Is the Success of Adaptive Therapy in Metastatic Castrate Resistant Prostate Cancer Influenced by Cell-Type-Dependent Production of Prostate Specific Antigen?

Monica Salvioli*,[1,2], Len Vandelaer*,[2], Katharina Schneider[2], Rachel Cavill[2], Kateřina Staňková[1]

[1] Department of Engineering Systems and Services, Delft University of Technology, Delft, The Netherlands
[2] Department of Data Science and Knowledge Engineering, Maastricht University, Maastricht, The Netherlands

*joint first authors

Abstract

Prostate-specific antigen (PSA) is the most common serum marker for prostate cancer. It is used to detect prostate cancer, to assess responses to treatment and recently even to determine when to switch treatment on and off in adaptive therapy protocols. However, the correlation between PSA and tumor volume is poorly understood. Moreover, even though there is empirical evidence that some cancer cell types produce more PSA than others, recent mathematical cancer models assume that all cell types contribute equally to the PSA level.

Here, we compare time to competitive release of the PSA-based adaptive therapy protocol to that of the standard of care with continuous maximum tolerable dose under different assumptions on PSA production. In particular, we assume that androgen dependent, androgen producing, and androgen independent may contribute to the PSA production to different extents.

Our results show that, regardless the assumption on how much each type contributes to PSA, adaptive therapy is always at least as good as standard of care in the sense that it prolongs the time of competitive release when resistant androgen independent cells outcompete the other types. The time to competitive release under adaptive therapy and standard of care coincides if the PSA dynamics are influenced only by the resistant cells. Furthermore, we observe that in the adaptive therapy protocol, the number of treatment cycles and their length strongly depend on the assumptions about the PSA contribution of the three types. Thus, our results suggest that investigating the patient-specific PSA dynamics is crucial to designing adaptive therapy protocols.

Keywords: Metastatic castrate-resistant prostate cancer, prostate-specific antigen, adaptive therapy, tumor composition, game theory

1. Introduction

Prostate-specific antigen (PSA) is an enzyme produced by prostate epithelial cells, both normal and cancerous ones [1]. The PSA level in blood is influenced by many factors, including the age

of the patient, the ethnic group, the size of prostate, the presence of prostate cancer and its stage and tumor volume [14, 16, 15]. For this reason, the precise correlation between the PSA level and the tumor volume remains poorly understood [21, 17, 2]. Nevertheless, PSA is currently the most widely used serum marker to diagnose, stage and monitor prostate cancer and to assess responses to treatment [1, 7, 18, 3]. With the advent of new treatment strategies such as adaptive therapy (AT), which modulates the treatment depending on the response of the specific patient [8], getting more information on tumor progression became even more crucial.

In a recent clinical trial applying AT in patients with metastatic Castrate-Resistant Prostate Cancer, decision-making was entirely PSA-based: The patients were treated by abiraterone until their PSA level dropped below half of its initial value when the treatment was discontinued until the PSA recovered to its initial value. This led to personalized schedules of on and off treatment cycles, where the length of the cycles varied per patient [26]. They showed that the AT protocol could double the time to progression, compared to the standard of care applying treatment at the maximum tolerable dose (MTD). The AT protocol was determined through a game-theoretical model of metastatic Castrate-Resistant Prostate Cancer, where three competing cancer cell types were identified: T^+ cells requiring exogenous androgen to survive, T^P cells producing testosterone due to the upregulation of the enzyme CYP17A and T^- cells which are androgen-independent. Zhang et al. (2017) assumed that each of these cell types produces one unit of PSA and that 50% of the PSA decays out of the blood serum per unit time:

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathrm{PSA}(t) = \sum_{i\in\mathcal{T}} x_i - 0.5 \cdot \mathrm{PSA}(t), \tag{1}$$

with $\mathcal{T} = \{T^+, T^P, T^-\}$ and x_i being the number of cells of the corresponding type [26].

The PSA dynamics have been explored in detail in many mathematical models. For instance, West et al. (2019) used the same assumptions of Zhang et al. (2017) and extended the formula to model four different cancer cell types [24]. Hansen et al. (2020) kept the 50% decay rate but assumed that each cell type produces two units of PSA per time unit [11]. As it is unclear how precisely the PSA level decays, Cunningham et al. (2018) and Cunningham et al. (2020) did not assume any decay rate but assumed that PSA simply measures $\sum_{i\in\mathcal{T}} x_i$ [5, 6].

Hirata et al. (2010) considered three slightly different cell types: androgen-dependent cells, androgen-independent cells resulting from reversible changes, and androgen-independent cells arising from irreversible changes of genetic mutations. Still they assumed that each type produces one unit of PSA without any decay, similarly to other works [12, 13, 19, 22, 20, 9, 23].

While assuming that all cell types equally contribute to PSA production seems a reasonable and established theoretical starting point, there is evidence that in reality this might not be the case. This is supported by in vitro experiments by Gustavsson et al. (2005), who cultured an androgen-dependent human prostate cancer cell line until the appearance of an androgen-independent subline and measured the corresponding PSA secretion [10]. His results suggest that in some cases the PSA dynamics, as introduced in [26, 5], might not reflect the actual tumor burden and that a more precise estimation of the PSA could be derived by accounting for the heterogeneity of the tumor cell population.

Consistent with this finding, we build on the model by Zhang et al. (2017) and Cunningham et al. (2018), assume that the three cell types can produce different amounts of PSA and explore different scenarios. In particular, we are interested in addressing and modelling the consequences of this assumption on the effectiveness of AT.

In the next section, we introduce the model and the parameters. Following [26, 5], we consider

three categories, based on the response to the treatment: best responders, responders and non-responders. In Section 3, we measure the superiority of AT over continuous MTD for each category assuming that the different cell types contribute to PSA production to different extents. Section 4 concludes by summarizing the main outcomes and discussing limitations and future research.

2. Model

We use the Lotka-Volterra competition model by [26, 5] to describe the interactions between the testosterone-dependent T^+, the testosterone-producer T^P and the testosterone-independent T^- cell types under abiraterone therapy. The instantaneous rate of change in the population size of each cell type $i \in \mathcal{T} = \{T^+, T^P, T^-\}$ is:

$$\frac{dx_i}{dt} = r_i x_i \Big(1 - \frac{\sum_{j \in \mathcal{T}} a_{ij} x_j}{K_i}\Big),$$

where r_i represents the growth rates, K_i the carrying capacities and a_{ij} the coefficients of the competition matrix

$$A = (a_{i,j}) = \begin{array}{c} \\ T^+ \\ T^P \\ T^- \end{array} \begin{array}{c} \begin{array}{ccc} T^+ & T^P & T^- \end{array} \\ \begin{pmatrix} a_{1,1} & a_{1,2} & a_{1,3} \\ a_{2,1} & a_{2,2} & a_{2,3} \\ a_{3,1} & a_{3,2} & a_{3,3} \end{pmatrix} \end{array}$$

As in Zhang et al. (2017) and Cunningham et al. (2018), we set the growth rates to $r_{T^+} = 0.27726$, $r_{T^P} = 0.0034657$ and $r_{T^-} = 0.0066542$, which are derived from the measured doubling times of representative cell lines [26, 5, 4].

Following [26, 5], we assume that abiraterone reduces the ability of T^+ and T^P cells to acquire testosterone and we model this effect as a reduction in the carrying capacity of these cell types. In particular, abiraterone diminishes the ability of T^P cells to exploit the CYP17A pathway to convert cholesterol into androgens and therefore inhibits the production of testosterone. For this reason, in the absence of treatment the carrying capacity of the T^P cells is set to $K_{T^P} = 10000$ while under treatment it is reduced to $K_{T^P} = 100$. As the T^+ cells rely on the endogenous testosterone produced by the T^P cells, following [26, 5] we assume that their carrying capacity is a linear function of the density of the T^P: $K_{T^+} = \mu x_{T^P}$, where $\mu = 1.5$ in the absence of therapy and $\mu = 0.5$ under therapy. As the T^- cells are not affected by abiraterone, their carrying capacity is always $K_{T^-} = 10000$.

Each competition coefficient $a_{i,j}$ describes the effect of cells of type j on the growth rate of cells of type i. The intra-cell type coefficients are set to $\alpha_{i,i} = 1$. Zhang et al. (2017), You et al. (2017) and Cunningham et al. (2018) assume that the inter-cell type coefficients have values from the set $\{0.4, 0.5, 0.6, 0.7, 0.8, 0.9\}$. Using these values they distinguish 22 cases, which they group into three categories, depending on the frequency of T^- cells at the equilibrium [26, 25, 5]:

- **Best responders**: twelve cases with a competition matrix promoting the absence of T^- and high frequencies of both T^+ and T^P. Like Cunningham et al. (2018) we use the following representative matrix for this category to explore model predictions [5]:

$$a_{i,j} = \begin{pmatrix} 1 & 0.7 & 0.8 \\ 0.4 & 1 & 0.5 \\ 0.6 & 0.9 & 1 \end{pmatrix}$$

- **Responders**: four cases with competition matrices resulting in low frequencies of T^- at initiation of therapy. Following [5] for this category we use this representative matrix:

$$a_{i,j} = \begin{pmatrix} 1 & 0.7 & 0.8 \\ 0.4 & 1 & 0.6 \\ 0.5 & 0.9 & 1 \end{pmatrix}$$

- **Non-responders**: six cases with a competition matrix resulting in high equilibrium frequencies of T^- ($\geq 20\%$). Like [5] for this category we use the following representative matrix:

$$a_{i,j} = \begin{pmatrix} 1 & 0.7 & 0.9 \\ 0.4 & 1 & 0.6 \\ 0.5 & 0.8 & 1 \end{pmatrix}.$$

The initial cell counts for each category are taken from [5] and illustrated in Table 1.

	$x_{T^+}(0)$	$x_{T^P}(0)$	$x_{T^-}(0)$
Best responder	606.06	757.58	$1.94 \cdot 10^{-10}$
Responder	560.36	747.59	47.10
Non-responder	319.63	707.76	273.97

Table 1: Initial cell counts, taken from [5]

As opposed to [26, 5, 6], where the PSA level at a certain time t is assumed to correspond to the total number of cancer cells at that time up to some decay, here we assume that the three cell types can produce different amounts of PSA, so that the PSA level at a certain time t corresponds to:

$$PSA(t) = \alpha x_{T^+}(t) + \beta x_{T^P}(t) + (1 - \alpha - \beta) x_{T^-}(t), \tag{2}$$

with $0 \leq \alpha \leq 1, 0 \leq \beta \leq 1 - \alpha$. For each representative case, we compare the outcome under continuous MTD to the outcome under AT, where the treatment is administered until the PSA drops to half of its initial value, then paused and readministered only when the PSA recovers to its initial level.

In our case studies, we measure the success of the treatment through the time to competitive release (TCR), defined as the time at which T^- cells become the majority of the tumor composition. Following [26], we define

$$\text{TCR} = \min \left\{ t \in [0, T] : \frac{x_{T^-}(t)}{\sum_{i \in \mathcal{T}} x_i(t)} \geq \frac{x_{T^+}(t) + x_{T^P}(t)}{\sum_{i \in \mathcal{T}} x_i(t)} \right\}.$$

3. Results

In the following sections, we compare the effectiveness of standard of care using MTD to AT depending on different assumptions on the PSA production. We present results for the three patient categories best responders, responders, and non-responders. In all scenarios, we consider four different assumptions on the PSA production: 1) all cell types contribute equally to PSA production, i.e., $\alpha = \beta = \frac{1}{3}$, 2) only T^+ cells produce PSA, i.e., $\alpha = 1, \beta = 0$, 3) only T^P cells produce PSA, i.e., $\alpha = 0, \beta = 1$, and 4) only T^- cells produce PSA, i.e., $\alpha = 0, \beta = 0$.

3.1. Best responders

Figure 1 illustrates the population size of the three different cell types T^+, T^P, and T^- as well as the total cell count when applying MTD (Figure 1A) or AT (Figures 1B-1E). Here, we focus on the best responder scenario only. TCR is highlighted with a yellow dot and the yellow-shaded area covers the time after competitive release, when the treatment protocol is continued but strategically the treatment has already failed.

We observe that in all cases AT can improve TCR compared to applying MTD, except if $\alpha = \beta = 0$. In this case, the adaptive treatment protocol coincides with applying MTD all the time as T^- cannot be targeted by the treatment and thus, the PSA level never drops to half of its value. Table 2 shows the improvement of applying AT instead of MTD: If only T^+ cells are contributing to PSA production, we observe 32% improvement, if only T^P cells are contributing to PSA production, we observe 14% improvement, and if all three types are contributing equally to PSA production, we observe 13% improvement.

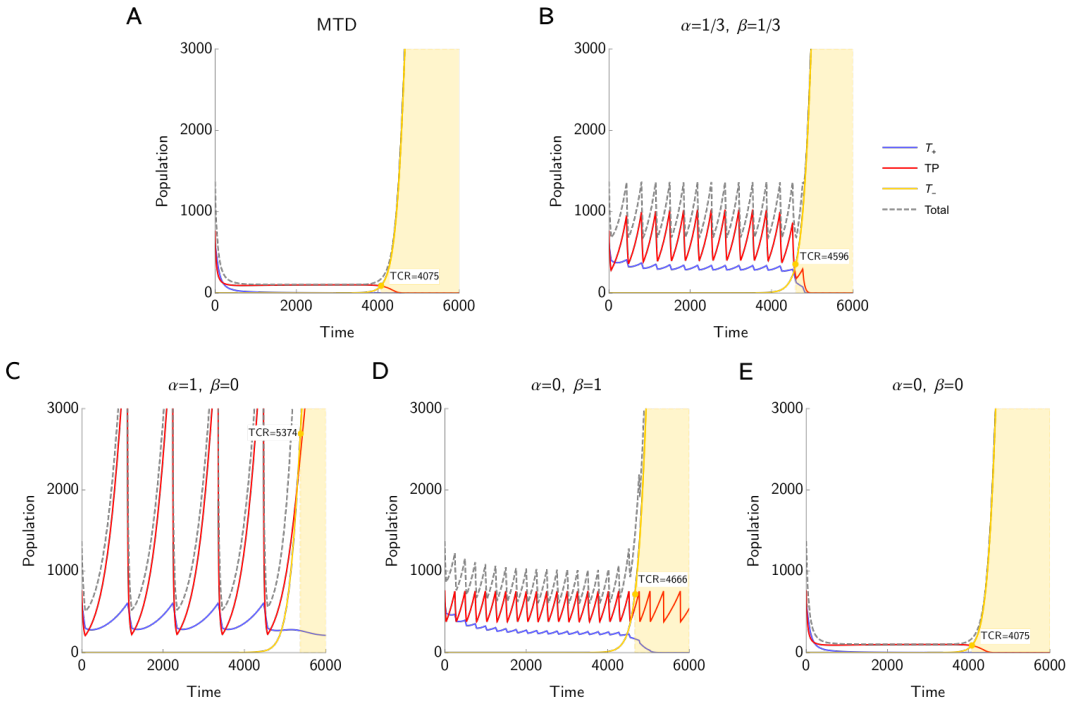

Figure 1: Best responders: Time to competitive release under MTD (A) and AT for different values of α and β (B-E). For all considered α and β values, AT is at least as good as standard of care using MTD. Only if $\alpha = \beta = 0$, i.e., T^- cells are the only PSA producers, we do not see any improvement when using AT instead of MTD, because we are following the same treatment protocol there. The number of treatment cycles as well as their length vary depending on α and β. It is important to note that treatment is continued after reaching TCR. After TCR, we observe oscillations in the population sizes of T^P only if T^P supports PSA production, i.e., $\beta > 0$.

The number of treatment cycles as well as their length vary dependent on α and β: We observe shorter treatment cycles leading to higher frequency in the oscillations of population sizes with increasing contribution of T^P cells to the PSA production. This is caused by the fact that T^P cells

are directly targeted by the treatment resulting in an immediate response in the PSA level if their contribution to PSA level is high. T^+ cells are only influenced by the treatment via the T^P cells and thus, there is a small delay in the drop of the PSA level leading to longer treatment cycles.

Treatment is continued after TCR. If $\alpha = 0$ and $\beta = 1$, we observe strong oscillations in the population size of T^P cells. As long as enough T^P cells are present and their contribution to PSA production is high enough, the PSA level can be influenced by the treatment and thus, the AT protocol will lead to treatment cycles after TCR. It is important to note that in our cases studies we do not define the tumor burden threshold corresponding to clinical progression or death, but we use the TCR as an early indicator of treatment failure.

While in Figure 1, we focus on the population size dynamics of a few selected values for α and β, Figure 2 shows a heat-map indicating the TCR for all possible values for α and β.

Parameter values	**TCR under MTD**	**TCR under AT**	**Improvement**
$\alpha = 1; \beta = 0$	4075	5374	32%
$\alpha = 0; \beta = 1$	4075	4665	14%
$\alpha = \frac{1}{3}; \beta = \frac{1}{3}$	4075	4596	13%
$\alpha = 0; \beta = 0$	4075	4075	0%

Table 2: Best responders: TCR under MTD or under AT including the improvement in percentage depending on different assumptions on PSA production. Applying AT increases TCR if T^- are not the only cells producing PSA. We observe the highest improvement in the TCR when applying AT instead of MTD for $\alpha = 1, \beta = 0$.

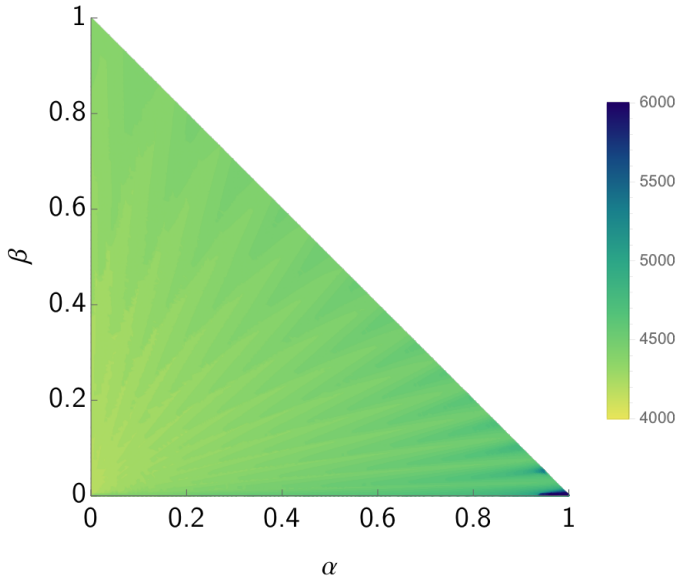

Figure 2: Best responders: Heat-map of TCR for different values of α and β.

3.2. Responders

Figure 3 shows the population dynamics for the three cell types in the responder scenario. Also in this scenario, AT improves on the TCR compared to applying MTD if at least one of either T^P or T^+ cells contribute to PSA production. Thus, the results are qualitatively similar to those for the best responders. However, quantitatively, a much lower TCR can be achieved in the responder scenario. This holds both for following an AT protocol as well as for applying MTD. While applying MTD leads to a TCR of 202, $\alpha = 1, \beta = 0$ and $\alpha = 0, \beta = 1$ following the AT protocol lead to the highest TCR of 499 and 497, respectively. Again, we observe the same results for applying MTD and for applying treatment based on the PSA level of the patient if $\alpha = \beta = 0$. The results in terms of TCR obtained by different assumptions on α and β as well as the improvement of applying AT compared to applying MTD are displayed in Table 3.

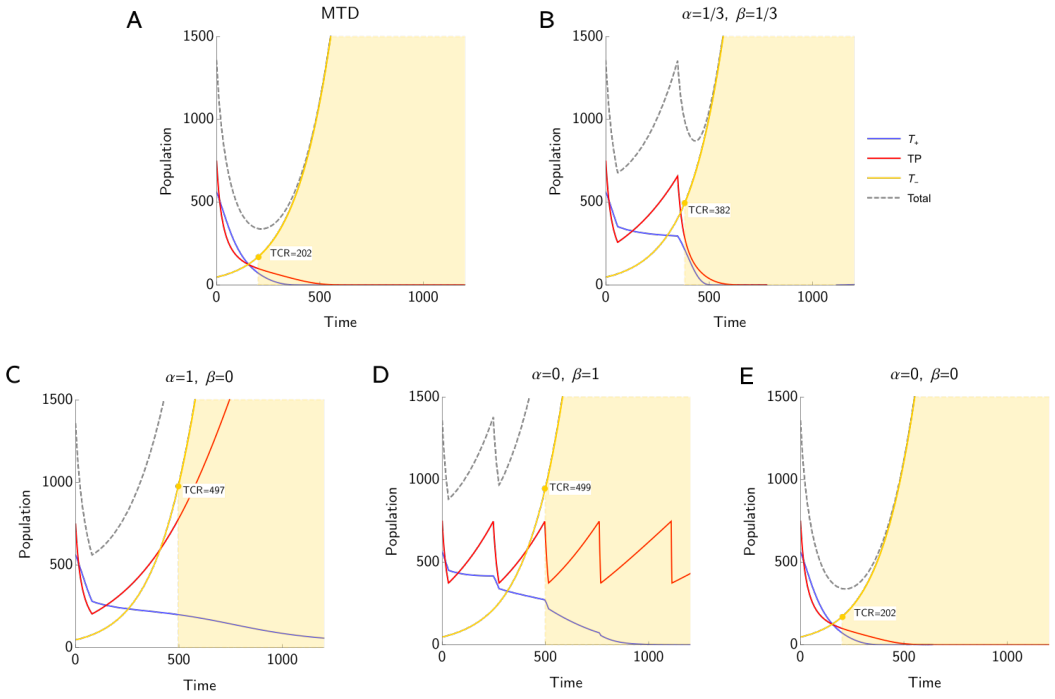

Figure 3: Responders: Time to competitive release under MTD (A) and AT for different values of α and β (B-E). For all considered α and β values, AT is at least as good as standard of care using MTD. Only if $\alpha = \beta = 0$, i.e., T^- cells are the only PSA producers, we do not see an improvement when using AT instead of MTD, because we are following the same treatment protocol there. We observe the highest TCR for $\alpha = 0, \beta = 1$, but considering $\alpha = 1, \beta = 0$, we achieve almost the same TCR.

For $\alpha = 1, \beta = 0$ and $\alpha = \beta = \frac{1}{3}$, the treatment is only stopped once in the AT before reaching TCR. For $\alpha = 0, \beta = 1$, there are at least two full treatment cycles. However, as expected, the number of cycles is much lower than the number in the best responder scenario.

Figure 4 illustrates TCR for all possible values for α and β. We observe the highest values for TCR if $\alpha > 0.6, \beta > 0.2$. Interestingly, if T^+ cells are the only PSA producers, i.e., $\alpha = 1$, the TCR is lower. If T^- cells contribute a lot to PSA production, i.e., $\alpha < 0.2, \beta < 0.2$, the results show the

lowest TCR.

Parameter values	**TCR under MTD**	**TCR under AT**	**Improvement**
$\alpha = 1;\ \beta = 0$	202	497	146 %
$\alpha = 0;\ \beta = 1$	202	499	147 %
$\alpha = \frac{1}{3};\ \beta = \frac{1}{3}$	202	382	89 %
$\alpha = 0;\ \beta = 0$	202	202	0 %

Table 3: Responders: TCR under MTD or under AT including the improvement in percentage depending on different assumptions on PSA production. Applying AT increases TCR if T^- are not the only cells producing PSA. We observe the highest improvement in the TCR when applying AT instead of MTD for $\alpha = 1, \beta = 0$ and almost the same improvement for $\alpha = 0, \beta = 1$.

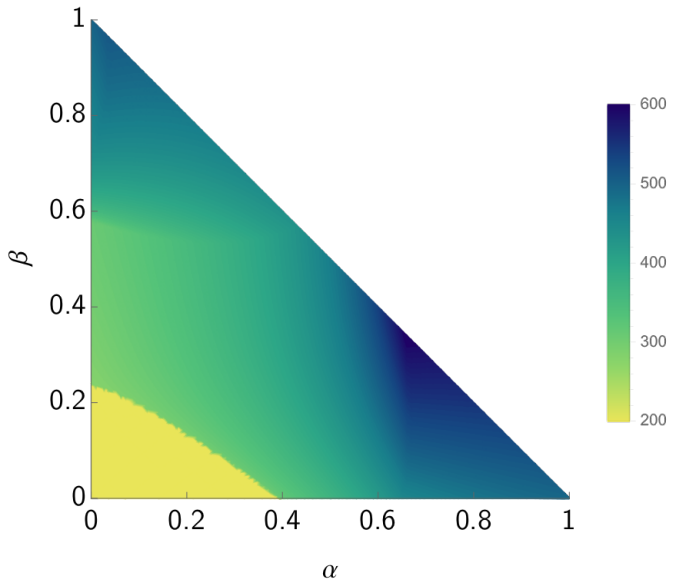

Figure 4: Responders: Heat-map of TCR for different values of α and β.

3.3. Non-responders

In Figure 5, the population size dynamics for T^P, T^+, and T^- in the non-responder scenario are displayed. As expected, the TCR decreases compared to the TCR obtained in the best responder and responder scenario. This holds both for applying AT and MTD. Also in the non-responder scenario, AT is at least as good as standard of care applying MTD, but in three of the four cases, AT cannot improve the TCR compared to the standard of care (see Table 4). However, if T^P cells are the only PSA producers ($\beta = 1$), AT can achieve a TCR that is about three times larger than standard of care. Only then, treatment is stopped at least once in the AT protocol before reaching TCR. In all other cases, treatment is not even stopped once before reaching TCR and thus, AT cannot improve the achieved TCR when applying MTD. Figure 6 supports the results displayed in Figure 5: The highest TCR can be achieved for $\alpha = 0, \beta = 1$, while in the other three scenarios, there is no difference in the TCR.

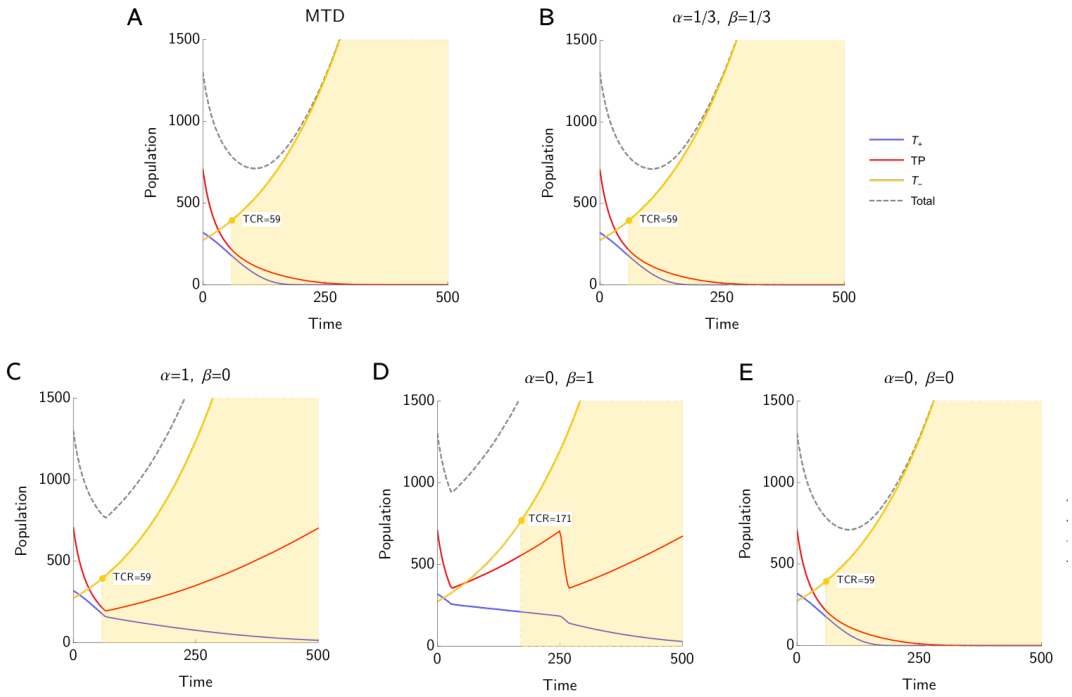

Figure 5: Non-responders: Time to competitive release under MTD (A) and AT for different values of α and β (B-E). For all considered α and β values, AT is at least as good as standard of care using MTD. If $\alpha = \beta = 0$ or $\alpha = \beta = \frac{1}{3}$ we do not see an improvement when using AT instead of MTD, because we are following the same treatment protocol there. In all other cases, AT outperforms standard of care using MTD. While the TCR obtained by applying MTD is 59, we observe the highest TCR of 171 for $\alpha = 1, \beta = 0$.

Parameter values	TCR under MTD	TCR under AT	Improvement
$\alpha = 1;\ \beta = 0$	59	59	0 %
$\alpha = 0;\ \beta = 1$	59	171	188 %
$\alpha = \frac{1}{3};\ \beta = \frac{1}{3}$	59	59	0 %
$\alpha = 0;\ \beta = 0$	59	59	0 %

Table 4: Non-responders. TCR under MTD or under AT including the improvement in percentage depending on different assumptions on PSA production. Applying AT increases TCR only if T^P cells are the only cells producing PSA. Then, we observe the highest improvement of 188% in the TCR when applying AT instead of MTD.

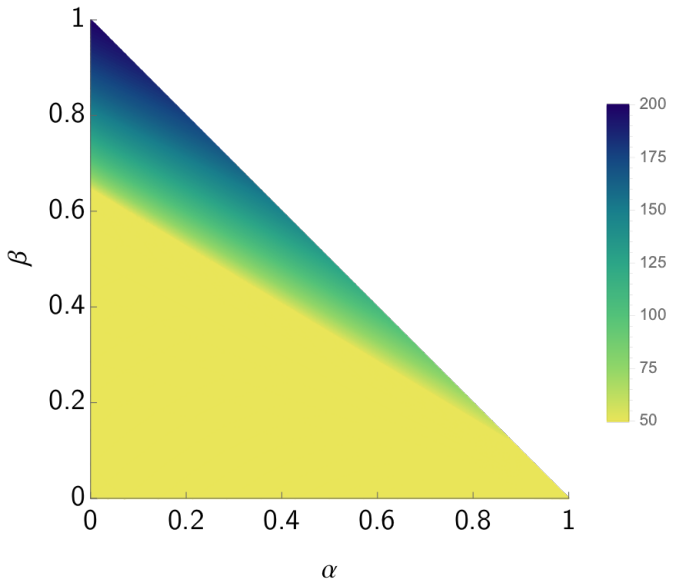

Figure 6: Non-responders: Heat-map of TCR for different values of α and β.

4. Discussion

Although its correlation with tumor volume remains unclear, the PSA has attracted significant attention as a biomarker for prostate cancer and has been used to modulate the treatment in protocols based on adaptive therapy [26]. While experimental studies revealed that the production of PSA depends on the tumor composition [10], mathematical models of adaptive therapy usually consider PSA as a surrogate for tumor burden and look only at the total cells count in order to determine when to pause or resume the treatment [26, 5, 24], putting further distance between the simulations and the clinical practice. Here we tried to disentangle the PSA dynamics from the tumor volume by weighting the contributions of the different cell types (Eq. 2). The rest of our modeling setup is based on [26, 5].

This work was designed to explore how different assumptions about the PSA producers can influence the superiority of adaptive therapy protocols over the standard of care based on maximum tolerable dose. To this aim, we compared the two protocols with a focus on four limit-cases:

1. All cell types contribute equally to PSA production;
2. T^+ cells are the only producers;
3. T^P cells are the only producers;
4. T^- cells are the only producers.

This was done for the three categories of patients analyzed in [5]: best responders, responders and non-responders, which differ in terms of the initial conditions: the responders have more T^- cells than the best responders and the non-responders have more T^- cells than all the others. Moreover, they differ in terms of the competition coefficients, which influence the population dynamics directly. Our results show that the protocol based on adaptive therapy outperforms the standard of care based on maximum tolerable dose in all the cases considered. The best responders have the longest time to competitive release under MTD compared to the other categories. Adaptive therapy can further improve it by 13-32% depending on the contribution of the different types to PSA production (Figure 1, Table 2). The greatest improvement is found in the case where the PSA is secreted almost only by the T^+ cells (Figure 2). There is only one case where the two protocols considered prove to be equivalent, which corresponds to the case where the PSA is produced only by the T^- cells, as shown in Figure 1.

For the responders, adaptive therapy can prolong the time to competitive release by 89-147% compared to MTD (Table 3). Similarly to the previous category, the most favourable outcome corresponds to the case where the PSA is secreted almost only by the T^+ cells, as shown in Figure 3 and Figure 4, while under the assumption that T^- are the only type contributing to PSA production adaptive therapy and MTD coincide.

As expected, the non-responders have the shortest time to competitive release under MTD compared to the other categories (Table 4). Figure 5 and Figure 6 show that for this category adaptive therapy would prolong the time to competitive release only in one case, where the PSA is produced mostly by the T^P type. In all the other cases the outcome obtained by applying adaptive therapy would coincide with the one obtained under MTD.

Overall, adaptive therapy proved to be at least as good as the standard of care in all the scenarios considered here. The evidence from these results suggests that the superiority of adaptive therapy over the standard of care does not depend on the specific assumptions about the contributions of the different cell types to the PSA production. Gustavsson et al. (2005) investigated PSA secretion in androgen-dependent and independent cells in vitro [10]. They reported that the level of PSA secreted by the androgen-dependent cells was tenfold higher than that by androgen-independent cells. This suggests that it might be unlikely to have the T^- cells as the main PSA producers, which corresponds to the case where adaptive therapy does not bring any improvements in any of the categories considered here.

An unsolved question remains whether the coefficients α and β governing the PSA dynamics (Eq 2) can change over time, especially as the tumor progresses to more advanced and aggressive states which are often characterized by androgen-independence. Similarly, we did not define any decay in this work. Considering time-dependent weights and including a decay rate in the PSA dynamics, which we leave for future works, would certainly improve the accuracy of the predictions about the benefit to adaptive therapy.

It has to be pointed out that the present work has focused on the time of competitive release and not on the clinical progression. While the time of competitive release can be considered, from a strategic point of view, as an early indicator of treatment failure, the idea of estimating it in the clinical practice is unrealistic. However, the fact that it happens probably much earlier than the real progression [6] means that physicians might have enough time to consider and intervene with

alternative treatment options.
Our results provide additional knowledge of the effectiveness of adaptive therapy compared to previous works, which primarily focused on the hypothesis that all the cell types produce the same amount of PSA. Future studies elucidating the mechanisms behind the PSA production or validating alternative biomarkers may enable the development of more effective and personalized AT protocols for prostate cancer.

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