Progress in Fractional Differentiation and Applications
An International Journal

http://dx.doi.org/10.18576/pfda/010401

Modeling Tumor Volume with Basic Functions of Fractional Calculus

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Received: 26 Jul. 2015, Revised: 7 Aug. 2015, Accepted: 8 Aug. 2015
Published online: 1 Oct. 2015

Abstract: In this paper, we introduce fractional sigmoidal curves and estimate their parameters to fit the given tumor volume data. We outline approximation techniques to choose the appropriate functions of discrete, discrete fractional and continuous fractional calculus. We demonstrate how to replace the exponential function e^{-ct} in the existing continuous time models with these functions. We use the tumor volume data which were taken over consecutive seventeen days, for twenty eight mice. We then compute residual sum of squares, standard error of the estimate, adjusted coefficient of multiple determination, and cross-validation methods to compare models on data fitting and predictive performances. Estrus cycle stages of measurement are also taken into account when comparing the models.

Keywords: Discrete fractional calculus, sigmoidal curves, data fitting.

1 Introduction

Tumor volume, a relationship between tumor size and time, is of special interest since volume estimation is very critical in a clinical practice. Determining and modeling tumor volume are useful and quantitative ways to monitor tumor progression. There are some mathematical models which describe tumor volumes and have prediction capabilities. Typically, there are three ways to model non-complex growth behavior: Exponential, logistic and sigmoidal. In 1825, Benjamin Gompertz introduced the Gompertz function in [1], a sigmoid function, which is found to be applicable to various growth phenomena, in particular tumor growth ([1], [2], [3], [4], [5]). Beside the Gompertz model which includes three parameters, Weibull and Richards models with four parameters are known as sigmoidal models.

Our aim in this paper is to introduce discrete, continuous fractional and discrete fractional models of the tumor volume and estimate parameters of these models in order to have better data fitting. It is important to point out that determining tumor volume over time can give a general overview of tumor destruction dynamics. Hence the models we develop here can be used to help physicians to choose the most appropriate treatment for patients and animals with malignant solid tumors.

We organize the paper as follows: In Section 2, we give a brief introduction about Mittag-Leffler functions of fractional calculus. Next, we introduce four types of sigmoidal curves with these functions, namely, continuous, discrete, continuous fractional, and discrete fractional for each of the sigmoidal curves of Gompertz and Logistics with three parameters and Richards and Weibull with four parameters. We first demonstrate fitting the mean data with the four curves in order to give the reader a feeling about how the models fits the raw data. Since a complete comparison of the fittings is mostly not possible with graphs, we use some statistical techniques. We compare continuous, discrete, continuous fractional, and discrete fractional forms of these sigmoidal curves by using the data on the tumor volume for twenty-eight controlled mice. These controlled and age-matched female CD_2F_1 mice had inoculated tumors but did not receive any subsequent treatment. Tumor volume was measured at 14HALO (hours after light on) daily until day 17 (for detailed information on the materials and methods used to measure the tumor volume see [6]. We use statistical computation techniques such as residual sum of squares, standard error of the estimate, adjusted coefficient of multiple determination, and cross-validation to compare fitting and predictive performances of these models. Besides the measurements on tumor volume, each mouse

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was observed on the estrus cycle stage of measurement. We compare the performance of different models by considering the estrus cycle stages. In Section 3, the results of the study are presented and analyzed. We close the paper with a discussion section.

2 Model Description

In the literature, continuous forms of the sigmoidal curves are used intensively in regression and data fitting analysis. In this section, we outline how to choose appropriate functions of discrete calculus and fractional calculus to replace the exponential function e^{-ct} which appears in the continuous forms of the sigmoidal curves.

First we recall some basic functions of fractional calculus.

The Mittag-Leffler function is named for Gösta Mittag-Leffler who defined and studied the special function [7]. The function is a direct generalization of the exponential function e^x, and it plays a major role in fractional calculus. The one and two-parameter representations of the Mittag-Leffler function can be defined in terms of a power series as

$$E_\alpha(x)=\sum_{k=0}^{\infty}\frac{x^k}{\Gamma(\alpha k+1)},$$

$$E_{\alpha,\beta}(x)=\sum_{k=0}^{\infty}\frac{x^k}{\Gamma(\alpha k+\beta)},$$

where α and β are positive real numbers. The Mittag-Leffler function with two-parameters was first defined by Wiman in [8].

We shall define the discrete Mittag-Leffler function with one and two-parameters in the following way. Related definitions are given by Nagai [9].

$$F_\alpha(at)=\sum_{k=0}^{\infty}\frac{a^k t^{\overline{k}}}{\Gamma(\alpha k+1)},$$

$$F_{\alpha,\beta}(at)=\sum_{k=0}^{\infty}\frac{a^k t^{\overline{k}}}{\Gamma(\alpha k+\beta)},$$

where α and β are positive real numbers and $|a|<1$. For any real number ν, the discrete Mittag-Leffler function was defined in [10]

$$F_{\alpha,\beta}(at^{\overline{\nu}})=\sum_{k=0}^{\infty}\frac{a^k t^{\overline{k\nu}}}{\Gamma(\alpha k+\beta)},$$

where the raising factorial power function $t^{\overline{\nu}}$ is defined by

$$t^{\overline{\nu}}=\frac{\Gamma(t+\nu)}{\Gamma(t)}.$$

2.1 Fractional Sigmoidal Curves

By use of the Mittag-Leffler functions, we present four different forms of the sigmoidal curves. Our study will include Gompertz, Logistics, Richards and Weibull models. Let $0<\alpha\leq 1$.

Continuous, discrete, continuous fractional, and discrete fractional forms of Gompertz curve are as follows:

$$Y(t)=e^{\ln a-e^{b}(e^{-c})^{t}} \qquad (continuous)$$

$$Y(t)=e^{\ln a-e^{b}(1-c)^{t}} \qquad (discrete)$$

$$Y(t)=e^{\ln a-e^{b}\sum_{n=0}^{\infty}(-c)^{n}\frac{t^{(n+1)\alpha-1}}{\Gamma((n+1)\alpha)}} \qquad (continuous\ fractional)$$

$$Y(t)=e^{\ln a-e^{b}\sum_{n=0}^{\infty}(-c)^{n}\frac{(t-n+1)^{\overline{(n+1)\alpha-1}}}{\Gamma((n+1)\alpha)}}. \qquad (discrete\ fractional)$$

Similarly continuous, discrete, continuous fractional, and discrete fractional forms of Logistic curve are as follows:

$$Y(t) = \frac{a}{1+e^{b}(e^{-c})^{t}} \qquad (continuous)$$

$$Y(t) = \frac{a}{1+e^{b}(1-c)^{t}} \qquad (discrete)$$

$$Y(t) = \frac{a}{1+e^{b}\sum_{n=0}^{\infty}(-c)^{n}\frac{t^{(n+1)\alpha-1}}{\Gamma((n+1)\alpha)}} \qquad (continuous\ fractional)$$

$$Y(t) = \frac{a}{1+e^{b}\sum_{n=0}^{\infty}(-c)^{n}\frac{(t-n+1)^{\overline{(n+1)\alpha-1}}}{\Gamma((n+1)\alpha)}}. \qquad (discrete\ fractional)$$

Gompertz and Logistics curves are known as sigmoidal curves with three parameters, a, b and c. In the continuous fractional and discrete fractional forms, α is also considered as a parameter.
Continuous, discrete, continuous fractional, and discrete fractional types of Richards curve are as follows:

$$Y(t) = \frac{a}{(1+e^{b}(e^{-c})^{t})^{\frac{1}{d}}} \qquad (continuous)$$

$$Y(t) = \frac{a}{(1+e^{b}(1-c)^{t})^{\frac{1}{d}}} \qquad (discrete)$$

$$Y(t) = \frac{a}{(1+e^{b}\sum_{n=0}^{\infty}(-c)^{n}\frac{t^{(n+1)\alpha-1}}{\Gamma((n+1)\alpha)})^{\frac{1}{d}}} \qquad (continuous\ fractional)$$

$$Y(t) = \frac{a}{(1+e^{b}\sum_{n=0}^{\infty}(-c)^{n}\frac{(t-n+1)^{\overline{(n+1)\alpha-1}}}{\Gamma((n+1)\alpha)})^{\frac{1}{d}}}. \qquad (discrete\ fractional)$$

Continuous, discrete, continuous fractional, and discrete fractional types of Weibull curve are as follows:

$$Y(t) = a - b(e^{-c})^{t^{d}} \qquad (continuous)$$

$$Y(t) = a - b(1-c)^{t^{d}} \qquad (discrete)$$

$$Y(t) = a - b(\sum_{n=0}^{\infty}(-c)^{n}\frac{t^{(n+1)\alpha-1}}{\Gamma((n+1)\alpha)})^{t^{d-1}} \qquad (continuous\ fractional)$$

$$Y(t) = a - b(\sum_{n=0}^{\infty}(-c)^{n}\frac{(t-n+1)^{\overline{(n+1)\alpha-1}}}{\Gamma((n+1)\alpha)})^{t^{d-1}}. \qquad (discrete\ fractional)$$

Richards and Weibull curves are known as sigmoidal curves with four parameters, a, b, c and d. In the continuous fractional and discrete fractional forms, α is also considered as a parameter.

2.2 Fitting mean data

In order to give the reader some idea about the distribution of the data points over a time interval (17 days) we plot mean tumor volume of twenty-eight mice by each day (y-value) and standard deviations of volume are represented by bars (see Figure 1). In fitting data, we use four different forms (continuous, discrete, continuous fractional, and discrete fractional) of each type of curves Gompertz, Logistic, Richards, and Weibull. Thus, for easy presentation, we call these curves as sub-models. We then try to fit different curves to mean tumor volume. In terms of residual sum of squares, continuous fractional Gompertz, continuous fractional Logistic, continuous Richards, and continuous Weibull sub-models fit the data best and these fits are plotted in Figure 1. In terms of notation, $y\_hat\_G, y\_hat\_L, y\_hat\_R$, and y_hat_W stand for fitted values using Gompertz, Logistic, Richards, and Weibull, respectively. The comparison of models can somewhat be done by looking at the graphs closely. However, it is hard to distinguish the fits of curves overall. In order to make a good judgment on model comparison, we use statistical methods mentioned earlier in the rest of the paper.

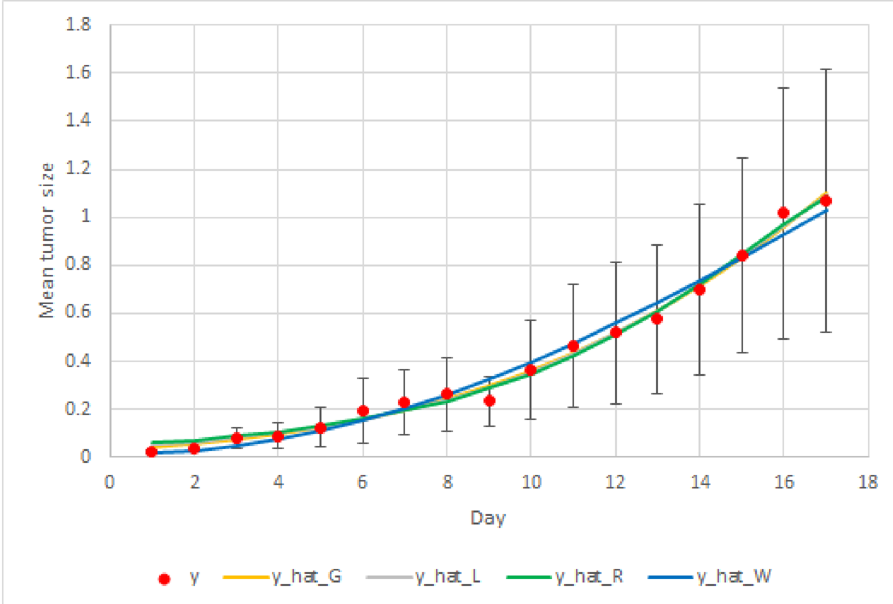

Fig. 1: Mean Tumor Volume with Standard Deviation by Day and Fits of curves

2.3 Model Fitting

To demonstrate how these models give new insights to the existing models, we use the tumor volume data for twenty-eight controlled mice. These controlled and age-matched female CD_2F_1 mice had inoculated tumors but did not receive any subsequent treatment. Tumor size was measured at 14HALO (hours after light on) daily until day 17 (for detailed information on the materials and methods used to measure the tumor volume see [6]).

We use Mathematica to estimate parameters for the continuous and discrete forms of the above curves. We first fix parameter c and compare graphs of the continuous and discrete forms of the curves (Richard and Weibul) to get better parameters a, b, d and α. Then we substitute the same parameters into continuous fractional and discrete fractional curves to find estimated data value $Y(t)$ for each iteration. We also use statistical computation techniques such as residual sum of squares, standard error of the estimate, adjusted coefficient of multiple determination, and cross validation to compare fitting and predictive performance of these models [4]. Residual sum of squares (RSS) is the sum of squares of residual. It is a measure of unexplained variation in tumor volume. In our study, RSS is considered as sum of squares of difference of original value y_i and estimated $Y(t)$ as predicted value, therefore,

$$RSS = \sum_{i=1}^{n} (y_i - Y(t))^2,$$

where n is the number of days observed. A smaller residual sum of squares indicates a better fit of the model to the data.

Standard error of the estimate (SE), which is derived from RSS, takes into account the number of parameters in the models (k) and eliminates the effects of number of observing points on RSS. A smaller value of SE indicates a better model.

$$SE = \sqrt{\frac{\sum_{i=1}^{n} (y_i - Y(t))^2}{n-k}}.$$

The third measure that we use to compare models is the adjusted coefficient of determination (r_a^2). The measure r_a^2 takes into account the percentage of variance in response variable that can be explained by a certain model and 'penalizes' model for using additional parameters. In other words, r_a^2 balance the cost of using more parameters against the gain in percentage of explained variance in tumor volume (r^2). Higher value of r_a^2 means a better fit.

$$r_a^2 = 1 - \frac{n-1}{n-k}(1-r^2),$$

where k is the number of parameters and r^2 is computed by:

$$r^2 = 1 - \frac{\sum_{i=1}^{n} (y_i - Y(t))^2}{\sum_{i=1}^{n} y_i^2 - (1/n)\left(\sum_{i=1}^{n} y_i\right)^2}.$$

RSS, SE and r_a^2 are used to access the fit of model. Sometimes, better fit does not mean good predictive performance because the model might 'overfit' the data by picking up to much random noise. In order to access predictive performance of models, we use k-fold cross-validation method. In k-fold cross-validation, the data is partitioned into k subsets. One of the k subsets is chosen for testing the model, namely validation set, and the remaining $k-1$ subsets are used as training data so it is called training set. The k-fold cross-validation process repeats k times. The advantage of this method is that all observations are used for both training and validation, and each observation is used for validation exactly once. In this study, we choose $k = n$, where n is the number of observations for each mouse and thus in each repetition of fitting models, the validation set contains one observation. We then use the predicted residual sum of squares (PRESS) to measure the ability of models in prediction.

$$PRESS = \frac{\sum_i (y_i - Y(t))^2}{n-1}.$$

A smaller value of PRESS indicates better performance of models in predicting missing value or future value of tumor volume.

3 Results

In Tables 1,2, and 3, we list the number of models with minimum RSS, minimum SE, and maximum r_a^2 which we obtain for the Gompertz, Logistic, Richards and Weibull curves for each mouse. The minimum residual sum of squares could be from continuous (C), discrete (D), continuous fractional (CF), discrete fractional (DF) or some of them at the same time.

Table 1: Number of Models with Minimum RSS

Model Type	*Gompertz*	*Logistic*	*Richards*	*Weibull*
Continuous	7	9	0	11
Discrete	8	14	22	12
Continuous Fractional	5	5	6	0
Discrete Fractional	10	4	0	5
Number of minimum RSS	3	1	16	8

Table 2: Number of Models with Minimum SE of the Estimate

Model Type	*Gompertz*	*Logistic*	*Richards*	*Weibull*
Continuous	12	14	8	14
Discrete	19	18	20	15
Continuous Fractional	0	0	0	0
Discrete Fractional	0	0	0	0
Number of minimum SE	6	17	3	2

In the next step, cross validation method is used to choose the models which are best at predictive performance. We tabulate the results in Table 4 in which each column represents number of minimum PRESS values for each model. Besides the measurements on tumor volume, each mouse was observed on the estrus cycle stage of measurement. Hence

Table 3: Number of Models with Maximum Adjusted Coefficient of Multiple Determination

Model Type	*Gompertz*	*Logistic*	*Richards*	*Weibull*
Continuous	6	9	1	10
Discrete	9	14	20	12
Continuous Fractional	5	5	7	3
Discrete Fractional	10	4	0	3
Number of maximum r_a^2	6	17	3	2

Tables 5, 6, and 7 list the number of times in which minimum residual sum of squares, minimum standard error of the estimate, and maximum adjusted coefficient of multiple determination are obtained for the Gompertz, Logistic, Richards and Weibull curves regarding the estrus cycle phases.

Table 4: Number of Minimum Multiple Residual Sum of Squares in Cross validation

Model Type	*Gompertz*	*Logistics*	*Richards*	*Weibull*
Continuous	5	1	8	10
Discrete	5	4	5	12
Continuous Fractional	10	16	5	1
Discrete Fractional	8	7	10	5

4 Discussion

Based on Table 1, the discrete-type models (discrete and discrete fractional) significantly outperform the continuous-type models (continuous and continuous fractional) in terms of data fitting (producing the minimum RSS) across all types of models we study in this paper. One of the reasons to explain such outcomes is the fact that time is measured on discrete

Table 5: Number of models with minimum RSS taking into account estrus cycle

Estrus Cycle	*Model Type*	*Gompertz*	*Logistic*	*Richards*	*Weibull*
Diestrus	*Continuous*	3	1	0	7
	Discrete	2	7	9	3
	Continuous Fractional	1	2	2	0
	Discrete Fractional	6	1	0	1
	min RSS	1	0	7	3
Metestrus	*Continuous*	1	3	0	1
	Discrete	3	5	7	6
	Continuous Fractional	3	2	1	1
	Discrete Fractional	1	0	0	0
	min RSS	2	0	4	2
Estrus	*Continuous*	3	3	0	1
	Discrete	1	1	3	2
	Continuous Fractional	1	1	3	0
	Discrete Fractional	2	3	0	3
	min RSS	0	1	3	2
Proestrus	*Continuous*	0	2	0	2
	Discrete	2	1	3	1
	Continuous Fractional	0	0	0	0
	Discrete Fractional	1	0	0	0
	min RSS	0	0	2	1

Table 6: Number of models with minimum SE of the estimate taking into account estrus cycle

Estrus Cycle	*Model Type*	*Gompertz*	*Logistic*	*Richards*	*Weibull*
Diestrus	*Continuous*	3	3	2	8
	Discrete	9	9	9	3
	Continuous Fractional	0	0	0	0
	Discrete Fractional	0	0	0	0
	min SE	2	7	2	0
Metestrus	*Continuous*	4	3	2	2
	Discrete	4	6	6	6
	Continuous Fractional	0	0	0	0
	Discrete Fractional	0	0	0	0
	min SE	2	5	0	1
Estrus	*Continuous*	5	6	3	3
	Discrete	3	2	3	4
	Continuous Fractional	0	0	0	0
	Discrete Fractional	0	0	0	0
	min SE	2	3	1	0
Proestrus	*Continuous*	0	2	1	1
	Discrete	3	1	2	2
	Continuous Fractional	0	0	0	0
	Discrete Fractional	0	0	0	0
	min SE	0	2	0	1

Table 7: Number of models with maximum adjusted coefficient of multiple determination taking into account estrus cycle

Estrus Cycle	*Model Type*	*Gompertz*	*Logistic*	*Richards*	*Weibull*
Diestrus	*Continuous*	3	1	0	7
	Discrete	2	7	9	2
	Continuous Fractional	1	2	2	1
	Discrete Fractional	6	1	0	1
	max r_a^2	2	6	2	1
Metestrus	*Continuous*	1	3	0	1
	Discrete	3	5	6	6
	Continuous Fractional	3	2	2	0
	Discrete Fractional	1	0	0	1
	max r_a^2	2	5	0	1
Estrus	*Continuous*	2	3	0	1
	Discrete	2	1	3	2
	Continuous Fractional	1	1	3	2
	Discrete Fractional	2	3	0	1
	max r_a^2	2	3	1	0
Proestrus	*Continuous*	0	2	1	1
	Discrete	2	1	2	2
	Continuous Fractional	0	0	0	0
	Discrete Fractional	1	0	0	0
	max r_a^2	0	2	0	1

scale. Thus the discrete-type models, which more precisely reflect the characteristics of the data, perform better. It also appears that the fractional models (both discrete and continuous) overall are not as good as the non-fractional models in terms of RSS. Within the non-fractional models, discrete models fit the data better. On the other hand, the fractional, discrete, and continuous models are comparative in fitting the data. Comparing across the model types, Richards curves appear to provide the best fit overall. Weibull curves are the second best in terms of fitting performance. Note that both Richards and Weibull models with 4-parameters provide more flexibility in terms of modeling and fitting the data comparing to Gompertz and Logistic models with 3-parameters.

Based on Table 2, taking into account the number of parameters in the models, the discrete models are again significantly better than continuous models in producing minimum SE of the estimate. Also note that none of the fractional models result in minimum SE of the estimate across all types. The important reveal in this table is that Richards curves are no longer the best fit models. Instead, Logistic curves outperform other curves in a wide margin. Thus, it can be concluded that Richards and Weibull curves with 4-parameter are penalized for using an additional parameter comparing to Gompertz and Logistic curves with 3-parameters.

Table 3 shows the number of models with maximum adjusted coefficient of multiple determination within each models. Here also the discrete-type models give better fit for the data. The non-fractional models are again fit better than fractional models. Within non-fractional model, discrete models fit better. For fractional models, discrete and continuous models are comparable in fitting data. Because the adjusted coefficient of multiple determination also penalizes models for using more parameters, Logistic curves appear to give the best fit for the data.

In short, comparing fitting performance of models, it appears that Logistic curves give the best fit in terms of residual sum of squares, standard error of estimate, and the adjusted coefficient of multiple determination. Also, the discrete-type models are seem to be outperformed the continuous-type models regarding all measures considered.

In Table 4, the results for comparing predictive performance among models using cross validation technique of four curves are presented. For all types of curves, fractional models do a better prediction than traditional models with a significant number of fractional models with minimum residual sum of squares. For Gompertz and Logistic curves, continuous-type models are better than discrete-type. On the other hand, for Richards and Weibull curves, discrete-type models perform better than continuous-type in terms of prediction. The four types of curves are comparable in terms of the number of models with minimum PRESS values, and thus are comparable in prediction capacity.

In Table 5, one can see that if we take the estrus cycle into account, the models with 4-parameters still dominate models with 3-parameter in terms of producing minimum residual sum of squares. The discrete models give better result in data fitting compared to continuous counterparts. For every estrus cycle, Richards curves mostly give the minimum residuals sum of squares. The second best is the Weibull curves. Hence, the pattern in model comparison in terms of RSS remains the same regardless of estrus cycles.

In Table 6, by taking the number of parameters in the models into account, Logistic curves prove to be the best curves in producing minimum SE of the estimate. Based on the minimum SE, discrete-type models perform better than continuous-type for all cycles except for estrus phase. Also, as in Table 2, none of the fractional models result in minimum SE compared to the traditional (non-fractional) models.

Table 7 again shows that Logistic curves is the best fit model in terms of adjusted coefficient of multiple determination. The continuous-type models and discrete-type models are comparative in terms of fitting for all estrus phases. Overall, the traditional models result in better fit than the fractional models.

Based on the above observations, this paper illustrates that beside the continuous models there are other models such as discrete, discrete fractional and continuous fractional which may serve better for modeling and data fitting.

Acknowledgement

This research supported in part of a grant from Kentucky Science and Engineering Foundation as per Grant Agreement KSEF-2488-RDE-014 with the Kentucky Science and Technology Cooperation.

Table 8: RSS for Gompertz, Logistic, Richards and Weibull Curves

id#	*Gompertz Curve*	*Logistic Curve*	*Richards Curve*	*Weibull Curve*	*Percentage of Reduction in RSS*
21	.09320807348 *C and D*	.07720652925 *D*	**.06293114988** *D*	.07048076018 *D*	32.48315566%
22	.3334575178 *C F*	.3258675032 *D*	**.3150651669** *D*	.7207975288 *C*	56.2893663877%
23	.099979266879 *D F*	.09474826414 *D*	**.09468867515** *D*	.1832135621 *C*	48.3178679216%
26	.01504232032 *D*	.01325261841 *C and D*	.01155143364 *D*	**.01112150576** *D*	26.0652244906%
27	**.05129960785** *C F*	.05247699452 *C F*	.05359189805 *D*	.05379376776 *D*	4.63652176425%
28	.09877841550 *D F*	.09269992014 *D*	**.09265786241** *D*	.4856070681 *C*	80.919169325%
29	.006858511228 *D F*	.006022041787 *D*	.006019138354 *D*	**.005935668825** *D*	13.4562160158%
30	.08160721610 *D*	.07976180993 *C*	**.0797249954** *D*	.09005716682 *C*	11.4729030291%
31	.08094056469 *D*	.07471837868 *D*	.07354750628 *D*	**.07221120207** *D*	10.78490452%
32	.00979888886 *D F*	.008848677223 *D*	**.008837102086** *D*	.01210950143 *D*	27.0234027628%
33	.04977301896 *D F*	.04950751166 *C*	**.04900239451** *D*	.05395346556 *D*	9.17655798124%
34	.3197937942 *C*	.3125897049 *D*	**.2951961514** *D*	.3196207032 *D*	7.691719866%
35	.04155372344 *C*	.03150005505 *C*	**.02468561651** *D*	.03038951321 *C*	40.59349087%
136	**.02069668479** *C*	.02091409925 *C F*	.02136563279 *C F*	.02133241926 *C*	3.130953371%
137	.2605491124 *C*	.2552786642 *C and D*	**.2517539004** *D*	.2526146358 *D F*	3.375644583%
138	.1689272298 *D F*	.1511871712 *D*	**.1510039993** *D*	.2413181123 *C*	37.4253354376%
139	.1444468940 *C*	.1389586529 *C*	**.1293800537** *D*	.1299003389 *D F*	10.43071255%
140	.05338370310 *D F*	.05156530341 *D F*	**.0512836781** *D*	.1677970703 *C*	69.437083729%
141	**.02861367403** *C F*	.02903453028 *C F*	.02963366498 *C F*	.02903453028 *D F*	3.44200068%
142	.003657090481 *D*	.003026069415 *D*	.003023604093 *D*	**.00259380003** *C*	29.0747646667%
143	.1279762340 *D F*	.1301131682 *D F*	.1333610592 *C F*	**.1217973994** *D F*	8.670941779%
144	.2024468349 *C and D*	.1942945348 *C*	**.1788737819** *D*	.2167948971 *C*	2.3573053%
145	.2808836341 *C F*	.2850144884 *C F*	.2920227196 *C F*	**.2758650186** *D F*	5.841223937%
146	.2419516991 *D F*	.2325981230 *D*	**.2300531995** *D*	.5407924771 *C*	57.459985254%
147	.03264789880 *D F*	.03702966456 *D F*	.04236747212 *C F*	**.03155296655** *D*	25.525491677%
148	.1113379834 *D*	.1077952924 *C*	**.1041125459** *D*	.1061510149 *D*	6.489642869%
149	.1394980990 *D*	.1242478059 *C and D*	.1140944052 *D*	**.1137031905** *D*	18.491225819%
150	.3029542604 *C F*	**.3004077982** *C F and D F*	.3031836220 *C F*	.3070499722 *D*	2.163222472%

Table 9: SE of the estimate for Gompertz, Logistic, Richards and Weibull Curves

id#	*Gompertz Curve*	*Logistic Curve*	*Richards Curve*	*Weibull Curve*	*Percentage of Reduction in SE*
21	0.081594849925 *C and D*	0.074261376834 *D*	**0.069576272414** *D*	0.073631494192 *D*	14.72958%
22	0.154336629274 *C*	**0.152565560428** *D*	0.155678457306 *D*	0.235469666314 *C*	35.20798%
23	0.084434139067 *D*	**0.082266233370** *D*	0.085344854809 *D*	0.124660537615 *D*	34.00780%
26	0.032778826267 *D*	0.030767118824 *D*	0.029808921793 *D*	**0.029248939179** *D*	10.76880%
27	**0.060533483220** *C*	0.061224688636 *C*	0.064207571384 *C*	0.064327149287 *D*	5.89746%
28	0.084007922165 *D*	**0.081372125861** *D*	0.084424687603 *D*	0.193272837858 *C*	57.89780%
29	0.022136274858 *D*	**0.020739957616** *D*	0.021517682092 *D*	0.021367963875 *C*	6.30782%
30	0.086132675723 *D*	**0.085153236169** *C*	0.089290256770 *C*	0.087633743678 *D*	4.63323%
31	0.076035971135 *D*	**0.073054959096** *D*	0.075215108343 *D*	0.074529912462 *D*	3.92053%
32	0.026433537456 *D*	**0.025140572250** *D*	0.026072535042 *D*	0.030520486726 *D*	17.62722%
33	0.059627328706 *D*	**0.059466384057** *C*	0.061395561422 *D*	0.064422562674 *D*	7.69323%
34	0.151137069812 *C*	**0.149425018201** *D*	0.150689735090 *D*	0.156799897763 *D*	4.70337%
35	0.054480483688 *C*	0.047434206351 *C*	**0.043576296053** *D*	0.048349300536 *C*	20.01485%
136	**0.038449117387** *C*	0.038650741020 *C*	0.040540944327 *C*	0.040508706813 *C*	5.15979%
137	0.141570616356 *C and D*	**0.140131439453** *C and D*	0.144842989820 *D*	0.145091495156 *C and D*	3.41857%
138	0.109861584278 *D*	**0.103918639604** *D*	0.107776120982 *D*	0.136245850268 *C*	23.72712%
139	0.101575761310 *C*	**0.099627396153** *C*	0.099761274165 *D*	0.100632454086 *C*	1.91814%
140	0.061756920555 *D*	**0.060690615567** *D*	0.062958086063 *D*	0.113611033558 *C*	46.58035%
141	**0.045208806727** *C*	0.045539304092 *D*	0.047745170469 *C*	0.047266144584 *C*	5.31229%
142	0.016162324976 *D*	0.014701966377 *D*	0.015250735400 *D*	**0.014125263791** *C*	12.60376%
143	**0.095612974015** *C*	0.096407243244 *C and D*	0.101289673671 *C*	0.097091220391 *D*	5.60442%
144	0.120251770079 *C and D*	0.117805691956 *C*	**0.117300987569** *D*	0.129137641864 *C*	9.16592%
145	**0.141644335876** *D*	0.142682970828 *C and D*	0.149882723333 *C*	0.145838953486 *C*	5.49656%
146	0.131462176282 *D*	**0.128895894593** *D*	0.133027816495 *D*	0.203959361921 *C*	36.80315%
147	**0.048291628800** *D*	0.051433723908 *C*	0.057108511470 *C*	0.049266127035 *D*	15.43882%
148	0.092544369151 *D*	**0.091060120630** *C*	0.093145292375 *D*	0.094052740036 *D*	3.18185%
149	0.118109313350 *D*	**0.111466499855** *C and D*	0.112592877809 *D*	0.112399678973 *D*	5.62429%
150	0.147104191622 *C*	**0.146484858945** *C*	0.152717975366 *C*	0.153685486077 *D*	4.68530%

Table 10: Adjusted coefficient of multiple determination for Gompertz, Logistic, Richards and Weibull Curves

id#	*Gompertz Curve*	*Logistic Curve*	*Richards Curve*	*Weibull Curve*	*Percentage of Improvement in* r_a^2
21	0.875576708450 *C and D*	0.896937141390 *D*	**0.909531267613** *D*	0.898678078451 *D*	3.87797%
22	0.913887734524 *CF*	**0.915847784358** *D*	0.912378723423 *D*	0.799542424038 *C*	14.54649%
23	0.948167714870 *DF*	**0.950787777278** *D*	0.947035552998 *D*	0.886997579679 *D*	7.19170%
26	0.953153210867 *D*	0.958726937939 *C and D*	0.961257684976 *D*	**0.962699618669** *D*	1.00156%
27	**0.959660165654** *CF*	0.958734318747 *CF*	0.954615883310 *CF*	0.954444930632 *D*	0.54642%
28	0.977987636496 *DF*	**0.979342204179** *D*	0.977763236309 *D*	0.883460190639 *C*	10.85301%
29	0.907013671671 *DF*	**0.918354357644** *D*	0.912116315795 *D*	0.913335035644 *C*	1.25033%
30	0.795175126623 *D*	**0.799806887185** *C*	0.779882302617 *C*	0.787973791478 *D*	2.55482%
31	0.730360795520 *D*	0.751088909937 *D*	0.736151266589 *D*	**0.871492336833** *CF*	19.32354%
32	0.967261358913 *DF*	**0.970378634044** *D*	0.968141796391 *D*	0.956344629902 *D*	1.46746%
33	0.978170454133 *DF*	**0.978286900833** *C*	0.976855238854 *D*	0.974516754010 *D*	0.38687%
34	0.887347108563 *C*	**0.889884873537** *D*	0.888012980577 *D*	0.878747166156 *D*	1.26745%
35	0.974393023894 *C*	0.980588474625 *C*	**0.983617619355** *D*	0.979832281166 *C*	0.94670%
136	**0.970745913446** *C*	0.970438605223 *CF*	0.967477329446 *CF*	0.967527886933 *C*	0.33785%
137	0.814855817720 *C and D*	**0.818600957411** *C and D*	0.806197762887 *D*	0.805535161649 *CF*	1.62200%
138	0.960512831514 *DF*	**0.964659615213** *D*	0.961987234579 *D*	0.939252146717 *C*	2.70507%
139	0.933103339405 *C*	**0.935645069393** *C*	0.935471994529 *D*	0.935218223864 *CF*	0.27240%
140	0.968603280203 *DF*	**0.969672741147** *DF*	0.967363269132 *D*	0.893721690468 *C*	8.49829%
141	**0.951442656867** *CF*	0.950730577633 *CF*	0.945843406303 *CF*	0.946938346619 *DF*	0.59198%
142	0.945913528509 *D*	0.955246002801 *D*	0.951842653145 *D*	**0.958688200381** *C*	1.35051%
143	**0.927035094804** *DF*	0.925816734203 *DF*	0.918116119435 *CF*	0.925216223046 *DF*	0.97144%
144	0.867718973914 *D*	0.873045777975 *C*	**0.874131245030** *D*	0.847447158036 *C*	3.14876%
145	**0.918048643639** *CF*	0.916843414599 *CF*	0.908244726297 *CF*	0.913321571961 *DF*	1.07944%
146	0.956885085930 *DF*	**0.958551859222** *D*	0.955851921143 *D*	0.896219878809 *C*	6.95499%
147	**0.966642898452** *DF*	0.962165947689 *DF*	0.953382357482 *CF*	0.965281739943 *D*	1.39089%
148	0.970344274342 *D*	**0.971287897257** *C*	0.969957893780 *D*	0.969369685109 *D*	0.19788%
149	0.910071904661 *D*	**0.919903076710** *C and D*	0.918276126086 *D*	0.918556346494 *D*	1.08026%
150	0.955994398393 *CF*	**0.956364284596** *CF and DF*	0.952573473449 *CF*	0.951968666503 *D*	0.46174%

Table 11: Parameter estimates and SEs for discrete and continuous Gompertz curve for mean data

Model type	*Parameter*	*Estimate*	*Standard error*
Discrete	a	16.859	19.2374
	b	1.83367	0.141244
	c	0.95235	0.0153967
Continuous	a	16.859	19.2374
	b	1.83367	0.141244
	c	0.0488226	0.0161671

A Appendix

In Table 8, the minimum RSS's for each model are presented. On average, the RSS's for Gompertz, Logistic, Richards, and Weibull curves are 0.2346, 0.2263, 0.2212, and 0.3219, respectively. Thus, among the four models, Richards curves result in the smallest average RSS's. It is interesting to note that the average RSS's for Weibull model is bigger than those of 3-parameter Gompertz and Logistic models, hence yields not good fitting on average. However, when considering the number of minimum RSS's, Weibull model results in larger number of minimum sum. This could be explained by the fact that Weibull curves yield minimum RSS's of wider range (more variability) than the ranges of 3-parameter Gompertz and Logistic models. If we compare the absolute values of RSS among models, the difference seems to be small. However, to show that there are a significant improvement using the best model, we compute the percentage of reduction in RSS, which are included in the last column of Table 8. The largest percentage of reduction in RSS is about 81%, which is a prominent and significant improvement in terms of model fitting.

Table 9 and Table 10 are similar to Table 8 with RSS's being replaced by SE of the estimate and adjusted coefficient of multiple determination.

From Table 9, on average, the SE of the estimate for Gompertz, Logistic, Richards, and Weibull curves are 0.0851, 0.0833, 0.0855, and 0.0995, respectively. Thus, among the four models, Logistic curves result in the smallest average SE. Note that average SE for 3-parameter models are smaller than those of 4-parameter models. This shows that SE penalizes the 4-parameter models for using extra parameters. In the last column of Table 9, we compute the percentage of reduction in SE. The largest percentage of reduction in SE is about 57.9%, which shows that there is a significant difference in terms of SE among different models.

From Table 10, on average, the adjusted coefficient of multiple determination for Logistic, Richards, and Weibull curves are 0.9245, 0.9285, 0.9248, and 0.9137, respectively. Logistic curves shows the best fitting performance in terms of both average r_a^2 and the number of models with maximum r_a^2. If the number of models with maximum r_a^2 is considered, Gompertz curves are the second best. While the average r_a^2 of Richards curves is the second largest, the number of models with maximum r_a^2 using Richards curve is far less than that of Gompertz curves. In the last column of Table 10, we compute the percentage of improvement in r_a^2. The largest percentage of improvement in r_a^2 is about 19.3%, which is still a substantial improvement in fitting performance to consider.

One further step is taken where we run a statistical random effect model using the same data. The model takes into account the effect of time on tumor volume. Moreover, since mice are chosen at random, they constitute the random factor in the model. It turns out that the random effect model yields a residual sum of squares of 0.336.

The mean tumor volume of all mice is computed and we fit all models to this mean data. In order to fit the fractional model, we use function(algorithm) named NonlinearModelFit in Mathematica to find the estimates for parameter a, b, and c. Then in the next step, value of α is searched using iteration. The parameter estimates and standard errors for continuous and discrete Gompertz curve for mean data are presented in Table 11.

We also fit all models to the mean tumor volume of mice against time. The result indicates that the continuous fractional Gompertz model fit data best in terms of all statistical measures RSS, SE, and r_a^2. The estimates and standard errors of parameters in continuous and discrete Gompertz curve are listed in Table 11. Except for the intercept, all parameters have small standard errors.

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