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Dynamics of Gompertzian tumour growth under environmental fluctuations

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\textbf{A B S T R A C T}

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 ($\tau$) to the steady-state distribution as a function of (i) the correlation strength ($\lambda$) between the additive noise and the multiplicative noise and (ii) as a function of the multiplicative noise intensity ($D$) and additive noise intensity ($\alpha$). It is observed that both the correlation strength and the intensities of additive and multiplicative noise, affect the relaxation time.

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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

\[ \frac{dx}{dt} = f(x) = ax - bx \ln(x), \quad x(0) = x_0. \]  

(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) 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 generalised 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,

\[ \frac{dx}{dt} = f(x) + x\sigma(t) - \Gamma(t), \]  

(2)

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

\[ \langle \Gamma(t) \rangle = \langle \sigma(t) \rangle = 0, \]  

(3a)

\[ \langle \sigma(t)\sigma(t') \rangle = 2D\delta(t - t'), \]  

(3b)
\[ (\Gamma(t) \Gamma(t')) = 2 \alpha \delta(t - t'), \quad (3c) \]
\[ (\sigma(t) \Gamma(t')) = \left( \Gamma(t) \sigma(t') \right) = 2 \lambda \sqrt{D \alpha} \delta(t - t'), \quad (3d) \]

and \( \alpha \) and \( D \) are the strengths of the additive and multiplicative noises respectively. The parameter \( \lambda \) denotes the degree of correlation between \( \sigma(t) \) and \( \Gamma(t) \) with \( 0 < \lambda \leq 1 \). Following the procedure \[38,49\], we may obtain the Fokker–Planck equation (FPE) of Eq. (2) for \( x \geq 0 \),

\[
\frac{\partial p(x, t)}{\partial t} = -\frac{\partial}{\partial x} [A(x)p(x, t)] + \frac{\partial^2}{\partial x^2} [B(x)p(x, t)], \quad (4)
\]
defined for \( x \in [x_{\min}, x_{\max}] \) and \( t \geq t_0 \). Here \( x_{\min} \) and \( x_{\max} \) are the arbitrary choices of the integration domain. The drift \( A(x) \) and the diffusion \( B(x) \) coefficients are given by,

\[
A(x) = ax - bx \ln(x) + Dx - \lambda \sqrt{D\alpha} \quad (5)
\]
and

\[
B(x) = Dx^2 - 2\lambda \sqrt{D\alpha} x + \alpha. \quad (6)
\]

These are time independent functions such that \( B(x) > 0 \) in the interval \( (x_{\min}, x_{\max}) \). The conditions imposed on the probabilistic solutions are

\[
p(x, t) \geq 0, \quad x_{\min} < x < x_{\max}, \quad t_0 \leq t, \quad (7)
\]
\[
\int_{x_{\min}}^{x_{\max}} p(x, t) \, dx = 1, \quad t_0 \leq t. \quad (8)
\]

From the Eq. (4), the second condition also takes the form

\[
\left[ -[A(x)p(x, t)] + \frac{\partial}{\partial x} [B(x)p(x, t)] \right]_{x_{\min} \rightarrow x_{\max}} = 0, \quad (9)
\]

for \( t_0 \leq t \) \[50\]. Suitable initial conditions may be used to produce the required evolution. We select the initial condition

\[
\lim_{t \rightarrow t_0^+} p(x, t_0) = \delta(x - x_0), \quad (10)
\]
for the transition probability distribution function \( p(x, t | x_0, t_0) \).

2.1. Eigenvalue problem for the Fokker–Planck equation

The probability density function \( p(x, t) \) is a solution of the Fokker–Planck equation of the form given by Eq. (4). To obtain an eigenvalue equation for the solution of time independent part of the FPE, we follow the procedure outlined in Ref. [50]. Here, it may be shown that the stationary solution of Eq. (4) is,

\[
p_\infty(x) = N^{-1} \exp \left[ \left( -\int [B'(x') - A(x')] / B(x') \, dx' \right) \right], \quad (11)
\]

with

\[
N = \int_{x_{\min}}^{x_{\max}} \exp \left[ \left( -\int [B'(x') - A(x')] / B(x') \right) \, dx' \right] \, dx,
\]
as the normalization constant. It may be pointed out that Eq. (4) is not in the standard self-adjoint form. However, if we define the function \( g(x, t) \) as,

\[
p(x, t) = \sqrt{p_\infty(x)} g(x, t) \quad (12)
\]
it is easy to show that \( g(x, t) \) obeys an equation of the form

\[
\partial_t g = \mathcal{L} g, \quad (13)
\]
where \( \mathcal{L} \) is defined by

\[
\mathcal{L} \phi = \frac{d}{dx} \left[ R(x) \frac{d\phi(x)}{dx} \right] - S(x) \phi(x), \quad (14)
\]
with

\[
R(x) = B(x) > 0,
\]
and
\[ S(x) = \frac{[B'(x) - A(x)]^2}{4B(x)} - \frac{[B'(x) - A(x)]}{2}. \] (15)

Hence Eq. (13) is now self-adjoint. Separating the variables by means of \( g(x, t) = \gamma(t)G(x) \), we have \( \gamma(t) = e^{-\epsilon t} \) while \( G \) is a solution of the typical Sturm–Liouville problem associated with the equation
\[ \mathcal{L}G(x) + \epsilon G(x) = 0 \] (16)
subject to the boundary conditions which may be obtained from Eq. (4),
\[ [B'(x_i) - A(x_i)]G(x_i) + 2B(x_i)G'(x_i) = 0, \]
\[ [B'(x_f) - A(x_f)]G(x_f) + 2B(x_f)G'(x_f) = 0. \] (17)
In Eq. (17) and for further use, we denote \( x_i = x_{\text{min}} \) and \( x_f = x_{\text{max}} \). It is easy to see that \( \epsilon = 0 \) is always an eigenvalue for the problem Eq. (16) and that the corresponding eigenfunction is \( \sqrt{p_{\text{st}}(x)} \) defined in Eq. (11).

According to Ref. [51] the differential problem defined by Eqs. (16) and (17) has simple eigenvalues \( \epsilon_n \) that constitute an infinite, increasing sequence and the corresponding eigenfunctions \( G_n(x) \) have \( n \) zeros in the interval \( (x_i, x_f) \). The lowest eigenvalues \( \epsilon_0 = 0 \), corresponds to the eigenfunction \( G_0(x) = \sqrt{p_{\text{st}}(x)} \) which never vanishes in \( (x_i, x_f) \) and is positive. These eigenfunctions constitute a complete orthonormal set of functions in \( L^2([x_i, x_f]) \) and the general solution of Eq. (4) has the form
\[ p(x, t) = \sum_{n=0}^{\infty} c_n e^{-\epsilon_n t} \sqrt{p_{\text{st}}(x)} G_n(x) \] (18)
with \( c_0 = 1 \) for normalization. The coefficients \( c_n \) for a particular solution are selected by the initial condition
\[ p(x, t_0^+) = p_0(x) \] (19)
which may be calculated from the orthonormality relations as
\[ c_n = \int_{x_i}^{x_f} p_0(x) \frac{G_n(x)}{\sqrt{p_{\text{st}}(x)}}. \] (20)

By solving Eq. (16), we obtain \( G_n(x) \) and the corresponding \( \epsilon_n \) and hence the probability density function \( p(x, t) \) at a particular time.

2.2. B-spline implementation

A complete description of B-splines and their properties can be found in deBoor’s book [52]. Here we summarise the main results from the application point of view. We start by defining a closed interval \( [x_i, x_f] \) and divide this interval into segments. The endpoints of these segments are given by the knot sequence \( \{t_i\}, i = 1, 2, \ldots, N + k \). A set of \( N \), B-splines of order \( k \), \( B_i^k(x) \), can be defined recursively on this knot sequence according to the formula,
\[ B_i^1(x) = \begin{cases} 1 & \text{if } t_i \leq x < t_{i+1}; \\ 0 & \text{otherwise}, \end{cases} \]
and
\[ B_i^k(x) = \frac{x - t_i}{t_{i+k} - t_i} B_i^{k-1}(x) + \frac{t_{i+k} - x}{t_{i+k} - t_{i+1}} B_{i+1}^{k-1}(x). \] (21)

We see that the \( B_i^k(x) \) is a piecewise polynomial of degree \( k - 1 \) that is non-negative everywhere. A B-spline is non-zero on \( k \) consecutive intervals \( [t_i, t_{i+1}) \) (i.e., in the interval \( t_i \leq x < t_{i+1} \)), so that two B-splines \( B_i^k(x) \) and \( B_j^k(x) \) overlap if \( |i - j| < k \), but they do not overlap when \( |i - j| \geq k \). Therefore, a B-spline basis of order \( k > 1 \) is not orthogonal. The sum at any point \( x \) of all of the B-splines that do not vanish at the point is unity. The set of B-splines of order \( k \) on the knot sequence \( \{t_i\} \) forms a complete basis for piecewise polynomials of degree \( k - 1 \) on the interval spanned by the knot sequence. In this work, the knots defining the grid have single multiplicity except at the end points \( x_i \) and \( x_f \) where it is \( k \)-fold, i.e., \( t_1 = t_2 = \cdots = t_k = x_i \) and \( t_{N+1} = t_{N+2} = \cdots = t_{N+k} = x_f \). When multiple knots are encountered, limiting forms of the above recursive definition of the B-splines must be used. For \( k > 1 \), the B-splines generally vanish at their endpoints; however, at \( x = x_i \) the first B-spline is equal to 1 (with all others vanishing) and at \( x = x_f \) the last B-spline has the same behaviour, which fact we will use below in implementing the boundary conditions. The choice of knot sequence is a matter of convenience. For our application the knots \( t_k, t_{k+1}, \ldots, t_N \) are distributed on a linear scale between the interval \( x_i \) and \( x_f \). Fig. 1 shows a B-spline basis set of order \( k = 9 \) using a linear knot sequence with \( N = 17 \) in the interval \( [x_i = 0, x_f = 10] \). As
Fig. 1. B-spline basis set in the interval [0, 10] obtained with a linear knot sequence, \( k = 9 \) and \( N = 17 \). Note that the borders of the interval have \( k \) multiplicity which explains the differences in the shape near \( x = 0 \) and \( x = 10 \). Note also that the first and the last B-splines are equal to 1 at \( x = 0 \) and \( x = 10 \).

may be seen, the B-spline functions are distributed all along the interval \([x_i, x_f]\), thus providing a similar degree of flexibility anywhere inside the interval.

There are a wide variety of finite basis sets that are commonly used in computational physics to solve eigenvalue problem. However, B-splines have a number of desirable properties that make them particularly useful. One advantage is the banded nature of the matrices one has to diagonalize. This allows the generation of very large basis sets with no complications in the linear dependence. A second advantage of B-splines is the flexibility afforded by the freedom to choose the radial grid points between which the B-splines are defined. Once coded using the recursive relations, the integrals involved can be evaluated to machine accuracy with Gaussian integration, making B-splines an accurate and easily set up basis set of wide utility.

2.3. Calculating eigenfunctions and eigenvalues of Sturm–Liouville equations using B-splines

We consider the Sturm–Liouville equation (16) and re-write,

\[
\mathcal{L}G(x) + \epsilon G(x) = 0, \tag{22}
\]

with

\[
\mathcal{L}G(x) = \frac{d}{dx} \left( R(x) \frac{dG(x)}{dx} \right) - S(x)G(x).
\]

Now we expand \( G(x) \) in terms of B-splines as,

\[
G(x) = \sum_{i=2}^{N-1} c_i B_k^i(x), \tag{23}
\]

where \( c_i \) are the coefficients of the B-splines to be determined. It may be noted that the first and the last B-splines are not included in the summation in Eq. (23) due to the fact that these two B-splines, \( B_k^1(x) \) and \( B_k^{N-1}(x) \) are generally used to modify \( B_k^2(x) \) and \( B_k^{N-2}(x) \) for the requirement of the boundary conditions Eq. (17). Substituting Eq. (23) into Eq. (22) and projecting with \( B_j^k \), we obtain equations in the form of \( N - 2 \times N - 2 \) symmetric generalized eigenvalue equations,

\[
\mathbf{Lc} = -\epsilon \mathbf{Qc}, \tag{24}
\]

where \( \mathbf{c} \) are the vector expansion coefficients given by

\[
\mathbf{c} = (c_2, c_3, \ldots, c_{N-1}). \tag{25}
\]

The matrices \( \mathcal{L}_{ij} \) and \( Q_{ij} \) are generally termed as interaction and overlap matrices respectively as,

\[
\mathcal{L}_{ij} = \int_{x_i}^{x_j} B_k^i(x) \mathcal{L} B_k^j(x) dx, \tag{26}
\]
and

\[ Q_{ij} = \int_{x_i}^{x_f} B_i^k(x)B_j^k(x)dx. \]  

(27)

Next we simplify the matrix \( L_{ij} \) by substituting the operator \( L \) from Eq. (14) into Eq. (26) and obtain

\[ L_{ij} = \int_{x_i}^{x_f} B_i^k(x) \left[ \frac{d}{dx} R(x) \frac{dB_j^k(x)}{dx} - S(x)B_j^k(x) \right] dx. \]

Using integration by parts in the first term of the above equation we obtain,

\[ L_{ij} = B_i^k(x)R(x) \frac{dB_j^k(x)}{dx} \bigg|_{x_i}^{x_f} - \int_{x_i}^{x_f} R(x) \frac{dB_j^k(x)}{dx} \frac{dB_i^k(x)}{dx} dx - \int_{x_i}^{x_f} S(x)B_j^k(x)B_i^k(x)dx. \]  

(28)

Since the product of \( B_i^k(x) \) and \( B_j^k(x) \) fail to vanish only when \( i \) and \( j \) differ by \( k \) or less, the matrices \( L \) and \( Q \) are sparse, diagonally dominant banded matrices. The solution to the eigenvalue problem for such matrices is numerically stable even when the matrices are very large. Solving the generalized eigenvalue equation, we obtain \( N - 2 \) real eigenvalues \( \epsilon_{\mu} \) and \( N - 2 \) eigenvectors \( c^\mu \). The eigenvectors satisfy orthogonality relations

\[ \sum_j c_i^\mu B_j^k(x)B_j^k(x)c_j^\nu = \delta_{\mu\nu}, \]

which leads to the orthogonality relations

\[ \int_{x_i}^{x_f} G^\mu(x)G^\nu(x) = \delta_{\mu\nu}. \]  

(29)

2.4. Eigenfunctions of Sturm–Liouville equation

A self-adjoint Sturm–Liouville problem is determined by the differential equation Eq. (16) and boundary conditions, similar to Eq. (17) or of a more general form. The spectrum of such problems is then known as consisting of only real values of the spectral parameter \( \epsilon \). An eigensolution to the problem is a pair \( (\epsilon, G(x)) \), where \( \epsilon \) is the eigenvalue for which the differential equation has a non-zero solution and \( G_n(x) \) is the eigenfunction, which satisfies the boundary conditions.

As expected, we obtain as shown in Fig. 2, that the eigenfunctions \( G_n(x) \) have \( n \) zeros in the interval \([x_i, x_f]\). It may be noted that we have taken care to ensure the convergence of the first eigenvalues in each of the cases, we considered, to an accuracy of the order of \( 1E - 05 \). To achieve this accuracy, we have chosen a linear knot sequence and used 500 B-splines in the domain \([0, 3000]\).

3. Results and discussion

3.1. Analysis of the probability density distribution of the cell population as a function of the correlation strength: The correlated case

We obtain the eigenfunctions and eigenvalues of the Fokker–Planck equation solving the Sturm–Liouville equation (Eq. (16)) with the boundary conditions defined in Eq. (17) to construct the probability density distribution function \( p(x, t) \) of tumour cell population as given by Eq. (18). It may be noted the boundary conditions change their values for each set of parameters we use. Here we present the results obtained from our numerical calculations. There are five parameters in our model namely \( a, b, \lambda, \alpha \) and \( D \). We use the fixed values for the growth and decay rates. It is known that from a biological point of view, a greater \( b \) value means a greater bio-availability of a drug. A smaller value of \( a \) means a slower initial growth rate of the tumour. Therefore a greater \( b \) value or a smaller \( a \) value indicates a greater anti-tumoural effect of the therapy. Here, we chose a greater \( a \) value and a smaller \( b \) value in this analysis to study the effect of external perturbation on a growing tumour.

Fig. 3 shows the time evolution of the probability density as a function of the cell number at different times, for four different values of the correlation strength between additive and multiplicative noise. In this figure we also show the corresponding steady-state probability \( p_{st}(x) \) for comparison. The figure shows that the cell density begins to grow in an initial state Eq. (10) and then relaxes to the steady state. Comparing the results for different values of \( \lambda \), it is observed that, the cell density takes about same time \( (t = 5) \) to relax to the steady state. This indicates that the relaxation time is largely unaffected with increasing \( \lambda \). However, it may be pointed out that the qualitative nature of the curves presented in Fig. 3 makes it difficult to derive a proper conclusion. Therefore, we compare the first statistical moments of the dynamical probability density distribution with those of the steady-state distribution as a function of time in Fig. 4. This figure shows that at \( t = 5 \), the moments of \( p(x, t) \) and \( p_{st}(x) \) are comparable in all cases of \( \lambda \) considered, but no quantification of
Fig. 2. Lowest five eigenfunctions corresponding to the parameters $\lambda = 0.0, a = 2.3, b = 1.0, D = 0.3$ and $\alpha = 3.0$.

Fig. 3. $p(x, t)$ and $p_{\infty}(x)$ (Dash-dot) versus $x$ for $t = 1$ (Solid curve), $t = 3$ (Dotted curve) and $t = 5$ (Dashed curve) for four different values of $\lambda$. The input model parameters are $\alpha = 1.0, D = 0.5, a = 2.3$ and $b = 1.0$.

The relaxation time can be made. To obtain a deeper insight, we plot the relaxation time ($\tau$) as a function of $\lambda$ in Fig. 5. This quantitative study of relaxation time is performed by calculating the norm $\|p(x, t) - p(x, \infty)\|^2 = \int_{x_{\min}}^{x_{\max}} |p(x, t) - p(x, \infty)|^2 dx = F(t)$ and fitting the $\sqrt{F(t)}$ with an exponential function $Ae^{-t/\tau}$. The qualitative nature of the curve in Fig. 6 shows that there is a decrease in $\tau$ as $\lambda$ increases. Quantitatively, we find that at $\lambda = 0.0$, the value of $\tau = 0.96$ and at $\lambda = 0.9$ then $\tau = 1.06$. Although this decrease is small, the overall trend of the curve suggests that the relaxation time is affected by correlation strength. High values of $\lambda$ push the system quickly to the steady state. The relaxation time is an important quantity which reflects the evolution velocity of the system from an arbitrary initial state to the stable state. In the present case of Gompertzian tumour growth, we have an equilibrium state that corresponds to the maximum cell density (at carrying capacity). For the cell density to reach its maximum value (steady state), we observe that the growth becomes faster since the relaxation time decreases as $\lambda$ increases. This indicates that there is an increase in cell number.

3.2. Analysis of the time evolution of the probability density distribution of the cell population as a function of noise intensities: The uncorrelated case ($\lambda = 0.0$)

In Figs. 6 and 7, we study the time evolution of the probability density distribution as functions of the intensities of the multiplicative and additive noises respectively. In Fig. 6 we perform simulations keeping $\lambda$ and $\alpha$ fixed and varying $D$. It may be observed from Fig. 6 that as the multiplicative noise intensities are increased, the system takes a little longer than $t = 4$
Fig. 4. The first moment of $p(x, t)$ (Solid curve) and $p_{st}(x)$ (Dotted curve) versus $x$ at $t = 5$ for four different values of $\lambda$. The input model parameters are $\alpha = 1.0, D = 0.5, a = 2.3$ and $b = 1.0$.

Fig. 5. Relaxation time $\tau$ as a function of $\lambda$. The input model parameters are $\alpha = 1.0, D = 0.5, a = 2.3$ and $b = 1.0$.

to relax to the steady state. Similar observations are found in the case where we perform simulations keeping $\lambda$ and $D$ fixed and varying $\alpha$ in Fig. 7. It can be seen in Fig. 7 that as $\alpha$ increases the probability density relaxes to the steady state longer than $t = 5$, which are particularly evident for the case of $\alpha = 2.0$ and $3.0$.

Although the time evolution of the probability distribution functions (Figs. 6 and 7) indicate that the relaxation time is affected by the noise intensities, it is worth analysing the results in detail in order to make them more conclusive. Therefore in Figs. 8 and 9, we compare the first moment of the dynamical probability density with those of steady-state density as a function of time. In Fig. 8, the results suggest that at $t = 4$, both the moments are comparable but not to a great extent. Similarly in Fig. 9, the results show an agreement at $t = 5$ which is again not convincing. Since no conclusions can be drawn from these results looking only at the qualitative nature of the curves, we perform a quantitative study of the relaxation time as a function of both the noise intensities.

Fig. 10 shows the plot of $\tau$ as a function of $D$ and $\alpha$. The results of $\tau$ as a function of noise intensities show that the relaxation time is of the order of unity. The plot $\tau$ as a function of $D$ shows that as $D$ increases, $\tau$ slowly increases. We find that the value of $\tau$ lies between 1.03 (for $D = 0.1$) and 1.07 (for $D = 1.0$). Similarly $\tau$ as a function of $\alpha$ shows that as $\alpha$ increases, there is an increase in the relaxation time. In this case the value of $\tau$ is found to be 1.0 (for $\alpha = 0.1$) and 1.1 (for $\alpha = 3$). Although in both these cases the relaxation time is of the order of unity, the general trend of our results suggests that the system becomes slower in reaching the steady state as we increase the noise intensities. These results indicate that
the evolution velocity of the cell population is slow which implies more intense noise may be useful to reduce the tumour cell population.

4. Summary and conclusions

In summary we have developed a stochastic Gompertzian model for avascular tumour growth to include environmental fluctuations. Our model is based on a numerical solution of the time-dependent Fokker–Planck equation using the B-spline approximation.

On analysing the results obtained from the equation for probability density distributions of tumour cell populations, we observe that the correlation between the two noises and the noise intensities affect the tumour cell number. The quantitative analysis of relaxation time as a function of the correlation parameter shows that the relaxation time decreases as we increase the correlation strength indicating an increase in the cell number. For the uncorrelated noise, similar analysis of relaxation time as a function of multiplicative noise intensity show that \( \tau \) increases slowly as \( D \) increases. In the case of additive noise, we also observe that \( \tau \) increases with \( \alpha \). The increase in the relaxation time as a function of noise intensities indicates that the growth becomes slower. Here our transient analysis of the tumour cell population density and the dependence of relaxation time on the noise parameters may provide some useful feedback in order to control the changes in the tumour cell number.
Fig. 8. The first moment of $p(x, t)$ (Solid curve) and $p_{\mu}(x)$ (Dotted curve) versus $x$ at $t = 4$ for four different values of $D$. The input model parameters are $\lambda = 0.0, \alpha = 1.0, a = 2.3$ and $b = 1.0$.

Fig. 9. The first moment of $p(x, t)$ (Solid curve) and $p_{\mu}(x)$ (Dotted curve) versus $x$ at $t = 5$ for four different values of $\alpha$. The input model parameters are $\lambda = 0.0, D = 0.5, a = 2.3$ and $b = 1.0$.

Fig. 10. $\tau$ as a function of $D$ (left figure) and $\alpha$ (right figure). The input model parameters are $\alpha = 1.0$ (left figure), $D = 0.5$ (right figure), $\lambda = 0.0, a = 2.3$ and $b = 1.0$. 
In this article we have studied the transient-state behaviour of the avascular tumour growth by considering Gaussian white noise sources that are correlated with each other. However, coloured noise sources have been rarely considered in the literature. A more realistic model of avascular tumour growth would require inclusion of the finite correlation time between noise sources. This would be an interesting extension of the present model.

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