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CHARACTERIZATION OF GLIOBLASTOMA GROWTH USING FIVE DIFFERENT MATHEMATICAL MODELS

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INTRODUCTION

Glioblastoma multiforme is the most common and most malignant primary brain tumor. Optimal therapy results in survival time of 15 months for newly diagnosed cancer and 5-7 months for recurrent disease [1]. Malignant glioma patients demonstrate limited response to conventional therapies which include surgery, radiation, and/or chemotherapy. New and improved methods of therapy are urgently needed. Physiological experiments using animal models are often used to study new chemotherapeutic agents. These studies are quite effective but often expensive and time consuming. Mathematical models are often used to augment physiological experiments. These models can both increase our understanding of tumor growth, as well as aid in the development and preliminary testing of treatment options [2]. In this research five ordinary differential equation models were used determine the cancer growth characteristics. Model parameters for glioblastoma multiforme were determined for each model and the best fitting model was identified.

METHODS

Five classical mathematical models were used to simulate tumor growth, the exponential, logistic, generalized logistic, Gompertz and von Bertalanffy models.

Exponential $$\frac{\mathrm{dV}}{\mathrm{dt}} = aV \quad (1)$$

Logistic $$\frac{dV}{dt} = aV\left(1 - \frac{V}{K}\right) \quad (2)$$

Generalized logistic $$\frac{dV}{dt} = aV\left(1 - \left(\frac{V}{K}\right)^{\upsilon}\right) \quad (3)$$

Gompertz $$\frac{dV}{dt} = ae^{-\beta t}V \quad (4)$$

Von Bertalanffy $$\frac{dV}{dt} = aV^{\gamma} - bV \quad (5)$$

For all the models V is the volume of the tumor in mm^3 and t is the time in days. The proliferation rate is a and K is the carrying capacity. In the Gompertz model the proliferation rate changes so a is the initial proliferation rate and β is the rate of exponential decay of this proliferation rate. Each of the ODEs was solved explicitly or using ode45 function in MATLAB.

In order to determine the unknown model parameters the modeled tumor growth behavior was compared to the results of data collected experimentally. An in-vivo experiment was previously conducted at Wake Forest University School of Medicine by one of our collaborators. In this study Luciferase-expressing G48a human GBM tumors were grown in nude mice [3]. Data from the control group (no treatment) was analyzed to determine the tumor growth rate. IVIS imaging data from the experiment is shown in Figure 1.

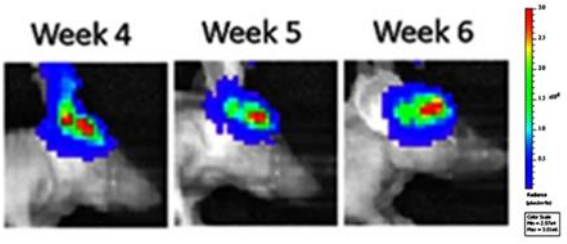

Figure 1: IVIS images of one of the nude mice with xenograft of human GBM tumor [3]

IVIS imaging measures the total photon flux emitted from the tumor. For the cell line used in the experiment there were 6.6 cells per photon, so the number of tumor cells could be estimated. The diameter of a glioblastoma cell was approximated to be $5x10^{-6}$ mm. Using this value, the tumor volume at each time step was calculated.

The tumor growth rate predicted by each mathematical model was compared to the growth rate found experimentally using an optimization cost function,

$$S = \sum (V_{e,i} - V_{m,i})^2$$

The tumor volume determine experimentally, $V_{e,i}$, at each time step, i, was compared to the modeled volume at each time step, $V_{m,i}$.

RESULTS

By minimizing the optimization cost function the unknown model parameters were found for each model. These model parameters characterize the growth rate of glioblastoma multiforme tumors under the conditions described in the experiment [3] and are shown in Table 1. The optimal model parameters were found using the MATLAB optimization tool box functions $lsqcurvefit$ and $fminsearch$. The goodness of fit for each model was also calculated (Table 1). Optimized mathematical models and experimental data are shown for each model type (Figure 2).

Table 1: Characteristic Model Parameter

Mathematical Model	Unknown Parameter	Unit	Parameter Values	Fit %
Exponential	a	[day^{-1}]	0.2265	92%
Logistic	a	[day^{-1}]	0.2655	84%
	K	[mm^3]	1322	
Generalized Logistic	a	[day^{-1}]	1400	86%
	K	[mm^3]	1300	
	υ	-	$4.56*10^{-5}$	
Gompertz	α	[day^{-1}]	0.2409	95%
	β	[day^{-1}]	0.0036	
Von Bertalanffy	a	[mm$^{3(1-\gamma)}$.day^{-1}]	0.7057	90%
	b	[day^{-1}]	0.5774	
	γ	-	0.9664	

DISCUSSION

The result from the optimized mathematical models is consistent with previous research results that modeled the growth of lung and breast cancer [4]. All models fit the experimental data well with fit data ranging from 84% to 95%. The best fitting model for glioblastoma growth was the Gompertz model.

With the characteristic parameters for untreated glioblastoma multiforme known, the next phase of the research will be to model the effects of chemotherapeutic agents on the growth rate. New models are currently being developed that characterize both the tumor growth and decay rates during chemotherapy.

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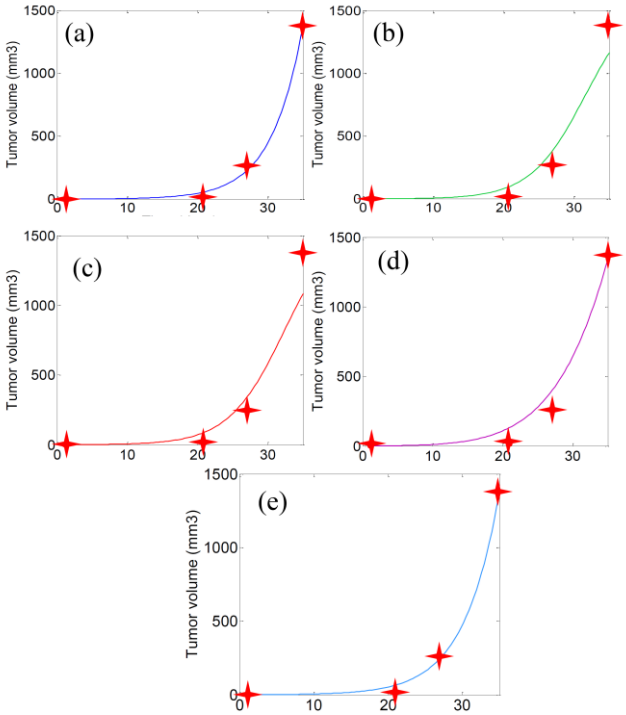

Figure 2: Tumor volume growth (vertical axis) vs. time (horizontal axis): (a) Exponential model (b) Logistic model (c) Generalized Logistic model (d) Von Bertalanffy model (e) Gompertz model, and the experimental data

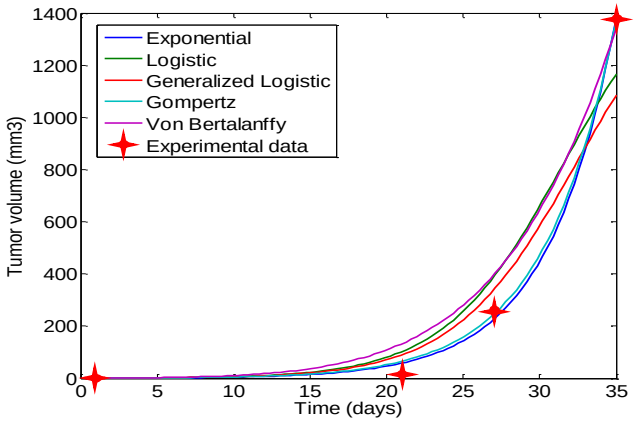

Figure 3: All the mathematical models and the experimental data (stars)

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