Biomedical Signal Processing and Control 24 (2016) 128–134

Contents lists available at ScienceDirect

Biomedical Signal Processing and Control

journal homepage: www.elsevier.com/locate/bspc

Optimal and receding horizon control of tumor growth in myeloma bone disease☆

João M. Lemos[a,*], Daniela V. Caiado[b], Rui Coelho[c], Susana Vinga[c]

[a] INESC-ID, Instituto Superior Técnico, Universidade de Lisboa, Rua Alves Redol 9, 1000-029 Lisboa, Portugal
[b] INESC-ID, Instituto Superior Técnico, Universidade de Lisboa, Lisboa, Portugal
[c] IDMEC, Instituto Superior Técnico, Universidade de Lisboa, Lisboa, Portugal

ARTICLE INFO

Article history:
Received 19 March 2015
Received in revised form 11 October 2015
Accepted 14 October 2015
Available online 8 November 2015

Keywords:
Optimal control
Receding horizon
Tumor
Bone remodeling

ABSTRACT

This article addresses the problem of designing therapies for the myeloma bone disease that optimize in a systematic way a compromise between drug toxicity and tumor repression. For that sake, the techniques of optimal control are applied to the dynamics of tumor growth, and the necessary conditions of Pontryagin's minimum principle are solved using a numerical relaxation algorithm. A therapy to accelerate bone mass recovery is applied in parallel, based on a PI control rule. Since the optimal controller provides an open-loop control, it is turned into a feedback law by following a receding horizon strategy. For that sake, an optimal manipulated variable profile is first computed over a time horizon, but only the initial part of this function is applied. The whole optimization procedure is then repeated starting at a time instant that corresponds to the end of the previously applied control.

1. Introduction

The micro-structure and evolution of the bone tissue depends of a complex process in which different cells interact through biochemical signaling substances [1]. The bone is continuously being degraded (resorption) and rebuilt, in a process called *remodeling*. In a healthy young human adult, bone formation and resorption are equilibrated along time.

The cells that are responsible for these two processes are osteoclasts and osteoblasts. Osteoblasts produce new bone by collagen synthesis and making it calcify. Opposite, osteoclasts are responsible for bone degradation. In the healthy body, the number of both types of these cells must be properly coordinated. For that sake, an important inducer of osteoclast differentiation is RANKL ([2], p. 706). When an osteoclast precursor comes in contact with RANKL molecules, this results in the maturation of an osteoclast. On the other way, osteoblasts produce also OPG that inhibits RANKL and prevents osteoclast maturation. The balance between RANKL and OPG signaling determines the degree of activation of osteoclasts and settles bone remodeling.

Cancer disrupts this balance and causes both bone disturbances and the emission of substances that favor the occurrence of metastases ([2], pp. 703–709). In particular, multiple myeloma is an hematological disease characterized by the unrelenting proliferation of plasma cells that causes destructive osteolytic lesions associated with severe pain and pathological fractures due to decreased osteoblastic and increased osteoclastic activity [3,4].

This article addresses the problem of designing therapies for the myeloma bone disease that are based on control techniques. It is stressed that the problem addressed has, as a consequence of the above remarks, an interest to cancers other then multiple myeloma. The use of optimal control allows to embed, in a systematic way, a compromise between drug toxicity and tumor repression. Furthermore, a therapy based on a PI control rule is applied in parallel to accelerate bone mass recovery.

Although optimal control provides a powerful tool to link clinical requirements to mathematical objectives, the resulting control law is open-loop, with all the inherent drawbacks. Since, in addition, some optimal drug administration profiles are such that, for a long period, the drug dose is kept at a minimum level, being only increased close to the end of the optimization time interval, this means that the patient will remain with little or no treatment at all for a significant period of time. To circumvent this problem [13], proposes to split the optimization interval in two parts.

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

* Corresponding author. Tel.: +351 213 100 322; fax: +351 213 145 843.
E-mail addresses: jlml@inesc-id.pt (J.M. Lemos), daniela.caiado@ist.utl.pt (D.V. Caiado), rui.coelho@tecnico.ulisboa.pt (R. Coelho), susanavinga@tecnico.ulisboa.pt (S. Vinga).

http://dx.doi.org/10.1016/j.bspc.2015.10.004
1746-8094/

To tackle the above problems, this article examines the possibility of using a receding horizon (RH) strategy [17], in which, at a given time t, an optimal control problem is solved in the time horizon between t and $t+T$, called the prediction horizon. Of the resulting control function, only the part between t and $t+\delta$ is actually used, with the whole procedure being repeated starting at $t+\delta$. This procedure has the advantage of performing a feedback action every δ units of time. Usually, RH control is considered in the framework of discrete-time predictive control [18]. Since the samples of the manipulated variable along the prediction horizon are left free, in nonlinear problems they can be stuck atlocal minima. In this paper, instead, Pontryagin's minimum principle is used to select them. Although the idea of using Pontryagin's principle together with RH control is not new [19,20], this approach is rather unexplored, and has not been previously considered for tumor growth control.

The contribution of this article consists therefore of the application of a receding horizon controller based on optimal control to the design of therapies for cancer that involves an interaction between bone remodeling and tumor growth.

The paper is organized as follows: After this introduction, a brief literature review is made in Section 2, and the tumor growth models considered are described in Section 3. Pontryagin's minimum principle (PMP) is reviewed in Section 4, together with a numerical solution algorithm for optimal control problems and application examples related to the control of tumor growth. Section 5 formulates the RH algorithm based on PMP and shows results on tumor growth, and in Section 6 the PI controller for the bone mass regulation is designed. Finally, Section 7 draws conclusions.

2. Literature review

The above process of bone remodeling can be represented by mathematical models that address both physiological and pathological situations. While many articles have been published addressing a variety of situations, we only cite here [5]. In this work, a lumped nonlinear state-space model, with state variables given by the number of osteoclasts and osteoblasts, has been developed, being able to predict a number of behaviors actually observed in patients, including nonlinear oscillations.

The above model has been extended in [6] for the myeloma bone disease, including the tumor size in the state and therapeutic drug administration as manipulated variables.

Although in [7] it has been pointed out, in a context other than cancer, that the bone remodeling problem can be envisaged as an optimal control problem, cancer in relation to this process has not yet been the subject of studies to design therapies based on the systematic application of control methods. Existing studies like [5,6,8] only exploit simulations under different scenarios, but without any reference to feedback or optimal control. On the other way, there is a rich bibliography on the design of therapies for tumor repression, some addressing the bone marrow, of which [9–14] are some examples. However, the interplay between bone remodeling and tumor evolution is not considered in this bibliography, despite this interaction being more and more recognized of upmost importance for several types of cancer. Indeed, as described in [2], p. 703, it has been observed that carcinomas of the lung, breast and prostate show a strong tendency to metastasize to the bone.

3. Bone remodeling and tumor growth dynamics

The model used for the simulation study in this paper corresponds to the one described in [5,6], with slight modifications. These modifications consist in the way that the drug affects the tumor growth equation, and also in the way the drugs affect the remodeling part of the model.

3.1. Bone remodeling model

The bone remodeling process involves the activity of osteoclasts, which are cells that breakdown the bone in a process called bone resorption, and osteoblasts, that are responsible for bone formation. The mathematical model that expresses the dynamic interaction between osteoclasts $C(t)$ and osteoblasts $B(t)$, described in [5], uses normalized variables and is

$$\dot{C}(t) = \alpha_1\, C(t)^{g_{11}} B(t)^{g_{21}} - \beta_1\, C(t), \tag{1}$$

$$\dot{B}(t) = \alpha_2\, C(t)^{g_{12}} B(t)^{g_{22}} - \beta_2\, B(t), \tag{2}$$

where the dot denotes derivative with respect to time, parameters α_i and β_i, with $i=1,2$, represent the activity of cell production and removal, and parameters g_{ij}, with $i,j=1,2$ describe the net effect of all the factors that are involved in osteoclasts and osteoblasts formation. For instance, the effect of all the factors produced by osteoclasts that regulate its own production are expressed by the parameter g_{11}, referred as autocrine regulation, while parameter g_{12} express the regulation of osteoclasts in the production of osteoblasts, referred as paracrine regulation. Conversely, parameters g_{21} and g_{22} are the paracrine and autocrine regulation, respectively, of all the factors produced by osteoblasts. In this model, the parameter g_{11} is responsible for the oscillatory mode of the bone remodeling process [5].

The bone mass $Z(t)$ is modeled by

$$\dot{Z}(t) = -\kappa_1\, C^*(t) + \kappa_2\, B^*(t), \tag{3}$$

where parameters k_i, for $i=1,2$, are the normalized activity of bone resorption and bone formation constants. In (3), the number of cells Y^* (with Y denoting either C or B) is given by

$$Y^*(t) = \begin{cases} Y(t) - Y_e & \text{if } Y(t) > Y_e, \\ 0 & \text{if } Y(t) \le Y_e, \end{cases} \tag{4}$$

where Y_e is the steady state of $\dot{Y}(t)$.

In the presence of bone pathologies, the bone remodeling dynamics is disrupted. In [6], the tumor size, $X(t)$, dynamics is incorporated in the bone remodeling process, and the osteoclasts and osteoblasts dynamics are described by

$$\dot{C}(t) = \alpha_1\, C(t)^{g_{11}\left(1+r_{11}\frac{X(t)}{L}\right)} B(t)^{g_{21}\left(1+r_{21}\frac{X(t)}{L}\right)} - \beta_1\, C(t), \tag{5}$$

$$\dot{B}(t) = \alpha_2\, C(t)^{g_{12}/(1+r_{11}\frac{X(t)}{L})} B(t)^{g_{22}-r_{22}\frac{X(t)}{L}} - \beta_2\, B(t), \tag{6}$$

where L and r_{ij}, with $i,j=1,2$, are nonnegative parameters.

The steady state solution of (5) and (6) is given by

$$C_e = \left(\frac{\beta_1}{\alpha_1}\right)^{\frac{1-(g_{22}-r_{22})}{\Delta}} \left(\frac{\beta_2}{\alpha_2}\right)^{\frac{g_{21}(1-r_{21})}{\Delta}}, \tag{7}$$

$$B_e = \left(\frac{\beta_1}{\alpha_1}\right)^{\frac{g_{12}}{(1+r_{12})\Delta}} \left(\frac{\beta_2}{\alpha_2}\right)^{\frac{1-g_{11}(1+r_{11})}{\Delta}}, \tag{8}$$

where

$$\Delta = \frac{g_{12}\, g_{21}(1-r_{21})}{1+r_{12}} - (1-g_{11}(1+r_{11}))(1-g_{22}+r_{22}), \tag{9}$$

and it is assumed that X is also in its steady state. This paper considers the bone remodeling dynamics in the presence of a tumor ((3)–(6)), as described in [6].