, glioblastoma) (Momand et al., 1998), mainly caused by gene amplification that contributes to enhanced p53 degradation and downregulation of its targets genes and cell control activities. Once p53 is downregulated, Mdm2 can be rise. It can be assumed that Mdm2 deregulation can leads to oncogenic behavior through p53 suppression.

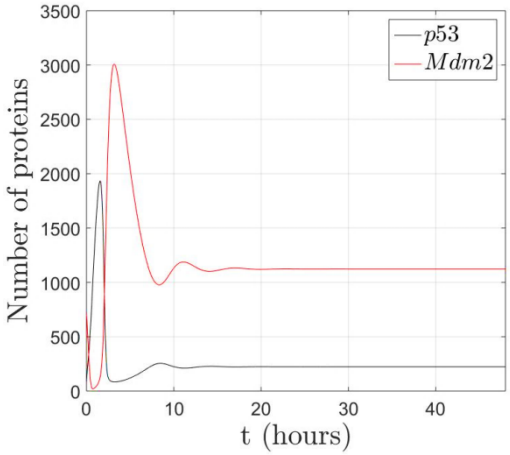


Fig. 2. Mdm2 overexpression and p53 downregulation.

Model (6) presents Mdm2 overexpression and p53 downregulation as can be seen in Fig. 2 with $k_1 = 1.9926x10^{-6}$/s, $d_p = 3.85x10^{-6}$/s, and $k_2 = 45x10^{-3}$/s.

3.3 Simulation Results

To illustrate regulated p53 behavior on the controlled network, two cases are included. For the first one, the network runs without any controller and the signal is given by overexpressed Mdm2 (oncogenic gene amplification); on the other hand, the second case uses cell death (apoptosis); with the control $u_i(t) \in \mathbb{R}$ (3) applied to p53.

The equation of the pinned network $\dot{x_1}$ is given by

$$\dot{x_1} = k_p - k_1 x_1 x_2 - d_p x_1 + u_1$$

$$\dot{x_2} = k_m + k_2 \frac{{x_1}^{1.8}}{{k_D}^{1.8} + {x_1}^{1.8}} - k_0 x_2$$

$$\dot{x_3} = k_0 x_2 - d_{rc} x_3$$

$$\dot{x_4} = k_T x_3 - k_i x_4$$

$$\dot{x_5} = k_i x_4 - d_{mn} {x_5}^2 - k_3 x_5 k_6$$

$$\dot{x_6} = k_a - d_a x_6 - k_3 x_5 k_6$$

Simulations are performed using Matlab/Simulink with the fourth order Runge–Kutta integration method and a fixed step size of $1x10^{-3}$. Starting on day 1, the network runs without any controller and represents the same behavior as in Fig. 2, where the network responds to Mdm2 overexpression and p53 downregulation. On day 2, the proposed control law is turned on, and the system gradually tracks the desired trajectory; in this case, with $k_0 = 8.0x10^{-6}$/s, apoptosis is induced because the damage is supposed to be non-repairable. The behavior for day 3, after the apoptosis induction, illustrates the lack of network activity, which can be interpreted as cell death (lack of system response) as can be seen in Fig. 3.

These results, clearly show that the proposed controller achieves regulation successfully for the p53-induced apoptosis response within the p53-Mdm2 network with Mdm2 in oncogenic behavior.

4. CONCLUSIONS

The proposed controller is evaluated via simulations as applied to the p53-Mdm2 network. Results illustrate good performance and effectiveness of the proposed controller, which

open a door for fighting diseases in which gene expression plays a fundamental role.

Furthermore, testing p53 degradation and the effect of such changes in other components of the regulatory network will help to reveal more specific mechanisms involved in the p53-Mdm2 network under disturbances that can lead to expected system reactions. One important question is how to decide which nodes are selected to apply the controller in different scenarios, such as specific variations in the p53-Mdm2 network in different cancer types as well as in other types of cellular stress. Future research should be able to integrate biological aspects, control theory concepts, and complex network analysis.

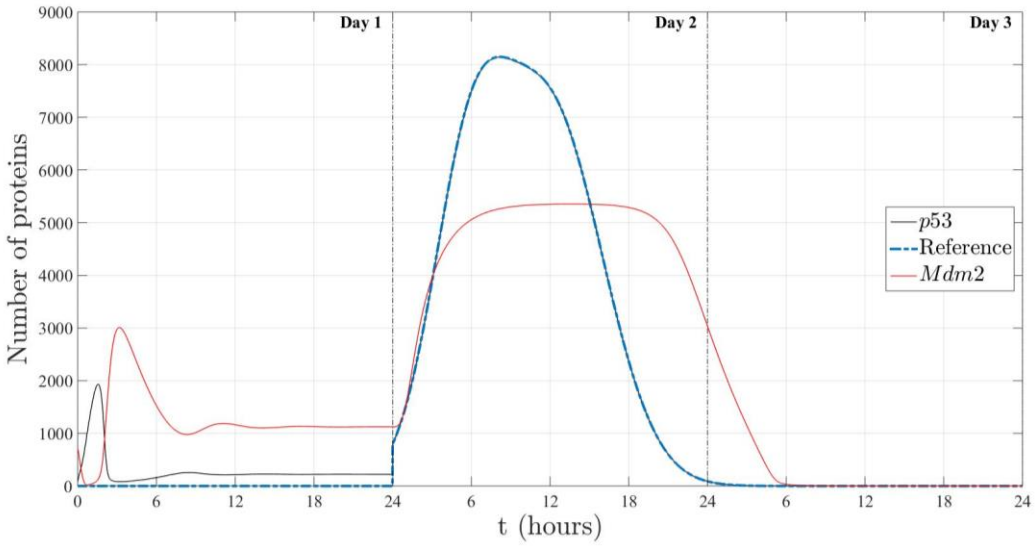


Fig. 3. Proposed scenarios simulations for abnormal p53 degradation (Day 1), and apoptosis induction under pinning control (Day 2).

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