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Stability Analysis of Gompertz Tumour Growth Model Parameters

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ABSTRACT

The stability analysis of Gompertz tumour growth model Parameter with respect to the tumour volume size leads us to conclude the constancy of Gompertz tumour growth parameter.

Keywords: Gompertz Model; Growth rate; Maximum Lifespan; Stability .

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INTRODUCTION

The serial determination of tumour volume is one of the few ways to study tumour behaviour and the analysis of growth curves from such data provides important theoretical and practical information for clinical and experimental oncology.

The Gompertz model of growth has been widely and successfully used as a simple, yet adequate descriptor of tumour growth curves [1–11]. Possible theoretical bases of this model have been addressed in the literature from various points of view, and it remains to be a topic of investigation [9, 12–24]. Most of the authors have attempted to derive the Gompertz model as an approximation (or a special case) of more general models, which are deemed to be based on accepted biological foundations. The Gompertz model is postulated (based on it empirical justification) and then the more general model is specified to yield the Gompertz model. Some complex models with more free parameters than the Gompertz model could not fit some tumour growth data adequately [9]. In fact many of those more complex models were not validated against data, as it is tacitly assumed that they have enough free parameters to _t simple sigmoidal growth curves. The Gompertz model have been almost universally used to describe the growth of organisms tissues, and populations of single cell organisms. Additionally the biological assumptions and mathematical generality of the Gyllenberg-Webb model [16] are sufficient to warrant its application to growth in general.

The approach to tumour growth presented in this paper uses a Gompertz tumour growth model parameter and it was introduced by Benjamin Gompertz (1825) [25] to analyse population dynamics and to determine life contingencies. Later, the Gompertzian model was found to fit well for diverse growth phenomena in nature, including tumour and embryonic growth. To the best of our knowledge, there have been few attempts to give biological, theoretical grounding to the Gompertz model ([1, 26–39]) in spite of its extensive use in biological and medical research. Especially in experimental oncology, the Gompertzian model is most widely used to describe in vivo tumour growth and expressed it mathematically by the equation if V (t) is the size of the tumour cell at time t, then

$$\frac{dV(t)}{dx} = A\,V(t) - \beta V(t)\,lnV^{*}(t) \qquad (1)$$

where A, the intrinsic growth rate of the tumor, is a parameter related to the initial mitosis rate and β, the growth deceleration factor is related to the antiangiogenic processes and $V^{*}(t) = V(t)/V_0$ define $V(0) = V_0$ is the volume at time t = 0. From a biological point of view, a greater β value means a stronger association constant between drug and angiogenic protein and/or a greater bio availability of the drug; a smaller *A* value means a slower initial grow rate of the tumor. Therefore, a greater β value or a smaller *A* value indicates a greater antitumoral effect of the therapy [40]. The growth deceleration factor, is related to the antiangiogenic processes. The solid tumour growth may be termed avascular or vascular, with angiogenesis facilitating the transformation form avascular to vascular growth. Avascular stage can be characterised by diffusion limited growth, with the tumour receiving vital nutrients and eliminating waste products via diffusion across its outer boundary and this stage tumours are usually harmless. To escape from the restriction of avascular growth a tumour must undergo angiogenesis. Once vascularised the rumour has access to an almost limitless supply of nutrients and is potentially life-threatening. However, it should be stressed that quite often discrepancies exist between clinical data and theoretical predictions, due to more or less intense environmental fluctuations.

This paper is organized as follows. In section 2, we outline the main features of the Gompertzian model and estimated the Gompertz parameters, given a uniqueness theorem for Gompertz parameters, in subsections we checked the existence of solid gompertz tumour growth parameter by theoretical, numerical methods. In the section 3, we checked the stability of Gompertz tumour growth parameter. In section 4, we given a conclusions.

2 ESTIMATION OF PARAMETERS

The Gompertz function describes an symmetrical type of sigmoidal growth is given by a Gompertz equation (1) of the following form

$$V(t) = V_0 e^{\frac{A}{\beta}(1-e^{-\beta t})} \qquad (2)$$

where V (t) is the volume of clonogenic tumour cell at time t; V_0 is the volume of clonogen number at time t = 0: *A* and β(> 0) are the Gompertz growth parameters. For tumour, size can be measured by volume, biomass or number of cells, since the number of tumour cells is equivalent to the volume of the tumour cells in a Gompertz tumour growth model [37]. For convenience, we will use volume (V (t)) as the measure of size of tumour cells.

Qualitatively, this model gives exponential growth at early time periods which then saturates at later time periods (decelerating growth). Using data obtained from a sequence of sampling times, the Gompertz parameter *A* and β have been estimated by various statistical methods like maximum likelihood, linear regression, non-linear regression [40].

In the following, we discussed the need to estimate the parameters *A* and β, also the details of a procedure for the estimation of parameters A and β in the absence of maximum volume data of the tumour cells then given the condition to exists such parameters. This method utilizes the cumulative volume rate (V_C)(i.e., defined by $V_c = \int_0^{\infty} V^{*}(t)\,dt$, where $V^{*}(t) = V(t)/V_0$) and the maximum lifetime of tumour cells (t_m) (at this time

the tumour reaches its maximum size of volume or maximum number of cells before disintegration and final effects).

The doubling time is a key parameter for assessing the impact of delays in cancer treatment. Most of the information about tumour growth rates comes from studies performed long ago and not known clearly the maximum volume size of individual tumours and groups of tumours. In general the time the tumour takes to double itself varies widely, such that in case of histological type of tumour the time distribution for tumour doubling itself is normally long [41–45]. The Gompertz model presents a doubling time (Volume Rate Doubling time (VRD)) which depends only on β. Comparisons of volume data of tumours in tumour growth model are aided by calculation of the VRD, because VRD changes in the same direction as lifespan of tumour cells. Solving equation (2) for VRD gives

$$VRD = -\frac{1}{\beta}\ln\left[1 - \frac{\beta}{A}ln(2)\right] \tag{3}$$

The above equation(3) fully depends on β; so we have to estimate β to calculate VRD in the absence of specific volume data of solid tumour cells , since VRD changes in the same direction as lifespan of tumour cells.

To estimate β, using equation (1) we get an exact mathematical descriptionof Gompertz model in the form of equation(2). Equation(2) gives

$$\frac{A}{\beta} = \frac{\ln(V^*(t))}{(1 - e^{-\beta t})'} \tag{4}$$

where $V^*(t) = V(t)/V_0$. Using the equation(4) we can find easily the value of unique A through the estimated unique β. The equation(4) depends more on measured tumour size $V^*(t)$ the ratio of Volume of tumour between initial and maximum size, so we must know the value of $V^*(t)$.

Table-1 Computations of Theoretical Gompertz Functions in terms of VRD(Volume Rate Doubling time) using equation(3).

Tumor	A	β	VRD
Mouse:			
Krebs	5.25	0.411	0.1357 hours
Ehrlich	0.078	0.009	9.26 hours
MC_1M,low dose	0.119	0.0147	6.09 hours
$6C_3HED$,high dose	0.0397	0.012	19.6 hours
$6C_3HED$, low dose	0.0626	0.0116	11.9 hours
DBA lymphoma	0.276	0.0238	2.59 hours
EI_4,low dose	0.207	0.019	3.46 hours
EI_4, high dose	0.172	0.023	4.23 hours
EO771	0.666	0.063	1.08 days
Osteosarcomas	1.02	0.159	0.7191 days
Rat:			
Walker, W26b1	0.220	0.0218	3.26 days
Walker, W12a7	0.342	0.0205	2.07 days
Walker, W10a6	0.362	0.039	1.99 days
Walker, W10b4	0.132	0.003	5.29 days
R39 Sarcoma, R3a7	1.28	0.124	0.56 days
R39 Sarcoma, R4c4	0.540	0.078	1.35 days
R39Sarcoma, a7R3	0.737	0.063	0.97 days
Flexner-Jobling	0.394	0.049	1.84 days
Rabbit:			
Brown-Pearce	1.262	0.0169	0.576 days

The source of data for each species is given in [1, 7].

Since tumour size can be measured by volume, biomass or number of cells, in a Gompertz tumour growth model [46], we assume $V(t_m)$ that maximum volume of tumour cells (where t_m is the time at which the tumour contains a cell number which is one less than its maximum i.e., one cell less to death, and which approximates the maximum lifespan of tumour

cells t_m). Thus

$$V(t^*_m) = V_0 e^{\frac{A}{\beta}(1-e^{-\beta t^*_m})} \tag{5}$$

after a few algebraic manipulations we get the formula to calculate the maximum lifespan of the tumour cell (approximate size at the time of death)

$$t^*_m = -\frac{1}{\beta}\ln\left[1 - \frac{\beta}{A} ln\left(\frac{V(t^*_m)}{V_0}\right)\right] \tag{6}$$

From equation (6) we calculate the approximate time of death, and maximum volume of the tumour can be calculated using equation(5). In the next step we estimate the growth rate of β of equation(1). The cumulative intrinsic volume rate V_c of the Gompertz model of equation(2), is already defined by

$$V_c = \int_0^\infty V^*(t)\,dt.$$

Substitute the value of $V^*(t)$ from the equation(2) in the above equation and apply a little algebra we get the following equatiaon

$$-\beta = \frac{1}{V_c} e^{-\frac{A}{\beta}} \int_{-\frac{A}{\beta}}^{\infty} \frac{e^{-z}}{z} dz \tag{7}$$

Where $z = -\frac{A}{\beta}e^{-\beta t}$

The above equation(7) is derived for the estimated term β by Gompertz tumour growth model. This estimation value β is substitute in equation(3) we will get the value of VRD and volume of the tumour. Clearly, the above integral in equation(7), exists, $\forall\, \beta \in R$.

Table-1 Computations of Theoretical Gompertz Functions in terms of VRD(Volume Rate Doubling time) from equation (3).

2.1 Uniqueness

The basic equation (7) is transcendental, involving an exponential integral, hence, its solution may not be unique. It thus becomes necessary to investigate the uniqueness of solution of equation(7).

Theorem 1: Equation(7) has a unique solution, if $\frac{2t_m}{V_c} < 1$ for $\beta > 0$

Theorem 2.: To have unique solution of Equation(7), it is necessary that $\frac{t_m}{V_c \ln\,[V^*(t)]} < 1$ for $\beta > 0$

From the above, we have proved the necessary condition for getting unique β through theorem 1 and theorem 2.

In order to examine the existence of Gompertz tumour growth model parameter by theoretically and satisfies the above conditions, we have used the results of experi-ments on the growth of tumours of different types of species Mouse, rat and rabbit in table-II.

Biological implication: The cumulative volume V_C is always greater than initial volume and towards maximum lifespan at time t_m. If this condition satisfies then only the theoretical existence is possible. For example, In table-II Mouse-Enrlich has $A = 0.078$, $V_C = 1.2883844 \times 10^6$ and DBA lymphoma has $A = 0.276$, $V_C = 20.71879 \times 10^6$ also EI_4 low dose- Mouse, Osteosarcomas-Mouse and all data's given in the table-I satisfies the condition.

We observed that, from theorem 1, it follows that to have a unique independent parameter A; it is necessary that $\frac{1}{V_c} \leq A$.

From theorem 1, the condition of unique β does not depends on tumour size $V^*(t)$ but from theorem 2 the necessary condition for unique β depends on the tumour size $V^*(t)$, hence theorem 1 is more useful than theorem 2. This property is very important, since even we do not know the maximum size of tumour, it is possible the check the existence of model and validity.

We verified the numerical solution values through the values of Table-II for the existence and validity of the data's of the parameter β. The numerical values from table-II were well fitted with growth curve and existing theoretically as well as

bio-logically. Hence the existence of solid Gompertz tumour growth parameter is justified.

Next section of this paper, we have proved a theorem on stability of time-dependent parameter β with respect to the volume size $V(t)$.

2.2 Existence of numberical values of estimated paratmeter:

Table-II Computation of reciprocal of cumulative volume rate $\frac{1}{V_c}$ and the maximum lifetime of tumour cells t_m

Tumour	A	β	V_0	$V(t_m)$	t_m hours/days	$1/Vc$
Mouse:						
Krebs	5.25	0.411	$2.7 X10^3$ cells	$800 X 10^6$ cells	3.9909 hours	$8.4567 X10^{-6}$
Ehrlich	0.078	0.009	$426 X10^3$ cells	$1593 X 10^6$ cells	331.1687 hours	$8.0750 X10^{-7}$
MC_1M,low dose	0.119	0.0147	$139 X 10^3$ cells	$467 X10^6$ cells	-	-
$6C_3HED$,high dose	0.0397	0.012	$50 X10^6$ cells	$890 X10^6$ cells	170.2028 hours	$33.0076X10^{-5}$
$6C_3HED$, low dose	0.0626	0.0116	$10X10^6$ cells	$776X10^6$ cells	141.5309 hours	$9.1051 X10^{-5}$
DBA lymphoma	0.276	0.0238	$10 X10^3$ cells	$1000X10^6$ cells	207.188 hours	$4.8265 X10^{-8}$
EI_4,low dose	0.207	0.019	$24 X10^3$ cells	$1260 X10^6$ cells	317.4464 hours	$6.0002 X10^{-6}$
EI_4, high dose	0.172	0.023	$695 X10^3$ cells	$1290 X10^6$ cells	-	-
EO771	0.666	0.063	$3 mm^3$	$31 cm^3$	32.9247 days	$2.9392 X10^{-6}$
Osteosarcomas	1.02	0.159	$0.01 cm^3$	$4.3 cm^3$	18.2688 days	$12.729 X10^{-5}$
Rat:						
Walker, W26b1	0.220	0.0218	0.4 g	175 g	42.3284 days	$5.3999 X10^{-5}$
Walker, W12a7	0.342	0.0205	$4.2 mm^3$	$212 cm^3$	51.0880 days	$3.87783 X10^{-5}$
Walker, W10a6	0.362	0.039	$418 mm^3$	$490 cm^3$	36.7349 days	$2.3222 X10^{-5}$
Walker, W10b4	0.132	0.003	$16.7 mm^3$	$196 cm^3$	79.8275 days	$1.06732 X10^{-6}$
R39 Sarcoma, R3a7	1.28	0.124	$8.36 mm^3$	$188 cm^3$	28.4854 days	$1.5610 X10^{-6}$
R39 Sarcoma, R4c4	0.540	0.078	$475 mm^3$	$276 cm^3$	32.2799 days	$5.3331 X10^{-5}$
R39Sarcoma, a7R3	0.737	0.063	$2.1 mm^3$	$202 cm^3$	62.7635 days	$1.6563 X10^{-7}$
Flexner-Jobling	0.394	0.049	0.015 g	18.3 g	43.9302 days	$1.865 X10^{-5}$
Rabbit:						
Brown-Pearce	1.262	0.0169	$18 mm^3$	$29.8 cm^3$	28.9986 days	$2.08294 X10^{-5}$

The source of data for each species is given in [1, 7].

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3 STABILITY OF GOMPERTZ TUMOUR GROWTH PARAMETER

Let β_1, β_2 be time-dependent parameters with volume of tumour size V_1, V_2 respectively, then

$$\beta_1 = \frac{-1}{V_c} e^{\frac{-\ln(V_1^*(t))}{(1-e^{-\beta_1 t_m})}} \int_{\frac{-\ln(V_1^*(t))}{(1-e^{-\beta_1 t_m})}}^{\infty} \frac{e^{-z}}{z} dz \ ,$$

$$\beta_2 = \frac{-1}{V_c} e^{\frac{-\ln(V_2^*(t))}{(1-e^{-\beta_2 t_m})}} \int_{\frac{-\ln(V_2^*(t))}{(1-e^{-\beta_2 t_m})}}^{\infty} \frac{e^{-z}}{z} dz \ ,$$

Consider

$$\beta_1 - \beta_2 = \frac{-1}{V_c} \left[\int_{x_1}^{\infty} \frac{e^{-z+x_1}}{z} dz - \int_{x_2}^{\infty} \frac{e^{-z+x_2}}{z} dz \right]$$
$$= \frac{-1}{V_c} \int_0^{\infty} e^{-u} \left[\frac{1}{u+x_1} - \frac{1}{u+x_2} \right] du, \qquad (8)$$

Where $x_i = \frac{-\ln(V^*(t))}{(1-e^{-\beta_i t_m})}$ for $i = 1,2$ and $u = (z - x_i)$ for $i = 1,2$ also $e^{-u} \geq 1, \forall u \leq 0.$

Set, $x_1 = \frac{x_1+x_2}{2} + \frac{x_1-x_2}{2}$, $x_2 = \frac{x_1+x_2}{2} - \frac{x_1-x_2}{2}$ (9)

Note that $\frac{x_1+x_2}{2}$ is the arithmetic mean and $\frac{x_1-x_2}{2}$ is the perturbation term of x_1, x_2.

Substitution of (9) into the equation (8), gives

$$\beta_1 - \beta_2 = \frac{-1}{V_c} \int_{\frac{x_1+x_2}{2}}^{\infty} \left[\frac{1}{y + \frac{x_1-x_2}{2}} - \frac{1}{y - \frac{x_1-x_2}{2}} \right] dy \qquad (10)$$

$$where \quad y = u + \frac{x_1+x_2}{2}$$

On the RHS of equation(10), the expression

$$\frac{1}{y + \frac{x_1-x_2}{2}} - \frac{1}{y - \frac{x_1-x_2}{2}} = \frac{1}{y}\left(1 - \frac{x_1-x_2}{2y} + \cdots\right) - \frac{1}{y}\left(1 + \frac{x_1-x_2}{2y} + \cdots\right) \qquad (11)$$

can be approximated to $-\left(\frac{x_1-x_2}{y^2}\right)$ by neglecting higher order perturbation terms in each expression on the RHS of (11), since $\left| \frac{x_1-x_2}{x_1+x_2} \right| < 1.$ On account of (11), equation (10) becomes

$$|\beta_1 - \beta_2| \leq \left| \left(\frac{-1}{V_c}\right) \int_{\frac{x_1+x_2}{2}}^{\infty} \left[\frac{x_1 - x_2}{y^2}\right] dy \right|$$
$$\leq \left(\frac{1}{V_c}\right) |x_1 - x_2| \int_{\frac{x_1+x_2}{2}}^{\infty} \left[\frac{dy}{y^2}\right].$$

Upon integration we get

$$|\beta_1 - \beta_2| \leq \frac{1}{V_c} \left| \frac{x_1 - x_2}{\frac{x_1+x_2}{2}} \right|. \qquad (12)$$

Retrieving x_i from (12) and substituting into equation (16), we get

$$|\beta_1 - \beta_2| \le \frac{1}{V_c}\left|\frac{\frac{-\ln(V_1^*(t))}{(1-e^{-\beta_1 t_m})}+\frac{\ln(V_2^*(t))}{(1-e^{-\beta_2 t_m})}}{2}\right|$$

$$= \frac{1}{V_c}\left|\frac{\ln(V_1^*(t))e^{-\beta_2 t_m}-\ln(V_2^*(t))e^{-\beta_1 t_m}-\ln(V_1^*(t))+\ln(V_2^*(t))}{\frac{\ln(V_1^*(t))e^{-\beta_2 t_m}+\ln(V_2^*(t))e^{-\beta_1 t_m}}{2}-\frac{\ln(V_1^*(t))+\ln(V_2^*(t))}{2}}\right| \quad (13)$$

Set, $\beta_1 = \frac{\beta_1+\beta_2}{2} + \frac{\beta_1-\beta_2}{2}$, $\beta_2 = \frac{\beta_1+\beta_2}{2} - \frac{\beta_1-\beta_2}{2}$ (14)

Sustitution of (14) into (13) and after a little algebra we obtain

$$|\beta_1 - \beta_2| = \frac{1}{V_c}\left|\frac{2\frac{\ln(V_1^*(t))\varphi - \ln(V_2^*(t))\psi}{\ln(V_1^*(t))+\ln(V_2^*(t))} - 2\eta\frac{\ln(V_1^*(t))-\ln(V_2^*(t))}{\ln(V_1^*(t))+\ln(V_2^*(t))}}{\frac{\ln(V_1^*(t))\varphi+\ln(V_2^*(t))\psi}{\ln(V_1^*(t))+\ln(V_2^*(t))}-\eta}\right| \quad (15)$$

where $\varphi = e^{\left(\frac{\beta_1-\beta_2}{2}\right)t_m}$, $\psi = e^{-\left(\frac{\beta_1-\beta_2}{2}\right)t_m}$, and $\eta = e^{-\left(\frac{\beta_1+\beta_2}{2}\right)t_m}$.

Since $e^{\pm\left(\frac{\beta_1-\beta_2}{2}\right)t_m} \approx 1 \pm \left(\frac{\beta_1-\beta_2}{2}\right)t_m$ (16)

(by neglecting higher order terms in $\beta_1 - \beta_2$)

Substituting (16) into equation (15) and simplifying we obtain

$$|\beta_1 - \beta_2| \le \frac{1}{V_c}\left|\frac{\frac{\ln(V_1^*(t))-\ln(V_2^*(t))}{\ln(V_1^*(t))+\ln(V_2^*(t))}\left(1-e^{-\left(\frac{\beta_1+\beta_2}{2}\right)t_m}\right)-2\left(\frac{\beta_1-\beta_2}{2}\right)t_m}{\left(1-e^{-\left(\frac{\beta_1+\beta_2}{2}\right)t_m}\right)+\left(\frac{\beta_1-\beta_2}{2}\right)t_m\frac{\ln(V_1^*(t))-\ln(V_2^*(t))}{\ln(V_1^*(t))+\ln(V_2^*(t))}}\right| \quad (17)$$

In (17) the last term in the denominator is a product of two perturbation terms. Weneglect this higher order term to get

$$|\beta_1 - \beta_2| \le \frac{1}{V_c}\left|\frac{\ln(V_1^*(t))-\ln(V_2^*(t))}{\frac{\ln(V_1^*(t))+\ln(V_2^*(t))}{2}}\right| + \frac{t_m}{V_c}\left|\frac{\beta_1-\beta_2}{\left(1-e^{-\left(\frac{\beta_1+\beta_2}{2}\right)t_m}\right)}\right| \quad (18)$$

Let

$$\frac{t_m/V_c}{\left(1-e^{-\left(\frac{\beta_1+\beta_2}{2}\right)t_m}\right)} < 1 \quad (19)$$

Then $0 < e^{-\left(\frac{\beta_1+\beta_2}{2}\right)t_m} < 1 - \frac{t_m}{V_c}$, which is true when $\frac{t_m}{V_c} < 1$.

If $\frac{t_m}{V_c} < 1$, further we have

$$-\left(\frac{\beta_1+\beta_2}{2}\right)t_m < \ln\left(1-\frac{t_m}{V_c}\right)$$

Which gives

$$\left(\frac{\beta_1+\beta_2}{2}\right)t_m > \frac{1}{t_m}\ln\left(\frac{1}{1-\frac{t_m}{V_c}}\right)$$

Note that the above estimation is independent of the volume size (t). Clearly the term $\frac{\beta_1+\beta_2}{2}$ is the mean of the time-dependent parameter.

3.1 Necessary for stability

Theorem-3 The time-dependent parameter β is stable for any volume size (t), provided $\frac{t_m}{V_c} < 1.$

Proof: When (19) holds, from (18) we get

$$|\beta_1-\beta_2| \le C\frac{1}{V_c}\left|\frac{\ln(V_1^*(t))-\ln(V_2^*(t))}{\frac{\ln(V_1^*(t))+\ln(V_2^*(t))}{2}}\right| \quad (20)$$

Where $C = \frac{1}{1-\left(\frac{t_m/V_c}{1-e^{-\left(\frac{\beta_1+\beta_2}{2}\right)t_m}}\right)} > 0$. Hence it follows from (20) that β is stable for any $V(t).$

Remark: When $\frac{t_m}{V_c} > 1$, we get

$$\frac{t_m/V_c}{1-e^{-\left(\frac{\beta_1+\beta_2}{2}\right)t_m}} \ge 1, \quad (21)$$

Since the function $\frac{1}{1-e^{-x}} > 1$ for every positive x and asymptotically goes to 1 (see figure 1)

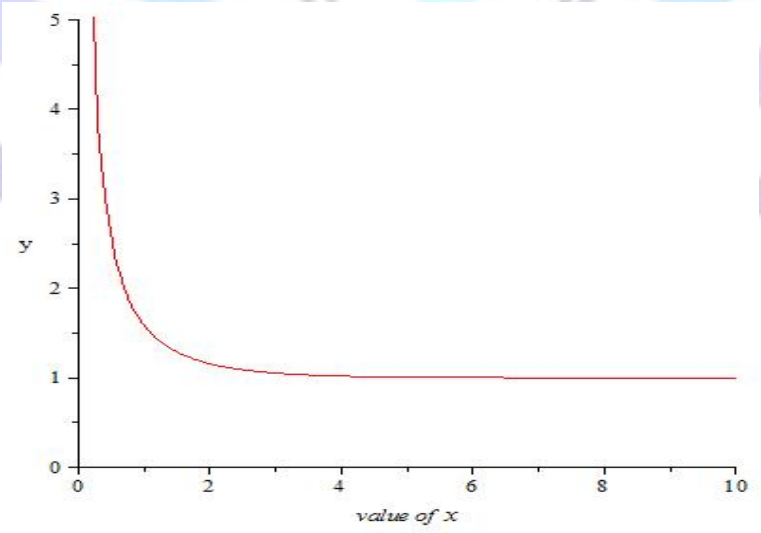

FIGURE:1: Graph of the function $y=1/(1-e^{-x})$

When (21) holds, it follows from (18).

Table-III Initial Mitosis Rate (A) was estimated at initial stage (equation (1)) VRD was calculated (equation (3)) from the time-dependent growth rate coefficient, β, t_m is calculated form reported β, *A* and V_0 for volume of dierent sizes V (t) (V (t_m) is approximate size at death and ∞ is theoretical upper limit.) The source of data for each tumour is given in [1,7]

	tumour type And Maximum volume	A (asymptotic)	β (asymptotic)	V_0 number of cells	t_m hours/days	VRD (asymptotic)
	Mouse:					
1.	Krebs V (t_m) = 800 _ 10^6 V *(t_m) = 952 _ 10^6	5.25	0.411	2:7 × 10^3	10.44 hours 24.04 hours	0.15675 hours
2.	Ehrlich V (t_m) = 1593 _ 10^6 V *(t_m) = 2300 _ 10^6	0.078	0.009	426 × 10^3	331.1687 hours 531.23 hours	9.88071 hours
3.	EI_4, low dose V (t_m) = 1260 _ 10^6 V *(t_m) = 1290 _ 10^6	0.207	0.019	24 × 10^3	317.4464 hours 438.213 hours	5.62582 hours
4.	Osteosarcomas V (t_m) = 4:3cm^3 V *(t_m) = 6:03cm^3	1.02	0.159	0.01 cm^3	18.27 days 38.92 days	0.75516 days
	Walker, W26b1					
5.	Rat: V (t_m) = 175 g V *(t_m) = 9600g	0.220	0.0218	0.4 g	42.33 days 341.23 days	4.03779 days
6.	Walker, W10a6 V (t_m) = 490cm^3 V *(t_m) = 1780cm^3	0.362	0.039	418 mm^3	36.73 days 59.12 days	2.02498 days
7.	R39 Sarcoma, R3a7 V (t_m) = 188cm^3 V *(t_m) = 241cm^3	1.28	0.124	8.36 mm^3	28.49 days 42.44 days	0.56666 days
8.	R39Sarcoma, a7R3 V (t_m) = 202cm^3 V *(t_m) = 252cm^3	0.737	0.063	2.1 mm^3	62.76 days 130.40 days	0.9851 days
9.	Flexner-Jobling V (t_m) = 18:3 g V *(t_m) = 465g	0.394	0.049	0.015 g	43.93 days 132.02 days	2.02099 days
	Rabbit:					
10.	Brown-Pearce V (t_m) = 29:8cm^3 V *(t_m) = 31:4cm^3	1.262	0.0169	18 mm^3	29.00 days 45.77 days	0.56168 days

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Theorem 4.: The time-dependent parameter β to be stable with respect to the population size V (t), it is necessary that β be a constant.

Corollary 1. Since β is a constant, it is clear that β is stable also with respect to the maximum life span t_m.

4 CLOSING COMMENTS

The purpose of this discussion has been to address the issue of parameter stability of a new method for estimating the time-dependent growth rate β of the Gompertz tumour growth rate model with deceleration factor. Such a method is necessary when attempting to estimate Gompertz tumour growth parameter coefficients in the absence of specific volume data of large number of tumour cells at particular time.

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