Qualitative Analysis of Gompertzian parameter in Brain Tumour

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Abstract

The Gompertz model, which is very helpful in explaining tumour dynamics, is based on a differential equation that is used to compute growth rates in a variety of domains. It is based on an exponential formula, and the values it generates are logically chosen depending on how the tumour behaves. The present study aims to analyze the qualitative properties of Gompertzian parameter in Brain Tumour growth model.

Keywords : Gompertz model, brain tumour, Gompertz parameter, uniqueness, stability.

1 Introduction

In order to understand the dynamic process of cancer cell formation and proliferation, mathematical models have been devised to aid in tumour size prediction. It has been demonstrated that differential equations can be used to forecast the growth curve of a variety of tumours. The Gompertz model is one that has been used for monitoring this prediction. The early stages of cancer progression are naturally represented by the exponential model. Any portion of the brain or skull can develop a brain tumour. Depending on the tissue from which they originate, the brain can develop any one of more than 120 different tumour forms.

Mathematics and computation can help in solving several growing problems in medical research by proposing models that allow us to formalize the cause-and-effect process and tie it to the biological observations. The process of mathematical modeling may be utilized to describe an object that exists in any area of science, not only mathematics. Models can describe interactions

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between biological components, which allow researchers to deduce the consequences of the interactions in medical and natural processes [3]. The basis of any mathematical model used to study the treatment of cancer is a model of tumor growth [6].The primary goals of a model of tumor growth are to predict the evolution of a tumor and optimize treatment regimens.

A mathematical system consists of a collection of assertions from which we derive consequences by logical arguments. The brain can be viewed as a system with various interacting regions that produce complex behaviors. Mathematical models have been developed to help predict tumor size and comprehend the dynamical process of cancer cell development and proliferation. The use of differential equations has been proven to predict the growth curve of various types of tumors [2]. One model that has been successfully used to manage this prediction is Gompertz model. In order to assess how accurate the growth over time results are, the Gompertz model is employed to study the growing brain tumour data over a period of seventy days. This article deals with qualitative analysis of Gompertzian brain tumour model.

2 Estimation of the parameter

The classical Gompertz differential equation is

$$\frac{dV}{dt} = (\alpha - \beta lnV^{'})V, \tag{1}$$

where
$V =$ volume in cubic milimetres, $V^{'} = \frac{V}{V_0}$, V_0 is the volume at time $t = 0$
$t =$ time in days,
$\beta =$ growth limit of the tumor and
$\alpha =$ constant growth rate. An exact mathematical description of our model of tumour cell proliferation is given by a Gompertz equation (1) of the following form

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

The Gompertz model presents a doubling time (Volume Rate Doubling time (VRD)) which depends only on β. Solving equation (2) for VRD gives

$$VRD = -\frac{1}{\beta} ln \left[1 - \frac{\beta}{\alpha} ln2 \right]. \tag{3}$$

Benjamin Gompertz (1825) [5] proposed that the growth of tumour volume increased exponentially with time for all tumours. Various subsequent researchers, especially in biology and gerontology, have viewed Gompertz observation as a law that describes the process of senescence in almost all type of tumours at any time after the onset of growth. As a rough approximation at initial growth, Gompertz exponential formula does capture the rise in growth in a great variety of tumours. Equation (2) gives

$$\frac{\alpha}{\beta} = \frac{ln[V^{'}(t)]}{(1-e^{-\beta t})} \tag{4}$$

and

$$V(t_m{}^{'}) = V_0 e^{\frac{\alpha}{\beta}(1-e^{-\beta t_m{}^{'}})} \tag{5}$$

(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

$$t_m{}^{'} = -\frac{1}{\beta} ln\left[1 - \frac{\beta}{\alpha} ln\left[\frac{V(t_m{}^{'})}{V_0}\right]\right]. \tag{6}$$

Finally the eatimation for β is given by

$$-\beta = \frac{1}{V_{cu}} e^{-\frac{\alpha}{\beta}} \int_{-\frac{\alpha}{\beta}}^{\infty} \frac{e^{-w}}{w} dw, \tag{7}$$

where $w = -\frac{\alpha}{\beta} e^{-\beta t}$.

Table 1 Data set of volume size of brain tumor
(reprinted from [7])

$Time(days)$	$Volume(V^{'}(t)),\ mm^2$
1	151
5	178
10	226
15	329
20	433
25	564
30	598
35	687
40	796
45	855
50	934
55	1001
60	1089
65	1143
70	1217

3 Existence of the parameter

The integral in the equation (7) exists if $\beta < 0$. If $\beta > 0$, then $\frac{e^{-w}}{w}$ has a pole at $w = 0$. Hence we take the principal value of the integral and prove its existence.

Theorem 3.1 Principal value of the integral $\int_{-\frac{\alpha}{\beta}}^{\infty} \frac{e^{-w}}{w} dw$ exists, if $\beta > 0$.

Proof: Now,

$$\int_{-\frac{\alpha}{\beta}}^{\infty} \frac{e^{-w}}{w} dw = \int_{-\frac{\alpha}{\beta}}^{-\epsilon} \frac{e^{-w}}{w} dw + \int_{-\epsilon}^{\epsilon} \frac{e^{-w}}{w} dw + \int_{\epsilon}^{\infty} \frac{e^{-w}}{w} dw. \tag{8}$$

Consider the middle term on the right hand side of the above integral

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

Hence the principal value of the above integral exists, if $\beta > 0$. The basic equation (7) is transcendental, involving an exponential integral. Hence, its solution may not be unique and so it is necessary to prove the uniqueness of β.

4 Uniqueness of the parameter

4.1 Uniqueness theorem

Note:
It may be observed that $\frac{1}{V_{cu}}$ cannot exceed α, as $\frac{1}{V_{cu}}$ represents contributions from α and β.
Proof:

$$-\beta = \frac{1}{V_{cu}} e^{-\frac{\alpha}{\beta}} \int_{-\frac{\alpha}{\beta}}^{\infty} \frac{e^{-w}}{w} dw \tag{9}$$

$$-\beta \leq \frac{1}{V_{cu}} e^{-\frac{\alpha}{\beta}} e^{\frac{\alpha}{\beta}} \left(-\frac{\beta}{\alpha} \right) \tag{10}$$

which implies that $\frac{1}{V_{cu}} \leq \alpha$.

Theorem 4.1 The equation (7) has a unique solution if $\frac{2t_m^{'}}{V_{cu}} < 1$ for $\beta > 0$.
Proof:
Let β_1 and β_2 be two distinct positive solutions of (7). Then

$$-\beta_1 = \frac{1}{V_{cu}} e^{-\frac{\alpha}{\beta_1}} \int_{-\frac{\alpha}{\beta_1}}^{\infty} \frac{e^{-w}}{w} dw$$

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$$-\beta_2 = \frac{1}{V_{cu}} e^{-\frac{\alpha}{\beta_2}} \int_{-\frac{\alpha}{\beta_2}}^{\infty} \frac{e^{-w}}{w} dw$$

Using (3) we have

$$-\beta_1 = \frac{1}{V_{cu}} e^{-\frac{lnV^{'}(t)}{(1-e^{-\beta_1 t_m^{'}})}} \int_{-\frac{lnV^{'}(t)}{(1-e^{-\beta_1 t_m^{'}})}}^{\infty} \frac{e^{-w}}{w} dw$$

$$-\beta_2 = \frac{1}{V_{cu}} e^{-\frac{lnV^{'}(t)}{(1-e^{-\beta_2 t_m^{'}})}} \int_{-\frac{lnV^{'}(t)}{(1-e^{-\beta_2 t_m^{'}})}}^{\infty} \frac{e^{-w}}{w} dw$$

Now

$$\begin{aligned} \beta_1 - \beta_2 &= -\frac{1}{V_{cu}} \left[\int_{z_1}^{\infty} \frac{e^{-w+z_1}}{w} dw - \int_{z_2}^{\infty} \frac{e^{-w+z_2}}{w} dw \right] \\ &= -\frac{1}{V_{cu}} \int_{0}^{\infty} e^{-x} \left[\frac{1}{x+z_1} - \frac{1}{x+z_2} \right] dx \end{aligned} \tag{11}$$

where $z_j = -\frac{lnV^{'}(t)}{(1-e^{-\beta_j t_m^{'}})}$ for $j = 1, 2$ and $x = (w - z_j)$ for $j = 1, 2$. Also, $e^{-x} \geq 1, \forall x \leq 0$. Hence we obtain

$$\begin{aligned} |\beta_1 - \beta_2| &\leq \frac{1}{V_{cu}} |z_1 - z_2| \int_{0}^{\infty} \frac{dx}{(x+z_1)(x+z_2)} \\ &= \frac{1}{V_{cu}} ln \left[\frac{z_1}{z_2} \right]. \end{aligned}$$

Therefore we get

$$\begin{aligned} |\beta_1 - \beta_2| &\leq \frac{1}{V_{cu}} \left| ln \left[\frac{1 - e^{-\beta_2 t_m^{'}}}{1 - e^{-\beta_1 t_m^{'}}} \right] \right| \\ &= \frac{1}{V_{cu}} \left| ln \left[\frac{e^{-\beta_2 t_m^{'}} (e^{-\beta_2 t_m^{'}} - 1)}{e^{-\beta_1 t_m^{'}} (e^{-\beta_1 t_m^{'}} - 1)} \right] \right| \\ &= \frac{1}{V_{cu}} \left| ln \left[\frac{e^{-\beta_2 t_m^{'}}}{e^{-\beta_1 t_m^{'}}} \right] + ln \left[\frac{e^{-\beta_2 t_m^{'}} - 1}{e^{-\beta_1 t_m^{'}} - 1} \right] \right| \\ &= \frac{1}{V_{cu}} \left| [\beta_1 t_m^{'} - \beta_2 t_m^{'}] + ln[e^{\beta_2 t_m^{'}} - 1] - ln[e^{\beta_1 t_m^{'}} - 1] \right|. \end{aligned}$$

Applying mean value theorem, we obtain

$$\begin{aligned} |\beta_1-\beta_2| &= \frac{1}{V_{cu}}\left[|\beta_1 t_m^{'}-\beta_2 t_m^{'}|+ln|e^{-\beta_2 t_m^{'}}-e^{-\beta_1 t_m^{'}}|\right] \\ &= \frac{1}{V_{cu}}[|\beta_1-\beta_2|t_m^{'}+|\beta_1-\beta_2|t_m^{'}] \\ &= \frac{2t_m^{'}}{V_{cu}}|\beta_1-\beta_2|. \end{aligned}$$

which gives

$$\left(\frac{2t_m^{'}}{V_{cu}}-1\right)|\beta_1-\beta_2|\geq 0. \tag{12}$$

But $\frac{2t_m^{'}}{V_{cu}}<1$. Hence the above inequality implies that $\beta_1\equiv\beta_2$, for $\beta>0$.

4.2 Necessary Condition for Uniqueness

Theorem 4.2 The necessary condition to have a unique solution for equation (7) is that $\frac{t_m^{'}}{V_{cu}ln[V^{'}(t)]}<1$ for $\beta>0$.

Proof:

Let β_1 and β_2 be two distinct positive solutions of (7). Then from (12) we have

$$\begin{aligned} \beta_1-\beta_2 &= -\frac{1}{V_{cu}}(z_2-z_1)\int_0^\infty \frac{e^{-x}}{(x+z_1)(x+z_2)}dx \\ &= -\frac{1}{V_{cu}}\left(\frac{1}{1-e^{-\beta_2 t_m^{'}}}-\frac{1}{1-e^{-\beta_1 t_m^{'}}}\right)(1-e^{-\beta_1 t_m^{'}})(1-e^{-\beta_2 t_m^{'}}) \\ &\times \int_0^\infty \frac{e^{-wln[V^{'}(t)]}}{(1+w(1-e^{-\beta_1 t_m^{'}}))(1+w(1-e^{-\beta_2 t_m^{'}}))}dy. \end{aligned}$$

Since

$$\frac{e^{-wln[V^{'}(t)]}}{(1+w(1-e^{-\beta_1 t_m^{'}}))(1+w(1-e^{-\beta_2 t_m^{'}}))}\leq 1, \tag{13}$$

we get

$$\begin{aligned} \beta_1-\beta_2 &\leq -\frac{1}{V_{cu}}\left(\frac{1}{1-e^{-\beta_2 t_m^{'}}}-\frac{1}{1-e^{-\beta_1 t_m^{'}}}\right)(1-e^{-\beta_1 t_m^{'}})(1-e^{-\beta_2 t_m^{'}})\int_0^\infty e^{-wln[V^{'}(t)]}dw \\ &= -\frac{1}{V_{cu}}\left(\frac{1}{1-e^{-\beta_2 t_m^{'}}}-\frac{1}{1-e^{-\beta_1 t_m^{'}}}\right)(1-e^{-\beta_1 t_m^{'}})(1-e^{-\beta_2 t_m^{'}})\frac{1}{ln[V^{'}(t)]}. \end{aligned}$$

Hence,

$$|\beta_1-\beta_2| \leq \frac{1}{V_{cu}ln[V^{'}(t)]}\left|(1-e^{-\beta_1 t_m^{'}})-(1-e^{-\beta_2 t_m^{'}})\right|$$

$$= \frac{1}{V_{cu} ln[V'(t)]} \left| (\beta_1 t_m^{'}) \frac{(1 - e^{-\beta_1 t_m{'}})}{\beta_1 t_m^{'}} - (\beta_2 t_m^{'}) \frac{(1 - e^{-\beta_2 t_m^{'}})}{\beta_2 t_m^{'}} \right|$$

$$= \frac{1}{V_{cu} ln[V'(t)]} \left| \frac{\beta_1 t_m^{'}}{\left(\frac{\beta_1 t_m^{'}}{1 - e^{-\beta_1 t_m^{'}}} \right)} - \frac{\beta_2 t_m^{'}}{\left(\frac{\beta_2 t_m^{'}}{1 - e^{-\beta_2 t_m^{'}}} \right)} \right|.$$

Thus

$$|\beta_1 - \beta_2| \leq \frac{t_m^{'} |\beta_1 - \beta_2|}{V_{cu}} ln[V^{'}(t)] max \left(\frac{\beta_1 t_m^{'}}{1 - e^{-\beta_1 t_m^{'}}}, \frac{\beta_2 t_m^{'}}{1 - e^{-\beta_2 t_m^{'}}} \right). \tag{14}$$

Suppose we have a unique solution of (7), it follows from (14) that

$$\frac{t_m^{'}}{V_{cu} ln[V'(t)] max \left(\frac{\beta_1 t_m^{'}}{1 - e^{-\beta_1 t_m^{'}}}, \frac{\beta_2 t_m^{'}}{1 - e^{-\beta_2 t_m^{'}}} \right)} < 1. \tag{15}$$

Since $\frac{\beta t_m^{'}}{1 - e^{-\beta t_m^{'}}} \geq 1, \forall \beta t_m^{'} \geq 0$, from (15) we get

$$\frac{t_m^{'}}{V_{cu} ln[V'(t)]} < min \left(\frac{\beta_1 t_m^{'}}{1 - e^{-\beta_1 t_m^{'}}}, \frac{\beta_2 t_m^{'}}{1 - e^{-\beta_2 t_m^{'}}} \right) < max \left(\frac{\beta_1 t_m^{'}}{1 - e^{-\beta_1 t_m^{'}}}, \frac{\beta_2 t_m^{'}}{1 - e^{-\beta_2 t_m^{'}}} \right)$$

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

Note that $\frac{\beta t_m^{'}}{1 - e^{-\beta t_m^{'}}}$ attains 1 only if $\beta t_m^{'} = 0$. Hence the above inequalities implies that $\frac{t_i m^{'}}{V_{cu} ln[V'(t)]} < 1$ for $\beta > 0$. Thus, to have a unique solution of equation (7) it is necessary that $\frac{t_m^{"}}{V_{cu} ln[V'(t)]} < 1$ for $\beta > 0$.

5 Stability Analysis

The stability theorem of the growth rate parameter of the Gompertz brain tumour model is investigated in this section [4, 1]. The stability examination of the parameter (in terms of tumour cell volume) leads to the conclusion that the parameter is constant.

5.1 Necessary condition for stability

Let $\beta 1$ and β_2 be two positive distinct solutions of equation (7) with tumour sizes $V_1^{'}$ and $V_2^{'}$ respectively. Then

$$\begin{aligned}\beta_1 &= -\frac{1}{V_{cu}} e^{-\frac{ln[V_1{}'(t)]}{(1-e^{-\beta_1 t'_m})}} \int\limits_{-\frac{ln[V_1{}'(t)]}{(1-e^{-\beta_1 t'_m})}}^{\infty} \frac{e^{-w}}{w} dw \\ \beta_2 &= -\frac{1}{V_{cu}} e^{-\frac{ln[V_2{}'(t)]}{(1-e^{-\beta_2 t'_m})}} \int\limits_{-\frac{ln[V_2{}'(t)]}{(1-e^{-\beta_2 t'_m})}}^{\infty} \frac{e^{-w}}{w} dw\end{aligned}$$

Consider

$$\begin{aligned}\beta_1 - \beta_2 &= -\frac{1}{V_{cu}} \left[\int\limits_{x_1}^{\infty} \frac{e^{-w+x_1}}{w} dw - \int\limits_{x_2}^{\infty} \frac{e^{-w+x_2}}{w} dw \right] \\ &= -\frac{1}{V_{cu}} \int\limits_{0}^{\infty} e^{-u} \left[\frac{1}{u+x_1} - \frac{1}{u+x_2} \right] du,\end{aligned}$$

where

$$x_i = -\frac{ln[V_i^{'}(t)]}{(1-e^{-\beta_i t'_m})} \tag{16}$$

for $i = 1, 2$ and $u = z - x_i$. Set

$$x_1 = \frac{x_1+x_2}{2} + \frac{x_1-x_2}{2}, \quad x_2 = \frac{x_1+x_2}{2} - \frac{x_1-x_2}{2}. \tag{17}$$

[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 (17) into the above equation results in

$$\beta_1 - \beta_2 = -\frac{1}{V_{cu}} e^{\frac{x_1+x_2}{2}} \int\limits_{\frac{x_1+x_2}{2}}^{\infty} e^{-y} \left[\frac{1}{y+\frac{x_1-x_2}{2}} - \frac{1}{y-\frac{x_1-x_2}{2}} \right] dy \tag{18}$$

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

On the RHS of (18), the expression

$$\frac{1}{y+\left(\frac{x_1-x_2}{2}\right)} - \frac{1}{y-\left(\frac{x_1-x_2}{2}\right)} = \frac{1}{y}\left(1 - \frac{x_1-x_2}{2y} + ...\right) - \frac{1}{y}\left(1 + \frac{x_1-x_2}{2y} + ...\right) \tag{19}$$

can be approximated to $-(\frac{x_1-x_2}{y^2})$ by neglecting higher order perturbation terms in each expression on the RHS of (19), since $\left|\frac{x_1-x_2}{x_1+x_2}\right| < 1$.

On account of (19), (18) becomes

$$\beta_1 - \beta_2 = -\frac{1}{V_{cu}} e^{\frac{x_1+x_2}{2}} \int_{\frac{x_1+x_2}{2}}^{\infty} -\left(\frac{x_1 - x_2}{y^2}\right) e^{-y} dy.$$

Further,

$$\begin{aligned} |\beta_1 - \beta_2| &\leq \frac{1}{V_{cu}} e^{\frac{x_1+x_2}{2}} \int_{\frac{x_1+x_2}{2}}^{\infty} \frac{|x_1 - x_2|}{y^2} e^{-y} dy \\ &\leq \frac{1}{V_{cu}} |x_1 - x_2| e^{\frac{x_1+x_2}{2}} e^{-\frac{x_1+x_2}{2}} \int_{\frac{x_1+x_2}{2}}^{\infty} \frac{dy}{y^2}. \end{aligned} \tag{20}$$

Upon integration we get

$$|\beta_1 - \beta_2| \leq \frac{1}{V_{cu}} \left| \frac{x_1 - x_2}{\frac{x_1+x_2}{2}} \right|. \tag{21}$$

Retrieving x_i from (16) and substituting into equation (21), we get

$$\begin{aligned} |\beta_1 - \beta_2| &\leq \frac{1}{V_{cu}} \left| \frac{lnV_1{}' (e^{\beta_2 t_m'} - 1) - lnV_2{}' (e^{\beta_1 t_m'} - 1)}{\frac{lnV_1{}' (e^{\beta_2 t_m'} - 1) + lnV_2{}' (e^{\beta_1 t_m'} - 1)}{2}} \right| \\ &= \frac{1}{V_{cu}} \left| \frac{lnV_1{}' e^{\beta_2 t_m'} - lnV_2{}' e^{\beta_1 t_m'} - (lnV_1{}' - lnV_2{}')}{\frac{lnV_1{}' e^{\beta_2 t_m'} + lnV_2{}' e^{\beta_1 t_m'}}{2} - \frac{(lnV_1{}' + lnV_2{}')}{2}} \right|. \end{aligned}$$

Dividing each term by $\frac{lnV_1{}' + lnV_2{}'}{2}$ and representing Gompertz parameter β as a sum of mean and perturbation as follows:

$$\beta_1 = \frac{\beta_1 + \beta_2}{2} + \frac{\beta_1 - \beta_2}{2}, \quad \beta_2 = \frac{\beta_1 + \beta_2}{2} - \frac{\beta_1 - \beta_2}{2}. \tag{22}$$

and after a little algebra we obtain

$$|\beta_1 - \beta_2| \leq \frac{1}{V_{cu}} \left| \frac{\frac{2lnV_1{}'}{lnV_1{}' + lnV_2{}'} P - \frac{2lnV_2{}'}{lnV_1{}' + lnV_2{}'} Q - \frac{lnV_1{}' - lnV_2{}'}{\frac{lnV_1{}' + lnV_2{}'}{2}} R}{\frac{lnV_1{}'}{lnV_1{}' + lnV_2{}'} P + \frac{lnV_2{}'}{lnV_1{}' + lnV_2{}'} Q - R} \right| \tag{23}$$

where we have denoted $P = e^{-\frac{\beta_1 - \beta_2}{2} t_m'}$, $Q = e^{\frac{\beta_1 - \beta_2}{2} t_m'}$ and $R = e^{-\frac{\beta_1 + \beta_2}{2} t_m'}$. Since

$$e^{\pm \frac{=\beta_1 - \beta_2}{2} t_m'} \approx 1 \pm (\frac{\beta_1 - \beta_2}{2}) t_m' \tag{24}$$

(by neglecting higher order perturbation terms in β_1, β_2) substituting (24) into equation (23) and simplifying further we obtain

$$|\beta_1 - \beta_2| \leq \frac{1}{V_{cu}} \left| \frac{\frac{lnV_1{'} - lnV_2{'}}{\frac{lnV_1{'} + lnV_2{'}}{2}}(1-R) - 2(\frac{\beta_1 - \beta_2}{2})t_m^{'}}{(1-R) + (\frac{\beta_1-\beta_2}{2})t_m^{'}(\frac{lnV_2{'} - lnV_1{'}}{lnV_1{'} + lnV_2{'}})} \right|. \tag{25}$$

In (25) the last term in the denominator is a product of two perturbation terms. We neglect this higher order term to get

$$|\beta_1 - \beta_2| \leq \frac{1}{V_{cu}} \left| \frac{lnV_1{'} - lnV_2{'}}{\frac{lnV_1{'} + lnV_2{'}}{2}} \right| + \frac{1}{V_{cu}} t_m^{'} \left| \frac{\beta_2 - \beta_1}{1 - e^{-\frac{\beta_1+\beta_2}{2}t_m^{'}}} \right|. \tag{26}$$

Let

$$\frac{t_m^{'}}{V_{cu}\left[1 - e^{-\frac{\beta_1+\beta_2}{2}t_m^{'}}\right]} < 1. \tag{27}$$

Then $0 < e^{-\frac{\beta_1+\beta_2}{2}t_m^{'}} < 1 - \frac{t_m^{'}}{V_{cu}}$, which is true when $\frac{t_m^{'}}{V_{cu}} < 1$.
If $\frac{t_m^{'}}{V_{cu}} < 1$, further we have

$$-\left(\frac{\beta_1+\beta_2}{2}\right)t_m^{'} < ln\left(1 - \frac{t_m^{'}}{V_{cu}}\right)$$

which gives

$$\frac{\beta_1+\beta_2}{2} > \frac{1}{t_m^{'}} ln\left(\frac{1}{1 - \frac{t_m^{'}}{V_{cu}}}\right).$$

Note that the above estimation is independent of the size $V^{'}(t)$.

Theorem 5.1
The growth rate parameter of Gompertz brain tumour model β is stable with respect to the tumour size $V^{'}(t)$, provided $\frac{t_m^{'}}{V_{cu}} < 1$.
Proof
When (27) holds, from (26) we get

$$|\beta_1 - \beta_2| \left\{ 1 - \left(\frac{t_m^{'}}{V_{cu}\left[1 - e^{-\frac{\beta_1+\beta_2}{2}t_m^{'}}\right]} \right) \right\} \leq \frac{1}{V_{cu}} \left| \frac{lnV_1{'} - lnV_2{'}}{\frac{lnV_1{'} + lnV_2{'}}{2}} \right|$$

or, equivalently

$$|\beta_1 - \beta_2| \leq K \frac{1}{V_{cu}} \left| \frac{lnV_1{'} - lnV_2{'}}{\frac{lnV_1{'} + lnV_2{'}}{2}} \right|, \tag{28}$$

where $K = \frac{1}{1-\left(\frac{t'_m}{V_{cu}}\left[1-e^{-\frac{\beta_1+\beta_2}{2}t'_m}\right]\right)} > 0$. Hence it follows from (28) that β is stable for any $V^{'}(t)$.

Theorem 2
The growth rate parameter of Gompertz brain tumour model β to be stable with respect to the tumour size $V^{'}(t)$, it is necessary that β be a constant.
Corollary :
Since β is a constant, it is clear that β is stable also with respect to $t^{'}_m$.

6 Sensitivity Analysis of the parameter

Sensitivity analysis can be used to project changes in tumour growth rate and volume as vital rates change and to identify the functional relationship between tumour volume or growth rate and the constituent rates (such as survival, growth, maturation, and migration). A sensitivity analysis is performed on the compartment dynamics to assess the effects of changing the parameters in brain tumour model.

In the standard Gompertz growth model the deceleration factor 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 [8]. Similarly we may consider how equation 7 behaves when $V^{'}(t), V_{cu}$ and $t^{'}_m$ are large.

To find the sensitivity changes, consider (7) and the partials of β with respect to $V^{'}(t), V_{cu}$ and $t^{'}_m$ are given by

$$-\frac{\partial\beta}{\partial V'(t)} = \frac{[V_0-(1/V_{cu})]/V^{'}(t)lnV^{'}(t)}{1+(e^{-\beta t'_m}/(e^{-\beta t'_m}-1))t'_m[V_0-(1/V_{cu})]},$$
$$-\frac{\partial\beta}{\partial V_{cu}} = \frac{-\beta/V_{cu}}{1+(e^{-\beta t'_m}/(e^{-\beta t'_m}-1))t'_m[V_0-(1/V_{cu})]},$$
$$-\frac{\partial\beta}{\partial t'_m} = \frac{-\beta(e^{-\beta t^{'}_m}/(e^{-\beta t^{'}_m}-1))/[(1/V_{cu})-V_0]}{1+(e^{-\beta t'_m}/(e^{-\beta t'_m}-1))t'_m[V_0-(1/V_{cu})]}.$$

It can be noted that

$$\frac{\partial\beta}{\partial V'(t)} = \frac{[V_0-(1/V_{cu})]/V^{'}(t)lnV^{'}(t)}{1+(e^{-\beta t'_m}/(e^{-\beta t'_m}-1))t_m'[V_0-(1/V_{cu})]} \geq 0 \;\; \forall V^{'}(t), \quad (29)$$
$$\frac{\partial\beta}{\partial V_{cu}} = \frac{-\beta/V_{cu}}{1+(e^{-\beta t'_m}/(e^{-\beta t'_m}-1))t'_m[V_0-(1/V_{cu})]} \leq 0, \quad (30)$$
$$\frac{\partial\beta}{\partial t'_m} = \frac{-\beta(e^{-\beta t^{'}_m}/(e^{-\beta t^{'}_m}-1))/[(1/V_{cu})-V_0]}{1+(e^{-\beta t'_m}/(e^{-\beta t'_m}-1))t'_m[V_0-(1/V_{cu})]} \leq 0. \quad (31)$$

As $V^{'}(t)$ tends to ∞ in (30), (31) and (31) we get

$$\lim_{V^{'}(t)\to\infty} \frac{\partial\beta}{\partial V^{'}(t)} = 0$$

$$\lim_{V^{'}(t)\to\infty} \frac{\partial\beta}{\partial V_{cu}} = 0$$

$$\lim_{V^{'}(t)\to\infty} \frac{\partial\beta}{\partial t_m^{'}} = 0.$$

Thus it is clear that β is insensitive to changes in $v^{'}(t) \to \infty$. That is β does not change rapidly as the volume of the tumour increases. On the other hand, if $V^{'}(t) \to 1$, from equation (30) we get

$$\lim_{V^{'}(t)\to 1} \frac{\partial\beta}{\partial V^{'}(t)} = \infty$$

since $1/V^{'}(t)lnV^{'}(t) \to \infty$ as $V^{'}(t) \to 1$. This in turn gives

$$\lim_{V^{'}(t)\to 1} \frac{\partial\beta}{\partial V_{cu}} = -\infty$$

$$\lim_{V^{'}(t)\to 1} \frac{\partial\beta}{\partial t_m^{'}} = -\infty.$$

Hence when the tumour growth rate decreases we see a substantial change in the sensitivity of β with respect to initial tumour volume V_0.

7 Conclusion

The major goal of this qualitative study is to gain a deeper knowledge of the Gompertzian brain tumour model so that we may use it as a platform for clinical applications. A study on asymptotic formulae will be dealt with in the near future because asymptotic solutions are helpful in the study of qualitative behaviour.

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