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Mathematical Approach to Optimizing the Hormonal Therapy of Prostate Cancer

Taiji SUZUKI*, Nicholas BRUCHOVSKI† and Kazuyuki AIHARA‡

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Abstract

Prostate cancer is one of the most common types of malignant neoplasm in men with an overall incidence of approximately 15% during the normal life span. Androgen-deprivation therapy (hormonal therapy) is an effective treatment of advanced prostate cancer. Despite impressive responses, such treatment when applied on a continuous basis is not curative and eventually culminates in androgen-independent disease. On the other hand, intermittent androgen suppression (IAS) was first conceived as a potential way of delaying progression to androgen-independence, in addition offering the possibility of reducing adverse effects and improving quality of life. Although the validity of this approach has been confirmed in several clinical studies, the optimal scheduling of the cycles of on- and off-treatment remains to be explored. In the present report, we show that intermittent androgen suppression lends itself to mathematical modeling and that the model we have developed can be used to select the best strategy for keeping prostate cancer in an androgen-dependent state for as long as possible. Our results also suggest that the current way of using intermittent androgen suppression exceeds what is necessary for optimal control; in fact, we have found that to achieve optimal control, the amount of therapy (dose and duration of drugs) can be reduced by a factor of one half. We believe that our theoretical methodology constitutes the first step towards refining the hormonal management of prostate cancer with intermittent androgen suppression.

1 Introduction

The success of androgen-deprivation therapy [12, 13] is based on the ability to induce apoptosis in prostatic epithelial cells, a cell death process that is regulated by the function of the androgen receptor and results in tumour regression when androgens are withdrawn.

Despite the fact that androgen withdrawal of approximately 6 months duration results in normal levels of the tumor marker, serum prostate-specific antigen (PSA), in about 90% of patients, the benefit of such therapy is usually temporary [20]. This is because under complete androgen withdrawal surviving tumor cells generally progress to an androgen-independent state; it is likely that permanent androgen ablation is the impetus for further growth and progression of androgen-independent cells [8]. However, if androgen-ablation therapy is stopped before the tumor cells progress to an androgen-independent state, the surviving cells may retain their androgen-dependent condition. In this regard, since pharmacological castration has proven

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effective, the androgen-deprivation routine can be stopped and re-started at any time as has been demonstrated in a number of clinical studies [1, 2, 6, 7, 9, 11, 17].

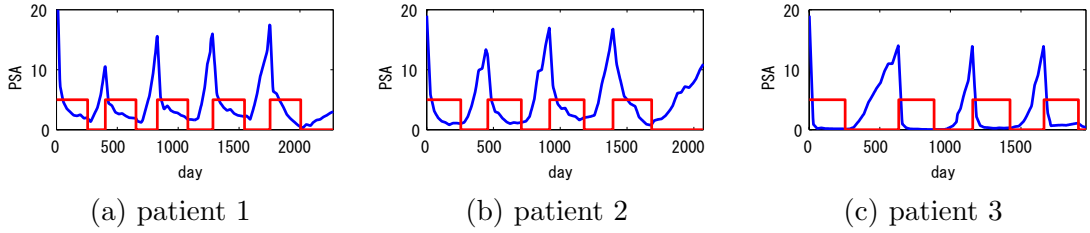


Figure 1: The transition of PSA during IAS. The blue line indicates the value of PSA. The red line indicates on-off of therapy, i.e. if the red line is up, medication is on; otherwise medication is off, or stopped.

Figure 1 shows the clinical data of the behavior of the serum PSA during intermittent androgen suppression covering a period of about 2000 days. It should be noted that the serum PSA was not allowed to exceed $20\mu\text{g}/\text{L}$ during the off-treatment periods of intermittent androgen suppression. The database was provided by the Department of Cancer Endocrinology at the British Columbia Cancer Agency in Vancouver, Canada. Although the on and off protocol of the intermittent androgen suppression is well designed [6], it is a challenging problem to optimize the protocol. We present herewith a computational approach to solve this optimization problem on the basis of a mathematical model.

2 Mathematical Model

Here we introduce a mathematical model that explains the dynamical behavior of prostate cancer [14, 18]. Let $x = (x_1, x_2)$ denote the subpopulations of cancer cells where x_1 and x_2 correspond to androgen-dependent cells and androgen-independent cells respectively. PSA is denoted by $y = c_1x_1 + c_2x_2$ where $c_1 = c_2 = 1$ is assumed for the sake of simplicity. u alternatively represents androgen withdrawal in the on and off modes, i.e.

$$u = \begin{cases} 1, & \text{(androgen withdrawal by on-treatment)} \\ 0, & \text{(off-treatment).} \end{cases}$$

Thus we obtain the following mathematical model [18]:

$$\frac{dx_1}{dt} = (\alpha_1(u) - \beta_1x_2 - m(u))x_1, \quad (1a)$$

$$\frac{dx_2}{dt} = m(u)x_1 + (\alpha_2 - \beta_2x_1)x_2, \quad (1b)$$

$$y = x_1 + x_2. \quad (1c)$$

Here we assume that the unit time of the above dynamics is four weeks (28 days). β_1 and β_2 are mutual suppression rates caused by competition between androgen-dependent cells and -independent cells for a nutrient resource inside a prostate tumor. $\alpha_1(u)$ represents the net growth rate of androgen-dependent cells, namely the difference between the proliferation and the apoptosis rates that depend on the serum androgen concentration. We assume α_1 as $\alpha_1(u) = \alpha_1^1 + \alpha_1^2u$, while α_2 is the net growth rate of androgen-independent cells. $m(u)$ denotes the mutation rate from androgen-dependent cells to androgen-independent cells, which is defined as $m(u) = m_0 + m_1u$.

The trajectory of intermittent androgen suppression starting from $x = (12, 0.25)$ is shown in Fig. 3 (a) where the parameter setting is as follows: $m_0 = 0$, $m_1 = 0.01$, $\beta_1 = 0.2$, $\beta_2 = 0.2$, $\alpha_1^1 = 0.55$, $\alpha_1^2 = -1.2$, and $\alpha_2 = 0.3$. Androgen withdrawal and replacement are switched according to a rule that (1) if y exceeds a given value r_1 during an off-administration period, we re-start withdrawal, and that (2) if y falls below another value r_0 during an on-administration period, then the dosing for androgen withdrawal is stopped. In Fig. 3 (a) r_0 and r_1 are set to be $r_0 = 0.4$ and $r_1 = 13$. The lines $y = r_0$ and $y = r_1$ are shown in red in Fig. 3 (a), which demonstrate that the state is confined to an area between the two red lines and converges to a stable limit cycle. Thus intermittent androgen suppression can be equated to therapy that keeps the state in a safety region by a stable limit cycle. Figure 2 (a) shows the temporal change of PSA under intermittent androgen suppression. It shows that our model can reproduce the dynamical behavior of PSA similar to clinically observed data in Fig. 1.

Next we show a relapse phenomenon in our model. In an actual clinical situation, permanent androgen withdrawal terminates in the appearance of recurrent disease in a majority of cases. Figure 2 (b) illustrates an example of such relapse behavior in our model. Here the androgen-dependent cells decrease, while the mutation to androgen-independent cells is enhanced due to the continuous androgen withdrawal; the system goes to relapse owing to an increase in androgen-independent cells as shown in Fig. 3 (b).

3 Optimal Scheduling

To optimize the medication schedule, we explore the possibility of reducing the system of prostate cancer in Eq. (1) to a simpler version that is more manageable. Here we employ a ‘‘piece-wise affine (PWA) hybrid system’’ [16, 19]. A hybrid system is one with both discrete and continuous variables [21] as exemplified in Eq. (1). In particular PWA hybrid systems are of a type where the state space is piecewisely divided into polyhedral regions, each of which is attached with affine dynamics. By introducing auxiliary discrete variables, we can describe discrete state-space transitions; driving a car with gear change is one example of such a PWA hybrid system. It is known that many kinds of problems appearing in analysis of PWA hybrid systems can be reduced to Mixed Integer Programming (MIP) [10] and solved by combinatorial optimization and discrete mathematics [4, 5].

The PWA hybrid systems modeling allows us to construct an explicit control law. The PWA hybrid system model introduced here is basically a Piece-Wise Affine (PWA) approximation of system (1) using the parameter setting described above. Let us define a feasible region $\mathcal{X} = [0, x_1^{\max}] \times [0, x_2^{\max}]$ where x_1^{\max} and x_2^{\max} are maximum values of x_1 and x_2 with $x_1^{\max} = 15$

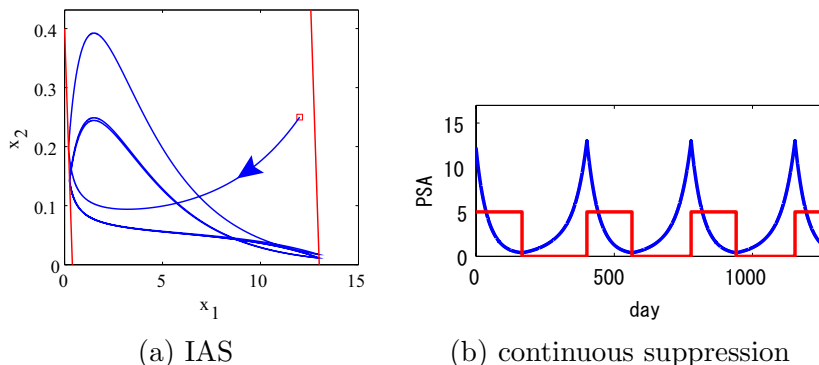


Figure 2: The temporal change of PSA in our model

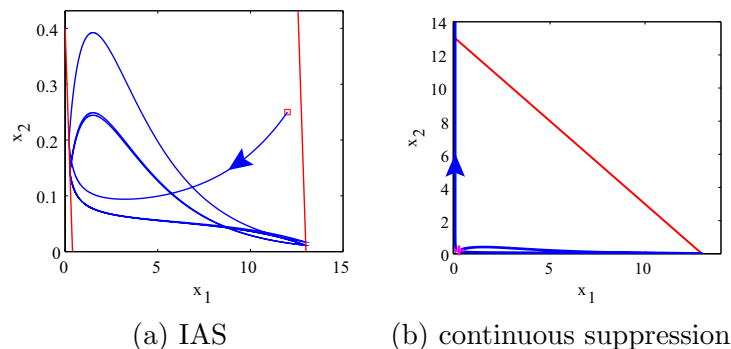


Figure 3: The trajectory in the state space

and $x_2^{\max} = 15$. The region is decomposed into polygons as shown in Fig. 4; splitting into polygonal regions makes the optimization procedure tractable. The decomposition is obtained by splitting the state space along the nullclines \mathcal{N}_1 and \mathcal{N}_2 with additional dividing lines so that the dynamics of the PWA hybrid system becomes close enough to that of the original nonlinear system (1). With the resultant polygons P_1, \dots, P_{10} , the PWA system which we consider here can be written as

$$\frac{dx}{dt} = A_i x + f_i, \quad \text{in } (x, u) \in P_i \text{ for } i = 1, 2, \dots, 10. \quad (2)$$

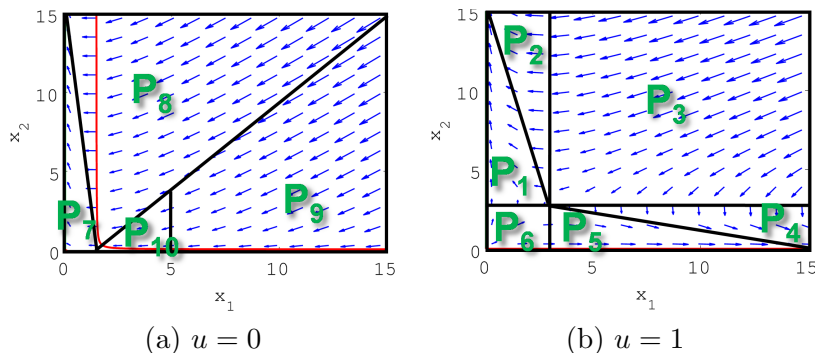


Figure 4: The decomposition of the feasible region \mathcal{X}

For each P_i ($i = 1, \dots, 10$), we determine affine dynamics (A_i, f_i) that are a local approximation of system (1). For this purpose, we employ a criterion of approximation, that is, each linear system well approximates the original nonlinear dynamics (1) on the boundary of the polygon.

Figure 5 shows an example of dynamical behavior of PSA in a model of the PWA hybrid system constructed so that it faithfully reproduces the real data. Then we consider how the optimal control law is suited to this model. Here we assume for simplicity that we can observe state x . To actually observe the internal state, an observer system like the Kalman filter is available [3, 15]. Hereafter the optimal control law is designed under this assumption of observability. To obtain the optimal control law [4, 5], the system is converted to a discrete-time system. On this discrete-time system, we consider the following optimization problem:

$$\min_u \sum_{k=0}^{T-1} \left\{ R|u(k)| + \|x(k)\|_1 \right\} + 2\|x(T)\|_1, \quad (3)$$

where $\|x\|_1 = |x_1| + |x_2|$, $T = 7$, and the time step of k , which corresponds to $t = 0.6$ in Eq. (2), represents the observation time of PSA. We can adjust the weight given to dosing schedule through R , which represents the therapeutic gain or loss related to the intensity of treatment as guided by clinical decision. For example, if the patient has an early stage cancer that can be managed conservatively but the side effects of treatment such as hot flushes are severe, then the use of large doses of drug might be avoided to reduce toxicity. In such a case R should be assigned a large value. On the other hand, if a higher priority is given to suppressing the patient's cancer than avoiding side effects, R should be assigned a small value. We solve the MIP problem to minimize the cost function of Eq. (3).

The results with $R = 4$ and $R = 9000$ are shown in Fig. 6. Figure 6 show the evolution of the optimal controlled solution from an initial state $(13, 2)$. Figures 6 (a1) and (b1) illustrate the temporal changes of x_1 and x_2 . Figures 6 (a2) and (b2) show the evolution of PSA. The red curves in Figs. 6 (a3) and (b3) are unsuccessfully treated trajectories resulting in a relapse under permanent androgen withdrawal. The blue curves inside the black arrowed circles, on the other hand, indicate the trajectories of stable limit cycles when optimal control is realized. Figures 6 (a4) and (b4) show the transitions of on- and off-medication periods denoted by u , i.e. when dosing is on, $u = 1$; otherwise $u = 0$. It should be noted that all of these results represent a type of intermittent androgen suppression with short periods of on-treatment. When R is large as in Fig. 6 (b), the amount of drug administered is less and peak values of PSA are higher. By comparison, when R is small as in Fig. 6 (a), the amount of drug administered is more and the PSA values are smaller. Also, in this situation, the optimal trajectory moves around the edge of a safety-danger boundary, that is the boundary between the 'danger area' where a relapse cannot be avoided and the 'safety area' where PSA can be well regulated. In contrast, when R is large (Fig. 6 (b)), the trajectory moves in a region of higher x_1 and lower x_2 . In this case, the androgen-independent cells are more suppressed. If we want to make the amount of drug as small as possible for constraining the number of tumor cells inside a safety region at any rate and simultaneously offering the possibility of a better quality of life, therapy with a large R is favored. From the shapes of the PSA time-series in Figs. 6 (a2) and (b2), we can see that conventional intermittent androgen suppression is approximately described as a case with large R . This implies that such therapy does not excessively suppress androgen, but rather keeps the PSA level inside a safety region by appropriately reducing the dose intensity of therapy. However, our predictions indicate that there is a room to improve the treatment schedule of intermittent androgen suppression by optimal control as follows.

The average amounts of drug dose and PSA over 2240 days (80 months) are summarized in Table 1. The average dosing rate is the rate of days with on-medication, which is expressed as $\sum_{t=1}^{2240} u(t)/2240$. Shown in the table are the average dosing rate and the average PSA under optimal control which is applied to the model of intermittent androgen suppression in Fig. 5. The corresponding data were also obtained from the simulation of Fig. 5 and an actual clinical

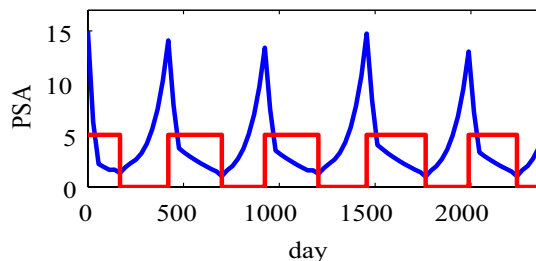


Figure 5: The temporal change of PSA in the PWA hybrid system

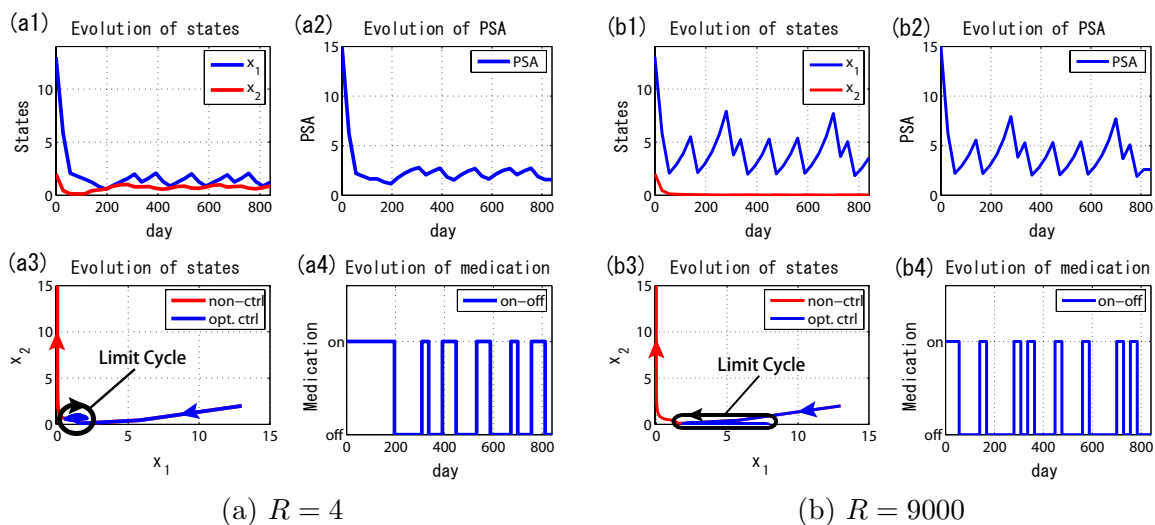


Figure 6: The optimal control when $R = 4$ (a) and 9000 (b)

Table 1: Comparison of average dosing rate and average PSA

	Under Control		IAS (simulation)	IAS (clinical data)
	$R = 4$	$R = 9000$		
average dosing rate	0.4375	0.2875	0.5750	0.5663
average PSA ($\mu\text{g/L}$)	2.4162	4.5293	4.2067	4.3190

case (Fig. 1 (b), patient 2) of intermittent androgen suppression. We can see that optimal control with $R = 9000$ yields an average dosing rate that is about one-half of the conventional dose of intermittent therapy (Table 1, clinical data). Moreover, it should be noted that even when $R = 4$, the average drug dosing rate is lower than that with conventional intermittent androgen suppression (Table 1, clinical data). With respect to the average level of PSA, it becomes optimal when $R = 4$ as expected. At this R value the average PSA is about two-thirds of the level achieved in the other treatments cases. This result strongly suggests that predictions based on optimal control can improve cyclic hormonal therapy for prostate cancer.

If we impose a high penalty with a large value of R for a decrease in drug dose, the on-treatment is terminated when the PSA level is still relatively high. The result implies that intermittent therapy with short periods of on-treatment that fails to achieve sufficiently low nadirs is still compatible with keeping PSA in the safety region. This is different from actual clinical practice as illustrated in Fig. 1. On the other hand, if we impose a low penalty with a small value of R for an increase in drug dose, the resultant data suggests that it is optimal to repeat androgen ablation while PSA is in a lower range taking care not to cross the separatrix in the state space. Our method makes it possible to flexibly derive optimal strategy according to clinical decisions that reflect the patient's condition by selecting the appropriate value for R . We believe that the combination of mathematical modeling and optimal control strategies as presented in this paper will lead to more sophisticated and individualized treatment regimens for prostate cancer.

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