Existence of Critical Gompertz Parameter for Solid Tumour Growth Model and Its Asymptotic Expression

M. Pitchaimani, G. Somasundara Ori

Abstract—In this paper we provide an interval of existence of critical Gompertz parameter of solid tumour growth model and their asymptotic formula for large number of tumour cells, in the absence of specific volume data at particular time.

I. INTRODUCTION

Cancer is a disease that may affect people at all ages. It causes about 13% of all human deaths. In the past two decades increasing attention has been paid to tumour growth, a major death cause in our society. It has long been documented that the growth of cancer tumours follows a sigmoidal growth curve, exhibiting at first a phase of exponential growth and later a phase of slowed growth. The character of such curves is simulated by various mathematical formulations, including deterministic models, stochastic models and cellular automata models. The most recognized pattern of tumour growth is Gompertz growth, which has been utilized by many researchers to provide a basis of description and prediction [1-17].

Broadly speaking solid tumour growth may be termed avascular or vascular with angiogenesis facilitating the transformation from avascular to vascular growth [18-21]. The 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 [21-23]. Since the size to which such tumours grow is limited (O(mm^3)), avascular tumours are usually harmless. To escape from the restrictions of avascular growth a tumour must undergo angiogenesis [18-21]. During this process the tumour induces blood vessels from the surrounding tissue to form a new capillary network that migrates towards, and ultimately penetrates, the tumour. Once vascularised the tumour has access to an almost limitless supply of nutrients and is potentially life-threatening for two reasons. Firstly, the rapid growth that results may impair the function of vital organs. Second, the development of secondary tumours or metastases is now a real threat; tumour fragments that enter the blood supply are transported to other parts of the body where if conditions are favourable they establish secondary tumour colonies that further threaten the host.

Traditionally mathematical models describing avascular tumour growth assume radial symmetry of the tumour and focus on its responses to various growth factors [24-26]. These models show excellent agreement with experimental results, reproducing the multi-layered structures that characterise avascular tumours and multicellular spheroids.

Manuscript received March, 2014. (Fill the Details)

M. Pitchaimani, Ramanujan Institute for Advanced study in Mathematics, University of Madras, Chennai 600005, India.

G. Somasundaraori. Ramanujan Institute for Advanced study in Mathematics, University of Madras, Chennai 600005, India.

However, the deterministic Gompertz law of population growth has been widely used to describe in vivo tumour growth in experimental oncology [27-32]. If V (t) is the volume of the tumour cell at time t, then the Gompertz law models the cell growth by the equation

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

where *A*; the intrinsic growth rate of the tumor, is a parameter related to the initial mitosis rate and β; the growth deceleration factor and $V^*(t) = V(t)/V_0$; define V (0) = V0, is the volume at time t = 0. From a biological point of view, a greater β value or a smaller *A* value indicates a greater antitumoral effect of the therapy [33].

The plan of this paper is as follows. In section 2 the details of a procedure for the estimation of parameters A and _ in the absence of specific volume data . This method utilizes the cumulative volume rate (Vc)(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 (tm) (at this time the tumour reaches its maximum size of volume or maximum number of cells before disintegration and final effects). Also given details about behaviour growth critical Gompertz parameter of solid tumour and proved the existence of critical time tk, critical Volume Nk. Section 3 presents the results for interval of existence of numerical solution. In section 4 we given a conclusion.

II. ESTIMATION OF PARAMETERS

An exact mathematical description of our model of tumour cell proliferation is given by a Gompertz equation (1) of the following form

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

where *V (t)* is the clonogenic tumour volume at time t; V0 is the clonogen number at time t = 0: A and β(> 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 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 [34-38]. The Gompertz model presents a doubling time (Volume Rate Doubling time (VRD)) which depends only on β.

Comparisons of volume data of solid tumours in tumour growth model are aided by calculation

of the VRD, because 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 [37]. Solving equation(2) for VRD gives

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

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. Equation (2) gives

$$\frac{A}{\beta} = \frac{\ln(V^*(t))}{(1-e^{-\beta t})}, \quad (4)$$

where $V^*(t) = V(t)/V_0$. We assume that V (tm); maximum volume of tumour cells (where tm 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

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

after a few algebraic manipulations we get,

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

The cumulative intrinsic volume growth rate Vc of the Gompertz model of equation (2), is defined $V_c = \int_0^\infty V^*(t)\,dt$ Substitute the value of $V^*(t)$from the equation (2) in the above equation and apply a little algebra we get the following equation

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

Where $z = -\frac{A}{\beta}e^{-\beta t}$. Clearly, the above integral (7), exists $\forall\ \beta \in R$.

Consider the initial volume of size V0 at initial stage. From the equation (1) the volume at which the growth rate of initial volume V0 has increasing or, equivalently, it tends to a V (t*m) is the time at which volume approximates the maximum number of tumour cells, is called a critical time, tk. The remaining tumour cells from an original volume size V (t) surviving at this critical time
is called critical volume Vk, and the corresponding Gompertz parameter in equation (1), is called critical Gompertz parameter βk.

2.1 Behaviour of solid tumour growth Gompertz parameter

To find the critical points of β we consider the partials of β with respect to V *(t),Vc and tm in equation (7). These are given by

$$\frac{\partial\beta}{\partial V^*(t)} = \frac{\left[A-\left(\frac{1}{V_c}\right)\right]/V^*(t)lnV^*(t)}{1+\left(\frac{e^{-\beta t_m}}{(e^{-\beta t_m}-1)}\right)t_m\left[A-\left(\frac{1}{V_c}\right)\right]} \quad (8)$$

$$\frac{\partial\beta}{\partial V_c} = \frac{-\beta/V_c}{1+\left(\frac{e^{-\beta t_m}}{(e^{-\beta t_m}-1)}\right)t_m\left[A-\left(\frac{1}{V_c}\right)\right]} \quad (9)$$

and

$$\frac{\partial\beta}{\partial t_m} = \frac{-\beta\left(\frac{e^{-\beta t_m}}{(e^{-\beta t_m}-1)}\right)/\left[\left(\frac{1}{V_c}\right)-A\right]}{1+\left(\frac{e^{-\beta t_m}}{(e^{-\beta t_m}-1)}\right)t_m\left[A-\left(\frac{1}{V_c}\right)\right]} \quad (10)$$

Here, βtm ≥1 and [A ≤ (1/Vc)] is positive, since $\left(\frac{1}{V_c}\right) \le A$

Therefore, for βtm ≥1 the value of $1+\left(\frac{e^{-\beta t_m}}{(e^{-\beta t_m}-1)}\right)t_m\left[A-\left(\frac{1}{V_c}\right)\right]$is positive.

This will give the result

$$\frac{\partial\beta}{\partial V^*(t)} \ge 0, \frac{\partial\beta}{\partial V_c} \le 0 \text{ and } \frac{\partial\beta}{\partial t_m} \le 0$$

.

It shows that the value of parameter β is increases when value of V *(t) is increases, β is decrease when the value of Vc increase and also β is decrease when the value of tm increases.

If we send $V^*(t)$ **to** ∞
in (8),(9) and (10) get that

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

Also we obtain,

$$\frac{\partial\beta}{\partial V^*(t)} = 0 \Leftrightarrow A = \frac{1}{V_c}, \quad \forall V^*(t),$$

$$\frac{\partial\beta}{\partial V_c} = 0 \Leftrightarrow \beta = 0,$$

$$\frac{\partial\beta}{\partial t_m} = 0 \Leftrightarrow A = \frac{1}{V_c} \text{ or } \beta = 0 \text{ or } \beta = -\infty.$$

Upon substitution $A = \frac{1}{V_c}$ in (4), we get

$$\frac{t_m}{V^*(t)lnV^*(t)} = \frac{\beta t_m}{(1-e^{-\beta t})} \quad (11)$$

from (11) it follows that,

$$\frac{t_m}{V^*(t)lnV^*(t)}\begin{Bmatrix} <1 \text{ if } \beta<0 \\ =1 \text{ if } \beta=0 \\ >1 \text{ if } \beta>0 \end{Bmatrix} \quad (12)$$

The point

$$\frac{t_m}{V_c lnV^*(t)} = 1$$

at which β changes sign is said to be the critical point βk.

From [39], Collins and his co-workers [40] were able to show that for a series of 206 children with Wilms' tumour that risk of recurrence agreed well with theoretical prediction by the method of Boag [41] and also the growth rate function approaches a constant with predictions on the basis of exponential growth at larger time. To determine the critical Gompertz parameter, βk, first we use the identity $\frac{t_m}{V_c lnV^*(t)} = 1$ to obtain critical values of β; namely critical volume, Vk and critical time tk. Since the partials of β with respect to $V^*(t), \frac{1}{V_c}$ and t_m become zero at $\frac{t_m}{V_c lnV^*(t)} = 1$.

Note that the condition $\frac{t_m}{V_c lnV^*(t)} = 1$
is necessary to have a constant growth rate function. Finally we obtain the asymptotic solution of (7), for the critical values, Vk and tk.Now we shall prove the existence of critical volume and critical time.

2.2 Critical volume Vk

For a given
$V^*(t), \frac{1}{V_c}$ and $t_m$with
$\frac{t_m}{V_c lnV^*(t)} > 1$
There exists a critical volume Vk and is given by
$e^{\frac{t_m}{V_c}}$. Indeed, since $lnV^*(t) < \frac{t_m}{V_c}$ we can take $lnV^*(t) = \frac{t_m}{V_c}$, or $V_k = e^{\frac{t_m}{V_c}}$. For instance,(see Table I in [42] when (Mouse Krebs)) A = 5:25, tm = 15; 20 and 25, we find that Vk = $927_x 10^6$ [6]; $949_x 10^6$ and $952_x 10^6$, respectively. Note that Vk is increases as tm. Thus the remaining volume (critical

volume)approximates 949 x 10^6 to 952 x 10^6 cells. Since the volume reaches its maximum size, the above said tm can be treated as critical time tk. From this we obtained tk = Vc ln [Vk]. To study the tumor growth rate of the remaining critical volume we need to consider critical Gompertz parameter βk because

$\frac{t_m}{V_c ln V^*(t)} = 1$

when $V^*(t) = V_k$. Thus, we conclude that when $\frac{t_m}{V_c ln V^*(t)} > 1$, tk = tm and $V_k = e^{\frac{t_m}{V_c}}$. Clearly , when $\frac{t_m}{V_c ln V^*(t)} > 1$, both tk and tm are same.

2.3 Critical growth time tk

On the contrary, when

$\frac{t_m}{V_c ln V^*(t)} < 1$

it is trivial to find the critical volume. As tm < Vc ln [Vk] we can take tk = Vc ln [Vk]. For instance,(see Table I in [42] when (Rat R39 Sarcoma,R3a7))
A = 1.28, tm = 42.44 days and $V^*(t)$=241 cm^3, we find that tk = 28.4854 . Thus we conclude that when

$\frac{t_m}{V_c ln V^*(t)} < 1$

,, tk = Vc ln [Vk], $V_k = e^{\frac{t_m}{V_c}}$ and $t_k \neq t_m$.
Clearly , when $\frac{t_m}{V_c ln V^*(t)} < 1$, tk < tm. Thus, in general, for any given $\frac{1}{V_c}$, tm and $V^*(t)$, we get
$t_k \leq t_m$.

III. INTERVAL OF EXISTENCE OF NUMERICAL SOLUTION

Recall that in [42-44] we obtained asymptotic solution of equation(7) for a large $V^*(t)$with $\frac{t_m}{V_c ln V^*(t)} > 1$ for β > 0. The asymptotic solution is given by

$$\beta = -\frac{1}{t_m} ln \left[1 - e^{\left(\frac{t_m}{V_c}\right)c / \left(\frac{t_m}{V_c}-1\right)} \left(ln V^*(t)\right)^{\left(\frac{t_m}{V_c}\right)/\left(\frac{t_m}{V_c}-1\right)}\right] \quad (13)$$

and

$$\beta = -\frac{1}{t_m} ln \left[1 - \frac{C\, ln V^*(t) - ln V^*(t) - 1}{ln\left(ln V^*(t)\right) + C}\right], \quad (14)$$

when $\frac{t_m}{V_c} \neq 1$ *and* $\frac{t_m}{V_c} = 1$ respectively, and
C = 0.577215; Euler's constant.
We remark that when $\frac{t_m}{V_c ln V^*(t)} < 1$
the above asymptotic formulae remain valid, provided $\frac{t_m}{V^*(t) ln V^*(t)} < 1$ or $V^*(t) > V_k$.
Our immediate concern is to extend the above formulae to $V^*(t) \geq V_k$. It is amazing to learn that
the formulae (13) and (14) derived for a large $V^*(t)$ equally hold good for $V^*(t) = V_k$Here is the
proof: Upon substitution $V^*(t) = V_k$ to (7), we get

$$\beta_k = \frac{-1}{V_c} e^{\frac{-ln(V_k)}{(1-e^{-\beta_k t_k})}} \int_{\frac{-ln(V_k)}{(1-e^{-\beta_k t_k})}}^{\infty} \frac{e^{-z}}{z} dz \quad (15)$$

where tk = tm , $\frac{t_m}{V_c ln V^*(t)} < 1$
and tk = Vc ln [Vk] when $\frac{t_m}{V_c ln V^*(t)} < 1$
Equation (15) gives

$$\beta_k \leq \frac{-1}{V_c} e^{\frac{-ln(V_k)}{(1-e^{-\beta_k t_k})}} \left(\frac{-(1-e^{-\beta_k t_k})}{ln(V_k)}\right) \int_{\frac{-ln(V_k)}{(1-e^{-\beta_k t_k})}}^{\infty} \frac{e^{-z}}{z} dz$$

$$= \frac{-1}{V_c} e^{\frac{-ln(V_k)}{(1-e^{-\beta_k t_k})}} \left(\frac{-(1-e^{-\beta_k t_k})}{ln(V_k)}\right) e^{\frac{ln(V_k)}{(1-e^{-\beta_k t_k})}}$$

Hence

$\beta_k t_k \leq \frac{t_k}{V_c}\left(\frac{1-e^{-\beta_k t_k}}{ln(V_k)}\right)$.

The above inequality ensures the existence of solution βk,provided

$\frac{t_m}{V_c ln V^*(t)} = 1$ As a consequence, we get

$$\beta_k t_k \leq \left(1 - e^{-\beta_k t_k}\right). \quad (16)$$

Obviously, any βk ≥ 0 will satisfy (16). To obtain the solution of (15) for every fixed V_c, t_k *and* V_k choose any β^* from the solution interval [0,∞). As every $\beta_k \geq \beta^*$ satisfies (15), let us find the largest possible of these. To achieve this, fix one such β^*. Substitute this into the right hand side of (15) to get

$$\beta_k = \frac{-1}{V_c} e^{\frac{-ln(V_k)}{(1-e^{-\beta^* t_k})}} \int_{\frac{-ln(V_k)}{(1-e^{-\beta^* t_k})}}^{\infty} \frac{e^{-z}}{z} dz \quad (17)$$

where

$\epsilon = (1 - e^{-\beta^* t_k})/(1 - e^{-\beta_k t_k}) \leq 1$, since $\beta_k \geq \beta^*$. We observe that by sending ϵ to zero in (17), one can obtain the asymptotic value of βk for a large $V^*(t) = V_k$, as we have

$$0 \leq \beta_k t_k \leq \frac{t_k}{V_c}\left(\frac{1-e^{-\beta^* t_k}}{\epsilon}\right), \quad (18)$$

from(16).
If we send ϵ to zero, on account of 8.212,1. in [45], we get

$$\beta_k = \lim_{\epsilon \to 0} -\frac{1}{t_k} ln\left[1 - \left(\frac{1-e^{-\beta^* t_k}}{\epsilon}\right)\right] \quad (19a)$$

$$= \lim_{\epsilon \to 0} -\frac{1}{t_k} ln\left[1 - \left(\frac{1-e^{-\beta^* t_k}}{\epsilon}\right)\right] - \lim_{\epsilon \to 0} -\frac{1}{t_k} ln\left[\left(\frac{\epsilon}{1-e^{-\beta^* t_k}}\right) - 1\right] \quad (19b)$$

And also from equation (17),

$$\beta_k = \lim_{\epsilon \to 0} \frac{-1}{V_c} e^{\left(\frac{-ln(V_k)}{(1-e^{-\beta^* t_k})}\right)\epsilon} \int_{\left(\frac{-ln(V_k)}{(1-e^{-\beta^* t_k})}\right)\epsilon}^{\infty} \frac{e^{-z}}{z} dz \quad (20a)$$

$$= \lim_{\epsilon \to 0} \frac{-1}{V_c} e^{\left(\frac{-ln(V_k)}{(1-e^{-\beta^* t_k})}\right)\epsilon} \left[C + ln\left[\frac{ln(V_k)}{1-e^{-\beta^* t_k}}\epsilon\right] + \int_0^{\left(\frac{ln(V_k)}{1-e^{-\beta^* t_k}}\right)\epsilon} \frac{e^{-\tau}-1}{\tau} d\tau\right] \quad (20b)$$

where C = 0:577215; Euler's constant.
In expressions (19b) and (20b) are equated to each other, i.e.,

$$\lim_{\epsilon \to 0} -\frac{1}{t_k} ln\left[1 - \left(\frac{1-e^{-\beta^* t_k}}{\epsilon}\right)\right] - \lim_{\epsilon \to 0} -\frac{1}{t_k} ln\left[\left(\frac{\epsilon}{1-e^{-\beta^* t_k}}\right) - 1\right] =$$

$$\lim_{\epsilon \to 0} \frac{-1}{V_c} e^{\left(\frac{-ln(V_k)}{(1-e^{-\beta^* t_k})}\right)\epsilon} \left[C + ln\left[\frac{ln(V_k)}{1-e^{-\beta^* t_k}}\epsilon\right] + \int_0^{\left(\frac{ln(V_k)}{1-e^{-\beta^* t_k}}\right)\epsilon} \frac{e^{-\tau}-1}{\tau} d\tau\right]$$

We expanding the a series and integrand in the value of β and the limit can be expressed then In the resulting equation retaining dominant $\ln(1/\epsilon)$ term only, after a little algebra, we get

$$\left(1 - \frac{t_k}{V_c}\right) ln \frac{1}{\epsilon} = -\frac{t_k}{V_c} C - \frac{t_k}{V_c} ln\left[\frac{ln(V_k)}{1-e^{-\beta^* t_k}}\right] - ln[1 - e^{-\beta^* t_k}] \quad (21)$$

or, equivalently,

$$\epsilon = exp\left\{ln[1 - e^{-\beta^* t_k}] - \frac{\frac{t_k}{V_c}(C + ln(ln(V_k)))}{\left(\frac{t_k}{V_c} - 1\right)}\right\}$$

A simple substitution of ϵ into $-\frac{1}{t_k} ln\left[1 - \left(\frac{1-e^{-\beta^* t_k}}{\epsilon}\right)\right]$
yields the required asymptotic formula

$$\beta_k = -\frac{1}{t_k} ln\left[1 - e^{\left(\frac{t_k}{V_c}\right)c / \left(\frac{t_k}{V_c}-1\right)} \left(ln V^*(t)^{\left(\frac{t_k}{V_c}\right)/\left(\frac{t_k}{V_c}-1\right)}\right)\right] \quad (22)$$

of (15) for large $V^*(t) = V_k$ with $\frac{t_k}{V_c \ln V^*(t)} = 1$

Strangely, on account of (21), the above formula fails at $\frac{t_k}{V_c} = 1$. But when $\frac{t_k}{V_c} = 1$, we have

$0 \le \beta_k \le \left(\frac{1 - e^{-\beta_k t_k}}{t_{kin[V_k]}}\right)$ from (16). Now setting $\left(\frac{1-e^{-\beta_k t_k}}{ln[V_k]}\right) = \frac{1}{\epsilon}$ substitute this into equation (15), to get

$$\beta_k = \lim_{\epsilon \to 0} \frac{-1}{t_k} e^{-\epsilon} \int_{-\epsilon}^{\infty} \frac{e^{-z}}{z} dz$$

If we send ϵ to zero, on account of 8.212,1. in [45], we get

$$\beta_k = \lim_{\epsilon \to 0} -\frac{1}{t_k} ln\left[1 - \left(\frac{ln[V_k]}{\epsilon}\right)\right] \qquad (23a)$$

$$= \lim_{\epsilon \to 0} -\frac{1}{t_k} ln\left[1 - \left(\frac{ln[V_k]}{\epsilon}\right)\right] - \lim_{\epsilon \to 0} -\frac{1}{t_k} ln\left[\left(\frac{\epsilon}{ln[V_k]}\right) - 1\right] \quad (23b)$$

And also from equation (17),

$$\beta_k = \lim_{\epsilon \to 0} \frac{-1}{t_k} e^{-\epsilon} \int_{-\epsilon}^{\infty} \frac{e^{-z}}{z} dz \qquad (24a)$$

$$= \lim_{\epsilon \to 0} \frac{-1}{t_k} e^{-\epsilon} \left[C + \ln(\epsilon) + \int_0^{\epsilon} \frac{e^{-\tau} - 1}{\tau} d\tau\right] \qquad (24b)$$

In expressions (23b) and (24b) are equated to each other, i.e.,

$$\lim_{\epsilon \to 0} -\frac{1}{t_k} ln\left[1 - \left(\frac{ln[V_k]}{\epsilon}\right)\right] - \lim_{\epsilon \to 0} -\frac{1}{t_k} ln\left[\left(\frac{\epsilon}{ln[V_k]}\right) - 1\right] =$$

$$= \lim_{\epsilon \to 0} \frac{-1}{t_k} e^{-\epsilon} \left[C + \ln(\epsilon) + \int_0^{\epsilon} \frac{e^{-\tau} - 1}{\tau} d\tau\right]$$

We expanding the a series and integrand in the value of β and the limit can be expressed. then in the resulting equation, as the dominant $\ln(1/\epsilon)$ term vanishes, we consider only ϵ-order term.

After a little algebra, we obtain

$$-\frac{1}{t_k} ln[(\ln(V_k))] - \frac{\epsilon}{t_k ln[V_k]} = \frac{1}{t_k}[(1-\epsilon)(C-\epsilon)]$$

Or

$$\epsilon = \frac{ln[(\ln(V_k))] + C}{C - 1 - (1/\ln(V_k))}$$

A simple substitution of ϵ into $-\frac{1}{t_k} ln\left[1 - \left(\frac{ln[V_k]}{\epsilon}\right)\right]$ yields the required asymptotic formula

$$\beta_k = -\frac{1}{t_k} ln\left[1 - \frac{C\, ln[V_k] - ln[V_k] - 1}{ln(ln[V_k]) + C}\right], \qquad (25)$$

of (15) for large $ln[V_k]$ when $\frac{t_k}{V_c} = 1$. summing up, we conclude the following.

THEOREM : For every fixed $V_c, t_k \text{ and } V^*(t)$, let I_1 and I_2 be intervals defined by

$$I_1 = \left[0, -\frac{1}{t_k} ln\left[1 - e^{\left(\frac{t_k}{V_c}\right)C/\left(\frac{t_k}{V_c}-1\right)}\left(lnV^*(t)^{\left(\frac{t_k}{V_c}\right)/\left(\frac{t_k}{V_c}-1\right)}\right)\right]\right]$$

$$I_2 = \left[0, -\frac{1}{t_k} ln\left[1 - \frac{C\, ln[V_k] - ln[V_k] - 1}{ln(ln[V_k]) + C}\right]\right]$$

where C = 0:577215; Euler's constant. Suppose there exists a unique solution of (7) in I_1, I_2 respectively, when $\frac{t_m}{V_c} \neq 1 \text{ and } \frac{t_m}{V_c} = 1$ Then it is necessary that $\frac{t_m}{V_c \ln V^*(t)} > 1$. Moreover, the asymptotic solution of (7) for a large $V^*(t) = V_k$ is given by (22), (25), respectively, when $\frac{t_m}{V_c} \neq 1 \text{ and } \frac{t_m}{V_c} = 1$.

Remark 1. Note that care must be taken while using the asymptotic solution (22) and (25), since the condition when $t_k = t_m$, $V_k = e^{\frac{t_m}{V_c}}$ and when $t_k = V_c \ln(V_k)$, $V_k = e^{\frac{t_m}{V_c}}$ and $t_k \neq t_m$ are crucially dependent on whether given $\frac{t_m}{V_c \ln V^*(t)} > 1$ or $\frac{t_m}{V_c \ln V^*(t)} < 1$.

Remark 2. From (4) it is easy to get the asymptotic formula of *A* using (22) and (25) for $V^*(t) = V_k$

Remark 3. We listed in table I the numerical values of asymptotic solution (22) for $V^*(t) = V_k$ for a comparison with that for a large $V^*(t)$

Remark 4. There were no recorded samples with $\frac{t_m}{V_c}$ =1 to compare with the asymptotic solution(25) for $V^*(t) = V_k$.

Remark 5. Asymptotic solution is useful in the study of qualitative behaviour of solution.

Remark 6. Using (13) or (14) from the values of $V_c, t_m \text{ and } V^*(t)$ we can calculate unique β then using that β substitute in (4) we will get the value of *A.*

Remark 7. Using (22) or (25) we can find critical Gompertz parameter βk for large number solid tumour growth cells, in the absence of specific volume data at particular time.

IV. CONCLUSION

The above theorem states that the asymptotic solution β of (7) is a continuous function in the variables $\frac{1}{V_c}, t_m \text{ and } V^*(t)$ from initial growth to critical growth time (or, $V^*(t) \ge V_k$). What happens to solution β when $V^*(t) \le V_k$ (below the critical volume)? As we have already equated t_m with t_k when $\frac{t_m}{V_c \ln V^*(t)} > 1$, what then is the actual maximum life time(theoretically exists) $t^*{}_m$? Such $t^*{}_m > t_m$ exists, How to determine this $t^*{}_m$?. All these questions remain to be addressed.

The purpose of this discussion has been to address the issue of existence of critical Gompertz parameter βk for large number solid tumour growth cells, in the absence of specific volume data at particular time. Such a method is necessary when attempting to estimate the growth decelaration rate parameter. From these analyses, 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.

ACKNOWLEDGEMENT

The work by **M.Pitchaimani** is supported by the **SERC-DST** (Ministry of Science and Technology, Government of India) Reference number:**SR/S4/MS-677/10**.

Table-1 Analysis of Theoretical Gompertz Functions in terms of t_m,t_k and VRD(asymptotic), VRD(critical) which depends on the tumour cell number at any time.

	tumour type	$\frac{1}{V_c}$	$t_m$days	$t_k$days	VRD (asymptotic)	VRD (critical)	V_k
	Mouse:						
1.	Krebs	$8.4567X10^{-6}$	-	10.4429	0.15675 hours	0.135 hours	800 X 10^6cells
2.	Ehrlich	$8.0750X10^{-7}$	-	331.1687	9.88071 hours	9.26 hours	1593 X 10^6cells
3.	MC_1M,low dose	$1.4616X10^{-6}$	-	-	6.5103 hours	6.09 hours	467X 10^6cells
4.	$6C_3HED$,high dose	$33.0076X10^{-5}$	425.9917	170.2028	20.01456 hours	19.6 hours	890 X 10^6cells
5.	$6C_3HED$,low dose	$9.1051X10^{-5}$	567.3520	141.5309	13.02839 hours	11.9 hours	4776 X 10^6cells
6.	DBA lymphoma	$4.8265X10^{-8}$	276.5147	207.188	2.68454 hours	2.59 hours	1000 X 10^6cells
7.	EI_4,low dose	$6.0002X10^{-8}$	438.213	317.4464	3.53419 hours	3.46 hours	1260 X 10^6cells
8.	EI_4,low dose high dose	$1.03297X10^{-5}$	-	-	5.62582 hours	4.23 hours	1290 X 10^6cells
9.	EO771	$2.9392X10^{-4}$	79.4302	32.9247	1.33441 days	1.08 days	31cm^3
10.	Osteosarcomas	$12.729X10^{-5}$	38.9177	18.2688	0.75516 days	0.719 days	4:3cm^3
	Rat:						
11.	Walker,W26b1	$5.3999X10^{-5}$	341.2281	42.3284	4.03779 days	3.26 days	175 g
12.	Walker,W12a7	$3.8778X10^{-5}$	342.2281	51.0880	2.2779 days	2.07 days	212cm^3
13.	Walker,W10a6	$2.3222X10^{-3}$	59.1180	36.7349	2.02498 days	1.99 days	490cm^3
14.	Walker,W10b4	$1.06732X10^{-4}$	-	79.8275	6.09501 days	5.29 days	196cm^3
15.	R39Sarcoma,R3a7	$1.5610X10^{-4}$	42.4407	28.4854	0.56666 days	0.56 days	188cm^3
16.	7R39Sarcoma,R4c4	$5.3331X10^{-3}$	-	32.2799	1.32498 days	1.35 days	276cm^3
17.	R39Sarcoma,a7R3	$1.6563X10^{-5}$	-	62.7635	0.9851 days	0.97 days	202cm^3
18.	Flexne-Jobling	$1.865X10^{-5}$	-	43.9302	2.02099 days	1.84 days	18.3 g
	Rabbit:						
19.	Brown-Pearce	$2.08294X10^{-3}$	45.7709	28.9986	0.56168 days	0.576 days	29:8cm^3

The source of data for each species is given in [9,42,46].

REFERENCES

1. Z.Bajer, Gompertizian growth as a self-similar and allometric process,Growth Dev. Aging63, pp.3-11, (1999).
2. Z.Bajzer, M.Marusic and S.AukPavlovic, conceptual Frameworks for mathematical modelling of tumour growth dynamics, Math. Comp.Mod. 23, pp.31-46, (1996).
3. N.Bellomo and L.Preziosi,Modelling and mathematical problems related to tumour evolution and its interaction with the immune system,Math.Comp,Mod32, pp.413-452,(2000).
4. S.Cooper, Distinguishing between linear and exponential cell growth during the division cycle: Single-cell studies, cell-culture studies and the object of cell-cycle research, Theor.Biol Med.Model3,p.10(2006).
5. D.Dingli, M.D.Cascino, K.Josic, S.J.Russell, and Z.Bajzer, Mathematical modelling of cancer radiovirotherapy,Math. Biosci.199, pp.55-78,(2006).
6. P.Hahnfeldt, D.Panigrahy, J.Folkman and L.Hlatky, Tumour development under angiogenic signaling: A dynamical theory of tumour growth, treatment response, and post vascular dormancy,Cancer Res.59,pp4770-4775, (1999).
7. A.R.Kansal, S.Torquato, G.R.Harsh, E.A.Chiocca and T.S.Deisboeck, simulated brain tumour growth dynamics using a three-dimensional cellular automaton,J.Theor. Biol203, pp 367-382,(2000).
8. F.Kozusko and Z.Bajzer, Combining Gompertizian growth and cell population dynamics, Math.Biosci.185, pp 153-167, (2003).
9. Anna Kane Laird. Dynamics of Tumour Growth. Br J Cancer. 18(3), 490-502 (September 1964).
10. Anna Kane Laird. Dynamics of Tumour Growth:Comparisons of growth rates and extrapolation of growth curve to one cell, Br J Cancer. 19, pp.278-291 (1965).
11. M.Marusic, Z.Bajzer, S.Vuk-Pavlovic and J.P.Freyer, Tumor growth in vivo and as multicellular spheroids compared by mathematical-models. Bull.Math.Biol56,pp.617-631, (1994).
12. J.A.McCredie, W.R.Inch, J.Kruuv and T.A Watson, The rate of tumour growth in animals, Growth 29, pp.331-347, (1965).
13. S.Michelson and J.Leith, Positive feedback and angiogenesis in tumour growth control,Bull.Math.Biol.59,pp.233-254,(1997).
14. L.Norton, R.Simson, H.D.Brereton and A.E.Bogden, Predicting the course of Gompertizian Growth, Nature264, pp.542-545, (1976).
15. C.Panetta, A Mathematical model of periodically pulsed chemotherapy: Tumour recurrence and metastasis in a competitive environment.Bull.Math.Biol58, pp425-447, (1996).
16. E.S.Lakshminarayanan and M.Pitchaimani. Existence of Gompertz parameters and its asymptotic formulae for a large population. Appl. Math. Lett. 17(2), 173 - 180 (2004).
17. X.Xu.The biological foundation of the Gompertz model .Int.J.Biomed. Comput. 20,pp.35-39,(1987).
18. Folkman.J. Tumour angiogenesis. Adv.Cancer.Res. 19,331-358,(1974).
19. Folkman.J. The vascularisation of tumours. In:Cancer Biology(edited by E.C.Friedberg),Scientific American 115-124,(1976).
20. Muthukarrupan V.R., Kubai.L and Auerbach. R.Tumour-induced neovascularisation in the mouse eye. J.Natl.Cancer Inst.69, 699-705,(1982).
21. Helen M.Byrne. A weakly nonlinear analysis of a model of avascular solid tumour growth.J.Math.Biol. 39:59-89, (1999).
22. Kerr.J.F.R. Shrinkage necrosis; a distinct mode of cellular death. J.Path. 105, 13-20, (1971).
23. Sutherland, R.M.Cell and environment interactions in tumour microregions: the multicell spheroid model. Science240, 177-184, (1988).
24. McElwain.D.L.S. and Morris.L.E. Apoptosis as a volume loss mechanism in mathematical models of solid tumour growth. Math.Biosci. 39, 147-157,(1978).
25. Maggelakis.S.A, and Adam.J.A. Mathematical model of prevascular growth of a spherical carcinoma. Math.Comput.Modelling. 13, 23-38,(1990).
26. Byrne.H.M and Chaplain.M.A. Growth of necrotic tumours in the presence and absence of inhibitors. Math.Biosci. 135, 187-216,(1996).
27. L.Bass H.S.Green and H.Boxenbaum, Gompertzian mortality derivedfrom competitionbetween cell-types: congenial, toxicologic and biometric determinants of longevity, J.Theor.Biol.140,p.263, (1989).
28. I. D. Bassukas. Comparative Gompertzian analysis of alterations of tumour growth patterns.Cancer Research, 54,p. 4385 - 4392 (1994).
29. P. Fuchshuber, M. Gunther, W. Feaux de Lacroix and R. Fischer.A Mathematical model for metastatic growth illustrated by in vivo and in vitro growth of a transplantable mammarycarcinoma in mice. Anticancer Research, 6,p. 819 - 828 (1986).
30. A.S.Qi, X.Zheng, C.Y.Du and B.S.An. A cellular automaton model of cancerous growth. J.theor. Biol. 161, 1 - 12 (1993).
31. K.Rygaard and M.Spang-Thomsen, Quantitationand Gompertzian analysis of tumour growth,Breast Cancer: Res.Treat. 46,p.303,(1997).
32. N.Y.Tyurin, A.Y.Yakovlev, J.Shi and L.Bass, Testing a model of aging in animal experiments,Biometics51,p.363,(1995).
33. L. Ferrante, S. Bompadre, L. Possati, and L. Leone. Parameter estimation in a Gompertzian stochastic model for tumor growth. Biometrics, 56, p.1076 - 1081 (2000).
34. Z.H.Levine, B.R.Borchardt, N.J.Brandenburg, C.W.Clark, B.Muralikrishnan, C.M.Shakarji Chen, J.J.Siege. E.L. RECIST versus volume measurement in Medical CT using ellipsoids ofknown size. Optics Express 18(8), 8151 8159 (April 12, 2010).
35. A.P.Peskin, K.Kafadar, A.M.Santos and G.G. Haemer. Robust Volume Calculations of Tumours of Various Sizes. The 2009 International Conference on Image Processing, Computer Vision, and Pattern Recognition. (July 2009).
36. Adele P. Peskin and Alden A. Dima. Modeling Clinical Tumours to Create Reference Data for Tumour Volume Measurement. Spriger-Verleg Berlin Heidelgerg, G.Bebis et.al.(Eds).ISVC(2010), part II, LNCS 6454 736-746 (2010).
37. C.E.Finch, M.C.Pike and M.Witten. Slow mortality rate accelerations during ageing in some animals approximate that of humans.Science, 249, 902 - 905 (1990).
38. F. M O Al-Dweri, D. Guirado, A. M. Lallena and V. Pedraza. E_ect on tumour control of time interval between surgery and postoperative radiotherapy: an empirical approach using MonteCarlo simulation. Phys. Med. Biol. 49, 2827 - 2839 (2004).
39. G.G.Steel and L.F.Lamerton, The Growth rate of Human tumours , Br J Cancer. 20(1):7486,(1966).
40. Boag, J.W. Maximum likelihood estimates of the proportion of patients cured by cancer therapy.J. R. Stat. Soc. 11, 15-53,(1949).
41. Collins. V. P., Loe_e. R. K. and Tivery H. Observations on growth rates of human tumors.Am.J. Roentgenol Radium Ther .Nucl Med..76(5),988-1000, (1956)
42. M. Pitchaimani,G.Somasundara Ori and T. Eakin, Unique Estimation and Sensitivity Behaviour of Gompertz Tumour Growth Model Parameter(Submitted).
43. E.S.Lakshminarayanan and M.Pitchaimani. Existence of critical Gompertz parameters and its asymptotic expression. Comp.Math. with applications 55,pp.1302-1309, (2008).
44. M. Pitchaimani , G.Somasundara Ori , Existence of solid tumour growth Gompertz parameter and its asymptotic expression, (Submitted).
45. I.S. Gradshteyn and I.M. Ryzhik. Table of Integrals, Series and Products Academic Press(1980).
46. K. C. Iarosz, C. C. Martins, A. M. Batista, R. L. Viana, S. R.Lopes, I. L. Caldas and T. J.P. Penna. On a cellular automaton with time delay for modelling cancer tumours Journal of Physics Conference Series 285 (2011).

AUTHORS PROFILE

M.Pitchaimani did M.Phil Mathematics and Ph.D Mathematics at Madurai Kamaraj University, Madurai, India. He is working as Assistant Professor in RIASM, Univeristy of Madras, Chennai, India. He published 24numbers of research papers in reputed Journals. His research areas are Stochastic differential equations and Mathematical modeling. He guided 13 M.Phil Students and guiding 07 Ph.D. Students. He awarded by young Scientist from DST.

G.Somasundara ori did M.Phil Mathematics at Madurai Kamaraj University, Madurai, India and he is Research Schlor in Mathematics at RIASM, Univeristy of Madras, Chennai, India. He published 2 numbers of research papers in reputed Journals. His research areas are Stochastic differential equations and Mathematical modeling.