A mathematical model to determine which pathway of castration resistance the patient will develop

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Abstract

Prostate cancer cells depend on androgen for proliferation and survival. Cancers that recur after first line treatment are then treated with androgen ablation. Although initially successful, this treatment modality inevitably fails because tumors become androgen-independent. A variety of pathways are known to lead to androgen independence. At present, however, no clinical method exists to predict which mode of resistance will develop. In this ongoing study, we propose a compartmental model that could potentially be used to determine which pathway of castration resistance the patient will develop. The model is structured by cell cycle stage. We use sensitivity analysis to test the biological validity of the model and parameters to ascertain when and how castration resistant prostate cancer occurs. Here we validate the model by fitting its solutions to a subset of data from a large-scale trial of intermittent androgen ablation therapy. Different resistance pathways yield different patterns of frequencies of cells in each cell cycle stage; therefore, the model should detect these patterns and subsequently the mechanism of resistance developing in an individual patient. Such a tool can provide oncologists critical information that they can use to plan treatment to avoid or delay resistance and increase both length and quality of life.

Key Words: Castration resistance, Cell cycle model, Androgen deprivation therapy, Prostate-specific antigen

Contents

1 Introduction

1.1 Background

Prostate cancer is the most common non-skin cancer in American men and the second leading cause of cancer mortality (Sung et al.). At least 85% of prostate cancer cases are treatable with surgery and radiation (John Hopkins Medicine, 2021). However, between 20% to 30% of patients with prostate cancer that have been treated the cancer returns (John Hopkins Medicine, 2021). Nearly all prostate cancers begin as androgen-dependent and are attacked with either radiation or androgen deprivation therapy (Feldman & Feldman, 2001). This treatment chemically castrates patients to lower prostate-specific antigen (PSA), an enzyme released by the prostate and is found in high concentrations in men with prostate cancer (Feldman & Feldman, 2001). Although there are improved clinical outcomes while on treatment, over time some cells survive and proliferate. This results in androgen-independent prostate cancer (AIPC), a fatal form of prostate cancer that metastasizes (Feldman & Feldman, 2001). There's no treatment for this form of cancer, thus, prostate cancer treatment focuses on reducing androgen levels right before androgen-dependent cells die.

For prostate cancer to progress, there must be more cells proliferating than dying (Hanahan & Weinberg, 2000). Androgen regulates this proportion by stimulating growth and hindering apoptosis (Feldman & Feldman, 2001). This means that prostate cancer requires a certain level of androgen for it to progress. The testes release testosterone and it circulates the blood. Since testosterone, the principal androgen, is removed from the body in androgen ablation the cancer regresses (Feldman & Feldman, 2001). When testosterone enters a prostate cell, about 90% gets converted to dihydrotestosterone (DHT) by an enzyme called 5α-reductase as it has five times a higher affinity for the androgen receptor (AR) (Feldman & Feldman, 2001). The AR is attached to heat-shock proteins but dissociates from them when it binds (Feldman & Feldman, 2001). This activation is regulated by protein kinase A and causes translocation to the nucleus (Feldman & Feldman, 2001).

Many studies show that although only a couple AR mutations have been found in primary prostate cancer, it is suspected that as much as up to 50% of metastatic prostate cancer cases have AR mutations (Feldman & Feldman, 2001). Intermittent androgen deprivation therapy tries to delay these mutations that would eventually lead to AIPC. There are five mechanisms by which AIPC can evolve: the hypersensitive pathway, the promiscuous pathway, the outlaw pathway, the bypass pathway, and the lurker cell pathway (Feldman & Feldman, 2001). In the hypersensitive pathway, the AR has increased sensitivity to androgen to make up for the lowered levels of testosterone, more AR is made by gene amplification, or the rate of converting testosterone to DHT is increased (Feldman & Feldman, 2001). In the promiscuous pathway, the specificity of the AR expands and leads to AR activation by molecules other than androgens (Feldman & Feldman, 2001). In the outlaw pathway, the AR is phosphorylated by the mitogen-activated protein kinase (MAPK) pathway or protein kinase B, creating a ligand-independent AR (Feldman & Feldman, 2001). In the bypass pathway, other survival mechanisms remove the need for the AR or the ligand (Feldman & Feldman, 2001). In the lurker cell pathway, cells that are androgen-independent exist in the prostate the entire time, even before therapy is introduced (Feldman & Feldman, 2001).

1.2 Life cycle

The cell cycle is a sequence of events that take place in a cell as it grows and later divides. Any given cell spends its time in a phase called interphase in which it grows, duplicates its chromosomes, and prepares for cell division (Alberts et al., 2002). It then leaves interphase to undergo mitosis and finish dividing. There are four stages to interphase: G1, G0, Synthesis (S), and G2 . The first stage, G1, is known as the growth phase since this is when the cell grows (Alberts et al., 2002). In this stage, the cell synthesizes nutrients and enzymes that will be needed later for replication and division (Alberts et al., 2002). During the S phase, the cell synthesizes a copy of the DNA in the nucleus. This extra copy of the DNA then gets condensed during G2, and the cell is preparing for division (Alberts et al., 2002). Once interphase is complete, the cell then moves on to mitosis (Alberts et al., 2002). Here, the cell splits to form two identical daughter cells. After mitosis concludes, the daughter cells enter their own interphase and begin a new round of the cell cycle (Alberts et al., 2002).

The type of cell determines how the time is split in each cell cycle phase. Some types of cells, such as embryo and tumor cells, divide quickly, where the daughter cells may potentially go through another round of the cell cycle instantly. However, other types of cells divide very slowly or do not divide at all. Those that do not divide exit the G1 phase and enter the resting stage of G0 (Alberts et a., 2002). A cell in G0 is not actively growing nor preparing to divide. It already has a specific purpose. For example, in G0 a liver cell will be helping to filter blood and a neuron will be conducting signals. G0 is the permanent phase for several cells, whereas clones may reenter the cell cycle by moving into the S phase.

1.3 Previous Works

In previous works, such as Portz and Ideta, the models predicted the behavior of AD and AI cells during Intermittent Androgen Suppression therapy. Within Portz, the dynamics of androgen suppression therapy are modeled through Androgen Dependent (AD) cells, Androgen Independent (AI) cells, and mutation rates. Existing models reflect the mutation of AD cells to AI cells during Androgen suppression treatment. Our model also recognizes the importance of androgen for proliferation and apoptosis and includes it as a parameter. Unlike previous models that include a rate for mutation of AD cells to AI cells to reflect the ratio of cells during treatment, the focus of our model is to predict the type of pathway an AD cell will change into an AI cell. Our model focuses on the phases that each cell resides in and hope to determine the behavior of malignant cancer cells.

2 Model

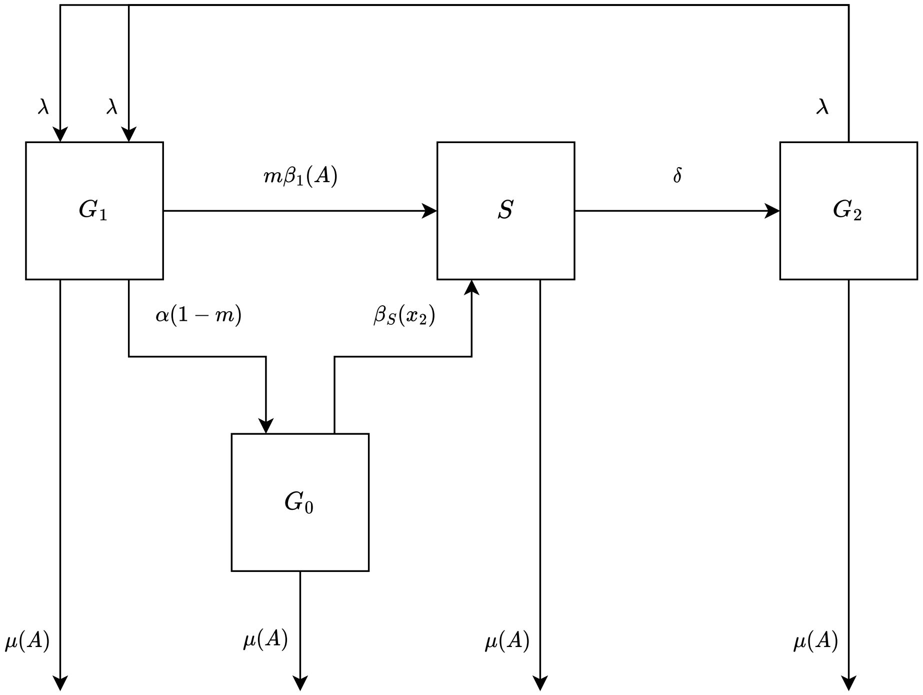

Figure 1: Life cycle graph of the stages of cell development.

Figure (1) outlines the cell cycle and notation. We assume that cells begin their life cycle in the G_1 stage (Alberts et al., 2002). This stage is the growth phase, and it is where cells synthesize RNA and proteins, and finish growing to their maximum size (Alberts et al., 2002). There is a checkpoint near the end of the G_1 stage that is regulated by retinoblastoma protein (pRb) (Hanahan and Weinberg, 2000). For a cell to enter the S stage, pRb allows E2 factors (E2F) to enable cells to multiply (Hanahan and Weinberg, 2000). Then, cells move to the G_0 stage. This stage is the resting phase, and it is where 99% of cells will spend the rest of their life, unless pRb enables E2 factors so a healthy cell may leave G_0 to enter S (Hanahan and Weinberg, 2000). The cell is busy working hard to maintain homeostasis here and does not begin to replicate chromosomes or divide (Alberts et al., 2002). Cells transition from G_1 to G_0 the rate $\alpha(1-m)$, where α is the basic rate modified by m which is a measure of malignancy (Table 1). The measure of malignancy determines the likelihood that a cell will bypass G_0. For example, should m be 1/2, we can assume that half of the cells will skip the G_0 stage and move right into S at rate $m\beta_1(A)$. The S stage is where cells begin replicating their chromosomes to prepare for mitosis (Alberts et al., 2002). The base transition rate, $\beta_1(A)$, is a function of androgen, A, as entry into this stage is highly dependent on androgen (Table 2) (Feldman & Feldman, 2001). On the other hand, healthy cells in G_0 will also transition to S when their density is below a carrying capacity, K. To reflect this transition from G_0 into S, we model this transition rate as a function $\beta_S(x_2)$, where x_2 is the number of cells in G_0 (Table 2). Cells in S then move into G_2 at rate δ. The G_2 stage is where cells complete replicating chromosomes and look for and repair errors. At the end of G_2, cells complete mitosis and cytokinesis at rate λ, and two daughter cells enter G_1 at rate 2λ (Table 1). Mitosis and cytokinesis occur during the G_2 stage; however, as these happen quickly, instead of representing them as compartments, we leave them as rate λ leaving the G_2 class. We assume in each of these stages that cells die at rate $\mu(A)$, which is a function of androgen since prostate cell survival is highly dependent on this hormone (Feldman & Feldman, 2001). When errors cannot be fixed, normal cells will induce apoptosis.

Let $\vec{x} \in \mathbb{R}^4_{\geq 0}$ be the cell population in each phase of the cell cycle. We define it as,

$$\vec{x} = [x_1, x_2, x_3, x_4]^{\intercal}\,. \tag{1}$$

Our x_i is used to represent each stage of the cell life cycle; the subscript states which stage in particular. Respectively, when i = 1, 2, 3, 4, the stage of the cycle is then G_1, G_0, S, and G_2.

Our model takes the following form: $\dfrac{d\vec{x}}{dt} = A\vec{x}$, where A is the following projection matrix:

$$\begin{pmatrix} -\left(\alpha(1-m) + m\beta_1(A) + \mu\right) & 0 & 0 & 2\lambda \\ \alpha(1-m) & -\left(\beta_S(x_2) + \mu\right) & 0 & 0 \\ m\beta_1(A) & \beta_S(x_2) & -\left(\delta + \mu\right) & 0 \\ 0 & 0 & \delta & -\left(\lambda + \mu\right) \end{pmatrix}. \tag{2}$$

We assume that healthy tissue homeostasis is regulated based on the number of cells in G_0. As the G_0 population approaches a fixed set point, K, the rate at which cells in G_0 commit to division decreases. When the G_0 population equals or exceeds K, normal cells will stop dividing and remain in G_0. We model this biological mechanism by making β_S a function of x_2, as follows:

$$\beta_S(x_2) = \hat{\beta_S}\left(1 - \frac{x_2}{K}\right). \tag{3}$$

As cell survival and transition from the growth phase to the synthesis phase are androgen-dependent, both β_1 and μ are functions of androgen (Feldman & Feldman, 2001). Specifically, we assume that the transition of malignant cells from G_1 to S can be modeled using Michaelis-Menten formalism; that is,

$$\beta_1(A) = \beta_{max}\left(\frac{A}{k_\beta + A}\right). \tag{4}$$

The mortality function, μ, is assumed to be an exponentially decreasing function of A, with a maximum death rate of μ_{max} when $A = 0$ and a minimum of μ_{min} as $A \to \infty$. We model these assumptions as follows:

$$\mu(A) = \mu_{max} e^{-\eta A} + \mu_{min}, \tag{5}$$

where η is the sensitivity of cell survival to androgen (Table 1).

Table 1: Parameters used in the model; their description, values, units and source.

Parameter	Description	Value	Unit	Source
α	Rate at which cells move from G_1 to G_0	1/4	hrs	[4]
δ	Rate at which cells move from S to G_2	1/11	hrs	[7]
λ	Rate at which cells move from G_2 to G_1	1/7	hrs	[4]
m	Measure of malignancy	0	1	
$\hat{\beta}_S$	Maximum Rate of Transition from G_0 to S	1	1	
k	Homeostatic set point	1	1	
β_{max}	Maximum growth rate of cells		1	
k_β	Androgen sensitivity of cells moving from G_1 to S		1	
μ_{max}	Maximum rate at which cells die with respect to androgen	1/60	1	
μ_{min}	Minimum rate at which cells die with respect to androgen	1/1000	1	
η	Sensitivity of cell survival to androgen	0	1	
$\beta_S(x_2)$	Rate at which cells move from G_0 to S	3	gm	
$\beta_1(A)$	Rate at which cells move from G_1 to S	4	gm	
$\mu(A)$	Rate at which cells die in all classes	5	gm	

Table 2: Variables, their meaning, equation and unit.

Variable	Description	Equation	Unit
t	Time		Hours
$\vec{x}(t)$	Population vector of cells in state $x_i(t)$ $i \in \{1, 2, 3, 4\}$ at time t	1	1
$X(t)$	Total mass of the tumor	$\sum 1$	gm
A(t)	Serum Androgen Concentration	4	μg/ml

3 Results

3.1 Mathematical

Given the life cycle model, we have the following differential equations:

$$\dot{x_1} = 2\lambda x_4 - (\alpha(1-m) + m\beta_1(A) + \mu)x_1 \tag{6}$$
$$\dot{x_2} = \alpha(1-m)x_1 - (\beta_s(x_2) + \mu)x_2 \tag{7}$$
$$\dot{x_3} = m\beta_1(A)x_1 + \beta_S(x_2)x_2 - (\delta + \mu)x_3 \tag{8}$$
$$\dot{x_4} = \delta x_3 - (\lambda + \mu)x_4. \tag{9}$$

We solve for the variables to obtain the fixed points,

$$E_0 = [0,\ 0,\ 0,\ 0] \tag{10}$$
$$E_1 = [x_1^*,\ x_2^*,\ x_3^*,\ x_4^*]. \tag{11}$$

Where in E^1, the equations for the equilibria are:

$$x_1^* = \frac{\frac{-2K\lambda\delta\mu}{\hat{\beta}_S}(\hat{\beta}_S + \mu)}{(\lambda + \mu)(\delta + \mu)(\alpha(1-m) + m\beta_1(A) + \mu)} \tag{12}$$
$$x_2^* = \frac{K}{\hat{\beta}_S}\left(\hat{\beta}_S + \hat{\mu}\right) \tag{13}$$
$$x_3^* = \frac{\frac{-K\mu}{\hat{\beta}_S}(\hat{\beta}_S + \mu)}{\delta + \mu} \tag{14}$$
$$x_4^* = \frac{\frac{-K\delta\mu}{\hat{\beta}_S}(\hat{\beta}_S + \mu)}{(\delta + \mu)(\lambda + \mu)}. \tag{15}$$

Consider the case when $\mu = 0$. We then have no dying cells, so it follows that there is an unceasing division of cells and eventually, x_2 will reach K and we get $\beta_S(x_2) = \hat{\beta}_S$ (Equation 3). Thus, the entire population will accumulate at stage x_2. Now, consider $\mu = 1$. We can immediately observe that no cells will proceed to the next stage since the cells will all die from whatever stage they are located at. Thus, having $0 < m < 1$ allows a flow between stages.

Consider when $m = 0$. Cells in stage x_1 proceeds directly to x_2. However, if $m = 1$ then cells skip x_2, and thus cells do not enter a resting phase and there is a greater division of cells. This may lead to cancer.

It was essential to calculate the Jacobian so that the eigenvalues could be obtained. With this, the properties of the linear stability of the system and the equilibrium can be found. We use the local stability theorem.

Theorem 1 (Local Stability Theorem) *If at least one eigenvalue of the Jacobian matrix of this system at x^* has a positive real part, the system is unstable. If all eigenvalues have negative real part, then the system is locally asymptotically stable.*

$$J = \begin{pmatrix} -(m\beta_1(A) + \alpha(1-m) + \hat{\mu}) & 0 & 0 & 2\lambda \\ \alpha(1-m) & -\left(\dfrac{\hat{\beta}_s}{k} + \hat{\mu}\right) & 0 & 0 \\ m\beta_1(A) & \dfrac{\hat{\beta}_s}{k} & -(\delta+\hat{\mu}) & 0 \\ 0 & 0 & \delta & -(\hat{\mu}+\lambda) \end{pmatrix}$$

Now with the Jacobian, we obtained the eigenvalues. However, given the complexity of these, we opted to evaluate these cases at specific numerical solutions so that the behavior of the system could be observed.

Following the structure of the life cycle model, a matrix model was implemented to help expand into the stability analysis of prostate cancer (Equation 2).

The R_0 of the model was calculated to better validate the behavior of the system. To do this, the probability that the cell will survive and transition to the next phase was calculated for each possible stage. As follows,

$$P\{x_1 \to x_2, x_2 \to x_3, x_3 \to x_4, x_4 \to x_1\} = \frac{\alpha}{\alpha+\mu}\frac{\hat{\beta}_S}{\hat{\beta}_S+\mu}\frac{\delta}{\delta+\mu}\frac{\lambda}{\lambda+\mu}.$$

Thus, we see that:

$$R_0 = \frac{2\alpha\hat{\beta}_S\delta\lambda}{(\alpha+\mu)(\hat{\beta}_S+\mu)(\delta+\mu)(\lambda+\mu)}. \tag{16}$$

When $R_0 > 1$, the tumor persists, but when $R_0 < 1$ there is extinction of the tumor. We see the same results when compared to the real part of the dominant eigenvalue.

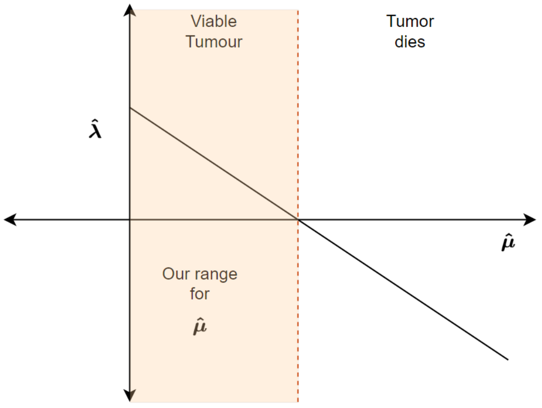

Figure 2: The real part of the dominant eigenvalue plotted against death.

Highlighted with orange in the figure above is the range of a viable tumor. Once it passes the bifurcation point, the tumor becomes extinct.

3.2 Computational

We began computational analysis after finishing our mathematical analysis. We started out by calculating the default solution, which tells us how our model should behave (Fig. 3, Tab. 3).

The default solution was done using MATLAB's ODE45 function, which is a fifth order Runga-Kutta method with six stages that is used to solve ordinary differential equations. Specifically, it uses the Runge-Kutta-Fehlberg method of integration. To do this, it calculates six slopes and multiplies each by the chosen time-step and then takes the weighted average of these.

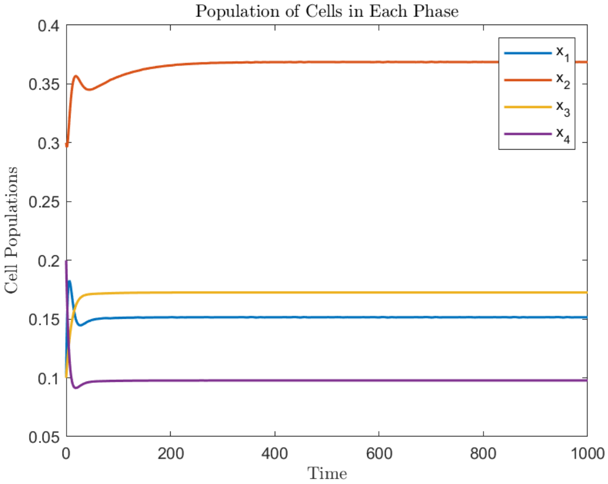

Figure 3: The default solution. The values for the parameters used are found in Table 3.

Table 3: Parameter values used in the default solution.

Parameter	Value
μ	0.01766666670
δ	1/11
β_1	1/6
λ	1/7
α	1/6
$\hat{\beta}_S(x_2)$	1/10
k	3/4
m	0

Recall that we have two fixed point, the trivial $E^0 = \vec{0}$ and interior $E^1 = \vec{x}^* \in \mathbb{R}^4$. The fixed points were calculated using the default solution's parameters to yield,

$$x_1^* = 0.15150 \tag{17}$$
$$x_2^* = 0.36860 \tag{18}$$
$$x_3^* = 0.17260 \tag{19}$$
$$x_4^* = 0.09780 \tag{20}$$

(Table 3). Which were graphed over the default solution to demonstrate that the populations indeed went to the above values (Fig. 3).

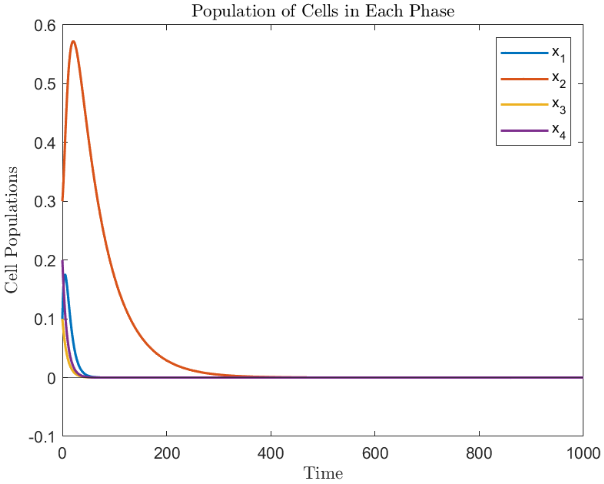

Figure 4: The default solution with calculated equilibria.

Recall that we calculated the basic reproduction number R_0,

$$R_0 = \frac{2\alpha\hat{\beta}_S\delta\lambda}{(\alpha+\mu)(\hat{\beta}_S+\mu)(\delta+\mu)(\lambda+\mu)}. \tag{21}$$

Recall that when $R_0 > 1$, we have a viable tumor, and when $R_0 < 1$, it dies off. From the default solutions parameters, we calculated its R_0 to get 1.1451. We see that on the default solution, it goes to equilibria and does not die off, which means that the trivial fixed point is unstable, the interior fixed point is stable, and $R_0 > 1$. We began doing some basic sensitivity analysis by testing out some different values for our parameters.

When we let $K = 0$, the trivial fixed point is stable, and the tumor becomes extinct. The interior fixed point does not exist, and $R_0 < 1$.

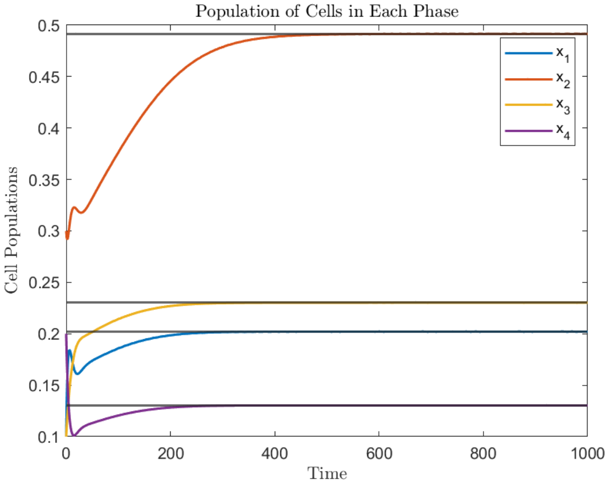

Figure 5: Default solution where $K = 0$.

When $K = 1$, the mass of the tumor is greater than the previous solution. The trivial fixed point is unstable, the interior fixed point is stable, and so the tumor persists and reaches equilibria. Here, R_0 is greater than 1.

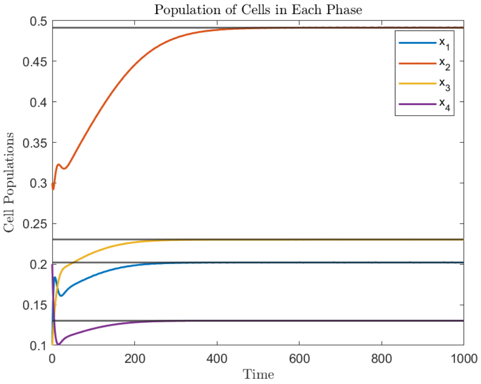

Figure 6: Graph when $K = 1$.

$$x_1^* = 0.20210 \tag{22}$$
$$x_2^* = 0.49150 \tag{23}$$
$$x_3^* = 0.23020 \tag{24}$$
$$x_4^* = 0.13040 \tag{25}$$

We let $m = 1/4$, and see that the interior fixed point is table, the trivial fixed point is unstable, and the solution oscillates before reaching equilibria.

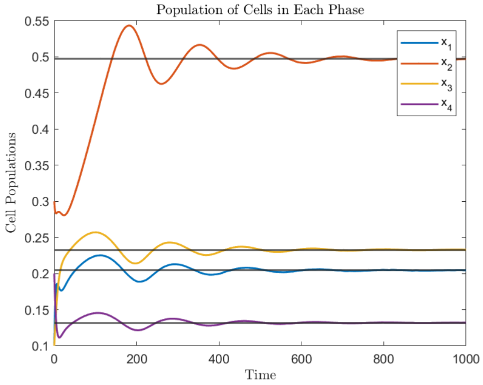

Figure 7: Graph when $m = 1/4$.

$$x_1^* = 0.20440 \tag{26}$$
$$x_2^* = 0.49710 \tag{27}$$
$$x_3^* = 0.23280 \tag{28}$$
$$x_4^* = 0.13180 \tag{29}$$

For both of these next graphs, where $\hat{\beta}_S$ is 1/4, and $\hat{\beta}_S$ is 3/4, the trivial and interior fixed points are unstable. The behavior of both solutions is a limit cycle. The mass of the tumor is greater when $\hat{\beta}_S$ is equal to 3/4, as it is the maximum transition rate from G_0 to S.

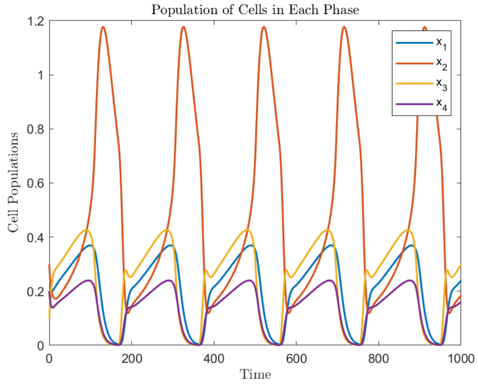

Figure 8: Graph when $\hat{\beta}_S = 1/4$.

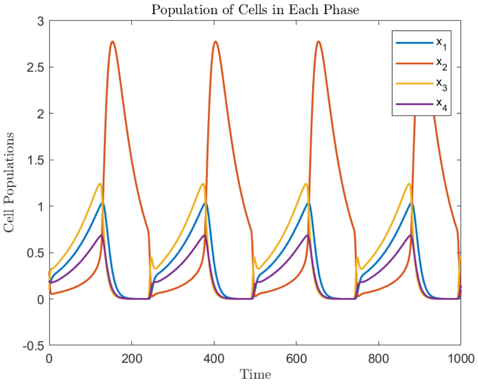

Figure 9: Graph when $\hat{\beta}_S = 3/4$.

Table 4: Parameter values used to calculate the above solutions.

Parameter	Value
μ	0.0176666667
δ	1/11
β_1	1/6
λ	1/7
α	1/6
$\hat{\beta}_S$	1/10, 1/4, 3/4
k	0, 3/4, 1
m	0, 1/4

Lastly, here is a table showing the different states and behaviors of the trivial and interior fixed points our model can have. We discovered these from testing different parameter values, as shown above in our solutions.

Table 5: Behavior of trivial and interior fixed points when stable or unstable.

Trivial	Interior	Behavior
Stable	DNE	Extinction
Unstable	Stable	Equilibria
Unstable	Unstable	Limit Cycle

3.3 Statistical

Initially, a preliminary statistical analysis was done on patient data. First, patient's serum PSA vs serum testosterone levels were plotted with a regression line. The equation for the regression line is:

$$\hat{y_i} = 2.10540 + 0.45419x\hat{\epsilon_i}, \tag{30}$$

where $\epsilon \sim N(0, 5.094^2)$.

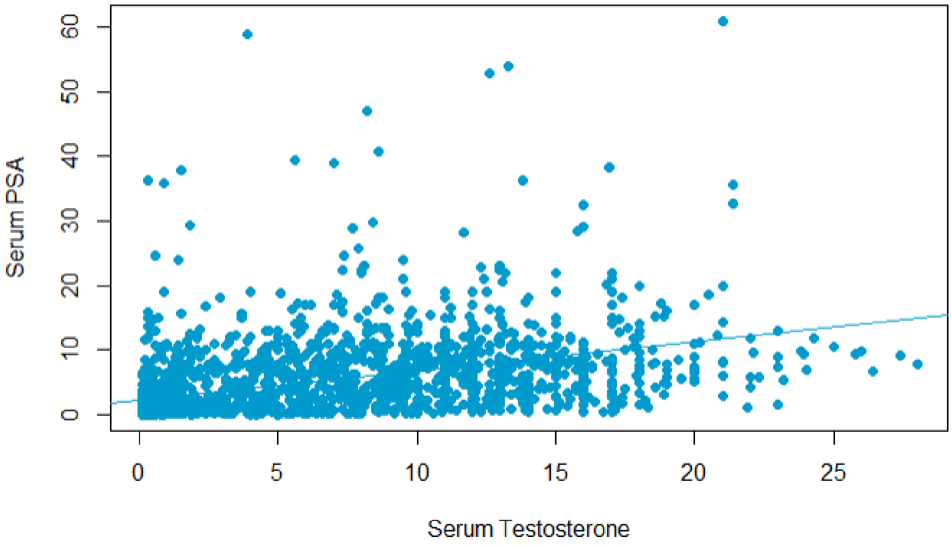

Figure 10: Plot of all patient Serum PSA vs Serum Testosterone data.

Next, the data was plotted by treatment cycle.

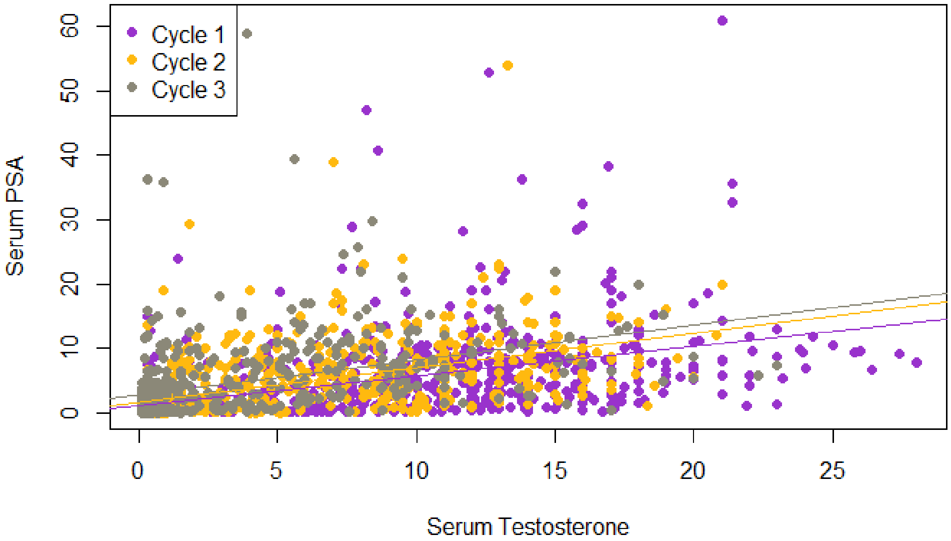

Figure 11: Plot of patient serum PSA vs serum testosterone data by treatment cycle.

The equations for the regression lines of each cycle in ascending order are:

$$\hat{y}_i = 1.21264 + 0.45665x + \hat{\epsilon}_i$$

where $\epsilon \sim N(0, 5.48^2)$,

$$\hat{y}_i = 1.74126 + 0.22534x + \hat{\epsilon}_i$$

where $\epsilon \sim N(0, 4.339^2)$, and

$$\hat{y}_i = 2.72088 + 0.54586x + \hat{\epsilon}_i$$

where $\epsilon \sim N(0, 5.371^2)$.

4 Discussion

4.1 Future Works

In our future works we will complete thorough sensitivity analysis and statistical analysis. Once completing our statistical analysis, we can begin to incorporate patient data to the model.

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6 References

[1] Alberts B, Johnson A, Lewis J, et al. Molecular Biology of the Cell. 4th edition. New York: Garland Science; 2002. An Overview of the Cell Cycle. Available from: https://www.ncbi.nlm.nih.gov/books/NBK26869/

[2] Feldman, B. J., & Feldman, D. (2001). The development of androgen-independent prostate cancer. Nature Reviews Cancer, 1(1), 34–45. doi:10.1038/35094009

[3] Hanahan, D., & Weinberg, R. A. (2000). The hallmarks of cancer. Cell, 100(1), 57–70. https://doi.org/10.1016/s0092-8674(00)81683-9

[4] Hume, S., Dianov, G. L., & Ramadan, K. (2020). A unified model for the G1/S cell cycle transition. Nucleic Acids Research, 48(22), 12483–12501. https://doi.org/10.1093/nar/gkaa1002

[5] John Hopkins Medicine. (2021, August 8). Prostate cancer prognosis. Johns Hopkins Medicine. Retrieved August 4, 2022, from https://www.hopkinsmedicine.org/health/conditions-and-diseases/prostate-cancer/prostate-cancer-prognosis

[6] Megretski, A. (2003, October 3). Dynamics of Nonlinear Systems. reading, Cambridge: Massachusetts Institute of Technology.

[7] Norbury , C., & Nurse, P. (1992). Animal Cell Cycles and Their Control. Annual Reviews, 441–470. QRLSSP PCa Prestentation July 8, 2022 32

[8] Pishro-Nik, H. (2014). Introduction to probability, statistics, and Random Processes. Blue Bell, PA: Kappa Research, LLC.

[9] Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global cancer statistics 2020: Globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians, 71(3), 209–249. https://doi.org/10.3322/caac.21660

[10] Megretski, A. (2003, October 3). Dynamics of Nonlinear Systems. reading, Cambridge: Massachusetts Institute of Technology.

7 Appendix

7.1 Proof of Expected Value of an Exponential Random Variable

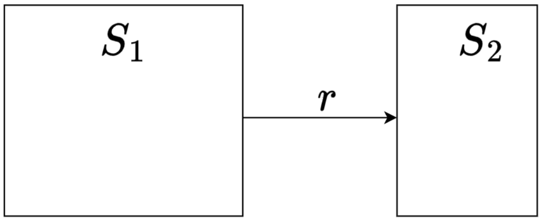

Figure 12: Image demonstrating exponential random variable r going from example classes S_1 to S_2.

The rate of the population leaving S_1 to S_2 is $\frac{dS_1}{dt} = -rt$. Using seperation of variables, we know that $S_1(t) = S_0 e^{-rt}$. We want to obtain the average time that a cell is in S_1. Thus, we can find the average time using the Expected value formula. $E[X] = \int_{xmin}^{xmax} xf(x)\,dx$. We use the probability distribution function $\mathcal{F}(t) = 1 - e^{-rt}$ and obtain the probability function as $f(t) = re^{-rt}, \quad t \geq 0$.

$$\begin{aligned} E[t] &= te^{-rt} + \int_{\infty}^{\infty} xf(x)\,dx \\ &= 0 + \frac{e^{-rt}}{-r} \\ &= \frac{1}{r}. \end{aligned}$$

Therefore, we see that the expected value of an exponential random variable is indeed $\frac{1}{r}$. ■

7.2 Code for the model

```
close all; clc; clear all;

% Initial values G1 = .1; G0 = .3; S = .1; G2 = .2;

% Parameter values
alpha = 1/6; lambda = 1/7; delta = 1/11;
k_1 = 1; bmax_1 = 0.1; A = 1;
eta = 0.025; umax = 0; umin = 0;
beta_hatS = 0.1; k = 3/4; m = 0;

% Michaelis-Menten and Death equations
betaA_1 = bmax_1 * (A / (k_1 + A));
muA_1 = umax * exp(-eta * A) + umin;

% Set the time span
tspan = 0:1000;

% Put parameters and initial values into arrays to pass into the model
y0 = [G1 G0 S G2];
parameters = [alpha lambda delta muA_1 beta_hatS k m betaA_1];

% Use ode45 to solve our system of equations.
[t,y] = ode45(@cancer,tspan,y0,[],parameters);
figure(1) % Gives the graph its own window
plot(t,y(:,1),’LineWidth’,1.5); hold on % this will graph our G1
plot(t,y(:,2),’LineWidth’,1.5); % this will graph our G0
plot(t,y(:,3),’LineWidth’,1.5); % this will graph our S
plot(t,y(:,4),’LineWidth’,1.5); hold off % this will graph our G2
title(’Population of Cells in Each Phase’,’Interpreter’,’latex’);
xlabel(’Time’,’Interpreter’,”latex”) % add a label to the x axis
ylabel(’Cell Populations’,’Interpreter’,”latex”) % add a label to the y axis
legend(’x_1’,’x_2’,’x_3’,’x_4’) % create the legend
saveas(gcf, ’bhs34new.png’) % saves a png of the graph

R0 = (2 * lambda * beta_hatS * alpha * delta) / ((alpha + muA_1) * (beta_hatS + muA_1) * (lambda+muA_1) * (delta + muA_1))

    % Plot all populations on a log plot
figure(3) % Gives the graph its own window semilogy(t,y(:,1),’LineWidth’,1.5); hold on % this will graph our G1
```

```
semilogy(t,y(:,2),’LineWidth’,1.5); % this will graph our G0
semilogy(t,y(:,3),’LineWidth’,1.5); % this will graph our S
semilogy(t,y(:,4),”LineWidth”,1.5); hold off % this will graph our G2
% title(’(Log) Population of Cells in each Phase’);
% Making the graph slightly nicer xlabel(’Time’,’Interpreter’,”latex”) % add a label to the x axis
ylabel(’Cell Populations’,’Interpreter’,”latex”) % add a label to the y axis
legend(’x_1’,’x_2’,’x_3’,’x_4’) % create the legend
saveas(gcf, ’k at 0.75.png’) % saves graph as a png

% Our main model. We pass in our initial populations values as an array to
% the ”y” parameter, and we pass in our parameter values as an array
% to the params parameter function dydt = cancer( ,y,params)

% Assign value to parameters using params vector
alpha = params(1); lambda = params(2); delta = params(3); muA_1 = params(4); beta_hatS =
params(5); k = params(6); m = params(7); betaA_1 = params(8);

% Assign values to proportions of cells in each stage from the y vector
x1 = y(1); x2 = y(2); x3 = y(3); x4 = y(4);

if (x2 >= 0) && (x2 <= k)

    beta_S = beta_hatS * (1 - x2/k);
else

    beta_S = 0;
end

dydt = [ 2*lambda*x4 - (1-m)*alpha*x1 - m*betaA_1*x1 - muA_1*x1; % dx1/dt

    (1-m)*alpha*x1 - beta_S*x2 - muA_1*x2; % dx2/dt

    m*betaA_1*x1 + beta_S*x2 - delta*x3 - muA_1*x3; % dx3/dt

    delta*x3 - lambda*x4 - muA_1*x4 % dx4/dt
];

end
```

7.3 Code to calculate fixed points

```
% Our model as a function of time
syms t ’real’

% Define variables for our state vector, to be used in the projection
% matrix in the for vec(x)(t) = P* vec(x)
syms x(t) [4,1]; % State vector
assume(x(t), ’real’);

% Define our general parameters
syms alpha beta_S beta_1 delta lambda ’real’
assume([alpha, beta_S, beta_1, delta, lambda] > 0);

% Define our mortality parameters, we will just use mu here syms mu ’real’ %mu_max mu_min eta A
’real’
assumeAlso(mu > 0);
%assumeAlso([mu, mu_max, mu_min, eta, A] > 0);
```

```
% New parameters for the betaS function
% beta_hat is the beta_hat_S
syms beta_hat m K ’real’
assumeAlso([beta_hat, m, K] > 0);

% Parameters for beta1 function
%syms A beta_max K_beta
%assumeAlso([A, beta_max, K_beta] > 0);

% Define the projection matrix
P = [-(mu + alpha*(1-m) + m*beta_1), 0, 0, 2*lambda; % G1 stage
alpha*(1-m), -(beta_hat*(1 - x2/K) + mu), 0, 0; % G0 stage
m*beta_1, beta_hat*(1 - x2/K), -(delta + mu), 0; % S stage
0, 0, delta, -(lambda + mu)]

% Now, use the diff function
modelP = diff(x, t) == P*x

% We just need to see the RHS of this eqn. So let’s do that
ModelPRHS = rhs(modelP)
% Let’s look for equilibria now
% Going to substitute ys in for our x_i(t)’s
syms y [4,1]
assumeAlso(y, ’real’)
assumeAlso(y >= 0)
ModelPRHSAuto = formula(subs(ModelPRHS, [x1, x2, x3, x4], [y1, y2, y3, y4]))

% Solving for x4
Solx4 = solve(ModelPRHSAuto(4) == 0, y4, ’ReturnConditions’, true);
% ReturnConditions means it tells us when this is true
Solx4.y4 % Print the solution

Solx4.conditions % What conditions is it true?

% Sub in x4, our goal is to have x1 be a function of x3, too.
Solx1 = subs(ModelPRHSAuto(1), y4, Solx4.y4)
% Solving for x1
Solx1 = solve(Solx1 == 0, y1, ’ReturnConditions’, true)
Solx1.y1 % x1 is now a function of x3
Solx1.conditions

% Sub in our solved x4
Solx2 = simplifyFraction(subs(ModelPRHSAuto(2), [y1 y4], [Solx1.y1 Solx4.y4]))

Solx2 = collect(Solx2, y2)
Solx2 = solve(Solx2 == 0, y2, ’ReturnConditions’,true)

Solx2.y2 = simplifyFraction(Solx2.y2)
Solx2.y2
% Sub in x1, x2, x4
Solx3 = subs(ModelPRHSAuto(3), y4, Solx4.y4)
Solx3 = subs(Solx3, y1, Solx1.y1)
Solx3 = subs(Solx3, y2, Solx2.y2)

test1 = simplify(Solx3(1))
```

```
test1 = simplifyFraction(test1)
test1 = collect(test1, y3)
test1 = solve(test1 == 0, y3, 'ReturnConditions',true)
test1.y3
test2 = simplify(Solx3(2))
test2 = simplifyFraction(test2)
test2 = collect(test2, y3)
test2 = solve(test2, y3, 'ReturnConditions',true);
test2.y3
test2.conditions
NewSolx3 = [test1.y3 test2.y3]
Evalx3pt1 = subs(NewSolx3,[alpha, beta_1, delta, lambda, beta_hat, m, K, mu],[1/6, 1/2, 1/11, 1/7,
1, 0, 3/4, 0.0176666667])
Evalx3pt2 = subs(NewSolx3, [alpha, beta_1, delta, lambda, beta_hat, m, K, mu], [1/11, 1/2, 1/8, 1/5,
1, 1/4, 3/4, 0.0176666667])
Evalx3pt3 = subs(NewSolx3,[alpha, beta_1, delta, lambda, beta_hat, m, K, mu],[1/6, 1/6, 1/11, 1/7,
0.25, 0, 3/4, 0.0176666667])
solnx3pt3_2 = double(Evalx3pt3(2))
solnx3pt2_2 = double(Evalx3pt3)

Ex3 = solnx3pt2_2(2)
solnx1 = subs(Solx1.y1,[alpha, beta_1, delta, lambda, beta_hat, m, K, mu, y3],[1/6, 1/6, 1/11, 1/7,
0.25, 0, 3/4, 0.0176666667, Ex3]);
Ex1 = double(solnx1)
solnx2 = subs(Solx2.y2,[alpha, beta_1, delta, lambda, beta_hat, m, K, mu, y3],[1/6, 1/6, 1/11, 1/7,
0.25, 0, 3/4, 0.0176666667, Ex3]);
Ex2 = double(solnx2(2))
solnx4 = subs(Solx4.y4,[alpha, beta_1, delta, lambda, beta_hat, m, K, mu, y3],[1/6, 1/6, 1/11, 1/7,
0.25, 0, 3/4, 0.0176666667, Ex3]);
Ex4 = double(solnx4)

Equilibria1 = [Ex1, Ex2, Ex3, Ex4]
```