The Use of Mathematical Models in Analyzing the Growth of Pancreatic Cancer and Response to Treatment

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Introduction

Pancreatic cancer is one of the leading causes of death due to cancer in the United States.

- Pancreatic cancer contains cancer stem cells (CSCs) which have been shown to have chemoresistance and plasticity. Along with CSCs, there are progenitor and differentiated cancer cells (DCCs) where the progenitor state is a halfway point from CSCs and DCCs. The ratio of CSCs is known to be less than 1% [1].
- **Goals:** Utilize the multicompartment growth model and the linear-quadratic model to elucidate the dynamics of pancreatic cancer cell growth and response to treatment.

Mathematical Growth Model

We model the growth through asymmetric division where CSCs can produce progenitor cells by producing one CSC and one progenitor cell. An equivalent incident happens with progenitor cells when dividing. Symmetric division results in an equivalent growth model [6]. In our growth model (Figure 1), C_0, C_1, and C_2 represent CSCs, progenitor cells, and DCCs, respectively. p_0 is the probability that CSCs self-renew upon division and p_1 is the probability that progenitor cells self-renew upon division. The death rate of DCCs is represented by d_2. v_0 and v_1, respectively, are the growth rates of CSCs and Progenitor cells.

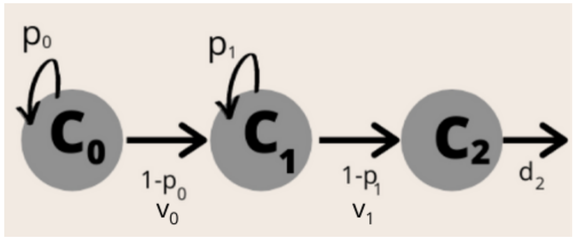

Figure 1: The Cancer Cell Hierarchal Model.

The mathematical growth model is constructed as

Cancer Stem Cells $\quad \frac{dC_0}{dt} = (2p_0 - 1)v_0C_0$

Progenitor Cells $\quad \frac{dC_1}{dt} = 2(1 - p_0)\, v_0C_0 + (2p_1 - 1)\, v_1C_1$

Differentiated Cancer Cells $\quad \frac{dC_2}{dt} = 2(1 - p_1)\, v_1C_1 - d_2C_2$

The values of p_0 and v_0 were obtained from references (p_0=0.505 and v_0=0.004), whereas v_1 and d_2 were assumed to be near the value of v_0 for simplification. P_1 is assumed to be less than 0.5 to allow for a possible decrease of progenitor cells due to radiation [2,3].

Sensitivity Analysis

A sensitivity analysis was done to explore how all parameters effect cancer cell growth. This was done through MATLAB with the initial conditions of $C_0(t=0)=1$ and $C_1(t=0)=C_2(t=0)=0$ as all other cancer cells arise from cancer stem cells.

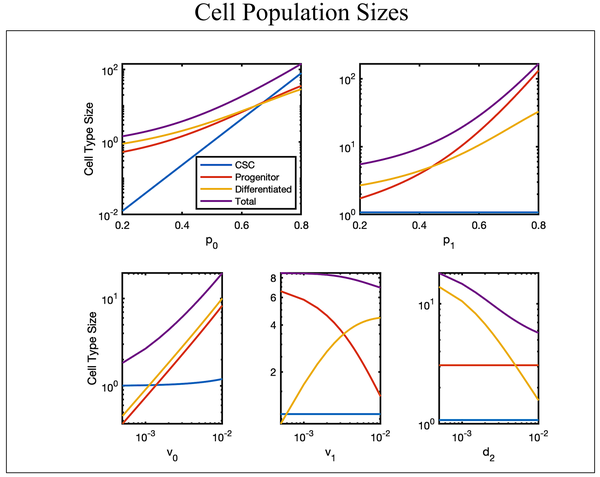

Figure 2: Dependence of cell population sizes of different cancer cell types on p_0, p_1, v_0, v_1, and d_2 at 5 years (t = 1825 days). The sizes of the cancer stem cells, progenitor cells, differentiated cancer cells, and total cancer cells are given by C_0, C_1, C_2, and $C_0 + C_1 + C_2$, respectively. The blue line is CSC, red is Progenitor, yellow is Differentiated, and purple is total.

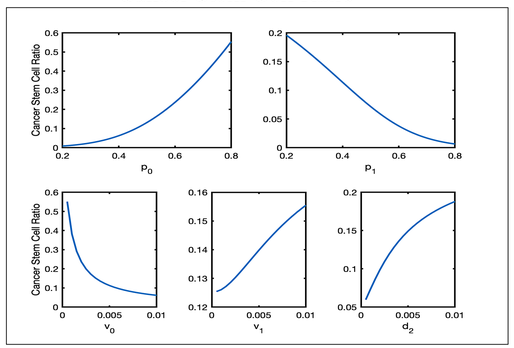

Figure 3: Dependence of the cancer stem cell ratio on p_0, p_1, v_0, v_1, and d_2, in order of figure (left to right), at 5 years (t = 1825 days). The ratio is given by $C_0/(C_0 + C_1 + C_2)$. Corresponding parameters chosen are: p_0=0.505, p_1=0.35, v_0=0.004, v_1=0.004, and d_2=0.004. Initial conditions: $C_0(t=0)=1$ and $C_1(t=0)=C_2(t=0)=0$.

Observations from the sensitivity analysis:

- Near-steady state analysis was done when p_1 was less than 0.5 and greater than 0.5 and the end CSC ratios were recorded.
- When $p_1 < 0.5$, steady states were obtained with an end CSC ratio of around 24% with the lowest being 12%.
- When $p_1 > 0.55$, steady states were obtained with an end CSC ratio of less than 1%
- In both simulations, the value of p_0 was fixed at 0.505 and v_0, v_1, and d_2 ranged from 0.002 to 0.008. However, the values of v_0, v_1, and d_2 did not greatly affect the result.

Discussion

- The treatment targeting to shrink the cancer size could focus on decreasing p_0, p_1, v_0 while increasing v_1 and d_2. The treatment targeting to kill the stem cells could focus on decreasing p_0 and v_0, though the effect of a decreasing v0 is not significant.
- The steady states obtained when $p_1 < 0.5$ ended in a ratio of CSCs of around 24% with the lowest at 12%, which means the cancer is not actively developing.
- The steady states obtained when $p_1 > 0.5$ ended in a ratio of CSCs less than 1% meaning the cancer is still developing.
- The analysis of the growth of pancreatic cancer can elucidate the response under specific treatments.

Future Direction

To implement radiotherapy, we will use the Linear-Quadratic Model (LQ model) [4].

- This model implements the biological effects radiotherapy has on cancer cells to show a survival fraction.
- Below is the LQ model for one compartment where D is the dose of radiation in Gy and α and β are radiobiological parameters of the cell.

$$SF(D) = e^{-\alpha D - \beta D^2}$$

- A multi-compartment LQ model derived from Sheng et. al will be used to represent the three types of cancer cells [5]. This will be done by putting 3 exponential terms in the equation above.
- Simulations can be done to analyze the most effective radiotherapy treatment.

Acknowledgements

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