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Dynamics of Gompertzian tumour growth under environmental fluctuations

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ABSTRACT

We investigate the effect of correlated additive and multiplicative Gaussian white noise on the Gompertzian growth of tumours. Our results are obtained by solving numerically the time-dependent Fokker–Planck equation (FPE) associated with the stochastic dynamics. In our numerical approach we have adopted B-spline functions as a truncated basis to expand the approximated eigenfunctions. The eigenfunctions and eigenvalues obtained using this method are used to derive approximate solutions of the dynamics under study. We perform simulations to analyze various aspects, of the probability distribution, of the tumour cell populations in the transient- and steady-state regimes. More precisely, we are concerned mainly with the behaviour of the relaxation time (τ) to the steady-state distribution as a function of (i) of the correlation strength (λ) between the additive noise and the multiplicative noise and (ii) as a function of the multiplicative noise intensity (D) and additive noise intensity (α). It is observed that both the correlation strength and the intensities of additive and multiplicative noise, affect the relaxation time.

1. Introduction

In recent years, much attention has been directed towards the application of nonlinear physics to uncover biological complexities. Studies have confirmed the role of noise in nonlinear stochastic systems [1]. Now it has been realized that the effects of noise have widely appeared in all kinds of nonlinear systems including bistable systems [2–5], laser systems [6,7] and biological systems [8–12]. Some of the notable examples of noise induced effects are stochastic resonance in biological systems. These effects are evident in sensory systems at tissue and subcellular levels [13], pattern formation in cancer growth [14] and the effect of cell-mediated immune response against cancer [15–17].

In this paper we are interested in studying a nonlinear stochastic system with noise to obtain a deeper understanding of the dynamics of avascular tumour growth under environmental fluctuations. Among avascular tumour growth laws the Gompertz model has been the most broadly and successfully applied to fit the experimental data [18–20] and is particularly consistent with the evidence of tumour growth [21–23]. Although this model is found to be consistent with the experimental data there exist some discrepancies between the theoretical values and experimental data [24] which are due to environmental fluctuations. Neglecting such fluctuations may lead to incorrect predictions of tumour growth dynamics and in some cases may suggest inadequate therapies [24]. In the present work, we develop a stochastic analogue of the Gompertz model which incorporates environmental effects (Section 2) in order to analyze the dynamical probability distribution of the tumour cell population. We consider that the origin of the fluctuations is due to the application of therapy in the tumour treatment.

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To date many studies have been carried out on the analysis of the steady state of the tumour growth [25–28] under the influence of environmental fluctuations. Yet there are many biological systems in which the interesting dynamics take place before the system has had time to reach the steady state. For example, the multi-peak structure of the probability density function generated by the cell fission as time evolves which is predicted by Lo [29] in a study based on the stochastic Gompertz model of tumour cell growth. In this work Lo [29] employed a functional Fokker–Planck equation originally proposed by Basse et al. [30,31], for which an analytical solution exists. However studies examining the behaviour of the growth of the tumour before it reaches the steady state under the influence of environmental fluctuations are still sparse in the literature.

Hence our motivation for this study is to investigate the non-steady-state behaviour of the tumour cell population under the influence of correlated additive and multiplicative Gaussian white noises. This calculation is based on a solution of the time-dependent Fokker–Planck equation. Obtaining the time-dependent solution of the FPE for a specific system, is a much more complicated problem than the steady-state case, since it is necessary to solve an eigenvalue problem and this often requires numerical implementation. The numerical solution of the FPE and in particular the nonlinear form of this equation, still remains a challenging problem. Various approaches have been explored for obtaining numerical solutions, for example Suzuki's scaling theory [32], normal mode analysis [33], cumulant moment method [34], path integral method [35,36], Monte Carlo techniques [37], continued-fraction method [38], finite-difference methods [39] and methods based on eigenfunction expansions [40,41]. The Monte Carlo techniques are useful for providing information about certain properties of the system in terms of the moments of the stochastic process without the need for direct reference to the probability density distribution. In the case where the entire distribution function is required, direct approaches, such as those based on an eigenfunction expansion or finite-difference methods are frequently used. Based on this approach, various spectral methods can be used to provide extremely accurate solutions of FPE. In the present article, we use the eigenfunction expansion method to solve the time-dependent FPE where, the eigenfunctions are constructed using a piecewise polynomial function called B-splines. Solving the FPE numerically using the B-spline method is a new development. The B-spline approximation is a very powerful numerical technique and has been widely applied in atomic physics for the calculations of the electronic structure of atoms, ions and plasmas [42,43].

In Section 2, we present the theoretical formulation of the stochastic model. For completeness we also introduce the B-spline approximation and discuss the procedure for obtaining the eigensolution of FPE in this section. In Section 3, we present our results and analyze them. Finally in Section 4 we present our summary and conclusions.

2. Stochastic model

Stochastic models of population growth have often been obtained by the randomisation of a growth rate or other parameter in a deterministic differential equation describing the temporal evolution of the population size. This approach has been used for example, in the study of Malthusian growth in randomly varying environments [44,45] and stochastic processes in the Gompertzian framework of birth–death paradigms [46–48]. The Gompertz law of tumour cell growth is given by

$$\frac{\mathrm{d}x}{\mathrm{d}t} = f(x) = ax - bx\ln(x), \qquad x(0) = x_0. \tag{1}$$

Here $x(t)$ represents the cell number at time t, $x(0)$ is the number at the initial time identified as the instant when the cancer is diagnosed. The parameter a is the intrinsic growth rate of the tumour related to the initial mitosis rate and b is the growth deceleration factor (regulation parameter). The solution of Eq. (1) is a sigmoidal function which shows that there exists a non-trivial equilibrium point $x_\infty = exp(a/b)$ which represents the largest tumour density (carrying capacity). In this model we assume that, (i) the tumour only contains one cell type, i.e., the proliferating cells, (ii) is spatially independent, (iii) does not explicitly mention nutrients, growth factors or host vasculature, (iv) tumour volume is proportional to $x(t)$.

Next, Eq. (1) is generalized to consider stochastic effects due to some external factors such as temperature or drugs or radiotherapy etc., noise which may represent fluctuations due to the treatment resulting in cell death. In other words, the fluctuations of these external factors can influence the growth parameter a generating a multiplicative noise and at the same time can restrain the cell growth giving rise to an additive noise. Here we have implicitly assumed both the multiplicative and additive noise are correlated since they have a common origin [27,28]. Thus the coupling parameter can be interpreted as the ability of a tumour to compensate the external interference due to treatment effects via internal reactions. As a result, we obtain a Langevin-type differential equation, corresponding to the deterministic growth law Eq. (1), driven by the correlated Gaussian white noise as,

$$\frac{\mathrm{d}x}{\mathrm{d}t} = f(x) + x\sigma(t) - \Gamma(t), \tag{2}$$

where $\sigma(t)$ and $\Gamma(t)$ are Gaussian white noises with the following properties:

$$\langle \Gamma(t) \rangle = \langle \sigma(t) \rangle = 0, \tag{3a}$$

$$\langle \sigma(t)\sigma(t') \rangle = 2D\delta(t - t'), \tag{3b}$$