A Mechanistic Model for Metastatic Tumor Growth and Treatment with Radiation Therapy

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Introduction

Cancer is a disease in which cells divide in an unregulated manner. Currently, the study of cancer rests on six distinguishing hallmarks that provide the foundation for understanding a cell's progression into the neoplastic disease: sustaining proliferative signaling, evading growth suppressors, activating invasion and metastasis, enabling replicative immortality, inducing angiogenesis, and resisting cell death [1].

Generally, cancer begins at the **primary tumor**, which is localized and can grow to a substantial size. From the primary tumor, certain cells **metastasize**, thus dispersing throughout the body. Often times, new metastatic tumors arise from existing ones, posing a particularly difficult problem for treatment intervention because metastases are often the cause for cancer's lethality. Therefore, treatment should ideally begin before primary tumor metastasizes.

Mathematical biologists have developed models to study the evolution of **micrometastases**: small metastatic tumors that are difficult to detect. Here, we investigated a mechanistic PDE model for cancer growth using the McKendrick-von Foerster equation. We are interested in using the model to understand the evolution of micrometastases in tandem with simulations of radiation therapy *in silico* at prescribed times. The goal is to better gauge how tumors are targeted in radiation therapy in order to improve treatment options.

Mathematical Model: Motivation and Derivation

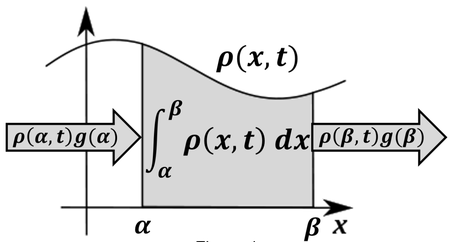

Figure 1

- Interested in $\boldsymbol{\rho(x,t)}$, the colony size distribution of metastatic tumors with x number of cells at time t
- Let $g(x)$ represent the tumor grow rate
- For arbitrary $\alpha < \beta$, the number of colonies of size $x \in [\alpha, \beta]$ is given by the area under the curve in Figure 1
- The rate of change of the colony size equals the net flux of colony size distribution: $\frac{\partial}{\partial t}\int_\alpha^\beta \rho(x,t)dx = \rho(\alpha,t)g(\alpha) - \rho(\beta,t)g(\beta)$
- By Gauss' theorem, we arrive at the **McKendrick-von Foerster equation**: $\frac{\partial}{\partial x}[\rho(x,t)g(x)] + \frac{\partial}{\partial t}\rho(x,t) = 0$

Obtaining An Analytic Solution

From the McKendrick-von Foerster equation along with its initial and boundary conditions:

$$\rho(x,0) = 0$$
$$g(1)\rho(1,t) = \int_1^\infty mx^{2/3}\rho(x,t)\,dx + m\left(x_p(t)\right)^{2/3}$$
$$\frac{dx_p}{dt} = g\left(x_p(t)\right)$$
$$x_p(0) = 1$$

where we prescribed $g(x) = ax\ln\frac{b}{x}$, the Gompertzian growth law (a, b, m are constants), we could use **Laplace transformation** to obtain an analytic solution for $\rho(x,t)$. However, this analytic formulation is not amenable for numerical evaluations [2]. Thus, we will solve the equation numerically.

Numerical Analysis

We used the **method of characteristics** to obtain a numerical scheme for which we can use for simulation *in silico*. We parameterized the PDE with a system of ODEs, where s is the parameter:

$$\begin{cases} \dot{x}(s) = g(x(s)) \\ \dot{t}(s) = 1 \\ \dot{\rho}\left(x(s),t(s)\right) = -\rho\left(x(s),t(s)\right)\dot{g}(x) \end{cases}$$

Let $x(s) = x_0$. The solution to the system of ODEs is:

$$\rho\left(x(s),t(s)\right) = \rho(x_0,0)e^{as}\left(\frac{x_0}{b}\right)^{1-e^{-as}}$$

From here, we used a numerical scheme to simulate the evolution of metastatic tumors with radiation therapy [3]. Figure 2 is a surface plot of $\rho(x,t)$ where no treatment has been given:

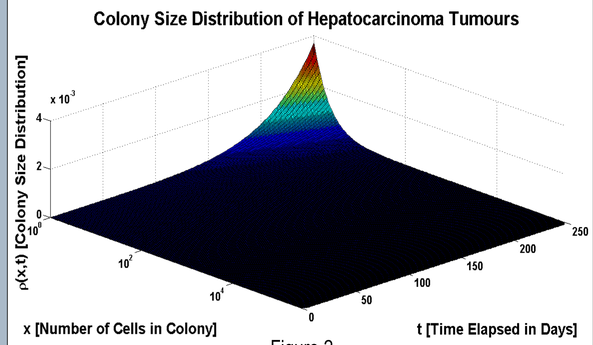

Figure 2

For this figure as well as all subsequent analyses, we used clinical data from **hepatocarcinoma** for the following constant values:
$a = 0.00286, b = 7.3 \times 10^{10}, m = 5.3 \times 10^{-8}$

Colony Growth Dynamics

Unfortunately, the surface plot provides little information regarding how detectable tumor colonies evolve over time. Rather, we look at the total number of colonies over a specific range of colony sizes. Particularly, we are interested in the following integral:

$$N_\lambda(t) = \int_\lambda^b \rho(x,t)dx$$

where λ is the minimum detectable size given in number of cancer cells per colony and b is the carrying capacity of the system given by clinical data. Figure 3 plots $N_1(t)$, the total number of colonies in the system, and a decomposition showing contributions from the primary tumor and metastatic tumors for hepatocarcinoma:

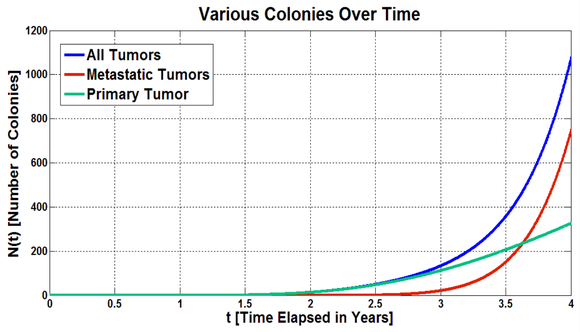

Figure 3

At **small times**, the contribution to the total number of colonies from the **primary tumor** is dominant, while at **large times**, that of **metastatic tumors** is dominant. This observation reaffirms that metastatic tumors arise from both the primary tumor as well as other metastatic tumors.

Treatment with Radiation Therapy

Clinical data revealed that the smallest detectable colony has **10^9 cells** [3]. Our radiation therapy treatment supposes **99%** of all detectable colonies are killed. Figure 4 describes the total number of colonies and the number of detectable colonies over time as a result of treatment at 3 and 5 years. It shows that the number of detectable colonies is small compared to the total number of colonies (vertical axis is log-scaled).

Effect of Delayed Treatment

- Treatment at a later stage of cancer (5 years) would kill more colonies than treatment at an earlier stage (3 years)
- Blue and red curves in Figure 4 do not converge or intersect at large times
- By 5 years, more colonies have grown to detectable sizes, increasing available colonies for targeted treatment
- However, treatment at large times only eliminates the number of tumors; does not address possible lethality of metastases
- Preventing metastasis should be the priority

Difficulties with Detection

- Metastases first occur at 1.34 years; no tumor has grown to a detectable size at this time
- Earliest time for any detection is 1.69 years; diagnosis and treatment cannot begin until after this time
- However, metastatic activities have already commenced and effective treatment becomes difficult

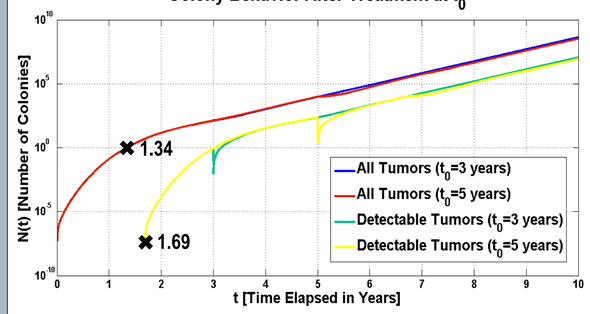

Figure 4

Conclusion

Implications

- Improve tumor detection capability, allowing for earlier treatment
- Supplement radiation therapy with chemotherapy to better target micrometastases

Limitation and Future Work

- Model only simulated one-time treatment
- Radiation therapy treatment administered multiple times over a long period
- Simulate radiation therapy with chemotherapy

References

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3. D. Barbolosi, A. Benabdallah, F. Hubert, and F. Verga. Mathematical and numerical analysis for a model of growing metastatic tumors. *Mathematical Biosciences*, 218:1-14, 2009.