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Change detection in the dynamics of an intracellular protein synthesis model using nonlinear Kalman Filtering

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Abstract: A method for early diagnosis of parametric changes in intracellular protein synthesis models (e.g. the p53 protein - mdm2 inhibitor model) is developed with the use of a nonlinear Kalman Filtering approach (Derivative-free nonlinear Kalman Filter) and of statistical change detection methods. By applying a diffeomorphism that is based on differential flatness theory a linearized form of such models can be obtained. For the linearized equivalent models, state estimation can be performed using the Kalman Filter recursion. By comparing the output of the Kalman Filter (which is assumed to correspond to the undistorted protein synthesis model) with measurements obtained from the monitored protein synthesis system, a sequence of differences (residuals) is obtained. The statistical processing of the residuals with the use of χ^2 change detection tests, can provide indication within specific confidence intervals about parametric changes in the considered biological system and consequently indications about the appearance of specific diseases (e.g. malignancies).

Keywords: detection of parametric changes, protein synthesis models, nonlinear Kalman Filtering, χ^2 test, p53 protein - mdm2 inhibitor model

1. INTRODUCTION

The paper studies the problem of parametric change detection in intracellular protein synthesis models, such as the model describing the p53 protein - mdm2 inhibitor dynamics (Jahoor Alam et al., 2012),(Elias et el., 2013),(Liu et al., 2011),(Wagner et al., 2005). The $P53$ protein is of major importance for preventing the development of tumors since it enhances cell-cycle arrest and apoptosis (Lillaci et al., 2006),(Peirce and Findley, 2010),(Qi et al., 2007),(Xin and Jia, 2010). By applying nonlinear estimation (identification) methods it has become possible to obtain numerical values for the parameters of the p53 protein - mdm2 inhibitor system (Meskin et al., 2013),(Quach et al., 2007),(Wang et al., 2009). However, the parameters of such a model are subjected to uncertainties and parametric changes. Actually, the deviation of the protein synthesis model parameters from their nominal values is associated with deregulation of the cells population and is likely to provoke the appearance of malignancies.

To detect pathological symptoms in the p53-mdm2 protein loop, a model of the system's dynamics is generated with the use of nonlinear Kalman Filtering and this is parameterized with the nominal values which are associated with the normal protein synthesis conditions. The considered filtering approach is the Derivative-free nonlinear Kalman Filter (Rigatos, 2013). This consists of the application of the standard Kalman Filter recursion on the linearized equivalent of the protein synthesis system which has been obtained after applying differential flatness theory (Chien et al., 2008), (Fliess and Mounier, 1999). Moreover, using an inverse transformation based again on differential flatness theory one can obtain estimates of the state variable of the initial nonlinear model.

For detecting abnormalities in the p53-mdm2 protein loop, two sequences of data are generated. The first sequence consists of real measurements of the p53 protein concentration with are obtained at specific sampling instances. The second sequence is the Kalman Filter's output, again sampled at the same time instances. By comparing the two signals, a residuals (estimation error) sequence is generated. The processing of the residuals with the use of statistical decision making criteria provides an indication about the existence of parametric changes (damages) in the p53-mdm2 protein synthesis model, which otherwise could not have been detected (Basseville and Nikiforov, 1993),(Rigatos and Zhang, 2009).

Thus, by applying fault detection tests based on the χ^2 distribution it can be concluded if the p53 protein-mdm2 inhibitor system remains healthy and if the nominal parameter values for its model still hold. Otherwise, abnormality can be detected.

2. DYNAMIC MODEL OF THE P53 PROTEIN - MDM2 INHIBITOR SYSTEM

The concentration of the P53 protein is mainly controlled by the levels of the mdm2 protein within a negative feed-

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back loop. The synthesis of the P53 protein is also affected by the ATM, ARF and E2F1 proteins through secondary feedback loops (Lillaci et al., 2006). The dynamic model of the p53 protein - mdm2 inhibitor system is described by Fig. 1. The meaning of the variables that appear in the p53 protein - mdm2 inhibitor dynamical system is as follows (Lillaci et al., 2006),(Qi et al., 2007),(Elias et el., 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.

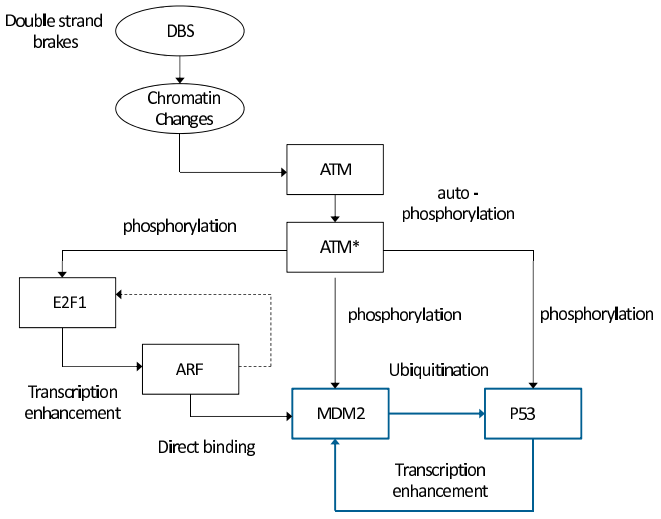

Fig. 1. Feedback control loop of the p53 protein - mdm2 inhibitor system

The following state variables are defined for the dynamic model of the $p53$ protein - $mdm2$ inhibitor system $x_1 = p53$, $x_2 = P53$, $x_3 = P53^*$, $x_4 = mdm2$, $x_5 = MDM2$, $x_6 = N$, $x_7 = e2f1$, $x_8 = E2F1$, $x_9 = E2F1^*$, $x_{10} = arf$, $x_{11} = ARF$. The system can be described using the following state-space equations Lillaci et al. (2006)

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

3. FEEDBACK LINEARIZATION OF THE P53-MDM2 PROTEIN SYNTHESIS MODEL

By defining the flat output $y = [P^*_{53}, N, E2F1^*, ARF]$, or $y = [x_3, x_6, x_9, x_{11}]$ and by differentiating it successively in time one obtains

$$
y_1^{(3)} = f(y, \dot{y}) + g(y, \dot{y})u \tag{2}
$$

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 defined as follows:

(i) function $f(y, \dot{y})$

$$
\begin{aligned}
f(y,\dot{y}) &= -\frac{2(K_{M_1}+x_2)\dot{x}_2 K_1 ATM K_{M_1}}{(K_{M_1}+x_2)^4}[a_{p53}\dot{x}_1 - \mu_{p53}\dot{x}_2 - \\
&v_{p53}\dot{x}_3 - \frac{K_1 ATM^* x_2}{K_{M_1}+x_2} - \frac{K_{cat}x_5 x_2}{aK_{13}+x_2}] + \frac{K_1 ATM^* K_{M_1}}{(K_{M_1}+x_2)^2}[a_{p53}\dot{x}_1 - \\
&\mu_{p53}\dot{x}_2 - v_{p53}\dot{x}_3 - \frac{K_1 ATM\dot{x}_2(K_{M_1}+x_2) - K_1 ATM^*\dot{x}_2}{(K_{M_1}+x_2)^2} - \\
&-\frac{K_{cat}(\dot{x}_5 x_2 + x_5\dot{x}_2)(aK_{13}+x_2) - K_{cat}x_5 x_2\dot{x}_2}{(aK_{13}+x_2)^2}] - \\
&-\frac{-K^*_{cat}aK_{13}\dot{x}_5(aK_{13}+x_3)^2 - K^*_{cat}aK_{13}x_5 2(aK_{13}+x_3)\dot{x}_3}{(aK_{13}+x_3)^4}\cdot \\
&\cdot[\frac{K_1 ATM^* x_2}{K_{M_1}+x_2} - v_{p53}x_3 - \frac{K_c at^* x_5 x_3}{aK_{13}+x_3}] - [v_{p53} + \frac{K^*_{cat}aK_{13}x_5}{(aK_{13}+x_3)^2}]\cdot \\
&\cdot[\frac{K_1 ATM^*\dot{x}_2(K_{M_1}+x_2) - K_1 ATM^* x_2\dot{x}_2}{K_{M_1}+x_2{}^2} - v_{p53}\dot{x}_3 - \\
&-\frac{K^*_{cat}(\dot{x}_5 x_3 + x_5\dot{x}_3)(aK_{13}+x_3) - K^*_{cat}x_5 x_3(aK_{13}+x_3)}{(aK_{13}+x_3)^2}] - \\
&-\frac{K^*_{cat}\dot{x}_3(aK_{13}+x_3) - K_c at^* x_3\dot{x}_3}{(aK_{13}+x_3)^2}\cdot[a_{MDM2}x_4 - \mu_{MDM2}x_5 - \\
&-\frac{K_2 ATM^* x_5}{K_{M_2}+x_5} - K_4 x_{11}x_5 - K_6 x_6 x_5] - \frac{K^*_{cat}x_3}{(aK_{13}+x_3)}\cdot[a_{MDM2}\dot{x}_4] - \\
&\mu_{MDM2}\dot{x}_5 - \\
&-\frac{K_2 ATM^* x_5 - K_{M_2} ATM^*\dot{x}_5}{K_{M_2}+x_5{}^2} - K_4(\dot{x}_{11}x_5 + x_{11}\dot{x}_5) \\
&-K_6 x_6\dot{x}_5] - \frac{K^*_{cat}x_3}{(aK_{13}+x_3)}[-\mu_N x_6 - K_6 x_6 x_5](-K_6 x_5)
\end{aligned}
$$

(ii) function $g(y, \dot{y})$

$$
g(y,\dot{y}) = -\frac{K^*_{cat}x_3}{aK_{13}+x_3}(-K_6 x_5) \tag{3}
$$

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 linearized form