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Adaptive Predictive Control Based Therapy of Bone Marrow Cancer ⋆

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Abstract: This paper starts by reviewing the mathematical model for tumor growth as well as the pharmacokinetics and pharmacodynamics models of the drug, so that the therapy can be as close as possible to reality. A Nonlinear Model Predictive Control algorithm (*NMPC*) is used to find the optimal drug dose, in order to reduce the bone marrow tumor density. The Recursive Least Squares algorithm is used to learn the parameters of the tumor growth model, in order to obtain an adaptive *NMPC* strategy. This control strategy is applied to a bone microenvironment model to schedule a therapy for reducing tumor density.

Keywords: Adaptive Predictive Control, Nonblinear Model Predictive Control, Nonlinear models, Pharmacodynamical models, Bone Marrow Cancer, Biomedical Systems.

1. INTRODUCTION

1.1 Motivation and literature review

A wide range of diseases that have in common an unusual and unnecessary cell reproduction beyond the organism needs are called cancer. This uncontrolled proliferation provokes the formation of a cellular mass called tumor. The bone microenvironment provides a fertile soil for cancer cells. The therapy to repress cancer growth has collateral toxic effects that affect the patient. To study that interaction, several studies were performed recently, using mathematical models and optimization solvers, allowing a deeper understanding and the design of control base therapies to repress tumor growth Michor *et al.* (2004); Domingues (2012); Martin *et al.* (1993); Ayati *et al.* (2010); Matveev *et al.* (2000); Chen *et al.* (2012); Bumroongsri *et al.* (2015); Florian *et al.* (2004); Lemos *et al.* (2015). Some of those studies have used Model Predictive Control (*MPC*) to compute an optimal therapeutic schedule. In Bumroongsri *et al.* (2015) an optimal chemotherapy dose is found by solving a convex optimization problem based on linear matrix inequalities; in Chen *et al.* (2012) it is shown that, even when the system states are not fully directly measurable and there are mismatches in the model parameters, *MPC* still provides an useful schedule for cancer treatment; in Florian *et al.* (2004) *MPC* is used to provide a chemotherapy schedule for mice with breast cancer. It has been assumed in many researches related to diseases that it is possible to directly control the effect of a drug on the target. The effect that the body has on the drug, and the effect that the drug has on the body, are called pharmacokinetics (*PK*) and pharmacodynamics (*PD*), respectively. After the administration of a drug there are natural processes, such as solubility, distribution, metabolism and elimination, that affect the amount of drug concentration that reaches the target organ. The work Jambhekar *et al.* (2009) suggests mathematical models to represent those interactions. Resistance to drugs is a natural process of the human body and is a major problem in cancer therapies Gottesman *et al.* (2002). In Lemos *et al.* (2012) a drug resistance model in the treatment of *HIV* is presented, based on the amount of drug concentration present in the bloodstream. A similar approach may be followed in cancer therapy.

Bone marrow cancer is a common type of cancer that may result in metastasis at the prostate and breast. Tt is crucial to better understand the interactions between osteoclasts, osteoblasts, bone density, and the tumor. In Komarova *et al.* (2003) a model to represent the microenvironment interactions between osteoclasts, osteoblasts and the bone mass density was developed. A tumor growth model is proposed in Ayati *et al.* (2010) and the model of Komarova *et al.* (2003) was adapted to show the relations that the tumor has with the bone microenvironment. A recent research Lemos *et al.* (2015) employs continuous time nonlinear optimal control to deal with this disease.

1.2 Paper contributions and structure

The main goal of this work is to develop an adaptive MPC law to schedule a therapy to reduce the density of a cancer tumor. The time evolution of the tumor density T, is represented by a nonlinear function, that depends on the tumor density itself and on the drug effect, u. To discover which drug effect u, should be applied, the

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MPC algorithm is used in order to solve an optimization problem. For that sake, a quadratic cost function that weights the drug effect u and the error between the tumor density T and a reference signal T_{ref} , is used. The *PK* and the *PD* of a drug are modeled. Since *MPC* computes an optimal drug effect u^*, but only the drug dose d can be manipulated, it is necessary to find the optimal drug effect u^* that corresponds to the optimal drug concentration c^*. To do so, the inverse *PD* model is defined and used. To discover which drug dose d is going to generate a drug concentration c as close as possible to the optimal drug concentration c^*, a controller with an asymptotic observer is designed. To find the tumor density model that best fits a patient, the Recursive Least Squares (*RLS*) algorithm is used to learn the model parameters from data, in real time, yielding an adaptive *MPC* algorithm.

After this introduction the paper is structured as follows: the mathematical models of *PK*, *PD* and drug resistance are defined as well as the tumor density time variation. Then, the *MPC* is formulated. Some *MPC* performance characteristics are studied.

2. MODELS

2.1 Pharmacological model

PK model This model relates the drug concentration c in the bloodstream as a function of time t with the therapy dose administered. Consider now the equivalent state space representation of the PK model, represented by matrices A, B and C in the model

$$\begin{aligned} \dot{x} &= Ax + B, \\ y &= Cx, \end{aligned} \tag{1}$$

where $x \in \Re^2$ is the state and y is the blood drug concentration. This system is fully controllable and observable and thus a controller with an asymptotic observer can be designed to discover the optimal drug dose d. Let the system dynamics with a controller and a observer be given by

$$\begin{aligned} d &= -K\hat{x}, \\ \dot{\hat{x}} &= (A - BK - LC)\hat{x} - Le, \end{aligned} \tag{2}$$

where K and L are gain vectors that may be computed using a pole placement technique. The closed loop system can be defined, in an equivalent way, by the following new matrices

$$\begin{aligned} A_{CL} &= A - BK - LC, \\ B_{CL} &= -L, \\ C_{CL} &= C. \end{aligned} \tag{3}$$

With the system defined by matrices (3), the drug concentration evolution in discrete time, for Dirac input signals $d(k)$, is given by

$$c(k+\Delta) = C_{CL} \cdot \left(e^{\Delta \cdot A_{CL}} x(k) + e^{\Delta \cdot A_{CL}} B_{CL} \cdot d(k)\right), \tag{4}$$

where Δ is the sampling time.

PD model The *PD* of a drug is represented by the *Hill* equation, assumed to be a static nonlinear relation given by

$$u(k) = \frac{c(k)}{c_{50}(k) + c(k)}, \tag{5}$$

where $c_{50} \in \Re^+$ is the drug concentration value for which the drug effect is half of the maximum drug effect. It is assumed that c_{50} may vary in time depending on the resistance model explained below.

Drug resistance model If the drug concentration c is below a given threshold c_{lim}, only *weak* cells are killed. The cells reproduced are resistant to that amount of drug concentration. This phenomenon is called drug resistance. Let $r(k)$ be the drug resistance level at time k

$$r(k) = r(k-1) + \delta \cdot \max(0, c_{lim} - c(k)), \tag{6}$$

where δ is the sampling interval and c_{lim} the limit above which no resistance to the drug is developed. When drug resistance is developed by the body, an higher drug concentration c is needed to perform the same drug effect u. This can be represented by increasing the c_{50} parameter proportionally to the drug resistance level Lemos *et al.* (2012). Let c_{50} be affected by the drug resistance r as follows

$$c_{50}(k) = c_{50}(0) \cdot (1 + K_r \cdot r(k)), \tag{7}$$

where $c_{50}(0)$ is the initial value of the c_{50} parameter and $K_r \in \Re_0^+$ is a parameter related to the ability of the disease to develop resistance to the drug.

2.2 Bone model with tumor and drug treatment

Tumor growth model It is assumed that a cell-kill drug is administered to the patient to diminishing the tumor density. For this sake, the tumor growth model used in Ayati *et al.* (2010) is slightly changed to a more realistic one Martin *et al.* (1993). Consider that the tumor density variation is given as a function of continuous time t by $T(t)$

$$\dot{T} = aT\log\left(\frac{\eta}{T}\right) - bTu_2, \tag{8}$$

where $a \in \mathbb{R}^+$ is a parameter related to the tumor growth rate, $b \in \mathbb{R}_0^+$ is the tumor sensitivity to the drug, $\eta \in \mathbb{R}^+$ is the *plateau* level, $T \in]0, \eta[$ is the tumor density and $u_2 \in \mathbb{R}_0^+$ is the tumor cell kill drug effect.

Bone microenvironment model Consider the following nonlinear model, presented in Ayati *et al.* (2010), where $C(t)$ and $B(t)$ represent, respectively, osteoclasts and osteoblasts activity, and $Z(t)$ represents the bone mass density, as a function of continuous time t

$$\begin{aligned} \dot{C} &= \alpha_1 C^{g_{11}\left(1+r_{11}\frac{T}{\eta}\right)} B^{g_{21}\left(1+r_{21}\frac{T}{\eta}\right)} - \beta_1 C, \\ \dot{B} &= \alpha_2 C^{g_{12}/\left(1+r_{12}\frac{T}{\eta}\right)} B^{g_{22}-r_{22}\frac{T}{\eta}} - (\beta_2 - u_1)B, \\ \dot{Z} &= -k_1 \cdot \max(0, C - \overline{C}) + k_2 \cdot \max(0, B - \overline{B}), \end{aligned} \tag{9}$$

where $g_{\bullet\bullet}$, $r_{\bullet\bullet}$, $\alpha_\bullet$, $\beta_\bullet$ and $k_\bullet$ are bone microenvironment model parameters, and $\overline{C}$ and $\overline{B}$ are the mean value of osteoclasts and osteoblasts function Komarova *et al.* (2003). The variable u_1 represents the osteoblasts recovery drug effect. Since the control algorithms used operate in discrete time, models (8) and (9) are approximated using the 4^{th} order Runge−Kutta method, with step size h. Hereafter, consider $y(k)$ as the discrete version of $T(t)$.

3. PARAMETER ESTIMATION

The adaptive *MPC* strategy is obtained by using the *RLS* method to estimate the model parameters. The new estimate of the parameters $\hat{\theta}(k+1)$ is found as a function of the previous estimate $\hat{\theta}(k)$, the system input $u(k)$ and system output $y(k+1)$ using

$$\begin{aligned}\hat{\theta}(k+1) &= \hat{\theta}(k) + K_g(k+1)[y(k+1) - \phi^T(k)\hat{\theta}(k)],\\ K_g(k+1) &= \frac{P(k)\phi(k)}{\nu + \phi^T(k)P(k)\phi(k)},\\ P(k+1) &= P(k) - \frac{P(k)\phi(k)\phi^T(k)P(k)}{\nu + \phi^T(k)P(k)\phi(k)},\end{aligned} \tag{10}$$

where K_g is the Kalman gain, P is the covariance matrix, ν is the forgetting factor and ϕ is the vector with the model dependent variables such that $y(k+1) = \phi(k)^T\theta$. By applying the 4^{th} order Runge-Kutta method to discretize the Gompertz model (8), the result is an accurate discrete model. However the model is nonlinear in the parameters. Thus, consider for the purpose of parameter estimation that the Gompertz model (8) is discretized by the Euler method, yielding

$$y(k+1) = y(k) + h\left(ay(k)\log\left(\frac{\eta}{y(k)}\right) - bu(k)y(k)\right), \tag{11}$$

where $h \in \Re^+$ is the discretization step size. Therefore

$$\begin{aligned}\phi(k) &= \begin{bmatrix} hy(k)\log\left(\frac{\eta}{y(k)}\right) & -hu(k)y(k)\end{bmatrix}^T,\\ \theta &= [a \quad b]^T.\end{aligned} \tag{12}$$

4. NONLINEAR MPC OF TUMOR GROWTH

4.1 MPC algorithm

At time k it is desired to discover which value should $u_2(k)$ be to reduce the tumor density. This is done by solving the following constrained optimization problem in a receding horizon strategy

$$\begin{aligned}\underset{U_k}{\text{minimize}} \quad & J(y(k), U_k)\\ s.t. \quad & U_{min} \leq U_k \leq U_{max}\end{aligned}, \tag{13}$$

where $U_{min} = u_{min}\cdot\mathbf{1}$ and $U_{max} = u_{max}\cdot\mathbf{1}$ are the constant constraint vectors with the same dimension as U. The cost function J is the quadratic cost function defined as

$$J(y(k), U_k) = (Y_{k+1} - Y^*_{k+1})^T(Y_{k+1} - Y^*_{k+1}) + \rho U_k^T U_k, \tag{14}$$

where Y_{k+1} is the predicted output vector

$$Y_{k+1} = [y(k+1|k) \;\; y(k+2|k) \;\; \ldots \;\; y(k+N|k)]^T, \tag{15}$$

N is the prediction horizon and $\rho \in \Re^+$ is a tuning parameter. The reference signal vector Y^*_{k+1} that Y_{k+1} should follow is given by

$$Y^*_{k+1} = [Y_{ref}(k+1) \;\; Y_{ref}(k+2) \;\; \ldots \;\; Y_{ref}(k+N)]^T, \tag{16}$$

and U_k is the virtual inputs control vector

$$U_k = [u_2(k) \;\; u_2(k+1|k) \;\; \ldots \;\; u_2(k+N-1|k)]^T. \tag{17}$$

Only the first element of U^*_k, $u^*_2(k)$, is actually applied to the system. According to a receding horizon strategy, the same procedure is repeated at time $k+1$.

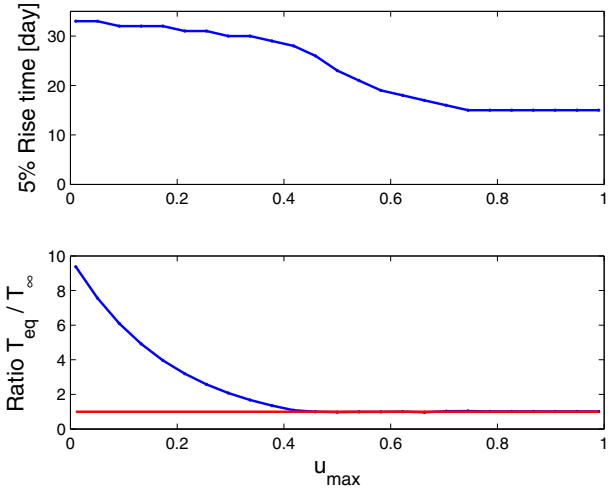

Fig. 1. 5% *rise time* as a function of u_{max}. Tumor growth parameters: $a = 0.15$, $b = 1.5$, $\eta = 1$, $h = 1/7$. Reference quickness parameter: $\lambda = 0.2$. *MPC* parameters: $\rho = 10^{-4}$, $N = 7$.

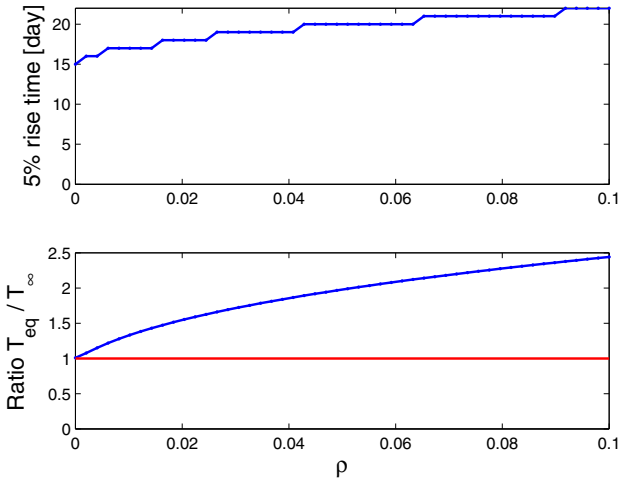

Fig. 2. 5% *rise time* as a function of ρ. *MPC* parameters: $u_{min} = 0$, $u_{max} = 0.99$, $N = 7$.

4.2 MPC performance and features

To study the performance of the controller, the system is simulated for different u_{max} with a fixed ρ and vice-versa. Figure 1 shows that as u_{max} decreases, the system response y is slower. However, when u_{max} is small, *MPC* cannot drive y to T_∞, even if the simulation time is increased. As seen, u_{max} is set to 1 and by inspection this value allows the *MPC* to drive y to T_∞ in an admissible time with no offset. Figure 2 shows that as ρ increases, the smaller is the bandwidth and the slower the system response will be. Furthermore, more robustness is given to the system because the high frequency dynamics is attenuated. Moreover, by increasing ρ, the bigger the offset will be.

Two other important characteristics to study are the relation between the simulation cost and simulation time as a function of the prediction horizon, N. When analysing

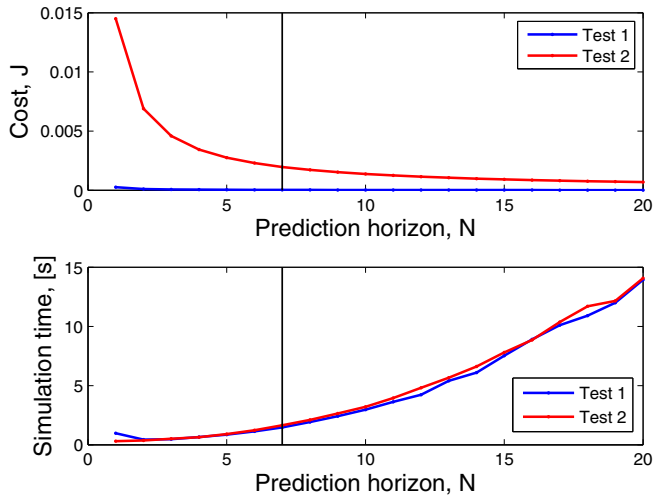

Fig. 3. Cost and simulation time of having a prediction horizon of size N. *MPC* parameters: $\rho = 10^{-4}$, $u_{min} = 0$, $u_{max} = 0.99$. The vertical black line is pointing at the chosen prediction horizon $N = 7$.

the cost as a function of the prediction horizon, two cases were considered: in *Test 1*, the *MPC* tumor density model has no parameter errors, while in *Test 2* *MPC* tumor density model has ±20% parameter errors. Let J be the cost that evaluates all the experience, with D samples, defined as

$$J(N) = \frac{1}{N}\left[\sum_{i=1}^{D}(Y_J(i) - Y_J^*(i))^2 + \rho U_J^2(i)\right], \qquad (18)$$

where Y_J is a vector that contains the system outputs, Y_J^* is a vector that contains the reference signal and U_J is a vector that contains the system inputs.

From figure 3 it is concluded that *Test 1* yields a smaller value of J than *Test 2*. This happens because the difference between T and T_{ref} does not vanish in *Test 2*, due to the differences between the model that *MPC knows* and the real system behaviour. There is no specific rule to choose the best number of predictors N. Although, there is a *rule of thumb* that suggests that the chosen N should be after the cost curve *knee*, because more predictors will cause a very small decrease of the cost. For the Test 1 case, the cost curve *knee* is at $N = 2$, which means that any $N > 2$ is probably a good choice (for the *Test 2* case, the cost curve *knee* is approximately at $N = 5$). Furthermore, when N increases, the simulation time increases exponentially (Figure 3). Thus, the prediction horizon N was set to 7. Since the algorithm step size h is expressed in days, this prediction horizon value means that *MPC* is observing one week in the future.

As seen from from figure 4 the results obtained for different values of $U_0(0)$ are almost equal.

5. BONE MICROENVIRONMENT

5.1 Bone mass recovery

In this section, the control algorithm described above is used with the model determined in Ayati *et al.* (2010) to

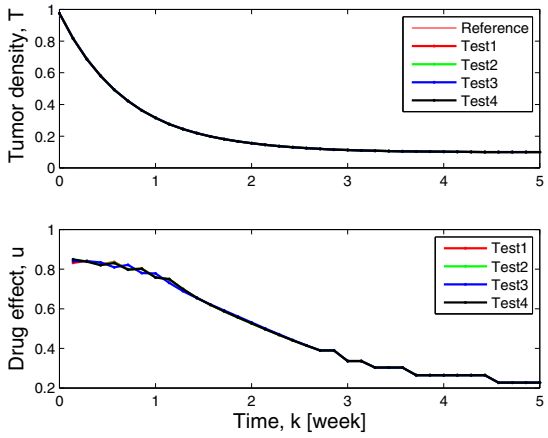

Fig. 4. System input and output for different optimization problem initializations. Test1: $U_0(0) = 0.1 \cdot \mathbf{1}$. Test2: $U_0(0) = 0.5 \cdot \mathbf{1}$, Test3: $U_0(0) = \mathbf{1}$, Test4: $U_0(0)$ is a random vector between 0 and 1, where its elements may be different.

decrease the tumor density and to recover bone mass. Two time instants were defined: k_1 is the same as in Ayati *et al.* (2010) and represents the beginning of both treatments (tumor cell kill drug and osteoblasts regulator drug), and k_2 is where it is considered that the tumor is eliminated. For the purpose of recovering the bone mass density, a discrete *PI* controller with forward Euler integrator is used to compute the drug effect u_1, assumed to be the manipulated variable.

The approach is the following: between k_1 and k_2 both the osteoblasts regulator drug and the tumor cell kill drug are administered to the patient, and after k_2 only the osteoblasts regulator drug is still administered. This decision is based on Zheng *et al.* (2013) that suggests that, to break the vicious cycle, the osteoclasts number must return to a normal value, so that excessive bone resorption stops making the tumor to not spread to other sites.

The presence of the vicious cycle is evident from figures 7 and 8. The amplitude of osteoclasts and osteoblasts dynamics is changed. Osteoclasts increase in number, destroying more bone than the one that is created and also the period of oscillations is affected. Between k_1 and k_2, where both drugs are applied, the tumor density decreases until the tumor is considered to be extinct ($T < 2\%$) following a reference signal and osteoclasts and osteoblasts balance starts to recover as also does the bone mass density. After k_2, where only the osteoblasts regulator drug is active, bone mass density continues to recover until it reaches the steady state $\bar{Z} = 100$. The variation of the cell kill drug concentration c, the c_{50} parameter and the drug resistance level r are shown in Figure 6. Those graphs only have meaning when the tumor cell kill drug therapy is on, this being the reason why those measures were set to 0 after k_2.

5.2 RLS method results

Cancer is a disease that have the ability to adapt to the environment where it is established. Consider that the consequences of those changes are expressed in the

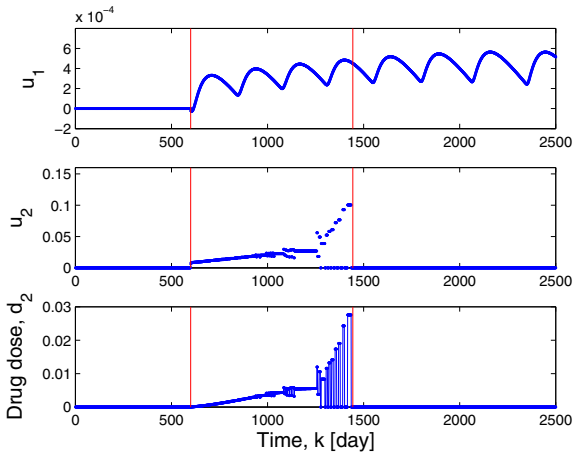

Fig. 5. Drug effects u_1 and u_2 and drug dose d_2 time variation. The vertical lines indicate the therapy time instants $k_1 = 600$ and $k_2 = 1435$. Discrete PID controller parameters: $K_d = 0$, $K_i = -10^{-8}$ and $K_p = -10^{-7}$.

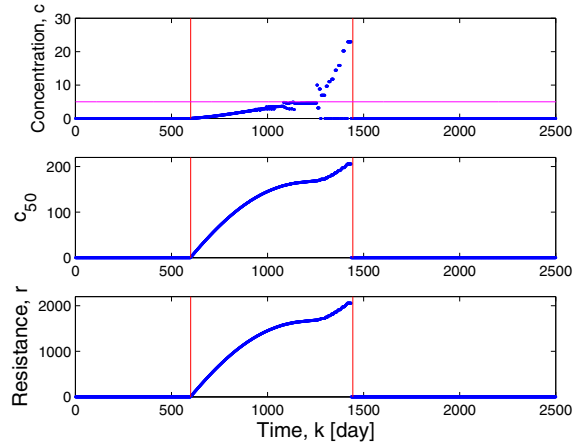

Fig. 6. Drug concentration, c_{50} and drug resistance time variation. The pink horizontal line, indicate the c_{lim} parameter. Controller and observer poles location on the complex plan $s = -50$ and $s = -100$ respectively. Controller and observer initial state $[0\ \ 0]^T$ and $[1\ \ 1]^T$ respectively. PK model sampling time: $\Delta = 1$. Resistance model parameters: $\delta = 1$, $c_{lim} = 5$, $K_r = 3$ and $c_{50}(0) = 1$.

Tracking quadratic error	Case B	Case C
Without *RLS*	1153	79.23
With *RLS*	$3.7 \cdot 10^{-3}$	9.34

Table 1.

tumor growth model parameter a, that now is changing in time. By applying the *RLS* method with an exponential forgetting factor, and measuring the tracking quadratic error between the tumor density and the reference signal, the results in Table I were achieved. The results are compared with the case where the *RLS* method is turned off.

In all the three cases, by using the *RLS* method, the tracking quadratic error was reduced approximately more than 90%, which shows the benefit of using a model parameters estimator.

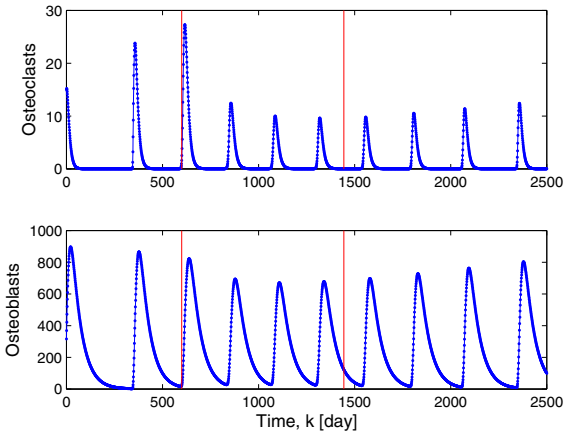

Fig. 7. Osteoclasts and osteoblasts activity. $\bar{C} = 5$, $\bar{B} = 316$, $\alpha_1 = 3$ cell day^{-1}, $\alpha_2 = 4$ cell day^{-1}, $\beta_1 = 0.2$ day^{-1}, $\beta_2 = 0.02$ day^{-1}, $g_{11} = 1.1$, $g_{12} = 0$, $g_{21} = -0.5$, $g_{22} = 0$, $r_{11} = 0.005$, $r_{12} = 0$, $r_{21} = 0$, $r_{22} = 0.2$, $C(0) = 15$, $B(0) = 316$, $y(0) = 1$.

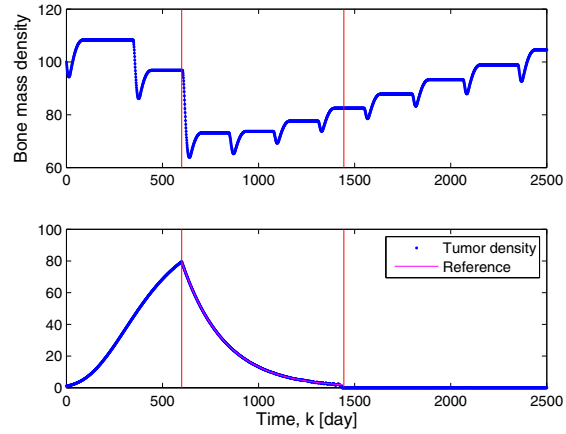

Fig. 8. Bone mass and tumor densities variation.

Figure 9 shows the simulation results with and without *RLS* identification. Note that the "Tumor density with *RLS*" signal is exactly tracking the "Reference" signal. Figures 10 and 11 show the parameter estimates.

6. CONCLUSIONS

The combination of both *MPC* and *RLS* methods provides an adaptive optimization solver, applied here to the treatment of bone marrow cancer. Optimizing the therapy can be formulated as a control problem whose solution provides a drug dose schedule. This open-loop solution can be transformed into a feedback control law, with all the inherent advantages, by using the receding horizon strategy. In the simulations presented, *MPC* can drive the tumor density to low values, interrupting the vicious cycle and stopping the tumor from spreading to other organs.

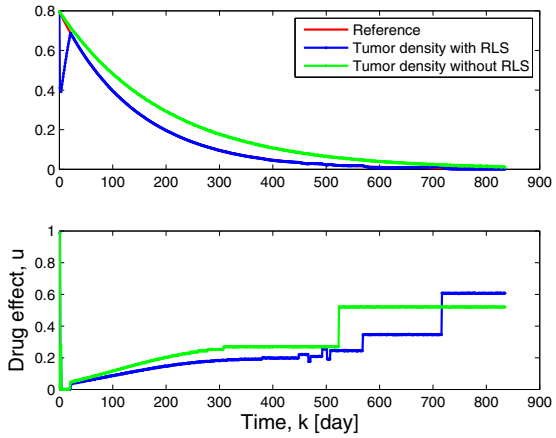

Fig. 9. Simulation of the system with (Case A) and without the *RLS* estimation. The "Tumor density with *RLS*" is following better the "Reference" than the "Tumor density without *RLS*".

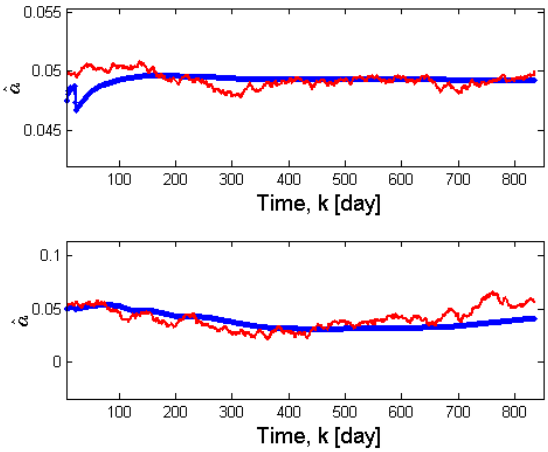

Fig. 10. Tumor growth model parameters (red) and the respective estimates (blue) for Case B.

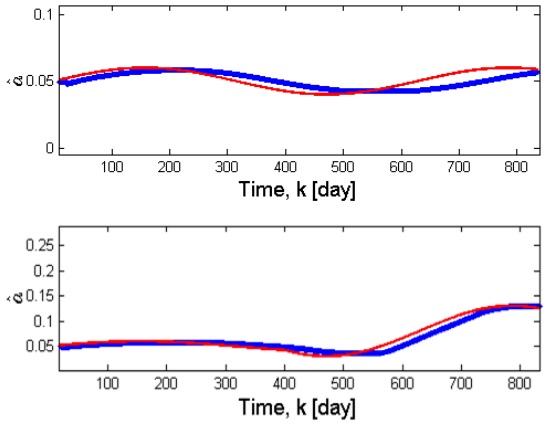

Fig. 11. Tumor growth model parameters (red) and the respective estimates (blue) for Case B.

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