

# Towards a General Model for Solid Tumor Growth

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## Introduction

Malignant Neoplasms are the 2<sup>nd</sup> leading cause of death in the United States (1), and rank among the top killers worldwide. Each year billions of dollars from both government and private funding sources are spent on Cancer research. For instance, the National Cancer Institutes 2002 budget amounts to \$5,030,000,000.(2) Great achievements have been made in the development of treatments for specific, individual cancer types, of which over 200 have been identified. However, despite tens of billions of dollars and decades of research relatively little progress has been made towards the construction of a general model describing tumor growth. The research presented in this paper will point towards a first general model for solid tumor growth.

The current position taken by most Cancer researchers is that few if any properties of tumor biology are common to all or even most types of cancer.(3) Therefore, arriving at a general definition for a tumor proves quite difficult. A common definition is the following: “A tumor is a purposeless growth of tissue that tends to be atypical, autonomous and aggressive.”(3) While accurate, this definition presents relatively insubstantial grounds from which further insight into general characteristics of tumor growth can be made. For this reason recasting the definition of tumor growth into a form with different points of emphasis can be useful.

An alternative definition stems from considering tumor growth in terms of energy use. The following working definition is introduced: “A tumor is a growth of tissue in which the normal consumption and allocation of metabolic and anabolic resources is altered, resulting in abnormal structural and functional properties.” A useful analogy describing the difference between normal growth and malignant growth is to consider two groups of individuals distributing and consuming food. The one representing normal growth structures distribution of food in a cooperative way that maximizes the overall efficiency of the group, with individuals modulating their consumption towards the benefit of the group. In contrast the individuals in the group representing a tumor simply try to consume as much food as possible for themselves, with little or no regard for the effect on others or the group as a whole. Thus follows the all-important difference between the sustainable growth of normal life and the unsustainable growth of malignant life.

## Tumor growth

The traditional approach to understanding tumor growth considers it in terms of cell birth and death rates. Tumor growth results from an imbalance in the normal harmony between cell birth and cell death. The rate of tumor growth is determined directly from the degree to which this harmony is disrupted. One can quite easily write down a basic equation for the rate of tumor growth:

$$dN^t/dt = (dN^t_b/dt) - (dN^t_d/dt). \quad \text{Eq.(1)}$$

where  $dN^t/dt$  is the rate of change of the total number of cancer cells,  $dN^t_b/dt$  is the rate of tumor cell birth and  $dN^t_d/dt$  the rate of tumor cell death. Solutions to this equation will be discussed later when the scaling of the birth and death rates with tumor size are considered.

The novel approach to tumor growth taken in this paper derives from considering how energy is used and distributed in tumors. Tumor growth results from an imbalance in the *allocation of energy* to growth, differentiation and maintenance. The dynamics of tumor growth fall out of a model for the dynamics of energy allocation. However, before this new line of thinking is pursued, we should review the present state of tumor growth models.

### Deficiencies in current understanding of solid tumor growth

To the knowledge of the author of this paper, there is no existing successful model for solid tumor growth based on fundamental, observable properties of tumor biology. Current models of tumor growth come mostly from curve fitting, computer simulation, or from differential equations based on gross simplification of the biology. The main reason for the lack of sophisticated, robust models is an inability to model the controls of growth. The theory presented here stems from the West et al. theory that growth, and life in general, is driven by metabolic demands and restraints. Two key deficiencies in current models of tumor growth underscore this idea.

Firstly, there is general ignorance as to how Host size affects neoplastic growth. For instance, even though most cancer research is conducted in animals significantly smaller than humans, primarily rats, there is no complete theory for predicting how tumor growth (or any other tumor property) scales from organism to organism based on size. Secondly, there is little understanding of how energy use in tumor cells determines growth of solid tumors. Despite a

large amount of research devoted to the metabolic aspects of cancer, no successful model of energy use in tumors has ever emerged. These two points ultimately stem from the same question: how do the metabolic resource limitations of a give tumor determine its metabolism and growth?

## Tumor Metabolism

Metabolism and growth are inextricably intertwined. Any change in metabolism must eventually reflect in a change in growth, and vice-versa. The observation that uncontrolled growth of bodily tissue ultimately underlay all cancers led to the logical hypothesis that the metabolic state of malignant tissue must be altered. Some of the earliest studies into tumor biology, conducted by the famous cellular physiologist Otto Warburg, focused on exploring this possibility. By the 1930's Warburg had proposed the "respiratory injury" hypothesis to account for his observations that tumors showed increased rates of glycolysis. The respiratory injury hypothesis explained this metabolic phenomenon by ascribing it a defect in cellular respiration. Other studies conducted contemporaneously that demonstrated that malignant growth could be induced in cell culture by prolonged oxygen deprivation seemed to support Warburg's hypothesis.

However, while it seems to be true that oxygen deprivation/respiratory malfunction plays an important role in most if not all cancers, Warburg's original hypothesis proved an oversimplification. The increased rates of glycolysis Warburg thought were cancer specific were found to be common to embryonic growth as well. Increased glycolytic activity appears to be common to all rapidly dividing cells. Rather than a cause, this particular metabolic attribute of tumor growth is now thought to be a consequence of some underlying departure from normality.

Although no causative role for tumor metabolism has been identified, the idea that the metabolic properties of tumors must differ from normal tissues still holds. In order for tissues to grow beyond the point of stasis they reach naturally they must achieve some alteration either in the total consumption of resources, the balance between allocation of resources to growth and maintenance or both. As use and allocation of energy forms the most fundamental level on which growth can be understood, metabolism is a logical beginning point for the construction of a general model of any type of growth. The absence of a theoretical model for tumor growth parallels the lack of a model for biological growth in general that existed before the construction of the West et al Model.

## Extension of West et al Model to tumor metabolism and growth

In 1997 Geoffrey West, Jim Brown and Brian Enquist proposed a model to explain the origin of allometric scaling laws from arguments based on the structure of biological distribution networks. From this model they constructed the first *apriori* model to explain biological growth across ontogeny. The West et al model of metabolic scaling derives from the basic supposition that metabolism, and therefore growth of any tissue is controlled by nutrient supply. Nutrient supply is in turn determined by the structure of the transport system of the organism. In the case of mammals, which will be the focus of this paper, the transport system is the vascular network. A detailed description of the West et al model is given in reference z.

The basic requirements a system must meet for the West et al model to be applicable are the following:

1. The transport system must be a hierarchical, self-similar tree.
2. The tree must be space filling

3. The network must be optimized to minimize energy expended in transport.
4. The terminal units must be invariant
5. The network must transport material vital to the functioning of the system it supports.

Hypothetically, any distribution network that obeys these rules can be analyzed according to the West et al. methodology. The next part of this paper investigates whether or not tumor vasculature conforms to these rules.

### Properties of tumor vasculature

In the late 1970's Judah Folkman, a cancer surgeon with Children's Hospital in Boston, made the observation that every tumor he had come across which had grown beyond 2 mm had developed its own circulatory system. Folkman proposed the idea that solid tumors could not grow beyond the size of 2 mm without inducing angiogenesis, the recruitment and construction of new blood vessels from surrounding vasculature. Today, cancer treatments focused on angiogenesis represent a promising area of cancer research. Understanding how the structure of tumor vasculature affects tumor growth is critical to this line of research, and to our understanding of cancer in general.

Tumor vascular architecture shows both similarities and differences from normal vascular design. In general, tumor vasculature appears to be hierarchical, tree like and scale invariant. Between tumors of different types and tumors in different organisms, there is only slight variation of capillary size, the terminal units of circulatory systems. So far these observations imply that the West et al model should be applicable to analyzing tumor metabolism and growth from tumor vasculature.

The main departure from normal vascular architecture is the non-space filling nature of tumor vasculature. However, vessel density has been observed to scale with area, so that over some fraction of the total mass of the tumor the vasculature is space filling, and this mass in turn scales with the total tumor mass. This scale invariance of the space-filling fraction should still allow application of the West et al model. Other deviations include increased vessel permeability, increased minimum path difference due to vessel tortuosity, altered branching ratios and radii ratios. The increased vessel permeability should only affect the intercept, and not the scaling of metabolism and the increased minimum path distance (1-3% difference) should only affect the scaling by about 1%. However these are still details that in the final analysis cannot be left out. For the simplicity of an initial treatment they will be ignored for the rest of this discussion. At present the author is investigating the effects of altered branching ratios and radii ratios, but these are observed to occur only occasionally, while in general tumor vasculature remains close to normal as far as these properties are concerned.

In summary, the scaling of the vascularized region of the tumor with the total mass should be observable, and therefore the scaling of metabolism with mass predictable.

Studies conducted by Vaupel et al. have demonstrated that, for tumors of the same type but different size, metabolism appears to follow a power law with mass. The power observed varies between  $\frac{1}{2}$  and  $\frac{2}{3}$  as opposed to the  $\frac{1}{3}$  observed for normal tissue. However the metabolism in these studies is averaged over the entire tumor mass, and does not take into account the presence of avascular or necrotic tissue. Accounting for these variables brings the scaling exponent closer to normal.

Experimental evidence suggests that the West et al model should be adaptable to tumor growth. Tumor vasculature seems to adhere closely enough to the requirements made by West et

al, and in addition preliminary research suggests that tumor metabolism does in fact follow a power law. Before I discuss the West et al growth model and its application to tumors a brief introduction of current growth models should be presented.

Two common models are extant in the literature, the exponential model, and the Gompertz model. The exponential model starts with

$$dN^t/dt = (dN_b^t/dt) - (dN_d^t/dt). \quad \text{Eq.(1)}$$

Assuming that  $dN_b/dt$  and  $dN_d/dt$ , the rate of birth and the rate of death, both scale linearly with the tumor mass  $m^t$ , then  $dm^t/dt = am^t - bm^t$ . An exponential function  $m^t = m_0 \text{Exp}[a-b]$  is the obviously solution to this equation. While this solution approximates the early behavior of solid tumor growth curves, it fails to capture the sigmoid form common to all solid tumors. Apparently the assumed scaling of rates of birth and death with mass is incorrect. Since no derivation of the scaling of birth and death rates with mass from biological considerations has ever been accomplished, no biological model for the sigmoid curve exists.

Along those lines, the most widely accepted model for tumor growth is the Gompertz curve, an exponentially growing term raised to an exponentially decaying term:

$$M = M_0 \text{Exp}[A/a(1 - \text{Exp}[-bt])].$$

The Gompertz equation, while very successful at fitting a wide range of tumor growth curves, is produced by curve fitting techniques, and not by any biological theory. (Examples of Cancers for which Gompertz works.) Presently, as far as this author is aware, no model successfully explaining tumor growth in terms of fundamental biological observable exists.

## General West et al Growth Equation

The general equation for ontogenetic growth is derived from simple considerations of energy use in organism<sup>1</sup>. Energy from metabolism is divided between growth and metabolism. The general equation, derived from Eq(2)

$$\mathbf{B} = (\mathbf{Bc/Mc}) \mathbf{M} + (\mathbf{Ec/Mc})(d\mathbf{M}/dt)$$

Where  $\mathbf{B}$ = total metabolism,  $\mathbf{Bc}$ =cellular metabolism,  $\mathbf{Ec}$  = energy required to create a cell,  $\mathbf{Mc}$ = mass of cell, and  $\mathbf{M}$  =total Mass.

$$\text{If } \mathbf{B} = \mathbf{B_0 M}^p$$

Then, solving for  $d\mathbf{M}/dt$  gives:

$$d\mathbf{M}/dt = (\mathbf{B_0 Mc/Ec})\mathbf{M}^p - (\mathbf{Bc/Ec})\mathbf{M}.$$

For tissue exhibiting normal vascular architecture,  $p=3/4$ .

The question is, if tumor metabolism does in fact follow a power law, what is  $p$ ?

## Brief Summary

Two major questions are under consideration, based one general assumption. The two questions that this paper will attempt to be addressed through an evolving series of models presented in the next few pages are: 1.How does Host size affect tumor growth? 2. How can tumor metabolism be predicted from tumor vasculature, and in turn how can tumor growth be predicted from tumor metabolism? The major assumption, based on empirical evidence, is that tumor metabolism follows a power law, whose exponent is determined by the tumor vascular architecture in the same way that normal metabolic scaling is determined. The concept of a

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<sup>1</sup> For a detailed treatment of the West et al. model see reference x

tumor metabolic mass, denoted  $M_m$ , is introduced. The metabolic mass of a tumor is the portion of the tumor within which the majority of the tumor's metabolism is occurring.

As metabolism necessitates the delivery of metabolites to tissue, the metabolic mass must be synonymous with the vascularized region of tumor. For fully vascularized tumors, the metabolic mass approaches the entire mass of the tumor. In general, since the vascularized region of tumors has been shown to be scale invariant, the metabolic mass must scale with the total mass. If, within the vascularized region of the tumor, vascular architecture falls into patterns that allow application of the West et al model, then the metabolism of the metabolic mass can be predicted and in turn the metabolism of the entire tumor predicted. From such a model of tumor metabolism this paper follows arguments along the lines of the West et al ontogenetic growth model to describe the groundwork for the first general model for solid tumor growth.

### Theoretical Tumor Growth Equations

The conservation of energy equation, adapted from the West et al equation, for an organism with a cancerous growth, is:

$$\mathbf{B} = \sum [\mathbf{N}_c^h \_ \mathbf{B}_c^h + \mathbf{E}_c^h \_ \mathbf{d} \mathbf{N}_c^h / \mathbf{d} \mathbf{t}] + \sum [\mathbf{N}_c^t \_ \mathbf{B}_c^t + \mathbf{E}_c^t \_ \mathbf{d} \mathbf{N}_c^t / \mathbf{d} \mathbf{t}] \quad (1)$$

where the “incoming rate of energy flow,  $\mathbf{B}$ , is the average resting metabolic rate” in this case of entire tumor at a time  $\mathbf{t}$ ,  $\mathbf{B}_c^h$  is the metabolic rate of a normal single cell,  $\mathbf{E}_c^h$  is the metabolic energy required to create a normal cell,  $\mathbf{N}_c^h$  is the total number of normal cells,  $\mathbf{B}_c^t$  is the metabolic rate of a single tumor cell,  $\mathbf{E}_c^t$  is the metabolic energy required to create a tumor cell, and  $\mathbf{N}_c^t$  is the number of tumor cells of a given cell type. The sum is over all cell types, first in the body, and second within the tumor. I assume an average cell type for the host and a separate average cell type for the tumor, representing that tumor's average differentiation state. This

average cancer cell type is considered tumor type specific, and therefore  $E_c^t$  is likewise tumor type specific. The  $E_c^t$  term will prove important in modelling different tumor types when growth rates of different tumors are considered.

By summing over all cell types  $N_c^h$  becomes the total number of cells for the host and  $N_c^t$  for the entire tumor, and since  $N_c^h m_c^h = m^h$ , where  $m_c^h$  is the mass of the average cell, and  $N_c^t m_c^t = m^t$ , equation (1) can be re-written as:

$$dM^t/dt = (M_c^t - B_c^t) - B - [(m_c^t - B_c^h) - (m_c^h - E_c^t)] - m^h - [(E_c^h - m_c^t) - (E_c^t - m_c^h)] - dm^h/dt - (B_c^t - E_c^t) - m^t \quad (2)$$

This equation forms the general framework from which all considerations of tumor growth in this paper will stem.

The  $dm^h/dt$  and  $B$  terms in this equation must be dealt with in order to analyze the growth dynamics of the tumor by solving for  $dM^t/dt$ . The first alteration that can be made to simply this equation is to assume that  $dm^h/dt = 0$ . That is, the size of the host minus the tumor does not change. This simplification assumes that tumors are either non-invasive, or that the invasion results in a mass loss that is significantly less than the size of the host. Qualitatively this is true at least up until advanced stages of cancer. Secondly,  $B$  must be expressed in terms of tumor and host size. Where West et al lets  $B = B_0 M^{\alpha}$ , having rigorously derived this relationship in previous work, the scaling of tumor metabolism with tumor and host mass, if existent at all, are not well established. For an accurate determination of such a scaling, a detailed analysis of both the interaction of the tumor with the host vascular network and of the properties of the tumor vascular architecture itself must be conducted. While such an analysis is beyond the scope of the current paper, some starting points will be introduced, and a rigorous treatment seems within reach in the near future.

A first approximation assumes that the growth of a tumor doesn't alter the symmetry of the host network, and therefore the overall metabolic properties remain unadulterated, that is  $\mathbf{B}$  is proportional to  $(\mathbf{m}^h + \mathbf{m}^t)$ . Substituting for  $\mathbf{B}$  and letting  $d\mathbf{m}^h/dt = 0$ , equation (2) becomes:

$$d\mathbf{M}^t/dt = (\mathbf{M}_c^t - \mathbf{B}_c^t) - \mathbf{m}_0 - (\mathbf{m}^h + \mathbf{m}^t) - [(\mathbf{m}_c^t - \mathbf{B}_c^h) - (\mathbf{m}^h - \mathbf{E}_c^t)] - \mathbf{m}^h - (\mathbf{B}_c^t - \mathbf{E}_c^t) - \mathbf{m}^t \quad (3)$$

Since  $\mathbf{m}^h + \mathbf{m}^t = \mathbf{m}^{\text{tot}}$ , and  $d\mathbf{m}^h/dt + d\mathbf{m}^t/dt = d\mathbf{m}^{\text{tot}}/dt$ , then, substituting in for  $d\mathbf{M}^t/dt$  and  $\mathbf{m}^t$ , and rearranging terms, equation (3) becomes

$$d\mathbf{m}^{\text{tot}}/dt = (\mathbf{M}_c^t - \mathbf{B}_c^t) - \mathbf{B}_0(\mathbf{m}^{\text{tot}})^{3/4} - (\mathbf{B}_c^t - \mathbf{E}_c^t) - \mathbf{m}^{\text{tot}} - \{[(\mathbf{m}_c^t - \mathbf{B}_c^h) - (\mathbf{m}^h - \mathbf{E}_c^t)] + (\mathbf{B}_c^t - \mathbf{E}_c^t)\} - \mathbf{m}^h \quad (4)$$

This equation can be rewritten in the form of the original West et al equation:

$$\frac{dm}{dt} = am^{3/4} \left[ 1 - \left( \frac{m}{M} \right)^{1/4} \right] \quad (5)$$

Integrating (5) yields:

$$\left( \frac{m}{M} \right)^{1/4} = 1 - \left[ 1 - \left( \frac{m_0}{M} \right)^{1/4} \right] e^{-at/4M^{1/4}} \quad (6)$$

The tumor mass can be solved for by letting the asymptotic mass of the host  $\mathbf{m}^h$  be the lower integration bound and letting the asymptotic host mass plus the asymptotic tumor mass be the upper integration bound, isolating  $m$  in the above equation, and subtracting off the asymptotic mass.

The analytical solution is pictured in figure 2 with average tumors from different size animals. While this solution misses the early stage exponential growth, it does seem to model late stage tumor growth fairly well. The obvious mathematical explanation is that the ratio of the initial size to the final size isn't large enough to produce an early exponential growth. However this curve also has biological corollaries. It either assumes that the new mass is distributed homogenously throughout the body, or it assumes that the allocation of resources in the tumor is determined by the allocation of resources in the host's normal tissue. That is, as the size of the host, and its stage in development, determines the proportions of energy awarded to growth and energy used for maintenance, this host size and developmental state also determines the relationship of growth to maintenance. Already we see that this cannot be true, because tumors in fully grown organisms do show exponential growth. However, since the doubling times of the tumor after the inflection point are well modeled by this equation, it suggests that at some point host size does play a controlling role in tumor resource allocation

The model does demonstrate the general effect of host size on tumor growth and to this author's knowledge is the first such model to do so. When the solution is plotted once with  $m^h$  equal to the mass of a rat, and then again with  $m^h$  equal to the mass of a human, the correct scaling of doublings times from rat to humans is roughly predicted, both in the exponential growth phase and in the late stage growth. That is, in the exponential stage, it overshoots for both rat and human, but that overshoot still reflects the experimentally determined scaling of doubling times from rat to human. Despite the assumptions made, this model begins to explain host effect on tumor growth.

While the first model clearly shows that tumor resource allocation is somewhat autonomously determined in early tumor growth, this may not preclude a general governing of

metabolic rate by the host. On the one hand, it makes sense that if the tumor isn't yet large enough for its allocations to be effected by the host, that it is also free of metabolic constraints applied by the host network, the mass dependant scaling of doubling times in this early exponential stage implies that the host metabolic properties still have some important effect.

One way to model a host determined metabolic resource environment without falling into the resource allocation trap is to write a differential equation in terms of the tumor mass, for which the boundary mass is that of the tumor, and not of the host plus the tumor as in eq (6), but where the mass specific metabolic rate of the tumor is the mass specific metabolic rate of the host. That is:

$B^t \_ m^t$  is proportional to  $B^h \_ m^h$ .

$$\Rightarrow B^t = B^t_0 (m^h + m^t)^{-1/4} \_ m^t \quad (7)$$

Substituting into the growth equation gives:

$$B^t_0 (m^h + m^t)^{-1/4} \_ m^t = (B^t_c \_ m^t_c) \_ m^t + (E^t_c \_ m^t_c) \_ dm^t/dt \quad (8)$$

In general,  $m^t \_ m^h \ll 1$ . Expanding this equation binomially and solving for  $dm^t/dt$  yields

$$dm^t/dt = a \_ (m^h)^{-1/4} \_ m^t \_ (a/4) \_ (m^t)^2 \_ (m^h)^{-5/4} \_ b \_ m^h \quad (9)$$

where  $a = B^t_0 \_ m^t_c \_ E^t_c$  and  $b = B^t_c \_ E^t_c$ .

This second equation models the actual behavior of tumor growth more closely, as shown in figure 2. It qualitatively captures the early exponential growth, missing the slope to small degree. It qualitatively predicts the scaling of tumor doubling time between organisms of different sizes, similarly to the first model. (They make the same assumptions about how tumor metabolism is driven by host, and actually this second model is derived straight from the first by

simply neglecting the first term of the binomial expansion and throwing out everything except terms pertaining to tumor mass and growth.) However, in addition to leaving out any consideration of the metabolic mass of the tumor, it points out major shortcomings of this approach: in order to fit the curve produced by this equation to the experimental data, unlikely values for the constants are required. While these values are not impossibly far off, they are at the edge of what might be considered the possible range for cellular metabolic rates and energy requirements for cell building. For all of its shortcomings, however, this model does present evidence that the general approach to understanding tumor growth through metabolism and host effects shows great promise, and has already shed light on previously unexplained findings.

Consideration of the metabolic mass is quite easily introduced by substituting in  $m_m^t$  the metabolic mass, for  $m^t$ , and then in turn letting  $m_m^t$  scale with  $m^t$  to some power.

$$m_m^t = m_0^t (m^t)^q.$$

Determination of the scaling exponent  $q$  is at the very least tumor type specific, and more likely variable even between tumors of the same type. Jain et al. have made extensive studies of this scaling exponent. Their experiments suggest that after an initial very early growth phase that this exponent converges on a constant. The range they have observed for tumors as diverse as --- - and ---- is ---. As the above general equation in terms of  $M_m$ ,  $M_h$ ,  $p$  and  $q$  is analytically intractable, I will present a few numerical solutions with values for  $q$  in the experimentally determined range.

(Van, I'm going to skip substituting this into the equation above, and look at how the metabolic mass changes the parameter values. I actually can't remember if letting the tumor mass go to some power less than one, modeling the "metabolic mass", makes the situation better

or worse, I have to go and redo that when I get back to school. Once I do that I'll include it and send it along. And, actually, I need to look to see if those parameter values really are as bad as I thought. Instead I'm skipping to just assuming that tumor metabolism scales with tumor mass to some power  $p$ , and letting the host influence come through in the cellular metabolic term. This is also problematic as if you plot tumor asymptotic size as a function of mass, you get a funny curve which can't be right. That was where I was right at the end of the summer, and I have to think about this again. Ultimately we need to do this thing ground up, the way Geoff did the original model, so this won't matter anyway. )

A third approach to modeling tumor growth, based on insights from the first two, is to assume that tumor metabolism scales with tumor metabolic mass to as power  $p$ , and that the host influence can be modeled by letting the cellular metabolic rate scale with the host mass-specific metabolic rate. So:

$$\mathbf{B}^t = \mathbf{B}_0^t (m^t)^{pq}, \text{ and } \mathbf{B}_c^t = \mathbf{B}_{c0}^t (m^h)^{-1/4}$$

Writing the growth equation:

$$\mathbf{B}_0^t (m^t)^{pq} = (\mathbf{B}_{c0}^t (m^h)^{-1/4} - m^t c)(m^t)^p - (E_c^t - m^t c) \frac{dm^t}{dt}$$

And solving for  $\frac{dm^t}{dt}$  yields

$$\frac{dm^t}{dt} = a - (m^t)^{pq} - b - (m^t)^p$$

where  $a$  and  $b$  are the same as in eq. (9), except with the new  $\mathbf{B}_c^t$ .

The obvious unknown is the value of  $p$ . At the present time, data has not yet confirmed values for  $p$ , although preliminary investigations suggest that it is often less than the  $\frac{1}{4}$  value for

normal tissues. However, those values do not factor in the scaling of metabolic mass, so it is possible that the actual value of  $p$  for the metabolic mass is close to the  $\frac{1}{3}$  of normal tissue. As stated towards the beginning of the paper, the value of  $p$  is the subject of further theoretical investigations into tumor vascular architecture, and experimental studies of tumor metabolism.

Instead of supplying theoretically derived values for  $p$  and  $q$ , as would be the ideal case, I instead vary these values within a realistic range to try to fit the growth equation to known tumor growth curves, to see if the parameter space offers the potential for quantitative modeling. I fit these curves to a set of experimental curves from one of the canonical papers on tumor growth, published in [1], as well as a human tumor growth curve from another famous paper. Results for the best fit to each experimental curve are displayed in chart 1. As can be seen, the curves fit fairly well, however the curvature of the curve in the first section of the exponential phase of growth is incorrect for each case. This suggests that some fundamental aspect of the model needs modification.

One possibility is that the scaling of tumor metabolism with mass undergoes some change, reflected in a change in scaling power, and resulting in a change in the slope of the tumor growth curve. The original West. et al model centers around a minimization of the energy lost through blood transport. For large vessels, wave reflection dominates energy lost, whereas for small vessels friction along vessel walls accounts for the major energy loss. The minimization, predicted by the West model, and observed for normal vasculature, results in a change from pulsatile to non-pulsatile flow through the vessel, as well as different inter-branch vessel radii ratios. Preliminary research into tumor vascular architecture suggests that such a changeover in branch radii ratio does occur, around the same value as for normal vascular systems. This suggests that initially, when the tumor is small, and connected to small vessels for

its blood supply, it receives only non-pulsatile flow. At some point, presumably where the observed change in branch radii ratio occurs, a switchover to pulsatile flow occurs.

Based on the West et al model, tumors which are subject to non-pulsatile flow would exhibit metabolisms which scale more closely to linear with tumor mass, as the metabolism of very small animals scales more closely to linear with mass. Factoring this into the model results in a set of two equations for tumor growth, one, in which is close to one, for tumors less than a certain mass, predicted to be 5 grams, which is also the size at which the preliminary data suggests that the branch radii ratio changes, and a separate equation, with  $p$  around .75 or less, for the tumor after 5 grams. These equations are plotted in Figure 2. The change over occurs where the two curves intersect. This intersection point between the exponential and sigmoidal growth curves, if it truly reflects the size at which a tumor's blood flow switches from non-pulsatile to pulsatile at the top level, should be relatively host independent, as it corresponds to the level of branching from the bottom up. As it turns out, the intersection point is relatively host-size independent, one more check that the model is somewhat consistent. Experimentally, this change over seems to occur at the same size as well, as is illustrated in figure 3.

As can be seen, the new curve fits the experimental curves much more closely. Actually, by slight variations in the parameters, quantitative fitting can be achieved. Results for the improved model appear in table 2. The doubling times for early growth now perfectly reflect the experimentally observed doubling times.

## Conclusion and Further Directions

The complexity and variability of cancer make it an extremely difficult system to model. Until now, no unified theoretical approach to understanding tumor growth has been created. The model presented in this paper starts with the West et al model of metabolism and ontogenetic

growth, and derives the framework of a general model for solid tumor growth. Although certainly rough, and built largely on approximations, this model, to the authors knowledge, already surpasses any other in terms of producing tumor growth curves from fundamental biological observables. It is also the first model to begin to explain the effects of host size on tumor growth. While the model is still relatively unproven, it makes testable predictions on a wide range of properties of tumors. For instance preliminary data shows that cancer risk seems to scale with body mass to the  $-1/16$ , whereas the predications of this approximate model, having to do with energy flux per unit mass and cell division rate per unit mass, suggest a  $-1/4$  scaling. On the other hand, preliminary data show that the scaling of tumor development time with body does appear to follow the  $+1/4$  scaling expected. Deviations from these laws present some of the most interesting areas of potential research: cats, for instance, show a much lower rate of cancer incidence than would be expected for their size.

The future of research in this area is wide open. The two most important tasks that need to be accomplished are:

1. the ground-up construction of a rigorous model of tumor vascular architecture, the resultant scaling of metabolism with tumor size, and interaction of the tumor vascular system with the circulatory system of the host.

2. The collection of more data:

- (a) on tumors, for which the growth curve and the necrotic/hypoxic fraction scaling is known.

- (b) on the scaling of tumor metabolism with host and tumor size

With this information the growth equations can be fitted to the experimental curves, and the necrotic/hypoxic fraction and metabolic scaling predicted and confirmed, or vice a versa. In

addition, the model needs to include explicit terms for cell birth and death rates, or at least we need to be able to solve for these from the model.

Overall, the preliminary results presented in this paper suggest that the application of the West. Et al model provides the first avenue towards building a general model of solid tumor growth.