Control of the p53 Protein - mdm2 Inhibitor System using Nonlinear Kalman Filtering

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Abstract: A nonlinear feedback control scheme for the p53 protein - mdm2 inhibitor system is developed with the use of differential flatness theory and of nonlinear Kalman Filtering. It is shown that by applying differential flatness theory the protein synthesis model can be transformed into the canonical form. This enables the design of a feedback control law that maintains the concentration of the p53 protein at the desirable levels. To estimate the non-measurable elements of the state vector describing the p53-mdm2 system dynamics and to compensate for modeling uncertainties and external disturbances that affect the p53-mdm2 system, the nonlinear Kalman Filter is re-designed as a disturbance observer. The proposed nonlinear feedback control and perturbations compensation method for the p53-mdm2 system can result in more efficient chemotherapy schemes where the infusion of medication will be better administered.

1 INTRODUCTION

The *P*53 protein has been identified as a key factor in the abatement of tumors since it enhances cell-cycle arrest and apoptosis. The concentration of the *P*53 protein in the cytoplasm is primarily controlled by another protein, known as inhibitor protein *mdm*2, within a feedback loop. When the concentration of the MDM2 protein increases, the concentration of the P53 protein is reduced (downregulation). The MDM2 protein binds ubiquitin molecules to P53 which result to the disintegration of the *P*53 protein. On the other side, the increase of the concentration of *P*53 enhances the transcription procedure of *mdm*2 and consequently the produced MDM2 protein will downregulate *P*53. In this manner the *p*53-*mdm*2 feedback loop converges to an equilibrium (Lillacci et al., 2006),(Qi et al., 2008),(Wagner et al., 2005). There are chemotherapy drugs that work by binding the *MDM*2 protein and consequently by preventing the *MDM*2 protein from disintegrating the *P*53 protein (ubiquitination) (Elias et al., 2013),(Abou-Jaoudé et al., 2010). This is a promising approach to the treatment of cancer. It is based on the infusion of *MDM*2 antagonists which are called Nutlins. By deactivating *MDM*2 these drugs restore the levels of concentration of the *P*53 protein and consequently contribute to the fighting against cancel cells (Jahoor Alam et al., 2012),(Pierce and Findley, 2010),(Leenders and Tuszynski, 2013).

In this paper it is shown that it is possible to control the levels of the concentration of the P53 protein through nonlinear feedback control, where the control input is the infusion rate of the chemotherapy drug. Previous results on nonlinear feedback control of biological oscillators and on control of protein synthesis processes can be found in (Rigatos, 2013),(Rigatos and Rigatou, 2013). The pharmacokinetics - pharmacodynamics model of the P53 protein is described by a complicated set of nonlinear differential equations. It is shown that with the use of differential flatness theory it is possible to transform this complicated model into the canonical Brunovsky form (Rudolph, 2003),(Sira-Ramirez and Agrawal, 2004),(Lévine, 2011),(Fliess and Mounier, 1999),(Rouchon, 2005),(Martin and Rouchon, 1999),(Bououden et al., 2011), (Laroche et al., 2007). In this latter form a single-input single output description between the output (P53 protein) and the input (drug's infusion rate) is obtained and this facilitates the design of a feedback control and state estimation scheme that can make the P53 protein concentration converge to the desirable levels. Moreover, disturbances estimation and compensation

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is performed with the use of nonlinear Kalman Filtering.

2 DYNAMIC MODEL OF THE p53 PROTEIN - mdm2 INHIBITOR SYSTEM

The meaning of the variables that appear in the p53 protein - mdm2 inhibitor dynamical system (see Fig. 1) is as follows (Lillacci et al., 2006), (Qi et al., 2008), (Elias et al., 2013), (Jahoor Alam et al., 2012): $p53$: mRNA concentration of the p53 gene after transcription, $P53$: concentration of the P53 protein in the cytoplasm after translation, $P53^*$: active form of the P53 protein that is produced after phosphorylation of P53, $mdm2$: mRNA concentration of the inhibitor protein mdm2 after transcription, $MDM2$: concentration of the MDM2 protein in the cytoplasm after translation, N: concentration of the chemotherapeutic drug, ATM: a protein that identifies the transcription of p53 and contributes to the phosphorylation of the P53 protein, ATM^*: concentration of the active form of the ATM protein. It contributes both to the phosphorylation of protein $P53$ and of protein $MDM2$, $e2f1$: mRNA concentration of the gene $e2f1$ after transcription, $E2F1$: concentration of the protein $E2F1$ after translation, $E2F1^*$: active form of the $E2F1$ protein, arf: mRNA concentration of the gene arf after transcription, ARF: concentration of the ARF protein after translation. The associated state-space model is (Lillacci et al., 2006):

$$
\begin{aligned}
&\dot{x}_1 = \lambda_{p53} - \mu_{p53}x_1\\
&\dot{x}_2 = a_{p53}x_1 - \mu_{53}x_2 - v_{p53}x_3 - \frac{K_1 ATM^* x_2}{K_{M_1}+x_2} - \frac{K_{cat}x_5 x_2}{aK_{13}+x_2}\\
&\dot{x}_3 = \frac{K_1 ATM^* x_2}{K_{M_1}+x_2} - v_{p53}x_3 - \frac{K_c at^* x_5 x_3}{aK_{13}+x_3}\\
&\dot{x}_4 = \lambda_{mdm2} - \mu_{mdm2}x_4 + \phi_{mdm2}\frac{x_3(t-r_1)^{n_1}}{x_2(0)^{n_1}+x_3(t-r_1)^{n_1}}\\
&\dot{x}_5 = a_{MDM2}x_4 - \mu_{MDM2}x_5 - \frac{K_2 ATM^* x_5}{K_{M_2}+x_5} -\\
&-K_4 x_{11}x_5 - K_6 x_6 x_5\\
&\dot{x}_6 = \lambda_N - \mu_N x_6 - K_6 x_6 x_5\\
&\dot{x}_7 = \lambda_{e2f1} - \mu_{e2f1}x_7\\
&\dot{x}_8 = a_{E2F1}x_7 - \mu_{E2F1}x_8 + v_{E2F1}x_9 - \frac{K_2 ATM^* x_8}{K_{M_3}+x_8}\\
&\dot{x}_9 = \frac{K_3 ATM^* x_8}{K_{M_3}+x_8} - v_{E2F1}x_9 - K_5 x_{11}x_9\\
&\dot{x}_{10} = \lambda_{arf} - \mu_{arf}x_{10} + \phi_{arf}\frac{x_9(t-r_2)^{n_2}}{x_8(0)^{n_2}+x_9(t-r_2)^{n_2}}\\
&\dot{x}_{11} = a_{ARF}x_{10} - \mu_{ARF}x_{11} - K_4 x_{11}x_5 - K_5 x_{11}x_9
\end{aligned}
\tag{1}
$$

where the state variables for the dynamic model of the $p53$ protein - $mdm2$ inhibitor system of Eq. (1) are defined as: $x_1 = p53$, $x_2 = P53$, $x_3 = P53^*$, $x_4 = mdm2$, $x_5 = MDM2$, $x_6 = N$, $x_7 = e2f1$, $x_8 = E2F1$, $x_9 = E2F1^*$, $x_{10} = arf$ and $x_{11} = ARF$. In matrix form, the state-space description of the system becomes

$$\dot{x} = f(x) + g(x)u \tag{2}$$

where $u = \lambda_N$ is the control input (drug infusion rate), and $f(x) \in R^{11\times 1}$, $g(x) \in R^{11\times 1}$ are vector fields.

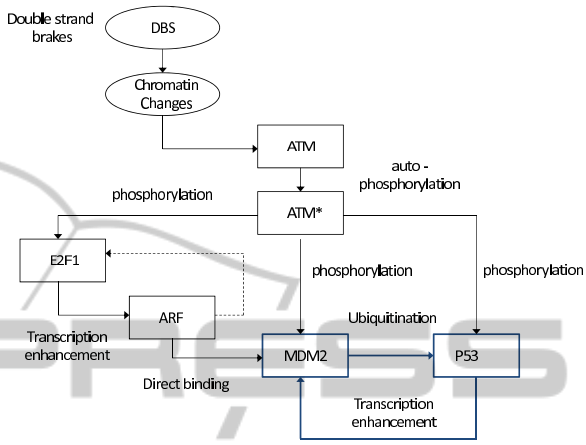


Figure 1: Feedback control loop of the p53 protein - mdm2 inhibitor system.

3 FLATNESS-BASED CONTROL OF THE p53 PROTEIN SYSTEM

First, it will be shown that the considered model of the $p53$ protein - $mdm2$ inhibitor system is a differentially flat one. The following flat output is defined $y = [p^*_{53}, N, E2F1^*, ARF]$ or $y = [x_1, x_6, x_9, x_{11}]$. Thus one has $y = [y_1, y_2, y_3, y_4]^T$. From the sixth row of Eq. (1) and by solving with respect to x_5 one obtains

$$
\begin{aligned}
&x_5 = \frac{\dot{x}_6 + \mu_N x_6}{-K_6 x_6} \Rightarrow x_5 = \frac{\dot{y}_2 + \mu_N y_2}{-K_6 y_2} \Rightarrow\\
&x_5 = \frac{[0\ 1\ 0\ 0]\dot{y} + \mu_N [0\ 1\ 0\ 0]y}{-K_6 [0\ 1\ 0\ 0]y} \Rightarrow x_5 = f_5(y, \dot{y})
\end{aligned}
\tag{3}
$$

From the third row of Eq. (1) and by solving with respect to x_2 one obtains

$$
\begin{aligned}
&x_2 = \frac{K_{M_1}\dot{y}_1 - v_{p53}K_{M_1}y_1 + K_{M_1}\frac{K^*_{cat} f_5(y,\dot{y})y_1}{aK_{13}+y_1}}{K_1 ATM^* + v_{p53}y_1 + \frac{K^*_{cat} f_5(y,\dot{y})y_1}{aK_{13}+y_1} - \dot{y}_1} \Rightarrow\\
&x_2 = f_2(y, \dot{y})
\end{aligned}
\tag{4}
$$

Equivalently, the second row of Eq. (1) is solved with respect to x_1. This gives

$$
\begin{aligned}
&x_1 = \dot{x}_2 + \mu_{p53}x_2 + v_{p53}x_3 + \frac{K_1 ATM^* x_2}{K_{M_1}+x_2} - \frac{K_{cat}x_2 x_5}{aK_{13}+x_2} \Rightarrow\\
&x_1 = f_1(y, \dot{y})
\end{aligned}
\tag{5}
$$

The fifth row of Eq. (1) is solved with respect to x_4

$$x_4 = \frac{\dot{x}_5+\mu_{MDM2}x_5+\frac{K_2ATM^*x_5}{K_{M_2}+X_5}+K_4x_{11}x_5+K_6x_6x_5}{a_{MDM2}} \Rightarrow \quad x_4 = f_4(y,\dot{y}) \tag{6}$$

The ninth row of Eq. (1) is solved with respect to x_8

$$K_{M_3}\dot{x}_9 + \dot{x}_9x_8 = K_3ATM^*x_8 - v_{E2F1}K_{M_3}x_9 - -v_{E2F1}x_8x_9 - K_5K_{M_3}x_{11}x_9 - K_5x_{11}x_9x_8 \Rightarrow$$
$$x_8 = \frac{K_{M_3}\dot{x}_9+v_{E2F1}K_{M_3}x_3+K_5K_{M_3}x_{11}x_9}{K_3ATM^*-\dot{x}_9-v_{E2F1}x_9-K_9x_{11}x_9} \Rightarrow \quad x_8 = f_8(y,\dot{y}) \tag{7}$$

The eighth row of Eq. (1) is solved with respect to x_7

$$x_7 = \frac{\dot{x}_8+\mu_{E2F1}x_8-v_{E2F1}x_9+\frac{K_2ATM^*x_8}{K_{M_3}+x_8}}{a_{E2F1}} \Rightarrow \quad x_7 = f_7(y,\dot{y}) \tag{8}$$

The eleventh row of Eq. (1) is solved for x_{10}

$$x_{10} = \frac{\dot{x}_{11}+\mu_{ARF}x_{11}+K_4x_{11}x_5+K_5x_{11}x_9}{a_{ARF}} \Rightarrow \quad x_{10} = f_{10}(y,\dot{y}) \tag{9}$$

Moreover, from the sixth row of Eq. (1) and using that $x_5 = f_5(y,\dot{y})$ and $x_6 = y_2$ one obtains about the control input $u = \lambda_N$

$$u = \lambda_N = \dot{x}_6 + \mu_N x_6 + K_6x_6x_5 \Rightarrow \quad \lambda_N = f_u(y,\dot{y}) \tag{10}$$

Thus one has that all state variables and the control input of the $p53$ protein - $mdm2$ inhibitor system are functions of the flat output y and of its derivatives. Consequently, the dynamical system of $P53$ protein is a differentially flat one.

Next, it will be shown that using the differentially flat description of the $p53$ protein - $mdm2$ inhibitor system it is possible to transform it to the canonical Brunovsky form. It holds that $y_1 = x_3$ therefore

$$\dot{y}_1 = \dot{x}_3 \Rightarrow \dot{y}_1 = \frac{K_1ATM^*x_2}{K_{M_1}+x_2} - v_{P53}x_3 - \frac{K^*_{cat}x_5x_3}{aK_{13}+x_3} \tag{11}$$

Consequently, the second derivative of y_1 is

$$\ddot{y}_1 = \frac{(K_1ATM^*\dot{x}_2)(K_{M_1}+x_2)-(K_1ATM^*x_2)\dot{x}_2}{(K_{M_1}+x_2)^2} - v_{p53}\dot{x}_3 - \frac{-K^*_{cat}(\dot{x}_5x_3+x_5\dot{x}_3)(aK_{13}+x_3)-(K^*_{cat}x_5x_3)\dot{x}_3}{(aK_{13}+x_3)^2} \tag{12}$$

After intermediate operations one obtains

$$\ddot{y}_1 = \frac{K_1ATM^*K_{M_1}}{(K_{M_1}+x_2)^2}\dot{x}_2 - v_{p53}\dot{x}_3 - \frac{K^*_{cat}aK_{13}x_5\dot{x}_3}{(aK_{13}+x_3)^2} - \frac{K^*_{cat}x_3}{(aK_{13}+x_3)}\dot{x}_5 \tag{13}$$

and after substituting $\dot{x}_3$ and $\dot{x}_5$ one gets

$$\ddot{y}_1 = \frac{K_1ATM^*K_{M_1}}{(K_{M_1}+x_2)^2}[a_{p53}x_1 - \mu_{p53}x_2 - v_{p53}x_3 - \frac{K_1ATM^*x_2}{K_{M_1}+x_2} - \frac{K_{cat}x_5x_2}{aK_{13}+x_2}] - [v_{p53} + \frac{K^*_{cat}aK_{13}x_5}{(aK_{13}+x_3)^2}]\cdot[\frac{K_1ATM^*x_2}{K_{M_1}+x_2} - v_{p53}x_3 - \frac{K^*_{cat}x_5x_3}{(aK_{13}+x_3)}] - \frac{K^*_{cat}x_3}{(aK_{13}+x_3)}[a_{MDM2}x_4 - \mu_{MDM2}x_5 - \frac{K_2ATM^*x_5}{K_{M_2}+x_5} - K_4x_{11}x_5 - K_6x_6x_5].$$

By differentiating once more with respect to time one obtains $y_1^{(3)} = f(y,\dot{y}) + g(y,\dot{y})u$, where the control input $u = \lambda_N$ is the input rate of the chemotherapy drug, while functions $f(y,\dot{y})$ and $g(y,\dot{y})$ are:

$$f(y,\dot{y}) = -\frac{2(K_{M_1}+x_2)\dot{x}_2K_1ATMK_{M_1}}{(K_{M_1}+x_2)^4}[a_{p53}\dot{x}_1 - \mu_{p53}\dot{x}_2 - v_{p53}\dot{x}_3 - \frac{K_1ATM^*x_2}{K_{M_1}+x_2} - \frac{K_{cat}x_5x_2}{aK_{13}+x_2}] + \frac{K_1ATM^*K_{M_1}}{(K_{M_1}+x_2)^2}[a_{p53}\dot{x}_1 - \mu_{p53}\dot{x}_2 - v_{p53}\dot{x}_3 - \frac{K_1ATM\dot{x}_2(K_{M_1}+x_2)-K_1ATM^*\dot{x}_2}{(K_{M_1}+x_2)^2} - \frac{K_{cat}(\dot{x}_5x_2+x_5\dot{x}_2)(aK_{13}+x_2)-K_{cat}x_5x_2\dot{x}_2}{(aK_{13}+x_2)^2}] - \frac{-K^*_{cat}aK_{13}\dot{x}_5(aK_{13}+x_3)^2-K^*_{cat}aK_{13}x_5 2(aK_{13}+x_3)\dot{x}_3}{(aK_{13}+x_3)^4}\cdot[\frac{K_1ATM^*x_2}{K_{M_1}+x_2} - v_{p53}x_3 - \frac{K_cat^*x_5x_3}{aK_{13}+x_3}] - [v_{p53} + \frac{K^*_{cat}aK_{13}x_5}{(aK_{13}+x_3)^2}]\cdot[\frac{K_1ATM^*\dot{x}_2(K_{M_1}+x_2)-K_1ATM^*x_2\dot{x}_2}{K_{M_1}+x_2{}^2} - v_{p53}\dot{x}_3 - \frac{K^*_{cat}(\dot{x}_5x_3+x_5\dot{x}_3)(aK_{13}+x_3)-K^*_{cat}x_5x_3(aK_{13}+x_3)}{(aK_{13}+x_3)^2}] - \frac{K^*_{cat}\dot{x}_3(aK_{13}+x_3)-K_cat^*x_3\dot{x}_3}{(aK_{13}+x_3)^2}\cdot[a_{MDM2}x_4 - \mu_{MDM2}x_5 - \frac{K_2ATM^*x_5}{K_{M_2}+x_5} - K_4x_{11}x_5 - K_6x_6x_5] - \frac{K^*_{cat}x_3}{(aK_{13}+x_3)}\cdot[a_{MDM2}\dot{x}_4] - \mu_{MDM2}\dot{x}_5 - \frac{K_2ATM^*x_5-K_{M_2}ATM^*x_5\dot{x}_5}{K_{M_2}+x_5{}^2} - K_4(\dot{x}_{11}x_5+x_{11}\dot{x}_5) - K_6x_6\dot{x}_5] - \frac{K^*_{cat}x_3}{(aK_{13}+x_3)}[-\mu_Nx_6 - K_6x_6x_5](-K_6x_5)$$

and $g(y,\dot{y}) = -\frac{K^*_{cat}x_3}{aK_{13}+x_3}(-K_6x_5)$. By defining the new control input $v = f(y,\dot{y}) + g(y,\dot{y})u$, the dynamics of the active $P53$ protein can be written in the form

$$y^{(3)} = f(y,\dot{y}) + g(y,\dot{y})u \Rightarrow y^{(3)} = v \tag{14}$$

A suitable feedback control law for the system of Eq. (14) is given by

$$v = y_d^{(3)} - k_1(\ddot{y}-\ddot{y}_d) - k_2(\dot{y}-\dot{y}_d) - k_3(y-y_d) \tag{15}$$

where the gains k_1, k_2 and k_3 are chosen such that the characteristic polynomial of the closed-loop system to be a Hurwitz-stable one. The dynamics of the tracking error is $e = y - y_d = P53^* - P53^*_d$ is given by $e^{(3)} + k_1\ddot{e} + k_2\dot{e} + k_3e = 0$, which finally results into $lim_{t\to\infty}e(t) = 0$. The control input that actually ap-

plied to the $p53$ protein - $mdm2$ inhibitor system is computed from $u = g(y,\dot{y})^{-1}[v - f(y,\dot{y})]$

4 DISTURBANCES COMPENSATION USING NONLINEAR KALMAN FILTERING

To apply the feedback control law of Eq. (15) to the system of the p53 protein synthesis it is possible to use measurements of the concentration of the active $P53^*$ protein concentration at the cytoplasm, however the derivatives of $P53^*$ with respect to time are missing. Moreover, the p53-mdm2 dynamic model is subjected to modeling uncertainties and external disturbances which are denoted by the aggregate term $\tilde{d}$ in the following equation:

$$y^{(3)} = f(y,\dot{y}) + g(y,\dot{y})u + \tilde{d} \tag{16}$$

The dynamics of the additive disturbance term $\tilde{d}$ can be equivalently represented through knowledge of the associated n-th order derivative. Here, without loss of generality it is considered that $n = 3$ thus one has $\tilde{d}^{(3)} = f_d$. Next, the system's state vector is extended so as to include the disturbance term's dynamics. The extended state vector contains the following state variables: $z_1 = y$, $z_2 = \dot{y}$, $z_3 = \ddot{y}$, $z_4 = \tilde{d}$, $z_5 = \dot{\tilde{d}}$ and $z_6 = \ddot{\tilde{d}}$. Then the dynamics of the $p53$ protein - $mdm2$ inhibitor system, including the modeling uncertainty and external disturbances terms is written in the following canonical Brunovsky form $\dot{z} = Az + Bv$ and $z_m = Cz$, or equivalently

$$\begin{pmatrix} \dot{z}_1 \\ \dot{z}_2 \\ \dot{z}_3 \\ \dot{z}_4 \\ \dot{z}_5 \\ \dot{z}_6 \end{pmatrix} = \begin{pmatrix} 0\,1\,0\,0\,0\,0 \\ 0\,0\,1\,0\,0\,0 \\ 0\,0\,0\,1\,0\,0 \\ 0\,0\,0\,0\,1\,0 \\ 0\,0\,0\,0\,0\,1 \\ 0\,0\,0\,0\,0\,0 \end{pmatrix} \begin{pmatrix} z_1 \\ z_2 \\ z_3 \\ z_4 \\ z_5 \\ z_6 \end{pmatrix} + \begin{pmatrix} 0\,0 \\ 0\,0 \\ 1\,0 \\ 0\,0 \\ 0\,0 \\ 0\,1 \end{pmatrix} \begin{pmatrix} v \\ f_d \end{pmatrix} \tag{17}$$

with measurement equation given by

$$z_m = \begin{pmatrix} 1 & 0 & 0 & 0 & 0 & 0 \end{pmatrix} z \tag{18}$$

For the dynamics of the $p53$ protein - $mdm2$ inhibitor that is described by Eq. (17) and Eq. (18) it is possible to perform simultaneous estimation of the non-measurable state variables as well as of the external disturbances using the Kalman Filter recursion. The application of Kalman Filtering on the linearized equivalent of the system and the use of an inverse transformation based on the expression of the initial state variables as functions of the flat output (see Eq. (3) to Eq. (7)) enables also to obtain estimates for the state variables of the initial nonlinear dynamical system. This recursive estimation and inverse transformation procedure constitutes the *Derivative-free nonlinear Kalman Filter*. The disturbance estimator is

$$\begin{aligned} \dot{\hat{z}} &= A_o\hat{z} + B_o u + K(z_m - \hat{z}_m) \\ \hat{z}_m &= C_o\hat{z} \end{aligned} \tag{19}$$

where $A_o = A$, $C_o = C$ and

$$B_o^T = \begin{pmatrix} 0\,0\,1\,0\,0\,0 \\ 0\,0\,0\,0\,0\,0 \end{pmatrix} \tag{20}$$

In the design of the associated disturbances' estimator one has the dynamics defined in Eq. (19), where $K \in R^{6\times 1}$ is the state estimator's gain and matrices A_o, B_o and C_o have been defined in Eq. (17) to Eq. (18). The discrete-time equivalents of matrices A_o, B_o and C_o are denoted as $\tilde{A}_d$, $\tilde{B}_d$ and $\tilde{C}_d$ respectively, and are computed with the use of common discretization methods (Rigatos, 2011),(Rigatos and Zhang, 2009). Next, a Derivative-free nonlinear Kalman Filter can be designed for the aforementioned representation of the system dynamics (Rigatos, 2011). The associated Kalman Filter-based disturbance estimator is given by the recursion (Rigatos and Tzafestas, 2007),(Bassevile and Nikiforov, 1993),(Rigatos and Zhang, 2009)

measurement update:

$$\begin{aligned} &K(k) = P^-(k)\tilde{C}_d^T[\tilde{C}_d \cdot P^-(k)\tilde{C}_d^T + R]^{-1} \\ &\hat{z}(k) = \hat{z}^-(k) + K(k)[\tilde{C}_d z(k) - \tilde{C}_d\hat{z}^-(k)] \\ &P(k) = P^-(k) - K(k)\tilde{C}_d P^-(k) \end{aligned} \tag{21}$$

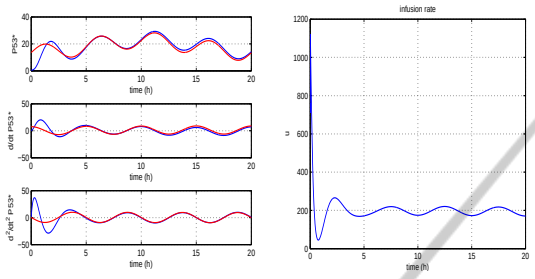
time update:

$$\begin{aligned} &P^-(k+1) = \tilde{A}_d(k)P(k)\tilde{A}_d^T(k) + Q(k) \\ &\hat{z}^-(k+1) = \tilde{A}_d(k)\hat{z}(k) + \tilde{B}_d(k)\tilde{v}(k) \end{aligned} \tag{22}$$

5 SIMULATION TESTS

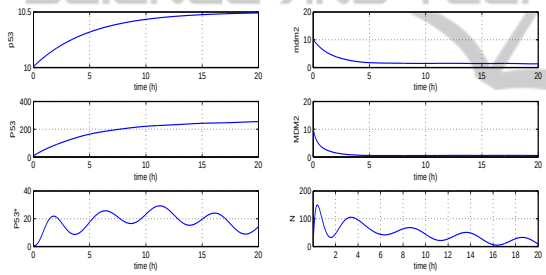
The test case considers that there are model uncertainties and external disturbances that affect the $p53$ protein - $mdm2$ inhibitor system. The use of the Derivative-free nonlinear Kalman Filter enables to perform simultaneous estimation of the non-measurable elements of the system's state vector as well as estimation of the disturbance terms. By identifying the perturbation parameters their compensation becomes possible. It suffices to include an additional control input that compensates for the disturbances effects. Thus, the new control input becomes

$v_1 = v - \hat{z}_4$, where $\hat{z}_4$ is the fourth element of the extended state vector and is an estimate of disturbance term $z_4 = \tilde{d}$. The associated results are depicted in Fig. 2 to Fig. 5. It can be observed that the proposed nonlinear feedback control scheme enables accurate tracking of the concentration of the $P53^*$ protein to the desirable concentration levels.



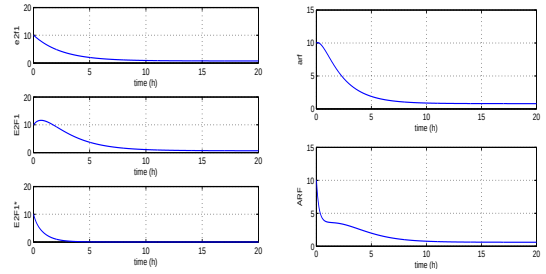
(a) **(b)**

Figure 2: Dynamical model with disturbances: (a) nonlinear feedback control of the $P53^*$ protein concentration (blue line) and convergence to the associated setpoints (red lines), (b) infusion rate as control input.



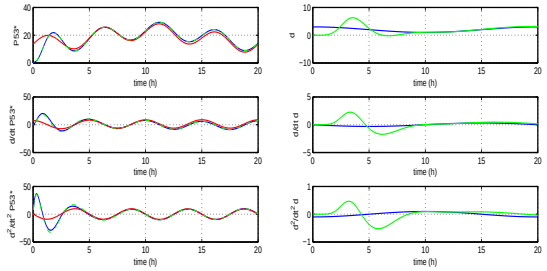
(a) **(b)**

Figure 3: Dynamical model with disturbances: (a) variation of the $p53$ mRNA concentration, $P53$ concentration in the cytoplasm and active $P53^*$ concentration, (b) variation of the $mdm2$ mRNA concentration, $MDM2$ concentration in the cytoplasm and active $MDM2^*$ concentration.



(a) **(b)**

Figure 4: Dynamical model with disturbances: (a) variation of the $e2f1$ mRNA concentration, $E2F1$ concentration in the cytoplasm and active $E2F1^*$ concentration, (b) variation of the arf mRNA concentration, ARF concentration in the cytoplasm.



(a) **(b)**

Figure 5: Dynamical model with disturbances: (a) convergence of the estimates of $P53^*$ concentration and of its derivatives (green lines) to the associated real parameter values (blue lines), (b) estimation of disturbance terms (green lines) that affect the model and convergence to the associated real parameter values (blue lines).

6 CONCLUSIONS

A nonlinear feedback control method has been proposed for the p53 protein - mdm2 inhibitor system. The control scheme is based on differential flatness theory and the Derivative-free nonlinear Kalman Filter. The first stage for the design of the control scheme was the transformation of the initial description of the system dynamics from a set of complex coupled nonlinear differential equations into a SISO model of the canonical Brunovsky form. The transformation was based on differential flatness theory. The latter model connected the infusion rate of the chemotherapy drug (control input) to the concentration of the P53 protein (system's output). For the transformed model the design of state feedback control was possible. Moreover, to make the control scheme robust to modeling uncertainty and external disturbances and to cope with the nonmeasurable elements of the state vector (derivatives of the P53 protein concentration), a disturbance estimator was designed with the use of the Derivative-free nonlinear Kalman Filter. The efficiency of the proposed control scheme was evaluated through simulation experiments.

REFERENCES

W. Abou-Jaoudé, M. Chavés and J. L. Gouzé, A theoretical exploration of birhythmicity in the p53-mdm2 network, INRIA Research Report No 7406, Oct. 2010.

M. Bassevile and I. Nikiforov, Detection of abrupt changes: Theory and Applications, *Prentice-Hall*, 1993.

S. Bououden, D. Boutat, G. Zheng, J. P. Barbot and F. Kratz, A triangular canonical form for a class of 0-flat nonlinear systems, International Journal of Control, Taylor and Francis, vol. 84, no. 2, pp. 261-269, 2011.

J. Elias, L. Dimitrio, J. Clairambault and R. Natalini, The p53 protein and its molecular network: modelling a missing link between DNA damage and cell fate, Biochimica and Biophysica Acta - Proteins and proteomics, 2013.

M. Fliess and H. Mounier, Tracking control and π-freeness of infinite dimensional linear systems, In: G. Picci and D.S. Gilliam Eds.,Dynamical Systems, Control, Coding and Computer Vision, vol. 258, pp. 41-68, *Birkhaüser*, 1999.

M. Jahoor Alam, N. Fatima, G. R. Devi and R. K. Brojen, The enhancement of stability of P53 in MTBP induced p53-MDM2 regulatory network, Biosystems, Elsevier, vol. 110, pp. 74-83, 2012.

B. Laroche, P. Martin, and N. Petit, Commande par platitude: Equations différentielles ordinaires et aux derivées partielles, Ecole Nationale Supérieure des Techniques Avancées, Paris, 2007.

G. B. Leenders and J. A. Tuszynski, Stochastic and deterministic models cellular p53 regulation, Frontiers of Oncology, vol. 3, article No 64, 2013.

J. Lévine, On necessary and sufficient conditions for differential flatness, Applicable Algebra in Engineering, Communications and Computing, Springer, vol. 22, no. 1, pp. 47-90, 2011.

G. Lillacci, M. Boccadoro and P. Valigi, The p53 network and its control via MDM2 inhibitors: insights from a dynamical model, Proc. 45th IEEE Conference on Decision and Control, San Diego, California, USA, Dec. 2006.

Ph. Martin and P. Rouchon, Systèmes plats: planification et suivi des trajectoires, Journées X-UPS,École des Mines de Paris, Centre Automatique et Systèmes, Mai,1999.

S. K. Peirce and H. W. Findley, Targetting the MDM2-p53 interaction as a therapeutic strategy for the treatment of cancer, Cell Health and cytoskeleton, Dove Medical Press, vol. 2, pp. 49-58, 2010.

J. Qi, S. Shao, Y. Shen and X. Gu, Cellular responding DNA damage: a predictive model of P53 Gene Regulatory Networks under continuous ion radiation, Proc. 27th Chinese Control Conference, Kunming Yunnan, China, July 2008.

J. Wagner, L. Ma, J.J. Rice, W. Hu, A.J. Levine and G.A. Stolovitzky, p53-mdm2 loop controlled by a balance of its feedback strength and effective dampening using ATM and delayed feedback, IEE Proceedings on Systems Biology, vol. 152, no.3, pp. 109-118, 2005.

G. G. Rigatos and S.G. Tzafestas, Extended Kalman Filtering for Fuzzy Modelling and Multi-Sensor Fusion, Mathematical and Computer Modelling of Dynamical Systems, *Taylor & Francis*, vol. 13, pp. 251-266, 2007.

G. Rigatos and Q. Zhang, Fuzzy model validation using the local statistical approach, Fuzzy Sets and Systems, Elsevier, vol. 60, no.7, pp. 882-904, 2009.

G. Rigatos, Modelling and control for intelligent industrial systems: Adaptive algorithms in robotics and industrial engineering, Springer, 2011.

G. Rigatos, Advanced models of neural networks: Nonlinear dynamics and stochasticity in biological neurons, Springer, 2013.

G. Rigatos and E. Rigatou, A Kalman Filtering approach to robust synchronization of coupled neural oscillators, ICNAAM 2013, 11th International Conference of Numerical Analysis and Applied Mathematics, Rhodes, Greece, Sep, 2013.

P. Rouchon, Flatness-based control of oscillators, ZAMM Zeitschrift fur Angewandte Mathematik und Mechanik, vol. 85, no.6, pp. 411-421, 2005

J. Rudolph, Flatness Based Control of Distributed Parameter Systems, Steuerungs- und Regelungstechnik, *Shaker Verlag*, Aachen, 2003.

H. Sira-Ramirez and S. Agrawal, Differentially Flat Systems, Marcel Dekker, New York, 2004.