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PHASE-SPACE ANALYSIS OF TUMOR GROWTH

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Abstract:

Beginning with this article we intend to investigate the problems of mathematical and biological approaches to model the cancer growth dynamics processes and operations. It is important to take into account "the nonlinear property of cancer growth processes" in construction of mathematical logistic models. The nonlinearity approach appears very convenient to display unexpected dynamics in cancer growth processes expressed in different reactions of the dynamics to different concentrations of immune cells at different stages of cancer growth developments [1-21]. Taking into account all the complex processes, nonlinear mathematical models can be estimated capable of compensation and minimization the inconsistencies between different mathematical models related to cancer growth-anticancer factor affections. The elaboration of mathematical non-spatial models of the cancer tumor growth in the broad framework of tumor immune interactions studies is one of intensively developing areas in the modern mathematical biology, see works [1-9]. Of course, the development of powerful cancer immunotherapies requires an understanding of the mechanisms governing the dynamics of tumor growth. One of main reasons for creation of non-spatial dynamical models of this nature is related to the fact that they are described by a system of ordinary differential equations, which can be efficiently investigated by powerful methods of qualitative theory of dynamical systems theory. Mathematical models for tumor growth have been extensively studied in the literature to understand the mechanism of the disease and predict its future behavior. Interactions of tumor cells with other cells of the body, i.e. healthy host cells and immune system cells are the main components of these models and these interactions may yield different outcomes. Some important phenomena of the tumor progression such as tumor dormancy, creeping through, and escaping from immune surveillance have been investigated by using these models. Kuznetsov et al. [1] proposed a model of second order ordinary differential equations (ODEs), which includes the effector immune cell and the tumor cell populations. They demonstrated that even with two cell populations, these models can provide rich dynamics depending on the system parameters and explained some important aspects of the stages of cancer progression. Three equation mathematical models of tumor growth with an immune responses were studied e.g. in [4, 5, 7, 9, 10]. For instance, Kirschner and Panetta [4] examined the tumour cell growth in the presence of the effector immune cells and the cytokine IL-2 which has an essential role in the activation and stimulation of the immune system. de Pillis and Radunskaya [5] included a normal tissue cell population in this model, performed phase space analysis and investigated the effect of chemotherapy treatment by using optimal control theory. In [9], interactions between cancer cells, effector cells, and cytokines (such as IL-2, TGF-β, IFN-γ) studied. In [7] interactions between cancer cells, effector cells, and normal tissue cells are investigated. In contrast to mentioned works, here mathematical analysis of multipoint IVP for (1.1), local and global stability

and the multiphase basins of attractions have been investigated. We prove that all orbits are bounded and must converge to one of several possible equilibria. Therefore, the long-term behavior of an orbit is classified according to the basin of multipoint attraction in which it starts. Here, we examine the dynamics of one cancer growth model proposed in [5], but possessing multiphase structure, i.e. we consider the following multipoint initial value problem (IVP) for dynamical system

$$T=r_1T(1-k_1^{-1}T)-a_{12}NT-a_{13}IT,$$

$$N=r_2N(1-k_2^{-1}N)-a_{21}NT,\ I=((r_3IT)/(k_3+T))-a_{31}IT-d_3I, \quad \#1.1$$

$$T(t_0)=T_0+\sum_{k=1}^{m}\alpha_{1k}T(t_{k}), \qquad N(t_0)=N_0+\sum_{k=1}^{m}\alpha_{2k}N(t_{k}), \quad \#1.0$$

$$I(t_0)=I_0+\sum_{k=1}^{m}\alpha_{3k}I(t_{k}),\ t_0\in[0,\eta),\ t_{k}\in O_{\delta}(t_0),$$

where $T=T(t)$, $N=N(t)$, $I=I(t)$ denote the densities of tumor cells, healthy host cells and the effector immune cells, respectively at the moment t, α_{jk} are real numbers, m is a natural number and

$$O_{\delta}(t_0)=\{t\in R:|t-t_0|<\delta\} \text{ for a } \delta>0. \quad \#1.2$$

The assumption (1.0) is given on coefficients

$$\alpha_{ij},\ t_0,t_1,t_2,\ldots t_{m},$$

where, (T_0,N_0,I_0) indicate the given pre-healing vector (or pre-healing vector state) such that T_0 is small enough but N_0, I_0 are big enough. The condition (1.2) links the values of vector function $V(t)=(T(t),N(t),I(t))$ at various points $t_0,t_1,\ldots,t_{m}$ to each other by healing vector (T_0,N_0,I_0); so, we called (1.2) a multipoint IVP. The first term of the first equation corresponds to the logistic growth of tumor cells in the absence of any effect from other cells populations with the growth rate of r_1 and maximum carrying capacity k_1. The competition between host cells and tumor cells $T(t)$ which results in the loss of the tumor cells population is given by the term $a_{12}NT$. Next, the parameter a_{13} refers to the tumor cell killing rate by the immune cells $I(t)$. In the second equation, the healthy tissue cells also grow logistically with the growth rate of r_2 and maximum carrying capacity k_2. We assume that the cancer cells proliferate faster than the healthy cells which gives $r_1>r_2$. The tumor cells also inactivate the healthy cells at the rate of a_{21}. The third equation of the model describes the change in the immune cells population with time t. The first term of the third equation illustrates the stimulation of the immune system by the tumor cells with tumor specific antigens. The rate of recognition of the tumor cells by the immune system depends on the antigenicity of the tumor cells. The model of the recognition process is given by the rational function which depends on the number of tumor cells with positive constants r_3 and k_3. The immune cells are inactivated by the tumor cells at the rate of a_{31} as well as they die naturally at the rate d_3. We suppose that the constant influx s of the activated effector cells into the tumor

microenvironment is zero. One of main aims is derivation of sufficient conditions under which the possible biologically feasible dynamics is local and globally stable, and a converges to one of equilibria. Since these equilibrium points have a biological sense, we notice that understanding limit properties of dynamics of cells populations based on solving problems (1.1)-(1.2) may be of an essential interest for the prediction of health conditions of a patient without a treatment, when the data (e.g. the status of blood cells shown above) that determines the conditions of the patient are compared at various times $t_0,t_1,...,t_{m}$ and correlated.

By scaling $x_1=Tk_1^{-1}$, $x_2=Nk_2^{-1}$, $x_3=Ik_3^{-1}$, $t=r_1t$ in (1.1) and omitting the tilde notation we get the multipoint IVP for the following dynamical system

$$x_1=x_1(1-x_1)-a_{12}x_1x_2-a_{13}x_1x_3,$$
$$x_2=r_2x_2(1-x_2)-a_{21}x_1x_2, \quad \#1.3$$
$$x_3=((r_3x_1x_3)/(x_1+k_3))-a_{31}x_1x_3-d_3x_3,\ t\in[0,\mid\mid T),$$
$$x_1(t_0)=x_{10}+\sum_{k=1}^{m}\alpha_{1k}x_1(t_{k}), \qquad x_2(t_0)=x_{20}+\sum_{k=1}^{m}\alpha_{2k}x_2(t_{k}), \#1.4$$
$$x_3(t_0)=x_{30}+\sum_{k=1}^{m}\alpha_{3k}x_3(t_{k}),\ t_0\in[0,\mid\mid T),\ t_{k}\in O_{\delta}(t_0).$$

We are interested in biologically relevant solutions of the system (1.3)-(1.4).
Conclusion. Taking into account different and effective features of mathematical modelling and its possibilities to figure out a problem in dynamics on the basis of its logic properties, it was surely pointed out the characteristics of a mathematical model to use in description of needed processes of a given dynamic system with identified problems. In this paper, a three dimensional model was devoted to mathematical description and regulation possibilities of uncontrolled tumor processes by organism as a complex system. The dynamics of interactions of the dimensions corresponded to tumor cells, immune cells and healthy -- "host" -- cells were given as forces of vectors, negatively or positively converging to basins of attractions, depending on their importance for the complex system. In order to make the model subjected to control, there was included multiphase IVP, describing the system's important parameters to operate with it in the farther processes of stages of development. The model was undergone different changes to determine its limits of survival: it was determined the conditions of boundedness the system can be restricted, invariance in non-negativity, which means the model keeps its properties of reactions to changing in proper way, being subjected to different analysis, and the circumstances the system can be forced to be dissipated in. The system was exposed to changing pressures to estimate its convenience to biologically important properties as points of equilibria and Lyapunov stability conditions. The next step in exploring of the model were very complex and logistic approaches to its properties for verification of the conditions, providing the global equilibria points and multimodal attraction sets, having biologically strong value in regulation of the processes towards the positive effects of feasible medical external implementation at the convenient stages, determined by multimodal attraction basins.

Biological implications. Here we study a multiphase host-tumor model that enhances the type of effector immune cells that can fight a tumor, and stimulates effector immune cells to proliferate. Interactions between cancer tumor cells, healthy host cells and the effector immune cells can explain long-term tumor relapse. Here, the sufficient conditions is derived that under which the possible biologically feasible dynamics is stable in the Lyapunov sense, and a converges to one of equilibrium points. Since these equilibrium points have a biological sense, we notice that

understanding limit properties of dynamics of cells populations based on solving the problem (1.3)-(1.4) may be of an essential interest for the prediction of health conditions of a patient without a treatment, when the data (e.g. the status of blood cells shown above) that determines the condition of the patient are compared at various times $t_0,t_1,...,t_{m}$ and correlated. In the section 3, we find the positively invariant domain $B_{\alpha,m}$ that depend on multipoint IVP condition parameters α_{k}, t_{k} and m. Moreover, the boundedness of orbits of the system (1.3)-(1.4) is derived. As a result, the future evolution of cells populations involved in this model is completely predictable in the following sense: by knowing the specific linear connection between the tumor, guest and immune cells at the t_0, $t_1,...t_{m}$ time phase densities, populations has an accurate and predictable estimate of its change. In the section 4, lyapunov stability of the system (1.3) at the corresponding equilibria points are studied. We show that the system (1.3) is global stable at the "free tumor " equilibria point $E_2(0,1,0)$. In the section 5, the basins of multiphase attractors of the system (1.3)-(1.4) are constructed dependent on multipoint parameters of IVP.

Keywords: Cancer growth processes, immune responses, nonlinear mathematical models
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