EVALUATION OF SOME MATHEMATICAL MODELS FOR TUMOR GROWTH

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A number of mathematical models for tumor growth have been proposed in the past to increase the understanding of the tumor growth process. This study evaluates the exponential, the Gompertz, the Bertalanffy and the logistic models. The data used for the evaluation of the models consists of: the untreated primary carcinoma of the human lung, and induced sarcoma in mice. The non-linear regression method was used for the analysis of the data. The logistic equation gave the best fit in the cases of all seven patients. However, the Bertalanffy equation was the best in seven out of 10 cases of mice. The models were also judged by comparing the percentage error in predicting the volume of a tumor.

Introduction

A tumor growth model is a mathematical expression describing the size of a tumor with respect to time. An ideal mathematical model for tumor growth should satisfy the following criteria:

(1) it should have a physiological basis;
(2) it should have a minimum number of arbitrary constants;
(3) variables described in the model should be measurable so that collection of experimental data is possible;
(4) it should give a good fit to the experimental data;
(5) it should be able to predict the tumor growth with reasonable accuracy;
(6) it should improve general understanding at microscopic as well as macroscopic level of tumor growth; and
(7) it should have breadth, in the sense that it should be applicable to different patients or animals with the same type of tumor. Since cancer is not one disease, it may not be possible to use one model for all types of tumors.

A number of mathematical models have been proposed to represent tumor growth; however, little is available in the way of a comparative study.

This study evaluates four continuous time mathematical models commonly used to describe tumor growth. The models used are: the exponential, the Gompertz, the

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Bertalanffy and the logistic. These are evaluated by comparing the results of: (1) non-linear regression analysis, and (2) the error in predicting a tumor volume. Data on human tumors as well as mouse tumors were used for the analysis.

Analysis of the models

1. Exponential model

This model assumes that the rate of increase in the volume (or number of cells) of a tumor is proportional to the volume (or number of cells) at that time. If the volume of a tumor, at time t is denoted by $V(t)$ and a constant of proportionality by λ, then mathematically

$$\frac{dV}{dt} = \lambda V \tag{1}$$

whose solution is:

$$V(t) = V_0 e^{\lambda t} \tag{2}$$

The time required for volume $V(t)$ to double is referred to as the doubling time DT and is given by:

$$DT = \ln 2/\lambda \tag{3}$$

Thus an exponential model implies constant doubling time.

The exponential model is of importance because it introduced the concept of doubling time. Even though it does not have a strong physiological basis, it starts with a reasonable assumption. It also has few arbitrary constants. However, its shortcomings become apparent when the tumor growth data is analyzed.

2. Gompertz equation

This equation was developed by Gompertz (1825) for studies on human mortality. Albert Casey (1934) was the first to use the Gompertz curve to fit tumor growth. The Gompertz equation in its differential form is given by:

$$\frac{dV}{dt} = V(A/B)\,(1 - (1 - B)\exp(-Bt)) \tag{4}$$

whose solution is

$$V = V_0 \exp[(A/B)\,(1 - \exp(-Bt))] \tag{5}$$

where V is the tumor volume at time t, V_0 is the initial tumor volume and, A and B are arbitrary constants.

The pattern of growth suggested by the Gompertz equation is close to exponential in the early stage but approaches a plateau as the tumor size increases. Such a curve is said to be sigmoid in shape.

In recent years, considerable work has been done using the Gompertz equation. Laird (1964, 1965) analyzed 19 examples of 12 different tumors in mice, rats and rabbits. She concluded that the growth of a transplanted, or primary, tumor is well described by the Gompertz equation. McCredie *et al.* (1965) found that the growth curves were better expressed by the Gompertz equation than by the exponential equation. Simpson-Herren *et al.* (1970) used the Gompertz equation to fit nine experimental tumors. This equation has also been used by Swan and Vincent (1977) for optimal control analysis in the chemotherapy of IgG multiple myeloma.

Even though it is reported that a good fit is obtained using the Gompertz equation, it is not free from shortcomings. One of the major drawbacks is that the equation is not derived from any physiological basis, although Swan (1977) suggests that it may be possible to derive this equation from thermodynamic considerations.

3. Bertalanffy equation

This equation was originally derived by Bertalanffy (1960) to describe animal growth. This equation can also be used to describe a tumor growth process, and in fact is one of the few models that has some basis in metabolic theory and which can be verified using experimental data. For the tumor growth process the derivation is based on the following assumptions:

(1) the growth rate is equal to the difference between the anabolic and catabolic rate;
(2) the rate of total volume loss is proportional to the volume of the tumor;
(3) the mass build up is limited by the capacity for respiration and ingestion. In other words, mass build up is proportional to the surface area; and
(4) the shape of the tumor does not change, and thus the anabolic growth rate is proportional to 2/3 power of the volume of the tumor.

These assumptions are combined in the following equation

$$\frac{dV}{dt} = nV^{2/3} - mV, \tag{6}$$

where n and m are proportionality constants.

Bertalanffy (1960) has shown that the solution of the eqn. (6) is of the following form

$$V = \left[\frac{n}{m} - \left(\frac{n}{m} - c \right) \exp \left(\frac{-mt}{3} \right) \right]^3 \tag{7}$$

where c is a constant. Or equivalently (Fabens, 1965)

$$V = b_1^3(1 - b_2 \exp(-b_3 t))^3 \tag{8}$$

Although this equation has not been widely used to describe the tumor growth process, the results presented here show that it performs quite well for this application.

4. Verhulst-Pearl or logistic equation

Swan (1977) gives the historical background for this equation. He writes that the expression

$$\frac{dN}{dt} = aN - bN^2. \tag{9}$$

where N is the number of cells and, a and b are constants, has been known for a long time. It appears to have been first considered by Verhulst in 1845 and was rediscovered by Pearl in 1924. Swan further writes '... the (N,t) graph is known as the logistic curve, for some unknown reason.'

The eqn. (9) can be written for volume V as

$$\frac{dV}{dt} = aV - bV^2 \tag{10}$$

whose solution is

$$V(t) = \frac{a}{\exp(-at)[(a/V_0) - b] + b} \tag{11}$$

where V_0 is the initial volume.

A comparison of the logistic equation to the Gompertz equation is done by Winsor (1932). The Bertalanffy equation is similar to the logistic equation except for the exponents in eqn. (10). However, there is no clear physiological basis for the selection of the exponents. This equation is highly flexible. If a set of data covers observations of an early stage, showing an approximate exponential increase, then one can choose b to be very small. The logistic equation in such cases is essentially identical to the

exponential equation. On the other hand, if the data cover observations up to the later stage of growth, then it is possible to see a plateau region. In this case, b can be chosen high to account for the retardation in the tumor growth.

Data

Schwartz (1961), in his analysis of exponential tumor growth model, has used growth data for primary carcinoma of the human lung. The same data have been used for the analysis presented here. Since the main interest of this work is the understanding of the course followed by the untreated tumor, it was necessary to neglect some data points.

Dr. K.E. Hellström (pers. comm.) from the Fred Hutchinson Cancer Research Center in Seattle, Washington, provided the data on induced sarcoma in mice.

Fitting of the models

1. Method of parameter estimation

The parameter estimates in this study were obtained using the SPSS non-linear regression package. This program uses Marquardt's method which combines the best features of the Gauss and Steepest descent method.

In order to run the *SPSS NONLINEAR* program it is essential to specify initial parameter estimates. Good initial estimates save considerable computer time.

2. Exponential equation

Equation (2) is a non-linear equation with V_0 and λ as parameters. However, a linear least square fitting problem is obtained if the equation is written in the form

$$\ln V = \ln V_0 + \lambda t \tag{12}$$

Note that this minimizes $\Sigma(\ln v_i - \ln v(t_i))^2$ rather than $\Sigma[v_i - v(t_i)]^2$. Therefore parameter values obtained by fitting eqn. (12) were only used to get initial values for the *SPSS* program.

3. Gompertz equation

For the Gompertz equation (eqn. 5) one needs to specify the initial estimates for parameters V_0, A and B. A good estimate for V_0 is the same as the volume at time $t = 0$. In cases where volume V suddenly jumps from a small value V' at $t = 0$ to a high value V'' for t less than a week, it is desirable to use the average of V' and V'' as an initial estimate. A value between 0.1 and 0.01 is generally a good starting point for B, whereas the starting value of A should be chosen after fitting the exponential equation. If this is done then A should be set equal to λ.

It is difficult to find good starting values for the Gompertz equation. One often has to try several different sets of starting values to achieve convergence.

4. Verhulst-Pearl equation

For eqn. (11) it is required to specify a, b and initial volume V_0. This is a problem of non-linear regression. Good starting values were obtained by first fitting the Gompertz equation to a given set of data. Then using the derivative form of the Gompertz equation to generate derivative values. A linear least squares fit was made using the differential equation form of the Verhulst-Pearl equation (eqn. 10). The value of a and b obtained were then used as initial values in the non-linear regression program for eqn. (11).

5. Bertalanffy equation

The Bertalanffy equation in its differential form (eqn. 6) is similar to the Verhulst-Pearl equation. (eqn. 10) The initial parameter estimation method described for the Verhulst-Pearl equaton also applies to the Bertalanffy equation.

In some cases, after getting the results the models were rerun using slightly different initial parameter estimates. This reduces the possibility of reaching a local minima and subsequently increases the possibility of reaching a global minima.

Predictability of a model

The degree to which a tumor growth model fits a given set of data is not the only measure of the efficacy of the model. Of at least as much importance is the extent to which the equation can predict the future course of a tumor from the early growth data.

To test the predictability, five out of 10 animal cases with at least 10 data points were selected. In each case, the first six data points were used for estimating the

TABLE 1

COMPARISON OF THE LEAST SUM OF SQUARES FUNCTION (HUMAN TUMOR)

Patient	Duration (weeks)	No of data points	LSSEBF	Exponential DLSS (%)	Bertalanffy DLSS (%)	Gompertz DLSS (%)	Logistic DLSS (%)
MM	20.7	9	4.5651E9	233.49	69.30	49.56	0.0
LH	53.0	9	3.1172E8	26.45	236.84	7.66	0.0
AC	11.28	6	1.754E10	20.65	0.62	0.41	0.0
RP	55.0	13	2.2505E8	4.79	24.33	0.0	3.62
JS.I.	15.0	5	3.0007E7	26.08	21.84	0.0	2.14
NC[a]	63.0	7	2.9782E9	93.10	107.03	19.71	0.0
JS.II.	169.28	9	3.1108E6	8.95	226.73	0.0	2.47

[a]Died one week after the last observation.

parameters of the equation to be fitted. The rest of the data points were not used at all. The parameters that gave the best fit to the six data points were used for extrapolating future tumor growth. The extrapolated values were compared to the corresponding actual values, which were unused in this analysis. The percentage difference between the observed volume and the extrapolated volume was calculated. The same procedure was also followed for patient RP.

The results of non-linear regression analysis

Final parameter values and the coefficient of variation are given in Table 3–6. The percentage difference between the least sum of squares function is calculated using the following definition: Let LSSEBF be the least sum of the squares of the errors of the best fitted model. Let LSSEMC be the least sum of the squares of the errors of the model under consideration. Then define the percentage difference between the least sum of the squares of the errors, DLSS, as follows:

$$\text{DLSS} = \frac{\text{LSSEMC} - \text{LSSEBF}}{\text{LSSEBF}} \times 100 \tag{13}$$

It is reasonable to assume that if a model has DLSS less than or equal to 5%, then for all practical purposes the model is as good as the one with 0% DLSS. With this criterion the following conclusions are drawn for the data on human tumors.

TABLE 2

COMPARISON OF THE LEAST SUM OF SQUARES FUNCTION (ANIMAL TUMOR)

Mouse No.	Duration (weeks)	No. of data points	LSSEBF	Exponential DLSS (%)	Bertalanffy DLSS (%)	Gompertz DLSS (%)	Logistic DLSS (%)
5806[a]	4.28	9	4.4137E4	4043.2	189.98	84.91	0.0
5818[a]	5.57	10	2.45E5	431.8	0.0	1.27	14.3
5821[e]	4.43	9	7.4361E4	22.98	87.65	0.0	13.48
5836[a]	6.00	10	2.5818E4	165.57	0.0	70.92	348.80
5845[d]	5.00	9	3.4898E5	42.91	0.0	10.30	30.59
5853[a]	5.14	9	7.7259E4	543.81	0.0	23.65	109.11
5854[a]	5.00	9	1.023E5	825.02	0.0	15.13	69.60
5873[b]	5.00	10	2.9431E5	146.18	0.0	10.24	37.62
5879[c]	6.00	12	2.8789E5	148.48	9.6	6.32	0.0
5894[a]	5.00	10	8.0431E4	1008.8	0.0	23.8	88.6

[a]Mouse died.
[b]Died 10 days after the last observation.
[c]Died 11 days after the last observation.
[d]Died 2 weeks after the last observation.
[e]Died 1 month after the last observation.

Among the four models tried, the logistic equation gives the closest fit to the human tumor data for all the patients. The Gompertz equation gives a good fit for four out of seven cases, whereas the Bertalanffy and the exponential model is found to be good for only one of the seven cases (See Table 1).

For animal tumor data the Bertalanffy equation is found to be best. It gives a good fit in seven out of 10 cases. The Gompertz and the logistic equation give a good fit to only two out of 10 cases, whereas the exponential model not give a close fit in any of the cases (See Table 2).

TABLE 3

BEST FITTED PARAMETERS FOR: EXPONENTIAL EQUATION

Patient	Parameters	
	V_0	λ
MM	34526.38	0.128384
LH	13918.25	0.04954
AC	809187.06	0.080761
RP	4317.21	0.058368
JS.I.	60090.65	0.076237
NC	249490.78	0.03329
JS.II.	318.118	0.025141
Coefficient of variation for epidermoid carcinoma[a]	191.14%	45.83%
Mouse No.		
5806	553.161	0.43515
5818	720.926	0.36371
5821	239.44	0.66733
5836	498.612	0.34731
5845	459.425	0.4633
5853	437.358	0.45585
5854	622.032	0.3409
5873	488.046	0.46047
5879	406.548	0.41483
5894	687.633	0.24892
Coefficient of variation for sarcoma	26.44%	25.0%

[a]Since patient NC has adenocarcinoma, corresponding parameters have been excluded for this calculation.

TABLE 4

BEST FITTED PARAMETERS FOR: BERTALANFFY EQUATION

Patient	Parameters		
	b_1	b_2	b_3
MM	106.558	0.914	0.05884
LH	2241.53	0.9913	0.000321
AC	544.32	0.8316	0.006934
RP	16420.78	0.999	0.0000462
JS.I.	811.81	0.995	0.000153
NC	24966.97	0.997	0.000043
JS.II.	14413.87	0.999	0.0000113
Coefficient of variation for epidermoid carcinoma[a]	119.64%	6.57%	194.7%
Mouse No.			
5806	15.1934	1.1153	0.8132
5818	23.769	0.7463	0.17765
5821	4137.2	0.999	0.000688
5836	19.607	0.7866	0.22
5845	77.738	0.91679	0.030315
5853	27.186	0.8226	0.14014
5854	15.6898	0.6806	0.45117
5873	31.479	0.81865	0.1106
5879	50.692	0.89497	0.04806
5894	12.9282	0.59543	0.76931
Coefficient of variation for sarcoma	279.30%	17.19%	103.03%

[a]Since patient NC had adenocarcinoma, corresponding parameters have been excluded for this calculation.

The results of predictability

The tumor volume was predicted using the exponential, the Bertalanffy, the Gompertz and the logistic model. The values obtained were compared with the actual recorded volume. The percentage error was calculated using the following formula:

$$\% \text{ PREDICTION ERROR} = \left[\frac{\text{Predicted Volume} - \text{Observed Volume}}{\text{Observed Volume}}\right] \times 100 \quad (14)$$

TABLE 5

BEST FITTED PARAMETERS FOR: GOMPERTZ EQUATION

Patient	Parameters		
	V_0	A	B
MM	4272.37	0.5791	0.11088
LH	16861.67	0.03783	–0.00725
AC	769853.43	0.10154	0.03469
RP	3070.86	0.078009	0.00629
JS.I.	58474.1	0.08545	0.013139
NC	227500.58	0.04176	0.006092
JS.II.	465.55	0.019318	–0.001978
Coefficient of variation for epidermoid carcinoma[a]	197.94%	129.06%	155.05%
Mouse No.			
5806	14.126	5.59735	1.0228
5818	259.336	1.156	0.3263
5821	182.140	0.8557	0.07601
5836	121.259	1.40145	0.3639
5845	313.97	0.7873	0.16828
5853	154.237	1.3048	0.31328
5854	171.035	1.8590	0.61385
5873	228.504	1.10147	0.27299
5879	175.926	0.94756	0.20515
5894	185.32	2.23771	0.91853
Coefficient of variation for sarcoma	42.29%	78.88%	79.91%

[a]Since patient NC had adenocarcinoma, corresponding parameters have been excluded for this calculation.

Tables 7–12 show the time, the observed volume and the percentage prediction error for each model.

Criterion for acceptable limits for the percentage error in prediction

A model will be considered to give satisfactory prediction results if the prediction error in volume is less than 10% in each forecasted value. The error can be either positive or negative.

Since first the diameter measurements are taken and then converted to volume, it is essential to know how the criterion translates into linear measurements. It can be

TABLE 6

BEST FITTED PARAMETERS FOR: LOGISTIC EQUATION

Patient	Parameters		
	a	V_0	b
MM	0.286	9668.4	5.41E-7
LH	0.0379	17046.72	−1.18E-7
AC	0.1185	769669.0	2.61E-8
RP	0.6433	3854.58	7.27E-8
JS.I.	0.8912	58666.45	1.04E-7
NC	0.419	227911.91	8.24E-9
JS.II.	0.0230	389.52	−1.89E-7
Coefficient of variation for epidermoid carcinoma[a]	97.93%	196.08%	320.33%
Mouse No.			
5806	1.758	95.902	5.618E-4
5818	0.773	345.144	1.269E-4
5821	0.730	212.026	2.57E-5
5836	0.779	217.277	1.813E-4
5845	0.577	393.796	4.819E-5
5853	0.813	239.582	1.394E-4
5854	1.108	258.6	3.525E-4
5873	0.751	310.964	1.098E-4
5879	0.679	225.087	9.88E-5
5894	1.38	266.096	6.734E-4
Ceofficient of variation for sarcoma	37.67%	30.29%	91.45%

[a]Since patient NC had adenocarcinoma, corresponding parameters have been excluded for this calculation.

easily shown that the 10% error in volume prediction is equivalent to 3.22% error in diameter prediction. Thus criterion for satisfactory prediction is very stringent.

Conclusion

There is no single model that commands universal superiority over the others. The sample used in this study was not large enough to draw any statistical conclusions. However, the results obtained do show a trend. It was found that in mice, the

Bertalanffy equation had an edge over the other models for the following reasons:

(1) it has a basis in metabolic theory;
(2) it fitted well in seven out of 10 cases; and
(3) it could predict volume within a 10% margin (i.e. 3.22% error in diameter prediction) in three out of five cases.

For the human tumor data, the logistic equation proved better because it fitted well in all the cases studied.

The data on human tumors were obtained from Schwartz (1961). He reports that a good fit is obtained by using the exponential model. However, the results presented here indicate that the exponential model gives a good fit only in the case of patient RP. Although the exponential equation is a close representation of the initial growth period, in general it is not a good model. This conclusion is in agreement with other worker's findings.

Emanuel and Evseenko (1973) have used the human tumor data reported by Schwartz (1961) for studying tumor growth kinetics. They conclude that for patients AC, JS.I, and NC the tumor grew as a linear function of its diameter. However, it was found that such relationship does not give a fit as good as the one obtained by the logistic equation.

Steel (1977) described the Bertalanffy, the logistic and the Gompertz equations. He further writes (p. 21):

> 'When the experimental data cover a narrow range of size (one decade or less), any of the equations that have just been described will usually fit well. When the data cover a wide range of sizes the Gompertz equation usually gives a better fit than either the logistic or the Bertalanffy equation'.

The human tumor data used here covers a range of more than a decade in all the cases except for the patient NC. Thus according to the statement quoted above, the data should give a better fit to the Gompertz equation than either the logistic or the Bertalanffy equation. However, it is seen that the logistic equation gives a good fit in all the cases. A similar comment can be made about the data on animal tumors, where the Bertalanffy equation was found to be the best.

Steel (1977) remarks that the Bertalanffy equation may be useful in studies of normal growth of organisms, but its behavior at early time intervals makes it less attractive as a tumor growth model. However, it was found that the Bertalanffy equation gives satisfactory results when used for tumor growth in mice.

The measurements of the diameter of the animal tumors were noted till the death of the host in six out of 10 cases. Among these six cases, only in one case was the Gompertz equation found to be better than the other models. The Bertalanffy was better in five cases and the logistic was better in one case. It is believed that the Gompertz equation does better when the complete history of the tumor growth is analyzed. Obviously this is not the case for the animal data used here.

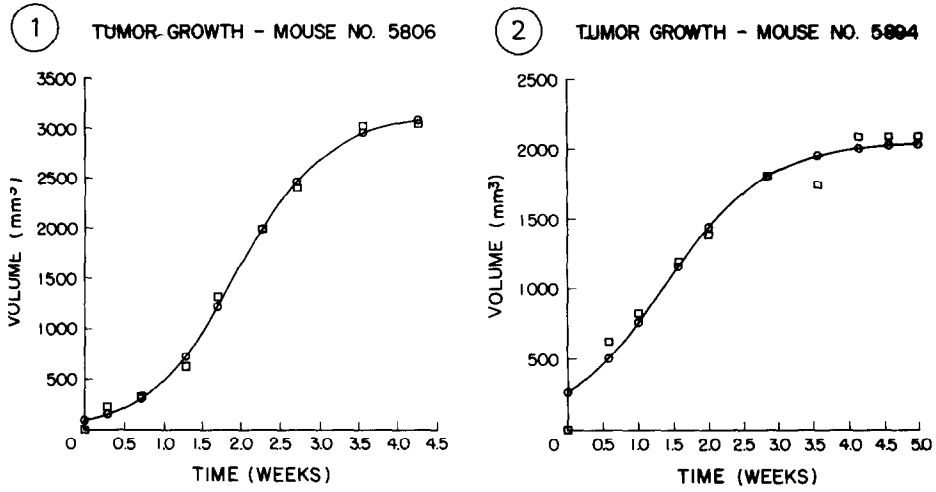

Fig. 1. Tumor growth – mouse No. 5806: □, time vs. observed; ○, time vs. logistic.

Fig. 2. Tumor growth – mouse No. 5894: □, time vs. observed; ○, time vs. logistic.

The Gompertz curve is sigmoid. Thus one would expect that the equation should do better where the plotted data has such a shape. It is seen from Figs. 1 and 2 that the data show a clear sigmoid shape. The data are approximately sigmoid in Fig. 3. However, in none of the three cases is the Gompertz model the best fitted among the four models analyzed here.

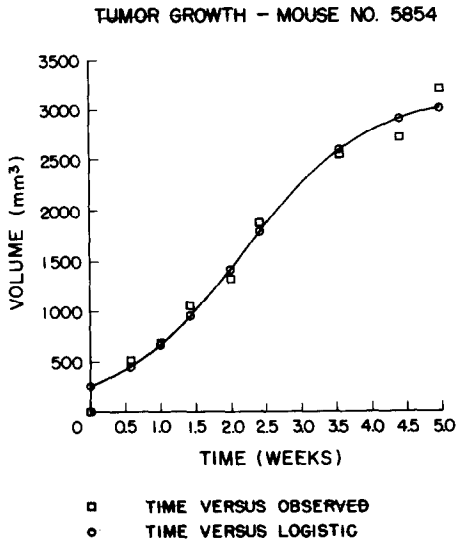

Fig. 3. Tumor growth – mouse No. 5854: □, time vs. observed; ○, time vs. logistic.

TABLE 7

RESULTS OF PREDICTION FOR PATIENT RP

Time (weeks)	Observed volume (mm^3)	Percentage error in prediction			
		Exponential	Gompertz[a]	Bertalanffy	Logistic
31.6	31059.35	−14.61	−56.38	−18.19	−17.52
38.0	44602.23	−7.31	−65.92	−22.44	−19.72
39.3	47712.93	−5.18	−67.53	−23.09	−20.26
41.0	54361.59	−6.36	−70.83	−27.21	−24.54
51.5	82447.95	27.89	−78.58	−26.43	−28.27
52.8	107536.19	7.30	−83.42	−40.77	−43.12
55.0	118846.97	13.09	−84.77	−41.89	−45.78

[a]Best fit was obtained using this equation (DLSS = 0).

TABLE 8

RESULTS OF PREDICTION FOR MOUSE NO. 5818

Time (weeks)	Observed volume (mm^3)	Percentage error in prediction			
		Exponential	Gompertz	Bertalanffy[a]	Logistic
4.0	3562.56	7.75	−7.08	−6.64	−9.01
4.6	3939.55	33.58	−2.60	−0.95	−8.74
5.0	4536.45	47.04	−7.21	−4.45	−16.50
5.6	5026.54	81.93	−7.17	−2.47	−21.12

[a]Best fit was obtained using this equation (DLSS = 0).

TABLE 9

RESULTS OF PREDICTION FOR MOUSE NO. 5836

Time (weeks)	Observed volume (mm^3)	Percentage error in prediction			
		Exponential	Gompertz	Bertalanffy[a]	Logistic
3.6	2010.61	26.72	−2.25	0.007	−7.52
4.0	2278.70	52.33	−3.00	1.45	−12.88
5.1	3053.62	158.91	−11.01	0.19	−30.25
6.0	3769.91	289.25	−21.20	−5.81	−42.71

[a]Best fit was obtained using this equation (DLSS = 0).

TABLE 10

RESULTS OF PREDICTION FOR MOUSE NO. 5873

Time (weeks)	Observed volume (mm^3)	Percentage error in prediction			
		Exponential	Gompertz	Bertalanffy[a]	Logistic
3.3	2228.43	63.50	−1.06	3.62	−11.54
4.0	3562.56	83.21	−30.57	−23.8	−42.78
4.6	3760.48	176.48	−30.46	−20.8	−45.32
5.0	4775.22	208.91	−43.67	−34.15	−56.82

[a]Best fit was obtained using this equation (DLSS = 0).

TABLE 11

RESULTS OF PREDICTION FOR MOUSE NO. 5879

Time (weeks)	Observed volume (mm^3)	Percentage error in prediction			
		Exponential	Gompertz	Bertalanffy	Logistic[a]
3.3	1334.12	36.87	−26.08	−24.39	−28.97
4.0	2563.53	10.27	−61.23	−60.08	−62.99
4.6	2883.98	38.97	−65.47	−64.35	−67.09
5.0	3524.86	47.80	−71.73	−70.78	−73.08
5.4	3901.85	73.45	−74.45	−73.58	−75.68
6.0	4576.25	109.79	−78.21	−77.46	−79.26

[a]Best fit was obtained using this equation (DLSS = 0).

TABLE 12

RESULTS OF PREDICTION FOR MOUSE NO. 5894

Time (weeks)	Observed volume (mm^3)	Percentage error in prediction			
		Exponential	Gompertz	Bertalanffy[a]	Logistic
3.6	1744.63	60.98	7.69	9.27	4.79
4.1	2089.15	80.51	−7.63	−5.43	−11.49
4.6	2089.15	125.25	−6.53	−3.77	−11.17
5.0	2089.15	181.08	−5.83	−2.6	−11.01

[a]Best fit was obtained using this equation (DLSS = 0).

Tables 3–6 give final parameter values and the coefficient of variation (CV). It is seen that the CV of the parameters is very high for all of the models. This fact indicates that the equations are very flexible and the parameters are arbitrary. Thus the equations do not apply universally.

Breur (1966) has given the data on doubling time for different types of malignancies. If one calculates the coefficient of variation for the doubling time, it is seen that CV varies from as low as 38.34% for adenocarcinoma solidium to as high as 127.5% for osteosarcoma. This indicates that it is not unusual to get high variation in the parameters.

Any individual's growth depends mainly upon environmental factors, genetic factors and eating habits. It would also be true for tumor growth. This may be the reason for the high CV. It would be difficult to develop a model that would account for the above mentioned factors and at the same time have fewer arbitrary constants.

The above explanation, however, is less likely to account for the high coefficient of variation noted for the animal tumor data. Since the experiments for animals are controlled, genetic factors and environmental factors vary to a lesser degree than for humans.

Another factor that could account for the high value of the CV is vascularization of the tumor. If the blood vessels grow to form a network throughout the tumor, then the malignant cells will proliferate. Without vascularization, the growth of the tumor will not be rapid. This explanation, however, is highly speculative and is not known to be verified experimentally.

Among the six models tried for predictability, the division according to the best fit obtained (DLSS = 0) was as follows (refer to Table 2): Bertalanffy four, Gompertz one, and Logistic one. The prediction results presented here show that the Bertalanffy equation satisfied the 10% error criterion in three out of the four best fitted cases. In mouse No. 5873 the Bertalanffy equation could not satisfy the criterion. However, its overall prediction error was less than the rest of the models. On the other hand, the prediction error using the Gompertz equation was the highest even though it was the best fitted model for patient RP. Thus the Gompertz model was the worst of all the four models in predicting the tumor volume of patient RP. A similar comment can be made for the logistic equation in the case of mouse No. 5879.

The Gompertz equation did satisfy the 10% criterion for mice Nos. 5818 and 5894. It is worth noting that even though a good fit was not obtained using the Gompertz equation for mouse No. 5894, it could predict the volume very well.

Another important point is that all the models, except the exponential equation, tend to underestimate the volume of a tumor. However, the exponential model invariably overestimates the volume.

There are advantages and disadvantages in using models with a strong basis in physiology. Although such models tend to give some insight into the growth process, they can not be verified using the experimental data. On the other hand the Gompertz model, which according to many researchers gives a good fit to the data, lacks a basis

in physiology. There is a need to bridge the gap between the two extremes. In some sense the Bertalanffy model achieves this. The model has some basis in metabolic theory, has few arbitrary constants, can be verified experimentally and gives good results in predicting the volume.

References

Bertalanffy, L. Von, Principles and theory of growth, in *Fundamental Aspects of Normal and Malignant Growth*, W.W. Nowinsky (Ed.), Elsevier, Amsterdam, 1960, pp. 137–259.

Breur, K., Growth rate and radiosensitivity of human tumors–I, *Eur. J. Cancer*, **2** (1966) pp. 157–171.

Casey, A.E., The experimental alteration of malignancy with an homologous mammalian tumor material–I, *Am. J. Cancer*, **21** (1934) pp. 760–775.

Emanuel', N.M. and Evseenko, L.S., Kinetics of tumor growth, in *Clinical Oncology – A Quantitative Approach*, Israel Program for Scientific Translations, Halsted Press, John Wiley and Sons, New York, 1973, pp. 12–16.

Fabens, A.J., Properties and fitting of the von Bertalanffy growth curve, *Growth*, **29** (1965) pp. 265–289.

Gompertz, B., On the nature of the function expressive of the law of human mortality and on a new model of determining life contingencies, *Philos. Trans. R. Soc. (Lond.)*, **115** (1825) pp. 513–585.

Laird, A.K., Dynamics of tumor-growth, *Br. J. Cancer*, **18** (1964) pp. 490–502.

Laird, A.K., Dynamics of tumor growth: Comparison of growth rates and extrapolation of growth curve to one cell, *Br. J. Cancer*, **19** (1965) pp. 278–291.

McCredie, J.A., Inch, W.R., Kruuv, J. and Watson, T.A., The rate of tumor growth in animals, *Growth*, **29** (1965) pp. 331–347.

Schwartz, M., A biomathematical approach to clinical tumor growth, *Cancer*, **14** (1961) pp. 1272–1294.

Simpson-Herren, L. and Lloyd, H.H., Kinetic parameter and growth curves for experimental tumor systems, *Cancer Chemother. Rep.*, Part 1, **54** (1970) pp. 143–174.

Steel, G.G., Growth rate of tumors, in *Growth Kinetics of Tumors*, Oxford University Press, Oxford, England, 1977, pp. 5–55.

Swan, G.W. and Vincent, T.L., Optimal control analysis in the chemotherapy of IgG multiple myeloma, *Bull. Math. Biol.*, **39** (1977) pp. 317–337.

Swan, G.W., Tumor cell population dynamics, in *Some Current Mathematical Topics in Cancer Research*. Monograph Publishing on Demand: Sponsor Series, University Microfilms International, Ann Arbor, Michigan, 1977, pp. 1–8.

Winsor, C.P., The Gompertz curve as a growth curve, *Proc. Natl. Acad. Sci.*, **18** (1932) pp. 1–8.