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A cancer model for the angiogenic switch

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HIGHLIGHTS

- A 4D dynamical model for a single tumor site.
- A novel model for describing the angiogenic switch.
- Describing interactions between endothelial, host, immune and tumor cells.
- Relating sensitivity to initial conditions of tumor growth to parameter values.

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ABSTRACT

The occurrence of metastasis is an important feature in cancer development. In order to have a one-site model taking into account the interactions between host, effector immune and tumor cells which is not only valid for the early stages of tumor growth, we developed in this paper a new model where are incorporated interactions of these three cell populations with endothelial cells. These latter cells are responsible for the neo-vascularization of the tumor site which allows the migration of tumor cells to distant sites. It is then shown that, for some parameter values, the resulting model for the four cell populations reproduces the angiogenic switch, that is, the transition from avascular to vascular tumor.

1. Introduction

Tumor growth is a complex process depending on various cell types as mutant (tumor) cells, host (normal-tissue) cells, immune cells (lymphocytes, macrophages), endothelial cells, etc. In order to get real insights into critical parameters that control system dynamics, theoretical models are required (Gatenby and Maini, 2003). They can also be used for designing new effective treatments without an extensive experimentation (Byrne, 1999). Typically, there are three levels for describing interactions among these cells, namely the cell-, tissue- and organ-level. At the individual-cell level, the complexity of the model increases in proportion to the number of specific cells which contribute to the tumor growth. These models are well suited for investigating in details a particular mechanism arising in a specific cancer. For instance, such an approach was used to describe the role of the Adenosine TriPhosphate (ATP) metabolism as the cellular energy carrier in tumor angiogenesis (Nagy and Armbruster, 2012): the corresponding cell energetics model is made of three ordinary differential equations. The ATP is thus used to drive a second model — at the tissue level — for tumor growth made of three other ordinary differential equations governing tumor mass, immature vascular endothelial cell mass and total microvessel length; the model depends on twenty-three parameters. Such a model type is necessarily specific to a given type of cancer since based on a description of interactions at the cell level. In order to have a generic model, the tissue level was here retained for modelling the tumor growth. This level of description was required to reduce the model complexity, thus avoiding a model too difficult to parametrize and to investigate (Eftimie et al., 2011).

Indeed, most of the models used to investigate tumor growth are at the tissue level as reviewed by Araujo and McElwain (2004) or by Eftimie et al. (2011): at this level of description unavoidable simplifications are made, focusing on some detailed mechanisms depending on the objectives. Most of the models are devoted to the interactions between tumor cells and immune cells (Eftimie et al., 2011). For a generic description of interactions between

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tumor and immune cells, the number of ordinary differential equations is at least two (Boon and van der Bruggen, 1996; Khar, 1997; d'Onofrio, 2008). Some specifications are developed for designing therapies in particular contexts for which specific cell types can be taken into account, thus increasing the model dimension (Byrne et al., 2004; Berner et al., 2007; Bunimovich-Mendrazitsky et al., 2007). Thus, a set of 11 ordinary differential equations can be obtained (de Boer et al., 1985). In these cases, models are specific to a given type of cancer. One of them was for instance developed for malignant melanoma (Eikenberry et al., 2009) by taking into account tumor cells, healthy cells, tumor angiogenic factor, blood vessel endothelial cells, necrotic debris, spatial pressure of oxygen and basement membrane: this model is made of partial differential equations for describing the spatial tumor growth as well as tumor angiogenesis. There are also some models combining a tissue-level description with some migrations among various organs to take into account the circulating endothelial progenitor cells (Stoll et al., 2003) since these cells may contribute to tumor angiogenesis (Rafii et al., 2002).

In our cases, we would like to develop a generic model (not specific to a given type of cancer) at the tissue level for a single tumor site, that is, ignoring for now the diffusion process. Our aim is to include the micro-environment (host or healthy cells) of the tumor cells as considered in Owen and Sherratt (1998) or in De Pillis et al. (2006). To overcome the limitation of these latter models which are only for avascular tumor growth, we introduced interactions between tumor, immune, host and endothelial cells as recommended by Merlo et al. (2006). Since we limit ourselves our model to a single tumor site, cell migration by diffusion or by circulating through the blood vessels is not considered in this paper. Nevertheless, we would like to have a model for which the presence (or not) of angiogenesis depends in a simple way on some parameters since angiogenesis is a relevant requirement for an expanding growth of multiple solid tumors (Folkman, 1989). The angiogenic switch is a fundamental step which allows a tumor whose size is less than 3 mm to switch from an avascular type (with a slow growth) to a vascular type through new blood vessels under the influence Tumor Angiogenesis Factor (TAF) like Vascular Endothelial Growth Factor (VEGF) produced by tumor cells. The new vessels allow the tumor to get a faster growth and to become more invasive (Folkman, 2002). The next step is the acquisition of a metastatic phenotype (Folkman, 1995) according to which cancer cells use neo-vessels to migrate at a significant distance from the initial tumor site, most often in other organs, to create new tumor sites (Weidner et al., 1991; Malanchi et al., 2012). Thus by introducing endothelial cells in the model initially proposed by De Pillis and Radunskaya (2001, 2003) we constructed a one-site cancer model which is also valid for vascular tumor growth. As performed in these works, we do not consider cellular interactions at the molecular level, such an approach necessarily leading to too complex models for simulating tumor growth at the organ level as we planned to do in further works.

Most of cancer models do not describe the interactions between tumor cells and the organism (the host cells). Among the very few models dealing with host cells (Owen and Sherratt, 1998; Eisen, 1979; Dibrov et al., 1985; Knolle, 1988) is the three-dimensional cancer model proposed by De Pillis and Radunskaya (2001, 2003) which retained our attention as explained below. It describes the interactions between tumor, immune and host cells. A chaotic regime was observed in this model (Itik and Banks, 2010) and some bifurcation diagrams were investigated in Letellier et al. (2013). Some clinical evidences were well reproduced by this model (De Pillis and Radunskaya, 2001; Letellier et al., 2013; Denis and Letellier, 2012a,b). In this latter study, it was shown that this model produces stiff oscillations of the population of tumor cells, corresponding to a fast-growing cancer after a quite long period of latency: it corresponds to tumor dormancy as discussed in De Pillis and Radunskaya (2001). We investigated this model using an observability analysis which consists in determining whether a given variable provides all the required information to distinguish states which are different in the original phase space. This is performed by investigating the property of the jacobian matrix of the coordinate transformation between the original phase space and the space reconstructed by using successive time derivatives of a given variable (Letellier and Aguirre, 2002; Letellier et al., 2005). Such an observability analysis of this cancer model showed that if one would like to investigate the dynamics of the system "tumor + organism", it would be better to "measure" the number of host cells (Letellier et al., 2013). It is rather hard to imagine how one could measure the number of host cells since all cells in the body can be considered as host cells but transposed to the clinical point of view, the host dynamics can be evaluated at the body level by the tumor-induced symptoms. For instance, if the population of host cells decreases, the tumor grows in size and symptoms appear. In the case of patients who received treatments for a lung cancer, we thus designed a follow-up based on weekly self-assessed symptoms (lack of appetite, fatigue, pain, cough, breathlessness) and weight to "evaluate" the environment (host cells) of the tumor: the reliability of such a follow-up is equivalent to those of a routine imaging (Denis et al., 2013, 2014).

Before considering spatio-temporal models for tumor growth, it is relevant to have a model which reproduces the angiogenic switch, an important feature inducing metastasis during tumor growth. It is therefore needed to introduce endothelial cells in the three-dimensional model proposed by De Pillis and Radunskaya. The subsequent part of this paper is organized as follows. Section 2 briefly introduces the three-dimensional model describing the interactions between host, immune and tumor cells. Section 3 briefly describes the dynamics in the "tumor-free-limit", that is, when there is no tumor cell in the site. Section 4 is devoted to the interactions between these first three types of cells with endothelial cells. A dynamical analysis of the resulting four-dimensional model is then performed. Section 5 gives some conclusions.

2. Three-dimensional cancer model

Mathematical cancer model taking into account normal (non malignant) cells interacting with immune and tumor cells are not numerous. There is one proposed by Owen and Sherratt (1998) which remains mainly focused on tumor–macrophage interactions, the normal cells being only considered for their ability to colonize the site studied. Some others only focused on tumor–host interactions (Eisen, 1979; Dibrov et al., 1985; Knolle, 1988). An interesting model by De Pillis and Radunskaya (2001, 2003) incorporates host (normal), immune and tumor cells to reproduce certain qualitative aspects as oscillations in tumor size (Jeff's phenomenon) (Tholimson, 1982) or tumor dormancy (Farrar et al., 1999). This model is rather generic in the sense that it is not specific to a given type of cancer. It is indeed based on quite common interactions between host, immune and tumor cells. The model is

$$\begin{cases} \dot{N} = \rho_2 N(1-b_2 N) - c_4 TN \\ \dot{T} = \rho_1 T(1-b_1 T) - c_2 IT - c_3 TN \\ \dot{I} = s + \dfrac{\rho IT}{\alpha + T} - c_1 IT - d_1 I \end{cases} \tag{1}$$

where N represents the population of normal (host) cells, T the population of tumor cells and I the population of immune cells. In this model, immune cells can be B- or cytotoxic T- lymphocytes, or even Natural Killer. This is a single tumor-site model where