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RESEARCH

Mathematical modeling of tumor growth as a random process

Fatemeh Beigmohammadi[1] · Amir A. Masoudi[1] · Mohammad Khorrami[1] · Amir H. Fatollahi[1]

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Abstract

A model is presented to study the random growth of the number of tumor cells. It contains deterministic growth and therapy terms, as well as a random term. The model is formulated as a Langevin equation and its corresponding Fokker–Planck equation is studied. Three forms for the time-dependence of the therapy are used and the results are compared to each other. Specifically, the ratio of the probability that the number of tumor cells be large to the probability that the number of tumor cells be small is investigated. The large time behavior of this ratio is considered as a figure of merit. Better therapies correspond to smaller values for this figure of merit. The behavior of this figure of merit in terms of various parameters of the therapy is investigated. It is seen that decreasing the amplitude or the period, decreases this figure of merit, hence improves the therapy.

Keywords Langevin equation · Tumor random growth · Fokker–Planck equation

Introduction

There have been significant developments in the mathematical modeling of tumor growth[1–4]. Simplest models deal with just the number of tumor cells, so that there is a single variable the time evolution of which is studied. More extended models involve several numbers (the number of tumor cells or other kinds of the cells, for example) which still depend on only time[5]. One could also study the spatial behavior of these numbers, so that the time evolutions of some fields are studied. One could investigate deterministic models, which result in ordinary or partial differential equations, depending on whether the spatial behavior is neglected or investigated. Finally, one could include random effects in the models. Including random effects through Gaussian white noises results in Langevin equations which correspond to equivalent Fokker–Planck equations for probability functions[6–10].

Here a simple model is studied which contains a single time-dependent variable, the number of the tumor cells, but contains random effects. The model contains a growth term which is of the form of a logistic function, a therapy term which could depend on time, and a white noise term. The Langevin equation corresponding to the system, and its equivalent Fokker–Planck equation are studied, and specifically the longtime behavior of the system is studied. To quantify the effect of various parameters on the therapy, a figure of merit r is introduced, which is the large time value of the ratio of the probability that the number of tumor cells be large to the probability that the number of tumor cells be small. Better therapies correspond to smaller values for this figure of merit. Three types of time-dependences are considered for the therapy function: sine, piecewise constant, and exponential, all of them periodic in time. Increasing the average of the therapy function, of course decreases the value of r, hence improving the therapy. It is shown that increasing the amplitude or the period increases r. Also, for similar parameters, it is seen that the exponential form and the sine form correspond to the smallest and largest values for r, respectively. So best therapies are achieved by exponential forms with small amplitudes and periods.

The scheme of the paper is the following. In Sect. 2 the mathematical tools and in Sect. 3 the model are introduced.

✉ Mohammad Khorrami
mamwad@alzahra.ac.ir

Fatemeh Beigmohammadi
f.beigmohammadi@alzahra.ac.ir

Amir A. Masoudi
masoudi@alzahra.ac.ir

Amir H. Fatollahi
fath@alzahra.ac.ir

[1] Department of Physics, Faculty of Physics and Chemistry, Alzahra University, Tehran, Iran

Section 4 is where periodic therapies are studied and the main results are presented. Section 5 is devoted to the discussion.

Mathematical tools

Mainly to introduce the notation, let us briefly review the Langevin equation and the equivalent Fokker–Planck method. A Langevin equation for a single variable x, with an additive Gaussian white noise, is of the form

$$\frac{\mathrm{d}\,x}{\mathrm{d}\,t} = f(t,x) + \xi(t), \tag{1}$$

where ξ is a Gaussian white noise satisfying

$$\langle \xi(t) \rangle = 0, \tag{2}$$

$$\langle \xi(t)\,\xi(t') \rangle = 2\,\Gamma\,\delta(t - t'), \tag{3}$$

where Γ is a positive constant. The corresponding Fokker–Planck equation is

$$\begin{aligned} \mathrm{D}_0\,P &= -\mathrm{D}\,J, \\ &=:\ H\,P, \end{aligned} \tag{4}$$

where D_0 and D are differentiation with respect to t and x, and the probability current J satisfies

$$J = f\,P - \Gamma\,\mathrm{D}\,P. \tag{5}$$

So,

$$H\,P = -\mathrm{D}\,(f\,P) + \mathrm{D}\,(\Gamma\,\mathrm{D}\,P). \tag{6}$$

J vanishes at the boundaries corresponding to x, so that the integral of P over x is a constant. (It should be one.) If f is time-independent, then there exists a time-independent solution for P. This time-independent solution corresponds to a vanishing J:

$$J = 0. \tag{7}$$

So, denoting the time-independent probability by P_{st}, one has

$$P_{\mathrm{st}}(x) = \mathcal{N}\,\exp\left[\frac{1}{\Gamma}\int^{x} \mathrm{d}\,x'\,f(x')\right], \tag{8}$$

where $\mathcal{N}$ is a normalization constant[11, 12].

In general, that f does depend on time, the time evolution of P is governed by

$$P(t,x) = \int \mathrm{d}\,x'\;U(t,x,x')\,P(0,x'), \tag{9}$$

or in a more compact form

$$P(t) = U(t)\,P(0), \tag{10}$$

where U is the evolution operator satisfying

$$\mathrm{D}_0\,U = H\,U, \tag{11}$$

$$U(0,x,x') = \delta(x - x'). \tag{12}$$

A special case is when f is periodic in time, say with the period T. In that case in large times P would be periodic with the same period. Denoting that P again with P_{st}, one has

$$P_{\mathrm{st}}(t + n\,T, x) = \int \mathrm{d}\,x'\;U(t,x,x')\,P_{\mathrm{st}}(0,x'), \tag{13}$$

where n is an integer. Also,

$$P_{\mathrm{st}}(0,x) = \int \mathrm{d}\,x'\;U(T,x,x')\,P_{\mathrm{st}}(0,x'), \tag{14}$$

meaning that P_{st} is an eigenvector of the evolution by the time T, with the eigenvalue 1. The time average of P_{st} would satisfy

$$\overline{P_{\mathrm{st}}}(x) = \frac{1}{T}\int_0^T \mathrm{d}\,t \int \mathrm{d}\,x'\;U(t,x,x')\,P_{\mathrm{st}}(0,x'). \tag{15}$$

The model

A complete model of the growth of a tumor, involves the tumor cells as well as the normal cells, with interaction between them. Here a very simple model is studied, in which the effect of the normal cells on the tumor cells is neglected, so that the equation for the evolution of the tumor contains only the tumor, and the therapy parameters.

Let us assume a logistic model for the deterministic growth of the tumor cells. This means that the growth rate is proportional to the number of cells, if the number of cells is small, but reaches a saturation. A therapy term c (in general a function of time and the number of tumor cells) is added to this. Finally, the stochastic effects are taken into account through a Gaussian white noise. One could use a more complex stochastic term, with the coefficient of the noise being a function of time and the number of tumor cells. Here, these dependencies have been neglected to make the model simpler, with fewer parameters, so that the effect of each parameter could be studied.

With this model, the evolution equation is

$$\frac{\mathrm{d}\,x}{\mathrm{d}\,t} = a\,x(1 - b\,x) + c(t,x) + \xi(t). \tag{16}$$

x is the number of tumor cells, a is the birth rate of the tumor cells, and b is the inverse of the carrying capacity.

The current J corresponding to the Fokker–Planck equation (4) satisfies

$$J = [a\,x(1 - b\,x) - c]\,P - \Gamma\,\mathrm{D}\,P, \tag{17}$$

so that the Fokker–Planck equation itself is

$$\mathrm{D}_0\,P = \mathrm{D}\{[-a\,x(1 - b\,x) + c]\,P\} + \Gamma\,\mathrm{D}^2\,P. \tag{18}$$

The dimensionless form of the above is

$$\mathrm{D}_0\,P = \mathrm{D}\{[-x(1 - x) + c]\,P\} + \Gamma\,\mathrm{D}^2\,P. \tag{19}$$

If c is independent of time, the time-independent probability P_{st} would satisfy

$$P_{\mathrm{st}}(x) = \mathcal{N} \exp\left\{\frac{1}{\Gamma}\left[\frac{x^2}{2} - \frac{x^3}{3} - \int^x \mathrm{d}\,x'\,c(x')\right]\right\}. \tag{20}$$

For example, for c being equal to a constant μ,

$$P_{\mathrm{st}}(x) = \mathcal{N} \exp\left[\frac{1}{\Gamma}\left(\frac{x^2}{2} - \frac{x^3}{3} - \mu\,x\right)\right]. \tag{21}$$

Periodic therapies

Consider a therapy function c which is a function of only time, and is periodic in time with the period T. The reason for choosing the therapy to be a periodic function of time, is that real therapies are like this. Of course real therapies could depend also on x. Here a very simple model is considered in which this dependence has been put aside.

Among the characteristics of these functions are the mean μ, the amplitude α, and the sharpness β. μ and α are defined as

$$\mu = \frac{1}{T}\int_0^T \mathrm{d}\,t\,c(t). \tag{22}$$

$$\alpha^2 = \frac{1}{T}\int_0^T \mathrm{d}\,t\,[c(t) - \mu]^2. \tag{23}$$

The sharpness β is defined as the inverse of the time (in a period), for which c is larger than μ.

Three kinds of such therapy functions are studied here: the sine function c_{s}, the piecewise-constant function c_{c}, and the exponential function c_{e}.

- The sine function

$$c_{\mathrm{s}}(t) = \mu + A\,\cos\frac{2\,\pi\,t}{T}. \tag{24}$$

$$|A| < \mu. \tag{25}$$

$$\alpha_{\mathrm{s}} = \frac{A}{\sqrt{2}}. \tag{26}$$

$$\frac{1}{\beta_{\mathrm{s}}} = \frac{T}{2}. \tag{27}$$

- The piecewise constant function

$$c_{\mathrm{c}}(t) = \mu + \begin{cases} \dfrac{B}{T_1}, & 0 < t < T_1 \\ -\dfrac{B}{T - T_1}, & T_1 < t < T \end{cases}. \tag{28}$$

$$B < \mu\,(T - T_1). \tag{29}$$

$$\alpha_{\mathrm{c}} = \frac{B}{\sqrt{T_1\,(T - T_1)}}. \tag{30}$$

$$\frac{1}{\beta_{\mathrm{c}}} = T_1. \tag{31}$$

- The exponential function

$$c_{\mathrm{e}}(t) = \mu\,\frac{T}{\tau}\left[1 - \exp\left(-\frac{T}{\tau}\right)\right]^{-1}\,\exp\left(-\frac{t}{\tau}\right). \tag{32}$$

$$\alpha_{\mathrm{e}} = \mu\left\{\frac{T}{2\,\tau}\left[1 - \exp\left(-\frac{T}{\tau}\right)\right]^{-1}\left[1 + \exp\left(-\frac{T}{\tau}\right)\right] - 1\right\}^{1/2}. \tag{33}$$

$$\frac{1}{\beta_{\mathrm{e}}} = -\tau\,\ln\left\{\frac{\tau}{T}\left[1 - \exp\left(-\frac{T}{\tau}\right)\right]\right\}. \tag{34}$$

Figure 1 shows the three therapy functions.

The aim is to study the effects of the functional types of the therapy and the involved parameters on the result. To do so, the time average of the large-time behavior of the probability is studied and a single parameter r is defined as a figure of merit for the therapy:

$$r = \frac{\overline{P_{\mathrm{st}}}(1)}{\overline{P_{\mathrm{st}}}(0)}. \tag{35}$$

Better therapies correspond to smaller values of r.

In the following the behavior of r is investigated. It is seen that the sine function and the exponential function contain three independent parameters, μ, α, and T. For these functions, β depends on the other three parameters. For the piecewise constant function, β is independent as well.

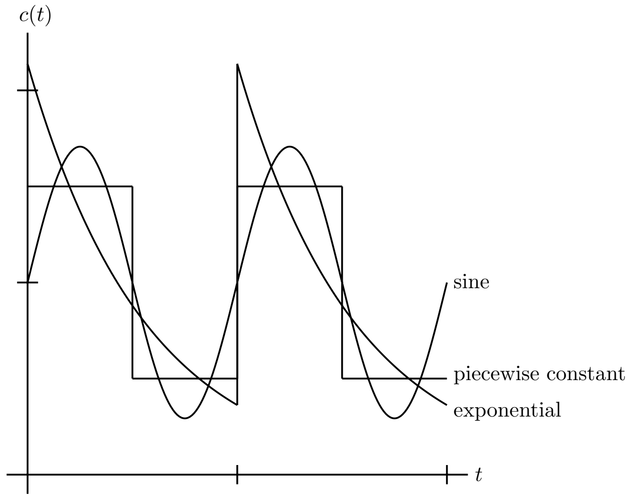

Fig. 1 The three therapy functions: sine, piecewise constant, and exponential

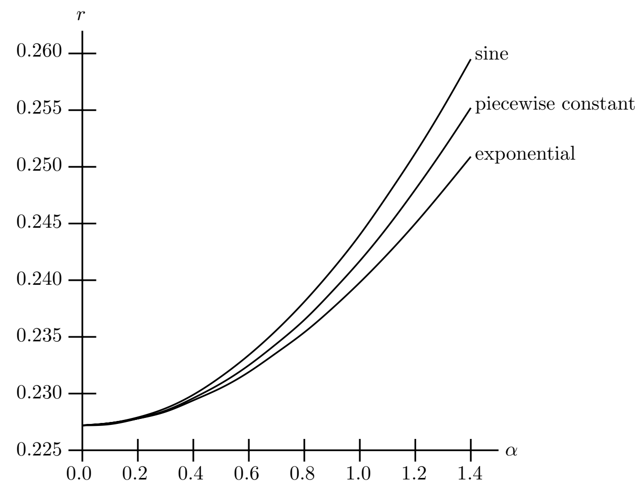

Fig. 2 The figure of merit r in terms of the amplitude α. Here $T = 1$. It is seen that the exponential function has the best (smallest) value of r, while the sine function has the worst (largest) value of r

However, the numerical results show that the effect of β_c on r is small. So, to simplify the comparison β_c is taken to equal to $(2/T)$, similar to the sine function. Also Γ is taken to be one. Finally, it is obvious that increasing the mean μ reduces r (improves the therapy). So in the following comparison μ is kept constant and the effects of α and T are studied. To summarize, the following parameters are used.

$$\Gamma = 1. \tag{36}$$

$$\mu = 2. \tag{37}$$

$$\frac{1}{\beta_c} = \frac{T}{2}. \tag{38}$$

Figure 2 shows the behavior of the figure of merit r in terms of the amplitude α with a constant period $T = 1$.

Figure 3 shows the behavior of the figure of merit r in terms of the period T with a constant amplitude $\alpha = 1$.

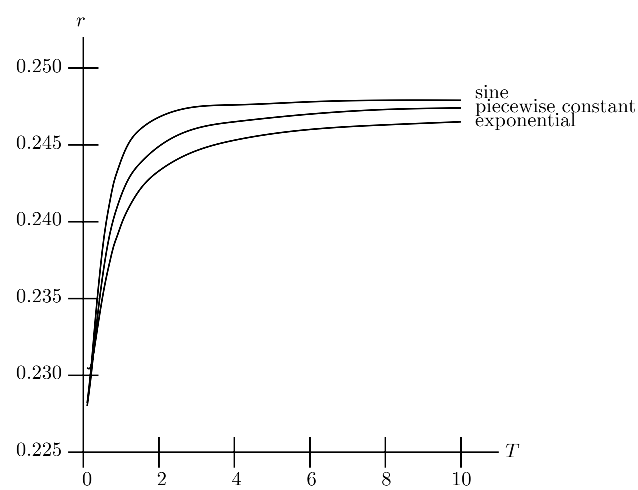

Fig. 3 The figure of merit r in terms of the period T. Here $\alpha = 1$. It is seen that the exponential function has the best (smallest) value of r, while the sine function has the worst (largest) value of r

Discussion

Increasing the average value of the therapy function, of courses decreases the figure of merit: makes things better, that is, decreases the probability of large number of tumor cells. The above diagrams show that decreasing the period and decreasing the amplitude have similar effects. So, if there are no other constraints, a better therapy is one that is constant in time. Practically, this may not be possible. If the therapy is administered in discrete batches, then it is better to shorten the time between the batches and decrease the amount of each batch. Finally, among the three time dependencies of the therapy, the exponential function seems to be the best. Incidentally, it is probably also the practical one: if the drug is given in a short time interval, then it is plausible to assume that the amount of the drug decreases exponentially with time, until the next batch.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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