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Cell death induction in p53-Mdm2 network regulated by p300 and HDAC1 using pinning control

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***Abstract*—Gene regulatory networks are important to understand cellular processes and open a door for fighting diseases in which these networks play a fundamental role. p53 has been named as "the guardian of the genome" and Mdm2 is its principal negative regulator. The p53-Mdm2 network is structurally and biologically well understood and known. In this paper, the p53-Mdm2 network regulated by p300 and HDAC1 is modeled by fourteen ordinary differential equations. Then, using such model, an oncogenic condition of Mdm2 overexpression and the functional suppression of p53 is simulated as one possible carcinogenic behavior. After that, the pinning control strategy to induce cell death is proposed using only two states (pinned nodes) of such network. The results are presented for in silico simulation and illustrate the effectiveness of the proposed controller to achieve cell death.**

***Index Terms*—Gene regulatory networks, pinning control, p53-Mdm2 network, cell death, in silico simulation.**

I. INTRODUCTION

Gene regulatory networks can be modeled and analyzed from data produced by experimental techniques and computational methods [1]. Understanding precise interaction and molecules regulation can exhibit the topological structure, dynamical behaviors, and organization of gene regulatory networks. This network includes components as nodes (representing molecules) and edges (establishing regulatory properties) that can be modeled as complex networks [2], [3].

$TP53$ (p53) is a very important regulatory gene since it allows the cell to execute tasks such as DNA repair induction, cell cycle arrest, senescence or cell death [4]. When cells present irreparable defects, survival signals are inhibited and the effector proteins of cell fate promote cell death mechanisms [5]. If the mechanisms of response to DNA damage are intact, the damaged cell will not promote carcinogenesis. On the other hand, cell death control will avoid passing new cells with damage to the following cell generations [6]. Numerous anti-tumor strategies have been increasing in recent years, including promoting and stimulating the anti-tumor activity of p53 and its regulatory network, thereby forcing cell death [7]. In this paper, a deterministic model of the p53-Mdm2 (Mouse double minute 2 homolog) network regulated by p300 (Histone acetyltransferase) and HDAC1 (Histone Deacetylase 1) under ionizing gamma-radiation is used. The idea is to propose a case of inactivation through the p53 inhibition by the Mdm2 protein as in [8], [9]; furthermore, using a simple and effective control technique named pinning control [10], which consists in applying a reduced quantity of controllers in order to produce cell death. The applicability of the proposed scheme is illustrated by simulation of a carcinogenesis case due to overexpression of the Mdm2 protein [11].

This paper contributes as part of the ongoing research where gene regulatory networks and control methodologies play important role. The novelty consists in developing a controller, which guarantees cell death induction in p53-Mdm2 network regulated by p300 and HDAC1 using a discontinuous feedback control law combined with pinning control. The paper outline is as follows: Section II contains mathematical preliminaries for gene regulatory networks and the pinning control strategy. In section III, the main contribution is presented; the p53-Mdm2 network regulated by p300 and HDAC1 is exhibited and the proposed control strategy is exemplified in silico simulation. Finally, conclusions are drawn in Section IV.

II. MATHEMATICAL FUNDAMENTALS

A. Mathematical model

In this paper, a mathematical model for gene regulatory networks is proposed by using the framework of complex networks [12], [13]. Consider a general network consisting of N non-identical nodes with nonlinear functions couplings, where each node is a scalar dynamical system. The proposed network is defined as

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

where $x_i \in \mathbb{R}$ is the own species (genes, proteins, messengers and others) for the network, $i = 1, 2, \ldots, N$, $f_i : \mathbb{R} \mapsto \mathbb{R}$ represents the self-dynamics of node i related to individual processes as: proteins, the production or degradation process of RNA, and so on, and $g_i : \mathbb{R}^N \mapsto \mathbb{R}$ denotes the nonlinear coupling function between nodes, associated with changes of x_i due to translation, transcription, activation, inhibition or other interaction processes.

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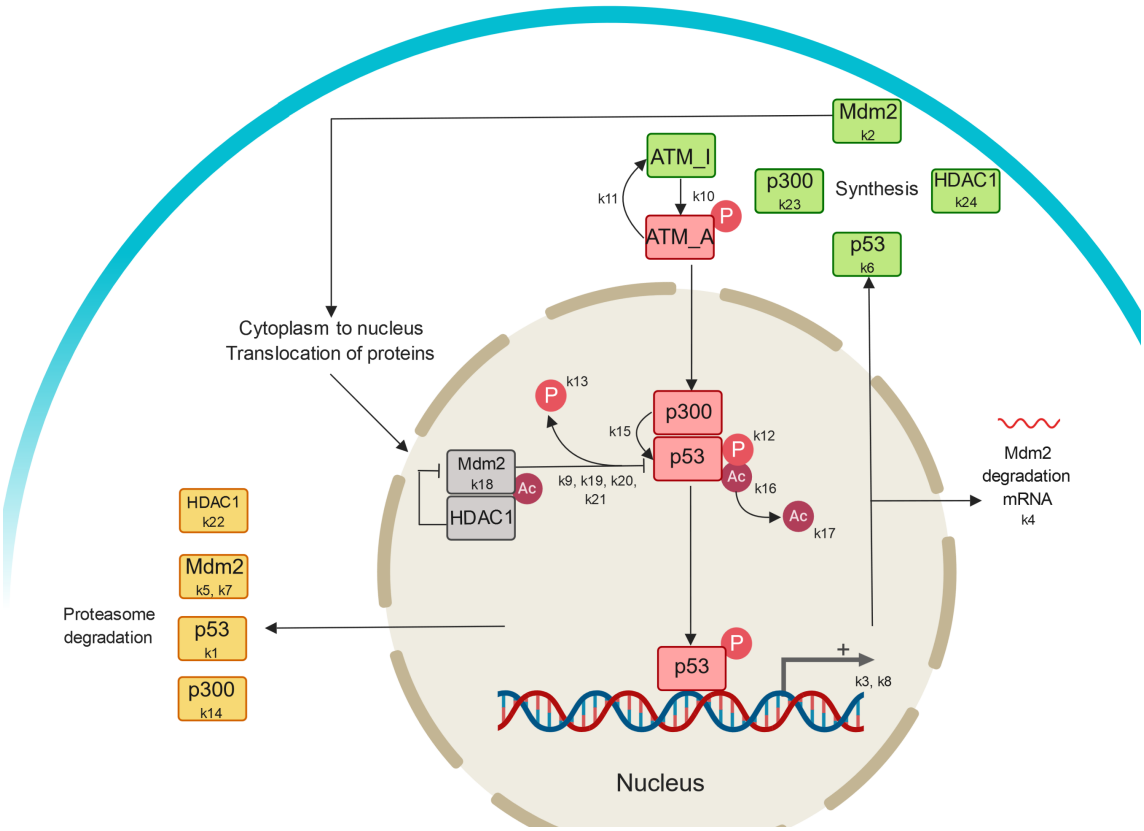

Fig. 1. Biochemical model of p53-Mdm2-p300-HDAC1 regulatory network.

B. Network control

To control (1) in a desirable manner for treatment or intervention purposes, the control goals is to force (1) to track a reference trajectory given as

$$y = y_r(t).$$

The above control objective is achieved by applying a reduced quantity of controllers in the network, according to the pinning control technique [14]–[16] as follows. Consider the first l nodes be selected to be pinned. The controlled network is given by

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

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

The discontinuous feedback control law is defined as:

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

where $K_i > 0$ is a positive control gain.

III. P53-MDM2 NETWORK CONTROL

In this section, the proposed control approach is provided for an example of the p53-Mdm2 network regulated by p300 and HDAC1 under ionizing gamma-radiation damage.

A. p53-Mdm2 network regulated by p300 and HDAC1

p53 is referred as "the guardian of the genome" because of its responses to different levels of stress, maintaining genome stability by preventing mutation and determining cell fate decisions. Mdm2 has been identified as a p53 interacting protein, which represses p53 transactivation activity and mediates p53 degradation [17]–[19]. p53 activation in genotoxic stresses is mediated through numerous protein interactions and gene transactivation, which induces DNA repair, cell cycle arrest, senescence or cell death [20]. In non-genotoxic conditions, p53 is expressed at very low levels thanks to direct inhibition by negative regulator Mdm2, which promotes p53 ubiquitination that leads to proteasomal degradation. The p53-Mdm2 interaction is related to different cell damage stimulus, such as DNA-induced damage, and alterations suffered by viral infections, among others [21], [22]. Another protein is p300, which binds to p53 and acts as co-activator in promoting p53-mediated transactivation and stabilization; additionally p53 can reduce the interaction with Mdm2 [23]. In response to DNA damage, it has been reported p300-mediated induction of p53 acetylation, then forming a complex union of Mdm2 and p53 [24]. In addition, Mdm2 recruit HDAC1, inhibiting p300-mediated acetylation of p53, which promote Mdm2-p53 mediated degradation. Finally, ATM (Ataxia Telangiectasia Mutated) protein has been related to p53 phosphorylation in response to ionizing radiation,

stabilizing and activating p53 [25]. In this way, the p53-Mdm2 network regulates post-translational modifications as specific responses mediated by genotoxic stressors [26].

In Figure 1, the interaction system of p53, Mdm2, p300, HDAC1, and ATM in the nucleus and the cytoplasm is represented. Proteins synthesis are highlighted by green color, activation proteins are illustrating by red color, while inhibition proteins by gray color. Protein degradation is representing by yellow color.

Taken from [27], based on standard principles of mass-action law and biochemical transcription kinetics, the behavior of p53-Mdm2 network regulated by p300 and HDAC1 can be mathematically described as follows:

$$
\begin{aligned}
\dot{x}_1 =& -k_{14}x_1 - k_{15}x_1x_7 - k_{19}x_4x_1 - k_{20}x_{11}x_1 + k_{23},\\
\dot{x}_2 =& -k_{18}x_{11}x_2 - k_{22}x_2 + k_{24},\\
\dot{x}_3 =& k_3x_8 - k_4x_3,\\
\dot{x}_4 =& -k_7x_4 + k_8x_8x_{11} - k_9x_4 - k_{19}x_4x_1,\\
\dot{x}_5 =& -k_{10}x_5 + k_{11}x_6,\\
\dot{x}_6 =& k_{10}x_5 - k_{11}x_6 - k_{12}x_8x_6,\\
\dot{x}_7 =& k_{12}x_8x_6 - k_{13}x_7 - k_{15}x_7x_1,\\
\dot{x}_8 =& -k_1x_8x_{14} + k_6 - k_8x_8x_{11} + k_9x_4 - k_{12}x_8x_6\\
&+ k_{13}x_7 + k_{17}x_{10}x_{12},\\
\dot{x}_9 =& k_{15}x_1x_7 - k_{16}x_9 + k_{21}x_{13},\\
\dot{x}_{10} =& k_{16}x_9 - k_{17}x_{10}x_{12},\\
\dot{x}_{11} =& k_2x_3 - k_5x_{11} + k_7x_4 - k_8x_8x_{11} + k_9x_4\\
&- k_{18}x_{11}x_2 - k_{20}x_{11}x_1 + k_{21}x_{13},\\
\dot{x}_{12} =& -k_{17}x_{10}x_{12} + k_{18}x_{11}x_2,\\
\dot{x}_{13} =& k_{19}x_4x_1 - k_{21}x_{13},\\
\dot{x}_{14} =& -k_1x_8x_{14} + k_{20}x_{11}x_1,
\end{aligned}
\tag{4}
$$

where, x_1, x_2, x_3, x_4, x_5, x_6, x_7, x_8, x_9, x_{10}, x_{11}, x_{12}, x_{13}, and x_{14} are p300 protein, HDAC1 protein, p53 protein, Mdm2 protein, Mdm2 messenger RNA, Mdm2 with p53 complex, inactivated ATM protein, activated ATM protein, phosphorylated p53 protein, phosphorylated p53-p300 complex, acetylated p53 protein, Mdm2 with HDAC1 complex, Mdm2-p53 with p300 complex, and Mdm2 with p300 complex respectively.

Parameters in (4) are as follows: k_1 the p53 polyubiquitination and degradation by Mdm2-p300 complex, k_2 the constant rate translation into Mdm2 protein, k_3 the constant rate transcription into messenger RNA, k_4 the degradation Mdm2-mRNA basal rate, k_5 the degradation Mdm2 basal rate, k_6 the creation p53 basal rate, k_7 the ubiquitination marks due to Mdm2 and generate p53 degradation rate, k_8 the interaction rate in Mdm2-p53 complex, k_9 the constant rate dissociation in Mdm2-p53 complex, ATM takes place with k_{10} activation and k_{11} deactivation respectively, and ATM-initiated phosphorylation reduces the affinity of p53 which generate the phosphorylation rate k_{12} and dephosphorylation rate k_{13}, k_{14} the degradation p300 basal rate, k_{15} the transcription activation rate of p53 binds tightly to p300, k_{16} the p53 acetylation constant rate, k_{17} the p53 deacetylation constant rate, k_{18} the interaction rate in Mdm2-HDAC1 complex, k_{19} the interaction rate in Mdm2-p53-p300 complex, k_{20} the interaction with constant rate between Mdm2 and p300, k_{21} the ternary complex dissociates into Mdm2 and p53-p300 complex, k_{22} the degradation HDAC1 basal rate, k_{23} the creation p300 basal rate, k_{24} the creation HDAC1 basal rate. The respective parameters are presented in Table I.

Parameter	Description	Value
k_1	p53 degradation	8.25×10^{-4}/s
k_2	Mdm2 creation	4.95×10^{-4}/s
k_3	Mdm2-mRNA creation	1.0×10^{-4}/s
k_4	Mdm2-mRNA degradation	1.0×10^{-4}/s
k_5	Mdm2 degradation	4.33×10^{-4}/s
k_6	p53 synthesis	0.078/s
k_7	Mdm2-p53 degradation	8.25×10^{-4}/s
k_8	Mdm2-p53 synthesis	11.55×10^{-4}/s
k_9	Mdm2-p53 dissociation	11.55×10^{-6}/s
k_{10}	ATM activation	1.0×10^{-4}/s
k_{11}	ATM deactivation	5.0×10^{-4}/s
k_{12}	Phosphorylation of p53	5.0×10^{-4}/s
k_{13}	Dephosphorylation of p53	5.0×10^{-1}/s
k_{14}	p300 degradation	1.0×10^{-4}/s
k_{15}	p53-p300 formation	1.0×10^{-4}/s
k_{16}	Acetylation of p53	1.0×10^{-4}/s
k_{17}	Deacetylation of p53	1.0×10^{-5}/s
k_{18}	Creation of Mdm2-HDAC1	2.0×10^{-4}/s
k_{19}	Creation of Mdm2-p53-p300	5.0×10^{-4}/s
k_{20}	Formation of Mdm2-p300	5.0×10^{-4}/s
k_{21}	Dissociation of Mdm2-p53-p300	1.0×10^{-4}/s
k_{22}	Degradation of HDAC1	1.0×10^{-4}/s
k_{23}	p300 synthesis	0.08/s
k_{24}	HDAC1 synthesis	2.0×10^{-4}/s

TABLE I
MODEL PARAMETERS.

B. p53-Mdm2 oscillation response

Model (4) presents oscillation response corresponding to an ionizing gamma-radiation dose, simulated over 48 hours using parameters of Table I. This response is the normal behavior under radiation effect. Oscillation pattern is presented in periods of 6.2 hours as can be seen in Fig. 2.

An increase gamma radiation doses are compatible with an increase in the number of damped pulses of p53 established in [28]. Gamma radiation causes a number of double-strand breaks (DSBs) in the DNA, which activate the p53-Mdm2 network. Cells detecting non-repaired DSBs along time, restart a new pulse of p53 activity. Only if the damage is still present, pulses in the oscillatory behavior can be repeated until is completely repaired or the cell starts a program to die. [28].

C. Mdm2 overexpression and p53 downregulation

Model (4) presents Mdm2 overexpression and p53 downregulation when $k_7 = 8.25 \times 10^{-5}$/s, $k_8 = 11.55 \times 10^{-5}$/s, $k_9 = 11.55 \times 10^{-5}$/s, and $k_{23} = 0.025$/s. This case represents an oncogenic scenario, where Mdm2 overexpression

suppress functions of p53 through an increase rate of degradation, leading to failure to genotoxic damage responses, which is validated in [11], [29], [30].

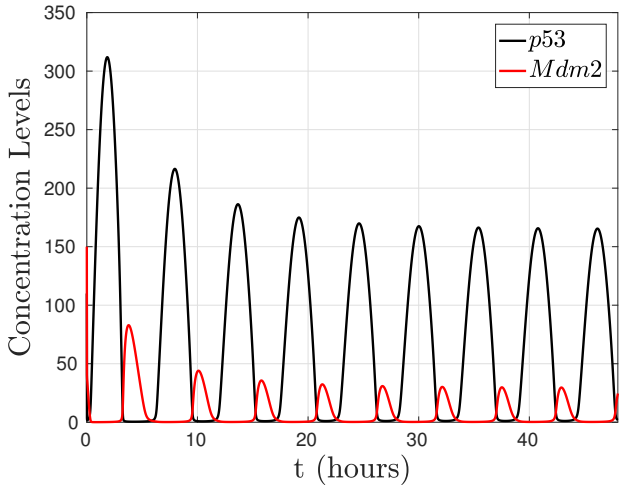

Fig. 2. p53 and Mdm2 oscillation response to ionizing radiation damage.

D. Cell death

Model (4) presents cell death (necrosis or apoptosis) when $k_1 = 1.25 \times 10^{-6}$/s, $k_6 = 0.2$/s, and $k_8 = 11.55 \times 10^{-2}$/s. This case represents the lack of network activity, where p53 and Mdm2 are inhibited, which is validated in [31]–[33].

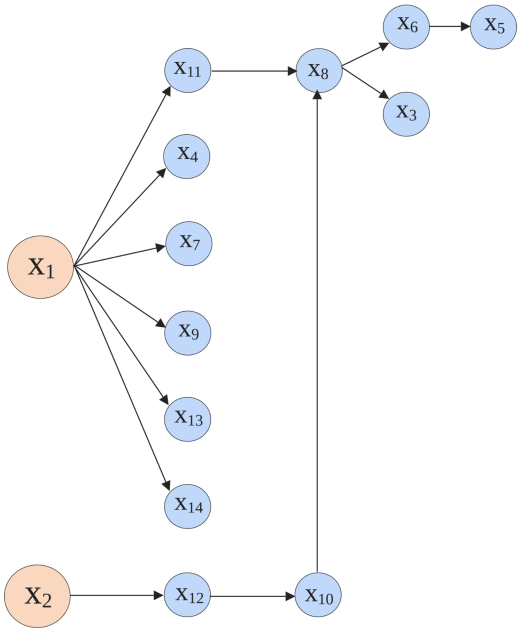

Fig. 3. Spanning tree of p53-Mdm2 network regulated by p300 and HDAC1.

E. Pinned Nodes

In order to select the pinned nodes, virtual leader methodology presented in [34], [35] is used. The spanning tree of the p53-Mdm2 network as can be seen in Fig. 3 is considered. Topologically, it is demonstrates that the nodes with the highest rate of interactions with other nodes can be pinned. Furthermore, proper dynamics of the nodes, biological meaning and the pinning control technique application are taken into account.

The equations of the pinned nodes p300 (x_1) and HDAC1 (x_2) are given by

$$
\begin{aligned}
\dot{x}_1 =& -k_{14}x_1 - k_{15}x_1x_7 - k_{19}x_4x_1 - k_{20}x_{11}x_1 + \boxed{k_{23}u_1}, \\
\dot{x}_2 =& -k_{18}x_{11}x_2 - k_{22}x_2 + \boxed{k_{24}u_2}, \\
\dot{x}_3 =& k_3x_8 - k_4x_3, \\
\dot{x}_4 =& -k_7x_4 + k_8x_8x_{11} - k_9x_4 - k_{19}x_4x_1, \\
\dot{x}_5 =& -k_{10}x_5 + k_{11}x_6, \\
\dot{x}_6 =& k_{10}x_5 - k_{11}x_6 - k_{12}x_8x_6, \\
\dot{x}_7 =& k_{12}x_8x_6 - k_{13}x_7 - k_{15}x_7x_1, \\
\dot{x}_8 =& -k_1x_8x_{14} + k_6 - k_8x_8x_{11} + k_9x_4 - k_{12}x_8x_6 \\
& + k_{13}x_7 + k_{17}x_{10}x_{12}, \\
\dot{x}_9 =& k_{15}x_1x_7 - k_{16}x_9 + k_{21}x_{13}, \\
\dot{x}_{10} =& k_{16}x_9 - k_{17}x_{10}x_{12}, \\
\dot{x}_{11} =& k_2x_3 - k_5x_{11} + k_7x_4 - k_8x_8x_{11} + k_9x_4 \\
& - k_{18}x_{11}x_2 - k_{20}x_{11}x_1 + k_{21}x_{13}, \\
\dot{x}_{12} =& -k_{17}x_{10}x_{12} + k_{18}x_{11}x_2, \\
\dot{x}_{13} =& k_{19}x_4x_1 - k_{21}x_{13}, \\
\dot{x}_{14} =& -k_1x_8x_{14} + k_{20}x_{11}x_1.
\end{aligned}
\tag{5}
$$

In order to control the network (5), it is necessary to increase the p300 and HDAC1 concentrations levels; therefore, k_{23} and k_{24} are selected due to they are the only terms preceded by a positive sign.

F. In Silico Results

Simulations are performed using Matlab/Simulink with the fourth order Runge-Kutta integration method and a fixed step size of 1×10^{-3}. Starting at 0 hours; the whole network runs without any control and the system presents Mdm2 overexpression and p53 downregulation (oncogenic scenario) as initial behavior. At 24 hours, the proposed control law is injected, consequently, the system gradually tracks the cell death reference (x_3=x_4=0) as can be seen in Figure 4; this behavior is induced because the DNA damage is assumed non-repairable. The behavior for 24 hours after control induction, illustrates the lack of network activity, which can be interpreted as cell death pathway (necrosis or apoptosis). Figure 5 illustrates simulation results for the control input signals $u_1(t)$ and $u_2(t)$ applied to the pinned nodes.

From these results, it is possible to see that the proposed controller, achieves cell death induction successfully for the p53-Mdm2 network regulated by p300 and HDAC1.

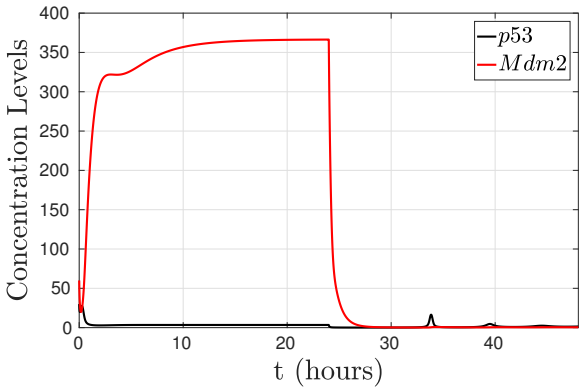

Fig. 4. Cell death induction under pinning control.

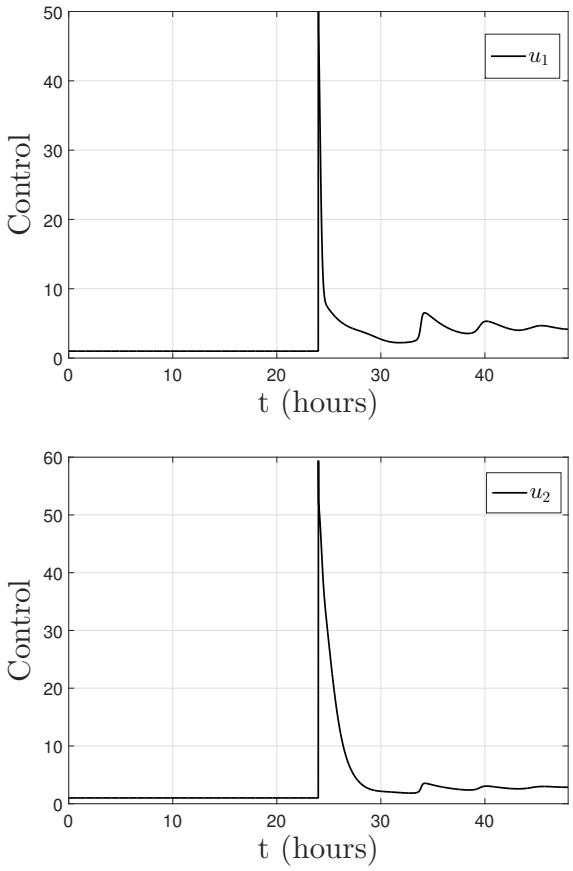

Fig. 5. Control signals $u_1(t)$ and $u_2(t)$.

IV. Conclusions

Cell death induction in p53-Mdm2 network regulated by p300 and HDAC1 using pinning control is achieved in silico simulation. To illustrate the p53 and Mdm2 protein modulation under pinning control, one case is considered. In this case, the control law ($u_1(t)$ and $u_2(t) \in \mathbb{R}$), are applied to p300 and HDAC1 in equation (5) and the network tracks a reference given by cell death pathway (necrosis or apoptosis).

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