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A HORMONE THERAPY MODEL FOR BREAST CANCER USING LINEAR CANCER NETWORKS

Michelle McDuffie

Abstract. Hormone therapy is a viable technique used to treat endocrine receptor positive cancers. Using the recently developed theory of cancer networks, we create a mathematical model describing the growth of an estrogen-receptive cancer governed by a linear cancer network. We then present hormone therapy as a drug that blocks the estrogen receptors of different cells in the network. Depending on the effectiveness of the drug, the model predicts coexistence of healthy and cancerous cells as well as a cure state. In the case of coexistence, the carrying capacities of all cancerous cells are reduced by hormone therapy, increasing effectiveness of other treatments such as surgery.

keywords: cancer stem cells, breast cancer, hormone therapy, tamoxifen

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1 Introduction

Cancer is an invasive disease of the body that is a result of a mutation or set of mutations in the healthy cells of an individual. This mutation prevents cells from carrying out apoptosis or cell death, instead causing them to grow rapidly and eventually form a tumor that, without treatment, kills the host [6, 7]. Many treatments have been developed to fight specific forms of cancer, yet there is still no cure for cancer.

With the exception of skin cancer, breast cancer is now the most common cancer among women [6]. Breast cancer starts in the cells of the ducts or lobes of the breast, known as the epithelial cells, and can invade the surrounding tissue. Breast cancer can occur in many forms including endocrine receptor positive for estrogen, endocrine receptor positive for progesterone, HER2 positive, or negative for all three [6]. The most common type of breast cancer forms when escalated levels of estrogen cause an increase in the rate of cellular division. The corresponding increase in DNA replication leads to mutations in healthy cells resulting in endocrine receptor positive breast cancer [1].

Currently, treatment options for breast cancer include radiation therapy, hormone therapy, targeted therapy, chemotherapy, and surgery. Hormone therapy only works for hormone receptive positive breast cancer and is typically used to help lower the risk of breast cancer reoccurring after surgery. Hormone therapy can be used in pre- and post-menopausal women to help in the breast cancer remission stage. One current area of research seeks to determine whether this form of treatment can help reduce the size of tumors in the breast so that breast conserving surgery may be performed [6].

There are different forms of hormone therapy. For example, specific drugs can prevent estrogen from binding to estrogen receptors in the cancerous epithelial cells or prevent the body from producing estrogen. The drug Tamoxifen has been used for over 30 years as an adjuvant treatment to lower the risk of breast cancer recurrence, as preventative medication for women who are at high risk of getting breast cancer, or as a way to slow down endocrine positive breast cancers that have metastasized. Tamoxifen attaches to estrogen receptors in endocrine receptor positive cancer to prevent the cells from dividing. Tamoxifen inhibits the estrogen receptors and induces apoptosis of the cancerous cells [2, 4].

In order to create a mathematical model of hormone therapy, we must select a framework to describe the onset of cancer and the fundamental interactions between healthy and cancerous cells. Recently, Eric Werner has proposed a new paradigm for cancer growth which suggests that cancer develops as a result of mutations to developmental control networks. He introduces various types of cancer networks that describe the behavior of cancer stem cells [7]. These stem cells divide based on instructions from their network to produce tumor cells. We consider linear cancer networks in which a cancer stem cell can either divide into itself or differentiate into a terminal tumor cell.

Once we establish a model of a linear cancer network, we extend the model to include the effects of estrogen availability and hormone therapy in the growth or cure of estrogen receptor positive breast cancer. The model establishes specific conditions on the effectiveness of a receptor-blocking drug on cancer stem cells and healthy epithelial cells that determine

whether the treatment fails, cures the cancer completely, or reduces final tumor size. In the latter case, reduction of the tumor size may allow for breast-conserving surgery.

In Section 2 we describe relevant mathematical models of breast cancer and establish a framework for a mathematical model of cancer stem cells, cancer tumor cells, and healthy epithelial cells in the breast. In Section 3 we present an original system of differential equations as a model for breast cancer dynamics and treatment via hormone therapy, which we simulate in Section 4 by choosing specific parameter values and producing graphs that show the behavior of our model both with and without treatment. In Section 5 we explore long-term behavior of the model with a local stability analysis and address the robustness of the model with a sensitivity analysis. We then in Section 6 discuss the biological significance of each equilibrium point and suggest possible insights into cancer recurrence and viability of neoadjuvant treatment. Finally, in Section 7 we provide some concluding remarks and outline potential future directions for research.

2 Background of Models

Many current mathematical models of cancer utilize systems of first-order differential equations to represent the populations of cancerous cells and healthy cells. For instance, in [3], Mufudza, Sorofa, and Chiyaka consider a Lotka-Volterra type system of four ordinary differential equations to describe the interactions among healthy, tumor, and immune cells, as well as excess estrogen levels in breast cancer. Shimada and Aihara [5] explore androgen suppression therapy by presenting a system of three ODEs that monitor androgen-dependent and independent cells in prostate cancer. Moreover, models that incorporate cancer stem cells have the potential to address open questions in cancer research, such as recurrence or spontaneous remission. Properly targeting cancer stem cells may lead to new treatment options that could eradicate tumors and offer longer periods of remission.

Our approach in creating a mathematical model of the interactions between cancer stem cells and cancer tumor cells will be to use linear cancer networks. As described by Werner [7], a linear cancer network occurs when a cancer stem cell (A) divides and produces another cancer stem cell and a cancer tumor cell (B). This means that the cancer stem cells will stay constant but the cancer tumor cells will be produced linearly by the cancer stem cells.

We use Werner's idea as a framework to create a set of two differential equations to model the growth of cancer stem cells (A) and cancer tumor cells (B). To anticipate the effect of hormone therapy both on cancerous and healthy cells, we include a third differential equation that describes the growth rate of healthy cells (H) within the breast tissue.

$$\begin{aligned}\frac{dA}{dt} &= kA \left(1 - \frac{A}{M_1}\right) \\ \frac{dB}{dt} &= kA \left(\frac{A}{M_1}\right) \left(1 - \frac{B}{M_2}\right) - nB \\ \frac{dH}{dt} &= qH \left(1 - \frac{H}{M_3}\right)\end{aligned}$$

The healthy cells of the model only refer to the epithelial cells of the breast that are near the site of the tumor, and we assume that these cells grow logistically at a rate of q . We also assume that cancer stem cells grow logistically at a rate of k . M_1 , M_2 , and M_3 refer to the carrying capacities of stem, tumor, and healthy cells, respectively. The fraction $\frac{A}{M_1}$ represents the proportion of stem cell divisions that differentiate into tumor cells. While k accounts for the net growth rate of A cells, it only describes the birth rate of B cells (recall that we follow Eric Werners assumption that B cells are terminal and do not divide on their own [7]); therefore, we include a natural death rate n of B cells.

3 Breast Cancer Model

The above models [3, 5] support the choice to represent the dynamics of estrogen (relative to a natural equilibrium level) explicitly with an ODE. In order to include linear cancer networks, our model also separates cancerous cells into two categories: cancer stem cells and tumor cells. However, we assume that Lotka-Volterra competition between cell populations is negligible and that all cell types are estrogen-dependent. Using Eric Werner's framework, we propose the following equations to reflect how levels of available estrogen affect cancer cell growth.

$$\begin{aligned}A' &= \left(\frac{kE}{E_0}\right) A \left(1 - \frac{A}{M_1}\right) - d_1 \left(1 - \frac{E}{E_0}\right) A \\ B' &= \left(\frac{kE}{E_0}\right) A \left(\frac{A}{M_1}\right) \left(1 - \frac{B}{M_2}\right) - nB - d_2 \left(1 - \frac{E}{E_0}\right) B \\ H' &= \left(\frac{qE}{E_0}\right) H \left(1 - \frac{H}{M_3}\right) - d_3 \left(1 - \frac{E}{E_0}\right) H \\ E' &= rE \left(1 - \frac{E}{E_0}\right) - sDE\end{aligned}$$

Since the model shows the growth of cells that are estrogen dependent, we had to consider how estrogen would effect how the cells grow. The term $\frac{E}{E_0}$ accounts for how estrogen helps the cells grow. E_0 serves as the carrying capacity for E . When $E < E_0$, then the rate that cells are dividing due to estrogen are slower than when $E > E_0$. When $E = E_0$, then the cells are dividing normally. The amount of available estrogen has logistic growth (with rate

A	=	Number of cancer stem cells
B	=	Number of tumor cells
H	=	Number of healthy cells
E	=	Amount of estrogen available to bind to estrogen receptors in the cells
k	=	Normal rate of division for A cells
E_0	=	Normal amount of estrogen needed for all cells to divide normally
$M_{1,2}$	=	Carrying capacities of cancer stem cells and tumor cells
$d_{1,2}$	=	Rate at which A and B cells are dying from lack of estrogen
n	=	Death rate of B
q	=	Normal growth rate of healthy cells
M_3	=	Carrying capacity of healthy cells
d_3	=	Rate that healthy cells are dying from lack of estrogen
r	=	Logistic growth rate of binding estrogen
s	=	Effectiveness of the Tamoxifen at blocking estrogen receptors
D	=	Dose of Tamoxifen

r) because as the cells use estrogen, more estrogen is being replenished by natural functions. In pre-menopausal women, the ovaries produce estrogen, and in post menopausal women estrogen is produced by fat tissue [6]. The term $\left(1 - \frac{E}{E_0}\right)$ found in the other equations describes the proportion of available estrogen that is unable to bind to receptors. As E decreases, this proportion grows larger and has an increasingly negative effect on cellular growth. The dosage (D) of Tamoxifen we assume constant because it is taken daily [6], and s describes the effectiveness of Tamoxifen at reducing available estrogen.

4 Results

With the model in place we now perform numerical simulations using *Mathematica 9*. We first simulate the model without treatment to visualize normal interactions between cancerous cells, healthy cells, and available estrogen.

4.1 Without Treatment

We let $D = 0$ to represent a no-treatment case. From a simple stability analysis we conclude that the only stable equilibrium point for this model is when the cells and estrogen co-exist. The graph in Figure 1 shows the dynamics of the model.

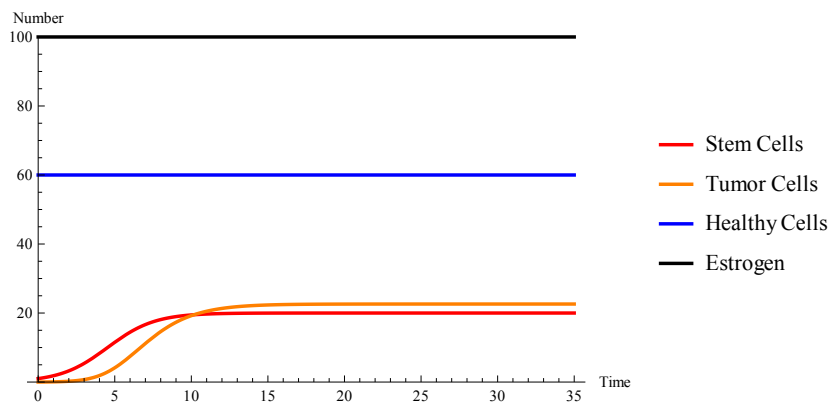


Figure 1: Breast cancer growth model before treatment

4.2 With Treatment

We then wanted to show the effects of introducing the drug Tamoxifen. Using the following set of parameters found in Table 1 we produced four graphs (see Figures 2, 3, 4, and 5) showing different outcomes of the model.

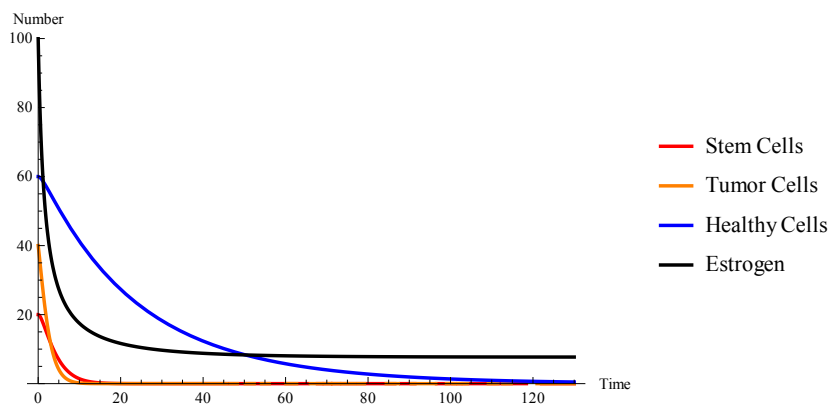


Figure 2: All cells are dead and only estrogen is available

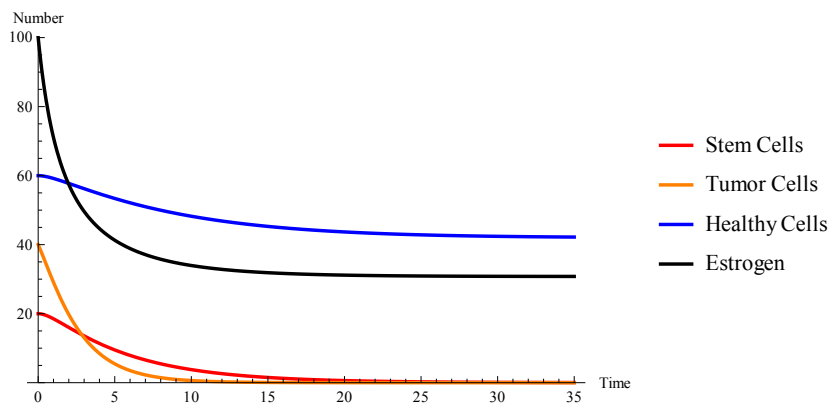


Figure 3: The cure state where all cancer cells are dead and healthy cells survive

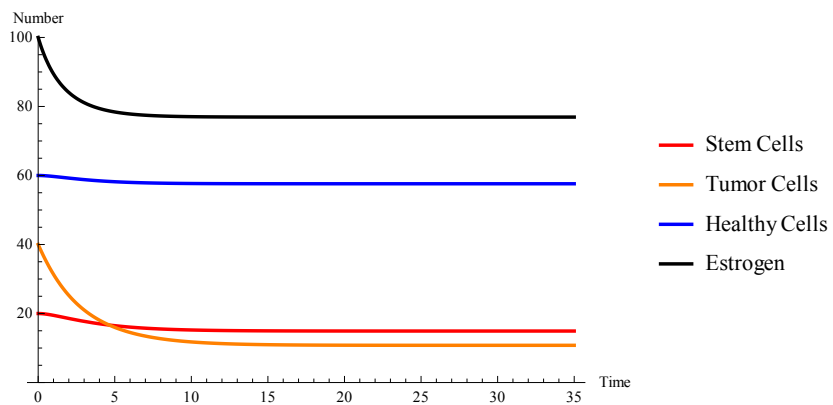


Figure 4: All cells and available estrogen coexist

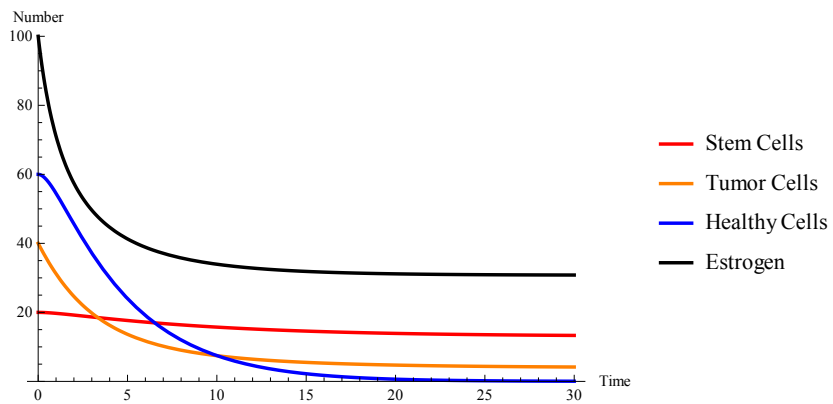


Figure 5: All healthy cells die and cancer cells live

Parameter	Graph 1	Graph 2	Graph 3	Graph 4
k	.65	.65	.65	.65
E_0	100	100	100	100
M_1	20	20	20	20
M_2	40	40	40	40
d_1	.55	.55	.55	.10
d_2	.65	.65	.65	.20
n	.25	.25	.25	.25
q	.75	.75	.75	.75
M_3	60	60	60	60
d_3	.1	.1	.1	.7
r	.65	.65	.65	.65
s	.60	.45	.15	.45
D	1	1	1	1

Table 1: Parameters for breast cancer growth model

5 Analysis of Model

To gain insight on how changing parameters in the model lead to each of the four distinct behaviors in Figures 2, 3, 4, 5, we place our system in dimensionless form and conduct stability and sensitivity analyses.

5.1 Dimensionless Form

The dimensionless form reduces the number of parameters in the model so that the analysis is easier to conduct.

$$x' = wx(1-x) - \delta_1(1-w)x \quad (1)$$

$$y' = \mu wx^2(1-y) - \eta y - \delta_2(1-w)y \quad (2)$$

$$z' = \gamma wz(1-z) - \delta_3(1-w)z \quad (3)$$

$$w' = \rho(1-w)w - \sigma w \quad (4)$$

where

5.2 Equilibrium Points

We set the differential equations 1, 2, 3, and 4 simultaneously equal to 0 in order to find the equilibrium points of our model. Let

$$\begin{aligned}
 x &= \frac{A}{M_1}, & \delta_i &= \frac{d_i}{k}, i = 1, 2, 3 \\
 y &= \frac{B}{M_2}, & \eta &= \frac{n}{k}, \\
 z &= \frac{H}{M_3}, & \gamma &= \frac{q}{k}, \\
 w &= \frac{E}{E_0}, & \rho &= \frac{r}{k}, \\
 \mu &= \frac{M_1}{M_2} & \sigma &= \frac{sD}{k}.
 \end{aligned}$$

$$\begin{aligned}
 \bar{x} &= \frac{\rho - \sigma - \delta_1\sigma}{\rho - \sigma} \\
 \bar{y} &= \frac{\mu(\rho - \sigma - \delta_1\sigma)^2}{\mu(\rho - \sigma - \delta_1\sigma)^2 + (\rho - \sigma)(\eta\rho + \delta_2\sigma)} \\
 \bar{z} &= \frac{\gamma\rho - \gamma\sigma - \delta_3\sigma}{\gamma(\rho - \sigma)} \\
 \bar{w} &= \frac{\rho - \sigma}{\rho}
 \end{aligned}$$

The dimensionless model gave 5 equilibrium points:

$$\begin{aligned}
 P_1 &= (0, 0, 0, 0) \\
 P_2 &= (0, 0, 0, \bar{w}) \\
 P_3 &= (\bar{x}, \bar{y}, 0, \bar{w}) \\
 P_4 &= (0, 0, \bar{z}, \bar{w}) \\
 P_5 &= (\bar{x}, \bar{y}, \bar{z}, \bar{w})
 \end{aligned}$$

We can then analyze the stability of each equilibrium point by plugging each one into the resulting Jacobian matrix, but first we will discuss the positivity of these points.

5.3 Positivity of Equilibrium Points

In order to determine when each of our populations can approach a non-negative steady state, we must establish conditions on our parameters to ensure that each point is located in

$$\mathbb{R}_+^4 = \{(x, y, z, w) : x, y, z, w \geq 0\}.$$

Clearly, $P_1 \in \mathbb{R}_+^4$. To guarantee that $\bar{w} > 0$ in the remaining four equilibrium points, we require that

$$\rho > \sigma \quad (5)$$

and we make this assumption for the remainder of the paper. Consequently, $P_2 \in \mathbb{R}_+^4$. Next, we note that $\bar{x} > 0$ whenever

$$\delta_1 < \frac{\rho - \sigma}{\sigma} \quad (6)$$

and $\bar{z} > 0$ whenever

$$\delta_3 < \frac{\gamma(\rho - \sigma)}{\sigma}. \quad (7)$$

Thus, assuming (7) holds, $P_4 \in \mathbb{R}_+^4$. From (5), (6) we conclude that $\bar{y} > 0$. Therefore $P_3, P_5 \in \mathbb{R}_+^4$.

5.4 Stability Analysis of Dimensionless Model

After establishing conditions that ensure the positivity of the equilibrium points, we find the Jacobian matrix of the dimensionless model. The Jacobian matrix will be used to analyze the local stability of each equilibrium point.

$$\begin{bmatrix} w - 2xw - \delta_1 + \delta_1 w & 0 & 0 & x - x^2 + \delta_1 x \\ 2\mu wx - 2\mu wxy & -\mu wx^2 - \eta - \delta_2 + \delta_2 w & 0 & \mu x^2 - \mu x^2 y + \delta_2 y \\ 0 & 0 & \gamma w - 2\gamma wz - \delta_3 + \delta_3 w & \gamma z - \gamma z^2 + \delta_3 z \\ 0 & 0 & 0 & \rho - 2\rho w - \sigma \end{bmatrix}$$

The four eigenvalues of the Jacobian matrix evaluated at P_1 follow:

$$\left\{ \begin{array}{l} \lambda_1 = -\delta_1 \\ \lambda_2 = -\delta_3 \\ \lambda_3 = -\delta_2 - \eta \\ \lambda_4 = \rho - \sigma \end{array} \right\}$$

Note λ_4 . Since we concluded that ρ has to be greater than σ the origin, or equilibrium point P_1 , will always be unstable. For the remaining four equilibrium points, inequalities (6, 7) lead to four cases where each equilibrium point becomes stable based on sign changes in the eigenvalues.

The four cases are:

- Case 1:

$$\delta_1 > \frac{\rho - \sigma}{\sigma} \text{ and } \delta_3 > \frac{\gamma(\rho - \sigma)}{\sigma}$$

- Case 2:

$$\delta_1 > \frac{\rho - \sigma}{\sigma} \text{ and } \delta_3 < \frac{\gamma(\rho - \sigma)}{\sigma}$$

- Case 3:

$$\delta_1 < \frac{\rho - \sigma}{\sigma} \text{ and } \delta_3 < \frac{\gamma(\rho - \sigma)}{\sigma}$$

- Case 4:

$$\delta_1 < \frac{\rho - \sigma}{\sigma} \text{ and } \delta_3 > \frac{\gamma(\rho - \sigma)}{\sigma}$$

For case 1, P_2 is the only point stable because when (6),(7) are reversed, then all other cases have a positive eigenvalue. All other cases follow a similar argument as the first.

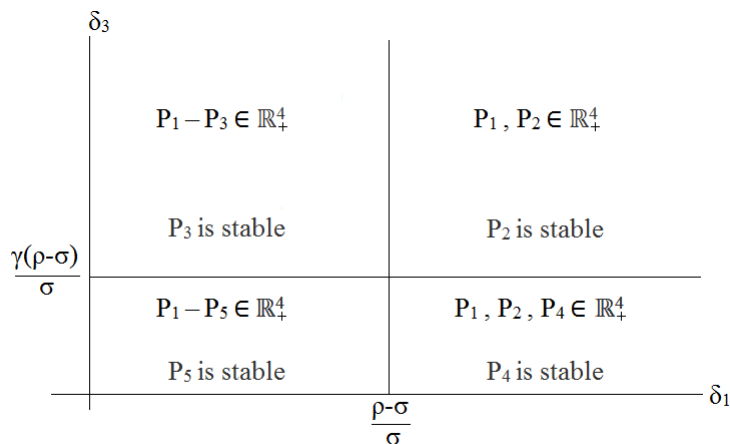


Figure 6: This graph shows the positivity and stability of our model.

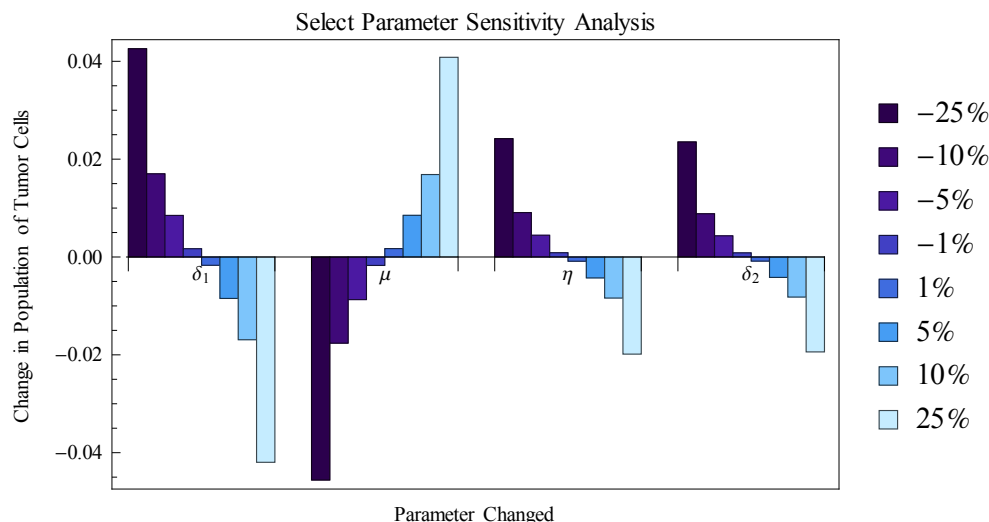
Since ρ and σ play an important role in the long term behavior of the model, we next perform a sensitivity analysis to explore how other parameters affect the model.

5.5 Sensitivity

For the sensitivity analysis, baseline parameters were chosen to place our model in case 3 of coexistence. We will be measuring the dimensionless fraction (y) of remaining tumor cells after an extended period of time. These parameters (found below in Table 2) gave a remaining fraction of the tumor cells of .221253. The parameters ρ and σ will be set to maintain coexistence. We will also fix the parameters γ and δ_3 that have no effect on the fraction of remaining tumor cells we are observing. The remaining values will be changed by a certain percentage from their baseline, and the change in the remaining fraction of tumor cells will be recorded.

Parameter	Baseline Value
ρ	.40
σ	.15
γ	.75
δ_3	.20
δ_1	.55
μ	.50
η	.25
δ_2	.65

Table 2: Fixed parameters for sensitivity analysis



6 Discussion

The analysis of the model produced five equilibrium points. All the points have biological meaning in relation to explaining the cancer growth dynamics. P_1 represents the situation where there are no cells (cancer, tumor, or healthy) and no binding estrogen. P_2 represents where all cells are dead and there is only estrogen available, while P_3 shows a case where the cancer cells (stem and tumor) are existing with available estrogen but all the healthy cells are dead. P_3 could describe the situation where cancer has killed the host. P_4 represents a cure state where the cancer has gone into permanent remission. This may be possible if the right drug/treatment is administered and is 100% effective but typically this does not happen with hormone therapy. This is because over time the cancer cells which are dependent on estrogen slowly develop into independent cells that grow regardless of estrogen binding to

receptors [5]. P_5 represents the coexisting state and in this state breast conserving surgery can be done.

Our stability analysis shows that two key inequalities determine the long term behavior of the model. It is interesting to reformulate these inequalities in terms of σ to reveal how the effectiveness of the drug impacts this behavior. For example, in the case where P_5 is stable and coexistence between healthy and cancerous cells occurs, we have:

$$\sigma < \frac{\rho}{\delta_1 + 1} \text{ and } \sigma < \frac{\gamma\rho}{\delta_3 + \gamma}$$

Notice that as δ_1 increases (i.e. stem cells are more negatively affected by blocked estrogen receptors), it becomes more likely that σ will instead exceed the threshold stated in the first inequality and transfer stability to the cure state P_4 . A corresponding risk occurs when increasing δ_3 ; a poorly targeted drug can cause significant damage to healthy cells. Perhaps the most interesting feature of these inequalities is the noticeable lack of δ_2 . No matter how effective the drug is at blocking estrogen receptors of tumor cells, unless δ_1 is large, the cancer will not be cured. However, larger values of δ_2 do succeed in decreasing the steady-state population of tumor cells, \bar{y} .

One possible consequence is that making \bar{y} sufficiently small may create the illusion of achieving remission. In such a case, though, recurrence of the cancer would inevitably follow if δ_1 (or σ) was not large enough to guarantee a stable cure state. This scenario may indeed be quite likely if the cells of a particular tumor contain significantly more estrogen receptors than the corresponding cancer stem cells. On the other hand, a diminished size of \bar{y} may make other treatment options such as surgery more plausible; our model thus predicts estrogen therapy can be useful as an option for neoadjuvant treatment.

7 Conclusion

Using a linear cancer network, we have produced a model which illustrates how hormone therapy can be used as a viable option for curing or reducing tumor sizes of estrogen receptor positive breast cancer. Future work will consist of finding more biologically realistic parameters, exploring other types of cancer networks, and incorporating interactions with immune cells or estrogen-independent cells.

Note: All graphs appearing in this paper were produced using *Mathematica 9*.

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