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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*

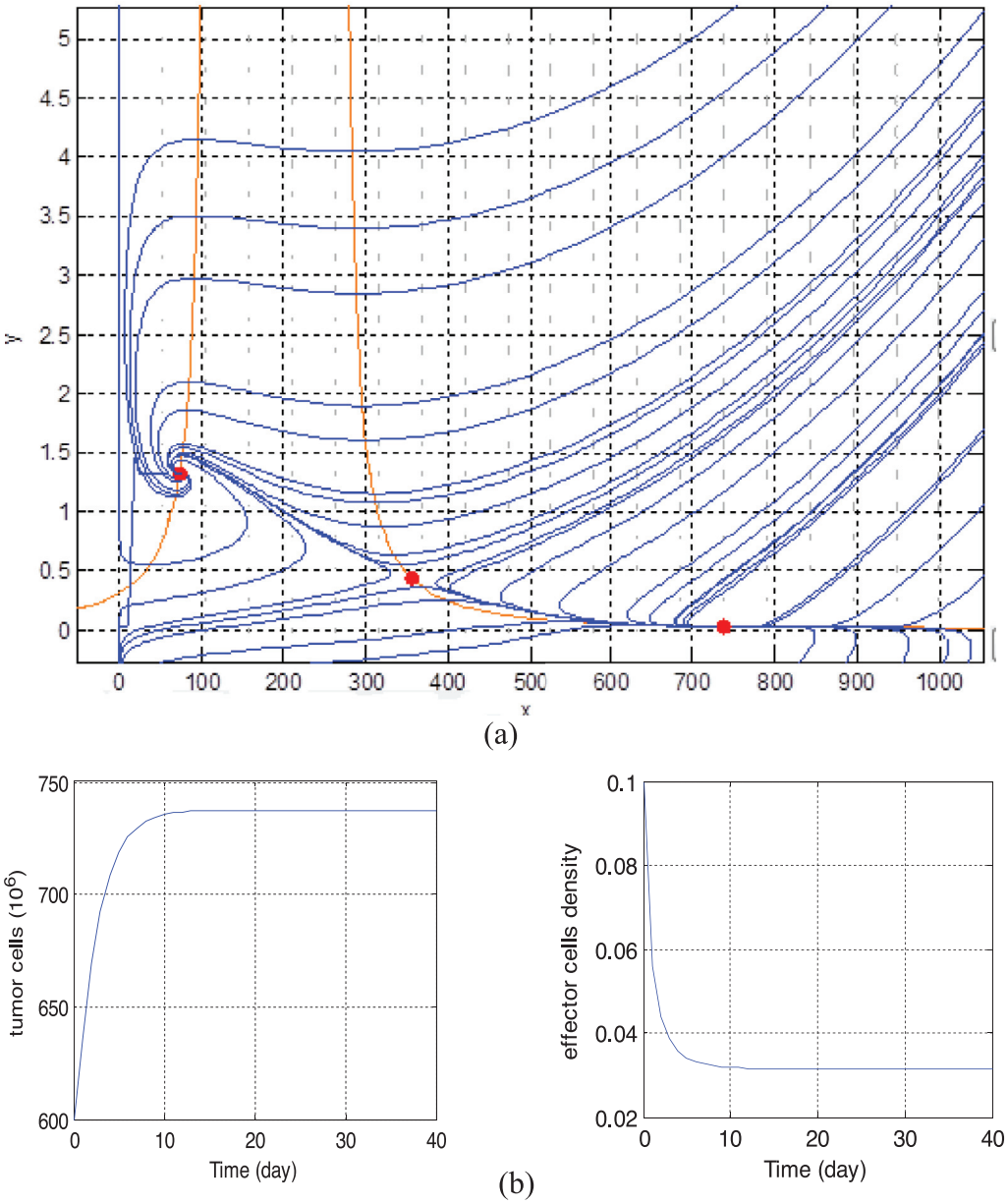

Fig. 1. (a) Phase portrait of the uncontrolled system (1) and (2), (b) dynamic profile of tumor cells and effector cells' density.