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Model predictive control for optimally scheduling intermittent androgen suppression of prostate cancer

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ABSTRACT

Mathematical modeling of prostate cancer under intermittent androgen suppression revealed that we may be able to delay relapse by optimally scheduling the hormone therapy for each patient. However, our previous study showed the difficulty of the scheduling by minimizing the maximal tumor growth rate because the transient dynamics is also important and can help to delay the relapse for a finite time. Here, we propose to use model predictive control for scheduling intermittent androgen suppression. We find that model predictive control tends to delay the relapse of prostate specific antigen more than the method with minimizing the maximal tumor growth rate. Therefore, model predictive control is a promising approach for practically applying the mathematical model to optimally schedule intermittent androgen suppression.

1. Introduction

Intermittent androgen suppression (IAS) was proposed to delay the relapse of prostate cancer [1]. In a conventional IAS, patients stop androgen suppression after their prostate specific antigen (PSA) levels decrease less than a certain lower threshold and a certain duration of time has passed after starting the androgen suppression. Then patients restart the androgen suppression after their PSA levels exceed an upper threshold. In the practical treatment by IAS, the times for starting and stopping the androgen suppression are decided based on medical doctors' experience and intuition about the thresholds.

We believe that mathematical modeling is necessary for IAS. There are two main reasons for the necessity. The first reason is that we may be able to delay the relapse of cancer as much as possible if we use a mathematical criterion for switching the medical regimens that is optimally personalized for each patient. The second reason is that medical doctors may be able to choose an appropriate treatment protocol for each patient because clinical trials show that IAS works effectively for some patients but not for the other patients [2,3]. In this paper, we assume that we select patients who can delay their relapse by IAS and explore how we can design the schedule of IAS.

In our previous study, we proposed a method for designing the schedule of IAS by minimizing the maximal growth rate of prostate cancer cells [4]. This design is mathematically equivalent to minimizing the maximal eigenvalue of tumor transition matrix for a period of IAS. Although this idea is natural in terms of asymptotic behavior, we found that the asymptotic behavior cannot fully explain the behavior within a finite time. Namely, there are some patients who can still have benefits from IAS even though in a long run, continuous androgen suppression can delay the relapse more than IAS [5].

Here, we propose to use model predictive control [6] for taking into account the behavior of cancer cells within a finite time and scheduling IAS optimally. Our numerical experiments show that the model predictive control tends to delay the relapse of cancer more than the method with minimizing the maximal growth rate of cancer cells. We will discuss advantages for the proposed framework.

2. Mathematical models for intermittent androgen suppression

In 2008, Ideta et al. [7] proposed the first mathematical model for IAS. This model includes three variables: one for androgen dynamics and the other two for population dynamics of cancer cells. This model explained a basic mechanism on why IAS can delay the relapse of cancer. Namely, androgen-dependent cancer cells decrease and androgen-independent cancer cells increase during

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the on-treatment periods, while androgen-dependent cancer cells increase and androgen-independent cancer cells decrease during the off-treatment periods.

Several extensions to the model of Ideta et al. [7] have been proposed [8–16]. Shimada and Aihara [8] considered the competition between androgen-dependent cancer cells and androgen-independent cancer cells. Guo et al. [9–11] extended the model of Ideta et al. [7] to partial differential equations, considering the spatial distribution of cancer cells. Hirata et al. [12] and Tanaka et al. [13] modified the model of Ideta et al. [7] in such a way that the model can explain the quantitative changes of the clinical PSA values. Jain et al. [14] and Portz et al. [15] considered more detailed dynamics related to androgens. Jain and Friedman [16] simplified the model of Jain et al. [14].

In this paper, we use the model of Hirata et al. [12] because it can describe the changes of clinical PSA values more quantitatively well. This model is composed of three variables: one type of androgen-dependent cancer cells x_0 and two types of androgen-independent cancer cells x_1 and x_2 (see Fig. 1). During the on-treatment periods, the androgen-dependent cancer cells x_0 change to two types of androgen-independent cancer cells x_1 and x_2. During the off-treatment periods, the androgen-independent cancer cells expressed by x_1 may become again the androgen-dependent cancer cells expressed by x_0, while the androgen-independent cancer cells expressed by x_2 do not change back to x_0 or x_1. Therefore, the androgen-independent cancer cells expressed by x_1 appear through reversible changes such as adaptation and epigenetic changes while those expressed by x_2 appear through irreversible changes of mutations. The model equations can be written by

$$\frac{dx}{dt} \equiv \frac{d}{dt}\begin{pmatrix} x_0 \\ x_1 \\ x_2 \end{pmatrix} = \begin{pmatrix} w^1_{0,0} & 0 & 0 \\ w^1_{1,0} & w^1_{1,1} & 0 \\ w^1_{2,0} & w^1_{2,1} & w^1_{2,2} \end{pmatrix}\begin{pmatrix} x_0 \\ x_1 \\ x_2 \end{pmatrix} \equiv W_1 x, \tag{1}$$

for the on-treatment periods, and by

$$\frac{dx}{dt} \equiv \frac{d}{dx}\begin{pmatrix} x_0 \\ x_1 \\ x_2 \end{pmatrix} = \begin{pmatrix} w^0_{0,0} & w^0_{0,1} & 0 \\ 0 & w^0_{1,1} & 0 \\ 0 & 0 & w^0_{2,2} \end{pmatrix}\begin{pmatrix} x_0 \\ x_1 \\ x_2 \end{pmatrix} \equiv W_0 x, \tag{2}$$

for the off-treatment periods. Here $w^m_{i,j}$ is the change rate from cancer cells j to i during either the on-treatment periods ($m = 1$) or the off-treatment periods ($m = 0$). Now we assume that the PSA level is expressed by $x_0 + x_1 + x_2$ for simplicity.

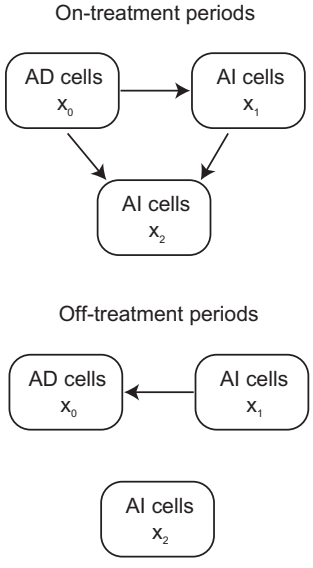

Fig. 1. Schematic diagram of the model of Hirata et al. [12] for intermittent androgen suppression of prostate cancer. AD cells stand for androgen-dependent cancer cells, and AI cells, androgen-independent cancer cells.

Letting $x(t_0)$ be an initial condition at time t_0, analytical solutions for on- and off-treatment periods after t days are provided by

$$x(t_0 + t) = \exp(W_1 t)x(t_0), \tag{3}$$

for on-treatment periods and

$$x(t_0 + t) = \exp(W_0 t)x(t_0), \tag{4}$$

for off-treatment periods, respectively. Thus, the PSA level at time $t_0 + t$ is given by $[1 \quad 1 \quad 1]x(t_0 + t)$.

We fit the mathematical model to the dataset of each patient so that we can select the optimal regimen and personally optimize the treatment schedule for him [12]. During the fitting, we enforce some constraints so that each variable is non-negative, each variable changes at most 20% within a day, and the PSA relapse occurs if patients continue the androgen suppression without interruption [12]. We can realize the first set of constraints that each variable is non-negative by applying the following conditions: $w^1_{1,0} \geqslant 0, w^1_{2,0} \geqslant 0, w^1_{2,1} \geqslant 0$, and $w^0_{0,1} \geqslant 0$; the second set of constraints are $|\sum_{i\in\{0,1,2\}} w^m_{i,j}| < 0.2$ for all $j \in \{0,1,2\}$ and $m \in \{0,1\}$, which realize that each variable changes at most 20% within a day; the third constraint realizing the relapse of PSA is mainly $w^1_{2,2} > 0$. We enforce these constraints with the penalty method [17] (Please find the detailed implementations in [12]).

We can classify each patient according to the values of the fitted parameters [12,5]. The classification is shown in Fig. 2. This classification was originally proposed in Ref. [5]. Type 1 patients are patients whose relapse can be prevented by optimally scheduling IAS. Type 2 patients are patients whose relapse cannot be prevented but can be delayed by IAS than by continuous androgen suppression. Type 3 patients are patients for whom continuous androgen suppression asymptotically can delay the relapse of cancer than IAS. We found that the classifications by these criteria agreed well with the classifications by the medical doctors who conducted the clinical trial [2,3].

Some applications were proposed based on the model of Hirata et al. [12]. One of such applications includes quantifying the uncertainty due to the short and noisy measurement of PSA by introducing a set of parameter sets [18]. One of the other applications is to delay the relapse of cancer by minimizing the maximal growth rate of cancer cells [4]. In the next section, we briefly discuss this second application.

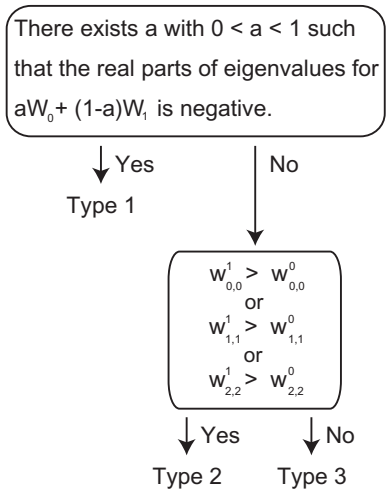

Fig. 2. Classification of patients according to the fitted parameter sets, which was originally proposed in Ref. [5].