DISCRETE AND CONTINUOUS
DYNAMICAL SYSTEMS SERIES B
Volume **18**, Number **4**, June **2013**

doi:10.3934/dcdsb.2013.18.945

pp. **945–967**

# MODELING PROSTATE CANCER RESPONSE TO CONTINUOUS VERSUS INTERMITTENT ANDROGEN ABLATION THERAPY

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Abstract. Due to its dependence on androgens, metastatic prostate cancer is typically treated with continuous androgen ablation. However, such therapy eventually fails due to the emergence of castration-resistance cells. It has been hypothesized that intermittent androgen ablation can delay the onset of this resistance. In this paper, we present a biochemically-motivated ordinary differential equation model of prostate cancer response to anti-androgen therapy, with the aim of predicting optimal treatment protocols based on individual patient characteristics. Conditions under which intermittent scheduling is preferable over continuous therapy are derived analytically for a variety of castration-resistant cell phenotypes. The model predicts that while a cure is not possible for androgen-independent castration-resistant cells, continuous therapy results in longer disease-free survival periods. However, for androgen-repressed castration-resistant cells, intermittent therapy can significantly delay the emergence of resistance, and in some cases induce tumor regression. Numerical simulations of the model lead to two interesting cases, where even though continuous therapy may be non-viable, an optimally chosen intermittent schedule leads to tumor regression, and where a sub-optimally chosen intermittent schedule can initially appear to result in a cure, it eventually leads to resistance emergence. These results demonstrate the model's potential impact in a clinical setting.

1. **Introduction.** The prostate gland is a vital component of the male reproductive anatomy. It's primary function is to produce an alkaline fluid that is one of the key components of semen. In addition, prostatic epithelia also produces prostate-specific antigen (PSA), a proteolytic glycoprotein that aids in semen motility [28]. Unfortunately, the prostate is one of the most common sites of cancer incidence, with prostate cancer (CaP) being second most common type of cancer affecting men in the United States. In 2010 alone, more than 200,000 cases were diagnosed in the United States, resulting in 32,000 deaths [6]. Thus, CaP remains a major public health challenge today.

2010 *Mathematics Subject Classification.* Primary: 92C40, 92C50; Secondary: 37N25.

*Key words and phrases.* Androgen ablation, androgen independent, androgen repressed, castration resistance, mathematical model, prostate cancer, PSA.

Initially, CaP cells, like the glandular cell from which they chiefly originate, are dependent on male sex hormones or androgens for growth and survival. The principle androgen is testosterone, mainly synthesized from cholesterol in the Leydig Cells of the testis under regulation by luteinizing hormone from the pituitary gland. Upon entering a prostate cell or a CaP cell, testosterone is mostly converted to dihydrotestosterone (DHT). Both testosterone and DHT bind to and activate intracellular androgen receptors, however DHT has a much greater binding affinity and forms a more stable complex with androgen receptors than testosterone. Activated androgen receptors undergo phosphorylation and dimerization in the cell cytoplasm before translocating to the nucleus where they promote transcriptional activity of genes associated with growth, survival and proliferation [10, 27].

Since CaP cells produce PSA, and CaP is associated with increased levels of serum PSA, the current guidelines in the United States for screening for prostate cancer in men 50 years of age or older include a PSA test, often coupled with a digital rectal exam [2]. Early stage CaP may be treated with surgery, or radiation, or both. Recurrent disease post-surgery or -radiation therapy is classified as advanced CaP. At this stage, cancer cells have already spread to tissues outside the prostate gland, forming lymph node or bone metastases [9].

Advanced cancer typically responds poorly to standard cytotoxic regimens. However, since cancer cells depend on androgens for growth and survival, the treatment of advanced CaP includes androgen-ablation, which typically consists of a combination of 2 drugs: a luteinizing hormone-releasing hormone agonist that down-regulates testosterone production such as goserelin or Zoladex, and a competitor of androgens at the receptor level such as bicalutamide or flutamide [9]. This treatment works well initially, but eventually cancer cells develop resistance, generally observed via the rise of PSA levels [8]. It has been proposed that mutations in the androgen receptor signaling pathway could contribute to castration-resistance [8], and that such mutations are associated with continuous hormone therapy [21]. Consequently, it has been proposed that constant androgen ablation be replaced with intermittent androgen suppression, where treatment is switched on and off depending on predefined clinical objectives such as threshold PSA levels.

A number of mathematical models have been proposed aimed at gaining a better understanding of the consequences of current clinical care, as well as investigating the therapeutic potential of intermittent hormone treatment. Models by Jackson [18, 19] were one of the first to consider the competitive interactions between androgen-dependent and mutated cancer cells and mutated cancer cells. In these models, cellular proliferation and survival rates are taken to be functions of androgen concentrations. Ideta et al. [17] subsequently modified the models of Jackson by including a rate of mutation from androgen-dependent to castration-resistant cancer cells that is assumed to be an increasing function of androgen concentration. With the aim of identifying optimal scheduling protocols with intermittent therapy, Hirata et al. [16] proposed a piecewise linear model of prostate cancer progression which separates the androgen-independent cells into two populations, those that have undergone a reversible change and those that are irreversibly mutated to a castration-resistant phenotype. In their model of early cancer development, Eikenberry et al. [7] were the first to include detailed intracellular signal transduction pathways relating to the interaction between androgens and their receptors. This model was subsequently modified by Portz et al. [24] to simulate the treatment of clinical disease.

We have previously developed a biochemically-motivated mathematical model of advanced CaP progression [20] with a number of patient-specific or personalized parameters which captured the heterogeneity that is a hallmark of CaP. Model simulations were able to reproduce a variety of clinically observed outcomes for patients on various therapeutic schedules. Crucially, we predicted that in the absence of a competitive advantage of androgen-dependent cells over castration-resistant cells, intermittent therapy could lead to more rapid treatment failure. In this paper, we use singular perturbations to simplify our model [20], reducing it to system of equations that describe the temporal dynamics of androgen-dependent and castration-resistant cancer cells and serum PSA. We begin our analysis of CaP response to treatment by deriving a necessary and sufficient condition for continuous androgen ablation to be a viable therapeutic option. Next, a variety of castration-resistant cell phenotypes are considered, and conditions derived under which intermittent therapy can lead to a delayed onset of castration-resistance in the absence of inter-cell competition, as compared to continuous therapy. We also prove necessary and sufficient conditions for a cure using intermittent therapy. Finally, we present numerical simulations illustrating our analytical results.

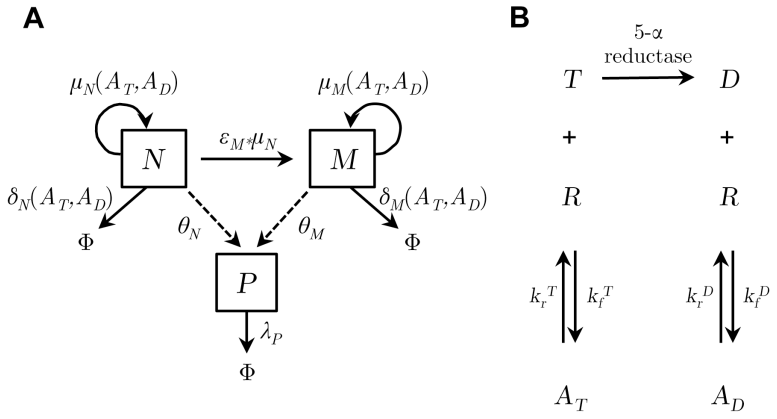


FIGURE 1. Model Schematic. **A**, Androgen-dependent cancer cells ($N$) and castration-resistant cancer cells ($M$) undergo proliferation at rates $\mu_N$ and $\mu_M$ respectively, and die at rates $\delta_N$ and $\delta_M$ respectively. Cellular proliferation and death rates are taken as functions of intracellular activated androgen receptor concentrations. Mutation to $M$ cells is assumed to occur as a result of aberrant proliferation in $N$ cells, with some probability $\epsilon_M$. Further, both cell types produce PSA ($P$) at rates $\theta_N$ and $\theta_M$. PSA undergoes decay and clearance from the body at a rate $\lambda_P$. **B**, Intracellular testosterone ($T$) is converted into its more active metabolite DHT ($D$) by the action of 5-$\alpha$ reductase. Both testosterone and DHT bind to free androgen receptors ($R$), resulting in testosterone-activated ($A_T$) and DHT-activated receptors ($A_D$) respectively. These reactions occur within both $N$ and $M$ cells.

2. **Model development.** Our model for CaP growth and treatment is derived from our previously published model of prostate cancer progression under androgen deprivation therapy [20]. The principal species of the model are: androgen-dependent cancer cell number in millions ($N$), castration-resistant cancer cell number in millions ($M$), serum PSA concentration in ng/ml ($P$), and intracellular chemical species with concentration measured in nM, namely testosterone ($T$), DHT ($D$), free androgen receptors ($R$), testosterone-activated androgen receptors ($A_T$) and DHT-activated androgen receptors ($A_T$). The equations governing the dynamics of these species are explained below.

2.1. **Tumor growth and PSA production.** Androgen-dependent cancer cells ($N$) and castration-resistant cancer cells ($M$) proliferate at rates $\mu_N$ and $\mu_M$ respectively, and have death rates $\delta_N$ and $\delta_M$ respectively. The cell proliferation and death rates are taken to be functions of intracellular testosterone-activated androgen receptor ($A_T$) and DHT-activated androgen receptor ($A_D$) concentrations. Mutations leading to castration resistance have been hypothesized to be an early event, and independent of androgen ablation [5]. To account for this, we assume that $N$ cells mutate irreversibly to an $M$ cell phenotype with probability $\epsilon_M$, as a result of aberrant proliferation. $N$ and $M$ cells also produce PSA ($P$) which is released into the blood stream, from where it is cleared from the body. Together, these processes translate into the following system of equations describing the dynamics of $N$, $M$ and $P$. A model schematic is shown in Figure 1A.

$$\begin{aligned}
\frac{dN}{dt} &= \underbrace{\mu_N(A_T,A_D)N}_{\text{proliferation}} - \underbrace{\delta_N(A_T,A_D)N}_{\text{death}} - \underbrace{\epsilon_M\mu_N(A_T,A_D)N}_{\text{mutation to castration-resistant phenotype}} \\
\frac{dM}{dt} &= \underbrace{\mu_M(A_T,A_D)M}_{\text{proliferation}} - \underbrace{\delta_M(A_T,A_D)M}_{\text{death}} + \underbrace{\epsilon_M\mu_N(A_T,A_D)N}_{\text{mutation from androgen-dependent phenotype}} \\
\frac{dP}{dt} &= \underbrace{\theta_N N + \theta_M M}_{\text{production}} - \underbrace{\lambda_P P}_{\text{degradation/ clearance}}
\end{aligned} \tag{1}$$

2.2. **Intracellular signal transduction.** Testosterone produced in the testes is released into the blood stream. From here, it enters the prostate as well as sites of metastasis, and is taken up by $N$ and $M$ cells. Intracellular testosterone ($T$) is converted into DHT ($D$) by the action of 5-$\alpha$ reductase. Testosterone and DHT both bind to androgen receptors ($R$), activating them. Testosterone-activated receptors ($A_T$) and DHT-activated receptors ($A_D$) induce proliferative and survival signal modulation in $N$ and $M$ cells [1, 15, 23]. This chemical reaction network is shown in Figure 1B. In our model, we also allow for the possibility of degradation of all molecular species. The reactions described above are translated into the following system of differential equations, using the Law of Mass Actions (see [20] for details):

$$\frac{dT}{dt} = \underbrace{f(t)\cdot\alpha_T}_{\text{supply from bloodstream}} - \underbrace{\lambda_T T}_{\text{degradation}} - \underbrace{\beta_T\frac{T}{K_T+T}}_{\text{conversion of testosterone to DHT}} - \underbrace{k_f^T RT + k_r^T A_T}_{\text{binding with androgen receptors}} \tag{2}$$

$$\frac{dD}{dt} = \underbrace{\beta_T \frac{T}{K_t + T}}_{\substack{\text{conversion of} \\ \text{testosterone to DHT}}} - \underbrace{\lambda_D D}_{\text{degradation}} \underbrace{- k_f^D RD + k_r^D A_D}_{\substack{\text{binding with} \\ \text{androgen receptors}}}$$

$$\frac{dR}{dt} = \underbrace{\alpha_R}_{\text{production}} - \underbrace{\lambda_R R}_{\text{degradation}} - \underbrace{k_f^T RT + k_r^T A_T}_{\text{binding with testosterone}} \underbrace{- k_f^D RD + k_r^D A_D}_{\text{binding with DHT}}$$

$$\frac{dA_T}{dt} = - \underbrace{\lambda_{A_T} A_T}_{\text{degradation}} + \underbrace{k_f^T RT - k_r^T A_T}_{\substack{\text{activation of androgen} \\ \text{receptors by testosterone}}}$$

$$\frac{dA_D}{dt} = - \underbrace{\lambda_{A_D} A_D}_{\text{degradation}} + \underbrace{k_f^D RD - k_r^D A_D}_{\substack{\text{activation of androgen} \\ \text{receptors by DHT}}}$$

For simplicity, following [8], we assume that the collective effect of androgen ablation therapy is to reduce the bio-availability of DHT to the cells by an average of 60%, which is simulated by a decrease in the production rate $\alpha_T$ of intracellular testosterone on the right hand side of the first equation of system (2), via a function $f(t)$. Therefore, $f(t)$ represents the application of hormonal therapy, and it's precise form is determined by the treatment schedule. We will consider the following three possible schedules:

1. Continuous androgen ablation starting at time $t_{on}$ that is simulated by defining:

$$f(t) = \begin{cases} 1, & \text{if } t < t_{on}, \\ \epsilon_T, & \text{if } t \geq t_{on}. \end{cases} \tag{3}$$

Here the constant $\epsilon_T < 1$ is chosen so that the net effect of therapy is to decrease intracellular DHT levels by 60% (see Table 1).

2. Intermittent androgen ablation applied starting at time $t_{on}$, where therapy is switched 'on' for a fixed length of time, say $\tau_{on}$ and switched 'off' for a fixed length of time, say $\tau_{off}$, and that is simulated by defining:

$$f(t) = \begin{cases} \epsilon_T, & t_{on} + (n-1)\tau_{on} + (n-1)\tau_{off} \leq t < t_{on} + n\tau_{on} + (n-1)\tau_{off}, \\ 1, & t_{on} + n\tau_{on} + (n-1)\tau_{off} \leq t < t_{on} + n\tau_{on} + n\tau_{off}. \end{cases}, \tag{4}$$

where $n \in \mathbb{Z}^+$.

3. Following [11, 12], we also consider intermittent androgen ablation based on serum PSA levels, where the therapy is switched 'on' if PSA rises above a critical threshold, say $P_{crit}$, and is administered for a preset period of time, say $\tau_{on}$. This schedule is simulated by defining:

$$f(t) = \begin{cases} 1 \to \epsilon_T, & \text{if } P(t) = P_{crit} \text{ and } dP/dt > 0, \\ \epsilon_T \to 1, & \text{if time on therapy} = \tau_{on}. \end{cases} \tag{5}$$

2.2.1. *Parameter estimation.* The values of the parameters appearing in the system of equations (2) have been previously estimated in [20], from experimental data on the rat prostate reported in [27] and taking into account human prostate characteristics. Table 1 lists the values and units of each parameter. A brief description of the parameter estimation follows, complete details of which are provided in the Supplementary Information of [20].

TABLE 1. List of parameter values for intracellular biochemical equations.

| Parameter | Value | Units | Source |
|---|---|---|---|
| $\alpha_T$ | 563.9316 | nM per day | [20, 27] |
| $\lambda_T$ | 5.5452 | per day | [7] |
| $\beta_T$ | 438.6336 | nM per day | [20, 27] |
| $K_T$ | 0.1042 | nM | [20, 27] |
| $k_f^T$ | 3.3600 | per nM per day | [26] |
| $k_r^T$ | 1.6560 | per day | [26] |
| $\lambda_D$ | 1.8484 | per day | [7] |
| $k_f^D$ | 1.2720 | per nM per day | [26] |
| $k_r^D$ | 0.4320 | per day | [26] |
| $\alpha_R$ | 306.4200 | nM per day | [20] |
| $\lambda_R$ | 5.5452 | per day | [7] |
| $\lambda_{A_T}$ | 5.5452 | per day | [20, 27] |
| $\lambda_{A_D}$ | 1.3836 | per day | [13] |
| $\epsilon_T$ | 0.2842 | dimensionless | see text |

In a set of experiments described in [27], 55-day-old male Sprague Dawley rats were castrated and treated with subcutaneously implanted testosterone pellets together with finasteride to ensure minimal or no conversion of testosterone to DHT in the prostate. The rats were sacrificed four days after castration, and intraprostatic testosterone and ventral prostate weights measured and recorded versus corresponding values of serum testosterone. This data was used to estimate the rate $\alpha_T$ of testosterone entry into the rat prostate, and the rate $\lambda_{A_T}$ of testosterone-activated androgen receptor decay. In a second set of experiments described in [27], the castrated rats were not treated with finasteride, allowing for the conversion of testosterone to DHT in the prostate. As before, the rats were sacrificed four days after castration, and intraprostatic DHT and ventral prostate weights measured and recorded versus corresponding values of serum testosterone. This data was used to estimate the parameters relating to the conversion of testosterone to DHT, namely $\beta_T$ and $K_T$. To better reflect the fact that humans produce a much higher level of testosterone than rats (serum testosterone concentration in adult males is ≈27-fold higher than in rats), at least 90% of which is in the form of DHT, the parameters $\alpha_T$ and $\beta_T$ are scaled up by factors of 27 and 4, respectively. Their values in Table 1 reflect this scaling.

2.2.2. *Nondimensionalization.* While the biochemical reactions described above take place on short time-scales on the order of seconds or minutes, we are interested in the longer time-scale that corresponds to tumor growth. We therefore rewrite the system of equations (2) in dimensionless variables, denoted by a bar. The following rescaling is chosen for the various molecular species and time.

$$t = \frac{1}{\tau_C}\bar{t}, \quad T = \bar{T}T_0, \quad D = \bar{D}D_0, \quad R = \bar{R}R_0, \quad A_T = \bar{A}_T R_0, \quad A_D = \bar{A}_D R_0.$$

Time is rescaled by the typical growth rate $\tau_C$ of CaP cells. The value of $\tau_C$ is estimated from data in [3]. $T_0$ and $D_0$ are the total amount of testosterone and DHT respectively in a healthy prostate and $R_0$ is the level of androgen receptors expressed in prostatic epithelial cells. We remark that $R_0$ has previously been estimated

in [20] and that $T_0$ and $D_0$ may be estimated numerically by solving the system of equations (2) to steady state. The dimensionless equations are listed below, with bars dropped for notational convenience. The values of scaling constants and the values and expressions for each dimensionless parameter are listed in Table 2.

$$\begin{aligned}
\epsilon\frac{dT}{dt} &= f(t)\cdot\sigma_1 - \sigma_2 T - \sigma_3\frac{T}{\sigma_4+T} - \sigma_5 RT + \sigma_6 A_T \\
\epsilon\frac{dD}{dt} &= \sigma_7\frac{T}{\sigma_4+T} - \sigma_8 D - \sigma_9 RD + \sigma_{10} A_D \\
\epsilon\frac{dR}{dt} &= \sigma_{11} - \sigma_{12} R - \sigma_{13} RT + A_T - \sigma_{14} RD + \sigma_{15} A_D \\
\epsilon\frac{dA_T}{dt} &= -\sigma_{16} A_T + \sigma_{13} RT - A_T \\
\epsilon\frac{dA_D}{dt} &= -\sigma_{17} A_D + \sigma_{14} RD - \sigma_{15} A_D
\end{aligned} \tag{6}$$

TABLE 2. List of scaling constants and non-dimensional parameter values appearing in the system of equations (6).

| Parameter | Source | Value |
|---|---|---|
| $T_0$ | see text | 23.2968 nM |
| $D_0$ | see text | 276.9988 nM |
| $R_0$ | [20] | 180 nM |
| $\tau_C$ | [3] | 0.0030 per day |

| Parameter | Expression | Value |
|---|---|---|
| $\epsilon$ | $\tau_C/k_r^T$ | 0.0018 |
| $\sigma_1$ | $\alpha_T/(T_0 k_r^T)$ | 14.6174 |
| $\sigma_2$ | $\lambda_T/k_r^T$ | 3.3486 |
| $\sigma_3$ | $\beta_T/(T_0 k_r^T)$ | 11.3696 |
| $\sigma_4$ | $K_T/T_0$ | 0.0045 |
| $\sigma_5$ | $k_f^T R_0/k_r^T$ | 365.2174 |
| $\sigma_6$ | $R_0/T_0$ | 7.7264 |
| $\sigma_7$ | $\beta_T/(D_0 k_r^T)$ | 0.9563 |
| $\sigma_8$ | $\lambda_D/k_r^T$ | 1.1162 |
| $\sigma_9$ | $k_f^D R_0/k_r^T$ | 138.2609 |
| $\sigma_{10}$ | $k_r^D R_0/(D_0 k_r^T)$ | 0.1695 |
| $\sigma_{11}$ | $\alpha_R/(R_0 k_r^T)$ | 1.0280 |
| $\sigma_{12}$ | $\lambda_R/k_r^T$ | 3.3486 |
| $\sigma_{13}$ | $k_f^T T_0/k_r^T$ | 47.2689 |
| $\sigma_{14}$ | $k_f^D D_0/k_r^T$ | 212.7604 |
| $\sigma_{15}$ | $k_r^D/k_r^T$ | 0.2609 |
| $\sigma_{16}$ | $\lambda_{A_T}/k_r^T$ | 3.3486 |
| $\sigma_{17}$ | $\lambda_{A_D}/k_r^T$ | 0.8355 |

We have introduced a small parameter $\epsilon = \tau_C/k_r^T = 1.8 \times 10^{-3} \ll 1$ in our nondimensional equations; $\epsilon$ is the ratio of tumor cell growth rate, and the dissociation rate of the testosterone-activated receptor into its constituent species. We exploit the appearance of this small parameter by setting the rates of change of the molecular species equal to 0 in equations (6), and approximating activated-androgen receptor concentrations in the cell equations by their steady-state values. Thus, our model for CaP progression in response to androgen ablation therapy reduces simply to the system of equations (1), where the rates of proliferation and death of $N$ and $M$ cells are constant, with different values for the on and off-treatment cases. For simplicity, we assume that the death rate of $N$ cells is negligible when treatment is off, and that their proliferation rate is negligible when treatment is on. That is,

$$\mu_N(A_T, A_D) = \begin{cases} \alpha_N, & \text{if therapy is off,} \\ 0, & \text{if therapy is on.} \end{cases}, \quad \delta_N(A_T, A_D) = \begin{cases} 0, & \text{if therapy is off,} \\ \beta_N, & \text{if therapy is on.} \end{cases}$$

Further, in the case of $M$ cells, we set

$$\mu_M(A_T, A_D) - \delta_M(A_T, A_D) = \begin{cases} \alpha_M, & \text{if therapy is off,} \\ \beta_M, & \text{if therapy is on.} \end{cases},$$

where $\alpha_N, \beta_N, \beta_M > 0$ and the choice of $\alpha_M$ determines the phenotype of the castration-resistant cells.

## 3. Analysis.

In this section, we shall explore the following questions analytically: (i) Whether continuous androgen inhibition is a viable option; and (ii) When is intermittent treatment preferable to continuous androgen deprivation. We first provide a definition of what we mean by a viable therapeutic option.

**Definition 3.1. Viability of Continuous Therapy:** Continuous androgen ablation is said to be a viable therapeutic option if it results in an eventual decrease in serum PSA concentration, while therapy is on. Mathematically, if $t_{on}$ is the time at which the current cycle of therapy has been started, then androgen ablation is defined to be viable if:

$$\exists\, t_v \in [t_{on}, \infty) \text{ such that } \left.\frac{dP}{dt}\right|_{t=t_v} < 0.$$

Consider now the simplified model of CaP growth derived in the previous section:

$$\begin{aligned} \frac{dN}{dt} &= \begin{cases} \alpha_N(1-\epsilon_M)N, & \text{if therapy is off,} \\ -\beta_N N, & \text{if therapy is on.} \end{cases}, \\ \frac{dM}{dt} &= \begin{cases} \alpha_M M + \alpha_N \epsilon_M N, & \text{if therapy is off,} \\ \beta_M M, & \text{if therapy is on.} \end{cases}, \\ \frac{dP}{dt} &= \theta_N N + \theta_M M - \lambda_P P \end{aligned} \tag{7}$$

The above system can be solved explicitly to give the following expressions. If therapy is switched off at some time $t_{off} > 0$, for $t \geq t_{off}$ and for as long as therapy

remains off we have:

$$\begin{aligned} N(t) =& N_{off} e^{\alpha_N(1-\epsilon_M)(t-t_{off})} \\ M(t) =& M_{off} e^{\alpha_M(t-t_{off})} + \rho_1 N_{off} \left( e^{\alpha_N(1-\epsilon_M)(t-t_{off})} - e^{\alpha_M(t-t_{off})} \right) \\ P(t) =& P_{off} e^{-\lambda_P(t-t_{off})} + \rho_2 \left( e^{\alpha_N(1-\epsilon_M)(t-t_{off})} - e^{-\lambda_P(t-t_{off})} \right) \\ &+ \rho_3 \left( e^{\alpha_M(t-t_{off})} - e^{-\lambda_P(t-t_{off})} \right) \\ &+ \rho_4 \left( \frac{e^{\alpha_N(1-\epsilon_M)(t-t_{off})}}{\alpha_N(1-\epsilon_M)+\lambda_P} - \frac{e^{\alpha_M(t-t_{off})}}{\alpha_M+\lambda_P} + \rho_5 e^{-\lambda_P(t-t_{off})} \right) \end{aligned} \tag{8}$$

where $N_{off} = N(t_{off})$, $M_{off} = M(t_{off})$, $P_{off} = P(t_{off})$, the constants $\rho_i$ are defined as:

$$\begin{aligned} \rho_1 =& \frac{\alpha_N \epsilon_M}{\alpha_N(1-\epsilon_M)-\alpha_M}, \qquad \rho_2 = \frac{\theta_N N_{off}}{\alpha_N(1-\epsilon_M)+\lambda_P}, \qquad \rho_3 = \frac{\theta_M M_{off}}{\alpha_M+\lambda_P}, \\ \rho_4 =& \theta_M \rho_1 N_{off}, \qquad \rho_5 = \frac{\alpha_N(1-\epsilon_M)-\alpha_M}{(\alpha_N(1-\epsilon_M)+\lambda_P)(\alpha_M+\lambda_P)}, \end{aligned}$$

and where we have assumed that $\alpha_N(1-\epsilon_M) \neq \alpha_M$, and that $\alpha_M \neq -\lambda_P$. It follows from (8) that left untreated, $N(t)$, $M(t)$ and $P(t) \to \infty$ as $t \to \infty$.

Likewise, If therapy is switched on at some time $t_{on} > 0$, for $t \geq t_{on}$ and for as long as therapy remains on we have:

$$\begin{aligned} N(t) =& N_{on} e^{-\beta_N(t-t_{on})} \\ M(t) =& M_{on} e^{\beta_M(t-t_{on})} \\ P(t) =& P_{on} e^{-\lambda_P(t-t_{on})} + \rho_6 \left( e^{-\beta_N(t-t_{on})} - e^{-\lambda_P(t-t_{on})} \right) \\ &+ \rho_7 \left( e^{\beta_M(t-t_{on})} - e^{-\lambda_P(t-t_{on})} \right) \end{aligned} \tag{9}$$

where $N_{on} = N(t_{on})$, $M_{on} = M(t_{on})$, $P_{on} = P(t_{on})$, the constants $\rho_i$ are defined as:

$$\rho_6 = \frac{\theta_N N_{on}}{\lambda_P - \beta_N}, \qquad \rho_7 = \frac{\theta_M M_{on}}{\beta_M + \lambda_P},$$

and where we have assumed that $\lambda_P \neq \beta_N$. It follows from (9) that under continuous androgen deprivation, $M(t)$ and $P(t) \to \infty$ as $t \to \infty$. Note that in the second equation in (8), $\rho_1 \left( e^{\alpha_N(1-\epsilon_M)(t-t_{off})} - e^{\alpha_M(t-t_{off})} \right)$ is positive regardless of the sign of $\alpha_N(1-\epsilon_M)-\alpha_M$. Hence we may assume in what follows that $\alpha_N(1-\epsilon_M) > \alpha_M$ and similarly that $\lambda_P > \beta_N$.

We now derive necessary and sufficient conditions for the viable application of continuous androgen ablation therapy.

**Theorem 3.2.** *Let $t_{on}$ be the time at which the application of therapy is being considered. Assume that at this time, serum PSA is increasing, that is $\left.\frac{dP}{dt}\right|_{t=t_{on}} > 0$. Then, necessary and sufficient conditions for androgen ablation to be a viable therapeutic option are:*

$$\begin{aligned} (\lambda_P + \beta_M)b - (\beta_N + \beta_M)c >& 0, \qquad \textit{and} \\ a - b\left(\frac{\lambda_P - \beta_N}{\beta_M}\right) x_m^{-(\lambda_P+\beta_M)/\beta_M} <& 0, \end{aligned}$$

*where* $x_m = \left[\dfrac{(\lambda_P+\beta_M)b}{(\beta_N+\beta_M)c}\right]^{\beta_M/(\lambda_P-\beta_N)}$, $a = \rho_7\beta_M$, $b = (\rho_6+\rho_7-P_{on})\lambda_P$ *and* $c = \rho_6\beta_N$.

*Proof.* From (9), the rate of change of PSA while therapy is on is given by $\dfrac{dP}{dt} = xg(x)$, where

$$\begin{aligned} x =& e^{\beta_M(t-t_{on})}, \text{ and} \\ g(x) =& a + bx^{-(\lambda_P+\beta_M)/\beta_M} - cx^{-(\beta_N+\beta_M)/\beta_M}. \end{aligned}$$

where $a$, $b$ and $c$ are as defined in the theorem statement. Note that $x \in [1,\infty)$ for $t \geq t_{on}$ and $g(1) = a+b-c > 0$ by assumption. Since $\lim_{x\to\infty} g(x) = a > 0$, $P(t)$ will decrease if and only if $g(x)$ has a minimum in $(1,\infty)$ at which $g$ is negative. Now,

$$\begin{aligned} g'(x) = 0 \Leftrightarrow & \frac{(\lambda_P+\beta_M)b}{\beta_M}x^{-(\lambda_P+2\beta_M)/\beta_M} = \frac{(\beta_N+\beta_M)c}{\beta_M}x^{-(\beta_N+2\beta_M)/\beta_M} \\ \Leftrightarrow & x^{(\lambda_P-\beta_N)/\beta_M} = \left(\frac{\lambda_P+\beta_M}{\beta_N+\beta_M}\right)\cdot\frac{b}{c} \end{aligned} \tag{10}$$

Thus, $g(x)$ has a (unique) extremum in $(1,\infty)$ if and only if $(\lambda_P+\beta_M)b-(\beta_N+\beta_M)c > 0$. In this case, $x_m$ as defined in the theorem statement is the point of extremum. Further,

$$g(x_m) < 0 \Leftrightarrow a + \left(b - cx_m^{(\lambda_P-\beta_N)/\beta_M}\right)x_m^{-(\lambda_P+\beta_M)/\beta_M} < 0$$

which, upon substituting for $x_m$ from (10), gives the second condition of the Theorem. □

We remark that the inequalities expressed in the above theorem do not have a direct physical interpretation; these inequalities are necessary and sufficient conditions for PSA to eventually decrease under androgen ablation. We next provide a definition of treatment failure.

**Definition 3.3. Treatment Failure:** Following [11], androgen ablation is said to have failed if serum PSA fails to attain a nadir below a critical threshold, say $P_{low}$ while therapy is on, or if serum PSA increases above $P_{low}$ while therapy is on, having already attained a minimum below $P_{low}$.

From the above definition, treatment failure times for continuous and intermittent therapy can be calculated as follows.

**Continuous Treatment Failure Time:** Suppose that continuous androgen ablation is switched on at time $t_{on}$. By the remark following (9), since $\lim_{t\to\infty} P(t) = \infty$, $\exists\, t_{min} \in [t_{on},\infty)$ at which $P(t)$ attains it global minimum. If $P(t_{min}) \geq P_{low}$, $t_{min}$ is the time of treatment failure. If $P(t_{min}) < P_{low}$, we can compute the time of treatment failure by solving the transcendental equation $P(t) = P_{low}$ where $P(t)$ is given by (9). This equation will have two roots if therapy is initially successful, and we seek the second of these, since at this time $dP/dt > 0$. Note further that continuous therapy will therefore always result in treatment failure, in finite time.

**Intermittent Treatment Failure Time:** If therapy is switched on at time $t_{on}$ and switched off at time $t_{off}$ such that $0 \leq t_{on} < t_{off} < \infty$, intermittent androgen

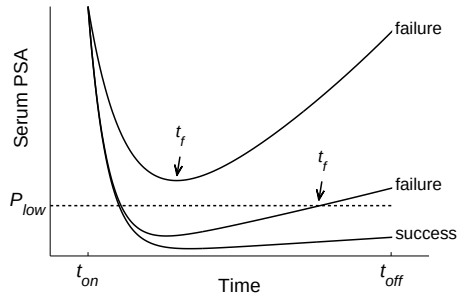


FIGURE 2. Successful versus unsuccessful application of androgen ablation. Androgen ablation is applied between time $t_{on}$ and $t_{off}$. If serum PSA is unable to attain a nadir below a critical threshold $P_{low}$ (first curve), or if it increases above $P_{low}$ while therapy is on (second curve), treatment is said to have failed, with times of failure $t_f$ indicated with arrows. Successful treatment requires PSA to reach a minimum below $P_{low}$ and subsequently remain below this threshold while therapy is on (third curve).

ablation has failed if:

$$\begin{aligned} &\text{either } P(t_{min}) \geq P_{low}, \\ &\text{or } \exists\, t_f \in (t_{min}, t_{off}) \text{ such that } P(t_f) = P_{low} \text{ and } \left.\frac{dP}{dt}\right|_{t=t_f} > 0, \end{aligned} \tag{11}$$

where $t_{min} \in [t_{on}, t_{off}]$ is the time at which $P(t)$ attains it (global) minimum. If $P(t_{min}) \geq P_{low}$, $t_{min}$ is defined as the time at which treatment fails, and if $P(t_{min}) < P_{low}$, $t_f$ is defined as the time at which treatment fails.

**Remark 1.** From definition 3.3, it naturally follows that androgen ablation is successful if PSA decreases below $P_{low}$, and stays bounded by $P_{low}$ for as long as therapy is applied. See Figure 2 for a graphical representation of the definitions of treatment failure and success.

Having established conditions under which continuous androgen ablation is a viable therapeutic option, we next compare continuous versus intermittent scheduling. We will consider two classes of castration-resistant cells: (i) Androgen-Independent Cells, whose growth rate is largely unaffected under androgen ablation, that is $\alpha_M \geq \beta_M > 0$ in equation (7), and (ii) Androgen-Repressed Cells, which have a negative growth rate in the presence of androgens, that is $\alpha_M < 0$ in equation (7). We remark that castration-resistant cells of the second type have been isolated from human tumors [30]. For each case, we will make predictions of optimal therapeutic choices. In order to be biologically realistic, we assume that in the case of intermittent therapy, the intervals of time for which therapy is on, and off are finite and bounded below by a constant, say $\tau > 0$. That is, if $\tau_{on,i}$ is the time on therapy and $\tau_{off,i}$ is the time off therapy in the $i$th cycle, then

$$\tau_{on,i} \text{ and } \tau_{off,i} > \tau > 0 \tag{12}$$

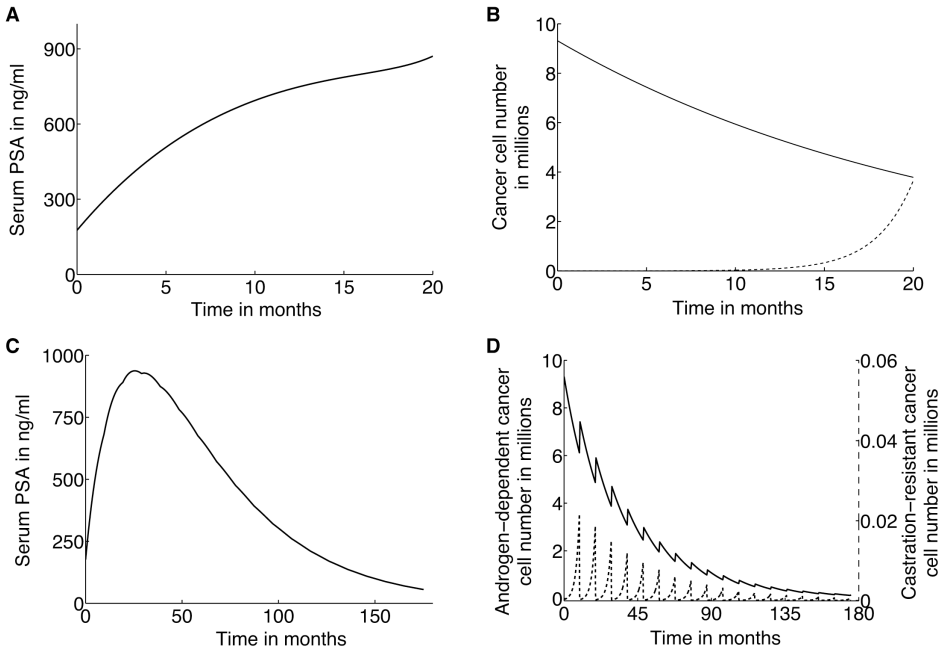


FIGURE 3. Numerical predictions of cancer response to therapy when androgen-dependent cells mutate to an androgen-repressed castration-resistant phenotype with parameter values $\alpha_N = 0.016$, $\beta_N = 0.0015$, $\gamma_M = 0.6$, $\beta_M = 0.016$, $\theta_N = \theta_M = 0.3329$, $\epsilon_M = 10^{-3}$, $\lambda_P = 0.0016$ and initial conditions $N_{on} = 9.3$, $M_{on} = 2.4 \times 10^{-4}$, $P_{on} = 176.3$ and $t_{on} = 0$. The conditions for viability of continuous therapy as derived in Theorem 3.4 are not satisfied $(a\beta_M - b\,(\lambda_P - \beta_N)\, x_m^{-(\lambda_P+\beta_M)/\beta_M} \approx 2 > 0)$, while the conditions for cure with an intermittent schedule as derived in Theorem 3.2 are satisfied $(0.0267 = \beta_M/\gamma_M < \beta_N/(\alpha_N(1-\epsilon_M)) = 0.0938)$. **A**, Predicted PSA values and **B**, androgen-dependent (solid line) and castration-resistant (dashed line) cancer cell number under continuous androgen ablation. Even under therapy, PSA continues to rise, as do castration-resistant cell numbers. **C**, Predicted PSA values and **D**, androgen-dependent (solid line) and castration-resistant (dashed line) cancer cell number under intermittent androgen ablation on a schedule where time on therapy = 9 months and time off therapy = 0.5 months. Even though there is a transient rise in PSA initially, it eventually decays to 0 in response to decresaing cell numbers.

3.1. **Androgen-independent castration-resistant cells.** We first consider the treatment of CaP in which the androgen-dependent cells mutate to a castration-resistant phenotype for whom $\alpha_M \geq \beta_M > 0$. In this case, both continuous and intermittent therapy lead to treatment failure. However, we claim that in terms of delaying the emergence of castration resistance, continuous androgen ablation is preferable to any intermittent strategy. The proof of this claim follows from the

following theorem, where we have used the following notation: let $t_{on}$ be the time at which treatment (whether given continuously or intermittently) is first applied. Let the number of androgen-dependent and castration-resistant cancer cells, and serum PSA concentration be denoted by $N_C(t)$, $M_C(t)$ and $P_C(t)$ under continuous therapy, and $N_I(t)$, $M_I(t)$ and $P_I(t)$ under intermittent therapy, respectively, at time $t \geq t_{on}$.

**Theorem 3.4.** *If, in* (7) $\alpha_M = \beta_M > 0$, *then* $P_C(t) \leq P_I(t)\ \forall\ t \geq t_{on}$.

*Proof.* Note that $N_C(t_{on}) = N_I(t_{on})$, $M_C(t_{on}) = M_I(t_{on})$ and $P_C(t_{on}) = P_I(t_{on})$. From (1), $P_j(t) = P_j(t_{on})e^{-\lambda_P(t-t_{on})} + e^{-\lambda_P t}\displaystyle\int_{t_{on}}^{t} (\theta_N N_j(s) + \theta_M M_j(s))\, e^{\lambda_P s} ds$, $j = C, I$. Comparing (8)and (9) it follows that $N_C(t) \leq N_I(t)$ and $M_C(t) \leq M_I(t)\ \forall\ t \geq t_{on}$, since during the off therapy periods in intermittent scheduling $dN_I/dt > 0$ while $dN_C/dt < 0$ and $dM_I/dt > dM_C/dt$. Therefore, $\theta_N N_C(t) + \theta_M M_C(t) \leq \theta_N N_I(t) + \theta_M M_I(t)\ \forall\ t \geq t_{on}$ and the theorem follows. □

**Remark 2.** From the above theorem it follows that if continuous androgen ablation is not a viable option as defined in 3.1, intermittent therapy will also fail.

3.2. **Androgen-repressed castration-resistant cells.** We next consider the treatment of CaP in which the androgen-dependent cells mutate to a castration-resistant phenotype for whom $0 > \alpha_M (= -\gamma_M$, say). In this case, we show that under certain conditions intermittent therapy can lead to a cure, defined as $\lim_{t\to\infty} N(t), M(t) = 0$.

**Theorem 3.5.** *If, in* (7) $\alpha_M = -\gamma_M < 0$ *and* $\beta_M > 0$ *and* (12) *is satisfied, then intermittent scheduling of androgen ablation can lead to a cure if and only if* $\beta_N\gamma_M > \alpha_N\beta_M(1-\epsilon_M)$.

*Proof.* First, assume that $\beta_N\gamma_M > \alpha_N\beta_M(1-\epsilon_M)$. Let androgen ablation be applied on an intermittent schedule where the time on therapy in the $i$th cycle, $\tau_{on,i}$ and time off therapy in the $i$th cycle, $\tau_{off,i}$ are chosen such that $\tau_{off,i} = \upsilon\tau_{on,i}$ for some constant $\upsilon$. From (12), $\tau_{on,i} \geq \tau > 0$. Further choose $\upsilon$ such that $\dfrac{\beta_M}{\gamma_M} < \upsilon < \dfrac{\beta_N}{\alpha_N(1-\epsilon_M)}$. Let $\kappa_{N,i} = \alpha_N(1-\epsilon_M)\tau_{off,i} - \beta_N\tau_{on,i}$, $\kappa_{M,i} = \beta_M\tau_{on,i} - \gamma_M\tau_{off,i}$ and let $t_i = \tau_{on,i} + \tau_{off,i}$ for $i \in \mathbb{Z}^+$, and $t_0 = t_{on}$, the time at which therapy was first started. From (8) and (9), the number of cancer cells at the end of the $n$th cycle of therapy are given by:

$$\begin{aligned} N(t_n) =& N(t_{n-1})e^{\kappa_{N,n}} \\ M(t_n) =& M(t_{n-1})e^{\kappa_{M,n}} + \rho_1 N(t_{n-1})e^{-\beta_N\tau_{on,n}}\left(e^{\alpha_N(1-\epsilon_M)\tau_{off,n}} - e^{-\gamma_M\tau_{off,n}}\right) \\ <& M(t_{n-1})e^{\kappa_{M,n}} + \rho_1 N(t_{n-1})e^{\kappa_{N,n}} \end{aligned}$$

In general,

$$\begin{aligned} N(t_n) =& N_{on}e^{\sum_{i=1}^{n}\kappa_{N,i}} \\ M(t_n) <& M_{on}e^{\sum_{i=1}^{n}\kappa_{M,i}} \\ &+ \rho_1 N_{on}\left(e^{\kappa_{N,1}+\sum_{i=2}^{n}\kappa_{M,i}} + e^{\kappa_{N,1}+\kappa_{N,2}+\sum_{i=3}^{n}\kappa_{M,i}} + \cdots + e^{\sum_{i=1}^{n}\kappa_{N,i}}\right) \end{aligned}$$

Let $(\alpha_N(1-\epsilon_M)\upsilon - \beta_N)\tau = \kappa_N$ and $(\beta_M - \gamma_M\upsilon)\tau = \kappa_M$. By choice, $\kappa_{N,i} \leq \kappa_N < 0$ and $\kappa_{M,i} \leq \kappa_M < 0$. Thus, as $n \to \infty$,

$$\begin{aligned} N(t_n) \leq & N_{on}e^{n\kappa_N} \to 0 \\ M(t_n) < & M_{on}e^{n\kappa_M} + \rho_1 N_{on}\left(e^{\kappa_N+(n-1)\kappa_M} + e^{2\kappa_N+(n-2)\kappa_N} + \cdots + e^{n\kappa_N}\right) \\ = & M_{on}e^{n\kappa_M} + \rho_1 N_{on}e^{\kappa_N}\frac{e^{n\kappa_M} - e^{n\kappa_N}}{e^{\kappa_M} - e^{\kappa_N}} \to 0 \end{aligned}$$

Again, from (8) and (9) observing that for $t \in [t_{n-1}, t_n]$, $N(t) \leq N_{n-1}e^{\alpha_N(1-\epsilon_M)\tau_{off,n}}$ and $M(t) \leq M_{n-1}e^{\beta_M\tau_{on,n}} + \rho_1 N_n$, our claim follows.

Conversely, let $\beta_N\gamma_M \leq \alpha_N\beta_M(1-\epsilon_M)$. Consider any intermittent schedule, where the time on therapy in the $i$th cycle is $\tau_{on,i}$ and time off therapy is $\tau_{off,i}$. We will show that either $N(t)$ or $M(t)$ is in fact unbounded on $[0,\infty)$, and hence a cure is not possible. Indeed suppose $N(t)$ and $M(t)$ are both bounded by some constant $\eta$. From (8) and (9), the number of androgen-dependent cancer cells at the end of the $n$th cycle of therapy is given by:

$$N(t_n) = N(t_{n-1})e^{\kappa_{N,n}} = \cdots = N_{on}e^{\sum_{i=1}^n \kappa_{N,i}},$$

where $\kappa_{N,i}$ and $\kappa_{M,i}$ are defined as in the previous case. Thus by assumption, $\forall\ n \in \mathbb{Z}^+$,

$$\begin{aligned} \sum_{i=1}^n \kappa_{N,i} \leq \ln(\eta/N_{on}) = & \bar{\eta}_N, \text{ say} \\ \Rightarrow \alpha_N(1-\epsilon_M)T_{off,n} - \beta_N T_{on,n} \leq & \bar{\eta}_N, \end{aligned} \tag{13}$$

by the definition of $\kappa_{N,i}$ and where $T_{off,n} = \sum_{i=1}^n \tau_{off,i}$, $T_{on,n} = \sum_{i=1}^n \tau_{on,i}$.

Again, from (8) and (9), the number of castration-resistant cancer cells at the end of the $n$th cycle of therapy is given by:

$$\begin{aligned} M(t_n) = & M(t_{n-1})e^{\kappa_{M,n}} + \rho_1 N(t_{n-1})e^{\kappa_{N,n}}\left(1 - e^{-\chi\tau_{off,n}}\right) \\ = & M(t_{n-2})e^{\kappa_{M,n-1}+\kappa_{M,n}} + \rho_1 N(t_{n-2})e^{\kappa_{N,n-1}+\kappa_{M,n}}\left(1 - e^{-\chi\tau_{off,n-1}}\right) \\ & + \rho_1 N(t_{n-2})e^{\kappa_{N,n-1}+\kappa_{N,n}}\left(1 - e^{-\chi\tau_{off,n}}\right) \\ & \vdots \\ = & M_{on}e^{\sum_{i=1}^n \kappa_{M,i}} + \rho_1 N_{on}\sum_{i=1}^{n-1} e^{\sum_{j=1}^i \kappa_{N,j}}e^{\sum_{j=i+1}^n \kappa_{M,j}}\left(1 - e^{-\chi\tau_{off,i}}\right) \\ & + \rho_1 N_{on}e^{\sum_{i=1}^n \kappa_{N,j}}\left(1 - e^{-\chi\tau_{off,n}}\right), \end{aligned} \tag{14}$$

where $\chi = \alpha_N(1-\epsilon_M) + \beta_N$. In particular, $\forall\ n \in \mathbb{Z}^+$, $M(t_n) > M_{on}e^{\sum_{i=1}^n \kappa_{M,i}}$. Thus by assumption, $\sum_{i=1}^n \kappa_{M,i} \leq \ln(\eta/M_{on}) = \bar{\eta}_M$, say. From the definition of $\kappa_{M,i}$ and (13), it follows that

$$\begin{aligned} \sum_{i=1}^n \kappa_{M,i} = & \beta_M T_{on,n} - \gamma_M T_{off,n} \\ \geq & \frac{(\alpha_N\beta_M(1-\epsilon_M) - \beta_N\gamma_M)}{\alpha_N(1-\epsilon_M)}T_{on,n} - \frac{\gamma_M\bar{\eta}_N}{\alpha_N(1-\epsilon_M)}. \end{aligned} \tag{15}$$

If $\beta_N\gamma_M < \alpha_N\beta_M(1-\epsilon_M)$, then from (15), $\sum_{i=1}^{n}\kappa_{M,i} \to \infty$ as $n \to \infty$, which contradicts the boundedness of $M(t)$.

If $\beta_N\gamma_M = \alpha_N\beta_M(1-\epsilon_M)$, then proceeding as in (15), $\forall\ n \in \mathbb{Z}^+$

$$\frac{-\beta_N\bar{\eta}_M}{\beta_M} < \sum_{i=1}^{n}\kappa_{N,i} \le \bar{\eta}_N \text{ and } \frac{-\gamma_M\bar{\eta}_N}{\alpha_N(1-\epsilon_M)} < \sum_{i=1}^{n}\kappa_{M,i} \le \bar{\eta}_M$$

From (12) and (14), for any $n \in \mathbb{Z}^+$,

$$M(t_n) > \rho_1 N_{on}\zeta\sum_{i=1}^{n}\left(1-e^{-\chi\tau_{off,i}}\right) > \rho_1 N_{on}\zeta\left(1-e^{-\chi\tau}\right)\sum_{i=1}^{n}1 \to \infty, \text{ as } n \to \infty,$$

where $\zeta = e^{-\beta_N\bar{\eta}_M/\beta_M}e^{-\gamma_M\bar{\eta}_N/\alpha_N(1-\epsilon_M)}$, which contradicts the boundedness of $M(t)$. □

**Remark 3.** From the proof of Theorem 3.5 it follows that when $\beta_N\gamma_M > \alpha_N\beta_M(1-\epsilon_M)$, an intermittent schedule chosen so that either $\frac{\beta_M}{\gamma_M} > \frac{\tau_{off,i}}{\tau_{on,i}}\ \forall\ i$, or $\frac{\tau_{off,i}}{\tau_{on,i}} > \frac{\beta_N}{\alpha_N(1-\epsilon_M)}\ \forall\ i$ will lead to eventual treatment failure due to unbounded cell growth.

**Remark 4.** For an androgen-repressed castration-resistant phenotype, non-viability of continuous androgen ablation does not necessarily imply intermittent treatment failure. In fact, it is possible to choose model parameters such that the viability condition in Theorem 3.2 is not satisfied, but the condition for intermittent treatment success in Theorem 3.5 is satisfied. In this case, the proof of Theorem 3.5 suggests a treatment schedule that will lead to a cure. This example is illustrated in Figure 3

In Theorem 3.5, we derived necessary and sufficient conditions for the possibility of a cure when androgen-dependent cells mutate to an androgen-repressed state. As we shall see from numerical examples in the next section, intermittent therapy can delay the onset of castration resistance as compared to continuous therapy even in the case when a cure is not possible.

TABLE 3. List of parameter values relating to cell growth and PSA dynamics.

| Parameter | Value | Units | Source |
|---|---|---|---|
| $\alpha_N$ | 0.0016 | per day | fit to data in [12] |
| $\beta_N$ | 0.0015 | per day | fit to data in [12] |
| $\theta_N$ | 1.6647 | ng/ml per million cells per day | fit to data in [12] |
| $\theta_M$ | 1.6647 | ng/ml per million cells per day | see text |
| $\lambda_P$ | 6.6542 | per day | [4] |
| $N_{on}$ | 100 | millions of cells | see text |
| $M_{on}$ | $10^{-5}$ | millions of cells | see text |
| $\epsilon_M$ | $10^{-5}$ | dimensionless | [22] |
| $P_{low}$ | 4 | ng/ml | [11, 12] |

4. **Numerical simulations.** In this section, we simulate numerically the various possible treatment outcomes in response to continuous versus intermittent androgen ablation, for the different types of castration-resistant cells discussed earlier. We begin with a brief description of parameter estimation.

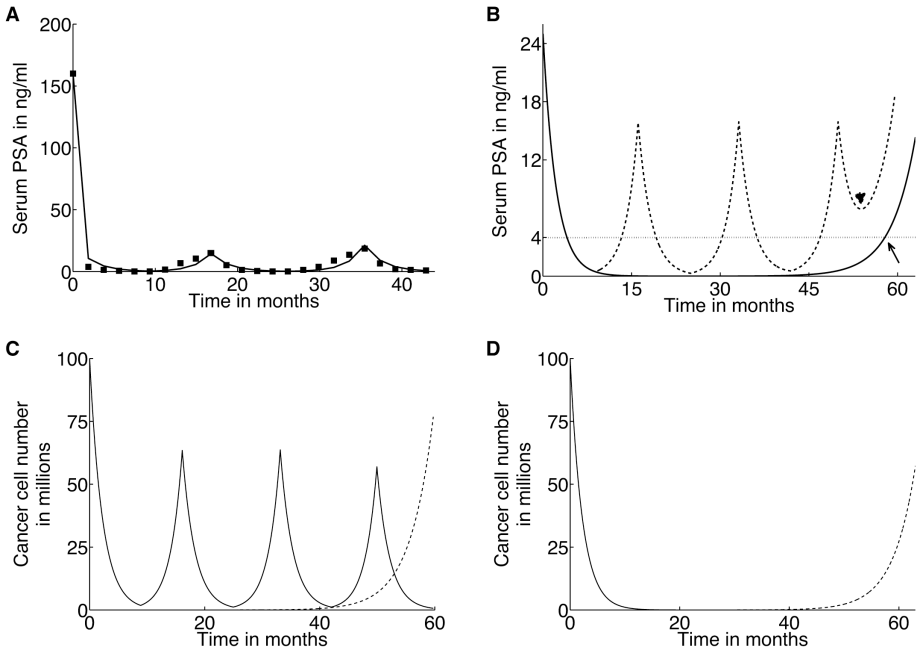


FIGURE 4. **A**, Fit to averaged patient PSA values as reported in [12] (see Table 4 for experimental data), in response to intermittent therapy based on the schedule that therapy is reinstituted with a PSA of 15 ng/ml, and remains on for 9 months, in order to estimate $N$ cell growth rates $\alpha_N$ and $\beta_N$, and PSA production rate $\theta_N$. **B,C,D**, Numerical predictions of cancer response to therapy when androgen-dependent cells mutate to an androgen-independent castration-resistant phenotype. **B**, Predicted PSA values under intermittent (dashed line) versus continuous (solid line) androgen ablation. Times to treatment failure are indicated by an arrow (continuous therapy) and arrowhead (intermittent therapy). Predicted androgen-dependent (solid line) and androgen-independent (dashed line) cancer cell numbers under: **C**, intermittent therapy; and **D**, continuous therapy.

4.1. **Model parametrization.** Parameters relating to androgen-dependent cancer cell growth and PSA dynamics are estimated form the literature, and by fitting PSA time-courses generated by our model to available clinical data. The values of these parameters and their sources are given in Table 3. $N$ cell proliferation rate $\alpha_N$ and death rate $\beta_N$, and PSA production rate $\theta_N$ are estimated from data in [12] as follows. In 1995, Goldenberg et al. [12] published one of the first studies of intermittent androgen ablation in the treatment of CaP. Two cycles of androgen

TABLE 4. Averaged patient time-course PSA data taken from [12] used to estimate parameters reported in Table 3. Best fits are shown in Figure 4A.

| Time in weeks from enrollment in study | Serum PSA concentration in ng/ml | Androgen ablation (on/off) |
|---|---|---|
| 0 | 160 | on (therapy initiation) |
| 8 | 3.9 | on |
| 16 | 1.4 | on |
| 24 | 0.7 | on |
| 32 | 0.2 | on |
| 40 | 0.2 | on $\rightarrow$ off |
| 48 | 1.6 | off |
| 56 | 6.8 | off |
| 64 | 10.5 | off |
| 72 | 15 | off $\rightarrow$ on |
| 80 | 5.2 | on |
| 88 | 1.4 | on |
| 96 | 0.5 | on |
| 104 | 0.2 | on |
| 112 | 0.2 | on $\rightarrow$ off |
| 120 | 1.4 | off |
| 128 | 3.9 | off |
| 136 | 8.9 | off |
| 144 | 13.6 | off |
| 152 | 18.6 | off $\rightarrow$ on |
| 160 | 6.6 | on |
| 168 | 2.0 | on |
| 176 | 1.4 | on |
| 184 | 0.9 | on |

ablation were performed, with time on treatment in each cycle fixed at 9 months, and androgen ablation reinstituted with a PSA greater than 15 ng/ml in the off treatment period. Time course PSA data, averaged across an initial cohort of 47 patients, was reported on an 8-week cycle (Figure 4A, black squares, and Table 4). The equations governing $N$ and $P$ dynamics given by (7) are solved and predicted PSA profiles are fit to the data in [12], using Matlab's in-built nonlinear curve fitting tool 'lsqcurvefit'. The intermittent schedule is simulated by implementing (5), with $P_{crit} = 15$ ng/ml and time on therapy $\tau_{on} = 9$ months. An initial tumor burden of 100 million cells is assumed corresponding to the smallest size of significant CaP detectable by T2-weighted MRI imaging [14], taking the average volume of a tumor cell to be $0.126 \times 10^{-6} \mu$l [29]. The best fit is shown in Figure 4A. In performing these fits, the number of castration-resistant cells is taken to be zero since we shall vary $M$ cell growth rates $\alpha_M$ and $\beta_M$ in the simulations that follow to generate the various castration-resistant phenotypes discussed in the previous section.

For simplicity, we assume that $N$ and $M$ cell PSA production rates are equal so that $\theta_N = \theta_M$ and the number $M_{on}$ of $M$ cells at the time of therapy initiation is

fixed at 10 cells. Unless otherwise indicated, the parameter values estimated here will remain unchanged in all numerical simulations that follow.

4.2. **Mutation to androgen-independent phenotype.** Consider first the case when $N$ cells mutate to $M$ cells whose growth rates $\alpha_M$ and $\beta_M$ in androgen-rich and androgen-deprived conditions respectively are such that $\alpha_M \geq \beta_M > 0$. For the purposes of illustration, we take $\beta_M = \alpha_M = \alpha_N/2$, since hormonally failing tumor cells are observed to have a lower net proliferation rate than cancer cells taken from treatment naive patients [3]. In this case, Theorem 3.4 predicts intermittent therapy to result in a quicker onset of castration-resistance as compared to continuous therapy. As can be seen from Figure 4B which shows simulated PSA time courses for the two schedules, continuous treatment is predicted to fail at 58 months post therapy initiation as compared with a failure time of 54 months for intermittent treatment based on the schedule in [12]. Figures 4C and 4D show time-course plots of cancer cell number for continuous and intermittent therapy, respectively. An approximate period of 24 months of disease-free survival is predicted in the continuous therapy case, with the number of castration resistant cells at the time of treatment failure = 16 million, and a negligible number of androgen-dependent cells ($<$ 1 cell). In contrast, the corresponding cell numbers are 18.6 million and 4 million respectively in the case of intermittent therapy at the time of treatment failure - a 40% higher tumor burden than in the continuous case.

4.3. **Mutation to androgen-repressed phenotype.** Consider next the mutation of $N$ cells to $M$ cells whose growth rates $(-\gamma_M)$ and $\beta_M$ in androgen-rich and androgen-deprived conditions respectively are such that $\beta_N\gamma_M \leq \alpha_N\beta_M(1-\epsilon_M)$. In this case, Theorem 3.5 predicts treatment failure for any intermittent schedule. For the purposes of illustration we take $\beta_M = \alpha_N$ and $\gamma_M = \beta_N$. PSA time-courses of intermittent androgen-ablation based on the schedule in [12], and continuous therapy are plotted in Figure 5A. Numerical simulations predict that continuous treatment fails 29 months post therapy initiation with the number of castration-resistant and androgen dependent cells at the time of failure = 16 million and 206, respectively (Figure 5C). In contrast, intermittent therapy fails 91.5 months post therapy initiation with the number of castration-resistant and androgen dependent cells at the time of failure = 13.8 million and 2.2 million, respectively (Figure 5B). Thus, even though both therapeutic approaches eventually fail, intermittent therapy has delayed the emergence of castration-resistance by 6 years.

Finally, consider the mutation of $N$ cells to $M$ cells whose growth rates are such that $\beta_N\gamma_M > \alpha_N\beta_M(1-\epsilon_M)$. In this case, Theorem 3.5 predicts that a cure is possible. For the purposes of illustration we take $\beta_M = \alpha_N$ and choose $\gamma_M = \beta_N = 0.0018$ per day. Consider an intermittent schedule as suggested in the proof of Theorem 3.5, where the time on therapy $(\tau_{on,i})$ in each cycle is fixed at = 9 months, and time off therapy $(\tau_{off,i})$ in each cycle is fixed at = 8.5 months. Then, $0.09080 = \dfrac{\beta_M}{\gamma_M} < \dfrac{\tau_{off,i}}{\tau_{on,i}} = 0.9474 < \dfrac{\beta_N}{\alpha_N(1-\epsilon_M)} = 1.1013$. As can be seen from Figure 6B, numerical simulations predict that serum PSA decreases to undetectable levels within 10 years of therapy initiation, and remains at these levels for as long as therapy is continued. However, if intermittent androgen-ablation is based on PSA thresholds as in [12], an infinite cycling of PSA values is predicted (Figure 6A, dashed line). The corresponding cancer cell numbers (not shown) also remain bounded throughout the course of therapy.

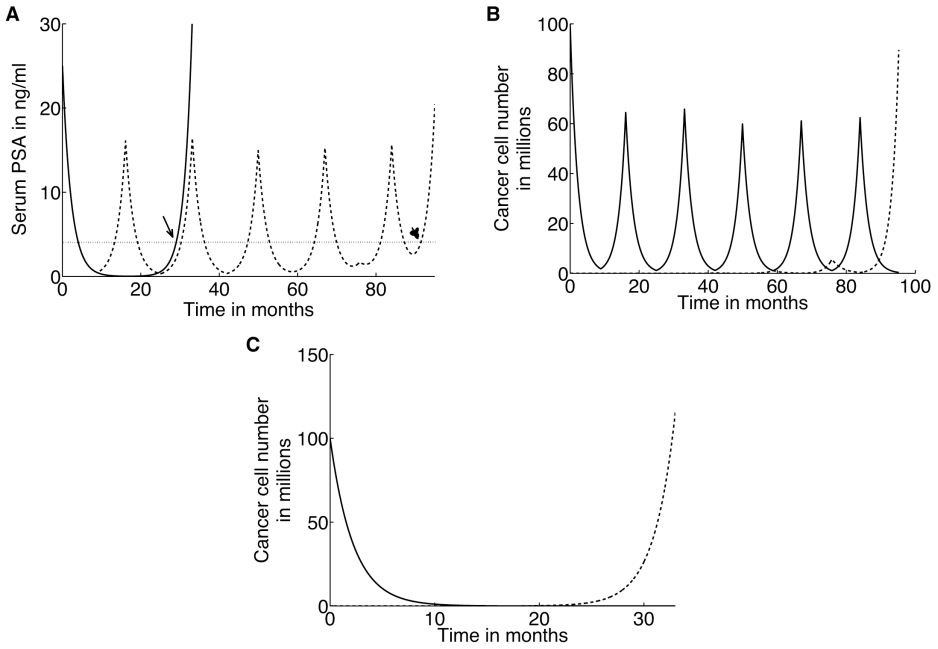


FIGURE 5. Numerical predictions of cancer response to therapy when androgen-dependent cells mutate to an androgen-repressed castration-resistant phenotype with $\beta_N\gamma_M \leq \alpha_N\beta_M(1-\epsilon_M)$. **A**, Predicted PSA values under intermittent (dashed line) versus continuous (solid line) androgen ablation. Times to treatment failure are indicated by an arrow (continuous therapy) and arrowhead (intermittent therapy). Intermittent therapy is based on the schedule that therapy is reinstituted with a PSA of 15 ng/ml, and remains on for 9 months. Predicted androgen-dependent (solid line) and androgen-independent (dashed line) cancer cell numbers under: **B**, intermittent therapy; and **C**, continuous therapy.

Most significantly, it is possible to choose an intermittent schedule that appears to result in initial treatment success, but leads to treatment failure eventually. For instance, if $\tau_{on,i}$ in each cycle = 9 months, and $\tau_{off,i}$ in each cycle = 6.5 months, serum PSA rapidly decreases to undetectable levels within 4 years of therapy initiation, as can be seen from Figure 6C. However, persisting with this schedule is predicted to result in treatment failure as soon as 10 years later, due to the emergence of castration-resistant cells. Now, $\dfrac{\tau_{off,i}}{\tau_{on,i}} = 0.7368 < \dfrac{\beta_M}{\gamma_M}$, for all $i$, and from remark following Theorem 3.5, failure is inevitable. We remark that continuous androgen ablation is predicted to fail 29 months post therapy initiation (Figure 6A, solid line), with the number of castration-resistant and androgen dependent cells at the time of failure = 16 million and 15, respectively. Cell profiles are similar to those for the earlier cases, and have consequently not been shown.

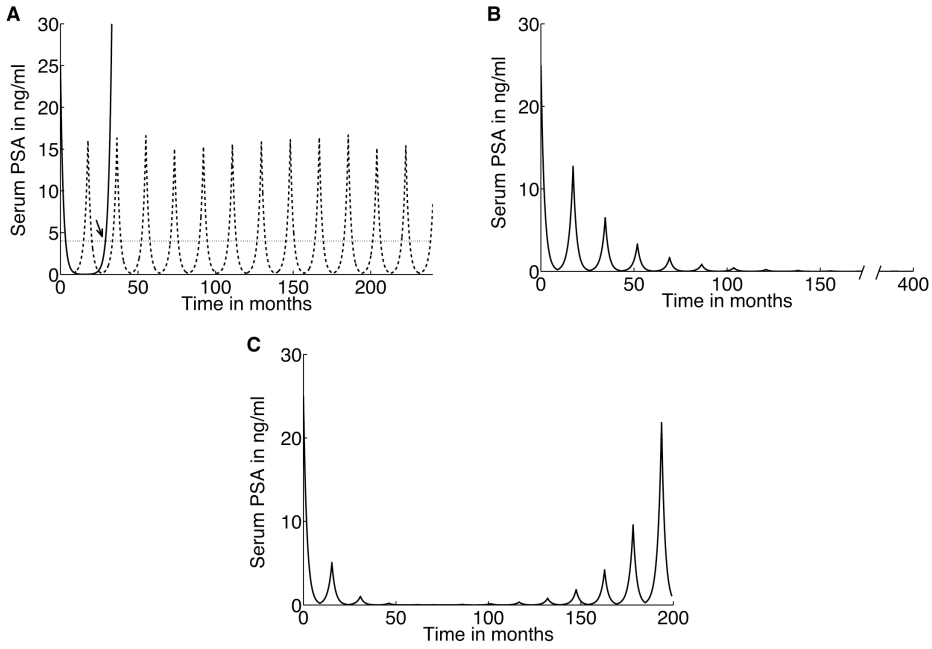


FIGURE 6. Numerical predictions of cancer response to therapy when androgen-dependent cells mutate to an androgen-repressed castration-resistant phenotype with $\beta_N\gamma_M > \alpha_N\beta_M(1-\epsilon_M)$. **A**, Predicted PSA values under intermittent (dashed line) versus continuous (solid line) androgen ablation. Time to treatment failure is indicated by an arrow (continuous therapy). Intermittent therapy based on the schedule that therapy is reinstituted with a PSA of 15 ng/ml, and remains on for 9 months results in infinite cycling of serum PSA. **B**, Intermittent therapy based on the schedule suggested in the proof of Theorem 3.5 so that $\dfrac{\beta_M}{\gamma_M} < \dfrac{\text{Time Off Therapy}}{\text{Time On Therapy}} < \dfrac{\beta_N}{\alpha_N(1-\epsilon_M)}$ leads to a cure. Here, time on therapy is 9 months and off is 8.5 months. **C**, An intermittent schedule during which time on therapy is 9 months and off is 6.5 months appears to lead to a cure initially. However, if this schedule is persisted with, it eventually results in the emergence of castration resistance.

5. **Discussion.** Androgen ablation remains the mainstay of advanced CaP treatment. However, treatment failure is nearly universal due to the selective pressures created by androgen-limiting conditions that give rise to castration-resistant cells. Consequently, it has been hypothesized that intermittent androgen ablation may delay the onset of castration resistance, as compared to continuous therapy. In order to assess conditions under which one or the other therapeutic strategy yields a longer remission period, we developed and analyzed a model of prostate cancer progression based on detailed intracellular androgen-mediated signaling in this paper.

Our model is formulated by a system of differential equations describing the temporal dynamics CaP cells, serum PSA, and intracellular androgens and their receptors. Using singular perturbation analysis, the full model comprising of eight equations was reduced to just three governing the dynamics of androgen-dependent and castration-resistant cells and serum PSA. By simply varying CaP cell growth rates in androgen-rich and androgen-depleted environments, we could simulate the emergence of a variety of castration-resistant phenotypes

We began our model analysis by deriving necessary and sufficient conditions for continuous androgen ablation to be a viable therapeutic option, evidenced by a decrease in serum PSA levels. We then investigated the emergence of castration-resistance under different therapy schedules. Conditions under which intermittent therapy is favorable as compared to continuous therapy in terms of delaying the onset of castration-resistance or even effecting a cure were derived. These results were illustrated with a number of numerical examples that simulated a variety of patient responses to different therapeutic schedules.

In particular, while considering the emergence of androgen-repressed castration-resistant cells, two interesting cases were observed:

1. The non-viability of continuous androgen ablation does not necessarily imply failure of intermittent therapy. As the numerical example shown in Figure 3 demonstrates, even though continuous therapy fails at the start of treatment, an optimally chosen intermittent schedule (as suggested by our analytical results) can eventually result in a cure.
2. It is possible to choose an intermittent schedule that appears to lead to a cure but fails eventually, even when a different schedule would have lead to a cure or controlled tumor growth (see Figure 6).

The above examples illustrate the potential of mathematical modeling such as that presented here to make significant contributions in a clinical setting. However, our predictions are crucially dependent on the observation of additional biomarkers such as cancer cell proliferation and death rates in androgen-rich and androgen-depleted environments. By incorporating these measurements with PSA tests results, our simplified model can be used to suggest optimal treatment protocols that are personalized for each patient. Such strategies however, will need to be examined using the full system of model equations.

**Acknowledgments.** The authors thank Prof Steven Clinton and Dr Arvinder Bhinder for many helpful discussions. This research has been supported in part by the Mathematical Biosciences Institute and the NSF (grant DMS 0931642).

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Received March 2012; revised April 2012.

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