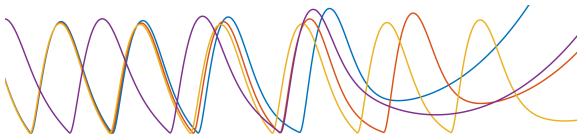
Research in Groups: Scientific Computing

The Evolution of Tumor Models



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1 Introduction

Cancer and the therapy thereof plays an increasingly important role in our everyday lives. Thus much scientific effort is dedicated to finding therapies that balance the negative side effects with effective treatment. In mathematics this effort is mainly undertaken in the formulation and analysis of models, that represent the behaviors of tumors in a simplified yet sufficiently complex way, and allow for the derivation of optimal treatment protocols.

The present work acts as a report on some of the considerations I made in a course on the simulation of evolution models, held by Professor Borzì. Overall I occupied myself with the study of various cancer models and their therapy. The first work I considered was [HPFH99] due to Hahnfeldt et al. in 1999, which included a general tumor model, incorporating vascular structure for the simulation of angiogenic inhibition as therapy. After programming the model and treatment in Matlab I was able to reproduce the results given in the paper. Then I considered the paper [ECM03] of Ergun et al. who deduced optimal protocols of angiogenic inhibition treatment for a tumor model, derived from Hahnfeldt's work. For further reading on optimal control of tumor models I consulted some of the work of Maurer et al. (see, e.g., [LMMS10], [LMS11] or [LMS19]). Subsequently came to my attention that some authors used partial differential equations to model the spatial evolution of tumors. This led to my initial contemplations on the numerics of partial differential equations.

Thereafter my focus shifted towards prostate cancer, a common kind of cancer restricted to the male population, whose dynamics evidentially depend on hormones. Therefore different kinds of hormonal therapy are applied to prostate cancer patients and have a realization in the corresponding tumor models. My first considerations were dedicated to the paper [FJ13] by Friedman et al., who introduced a partial differential equation framework for the analysis of prostate tumors. Since no explicit tumor dynamics were given in the model I was tasked with surveying the dynamics established by other authors. While considering the different prostate cancer models of Portz et al. and Ideta et al. (see [PKN12] and [ITTA08]) I encountered some differing assumptions on the dynamics of the cancer cell populations. To analyze the effect of these differences on the tumor evolution I implemented the models and ran simulations of both in Matlab. To illustrate my findings I want to present both models seperately and describe their general behaviors under therapy. Then I convey a comparison of the two models, after some parameter adjustments. Each simulation is visualized with plots generated by Matlab. The parameter values used for the simulations can be found in the Appendix.

2 General Assumptions on Prostate Cancer

The prostate is a male gland, essential to human reproduction. For operation and preservation the prostate is dependent on hormones, e.g., Testosterone, which are commonly refered to as androgens. Since the malignant prostate cancer cells develop from prostate cells, at first they also depend on androgen stimulation. An applied method of treatment consists of continuous androgen suppression (CAS) to inhibit the growth of the androgen dependent (AD) tumor cells. The deprivation was attained by means of physical or chemical castration. The therapy often resulted in an initial improvement of the patients condition until a relapse by development of seemingly androgen independent (AI) tumor cells took place. To describe this phenomenon a relapse is defined to be the point in time from which the tumor volume grows exponentially, after the application of treatment to the patient has been initiated. As a result of the distinct behaviors of tumor cells, prostate cancer is generally modeled by means of two seperate cancer cell populations, the AD and AI populations. The AD population is assumed to proliferate at normal androgen levels and to deteriorate at low androgen levels. However under androgen suppression the AD cancer cells are presumed to mutate from AD to AI cells. Unlike the name would suggest, the dynamics of the AI population are commonly hypothesized to depend on androgen levels, but the details of this dependence remain unclear. In fact different authors assumed fundamentally different behaviors for the AI population while exposed to high androgen concentration (see [PKN12] and [ITTA08]). However the different models all assumed the AI cancer cells to proliferate in an androgen poor environment which conforms to scientific evidence. To delay the relapse it was proposed by Bruchovsky et al. in [BRC$^+$90] to temporarily suspend the androgen suppression, to inhibit the mutation towards androgen independence, and to continue therapy before the tumor could proliferate to a high volume. This switching procedure is called intermittent androgen suppression (IAS) therapy and has been applied to patients in clinical trials to various degrees of success (see [Tun07]). Optimally the IAS therapy would increase the patient's quality of life during off-treatment periods, and would result in a delay of the relapse, if not its aversion. The difficult question to answer is how to derive an optimal treatment protocol to comply with the patients individual needs, which largely remains unanswered today. The uncertainty about the behavior of the AI tumor cells at high androgen levels is a major hurdle to take when modeling prostate tumors and their IAS therapy. In the following I aim to shed some light on the differences of two major models of prostate cancer which used different assumptions on the AI tumor cell dynamics.

3 Portz' Tumor Model

3.1 Tumor Dynamics

First I want to present Portz et al.'s tumor model (see [PKN12]). The model incorporates two seperate populations X_1 and X_2 of cancer cells, the androgen dependent (AD) and the androgen independent (AI) cancer cells. In Portz' model the AD population proliferates in presence of high androgen concentration and declines while androgen is suppressed. The AI population differs from the AD population insofar that low androgen concentration, i.e., the androgen concentration during suppression, is sufficient to cause an increase of the population (see figure 1). Though a major difference from other models is the assumption, that a higher concentration of androgens also increases the proliferation of AI cells (see section 5). In fact Portz called other assumption biologically unlikely, since AI tumor cells typically have androgen receptors with increased sensitivity. However Portz admits that this premise causes an acceleration of the disease progression when applying IAS therapy in comparison to CAS therpy (see [PKN12, p. 2]). It is further assumed, that the AD cells mutate to AI cells from lack of androgen at a rate given by the function λ_1 and mutate from AI to AD cells in an androgen rich environment by the rate λ_2. One of the major advances of Portz' model was the introduction of androgen cell quotas, which were first proposed by Droop in [Dro68]. They were established to differ between the

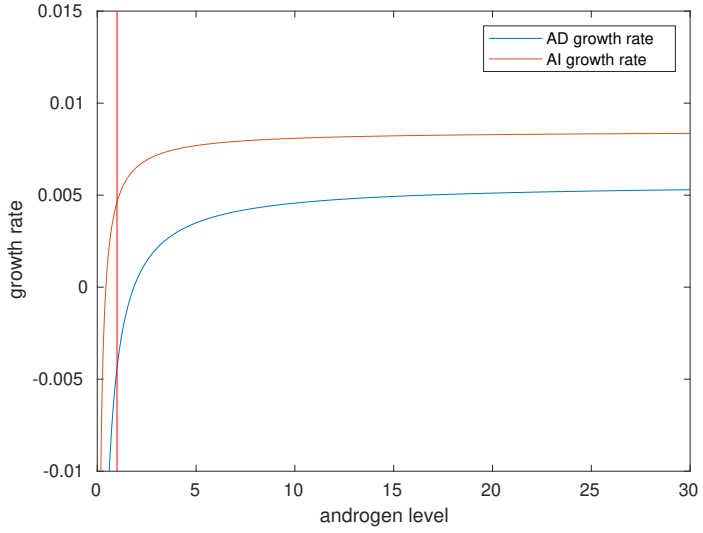

Figure 1: Portz' growth rates for the AD and AI populations with respect to constant androgen level; Red vertical indicates minimal androgen level at $A_1 = 1$.

androgen concentration in the blood serum, which is the measured concentration, and the intercellular androgen concentration, which contributes to the tumor dynamics. Therefore he considered two seperate cell quotas of androgen, Q_1 for the AD cells, and Q_2 for the AI cells. This cell quota model caused a delay in the adaptation of the AD and AI populations to varying androgen levels, which the authors probably intended to more accurately reproduce experimental reaction times of tumors within patients. Finally Portz introduced a new model for the concentration of the Prostate Specific Antigen (PSA) which also depended on the androgen cell quotas. More specifically the PSA concentration P in the tumorcells was assumed to increase with high androgen concentration within the cells in addition to a constant proliferation rate. In total Portz' model was constituted from the following system of dynamics:

$$\begin{aligned}
\frac{dX_1}{dt} &= \mu_m \left(1 - \frac{q_1}{Q_1}\right) X_1 - d_1 X_1 - \lambda_1(Q_1) X_1 + \lambda_2(Q_2) X_2, && \text{(AD volume)} \\
\frac{dX_2}{dt} &= \mu_m \left(1 - \frac{q_2}{Q_2}\right) X_2 - d_1 X_2 + \lambda_1(Q_1) X_1 - \lambda_2(Q_2) X_2, && \text{(AI volume)} \\
\frac{dQ_1}{dt} &= \nu_m \frac{q_m - Q_1}{q_m - q_1} \frac{A}{A + \nu_h} - \mu_m (Q_1 - q_1) - b Q_1, && \text{(AD quota)} \\
\frac{dQ_2}{dt} &= \nu_m \frac{q_m - Q_2}{q_m - q_2} \frac{A}{A + \nu_h} - \mu_m (Q_2 - q_2) - b Q_2, && \text{(AI quota)} \\
\frac{dP}{dt} &= \sigma_0 (X_1 + X_2) + \sigma_1 X_1 \frac{Q_1}{Q_1 + \rho_1} + \sigma_2 X_2 \frac{Q_2}{Q_2 + \rho_2} - \delta P, && \text{(PSA level)}
\end{aligned}$$

where the mutation rates are given by

$$\begin{aligned}
\lambda_1(Q) &= c_1 \frac{K_1}{Q + K_1}, && \text{(AD to AI mutation rate)} \\
\lambda_2(Q) &= c_2 \frac{Q}{Q + K_2}. && \text{(AI to AD mutation rate)}
\end{aligned}$$

Notably, the dependence of the dynamics on the androgen quotas, instead of the explicit androgen levels, hinder a transparent representation of the growthrates. This motivates the derivation of stabilized quotas with respect to a constant androgen concentration, as discussed in section 5.1. With the help of these quotas one can deduce growth rates of the AD and AI populations depending on androgen for improved visualization (see figure 1).

3.2 Androgen Dynamics and IAS Therapy

One notices the abscence of androgen dynamics in the above model, which was substituted in Portz' model by extrapolated patient data. Since this

data wasn't available to me I assumed an exponential fit for the androgen dynamics, depending on a switch function $u(t)$ which indicated androgen suppression if $u(t) = 1$ and abscence of treatment if $u(t) = 0$, similar to Ideta's androgen model (see [ITTA08, p.603]). Without treatment the androgen is assumed to remain at a constant level $A_0 = 30\frac{nmol}{l}$, a feasible assumption for healthy, middle-aged men, as in [ITTA08]. By switching on the treatment the androgen level exponentially decreases to $A_1 = 1\frac{nmol}{l}$, which lies well between the commonly assumed castration level of $1.7\frac{nmol}{l}$ and the lowest reported androgen levels in [Nas14] of about $0.4\frac{nmol}{l}$. This assumption was chosen according to the data used by Portz.

Since the PSA concentration is considered to be an indicator towards the development of a tumor, it is usual to choose the therapy protocol in dependence on the measured PSA levels of the patient. Thus it seems feasible to model intermittent androgen suppression (IAS) therapy as a feedback loop depending on the PSA evolution. As in Ideta's model, the IAS therapy u is turned on if the PSA level increases above a certain threshold r_1 and is switched off if the PSA level decreases below a lower threshold r_0. With the above assumptions the androgen dynamics and therapy function are given by the following equations:

$$\frac{dA}{dt} = -\gamma(A - A_0) - \gamma(A_0 - A_1)u(t), \qquad \text{(androgen level)}$$

$$u(t) = \begin{cases} 0 \to 1, \text{ if } P(t) \geq r_1 \text{ and } \frac{dP}{dt}(t) > 0, \\ 1 \to 0, \text{ if } P(t) \leq r_0 \text{ and } \frac{dP}{dt}(t) < 0. \end{cases} \qquad \text{(therapy control)}$$

Note that continuous androgen suppression (CAS), i.e., permanent castration, is contained in the above IAS therapy by choosing $r_0 = 0$. Similar to the values considered in [ITTA08], I chose $r_0 = 20$ and $r_1 = 15$ for the numerical simulations. These Parameters are probably not optimal and are solely chosen for illustriation of the general behavior under treatment.

3.3 Numerical Simulation

In the following section I present my numerical results of the simulations of Portz' tumor model. The section is separated into the simulations of the model without therapy, with CAS therapy and with IAS therapy. All parameter values can be found in the tables 2 and 3. Furthermore I considered the following initial conditions:

$$\begin{aligned} X_1(0) &= 100, & X_2(0) &= 0, \\ Q_1(0) &= 1.5942, & Q_2(0) &= 1.5202, \\ P(0) &= 35, & A(0) &= A_0. \end{aligned}$$

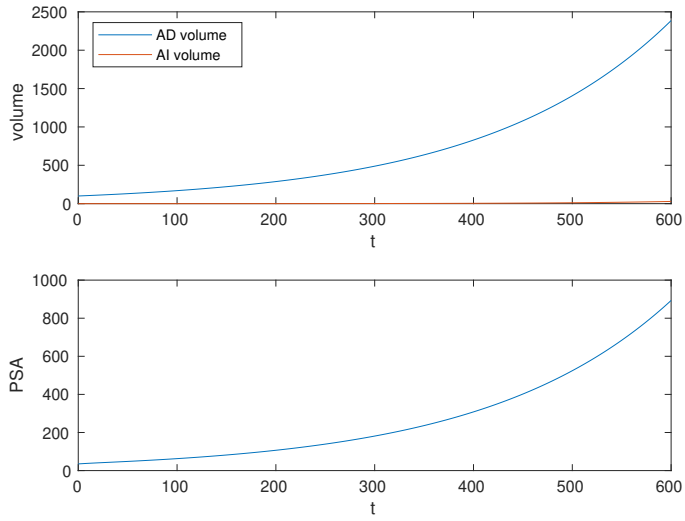

Figure 2: Evolution of Portz' tumor model (no therapy) with cancer volumes (top) and PSA level (bottom).

No Therapy (see figure 2) The model showed the expected exponential growth of the AD population. Notably also the AI population developed, which is due to the positive mutation rate from the AD to the AI population even at high androgen levels of $A_0 = 30$. The positive growth of the AI population during high androgen concentration, that is the unique assumption of the model, then caused the inclination of the AI population. Though in comparison to the numerical values of the AD population, the AI population seems neglectable. The PSA level develops parallel to the total tumor volume.

Continuous Androgen Suppression Therapy (see figure 3) Under CAS therapy the AI population declined from lack of androgens, whereas the mutation towards androgen independence and the positive growth of the AI population caused a relapse of the cancer at around 720 days. Afterwards the tumor grew exponentially and was fully independent of androgens.

Intermittent Androgen Suppression Therapy (see figure 4) The IAS therapy is switched on from the start up until around day 215. Afterwards begin four phases of suspension, which last around 17 days each, and the consecutive continuation of the therapy for about 120 days. At day 668 the IAS therapy was permanently switched on and the AI population grew exponentially. Over the course of the therapy the AD population eventually declined to zero after short periods of inclination during suspension of the therapy. The AI population on the other hand continuously increased in

volume since the assumptions on it effectuated positive growth for all attained levels of androgen. One can see that IAS therapy actually accelerates the disease progression and can never lead to a cure of the patient in Portz' model, as noted already in section 3.1.

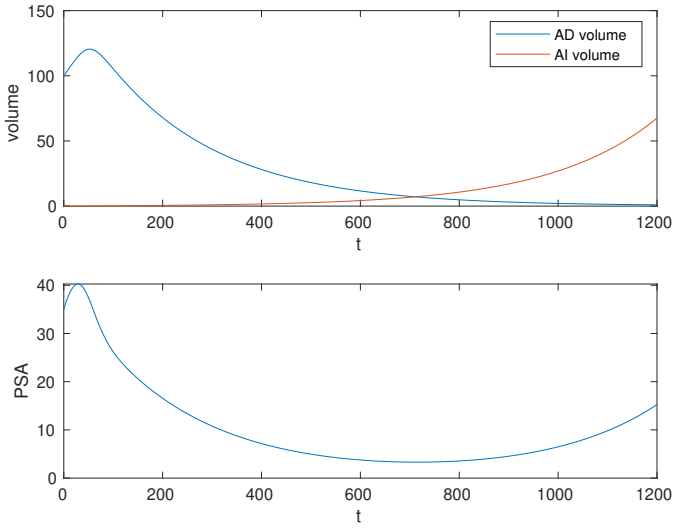

Figure 3: Evolution of Portz' tumor model (CAS therapy) with cancer volumes (top) and PSA level (bottom).

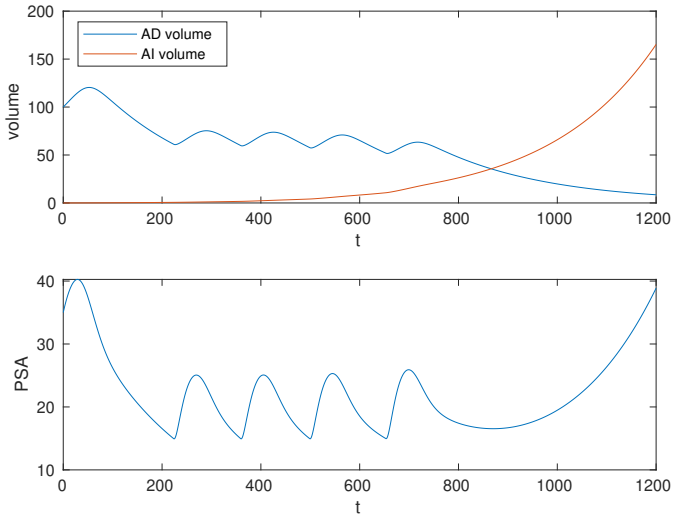

Figure 4: Evolution of Portz' tumor model (IAS therapy) with cancer volumes (top) and PSA level (bottom).

4 Ideta's Tumor Model

4.1 Tumor Dynamics

The second prostate cancer model I want to present was proposed by Ideta et al. in [ITTA08]. Ideta defined the dynamics of the two different AD and AI cancer cell populations X_1 and X_2 as well as mutation between the two at a rate m depending on the androgen concentration. The AD population was assumed to decrease exponentially at low androgen concentracions, whereas for the AI population three different androgen-dependent dynamics were considered (see figure 5). The first growth model g_1 assumed constant proliferation for all androgen levels. The next model g_2 assumed increased growthrates for low androgen concentration and no proliferation at high androgen levels. The last model g_3 assumed positive growth during androgen deprivation and negative growth in the abscence of androgen deprivation, i.e., degradation of the AI population without therapy. Ideta considered the three different dynamics for the AI population, to analyze the effect of the different hypotheses on the tumor development. According to the authors, the last two assumption are supported by biological evidence (see [ITTA08, pp. 600-602]). The first assumption is studied to illustrate the behavior of a truly androgen independent AI population. Since I wanted to consider the development of the same patient as for Portz' tumor model, the dynamics of the androgen level A are assumed to be the same as in section 3.2. To summarize Ideta's prostate cancer model, the following dynamics were considered:

$$\begin{aligned}
\frac{dX_1}{dt} &= \left(\alpha_1 \frac{A}{A+k_1} - \beta_1 \left(k_2 + (1-k_2)\frac{A}{A+k_3}\right) - m(A)\right) X_1, && \text{(AD volume)} \\
\frac{dX_2}{dt} &= m(A)X_1 + \left(\alpha_2\, g_i(A) - \beta_2\right) X_2, && \text{(AI volume)}
\end{aligned}$$

where the growth rates g_i of the AI population are given by

$$g_i(A) = \begin{cases} 1 & \text{if } i = 1, \quad \text{(constant growth)} \\ 1 - \left(1 - \frac{\beta_2}{\alpha_2}\right)\frac{A}{A_0} & \text{if } i = 2, \quad \text{(stationary at max. androgen)} \\ 1 - \frac{A}{A_0} & \text{if } i = 3, \quad \text{(decreasing at max. androgen)} \end{cases}$$

and the mutation rate from the AD to the AI population is given by

$$m(A) = m_1 \left(1 - \frac{A}{A_0}\right) X_1.$$

Furthermore the PSA level is defined to depend proportionally on the AD and AI cell populations, namely

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

which also was the PSA model initially considered by Portz.

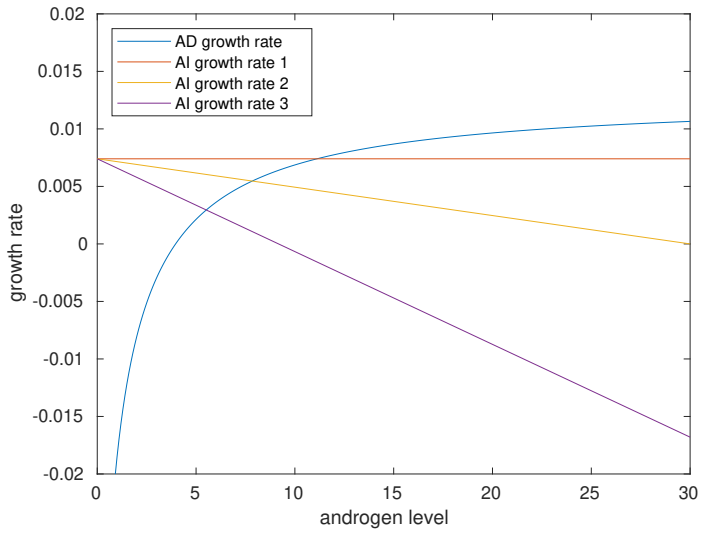

Figure 5: Ideta's growth rates for the AD population and the three different AI populations with respect to A.

4.2 Numerical Simulation

In this section I present my numerical results from the simulations of Ideta's tumor model with the three different growth models for the AI population. It is divided into the simulations of the model without therapy, with CAS therapy and with IAS therapy. For the parameter values one can consult the tables 3 and 4. The following initial conditions were considered for the simulations:

$$\begin{aligned} X_1(0) &= 100, \\ X_2(0) &= 0, \\ A(0) &= A_0. \end{aligned}$$

Because the PSA level moves in tandem with the total tumor volume, it follows the same increases and decreases. Therefore it is of no particular interest to discuss the PSA development separately when discussing the effect the different treatments on the tumor model. Though it is still serves as a means to illustrate the IAS treatment protocol.

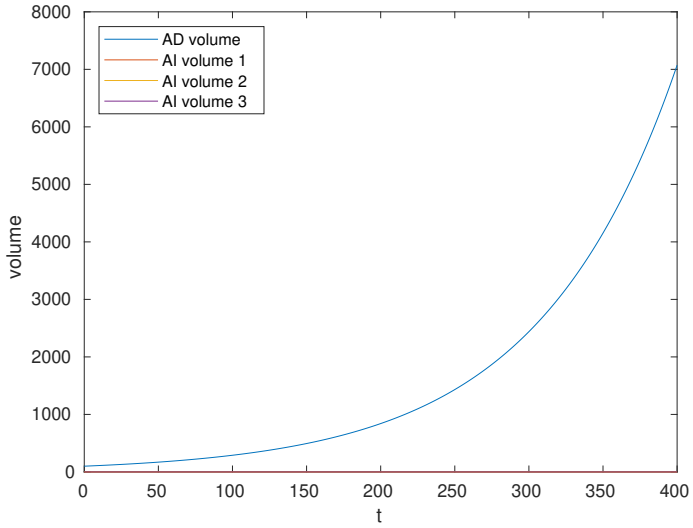

Figure 6: Evolution of Ideta's tumor model (no therapy).

No Therapy (see figure 6) Without therapy the AD tumor volume grew exponentially. For neither of the growth models the system showed any development of the the AI population, because the mutation rate from AD to AI population was identically zero at all times.

Continuous Androgen Suppression Therapy (see figure 7) After an initial increase the AD population rapidly decreased to zero. Whereas the AI population increased from the beginning, due to the mutation towards androgen independence, causing a relapse of the patient at around 300 days. For all different growth models the AI population increased exponentially at a constant rate, that only differed in its magnitude. No fundamental differences can be observed in the general profiles of the evolution graphs.

Intermittent Androgen Suppression Therapy The simulation with the first growth function g_1, that assumed constant proliferation at all androgen levels, showed how the AI population increased exponentially (see figure 8). The IAS protocol still allotted five cycles of treatment starting at day 95, which eventually caused the AD populatin to decrease to zero. The off-treatment peroids had a duration of about 34 days and the on-treatment periods took around 75 days, with the last one beeing slightly longer at 95 days.

The second simulation, assuming AI proliferation with the growth function g_2, which implied a stationary AI population at high androgen levels, resulted in a prolongation of the disease progression in comparison to CAS therapy (see figure 9). However the therapy could not avert the relapse of

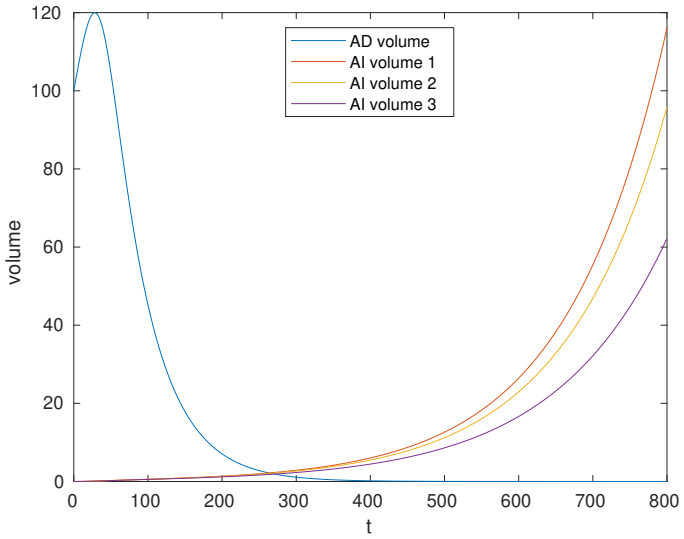

Figure 7: Evolution of Ideta's tumor model (CAS therapy).

the patient. After 95 days the IAS therapy was suspended six times for a duration ranging from 35 to 40 days and one last time for 57 days, while the duration of the treatment periods inbetween increased from 72 to 109 days. After the seven treatment cycles, at day 854, the therapy was permanently switched on, which caused exponential growth of the AI population and apoapsis of the AD population.

For the third simulation the growth function g_3 was considered for the AI population, that effectuated decline of the population at high androgen concentrations and proliferation at low androgen levels. This assumption produced periodic behaviour of the tumor populations where the AD population oscillated between 77 and 47 mm^3 and the AI population oscillated between 1 and 2 mm^3 (see figure 10). Notably the treatment didn't result in a cure in this model, but neither in a deterioration of the patient's condition. The tumor seemed to be stabilized indefinitely without noticable development of androgen independent tumor cells. The IAS protocol started at day 95 with suspension of the therapy for 34 days, followed by a continuation of the therapy for about 71 days. Eventually the periods of therapy omission stabilized at 36 days and the periods of therapy continuance stabilized at 72 days, yielding a full therapy cycle every 108 days. This syncronization of the therapy and tumor volumes is in fact not a singular case, as further testing with different therapy parameters showed. Various combinations of values for r_0 and r_1 were considered and all led to similar results, with the exception of the choices including $r_1 \leq 2$, where the IAS therapy effectively became CAS therapy and showed the same behavior as discussed already.

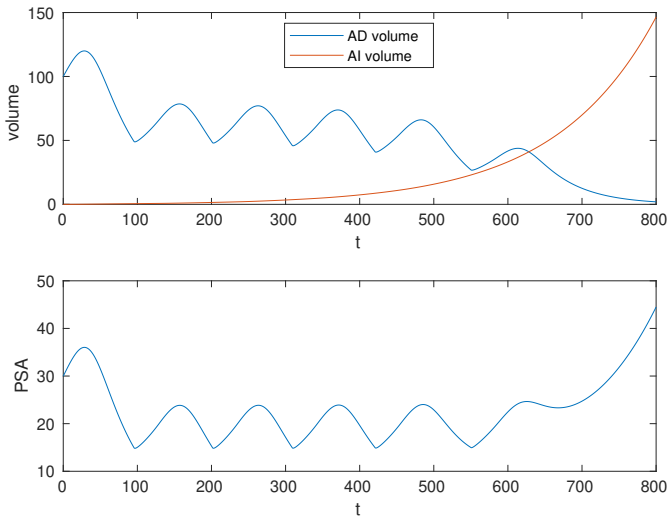

Figure 8: Evolution of Ideta's tumor model (IAS therapy) with growth function g_1 for the AI population; Cancer volumes (top) and PSA level (bottom).

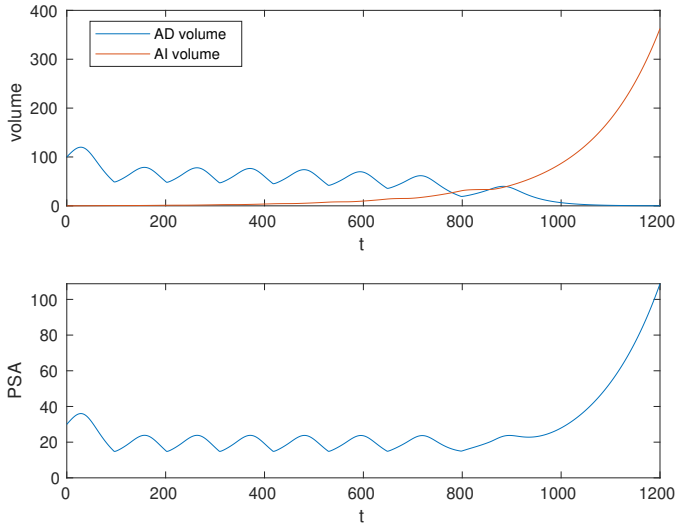

Figure 9: Evolution of Ideta's tumor model (IAS therapy) with growth function g_2 for the AI population; Cancer volumes (top) and PSA level (bottom).

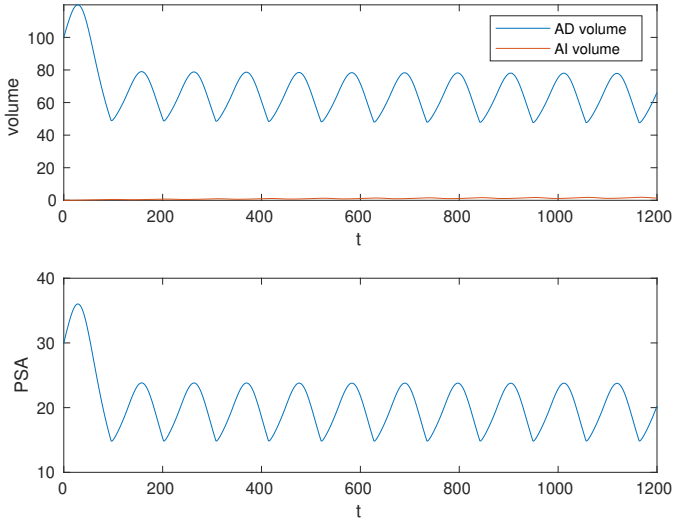

Figure 10: Evolution of Ideta's tumor model (IAS therapy) with growth function g_3 for the AI population; Cancer volumes (top) and PSA level (bottom).

5 Comparison of Tumor Models

5.1 Parameter Estimation and Adaptation

The goal of the comparison of tumor models is to illustrate the effect of the different assumptions concerning the behavior of the AI population on the IAS therapy protocols derived for a given patient. But as could be seen in the sections 3.3 and 4.2 the numerical values for Portz' and Ideta's model differed significantly. Particularly for CAS therapy or without treatment the models yielded different data but not generally different behaviors. To attain comparable values under these somewhat more trivial conditions, altering the parameters seemed necessary. This would ultimately allow the comparison of the IAS protocols between the models. Changing the growth parameters could be interpreted as tailorfitting the models to the same patient. While being unsure how the AI population of said patient would develop, which is why multiple growth models are considered in the first place, the development of the AD population should coincide for all models, since the assumptions on it are equivalent. Now I could have chosen either AD population to match the behavior of the other, but since Portz' parameters seemed to be more accurately fitted to real patient data, I chose to alter the parameters in Ideta's model. To this end I first considered the stationary solutions to the AD cell quota Q_1 in Portz' model depending on the androgen level A, i.e., I solved

$$0 = \nu_m \frac{q_m - Q_1}{q_m - q_1} \frac{A}{A + \nu_h} - \mu_m (Q_1 - q_1) - bQ_1,$$

for Q_1 to obtain the stabilized quota in the presence of constant androgen concentration A. The effective growth rate of the AD population in Portz' model is

$$g_{portz}(Q) = \mu_m \left(1 - \frac{q_1}{Q}\right) - d_1.$$

Inserting the stabilized quotas for $A_0 = 30$ and $A_1 = 1$ yielded an approximation of the maximal and minimal values for the growth rate of the AD population

$$\begin{aligned} g_{max} &:= g_{portz}(Q_1(A_0)) = g_{portz}(Q_1(30)) \approx 0.0052954, \\ g_{min} &:= g_{portz}(Q_1(A_1)) = g_{portz}(Q_1(1)) \approx -0.0043956. \end{aligned}$$

I further deduced the growth rate g of the AD population in Ideta's model given by

$$g_{ideta}(A) = \alpha_1 \frac{A}{A + k_1} - \beta_1 \left(k_2 - (k_2 - 1)\frac{A}{A + k_3}\right).$$

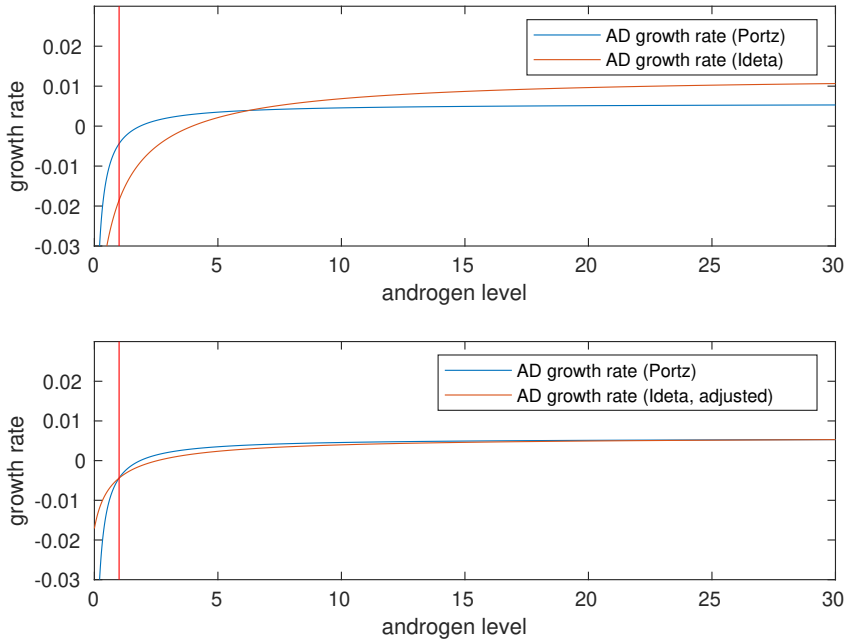

Figure 11: Growth rates for the AD populations in dependence on the androgen level with original parameters (top) and adjusted parameters (bottom); Red vertical indicates minimal androgen level at $A_1 = 1$.

Now, solving

$$g_{ideta}(A_0) = g(30) = g_{max},$$
$$g_{ideta}(A_1) = g(1) = g_{min},$$

for α_1 and β_1 yielded

$$\alpha_1 \approx 0.0081898,$$
$$\beta_1 \approx 0.0021377.$$

Adjusting the parameters in Ideta's model according to the above calculations resulted in almost identical behaviour of the AD population as for the one in Portz' model under the influence of the constant androgen concentrations $A_0 = 30$ and $A_1 = 1$ (see figure 11).

Since the parameters α_1 and β_1 have biological interpretations as proliferation and death rates of the AD population, it seemed reasonable, that in order to preserve the global balance of the ecosystem I would have to adjust the growth and death rates α_2 and β_2 of the AI population accordingly. This was achieved by rescaling them with the proportional adjustment made to

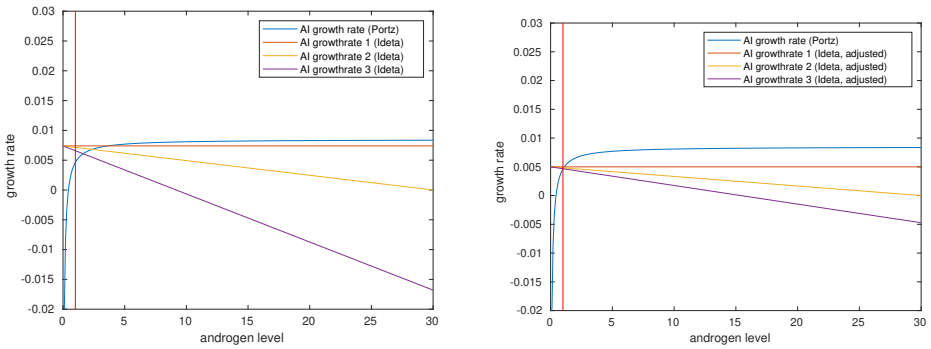

Figure 12: Growth rates for the AI populations in dependence on the androgen level with original parameters (left) and adjusted parameters (right); Red vertical indicates minimal androgen level at $A_1 = 1$.

α_1 and β_1, i.e., I wanted to preserve the ratios

$$\frac{\alpha_2^{old}}{\alpha_1^{old}} = \frac{\alpha_2^{new}}{\alpha_1^{new}} \iff \alpha_2^{new} = \alpha_2^{old} \cdot \frac{\alpha_1^{new}}{\alpha_1^{old}} \approx \alpha_2^{old} \cdot 0.40146,$$
$$\frac{\beta_2^{old}}{\beta_1^{old}} = \frac{\beta_2^{new}}{\beta_1^{new}} \iff \beta_2^{new} = \beta_2^{old} \cdot \frac{\beta_1^{new}}{\beta_1^{old}} \approx \beta_2^{old} \cdot 0.28128.$$

Inserting the values $\alpha_2^{old} = 0.0242$ and $\beta_2^{old} = 0.0168$ resulted in the new values

$$\alpha_2^{new} \approx 0.0081898,$$
$$\beta_2^{new} \approx 0.0047255.$$

These parameter estimations led to equal magnitude of the growth rates in Portz' and Ideta's model under constant androgen suppression while still reflecting the different assumptions made on the behavior of the AI population at high androgen concentrations. In fact the AI growth rates almost coincide for $A_1 = 1$ and are equally spaced for $A_0 = 30$ (see figure 12).

Finally it remains to mention the differences in the PSA models established by Portz and Ideta, since they are fundamental to deriving the IAS protocol. Actually Portz started with the same PSA model as Ideta but eventually derived an improved model, which more accurately matched real patient data. Said improvements are due to PSA dynamics, depending on the local androgen concentration by means of cell quotas. Thus I established the androgen cell quotas and the PSA dynamics as in section 3.1 for Ideta's tumor model, with the corresponding Parameter values in table 2. This altered tumor model, with the new parameter values from table 1, was considered for the comparison to Portz' tumor model.

Table 1: Ajusted parameter values chosen for the numerical simulation of Ideta's tumor model for the comparison to Portz' tumor model

Parameter	New Value	Old Value
α_1	0.0081898	0.0204
α_2	0.0097153	0.0242
β_1	0.0021377	0.0076
β_2	0.0047255	0.0168

5.2 Comparison of Numerical Simulations

In the following I discuss my findings on the differences and similarities of the simulations of the various tumor models by Portz and Ideta. To this end the models have been simulated with the respective parameter values from the tables 1, 2, 3 and 4, as discussed in section 5.1. The same initial conditions as in section 3.3 and section 4.2 have been chosen for consistency.

No Therapy (see figure 13) All models attained almost identical, exponentially growing values for the tumor volumes and consequently for the PSA levels. This was to be expected from the previous parameter estimations.

Continuous Androgen Suppression Therapy (see figure 14) During continuous androgen deprivation all models responded with a delayed de-

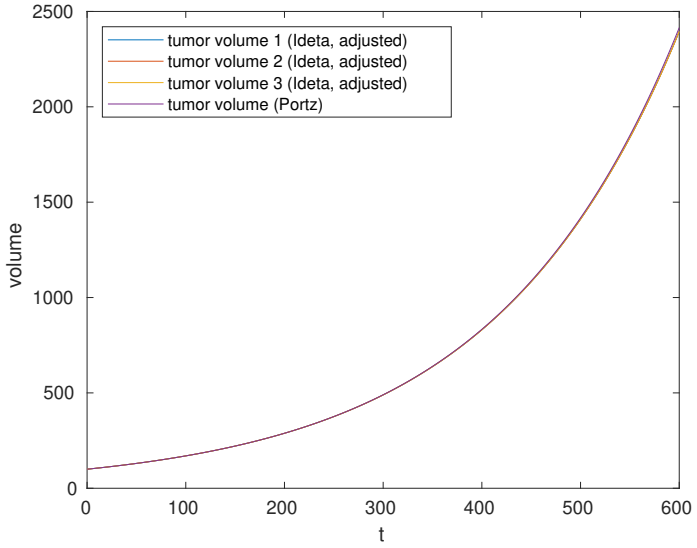

Figure 13: Evolutions of Portz' and Ideta's adjusted tumor models (no therapy).

cline of the tumor volume, which was caused by the receding AD populations. The magnitudes of the attained values were equal up until the relapses occured, which were due to an increasing AI population for all models. Only the timings of the relapses, starting from 500 days, differed by about half a year. Furthermore the chronological order of relapses conincided with the decreasing order of the growth rates of the AI populations at low androgen levels. More explicitly, the tumor populations grew exponentially with Ideta's growth model g_1 having the strongest growth, followed by the gowth models g_2 and g_3 and with Portz' model having the weakest growth. Generally speaking the tumor models all had similar developments, differing only in the magnitude of their proliferation.

Intermittent Androgen Suppression Therapy (see figure 15) The Ideta model with the first growth function g_1 for the AI population was the one to experience the fastest growth overall and experienced only five IAS off-treatment cycles. The first break of the treatment was initiated after 191 days. On average the off-therapy periods took around 16 days and were followed by peroids of androgen suppression, which increased from 96 to 125 days. The evolution of the second Ideta model with the function g_2 as growth rate of the AI population had the second fastest growth overall and received six periods of treatment suspension, which lasted 15 to 18 days each, starting at day 191. Between each of these periods the treatment was continued for 95 to 128 days. The last of the simulations of Ideta's model

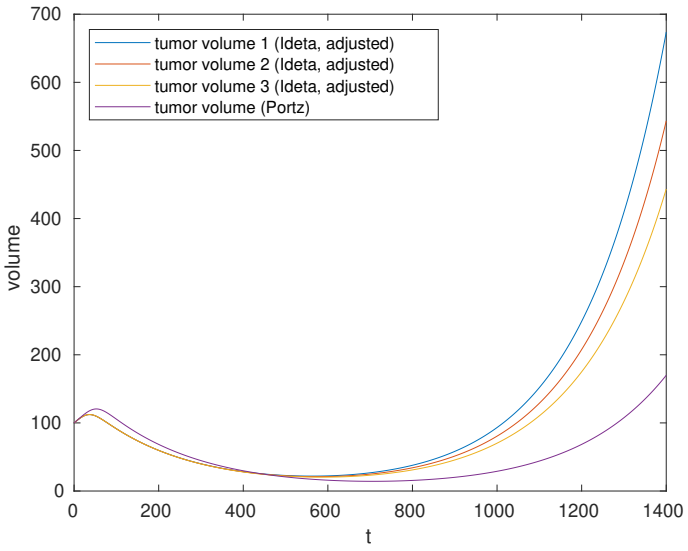

Figure 14: Evolutions of Portz' and Ideta's adjusted tumor models (CAS therapy).

utilized dynamics following the funcion g_3 as growth for the AI cells. Under these assumptions a total of seven treatment omissions were allocated by the IAS protocol, beginning after 190 days. The duration of periods without treatment ranged from 16 to 18 days, while the consecutive periods of androgen suppression took around 95 days for the first four treatment cycles and increased to 101 and 113 days for the last two interim applications. Remarkably the system did not enter the cyclic behavior oberved in section 4.2 for any tested set of therapy parameters, which is due to the alteration of growth parameters. For a description of Potz' tumor model and its IAS protocol see section 3.3, since the tumor dynamics were unchanged.

In common the simulations all had the duration of the therapy intermissions of around 17 days. Notably, none of the models predicted a cure of the patient by hormonal therapy, because the mutation towards androgen independence and the final period of constant androgen suppression eventually dominated the tumor dynamics.

A minor difference between the simulations was the initiation of the first therapy intermission phase for Portz' model after 215 days and for Ideta's model after only 190 days, regardless of the assumption made on the AI growth. One of the most prominent differences of the simulations were the different IAS protocols. While Portz' model received four periods off treatment, the different growth models based on the functions g_1, g_2 and g_3 each had five, six and seven periods without androgen deprivation. This order also coincides with the decreasing order of growth rates for the AI population at high levels of androgen (see figure 12), which are the characterizing differences of the models. Also the interim treatment periods of the different simulations were generally decreasing in length with increasing number of treatment cyles. Furthermore the IAS therapy had a positive impact on delaying the tumor relapse in all cases except in the case of Portz' model, where the relapse was accelerated by about half a year in comparison to CAS (see section 3.3). Thus one can see, how fundamental the impact of the different assumptions on the AI populations were for deriving the IAS treatment protocol and the effectiveness of the therapy.

Summary To sum up the comparison one could describe the behaviors of the various tumor models as almost equivalent under CAS therapy and without therapy. The different assumptions on the AI population further implied the derivation of different numbers of treatment cycles during the IAS therapies. None of the hormonal treatments led to a cure of the patient. Hence a combined therapy with, e.g., chemo- or radiation therapy could be advisable for the patient. Though, one could still surmise that IAS therapy had a positive effect on the patient, since the relapse was delayed in three of four cases, and at least the quality of life was improved in comparison to CAS therapy.

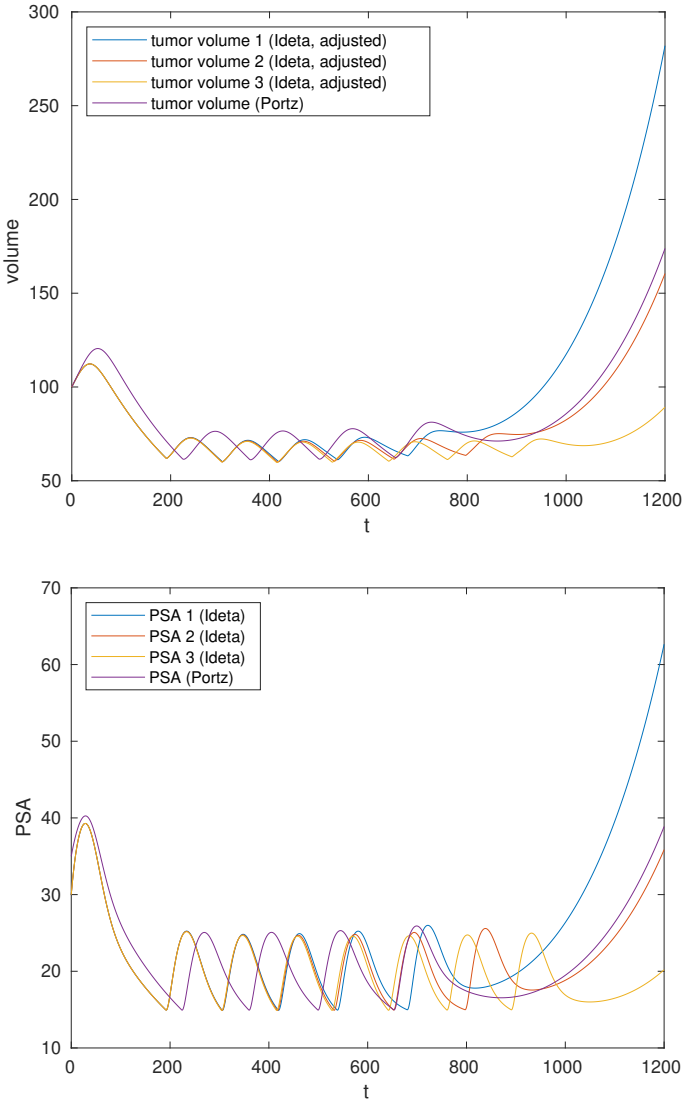

Figure 15: Evolutions of Portz' and Ideta's adjusted tumor models (IAS therapy).

Appendix

Table 2: Parameter values chosen for numerical simulation of Portz' tumor model (source: [PKN12]).

Parameter	Value	Description
ν_m	0.275	maximum cell quota uptake rate
q_m	5	maximum cell quota
μ_m	0.025	maximum cell proliferation rate
ν_h	4	uptake rate half-saturation level
q_1	0.3	minimum AD cell quota
q_2	0.1	minimum AI cell quota
b	0.09	cell quota degradation rate
d_1	0.015	AD cell apoptosis rate
d_2	0.015	AI cell apoptosis rate
c_1	0.00015	maximum AD to AI mutation rate
c_2	0.0001	maximum AI to AD mutation rate
K_1	0.08	AD to AI mutation half-saturation level
K_2	1.7	AI to AD mutation half-satutation level
σ_0	0.004	baseline PSA production rate
σ_1	0.05	AD PSA production rate
σ_2	0.05	AI PSA production rate
ρ_1	1.3	AD PSA production half-saturation level
ρ_2	1.1	AI PSA production half-saturation level
δ	0.08	PSA clearance level
γ	0.08	androgen proliferation rate

Table 3: New parameter values chosen for numerical simulations of Portz' and Ideta's tumor model.

Parameter	Value	Description
A_0	30	maximum androgen level
A_1	1	minimum androgen level
r_0	20	IAS control switch-on threshold
r_1	15	IAS control switch-off threshold

Table 4: Parameter values chosen for initial numerical simulation of Ideta's tumor model (source: [ITTA08]).

Parameter	Value	Description
α_1	0.0204	maximum AD proliferation rate
α_2	0.0242	maximum AI proliferation rate
β_1	0.0076	AD cell death rate
β_2	0.0168	AI cell death rate
k_1	2	AD proliferation rate half-saturation level
k_2	8	Effect of low androgen level on AD apoptosis rate
k_3	0.5	AD apoptosis rate dependence on androgen
m_1	0.00005	AD to AI mutation rate
c_1	0.3[1]	PSA dependence on AD cells
c_2	0.3[1]	PSA dependence on AI cells
γ	0.08	androgen proliferation rate

[1]The values were not explicitly given by Ideta, and were chosen to conform with Portz' PSA model

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