A Mathematical Model for Microenvironmental Control of Tumor Growth

A.R. Galante, D. Levy, and C. Tomasetti

Department of Mathematics and Center for Scientific Computation and Mathematical Modeling (CSCAMM), University of Maryland, College Park, MD, USA

Abstract— **One of the most intriguing questions related to cancer is why approximately two out of three people never develop cancer? It has been proposed that this variability in cancer resistance may be due to differences in the efficiency of certain protective mechanisms, which are known to inhibit the growth of neoplastic cells. Here we focus on the mechanism known as microenvironmental control. There is a large amount of evidence that a majority of disseminated tumor cells present in the human body never develop into clinical tumors, and that the direct physical contact between normal and tumoral cells appears to be a necessary condition for such resistance to cancer. By using a system of ordinary differential equations, we model contact-controlled tumor growth and are able to simulate the three expected modes of growth: expansive, contractive and stable, thus mathematically supporting the feasibility of microenvironmental control.**

Keywords— **Cancer, Cancer Resistance, Microenvironmental Control, Ordinary Differential Equations.**

I. Introduction

It is known that the majority of the tumors are monoclonal [1], that is, cancer generally develops starting from a single cell that has undergone some specific kind of mutation. However it is calculated that 3 mutations occur on average every time the cell's DNA base pairs are duplicated, an event that occurs 10^{16} time in the life of a person [2]. Furthermore, there are a lot of genetic and epigenetic changes that can promote cancer [3]. This raises one of the most challenging questions related in cancer studies: why do approximately two out of three people never develop cancer? Furthermore, why does it appear that at least for some types of tumors, the disease progresses for some patients while remains latent in others?

It is a striking fact, supported by a large amount of evidence, that the majority of disseminated tumor cells present in the human body never develop into clinical tumors. Some examples are the cancerous cells found in the prostate, the mammary gland, and the epithelium [4-6]. Based on recent data it has been proposed that one possible explanation may be the variability in the efficiency of certain protective mechanisms, which are known to inhibit the growth of neoplastic cells.

In a timely PNAS article [4], Klein lists some of the mechanisms that cause resistance to cancer: *immunological* (T cells targeting non-self proteins), *genetic* (genes that control the fidelity of DNA replication), *epigenetic* (lack of impairment of normal parental epigenetic imprinting), *intracellular* (triggering of apoptosis in cells with DNA damage or illegitimate activation of oncogenes) and *intercellular* (healthy neighboring cells inhibiting neoplastic growth). It is on this last mechanism, also known as "microenvironmental control" that we would like to focus our attention.

The first evidence of such an inhibition mechanism activated by normal cell was given in a paper by Stoker et al. in 1966 [7]. There it was shown that the inhibition was working by direct contact between the healthy and neoplastic cells. Further evidence in this direction was given, for example, by [8-9] for the case of the epithelium and stroma. Other types of contactual interactions may play a relevant role. One known example is that of the adherence junctions: e-cadherin, which is a major component of such junctions, is down regulated in most epithelial tumors [4]. It is important to note that the direct physical contact between normal and tumoral cells appears to be a necessary condition for the microenvironmental control to be functional (see [10]). This type of mechanism is what we would like to model.

While there are a number of mathematical models focusing on the immunological mechanism of resistance to cancer (see for example [11-12] and the references therein), environmental control has not been the focus of mathematical studies. We would like to mention a few. For example, in 1980 Cox et al. [13] presented a model where the size of the reproducing tumor population is proportional to the number of unoccupied receptors for inhibitors. Chaplain et al. [14] instead have included in their model a variable for the diffusion of inhibitors. Finally, Bajzer et al. [15] considered the contribution of paracrine interactions as a regulatory feedback in cell-cell interaction.

We would like to model resistance to cancer due to microenvironmental control. We will take the simplest point of view, that is, we will not assume (and thus include) any specific role of nutrients, growth factors, and so forth. We will only consider direct physical contact, and show that this is a sufficient mechanism for explaining the observed dynamics.

K.E. Herold, W.E. Bentley, and J. Vossoughi (Eds.): SBEC 2010, IFMBE Proceedings 32, pp. 213–216, 2010.
www.springerlink.com

II. A MATHEMATICAL MODEL

A. Derivation

To derive our model for microenvironmental control of a solid tumor, we begin by assuming that the tumor is spherical with radius R and is composed of approximately spherical cells of radius r (consult Figure 1). Hence, the volume of the tumor is given by

$$V_T = \frac{4}{3}\pi R^3, \tag{1}$$

and the volume of a cancer cell is

$$V_C = \frac{4}{3}\pi r^3. \tag{2}$$

Assuming a packing factor of ¾, we can determine that the total number of cancer cells, T, is given by the volume of the tumor, equation (1), divided by the volume of a single cell:

$$T = \frac{3}{4}\left(\frac{R}{r}\right)^3. \tag{3}$$

In tumor spheroids, the majority of the proliferating cancer cells are located in the outer three to five cell layers [16]. For the sake of simplicity, we assume that only the outer layer of tumor cells is capable of proliferating; we denote this population of proliferating cancer cells on the rim of the tumor by S. To allow for microenvironmental control by physical contact, we allow normal cells, denoted by N, to interact with the cancer cells on the surface of the tumor. Upon interaction of one normal cell and one cancer cell, we allow for the formation of a two-cell complex which can either dissociate or result in the death of the cancer cell. We denote the population of complexes by X. When a cancer cell is in a complex with a normal cell, we do not allow the cancer cell to proliferate. These cell populations in and around our spherical tumor model are illustrated in Figure 1. The volume of the cancer cells in the non-proliferating core of the tumor is quantified by

$$V_{T-(S+X)} = \frac{4}{3}\pi(R-2r)^3. \tag{4}$$

Again assuming a packing factor of ¾, equation (4) can be used to determine the number of cells in the non-proliferating region:

$$T-(S+X) = \frac{3}{4}\frac{(R-2r)^2}{r^3}. \tag{5}$$

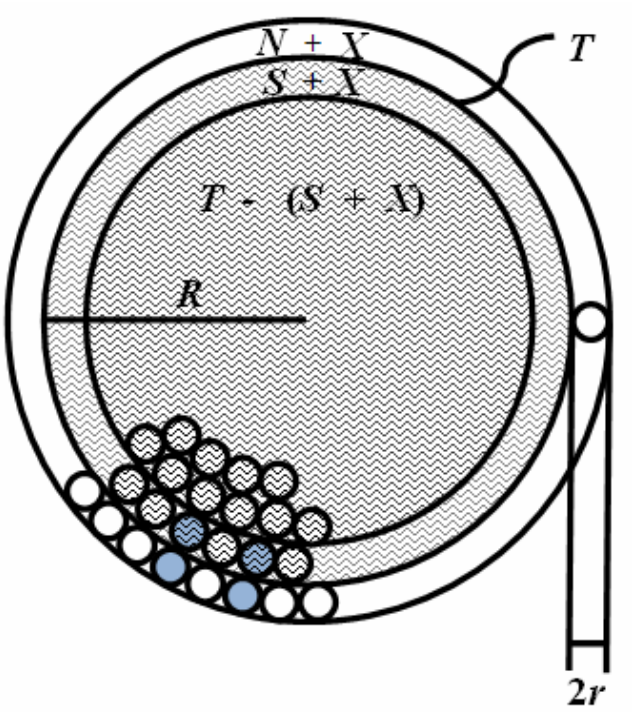

Fig. 1 A 2-D depiction of a 3-D spherical tumor of radius R composed of spherical cells of radius r. The two-cell complexes, X, are shown shaded in blue. The cancer cells and necrotic core, T, are shown with a wave pattern while the normal cells have no pattern

Using equation (3) to solve for R in terms of T, a formula for the number of "uncomplexed" cancer cells on the surface of spherical tumor, S, can be derived from Eqn. (5):

$$S = 6\left(\frac{3}{4}\right)^{\frac{1}{3}} T^{\frac{2}{3}} - 12\left(\frac{3}{4}\right)^{\frac{2}{3}} T^{\frac{1}{3}} + 6 - X. \tag{6}$$

Assuming the number of normal cells on the surface of the tumor, N, is greater than S and following a similar logic as above, we can derive an analogous expression for N:

$$N = \frac{3}{4}\left(\left(\frac{4}{3}T\right)^{1/3} + 2\right)^3 - T - X. \tag{7}$$

This allows us to develop the dynamic equations for spherical tumor growth within a microenvironment. Let C be cancer cells not in complexes, i.e., $C=T - X$. We assume that the cancer cells in population S are the only cancer cells undergoing mitosis, at rate k. Let h and k_0 be the rate constants for the formation and dissociation of complexes, respectively. Hence, the dynamic equation for $C(t)$ reads

$$\frac{dC}{dt} = kS - hSN + k_0 X. \tag{8}$$

The dynamic equation for complexes X allows for the association and dissociation of complexes as well as the death of a cancer cell, resulting in the elimination of a complex (with rate k_2):

$$\frac{dX}{dt} = hSN - (k_2 + k_0)X. \quad (9)$$

Note that since $C+X=T$, a dynamic expression for T can be derived from equations (8) and (9):

$$\frac{dT}{dt} = kS - k_2 X. \quad (10)$$

Considering that S and N are functions of T and X, we have derived a nonlinear system of ODEs with two equations and two variables.

B. *Analysis of the Model*

We can define the functions $f(T) = S+X$ and $g(T)=N+X$ to be the number of cancer cells and normal cells on the surface of the tumor, respectively. It is important that if a steady state (X^*,T^*) exists, it must be such that $X^* \le f(T^*)$. Otherwise, the model would allow for the number of "uncomplexed" cancer cells on the surface of the tumor to be negative. Noting that both f and g are always positive, it is easy to show that any solution to both nullclines $\dot{X} = 0$ and $\dot{T} = 0$ satisfy this condition. The two nullclines must cross, yielding a steady state; this must occur on the line given by

$$N^* = \frac{k(k_0 + k_2)}{hk_2}, \quad (11)$$

which is a translation of $g(T)$ to the left by exactly N^*. According to the value of N^*, the steady state may be found numerically for large values of T. In these cases, however, the steady state is outside of the feasible area for the model assumptions; tumors tend to undergo angiogenesis when they are approximately 1mm in diameter or 10^5 cells [16]. Thus, depending on the value of the parameters and, hence, the value that N^* takes, either the tumor will reach a steady state or will grow uncontrolled (due to the fact that the steady state is outside of the feasible region). Of course, parameter values can also be selected to force the steady state to be approximately zero.

III. Results and Discussion

To assess the feasibility of our model, we must capture the three tumor growth modes: controlled, suppressed, and uncontrolled. Indeed, we were able to show that all three modes of interest can be obtained by varying the model parameters. Each simulation was run in MATLAB using *ode45* using the arbitrary initial condition of 700 cancer cells and 10 cells in complexes.

In Figure 2, tumor stability is simulated. With the chosen parameters, it is noteworthy that the tumor continues to grow until a sufficient number of complexes are formed and then it contracts in size until reaching the steady state.

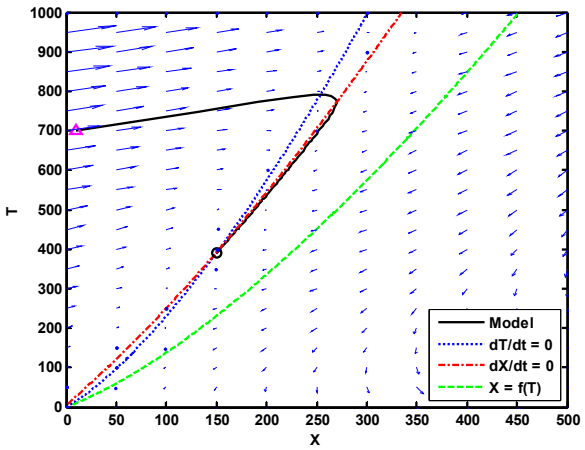

Fig. 2 Model simulation demonstrating tumor stability. Parameter values used were $k = 2$, $h = 0.01$, $k_0=0.1$, and $k_2=1$

In Figure 3, tumor suppression is simulated. In this case, the parameters are such that the tumor barely grows before reaching the line for $\dot{X} = 0$, at which point the complexes slowly suppress the tumor to a steady state of approximately zero.

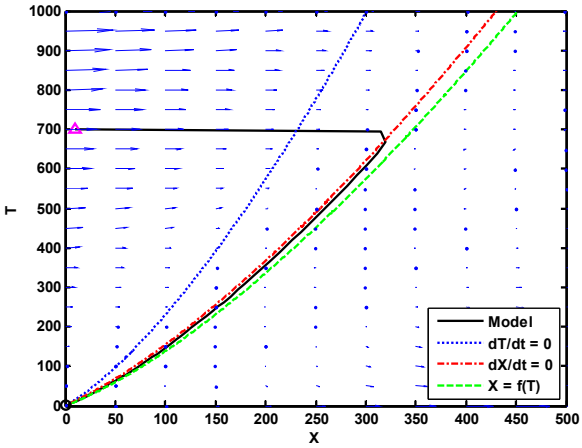

Fig. 3 Model simulation demonstrating tumor suppression. Parameter values used were $k = 2$, $h = 0.1$, $k_0=0.1$, and $k_2=1$

In Figure 4, the phenomenon of uncontrolled tumor growth can be seen. In this case, it is noteworthy that the

line for $\dot{X} = 0$ is to the left of the line $\dot{T} = 0$. We know that these nullclines must intersect because of the dynamics of the system. Hence, while not visible in the figure, a very large steady state does in fact exist.

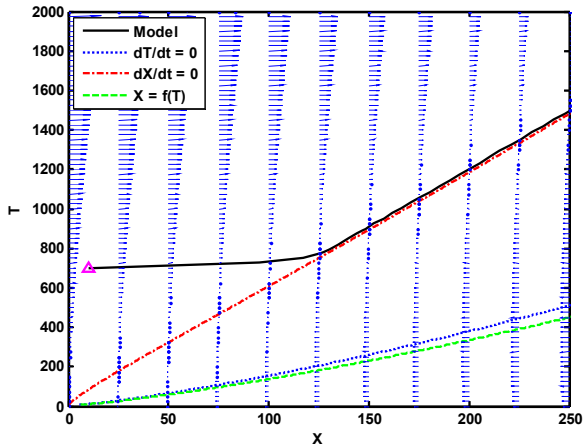

Fig. 4 Model simulation demonstrating uncontrolled tumor growth. Parameter values used were $k = 1$, $h = 0.01$, k_0=8, and k_2=0.1

Note that it is not necessary to assume that the complexes are capable of killing cancer cells; this assumption can be relaxed to a situation where cancer cells in complexes are put into a quiescent state. Since the focus of our paper has been on microenvironmental control, we have considered small tumors which have not yet undergone angiogenesis. As we have been able to capture each expected trend, we can conclude that our model supports the feasibility of contact-based microenvironmental control.

Acknowledgment

This work was supported in part by the joint NSF/NIGMS program under Grant Number DMS-0758374 and in part by Grant Number R01CA130817 from the National Cancer Institute. The content is solely the responsibility of the authors and is does not necessarily represent the official views of the National Cancer Institute or the National Institute of Health.

References

1. Klein G (2009) Reply to Bredberg: the voice of the whale. Proc Natl Acad Sci USA 106:E52
2. Bredberg A (2009) Cancer resistance and Peto's paradox. Proc Natl AcadSci USA 106:E51
3. Weinberg RA (2007) The biology of cancer. Garland Science Publishers, New York
4. Klein G (2009) Toward genetics of cancer esistance. Proc Natl Acad Sci USA 106:859-863
5. Naumov GN et al. (2002) Persistence of solitary mammary carcinoma cells in a secondary site: a possible contributor to dormancy. Cancer Res 62:2162-2168
6. Zhang W (2001) Escaping the stem cell compartment: sustained UVB exposure allows p-53 mutant keratinocytes to colonize adjacent epidermal proliferating units without incurring additional mutations. Proc Natl Acad Sci USA 98:13948-13953
7. Stoker MG, Shearer M, O'Neill C (1966) Growth inhibition of polyoma-transformed cells by contact with static normal fibroblasts. J Cell Sci 1:297-310
8. Glick AB, Yuspa SH (2005) Tissue homeostasis and the control of the neoplastic phenotype in epithelial cancer. Semin Cancer Biol 15:75-83
9. Alt-Holland A, Zhang W, Marguilis A, Garlick JA (2005) Microenvironmental control of premalignant disease: the role of intercellular adhesion in the progression of squamous cell carcinoma. Semin Cancer Biol 15:84-96
10. Alexander DB et al. (2004) Normal cells control the growth of neighboring transformed cells indipendent of gap junctional communication and Src activity. Cancer Res 64:1347-1358
11. Adam JA, Bellomo N (1996) A survey of models for tumor-immune system dynamics. Birkhauser, Boston
12. Arciero JC, Jackson TL, Kirschner DE (2004) A mathematical model of tumor-immune evasion and siRNA treatment. Discrete and Continuous Dynamical Systems 4:39-58
13. Cox EB, Woodbury MA, Myers LE (1980) A new model for tumor growth analysis based on a postulated inhibitory substance. Compd. Biomed. Res. 13:437-445
14. Chaplain MAJ, Benson DL, Maini PK (1994) Nonlinear diffusion of a growth inhibitory factor in multicell spheroids. Math. Biosci. 121:1-13
15. Bajzer Z, Vuk-Pavlovic S (2005) Modeling positive regulatory feedbacks in cell-cell interactions. BioSystems 80:1-10
16. Sutherland, RM (1988) Cell and Environment Interactions in Tumor Microregions: The Multicell Spheroid Model. Science 240: 177-184

Author: Cristian Tomasetti
Institute: Department of Mathematics, University of Maryland
Street: Paint Branch Drive
City: College Park
Country: USA
Email: cristian@math.umd.edu