Article Title: The Dynamics of War between Benign and Malignant Cells

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Abstract

This article provides a mathematical dynamic description of the interaction of two types of cells, malignant cells (cancer) and benign cells. Considering a living tissue at the system theoretical level as a collection of these two types of cells, we analyse the dynamics of cell interaction using ordinary differential equations. We show that in a living tissue equilibrium between the two types of cells is possible. Cyclic oscillations are not possible. Suitably adjusting the mitosis ratio or the death ratio for benign and malignant cells, the article demonstrates the dynamics by which malignant cells can be completely removed by chemical treatment.

1 Introduction

This article conceptualizes a war between benign and malignant cells within a living tissue. The benign cells may be supported by killer agents. There is a growing realization in cancer research that the attack on malignant cells by so-called "killers", most recently suggested in the form of engineered bacteria, may "represent a new weapon in the war against cancer" (Jain and Forbes 2001:1).[1] A considerable amount of experiments have been carried out to test the growth and proliferation of benign and malignant cells. Although this literature is quantitative and technical in nature, with suggested polynomials describing the cell growth and cell proliferation, lacking is to our knowledge the operational approach to this type of problem.[2] By considering a living tissue at the system theoretical level as a collection of only these two types of cells (benign and malignant), we analyse the dynamics of cell interaction using ordinary differential equations. This approach is to our knowledge new within the field oncology, but has been quite common in other fields of science. Generally, differential equations have over the last centuries gained a prominent position within mathematics mainly due to many physical, chemical, biological, and also social laws and relations appearing on this form. Differential equations are believed to explain, in principle, all phenomena where at least one variable varies with respect to another variable. The lesson from nature is that complex time relations are constituted such that values of the different variables at a given time are exclusively given by the values at the previous time when the intervening time interval approaches zero. This phenomenon has today been built into mathematical models by using differential equations, providing mathematical models with more predictive power than algebraic relations. In this sense differential equations are more foundational than algebraic expressions. The approach in this article is similar to the approach of Braun (1983) who applies differential equations in fascinating manners to a variety of different phenomena (war, ecology, population, disease, pollution, spread of technological innovations, atomic waste disposal problems). Braun (1983:52ff) also analyzes the growth of a tumor (Gompertzian relation), but without focusing on how the tumor cells interact with benign

[1] Dang et al. (2001:) describe how such killers localize and proliferate in the hypoxic regions of tumors.
[2] See Panetta (1995, 1997) for an analysis of the logistic model.

cells, which is the focus of this article.

This article addresses the following problems. 1. What is the nature of the equilibrium between benign and malignant cells? Defining cancer as the presence of malignant cells, what kinds of changes in parameters cause the tissue to move from being cancer-free to acquire cancer with possible subsequent death? How are the acquisition and proliferation of cancer controlled by benign natural and engineered agents? Which parameters typically change during chemical treatment and X-ray radiation?

We show that in a living tissue equilibrium between the two types of cells is possible. Cyclic oscillations are not possible. Suitably adjusting the mitosis (birth) ratio or the death ratio for benign and malignant cells, the article demonstrates the dynamics by which malignant cells can be completely removed by chemical treatment.

Section 2 provides the theoretical model. Section 3 discusses the effect of various clinical treatments. Section 4 concludes.

2 The model

Let $\rho_1(t)$ be the density of the benign living cells defined as the expected number of benign living cells pr unit volume, and $\rho_2(t)$ be the density of the malignant living cells defined as the expected number of malignant living cells pr unit volume in a tissue at time t. This section applies expected values for all variables and we suppress the word expectation hereafter. Generally we assume that

$$\dot{\rho}_i(t) \overset{\text{mod}}{=} f_i\left(\rho_1(t),\rho_2(t)\right),\ i=1,2, \tag{2.1}$$

Taylor expansion up to the second order gives[3]

[3] The constant term in the Taylor expansion is removed since we cannot give it any population dynamic interpretation.

$$\begin{aligned}\dot{\rho}_1(t) &= a_1\rho_1(t) - b_1\rho_1(t)^2 - c_1\rho_1(t)\rho_2(t) - d_1\rho_2(t)^2 - e_1\rho_2(t),\\ \dot{\rho}_2(t) &= a_2\rho_2(t) - b_2\rho_2(t)^2 - c_2\rho_1(t)\rho_2(t) - d_2\rho_1(t)^2 - e_2\rho_1(t),\end{aligned} \tag{2.2}$$

where we now proceed to argue for the chosen signs of the parameters a_i, b_i, c_i, d_i, e_i.

Empirics from in vitro experiments (Haux et al. 1999, and many others) shows unequivocally that the density of living cells left by themselves under favourable constant external circumstances (constant temperature and constant supply/availability of oxygen and other nutrients) grow or decrease exponentially when the density is low. The explanation is as follows: Consider an arbitrary cell. Let p_{ib} and p_{id} be the probabilities that the cell of type i divides (causing birth of two new cells) and dies, respectively, in the time interval from t to t+Δt. It seems reasonable to let both the probability of division and the probability of death be proportional to Δt, i.e.

$$p_{ij} \overset{\text{mod}}{=} c_{ij}\Delta t,\ i = 1,2,\ j = b,d, \tag{2.3}$$

where mod means that this is a model assumption, and j and d denotes birth and death respectively. For a large group the relative increase of type i cells is

$$\frac{\Delta\rho_i}{\rho_i} = p_{ib} - p_{id} = (c_{ib} - c_{id})\Delta t, \quad c_{ib} - c_{id} \overset{def}{=} a_i, \quad i = 1,2, \tag{2.4}$$

which gives exponential increase when a_i is positive. After some time the exponential growth slows down and the density approaches an asymptote. Also in a tissue there is an upper bound on the density $\rho_i(t)$ of living cells. This negative impact in (2.2) is caused by the contact inhibition which gets initiated when the density is so high that the cells are more or less in contact at all time. The inhibition is furnished by a reduction in the mitosis (birth) rate of the cells, i.e. a reduction in the parameter c_{ib}. This phenomenon can be taken into account

by subtracting a logistic dampening term[4] of the kind $b_i \rho_i(t)^2$ with negative impact in (2.4). This gives the equation $\dot{\rho}_i(t) = (c_{ib} - c_{id})\rho_i(t) - b_i\rho_i(t)^2$. This equation can be written as $\dot{\rho}_i(t) = a_i\rho_i(t)[1 - \rho_i(t)b_i/a_i]$. The well known solution is that the density of cells increases in an S-shaped manner from $\rho_i(0)$ toward the asymptote a_i/b_i.

Benign cells also feel a contact inhibition against malignant cells, while malignant cells do not feel any contact inhibition against benign cells. A simple equation that takes this into account for the benign cells is $\dot{\rho}_1(t) = a_1\rho_1(t)\left[1 - \left(\rho_1(t) + (c_1/b_1)\rho_2(t)\right)b_1/a_1\right]$. By expanding the term on the right hand side, parts of (2.2) follows. Usually the malignant cells have approximately the same dimension as the benign cells, and therefore $c_1 \approx b_1$.

Within a tissue we denote $\rho'_1(t)$ as the density of a relatively small but special subgroup of benign killer agents, i.e. killers. These special killers interact directly with the malignant cells, attempting to eliminate the latter. If the malignant cells become numerous they inhibit the normal functioning of the benign cells and the tissue acquires a cancer condition. If the density of benign cells gets sufficiently reduced, the tissue may stop to function properly. Observe the analogy between this interaction between malignant cells and Lanchester (1914) linear warfare.[5] Analogous to Lanchester linear warfare, the following interpretation can be given based on Lotka's (1924) theory. Consider a malignant cell. Define p_{2a} as the probability that this cell gets attacked by the killers during the time interval from t to $t+\Delta t$. It seems reasonable to let this probability be proportional to Δt and proportional to the number of killers where we assume that all killers operate independently of each other. Hence

[4] For a discussion of the history of the logistic hypothesis, first presented by Verhulst (1845) and developed by Lotka (1924), in population ecology see Kingsland (1985:64-97). Logistic increase has found its application in many fields.

[5] In Lanchester linear (guerilla) warfare agents in one group shoot into an area where they do not know where the agents in the other group are located, and thus cannot know when a hit has been made. The loss rate for group 1 with n_1 members is proportional to the number n_2 of members in group 2, since a larger group 2 is likely to produce a larger number of n_1-casualties. It is further reasonable to let the loss rate for group 1 be proportional to n_1, since the larger is n_1, the larger is the point probability that a shot from group 2 will hit. This gives $d\rho_1/dt = -\mu_1\rho_2\rho_1$, $d\rho_2/dt = -\mu_2\rho_1\rho_2$. In other words, the loss rate of group 1 depends on the number of contacts between groups 1 and 2, where a larger ρ_2 is likely to produce a larger number of shots against group 1, and a larger ρ_1 is likely to absorb a larger number of these shots from group 2.

$$p_{2a} \overset{\text{mod}}{\sim} \Delta t \rho'_1 . \tag{2.5}$$

For a large number of killers the law of large numbers allows us to state that

$$p_{2a} \sim \frac{\Delta \rho_2}{\rho_2}, \tag{2.6}$$

which gives

$$\frac{\Delta \rho_2}{\rho_2} \sim \Delta t \rho'_1 \quad \Leftrightarrow \quad \dot{\rho}_2 \sim \rho_2 \rho'_1 . \tag{2.7}$$

A loss term of the kind $c_2 \rho_1^{'}(t) \rho_2(t)$ thus appear, where c_2 is a positive constant.

The parameters d_i and e_i do not have a straightforward population dynamic interpretation and we set $d_i=0=e_i$ which, when inserted into (2.2), gives

$$\dot{\rho}_1(t) = \rho_1(t)\left(a_1 - b_1\rho_1(t) - c_1\rho_2(t)\right), \ \dot{\rho}_2(t) = \rho_2(t)\left(a_2 - b_2\rho_2(t) - c_2\rho_1^{'}(t)\right). \tag{2.8}$$

The model of the density $\rho'_1(t)$ of the killers is important to establish. It is well known that in a tissue an amount of so-called natural killer cells appears. Recent developments in cancer research suggest injecting engineered bacteria into a tissue with the objective of attacking malignant cells (Dang et al. 2001, Jain and Forbes 2001). The remainder of the article considers the simple model $\rho_1'(t) = a_k \rho_1(t)$, where a_k is a constant. Inserting into (2.8) gives

$$\dot{\rho}_1(t) = \rho_1(t)\left(a_1 - b_1\rho_1(t) - c_1\rho_2(t)\right), \ \dot{\rho}_2(t) = \rho_2(t)\left(a_2 - b_2\rho_2(t) - c_2\rho_1(t)\right), \tag{2.9}$$

where c_2 is redefined. (2.9) is mathematically equivalent to the equations presented by Volterra (1931) for two species competing for the same limited food supply. Although these

equations have been analyzed in the literature (Braun 1983:449-456), section 3 uses phase diagrams to analyze the equations in a manner that we believe is brief and sufficient to understand the interaction between benign and malignant cells.

3 Interpretation of the model

We define the following two lines labelled l_1 and l_2 in the phase diagram ρ_1 versus ρ_2,

$$l_1 : a_1 - b_1\rho_1 - c_1\rho_2 = 0, \quad l_2 : a_2 - b_2\rho_2 - c_2\rho_1 = 0. \tag{3.1}$$

Inserting $\dot{\rho}_1(t) = \dot{\rho}_2(t) = 0$ into (3.1) gives the equilibrium solutions

$$(0,0),\ \left(\frac{a_1}{b_1},0\right),\ \left(\frac{a_2}{b_2},0\right),\ \left(\frac{a_1b_2 - c_1a_2}{b_1b_2 - c_1c_2}, \frac{a_2b_1 - c_2a_1}{b_1b_2 - c_1c_2}\right). \tag{3.2}$$

The equilibrium solutions are interesting since these represent steady state values for the densities of benign and malignant cells in the tissue. Figs. 1-4 show the lines l_1 described by $\rho_2=a_1/c_1-b_1\rho_1/c_1$ and l_2 described by $\rho_2=a_2/c_2-c_2\rho_1/b_2$ in the phase diagram ρ_1 versus ρ_2 for these four topologically different cases. Fig. 1 assumes $a_1/b_1>a_2/c_2$ and $a_1/c_1>a_2/b_2$, where the phase diagram is divided into the three areas (a): $\dot{\rho}_1(t) < 0$, $\dot{\rho}_2(t) < 0$, (b): $\dot{\rho}_1(t) > 0$, $\dot{\rho}_2(t) < 0$, (c): $\dot{\rho}_1(t) > 0$, $\dot{\rho}_2(t) > 0$.

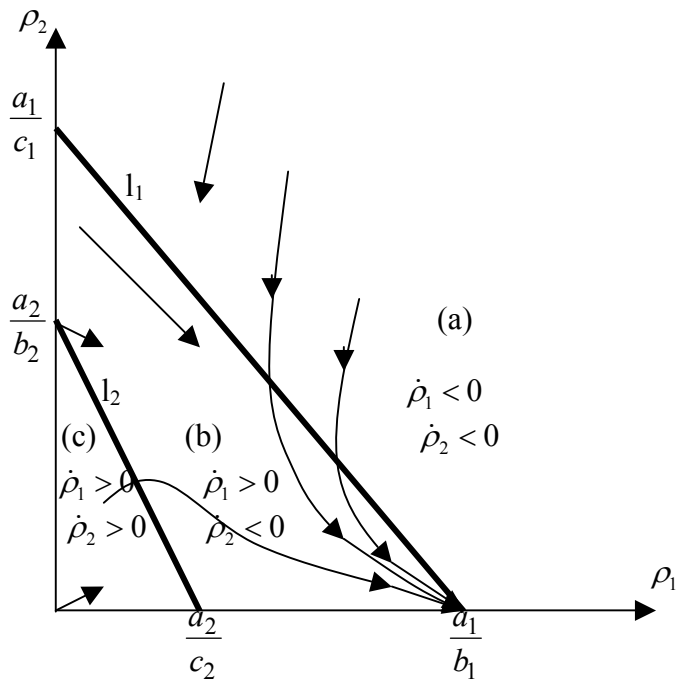

Fig. 1. Phase diagram when $a_1/b_1>a_2/c_2$ and $a_1/c_1>a_2/b_2$.

Fig. 1 reveals the three equilibria (0,0), $(a_1/b_1,0)$, and $(0,a_2/b_2)$, where the first and third are unstable. Observe that any starting point (ρ_1,ρ_2) outside the equilibrium points causes movement toward $(a_1/b_1,0)$. Assuming that the partial derivatives of $f_i\left(\rho_1(t),\rho_2(t)\right)$ in (2.1) are continuous it possible to show that the phase lines do not cross each other except in the equilibrium points. This implies that phase lines from starting points outside the axes $\rho_1=0$ and $\rho_2=0$ cannot touch any of the axes outside the equilibria (0,0), $(a_1/b_1,0)$, and $(0,a_2/b_2)$ since such a phase line would coincide with another phase line along one of the axes.

The instability of the equilibria (0,0) and $(0,a_2/b_2)$ means that any small perturbation from those equilibrium points causes movement toward $(a_1/b_1,0)$. Hence all the malignant cells die ($\rho_2=0$) with subsequent healing of the tissue. Fig. 1 thus represents the preferable situation where the tissue gets healed for all initial values of the malignant cells.

Fig. 2 assumes $a_1/b_1>a_2/b_2$ and $a_1/c_1>a_2/b_2$, where the phase diagram is divided into the four areas (a): $\dot{\rho}_1(t)<0$, $\dot{\rho}_2(t)<0$, (b): $\dot{\rho}_1(t)>0$, $\dot{\rho}_2(t)<0$, (c): $\dot{\rho}_1(t)>0$, $\dot{\rho}_2(t)>0$, (d): $\dot{\rho}_1(t)<0$, $\dot{\rho}_2(t)>0$.

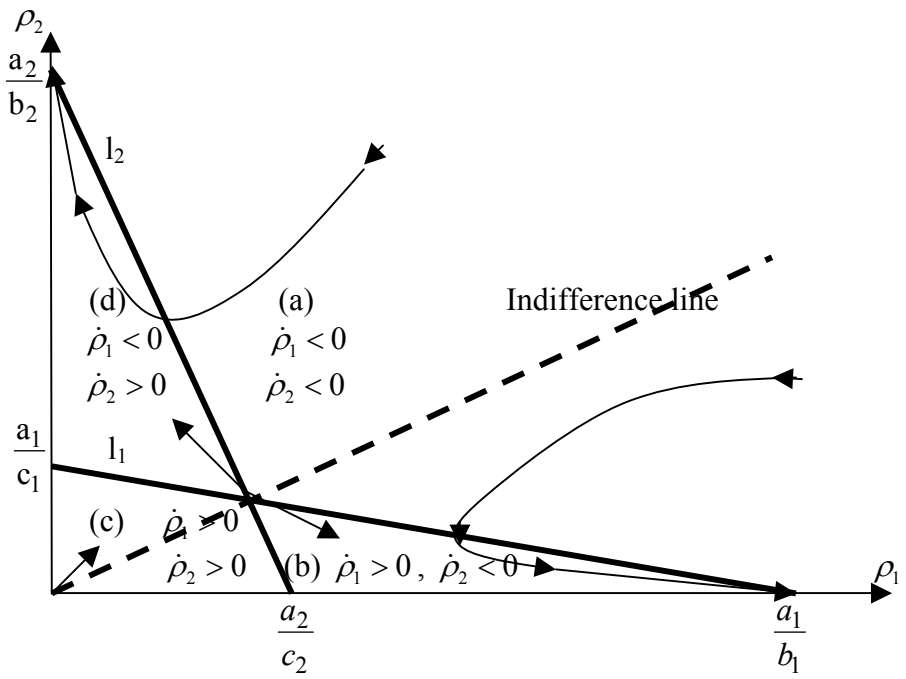

Fig. 2. Phase diagram when $a_1/b_1 > a_2/c_2$ and $a_1/c_1 < a_2/b_2$.

Fig. 2 reveals the four equilibria (0,0), $(a_1/b_1,0)$, $(0,a_2/b_2)$ and $\left(\frac{a_1b_2 - c_1a_2}{b_1b_2 - c_1c_2}, \frac{a_2b_1 - c_2a_1}{b_1b_2 - c_1c_2}\right)$, where the first and fourth are unstable. Any starting point (ρ_1, ρ_2) outside the two equilibria $(a_1/b_1,0)$ and $(0,a_2/b_2)$ causes, dependent on the starting point, movement toward $(a_1/b_1,0)$ or $(0,a_2/b_2)$, as time approaches infinity. The stapled "indifference line" in Fig. 2 delimiting the two regions of attraction, defined as the line where the phase lines are indifferent between making a rightward turn toward the equilibrium $(0,a_2/b_2)$ and a leftward turn toward the equilibrium $(a_1/b_1,0)$, is approximately given by a straight line through the origin and the crossing point between the two lines l_1 and l_2. The functional form is

$$f(\rho_2(t)) = \frac{a_2b_1 - c_2a_1}{a_1b_2 - c_1a_2}\rho_2(t). \tag{3.3}$$

The cancer-free equilibrium $(a_1/b_1,0)$ where the tissue is free from malignant cells ($\rho_2=0$) is the preferable equilibrium. The equilibrium $(0,a_2/b_2)$ where the malignant cells eventually take over the entire tissue causing it to die ($\rho_1=0$), is not preferable.

Fig. 3 assumes $a_1/b_1 < a_2/b_2$ and $a_1/c_1 < a_2/b_2$, where the phase diagram is divided into the three areas (a): $\dot{\rho}_1(t) < 0$, $\dot{\rho}_2(t) < 0$, (b): $\dot{\rho}_1(t) < 0$, $\dot{\rho}_2(t) > 0$, (c): $\dot{\rho}_1(t) > 0$, $\dot{\rho}_2(t) > 0$

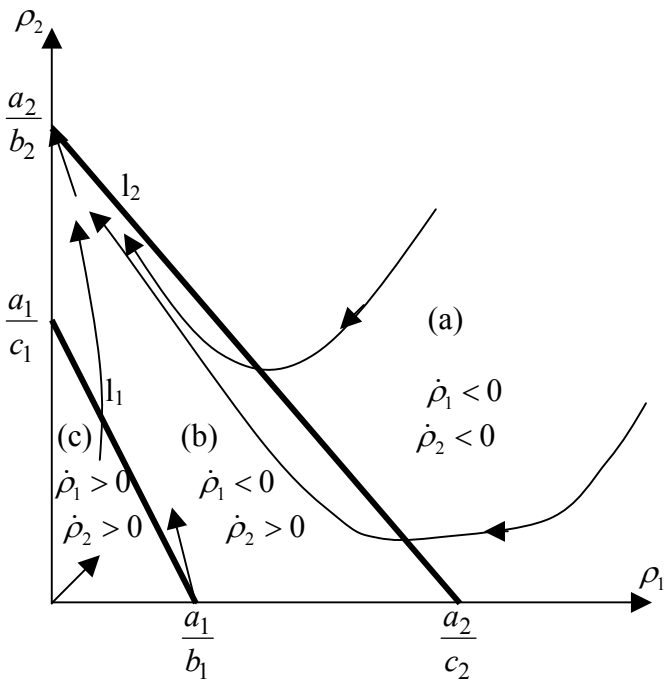

Fig. 3. Phase diagram when $a_1/b_1<a_2/c_2$ and $a_1/c_1<a_2/b_2$.

Observing that the two equilibra (0,0), $(a_1/b_1,0)$ are unstable, any starting point (ρ_1, ρ_2) outside the equilibrium $(0,a_2/b_2)$ in Fig. 3 causes movement to the unbeneficial unique equilibrium $(0,a_2/b_2)$ where the tissue dies of cancer since the density of begin cells approaches zero.

Fig. 4 assumes $a_1/b_1<a_2/b_2$ and $a_1/c_1>a_2/b_2$, where the phase diagram is divided into the four areas (a): $\dot{\rho}_1(t) < 0$, $\dot{\rho}_2(t) < 0$, (b): $\dot{\rho}_1(t) < 0$, $\dot{\rho}_2(t) > 0$, (c): $\dot{\rho}_1(t) > 0$, $\dot{\rho}_2(t) > 0$, (d): $\dot{\rho}_1(t) > 0$, $\dot{\rho}_2(t) < 0$.

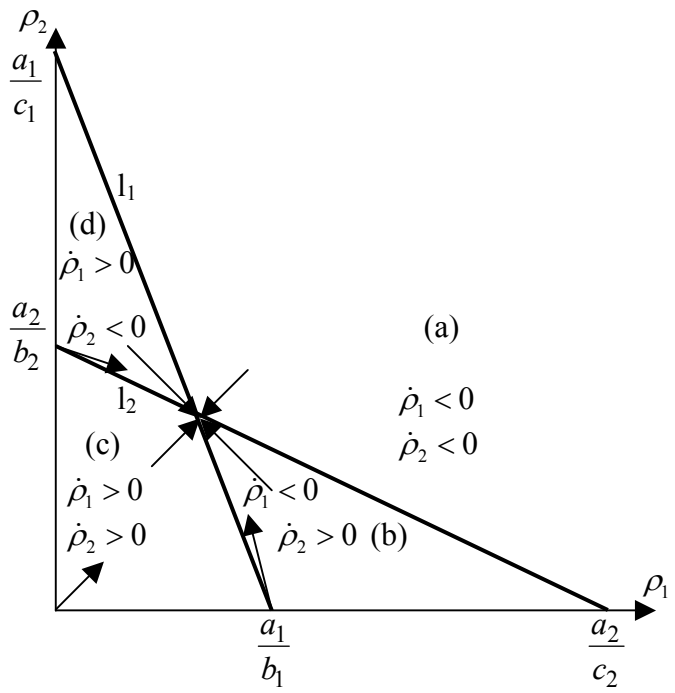

Fig. 4. Phase diagram when $a_1/b_1<a_2/c_2$ and $a_1/c_1>a_2/b_2$.

Observing that the three equilibria (0,0), $(a_1/b_1,0)$, $(0,a_2/b_2)$ are unstable. Hence any starting different from those equilibrium points causes movement to the unique equilibrium $\left(\frac{a_1b_2-c_1a_2}{b_1b_2-c_1c_2},\frac{a_2b_1-c_2a_1}{b_1b_2-c_1c_2}\right)$, where the tissue is alive in an equilibrated state with both benign and malignant cells as time approaches infinity. Comparing with Fig. 2, the manner in which the lines l1 and l2 cross causes a stable interior equilibrium in Fig. 4, and an unstable interior equilibrium in Fig. 2.

Observe that decline of c_2 toward zero does not necessarily mean that the tissue dies since the topological case in Fig. 4 may arise if $a_1/a_2<c_1/b_2$. Assuming a sufficiently low c_2 such that $a_2/c_2>a_1/b_1$ makes only Figs. 3 and 4 possible. Surgery may drastically reduce the ratio a_1/a_2 due to wounds, reduced healing capacity, etc. Such a reduction of a_1/a_2 may cause a switch from the partly beneficial case in Fig. 4 to the unbeneficial case in Fig. 3 where $a_1/a_2>c_1/b_2$ and the tissue dies.

4 Simulations of treatment

This section focuses on which parameters a_i, b_i, c_i, i=1,2 in (2.8) are crucial in attempts, through chemotherapy (chemical treatment), surgery, and X-ray treatment, to treat a tissue where the density of malignant cells tends to increase causing the density of benign cells to

decrease. In chemotherapy malignant cells are attempted attacked by the use of drugs. The drawback of this procedure is the difficulty of avoiding impact also on benign cells. Benign cells and malignant cells have many common features. The challenge in chemotherapy is to design drugs equipped with the targeted or selective ability of reducing the density of malignant cells without affecting the benign cells.

The majority of cytostatica today attack the cells by reducing the mitosis rate, but some also affect the death rate by increasing the apoptosis of the cells (programmed cell death). It seems reasonable to describe chemotherapy mathematically by subtracting a term of the type $f_1\rho_1(t)$ and $f_2\rho_2(t)$, respectively, in the two equations in (2.2). Mathematically this simply amounts to redefining a_i to $a_i'=a_i-f_i$, i=1,2. Observe that regardless of the state of the tissue an increase of the ratio $a_1'/a_2'= (a_1-f_1)/(a_2-f_2)$ is beneficial. The challenge in chemotherapy is thus to ensure $f_1>f_2$. Graphically this means moving the crossing point between the lines l_1 and l_2 in Fig. 2 upwards changing the regions of attraction such that some of the phase lines that make a rightward turn toward the equilibrium $(0,a_2/b_2)$ instead make a leftward turn toward the equilibrium $(a_1/b_1,0)$. If the crossing point is moved sufficiently high up, a transition from the topological case in Fig. 2 to the topological case in Fig. 1 occurs. Observe that the density of malignant cells may decline also when a_2 is positive given that, in accordance with (2.8), that $a_2 < c_2\rho_1(t)+b_2\rho_2(t)$. In vitro experiments where the malignant cells are separated from the benign cells may thus cause an increase in the density of malignant cells for this a_2. This means that a categorical requirement that the density of malignant cells needs to decrease (a_2 is negative) is not necessary to cure the tissue. The presence of the benign cells and the influence of these through the immune system on the malignant cells may facilitate curing the tissue despite a_2 being positive.

In surgery the area infected by malignant cells is attempted removed physically from the tissue. When successful this means reducing a_2. The risk is that other factors may cause an increase in a_2 that outweighs the reduction in a_2 achieved by the surgical removal. One such factor may be the inadvertent or unavoidable introduction of wounds which may not heal properly. Another factor may be that surgery does not succeed in removing the entire affected area causing a bleeding area which may give extra nourishment to the malignant cells with concomitant increase of a_2. This may cause a transition from the partly beneficial topological case in Fig. 4, or the “unstable” topological case in Fig. 2, to the unbeneficial topological

case in Fig. 3 where the tissue dies. The maximal density of the cells of a given type (benign or malignant) operating in isolation is given by the ratio a_i/b_i, which is the asymptote of the logistic equation $\dot{\rho}_i(t) = a_i\rho_i(t) - b_i\rho_i(t)^2$ given by the first two terms on the right hand side in (2.8). We interpret the inverse of the maximal density a_i/b_i, i.e. b_i/a_i, as the minimum volume for a given cell. Defining r_i as the radius of this cell, we express this minimum volume as

$$\frac{b_i}{a_i} = \frac{4\pi r_i^3}{3}. \tag{4.1}$$

Lets say that a typical cell dimension is r_i = 5 10^(-6) metres which gives b_i/a_i= 2 10^9/ml. We consider the topological case in Fig. 2 to be the most typical situation since almost every tissue eventually acquires a cancer-condition if the initial density $\rho_2(t)$ of malignant cells is sufficiently large. Following the discussion in section 2 we set $c_1 \approx b_1$ for benign cells which causes $a_1/c_1 \approx a_1/b_1$ describing where l_1 crosses the two axes in Fig. 2. From the assumption that the sizes of benign and malignant cells are approximately equal, it follows that $a_1/b_1 \approx a_2/b_2$, which causes l_1 and l_2 in Fig. 2 to be close to parallel. To the extent l_1 and l_2 are not parallel, they cross each other either at the upper left or the lower-right part of the first quadrant in Fig. 2. Given excessive proliferation of malignant cells and possible pessimistic prospects for the tissue, we believe a crossing point in the lower-right part in Fig. 2 is the most realistic assumption. As an example lets say that malignant cells have proliferation rates of a_2=10/month, while typical values for benign cells could be a_1 = 2/month. Figs. 5-7 illustrate a typical situation where the tissue dies of cancer after 23 months. Observe the dramatic worsening of the disease after approximately 20 months. The solution starts in region (c) of the topological case in Fig. 2 and moves into region (d). $\rho_2(0)/\rho_1(0)$ is only 0.01, which illustrates that a very small initial "jump" in $\rho_2(t)$ is sufficient to initiate an unstable situation.

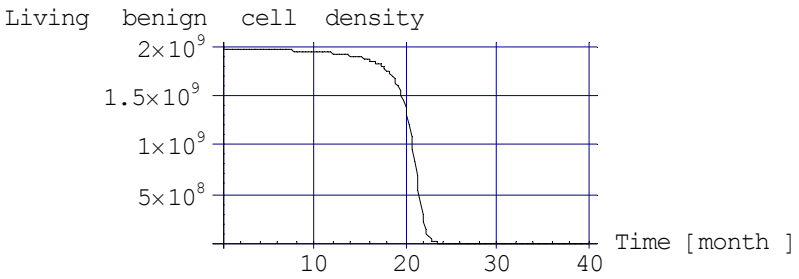

Fig. 5: Benign cells, a_1=4.4/month, a_2=11/month, b_1=2.2 10^(-9)/month/ml, b_2=5.5 10^(-9)/month/ml, c_1=3.3 10^(-9)/month/ml, c_2=5.50028 10^(-9)/month/ml, $\rho_1(0)$=1.98 10^9/ml, $\rho_2(0)$=1.9997 10^7/ml.

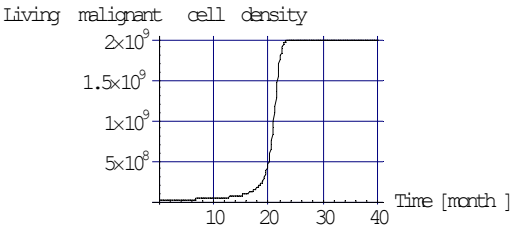

Fig. 6: Malignant cells, a_1=4.4/month, a_2=11/month, b_1=2.2 10^(-9)/month/ml, b_2=5.5 10^(-9)/month/ml, c_1=3.3 10^(-9)/month/ml, c_2=5.50028 10^(-9)/month/ml, $\rho_1(0)$=1.98 10^9/ml, $\rho_2(0)$=1.9997 10^7/ml.

Assume that the tissue is treated with chemotherapy after 22.5 months. It is convenient to interpret such treatment mathematically as reducing the parameter a_2. It follows from (2.8) that a necessary condition for reducing the density of malignant cells at a specific time is

$$a_2 < c_2\rho_1(t) + b_2\rho_2(t) = a_{2c}. \tag{4.2}$$

Fig. 7 shows a_{2c}/a_2, i.e. the necessary relative reduction of a_2 as a function of time required to initiate a reduction in the density of malignant cell. Note that according to the model the reduction has a maximum approximately at the time when the decease initiates its worsening.

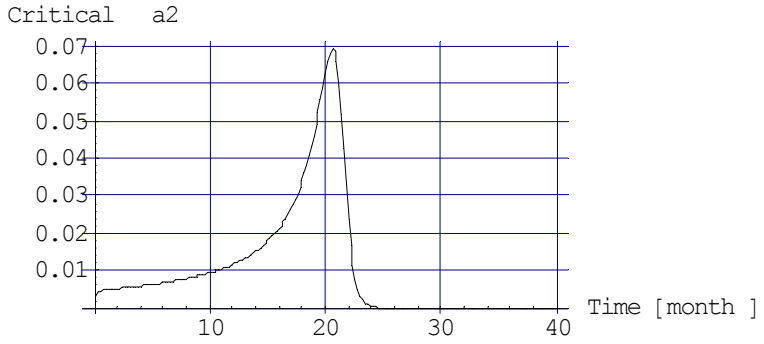

Fig. 7: Necessary relative reduction in the parameter a_2 in order to reduce the density of malignant cells.

Figs. 8-10 illustrate a situation where the parameter a_2 is reduced with 50 percent after 22.5 months. Observe the increasing density of benign cells.

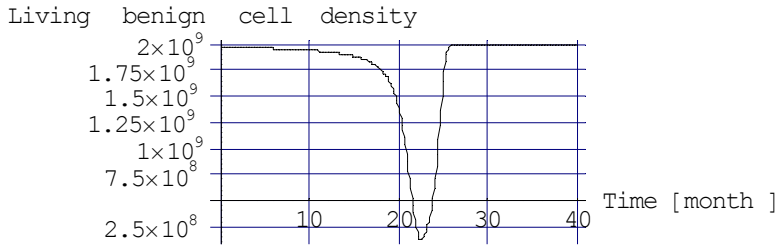

Fig. 8: Benign cells, a_1=4.4/month, a_2=11/month, b_1=2.2 10^(-9)/month/ml, b_2=5.5 10^(-9)/month/ml, c_1=3.3 10^(-9)/month/ml, c_2=5.50028 10^(-9)/month/ml, $\rho_1(0)$=1.98 10^9/ml, $\rho_2(0)$=1.9997 10^7/ml, a_2=5.5/month after 22.5 months.

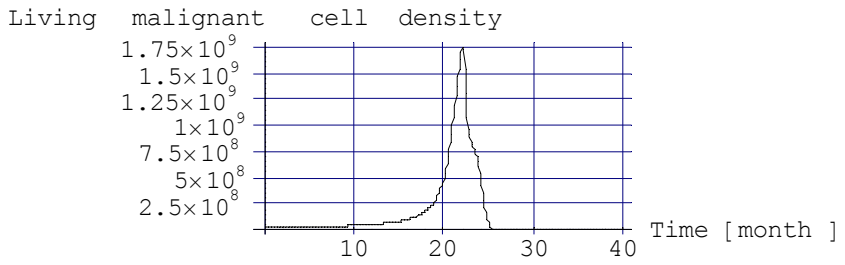

Fig. 9: Malignant cells, a_1=4.4/month, a_2=11/month, b_1=2.2 10^(-9)/month/ml, b_2=5.5 10^(-9)/month/ml, c_1=3.3 10^(-9)/month/ml, c_2=5.50028 10^(-9)/month/ml, $\rho_1(0)$=1.98 10^9/ml, $\rho_2(0)$=1.9997 10^7/ml, a_2=5.5/month after 22.5 months

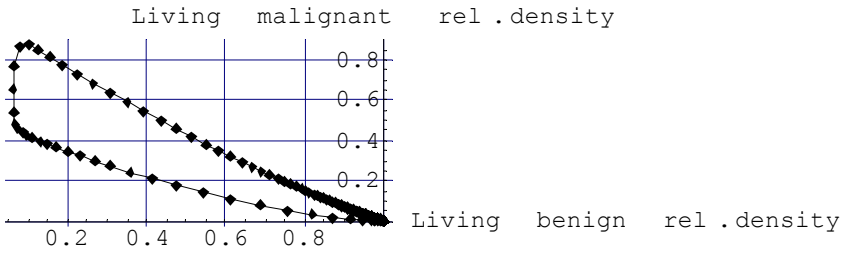

Fig. 10: Benign cells-Malignant cells, a_1=4.4/month, a_2=11/month, b_1=2.2 10^(-9)/month/ml, b_2=5.5 10^(-9)/month/ml, c_1=3.3 10^(-9)/month/ml, c_2=5.50028 10^(-9)/month/ml, $\rho_1(0)$=1.98 10^9/ml, $\rho_2(0)$=1.9997 10^7/ml, a_2=5.5/month after 22.5 month.

From the indifference line defined in (3.3) as the straight line through the origin and the cross point between the two lines l_1 and l_2, the restriction $\rho_2(t) < f(\rho_2(t))$ follows to ensure a cure of the tissue.

Fig. 11 shows $Log[\rho_2(t)/f(\rho_2(t))]$ as a function of time. The path crosses the horizontal axis downwards at time 25 months. Consequently, chemotherapy initiated after 22.5 months, causing a reduction in a_2 with 50%, must proceed for at least 2.5 months in order to complete cure the tissue.

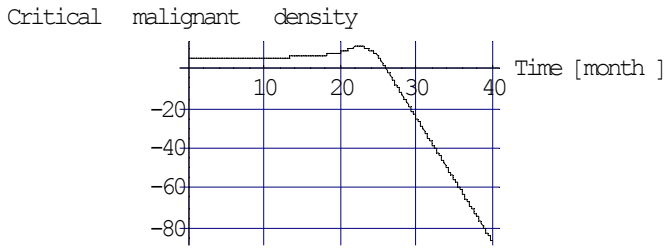

Fig. 11: $Log[\rho_2(t)/f(\rho_2(t))]$ as a function of time.

5 Conclusion

The article provides a mathematical description based on the theory of differential equations for one of mankind's greatest problem, cell proliferation of malignant cells (cancer). A model is developed enabling us to describe the relation between benign and malignant cells at an overall operational level. The model is studied in some detail when the density of killer agents is proportional to the density of benign cells in a given tissue. The theoretical results and considerations are in agreement with clinical experiences. We find that in a living tissue there can exist a static equilibrium between the two types of cells, and that cyclic oscillations are never possible. By changing the proliferation ratio between the two different types of cells, the malignant cells in a tissue can be completely removed.

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