Journal of Theoretical Biology 350 (2014) 1–16

Contents lists available at ScienceDirect

Journal of Theoretical Biology

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

A new protocol for intermittent androgen suppression therapy of prostate cancer with unstable saddle-point dynamics

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HIGHLIGHTS

- We propose a new protocol for intermittent hormonal therapy for prostate cancer.
- Tumor cell population dynamics are modeled by a hybrid dynamical system.
- Dynamics are determined by event-driven transition between two unstable subsystems.
- Saddle-point dynamics of the subsystems are deeply involved in the stabilization.
- Clever use of the stable manifold provides robust stability and successful therapy.

ARTICLE INFO

Article history:
Received 9 September 2013
Received in revised form
1 February 2014
Accepted 3 February 2014
Available online 10 February 2014

Keywords:
Prostate cancer
Intermittent androgen suppression
Mathematical model
Hybrid dynamical system
Intermittent control

ABSTRACT

Intermittent androgen suppression (IAS) therapy is a class of hormonal treatment for prostate cancer, in which a drug-induced androgen deprivation can reduce the population of prostate cancer cells. In IAS therapy, drugs are administrated only in on-treatment periods that are separated intermittently by off-treatment periods. The presence of off-treatment periods may be beneficial for maintaining the sensitivity of the tumor cells to androgen deprivation. Thus, IAS can be superior to continuous androgen suppression (CAS) for delaying or possibly preventing relapse of a tumor. IAS therapy usually monitors the level of serum prostate-specific antigen (PSA), which is related to the population of tumor cells. Each on-treatment period begins when the PSA level is greater than an upper threshold; treatment results in a decrease in the PSA level. The on-treatment period is suspended when the PSA level falls below a lower threshold; the PSA level then rises again until the beginning of the next on-treatment period. To determine the transitions between on- and off-treatment periods, we propose a new IAS protocol that uses a model-based estimate of the state point in the phase space of the tumor dynamics. We show that the proposed protocol is effective if, in each of the on- and off-treatment periods, the tumor dynamics exhibits a saddle-point instability accompanied by a stable manifold. Mathematical analysis reveals that tumor dynamics can be controlled in a more effective and robust manner with the proposed protocol than with conventional IAS. We also discuss the clinical feasibility of the proposed protocol as an alternative to conventional IAS therapy.

1. Introduction

The number of patients with prostate cancer is increasing worldwide (Siegel et al., 2011). In many cases, patients with prostate cancer have few if any specific symptoms (Pentyala et al., 2000). Therefore, early detection is often achieved by the measurement of prostate-specific antigen (PSA) in the blood (Pentyala et al., 2000), and appropriate treatment can follow detection.

It is known that androgen, the male hormone, enhances the growth of prostate cancer (Charles and Clarence, 1941; Tan et al., 2012). Thus, deprivation of androgen can be an efficient treatment for prostate cancer. Continuous androgen suppression (CAS) therapy is a class of hormonal treatment that exploits the fact that androgen deprivation, which is achieved by administration of pharmacological agents, can reduce the population of tumor cells in advanced prostate cancer. However, many patients suffer from a relapse of the cancer (Pollack et al., 1994; Yu et al., 1995; Feldman and Feldman, 2001; Heidenreich et al., 2008), which is clinically recognized by a re-increase in the concentration of PSA. Relapse is rooted in a mutation of the prostate cancer from androgen

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http://dx.doi.org/10.1016/j.jtbi.2014.02.004
0022-5193

dependent (AD) cancer cells to androgen independent (AI) cancer cells (Feldman and Feldman, 2001; Edwards and Bartlett, 2005). Prevention of relapse is one of the primary issues in the treatment of cancer (Sharifi et al., 2005; Oudard, 2013).

Intermittent androgen suppression (IAS) is a strategy to delay or possibly prevent the relapse (Akakura et al., 1993; Gleave et al., 1998; Mackean et al., 1998; Crook et al., 1999; Mottet et al., 2012). In IAS therapy, drugs are administrated only in intermittent on-treatment periods, which are separated by off-treatment periods. Recent studies have revealed that the off-treatment periods in IAS therapy help to maintain the sensitivity of the tumor cells to androgen deprivation; i.e., the off-treatment periods inhibit the mutation from AD to AI cells.

Ideta et al. (2008) were the first to mathematically describe the dynamics of a tumor being treated by IAS. They analyzed the population dynamics of AD cells, AI cells, and androgen, and demonstrated that IAS therapy was superior to CAS therapy. The model of Ideta et al. (2008) has been extended in various ways (Shimada and Aihara, 2008; Guo et al., 2008; Tao et al., 2009, 2010; Hirata et al., 2010; Jain et al., 2011; Portz et al., 2012; Jain and Friedman, 2013; Tao et al., in press). Among these, Hirata et al. (2010) performed nonlinear system identification on clinical time-series data of PSA in patients with prostate cancer under IAS therapy. They obtained dynamical system models that described the population dynamics of AD cells and two types of AI cells and that quantitatively reproduced the clinical data. In the studies of Ideta et al. (2008) and Hirata et al. (2010), the population dynamics of tumor cells with IAS therapy was modeled by hybrid dynamical systems. Specifically, tumor dynamics during on-treatment periods was modeled by one system, referred to here as the *on-model*, and that in off-treatment periods by another system, referred to as the *off-model*; thus, these two subsystems are alternated in governing the overall dynamics.

Thus far, in conventional IAS therapy and thus also in the mathematical models of Ideta et al. (2008) and Hirata et al. (2010), each on-treatment period begins when the PSA level grows beyond a predetermined upper threshold, and results in a decrease in the PSA level. Treatment is suspended when the PSA level falls below a lower threshold; this is the onset of an off-treatment period during which the PSA level increases. Those two types of threshold-crossing events trigger the transitions between the on-model and the off-model. We refer to this control protocol as the *threshold method*. Typically, the threshold method induces a sustained oscillation in the PSA level, in which the maximum and minimum levels are roughly determined by the upper and the lower thresholds, respectively. Mathematically, this oscillation corresponds to a limit cycle of the hybrid dynamical system model. In this way, IAS therapy with the threshold method achieves a bounded population of cancer cells.

In this paper, we focus on the fact that the dynamics of each of the on-models and the off-models has a saddle-point instability for the typical cases explored in Ideta et al. (2008) and Hirata et al. (2010). In each on-treatment period of either IAS or CAS therapy, the effective degradation rate of the AD cells is responsible for the decrease in the PSA level during the early phase of the treatment, and this process is accompanied by a gradual increase in the number of AI cells. The corresponding dynamics is represented as follows: while moving along the stable manifold toward the saddle-point equilibrium located at the origin, the state point of the on-model is attracted by the unstable manifold.[1] The increase in AI cells during the later phase of the treatment is responsible for a relapse; this decrease is represented by the movement of the state point away from the origin along the unstable manifold. Similarly, in the absence of treatment (during each off-treatment period of IAS therapy), the population growth of AD cells is responsible for an increase in the PSA level; this is represented by the movement of the state point along the unstable manifold of the off-model. At the same time, the population of AI cells decreases; this is represented by the movement of the state point along the stable manifold of the off-model. In this way, the decrease and increase of the PSA level in the limit-cycle oscillation of IAS therapy, respectively, correspond to the movement of the state point along the stable manifold of the on-model and the unstable manifold of the off-model.

Here, based on dynamics that was revealed in previous studies, we propose a new IAS-based tumor control protocol, which we will call the *region-dividing method*. In this method, we combine the unstable saddle-point dynamics of the on- and off-models in order to stabilize the overall dynamics of IAS therapy. We modify the IAS models of Ideta et al. (2008) and Hirata et al. (2010) in order to examine the proposed control protocol. In Section 2, we introduce the original IAS models. In Section 3, we illustrate how the new protocol can stabilize an equilibrium point located at the origin of the hybrid dynamical system for IAS therapy, and provide a theoretical basis for the region-dividing method. Then, in Section 4, we define modified IAS models that include the region-dividing method and are based on Ideta et al. (2008) and Hirata et al. (2010). In Section 5, we investigate the dynamics of the modified IAS models, and compare that with the dynamics of the original threshold method. In Section 6, we compare the stability of the models that use the region-dividing method with those that use the threshold method, when values of important parameters are changed. We also show that the parameter regions where tumor growth is successfully controlled by the region-dividing method are almost identical to the parameter regions where both the on- and off-models have saddle-point equilibrium points. We then discuss, in Section 7, the clinical feasibility of using the proposed protocol as an alternative to conventional IAS therapy.

2. Models of conventional IAS therapy

In this section, we briefly introduce the two mathematical models of conventional IAS therapy that were proposed by Ideta et al. (2008) and Hirata et al. (2010); we will refer to them as the *ITTA model* and *HBA model*, respectively. In each model, the dynamics of the IAS therapy are described by a hybrid dynamical system consisting of an on-model and an off-model. Transitions between the on-model and the off-model are triggered by threshold-crossing events in the serum PSA concentration, as monitored by a blood test.

2.1. ITTA model

The ITTA model describes the androgen dynamics, the population dynamics of AD and mutated AI cells, and the serum concentration of PSA. The androgen dynamics in the presence of treatment is described by

$$\frac{d}{dt}a(t) = -\gamma a(t), \tag{1}$$

where $a(t)$ represents the serum concentration of androgen, which decays to zero during the on-treatment period with a time constant of $1/\gamma$. In the absence of treatment, the androgen concentration is regulated at a constant value of the normal androgen concentration in the untreated condition, a_0, as follows:

$$\frac{d}{dt}a(t) = -\gamma(a(t) - a_0). \tag{2}$$

[1] In general, an unstable manifold of a saddle-point equilibrium is attractive. Thus, a state point approaches an unstable manifold as it moves away from such an equilibrium point.