Identifiying Personalized Hormone Therapy Schedules for Prostate Cancer Using Delta-Decisions*

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ABSTRACT

Recent clinical studies suggest that the efficacy of hormone therapy for prostate cancer depends on the characteristics of individual patients. In this paper, we develop a computational framework for identifying patient-specific androgen ablation therapy schedules for postponing the potential cancer relapse. We model the population dynamics of heterogeneous prostate cancer cells in response to androgen suppression as a nonlinear hybrid automaton and estimate personalized parameters to characterize patients. We employ a delta-complete decision procedures based approach to synthesize patient-specific therapeutic strategies. The results show that our framework is promising and may lead to a prognostic tool for personalized cancer therapy.

Categories and Subject Descriptors

D.2.4 [**Software Engineering**]: Software/Program Verification—*Model checking*; J.3 [**Life and Medical Sciences**]: Biology and genetics

General Terms

Theory, Verification

Keywords

hybrid systems, parameter synthesis, decision procedures, systems biology, prostate cancer

1. INTRODUCTION

Prostate cancer is the second leading cause of cancer-related deaths among men in United States [13]. Hormone therapy in the form of androgen deprivation has been a cornerstone of the management of advanced prostate cancer for several decades. However, controversy remains regarding its optimum application [5]. Continuous androgen suppression (CAS) therapy has many side effects including anemia, osteoporosis, impotence, etc. Further, most patients experience a relapse after a median duration of 18-24 months of CAS treatment, due to the proliferation of androgen-independent (AI) cancer cells.

In order to reduce side effects of CAS and to delay the time to relapse, intermittent androgen suppression (IAS) was proposed aiming to limit the duration of androgen-poor conditions and avoid emergence of AI cells [2]. In details, IAS therapy switches between on-treatment and off-treatment modes by monitoring the serum level of a tumor marker called prostate-specific antigen (PSA): (i) when the PSA level decreases and reaches a lower threshold value r_0, androgen suppression is suspended; (ii) when the PSA level increases and reaches a upper threshold value r_1, androgen suppression is resumed by the administration of medical agents.

Recent clinical phase II and III trials confirm that IAS has significant advantages in terms of quality of life and cost. However, with respect to time to relapse and cancer-specific survival, the clinical trials suggest that to what extent IAS is superior to CAS depends on the individual patient and the on- and off-treatment scheme [3, 4, 7]. Thus, a crucial unsolved problem is how to design a personalized treatment scheme for each individual to achieve maximum therapeutic efficacy.

To answer this question, mathematical models have been developed to study the dynamics of prostate cancer under androgen suppression [11, 10, 8, 12]. Recently, attempts have been made to computationally classify patients and obtain the optimal treatment scheme [9, 14]. However, these results relied on simplifying nonlinear hybrid dynamical systems to more manageable versions such as piecewise linear models [9]

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and piecewise affine systems [14]. In this section, we show that our δ-decision based parameter synthesis approach can help to design personalized treatment scheme based on nonlinear hybrid systems with arbitrary computable real functions. Here we focus on the hybrid model presented by [10], which describes the growth of a prostate tumor as the dynamics of a mixed population of androgen-dependent (AD) and androgen-independent (AI) cells.

Contribution.

Releated work.

Organization.

2. MODEL

The model has two modes which are shown in Figure 1. $x(t)$, $y(t)$, and $z(t)$ represent the population of AD cells, the population of AI cells, and the serum androgen concentration, respectively. The growth dynamics of AD and AI cells are governed by their proliferation rate, apoptosis rate and mutation rate from AD to AI phenotype, depending on androgen concentration $z(t)$. The PSA level v (ng ml^{-1}) is defined as $v(t) = x(t) + y(t)$. The treatment is suspended or restarted according to the value of v and dv/dt. In mode 2 (off-treatment), the androgen concentration is maintained at the normal level z_0 by homeostasis. In mode 1 (on-treatment), the androgen is cleared at a rate $1/\tau$. Table 1 lists the values of model parameters.

Table 1: Prostate cancer model parameter values

Parameter	Bone metastasis	Lymph node metastasis
α_x	0.0204 d^{-1}	0.0168 d^{-1}
α_y	0.0242 d^{-1}	0.0277 d^{-1}
β_x	0.0076 d^{-1}	0.0085 d^{-1}
β_y	0.0168 d^{-1}	0.0222 d^{-1}
k_1	0.0 nM	0.0 nM
k_2	2.0	2.0
k_3	8.0 nM	8.0 nM
k_4	0.5	0.5
m_1	0.00005 d^{-1}	0.00005 d^{-1}
z_0	20.0 nM	20.0 nM
τ	62.5 d	62.5 d

3. RESULTS

We have developed an open-source tool dReach using OCaml to perform δ-complete reachability analysis for hybrid systems. dReach is built upon our SMT solver dReal [6] that implements a δ-complete decision procedure. All the experiments reported below were done using a machine with two Intel Xeon E5-2650 2.00GHz processors and 64GB RAM.

3.1 Model selection

Based on different assumptions of the proliferation dynamics of AI cells, the above model has three variations, denoted as H_1, H_2, and H_3, which are discriminated by the value of d, i.e.:

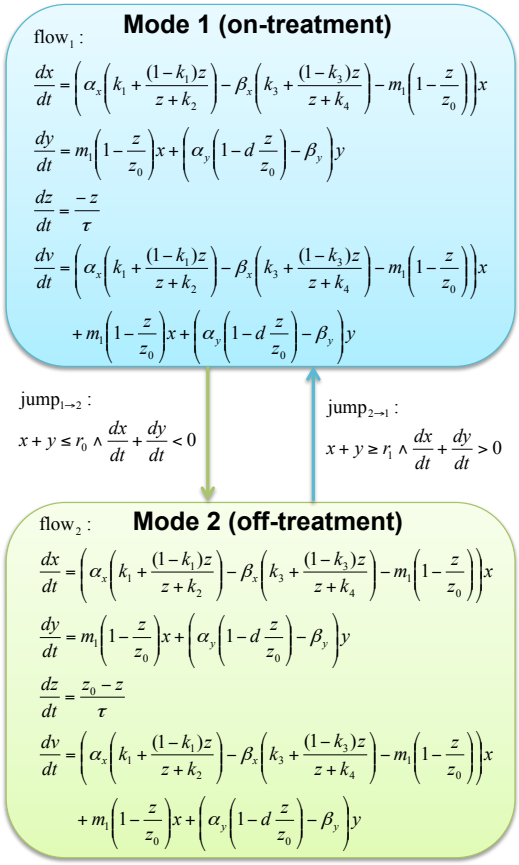

Figure 1: The prostate cancer treatment model.

- H_1: AI cells grow at the constant rate independent of the androgen level ($d = 0$)
- H_2: AI cells do not grow when the androgen level is normal ($d = 1 - \beta_2/\alpha_2$)
- H_3: AI cells decrease when the androgen level is normal ($d = 1$)

In order to perform model selection using δ-decision procedures, we specified the cancer relapse as a state with "$v > 30$", since the PSA level v reflects the total number of tumor cells. We then checked whether each of the model candidates can reach a relapse state within a bounded time of 1000 days. Here the treatment scheme threshold parameters were fixed as $r_0 = 4$ (ng ml^{-1}) and $r_1 = 10$ (ng ml^{-1}). The range of the initial concentration of androgen was given as $[10, 20]$ (nM).

Given the invariant $v \in [0, 30]$, H_1 and H_2 are unable to reach a state with $t = 1000$. In other words, H_1 and H_2 will always lead to cancer relapse state no matter which initial androgen concentration was chosen. This is conflict with the clinical observations by [3, 4]. In contrast, H_3 is able to avoid the relapse state and reproduce the experimental observation (see Figure 2). Thus, we completed the model

selection process by ruling out H_1 and H_2 and choose H_3 for further analysis.

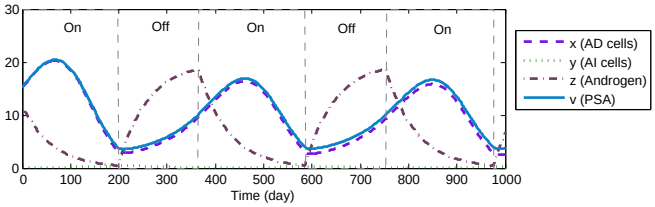

Figure 2: Simulated time profiles of H_3 model.

3.2 Personalized therapy design

We next apply our parameter synthesis method to selecting suitable therapy and designing personalized treatment scheme for individual patients. Note that the parameter values in Table 1 were estimated from clinical data of hundreds of patients [4]. Among patients, the values of some parameters vary, which causes the variability in responsiveness to hormone therapy. We select a set of "personalized parameters" including α_y (the proliferation rate of AI cells), β_y (the apoptosis rate of AI cells), m_1 (the mutation rate from AD to AI cells), and $z(0)$ (the initial androgen level). The values of these parameters can be either experimentally measured [1] or computationally determined from PSA time serials data [8].

Figure 3(a-c) illustrates the PSA dynamics of 3 patients with different personalized parameters under the same IAS treatment scheme ($r_0 = 4$, $r_1 = 10$). IAS prevents the relapse for Patient#1 and delays the relapse for Patient#2, but does not help Patient#3. Figure 3(d) shows that, by modifying the IAS scheduling parameters r_0 and r_1, the relapse of Patient#3 can be avoided or delayed. Thus, we can formulate the personalized therapy design problem as a parameter synthesis procedure: (i) fill in parameter values of a patient to H_3; (ii) set the ranges of scheduling parameters as $r_0 \in [0, 8)$ (nM) and $r_1 \in [8, 15]$; (iii) check if H_3 can reach a state with $t = 1000$ given the invariant $v \in [0, 30]$ (i.e. no relapse). If the δ-decision procedure returns False, it means that androgen suppression therapy is not suitable for the patient. Otherwise, a treatment scheme containing feasible values of r_0 and r_1 will be returned, which could prevent or delay the relapse of the patient. Note that if $r_0 = 0$ is returned, it refers to the CAS scheme.

We tested our method on real patients data collected by [4]. The values of α_y, β_y, m_1, and $z(0)$ for each selected patient were estimated by fitting the model to the PSA time serials data under the first 1.5 cycles of IAS therapy (data available at http://www.nicholasbruchovsky.com/clinicalResearch.html). Table 2 summarized the suggested treatment scheme for selected patients. The in silico validation results are shown in Supplementary Materials.

4. CONCLUSION

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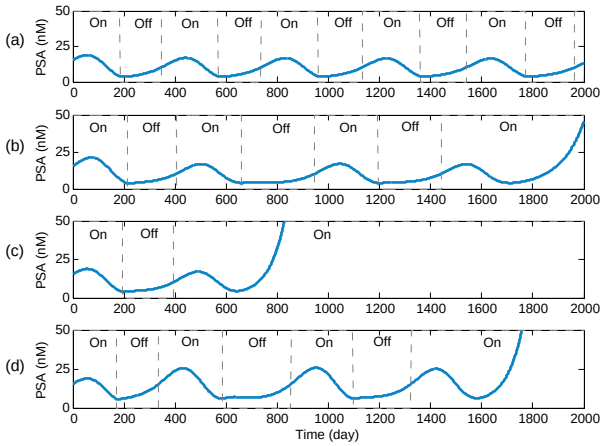

Figure 3: Simulated PSA profiles of patients with different parameters. (a) Patient#1: $\alpha_y = 0.0242$, $\beta_y = 0.0168$, $m_1 = 0.00005$, $z(0) = 12$, $r_0 = 4$, $r_1 = 10$ (b) Patient#2: $\alpha_y = 0.24$, $\beta_y = 0.13$, $z(0) = 13$, $m_1 = 0.0001$, $r_0 = 4$, $r_1 = 10$ (c) Patient#3: $\alpha_y = 0.35$, $\beta_y = 0.187$, $m_1 = 0.00005$, $z(0) = 10$, $r_0 = 4$, $r_1 = 10$ (d) Patient#3: $\alpha_y = 0.035$, $\beta_y = 0.187$, $m_1 = 0.00005$, $z(0) = 10$, $r_0 = 6$, $r_1 = 15$.

Table 2: Personalized hormone therapy scheme for selected patients

Patient ID	α_y	β_y	m_1	$z(0)$	Suggested scheme
#8	0.025	0.021	3.0E-5	8.23	$r_0 = 5.0$, $r_1 = 11.2$
#10	0.019	0.009	5.9E-5	9.44	$r_0 = 4.1$, $r_1 = 9.4$
#45	0.012	0.041	1.0E-5	12.61	$r_0 = 3.8$, $r_1 = 12.2$
#97	0.031	0.015	2.3E-5	10.61	–

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