A mathematical model of cancer networks with radiation therapy

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A theory of mutated developmental control networks has been developed by Oxford scientist Eric Werner and proposed as an alternative to the traditional explanation of cancer as the result of mutated genes that cause uncontrolled cell growth. This research examined one such control network and proposed a mathematical model that depicts the behavior described by this new paradigm of cancer growth. Treatment in the form of radiation therapy was introduced, and the resulting effects on each cell population were explored. Proton therapy was also considered as an alternative to traditional radiation therapy. This research will aid in the understanding of cancer, its growth, and how treatment may interact with it. The proposed mathematical model used a nonlinear system of three ordinary differential equations that describe the growth of cancer stem cells, tumor cells, and healthy cells. Equilibrium points were analyzed and examined to uncover the behavior of the model. The model was able to predict failed treatment, cure states, and tumor recurrence, providing new mathematical explanations for these events.

Keywords: cancer stem cells, developmental control networks, radiation therapy, recurrence

INTRODUCTION

Cancer is typically thought to be the result of one or more mutations in a cell's genes that cause uncontrolled cell division (Evan & Vousden, 2001). Werner (2011) proposed a new way to explain the growth and development of cancer. Rather than focusing on genetic mutations, he suggested that cancer is caused by specific mutations in developmental control networks, which are like instructions for growth and development that are carried out by the cells. Not all networks are cancerous. Developmental networks describe how normal, noncancerous cells divide and differentiate. Developmental networks can be activated by signals from inside the cell, from other cells, and from the cell's environment. These cues are how normal cells are prompted to divide or differentiate. Specific mutations change the way a cell is told to divide and differentiate and cause the network and cell to become cancerous. Rather than random, uncontrolled growth, Werner described cancer as a highly regulated process in which the new instructions tell the cell to grow abnormally.

Linear Cancer Networks

Werner (2011) presented various types of developmental control networks that, if mutated, can direct a cell to produce cancer. Our research focused on linear cancer networks. A linear cancer network is a type of network where the number of cells grows linearly with respect to time. They are described as having a slower growth rate than other cancerous network types.

Linear cancer networks begin with one type of cancerous cell (hereafter A cell). When A cells divide into two cells, they produce another A cell and an A cell that differentiates into another type of cell (hereafter B cell). The A cells are cancer stem cells. The B cells are terminal, which means they do not divide. This asymmetrical division results in the number of A cells staying constant and the number of B cells growing linearly. In this case, A cells are the cells that are cancerous because they are responsible for producing the unlimited growth of B cells, and the B cells are not necessarily cancerous because they do not produce growth. This results in a tumor that consists of mostly B cells but is sustained by the A cells. These linear networks are not limited to only two cell types. There can be many different types of cell that divide and differentiate into other types of cells, but for the simplicity of the models, the only network considered was the linear network consisting of cells of type A and type B.

Cancer Stem Cells

Werner suggested that the A cell is a cancer stem cell. Normal stem cells are unique cells in that they have the ability to undergo self-renewal, where they create more of themselves, and they can also differentiate, where they turn into other types of cells after cell division. They are unspecialized cells that are responsible for maintaining the equilibrium number of cells of different types in the human body, replacing normal cells lost from injury or apoptosis, scheduled cell death. They do this by differentiating from their unspecialized forms to more specific types of normal cells found throughout the body. They are often tissue specific, meaning they differentiate into different types of cells that contribute to one type of tissue (Li & Xie, 2005).

Normal cells undergo apoptosis after they have been dividing for long periods of time. The more a cell divides, the more likely it is to lose parts of its DNA or create defective cells. Normal cells cannot proliferate forever. Stem cells, however, can. Stem cells have larger amounts of a specific enzyme that prevents their DNA from being damaged during cell division. For this reason, stem cells are able to live and divide indefinitely (Soltysova, Altanerova, Altaner, 2005). If stem cells become damaged and die, some of

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the other stem cells will stop differentiating and will produce more stem cells to replace those lost to return to the appropriate number of cells (Li & Xie, 2005).

It has been hypothesized that a cancer stem cell may be the result of either a mutated stem cell or a mutated normal cell that causes it to reproduce abnormally. There is a growing amount of evidence that supports the existence of cancer stem cells in several types of cancer, including Dingli and Michor (2006) and Milas and Hittelman (2009). Cancer stem cells can differentiate into other cells, just like noncancerous stem cells (Soltysova, Altanerova, Altaner, 2005). This agrees with Werner's assertion (2011) that the A cells are cancerous stem cells. They differentiate into non-cancerous B tumor cells that make up the majority of the tumor. However, in Werner's description of a linear cancer network, he did not allow for the possibility that cancer stem cells may divide without differentiating, meaning they may increase the population of A cells.

Cancer Treatments

Radiation therapy is a form of cancer treatment that delivers photons to a tumor, and the photons release energy to break apart a cell's DNA. Once its DNA is damaged, the cell can no longer reproduce and will eventually die (Sachs, Hlatky, Hahnfeldt, 2001). A downside to radiation therapy is that it penetrates all the way through the body and deposits radiation in all of the cells it passes. This means the beam harms healthy tissues, even past the tumor. Photons can travel through the tumor and continue destroying tissue (Suit, 2003). But, the strength of the beam decreases exponentially as it travels. Radiation works best for tumors near the surface of the body where it still has the most energy, and deeper tumors are problematic to treat (Castellucci, 1998). Although it is an effective method to treat cancer, radiation therapy has many drawbacks.

Proton therapy is similar to traditional radiation therapy in how it destroys the cell. It is a form of radiation that shoots a beam of protons at the tumor, rather than photons like in traditional radiation therapy (Castellucci, 1998). Proton therapy has been shown to be more effective than other forms of radiation. In a study by Mu et al. (2005), the mean dose of radiation absorbed by surrounding organs was about 0.0 Gy, which was significantly lower than other forms of radiation treatment. Proton therapy delivers a larger dose of radiation to the tumor and harms the surrounding healthy organs and tissues less than photon radiation that uses X-rays. The greatest dosage is delivered at the end of the beam (Chen et al., 2012). Since protons have mass, they only travel a specific distance into the body and do not travel all the way through. The depth of the beam may be controlled by how much energy the protons start with, and that can be easily calculated and controlled. The maximum dosage of radiation can be administered to the tumor itself, rather than wasted on the surface of the skin (Castellucci, 1998). Proton therapy is more effective in killing cancer cells than traditional photon therapy because it can deliver more radiation to the tumor itself and less to the nearby healthy cells. Suit (2003) predicted proton therapy would largely replace photon

therapy over the next 10 to 20 years.

The goal of this research was to mathematically model a linear cancer network as described by Werner (2011). Once the model of this network was established, the effects of radiation treatment and how it interacted with the network was explored, and mathematical models that show the effects of treatment on cancer stem cells, tumor cells, and healthy cells were created.

PREVIOUS MODELS

There are many mathematical models of radiation treatment for cancer, including Sachs et al. (2001), Dingli and Michor (2006), Belostotski and Freedman (2005), Freedman and Belostotski (2009), and Freedman and Pinho (2009).

Sachs, Hlatky, and Hahnfeldt (2001) presented a linear-quadratic model of radiation therapy that focused on how the cell is damaged. Logistic growth was used with the rationale that tumor growth slows over time as the tumor becomes larger. Tumors rarely produce exponential growth. They grow rapidly in their initial stages but slow over time (Skehan, 1986), which supports the assumption of logistic growth.

In the work by Dingli and Michor (2006), a model was proposed that includes cancer stem cells. They described normal healthy cells, healthy stem cells, normal cancerous cells, and cancerous stem cells, and they modeled several forms of treatment. However, radiation therapy was not included in their models. It was concluded that one of the most important factors in treating cancer is destroying the cancer stem cells. If these cancer stem cells remain in the body, the tumor can grow back rapidly. In two works, Freedman and Belostotski (Belostotski & Freedman, 2005; Freedman & Belostotski, 2009) developed a model for radiation treatment using a system of two differential equations, where one considered healthy cells and the other accounted for cancerous cells. They assumed each cell population grows logistically and cancer cells and healthy cells each inhibit the growth of the other. They used four different methods of describing how the radiation dose was administered – as a constant, proportional to the number of cancer cells, proportional to the ratio of cancer cells to healthy cells, and periodically.

The model proposed in this paper expanded upon these previous models by incorporating the idea of cancer stem cells and cancerous developmental control networks. It drew support from these models in its depiction of radiation and cell division.

MODELS

Basic Linear Cancer Network Model

For a linear cancer network, Werner (2011) described a system where the population of A cells stayed constant and the population of B cells increased at a rate proportional to the number of A cells. B cells were terminal, so they did not divide, and they were produced indefinitely. Also, all the cancer cells lived forever. This can be modeled by the system of differential equations,

$$\frac{dA}{dt} = 0 \qquad \frac{dB}{dt} = k_1 A$$

where

A	represents the number of A cancer stem cells,
B	represents the numbers of B tumor cells, and
k_1	is the rate that A stem cells are dividing.

Refined Linear Cancer Network Model

The previous system of Eq. 1-2 was slightly changed to make it more realistic. The new assumption was made that all cells grow logistically. Works by Skehan (1986) and Laird (1964) supported this assumption, as a tumor's growth rate was shown to slow as it grows larger, and it was in accordance with many other models of cancer growth, such as Sachs et al. (2001), Belostotski and Freedman (2005), Freedman and Belostotski (2009), Freedman and Pinho (2009), and Dingli et al. (2006). Also included were healthy cells (H). These were only the healthy cells adjacent to the tumor that were close enough to be vulnerable to radiation. Although healthy cells are not part of a linear cancer network, they were included because the effect of radiation on these cells is important to monitor. It was assumed that they do not interact with the cancerous cells and vice versa for the simplicity of an analysis.

Our refined model is as follows:

$$\frac{dA}{dt} = k_1 A\left(1 - \frac{A}{S}\right)$$

$$\frac{dB}{dt} = k_1 A\left(\frac{A}{S}\right)\left(1 - \frac{B}{M_1}\right)$$

$$\frac{dH}{dt} = k_2 H\left(1 - \frac{H}{M_2}\right)$$

where

A	represents the number of A cancer stem cells,
B	represents the numbers of B tumor cells,
H	represents the number of healthy cells vulnerable to radiation,
k_1	is the rate that A stem cells are dividing,
k_2	is the rate that H cells are growing,
S	is the desired number of A stem cells in the tumor,
AS	is the fraction of A cell divisions producing B cells,
$M_{1,2}$	are the carrying capacities of B and H, respectively, and
d	is the death rate of B cells.

Werner (2011) suggested that cancer starts off as one mutated cell, which is the first A cell, and that the A cell always divides asymmetrically, producing one A cell and one B cell, exemplified in the system of Eq. 1-2. It was then assumed in our model that the first A cell produced more A cells before differentiating into B cells, similar to how normal stem cells behave (Soltysova, Altanerova, Altaner, 2005). In the system of Eq. 3-5, A cells grew to a specific number by dividing to produce two daughter A cells rather than one A cell and one B cell until they reached the desired number (S). The fraction $\frac{A}{S}$ in the $\frac{dB}{dt}$ equation represents the fraction of A cell divisions that differentiate into B cells. If A<S, some A cells produce more A cells and some produce B cells. If A=S, all of the A cells produce B cells. It was assumed that A will never exceed S because A cells will not produce more A cells if they are at their capacity.

A death rate was incorporated in Eq. 4. While k_2, the growth rate of H, accounted for the birth rate and death rate of H cells,

k1 only described the division rate of A cells, which was also the birth rate of B cells. Therefore, it was important to include the -dB term in the equation for B cells to account for their natural death over time. Many types of cancer cells cease to undergo apoptosis, but there are other proposed mechanisms by which the cells can die (Brown & Attardi, 2005). Some oncogenes actually promote cell death (Lowe & Lin, 2000). Other causes for cancer cell death include natural immune responses to the cancer (Usman, Jackson, Cunningham, 2009). However, these occurrences would be relatively slow, so d was assumed to be a very small number.

To depict the growth of a tumor from its initiation, the initial conditions, which were denoted by $A(0)= A_0$, $B(0)= B_0$, and $H(0)= H_0$, described the tumor at the point immediately after the first A cell was created. This meant initial conditions $A_0=1$, $B_0=0$, and $H_0=M_2$.

Radiation Treatment Model

The goal of this research was to describe the effect of radiation therapy on these cancer networks with a mathematical model. The model proposed here considered only radiation delivery as a constant in its differential equations, as proposed in the work of Freedman and Belostotski (2009) and Freedman and Pinho (2009). The model is as follows:

$$\frac{dA}{dt} = k_1 A\left(1 - \frac{A}{S}\right) - r_1,$$

$$\frac{dB}{dt} = k_1 A\left(\frac{A}{S}\right)\left(1 - \frac{B}{M_1}\right) - dB - r_2,$$

$$\frac{dH}{dt} = k_2 H\left(1 - \frac{H}{M_2}\right) - r_3,$$

where $r_{1,2,3}$ are the respective effects of radiation.
It is important to note the initial conditions of the treatment models may not start at $A_0=1$, $B_0=0$, and $H_0=M_2$. Starting at these initial conditions would imply that a cancer cell is being treated immediately after it is formed, which is unreasonable. The cancer must grow large enough to be noticed before treatment may begin. It is more reasonable for treatment to begin when the populations are beginning to reach their carrying capacities. The simulations start with each cell population at carrying capacity.

Dimensionless Form

The model was nondimensionalized to reduce the number of parameters and simplify the calculation of equilibrium points. The dimensionless model is shown below.

$$\frac{dx}{d\tau} = x(1 - x) - \varrho_1$$

$$\frac{dy}{d\tau} = \alpha x^2(1 - y) - \delta y - \varrho_2$$

$$\frac{dz}{d\tau} = \beta z(1 - z) - \varrho_3$$

where

$$x = \frac{A}{S}, \quad \delta = \frac{d}{k_1},$$

$$y = \frac{B}{M_1}, \quad \beta = \frac{k_2}{k_1},$$

$$z = \frac{H}{M_2}, \quad \varrho_1 = \frac{r_1}{k_1 S}$$

It is important to note that the dimensionless system produces the same behavior as the original treatment system (Eq. 6-8). Also, the parameters are all still positive. For more about nondimensionalization, see A First Course in Mathematical Modeling (Giordano, Fox, Horton, 2013).

ANALYSIS

Equilibrium Points

Equilibrium points were calculated by setting the growth rate equations in the dimensionless form (Eq. 9-11) equal to zero and solving in Mathematica 8. The equilibria helped in predicting the long-term behavior of the model. This produced four equilibrium points E_n of the form:

$$E_1 = (x^-, y^-, z^-)$$
$$E_2 = (x^-, y^-, z^+)$$
$$E_3 = (x^+, y^+, z^-)$$
$$E_4 = (x^+, y^+, z^+)$$

where

$$x^{\pm} = \tfrac{1}{2}(1 \pm \sqrt{1-4\varrho_1}), \quad y^{\pm} = \frac{\alpha(x^{\pm})^2 - \varrho_2}{\alpha(x^{\pm})^2 + \delta}, \quad z^{\pm} = \frac{\beta \pm \sqrt{\beta^2 - 4\beta\varrho_3}}{2\beta}$$

Positivity of Equilibria

It is interesting to establish conditions for the parameters of the model that determine whether the equilibrium points are positive or negative. This model did not include an equilibrium point where any of the populations are zero, which is typically thought of as a population dying. Whenever a population approaches a negative equilibrium value, it will die in a finite amount of time. When such a population reached zero, it was understood that it would not decrease further.

Let $R^+ = \{x \in R : x > 0\}$. If it was assumed that $\varrho_1 \leq 1/4$ and $\varrho_3 \leq \beta/4$, it was clear that $x^{\pm}, z^{\pm} \in R^+$. Note that A cell and healthy cell (x and z) populations were positive only if they are real-valued. However, the positivity of $y^{\pm}$ was less clear than the other two populations.

The denominator of $y^{\pm}$ was clearly positive, but the numerator may not be. To eventually kill all the B cells, the numerator must be negative, so it must be true that $\varrho_2 > \alpha(x^{\pm})^2$. That meant for E_1 and E_2, it must be true that $\varrho_2 > \alpha(x^-)^2$, and for E_3 and E_4, it must be true that $\varrho_2 > \alpha(x^+)^2$ for the B cell population to die out in the long term. The effects of this inequality will be further examined at a later point in this paper.

Jacobian Matrix

To analyze the stability of each equilibrium point, the Jacobian matrix of the model was calculated by taking the partial derivatives of the system of Eq. 9-11 in Mathematica 8.

$$J_1 = \begin{bmatrix} 1-2x & 0 & 0 \\ 2\alpha x - 2\alpha xy & -\alpha x^2 - \delta & 0 \\ 0 & 0 & \beta - 2\beta z \end{bmatrix}$$

Stability

Upon substituting each equilibrium point into the Jacobian matrix in Mathematica 8, the positive eigenvalues produced from E_1, E_2, and E_3 revealed that these equilibrium points were always unstable. E_4 was the only stable equilibrium point, as eigenvalues of this equilibrium point substituted into the Jacobian matrix are all negative. This stable equilibrium point was then further examined.

NUMERICAL SIMULATIONS

Low Radiation Effect on Nondividing Cells

All cell types will reach an equilibrium at the stable equilibrium point, E_4, when the inequalities $\varrho_1 \leq 1/4$, $\varrho_3 \leq \beta/4$, and $\varrho_2 < \alpha(x^+)^2$ are satisfied. It was assumed that $\varrho_2 < \alpha(x^+)^2$ because radiation affects cells that are nondividing less than cells that are quickly dividing (Santini, Rainaldi, Indovina, 2000). However, it is interesting to consider the behavior of the system when one or both of the inequalities $\varrho_1 \leq 1/4$ and $\varrho_3 \leq \beta/4$ are violated.

Consider $\sqrt{1-4\varrho_1}$ in x^+ and y^+, and $\sqrt{\beta^2 - 4\beta\varrho_3}$ and in z^+. If $\varrho_1 > 1/4$, then x^+, $y^+ \notin R$. Likewise, if $\varrho_3 > \beta/4$, then $z^+ \notin R$. To investigate the effect these inequalities have on the behavior of the model, four cases were developed (Figure 1):

Case 1: $x^+, y^+, z^+ \in R$
Case 2: $x^+, y^+ \in R$ and $z^+ \notin R$
Case 3: $z^+ \in R$ and $x^+, y^+ \notin R$
Case 4: $x^+, y^+, z^+ \notin R$

The dimensionless parameters were used to find numerical values for the original parameters that fit each case (Table 1). They were chosen arbitrarily, simply to describe each case. More realistic numbers may be acquired through biological study.

The rate of division of A cells was arbitrarily chosen. For Cases 1 and 3, the growth rate of the healthy cells was chosen to be similar to the division rate of the cancerous cells. This was because studies have shown that individual cancer cells usually do not appear to divide more quickly than healthy cells (Santini, Rainaldi, Indovina, 2000). This meant that B cells and H cells were likely
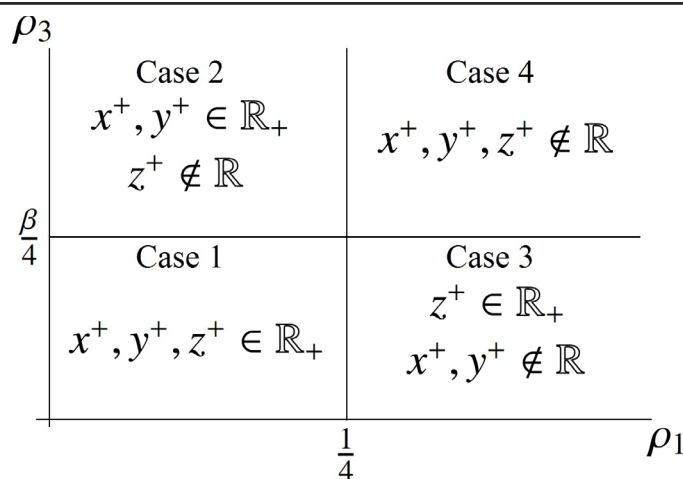

Figure 1. A plot of ϱ_1 vs. ϱ_3 that describes the characteristics of each of the four cases when it is assumed that $\varrho_2 \leq \alpha(x^-)^2$.

Parameter	Case 1	Case 2	Case 3	Case 4
A_0	15	15	15	15
B_0	47	47	43	43
H_0	110	110	110	110
k_1	.6	.6	.5	.5
k_2	.4	.06	.4	.06
S	15	15	15	15
M_1	100	100	100	100
M_2	110	110	110	110
d	.1	.1	.1	.1
r_1	2	2	2	2
r_2	.5	.5	.5	.5
r_3	1.5	1.98	1.5	1.98

Table 1. Numerical values of parameters for each case.

Case (revisited)	1	2	3	4
r_2 Value	4.5	4.1	3	3

Table 2. Values of r_2 in Figures 6-9.

produced at the same rate, so the death rate of B cells was chosen to bring the overall growth rate closer to the overall growth rate of H cells. For Cases 2 and 4, the value of k_2 was chosen simply to display the desired behavior of each case.

In our simulations, all populations started at their carrying capacity, but note that $B \neq M_1$. This occurred because k_1, which is the rate that A cells are dividing and B cells are being produced, does not account for the death rate of B like a typical logistic growth rate would because it is merely the rate of A cell division. On the other hand, k_2 accounts for the birth rate and death rate of H cells, so $H = M_2$. In our simulations, the initial population of B cells started at its true carrying capacity, which is a combination of M_1 and d that can be uncovered by graphing Eq. 4 and approximating the number it approaches.

The carrying capacities were chosen so that the A cell population was much smaller than both the B and H cell populations, to support the assumption that the growth of the tumor is maintained by only a small number of A cells.

The radiation constants represented the number of cells killed per time step. r_1 was largest because cells that are actively dividing are more easily harmed than cells that are not (Santini, Rainaldi, Indovina, 2000), and all A cells are dividing. r_2 was very small, especially in relation to the large number of B cells, because the

B cells are terminal, therefore the radiation was assumed to affect them very little. r_3 was also small with respect to the number of H cells, but it was larger than r_2 because many H cells do divide, but not all. However, r_3 was not as large as r_1 because healthy cells are better able to repair the damage from radiation than cancerous cells, as many cancer cells lack damage control checkpoints that normal cells have (Bao et al. 2006), so the radiation does not kill the healthy cells as frequently as it kills cancerous cells. This meant the fraction of healthy cells killed was smaller than the fraction of A cells killed.

Each case was graphed in Mathematica 8 using the appropriate parameters shown in Table 1 to visualize the behavior the various real or nonreal elements of the equilibrium points created (Figures 2-5).

These graphs revealed that an equilibrium containing a nonreal number resulted in the population reaching a negative number, though it was understood that the population would remain zero when it is reached. The number of B cells in Case 3 (Figure 4) and both B cells and healthy cells in Case 4 (Figure 5) would continue to decline until they reach zero. However, the number of A cells reached zero first, and the graphs cannot continue when the A cell population becomes negative because the negative population values produced unrealistic behavior.

High Radiation Effect on Nondividing Cells

Each case's behavior can vary further. Above, it was assumed that $\rho_2 < \alpha(x^+)^2$. This meant that the radiation had very little effect on the B cells, since the B cells are terminal (Santini, Rainaldi, Indovina, 2000). While this could still be true for some types of cancer, investigating the effects of $\rho_2 > \alpha(x^+)^2$ produced more interesting and biologically relevant behavior. This meant assuming radiation has a slightly larger effect on the B cells than before, which was highly plausible.

The following graphs (Figures 6-9) for each of the cases with large ρ_2 ($\rho_2 > \alpha(x^+)^2$) were developed in Mathematica 8. The only difference between the parameters used for these graphs and the previous (Figures 2-5) was that ρ_2 was increased, as shown in Table 2. Figures 6-9 were generated by plotting Eq. 6-8 with the initial populations, each at their equilibrium. When the population of B cells reached zero, the simulation was stopped and Eq. 7 was replaced with $\frac{dB}{dt} = 0$, to keep the B cell population from continuing into negative values. Then, the graph was allowed to continue until the next population reached zero or a nonzero equilibrium. Each revisited case resembled the previous graphs of each original case (Figures 2-5), except the B cells died out much more quickly. These graphs showed that it is possible for B cells to die out before A cells do.

Changing ρ_2 did not affect the previously discussed inequalities $\rho_1 \leq 1/4$ and $\rho_3 \leq \beta/4$. Changing ρ_2 merely affected the rate at which B cells died off. Although increasing ρ_2 even slightly had a dramatic effect on the behavior of the B cell population, there was no effect on the overall survival of the entire tumor. The difference was that A cells could then outlive the B cells, and if the A cells were not killed, they would repopulate the B cells and the tumor
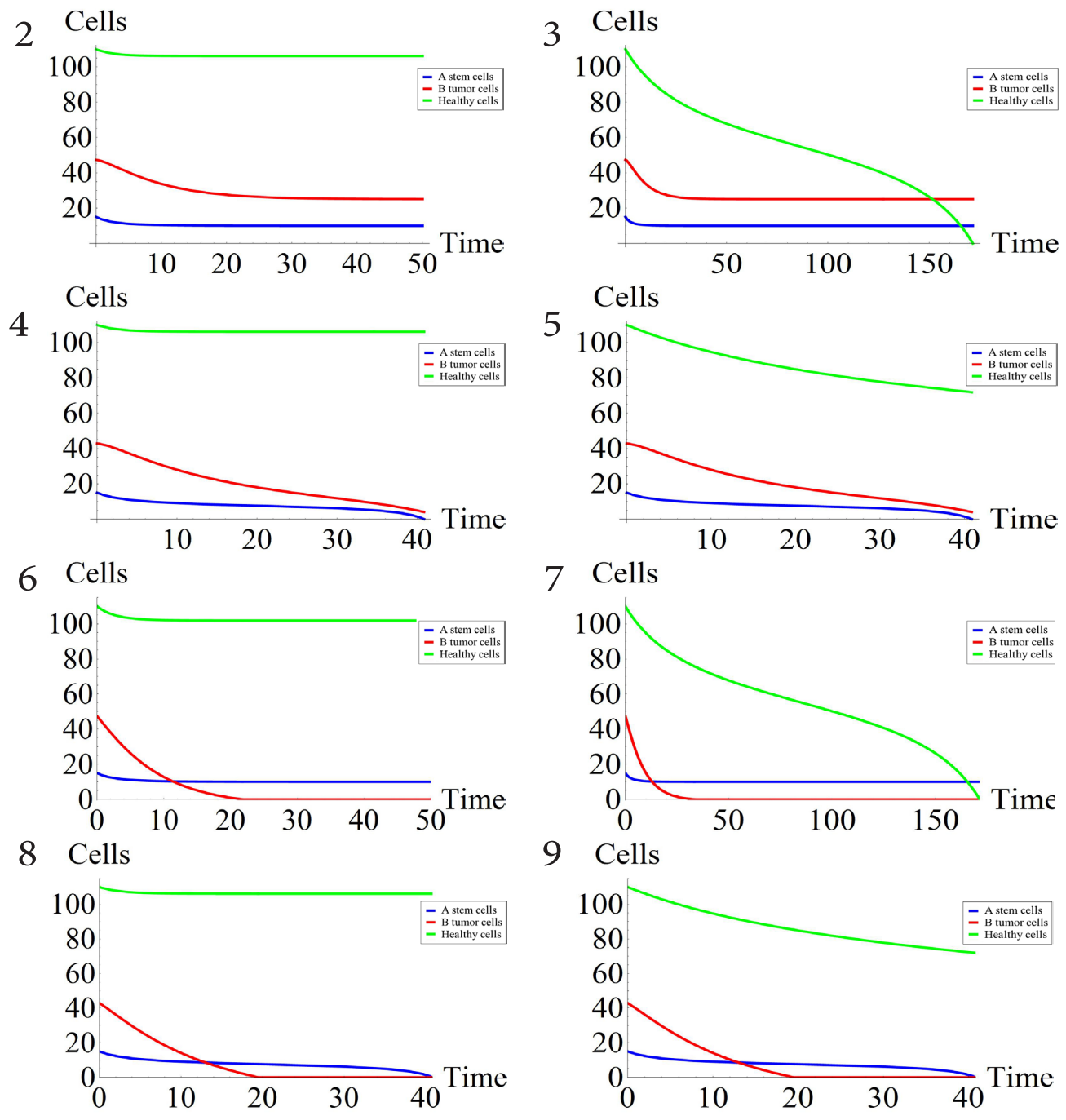
The number of cells in each population on an arbitrary scale.
Figure 2. Case 1 is shown in this plot, where all equilibria are real numbers. $Q_1 < 1/4$, $Q_3 < \beta/4$ **Figure 3.** Case 2 is shown in this plot, where x and y are real, z is nonreal. $Q_1 < 1/4$, $Q_3 > \beta/4$ **Figure 4.** Case 3 is shown in this plot, where x and y are nonreal, z is real. $Q_1 > 1/4$, $Q_3 < \beta/4$ **Figure 5.** Case 4 is shown in this plot, where aAll equilibria are nonreal numbers. $Q_1 > 1/4$, $Q_3 > \beta/4$ **Figure 6.** Case 1 revisited is shown in this plot, where all equilibria are real numbers. $Q_1 < 1/4$, $Q_3 < \beta/4$, and $Q_2 > \alpha(x^-)^2$ **Figure 7.** Case 2 revisited is shown in this plot, where x and y are real, z is nonreal. $Q_1 < 1/4$, $Q_3 > \beta/4$, and $Q_2 > \alpha(x^-)^2$ **Figure 8.** Case 3 revisited is shown in this plot, where x and y are nonreal, z is real. $Q_1 > 1/4$, $Q_3 < \beta/4$, and $Q_2 > \alpha(x^-)^2$ **Figure 9.** The number of cells in each population on an arbitrary scale. Case 4 revisited is shown in this plot, where all equilibria are nonreal numbers. $Q_1 > 1/4$, $Q_3 > \beta/4$, and $Q_2 > \alpha(x^-)^2$

would grow back, which describes recurrence.

DISCUSSION

Implications

The model predicted many possible outcomes of radiation treatment, including a cure, failed treatment, and cancer recurrence. The dimensionless parameter values for ϱ_1 and ϱ_2 that correspond to the outcome of each treatment is shown in Figure 10.

Three important outcomes of treatment explained by the model – tumor survival, tumor death, and recurrence – are summarized in Figure 10. Too small of a value of ϱ_1 resulted in the tumor surviving. This was exemplified in Case 1 (Figures 2 and 6) and Case 2 (Figures 3 and 7). In Case 2, realistically, the radiation would be stopped before the healthy cell population reached zero because the patient would be unable to physically withstand any more treatment. Biologically, in Case 1 and 2, the dose of radiation delivered to the A cells was not great enough. The radiation decreased the population of A cells but did not kill them all. Also, the effect of radiation on the B cells, ϱ_2, was not great enough to reduce the B cell population to zero. Radiation in this range merely shrunk the tumor, or lowered all populations' equilibria without decreasing them to zero. If radiation were stopped, the remaining A cells would regenerate and the tumor would grow back to its pre-treatment size or larger.

Another possible outcome of the treatment the model can predict is recurrence. This is when there is not enough radiation delivered to the A cells, allowing them to survive, but the B cells receive enough radiation and are killed. This was shown in revisited Cases 1-4 (Figures 6-9), where the B cells died out before the A cells. Since there was such a massive number of B cells relative to the number of A cells in the tumor prior to treatment, if all of the B cells were killed by the treatment, the tumor would be too small to identify. This may be misidentified as a cure state, and radiation would be discontinued. The remaining A cells could regrow the tumor, and the cancer would return, as the model suggested. Even in revisited Cases 3 and 4 (Figures 8 and 9), where the A cells would eventually be killed, radiation may likely be halted before the A cells have time to die off because the B cells, the visible bulk of the tumor, will die first. The course of recurrence is exemplified in Figure 11, where treatment is ceased at time 30. The remaining cancer stem cells were able to quickly regenerate the tumor. Supporting this idea of recurrence, Werner (2011) stated that the goal of treatment is to remove all the cells that are actually dividing. It is important to kill the A cells, since they are the driving force behind the tumor and responsible for its growth and survival.

To prevent the previous two outcomes, radiation must be delivered so that the previously discussed inequality $\varrho_1 > 1/4$ is true, demonstrated by original Case 3 and Case 4 (Figures 4 and 5) and revisited Case 3 and Case 4 (Figures 8 and 9), as long as radiation is continued for an adequate amount of time to kill the A and B cells. The ideal case was Case 3, where the tumor cells were killed by the radiation but the healthy cells survived. Converting the dimensionless inequalities back to the original, biologically

meaningful form resulted in the following Case 3 inequalities:

$$\varrho_1 > \frac{1}{4} \qquad \varrho_3 \leq \frac{\beta}{4}$$

$$\frac{r_1}{k_1 S} > \frac{1}{4} \qquad \frac{r_3}{k_1 M_2} \leq \frac{k_2}{4k_1}$$

$$r_1 > \frac{k_1 S}{4} \qquad r_3 \leq \frac{k_2 M_2}{4}$$

The first inequality ($\varrho_1 > 1/4$) suggests that in order to kill the cancer, the dose of radiation must exceed one-fourth of the growth rate times the carrying capacity of A cells. This makes sense biologically because increasing the size of the tumor (increasing S) or increasing the rate at which the tumor is growing (increasing k_1) will require a larger amount of radiation. The maximum number of A cells and the rate at which they are dividing are what determine the size and growth of the tumor. A large S means that there are many A cells to produce B cells and that the tumor will grow faster
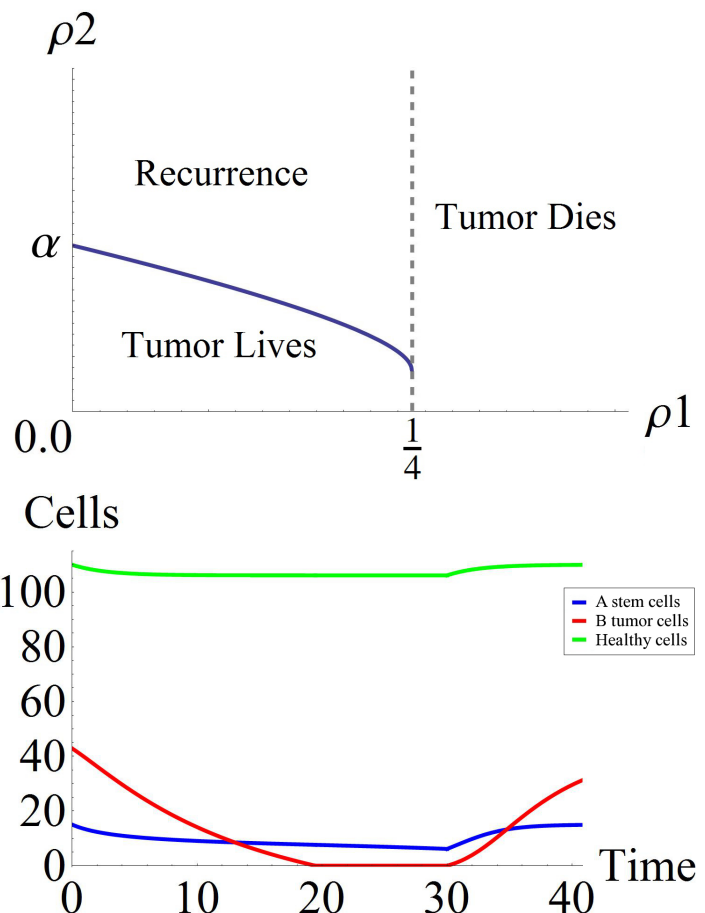

Figure 10. A graph of ϱ_1 vs. ϱ_2 describing the result of treatment based upon the numerical values of the parameters. **Figure 11.** A plot of the number of cells in each population over time depicting the course of recurrence. After all of the B cells are killed, the tumor is too small to detect, and treatment is stopped at time 30. The A cells are able to quickly regrow the tumor.

and larger. Similarly, a large k_1 indicates that A cells can produce B cells and reproduce other A cells very rapidly. The dose of radiation (r_1) must be large enough to combat those factors to result in the cure state.

The second inequality ($\varrho_3 \leq \beta/4$) suggests that the dose of radiation may not exceed one-fourth of the growth rate times the carrying capacity of healthy cells in order for the healthy cells to live. Increasing the total number of healthy cells (increasing M_2, because the initial population of healthy cells will be at the carrying capacity) or increasing the rate at which the cells can recover (increasing k_2, the rate they divide and regenerate) will result in a population of healthy cells that can withstand and recover from larger amounts of radiation. This inequality being true protects the healthy cells from dying. However, a cure state can be reached even when the inequality $\varrho_3 \leq \beta/4$ is not true as long as $\varrho_1 > 1/4$ is satisfied. This was exemplified by the original and revisited Case 4 (Figures 5 and 9). If radiation can be stopped after the cancerous A cells are killed but before too many of the healthy cells are, then a successful cure state will be reached.

Proton Therapy

Proton therapy does not greatly differ from typical radiation therapy in terms of the mathematical model, but there are differences in the parameters that distinguish the two from each other. Since proton therapy is much more selective toward the tumor (Chen et al., 2012), the value of r_3 would be significantly lower when modeling proton therapy than when modeling radiation therapy. The corresponding r_1 and r_2 could be much greater since a larger dose of radiation can be delivered to the tumor while affecting the healthy tissues less when treated with proton therapy (Suit, 2003). The predicted benefits of proton therapy for the model are that the inequality $\varrho_3 \leq \beta/4$ will be violated less frequently and the population of healthy cells will be less affected. Cases 2 and 4 (Figures 3, 5, 7, 9), where the healthy cells are greatly damaged, could be avoided. This would result in more successful treatments that would not have to be stopped because too many of the patient's healthy tissues were being harmed. The patient is predicted to undergo less physical stress on his or her body with proton therapy. More realistic use of the model may show that it is difficult to kill the cancer stem cells without greatly harming the healthy cells with radiation. Proton therapy has been shown to greatly reduce the toxicity to healthy cells and may be much more effective at targeting cancer stem cells (Milas & Hittelman, 2006). Overall, proton therapy is much more effective than radiation therapy.

Strengths of the Model

A major strength of the model is that it uses the idea of cancer stem cells and developmental control networks. Few models have used the idea of cancer stem cells. One of the few mathematical models of cancer stem cells is Dingli and Michor (2006). But, our proposed model incorporated the idea of developmental control networks. Developmental control networks are a new idea on which very little research has been conducted, but they offer many explanations for the behavior of cancer (Werner, 2011). This is important because it allows the model to predict recurrence. Pro-

viding a mathematical explanation of this phenomenon is a great contribution from cancer control networks.

The treatment model (Eq. 6-8) and the related inequalities may also be used to predict the time required to kill all tumor cells and prevent tumor recurrence. This will be of great help to the medical field, because recurrence is a major problem for many types of tumors (Lin, 1999). Several measurements of a patient's tumor progression over time may provide realistic, individualized parameters to be used in this model. Using realistic and accurate parameters, the time it takes to kill all of the tumor cells, including the cancerous stem cells, may be calculated, and radiation can be delivered to a patient accordingly. Also, if it is shown that the A cells die before the B cells, treatment may be stopped after killing all of the A cells, since the B cells will eventually die out. This could save a patient money and the stress of undergoing unnecessary radiation treatments.

Limitations of the Model

Although the model explained many new concepts, Werner proposed many types of cancer networks, such as linear, exponential, geometric, stochastic, and more. There are even expansions of the basic linear cancer network, called linear mixed cell networks, where there are more than A and B cells (Werner, 2011). These other types of cancer networks may be better predictors of actual cancerous behavior than the most basic linear network.

The model became unrealistic once any population reached zero. Realistically, the treatment would cease to affect a population of cells once that population reached zero. Instead, the model continued to subtract $r_{1,2,3}$ from the negative cell populations. This behavior was not biologically meaningful.

Another factor limiting the model was how the radiation is administered. In reality, radiation is not a one-time occurrence. It is delivered periodically, with breaks between treatments to allow the patient to recover from the previous treatment. Unfortunately, the model did not take this into account. The model depicted radiation as a singular treatment that either killed or failed to kill the cancer over time. The model was still very effective, because it described an overall, average effect of radiation in the long term, but it would be more realistic for a model to describe a periodic administration of treatment.

Also, there are different characteristics of cancer that can be modeled. One is competition between the cancerous cells and the healthy cells, like in Sachs et al. (2001), Belostotski and Freedman (2005), Freedman and Belostotski (2009), and Freedman and Pinho (2009), which can explain cancerous and healthy cells fighting for resources, healthy cells being negatively affected by byproducts of the cancerous cells, and more. The terms that model these interactions can get incredibly complicated and nonlinear. Unfortunately, competition was ignored for the sake of the analysis.

Future Work

There is much to expand on with this basic model of cancer networks and cancer treatment. First, the proposed model was of the simplest type of cancer network – a linear cancer network. As mentioned above, there are a seemingly endless number of net-

works that could all be modeled by differential equations. In the future, these could each be mathematically modeled.

As previously mentioned, the one-time administration of radiation depicted by the model was not entirely realistic. Though still meaningful, the model could be made more realistic if radiation was delivered periodically, similar to the fourth control in the work of Freedman and Belostotski (2009). This would be an interesting direction to take this research in the future.

However, Werner (2011) stated that radiation may not be the best way to treat a cancer that fits into the category of a linear cancer network because the radiation may mutate B cells into A cells instead of killing them. This is a common fear of radiation therapy. Radiation has been shown to sometimes mutate healthy cells into cancerous cells and cause a secondary cancer (Hall 2006). The model did not account for this mutation into A cells, and developing a model that does may be of interest. Although proton therapy reduces the risk of mutating other cells into cancerous cells, investigating and modeling other treatments and how they affect healthy cells, cancer stem cells, and developmental control networks could be beneficial.

CONCLUSION

The model was an effective depiction of a linear cancer network and radiation treatment, and it provided a mathematical explanation for recurrence, resulting from the incorporation of cancerous developmental control networks in the model. The model also can be used to predict the time and dose of radiation necessary to prevent negative results of treatment. This will be a great aid to medical professionals, but to properly utilize this model, realistic numerical values for the parameters must be found. Also, there is much more to investigate about these developmental control networks, like other types of networks, cells, cell interactions, and cancer treatments. Ideally, this research is a launching pad for future study.

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