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Multimodal therapy for complete regression of malignant melanoma using constrained nonlinear optimal dynamic inversion

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ABSTRACT

Using a realistic nonlinear mathematical model for melanoma dynamics and the technique of optimal dynamic inversion (exact feedback linearization with static optimization), a multimodal automatic drug dosage strategy is proposed in this paper for complete regression of melanoma cancer in humans. The proposed strategy computes different drug dosages and gives a nonlinear state feedback solution for driving the number of cancer cells to zero. However, it is observed that when tumor is regressed to certain value, then there is no need of external drug dosages as immune system and other therapeutic states are able to regress tumor at a sufficiently fast rate which is more than exponential rate. As model has three different drug dosages, after applying dynamic inversion philosophy, drug dosages can be selected in optimized manner without crossing their toxicity limits. The combination of drug dosages is decided by appropriately selecting the control design parameter values based on physical constraints. The process is automated for all possible combinations of the chemotherapy and immunotherapy drug dosages with preferential emphasis of having maximum possible variety of drug inputs at any given point of time. Simulation study with a standard patient model shows that tumor cells are regressed from 2×10^7 to order of 10^5 cells because of external drug dosages in 36.93 days. After this no external drug dosages are required as immune system and other therapeutic states are able to regress tumor at greater than exponential rate and hence, tumor goes to zero (less than 0.01) in 48.77 days and healthy immune system of the patient is restored. Study with different chemotherapy drug resistance value is also carried out.

1. Introduction

Melanoma is a malignant skin tumor from melanocytes, which are the cells that produce dark pigment melanin, responsible for the color of the skin. It is fatal and causes the majority (approximately 75%) of deaths related to skin cancer [1,2]. In current practice of cancer therapy, which is based on the inferences drawn from 'open-loop' clinical studies, high dosages of drugs are given at different points of time. However, this strategy has serious drawbacks. First, since it is based on mere open loop studies, the success rate turns out to be not high as the drug dosage is not patient condition specific in a closely monitored sense. Toxicity levels can cross the maximum prescribed values, leading to potentially dangerous side effects. A high dosage of chemotherapy drugs can kill the immune system cells as well. Instead of the currently practiced strategy, if a patient condition dependent (i.e., state feedback) low dosages of drugs are infused to the patient's body on a continuous basis, then the treatment strategy will be substantially more effective with much lesser side effects. However, frequent monitoring of the patient condition, followed by carefully computed low dosage of various drugs magnitude is possible only when the entire process is made automatic. Such an automated system will compute the appropriate quantity of drug dosages which needs to be given at that point of time, depending upon the patient's condition throughout the treatment period, resulting in a feedback control system mechanization. In this work, we propose a state feedback solution which ensures (i) complete regression of tumor and (ii) drug dosages are given within their toxicity limits. These two points are not concurrently taken care by current clinical practice.

Typical treatment procedures for solid tumors include treatment with chemo and immunotherapy drugs, after surgical removal of the tumor and/or radio therapy (which are not within the scope of this paper). The immune system has shown notable role in fighting against tumor [3–6]. Effect of immunotherapy on tumor growth is studied in [7–9]. Mathematical model for

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chemotherapy and immunotherapy effect on tumor growth is presented in [10]. In fact, recently attempts are being made to propose control theory based regimens for tumor control with chemo and immuno therapies. Optimal control of bang bang type is applied for tumor control with chemotherapy [11]. In another approach, for tumor control with chemotherapy, optimal control is considered with linear and quadratic cost functional [12]. However, the proposed optimal control solutions in [11,12] are in 'open loop'. To make it operate on a feedback scheme, a nonlinear model predictive control (NMPC) has also been proposed in the literature [13]. In [14], nonlinear tumor model is approximated by sequence of linear time varying models and then, state dependent Riccati equation (SDRE) based nonlinear suboptimal controller has been proposed. Optimal control based control solutions offer several advantages. However, they also suffer from several potential drawbacks, one being the fact that they are computationally quite intensive. Hence they are not easy to implement in embedded microchips, which can be a potential limitation if the ultimate aim is to implement the drug infusion through portable devices with limited computational power and energy source. More importantly, there is the big dilemma of either to take into account the nonlinear dynamics and land up with an 'iterative' solution scheme or to take approximate linearized dynamics, thereby degrading the solution quality.

In this paper, on the other hand, we propose an alternate drug infusion strategy based on the nonlinear state feedback control design philosophy called 'optimal dynamic inversion' (exact feedback linearization with static optimization), which leads to a closed form expression of the controller in state feedback form, which has previously been used for a treatment strategy for 'chronic myelogenous leukemia' [15]. However, one substantial improvement in this paper is to implement control constraints and to ensure that computed drug dosages does not violate the toxicity limits at any point of time. Furthermore, the lymphocyte population after recovery should develop towards a natural count (a finite positive value), thereby ensuring a healthy state of the patient (in control theory language, the internal dynamics must remain stable and bounded). To ensure that tumor cells are driven to zero without crossing drug toxicity limits, the problem has been formulated in the framework of optimal dynamic inversion [15], which in turn is based on the philosophy of feedback linearization [16] (feedback linearization is known as dynamic inversion in aerospace community). One should also note that drug input design is carried out using a 'outer loop–inner loop' philosophy (see Fig. 1; described in Section 3.1), which is inspired from what is routinely done in synthesizing guidance and control loops in aerospace technology. This essentially exploits the cause-and-effect relationship in the model extensively, making the proposed drug design approach very effective. Moreover, it avoids the important issue of instability of 'internal dynamics' [17]. This essentially correlates to the dynamics (Eqs. (1)–(6)) of natural killer cells (N), CD8$^+$T cells (L) and circulating lymphocytes (C) in this problem, which must remain bounded at all time. To drive number of tumor cells to zero, outermost loop is formulated with $T^* = 0$ (T^* is desired tumor value). Thus, tumor goes to zero asymptotically at exponential rate, see Fig. 2 in Section 3. It can be shown from theoretical analysis (see Section 3 for details) that when $T = 0$ and external inputs, $\upsilon_L = \upsilon_M = \upsilon_I = 0$ (Eqs. (1)–(6)), both $M, I \to 0$ and, subsequently, all other remaining states that constitute the internal dynamics (i.e., N, L and C) remain bounded. This has been validated from simulation results as well. Note that, optimal dynamic inversion is applicable, provided: (i) the model is in control affine form, i.e., the control variables (drug input terms) should appear linearly and (ii) number of control variables should be greater than or equal to the number of performance outputs (outputs to be controlled) that must be driven towards an objective. The model considered here satisfies both of these requirements

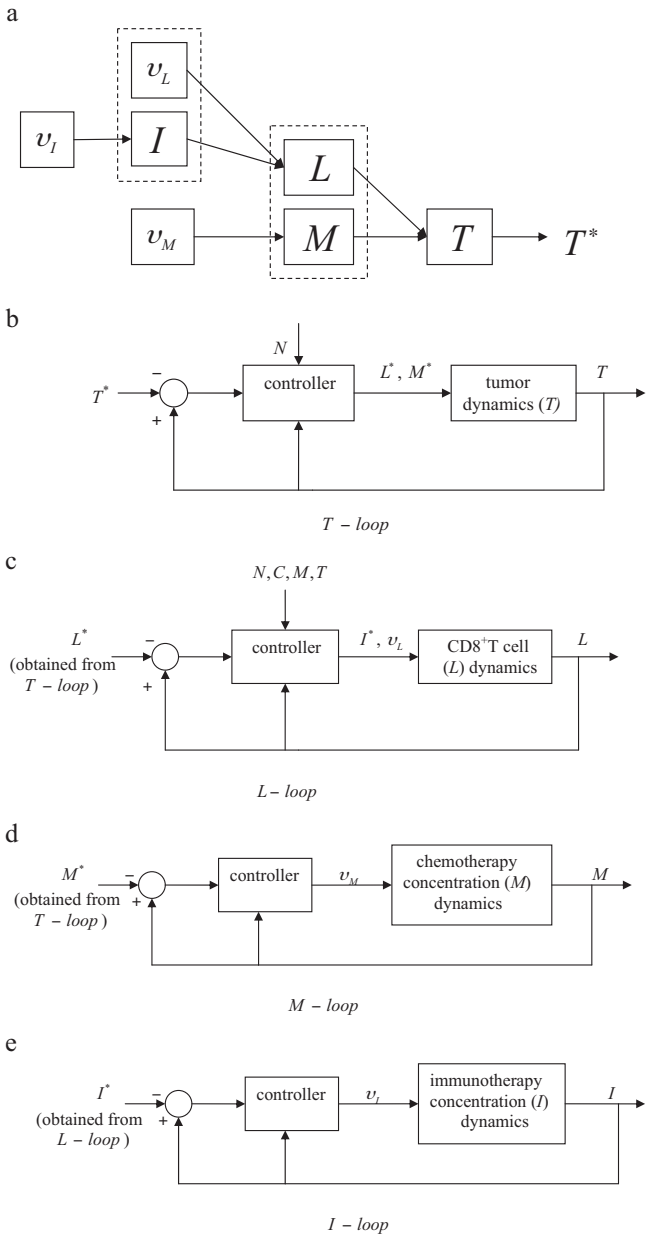

Fig. 1. Philosophical and block diagram representation of various loops in control design. (a) Cause and effect relationship between inputs and output through different states. (b) *T-loop*, (c) *L-loop*, (d) *M-loop*, and (e) *I-loop*.

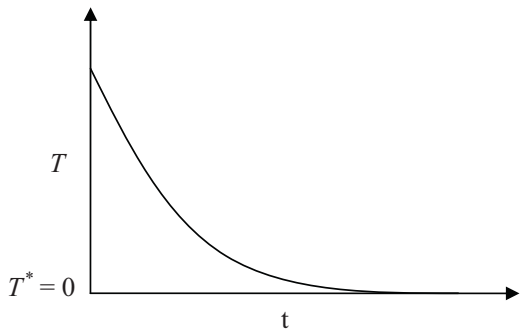

Fig. 2. Exponential tumor decay rate with $T^* = 0$.