Abstract. In this paper we investigate some stochastic model for tumour-immune system. To describe this model we used a Wiener process, as the noise has a stabilization effect. Their dynamics are studied in terms of stochastic stability in the equilibrium points, by constructing the Lyapunov exponent, depending on the parameters that describe the model. We have studied and analyzed a Kuznetsov-Taylor like stochastic model for tumour-immune systems. These stochastic models are studied from stability point of view and they were represented using the Euler second order scheme.

Keywords: tumour-immune system, modelling and simulation, stochastic model, Kuznetsov-Taylor model, Wiener process, Lyapunov exponent.

1 Introduction

Millions of people die from cancer every year. And worldwide trends indicate that millions more will die from this disease in the future. Great progress has been achieved in fields of cancer prevention and surgery and many novel drugs are available for medical therapies [4,10,12]. Biophysical models may prove to be useful in oncology not only in explaining basic phenomena [1], but also in helping clinicians to better and more scientifically plan the schedules of the therapies [12]. An interesting therapeutic approach is immunotherapy [4], consisting in stimulating the immune system in order to better fight, and hopefully eradicate, a cancer. In particular, in this paper I will be referring to generic immunostimulations, for example, via cytokines, but for the sake of simplicity I will use the term “immunotherapy”. The basic idea of immunotherapy is simple and promising but the results obtained in medical investigations are globally controversial, even if in recent years there has been evident progress.

From a theoretical point of view, a large body of research has been devoted to mathematical models of cancer-immune system interactions and to possible applications to cure the disease. Analyzing the best known finite dimensional models [4,10], we note that their main features are the following:

- existence of a tumor free equilibrium;
- depending on the values of parameters, there is the possibility that the tumor size may tend to $+\infty$ or to a macroscopic value;
- possible existence of a “small tumor size” equilibrium, which coexists with the tumor free equilibrium.

Stochastic modelling plays an important role in many branches of science. In many practical situations perturbations appear and these are expressed using white noise, modelled by Brownian motion. We will study stochastic dynamical systems that are used in medicine, in describing a tumour behaviour, but still we don't know much about the mechanism of destruction and establishment of a cancer tumour, because a patient may experience tumour regression and later a relapse can occur. The need to address not only preventative measures, but also more successful treatment strategies is clear. Efforts along these lines are now being investigated through immunotherapy ([10], [12]). This tumour-immune study, from theoretical point of view, has been done for two cell populations: effectors cells and tumour cells. It was predicted a threshold above which there is uncontrollable tumour growth, and
below which the disease is attenuated with periodic exacerbations occurring every 3-4 months. There was also shown that the model does have stable spirals, but the Dulac-Bendixson criterion demonstrates that there are no stable closed orbits. It is consider ODE’s for the populations of immune and tumour cells and it is shown that survival increases if the immune system is stimulated, but in some cases an increase in effectors cells increases the chance of tumour survival.

In the last years, stochastic growth models for cancer cells were developed, [1], [2], [3], [4], [5], [6].

Our goal in this paper is to construct stochastic model and to their behaviour around the equilibrium point. In these points stability is studied by analyzing the Lyapunov exponent, depending of the parameters of the models. Numerical simulations are done using a deterministic algorithm with an ergodic invariant measure.

In this paper the authors studied and analyzed one stochastic model. In Section 2, we considered a Kuznetsov and Taylor stochastic model [9]. Beginning from the classical one, we have studied the case of positive immune response. We gave the stochastic model and we analyzed it in the state such that the system (2) admits the equilibrium point

2 Problem Formulation

We will begin our study from the model of Kuznetsov and Taylor given by (1) if \(a_3 > 0\) that means that immune response is positive. For the equilibrium states \(P_1\) and \(P_2\): we study the asymptotic behaviour with respect to the parameter \(a_1\) in (1). For \(b_{a2}<a_1\;\text{the system (1) has the equilibrium states}\; P_1(x_1, y_1)\;\text{and}\; P_2(x_2, y_2)\;\text{with}\; x_1, y_1, x_2, y_2\;\text{given in [9].}

In [9] it is shown that there is an \(a_{10}\) such that if \(a_1 < a_{10}\;\text{the equilibrium state}\; P_1\;\text{is asymptotical stable, for}\; a_1 > a_{10}\;\text{the equilibrium state}\; P_1\;\text{is unstable and if}\; a_1 < a_{10}\;\text{the equilibrium state}\; P_2\;\text{is unstable and for}\; a_1 > a_{10}\;\text{the equilibrium state}\; P_2\;\text{is asymptotical stable.}

In the following, we associate a stochastic system of differential equations to the classical system of differential equations (1). Let us consider (Omega: Ft>0; \(P\) a filtered probability space and \(W(t)>0\) a standard Wiener process adapted to the filtration (F)t>0: Let \(\{X(t) =(x(t); y(t))t \geq 0\) be a stochastic process.

The system of Ito equations associated to system (1) is given by

\[
x(t) = x_0 + \int_0^t \left( a_1 - a_2x(s) + a_3x(s)y(s) \right) ds + \int_0^t g_1(x(s), y(s))dW(s)
\]

\[
y(t) = y_0 + \int_0^t \left( b_1y(s)(1-b_2y(s)) - x(s)y(s) \right) ds + \int_0^t g_2(x(s), y(s))dW(s)
\]

where the first integral is a Riemann integral, and the second one is an Ito integral. \(\{W(t); t \geq 0\) is a Wiener process [11].
The functions $g_1(x(t), y(t))$ and $g_2(x(t), y(t))$ are given in the case when we are working in the equilibrium state. In $P_1$ those functions have the following form

$$
g_1(x(t), y(t)) = b_{11}(x(t)-x_1) + b_{12}(y(t)-y_1)$$
$$g_2(x(t), y(t)) = b_{21}(x(t)-x_1) + b_{22}(y(t)-y_1)$$

In the equilibrium state $P_2$, the functions $g_1(x(t), y(t))$, and $g_2(x(t), y(t))$ are given by

$$g_1(x(t), y(t)) = b_{11}(x(t)-x_2) + b_{12}(y(t)-y_2)$$
$$g_2(x(t), y(t)) = b_{21}(x(t)-x_2) + b_{22}(y(t)-y_2)$$

The functions $g_1(x(t), y(t))$ and $g_2(x(t), y(t))$ represent the volatilizations of the stochastic equations and they are the therapy test functions.

### 3 Problem Solution

Using the formulae from [8], [10] and Maple 12 software, we get the following results, illustrated in the figures below. For numerical simulations, we use the following values for the parameters of the system (1):

- $a_1 = 0.1181$; $a_2 = 0.3747$; $a_3 = 0.01184$; $b_1 = 1.636$; $b_2 = 0.002$

Using the second order Euler scheme for the ODE system (1), respectively SDE system (2), we get the following orbits.
Fig. 6 displays the optimal behavior of the tumor cells vis. the effectors cells for SDE(2) in $P_1$.

Fig. 7 displays the optimal behavior of the tumor cells for ODE(1) in $P_2$.

Fig. 8 displays the optimal behavior of the tumor cells for SDE(2) in $P_2$.

Fig. 9 displays the optimal behavior of the effectors cells for ODE(1) in $P_2$.

Fig. 10 displays the optimal behavior of the effectors cells for SDE(2) in $P_2$.

Fig. 11 displays the optimal behavior of the tumor cells vis. the effectors cells for ODE(1) in $P_2$.

Fig. 12 displays the optimal behavior of the tumor cells vis. the effectors cells for SDE(2) in $P_2$. 
The Lyapunov exponent variation, with $b_{11}=\alpha$ a variable parameter, is given in Figure 13 for the equilibrium point $P_1$, and in Figure 14 for the equilibrium point $P_2$:

From the figures above, the equilibrium points $P_1$ and $P_2$ are asymptotically stable for all $\alpha$ such that the Lyapunov exponents $\lambda(\alpha) < 0$; and unstable otherwise. So $P_1$ is asymptotically stable for $\alpha$ from ($-\infty$, -1.78)$U(2.02, \infty)$ and $P_2$ is asymptotically stable for $\alpha$ from ($-\infty$; -1.62)$U(1.88, \infty)$:

4 Conclusion

It is interesting to use well established conceptual frameworks of ecological models to model competition phenomena in human biology, but it is important to pay attention to the whole ecological modeling aspect, such as the basic requirement of the positivity of the solutions. Even if model [12] violates the positivity rule, it is valuable because it may be read as a model which takes into account a disease-induced depression in the influx of lymphocytes. Then, instead of proposing another specific model, we preferred to add this new feature to a family of equations, and to analyze its properties. We stressed also that models which do not allow the possibility to have LAS tumor-free solutions should be cautiously considered. The general family [4] and [9] may be, of course, further generalized following Volterra’s ecological theory, i.e. by considering that there may be a delay between the consumption of a prey and the birth of a predator. This delayed model and stochastic models will be the subject of further investigations.

In this paper we focused on important tumour-immune systems, presented from stochastic point of view: a Kuznetsov-Taylor model, that belongs to a general family of tumour-immune stochastic systems. We have determined the equilibrium points and we have calculated the Lyapunov exponents. These exponents help us to decide whether the stochastic model is stable or not. For numerical simulations we have used the Euler scheme and the implementation of this algorithm was done in Maple 12. In a similar way other models can be studied. The model given by the SDE (2) allows the control of the model given by ODE (1) with a stochastic process.

Finally, we would like to illustrate some qualitative medical inferences from the investigations that we have here proposed. The main problem of immunotherapy is that, as it is clear from our analysis and simulations, in general, eradication may be possible but is dependent on the initial conditions ($x_0$, $y_0$). However, the Ics are in medical practice unknown or known with very large confidence intervals (for the cancer cells at the start of a radiotherapy and). This makes it impossible to plan an anticancer therapy based solely on this therapy. This is a peculiarity of immunotherapy, since there are other kinds of anticancer cures for which a globally stable eradication is possible [4]. However, in our simulations we have seen that in some particular cases the model [9] predicts that globally stable eradication is possible also in case of immunotherapy, but that it depends on the “degree of aggressiveness” of the cancer.

If in the future it might be possible, the option to use immunotherapy as main strategy, for relatively small “non-aggressive” tumors, could be seriously considered bolus based therapy. This result may be of interest, since continuous intravenous infusion may cause major practical problems to the patients.

References:


