Available online at www.sciencedirect.com

ScienceDirect

IFAC Papers Online CONFERENCE PAPER ARCHIVE

IFAC-PapersOnLine 49-13 (2016) 330–335

Adaptive Predictive Control Based Therapy of Bone Marrow Cancer ⋆

H. G. Silva * **J. M. Lemos** ** **B. A. Costa** ***

* *INESC-ID/Instituto Superior Técnico, Universidade de Lisboa, Portugal, (e-mail: hugo.g.silva@tecnico.ulisboa.pt).*
** *Corresponding author, INESC-ID/Instituto Superior Técnico, Universidade de Lisboa, Portugal, (e-mail: jlml@inesc-id.pt)*
*** *INESC-ID/Instituto Superior Técnico, Universidade de Lisboa, Portugal, (e-mail: bac@comp.ist.utl.pt)*

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

⋆ This work was supported by FEDER and Fundação para a Ciência e Tecnologia (Portugal) under contracts EXPL/EMSSIS/1954/2013 (CancerSys), PTDC/EMS-SIS/0642/2014 (PERSEIDS), and UID/CEC/50021/2013.

10.1016/j.ifacol.2016.07.989

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 $T(t)$.