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Unique Estimation of Solid Tumour Growth Gompertz Parameter and Its Sensitivity Behaviour

M. Pitchaimani[1], G. Somasundara Ori[1*] and Tim Eakin[2]

[1] *Ramanujan Institute for Advanced study in Mathematics, University of Madras, Chennai 600005, India.*

[2] *The University of Texas at Austin, Department of Kinesiology and Health Education, Austin TX 78712, USA.*

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Abstract

In this paper we estimate the growth rate parameter of Gompertz tumour growth model and prove the uniqueness theorem and discuss the sensitivity analysis for same.

Keywords: Gompertz model, growth deceleration parameter, maximum lifetime of tumour cells, sensitivity, tumour doubling time, uniqueness.

2010 Mathematics Subject Classification: 92B05;35A02.

1 Introduction

Cancer is a collection of diseases with the common feature of uncontrolled cellular growth. Many tissues in the body can give rise to cancer. There are certain types of tissue which are prone to cancer, and each cancer has unique features. The salient feature of cancer cells is that the mechanisms that control growth, proliferation and death of cells in a multicellular organism are disrupted and are the result of mutations. The $\approx 10^{13}$ cells in the human body are subject to numerous checks and balances that, to varying degrees, are absent, ignored or affirmatively avoided during cancer development. In effect, cancer cells escape the usual controls on cell proliferation and proliferate excessively to form a neoplastic growth or tumour [1].

In the early 1970s, Folkman [2] hypothesized that most, if not all, solid tumor growth occurs in two phases: the avascular phase and the vascular phase. In the first (avascular) phase, the tumour reaches nutrients and eliminates wastes by diffusion transport processes alone. At this stage, the tumour growth is diffusion limited; the tumour maybe considered roughly spherical in shape and

**Corresponding author: E-mail: somasundaraori@yahoo.co.in*

cannot expand more than a few millimetres in diameter. This occurs because the tumour consumes nutrients at a rate proportional to its volume, whereas the supply of nutrients is delivered at a rate proportional to its surface area. An avascular nodule consists of a central necrotic core surrounded by a layer of quiescent cells that are in turn surrounded by a layer of proliferating cells. Although a tumor still contains live dividing cells, in this phase, it does not expand.

The second and clinically more important phase is the vascular phase , which can occur only in *vivo.* This phase involves the blood supply which provides cancer cells with oxygen, the necessary nutrients, and factors required for replication and survival. A given tissue or organ must have a sufficient blood supply in order to function. No extra blood supply is available though, which will hinder any potential abnormal growth. Cancer cells have to induce the generation of new blood supply in order to sustain their growth. This process is called angiogenesis , and it is important to state that solid tumour growth is angiogenesis dependent [3,4]. Research on the role of angiogenesis for cancer progression has been pioneered by Judah Folkman in the 1960s and 70s [2], and work from his laboratory has been dominating the literature up to now. In early experiments, Folkman and colleagues placed a small number of rabbit melanoma cells on the surface of the rabbit thyroid gland. They observed that the tumour cells initially grew but subsequently stopped growing once they reached a relatively small size comparable to that of a pea. The reason is that the tumour cells run out of blood supply. It is now clear that growth to larger sizes requires the emergence of so-called angiogenic tumour cells. The ability of the cancer to grow depends on the balance between so-called angiogenesis inhibitors, and angiogenesis promoters.

It is now well established [5, 6] that solid tumours initiate the neovascularization process, secreting a number of diffusible chemical compounds into the surrounding tissues and extracellular matrix. These compounds are called angiogenic factors, and angiogenic processes have been exploited in order to control, or even stop altogether any subsequent tumour growth. Drugs have been discovered that are able to prevent the formation of new capillary growth. Therefore, antiangiogenesis has been proposed as a potential target for the treatment of cancer [7].

For blocking tumour angiogenesis, one of the main targets of the antiangiogenic drugs is the inactivation of angiogenic factors released from tumour cells into the host tissues. Angiogenesis, tumour growth, and antiangiogenesis processes are very complicated. However, their main features can be described in a few relatively simple statements that allow us to describe tumour growth by the following Gompertz tumour growth model. If $V(t)$ is the volume of the tumour at time t, then we obtain the model

$$\frac{dV(t)}{dt} = AV(t) - \beta V(t) \ln V^*(t), \tag{1.1}$$

where A, the intrinsic growth rate of the tumour, is a parameter related to the initial mitosis rate and β, the growth deceleration factor is related to the antiangiogenic processes and $V^*(t) = \frac{V(t)}{V_0}$, 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 between drug and angiogenic protein and/or a greater bio availability of the drug; a smaller A value means a slower initial growth rate of the tumour. Therefore, a greater β value or a smaller A value indicates a greater anti-tumorous effect of the therapy [8]. So it's very useful to study about the Gompertz parameters β and A.

The plan of this paper is as follows. In section 2, we describe the Gompertz model and 2.1, we give the detailed procedure to estimate parameters A and β. In this method we used the cumulative volume rate (V_c) and the maximum lifespan of tumour cells (t_m), where (t_m) is the time at which tumour reaches its maximum volume just before disintegration (at time of death). In section 3 we have proved the uniqueness theorem for Gompertz parameters and in the section 4, we perform

sensitivity analysis of Gompertz parameter β. Finally, in section 5 we have a discussion.

2 Gompertzian Model

The mathematical models are useful to describe the general size of a tumour under relatively simple conditions (two populations, Fickian diffusion), but have yet to be extended to multiple populations or active cellular motility. A review of several other mathematical models is contained in [9–11].

The Gompertzian model is a classical continuous model useful in describing population dynamics; in particular, it is a very efficient mathematical model to describe tumour growth in humans and animals [12, 13]. It was introduced by Benjamin Gompertz (1825) [14] 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 [15–18] 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.

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 [8].

In section 2.1, the procedure of estimation of parameters A and β are discussed.

2.1 Estimation of parameters

An exact mathematical description of our model of tumour cell proliferation is given by a Gompertz equation (1.1) of the following form

$$V(t) = V_0 e^{\frac{A}{\beta}(1-e^{-\beta t})}, \tag{2.1}$$

where $V(t)$ is volume of the clonogenic tumour cell at time t, V_0 is the clonogen volume at time $t = 0$. A and $\beta(> 0)$ are the Gompertz growth parameters.

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 the data on the maximum volume before disintegration of an individual/groups of tumour cells is unknown. 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 [19–23]. The Gompertz model presents a doubling time (Volume Rate Doubling time (VRD)) which depends only on β. Comparing volume of solid tumours in tumour growth model is aided by calculation of the VRD, *as VRD changes in the same direction as lifespan of tumour cells*. The growth rate of the tumour may also be described by additional coefficients (Gompertz-Makeham model) or by other power functions (Weibull model), in which the VRD changes with time [17]. Solving equation (2.1) for VRD gives

$$VRD = -\frac{1}{\beta}\ln\left[1 - \frac{\beta}{A}\ln(2)\right]. \tag{2.2}$$

The equation (2.2) is the key term of our model, which depends only on β. Therefore, we are going to estimate the value of β.

Equation (2.1) gives

$$\ln [V^*(t)] = \frac{A}{\beta}(1 - e^{-\beta t}),$$

or

$$\frac{A}{\beta} = \frac{\ln [V^*(t)]}{1 - e^{-\beta t}}, \tag{2.3}$$

where $V^*(t) = \frac{V(t)}{V_0}$.
From equation(2.1)

$$V(t_m^*) = V_0 e^{\frac{A}{\beta}(1-e^{-\beta t_m^*})}, \tag{2.4}$$

(where t_m is the time at which the tumour contains a cell volume which is one less than its maximum and which approximates the maximum lifespan of tumour cells t_m^*). After a few algebraic manipulations we get

$$t_m^* = -\frac{1}{\beta} \ln \left[1 - \frac{\beta}{A} \ln \left[\frac{V(t_m^*)}{V_0} \right] \right]. \tag{2.5}$$

The cumulative intrinsic volume growth rate of the Gompertz model equation (2.1), is defined by $V_c = \int_0^\infty V^*(t)dt$.
After a little algebra we get the following equation

$$-\beta = \frac{1}{V_c} e^{-\frac{A}{\beta}} \int_{-\frac{A}{\beta}}^{\infty} \frac{e^{-z}}{z} dz, \tag{2.6}$$

where $z = -\frac{A}{\beta} e^{-\beta t}$.
Here, we estimate the parameter β to calculate the value of VRD, which is the key term of our model. Now, we check the existence of the parameter β by analytical method. Clearly, the above integral in equation (2.6), exists, if $\beta < 0$. If $\beta > 0$ then, $\frac{e^{-z}}{z}$ has a pole at $z = 0$, and hence we take the principal value of this integral. The existence of the principal value of the integral is proved by the following lemma.

Table-1 Computations of theoretical Gompertz functions in terms of VRD (Volume Rate Doubling time) which depends on the tumour cell volume at any time from equation (2.2).

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
$6C_3$HED, low dose	0.0626	0.0116	11.9 hours
DBA lymphoma	0.276	0.0238	2.59 hours
El_4,low dose	0.207	0.019	3.46 hours
El_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 [24, 25].

Lemma: Principal value of the integral $\int_{-\frac{A}{\beta}}^{\infty} \frac{e^{-z}}{z} dz$ exists, if $\beta > 0$.

Proof: Consider

$$\int_{-\frac{A}{\beta}}^{\infty} \frac{e^{-z}}{z} dz = \int_{-\frac{A}{\beta}}^{-\epsilon} \frac{e^{-z}}{z} dz + \int_{-\epsilon}^{\epsilon} \frac{e^{-z}}{z} dz + \int_{\epsilon}^{\infty} \frac{e^{-z}}{z} dz.$$

Now, we consider only the middle of the RHS of the above integral

$$\begin{aligned} \lim_{\epsilon \to 0} \int_{-\epsilon}^{\epsilon} \frac{e^{-z}}{z} dz &= \lim_{\epsilon \to 0} \left[\int_{-\epsilon}^{0} \frac{e^{-z}}{z} dz + \int_{0}^{\epsilon} \frac{e^{-z}}{z} dz \right] \\ &= \lim_{\epsilon \to 0} \left[-\int_{0}^{\epsilon} \frac{e^{-z}}{z} dz + \int_{0}^{\epsilon} \frac{e^{-z}}{z} dz \right] \\ &= 0. \end{aligned}$$

Hence the principal value of the above integral exists, if $\beta > 0$. The basic equation (2.6) is transcendental, involving an exponential integral. Hence, its solution may not be unique. It thus becomes necessary to investigate the uniqueness of β.

3 Uniqueness

Before proving the uniqueness theorem, we observe that $\frac{1}{V_c}$ cannot exceed A, because the former represents contributions from A and β.

Here is the proof:

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

$$-\beta \leq \frac{1}{V_c} e^{-\frac{A}{\beta}} e^{\frac{A}{\beta}} \left(-\frac{\beta}{A}\right),$$

which implies $\frac{1}{V_c} \leq A$.

Theorem 1: Equation (2.6) has a unique solution, if $\frac{2t_m}{V_c} < 1$ for $\beta > 0$.
Proof: Suppose β_1, β_2 are two positive distinct solutions of equation (2.6), that is

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

$$\beta_2 = -\frac{1}{V_c} e^{-\frac{\ln[V^*(t)]}{(1-e^{-\beta_2 t_m})}} \int_{-\frac{\ln[V^*(t)]}{(1-e^{-\beta_2 t_m})}}^{\infty} \frac{e^{-z}}{z} dz.$$

Consider

$$\beta_1 - \beta_2 = -\frac{1}{V_c} \left[\int_{x_1}^{\infty} \frac{e^{-z+x_1}}{z} dz - \int_{x_2}^{\infty} \frac{e^{-z+x_2}}{z} dz \right]$$

$$= -\frac{1}{V_c} \int_0^{\infty} e^{-u} \left[\frac{1}{u+x_1} - \frac{1}{u+x_2} \right] du, \tag{3.1}$$

where $x_i = -\ln[V^*(t)]/(1-e^{-\beta_i t_m})$ for $i = 1, 2$ and $u = (z - x_i)$ for $i = 1, 2$ also $e^{-u} \geq 1, \forall u \leq 0$, (by lemma:1) we obtain

$$|\beta_1 - \beta_2| \leq \frac{1}{V_c} |x_1 - x_2| \int_0^{\infty} \frac{du}{(u+x_1)(u+x_2)} = \frac{1}{V_c} \ln \left[\frac{x_1}{x_2} \right].$$

Therefore,

$$|\beta_1 - \beta_2| \leq \frac{1}{V_c} \left| \ln \left[\frac{1-e^{-\beta_2 t_m}}{1-e^{-\beta_1 t_m}} \right] \right|$$

$$= \frac{1}{V_c} \left| \ln \left[\frac{e^{-\beta_2 t_m}(e^{\beta_2 t_m} - 1)}{e^{-\beta_1 t_m}(e^{\beta_1 t_m} - 1)} \right] \right|$$

$$= \frac{1}{V_c} \left| \ln \left[\frac{e^{-\beta_2 t_m}}{e^{-\beta_1 t_m}} \right] + \ln \left[\frac{e^{\beta_2 t_m} - 1}{e^{\beta_1 t_m} - 1} \right] \right|$$

$$= \frac{1}{V_c} \left| [\beta_1 t_m - \beta_2 t_m] + \ln \left[e^{\beta_2 t_m} - 1 \right] - \ln \left[e^{\beta_1 t_m} - 1 \right] \right|.$$

Applying the mean value theorem, we get

$$|\beta_1 - \beta_2| = \frac{1}{V_c} \left[|\beta_1 t_m - \beta_2 t_m| + \ln \left| e^{-\beta_2 t_m} - e^{-\beta_1 t_m} \right| \right]$$

$$= \frac{1}{V_c} \left[|\beta_1 - \beta_2| \, t_m + |\beta_1 - \beta_2| \, t_m \right]$$

$$= \frac{2t_m}{V_c} |\beta_1 - \beta_2|.$$

That is,

$$\left(\frac{2t_m}{V_c} - 1\right)|\beta_1 - \beta_2| \geq 0.$$

Since $\frac{2t_m}{V_c} < 1$, the last inequality implies that $\beta_1 \equiv \beta_2$ for $\beta > 0$.
Hence, we conclude that the equation (2.6) has uniqueness solution if $\frac{2t_m}{V_c} < 1$ for $\beta > 0$.

3.1 A necessary condition for uniqueness

Theorem 2: To have a unique solution of equation (2.6), it is necessary that $\frac{t_m}{V_c \ln[V^*(t)]} < 1$, $\beta > 0$.
Proof: Suppose β_1, β_2 are two positive distinct solutions of equation (2.6), that is from equation (3.1)

$$\beta_1 - \beta_2 = -\frac{1}{V_c}(x_2 - x_1)\int_0^\infty \frac{e^{-u}}{(u+x_1)(u+x_2)}du$$

$$= -\frac{1}{V_c}\left(\frac{1}{1-e^{-\beta_2 t_m}} - \frac{1}{1-e^{-\beta_1 t_m}}\right)(1-e^{-\beta_1 t_m})(1-e^{-\beta_2 t_m})$$

$$\times \int_0^\infty \frac{e^{-z\ln[V^*(t)]}}{(1+z(1-e^{-\beta_1 t_m}))(1+z(1-e^{-\beta_2 t_m}))}dz,$$

since

$$\frac{e^{-z\ln[V^*(t)]}}{(1+z(1-e^{-\beta_1 t_m}))(1+z(1-e^{-\beta_2 t_m}))} \leq 1.$$

We get

$$\beta_1 - \beta_2 \leq -\frac{1}{V_c}\left(\frac{1}{1-e^{-\beta_2 t_m}} - \frac{1}{1-e^{-\beta_1 t_m}}\right)(1-e^{-\beta_1 t_m})(1-e^{-\beta_2 t_m})\int_0^\infty e^{-z\ln[V^*(t)]}dz$$

$$= -\frac{1}{V_c}\left(\frac{1}{1-e^{-\beta_2 t_m}} - \frac{1}{1-e^{-\beta_1 t_m}}\right)(1-e^{-\beta_1 t_m})(1-e^{-\beta_2 t_m})\frac{1}{\ln[V^*(t)]}.$$

Hence,

$$|\beta_1 - \beta_2| \leq \frac{1}{V_c \ln[V^*(t)]}\left|(1-e^{-\beta_1 t_m}) - (1-e^{-\beta_2 t_m})\right|$$

$$= \frac{1}{V_c \ln[V^*(t)]}\left|(\beta_1 t_m)\left(\frac{(1-e^{-\beta_1 t_m})}{\beta_1 t_m}\right) - (\beta_2 t_m)\left(\frac{(1-e^{-\beta_2 t_m})}{\beta_2 t_m}\right)\right|$$

$$= \frac{1}{V_c \ln[V^*(t)]}\left|\frac{\beta_1 t_m}{\left(\frac{\beta_1 t_m}{1-e^{-\beta_1 t_m}}\right)} - \frac{\beta_2 t_m}{\left(\frac{\beta_2 t_m}{1-e^{-\beta_2 t_m}}\right)}\right|.$$

Thus,

$$|\beta_1 - \beta_2| \leq \frac{t_m |\beta_1 - \beta_2|}{V_c \ln[V^*(t)] \max\left(\frac{\beta_1 t_m}{(1-e^{-\beta_1 t_m})}, \frac{\beta_2 t_m}{(1-e^{-\beta_2 t_m}1)}\right)}. \tag{3.2}$$

Suppose we have a unique solution of (2.6). It follows from (3.2) that

$$\frac{t_m}{V_c \ln[V^*(t)] \max\left(\frac{\beta_1 t_m}{(1-e^{-\beta_1 t_m})}, \frac{\beta_2 t_m}{(1-e^{-\beta_2 t_m})}\right)} < 1. \tag{3.3}$$

Since $\frac{\beta t_m}{1-e^{-\beta t_m}} \geq 1, \forall \beta t_m \geq 0$, from (3.3) we get

$$\frac{t_m}{V_c \ln[V^*(t)]} < \min\left(\frac{\beta_1 t_m}{(1-e^{-\beta_1 t_m})}, \frac{\beta_2 t_m}{(1-e^{-\beta_2 t_m})}\right) < \max\left(\frac{\beta_1 t_m}{(1-e^{-\beta_1 t_m})}, \frac{\beta_2 t_m}{(1-e^{-\beta_2 t_m})}\right), \tag{3.4a}$$

$$1 \leq \min\left(\frac{\beta_1 t_m}{(1-e^{-\beta_1 t_m})}, \frac{\beta_2 t_m}{(1-e^{-\beta_2 t_m})}\right) \leq \max\left(\frac{\beta_1 t_m}{(1-e^{-\beta_1 t_m})}, \frac{\beta_2 t_m}{(1-e^{-\beta_2 t_m})}\right) \tag{3.4b}$$

Note that $\max\left(\frac{\beta t_m}{1-e^{-\beta t_m}}\right)$ attains 1 only if $\beta t_m = 0$.

Hence, the above inequalities (3.4a) and (3.4b) implies that $\frac{t_m}{V_c \ln[V^*(t)]} < 1, \beta > 0$.
We conclude that to have uniqueness solution of equation (2.6), it is necessary that $\frac{t_m}{V_c \ln[V^*(t)]} < 1, \beta > 0$.

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

Remark 2: From theorem 1, the condition of unique β does not depend on tumour volume $V^*(t)$, but from theorem 2 the necessary condition for unique β depends on the tumour volume $V^*(t)$, hence theorem 2 is more useful than theorem 1.

Remark 3: The unique value of A can be calculated through the unique value of β.

Remark 4: Using lemma, theorem 1 and theorem 2 we proved the existence of the parameter β by theoretical analysis method.

Remark 5: 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.

4 Sensitivity of Parameter Changes

Sensitivity analysis can be used to determine the functional relationship between tumour volume or growth rate and the constituent rates (e.g., fecundity, survival, growth, maturation, recruitment, movement), and to project changes in tumour growth rate and volume as vital rates change.

From the work of Witten and Satzer [15] we know that in the standard Gompertz growth model the deceleration factor β becomes insensitive to change in initial tumour volume V_0 if V_0 approaches a very large value, but becomes very sensitive to changes in V_0 if V_0 approaches 1. Similarly we may consider how equation (2.6) behaves when $V^*(t)$, V_c and t_m are large. To do this we consider equation (2.6) and the partials of β with respect to $V^*(t)$, V_c and t_m,

$$-\frac{\partial \beta}{\partial V^*} = \frac{[A-(1/V_c)]/V^* \ln V^*}{1+(e^{-\beta t_m}/(e^{-\beta t_m}-1))t_m[A-(1/V_c)]}, \tag{4.1}$$

$$-\frac{\partial \beta}{\partial V_c} = \frac{-\beta/V_c}{1+(e^{-\beta t_m}/(e^{-\beta t_m}-1))t_m[A-(1/V_c)]}, \tag{4.2}$$

$$-\frac{\partial \beta}{\partial t_m} = \frac{-\beta(e^{-\beta t_m}/(e^{-\beta t_m}-1)/[(1/V_c)-A]}{1+(e^{-\beta t_m}/(e^{-\beta t_m}-1))t_m[A-(1/V_c)]}, \tag{4.3}$$

respectively.

4.1 Existence of numberical values of estimated paratmeter:

Table-II Computation of cumulative volume rate (V_c) and the maximum lifetime of tumour cells (t_m) from equation (2.5).

Tumour	A	β	V_0	$V(t_m)$	t_m days	$\frac{1}{V_c}$ time $^{-1}$
Mouse:						
Krebs	5.25	0.411	2.7 $\times 10^3$ cells	800×10^6 cells	3.9909	8.4567 $\times 10^{-6}$
Ehrlich	0.078	0.009	426 $\times 10^3$ cells	1593×10^6 cells	331.1687	8.0750 $\times 10^{-7}$
MC_1M,low dose	0.119	0.0147	139×10^3 cells	467 $\times 10^6$ cells	-	-
6C_3HED,high dose	0.0397	0.012	50 $\times 10^6$ cells	890 $\times 10^6$ cells	170.2028	33.0076 10^{-5}
$6C_3$HED, low dose	0.0626	0.0116	10 $\times 10^6$ cells	776 $\times 10^6$ cells	141.5309	9.1051 $\times 10^{-5}$
DBA lymphoma	0.276	0.0238	10 $\times 10^3$ cells	1000 $\times 10^6$ cells	207.188	4.8265 $\times 10^{-8}$
El_4,low dose	0.207	0.019	24 $\times 10^3$ cells	1260 $\times 10^6$ cells	317.4464	6.0002 10^{-8}
El_4, high dose	0.172	0.023	695 $\times 10^3$ cells	1290 $\times 10^6$ times	-	-
EO771	0.666	0.063	3 mm^3	31 cm^3	32.9247	2.9392 $\times 10^{-6}$
Osteosarcomas	1.02	0.159	0.01 cm^3	4.3 cm^3	18.2688	12.729 $\times 10^{-5}$
Rat:						
Walker, W26b1	0.220	0.0218	0.4 g	175 g	42.3284	5.3999 $\times 10^{-5}$
Walker, W12a7	0.342	0.0205	4.2 mm^3	212 cm^3	51.0880	2.5787 $\times 10^6$
Walker, W10a6	0.362	0.039	418 mm^3	490 cm^3	36.7349	2.3222 $\times 10^{-5}$
Walker, W10b4	0.132	0.003	16.7 mm^3	196 cm^3	79.8275	1.06732 $\times 10^{-6}$
R39 Sarcoma, R3a7	1.28	0.124	8.36 mm^3	188 cm^3	28.4854	1.5610 $\times 10^{-6}$
R39 Sarcoma, R4c4	0.540	0.078	475 mm^3	276 cm^3	32.2799	5.3331 $\times 10^{-5}$
R39Sarcoma, a7R3	0.737	0.063	2.1 mm^3	202 cm^3	62.7635	1.6563 $\times 10^{-7}$
Flexner-Jobling	0.394	0.049	0.015 g	18.3 g	43.9302	1.865 $\times 10^{-5}$
Rabbit:						
Brown-Pearce	1.262	0.0169	18 mm^3	29.8 cm^3	28.9986	2.08294 $\times 10^{-5}$

The source of data for each species is given in [24, 25].

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We get that

$$\frac{\partial\beta}{\partial V^*(t)} = \frac{[A-(1/V_c)]/V^*(t)\ln V^*(t)}{1+(e^{-\beta t_m}/(e^{-\beta t_m}-1))t_m[A-(1/V_c)]} \geq 0, \forall V^*(t), \tag{4.4}$$

$$\frac{\partial\beta}{\partial V_c} = \frac{-\beta/V_c}{1+(e^{-\beta t_m}/(e^{-\beta t_m}-1))t_m[A-(1/V_c)]} \leq 0, \tag{4.5}$$

and

$$\frac{\partial\beta}{\partial t_m} = \frac{-\beta(e^{-\beta t_m}/(e^{-\beta t_m}-1)/[(1/V_c)-A]}{1+(e^{-\beta t_m}/(e^{-\beta t_m}-1))t_m[A-(1/V_c)]} \leq 0. \tag{4.6}$$

If we send $V^*(t)$ to ∞ in (4.4),(4.5) and (4.6) get that

$$\lim_{V^*(t)\to\infty}\frac{\partial\beta}{\partial V^*(t)} = 0, \quad \lim_{V^*(t)\to\infty}\frac{\partial\beta}{\partial V_c} = 0, \quad \lim_{V^*(t)\to\infty}\frac{\partial\beta}{\partial t_m} = 0.$$

. Thus, we see that β is relatively insensitive to changes in $V^*(t) \to \infty$. That is, β does not change rapidly as the number of tumour cells becomes larger.
If we sent $V^*(t)$ to 1 in equation (4.4), we get

$$\lim_{V^*(t)\to 1}\frac{\partial\beta}{\partial V^*(t)} = \infty,$$

because $1/V^*(t)lnV^*(t) \to \infty$ as $V^*(t) \to 1$. This , will gives

$$\frac{\partial\beta}{\partial V_c} \quad \text{and} \quad \frac{\partial\beta}{\partial t_m} = -\infty, \quad \text{as} \quad V^*(t) \to 1.$$

Hence, as the tumour size $V^*(t)$ decreases, we see a greater change in the sensitivity of β with respect to the initial tumour size V_0.

4.2 Existence of graphical interpretation of estimated parameter:

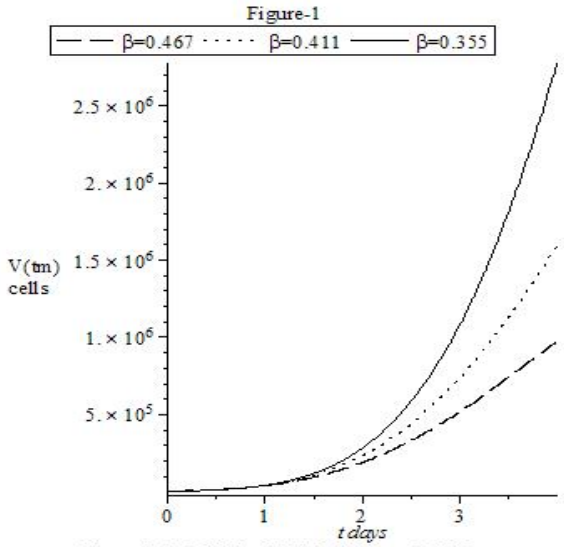

Figure-1 A=3.25, β=0.411±0.056, tm=3.9909

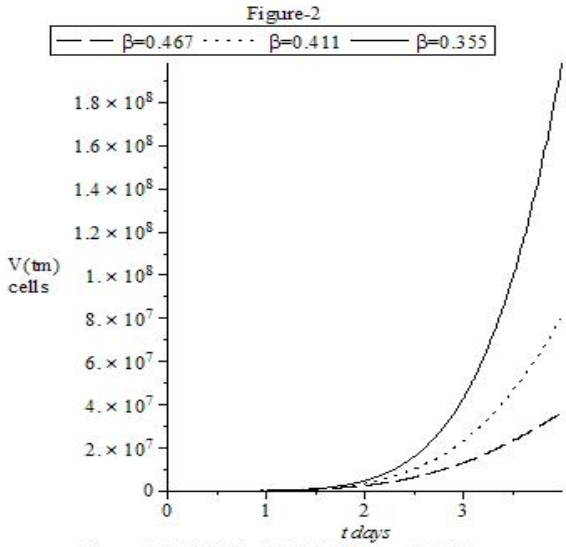

Figure-2 A=5.25, β=0.411±0.056, tm=3.9909

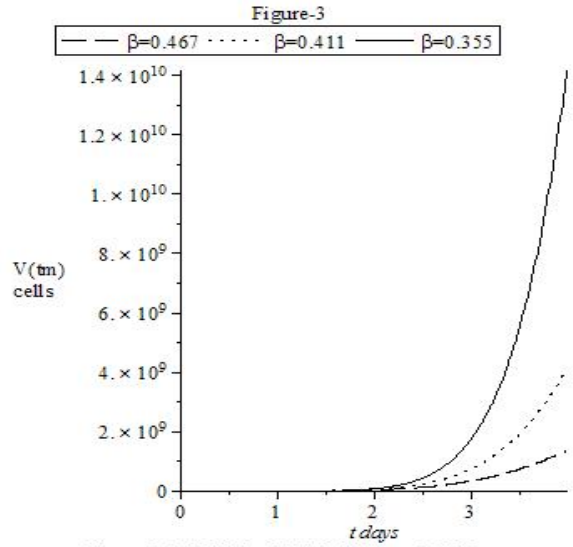

Figure-3 A=7.25, β=0.411±0.056, tm=3.9909

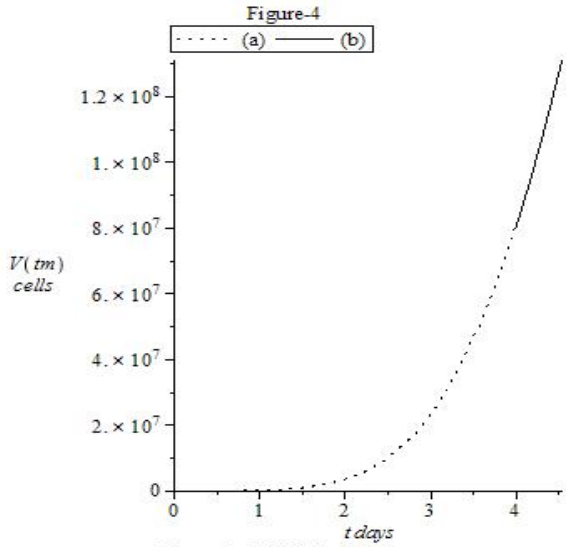

Figure-4 A=5.25, β=0.411

Classifications: Above figures of Gompertzian Tumour Growth of Mouse - Krebs were plotted from data [25] using equation (2.4) and (2.5).
Figure-1 For a constant $A = 3.25$, different $\beta = 0.411 \pm 0.055$ the growth curve is plotted.
Figure-2 For a constant $A = 5.25$ and different $\beta = 0.411 \pm 0.055$ the growth curve is plotted. The curve is increasing like the previous curve.
Figure-3 For a constant $A = 7.25$, different $\beta = 0.411 \pm 0.055$ the growth curve is plotted. This curve also, increasing like previous curves.
Figure-4 (a) Is the curve depicting the biological existence of tumour when $t_m = 0$ to 3.9909 days and **(b)** Is the curve depicting the biological existence of tumour to theoretically existence of tumour (t_m= 3.9909 upto maximum lifetime 4.53 days) of the curve.
For different A values($A = 5.35 \pm 2.00$) and different β values ($\beta = 0.411 \pm 0.055$) the curves were plotted and growth of the curve followed the same pattern. This illustrated that when the entire tumour volume was growing exponential growth was expected, but with the growth rate gradually reducing as the tumour volume of active growth was progressively restricted to decreasing size, utimately arriving at a linear growth rate. The observation that the Gompertz tumour growth model, as it implies the existence of a common upper limit of tumour size that the tumours may reach in time. However, our analysis showed that this general rule apply for all rumours. The data presented in this study suggest that the maximum volume size varies within the tumour sub-populations.

Remark 6: We verified the existence of numerical solution values through the graphical comparison and fitting the curve with classification based on the values of Table-II for the validity of a data of the parameter β.
The numerical values from table-II were fit well with growth curve and exist theoretically as well as biologically. In the above figures we plotted only the tumour growth of Mouse-Krebs and also we checked the remaining data in the same manner. The output supported our claim in the degree of acceptable level. Hence the existence of solid Gompertz tumour growth parameter is justified.

5 Discussion and Conclusions

The growth of nearly all tumours reported in the literature is characterized by a continuous deceleration from the earliest periods of observation. Growth of this nature is well described by a Gompertz function by equation (1.1). Such a function fits to the growth data of a volume of tumours in the mouse, rat and rabbit, and has been shown to follows growth through a 1000-fold increase in tumour volume size. A Gompertz function of this type has an asymptote solution; this fact implies that growth rate of tumours progresses towards an upper limit of volume size. The expectation that tumour growth under ideal conditions would prove to be exponential until it terminates with the exhaustion of the host has not been borne out in many careful studies of the growth of a wide variety of tumours. The growth rate of tumours is usually not constant even for a short time, but decreases steadily. In the present study we have shown that tumour growth is well described by a Gompertz function, according to which the time required to double the tumour volume (VRD)increase according to an exponential function.

A Gompertz function used here is a theoretical projection based on the measured growth of the tumour. The approximate size at death for those tumours were computed. For all the tumours included in the present survey, enough data were presented in the original studies to allow us to fit such a function to the data, and to project the maximum lifespan to tumour cell at approximate size at death. For most of the tumours the growth actually observed before the death of the host was a large fraction of the projected growth, falling short of the asymptote by only one or at most two doublings of tumour size. Only on special case we may conclude that the slowing of tumour growth simply reflects a terminal failure of the host to give nutritional support to the tumour. However, for several of the tumours, the observed growth fell far short of the projected upper limit, although the tumours all reached about the same size before the death of the host.

In table-1 the theoretical Gompertz parameter in terms of VRD of the tumour cell volume were calculated. In table-II we calculated the numerical data of our model. The existence of these data were checked with existing clinical data and they were observed to fit well. Using the theoretical existence formula we checked the numerical existence of clinical data.

We calculated the partials of β with respect to $V^*(t)$, V_c and t_m, to project changes in tumour growth rate and volume as vital rates change. In table-II, maximum time for approximate size at death t_m for Mouse-MC_1M-low dose, was not obtained, as because if $V^*(t) \to 1$ then $t_m \to \infty$ using equation (4.4). In table-II, Mouse-El_4-low dose, $V(t_m)$ is very close to V_0, and therefore we are unable to calculate its t_m. The source of data for each species is given in [24, 25].

The theoretical Gompertz curve gives the best fit by the method of least squares to the experimental data. The values for A lie generally between 0.08 and 0.36, and for β between 0.01 and 0.02. But several exceptions stand out notably like the high values for A and β found for the Kerbs tumour, and the very low value for β found for one for the Walker tumours. The ratio A/β, which determines the asymptote of the growth curve, is remarkably similar in spite of the differences in the individual values for A and β. Figure-1, Figure-2 and Figure-3 are plotted using the data from [24] of the tumour Kerbs ascites carcinoma $A = 5.25 \pm 2.00$, $\beta = 0.411 \pm 0.056$ and $t_m = 3.9909$ calculated through equation (2.4) and (2.5) and the remaining data also fit well. This shows that the numerical data of estimated Gompertz tumour growth parameters are very well supported by the graphical interpretations. The well fitting curves demonstrates, the existence of the estimated Gompertz tumour growth model parameter and its behaviour.

The condition of uniqueness β does not depends on tumour volume $V^*(t)$, but from theorem 2 the necessary condition for unique β depends on the tumour volume $V^*(t)$. The tumour

volume $V^*(t)$ was limited to an imaginable big tumour size (does not include unbelievable size of tumour growth, or biologically not possible growth, etc.,) by the necessary condition, and this must be satisfy for the existence of valid tumour growth parameter.

Also observed that, from theorem 1, it follows that to have a unique independent parameter A, it is necessary that $\frac{1}{V_c} \leq A$. But this data is not dependent on the value of $V^*(t)$, so it is not affected by any large number of solid tumour cells. So we calculate the unique β by Gompertz tumour growth model. We can estimate the growth deceleration parameter using the equation (2.6) and with this the value of A can be calculated.

A possible approach to examine the relationship between labelling index and tumour doubling time has been suggested by [26]. A relationship can be demonstrated theoretically for certain model cell population and if a sufficient variety of tumorous can be found in which both doubling time and labelling index are measurable the experimental confirmation should be possible. If such relationship value exists then with the tumour doubling time the growth rate of most tumours can be calculated using Gompertz growth model. In figure-4 **(a)** we plotted biologically existence curve when $t_m = 0$ to 3.9909 days and **(b)** From biologically existence curve to theoretically existing value (t_m= 3.9909 upto maximum lifetime 4.53 days) of the curve. This curve shows the existence of theoretical and biological curves. The biological existence of the curve will help in quantitative analysis of tumour growth and response to therapy. The measure formulated in this work can be used for future clinical trails on novel, or combinations of, anticancer therapeutic modalities.

The purpose of this discussion is to provide a method to estimate the unique growth rate β of the Gompertz tumour growth model. Such a method is necessary when attempting to estimate the growth rate in a Gompertz tumour growth model, at their maximum lifespan. Furthermore, a sensitivity analysis is performed. From these analysis, we believe that our model and methods will provide a useful approach to prediction of experimental and clinical tumour growth. For further applications more research is needed, and it may be started with the questions:
1) How can one apply this model and methods to develop efficient procedures for controlling tumour growth ?
2) Is it worthwhile to study asymptotic behaviour of the solution for the
equation (2.6)?.

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Competing Interests

The authors declare that no competing interests exist.

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