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Functional Fokker-Planck Equation Approach for a Gompertzian Model of Tumour Cell Growth

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Abstract

In this communication, based upon the deterministic Gompertz law of cell growth, a stochastic model in tumour growth is proposed. This model takes account of both cell fission and mortality too. The corresponding density function of the size of the tumour cells obeys a functional Fokker-Planck equation which can be solved analytically. It is found that the density function exhibits an interesting "multi-peak" structure generated by cell fission as time evolves.

Keywords: Tumor cell growth; Gompertz law; Fokker-Planck equation.

1. Introduction

Since cancer is a major death cause in our society, mathematical modelling of tumour growth has become a fast-growing area of research. Most studies stem out of mechanistic population growth models which consist of one or more differential equations, and such models have proved to be appropriate to predict the evolution of numerous biological phenomena.[1] However, it should be stressed that quite often discrepancies exist between clinical data and theoretical predictions, due to more or less intense environmental fluctuations. To take into account such environmental fluctuations, the tumour growth process could be described by a stochastic process.[2] Recently the one-dimensional archetype functional Fokker-Planck equation (FPE) of the form

$$\begin{aligned}\frac{\partial P(x,t)}{\partial t} &= \frac{\partial^2}{\partial x^2}\left\{D\left(x,t\right)P(x,t)\right\} - \\ &\quad \frac{\partial}{\partial x}\left\{g\left(x,t\right)P(x,t)\right\} + \\ &\quad \alpha^2 B\left(\alpha x,t\right)P\left(\alpha x,t\right) - \\ &\quad \left\{B\left(x,t\right)+\mu\left(x,t\right)\right\}P\left(x,t\right) \qquad (1)\end{aligned}$$

was used by Basse *et al.* to model the cell growth in plankton and human tumours under the assumption that the cells are assumed to be undergoing growth, fission and mortality at given rates.[3,4] The functional FPE is a modification of the conventional FPE when the "action at a distance" effect (*i.e.* cell fission in this case) is present. Accordingly, $P\left(x,t\right)$ denotes the density function of cells of size $x \geqslant 0$ at time $t \geqslant 0$, $D\left(x,t\right)$ is the dispersion coefficient, $g\left(x,t\right)$ is the rate of growth, $\mu\left(x,t\right)$ is the rate of death, and $B\left(x,t\right)$ is the rate at which cells divide into α equally sized daughter cells. Here $\alpha > 1$ is regarded as a constant, and the functions $D\left(x,t\right)$, $g\left(x,t\right)$, $\mu\left(x,t\right)$ and $B\left(x,t\right)$ are all non-negative. The partial differential equation in Eq.(1) is supplemented by the boundary conditions:

$$\begin{aligned}&\frac{\partial}{\partial x}\left\{D\left(x,t\right)P(x,t)\right\} - g\left(x,t\right)P(x,t)\Big]_{x=0} = 0 \\ &\lim_{x\to\infty}\frac{\partial P(x,t)}{\partial x} = \lim_{x\to\infty}P(x,t) = 0 \qquad . \qquad (2)\end{aligned}$$

These conditions ensure the decay conditions on $P(x,t)$ as $x \to \infty$ for any time $t \geqslant 0$, and that cells may never have negative size — a "no flux" condition on the boundary $x = 0$.

Beyond question, the "action at a distance" effect would make the functional FPE much more challenging to treat (both analytically and numerically). The special case of constant $D \neq 0$, g and B with $\mu = 0$ was studied by Wake *et al.*[5] and

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Kim[6], who examined the steady size distributions for the number density function. In this communication we examine a particular class of the functional FPE characterized by the following specification of the variable coefficients: $D(x,t) = D_0(t)\,x^2$, $g(x,t) = [g_0(t) - g_1(t)\ln x]\,x$, $B(x,t) = B_0(t)$ and $\mu(x,t) = \mu_0(t)$, and derive the exact analytical solution, which provides us a complete picture of the time evolution of the number density function. This special case is based upon the well-known deterministic Gompertz law of cell growth, which models the cell growth by the equation:

$$\frac{dx}{dt} = A_1 x - A_2 x \ln x \qquad \text{for} \quad A_2 > 0 \qquad , \tag{3}$$

and appears to be particularly consistent with the evidence of tumour growth[7-9]. The inclusion of these variable coefficients would escalate the complexity of the problem dramatically, and thus the system are expected to exhibit more interesting properties. Furthermore, the knowledge of the exact solution in closed form not only provides a conceptual basis for understanding the physics behind the FPE but it can also be useful as a benchmark to test approximate numerical or analytical procedures.

2. Stochastic Gompertz Model

By a change of variables $x = \exp(z)$ we could rewrite the functional FPE in Eq.(1) as follows:

$$\begin{aligned}
&\frac{\partial P(z,t)}{\partial t} \\
&= D_0(t)\frac{\partial^2 P(z,t)}{\partial z^2} + [3D_0(t) - g_0(t) + \\
&\quad g_1(t)\,z]\frac{\partial P(z,t)}{\partial z} + [2D_0(t) - g_0(t) + g_1(t) - \\
&\quad B_0(t) - \mu_0(t)]\,P(z,t) + g_1(t)\,zP(z,t) + \\
&\quad \alpha^2 B_0(t)\,P(z + \ln(\alpha), t)
\end{aligned} \tag{4}$$

for $-\infty < z < \infty$. Then, we define $P(z,t) = \exp\left\{C_6(t)\,z\frac{\partial}{\partial z}\right\}\exp\{C_5(t)\,z\}\,\tilde{P}(z,t)$, where $\tilde{P}(z,t)$ satisfies the equation

$$\begin{aligned}
\frac{\partial \tilde{P}(z,t)}{\partial t} &= D_0(t)\exp\{2C_6(t)\}\frac{\partial^2 \tilde{P}(z,t)}{\partial z^2} + \\
&\quad F_1(t)\frac{\partial \tilde{P}(z,t)}{\partial z} + F_2(t)\,\tilde{P}(z,t) + \\
&\quad C_4(t)\,\tilde{P}\left(z + \ln(\alpha)\,e^{C_6(t)}, t\right)
\end{aligned} \tag{5}$$

and

$$\begin{aligned}
C_4(t) &= \alpha^2 B_0(t)\exp\left\{\ln(\alpha)\,C_5(t)\,e^{C_6(t)}\right\} \\
C_5(t) &= \int_0^t g_1(t')\exp\{-C_6(t')\}\,dt' \\
C_6(t) &= \int_0^t g_1(t')\,dt' \\
F_1(t) &= 2C_5(t)\,D_0(t)\exp\{2C_6(t)\} + \\
&\quad [3D_0(t) - g_0(t)]\exp\{C_6(t)\} \\
F_2(t) &= C_5^2(t)\,D_0(t)\exp\{2C_6(t)\} + \\
&\quad [3D_0(t) - g_0(t)]\,C_5(t)\exp\{C_6(t)\} + \\
&\quad 2D_0(t) - g_0(t) + g_1(t) - B_0(t) - \\
&\quad \mu_0(t) \qquad .
\end{aligned} \tag{6}$$

Making use of the identities:

$$\begin{aligned}
&\exp\left(\eta\frac{\partial^2}{\partial z^2}\right) f(z) \\
&= \int_{-\infty}^{\infty} \frac{1}{\sqrt{4\pi\eta}}\exp\left\{-\frac{(z-z')^2}{4\eta}\right\} f(z')\,dz'
\end{aligned}$$

$$\begin{aligned}
&\exp\left(\eta\frac{\partial}{\partial z}\right) f(z) = f(z+\eta) \\
&\exp\left(\eta z\frac{\partial}{\partial z}\right) f(z) = f(z\exp(\eta)) \qquad ,
\end{aligned} \tag{7}$$

the solution of Eq.(4) is found to be

$$\begin{aligned}
&P(z,t) \\
&= \exp\left\{C_6(t)\,z\frac{\partial}{\partial z}\right\}\exp\{C_5(t)\,z\} \times \\
&\quad \exp\left\{\int_0^t dt' C_4(t')\exp\left(\ln(\alpha)\,e^{C_6(t')}\frac{\partial}{\partial z}\right)\right\} \times \\
&\quad \exp\left\{C_1(t)\frac{\partial^2}{\partial z^2} + C_2(t)\frac{\partial}{\partial z} + C_3(t)\right\} P(z,0) \\
&= \exp\{C_3(t)\}\exp\{zC_5(t)\exp\{C_6(t)\}\} \times \\
&\quad \sum_{n=0}^{\infty}\frac{1}{n!}\int_0^t dt_1\int_0^t dt_2\cdots\int_0^t dt_n\left\{\prod_{k=1}^{n} C_4(t_k)\right\} \\
&\quad \times \int_{-\infty}^{\infty} K(z,z',t,\{t_k\})\,P(z',0)\,dz' \qquad ,
\end{aligned} \tag{8}$$

where

$$\begin{aligned}
&K(z,z',t,\{t_k\}) \\
&= \frac{1}{\sqrt{4\pi C_1(t)}}\exp\left\{-\frac{[Q(z,z',t,\{t_k\})]^2}{4C_1(t)}\right\}
\end{aligned}$$

$$Q(z,z',t,\{t_k\}) = z\exp\{C_6(t)\} - z' + C_2(t) + \ln(\alpha)\sum_{m=1}^{n}\exp\{C_6(t_m)\}$$

$$C_1(t) = \int_0^t D_0(t')\exp\{2C_6(t')\}\,dt'$$

$$C_2(t) = \int_0^t F_1(t')\,dt'$$

$$C_3(t) = \int_0^t F_2(t')\,dt' \quad . \tag{9}$$

It is straightforward to show that the prescribed boundary conditions in Eq.(2) are satisfied by this solution.

3. Numerical Results

In Figure 1 and Figure 2 we plot the density function $P(z,t)$ versus z for different time t, provided $P(z,0) = \delta(z)$. In Figure 1 the input model parameters are selected as follows: $\alpha = 2$, $D_0(t) = 0.01$, $B_0(t) = 0.1$, $\mu_0(t) = 1$, $g_0(t) = 0.5$ and $g_1(t) = 0$. It is observed that the density function $P(z,t)$ has a number of peaks of different heights. As time evolves, these peaks diminish in height and spread to both sides rather rapidly. In Figure 2 we suppress the growth of cells and set $g_0(t)$ equal to zero as well, while other parameters remain unchanged. This figure also exhibits a similar multi-peaked density function $P(z,t)$, but with taller peaks and biased spreading to the left. Moreover, taking a closer look at the solution, it is not difficult to see that if the cells can live forever, *i.e.* $\mu_0(t) = 0$, the density function $P(z,t)$ in these figures will experience an overall increase in magnitude. Hence, it can be concluded that the cell fission creates the "multi-peak" structure of the density function and the mortality rate affects its magnitude. Both the dispersion coefficient and the growth rate are responsible for the fine tuning of the structure only.

Figure 3 and Figure 4 show the results when the mean-reverting process specified by $g_1(t)$ is turned on. It is obvious that Figure 2 and Figure 3 show great resemblance in shape and that the spreading of the density function $P(z,t)$ in Figure 3 is severely clamped by the mean-reverting force. In both figures the density function $P(z,t)$ has the main peak located at the origin, *i.e.* $z = 0$. When we compare Figure 1 and Figure 4, we observe the same resemblance in the shape of the density function $P(z,t)$ and similar discrepancies in the spreading. In both of these two figures the main peak of the density function $P(z,t)$ stays around $z = 0.5$.

3. Conclusion

Based upon the deterministic Gompertz law of cell growth, we have proposed a stochastic model in tumour cell growth, which also takes account of both cell fission and mortality. The corresponding density function $P(z,t)$ of the size of the tumour cells obeys a functional Fokker-Planck equation which can be solved analytically. It is found that the density function exhibits an interesting "multi-peak" structure generated by cell fission as time evolves.

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Figure 1 : P(z,t) versus z for t=1, 1.5 and 2. The input model parameters are: α=2, $D_0(t)$=0.01, $B_0(t)$=0.1, $\mu_0(t)$=1, $g_0(t)$=0.5 and $g_1(t)$=0

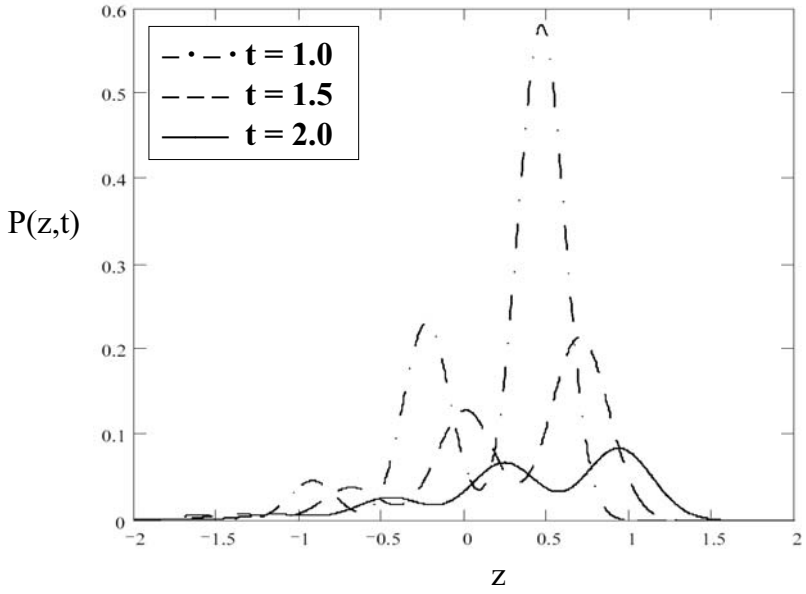

Figure 2 : P(z,t) versus z for t=1, 1.5 and 2. The input model parameters are: α=2, $D_0(t)$=0.01, $B_0(t)$=0.1, $\mu_0(t)$=1, $g_0(t)$=0 and $g_1(t)$=0

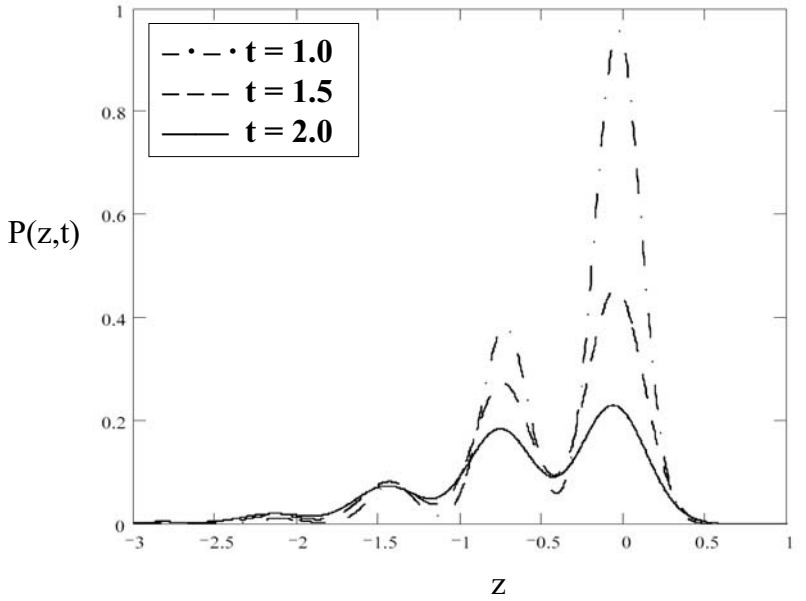

Figure 3 : P(z,t) versus z for t=1, 1.5 and 2. The input model parameters are: α=2, $D_0(t)$=0.01, $B_0(t)$=0.1, $\mu_0(t)$=1, $g_0(t)$=0 and $g_1(t)$=0.5

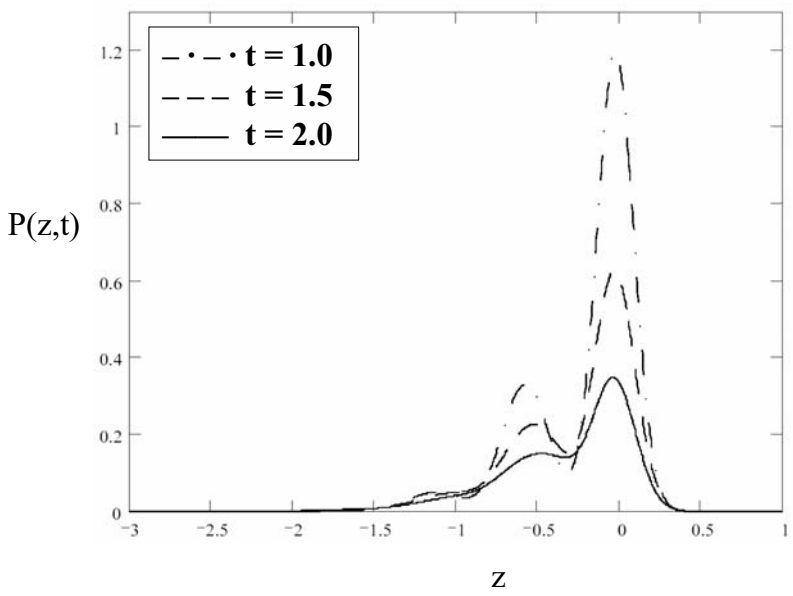

Figure 4 : P(z,t) versus z for t=1, 1.5 and 2. The input model parameters are: α=2, $D_0(t)$=0.01, $B_0(t)$=0.1, $\mu_0(t)$=1, $g_0(t)$=0.5 and $g_1(t)$=0.5