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Multiple model predictive control for optimal drug administration of mixed immunotherapy and chemotherapy of tumours

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ABSTRACT

Background: Mixed immunotherapy and chemotherapy of tumours is one of the most efficient ways to improve cancer treatment strategies. However, it is important to 'design' an effective treatment programme which can optimize the ways of combining immunotherapy and chemotherapy to diminish their imminent side effects. Control engineering techniques could be used for this.

Methods: The method of multiple model predictive controller (MMPC) is applied to the modified Stepanova model to induce the best combination of drugs scheduling under a better health criteria profile. The proposed MMPC is a feedback scheme that can perform global optimization for both tumour volume and immune competent cell density by performing multiple constraints.

Results: Although current studies usually assume that immunotherapy has no side effect, this paper presents a new method of mixed drug administration by employing MMPC, which implements several constraints for chemotherapy and immunotherapy by considering both drug toxicity and autoimmune. With designed controller we need maximum 57% and 28% of full dosage of drugs for chemotherapy and immunotherapy in some instances, respectively. Therefore, through the proposed controller less dosage of drugs are needed, which contribute to suitable results with a perceptible reduction in medicine side effects.

Conclusion: It is observed that in the presence of MMPC, the amount of required drugs is minimized, while the tumour volume is reduced. The efficiency of the presented method has been illustrated through simulations, as the system from an initial condition in the malignant region of the state space (macroscopic tumour volume) transfers into the benign region (microscopic tumour volume) in which the immune system can control tumour growth.

1. Introduction

Since cancer is the second cause of death worldwide, many researchers mainly focus on the modelling and treatment of cancer. Currently, some crucial clinical practices have been performed to determine abnormal conditions, especially tumours and cancers [1]. Also, pathologists are used to distinguish between structure and function in tissues, and, thus, they describe a general approach of how to derive biological functions from structures [2].

Clinical evidence, indicating the potential of the immune system to eliminate cancer, propels vast research in immunotherapy. Therefore, many studies have been conducted to utilize the most appropriate control strategies to acquire different performance objectives. However, the optimal way to combine multiple cancer therapies remains an open issue.

The mathematical modelling of the entire immune system can be a very complex task; therefore, researchers have tried to find models that would describe the immune system responses to a tumour that focus on elements having more important effects on controlling tumour growth [3]. Kirschner and Panetta [4] proposed a mathematical model that concentrates on tumour-immune interaction. A more detailed model for such interactions has been considered by de Pillis [5,6]. Also, a general class of models with a small number of parameters, which captures the most important features of tumour-immune interactions, has been formulated by d' Onifrio [7].

On the other hand, optimal control is a useful method for combining chemotherapy and immunotherapy. Considerable researches have been carried out to achieve the optimal injection methods [8–12]. However, some of these control injection approaches are in an open loop mode that increases the sensitivity of the entire result to parametric uncertainties and modelling errors.

Recently, the property of model predictive control design is to be a feedback scheme that needs optimal control at each decision

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Table 1
Numerical values for the variables and parameters used in simulations [7].

Variable/Parameter	Interpretation	Numerical value	Dimension
x	*Tumor volume*	–	10^6 *cells*
x_0	*Initial value for x*	600	10^6 *cells*
y	*Immune-competent cell density*	–	*Non-dimensional*
y_0	*Initial value for y*	0.10	*Non-dimensional*
α	*Rate of influx*	0.1181	1/day
β	*Inverse threshold for tumor suppression*	0.00264	*Non-dimensional*
γ	*Interaction rate*	1	10^7 *cells/day*
δ	*Death rate*	0.37451	1/day
μ_C	*Tumor growth parameter*	0.5599	10^7 *cells/day*
μ_I	*Tumor stimulated proliferation rate*	0.00484	10^7 *cells/day*
x_∞	*Fixed carrying capacity*	780	10^6 *cells*
k_x	*killing parameter*	1	10^7 *cells/day*

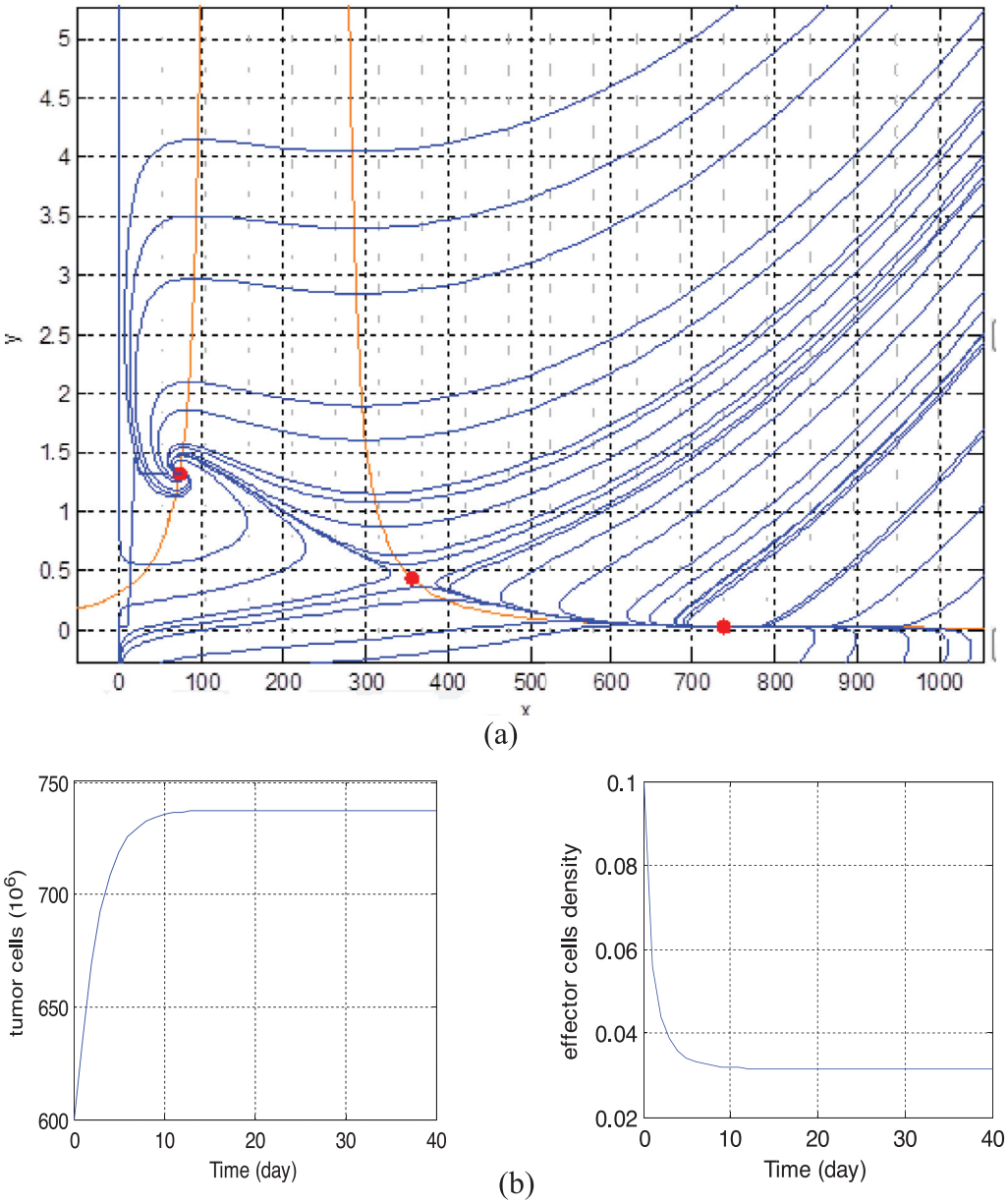

Fig. 1. (a) Phase portrait of the uncontrolled system (1) and (2), (b) dynamic profile of tumor cells and effector cells' density.

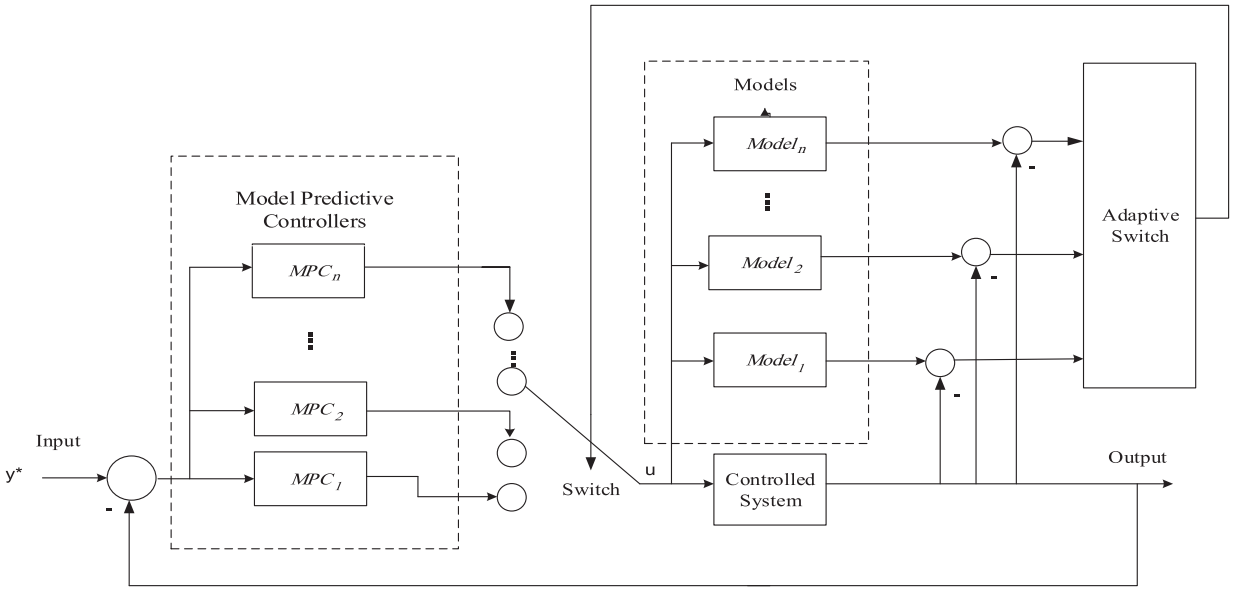

Fig. 2. Multiple model predictive control algorithm.

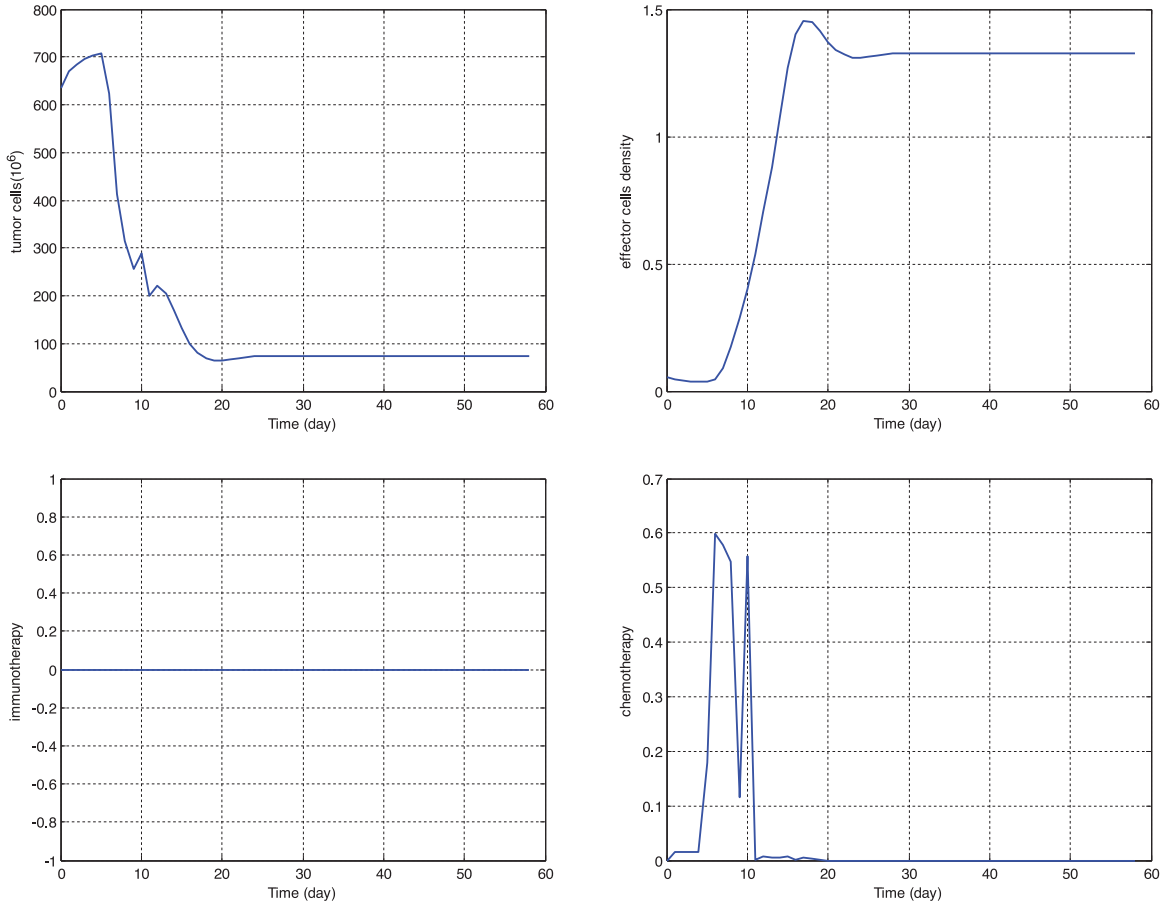

Fig. 3. Successful treatment when using exclusively chemotherapy in the initial condition ($x_0 = 600$, $y_0 = 0.1$).

instant. Model predictive control has been used to achieve an optimal dosing of cancer chemotherapy [13]. In addition, Chareyron and Alamir [14,15] propose a method based on NMPC for mixed immunotherapy and chemotherapy of tumours. In all cases, only chemotherapy has been considered. However, from a clinical view point, immunotherapy is considered as a drug therapy with side effects derived from revving up the immune system and could not be considered without limitations.

According to the previously mentioned review, most of the presented methods were open-looped or did not consider the model predictive control for the immune boost. This paper presents a feedback scheme that incorporates both the advantages of the

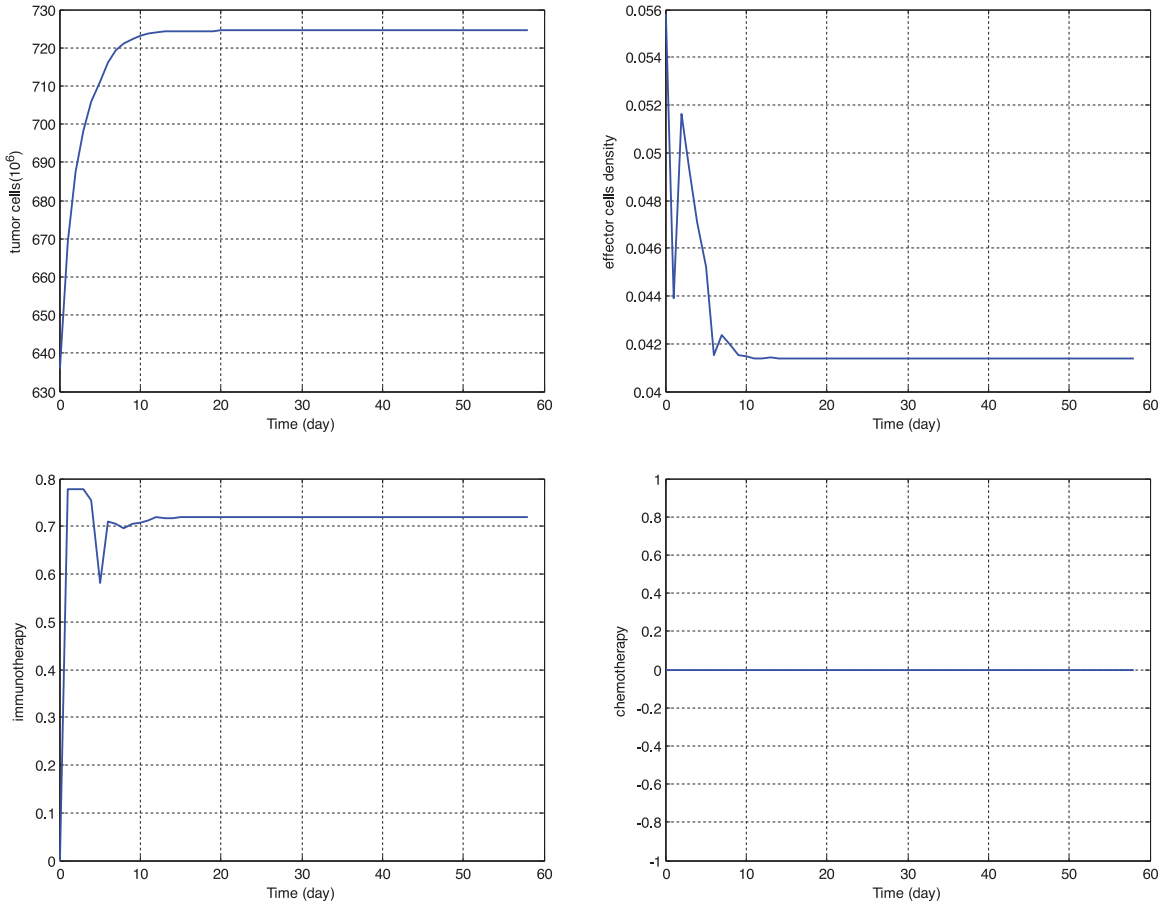

Fig. 4. Unsuccessful treatment when using exclusively immunotherapy in the initial condition ($\boldsymbol{x}_0 = 600$, $\boldsymbol{y}_0 = 0.1$).

optimal control theory and the feedback form. Also, MMPC is suggested to achieve this end, which could be used for both immunotherapy and chemotherapy. The efficiency of the method is illustrated through simulations. As shown here, these results help to guide the development of mixed therapies.

The rest of this paper is organized as follows: Section 2 provides a description of the model and the control problem. In Section 3, a controller based on the MMPC scheme has been designed. The simulation results are discussed in Section 4. Finally, some conclusion remarks are given in Section 5.

2. Model description and the control problem

In this section, the model of the system is described and then the control issue is presented.

2.1. Model of tumor-immune system interaction

We consider a modified version of Stepanova's model, which is proposed by d' Onifrio and Schattler [7]:

$$\dot{x} = -\mu_c x ln\left(\frac{x}{x_\infty}\right) - \gamma xy - k_x xu \tag{1}$$

$$\dot{y} = \mu_I\left(x - \beta x^2\right)y - \delta y + \alpha + k_y yv \tag{2}$$

where x and y represent the 'size' of tumour cells and effector cells (ECs) of the immune system, respectively. Control agents u and v, respectively, show the blood profiles of a cytotoxic agent and a generic immune stimulation agent. α is also a positive constant that models a constant influx of effector cells from the primary organs. All variables and parameters used in the simulations are given in Table 1.

Fig. 1 shows the dynamic profile of tumour cells as well as the immune system's density and its phase portrait at the initial condition $(x_0, y_0) = (600, 0.1)$. The tumour volume is measured in multiples of 10^6, while the immune competent cell density is on a scale relative to 1. As shown in Fig. 1(a), the uncontrolled system in the absence of treatment has two locally asymptotically stable equilibria—one microscopic at (73, 1.32) and the other macroscopic at (737.3, 0.032)—which are regions of attraction corresponding to the benign and malignant situations. Also, these attraction regions are separated by the stable manifold of an intermediate saddle point at (356.2, 0.439), and Fig. 1(b) shows that tumour grows enough to reach an equilibrium in case of it being malignant in the absence of any treatment.

2.2. Statement of the problem

The basic objective of cancer therapy drug administration is to decrease the number of tumour cells x while checking the number of immune-competent cell densities y. Owing to the damaging side effects of both cytotoxic chemotherapy and immunotherapy, it is not feasible to consider indefinite administrations of agents. Hence, the aim of applying MPC is to determine the ideal mix of treatment that minimizes both tumour volume and negative effects of combined drugs.

3. Controller design

In this section, we use a centralized manner for constrained control problems through a multivariable minimization. The main

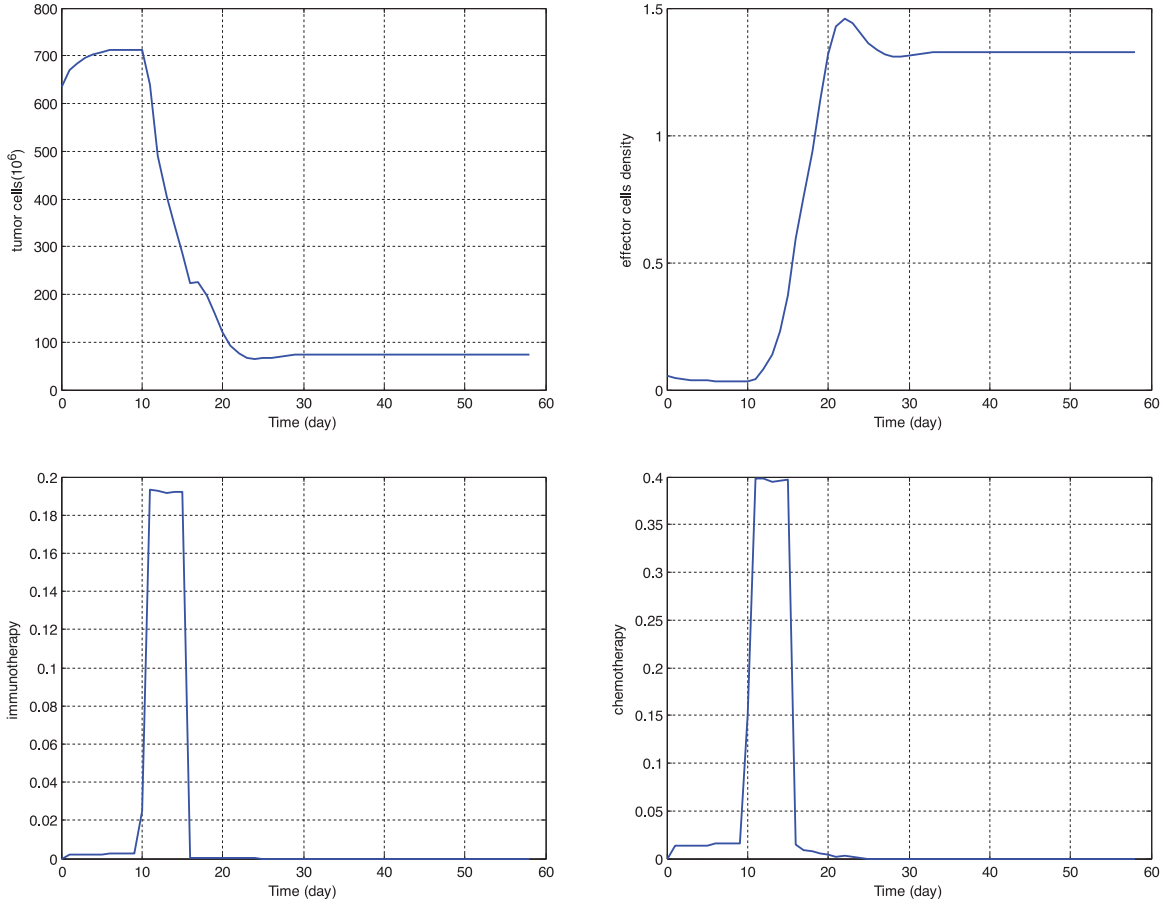

Fig. 5. Successful treatment when using combined immunotherapy and chemotherapy in the initial condition ($\boldsymbol{x}_0 = 600$, $\boldsymbol{y}_0 = 0.1$).

advantage of MPC over other control schemes is its ability to deal with constraints in an efficient and direct method [16].

The MMPC algorithm is shown in Fig. 2, as described in [17]. It has four major subsystems, namely models, MPCs, adaptive switch, and the controlled system. The system to be controlled has input u and output y. The purpose is to make the control error $e_c = y^* - y$ converge to zero, where y^* is the desired output.

There are n linear models and corresponding MPCs in the system. As seen in Fig. 2, $M_i (i = 1, 2, \ldots, n)$ is the i^{th} linear model of the controlled system at a typical operating zone and MPC_i is an MPC designed for the corresponding M_i.

The decision unit is the adaptive switch that determines the most proper MPC to control the tumour-immune system during each control period. Briefly, the operation of this unit consists of three steps: applying the control signals into the tumour-immune system and each model, comparing the output of each model with the output of the system, and choosing the model that best describes the actual system's performance at any instant in accordance to the errors and then switching on the corresponding MPC.

3.1. Model predictive controller design

Basically, the output trajectory of a process should be predicted by MPC and subject to constraints, and a series of control actions, which minimize the difference between the predicted trajectory and the desired trajectory, are computed. The MPC strategy comprises output prediction and control signal implementation. An important step to design MPC is to set an objective function, which is defined as follows:

$$min_{u(k),\ldots,u(k+N_u-1)} J = \sum_{j=1}^{N_u} \left(\begin{array}{c} \left(\hat{y}(k+j) - y_r(k+j)\right)^T Q \left(\hat{y}(k+j) - y_r(k+j)\right) \\ + u^T(k+j) R u^T(k+j) \end{array} \right) \quad (3)$$

where $\hat{y}(k+j)$ is the estimated output of the system at instant $k+j$, $y_r(k+j)$ is the desired output, and N_u is the prediction horizon. $Q \in \mathbb{R}^{2*2}$ and $R \in \mathbb{R}^{2*2}$ are weighting matrices on output errors and control signals, respectively. We define $Q = diag(\delta_x\ \delta_y)$ and $R = diag(\lambda_u\ \lambda_v)$, where δ_x and δ_y are penalties on errors in tumour cells (x) and immune competent density (y), respectively. λ_u and λ_v are penalties on u and v, correspondingly.

In the tumour-immune interaction system, there are several constraints as follows:

If we normalize the maximum dose rates to 1, the chemotherapy and immunotherapy agents, by definition, satisfy the following inequalities:

$$0 \le u \le 1 \quad (4)$$

$$0 \le v \le 1 \quad (5)$$

From the clinical point of view, the tumour volume and the immune-competent cell density, x and y, cannot be negative.

$$0 \le x < x_{max} \quad (6)$$

$$y_{min} \le y \quad (7)$$

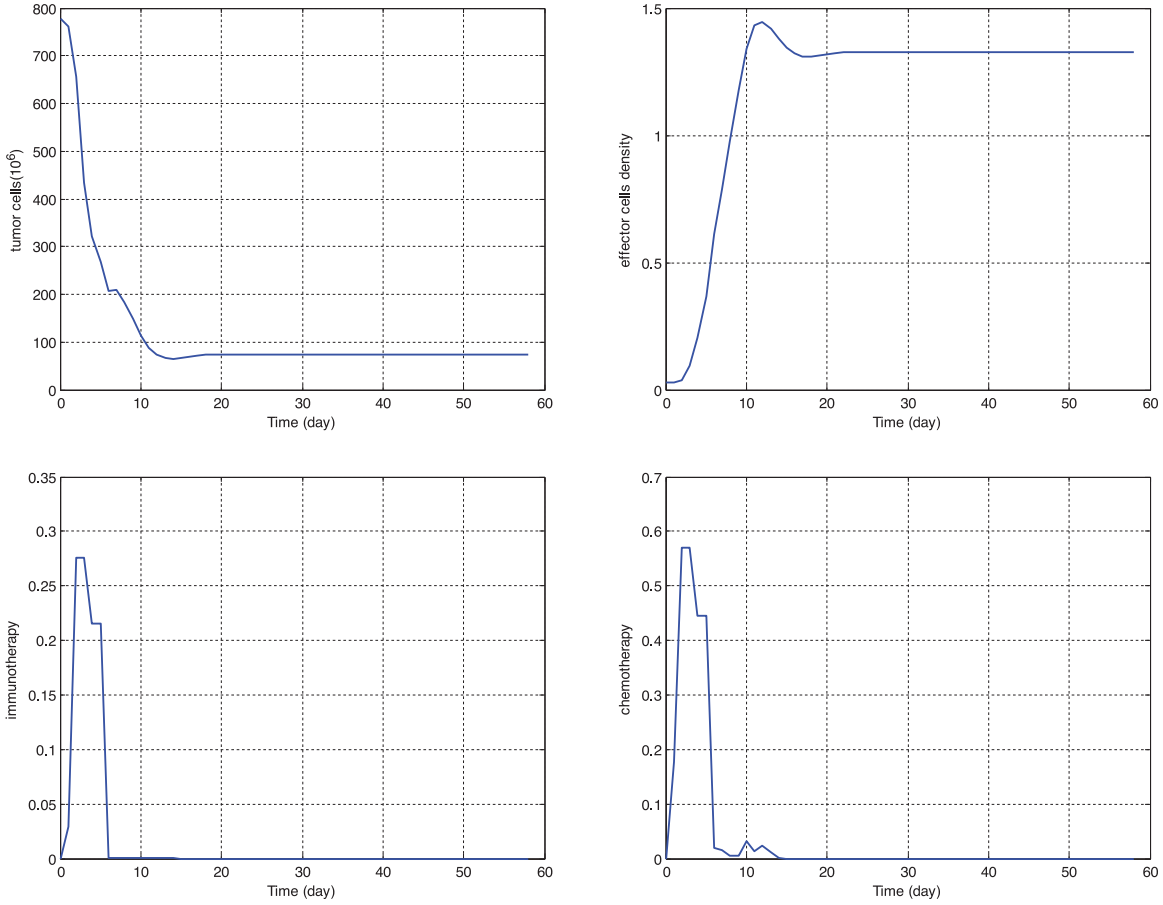

Fig. 6. Successful treatment when using combined immunotherapy and chemotherapy in the initial condition ($\boldsymbol{x}_0 = 780$, $\boldsymbol{y}_0 = 0.007$).

3.2. Adaptive switch design

If we consider $e_i(k)$ as the error between the output of the ith model and the output of the practical system, for the adaptive switch that defines which MPC would operate during the control period, we see the performance criterion function of the ith model as the following:

$$J_i = \gamma e_i^2(k) + \mu \sum_{j=k-l+1}^{k} e^{-\tau(k-j)} e_i^2(j), \quad i = 1, \ldots, n \tag{8}$$

where γ, μ, τ are constants and l is an integer. All these are free design parameters.

The performance criterion function sporadically compares by the adaptive switch controller and switches on the MPC designed for the j[th] model:

$$j = arg_i min_{i=1}^{n} J_i \tag{9}$$

4. Simulation result

In this section, for the parameter values and the initial condition given in Table 1, we give the algorithm to reach the best drugs administration. The experiments and simulations described in this section relied on MATLAB and were developed in a major step that was designed by multiple models-based MPCs to control the tumour-immune system. And based on the weighting matrixes $Q = diag(\delta_x\ \delta_y)$ and $R = diag(\lambda_u\ \lambda_v)$, and different sample time (τ_s), strategies were devised for a mixed-therapy.

Fig. 3 shows the singular chemotherapy treatment. There is a condition for which chemotherapy alone can control a growing tumour.

By using individual immunotherapy we observed an unsuccessful treatment, as shown in Fig. 4. A combined treatment would be essential for the success of the treatment, with decreases in both the dose rate of drugs and instant variations, as illustrated in Fig. 5.

By considering a different initial condition (x_0, y_0)=(780, 0.007), Fig. 6 shows excellent results derived from the mixed treatment of tumour in this condition.

5. Discussion

As simulation results show, the singular chemotherapy is a case for which chemotherapy alone can control a growing tumour and transfer the system from an initial condition in the malignant region to the benign region. Although this method lead to reach the desirable states, we need instant variation for chemotherapy dose rate u. Also, by using individual immunotherapy when the initial condition is in the malignant region, the immune system cannot control tumour growth and progresses to reach the malignant state.

It is interesting to observe that when using the mixed-therapy by the proposed method, immunotherapy plays a significant role to optimize the success of the administration. In this case, in the initial condition (x_0, y_0)=(600, 0.1), which is in the malignant situation after applying the proposed controller, the tumour converges to the locally asymptotically stable equilibrium in the benign region. From the clinical viewpoint, the benign state of the cancer represents the concept that activities of the immunity system can control its growth and prevent the disease from spreading further.

Compared to the work of [11], which is done on the same model, with the same initial condition(x_0, y_0)=(600, 0.1), the

proposed model needs less drugs dosage in some instances. As the simulation result shows, maximum 40% and 19% of full dosage of drugs for chemotherapy and immunotherapy are need, correspondingly, that contribute to acceptable results with tangible reduction in medicine side effects.

Likewise, Fig. 6 shows that for initial condition$(x_0, y_0)=(780, 0.007)$ which is in the malignant region mixed-therapy of tumour could be outstanding way. We need maximum 57% and 28% of full dosage of drugs for chemotherapy and immunotherapy in some instances, respectively. Although this initial condition is close to the macroscopic equilibrium point, which is the region of attraction corresponding to the malignant situation, we could optimize the way to converge the tumour to the locally asymptotically stable equilibrium in the benign region by applying the proposed controller.

6. Conclusions

Based on the modified Stepanova's mathematical model, which is in [7], we designed MMPC to reach an enhanced schedule therapy for mixed immunotherapy and chemotherapy. In the proposed scheme, we consider some constraints to avoid drug toxicity and autoimmune owing to chemotherapy and immunotherapy. This strategy reveals particularly good performance in the sense that it requires not only a low amount of drug doses in each instance, but also leads to tumour regression. Hence, this paper determines an optimal way to transfer the system from an initial condition in the malignant region of the state space to the benign region in which the immune system can control its growth.

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