Modeling the Dynamics of Cancerous Tumors *in Vivo*

Thesis for Graduation with Distinction in Mathematics

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Abstract

A key area of interest in cancer research is understanding tumor dynamics, so that tumor growth can be predicted more easily and treated more reliably. We explored *in vivo* tumor dynamics starting from simple exponential and logistic growth and progressing to more general models. We then applied these models to analyze the growth of breast cancer, liver cancer, and two types of neurological cancer using five data sets. We found that exponential growth gave the best fit to breast and liver cancers, while surface growth (a 2/3's power law) gave the best fit to neurological cancers.

Introduction

Biological Background

Patterns of cancer growth have been studied mathematically as an object of interest in the sense of seeming to grow as cells double or divide infinitely. As the tumors get larger, and begin to inhibit bodily functions, we may wonder, could this possibly go on forever? Is infinite growth possible? These tumors thrive on the resources of the environment within the body, or the patient may die before tumor can fully take over this environment. Needless to say,

understanding such dynamics is critical to projecting the outlook for a patient, and proposing a plan for treatment.

Glioblastomas are found in the brain, where they have ample room and resources to grow rapidly in all directions. They may begin to inhibit bodily functions when they press on parts of the brain. Breast cancers, by contrast, grow along ducts until they invade the surrounding tissue. Thus, larger breast cancer tumors are more likely to be ellipsoid than spherical. Acoustic neurinomas, though they affect the nervous system, are often benign unless they press against and inhibit important brain functions.

Generally, the type of tumor and its location affect its dynamics, and which model is considered the "best" overall to investigate tumor dynamics. Understanding this aspect of growth can aid in working towards a treatment. Previous work has described *in vitro* data [11], but we propose a method to describe the dynamics of tumor growth in the human body.

Mathematical Background

The simplest model for tumor growth is the exponential model. This model assumes that the tumor grows according to an unlimited cell division process. The equation and its solution are presented below:

$$\frac{dV}{dt} = rV$$

$$V(t) = V_0 e^{rt}$$

The power law model (again shown below with its solution) is a modification of the exponential growth law, with an additional parameter to restrict growth and account for the less than ideal factors in the system.

$$\frac{dV}{dt} = rV(t)^{\alpha}$$

$$V(t) = (V_0^{1-\alpha} + (1-\alpha)rt)^{1/(1-\alpha)}$$

Values of $\alpha<1$ indicate lack of efficiency in the tumor's use of the resources in the local environment of the body, or lack of sufficient resources. When the tumor reaches a threshold size, for example, and the inner cells are no longer able to receive blood through diffusion, angiogenesis occurs. The tumor must deliver blood to its core via transport vessels. Creating these vessels requires energy and resources, but the payoff of sustaining the tumor in the long term is sufficient to warrant this expenditure. The process, however, may halt or slow the tumor's growth, or create an imbalance with disproportionately fast growth externally, expanding surface area, and slow growth internally, restricting volume. The specific threshold is tumor-dependent, and variable according to patient demographic data as well as the extreme variability found in cancer genomes. We consider the power law case where $\alpha=2/3$ in particular. This power represents two-dimensional growth on the surface of a three-dimensional tumor. Biologically, this means that the tumor is expanding outward, but the cells at its core are no longer dividing, likely due once again to angiogenesis.

Power law growth is still infinite although it is slower than exponential, and can be thought of as a proportion of the total growth rate potential that the tumor is realistically able to attain.

In the long term, infinitely growing tumors are biologically implausible. Thus, we consider adjusting our growth formulas with an asymptote to represent the realistic limitations of the stress on the body. First we examine the generalized logistic formula below.

$$\frac{dV}{dt} = rV(t)\left(1-(V(t)/K)^{\beta}\right).$$

$$V(t) = K[1+Q\exp(-\beta rt)]^{-1/\beta};\ Q = [(K/V_0)^{\beta}-1]$$

The standard logistic growth formula is a simplified version of this model (β=1).

$$V(t) = \frac{KV_0e^{rt}}{K+V_0(e^{rt}-1)}$$

Here the point of inflection occurs at half the maximal volume.

Spratt et al. presented a special case of the general logistic model where $\beta = 1/4$.

$$V(t) = \frac{V_{\infty}}{\left[1+\left((V_{\infty}/V_0)^{1/4}-1\right)e^{-0.25rt}\right]^4},$$

Their variant of the model

$$V(t) = (1.1\times10^6)[1+1023e^{-0.25rt}]^{-4}.$$

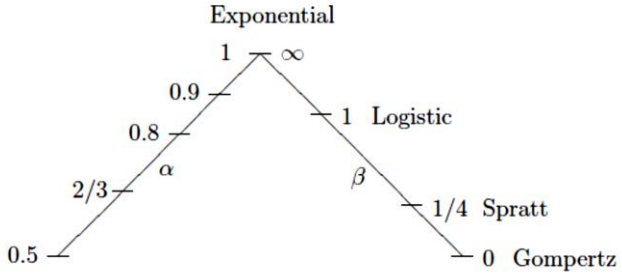
is derived from the volume of a cell and the maximal number of cells a tumor can sustain [1, 12, 13].

The limit as $\beta\to\infty$ yields exponential growth. As $\beta\to0$, we see Gompertzian growth, which is similar to the logistic sigmoidal growth pattern but with a flexible inflection point [2, 5, 8, 9].

$$\frac{dV}{dt} = \alpha(t)V(t); \quad \frac{d\alpha}{dt} = -r\alpha(t).$$

$$V(t) = V_0 \exp\left(\frac{\alpha_0}{r}(1-e^{-rt})\right)$$

As α and β vary, we see that the models lie along a spectrum divided into two branches, representative of limited and unlimited growth. The following graphic relates the models we focused on in greater detail and potential for clinical application.



Note that all of the growth formulas are of the form

$$\frac{V'(t)}{V(t)} = rf(V(t))$$

In other words, the growth rate can be modified and expressed as a function or a proportion of the total maximal growth, or ideal growth under optimal conditions.

Clinical Data

We obtained measurements of tumor growth from the work of Nakamura, Laasonen, Heuser, Saito, and Nakajima [3, 4, 6, 7, 10]. In all cases the data represents measurements taken at two

time points. The first corresponds with initial diagnosis of the tumor, and the second corresponds to delayed treatment. For breast cancer, we see the mammograms when the tumor was detected and then when it became more visible. Because of this data collection method, there is some degree of bias in data collection. As a potential confounding factor, some of the patients were too sick to receive treatment, or otherwise refused treatment. We are able to generalize within groups, but it is difficult to draw broad conclusions because of the large number of variables. We are seeking to understand and measure or control for variability due to location of the tumor, but demographic factors (such as the patient's age, medical history, and lifestyle) are unknown.

Our biggest challenge was developing a systematic method for implementing continuous-time models when only two (time, volume) points are known. To address this systematically, we used the solutions to the differential equations to approximate the tumor's growth rate. We then assessed the model fit via the growth rate constant, *r*, as a function of volume [1]. To evaluate our models, then, the "best" model was able to provide the most constant growth parameter. Statistically, this was the least correlated with volume. We implemented a basic two-tailed t test to check if the slope of *r* vs. *V* was statistically significantly different from 0 at a 0.05 and 0.1 significance level. Models with a slope that deviated significantly from 0 were not considered a good fit.

After we classified the equations as suitable or non-suitable for a particular tumor or data group, we investigated the values of the rate constant. We used the "average" *r* at the "average" tumor volume as follows.

$$\hat{r}_E = \frac{\log V(t_2) - \log V(t_1)}{t_2 - t_1} = r \cdot \frac{1}{t_2 - t_1} \int_{t_1}^{t_2} f(V(s))ds$$

Where $\int_{t_1}^{t_2} f\big(V(s)\big)ds \approx (f(V_1)+f(V_2))/2$

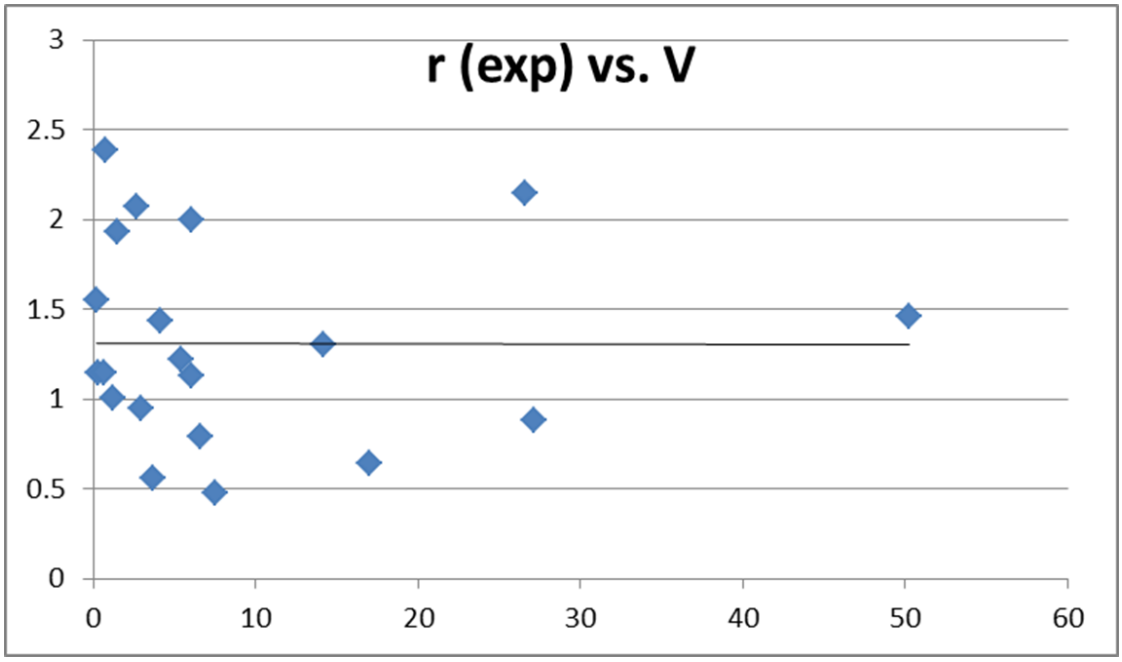
Analysis of the Models

Here we present the data for tumor growth *in vivo* and our analysis through the spectrum of limited and unlimited growth models.

Heuser (breast cancer)

Model	Significance	Normalized slope vs. V_1
.5	0.001**	0.478
2/3	0.011**	0.386
.8	0.092*	0.274
.9	0.396	0.148
Exp	0.915	-0.019
Spratt	0.669	0.078
Gompertz	0.206	0.209

Here and in the subsequent tables, * indicates significance at 0.1 and ** indicates significance at 0.5.

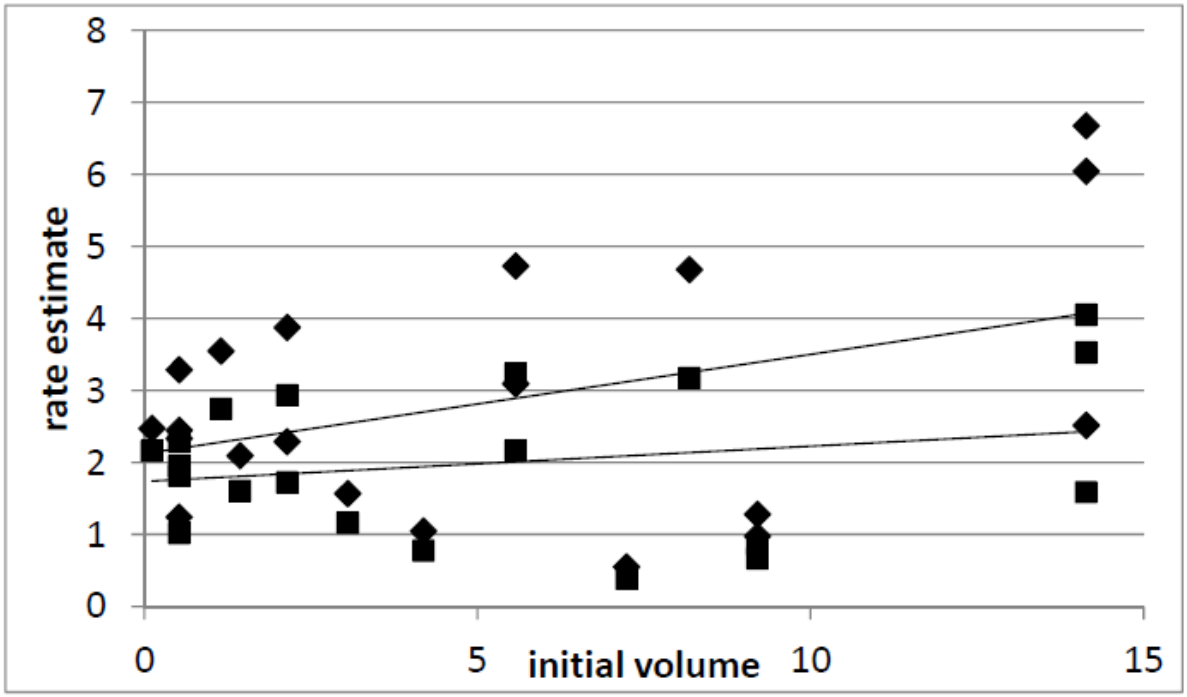


We can graphically confirm the result in the table for the exponential model. Tumor growth rate for the breast cancer data is not significantly influenced by tumor volume. This model is a good fit because *r* does not have to compensate for the value of *f(V)* being too low or too high, and thus increase or decrease with volume.

Saito (hepatocellular carcinoma)

Model	Significance	Normalized slope vs. V_1
.5	0.001**	0.537
2/3	0.004**	0.466
.8	0.021**	0.380
.9	0.032**	0.293

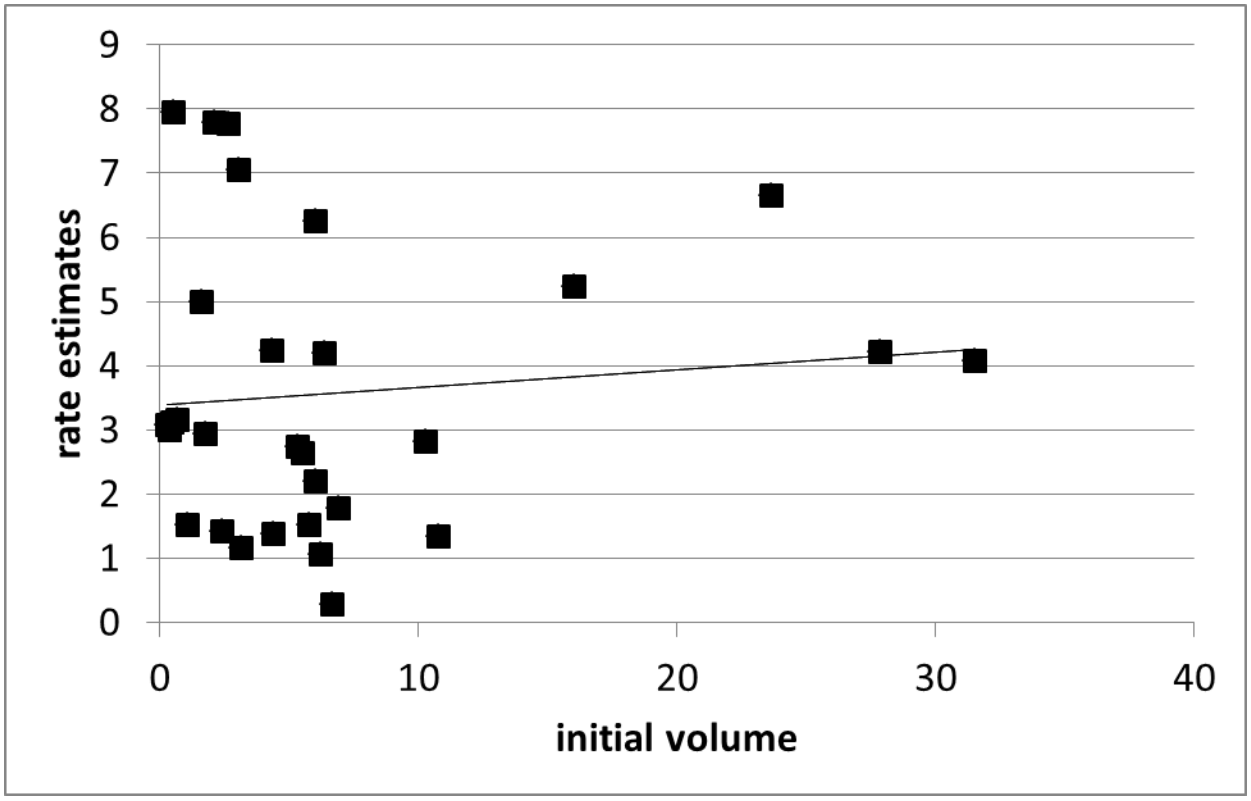
Exp	0.327	0.170
Spratt	0.880	0.291
Gompertz	0.379	0.382



In this comparison of the exponential (squares) and Spratt (diamonds) values of *r* for the Saito data set, we see regression lines with slopes 0.0488 and 0.1337, respectively. Note that the Spratt rate estimates are increasingly larger, and this discrepancy increases as the initial size of the tumor increases.

Nakajima (neurinoma)

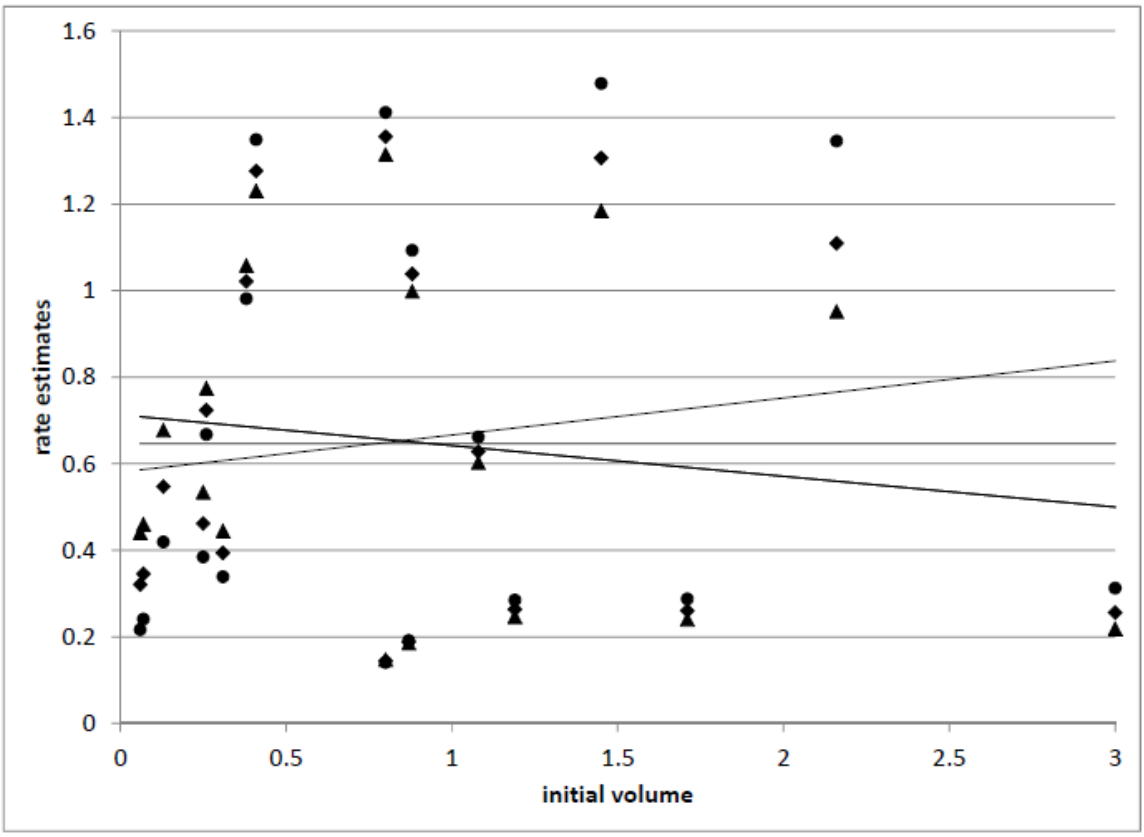
Model	Significance	Normalized slope vs. V_1
.5	0.0005**	0.616
2/3	0.0057**	0.522
.8	0.0463**	0.409
.9	0.196	0.286
Exp	0.6061	0.107
Spratt	0.1503	0.312
Gompertz	0.0324**	0.428



Like the Heuser data set, the exponential model has a slope that deviates the least from 0 in the Nakajima data.

Laasonen (neurinoma)

Model	Significance	Normalized slope vs. V_1
.5	0.577	0.155
2/3	0.997	0.00128
.8	0.565	-0.1622
Exp	0.091*	-0.454
Spratt	0.1647	-0.375
Gompertz	0.3794	-0.244

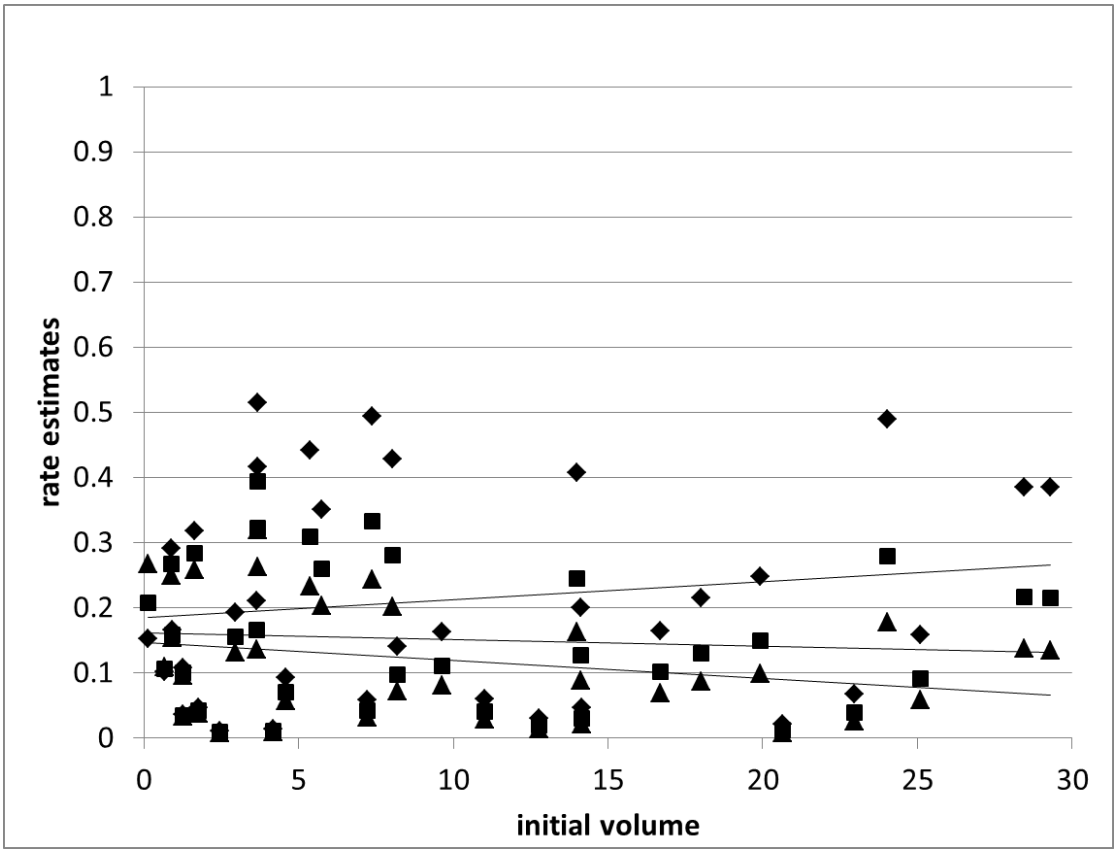


Here we notice that the slopes decrease as the power increases. At α=0.5, the power is too low (positive slope), and at α=0.8, the power is too high (negative slope). This data set is best modeled by a 2/3 power law.

Nakamura (meningioma)

Model	Significance	Normalized slope vs. V_1
.5	0.377	0.1582
2/3	0.635	-0.074

.8	0.116	– 0.246
Exp	0.009**	– 0.263
Spratt	0.041**	– 0.316
Gompertz	0.151	– 0.233



Like the Laasonen data, the Nakamura data is best fit to a 2/3 power law as illustrated by the decreasing slopes.

Value of the rate parameter

We previously determined that the fixed value of the rate parameter is constant for a particular data set, for a particular model. We then considered the possibility of constant rates between data sets, or similar values between models.

As we see below, the normalized data is comparable to an extent. However, the values are more similar between models for a particular data set than between data sets for a particular model. From this, we conclude that there are significant factors affecting the tumor development in each category, or distinct methods of data collection unique to each study that renders them generally incomparable. We must therefore focus on trends rather than fixate on exact values. The ability of the growth parameter to remain constant is more important than the precise calculation, which can vary with each study conducted.

Rate parameter estimates for each model and data set:

	Nakamura	Laasonen	Heuser	Saito	Nakajima
$\tilde{r}_{0.5}$	0.1034	0.8592	1.3442	2.6656	4.8215
$\tilde{r}_{2/3}$	0.0833	0.7238	1.0969	2.2387	4.0708
$\tilde{r}_{0.8}$	0.0845	0.6704	0.9948	2.0585	3.7296
$\tilde{r}_{0.9}$	0.0856	0.6593	0.9607	1.9953	3.6074
$\tilde{r}_{E}$	0.0896	0.6617	1.0514	1.9896	3.5957
$\tilde{r}_{S}$	0.0841	0.6700	1.1533	2.0408	3.6888
$\tilde{r}_{G}$	0.0158	0.6588	1.1847	2.1666	3.9164

In summary, we observed that in the case of breast cancer and brain cancer, an exponential model seems appropriate, whereas for neurinomas, a power law is appropriate where $\alpha=2/3$.

Conclusions

We have observed that exponential and power law models seem to describe the progression of tumors in the patients we studied. We speculate that these tumors are in an early growth phase, and relatively small compared to Spratt's projection of an asymptote, so they have not likely encountered resource shortage in this stage. Further experimentation or data collection would be necessary to draw further conclusions about the usefulness of the models. Controlling the groups of patients poses logistical and ethical constraints, and data we obtained from *in vivo* mouse trials is not necessarily comparable to the human body, so this would be an area with room for further exploration. We are also speculating about a detection model. This idea has been discussed and is potentially useful because tumors can stop growing, be missed, or be benign; the power of technology plays an important role in determining which tumors are critical to model as a potential health threat. Finally, we are proposing a further developed system of ODEs that accounts for immune response, and ways in which cellular interactions inhibit (or promote) the growth of tumors. Understanding phenomena in cancer biology mathematically can help contribute to a mechanistic understanding of current medical mysteries.

References

1. Chingola, R., and Foroni, R.I. (2005) Estimating the growth kinetics of experimental tumors from as few as two determinations of tumor size: Implications for clicnical oncology. *IEEE Transactions on Biomedical Engineering.* 52, 808–815
2. Gompertz, B. (1825) On the nature of the function expressive of the law of human mortality, and on a new mode of determining the value of contingencies. *Phil. Trans. Roy. Soc.* 115, 513-583
3. Hueser, L., Spratt, J.S., and Polk, H.C. Jr. (1979) Growth rates of primary breast cancers. *Cancer.* 43, 1888-1894
4. Laasonen, E.M., and Troupp, H. (1986) Volume growth of acoustic neurinomas. *Neuroradiology.* 28, 203–207
5. Laird, A.K. (1963) Dynamics of tumor growth. *British J. Cancer.* 18, 490–502
6. Nakajima, T., et al. (2002) Simple tumor profile chart based on cell kinetic parameters and histologic grade is useful for estimating the natual growth rate of hepatocellular carcinoma. *Human Pathology.* 33, 92–99
7. Nakamura, M., Roseer, F., Michel, J., Jacobs, C., and Samii, M. (2003) The natural history of incidental meningiomas. *Neurosurgery.* 53, 62–71
8. Norton, L. (1988) A Gompertzian model of human breast cancer growth. *Cancer Research.* 48, 7067–7071
9. Norton, L, Simon, R., Brereton, H.D., and Bogden, A.E. (1976) Predicting the course of Gompertzian growth. *Nature.* 264, 542–545
10. Saito, Y., et al. (1998) Multiple regression analysis for assessing the growth of small hepatocellular carcinomas. *J. Gastroenterology.* 33, 229–235

11. Sarapata, E.A., and de Piliis, L.G. (2014) A comparison and catalog of intrinsic tumor growth models. *Bulletin of Mathematical Biology*, to appear

12. Spratt, J.A., von Fournier, D., Spratt, J.S., and Weber, E.E. (1992) Decelerating growth and human breast cancer. *Cancer*. 71, 2013-2019

13. Spratt, J.A., von Fournier, D., Spratt, J.S., and Weber, E.E. (1992) Mammographic

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