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Stochastic Nonlinear Gompertz Model of Tumour Growth

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Abstract

In this communication, based upon the deterministic Gompertz growth law, a stochastic nonlinear model of tumour growth is proposed to model the conventional size-dependent therapy strategy of tumours. The probability density function of the size of the tumour obeys a nonlinear Fokker-Planck equation which can be solved analytically. It is found that during the cancer treatments the dose intensity should not be decreased at any time because this will allow the tumour to relapse, and that the late logarithmic intensification therapy could be the optimal therapeutic strategy.

Keywords: Gompertz law; Tumour growth; Fokker-Planck equation.

1. Introduction

Modelling tumour growth and treatment has become one of the leading research areas since cancer is a major cause of death in our modern society. Today most studies stem out of mechanistic population growth models which consist of one or more differential equations. Despite their simplicity, such models have proved to be appropriate to predict the evolution of numerous biological phenomena (Preziosi, 2003). Among the proposed models those based upon the deterministic Gompertz growth law appears to be particularly consistent with the evidence of tumour growth (Fuchshuber *et al.*, 1986; Bassukas, 1994; Rygaard and Spang-Thomsen, 1997; Bass and Green, 1989; Qi *et al.*, 1993; Tyurin *et al.*, 1995). If $x(t)$ is the volume of the tumour at time t, then the deterministic Gompertz growth law is defined by the differential equation:

$$dx = \{A_1 x - A_2 x \ln(x)\}\, dt \qquad , \qquad (1)$$

where A_1 is the intrinsic growth rate of the tumour (related to the initial mitosis rate) and A_2 is the growth deceleration factor (related to the antiangiogenic processes). The parameters A_1 and A_2 characterize the evolution of different tumour types. Eq.(1) admits the solution of the form of a sigmoidal function:

$$x(t) = \exp\left\{\frac{A_1}{A_2} - \left[\frac{A_1}{A_2} - \ln(x_0)\right]\exp(-A_2 t)\right\} \quad (2)$$

where $x_0 \equiv x(0)$. From the solution one can easily see the non-trivial equilibrium point $x(\infty) = \exp(A_1/A_2)$ representing the largest tumour size that an organism can tolerate (*i.e. carrying capacity*). There also exists an inflection point $x^* = \exp(A_1/A_2 - 1)$ corresponding to the maximum growth rate, which reflects the *self regulation effect* by an intrinsic growth control mechanism. However, it is quite often that discrepancies are found to exist between clinical data and theoretical predictions due to intense environmental fluctuations. For instance, Ferreira *et al.* (2003) analyzed the effect of distinct chemotherapeutic strategies for the growth of avascular tumours, and confirmed that an environment like chemotherapy would affect tumour growth behaviour and lead to morphological transitions under certain conditions. Therefore, a better model is needed to reflect the external randomness that affects the tumour growth behaviour.

A few years ago Ferrante *et al.* (2000) proposed a stochastic version of the Gompertz law to account for random fluctuations of the model parameters. They assume that the growth deceleration factor A_2 does not change, while the variability of environmental conditions induces fluctuations in the intrinsic growth rate A_1. By assuming that the intrinsic growth rate

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varies in time according to

$$\theta(t) = A_1 + \sigma\,\epsilon(t) \quad , \tag{3}$$

where A_1 is the constant mean value of $\theta(t)$, σ is the diffusion coefficient, and $\epsilon(t)$ is a Gaussian white noise process, the proposed stochastic model is defined by the stochastic differential equation

$$dx = \{A_1 x - A_2 x \ln(x)\}\,dt + \sigma x\,dZ \quad , \tag{4}$$

where dZ denotes the standard Wiener process. By Ito's lemma Eq.(4) implies that the exponent $\psi \equiv \ln x$ follows the Ornstein-Uhlenbeck process:(Gardiner, 1985)

$$d\psi = \left\{A_1 - \frac{1}{2}\sigma^2 - A_2\psi\right\}dt + \sigma\,dZ \tag{5}$$

with the long term mean $\left(A_1 - \frac{1}{2}\sigma^2\right)/A_2$. This model has been applied to simulate the effects of a time-dependent therapy for the case of a parathyroid tumour via adding a suppresion factor to moderate the intrinsic growth rate (Albano and Giorno, 2006).

In the administration of cancer treatments it is conventional that strategic dosing is used to maximize anticancer-drug effects while minimizing host toxicity (Sanga *et al.*, 2006). Accordingly, many therapy schedules employ intensive therapy initially, when the tumour is largest, and then the dose is decreased as the tumour is reduced. For example, in the post-surgical setting only microscopic foci of tumour are left residual, and the dose schedule of adjuvant chemotherapy chosen is often less intense in comparison with the case of a larger tumour of equivalent type. In this communication we propose that in order to model this size-dependent therapy strategy, a nonlinear tumour regression rate $A_3\langle\psi(t)\rangle$ is incorporated into the intrinsic growth rate as follows:

$$d\psi = \left\{A_1 - \frac{1}{2}\sigma^2 - A_3\langle\psi(t)\rangle - A_2\psi\right\}dt + \sigma\,dZ \tag{6}$$

where $\langle\psi(t)\rangle$ is the first moment of the probability density function $Q(\psi,t)$:

$$\langle\psi(t)\rangle = \int \psi Q(\psi,t)\,d\psi \quad , \tag{7}$$

and without loss of generality A_3 is assumed to be a constant. The corresponding Fokker-Planck equation governing the probability density function $Q(\psi,t)$ is then given by

$$\begin{aligned}\frac{\partial Q(\psi,t)}{\partial t} &= \frac{1}{2}\sigma^2\frac{\partial^2 Q(\psi,t)}{\partial\psi^2} - \frac{\partial}{\partial\psi}\left\{\left[A_1 - \frac{1}{2}\sigma^2\right.\right. \\ &\quad \left.\left. -A_3\langle\psi(t)\rangle - A_2\psi\right]Q(\psi,t)\right\}\end{aligned} \tag{8}$$

which is manifestly nonlinear. The inclusion of the nonlinear tumour regression rate would inevitably escalate the complexity of the problem dramatically, and thus the system is expected to exhibit more interesting properties. Following the method of Lo (2005), the solution $Q(\psi,t)$ of Eq.(8) can be easily found to be

$$Q(\psi,t) = \int_{-\infty}^{\infty} K\left(\psi,t;\psi',0\right)\,Q(\psi',0)\,d\psi' \tag{9}$$

where

$$\begin{aligned}&K\left(\psi,t;\psi',0\right) \\ &= \frac{1}{\sqrt{4\pi\eta(t)}}\exp\{A_2 t\}\times \\ &\quad \exp\left\{-\frac{\left[\psi\exp(A_2 t)+\xi(t)-\psi'\right]^2}{4\eta(t)}\right\}\end{aligned} \tag{10}$$

$$\xi(t) = -\int_0^t \mu(t')\exp(A_2 t')\,dt' \tag{11}$$

$$\eta(t) = \frac{\sigma^2}{4A_2}\{\exp(2A_2 t)-1\} \quad . \tag{12}$$

Obviously, this solution corresponds to the so-called natural boundary condition.

We suppose that the random variable ψ initially has the value ψ_0, *i.e.* $Q(\psi,0) = \delta(\psi-\psi_0)$. Then, $Q(\psi,t) = K(\psi,t;\psi_0,0)$, and

$$\langle\psi(t)\rangle = -\{\xi(t)-\psi_0\}\exp(-A_2 t) \tag{13}$$

which in turn yields

$$\begin{aligned}\frac{d\xi(t)}{dt} &= -A_3\{\xi(t)-\psi_0\} - \\ &\quad \left(A_1 - \frac{1}{2}\sigma^2\right)\exp(A_2 t) \quad .\end{aligned} \tag{14}$$

Eq.(14) can be easily solved to give

$$\begin{aligned}\xi(t) &= \psi_0\{1-\exp(-A_3 t)\} + \frac{A_1 - \frac{1}{2}\sigma^2}{A_2 + A_3}\times \\ &\quad \{\exp(-A_3 t) - \exp(A_2 t)\}\end{aligned} \tag{15}$$

$$\begin{aligned}\Longrightarrow\quad \langle\psi(t)\rangle &= \left(\psi_0 - \frac{A_1 - \frac{1}{2}\sigma^2}{A_2 + A_3}\right)\times \\ &\quad \exp\{-(A_2+A_3)t\} + \frac{A_1 - \frac{1}{2}\sigma^2}{A_2 + A_3}\ .\end{aligned} \tag{16}$$

The solution $Q(\psi,t)$ can then be expressed as

$$Q(\psi,t) = \frac{1}{\sqrt{4\pi\Omega^2(t)}}\exp\left\{-\frac{\left[\psi - \langle\psi(t)\rangle\right]^2}{4\Omega^2(t)}\right\} \tag{17}$$

where

$$\Omega(t) = \frac{\sigma}{2}\sqrt{\frac{1-\exp(-2A_2t)}{A_2}} \quad . \tag{18}$$

Obviously, as $t \longrightarrow \infty$, we have

$$\Omega(t) \longrightarrow \Omega_\infty \equiv \frac{\sigma}{2\sqrt{A_2}} \tag{19}$$

$$\langle\psi(t)\rangle \longrightarrow \psi_\infty \equiv \frac{A_1 - \frac{1}{2}\sigma^2}{A_2 + A_3} \quad . \tag{20}$$

As a result, the probability density function $Q(\psi,t)$ will asymptotically approach the steady-state limit $Q_\infty(\psi)$:

$$\begin{aligned} Q_\infty(\psi) &\equiv \lim_{t\longrightarrow\infty} Q(\psi,t) \\ &= \frac{1}{\sqrt{4\pi\Omega_\infty^2}}\exp\left\{-\frac{(\psi-\psi_\infty)^2}{4\Omega_\infty^2}\right\} \end{aligned} \tag{21}$$

It should be noted that increasing A_3 will eventually push the ψ_∞ towards zero.

For comparison, we consider a therapy in which the dose is linearly increasing in time (Albano and Giorno, 2006). This can be implemented by simply replacing the nonlinear tumour regression rate $A_3\langle\psi(t)\rangle$ by $A_3(1+\beta t)$, where β is an adjustable positive parameter monitoring the rate. In this case the desired $Q(\psi,t)$ is given by

$$\begin{aligned} Q(\psi,t) &= \frac{1}{\sqrt{4\pi\Omega^2(t)}} \times \\ &\exp\left(-\frac{\{\psi-[\psi_0-\omega(t)]\exp(-A_2t)\}^2}{4\Omega^2(t)}\right) \end{aligned} \tag{22}$$

where

$$\begin{aligned} \omega(t) &= \frac{A_3\beta}{A_2}t\exp(A_2t) - \\ &\left[A_1 - \frac{\sigma^2}{2} - A_3\left(1-\frac{\beta}{A_2}\right)\right]\times \\ &\left\{\frac{\exp(A_2t)-1}{A_2}\right\} \quad . \end{aligned} \tag{23}$$

Then the first moment $\langle\psi(t)\rangle$ of the probability density function $Q(\psi,t)$ can be easily evaluated as

$$\langle\psi(t)\rangle = [\psi_0 - \omega(t)]\exp(-A_2t) \quad . \tag{24}$$

For $A_2t \gg 1$, we have

$$\begin{aligned} \langle\psi(t)\rangle &\approx \Psi(t) \equiv \frac{1}{A_2}\left[A_1 - \frac{\sigma^2}{2} - \right. \\ &\left. A_3\left(1-\frac{\beta}{A_2}\right)\right] - \frac{A_3\beta}{A_2}t \end{aligned} \tag{25}$$

and

$$Q(\psi,t) \approx \frac{1}{\sqrt{4\pi\Omega_\infty^2}}\exp\left\{-\frac{[\psi-\Psi(t)]^2}{4\Omega_\infty^2}\right\} \quad . \tag{26}$$

It is clear that $\langle\psi(t)\rangle$ is a monotonically decreasing function of t. Nevertheless, for the special case of constant dose, *i.e.* $\beta = 0$, $\langle\psi(t)\rangle$ attains an asymptotic limit Ψ_∞:

$$\Psi_\infty \equiv \frac{1}{A_2}\left(A_1 - \frac{\sigma^2}{2} - A_3\right) \tag{27}$$

as $t \longrightarrow \infty$, while $Q(\psi,t)$ approaches the steady-state limit $\mathcal{Q}_\infty(\psi)$:

$$\mathcal{Q}_\infty(\psi) \equiv \frac{1}{\sqrt{4\pi\Omega_\infty^2}}\exp\left\{-\frac{(\psi-\Psi_\infty)^2}{4\Omega_\infty^2}\right\} \quad . \tag{28}$$

Accordingly, one needs a sufficiently high-dose therapy, *i.e.* $A_3 \gg A_1$, in order to reduce the tumour size to a desired level.

Next, we also examine the late logarithmic intensification therapy proposed by González *et al.* (2003). It has been shown that by using the same amount of threapy, a logarithmic therapy not only induces a larger reduction of the tumour size than a constant therapy, but it is also expected to be more tolerable than the one in which the dose is linearly increasing in time. In order to model such a logarithmic therapy, we replace the nonlinear tumour regression rate $A_3\langle\psi(t)\rangle$ by $A_3\ln(e+\Gamma t)$, where e is the Neper constant and the adjustable positive parameter Γ controls the rate. The corresponding probability density function $Q(\psi,t)$ is thus found to be

$$\begin{aligned} Q(\psi,t) &= \frac{1}{\sqrt{4\pi\Omega^2(t)}} \times \\ &\exp\left(-\frac{\{\psi-[\psi_0-\chi(t)]\exp(-A_2t)\}^2}{4\Omega^2(t)}\right) \end{aligned} \tag{29}$$

where

$$\begin{aligned} \chi(t) &= -\left(A_1 - \frac{\sigma^2}{2}\right)\left\{\frac{\exp(A_2t)-1}{A_2}\right\} + \\ &A_3\int_0^t \ln(e+\Gamma\tau)\exp(A_2\tau)\,d\tau \quad . \end{aligned} \tag{30}$$

Accordingly, the first moment $\langle\psi(t)\rangle$ is given by

$$\langle\psi(t)\rangle = [\psi_0 - \chi(t)]\exp(-A_2t) \tag{31}$$

from which the special case of contant-dose therapy discussed above can be recovered by setting $\Gamma = 0$.

It is obvious that the late logarithmic intensification therapy is capable of further reducing the tumour size by the amount

$$\frac{A_3\Gamma}{A_2}\int_0^t \frac{1-\exp\left\{-A_2\left(t-\tau\right)\right\}}{e+\Gamma\tau}\,d\tau$$

in comparison with the constant-dose therapy.

For illustration, in Figures (1) and (2) we plot $\langle\psi\left(t\right)\rangle$ (*i.e.* the expectation value of the tumour size at time $t \geqslant 0$) versus time t for various values of ψ_0 (*i.e.* the initial tumour size) under the four different kinds of therapy. In Fig.(1) we consider the case of a large tumour, namely $\psi_0 = 5$. Other input model parameters are selected as follows: $A_1 = A_2 = A_3 = \sigma = \beta = \Gamma = 1$. According to the figure, the size-dependent therapy is most effective in reducing the tumour size during the initial stage, *i.e.* $0 \leqslant t \lesssim 1$, in comparison with the other three treatments. After the initial stage the dose of the size-dependent therapy is reduced by a significant amount and the tumour size is maintained at the limit $\psi_\infty = 1/4$. On the other hand, while the constant-dose therapy can shrink the tumour size a bit more till the limit $\Psi_\infty = -1/2$, the treatment with linearly enhancing intensity is able to reduce the tumour size monotonically. As expected, the late logarithmic intensification therapy is more effective than the constant-does therapy, but it is outperformed by the one with linearly increasing intensity. Fig.(2) shows the results for the case of a tumour of moderate size, *i.e.* $\psi_0 = 1$. A similar pattern of the reduction of the tumour size is observed for the four different treatments, but the size-dependent therapy is obviously not so effective as the other three.

In summary, based upon the deterministic Gompertz growth law, we have proposed a stochastic nonlinear model of tumour growth to model the size-dependent therapy strategy. The probability density function $Q\left(\psi,t\right)$ of the tumour size obeys a nonlinear Fokker-Planck equation which can be solved analytically. The model is able to simulate the conventional size-dependent therapy strategy of tumours. It is found that during the cancer treatments the dose intensity should not be decreased at any time because this will allow the tumour to relapse, and that the therapy intensity should be continuously increased if possible. However, clinically a therapy with linearly increasing intensity could well be fatal to the patient. Hence, the late logarithmic intensification therapy could turn out to be the optimal therapeutic strategy, as evidenced by the numerical results.

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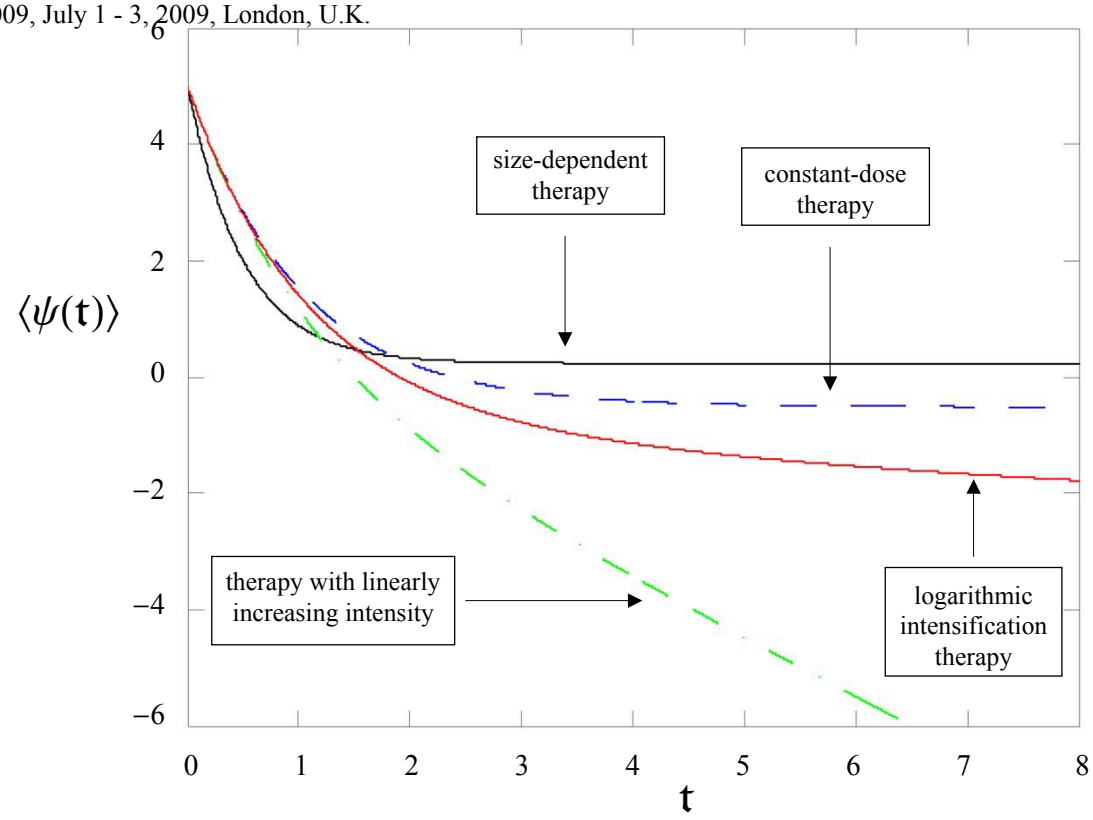

Figure 1 : $\langle\psi(t)\rangle$ versus time t for $\psi_0 = 5$ under the four different kinds of therapy. The input model parameters are: $A_1 = A_2 = A_3 = \sigma = \beta = \Gamma = 1$.

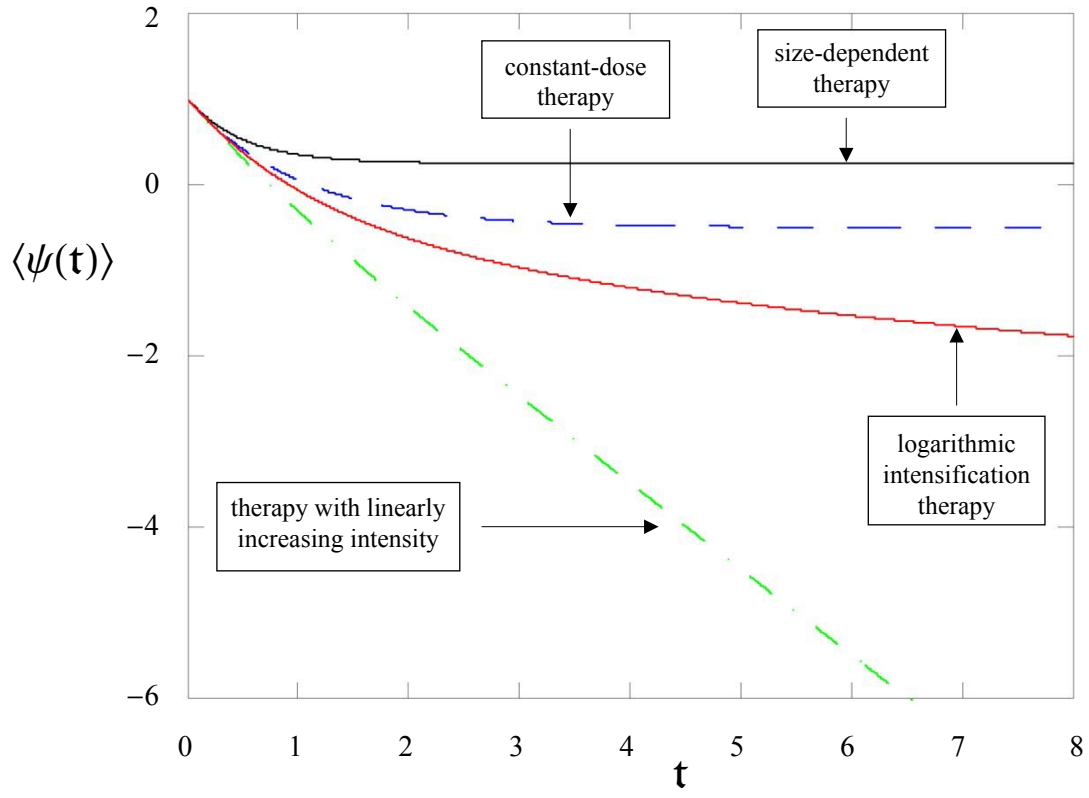

Figure 2 : $\langle\psi(t)\rangle$ versus time t for $\psi_0 = 1$ under the four different kinds of therapy. The input model parameters are: $A_1 = A_2 = A_3 = \sigma = \beta = \Gamma = 1$.

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