Modeling Prostate Cancer Dynamics

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Abstract

Prostate cancer is the most common cancer in men aside from skin cancer and has the potential to progress into advanced, metastatic disease in some patients. Initially, prostate cancer is testosterone-dependent; therefore, androgen deprivation therapy (ADT), which lowers testosterone production and blocks androgen receptors, effectively reduces tumor burden. However, essentially all tumors treated with ADT eventually progress into castration-resistant prostate cancer (CRPC). In addition, ADT significantly lowers patient quality of life. An "early-warning" system that can accurately predict approaching CRPC could enable clinicians to refine treatment strategies and enhance both the length and quality of life for patients. Here we show that signals of castration resistance are present in serum PSA dynamics data. First, the decay rate of PSA during treatment correlates with CRPC progression. Second, a simple mathematical model of evolving CRPC fit to serum PSA data from the first cycle of ADT can accurately predict the subsequent cycle dynamics, including onset of CRPC in some patients. This result demonstrates the potential of mathematical models to predict treatment response in a given cycle using information from preceding cycles. Our model, however, was not universally accurate; predictions failed dramatically in a subset of patients. Nevertheless, our simple model is general enough to allow its application to study treatment resistance in most cancers with minimal adjustments. This model takes another step along the path towards personalized therapeutic strategies in oncology, and can be applied to improve adaptive therapy, allowing clinicians to better plan treatment to delay progression of treatment resistance.

1 Introduction

Cancer treatment resistance poses a significant challenge in achieving favorable patient outcomes and prolonging survival. The evolution of resistance to drug therapies often leads to tumor progression and diminished effectiveness of treatments. To address this pressing issue, there is a growing need for the development of robust models that can predict and monitor treatment resistance in individual patients, facilitating personalized treatment strategies and improved quality of life [3].

Cancer is defined as the uncontrollable growth of cells – the absence of cellular homeostasis. Likewise, prostate cancer is the abnormal, uncontrollable growth of cells within the prostate gland. Prostate cancer is caused by mutations in the genome that are responsible for the universal "6 Hallmarks of Cancer" : evasion of cell death, limitless replicative potential, sustained angiogenesis, tissue evasion, metastasis, insensitivity to antigrowth signals, and self sufficiency in growth signals [2]. However, prostate cancer is unique as the factor of testosterone compounds cellular growth and longevity. Testosterone enters the cell membrane of a prostate cell and is converted into DHT(dihydrotestosterone) via the 5 α reductase, which can then bind with an (AR) androgen receptor, phosphorylating the AR. After the phosphorylation of the AR, the AR can then bind to the DNA and with the help of transcription factors can activate the oncogenes responsible for enhanced cellular growth and longevity.

Due to testosterone inadvertently activating the fore-mentioned oncogenes being the driver of prostate cancer, most modern treatment consists of eliminating the production of testosterone in the testes, adrenal gland, and from prostate cells themselves. This treatment is referred to as androgen deprivation therapy(ADT), and a combination of cyproterone, leuprolide acetate, and abiraterone are used in this treatment plan. Cyproterone (CPA), The most common execution of this treatment is maximum tolerated dose (MTD), where the patient is continuously prescribed the maximum dosage of ADT medication that they can tolerate until the prostate cancer, inevitably, becomes resistant.

There are 6 pathways to treatment resistance in prostate cancer cells: hypersensitive pathway, promiscuous pathway, outlaw pathway, bypass pathway, and the lurker cell pathway. The hypersensitive pathway is a mechanism where the AR becomes more sensitive to the presence of DHT via a higher population of ARs to intercept DHT, increased sensitivity to DHT, or increased enzyme activity to convert testosterone into DHT. The "promiscuous pathway" allows for ligands outside of DHT to bind to the AR and activate the same set of oncogenes responsible for prostate cancer.

In this study, our focus lies in optimizing the administration of drug medications for prostate cancer to enhance patient outcomes and extend lifespan. Specifically, we aim to create a predictive model that utilizes prostate-specific antigen (PSA) as an indicator to assess treatment resistance. PSA, a biomarker commonly used in prostate cancer management, holds promise as a valuable tool in understanding the response of cancer cells to treatment interventions. By monitoring PSA levels during treatment cycles, we can potentially identify early signs of treatment resistance, allowing for timely adjustments to the therapeutic approach.

The significance of this research lies in the potential to provide medical scientists and clinicians with a universally applicable model that takes into account individual patient parameters, including PSA levels and other relevant blood markers. By incorporating these parameters into a robust predictive model, we can improve our understanding of how cancer cells develop resistance to treatment regimens and optimize drug administration strategies accordingly. This, in turn, has the potential to enhance the quality of life for cancer patients and extend their lifespan.

The current challenge lies in finding a model that can effectively capture the complexities of treatment resistance across various patients and cancer types. Each patient presents a unique biological landscape, and capturing this heterogeneity is crucial in developing a comprehensive and accurate predictive model. Through careful statistical tests, dynamic modeling and multi-linear regression analyses, we aim to validate the parameter values for our model and ensure its reliability and applicability in diverse clinical scenarios.

2 Data

The data we are using comes from "Canadian Prospective Phase II Trial of Intermittent Androgen Suppression" [1], a clinical study on advanced prostate cancer patients with recurring prostate cancer after radiation therapy. The data set includes information on PSA levels, testosterone levels, cycles, periods, medicine administered, dates, notes, and hematology. In this study, patients receive treatment for prostate cancer and their PSA is monitored, if at 24 and 32 weeks PSA is not normalized they are classified as treatment resistant and pulled from the study. If PSA is normalized at these benchmarks, then they are withdrawn from treatment after 36 weeks and their PSA is monitored every 4 weeks. Once the PSA surpasses a threshold of 10 ng/ml, treatment is resumed.

2.1 Data analysis methods

The data were initially filtered to remove patients with sparse data. To model the off and on phases, we use the exponential and Gompertz model respectively. The Gompertz model is represented by the following differential equation:

$$N'(t) = \hat{\alpha} N(t) \ln\left(\frac{K}{N(t)}\right). \tag{1}$$

Table 1 describes each parameter in the Gompertz model.

For both the on and off treatment phases, we look for a signal of oncoming treatment resistance by investigating how the mean/medians of the decay rates, basic growth rates, and carrying capacities of the groups—progressor, non-progressor, death/illness, and miscellaneous—compare to each other.

For the Off treatment phases, MATLab was used to fit both the Gompertz and exponential model to the patients PSA quantity within a given time interval. The Gompertz model gives us the best fitting because it accounts for the inflections and the sigmoidal nature of our data, although the basic growth rate from this model does not agree with our mechanistic model. Thus, the basic growth rate was derived from the

Table 1: Description of parameters from Gompertz Model (**??**).

Parameter	**Description**	**Units**	**Value**
$N(t)$	Number of Cancerous Cells	# of cells	$\mathbb{R}_+$
α	Growth Rate of Cancerous Cells	1/time(s)	$\mathbb{R}_+$
K	Carrying Capacity	# of cells	$\mathbb{R}_+$

exponential model. The basic growth rate, $\hat{\alpha}$, and the carrying capacity, K, from the Gompertz model needed to be filtered due to anomalies that contradicted the biology of cancer growth

There were scenarios where negative $\hat{\alpha}$ values occurred, the corresponding patient - cycle was removed as cancer growth should not be decreasing when off treatment.

A significant amount of the data yielded K values that were abnormally large and had no biological significance, these values were disregarded when doing further analysis. The justification removing these K values are as follows: time does not go on long enough for there to be an observable inflection point, there is not enough data to make a sensible fitting with, and there are strange fluctuations that lead to a complex r^2 values. The process for determining which K values are "abnormal" involved analyzing instances where K values exceeded 100. It was thus determined that K values above 118 ng/ml should be disregarded due to time not progressing far enough to have an observable inflection point.

After filtering the data, the data was then transported to the Python workspace using the Pandas library and the statistical analyses were performed. The ANOVA is used on both the $\hat{\alpha}$ and K values, the QQ - plot and Bartlett tests were used to test the assumptions of the ANOVA. The ANOVA, Q-Q plot, and Bartlett test were functions imported from the statistics library by SciPy. All figures/graphs were created using Matplotlib.

3 Mechanistic model

In addition to fitting these essentially phenomenological mathematical expressions to the data, we also attempted to develop a more detailed model that captures the underlying biology of the evolution of treatment resistance.

3.1 Derivation

We assume that the resistant prostate cancer cells and the sensitive prostate cancer cells are competing for the same resources. The well-known Lotka-Volterra competition model describes the dynamics of two competing species. Let $x(t)$ and $y(t)$ be the populations of the sensitive cells and resistant cells at time t, respectively. The model can be represented by the following system of ordinary differential equations:

$$\frac{dx}{dt} = rx\left(1 - \frac{x + \alpha y}{K}\right),$$
$$\frac{dy}{dt} = ry\left(1 - \frac{y + \beta x}{K}\right),$$

where r is the instrinsic growth rate of the cancer cells, α and β represent the effects of interspecific competition, and K is the carrying capacity of the cells. We introduce a new parameter μ, which is a function of time that is 0 when a patient is off treatment, and when a patient is on treatment, it is a positive constant that represents the per capita death rate caused by treatment. Next we assume that treatment causes a linear increase in the death rate of sensitive cells. We also introduce a new parameter, s, which measures the physiological effect of resistance. We will assume that the death rate caused by treatment is decreased

by e^{-s} in the resistant cells. Our model then becomes the following:

$$\frac{dx}{dt} = rx\left(1 - \frac{x + \alpha y}{K}\right) - \mu x,$$
$$\frac{dy}{dt} = ry\left(1 - \frac{y + \beta x}{K}\right) - \mu e^{-s} y.$$

We then introduce a new parameter, η, which represents how much the resistance mechanism affects the sensitive cell's ability to compete. We assume that resistance can increase death rate from competition by ηs. Also, we assume that resistant cells can have a lower instrinsic growth rate as they are mutated and less competant. The final parameter we introduce is ψ, which is a proportion that is a measures of cost to the resistant cell's instrinsic growth rate. The final assumption we make is that the cell's resistance mechanism can decrease its intrinsic growth rate by $e^{-\psi s}$. Thus our final model is the following:

$$\frac{dx}{dt} = rx\left(1 - \frac{x + \alpha y}{K}\right) - \mu x, \tag{2a}$$
$$\frac{dy}{dt} = re^{-\psi s} y\left(1 - \frac{y + (\beta + \eta s)x}{K}\right) - \mu e^{-s} y. \tag{2b}$$

Table 2: Description of parameters from Model (2).

Parameter	Description	Value	Units
r	intrinsic cell growth rate of sensitive cells	$(0, \infty)$	per time
K	carrying capacity	$(0, \infty)$	cells
μ	death rate caused by treatment	$(0, \infty)$	per time
η	measures how the cell's resistance mechanism affect its ability to compete	$[0, \infty)$	unitless
s	physiological measure of the cell's resistance to treatment	$(0, \infty)$	unitless
α	competition coefficient between resistant cells and sensitive cells	$(0, \infty)$	unitless
β	competition coefficient between sensitive cells and resistant cells	$(0, \infty)$	unitless
ψ	measure of cost to the resistant cells' intrinsic growth rate	$[0, \infty)$	unitless

3.2 Model analysis

Here we analyze the dynamical properties of our mechanistic model.

3.2.1 On treatment

In this subsection we analyze the on-treatment case; that is, consider model (2) where $t \in T_x$ (i.e., $\mu > r$). In this case, system (2) has the following equilibria:

$$\mathbf{E_0} = (0, 0),$$
$$\mathbf{E_1} = \left(\frac{K(r - \mu)}{r}, 0\right),$$
$$\mathbf{E_2} = \left(0, \frac{K(r - \mu e^{s(\psi - 1)})}{r}\right),$$
$$\mathbf{E_3} = \left(\frac{K(-\alpha\mu r + \alpha + \mu r - 1)}{\alpha\beta + \alpha\eta s - 1}, \frac{K(-\beta\mu r + \beta - \eta\mu r s + \eta s + \mu r - 1)}{\alpha\beta + \alpha\eta s - 1}\right).$$

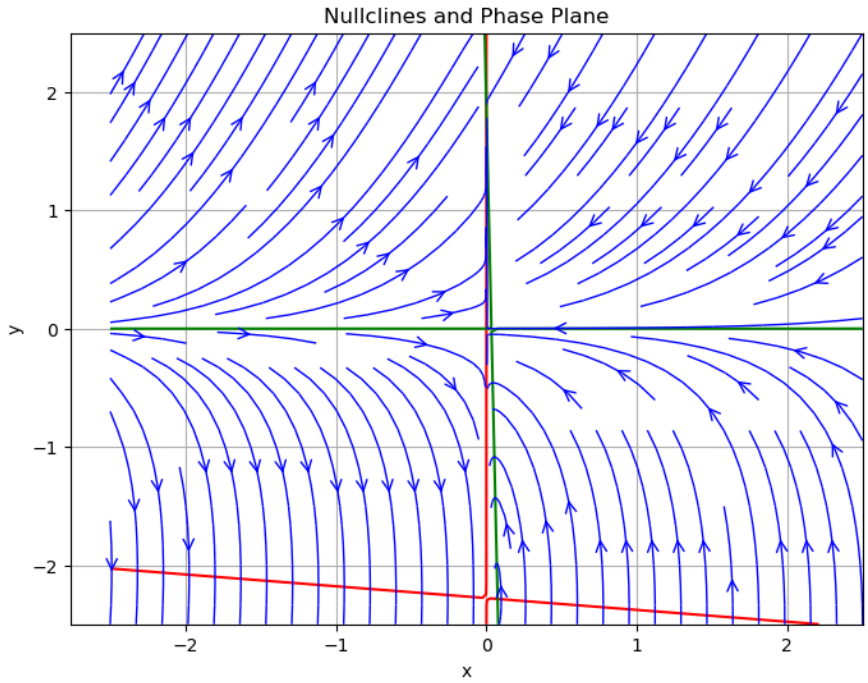

Figure 1: The parameter values used to create the graph above were $r = 3$, $\alpha = 10$, $\beta = 15$ $\eta = 50$, $K = 33.8466$, $\mu = 5.02$, $s = 0.8167$, and $\psi = 0.3$.

Theorem 3.1 (Equilibria Dynamics On Treatment)**.** *E_0 always exists, and it is locally asymptotically stable if and only if $\mu > re^{-s(\psi+1)}$. E_2 only exists when $-\mu e^{\psi-1} + r < 0$, and it is always locally asymptotically stable when it exists. E_1 and E_3 never exist in the positive cone.*

Proof. Since $\mu > r$, E_1 will always be negative, so we can disregard it. Let $\mathcal{N}_x$ be the set of points in the phase plane that satisfy $\frac{dx}{dt} = 0$. This set can be partitioned into 2 distinct subsets:

$$\mathcal{N}_{x1} := \{y\,;\, x = 0\}, \text{and}$$
$$\mathcal{N}_{x2} := \left\{(x, y)\,;\, y = \frac{K}{r}(r - \mu e^{s(\psi-1)}) - (\beta + \eta s)x\right\}.$$

Similarly, we define the set $\mathcal{N}_y$ as the set of points such that $\frac{dy}{dt} = 0$, which also can be partitioned as follows:

$$\mathcal{N}_{y1} := \{x\,;\, y = 0\}, \text{and}$$
$$\mathcal{N}_{y2} := \left\{(x, y)\,;\, y = \frac{K(r - \mu)}{\alpha r} - \frac{1}{\alpha}x\right\}.$$

Both $\mathcal{N}_{x2}$ and $\mathcal{N}_{y2}$ are decreasing linear functions of x. Since the x-intercept of $\mathcal{N}_{y2}$ is negative, no point in this set is positive. Therefore, the E_3 fixed-point, which occurs at the intersection of $\mathcal{N}_{x2}$ and $\mathcal{N}_{y2}$, never exists in a biologically relevant portion of the phase plane.

The general Jacobian matrix of this system is the following:

$$\mathbf{J}_{\text{on}}(x, y) = \begin{bmatrix} r\left(1 - \dfrac{(\alpha y + x)}{K}\right) - \dfrac{rx}{K} - \mu & -\dfrac{\alpha r x}{K} \\ -\dfrac{ry(\beta + \eta s)e^{-\psi s}}{K} & r\left(1 - \dfrac{(x(\beta + \eta s) + y)}{K}\right)e^{-\psi s} - \dfrac{rye^{-\psi s}}{K} - \mu e^{-s} \end{bmatrix}, \tag{3}$$

which when evaluated at E_0 becomes

$$\mathbf{J}_{\text{on}}(0, 0) = \begin{bmatrix} r - \mu & 0 \\ 0 & e^{-s}\left(re^{-s(\psi-1)} - \mu\right) \end{bmatrix}.$$

The eigenvalues are easily seen to be $r-\mu$ and $e^{-s}(re^{-s(\psi-1)}-\mu)$. The first eigenvalue is always negative because, by assumption, $\mu > r$. The second eigenvalue is negative when $re^{-s(\psi-1)}-\mu<0$. Also, E_0 must always exist because $\mathcal{N}_{x1}$ and $\mathcal{N}_{y1}$ always exist and they intersect at exactly $(0,0)$. Thus E_0 always exists, and it is locally asymptotically stable when $re^{-s(\psi-1)}-\mu<0$.

At E_2,

$$\mathbf{J}_{\text{on}} = \begin{bmatrix} r-\mu-\alpha\left(-\mu e^{s(\psi-1)}+r\right) & 0 \\ -(\beta+\eta s)\left(-\mu e^{s(\psi-1)}+r\right)e^{-\psi s} & e^{-s}\left(-\mu+re^{-s(\psi-1)}\right) \end{bmatrix}.$$

The eigenvalues of this matrix are: $[e^{-s}\left(\mu-re^{s(\psi-1)}\right),\ \alpha\left(\mu e^{s(\psi-1)}-r\right)+r-\mu]$. The first eigenvalue is negative when $\mu-re^{s(1-\psi)}<0$. This inequality is equivalent to $\mu e^{s(\psi-1)}-r<0$, so if the first eigenvalue is negative, the second eigenvalue must also be negative. E_2 exists when $r-\mu e^{s(\psi-1)}>0$ because that is when the point is positive. This inequality is also equivalent to the previous one, so E_2 exists when $r-\mu e^{s(\psi-1)}>0$, and it is always locally asymptotically stable when it exists. □

Table 3: Summary of boundary equilibrium dynamics for Model (**??**). LAS: locally asymptotically stable.

Equilibrium	**Existence**	**Stability**
$\mathbf{E_{0,0}}$	Always	• LAS iff $r-\mu e^{s(\psi-1)}<0$, otherwise it is unstable.
$\mathbf{E_{0,y^*}} = \left(0, \frac{K(r-\mu e^{s(\psi-1)}}{r}\right)$	$r-\mu e^{s(\psi-1)}>0$	• Always LAS when it exists.

Theorem 3.2. *If E_0 is the only equilibrium point that exists on treatment, it is globally asymptotically stable.*

Proof. When $x=0$ and arbitrary initial condition $y(0)\geq 0$, the solution of the system will be $(0, y(t))$. Thus, the solution will stay on the y-axis. By the uniqueness theorem of ODEs, no solution whose initial conditions are positive can cross the y-axis. We can use the same reasoning to show that no solution whose initial conditions are positive can cross the x-axis. Thus the positive quadrant of the phase plane is positively invariant. We seek to apply the theorem of Lyapunov, which requires that we find a positive definite function.

Definition 1 (Positive definite function)**.** *Let Ω be an open subset of $\mathbb{R}^2$ that contains a point, $\mathbf{p}$. Consider a C^1 function, $V(x,y)$, defined on Ω. This function $V(x,y)$ is **positive definite** on Ω if*

1. *$V(\mathbf{p})=0$; and*
2. *$V(\mathbf{p})>0$ for all $(x,y)\in\Omega$ such that $(x,y)\neq\mathbf{p}$.*

Let us first consider the case when E_2 does not exist. Let

$$V(x,y)=x^2+y^2. \tag{4}$$

Note that $V(x,y)\in C^1$, $V(0,0)=0$ and $V(x,y)>0$ everywhere else. Therefore, $V(x,y)$ is positive definite in $\mathbb{R}^2$.

Lemma 3.3 (Lyapunov's Theorem)**.** *Suppose $\mathbf{p}$ is a fixed point of model (2). If $V(x,y)$ is a positive definition function on domain Ω containing $\mathbf{p}$ and $V'(\mathbf{q})<0$ for all $\mathbf{q}\in\Omega$ such that $\mathbf{q}\neq\mathbf{p}$, then $\mathbf{p}$ is an asymptotically stable fixed point in which all solutions with $(x(0),y(0))\in\Omega$ approach $\mathbf{p}$ asymptotically.*

Consider the positive definite function $V(x,y)$ in equation (4), and note that

$$\frac{dV}{dt} = 2x\frac{dx}{dt}+2y\frac{dy}{dt} \tag{5a}$$

$$= 2x\left(rx\left(1-\frac{x+\alpha y}{K}\right)-\mu x\right)+2y\left(re^{-\phi s}y\left(1-\frac{y+(\beta+\eta s)x}{K}\right)-\mu e^{-s}y\right) \tag{5b}$$

$$= 2x^2(r-\mu)-2x\left(\frac{x+\alpha y}{K}\right)+2y^2e^{-s}\left(re^{s(-\psi+1)}-\mu\right)-2y^2re^{-\psi s}\left(\frac{y+(\beta+\eta s)x}{K}\right). \tag{5c}$$

By assumption, $x(0)$ and $y(0)$ are positive; since the positive quadrant is positively invariant, $x(t)$ and $y(t)$ must be positive for all t. Since $\mu > r$, the first term in expession (5c) must be negative. Since the second term only contains positive numbers, it must also be negative. The third term will be negative if $re^{s(-\psi+1)} - \mu < 0$, which is the same as the condition for when E_0 is the only non-negative equilibrium point. Finally, the fourth term will also be negative as all the terms in it are positive. Thus $\frac{dv}{dt} < 0$, so by Lemma (3.3) E_0 is globally asymptotically stable. □

Theorem 3.4. *If E_2 exists, it is globally asymptotically stable.*

Proof. Let f be our system on treatment, and let $u = \frac{dx}{dt}$ and $v = \frac{dy}{dt}$. We begin by showing that $f \in C^1(\Omega)$, where we define Ω to be the positive cone.

$$\frac{\partial u}{\partial x} = r - \mu - \frac{2rx}{K} - \frac{r\alpha y}{K}$$

This is a linear function of x, so it must be continuous.

$$\frac{\partial u}{\partial y} = \frac{r\alpha x}{K}$$

This is a constant function, so it must be continuous. By the same reasoning, the first order partial derivatives of u must be continuous, so we can conclude that f is C^1.

Lemma 3.5 (Bendixon's Criterion)**.** *Let $f \in C^1(\Omega)$. If $divf = \frac{\partial u}{\partial x} + \frac{\partial v}{\partial y}$ is non-zero and does not change sign Ω, then there are no limit cycles in Ω.*

When we expand and simplify div f we get the following:

$$\text{div}f = (r-\mu)(1+e^{-s}) - \frac{r\left(e^{-s}\left(2y + (\beta+\eta s)x\right) + 2x + \alpha y\right)}{K}$$

Since $\mu > r$, the first term is always negative. Previously, we showed that x and y are positively invariant, so the second term must also always be negative. Thus we can conclude that div f is non-zero and remains negative throughout the whole solution set, which shows that no limit cycles can exist.

Lemma 3.6 (Poincaré-Bendixson Theorem)**.** *Consider a planar system of differential equations:*

$$\frac{dx}{dt} = f_1(x,y), \tag{6}$$
$$\frac{dy}{dt} = f_2(x,y), \tag{7}$$

and suppose $f_1, f_2 \in C^1$. Let Ω be a positively invariant region of the phase space for system (6) containing a finite number of fixed points. Let $\Gamma(x,y)$ be a solution through point $\mathbf{p} \in \Omega$. Then the asymptotic limit of $\Gamma(x,y)$ is either (1) an asymptotically stable fixed point, or (2) an asymptotically stable limit cycle.

$\frac{dx}{dt}$ is negative throughout the whole first quadrant. If the solution is above E_2, $\frac{dy}{dt}$ is negative, and if the solution is below E_2, $\frac{dy}{dt}$ is positive. We also know that the solution set is positiveley invariant. All of this shows that solutions cannot diverge to infinity in the x direction or the y direction, and they must stay in a bounded region. Since there are no limit cycles, every solution will converge to a locally asymptotically stable equilibrium point. From our previous analysis, we know that when E_2 exists, it is the only locally asymptotically stable equilibrium, so E_2 will be globally stable. □

Table 4: Summary of boundary equilibrium dynamics for Model (**??**). Globally stable: globally asymptotically stable.

Equilibrium	**Existence**	**Stability**
$\mathbf{E_{0,0}}$	Always	• GAS if $r - \mu e^{s(\psi-1)} < 0$, otherwise it is unstable.
$\mathbf{E_{0,y^*}} = \left(0, \frac{K(r-\mu e^{s(\psi-1)}}{r}\right)$	$r - \mu e^{s(\psi-1)} > 0$	• Always GAS when it exists.

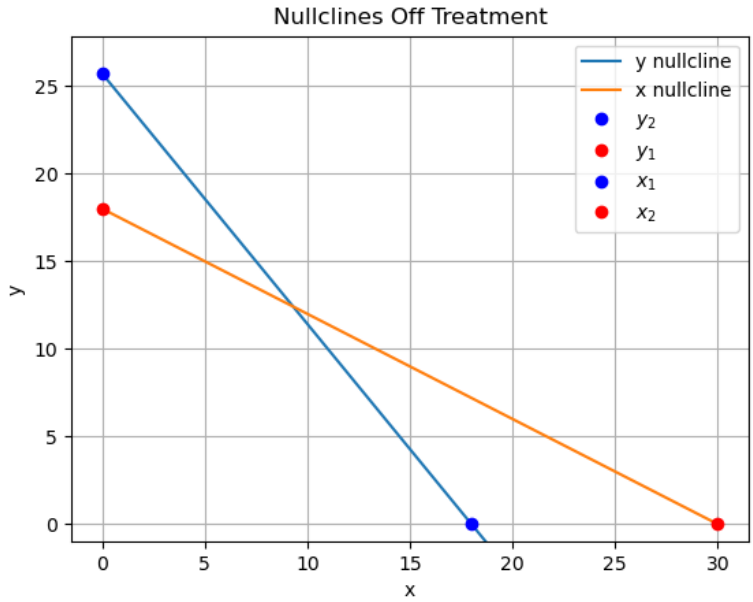

Figure 2: The parameter values used to create the graph above were alpha = .7, beta = .4, eta = .2, K = 18, and s = 1.

3.3 Off Treatment

The equilibrium points for the off treatment system are the following:

$$\begin{aligned}
\boldsymbol{E_0} &= (0,0),\\
\boldsymbol{E_1} &= (K,0),\\
\boldsymbol{E_2} &= (0,K),\\
\boldsymbol{E_3} &= \left(\frac{K(\alpha-1)}{\alpha\beta+\alpha\eta s-1}, \frac{\beta K+\eta K s-K}{\alpha\beta+\alpha\eta s-1}\right),
\end{aligned}$$

Theorem 3.7. *When a patient is off treatment E_0 always exists, and it is always unstable. E_1 and E_2 both always exist, and are stable when $\alpha > 1$ and $\beta+\eta s > 1$ respectively. E_3 exists when $\alpha < 1$ and $\beta+\eta s < 1$ OR $\alpha > 1$ and $\beta+\eta s > 1$. It is stable when $\alpha < 1$ and $\beta+\eta s < 1$, and it is unstable otherwise.*

Proof. The general Jacobian matrix, J, of the off treatment system is the following:

$$J = \begin{bmatrix} r\left(1-\dfrac{\alpha y+x}{K}\right)-\dfrac{rx}{K} & -\dfrac{\alpha r x}{K} \\ \dfrac{-ry(\beta+\eta s)e^{-\psi s}}{K} & e^{-\psi s}r\left(1-\dfrac{x(\beta+\eta s)}{K}\right) \end{bmatrix}.$$

Evaluated at E_0, J becomes

$$J_0 := \begin{bmatrix} r & 0 \\ 0 & re^{-\psi s} \end{bmatrix},$$

which has eigenvalues $[r,\ re^{-\psi s}]$. By assumption, $r > 0$; therefore, both eigenvalues are always positive, and E_0 always exists and is always unstable.

The other two boundary fixed points, E_1 and E_2, must always exist because, by assumption, $K > 0$. At E_1 the Jacobian matrix becomes

$$J_1 := \begin{bmatrix} -r & -\alpha r \\ 0 & r(1-(\beta+\eta s))e^{-\psi s} \end{bmatrix},$$

with eigenvalues $[-r,\ e^{-\psi s}r(1-(\beta+\eta s))]$. The first eigenvalue is always negative and the second is negative when $\beta+\eta s>1$. Thus E_1 is locally asymptotically stable when $\beta+\eta s>1$. At E_2 we have

$$J_2 := \begin{bmatrix} r\,(1-\alpha) & 0 \\ r(\beta+\eta s)e^{-\psi s} & -re^{-\psi s} \end{bmatrix},$$

which has eigenvalues $[r(1-\alpha), -re^{-\psi s}]$. The first eigenvalue is negative when $\alpha>1$, and the second eigenvalue is always negative. Thus, E_2 is locally asymptotically stable when $\alpha>1$.

Figure 2 is a graph that displays the nullclines off treatment, and their intersection, E_3.

□

$$\text{y intercept of x nullcline} = y_1 = (0, K)$$
$$\text{y intercept of y nullcline} = y_2 = \left(0, \frac{K}{\alpha}\right)$$
$$\text{x intercept of x nullcline: } = x_1 = \left(\frac{K}{\beta+\eta s}, 0\right)$$
$$\text{x intercept of y nullcline} := x_2 = (K, 0)$$

In order for E_3 to exist in the first quadrant, $y_1>y_2$ and $x_2>x_1$ or the inverse must be true. This means that either $\alpha<1$ and $\beta+\eta s<1$ OR $\alpha>1$ and $\beta+\eta s>1$. When we evaluate the Jacobian at E_3 and find its characteristic polynomial we get the following:

$$\lambda^2 + \frac{re^{-\psi s}\left((\alpha-1)e^{\psi s}+\beta+\eta s-1\right)}{\alpha\,(\beta+\eta s)-1}\lambda - \frac{r^2e^{-\psi s}(\alpha-1)(\beta+\eta s-1)}{\alpha\,(\beta+\eta s)-1}$$

We can use the Routh-Hurwits theorem to show the local stability of this point. This theorem states that if both coefficients of the characteristic polynomial are positive, then the point is locally stable. If evaluate the coefficients when $\alpha<1$ and $\beta+\eta s<1$, we can see that both coefficients of the characteristic polynomial are positive. If evaluate the coefficients when $\alpha>1$ and $\beta+\eta s>1$, we can see that both coefficients of the characteristic polynomial are negative. Thus, E_3 exists when $\alpha<1$ and $\beta+\eta s<1$ OR $\alpha>1$ and $\beta+\eta s>1$. It is locally asymptotically stable when $\alpha<1$ and $\beta+\eta s<1$, and it is unstable otherwise.

Table 5: Summary of boundary equilibrium dynamics for Model (**??**) (*off treatment*). LAS: locally asymptotically stable.

Equilibrium	**Existence**	**Stability**
$\mathbf{E_0} = (0,0)$	Always	• Unstable
$\mathbf{E_1} = (K,0)$	Always	• GAS if $\beta+\eta s>1$ and $\alpha<1$
$\mathbf{E_2} = (0,K)$	Always	• GAS if $\beta+\eta s<1$ and $\alpha>1$
$\mathbf{E_3} = \left(\frac{K(\alpha-1)}{\alpha(\beta+s\eta)-1}, \frac{K(\beta+s\eta-1)}{\alpha(\beta+s\eta)-1}\right)$	$\alpha<1$ and $\beta+\eta s<1$ OR $\alpha>1$ and $\beta+\eta s>1$	• GAS if $\alpha<1$ and $\beta+\eta s<1$

Table 6: Global Stability Conditions for Different Cases

Case	**Global Stability**
$\alpha>1$ and $\beta+\eta s<1$	E_1 is *GAS*
$\alpha<1$ and $\beta+\eta s>1$	E_2 is *GAS*
$\alpha<1$ and $\beta+\eta s<1$	E_3 is *GAS*
$\alpha>1$ and $\beta+\eta s>1$	E_1 or E_2 is *GAS*

Table 7: Description of parameters from Gompertz Model (**??**).

Parameter	Description	Units	Value
$N(t)$	Number of Cancerous Cells	# of cells	$\mathbb{R}_+$
α	Growth Rate of Cancerous Cells	1/time(s)	$\mathbb{R}_+$
K	Carrying Capacity	# of cells	$\mathbb{R}_+$

4 Searching for Signals of Treatment Resistance

4.1 On Treatment

We aimed to investigate the dynamics of sensitive cells and treatment resistance in prostate cancer patients during the On-Treatment phase. We focused on monitoring the changes in PSA levels as a reflection of the underlying cell behavior.

During the On-Treatment phase, it was anticipated that the population of sensitive cells would diminish as a result of the therapeutic interventions. Accordingly, we employed an exponential decay model, represented by the equation $y = x_0 e^{-rt}$, where y represents the PSA level, x_0 is the initial PSA level, r denotes the decay rate, and t signifies the elapsed time during the treatment phase.

To estimate the decay rate (r) during the On-Treatment phase, we utilized the mean slope of the log-transformed prostate-specific antigen (PSA) values for each patient and treatment cycle. This approach allowed us to capture the overall trend of PSA level changes over time and obtain a quantitative measure of the decline in the population of sensitive cells.

However, it was noted that in a subset of patients, treatment resistance emerged, leading to a lack of response or even an increase in PSA levels. In these cases, the PSA levels remained relatively stable or exhibited an upward trend, suggesting the persistence or growth of treatment-resistant cells.

To ensure the accuracy and reliability of our analysis, certain data preprocessing steps were implemented prior to calculating the decay rate. These steps were aimed at addressing potential sources of bias and noise in the dataset.

First, it was observed that the initial PSA value in each treatment cycle often deviated significantly from the subsequent measurements. Consequently, to minimize bias, the first PSA value within each cycle was excluded from the analysis. This step was necessary to prevent the abnormal initial value from affecting the estimation of the decay rate.

Additionally, values below 0.02 were removed from the dataset. These values were considered noise as they fell below the threshold of sensitivity for the assay used to measure PSA levels. Including such values could introduce inaccuracies and adversely impact the linear regression analysis.

4.2 Off Treatment

During the Off - Treatment phase, sensitive cells will begin to increase in growth at a rate $\hat{\alpha}$. This growth has a sigmoidal shape over time, and can best be approximated with the "Gompertz" equation:

$$N'(t) = \hat{\alpha} N(t) \ln\left(\frac{K}{N(t)}\right) \tag{8}$$

4.2.1 Basic growth rate, α

Parameter, $\hat{\alpha}$, is the growth rate for both the sensitive and resistant cells when on off period but is not used in the model

The alpha values collected from data set range from 0.00018 to 0.0614. The mean $\hat{\alpha}$ value is 0.00882, meaning the average growth rate of cancer growth during the off-cycle is 0.00882.

The distribution is right-skewed as depicted by Figure **??**. The mean $\hat{\alpha}$ value is 0.00882 and ranges from 0.000183 to 0.0614. Initially, it was expected that $\hat{\alpha}$ would act as a good r parameter for the mechanistic model but it failed considerably in application with simulations and fitting. Instead, the growth rate from the exponential model is used in the mechanistic model (see section 5.2.3).

Table 8: Description of parameters from Gompertz Model (**??**).

Parameter	**Normality**	**Variance (Bartlett)**	**Test**	**p-value**
r	Non-Normal	Non-homogeneous	Tukey's HSD	0.015
dr	Non-Normal	Non-homogeneous	Mann-Whitney	0.0369
$ln(\hat{\alpha})$	Normal	Homogeneous	One Way ANOVA	0.4707
$ln(K)$	Normal	Homogeneous	One Way ANOVA	0.1343

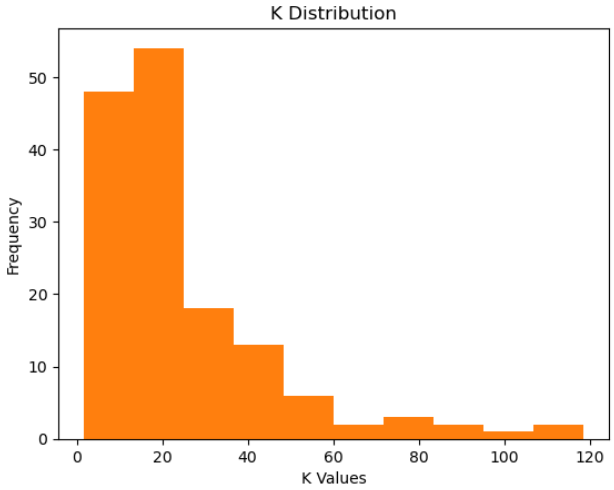

Figure 3: Histogram depicting the distribution of K values after abnormalities were removed

To investigate possible signals of oncoming treatment resistance within the off-cycle, $\hat{\alpha}$ is analyzed to observe a significant difference in the means of $\hat{\alpha}$ values in the groups progressors, non-progressors, death/illness, and miscellaneous. A one-way ANOVA is used to perform such analysis and assumptions made by the one-way ANOVA were validated. A QQ plot is used to check for normality in the distribution of $\hat{\alpha}$ residuals values, it is found that the distribution is not normal so a logarithmic transform is applied to normalize the distribution. To confirm homogeneity in variance, a Bartlett test is performed yielding a value of 0.186, which affirms the null hypothesis that the variance amongst the groups is homogeneous. After both conditions were affirmed, a one-way ANOVA was applied, resulting in a p-value of 0.596 which agrees with the null hypothesis that there is no significant difference in the means of the aforementioned groups. The analysis implies that there is no signal within the $\hat{\alpha}$ values of oncoming treatment resistance.

4.2.2 Carrying capacity, K

Parameter K is the carrying capacity or asymptotic limit of the cancer growth for a patient on a particular cycle during the off-period. K is also a parameter used in the mechanistic model. The distribution of the K values from applying the Gompertz model to the data is heavily-right skewed . This is due to there being instances where K is abnormally large and the Gompertz model behaving as an exponential model when there is no indication of an inflection (see section 5.2)

K is further analyzed to observe whether or not it acts as a reliable signal for anticipating the development of treatment resistance. To check for normality in the distribution of Ks, a QQ plot is used to observe how the data maps to the line representing normally distributed data. A natural log transform is applied in an

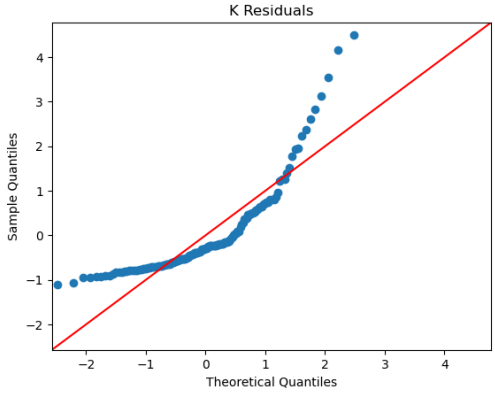

Figure 4: QQ Plot of log K values depicting non-normality

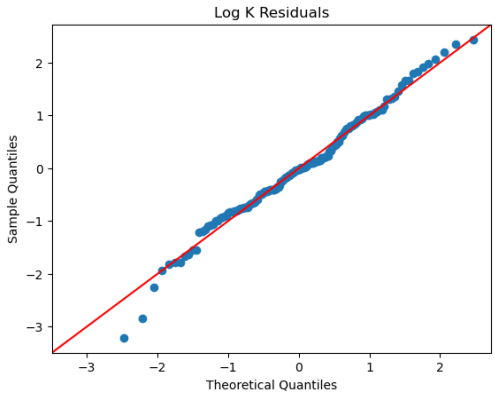

Figure 5: QQ Plot of log transformed K values depicting normality

attempt to normalize the data

Figure 4 shows how the K residuals by themselves are not normally distributed, hence the reason behind performing a log transform in Figure 5 to get a distribution that is more normalized. A Bartlett test is performed on the log transformed K values of groups progressors, non-progressors, death/illness, and miscellaneous. The Bartlett test yielded a p-value of 0.487, which affirms the null hypothesis and indicates homogeneous variance within the groups of K values. Due to both conditions now being met, a one-way ANOVA is performed on the groups of K values to check whether or not the null hypothesis that there is no significance in the means of the groups is true. After applying the ANOVA using the statistics library from SciPy, it is observed that the p-value is 0.097 therefore the null hypothesis is rejected. Thus, there is no indication within the carrying capacity values during the off period that there is oncoming treatment resistance.

4.2.3 Intrinsic growth rate, r

It was found that $\hat{\alpha}$ does not perform well as a growth rate in our mechanistic model, instead we took instances where the cancer growth resembled exponential growth (we defined this threshold to be when carrying capacity was past 118 ng/ml) and used the corresponding mean growth rate from the exponential fittings as the growth rate for our mechanistic model.

References

[1] Klotz L. Crook J. Malone S. Ludgate C. Morris W.J. Gleave M.E. Bruchovsky, N. and S.L. Goldenberg. Final results of the canadian prospective phase ii trial of intermittent androgen suppression for men in

biochemical recurrence after radiotherapy for locally advanced prostate cancer. *Cancer*, 107(2):389–395, 2006.

[2] Douglas Hanahan, , and Robert A Weinberg. The hallmarks of cancer. *Cell*, 100(1):57–70, 2000.

[3] Jingsong Zhang, Jessica J Cunningham, Joel S Brown, and Robert A Gatenby. Integrating evolutionary dynamics into treatment of metastatic castrate-resistant prostate cancer. *Nature communications*, 8(1):1816, 2017.