

Introduction

The Goal: To develop and analyze mathematical models of the interplay between tumor cells, immune cells, chemotherapy, and immunotherapy drug treatments. A good model has predictive power that enables us to test an array of new treatment approaches without causing harm to live subjects.



The tumor cell has been completely destroyed by the T cells. (Thanks: <http://www.cancer-info.com>)



Healthy cancer cell surrounded by killer T cells, which attack the tumor. (Thanks: <http://www.cancer-info.com>)

The Challenges: Though cancer researchers have made great strides in the search for a cure, overall cancer survival rates have not significantly declined over the past 50 years. It is therefore not surprising that we face the following challenges:

- Representing complex biological interactions with new mathematical systems requires synthesizing knowledge from a variety of medical and mathematical disciplines, including cancer biology, immunology, dynamical systems, optimal control, and differential geometry.
- Medical researchers have yet to fully understand how chemotherapy and immunotherapy function together to eradicate cancer.



Colon cancer cells. (Thanks, <http://www.medphoto.wellcome.ac.uk/>)

- Mathematical models should not be "literal" translations of biology, as they would not yield clear answers in a timely manner; as a result, careful simplifications and approximations must be enacted to make the problem tractable and useful.

Our Solution: We have constructed mathematical tools that have the potential to provide clinical guidance in the creation of new combination treatment protocols. In particular, we have

- Developed new mathematical models that reflect key biological system features
- Obtained realistic biological parameter estimates (e.g. the rate at which cancer cells multiply)
- Discovered more effective treatment strategies and proved they must exist for any tumor
- Investigated and catalogued emergent behaviors of our model, including relapse potential
- Created reusable computer code to simulate tumor-immune activity under customizable treatment schema
- Pioneered numerical analysis techniques allowing a 3D geometrical realization of tumor surface evolution

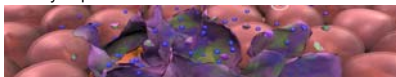
The Challenge: Finding precise biological parameters of the system can be difficult. System parameters may include cell-division rates, immune-tumor kill rates, and chemotherapy decay rates. These parameters may

- Be difficult or impossible to obtain (e.g. because methods have not been developed to ascertain some biological reaction rates)
- Vary from person to person as a function of genetics and environment (e.g. immune system strength)
- Fail to be sufficiently accurate; some models are highly sensitive to slight changes in certain parameters, so more precise measurements may be needed than are currently available

Our Solution: We use dynamical analysis to predict

- The outcome of selected therapies in terms of model parameters
- The parameters that are most important to the long-term survivability of the tumor
- The critical amount of therapy necessary to prevent relapse

An artist's rendition of a tumor cell dying. (Thanks: http://www.newsweek.com/images/upload/2006/09/12/fullsize/NoLabelBoxes_1600x1200.jpg)

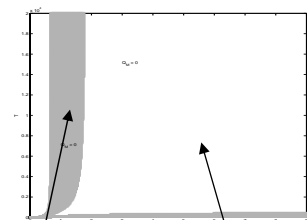


Optimal Control: Finding Treatment Strategies

The Goal: To determine the ideal combination of chemotherapy and immunotherapy needed to minimize tissue damage while quickly killing the tumor.

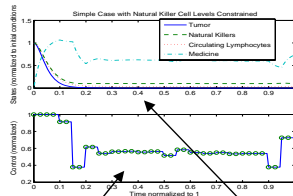
The Challenge: Both the immune system and chemotherapy are effective at killing tumor cells; however, chemotherapy severely damages the immune system. The interactions and synergies between immunotherapy and chemotherapy are not yet well established, so there are few data on which we may base our analysis.

Our Solution: We use methods from optimal control to mathematically define a context-specific cost-benefit analysis protocol and then apply this system to the immunotherapy model. The results of optimal control computations are shown below.



In this region a continuous chemotherapy treatment is best.

In this region an on-off treatment of chemotherapy is ideal.



This region is a completely novel treatment scheme discovered through optimal control.

The treatment maintains natural killer cells (which help destroy tumors) above a minimum level while dramatically reducing the tumor size.

The Models: Capturing the Biology

The Goal: To create a model of cancer that both produces results in agreement with clinical data and yet is sufficiently streamlined so as to make tractable optimal control, dynamical analysis, and geometric modeling, three mathematical tools that are used to glean clinically relevant outcomes.

$$\begin{aligned} \frac{dT}{dt} &= \alpha T(1 - \beta T) - cNT - DT - K_T(1 - e^{-\delta r M})T \\ \frac{dN}{dt} &= f\left(\frac{c}{\gamma}C - N\right) - \rho NT + \frac{\rho N I}{gN + I} - K_N(1 - e^{-\delta n M})N \\ \frac{dL}{dt} &= -\frac{\theta m L}{\theta + I} + j\frac{T}{k + T}L - qLT + (r_1 N + r_2 C)T - \frac{uL^2 C I}{k + I} - K_L(1 - e^{-\delta_L M})L + \frac{\rho I L I}{\theta + I} + \eta L v_L(t) \\ \frac{dC}{dt} &= \beta\left(\frac{\alpha}{\gamma}C - C\right) - K_C(1 - e^{-\delta_C M})C \\ \frac{dM}{dt} &= -\gamma M + \eta M v_M(t) \\ \frac{dI}{dt} &= -\mu I + \frac{\omega L I}{\zeta + I} + \eta I v_I(t) \\ D &= d\frac{(L/T)^y}{1 + (L/T)^y} \end{aligned}$$

The mathematical form of the immuno-chemotherapy model. The variables $T, N, L, C, M,$ and I denote biological quantities that we track. (Top) Breast cancer cells. (Right, Thanks: <http://www.medphoto.wellcome.ac.uk/>)

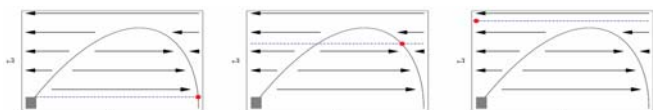


Our Solution: We developed three models, each of which consists of a system of interconnected nonlinear differential equations. Differential equations are mathematical tools used to describe and predict change. The models are

- The Chemotherapy Model:** A simpler model that allows for more complex optimal control analysis. It does not include immunotherapy and therefore does not closely track immune cell populations.
- The Immuno-Chemotherapy Model:** A more sophisticated form of the chemotherapy model designed for the exploration of combination chemotherapy and immunotherapy. This model includes immune cell populations and the important immunity stimulating molecule interleukin-2 (IL-2).
- The Spatial Model:** An immuno-chemotherapy model in 3D space. This model allows us to create visual realizations of the growth of a tumor starting from an initial shape of our choice.

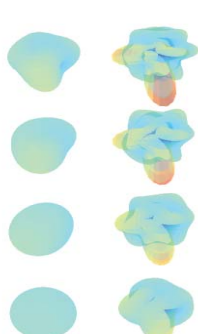
Dynamics: Predicting Outcomes

The Goal: To predict the future state of a tumor given current tumor data. This allows for the determination of the prognosis of the patient under a variety of treatment regimes.



The three frames above show the way in which immune cells (L) and tumor cells(T) change at three different drug concentrations. The picture shows that chemotherapy will not kill the tumor unless it reaches a certain level.

Geometry: Moving into 3D



Going up the columns, starting on the left, we increase the number of spherical harmonics used to represent a tumor.

The Goal: To simulate the changing surface of a tumor, taking into account the effects of the tumor's 3D structure. This approach will enable doctors to predict the future spatial configuration of a tumor given a snapshot image of its shape taken with medical imaging technology. Spatial predictive power will allow for more informed localized treatment schemes.

The Challenge: The boundary of a tumor fluctuates according to how pressure is distributed throughout the interior. However, the distribution of cells and molecules responsible for producing the pressure is dictated at any given moment by the shape of the tumor at that time. In short, the mathematical methods needed to produce results are sophisticated and relatively untested.

Our Solution: We approximate the tumor boundary by a sum of smaller parts that are analytically tractable. With enough of these parts (called spherical harmonics) we can depict the tumor and its transformation by means of computer simulation using MATLAB software.

Summary

Our research provides a foundation for continued development of more accurate and sophisticated models, which will ultimately lead to a paradigm as useful as a human test subject.

- Optimal control applied to an accurate cancer model produces clinically relevant treatment strategies.
- We have combined several computational techniques for a novel numerical approach to geometrical analysis, reducing a historically difficult problem into a tractable one.

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