STOICHIOMETRIC MODEL OF TUMOR GROWTH AND TREATMENT

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Abstract. We are working to create a stoichiometric model of organ and tumor growth within a human system. The model we are looking at is fairly general and can be modified for use with different organs. We establish a closed system similar to a chemostat in order to trace the flow of phosphorus and the effects of phosphorus deficiency and possibly toxicity on the organ. Our model simulates a healthy, whole bodily system comprised of an organ, which will eventually be the site of the new tumor growth, the effector or immune system cells and the rest of the healthy cells in the body. The model is primarily based on the flow of phosphorus in the bloodstream. The arteries supply the available phosphorus to the organ, tumor, and other quantities considered. The organ and tumor grow within the system based on the availability of phosphorus and space. Phosphorus is also continually supplied into the system and a fraction is continually flowing out of the system through the veins. The tumor in our model is able to vascularize, thus we also track the growth and decay of the tumor's vascular system. Finally, we discuss the influence of naturally occurring effector cells and immunotherapy to obtain the current state of the model.

An increasing number of models concerning tumor growth have surfaced in the past few years. All but a handful of these take into account the stoichiometric constraints of the system. It should be taken into account that some models begin with existing data and engineer a model that fits those specific experimental results. What we hope to do here is attack the problem from the opposite direction. That is; present a model that is independent of empirical data and that can be easily modified to reflect different forms of tumor growth based on patient specific parameters.

In this paper, we are primarily concerned with the flow of phosphorus throughout the system considered. Phosphorus was chosen because it is, after calcium, the most abundant nutrient in the body. Phosphorus is essential for energy conversion, providing the phosphate in ATP to run many metabolic cycles within the body. Most importantly; the inorganic phosphate in ATP is required to produce the nucleic acids and proteins used in DNA and RNA replication ([3], Haas, 1991). We take into account that the immune system can, in some cancers, recognize the tumor cells and target them for destruction. The immune system cells which do this are called effector cells. Within the body the effect of these cells is minuscule, but it can be isolated and then grown in a lab and re-introduced into the system in forms of immunotherapy (University of Washington, 1997) thus amplifying its power. We include the possible influence of effector cells and immunotherapy.

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The core of our model is the *Holling disc equation*. This equation is used to represent growth rates of cell quantities that will be introduced in the succeeding paragraphs.

We begin our model, which is ultimately the human body, by looking at the healthy cells outside of the organ, H, healthy cells that make up the organ, O, and the phosphorus cycling in the bloodstream, P. The mass of both sets of healthy cells is measured in grams of phosphorus. This can be done as a result of the empirical evidence of phosphorus content in a cell being constant. The measurements are obtainable given that 1% of healthy cell matter and 2% of tumor cell matter is phosphorus ([4], Kuang et al. 2004, [5], Williams, 2002). The cells grow by capturing phosphorus from the bloodstream. This process can be looked at as predation on phosphorus. We use the Holling disc equation to represent the growth rate of healthy cells outside of the organ and the healthy cells making up the organ.

The general form of the growth rate terms will be:

$\frac{dX}{dt} = \frac{c_X P}{s_X + P}$

Variables: X = cell quantity, P = phosphorus.

Constants: c_X = maximum growth rate, s_X = half saturation.

A constant rate of phosphorus ingestion and an excretion rate that is proportional to the amount of phosphorus present in the bloodstream, is introduced into the model. This biological process is approximated by 3 equations:

$$\frac{dH}{dt} = \frac{c_H P}{s_H + P}$$

$$\frac{dO}{dt} = \frac{c_O P}{s_O + P} O$$

$$\frac{dP}{dt} = P_0 - \sigma P - \frac{c_H P}{s_H + P} H - \frac{c_O P}{s_O + P} O$$

Both sets of healthy cells are assumed to have death rates that are proportional to the quantity of the cells in the given set i.e. each cell has the same constant death rate. The healthy cells also have a genetically determined maximum size hence we include crowding rates. For a given cell, its crowding rate is a fraction of the size of the population that the cell is part of. The healthy cells crowd themselves for space and nutrients, however they are idependent of one another, with respect to growth and space so neither crowds the other. The daily death rates of the cells are generally attributed to apoptosis. In the equation for the dynamics of phosphorus in the bloodstream we add the phosphorus that is liberated by the deaths in both healthy cell masses, but we assume that only a fraction, r, is reusable i.e. recycled by the human body. The remaining liberated phosphorus *not* used is either excreted from the system, or phagycytized during apoptosis. The bones contain a significant amount of phosphorus. In order for us to study precisely the dynamics of the tissue cells, we exclude the bones from our system. If we input these equations into Matlab we find they do indeed exhibit stable behavior with each mass staying constant at the initial healthy mass:

$$\frac{dH}{dt} = \frac{c_H P}{S_H + P} H - d_H H - m_H H^2$$

$$\frac{dO}{dt} = \frac{c_O P}{S_O + P} O - d_O O - m_O O^2$$

$$\frac{dP}{dt} = P_0 - \frac{c_H P}{S_H + P} H - \frac{c_O P}{S_O + P} O + r(d_H H + d_O O + m_H H^2 + m_O O^2) - \sigma P$$

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We now introduce the tumor into the system. Since the tumor in consideration is able to vascularize, we also insert the vascular system of the tumor into the model. Tumors can grow without blood vessels, but researchers believe that a tumor will not be able to grow much larger than the size of a pin head without the formation of a vascular system i.e. angiogenesis, to bring nutrients and oxygen to the interior of the tumor ([1], Cancer Research UK, 2001). We include only vessel dependent tumor growth on the assumption that the tumor is already large enough to be vascularized. The growth terms for the tumor and its vessels have the same flavor as the previous growth rates. Death rates and genetic crowding rates also have the same form. Unlike the previous quantities, the tumor can *act directly* upon the healthy cells. The tumor physically crowds the healthy cells but the healthy cells cannot physically crowd the tumor ([4], Kuang et al. 2004). Inserting the equations for tumor and vascular system dynamics as well as the death and crowding rates, the model takes the form:

$$\frac{dH}{dt} = \frac{c_H P}{s_H + P} H - d_H H - m_H H^2$$

$$\frac{dO}{dt} = \frac{c_O P}{s_O + P} O - d_O O - m_O O^2 - m_C (T + V) O$$

$$\frac{dT}{dt} = \frac{c_T P \left(\frac{\mu V}{\alpha H + \beta O + \mu V} \right)}{s_T + P \left(\frac{\mu V}{\alpha H + \beta O + \mu V} \right)} T - d_T T - m_T T^2$$

$$\frac{dV}{dt} = \frac{c_V P}{s_V + P} T - d_V V$$

$$\frac{dP}{dt} = P_0 - \sigma P - \frac{c_H P}{s_H + P} H - \frac{c_O P}{s_O + P} O - \frac{c_T P \left(\frac{\mu V}{\alpha H + \beta O + \mu V} \right)}{s_T + P \left(\frac{\mu V}{\alpha H + \beta O + \mu V} \right)} T - \frac{c_V P}{s_V + P} T$$

$$+ r(d_H H + d_O O + d_T T + d_V V + m_H H^2 + m_O O^2 + m_T T^2 + m_C (T + V) O)$$

Note that the functions used to represent tumor and vascular growth do not follow the pattern that was established for the growth of healthy cells. The function used for tumor growth takes the form:

$$\frac{c_T P \left(\frac{\mu V}{\alpha H + \beta O + \mu V} \right)}{s_T + P \left(\frac{\mu V}{\alpha H + \beta O + \mu V} \right)} T$$

As we mentioned previously, this term takes into account the vascular system. The tumor growth depends on the phosphorus brought into the tumor by the blood vessels. We take the amount of phosphorus available to the tumor to be proportional to the ratio between tumor blood vessels and all blood vessels present. This equation expresses a per capita growth rate.

From the model above, the function for the growth rate of vessels is:

$$\frac{c_V}{s_V + P} T$$

Unlike all of the previous equations, the growth of the vessels is not proportional to amount of vessels, instead it is proportional to the amount of tumor cells present. This is to represent the idea that vessel cells do not replicate independently. These cells ”need to be told” to replicate. Healthy cells have angiogenic genes that govern the state of blood vessel production i.e. they ”tell” the blood vessels when to grow and when not to grow. Scientists assert that tumor cells either lack the anti-angiogenic genes or their angiogenic genes are permanently switched on (Cancer Research UK 2001). From this it is apparent that vessel growth in the tumor needs to be regulated by the tumor cells. Blood vessels are healthy cells and so they also have a constant death rate, however since vessels are induced to grow by the tumor we do not include any crowding effects from the tumor on the vessels. In tumor-induced vessel cells it appears that the vessel cells will keep growing if such a right is granted to them by the tumor cells and there is enough phosphorus present to support their replication.

We add one more equation to our model before we consider it complete. This is an equation for the immune system response which includes a term for immunotherapy. Various tumors produce proteins that act like antigens. The body can recognize these antigens and mount a response to the growing tumor population. It seems, however that the bodily immune response alone has little effect slowing the tumor growth (University of Washington 1997). The cells we are concerned with here are effector cells, specifically NK cells which are mainly involved in the elimination of tumor cells. The exact mechanism with which these cells destroy tumor cells is unknown, but is presumed to be similar to Cytotoxic T-Lymphocytes. This means that the effector cells recognize the cancer through specific receptor cites, which creates a perforin channel through the tumor cell's membrane and causes it to lyse (Douglas F. Fix 2004).

The effector cells have a growth term that depends on the amount of tumor present. Effector cells are always present in the body, though at very small levels. As they float through the system they are "turned off ," but still growing, as resembled by:

$$\frac{c_{E_1} P}{s_{E_1} + P} E$$

Contact with a tumor cell (i.e. recognition of the antigen) switches these cells on. By "switch on" we mean two things. First they begin proliferating to mount an attack on the tumor cell. Second, they are activated to be able to attack the tumor/foreign cell with the appropriate antigen/lack of antigen. The rate at which each effector cell attacks does not only depend on the amount of tumor cells present but also on time. Each effector cell has a rate of discovery of tumor that will change as time passes. If we use the regular Holling derivation we see that:

$$T_{\text{destroyed}} = (t - t_h T_{\text{destroyed}}) a T$$

With previous derivations for growth terms, a has always been a constant but with the effector cells things are a little different. The term a is directly related to the rate of discovery of prey. This term will now depend on time. This is because as time passes, the tumor becomes more differentiated and the effector cells will recognize the tumor cells quicker. Again we use a Holling equation for the term:

$$a = \beta \frac{t}{s_{ET} + t}$$

Substituting this value for a:

$$T_{\text{destroyed}} = \frac{c_{ET} T t^2}{a_{ET}(s_{ET} + t) + Tt} = A(T,t)$$

Where c_{ET}, a_{ET}, s_{ET} are constants.
As we mentioned when the effector cells are "turned on", they are able to proliferate much quicker. The rate of proliferation actually depends on the rate at which the effector cells destroy the tumor cells. We assume that again the rate per capita will be a Holling equation but now only a fraction of our capita are working. This fraction is directly proportional to the rate of destruction. The term appearing in the equation for this growth will be:

$$\frac{c_{E_2} P}{s_{E_2} + P} \cdot ind \cdot \frac{\partial A(T,t)}{\partial t} E$$

The two sorts of immune system cells that are most active in tumor detection are the cytotoxic T-cells and Natural Killer cells, both here referred to as effector cells. They compliment each other in that cytotoxic T-cells recognize infected cells by the antigen present, while NK cells look for tumor cells that are missing a healthy cell receptor (Thornthwaite, 2000?). Here we assume they both work in very similar manners and so can both be modelled under immune response.

$$\frac{dH}{dt} = \frac{c_H P}{s_H + P} H - d_H H - m_H H^2$$

$$\frac{dO}{dt} = \frac{c_O P}{s_O + P} O - d_O O - m_O O^2 - m_C (T + V) O$$

$$\frac{dT}{dt} = \frac{c_T P \left(\frac{\mu V}{\alpha H + \beta O + \mu V}\right)}{s_T + P \left(\frac{\mu V}{\alpha H + \beta O + \mu V}\right)} T - d_T T - m_T T^2 - \frac{\partial A(T,t)}{\partial t} E$$

$$\frac{dV}{dt} = \frac{c_V P}{s_V + P} T - d_V V$$

$$\frac{dE}{dt} = \frac{c_{E_1} P}{s_{E_1} + P} E - d_E E - m_E E^2 + \frac{c_{E_2} P}{s_{E_2} + P} \cdot ind \cdot \frac{\partial A(T,t)}{\partial t} E + I(t)$$

$$\frac{dP}{dt} = P_0 - \frac{c_H P}{s_H + P} H - \frac{c_O P}{s_O + P} O - \frac{c_T P \left(\frac{\mu V}{\alpha H + \beta O + \mu V}\right)}{s_T + P \left(\frac{\mu V}{\alpha H + \beta O + \mu V}\right)} T - \frac{c_V P}{s_V + P} T - \frac{c_{E_1} P}{s_{E_1} + P} E$$

$$- \frac{c_{E_2} P}{s_{E_2} + P} \cdot ind \cdot \frac{\partial A(T,t)}{\partial t} E + r(d_H H + d_O O + d_T T + d_V V + d_E E$$

$$+ m_H H^2 + m_O (O + T + V) + m_T T^2 + m_E E^2 + \frac{\partial A(T,t)}{\partial t} E) - \sigma P$$

In our calculations we can take the I(t) term to be zero, if there is no immunotherapy, or alter it according to the agressiveness of the tumor and the frequency of immunotherapy. Immunotherapy is when effector cells, specific for the identified cancer are removed from the system, replicated in large quantities in vitro and introduced back into the system in hopes of boosting the body's own defense mechanism. We include immunotherapy here because it has less of an effect on the remaining healthy and organ tissues compared to other tumor treatments such as chemotherapy and radiation which are both cytotoxic to the healthy cells as well as the immune cells. Also, we note that the I(t) term does not take any phosphorus out of the system because these cells were replicated in vitro. They will, however, contribute to the phosphorus flow when they expire.

The difficulty with running this model to obtain graphical representations of the dynamics, is the amount of parameters. After hours of searching we have determined the values of many of these parameters, albeit not to the exact accuracy we would hope. This is because much research has not examined these parameters exactly. The growth rates and death rates for particular organs were fairly easy to identify. In our models we use growth and death rate data of the liver for the parameters of the organ. For those of the whole body, or rest of the cells we reviewed many different cell growth and death rates and approximated the value for the body as a whole. Dialy intake of phosphorus into the system was taken from information on daily recommended values of phosphorus and how much the average American usually intakes. With the advent of soda it seems that the phosphorus uptake has increased dramatically. We note in our model that the intake of phosphorus remains fairly constant throughout the duration. It is reasonable to assume that one's eating habits do not change dramatically from day to day.

For tumor growth we note that our model assumes that the tumor has already reached a detectible size, approximately 10 grams, and has thus already vascularized. The tumor can also be located anywhere in the body, and with slight modifications may also be used to model non-tumorous cancer growth. This isn't so far a stretch as we only include the phosphorus flow to the tumor through the vessels. Another sort of cancer, a lyphocytic cancer like leukemia, is already found in the bloodstream, so to alter the model we only need to remove the tumorous vascular term and alter the term for tumor growth slightly.

The following are simulations made using Matlab:

GRAPHS SHOULD BE HERE.

References

[1] Cancer Research UK (2001): *How a Cancer Gets Its Blood Supply*, http://www.cancerhelp.org.uk/help/default.asp?page=99

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[3] Elson M. Haas M.D. (1991): *Staying Healthy with Nutrition: The Complete Guide to Diet and Nutritional Medicine*, Celestial Arts

[4] Yang Kuang, John D. Nagy, James J. Elser (2004): *Biological Stoichiometry of Tumor Dynamics: Mathematical Models and Analysis*. Discrete and Continuous Dynamical Systems-Series B, **4**, 1, 221-240

[5] Scott Williams M.D. (2002): *Radionuclide Therapy for Tumors: Phosphorus-32 sodium phosphate*, http://www.auntminnie.com/ScottWilliamsMD2/nucmed/Tumor/Therapy/P32/P32.htm