# Final Report

Modeling the Effects of Proton Therapy on Cancer Stem Cells

By:

Rose Boch  Noelle Brokamp  Roger Rocha-Claros

## Contributions

**Rose Boch:**
Introduction, background, analysis of healthy cells, and proofread/edited.
**Noelle Brokamp:**
Analysis of non-proliferating cancer cells, assumptions paragraph under "Discrete Proton Therapy Model", and paragraphs explaining implications of fixed points and stability.
**Roger Rocha-Claros:** Analysis of cancer stem cells and discussion on possible therapy range for patient

MATH 434, Section 001, Spring 2025

May 8th, 2025

# 1 Introduction

Proton therapy is a form of radiation therapy primarily used for treating types of cancer near serially organized tissues such as the liver and the brain. These tissues, if damaged, will cause the patient severe secondary side effects including death. Proton therapy has extreme precision and is able to send treatment to narrow regions of tissues. Other advantages is it minimizes the amount of healthy cells dying so patients can be treated with higher dosages for fewer treatments without increasing side effects.

For a synopsis, beams of high-energy protons are precisely fired from a particle accelerator to a particular depth in the tumor. Majority of the dose occurs at the proton beam's endpoint which is dependent on the initial amount of energy chosen. For a singular beam, to eliminate the cancer cells, it is crucial that the beam ends at the optimal depth called the target depth. If the beam is too short, the therapy is not as effective. However, if the beam surpasses the target depth, the therapy's ability to eliminate the cancer cells quickly goes to zero. The maximum dosage of one beam is only capable of treating a small range of the tumor called the Bragg's peak region. This is typically unrealistic since most tumors are larger than one proton beam's Bragg's peak region. In order to have the majority of the dosage covering the full tumor, a proton beam is then modulated to create a spread out Bragg Peak (SOBP). Though important to understand, we will not focus on the (SOBP).

To analyze the effects of proton therapy, we will examine the densities of the cancer stem cells ($A$), the non-proliferating cancer cells ($B$), and the healthy cells ($H$) at each time step using the provided difference equations. We will use cobweb diagrams to help us analyze each cell type's steady state and use bifurcation graphs to see how the amount of therapy will change the orbits.

# 2 Discrete Proton Therapy Model

Using the provided difference equations, we will model the change of densities in discrete time and space. For the initial conditions for each cell, we assumed $H_0 = 1 - A_0 - B_0$, same as the researchers. To simplify the complexity of the equations we made further assumptions. Instead of once every 24 hours, we are assuming the same amount of proton therapy $P_t$ is applied every hour $t$. Instead of changing between depths of tissue $i$, we are only modeling at a constant tissue depth of $i = 1$ mm. Originally, diffusion was used to show cells diffusing from tissue depths of high concentration to depths of low concentration. Already, the diffusion of the non-proliferating cells was negligible because the researchers assumed the non-proliferating cells make the bulk of the tumor. To simplify, we are further going to assume the diffusion of the cancer stem cells and the healthy cells are also negligible due to our constant depth. We will be using a technique called time scale separation because the cancer stem cells are growing drastically faster per each time step than the healthy cells. Therefore, we will let the system $A$ reach equilibrium before starting systems for $B$ and $H$. Then we will let the system $B$ reach equilibrium. Finally, after letting systems $A$ and $B$ go to equilibrium, we will start system $H$ and find its equilibrium. This allows us to

use $A^*$ as the $A_t$ in equations $B^i_{t+1}$ and $H^i_{t+1}$ and $B^*$ as our value for $B_t$ in the equation $H^i_{t+1}$.

To represent the densities of the three cells for each time stamp, we have our first-order Discrete Proton Therapy Model.

$$A^i_{t+1} = A^i_t + k_A A^i_t \left(1 - \frac{A^i_t}{M_A}\right) - A^i_t P^i_t + d_A \sum (A^j_t - A^i_t) e^( - (j-i)^2/\mu_A$$
$$B^i_{t+1} = B^i_t + k_A A^i_t \left(\frac{A^i_t}{M_A}\right)\left(1 - \frac{B^i_t}{M_B}\right) - B^i_t P^i_t$$
$$H^i_{t+1} = H^i_t + k_H H^i_t \left(1 - \frac{H^i_t}{1 - A^i_t - B^i_t}\right) - H^i_t P^i_t + d_H \sum (H^j_t - H^i_t) e^( - (j-i)^2/\mu_H$$

Where $i$ represents the depth of tissue in mm, $t$ represents the time at each step in hours, and both $i, t \in \mathbb{Z}$. $M_A, M_B$ are the relative carrying capacities for $A, B$ and $k_A, k_H$ are the intrinsic growth rates for $A, H$. $P^i_t$ represents the dose or proton therapy and $d_A, d_H$ represents $A, H$ diffusing.

Recall, we removed the diffusion variables, assumed a constant $i = 1$ mm, used time scale separation, and assumed $P_t$ is a constant. Therefore our simplified equations are

$$A_{t+1} = A_t + k_A A_t \left(1 - \frac{A_t}{M_A}\right) - A_t P_t \tag{1}$$

$$B_{t+1} = B_t + k_A A_t \left(\frac{A_t}{M_A}\right)\left(1 - \frac{B_t}{M_B}\right) - B_t P_t \tag{2}$$

$$H_{t+1} = H_t + k_H H_t \left(1 - \frac{H_t}{1 - A_t - B_t}\right) - H_t P_t \tag{3}$$

# 3 Stability of Fixed Points

Finding fixed points for our model and analyzing their stability will help us to see how various proton therapy dosages ($P_t$) will effect the densities of the different types of cells. A fixed point indicates that the cell density is not changing and has reached a steady state. For both types of cancer cells, $A$ and $B$, this steady-state would indicate that a tumor is neither growing or shrinking, therefore remaining constant in size. For $H$ cells, this would indicate that the of level healthy cells is neither increasing nor decreasing. A $P_t$ level that is too low could cause levels of cancer cells to reach an equilibrium at a high level of cancer cell density, indicating that the tumor would grow very large before stopping. And therefore, because the cancer cells grow much faster than the healthy cells, the cancer cells will over power the healthy cells leading to death. On the contrary, a $P_t$ level that is too high may cause cancer cells to stop growing at a lower density, but this could affect healthy cells negatively by causing healthy cells to also stop growing at a lower density.

A stable fixed point would indicate that the equilibrium is attracting, therefore the cell density level would continue to reach that equilibrium despite small increases or decreases in cell density levels, which are dependent on $P_t$ . An unstable fixed point, or repelling equilibrium, would mean that small levels of change in cell density could cause the cell levels to rapidly increase or decrease.

## 3.1 Cancer Stem Cells

### Equation (1)

In order to find $A^*$ we have to set

$$A_{t+1} = A^*, A_t = A^*$$
$$A^* = A^* + k_A A^*(1 - \frac{A^*}{M_A}) - A^* P_t$$
$$A^* = \begin{cases} 0 \\ M_A \left(1 - \frac{P_t}{k_A}\right) \end{cases}$$

To analyze whether the fixed point is stable we have to find the derivative of the difference equation given by:

$$f'(A_t) = 1 - k_A - P_t - \frac{2k_A A_t}{M_A}$$

To determine the stability of a fixed point we can compute:

$$f'(A^*) = 1 - k_A - P_t - \frac{2k_A}{M_A}$$

$$f'(0) = 1 - k_A - P_t$$
$$|f'(0)| < 1, \text{ satisfies the stability criterion}$$
$$k_A < P_t < K_A + 2, \text{ is stable when } A^* = 0$$

$$f'(A^*) = 1 - k_A + P_t, \text{ when } A^* > 0$$
$$|f'(A^*)| < 1, \text{ satisfies the stability criterion}$$
$$k_A - 2 < P_t < K_A, \text{ is stable when } A^* > 0$$

## 3.2 Non-proliferating Stem Cells

### Equations (2)

To find the fixed points for non proliferating cancer cells, $B$, let $B_{t+1} = B_t = B^*$, and let $A_t = A^*$. Therefore, the fixed point is given by

$$B^* = \frac{(A^*)^2 \cdot M_B \cdot k_A}{k_A \cdot (A^*)^2 + M_A \cdot M_B \cdot P_t}$$

To analyze stability, we must find the derivative of the difference equation $B_{t+1}$. This is given by:

$$f'(B) = 1 - \frac{(A^*)^2 k_A}{M_A M_B} - P_t$$

To determine the stability of the a fixed point, we can compute:

$$f'(B^*) = 1 - \frac{(A^*)^2 k_A}{M_A M_B} - P_t$$

According to Theorem 4.1, a stable fixed point satisfies:

$$|f'(B^*)| < 1$$

Thus, we have

$$|1 - \frac{(A^*)^2 k_A}{M_A M_B} - P_t| < 1$$

$$-1 < 1 - \frac{(A^*)^2 k_A}{M_A M_B} - P_t < 1$$

By simplifying the inequality, we get

$$\frac{(A^*)^2 k_A}{M_A M_B} < P_t < 2 - \frac{(A^*)^2 k_A}{M_A M_B}$$

Therefore, the equilibrium is stable when

$$\frac{(A^*)^2 k_A}{M_A M_B} < P_t < 2 - \frac{(A^*)^2 k_A}{M_A M_B}$$

## 3.3 Healthy Cells

### Equations (3)

Now we want to find the fixed points for the density of healthy cells.

Let, $H^* = H_{t+1} = H_t, A^* = A_t, B^* = B_t$

$$\Rightarrow H^* = H^* + k_H H^* \left(1 - \frac{H^*}{1 - A^* - B^*}\right) - H^* P_t.$$

Then solving for $H^*$, we get

$$\Rightarrow H_1^* = 0, H_2^* = \frac{(1 - A^* - B^*)(k_H - P_t)}{k_H}.$$

Using our previously found fixed points, we can plug in the respective $A^*, B^*$ to dive more into our second fixed point $H_2^*$.

If $A^* = 0 \Rightarrow B^* = 0$,

$$\Rightarrow H_2^* = \frac{k_H - P}{k_H}.$$

And if $A^* = M_A\left(1 - \frac{P}{k_A}\right) \Rightarrow B^* = \frac{\left(M_A\left(1 - \frac{P}{k_A}\right)^2\right) M_A k_A}{k_A\left(M_A\left(1 - \frac{P}{k_A}\right)\right)^2 + M_A M_B P}$,

$$\Rightarrow H_2^* = \frac{(k_H - P)\left(M_A\left(\frac{P}{k_A} - 1\right) - \frac{k_A M_A^2 M_B\left(\frac{P}{k_A} - 1\right)^2}{M_A M_B P + k_A M_A^2\left(\frac{P}{k_A} - 1\right)^2}\right)}{k_H}$$

$$\Rightarrow = \frac{\left((k_H - P)\left(k_A^3 M_A - 2k_A^3 M_A^2 + M_A^2 P^3 - 4k_A M_A^2 P^2 + 5k_A^2 M_A^2 P + k_A M_A P^2 - 2k_A^2 M_A P + k_A^2 M_B P + k_A M_A M_B P^2 - k_A^2 M_A M_B P\right)\right)}{\left(k_A k_H\left(k_A^2 M_A + M_A P^2 - 2k_A M_A P + k_A M_B P\right)\right)}$$

So, unlike the fixed points to the other types of cells, the healthy cells will always have at least one equilibrium $H^* = 0$. The body is always guaranteed healthy cells until we approach death. Since we are using time scale separation, we will always have a second equilibrium depending on which previous fixed points we use. Even if we were not implementing time scale separation, our map has a bounded time interval (we are specifically choosing the start and finish time of the simulation), so we are guaranteed a second equilibrium.

Now, find the stability of $H^*$ by using theorem 4.1.

Let $H_{t+1} = F(H)$,

$$F(H) = H + k_H H\left(1 - \frac{H}{1 - A^* - B^*}\right) - HP$$

$$F'(H) = 1 + k_H - \frac{2k_H H}{1 - A^* - B^*} - P$$

The equilibrium is stable when $|F'(H^*)| < 1$

$$\Rightarrow |F'(H^*)| = \begin{cases} |F'(H_1^*)| = |k_H - P + 1| \\ |F'(H_2^*)| = |P - k_H + 1| \end{cases}$$

After reducing, we solve the inequality to determine the necessary dosage for healthy cells to be stable

$$\Rightarrow H^* = \begin{cases} 0, & \text{stable if } k_H < P < 2 + k_H \\ \frac{(1-A-B)(k_H - P)}{k_H}, & \text{stable if } k_H - 2 < P < k_H. \end{cases}$$

We can see that although we found two different equations for the healthy cell's second fixed

point depending on which cancer cells fixed points we choose, both $H_2^*$ are stable under the same conditions.

# 4 Simulations

## Parameters

| Parameter | | Value |
|---|---|---|
| $k_A$ | Cancer cell growth rate (hours$^-$1) | 3 |
| $k_H$ | Healthy cell growth rate (hours$^-$1) | 2 |
| $M_A$ | Relative carrying capacity of $A$ cells in 1 mm layer of tissue | 1 |
| $M_B$ | Relative carrying capacity of $B$ cells in 1 mm layer of tissue | 2 |
| $A_0$ | Initial density of $A$ | 0.1 |
| $B_0$ | Initial density of $B$ | 0.1 |
| $H_0$ | Initial density of $H$ | 0.8 |

## 4.1 Cancer Stem Cells

### 4.1.1 Cobweb Diagrams

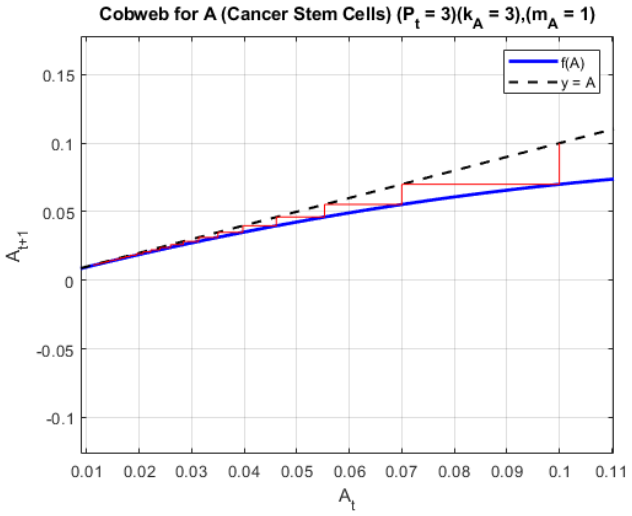


Figure 1: This cobweb show us the behavior at $t = 1$ and layer $i = 1$. When $P_t = 3$ and $k_A = 3$

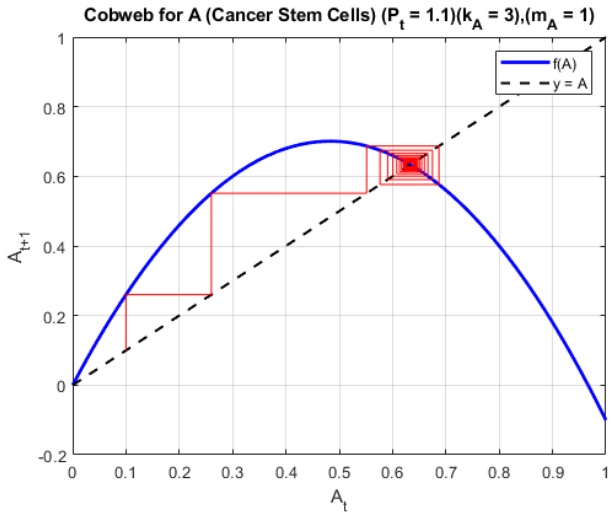


Figure 2: This cobweb show us the behavior at $t = 1$ and layer $i = 1$. When $P_t = 1.1$ and $k_A = 3$

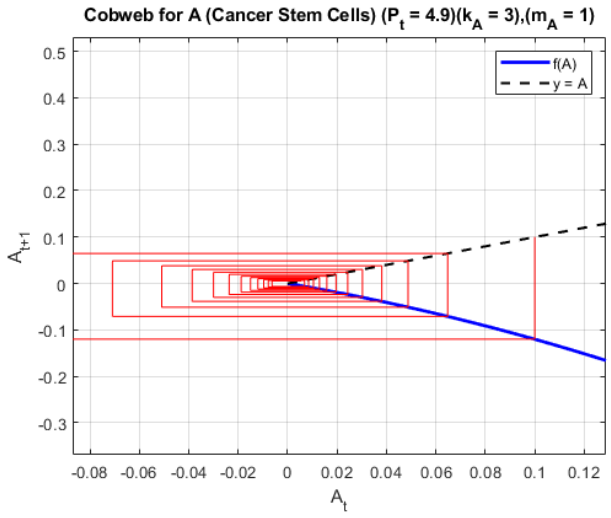


Figure 3: This cobweb show us the behavior at $t = 1$ and layer $i = 1$. When $P_t = 4.9$ and $k_A = 3$

**The goal is to demonstrate in the cobwebs is what the behavior is of $A_t$ when we produce a therapy strength that lies close to the boundaries of the stability criterion. We assume the cobwebs are a screenshot of a fixed time and fixed layer. For this situation since we are not calculating the proton strength as is travels through each layer and repeated dosages we can assume $t = 1$ and $i = 1$. Figure 1 is special because the cobweb doesn't explicitly show a convergence or divergence.**

### 4.1.2 Bifurcation Diagram

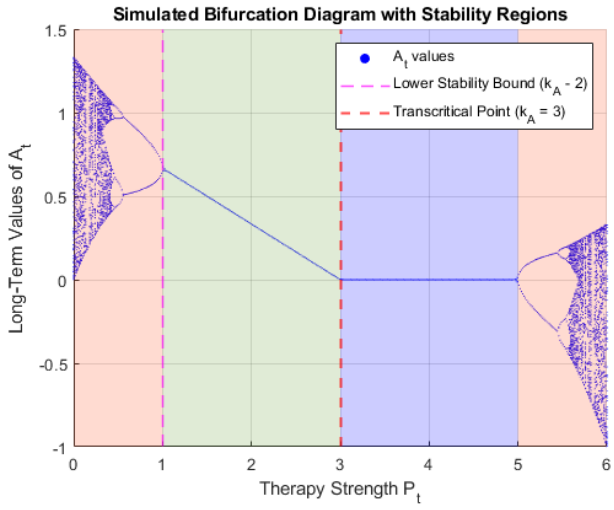


Figure 4: This diagram uses the fixed parameters $k_A = 3$, $M_A = 1$, and a varying therapy strength $0 < P_t < 6$ to demonstrate the long term behavior of $A_t$ when a constant therapy strength is applied.

**This bifurcation shows us the long term behavior of $A_t$ when the therapy is applied constantly ever hour for one layer, in this case layer $i = 1$. Earlier we looked at figure 1 when the therapy strength equaled the growth rate, $P_t = k_A$. The bifurcation shows us here that we experience a transcritical point. This means once we pass the threshold when $P_t = k_A$ the stability of our fixed points are being exchanged, which is why when we look at cobweb at that point, we can't tell if it is converging or diverging. $A^* > 0$ are stable until $P_t = k_A$ then becomes unstable. Also $A^* = 0$ is unstable until $P_t = k_A$, then becomes stable. We must stay in the stability criterion, because there are fixed points, $A^*$ that make $A_t$ go to zero or even oscillate, which does not make sense biologically. A therapy strength of $0.5\ hr^{-1}$ makes the density of cancer stem cells, $A_t$ in one layer go to 0.5 and 1. This just shows us that the therapy strength is too weak to allow us to study the behavior of $A_t$, which means we can't tell if the therapy is working.**

## 4.2 Non-proliferating Stem Cells

### 4.2.1 Cobweb Diagrams

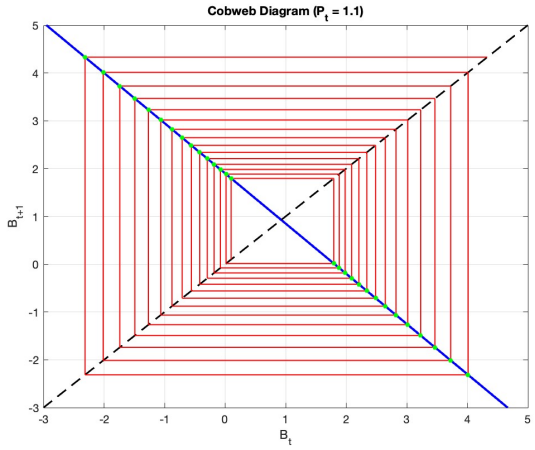


Figure 5: This cobweb diagram shows us the behavior of $B$ cells at $t = 1$ and layer $i = 1$ when $P_t = 1.1$ and $k_A = 3$

.

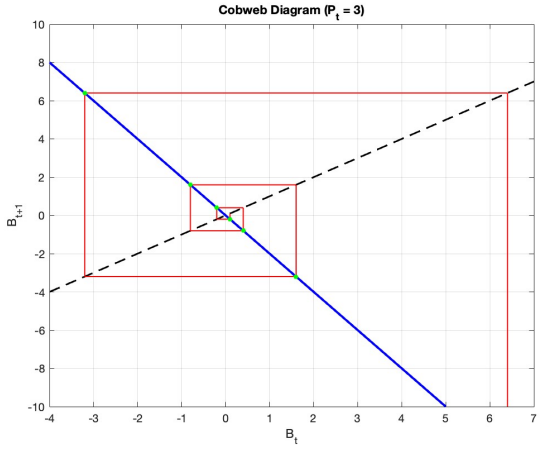


Figure 6: This cobweb diagram shows us the behavior of $B$ cells at $t = 1$ and layer $i = 1$ when $P_t = 3$ and $k_A = 3$

.

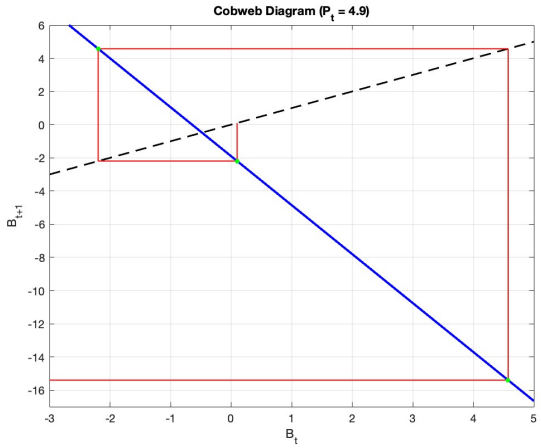


Figure 7: This cobweb diagram shows us the behavior of $B$ cells at $t = 1$ and layer $i = 1$ when $P_t = 4.9$ and $k_A = 3$ .

**In the cobweb diagrams, we demonstrate the behavior of $B_t$ at a fixed time, cell layer, and therapy strength. We used an initial condition of $B_t = 0.1$. We show three different values for $P_t$: the first where $P_t < k_A$, the second where $P_t = k_A$, and the third where $P_t > k_A$. All three diagrams appear to display unstable fixed points, as the the cobweb diagrams show the cobweb spiraling outward around the intersection between $F(B)$ and $y = x$. Intersections, or fixed points, occur at $B^* = 0.92683$, $B^* = 0$, and $B^* = -0.48101$, respectively. Although axis limits show ranges in negative values in order to more clearly see the behavior of the spiral, the domain of all variables is between $[0, \infty)$, so negative fixed points should be neglected.**

### 4.2.2 Bifurcation Diagram

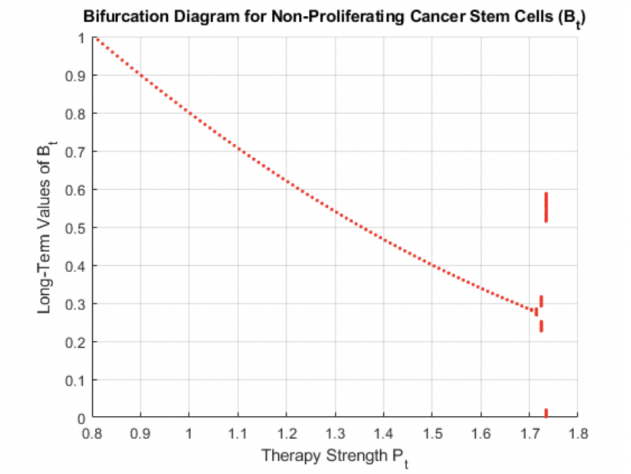


Figure 8: This bifurcation diagram uses the fixed parameters $k_A = 3$, $M_A = 1$, and a varying therapy strength $0 < P_t$ to demonstrate the long term behavior of $B_t$ when a constant therapy is applied every hour.

The bifurcation diagram for $B$ cells shows the long term behavior of $B_t$ for varying values of proton therapy dose $(P_t)$, where $B_t$ is cell density and $P_t$ is in $hr^{-1}$ units. We assume proton therapy is applied every hour at a cell depth of $i = 1$ mm. As therapy strength increases, the long-term value of $B_t$ decreases up until a value of around 1.74 $hr^{-1}$, where the values of $B_t$ begin to vary unpredictably between very large positive and negative values of $B_t$. This can be interpreted as increased proton therapy strength successfully lowering non-proliferating cancer cell density up until a certain point, where a value of $P_t$ exceeding this threshold begins to result in unpredictable, chaotic behavior in $B$ cell density. Proton therapy treatment above that point would not be ideal for a patient, as increases in $P_t$ could result in unpredictable growth or death of $B$ cells.

## 4.3 Healthy Cells

### 4.3.1 Cobweb Diagrams

For all cobwebs, dotted black represents $y(x) = x$, dark blue represents $y = F(H)$, red has $H_0 = 0.8$, purple has $H_0 = 0.1$, and light blue has $H_0 = -0.1$. I used $k_H = 6$ to see how the dosage of therapy effects both fixed points. Although it is unrealistic to have a negative amount of initial healthy cell density, I wanted to display more on what's happening at the fixed point. Since we used time scale separation and plugged in the previously found fixed points, I wanted to show how choosing different fixed points would effect the healthy cells. Therefore, the cobwebs on the left use $A_1^* = 0, B_1^* = 0$ and the cobwebs on the right use $A_2^*, B_2^*$

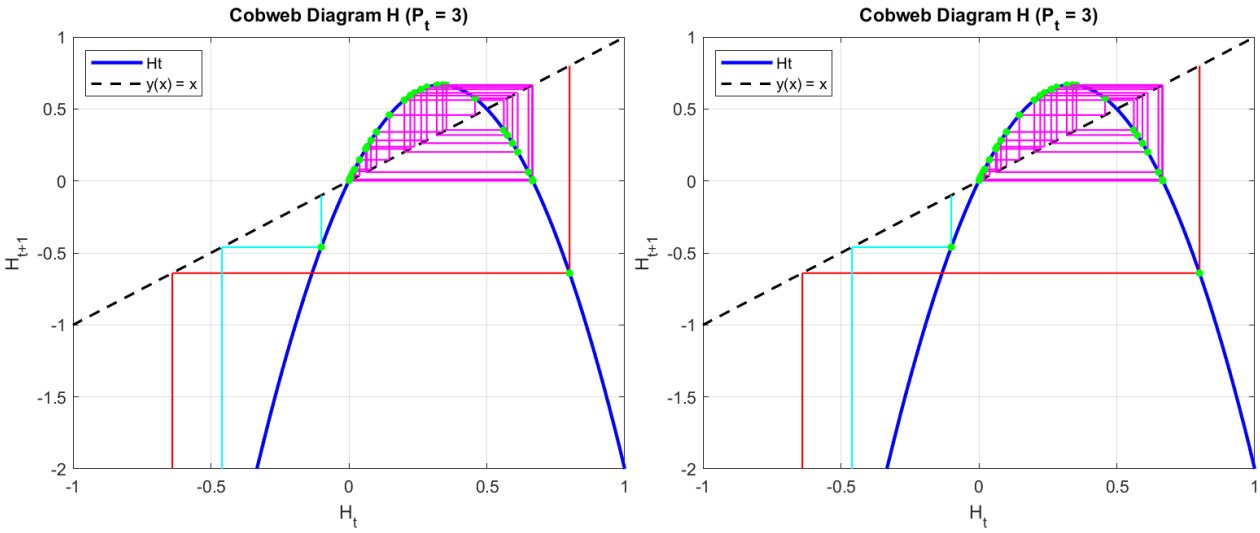


Figure 9: The fixed points for both cobwebs were $H_1^* = -1.8e^{-21}, H_2^* = 0.5$, where $H_1^*$ is semi-stable from below, and $H_2^*$ is a reseller.

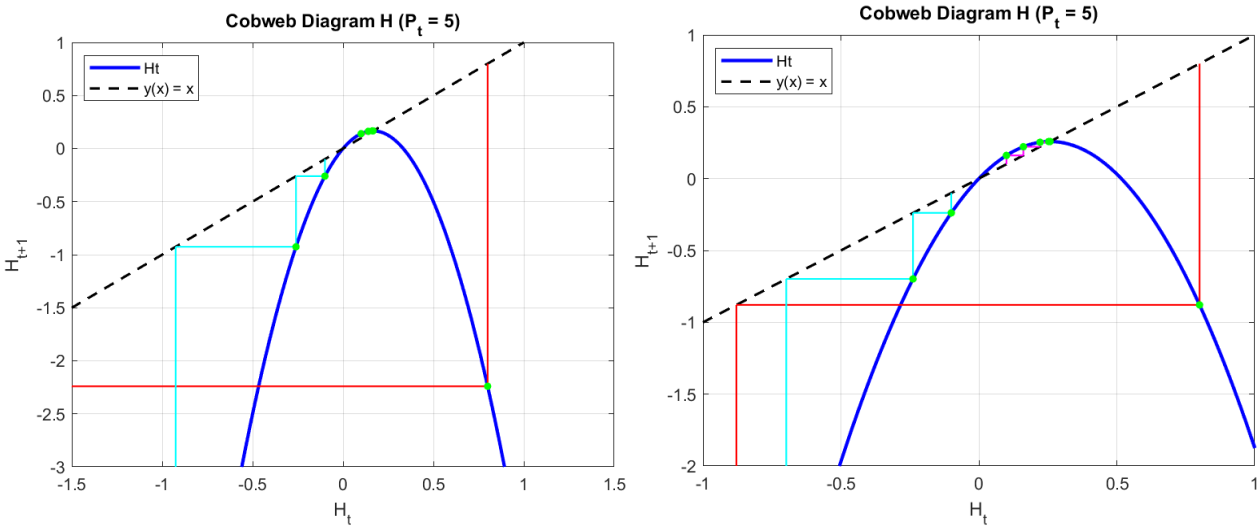


Figure 10: The fixed points for the left cobweb were $H_1^* = -6.03e^{-22}, H_2^* = 0.167$ and the fixed points for the right were $H_1^* = -1.06e^{-16}, H_2^* = 0.258$, where both $H_1^*$ are semi-stable from the left and both $H_2^*$ are repellers.

[H]

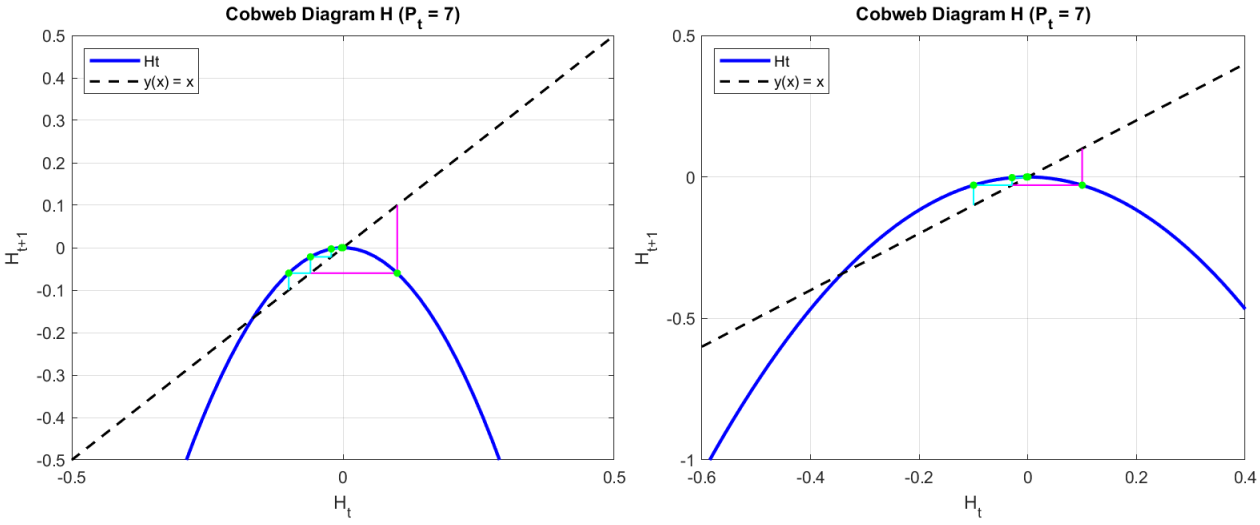


Figure 11: The fixed points for the left cobweb were $H_1^* = -0.167, H_2^* = 6.03e^{-22}$ and the fixed points for the right were $H_1^* = -0.343, H_2^* = -1.76e^{-16}$. Both $H_1^*$ are repellers, and $H_2^*$ are attractors.

Since physically, bodies cannot have a negative amount of healthy cells, we can conclude the densities of healthy cells stayed at zero as time went on. Many of the other fixed points were exponentially small, which is also unrealistic for a living body, so we can conclude these too approach zero over time. This leaves us with only three viable fixed points of healthy cells with large enough densities to fight back the cancer. This shows how important it is to be at the target depth. I want to take note that even though we used different $A^*, B^*$, the cobwebs for healthy cells were still about the same implying as long as the cancer cells are stable, the stability of the healthy cells is the same. When considering the real world, this makes sense. We can also notice that there was always a fixed point relatively close to zero that was attracting. Whether or not people have cancer, we have healthy cells that are dying and we all eventually die.

### 4.3.2 Bifurcation Diagram

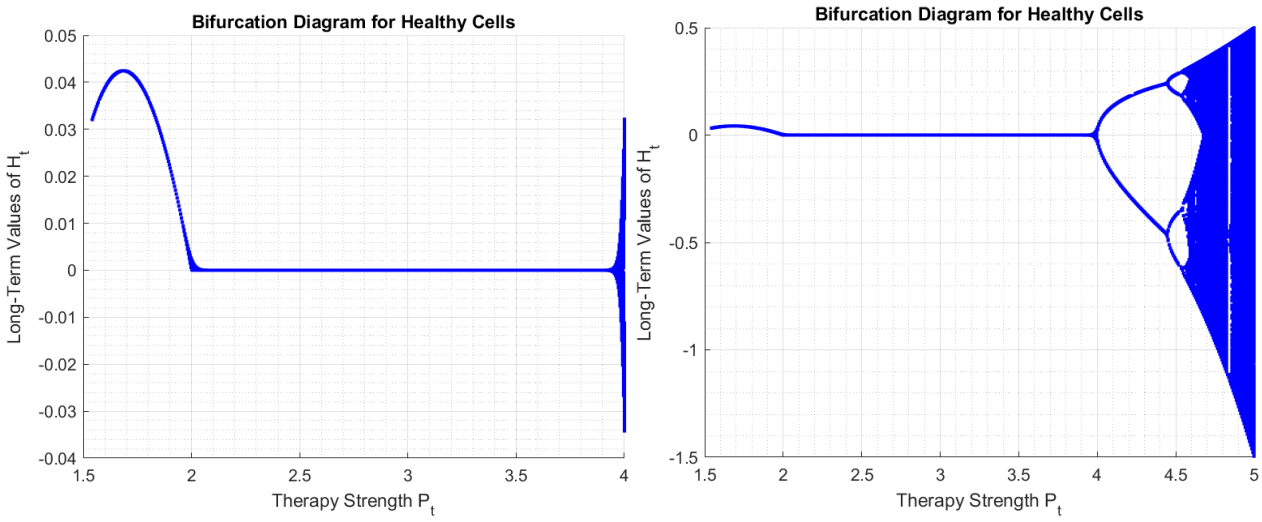


Figure 12: The first Bifurcation follows our simulation using $P = (0, 4)$. Our chosen $P$ values fit perfectly with the necessary bounds for the healthy cells to be stable when $k_H = 2$, so we can't get too much information. The right bifurcation I used $P = (3, 9)$ and assumed $k_H = 6$ to better show the change of stability.

The left bifurcation diagram of the healthy cells show the long term behavior of density depending on the dosage of proton therapy $P$ applied every hour. If $1.5 < P < 1.75$, the density increasing, meaning the therapy is very effective. If $1.75 < P < 2$, the density is decreasing, implying the therapy is not effective at all and leading to death. Then from $2 < P < 3.8$, the density is staying constant, meaning the dosage is "good enough" to stop the cancer from growing too fast; however, the cancer is still growing. Once $P > 3.8$, the density is unpredictable. Therefore, for our simulation, it's optimal to use a dosage between $1.5 < P < 1.75$. This makes sense because $k_H = 2$ For the right bifurcation diagram, a dosage of $P > 4$ is needed in order for the healthy cells not to go to 0. This makes sense because $k_H = 6$. (Recall from finding the stability of the fixed points previously).

# 5 Discussion/Conclusion

**There could be a possible range of therapy strength that is safe to the patient. Assuming giving a dose every hour safe and ethical. The figure 13 shows us a therapy strength in the range from (1.5, 1.75) that could work to help reduce cancer stem cells and non-proliferating cancer cells, while minimizing damage to the density of health cells in the one layer of tissue. In the diagram we can see the density of healthy cells in one layer go to zero until the therapy reaches about 1.5. This is the case, because before $P_t = 1.5$ the therapy is too weak this implies the layer of tissue is packed with non proliferating cells and cancer stem cells. We can assume the layer tissue is dead.**

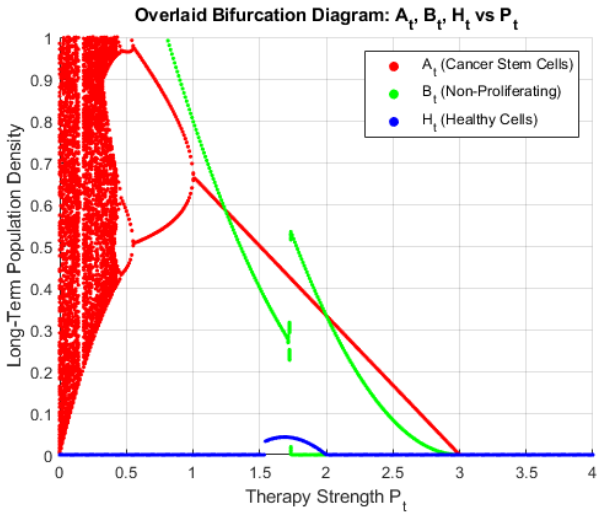


Figure 13: This diagram shows an overlap off all past bifurcations for cancer stem cells, non-proliferating cells, and healthy cells.

**In this model, proton therapy is applied every hour, which is most likely not realistic or ethically feasible in a clinical setting. Our analysis is limited to a single, fixed tissue depth (layer $i$).To simplify the dynamics, we applied a technique known as Time Scale Separation, allowing us to study the long-term behavior of each population under constant conditions.**

# Reference

Erin N. Bodine and K. Lars Monia, "A proton therapy model using discrete difference equations with an example of treating hepatocellular carcinoma" (2017)