Mathematical models and numerical simulations for the $P53 - Mdm2$ network

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Abstract. Guardian of the genome, p53 gene, and its partners that form the complex network involved in apoptosis and cell cycle arrest, is put under investigation. Some relevant mathematical models are described and each of them contains variables with time delay. For given values of the models parameters, numerical simulations and conclusions are made.

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Introduction

In every normal cell, there is a protective mechanism against tumoral degeneration. This mechanism is based on the p53 network. p53, also known as "the guardian of the genome", is a gene that codes a protein in order to regulate the cell cycle. The name is due to its molecular mass: it is a 53 kilo Dalton fraction of cell proteins. mdm2 gene plays a very important role in p53 network. It regulates the levels of intracellular P53 protein concentration through a feedback loop. Under normal conditions the P53 levels are kept very low. When there is DNA damage the levels of P53 protein rise and if there is a prolonged elevation the cell shifts to apoptosis, and if there is only a short elevation the cell cycle is arrested and the repair process is begun. The first pathway protects the cell from tumoral transformation when there is a massive DNA damage that cannot be repaired, and the second pathway protects a number of important cells (neurons, myocardic cells) from death after DNA damage. In these cells first pathway, apoptosis, is not an option because they do not divide in adult life and their importance is obvious. Due to its major implication in cancer prevention and due to the actions described above, p53 has been intensively studied in the last two decades.

During the years, several models which describe the interaction between p53 and mdm2 have been studied. We mention some of them in references [2], [3], [4], [6], [11], [12], [13], [14], [15].

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1. Model 1. The protein interaction between P53-Mdm2

This section gives a mathematical approach to the model described in [14]. The authors of paper [14] make a molecular energy calculation based on the classical force fields, and they also use chemical reactions constants from literature. Their results obtained by simulations in accordance with experimental behavior of the P53-Mdm2 complex. The analyze of the Hopf bifurcation with time delay as a bifurcation parameter can be done using the methods from [1], [7], [8].

1.1. The mathematical model

The state variables are: $y_1(t), y_2(t)$ the total number of P53 molecules and the total number of Mdm2 proteins.

The interaction function between P53 and Mdm2 is $f : \mathbf{R}_+^2 \to \mathbf{R}$ given by [14]:

$$f(y_1, y_2) = \frac{1}{2}(y_1 + y_2 + k - \sqrt{(y_1 + y_2 + k)^2 - 4y_1y_2}). \tag{1.1}$$

The parameters of the model are: s the production rate of P53, a the degradation rate of P53 (through ubiquitin pathway), and also the rate at which Mdm2 re-enters the loop, b the spontaneous decay rate of P53, d the decay rate of the protein rate Mdm2, k_1 the dissociation constant of the complex P53-Mdm2, c the constant of proportionality of the production rate of mdm2 gene with the probability that the complex P53-Mdm2 is build. These parameters are positive numbers.

The mathematical model is described by the following differential system with time delay [14]:

$$\begin{aligned} \dot{y}_1(t) &= s - af(y_1(t), y_2(t)) - by_1(t), \\ \dot{y}_2(t) &= cg(y_1(t-\tau), y_2(t-\tau)) - dy_2(t), \end{aligned} \tag{1.2}$$

where f is given by (1.1) and $g : \mathbf{R}_+^2 \to \mathbf{R}$, is

$$g(y_1, y_2) = \frac{y_1 - f(y_1, y_2)}{k_1 + y_1 - f(y_1, y_2)}. \tag{1.3}$$

For the study of the model (1.2) we consider the following initial values:

$$y_1(\theta) = \varphi_1(\theta), y_2(\theta) = \varphi_2(\theta), \theta \in [-\tau, 0],$$

with $\varphi_1, \varphi_2 : [-\tau, 0] \to \mathbf{R}_+$ are differentiable functions. In the second equation of (1.2) there is delay, because the transcription and translation of Mdm2 last for some time after that P53 was bound to the gene.

1.2. Numerical simulations

Let $X_0 = (y_{10}, y_{20})^T$ be the equilibrium state. For the numerical simulations we use Maple 11 and the data from [14]: the degradation of P53 through the ubiquintin

pathway $a = 3\times10^{-2}\text{sec}^{-}1$, the spontaneous degradation of P53 is $b = 10^{-4}\text{sec}^{-1}$, the dissociation constant between P53 and Mdm2 protein is $k_1 = 28$, the degradation rate of Mdm2 protein is $d = 10^{-2}\text{sec}^{-1}$, and the production rate of Mdm2 is $c = 1\text{sec}^{-1}$. For this data we consider different values for the constant k. Also, we have three cases: $s = 0.01$, $s = 0.1$, respectively $s = 10$ and obtain Table 1, Table 2, respectively Table 3.

Table 1.

$s = 0.01$	$k = 0.18$	$k = 18$	$k = 180$	$k = 1800$
y_{10}	0.51621	1.69276	4.67125	15.11336
y_{20}	0.65496	4.64864	13.45601	34.62588

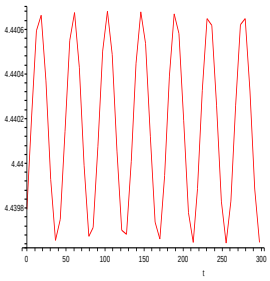
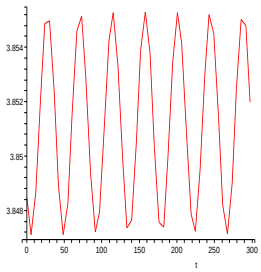
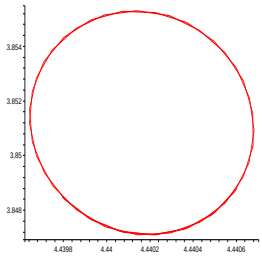
Table 2.

$s = 0.1$	$k = 0.18$	$k = 18$	$k = 180$	$k = 1800$
y_{10}	4.44004	8.31659	20.28508	81.19699
y_{20}	3.85114	15.17973	37.80454	73.61833

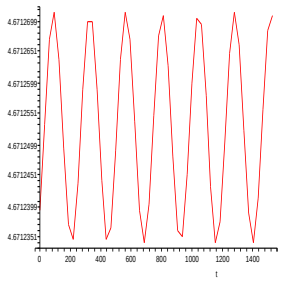
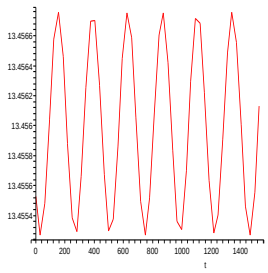
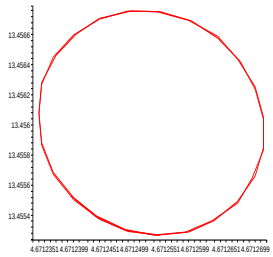
Table 3.

$s = 10$	$k = 0.18$	$k = 18$	$k = 180$	$k = 1800$
y_{10}	70012.08748	70756.83349	70088.92309	70019.72701
y_{20}	99.95996	99.95997	99.96009	99.960388

We consider the case $s = 0.1$, $k = 0.18$ and obtain Fig.1.1, Fig.1.2, Fig.1.3.

Fig.1.1 $(t, P53(t))$	Fig.1.2. $(t, Mdm2(t))$	Fig.1.3. $(P53(t), Mdm2(t))$
		

For the case $s = 0.01$, $k = 180$ we obtain Fig.1.4, Fig.1.5, Fig.1.6.

Fig.1.4. $(t, P53(t))$	Fig.1.5. $(t, Mdm2(t))$	Fig.1.6. $(P53(t), Mdm2(t))$
		

For the present model, we obtain an oscillatory behavior similar with the findings in [14].

2. Model 2. The mRNA and protein interaction between P53-Mdm2

2.1. The mathematical model

The tumour suppresser gene p53 and the mdm2 oncogene have important role in cell cycle checkpoints, apoptosis, growth control and oncogenesis [4]. There exists also an autoregulatory feedback loop between p53 and mdm2, implied in regulation of growth control by p53 [4]. Namely the mdm2 protein promotes the rapid degradation of the P53 protein, while P53 protein activates the transcription of the mdm2 gene [15]. This type of feedback loop could, in principle, give rise to an oscillatory behavior in the activity of the two genes.

In this section we use the p53-mdm2 interaction model with time delay given in [12].

Let y_1, y_2 be the concentrations of P53, Mdm2 proteins, let x_1, x_2 be the concentrations of the corresponding mRNA, b_1, b_2 the degradations and a_1, a_2, a_{12} the proteins degradations. The p53-mdm2 interaction model with delay is given by:

$$\begin{aligned} \dot{x}_1(t) &= 1 - b_1 x_1(t), \\ \dot{y}_1(t) &= x_1(t) - (a_1 + a_{12} y_2(t)) y_1(t), \\ \dot{x}_2(t) &= f(y_1(t-\tau)) - b_2 x_2(t), \\ \dot{y}_2(t) &= x_2(t) - a_2 y_2(t) \end{aligned} \tag{2.1}$$

with initial values:

$$x_1(0) = x_0, y_1(\theta) = \varphi(\theta), \theta \in [-\tau, 0], x_2(0) = x_{20}, y_2(0) = y_{20},$$

where $f : \mathbf{R}_+ \to \mathbf{R}$, is the Hill function, given by:

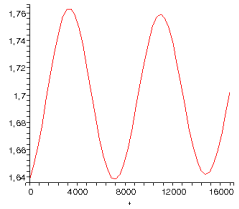
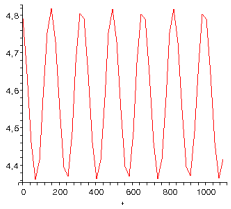
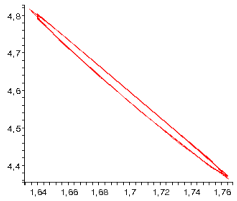
$$f(x) = \frac{x^n}{a + x^n} \tag{2.2}$$

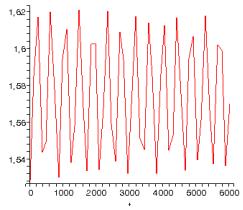
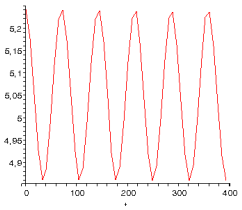
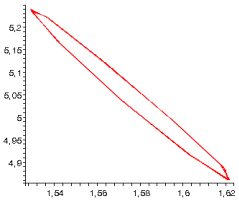
with $n \in \mathbf{N}^*, a > 0$.

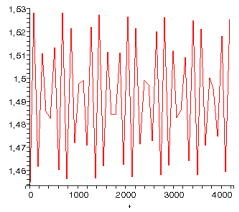
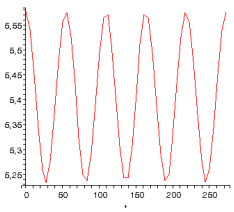
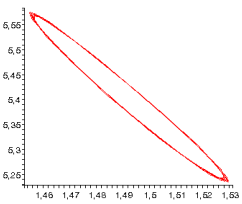
There is a time delay τ, because the interaction between proteins is not instantaneous. The parameters of the model are assumed to be positive numbers less or equal than 1.

2.2. Numerical simulations

In this section, we consider system (2.1) with $a_1 = a_2 = 0.13$, $b_1 = b_2 = 1$, $a = 4$.

	Waveplot (t, y_1)	Waveplot (t, y_2)	Phaseplot
$n = 3$			

	Waveplot (t, y_1)	Waveplot (t, y_2)	Phaseplot
$n = 4$			

	Waveplot (t, y_1)	Waveplot (t, y_2)	Phaseplot
$n = 5$			

Our simple model with two interrelated genes p53 and mdm2 can account for several type of behavior: evolution and maintaining of steady states, damped oscillations or sustained oscillations, all tangible by modifications of some parameters.

3. Model 3. P53-Mdm2 interaction with three delays

3.1. The mathematical model

Biological interaction do not take place instantaneous and therefore some amount of time is required. For a better modelling of p53-mdm2 interaction we introduced in previous model three delays in order to describe more specific the important processes that took place.

We used as a base for our model the model described in [12]. Our model is:

$$\begin{cases} \dot{x}_1 = \varphi A_1 - \eta_1 x_1(t) \\ \dot{y}_1 = \psi x_1(t) - (\lambda_1 + \lambda_{12} y_2(t-\tau_1)) y_1(t) \\ \dot{x}_2 = \varphi f(y_1(t-\tau_2)) - \eta_2 x_2(t) \\ \dot{y}_2 = \psi x_2(t) - (\lambda_2 + \lambda_{21} y_1(t-\tau_3)) y_2(t) \end{cases}$$

The notations are identical as the previous section and: τ_1 is the delay required for Mdm2 to bind P53 plus the time required for the interaction (under research) between P76MDM2 - P90MDM2, and also include the time for translocation of P53 in cytosol [9] (this is also a mechanism for the down-regulation of P53); τ_2 is the delay required for P53 to enter in the nucleus to bind P2 promoter of the mdm2 gene; τ_3 is the delay required for the HAUSP to interact with P53 and Mdm2 and to deubiquinate both proteins; λ_{21} is degradation rate for Mdm2 protein induced by P53. Recent findings show that HAUSP (also known as USP7), an ubiquitin hydrolase, plays a role in P53-Mdm2 degradations. Its role, in the presence of P53, is to deubiquinate Mdm2 and keeps a high Mdm2 level. To simplify the expressions that will appear in the calculus we use some notations: $\eta_1 = b_1$, $\lambda_1 = a_1$, $\lambda_{12} = a_{12}$, $\eta_2 = b_2$, $\lambda_2 = a_2$, $\lambda_{21} = a_{21}$ and also put numerical values for some parameters as follows: $\varphi = 1$, $\psi = 1$, $A_1 = 1$. These changes have no mathematically effect on our system. Finally, we will consider $\tau_1 = \tau_2 = \tau_3 = \tau$, the reason is that without this hypothesis the calculus become extremely complicated and the final result will not differ qualitatively from the calculus with this hypothesis. With these specifications made, our system became:

$$\begin{aligned} &\dot{x}_1(t) = 1 - b_1 x_1(t), \\ &\dot{y}_1(t) = x_1(t) - (a_1 + a_{12} y_2(t-\tau)) y_1(t), \\ &\dot{x}_2(t) = f(y_1(t-\tau)) - b_2 x_2(t), \\ &\dot{y}_2(t) = x_2(t) - (a_2 + a_{21} y_1(t-\tau)) y_2(t) \end{aligned} \tag{3.1}$$

where $f : \mathbf{R}_+ \to \mathbf{R}$, is the Hill function, given by:

$$f(x) = \frac{x^n}{a + x^n} \tag{3.2}$$

with $n \in \mathbf{N}^*, a > 0$. The parameters of the model are assumed to be positive numbers less or equal than 1.

For $\tau_1 = 0$, $\tau_2 = 0$, $a_{21} = 0$ in our model, we obtain the model from [12].

For the model (3.1) we consider the following initial values:

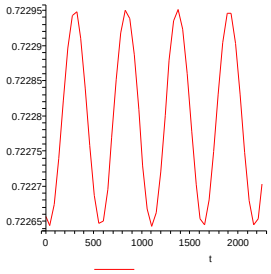
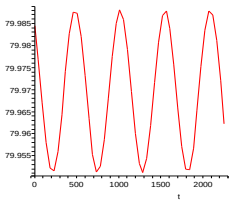
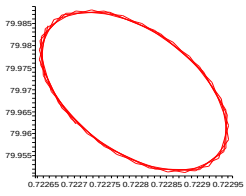
$$x_1(0) = \bar{x}_1, y_1(\theta) = \varphi_1(\theta), \theta \in [-\tau, 0], x_2(0) = \bar{x}_2, y_2(\theta) = \varphi_2(\theta), \theta \in [-\tau, 0],$$

with φ_1, φ_2 differentiable functions.

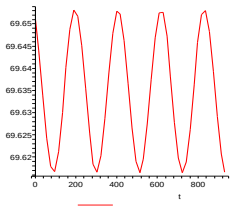
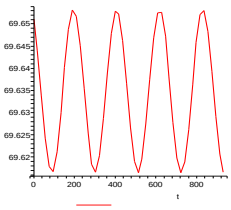
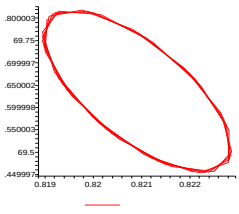
3.2. Numerical simulations

For the numerical simulations we use Maple 11. In this section, we consider system (3.1) with $a_1 = a_2 = 0.13$, $a_{12} = 0.02$, $a_{21} = 0.02$, $b_1 = 0.8$, $b_2 = 0.01$, $a = 4$; $a_{12} = a_{21}$ because there is molecular interaction between Mdm2 and P53, one molecule to one molecule. Let $X_0 = (x_{10}, y_{10}, x_{20}, y_{20})^T$ be the equilibrium state.

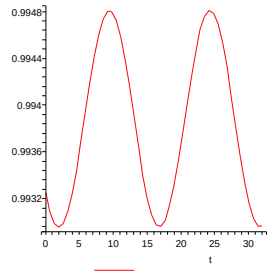
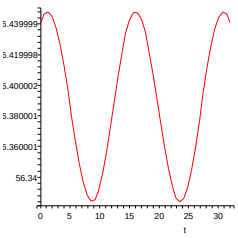
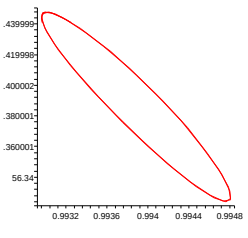
For $n = 2$ we obtain: $x_{10} = 1.2500000$, $y_{10} = 0.72279716$, $y_{20} = 79.96962531$, $x_{20} = 11.55208766$. The wave plots and the phase plot are:

Waveplot (t, y_1)	Waveplot (t, y_2)	Phaseplot (y_1, y_2)
		

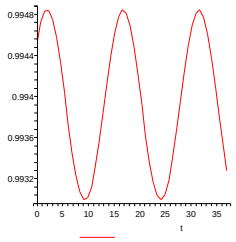
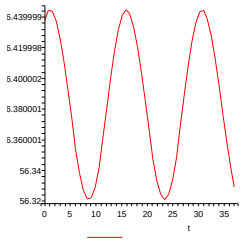
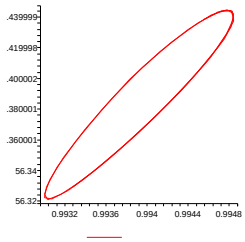
For $n = 4$ we obtain:$x_{10} = 1.2500000$, $y_{10} = 0.82091152$, $y_{20} = 69.63487984$, $x_{20} = 10.19581588$. The wave plots and the phase plot are:

Waveplot (t, y_1)	Waveplot (t, y_2)	Phaseplot (y_1, y_2)
		

For $n = 163$ we obtain:x_{10}=1.2500000, y_{10}=0.99390609, y_{20}=56.38320475, $x_{20} = 8.45060883$. The wave plots and the phase plot are:

Waveplot (t, y_1)	Waveplot (t, y_2)	Phaseplot (y_1, y_2)
		

For $n = 164$ we obtain:x_{10}=1.2500000, y_{10}=0.99394289, y_{20}=56.38087608, x_{20} = 8.45030131. The wave plots and the phase plot are:

Waveplot (t, y_1)	Waveplot (t, y_2)	Phaseplot (y_1, y_2)
		

Recent dynamic studies of P53 and Mdm2 proteins suggest that their responses in individual cells have cyclic behavior and their characteristics are compatible with a digital clock [3]. Similar behavior we obtained in our mathematical model.

4. Model 4. P53-Mdm2 with distributed time delay

4.1. The mathematical model

In the last years, the approaches of P53 dynamics as response to DNA damage comprise modelings in which are described three distinct subsystems: a DNA damage repair module, an ataxia telengiectasia mutated (ATM) switch and the P53-Mdm2 oscillator.

The DNA damage repair module includes a set of reactions which contain the repair proteins formed at eukaryotes by Mre11, Rad50 and NBS1 (which form the MRN complex). They come into action in DSB lesions of DNA and they will be called DSB-repair protein complex.

The second module, ATM switch is formed by the reactions which lead to ATM activation. In the cells under genetic stress, the initial signal of ATM activation is induced by DSB-repair protein complex and then the activation of ATM is given by intermolecular autophosphorylation, which is a quick process.

The third module, the P53-Mdm2 oscillator, includes the feedback loop between P53 and its principal antagonist, Mdm2, a P53-specific ubiquitin ligase that is transactivated by P53 [3], [6], [9].

Based on these three modules approach of the P53 dynamics, in the paper [11] it is described an interaction model of P53-Mdm2 and $P53^*$, taking into account ATMD, ATM and ATM^* and it is given by the following differential equations with time

delay:

$$
\begin{aligned}
&\dot{z}_1(t) = -c_1 z_1(t) + \frac{1}{2} c_2 z_2(t)^2,\\
&\dot{z}_2(t) = 2c_1 z_1(t) - \alpha_1 c c_3 z_2(t) + c_4 z_3(t) - c_2 z_2(t)^2 - c_3(\alpha_2 c + \alpha_3) z_2(t) z_3(t),\\
&\dot{z}_3(t) = \alpha_1 c c_3 z_2(t) - c_4 z_3(t) + c_3(\alpha_2 c + \alpha_3) z_2(t) z_3(t),\\
&\dot{x}_1(t) = a_1 - a_2 x_1(t),\\
&\dot{x}_2(t) = b_1 - b_2 x_2(t) + b_3 \frac{y_3(t-\tau_1)^n}{y_3(t-\tau_1)^n + k_1^n}\\
&\dot{y}_1(t) = d_1 x_1(t) - d_2 y_1(t) + d_3 y_3(t) - d_4 \frac{y_1(t) y_2(t)}{y_1(t) + k_2} - d_5 \frac{y_1(t) y_3(t)}{y_1(t) + k_3},\\
&\dot{y}_2(t) = l_1 x_2(t-\tau_2) - l_2 y_2(t) + (l_3 - l_4) \frac{z_3(t) y_2(t)}{z_3(t) + k_4},\\
&\dot{y}_3(t) = -d_3 y_3(t) + d_5 \frac{z_3(t) y_1(t)}{y_1(t) + k_3} - d_6 \frac{y_3(t) y_2(t)}{y_3(t) + k_5},
\end{aligned}
\tag{4.1}
$$

where $z_1(t)$, $z_2(t)$, $z_3(t)$ are the concentrations of ATMD, ATM, ATM^* and $x_1(t)$, $x_2(t)$, $y_1(t)$, $y_2(t)$, $y_3(t)$ are the concentrations of p53, mdm2, P53, Mdm2 and P_{53}^*, $\tau_1 > 0$, $\tau_2 > 0$ and the coefficients are the degradation rates. The numerical simulation and the specific interpretations are investigated in [11].

The models for P53-Mdm2 interaction were described in [5], [14].

In what follows we will consider a model only for the third module. The variables of the model are: x_1 p53-mRNA concentration, x_2 mdm2-mRNA concentration, y_1 P53-protein concentration and y_2 Mdm2-protein concentration.

We consider P53-Mdm2 model with distributed delay given by:

$$
\begin{aligned}
&\dot{x}_1(t) = c_1 - b_1 x_1(t),\\
&\dot{y}_1(t) = x_1(t) - (a_1 + a_{12} y_2(t)) y_1(t),\\
&\dot{x}_2(t) = \alpha f(y_1(t)) + (1-\alpha) f(\textstyle\int_{-\infty}^{t} G(t-s) y_1(s) ds) - b_2 x_2(t),\\
&\dot{y}_2(t) = x_2(t) - (a_2 + a_{21} y_1(t)) y_2(t)
\end{aligned}
\tag{4.2}
$$

where: b_1, b_2 are the rates for mRNA degradation, a_1, a_2, a_{12}, a_{21} are the rates for proteins degradation. The function $f : \mathbf{R}_+ \to \mathbf{R}$, is the Hill function, given by:

$$
f(x) = \frac{x^n}{a + x^n} \tag{4.3}
$$

with $n \in \mathbf{N}^*, a > 0$. The parameters a_1, a_2, b_1, b_2, c_1, a_{12}, a_{21} of the model are assumed to be positive numbers less or equal to 1, $\alpha \in [0, 1]$ and $\tau > 0$.

The memory function $G(s)$ that reflect the influence of the past states on the current dynamics is a nonnegative bounded function defined on $[0, \infty)$ and

$$
\int_0^{\infty} G(s) ds = 1.
$$

The memory function is called delay kernel. The delay becomes a discrete one when the delay kernel $G(s)$ is a delta function at a certain time. Usually, we employ the following form:

$$
G(s) = \frac{q^{p+1}}{p!} s^p e^{-qs}
$$

for the memory function. When $p = 0$ and $p = 1$ the memory function are called "weak" and "strong" kernel respectively.

From (4.2), for $\alpha = 1$, $a_{21} = 0$, $c_1 = 1$, we obtain the model from [12], which suggests that there is an oscillatory behavior based on using only numerical simulations.

If G(s) is given by:

$$G(s) = \begin{cases} \frac{1}{\tau}, & s \in [0, \tau] \\ 0, & s > \tau, \end{cases}$$

where $\tau > 0$, then we consider a dynamic P53-Mdm2 model with uniform distributed time delay:

$$\begin{aligned} &\dot{x}_1(t) = c_1 - b_1 x_1(t), \\ &\dot{y}_1(t) = x_1(t) - (a_1 + a_{12} y_2(t)) y_1(t), \\ &\dot{x}_2(t) = \alpha f(y_1(t)) + (1-\alpha) \int_0^\infty G(s) f(y_1(t-s)) ds - b_2 x_2(t), \\ &\dot{y}_2(t) = x_2(t) - (a_2 + a_{21} y_1(t)) y_2(t). \end{aligned} \tag{4.4}$$

In this paper, the model with uniform distributed time delay is investigated using the method from [1]. For $c_1 = 1$, $a_{12} = a_{21}$ the system (4.4) is given by:

$$\begin{aligned} &\dot{x}_1(t) = 1 - b_1 x_1(t), \\ &\dot{y}_1(t) = x_1(t) - (a_1 + a_{12} y_2(t)) y_1(t), \\ &\dot{x}_2(t) = \alpha f(y_1(t)) + \frac{(1-\alpha)}{\tau} \int_0^\tau f(y_1(t-s)) ds - b_2 x_2(t), \\ &\dot{y}_2(t) = x_2(t) - (a_2 + a_{12} y_1(t)) y_2(t). \end{aligned} \tag{4.5}$$

The function f is the Hill function and it is given by (4.3).

For the study of the model (4.5) we consider the following initial values:

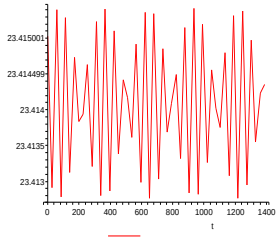
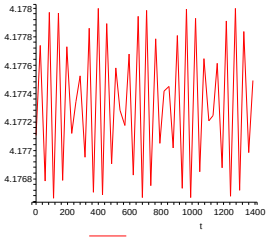
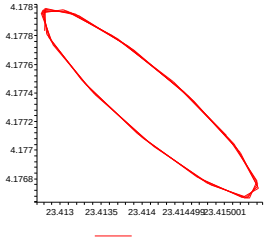
$$x_1(0) = \bar{x}_1, y_1(\theta) = \varphi_1(\theta), \theta \in [-\tau, 0], x_2(0) = \bar{x}_2, y_2(0) = \bar{y}_2,$$

with $\bar{x}_1 \geq 0$, $\bar{x}_2 \geq 0$, $\bar{y}_2 \geq 0$, $\varphi_1(\theta) \geq 0$, for all $\theta \in [-\tau, 0]$ and φ_1 is a differentiable function.

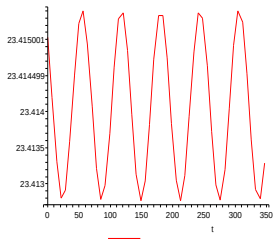
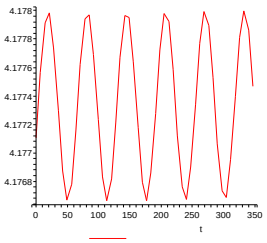
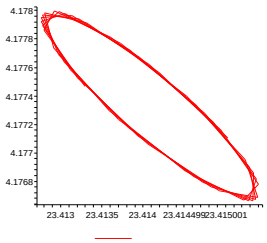
4.2. Numerical simulations

For the numerical simulations we use Maple 11. In this section, we consider system (4.5) with $a_1 = a_2 = 0.13$, $a_{12} = 0.02$, $b_1 = 0.2$, $b_2 = 0.4$, $a = 4$, $n = 3$. Let $X^* = (x_{10}, y_{10}, x_{20}, y_{20})^T$ be the equilibrium state.

For $\alpha = 0.2$ we obtain: $x_{10} = 5$, $y_{10} = 23.41409107$, $y_{20} = 4.177330982$, $x_{20} = 2.499221188$. The waveforms are displayed in Fig 4.1 and Fig 4.2 and the phase plane diagram of the state variables $y_1(t)$, $y_2(t)$ are displayed in Fig 4.3:

Fig.4.1. $(t, y_1(t))$	Fig.4.2. $(t, y_2(t))$	Fig.4.3. $(y_1(t), y_2(t))$
		

For $\alpha = 0.8$ we obtain: $x_{10} = 5$, $y_{10} = 23.41409107$, $y_{20} = 4.177330982$, $x_{20} = 2.499221188$. The wave plots are displayed in Fig4.4 and Fig4.5 and the phase plane diagram of the state variables $y_1(t)$, $y_2(t)$ are displayed in Fig4.6:

Fig.4.4. $(t, y_1(t))$	Fig.4.5. $(t, y_2(t))$	Fig.4.6. $(y_1(t), y_2(t))$
		

4.3. Discussions and conclusions

This new model is based on [13] and Model 3. Here we achieve a smoother modelling of the phenomenon, i.e. the interaction p53-mdm2. The production of P53 protein is continuous, so is the binding between P53 and the promoter of the mdm2. The difference from Model 3 lies in the introduction of the integral form in the third equation, which is the natural way of modelling a continuous process.

Using the integral form is better than using a simple time delay. From biological point of view we explain the use of integral form as in the pool of P53 protein, molecules has entered at different times.

For a better mathematical modelling we introduce the convex combination $\alpha X + (1-\alpha)Y$ in the third equation of system (4.5). Thus, it can be controlled the weigh of current P53 protein concentration and the weigh of previous P53 protein concentration. To sustain this statement, we say only that in spite of no biological meaning of the two extreme values $\alpha = 0$ and $\alpha = 1$ there is a mathematical meaning. The third equation of system (4.5) will not take into account the previous concentration of P53 protein for $\alpha = 1$ and current concentration of P53 protein for $\alpha = 0$.

In (4.2), the term $f(\int_{-\infty}^{t} G(t-s)y_1(s)ds)$ is justified by the fact that the variable $y_1(t)$ which characterize the P53 protein concentration is evaluated on $(-\infty, t)$ with

the help of delay kernel G(s), after that we apply the activation function. The delay kernels G for (4.2) are only of the Dirac type, weak and strong. To (4.4), we apply the activation function to variable $y_1(t)$, after that the result is evaluated on $[0, \tau]$ and G is given by the uniform distribution.

If we replace the quadratic terms with the terms which contain Hill functions in (4.2), then we obtain the model from [11] where it is eliminated ATM and $P53^*$.

In our future papers we will do a qualitative analysis of the model from [11].

As in our previous models, we obtain an oscillatory behavior similar to that observed experimentally [3]. The conclusion is not surprising, but is useful as this model provides a more accurate approach of the interaction P53-Mdm2. We can conclude that the transformation made by us to the continuous model with distributed time of the interaction P53-Mdm2, which actually is more real, did not alter the behavior of the system.

Taking into account that in this paper we modelled only the third module (P53-Mdm2 oscillator) and we have not introduced the ATM, we have not obtained the digital clock behavior of the process, but we obtained oscillations similar with those observed experimentally. Based on the recent experimental results and on the new approaches of the process modelling we intend in the future to do a qualitative analysis of a model which contain all the three modules.

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