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Nonlinear system identification for prostate cancer and optimality of intermittent androgen suppression therapy

Taiji Suzuki [a], Kazuyuki Aihara [a,b,*]

[a] Department of Mathematical Informatics, Graduate School of Information Science and Technology, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8656, Japan
[b] Institute of Industrial Science, The University of Tokyo, 4-6-1 Komaba, Meguro-ku, Tokyo 153-8505, Japan

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ABSTRACT

These days prostate cancer is one of the most common types of malignant neoplasm in men. Androgen ablation therapy (hormone therapy) has been shown to be effective for advanced prostate cancer. However, continuous hormone therapy often causes recurrence. This results from the progression of androgen-dependent cancer cells to androgen-independent cancer cells during the continuous hormone therapy. One possible method to prevent the progression to the androgen-independent state is intermittent androgen suppression (IAS) therapy, which ceases dosing intermittently. In this paper, we propose two methods to estimate the dynamics of prostate cancer, and investigate the IAS therapy from the viewpoint of optimality. The two methods that we propose for dynamics estimation are a variational Bayesian method for a piecewise affine (PWA) system and a Gaussian process regression method. We apply the proposed methods to real clinical data and compare their predictive performances. Then, using the estimated dynamics of prostate cancer, we observe how prostate cancer behaves for various dosing schedules. It can be seen that the conventional IAS therapy is a way of imposing high cost for dosing while keeping the prostate cancer in a safe state. We would like to dedicate this paper to the memory of Professor Luigi M. Ricciardi.

1. Introduction

The purpose of this paper is to propose methods to predict the behavior of prostate cancer by identifying its dynamics. On the basis of the identified dynamics, we analyze the effect of *intermittent androgen suppression (IAS) therapy* in comparison to *continuous androgen suppression (CAS) therapy* on the trade-off between the amounts of cancer cells and dosing. In IAS therapy, dosing is intermittently ceased to avoid the proliferation of drug-resistant cancer cells.

The American Cancer Society estimates that prostate cancer strikes approximately 16% of American men [29]. Prostate cancer continues to be the most common type of cancer in men and the second leading cause of cancer death, after lung cancer, in the United States.

Androgen ablation therapy has been the mainstay of treatment for advanced prostate cancer, following the pioneering work of Huggins and Hodges [19,20], and it makes use of the amenability of prostate cancer to androgen. Secretory epithelial cells included in the prostate have androgen receptors, which are responsible for the androgen dependence of the growth of prostate cancer. When androgen is withdrawn, the secretory epithelial cells go into apoptosis [7,26]. This phenomenon is a key point of androgen ablation therapy. In the treatment, the amount of androgen is decreased through medical castration, and the withdrawal causes a decrease of androgen-dependent tumor cells. In fact, CAS therapy for 3 months lets about 90% of patients have normal levels of the serum prostate-specific antigen (PSA), which is a tumor marker. However, the CAS therapy often results in recurrence, where the growth of prostate cancer cannot be managed by the hormone therapy. The main reasons for the ineffectiveness of the CAS therapy are adaptation and mutation to *androgen-independent* cells as well as clonal selection. Upon complete androgen withdrawal, the surviving tumor cells generally adapt to the androgen-depleted environment and progress to an androgen-independent state. Furthermore, permanent androgen ablation might even promote growth and progression of androgen-independent cells [11,25]. However, if androgen ablation therapy is stopped before the clonogenic tumor cells progress to an androgen-independent state, we may retain the amenability of the surviving cells to androgen and avoid the selective survival of preexisting androgen-independent cells and the mutation of androgen-dependent cells to the androgen-independent state [14]. Since excellent treatment involving pharmacological castration has been developed, we can stop and restart androgen ablation at any time. Recently, many

* Corresponding author at: Institute of Industrial Science, The University of Tokyo, 4-6-1 Komaba, Meguro-ku, Tokyo 153-8505, Japan. Tel.: +81 3 5452 6691; fax: +81 3 5452 6692.
E-mail address: aihara@sat.t.u-tokyo.ac.jp (K. Aihara).

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articles have shown the effectiveness of the IAS therapy [2,10,12,14,15,17,21,23] in clinical studies, and the methodology of the treatment has been well established.

Another reason why intermittent therapy is preferred is because it prevents side effects. Androgen withdrawal can cause several side effects such as hot flashes, loss of libido, impotence, adynamia, osteoporosis, fatigue, cognitive dysfunction, and depression. Severe side effects pose serious problems since they can impair the quality of life. Thus, it is noteworthy that well-manipulated IAS can not only lead to prolongation of the androgen-dependent state but also improve the quality of life.

Along with clinical study, it would be useful to devise a method for identifying the dynamics of the tumors and predicting their future behavior [18,22]. Toward this purpose, we utilize techniques developed in computer science. In this paper, we consider prostate cancer as a system that is driven by unknown dynamics. The identification of unknown dynamics of a system is called "system identification." There are two main approaches for general system identification. One is a bottom–up approach, which is used to construct a model from previous knowledge about an objective system. This is strongly dependent on the pertinency of the modeler's knowledge. If the objective system is not well investigated or the model is not sufficiently polished, this approach fails. The other approach is a black-box (or a non-parametric) approach, which is used to construct a model by investigating only input–output relations with minimum assumptions on an objective system. In other words, the black-box approach aims to directly predict the future values of PSA given the medical history observed so far. This is essentially the non-parametric estimation of a functional that maps an input sequence (medical history) to an output sequence (future values of PSA). Each of these two approaches has both pros and cons. In this paper, we investigate the black-box approach. In particular, we discuss two methods, namely, a variational Bayesian (VB) method and a Gaussian process method. In the former method, we employ a piecewise Affine (PWA) system to model the dynamics of prostate cancer. The PWA system is one of the *hybrid systems* [1,16,30,34]. Recently, a method with the optimal control of a PWA hybrid system model was proposed to control the behavior of prostate cancer [31]. The Gaussian process method, on the other hand, is based on the Gaussian process regression technique [27]. Gaussian process regression is one of the most popular methods for non-parametric regression in statistics and machine learning. This method is computationally efficient and has a solid theoretical basis. We compare these two methods in terms of their predictive accuracy.

The second purpose of this paper is to evaluate the conventional IAS therapy from the viewpoint of optimality. We will show that the system identification methods described above can reconstruct the real evolution of the PSA well. On the basis of the model constructed in the black-box approach, we compare the IAS therapy with the CAS therapy by determining a weighted sum of the PSA value and the dosing amount. It is observed that the conventional IAS treatment in a clinical situation can be said to be a therapy that minimizes dosing while keeping the PSA in a safe state.

2. Modeling prostate cancer's dynamics with a nonlinear auto-regressive eXogeneous model

In this section, we discuss the modeling of the dynamics of the PSA with a nonlinear *Auto-Regressive eXogeneous* (ARX) model (see Fig. 1 for actually observed data). Then, we show two *non-parametric* system identification methods based on a nonlinear ARX model: a variational Bayesian method utilizing PWA regression and a Gaussian process regression method. Roughly speaking, the nonlinear ARX model describes a nonlinear relation between the future PSA values and the medical history (PSA and dosing history). The system identification problem of a nonlinear ARX model can be reduced to a (nonlinear) regression problem. The first approach with the variational Bayesian method can be used along with the PWA regression model for solving the regression problem. The PWA model is particularly important in the context of optimal control [4,5]. In the second approach with the Gaussian process method, a smooth function is fit to the data in a nonparametric Bayesian manner with Gaussian process priors.

2.1. ARX model for PSA dynamics

Here, we introduce the ARX model that describes the dynamics of the PSA. Now, we assume that patients' PSA values are observed on a regular schedule.[1] We denote by q_t the actual PSA value at the tth time step. Let $y_t \in \mathbb{R}$ be the log of the PSA value at time step t and let it be given by $y_t = \log(q_t)$.[2] Let $u_t \in \{0,1\}$ represent the on–off state of the androgen ablation: $u_t = 1$ for on treatment and $u_t = 0$ for off treatment. Then the nonlinear ARX model can be described as

$$y_t = f(y_{t-1}, y_{t-2}, \ldots, y_{t-m}, u_t, \ldots, u_{t-m}) + \epsilon_t,$$

where m is the maximum time delay, f is an unknown nonlinear function, and ϵ_t is i.i.d. Gaussian noise with mean 0 and unknown variance. By identifying f, it becomes possible to predict the future value of PSA given the medical history. The estimation of the dynamics is reduced to the estimation of the nonlinear function f (and the unknown variance of the noise), which is a regression problem. We estimate f from the observed data $\mathcal{D} = \{y_t, u_t\}_{t=1}^{T}$. We propose two approaches based on *Bayesian estimation* to estimate f.

2.2. Piecewise affine ARX model by variational Bayesian inference

Here, we introduce the PWA model for the auto-regressive function f. Let x_t be given by

$$x_t = [y_{t-1}, y_{t-2}, \ldots, y_{t-m}, u_t, u_{t-1}, \ldots, u_{t-m}]^\top.$$

The ordinary (linear) ARX model employs a linear function as the function f as follows:

$$f(x_t) = w^\top x_t,$$

where $w \in \mathbf{R}^{2m+1}$. In the case of the PWA model that is of interest to us, f is given as

$$f(x_t) = w_i^\top \begin{bmatrix} x_t \\ 1 \end{bmatrix}, \quad \text{if } x_t \in \mathcal{X}_i,$$

where $w_i \in \mathbf{R}^{2m+2}$, $\{\mathcal{X}_i\}_{i=1}^{M}$ is a polyhedral decomposition of the state space $\mathbb{R}^{2m+1}$, that is, $\bigcup_{i=1}^{M} \mathcal{X}_i = \mathbb{R}^{2m+1}, \mathcal{X}_i \cap \mathcal{X}_j = \emptyset (i \neq j)$, and each $\mathcal{X}_i$ can be represented as $\mathcal{X}_i = \{z \in \mathbf{R}^{2m+1} | H_i z \leqslant K_i, F_i z < G_i\}$ for appropriate H_i, K_i, F_i, and G_i. It is known that many kinds of problems appearing in the analysis of a PWA hybrid system can be reduced to mixed integer programming (MIP) problems. In particular, the optimal control problem of a PWA hybrid system is reduced to a MIP problem [4,5].

We need to determine the number M of polyhedral regions, the polyhedral decompositon $\{\mathcal{X}_i\}_{i=1}^{M}$, and the parameters $\{w_i\}_{i=1}^{M}$. Here, we propose a method that uses a variational Bayesian technique to identify the PWA system. Now, let $d = 2m + 1$ and

[1] In this paper, the time interval between each observation is 21 days.

[2] Because of the log-transformation, y_t can take any real value while the PSA value $q_t = \exp(y_t)$ is always ensured to be positive. Therefore, if we estimate the dynamics of y_t instead of that of q_t, we do not need to impose any constraint on the dynamics such as positivity. This gives us much flexibility to develop a non-parametric system identification method. This technique is often utilized to model a positive time series, e.g., stock prices.

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