

Models of Hormone Treatment for Prostate Cancer: Can Mathematical Models Predict the outcomes?

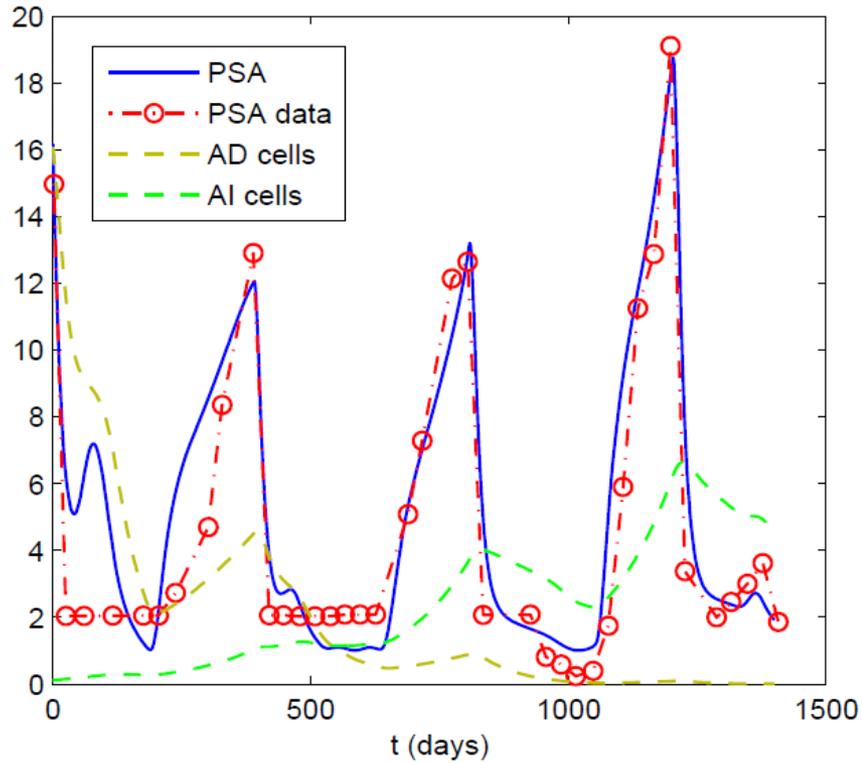


YANG KUANG
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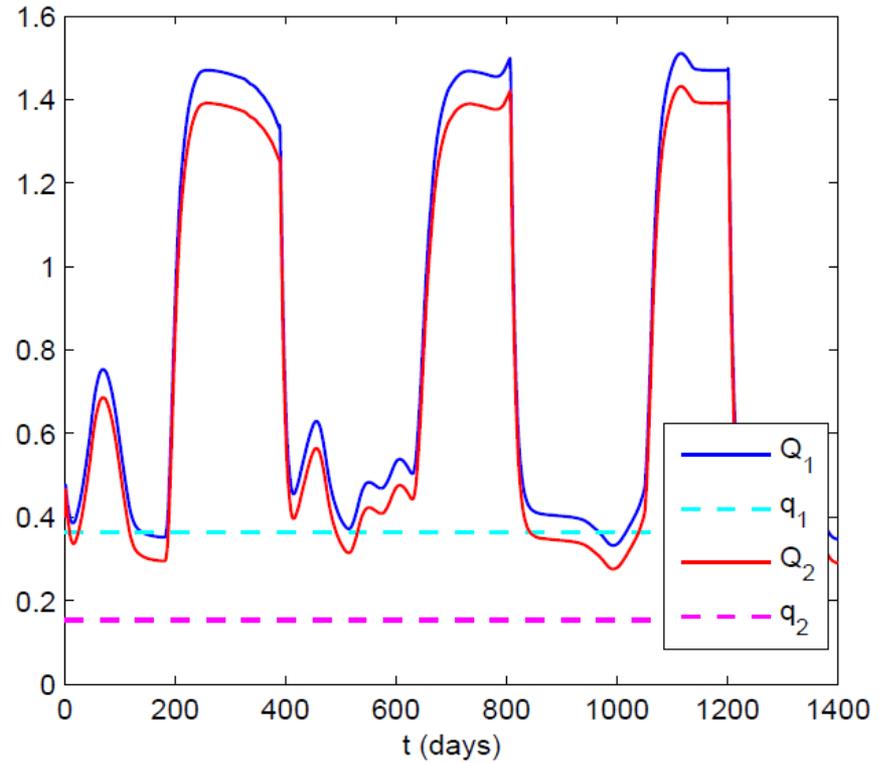
Based on results obtained jointly with
Travis Portz, John Nagy, and Javier Baez

Main reference: Travis Portz, Yang Kuang and John D. Nagy, 2012. A clinical data validated mathematical model of prostate cancer growth under intermittent androgen suppression therapy. AIP Advances 2, 011002; doi: 10.1063/1.3697848. OPEN ACCESS.

Model validation

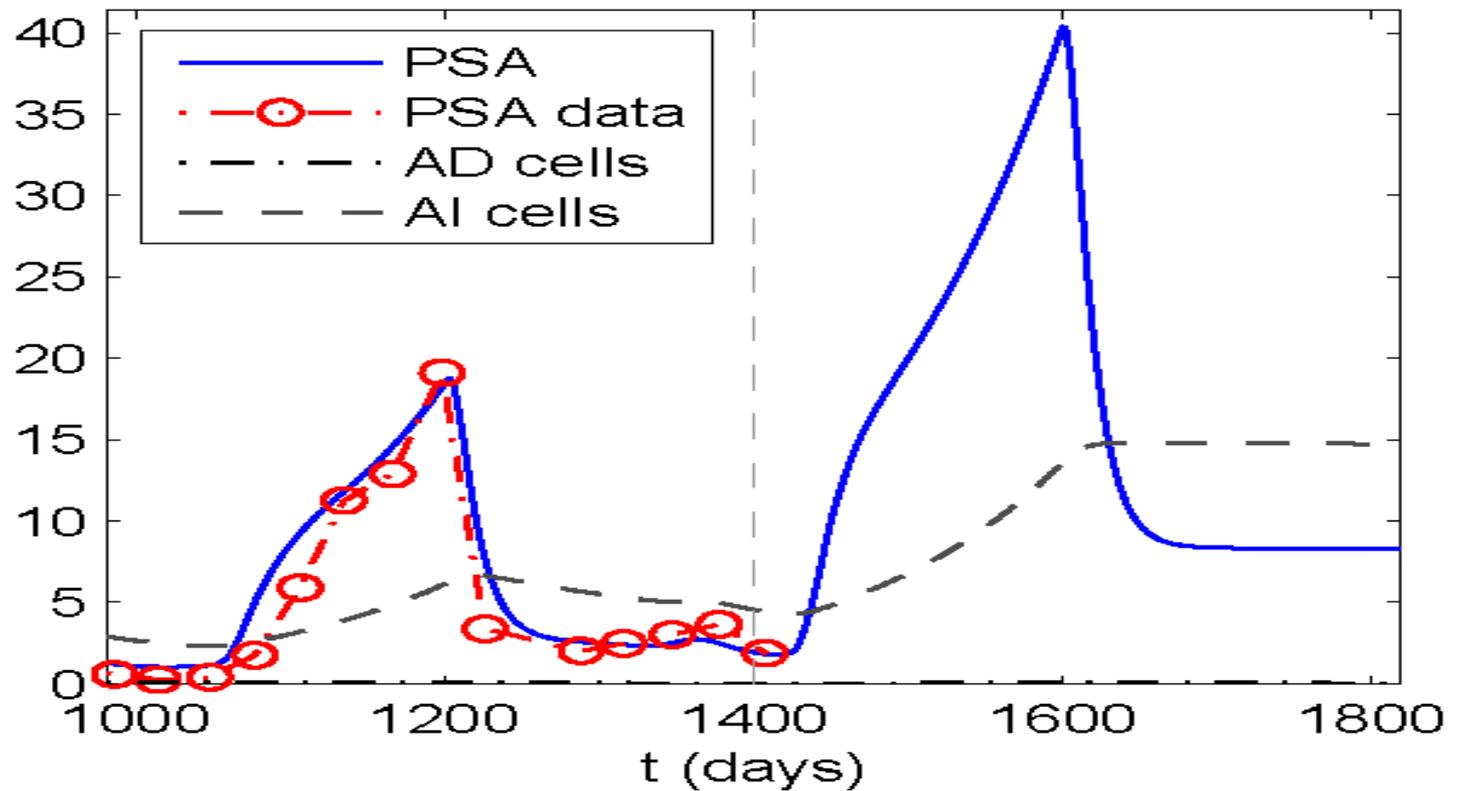


Case 1



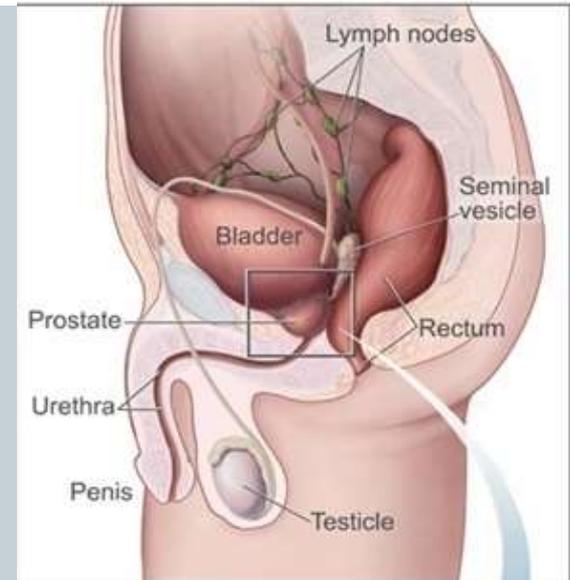
Cell quotas

Model Prediction

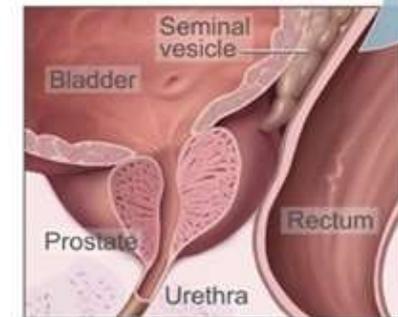


Prostate

- Store and secrete seminal fluids.



This shows the prostate and nearby organs.



This shows the inside of the prostate, urethra, rectum, and bladder.

(From Wikipedia)

Prostate Cancer



- Most common non-skin cancer in American men
- Slow-growing
 - Generally only affects older men
 - Limits the efficacy of chemotherapy
- Screening
 - Elevated prostate-specific antigen (PSA) levels
 - Controversy:
 - ✦ False positives and negatives
 - ✦ Early detection reduces mortality rates

Treatments



- **Localized cancer:**
 - Surgical removal of prostate
 - Radiation therapy
- **Advanced (metastatic) cancer:**
 - Endocrine therapy, known as hormone therapy or androgen ablation therapy, is the main treatment for advanced prostate cancer.
 - Chemotherapy?
 - Different method needed

Androgen Deprivation Therapy



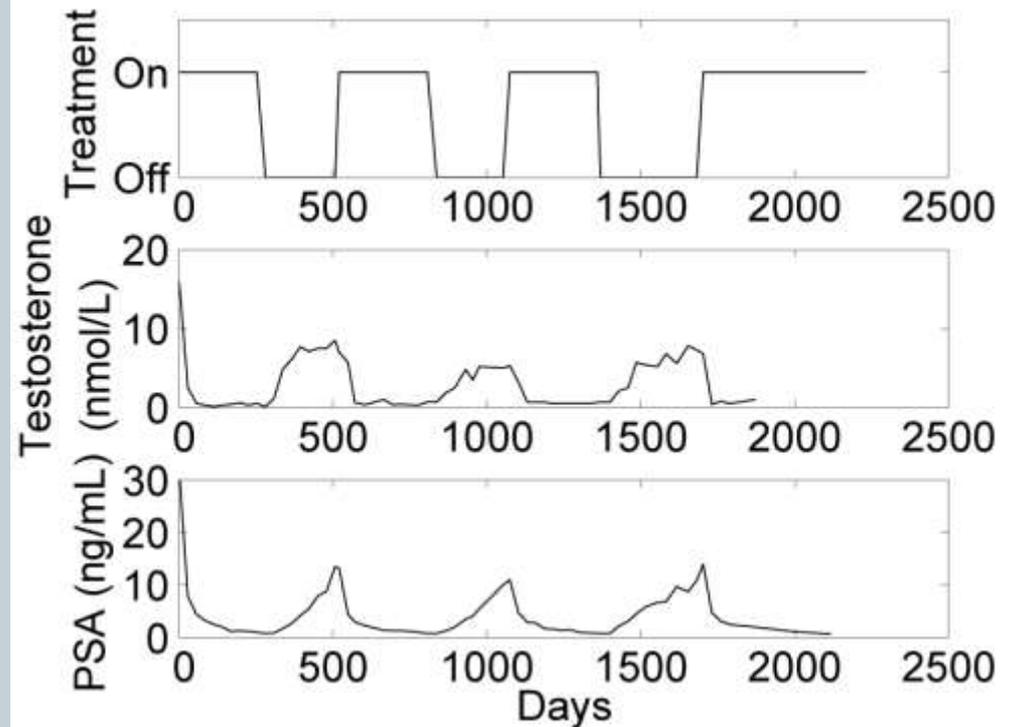
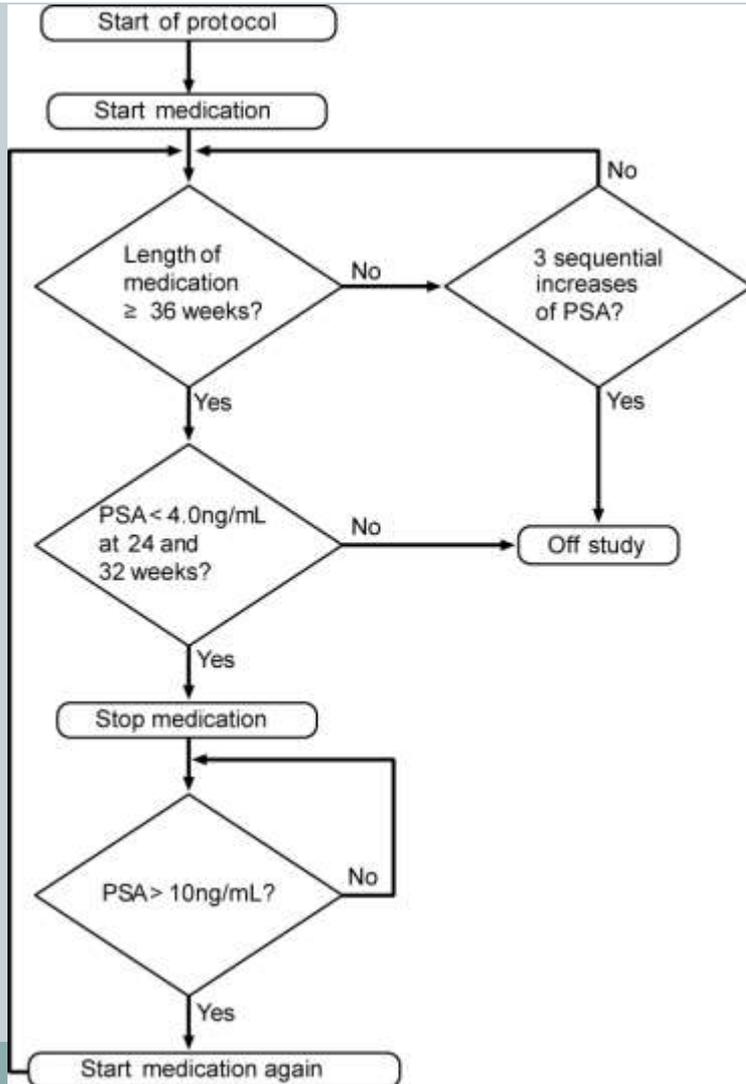
- **Eliminate androgen → Eliminate prostate cells**
 - Surgical castration
 - More commonly: androgen deprivation drugs
 - ✦ Luteinizing hormone-releasing hormone (LHRH) agonists/analogs inhibit production
 - ✦ Antiandrogens prevent stimulation of AR
- **Adverse effects**
 - Short term
 - ✦ Sexual dysfunction, hot flashes, fatigue
 - Long term
 - ✦ Osteoporosis, muscle loss, anemia, etc.
 - Androgen “independent” relapse

Intermittent Therapy



- Stop treatment before AI relapse
- Restart treatment after rise in PSA level
- Improved QoL during off-treatment periods
- Possibly delay progression of AI cancer

Example of intermittent therapy



Bruchovsky et al (2006; 2007)

Intermittent androgen suppression (IAS) vs continuous androgen suppression (CAS)



A phase III randomized trial comparing intermittent versus continuous androgen suppression for patients with PSA progression after radical therapy: NCIC CTG PR.7/SWOG JPR.7/CTSU JPR.7/UK Intercontinental Trial CRUKE/01/013.

L. Klotz, C. J. O'Callaghan, K. Ding, D. P. Dearnaley, C. S. Higano, E. M. Horwitz, S. Malone, S. L. Goldenberg, M. K. Gospodarowicz, J. M. Crook,
J Clin Oncol 29: 2011 (suppl 7; abstr 3)

Results: 1,386 patients were randomized to IAS (690) or CAS (696) arms. Median follow up was 6.9 years. IAS patients completed a median of 2 x 8 month cycles (range: 1-9). 524 deaths were observed (268 on IAS vs 256 on CAS). Median OS was 8.8 vs 9.1 years on IAS and CAS arms, respectively. The IAS arm had more disease related (122 vs 97) and fewer unrelated (134 vs 146) deaths. **Conclusions:** In men with PSA recurrence after RRT, IAS is non-inferior to CAS with respect to OS.

RESEARCH

Open Access

The evolutionary impact of androgen levels on prostate cancer in a multi-scale mathematical model

Steffen E Eikenberry^{1,2}, John D Nagy³ and Yang Kuang*¹

Abstract

Background: Androgens bind to the androgen receptor (AR) in prostate cells and are essential survival factors for healthy prostate epithelium. Most untreated prostate cancers retain some dependence upon the AR and respond, at least transiently, to androgen ablation therapy. However, the relationship between endogenous androgen levels and cancer etiology is unclear. High levels of androgens have traditionally been viewed as driving abnormal proliferation leading to cancer, but it has also been suggested that low levels of androgen could induce selective pressure for abnormal cells. We formulate a mathematical model of androgen regulated prostate growth to study the effects of abnormal androgen levels on selection for pre-malignant phenotypes in early prostate cancer development.

Results: We find that cell turnover rate increases with decreasing androgen levels, which may increase the rate of mutation and malignant evolution. We model the evolution of a heterogeneous prostate cell population using a continuous state-transition model. Using this model we study selection for AR expression under different androgen levels and find that low androgen environments, caused either by low serum testosterone or by reduced 5 α -reductase activity, select more strongly for elevated AR expression than do normal environments. High androgen actually slightly reduces selective pressure for AR upregulation. Moreover, our results suggest that an aberrant androgen environment

Effects of Intermittent Androgen Suppression on Androgen-Dependent Tumors

Apoptosis and Serum Prostate-Specific Antigen

Koichiro Akakura, M.D.,*† Nicholas Bruchovsky, M.D.,*

S. Larry Goldenberg, M.D.,*‡ Paul S. Rennie, Ph.D.,* Anne R. Buckley, M.D.,¶ and Lorne D. Sullivan, M.D.‡

Background. Since postcastration progression of tumors to an androgen-independent state appears to be linked to the cessation of androgen-induced differentiation of tumorigenic stem cells, the authors hypothesized that the replacement of androgens at the end of a period of apoptotic regression might result in the regeneration of differentiated tumor cells with further apoptotic potential.

Methods and Results. To determine the effect of intermittent exposure of androgens on the androgen-dependent Shionogi carcinoma, the tumor was transplanted into a succession of male mice, each of which was castrated when the estimated tumor weight became about 3 g. After the tumor had regressed to 30% of the original weight, it was transplanted into the next noncastrated male. This cycle of transplantation and castration-induced apoptosis was repeated successfully four times before growth became androgen-independent during the fifth cycle. In four of Stage C and three of Stage D patients with prostate cancer, androgen withdrawal was initiated with cyproterone acetate (100 mg/d) and diethylstilbestrol (0.1 mg/d) and then maintained with cyproterone acetate in combination with the luteinizing hormone-releas-

ing hormone agonist, goserelin acetate (3.6 mg/month). After 6 or more months of suppression of serum prostate-specific antigen (PSA) into the normal range, treatment was interrupted for 2 to 11 months. After recovery of testicular function, androgen-withdrawal therapy was resumed when serum PSA increased to a level of about 20 $\mu\text{g/l}$. This cycle was repeated sequentially to a total of two to four times over treatment periods of 21 to 47 months with no loss of androgen dependence.

Conclusions. These results demonstrate that intermittent androgen suppression can be used to induce multiple apoptotic regressions of a tumor; they also suggest that the cyclic effects of such treatment on prostate cancer can be followed by the sequential measurement of serum PSA levels. *Cancer* 1993; 71:2782-90.

Key words: intermittent androgen suppression, prostate, Shionogi carcinoma, apoptosis, prostate-specific antigen.

Apoptotic regression of an androgen-dependent tumor can be induced by any procedure which reduces the intracellular concentration of dihydrotestosterone by 80% or more.^{1,2} The benefit of such therapy usually is temporary, despite a high initial response rate, owing to the fact that surviving tumor cells generally progress to an androgen-independent condition.³⁻⁵ In studying progression of the androgen-dependent Shionogi carcinoma, we found previously that androgen withdrawal alters the ratio of stem cells in the tumor cell population, as shown in Figure 1.⁶ During the initial apoptotic phase, the changes include the elimination of differentiated cells and a decrease in the proportion of tumorigenic stem cells. With progression and recurrence, a marked 20-fold increase in the proportion of total stem cells (Fig. 1) and a massive 500-fold increase in the proportion of androgen-independent stem cells⁶ are ob-

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† Recipient of a Berlex Canada Fellowship in Urologic Oncology.

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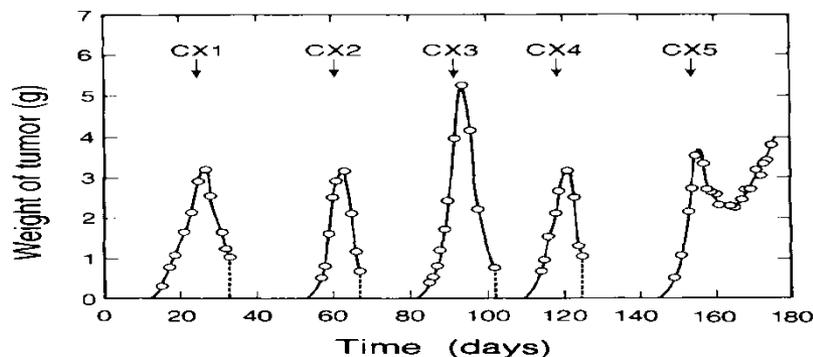


Figure 3. Effects of intermittent androgen withdrawal on Shionogi carcinoma. About 5×10^6 cells of the Shionogi carcinoma were injected into a male DDS strain mouse. When the tumor reached a weight of 3 g, the host animal was castrated (CX1-5). After the tumor had regressed to a weight of 1 g, it was implanted into a noncastrated male mouse. This cycle of transplantation and castration was repeated five times.

of the parent Shionogi carcinoma to androgens, the tumor was transplanted into a succession of male animals, each of which was castrated when the estimated tumor weight became about 3 g. The results of this experiment are shown in Figure 3.

After the initial implant, the parent Shionogi carcinoma became palpable after an interval of about 15 days and reached a weight of 3 g after another 10 days. After castration of the host animal (CX1), the tumor continued to grow for 1 to 2 days before the onset of apoptosis was evident. About 6 days after castration, the tumor regressed to 30% of its precastration weight. After transplant of this tumor into a second male host, the latent interval before development of the next tumor was slightly longer at 23 days. Castration (CX2) was again followed by involution of the tumor. Transplant of the regressed cells into a third male host resulted in the development of a palpable tumor after 18 days. A third castration (CX3) resulted in yet another regression of tumor cells. Transplant of the surviving tumor cells into a fourth host was followed by a short latent period of only 11 days before a tumor mass was palpable. The doubling time of 24 to 48 hours essentially was the same as that observed during previous growth periods. Regression of tumor was induced by castration (CX4), and after a latent period of 24 days, the transplanted regressed cells gave rise to a new tumor mass. Castration (CX5) brought about a partial

40% regression of the tumor after which autonomous growth abruptly supervened.

These results demonstrate that apoptotic potential can be reintended in a tumor cell population at least five times by replacement and withdrawal of endogenous testosterone. A similar pattern of consecutive responses has been reproduced in 16 different tumors with a mean time to androgen independence of 150 days. In keeping with the hypothesis outlined in Figure 1, these experimental results imply that progression of the Shionogi carcinoma is averted when androgens are replaced early, i.e., 6 days after castration (Fig. 3) rather than after a lengthy delay of 50 days (Fig. 2).

Case Reports

Case 1

The patient was a 57-year-old man with local progression of previously irradiated, Stage C, moderately differentiated adenocarcinoma. During the observation period described in Figure 4, he underwent four courses of androgen-withdrawal therapy. Serum PSA was suppressed with each treatment (A) in synchrony with the suppression of serum testosterone. In contrast, the rise in PSA after interruption of treatment (B) lagged behind the recovery of testosterone affording no-treatment periods of 7, 7, and 6 months, respectively. The volumes of the prostate before and at the end of the fourth treatment estimated by ultrasonography were 25 ml and 11 ml, respectively. Such regression of prostate associated with a decline in

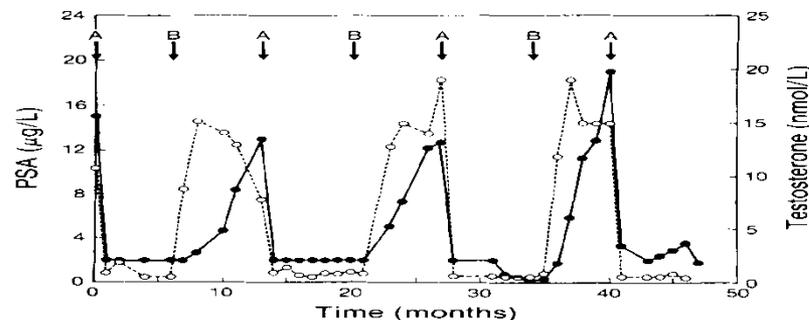


Figure 4. Effects of intermittent androgen withdrawal: Case 1. A 57-year-old man with local progression of previously irradiated, Stage C, moderately differentiated adenocarcinoma. Androgen withdrawal started at time A and interrupted at time B, yielding treatment intervals of 6, 7, 7, and 7 months and no-treatment intervals of 7, 7, and 6 months, respectively. ○: serum testosterone; ●: serum PSA.

Necessity of mathematical models



- Currently the timing of switching between on- and off-treatments is decided on doctors' experience and intuition. If we use a mathematical model, we may be able to optimize the switching on on- and off-treatments.
- For some patients, intermittent hormone therapy is effective, but may not be for the others. Can we distinguish these patients from observations of PSA?

Existing Mathematical Models



- **Swanson et al (2001) PSA model**
 - Continuous production rate
 - PSA concentration tracks tumor volume after initial delay
- **Jackson model (2004, DCDS-B and Neoplasia)**
 - PDE model
 - Continuous therapy
 - Predicts successful treatment for limited range of parameters
- **Ideta model (2008, Nonlinear Science)**
 - ODE version of Jackson model
 - Intermittent therapy
 - Predicts successful treatment only when androgen has a negative effect on AI population

Existing Models (continued)



- **Eikenberry AR model**
 - Role of androgen levels and AR in evolution of prostate cancer
 - Low androgen levels during development of cancer results in more aggressive tumor
 - **S.E. Eikenberry, J.D. Nagy, and Y. Kuang.** The evolutionary impact of androgen levels on prostate cancer in a multi-scale mathematical model. 2010. *Biology Direct* 2010, 5:24 doi:10.1186/1745-6150-5-24.
- **Jain, Friedman and others 2012 DCDSB, 2013, MBE)**
 - PNAS 2011: Jaina, Clinton, Bhinder, and Friedmana, multi-scale models for both continuous and intermittent treatments. Clinical implications.
 - DCDSB, 2012: multi-scale models for both continuous and intermittent treatments. New mathematical concepts and results.
 - **MBE 2013: PDE model.**

Model 1



- Based on Jackson and Ideta models
 - No negative effect of androgen on AI cells
- Androgen dependent (AD) population: $X_1(t)$
- Androgen independent (AI) population: $X_2(t)$
- Serum androgen concentration: $A(t)$
- Serum PSA concentration: $P(t)$
- **Assumptions:**
 - AI population has constant net growth rate
 - Constant PSA production rate

Model 1: AD Population



$$\frac{dX_1}{dt} = \alpha_1 p(A) X_1 - \beta_1 q(A) X_1 - m(A) X_1$$

$$p(A) = \frac{A}{A + k_1}$$

Proliferation

$$q(A) = k_2 + (1 - k_2) \frac{A}{A + k_3}$$

Death, $k_2 > 1$

$$m(A) = m_1 \left(1 - \frac{A}{a_0} \right)$$

Mutation

Model 1: AI Population, Androgen, PSA



$$\frac{dX_2}{dt} = \alpha_2 X_2 - \beta_2 X_2 + m(A) X_1$$

AI population

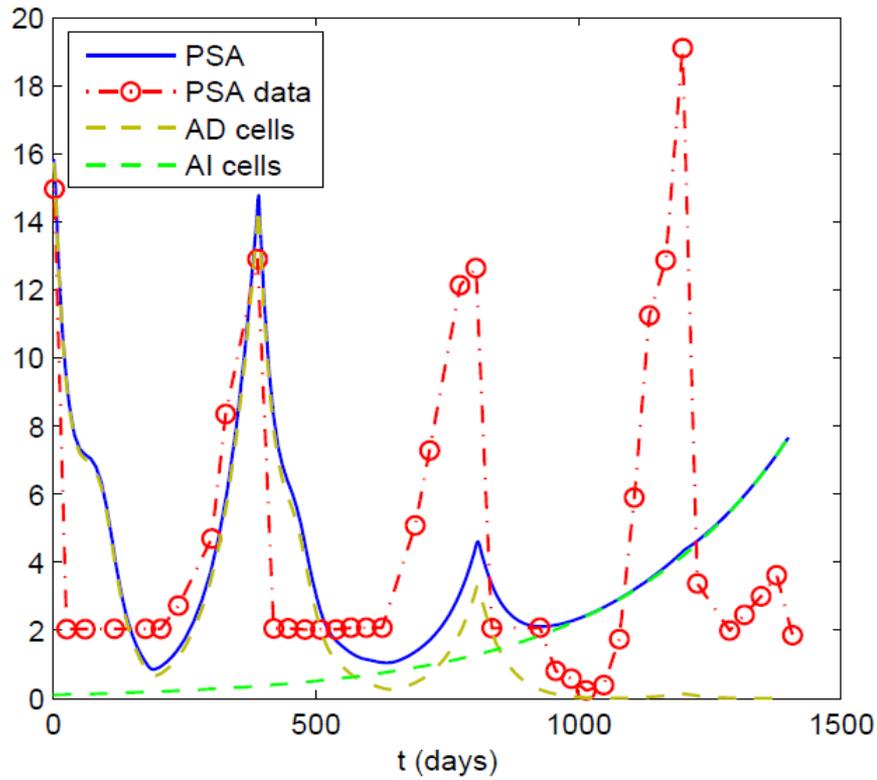
$$\frac{dA}{dt} = \gamma(a_0 - A) - \gamma a_0 u(t)$$

Androgen homeostasis

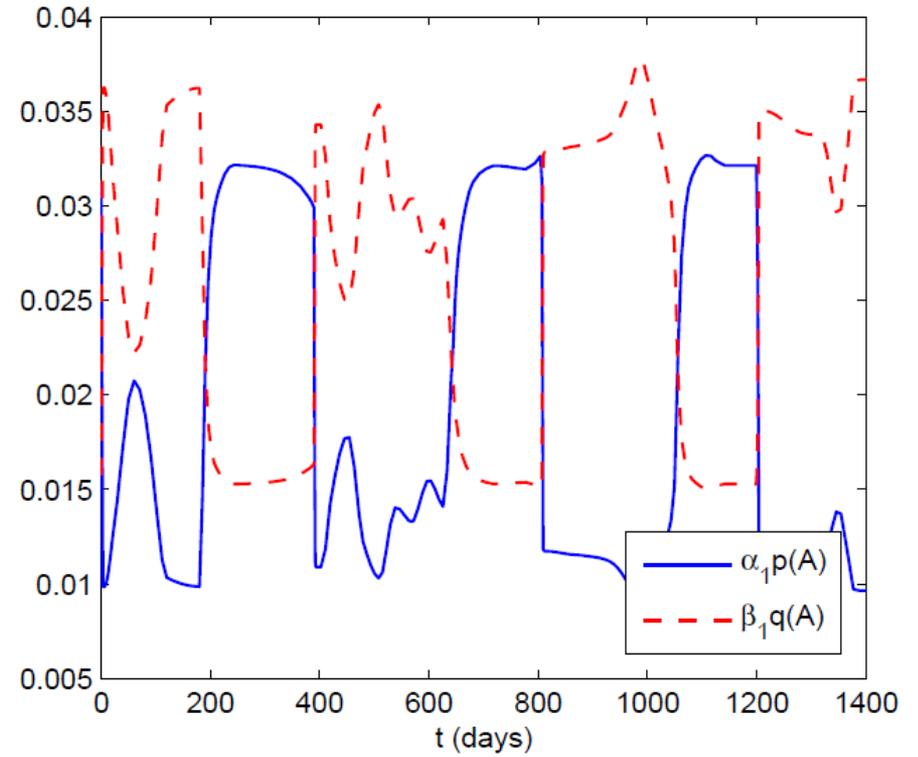
$$P(t) = c_1 X_1(t) + c_2 X_2(t)$$

PSA production

Model 1



Case 1



Growth and death rates

Model 2



- **Changes from Model 1:**
 - Cell quota model for AD population
 - New variable, cell quota for androgen: $Q(t)$
 - Mutation from AD to AI and AI to AD
- **Assumptions**
 - Model 1 assumptions
 - Switching behavior between cell populations

Model 2: Cell Populations



$$\frac{dX_1}{dt} = \mu_m \left(1 - \frac{q}{Q}\right) X_1 - \delta X_1 - m_1(Q)X_1 + m_2(Q)X_2$$

AD population

$$\frac{dX_2}{dt} = rX_2 - m_2(Q)X_2 + m_1(Q)X_1$$

AI population

$$m_1(Q) = k_1 \frac{K_1^n}{Q^n + K_1^n}$$

AD to AI mutation

$$m_2(Q) = k_2 \frac{Q^n}{Q^n + K_2^n}$$

AI to AD mutation

Model 2: Cell Quota, PSA



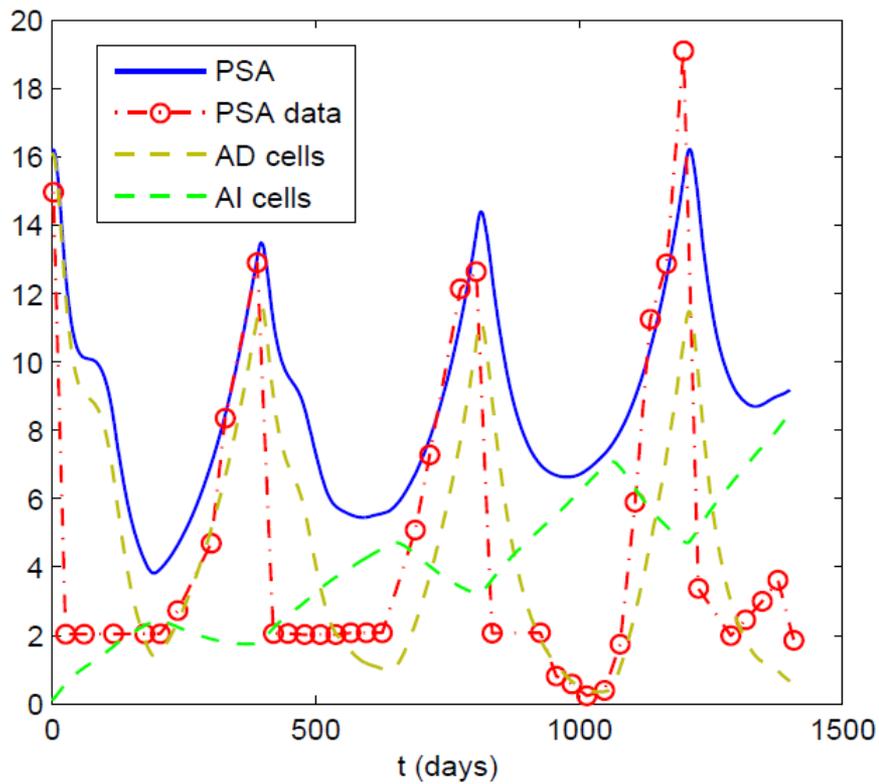
$$\frac{dQ}{dt} = v_m \frac{q_m - Q}{q_m - q} \frac{A}{A + v_h} - \mu_m(Q - q) - bQ$$

Cell quota

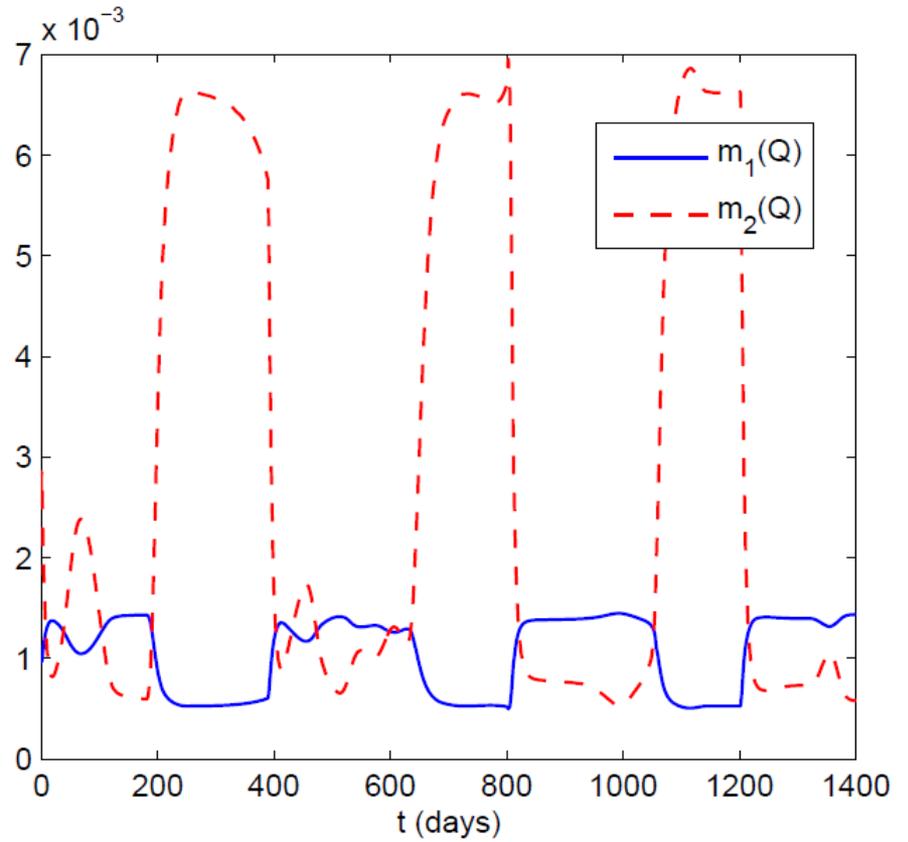
$$P(t) = c_1 X_1(t) + c_2 X_2(t)$$

PSA production

Model 2



Case 1



Mutation rates

Final Model



- **Changes from Model 2**
 - Cell quota model for both AD and AI populations
 - Cell quota variables $Q_1(t)$ and $Q_2(t)$
 - New model for PSA production
- **Assumptions**
 - AI population has increased sensitivity to androgen (can survive at lower levels)
 - PSA production is dependent on androgen

Model: Cell Populations



$$\frac{dX_1}{dt} = \mu_m \left(1 - \frac{q_1}{Q_1} \right) X_1 - d_1 X_1 - \lambda_1(Q_1) X_1 + \lambda_2(Q_2) X_2$$

AD population

$$\frac{dX_2}{dt} = \mu_m \left(1 - \frac{q_2}{Q_2} \right) X_2 - d_2 X_2 - \lambda_2(Q_2) X_2 + \lambda_1(Q_1) X_1$$

AI population

$$\lambda_1(Q) = c_1 \frac{K_1^n}{Q^n + K_1^n}$$

AD to AI mutation

$$\lambda_2(Q) = c_2 \frac{Q^n}{Q^n + K_2^n}$$

AI to AD mutation

Model: Cell Quotas, PSA



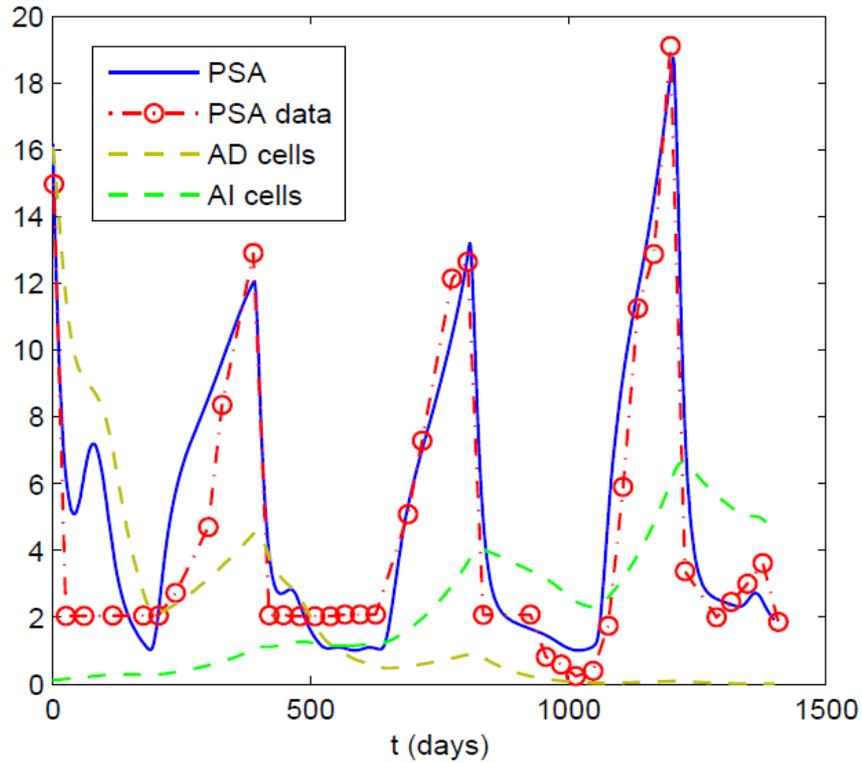
$$\frac{dQ_i}{dt} = v_m \frac{q_m - Q_i}{q_m - q_i} \frac{A}{A + v_h} - \mu_m(Q_i - q_i) - bQ_i$$

Cell quotas

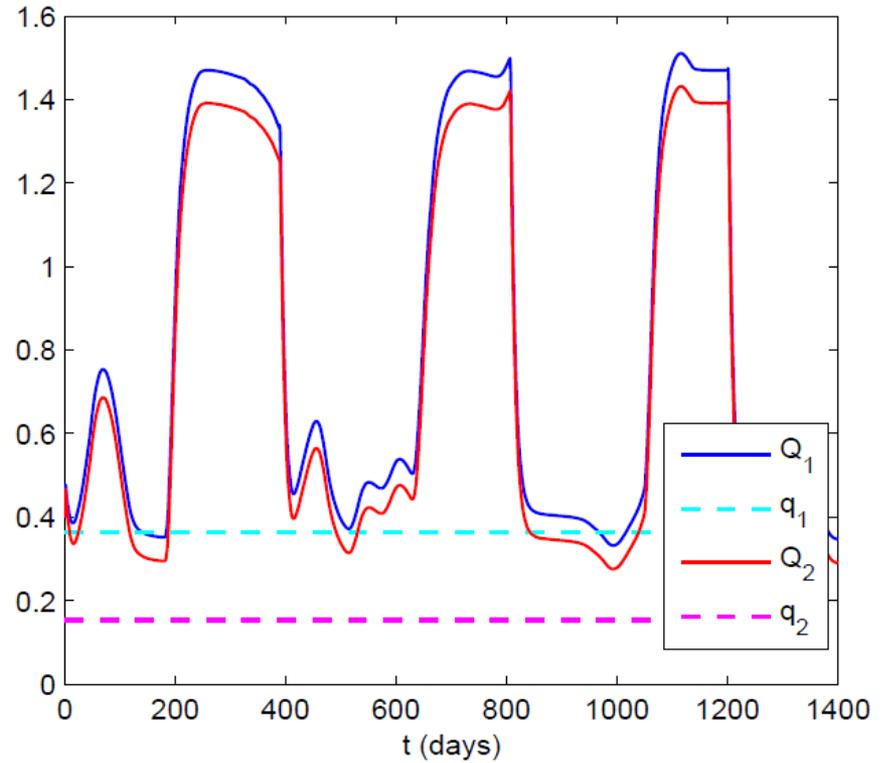
$$\frac{dP}{dt} = \sigma_0(X_1 + X_2) + \sigma_1 X_1 \frac{Q_1^m}{Q_1^m + \rho_1^m} + \sigma_2 X_2 \frac{Q_2^m}{Q_2^m + \rho_2^m} - \delta P$$

PSA production

Model validation

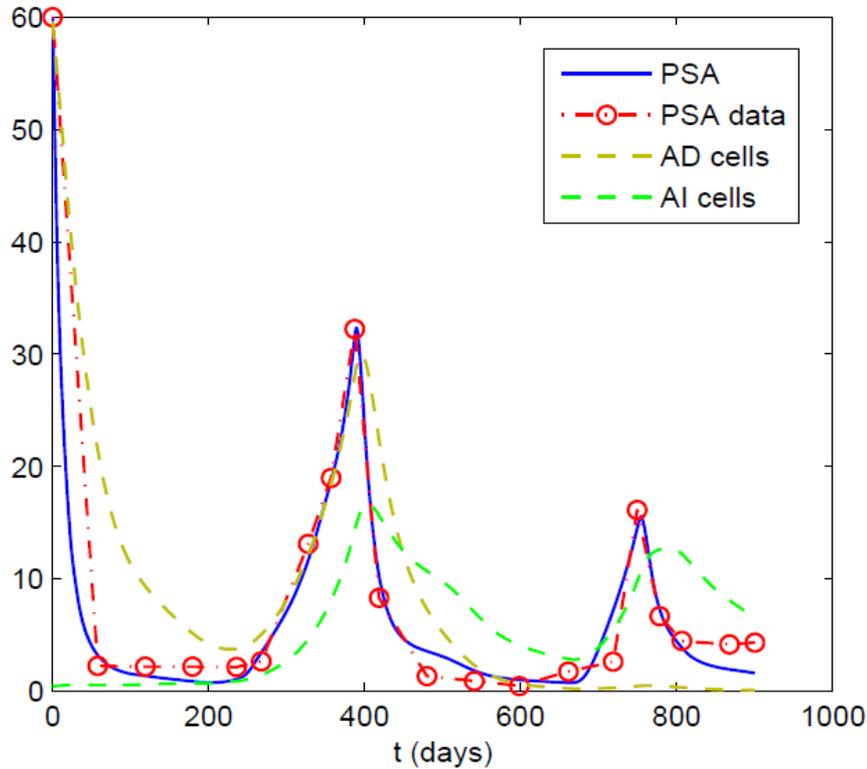


Case 1

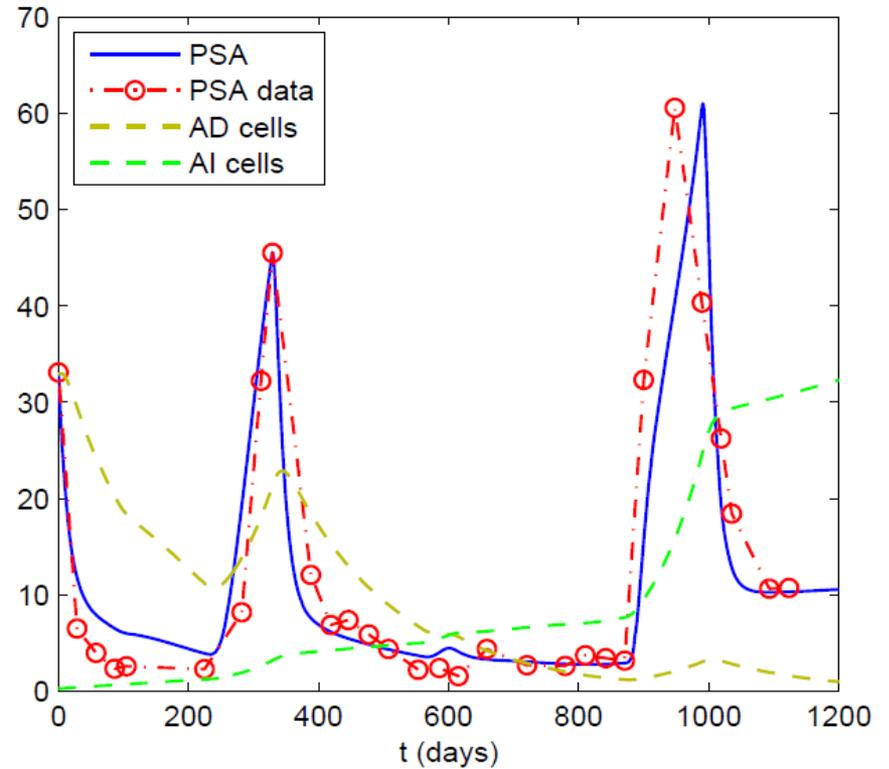


Cell quotas

More on model validation

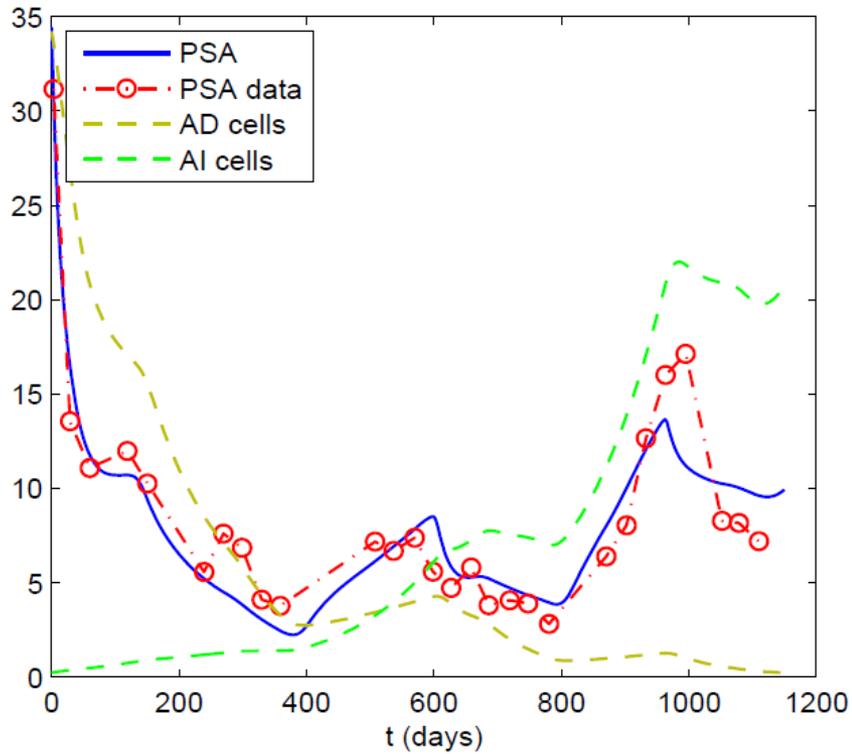


Case 2

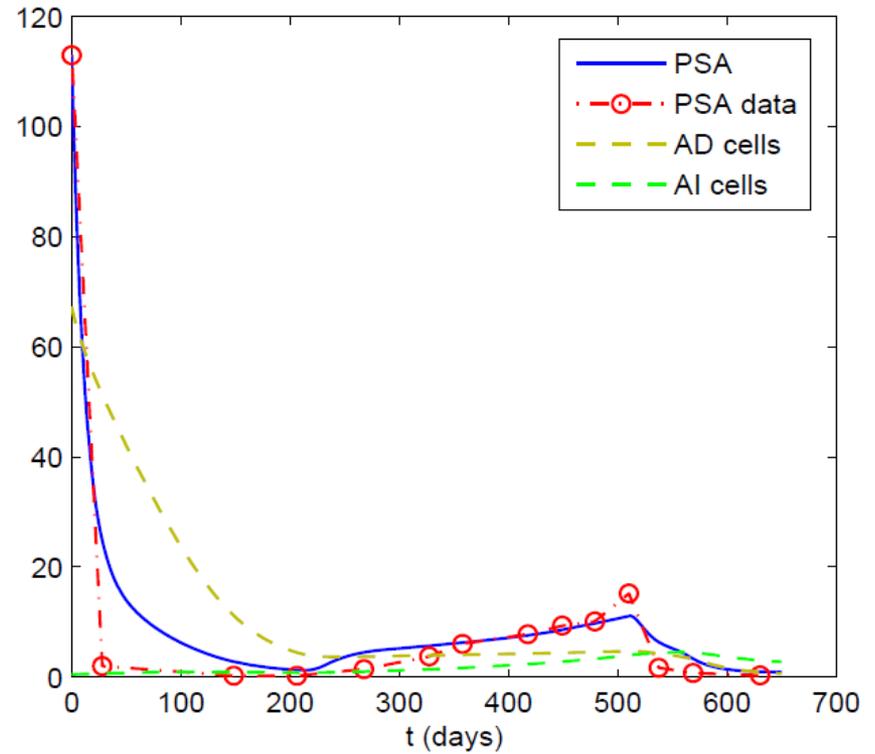


Case 3

More on model validation

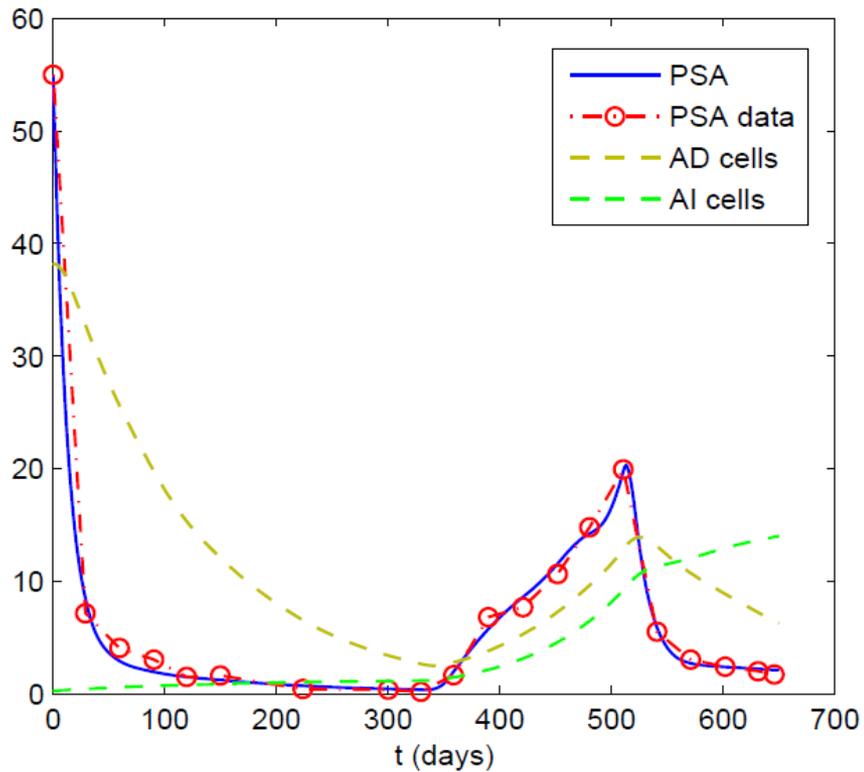


Case 4

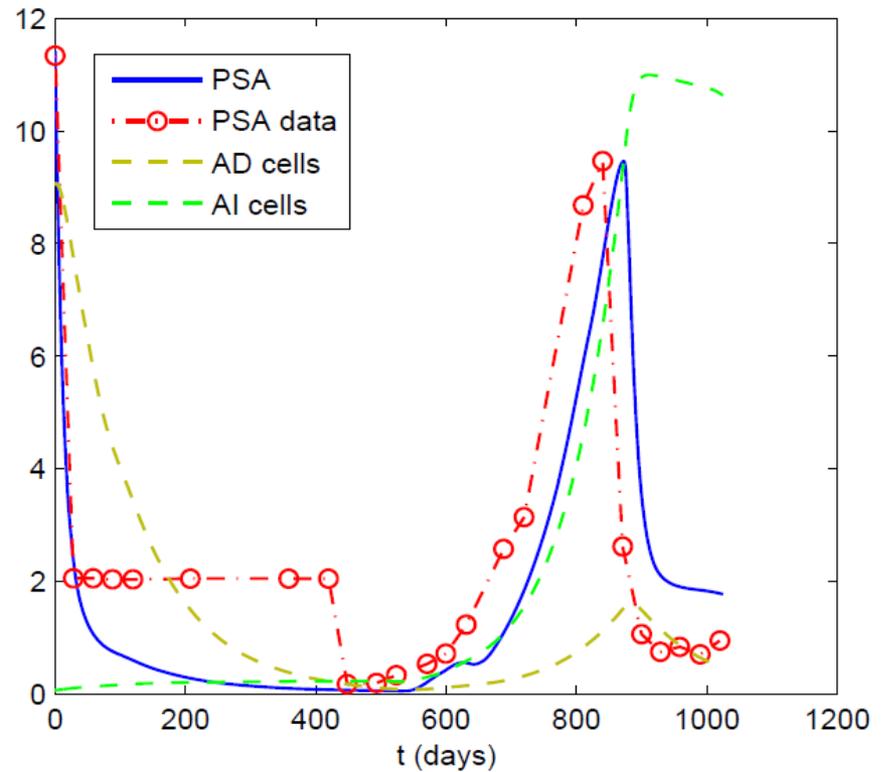


Case 5

More on model validation



Case 6



Case 7

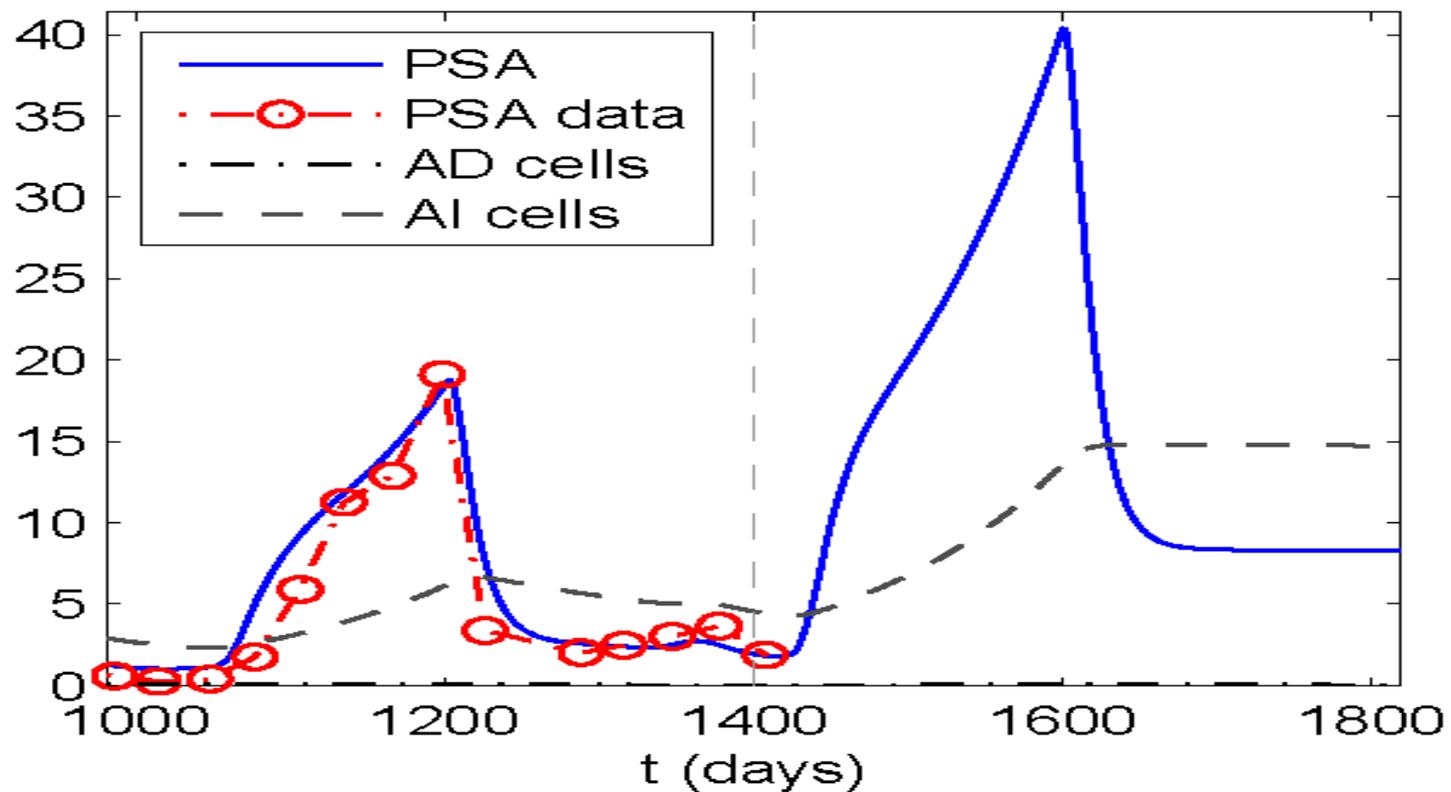


Error Comparison

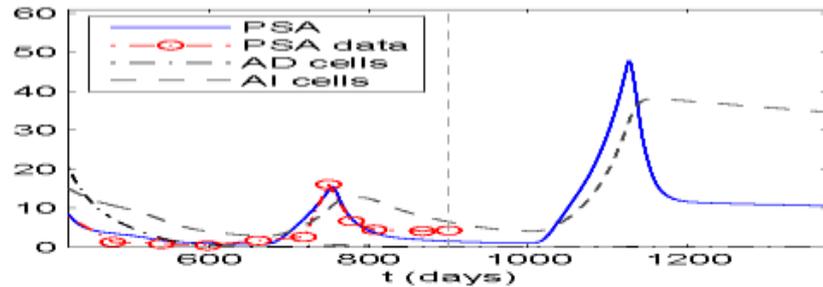
Final model has much lower average MSE with its fits

Case	MSE		
	Model 1	Model 2	Final Model
1	21.2089	30.6054	2.9606
2	25.6481	96.0505	2.7896
3	216.5615	238.1598	46.4210
4	12.2631	13.5954	3.9237
5	358.0592	497.2787	41.8106
6	44.5925	41.9082	0.3985
7	6.6549	6.5879	3.7098
Average	97.8554	132.0265	14.5734

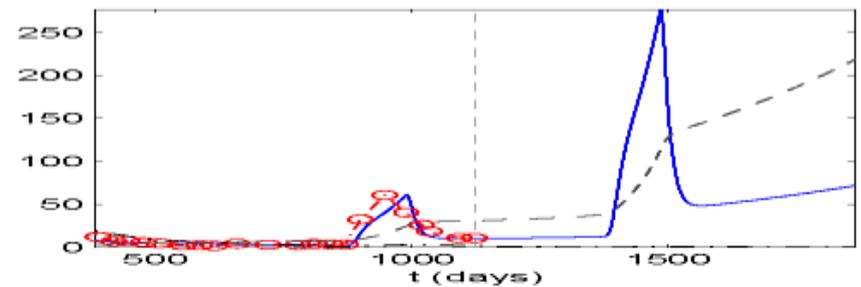
Model prediction for subject 1



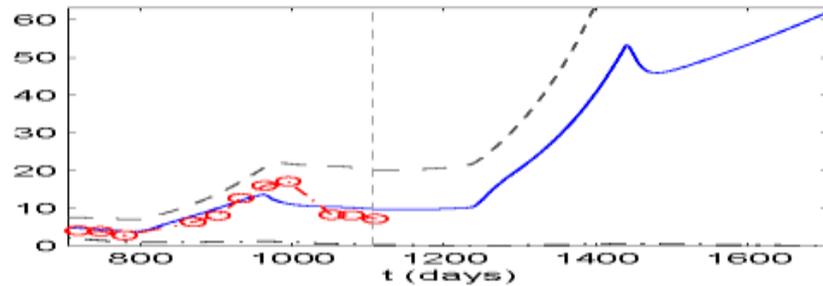
Prediction for other subjects



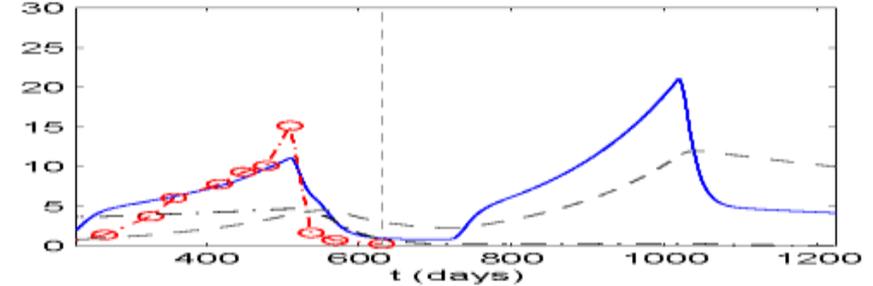
(a) Case 2



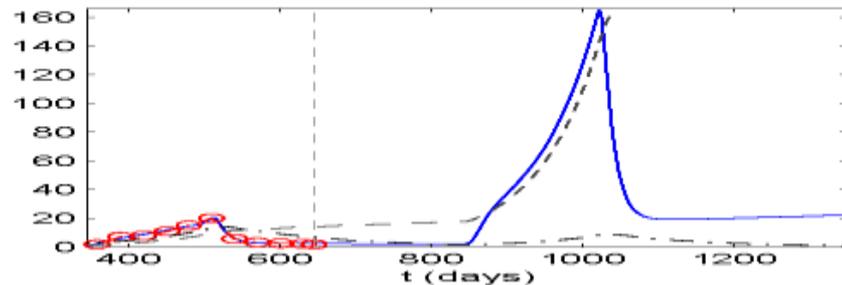
(b) Case 3



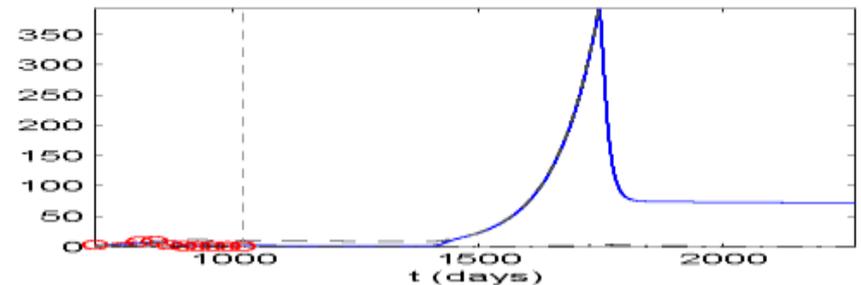
(c) Case 4



(d) Case 5



(e) Case 6



(f) Case 7

Prediction



The results of running the final model for another treatment cycle beyond the clinical data are shown in the next two slides. We note that the patients in cases 1, 2, 3, and 5 had stage C cancer, while the patients in cases 4, 6, and 7 had stage D (metastatic) cancer.

Our model predicts uncontrolled growth in the AI population for the stage D cases even though the PSA concentrations do respond to the final on-treatment period in cases 6 and 7. The model also predicts a poor response to another treatment cycle for the patient in case 3, who had already undergone two long treatment cycles.

A simple model with only AD cells

$$\begin{aligned}
 \frac{dx}{dt} &= \underbrace{\mu_m \left(1 - \frac{q}{A}\right)x}_{\text{growth}} - \underbrace{\left(d \frac{R}{A+R} + \delta\right)x}_{\text{death}} \\
 \frac{dA}{dt} &= \underbrace{\gamma}_{\text{production}} \underbrace{\frac{Q-A}{Q-q}}_{\text{cell limitation}} - \underbrace{\mu_m(A-q)x}_{\text{uptake}} \\
 \frac{dP}{dt} &= \underbrace{\sigma_0(x)}_{\text{baseline production}} + \underbrace{\left(\sigma_1 \frac{A^3}{A^3 + \rho^3}\right)x}_{\text{androgen-dependent production}} - \underbrace{\epsilon P}_{\text{clearance}}
 \end{aligned}$$

where, $\gamma = \gamma_1 u(t) + \gamma_2$

$$u(t) = \begin{cases} 1, & \text{on treatment} \\ 0, & \text{off treatment} \end{cases}$$

Full model with both AD and AI cells

$$\frac{dx_1}{dt} = \underbrace{G_1(A)x_1}_{\text{growth}} - \underbrace{D_1(A)x_1}_{\text{death}} - \underbrace{\lambda_1(A)x_1 + \lambda_2(A)x_2}_{\text{switching}}$$

$$\frac{dx_2}{dt} = \underbrace{G_2(A)x_2}_{\text{growth}} - \underbrace{D_2(A)x_2}_{\text{death}} - \underbrace{\lambda_2(A)x_2 + \lambda_1(A)x_1}_{\text{switching}}$$

$$\frac{dA}{dt} = \underbrace{\gamma}_{\text{production}} \underbrace{\frac{Q-A}{Q-q_2}}_{\text{cell limitation}} - \underbrace{G_1(A)Ax_1 + G_2(A)Ax_2}_{\text{uptake}}$$

$$\frac{dP}{dt} = \underbrace{\sigma_0(x_1 + x_2)}_{\text{baseline production}} + \underbrace{P_1(A)x_1 + P_2(A)x_2}_{\text{androgen-dependent production}} - \underbrace{\epsilon P}_{\text{clearance}}$$

$$G_i(A) = \begin{cases} \mu_m(1 - \frac{q_i}{A}), & A > q_i \\ 0, & A \leq q_i, \end{cases} \quad D_i(A) = d_i \frac{R_i^3}{A^3 + R_i^3} + \delta_i, \quad i = 1, 2$$

$$\lambda_1(A) = c_1 \frac{K_1^3}{A^3 + K_1^3}, \quad \lambda_2(A) = c_2 \frac{A^3}{A^3 + K_2^3}, \quad P_i(A) = \left(\sigma_i \frac{A^3}{A^3 + \rho_i^3} \right), \quad i = 1, 2.$$

PSA data fitting for patients

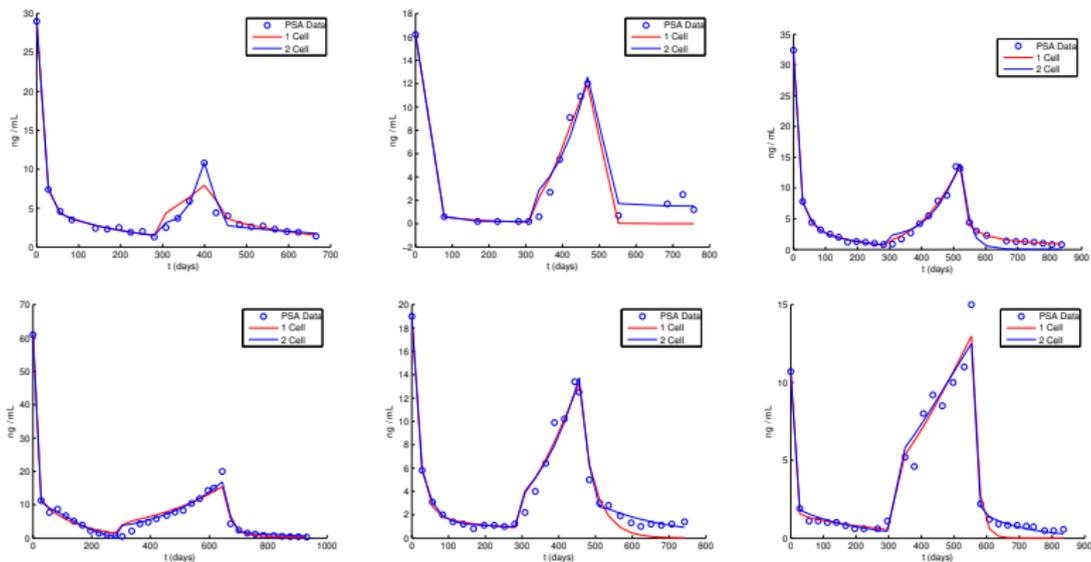


Figure 1: Simulation results for PSA data fitting for for patients 1 (top left), 8(top right), 15(mid left), 28(mid right), 39(bottom left), and 55 (bottom right)

Androgen data fitting for patients

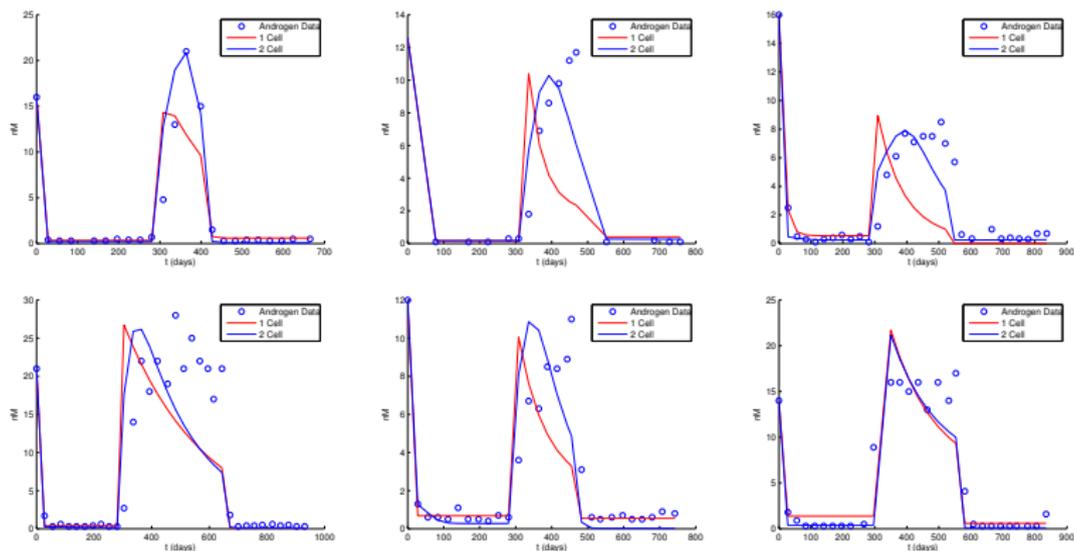


Figure 2: Simulation results for androgen data fitting for for patients 1 (top left), 8 (top right), 15 (mid left), 28 (mid right), 39 (bottom left), and 55 (bottom right)

Recent and Future Projects



- **Models for specific clinical data sets**
 - Identify death and proliferation rate profiles
 - Understand pathways to resistance
 - Identify mechanisms leading to resistance

Jason D. Morken, Aaron Packer, Rebecca A. Everett, John D. Nagy, and Yang Kuang, 2014. Mechanisms of resistance to intermittent androgen deprivation in patients with prostate cancer identified by a novel computational method, [Cancer Research](#), 74(14); 3673–83.

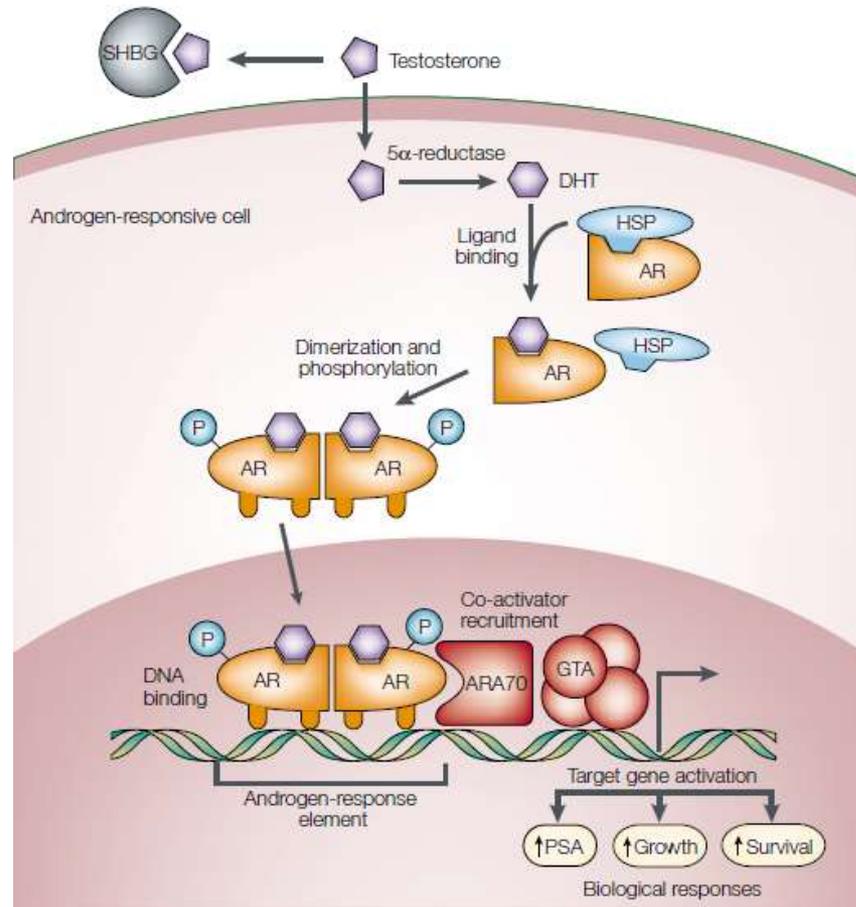
- **Use the models to make predictions**
 - Establish accuracy of treatment prediction with limited available data
 - Model may be used as a clinical tool for scheduling treatments

Prostate cells require androgens (testosterone and DHT) for growth and survival

Androgen:

Stimulates proliferation

Inhibits apoptosis



Androgen dependence of prostate cells (Feldman 2001)

Abi Model

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1 Introduction

What follows is a brief discussion of the biological system we wish to model and brief elucidation of the current mathematical model—the “abi model”—we are using to simulate the Mayo Clinic abiraterone data. Finally, we present some preliminary simulation results for a few of the patients. More work to come.

This section will be revised and expanded later.

2 Abiraterone Mechanism of Action

Note that all patients are on LHRH analogues (standard care androgen ablation) throughout the entire duration of the data sets. However, although chemical castration depletes blood serum testosterone levels by >90%, intraprostatic androgen concentrations remain at 20% to 50% [1-5]. In spite of depleted androgen levels from androgen ablation, the up-regulation of enzymes involved in androgen biosynthesis within tumor cells has been shown to be quite common and result in intratumoral androgen levels much higher than serum levels [6-8].

The mechanism of androgen production we consider is the conversion of pregnenolone to dehydroepiandrosterone (DHEA) by the 17α -hydroxylase/C $17,20$ lyase moieties of the cytochrome P450 enzyme CYP17A1, which is expressed in testicular, adrenal, and prostatic tumor tissues. DHEA is an androgen and precursor of testosterone. The mechanism of action of abiraterone—the active metabolite of pro-drug abiraterone acetate (trade name Zytiga)—is competitive inhibition of CYP17A1. Abiraterone binds to the active site of CYP17A1 and coordinates the heme iron through its pyridine nitrogen, mimicking the substrate.

To capture this reality, we’ve added a term that represents intratumoral androgen production to previous dynamical PSA model [5]. Here, we assume that Zytiga completely inhibits intratumoral androgen production for model simplicity.

This section will be revised and expanded later.

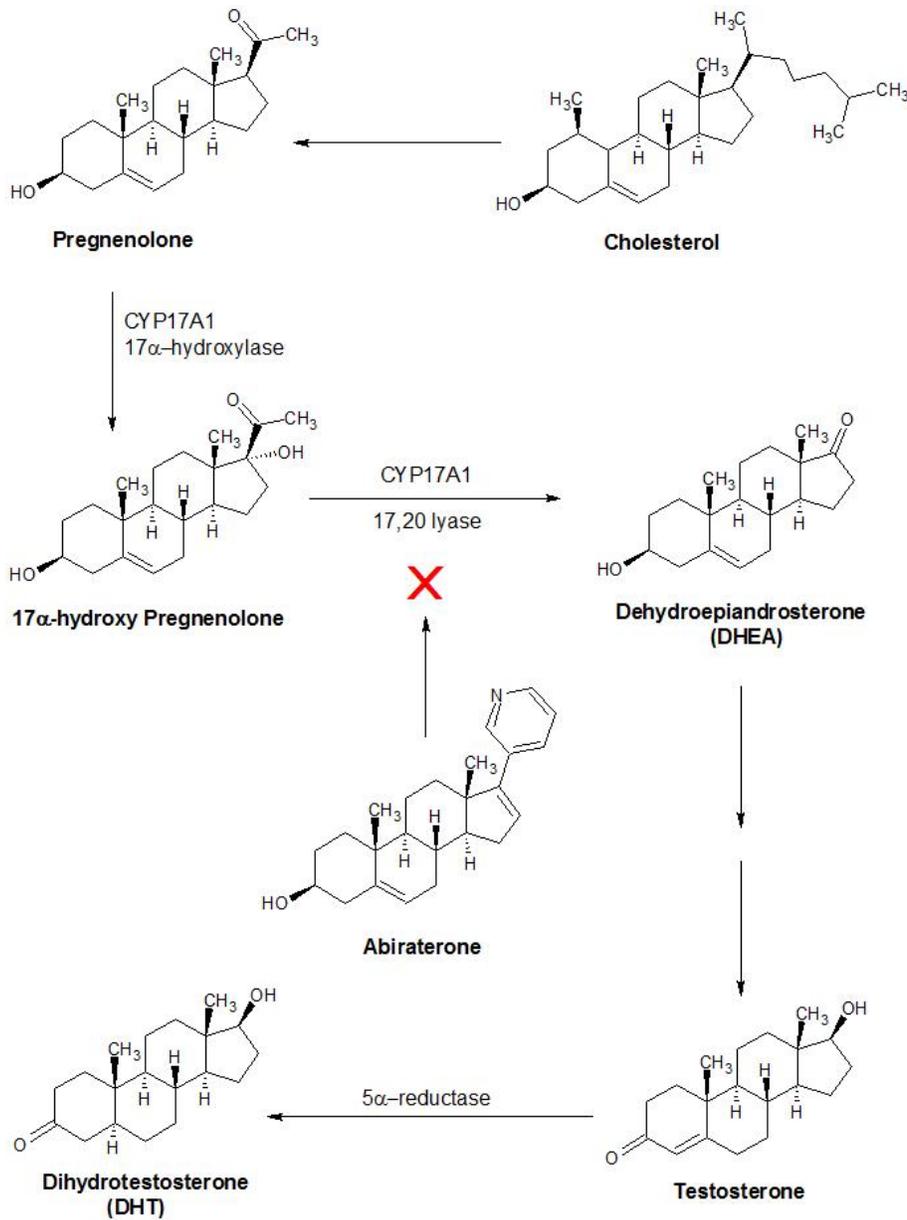


Figure 1: Abiraterone mechanism of action in androgen biosynthesis pathway. Abiraterone is an analogue of 17Preg and competes with 17Preg for the active site of the 17,20 lyase moiety of enzyme CYP17A1, thus inhibiting the illustrated lyation reaction and preventing the conversion of 17Preg to DHEA. Patients whom respond well to abiraterone show drastically reduced the levels of intratumoral androgen due to the inhibition of intratumoral androgen production by the illustrated metabolic pathway.

3 Current Abi Model

The Abi Model equations are as follows.

$$\frac{dX_1}{dt} = \mu_m \left(1 - \frac{q_1}{Q}\right) - D_1(Q)X_1 - \lambda_1(Q)X_1 + \lambda_2(Q)X_2, \quad (1)$$

$$\frac{dX_2}{dt} = \mu_m \left(1 - \frac{q_2}{Q}\right) - D_2(Q)X_2 + \lambda_1(Q)X_1 - \lambda_2(Q)X_2. \quad (2)$$

Equations (1) and (2) define the castration sensitive (CS) and castration resistant (CR) cell populations, respectively.

$$D_i(Q) = d_i \frac{R_i^\alpha}{R_i^\alpha + Q^\alpha} + \delta_i. \quad (3)$$

Equation (3) defines the cell death rate (CDR) in the i^{th} cell population, $i = 1, 2$.

$$\lambda_1(Q) = c_1 \frac{K_1^n}{K_1^n + Q^n}, \quad (4)$$

$$\lambda_2(Q) = c_2 \frac{Q^n}{K_2^n + Q^n}. \quad (5)$$

Equations (4) and (5) describe the phenotype “switching” process from CS cells to CR cells and vice versa. Androgen dynamics are modeled by

$$\frac{dQ}{dt} = \nu_m \frac{q_m - Q}{q_m - q_s} \frac{A}{A + \nu_h} + I(Q) - \mu_m(Q - q_1)X_1 - \mu_m(Q - q_2)X_2 - bQ, \quad (6)$$

$$q_s = \min(q_x, q_y),$$

$$I(Q) = \psi \left(\nu_c (q_m - Q) \right), \quad \psi = \begin{cases} 1, & \text{off Zytiga,} \\ 0, & \text{on Zytiga.} \end{cases} \quad (7)$$

where equation (6) describes the intratumoral androgen concentration dynamics where the first term captures the uptake of androgens from the blood serum (i.e., the diffusion of androgens into tumors) and the last two terms represent the degradation of androgen following proliferation. Equation (7) describes intratumoral androgen production which for simplicity is assumed to be completely inhibited in the presence of abiraterone. ψ represents a “switch” whereby intracellular androgen production is turned on when $\psi = 1$ and off when $\psi = 0$.

$$\frac{dA}{dt} = 0, \quad A(0) = A_0. \quad (8)$$

Equation (8) describes the blood serum androgen dynamics which are assumed to be constant since all patients are on LHRH analogues throughout the duration of the collected data. PSA dynamics are modeled by

$$\frac{dP}{dt} = \sigma_0(X_1 + X_2) + \sigma_1 X_1 \frac{Q^m}{Q^m + \rho_1^m} + \sigma_2 X_2 \frac{Q^m}{Q^m + \rho_2^m} - \epsilon P. \quad (9)$$

All free parameters—currently 14 total—are highlighted in red, whereas all static parameters that remain fixed are left black.

See [5] for parameter interpretations and [5,9] for additional elucidation of model formulations and assumptions.

This section will be revised and expanded later.

4 MATLAB Code

What follows is the code I've written to run the simulations for the abi model. The entire algorithm consists of 15 programs all of which depend on each other.

4.1 ABI_MODEL

4.2 ABI_MODEL_FIT

4.3 PLOT_PSA

5 Simulation Results

5.1 Patient 12

Results for patient 12 are as follows. All parameters and variables are within biologically appropriate ranges reported in the literature.

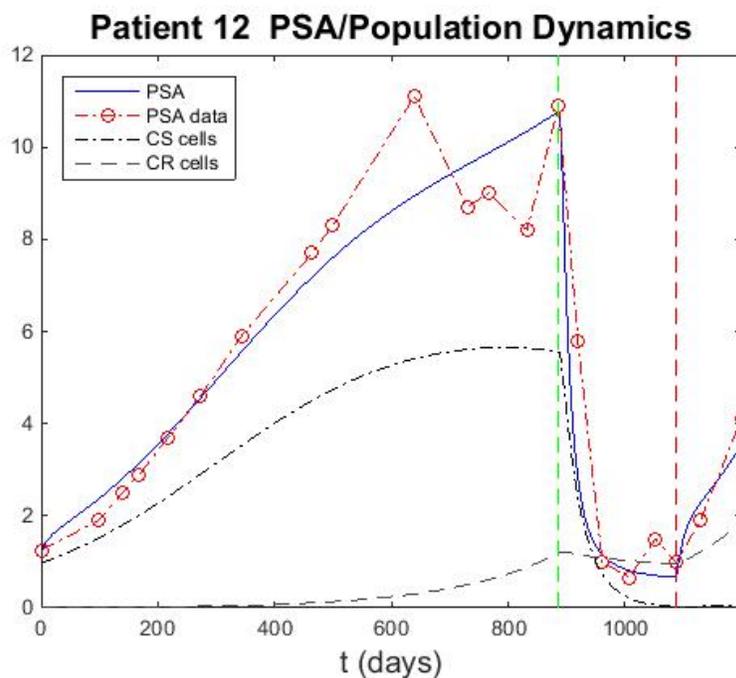


Figure 2: PSA fit for patient 12. **Green** vertical lines indicate **start** of Zytiga treatment and **dark red** vertical lines indicate the **stop** of Zytiga treatment. Notice how the model captures the PSA dynamics very well during the on-treatment period with Zytiga due to the new intratumoral androgen production switch.

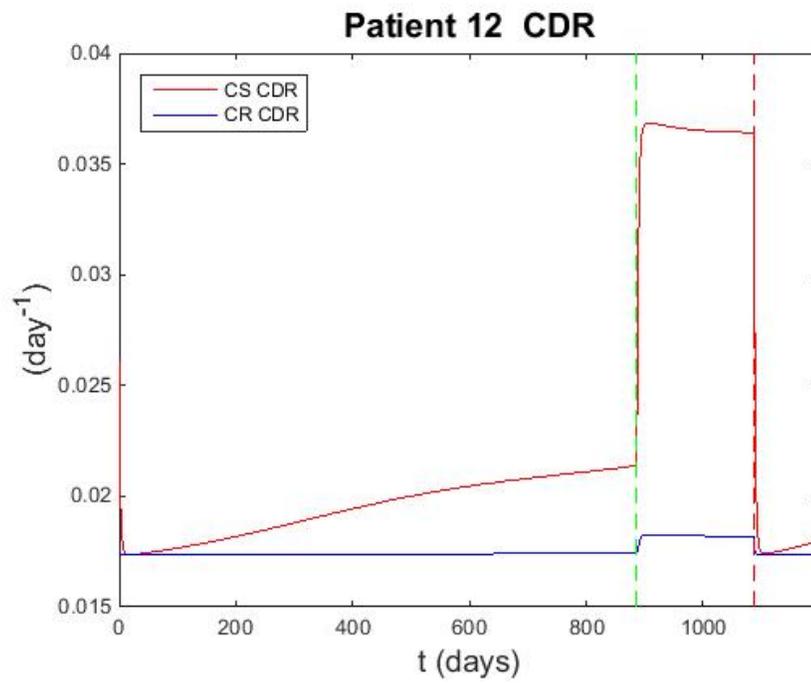


Figure 3: CDRs for patient 12. Notice CDRs go up during Zytiga treatment. This is consistent with patient responding well to Zytiga. However, the patient does seem to be developing resistance to the LHRHa's which is reflected by the relatively constant CDRs when off Zytiga and by the increasing PSA levels while off Zytiga (see Fig. 2).

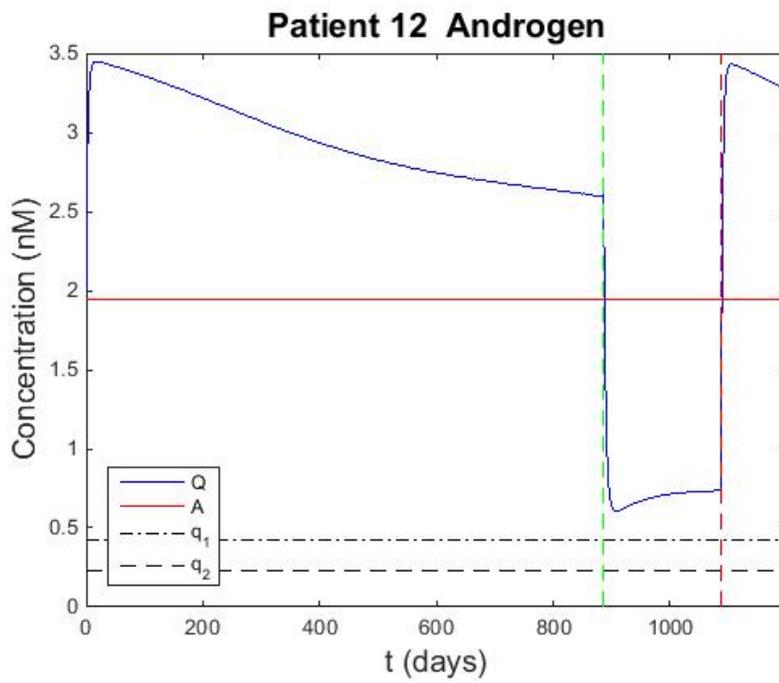


Figure 4: Intratumoral and serum androgen concentrations for patient 12. Notice androgen concentrations decrease with respect to time on LHRHa's and the dramatic reduction in intratumoral androgen during Zytiga treatment consistent with the notion that patient 12 responded well to Zytiga.

5.2 Patient 34

Results for patient 34 are as follows. One parameter is out of range. Still working on finding the right parameters.

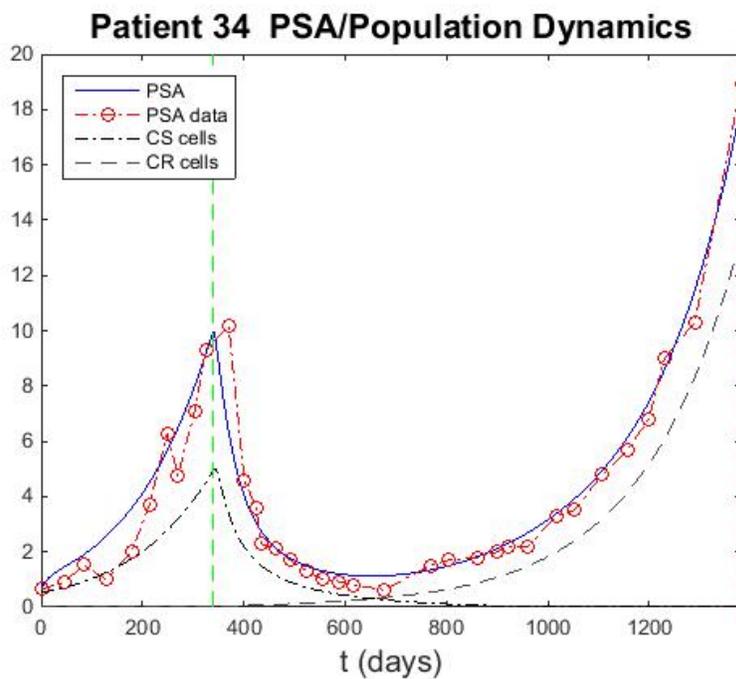


Figure 5: PSA fit for patient 34. Green vertical lines indicate start of Zytiga treatment and dark red vertical lines indicate the stop of Zytiga treatment. Notice how the model captures the PSA dynamics very well during the on-treatment period with Zytiga due to the new intratumoral androgen production switch. The castration resistant population rises dramatically with PSA toward the end of Zytiga treatment.

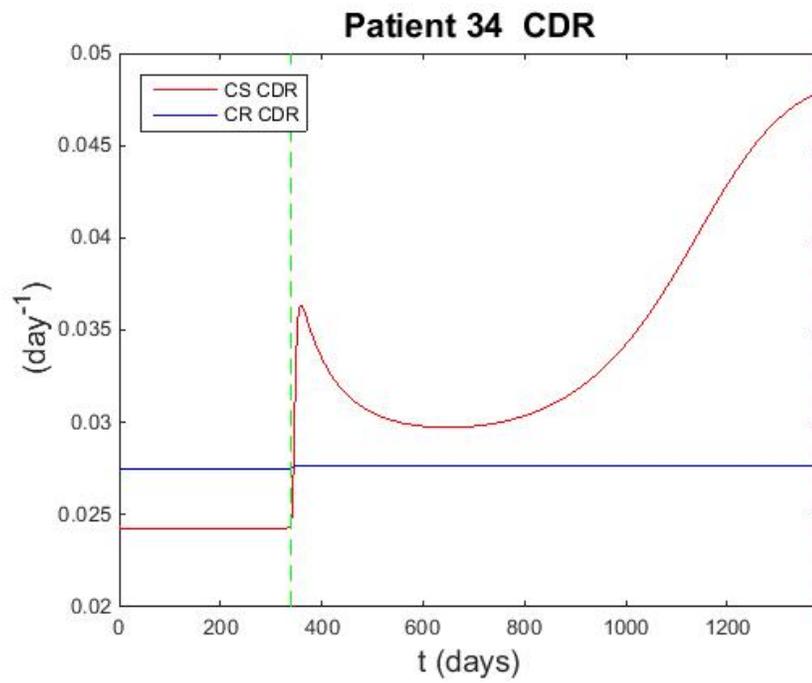


Figure 6: CDRs for patient 34. Notice CDR goes up only for the castration sensitive population during Zytiga treatment. Resistant population has a relatively constant CDR. This is consistent with patient NOT responding well to Zytiga.

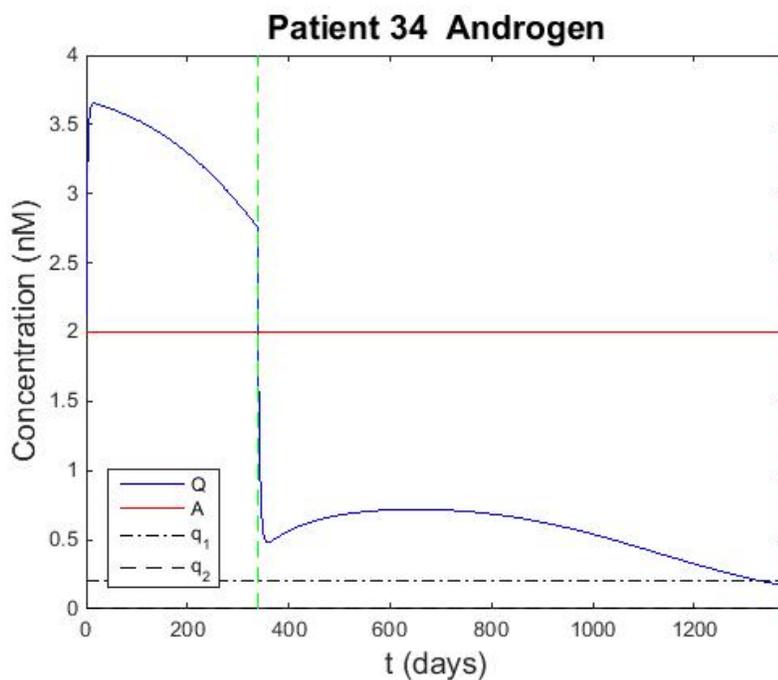


Figure 7: Intratumoral and serum androgen concentrations for patient 34. Notice androgen concentrations decrease with respect to time on LHRHa's and the dramatic reduction in intratumoral androgen during Zytiga. However, due to the near constant CDR in the CR population, we may conclude that patient 34 develops resistance not through increased intratumoral androgen production but by acceleration of the AR axis.

This section will be revised and expanded later.

6 Conclusion

I'm close to getting a good fit for patient 34. There's only one parameter out of range with MSE 0.8401. Patient 12 is done and the fit is great with all parameters/variables biologically relevant. Notice patients 12 and 34 are radical opposites. Patient 12 responds to Zytiga fantastically while patient 34 clearly develops massive resistance to Zytiga. That is why I'm trying so hard with these two patients because I feel that if the model can get a good fit with them, then the model can fit anything in between these two extreme cases.

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