B

MODELING INTERACTIONS BETWEEN TUMOR CELLS AND IMMUNE CELLS

MATH 221

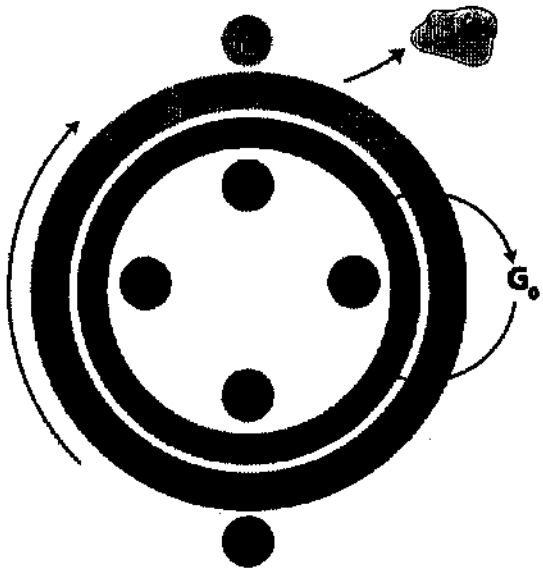
Fall 2010

Introduction

Cancer is a ferocious killer. Although the number of cancer deaths per year in the United States has slowly, yet steadily, decreased over the past three decades, the statistics are still overwhelming. Based on data published by the U.S. National Institute of Health, in 2007 there were approximately 180 cancer deaths per 100,000 people. To the arithmetically challenged, this may not sound like a staggering figure. However, the U.S. population was approximately 302.2 million in 2007, which translates to over 540,000 deaths that year [4]. A seemingly uncountable number of scientists and medical professional have been struggling for decades to develop new technologies to battle this dynamically pervasive disease. Multitudes of mathematical models have been developed to try and come up with more effective treatments to better a patient's quality of life or wipe out the disease altogether.

The model that I have been investigating deals with the "effects and interactions between tumor cells and immune cells, clearly differentiating between phases for subsequent treatment with a cycle-phase-specific drug" [1]. In other words, this approach uses different drugs to act on and during different phases of the cell cycle.

In order to comprehend the intricacies of the model, one must first understand the basics of the cell cycle. This topic alone could warrant hundreds of pages of descriptions and explanations, but I will only briefly describe the underlying key details. In the diagram below, there are two rings.



The outer displays two components, interphase and mitosis, denoted I and M, respectively. Interphase consists of three parts; gap 1, synthesis, and gap 2, denoted G_1, S, and G_2, respectively. During interphase, cells grow in size, replicate DNA, and grow some more. In mitosis, the cells divide themselves into two daughter cells. In between all four phases of the cycle, there are so called "checkpoints" that ensure the cells are developmentally ready to continue to the next phase. The component labeled G_0, typically called the quiescent phase, refers to a resting period, in which the cell has left the cycle. The model I have been investigating ignores this phase, so I will too.

Now that we are accustomed to the basics of the cell cycle, we can investigate the governing equations for this model. In the most rudimentary case, absent of any external forces or limiting factors, populations typically grow at a rate proportional to the existing population. This model is a very simple ordinary differential equation:

$$\frac{\partial P}{\partial t} = kP,$$

where P is the population at time t, and k is the growth rate constant. This is easily solvable, using your favorite O.D.E. method, resulting as

$$P(t) = P_0 e^{kt},$$

where $P(0) = P_0$. One can see that $k > 0$ results in population growth, and $k < 0$ results in population decay. Of course, almost every real world system is far more complicated. In fact, I recently heard a math professor say that when she visited a conference on applied sciences, most of the scientists she talked to said that they had to get over their fear of partial differential equations to solve any real world scientific problems. With that in mind, let's take a look at the equations for this system.

$$T_I' = 2a_4 T_M - (c_1 I + d_2)T_I - a_1 T_I(t-\tau)$$
$$T_M' = a_1 T_I(t-\tau) - d_3 T_M - a_4 T_M - c_3 T_M I - k_1(1-e^{-k_2 u})T_M$$
$$I' = k + \frac{\rho I(T_I + T_M)^n}{\alpha + (T_I + T_M)^n} - c_2 I T_I - c_4 T_M I - d_1 I - k_3(1-e^{-k_4 u})I$$
$$u' = -\gamma u$$

Initial data is given by:

$$T_I(t) = \phi_1(t) \text{ for } t \in [-\tau, 0]$$
$$T_M(t) = \phi_2(t) \text{ for } t \in [-\tau, 0]$$
$$I(t) = \phi_3(t) \text{ for } t \in [-\tau, 0]$$
$$u(0) = u_0$$

T_I(t) and $T_M(t)$ represent the tumor population during interphase and mitosis; $I(t)$ is the immune system population; $u(t)$ is the amount of the drug present; τ is the time delay; a_i's are rates at which cells cycle; d_i's are proportions of natural cell death; c_i's are losses from encounters of tumor cells with immune cells; k is the immune cells growth rate in the absence of tumor cells; $\frac{\rho I(T_I + T_M)^n}{\alpha + (T_I + T_M)^n}$ represents nonlinear growth of the immune population due to the stimulus by tumor cells, with ρ, α, n parameters that depend on the type of tumor and the health of the immune system.

Results

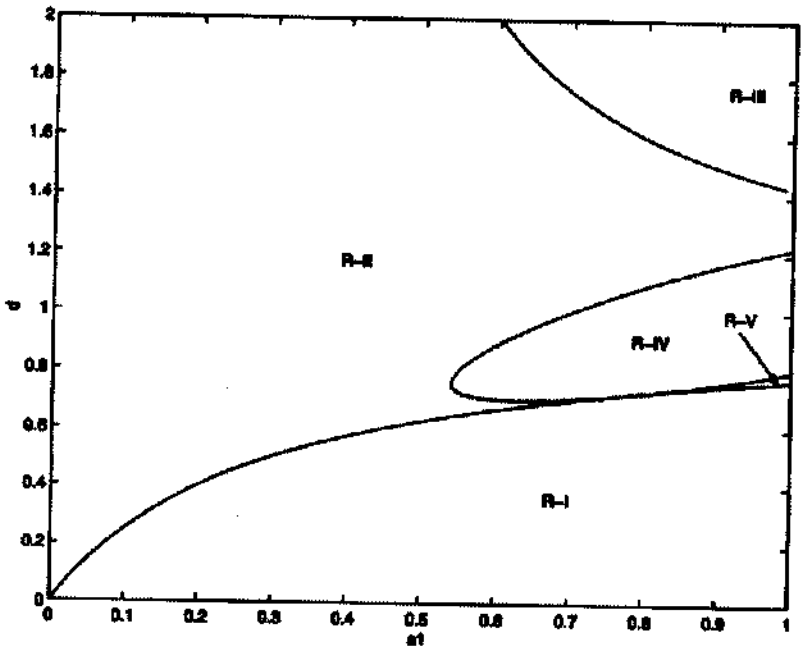
Due to the limitations of my own understanding, and the scope of this project, I will just briefly mention a couple stability results found. Note, all of these numerical results and figures come from [1]. Case 1 looks at a drug-free model, with

no time delay, and an absence of immune response. It turns out to be a simple set of linear ordinary differential equations:

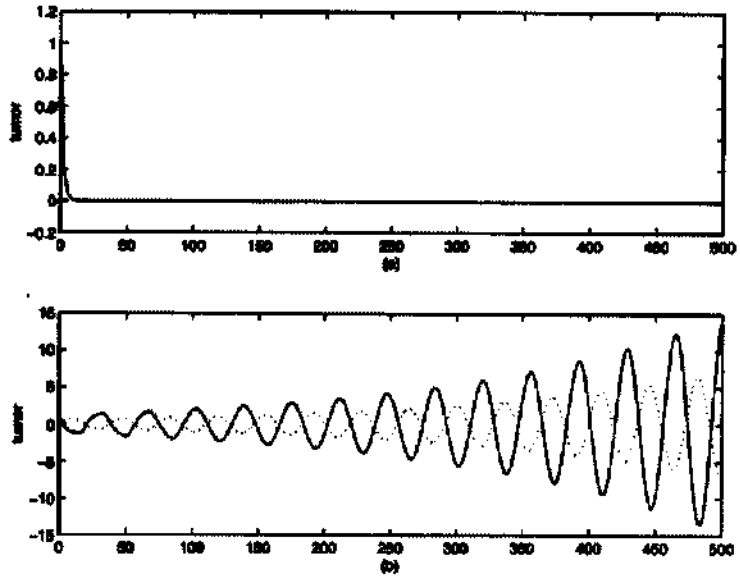
$$T_I' = 2a_4 T_M - (d_2 + a_1)T_I,\ T_I(0) = \phi_0$$
$$T_M' = a_1 T_I - dT_M,\qquad T_M(0) = \phi_1$$

Upon solving this system, the solutions give that tumor growth occurs if $(d_3 + a_4)(d_2 + a_1) < 2a_1a_4$. Otherwise, there will be a stable tumor-free environment. Case 2 is also a drug-free model with an absence of immune response, but includes the delay effect. The equations contain more aspects, and therefore the calculations are much more involved than the previous case, so I will leave them out. However, the following figure, showing stability regions in the parameter $a_1 - d$ plane are interesting:

For different delay values, the stability regions vary. For example, when τ=0 the tumor decay region is the union of II, III, IV, and V. But, when τ>0, the decay region is the union of just II and IV; in III and V, the stability can switch, but eventually remains unstable for sufficiently large τ. This can be seen in the following diagram:



(a) shows tumor decay when we set τ = 1 (days) and the parameter values in region R-IV from the above diagram. (b) is the result of the numerical integration for τ = 11 (days). The oscillations are predicted by a pair of purely imaginary eigenvalues.



There are many other results that I have been reading, but I will exclude them to maintain a relatively brief paper.

Discussion

This method of using delay differential equations that incorporate time-lags in the phases of cell division is "more consistent with certain reported data than the classic exponential growth model" [2]. These DDE's can make estimations on things other models cannot, such as the fraction of dividing cells, rate of commitment of cells to cell division, initial distribution of cells in the cycle, and the degree of synchronization of cells in the initial population [2]. These models can potentially be used in the hopefully near future to determine how to reduce tumor size by administering drugs that were designed based on the different parameter values calculated [3]. Since different types of cancerous tumors behave in different ways, these models will need to be adjusted appropriately, using the various characteristics of any particular given cancer. In closing, I think these processes of mathematical modeling are extraordinarily crucial to develop new medical breakthroughs, and, in turn, saving lives.

References

1. Villasana, M., Radunskaya, A.: A delay differential equation model for tumor growth. J. Math. Biol. **47**, 270-294 (2003)

2. Baker, C.T.H., Bocharov, G.A., Paul, C.A.H, Rihan, F.A.: Modeling and analysis of time-lags in some basic patterns of cell proliferation. J. Math. Biol. **37**, 341-371 (1998)

3. de Pillis, L., Radunskaya, A.: A mathematical tumor model with immune resistance and drug therapy: an optimal control approach. J. Theor. Med. Vol. 3.2 2001.

4. U.S. National Institutes of Health, National Cancer Institute, http://seer.cancer.gov