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A cancer model including tumor angiogenesis agents

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Abstract

Vascular tumor growth is a dangerous stage of cancer diseases. The growth of solid tumors beyond the critical size does indeed depend on angiogenesis. The angiogenesis process causes metastasis which leads to tumor migration. In this paper, a cancer model considering the role of tumor angiogenesis agents is developed to highlight better these chemical substances in the process of vascular tumor growth. The proposed model comprises four variables: endothelial cells, tumor angiogenesis agents, tumor cells, and effector immune cells. This paper investigates the avascular and vascular stages of tumor growth with the chaotic analysis of the model dynamics. The results show that the proposed model with the existence of tumor angiogenesis agents could capture the states of tumor growth and angiogenesis. It is also demonstrated that the tumor-secreted inhibitor factors are essential to regulate the angiogenesis process; however, an increase of inhibitor factors would be effective in the termination of metastasis.

Keywords: Chaos, Angiogenesis, Mathematical model, Vascular tumor, Tumor angiogenesis agents, numerical simulation.

1. Introduction

A solid mass is a mass of neoplastic tissue (newly formed tissue) that resulted from uncontrolled cell division. Solid tumors can take two forms, benign or malignant. Solid tumors can attack the surrounding tissue, thus the tumor grows. Tumor cells need oxygen and nutrients to penetrate and remove waste products to grow (Sutherland, 1988). The need for nutrients in the tumor is proportional to the volume of the tumor; however, its absorption is proportional to its surface. There are two stages of solid tumor growth: avascular growth and vascular growth, both of which are related to the blood supply to the tumor. New blood vessels provide nutrients, oxygen, and access to pathways through which tumor cells may travel to other locations in the host

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(metastasis). Angiogenesis is the formation of new capillaries from the existing blood vessels. This process plays an important role in physiological events such as growth, wound healing, and reproduction (Folkman, 1995). Angiogenesis depends on the exact balance between its natural stimulants and inhibitors in the body. If this balance is perturbed, conditions for diseases such as endometriosis, obesity, atherosclerosis, psoriasis, tumor growth, and metastasis are provided. In general, this process involves a series of cellular events such as migration, proliferation, and differentiation of endothelial cells and ultimately vascular formation (Folkman, 1995). The complex and fascinating process of angiogenesis and neo-vascularization has also aroused the interest of researchers in the field of mathematical biology. The challenge in mathematical biology is to produce a model that captures the basic elements and dependencies of a biological system. Such a mathematical model can give real comprehension of the parameters and may eventually be used as a forecasting tool.

In 1971, Folkman published a paper discussing a new theory of angiogenesis (Folkman, 1971). It was stated in this work that "Tumors never grow beyond a certain size unless their arteries enlarge.". Endothelial cells are genetically more stable than cancer cells. This stability has the advantage of targeting endothelial cells using anti-angiogenic drugs compared to chemotherapy for cancer cells, which mutate rapidly and cause drug resistance (Bagri et al., 2010). Because of this, endothelial cells are an ideal target for therapies. The angiogenesis process is extensively modeled by Anderson and Chaplain (1998). This model incorporates both continuous and discrete mathematical models that represent the formation of a capillary network in response to chemical stimuli (Tumor Angiogenic Factor, TAF) fed by a solid tumor. By properly separating their continuous mixed differential equations model, they created a continuous stochastic model that allows them to track the motion of individual cells. This provides a modeling framework that can include anastomosis and branching.

Over the past 30 years, several mathematical models have been proposed to explain the various stages of tumor growth. Continuous cell population models classically consider interactions between cell concentrations and some form of chemical stimulus (e.g., oxygen or nutrients). These models generally consist of reaction-diffusion-convection equations (Casciari, 1992). Previous models of this form calculated the nutrient concentration profile as a factor of the spherical radius of the tumor, which varied according to the rate of cancer cell proliferation (Adam and Maggelakis, 1989; Burton ,1966). Subsequent models cover some aspects of cellular movement and are divided into one of three forms: exposure (Byrne and Chaplain, 1997), active penetration (Sherratt, 2000), or chemotactic (Marchant et al., 2001). Discrete cell population models could simulate cancer growth on a single-cell scale (Dormann and Deutsch, 2002; Düchting and Vogelsaenger, 1985; Stott et al., 1999). In general, this type of model uses the cellular automaton model to simulate cell behavior, although there are other possibilities, such as the Potts method (Potts, 1952) and the Fokker-Planck method (Fokker, 1914; Planck, 1917).

In 2003, a model for tumor growth was introduced based on three variables as normal cells, tumor cells, and immune cells (De Pillis and Radunskaya, 2003). This model was developed from a two-variable model consisting of a pair of ordinary first-order differential equations introduced by Kuznetsov et al. (1994) for two cell populations, namely effective immune cells and tumor cells. Even for just two cell populations, the model can show rich dynamics and explain important aspects of cancer progression. De Pillis and Radunskaya (2003) were interested in studying how to keep cell population fluctuations to a minimum and finding ways to move the system into the basin of absorbing stable and healthy equilibrium states. The main emphasis of phase space analysis is to classify fixed locations and fixed points and perform traditional linear analysis with the help of powerful theorems. Itik and Banks (2010) reported specific chaos in the cancer model proposed by De Pillis and Radunskaya. They found a chaotic attractor for a particular point in the parameter space, calculated Lyapunov indices for this point, and argued that the system is what they refer to as a Shilnikovlike connection. Their work was completed and expanded by Duarte et al. (2013), who reported turbulence at certain intervals in the control space. It introduces the authors to the chaos using symbolic dynamics and Lyapunov's indicators. At the same time, Letellier et al. (2013) performed a topological analysis of the model to show that there is a new trend in understanding interactions between tumor cells. Instead of a single interval, chaos is reported for intervals of

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specific parameters of host cell growth rate and tumor cell killing rate. In particular, they showed that increasing the growth rate of host cells increases population fluctuations and creates rare but rapid tumors. Lopez et al. (2014) further found chaotic behavior by selecting specific parameters of the system. As the immune system's response to tumor cells diminished, they found a boundary crisis that led to transient chaotic dynamics, with the system behaving chaotically for a limited time to avoid the inevitable extinction of healthy and immune cell populations. They proposed a control method to prevent extinction. The well-known cancer tumor model studied by De Pillis and Radunskaya (2003) is a chaotic dynamic tumor model. However, this model cannot absorb angiogenesis, which is an important issue in malignant tumor growth. There is an alternative biological model of metastases in cancer that suggests that these complex organs in dynamic equilibrium are close to a chaotic boundary. Besides, mathematics learns the nonlinear dynamics of chaos theory to describe the natural history of these organs. The main task in understanding this model was Folkman's pioneering work in tumor angiogenesis (Folkman, 1995a,b). Baum et al. (1999) proposed a mathematical model that describes chaos as working with micrometastatic tumor angiogenesis.

Anderson and Chaplain (2000) also proposed a mathematical model that describes the angiogenic response of endothelial cells to a secondary tumor. Their model assumes that endothelial cells react chemically to two opposing chemical gradients: the tumor angiogenic gradient, which is produced by the secretion of angiogenic cytokines from the secondary tumor; and a gradient of angiostatin (a specific angiogenesis inhibitor), which is located in the tissue around nearby arteries. In a study by O'Reilly et al. (1994), it is proved that the tumor is also producing substances like angiostatin as an inhibitor to regulate the formation of neovascularization. In another study by Maggelakis (1996), they examined the effect of TAF and tumor inhibitor factors (TIFs) on neovascularization via a mathematical model. They believe that in the pre-vascular stage, the tumor produces both TAF and TIFs.

A 4-dimensional mathematical model including host cell status, immune cells, tumor cells, and endothelial cells was introduced by Viger et al. (2014). This model was developed from the three-dimensional cancer model performed by De Pillis and Radunskaya. They examined their model to show the change in non-vascular and vascular phases of tumor growth (angiogenic switch) with chaotic dynamics. In the vascular phase of tumor growth, the tumor cell population and endothelial cells have chaotic behavior (Viger et al., 2014). Letellier et al. (2017) added a therapy action into the Viger's cancer model to study the impact of chemotherapy and antiangiogenic drugs in the cancer model.

The modeling of the tumor growth process and angiogenesis by considering the endothelial cell population has been performed by Viger et al. (2014); however, the impact of tumor angiogenesis agents in the model is also essential to study the angiogenesis phenomena. The innovation of this paper is to explore the effect of tumor angiogenesis agents on tumor vascularization. We introduced a four-dimensional single tumor site model by including tumor angiogenesis agents that make our model different from the Viger model. The other difference between our model and Viger's model is that in the presented model, the impact of the tumor cells on the endothelial cells' proliferation is indirect via tumor angiogenesis agents. We considered four populations including endothelial cells, tumor angiogenesis agents, tumor cells, and immune cells. TAF and TIF as tumor angiogenesis agents were introduced to the model. Then, we investigate the avascular and vascular stages of tumor growth with the chaotic analysis of the model dynamics.

2. Material and methods

The proposed cancer model by De Pillis and Radunskaya (2003) is a biologically plausible model including tumor, immune, and host cell populations. Viger et al. (2014) added the population of endothelial cells to make a 4-dimensional cancer model including qualitative aspects of angiogenesis. We proposed a cancer model that

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can make a better understanding of the angiogenesis process by taking into account the tumor angiogenesis agents besides the endothelial cells. The proposed model incorporates TAF and TIF as tumor angiogenesis agents which are effective in the onset of vascularization. Unlike the presented model by Viger et al., in our model, due to the existence of tumor angiogenesis agents' variable, the tumor has no direct impact on endothelial cell proliferation in the endothelial cell equation. The tumor cells are producing tumor angiogenesis agents via the term $\frac{\rho_2 Tc}{1+T}$. Instead, the tumor-induced angiogenesis agents have a direct impact on endothelial cell proliferation via the term $\frac{\rho_1 cn}{1+c}$. Most cancer models do not consider the interactions between tumors and host cells (Viger et al., 2014). Our main focus is to reproduce tumor angiogenesis; so, the interactions with host cells are not relevant in the context of our presented model. Based on the flow graph in Fig.1, our 4-dimensional model (1) is written as:

$$\begin{cases} \dot{n} = \dfrac{\rho_1 cn}{1+c} - \delta_1 n - \alpha_{11} cn \\ \dot{c} = \dfrac{\rho_2 Tc}{1+T} - \alpha_{22} nc \\ \dot{T} = \rho_3 T(1-T) - \alpha_{31} IT + \dfrac{\alpha_{32} nT}{1+n} - \alpha_{33} cT \\ \dot{I} = \dfrac{\rho_4 IT}{1+T} - \alpha_{41} TI - \delta_2 I + \alpha_{42} nI \end{cases} \quad (1)$$

where n is the population of endothelial cells, c corresponds with tumor angiogenesis agents secreted by the tumor in the pre-vascular stage, T represents the population of tumor cells, and I is the population of effector immune cells.

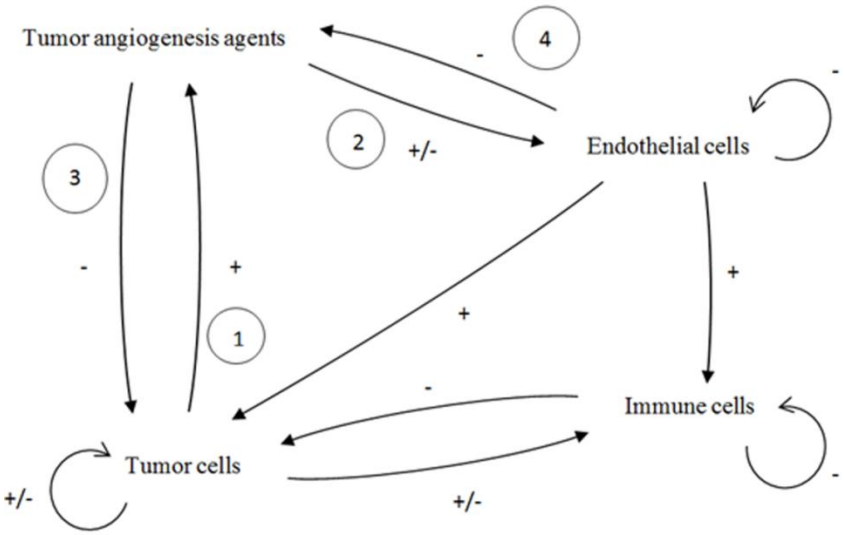

Fig.1. The flow graph of the proposed model describing the interactions between tumor cells, tumor angiogenesis agents (TAF/TIF), endothelial cells, and effector immune cells.

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In the process of tumor growth, tumor cells produce TAF substances, such as vascular endothelial growth factors (VEGF), to stimulate vascularization. However, tumor cells also produce smaller amounts of inhibitors which are called tumor inhibitor factors (TIFs) such as angiostatin that can regulate the formation of new blood vessels (O'Reilly et al., 1994). The equation for tumor angiogenesis agents (c) is our contribution to the model. When a tumor reaches a critical size, it begins to spread tumor angiogenesis agents with growth rate $\boldsymbol{\rho_2}$ to surrounding tissues, which spread to neighboring blood vessels, creating a chemical gradient. This interaction is shown in arrow 1 on the flow graph (Fig.1). VEGF molecules bind to the receptor of endothelial cells to make them proliferate; however, there exists a negative impact on endothelial proliferation by TIF agents. The tumor angiogenesis agents' interactions with endothelial cells are shown by arrow 2 in Fig.1. When endothelial cells migrate through the extracellular matrix, the endothelial cells consume tumor angiogenesis agents via the rate of $\boldsymbol{\alpha_{22}}$. The minor negative effect of TIF secreted by tumor cells on endothelial cells is considered by additional term $\boldsymbol{\alpha_{11}cn}$ to the first equation. This minor negative effect is also considered on the tumor cell population with $\boldsymbol{\alpha_{33}cT}$ additional term**.** This interaction corresponds to arrow 3 in Fig.1. There is no positive feedback loop of tumor angiogenesis agents to themselves since their proliferation is only related to the tumor cells. In our model, the stimulation impact of TAF agents on tumor cells is considered by the indirect impact through endothelial cells. Capillary sprouts form in the walls of blood vessels and release endothelial cells. The sprouts then grow toward the tumor and each other; so, the rings are formed in a process known as anastomosis, creating the source of blood for the tumor (Hillen and Griffioen, 2007). The proliferation rate of the endothelial cell population via tumor angiogenesis agents is considered by $\boldsymbol{\rho_1}$. Then the endothelial cells intake tumor angiogenesis agents while traveling to the tumor site (Bagri et al., 2010). This interaction corresponds to arrow 4 depicted in the flow graph (Fig.1) and is considered with term $\boldsymbol{\alpha_{22}nc}$. The endothelial cells' natural death is quantified by the coefficient $\boldsymbol{\delta_1}$. The endothelial cells have no positive impact on themselves since their growth depends on their interactions with tumor angiogenesis agents. The tumor cells have a logistic growth with the growth rate of $\boldsymbol{\rho_3}$. The tumor cell proliferation is also related to the presence of the endothelial cells in a Hill-function as $\frac{\alpha_{32}nT}{1+n}$. The impact of endothelial cells on the immune cells is positive since the effector immune cells are migrating through new blood vessels to reach the tumor cells [29]. So, this interaction is considered via parameter $\boldsymbol{\alpha_{42}}$. In the context of our model, the other interactions between immune cells and endothelial cells are not relevant because this work aims to model tumor angiogenesis. For example, we assume that the impact of effector immune cells on the production of endothelial cells is very limited or nothing; so, we neglected that which has been done in the study by (Brazzoli et al., 2010). Besides, in our model, the tumor angiogenesis agents have an indirect impact on effector immune cells. This indirect interaction corresponds to the interactions that they have with the endothelial cell population.

Table 1. The parameter values of model (1).

Parameters	Descriptions	Values
$\boldsymbol{\rho_1}$	Endothelial cell growth rate;	$\boldsymbol{0.92}$
$\boldsymbol{\delta_1}$	Endothelial cell natural death rate;	$\boldsymbol{\frac{1}{11}}$
$\boldsymbol{\alpha_{11}}$	Endothelial cell inhibition rate by tumor angiogenesis agents;	$\boldsymbol{0.02}$
$\boldsymbol{\rho_2}$	Tumor angiogenesis agents' growth rate;	$\boldsymbol{0.718}$
$\boldsymbol{\alpha_{22}}$	Tumor angiogenesis intake rate by endothelial cells;	$\boldsymbol{1}$
$\boldsymbol{\rho_3}$	Tumor growth rate;	$\boldsymbol{1}$

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α_{31};	Tumor cell killing rate by immune cells;	**2.5**
α_{32}	Tumor cell growth rate due to vascularization by endothelial cells;	**0.75**
α_{33}	Tumor cell inhibition rate via tumor angiogenesis agents;	**0.07**
ρ_4	Immune cell growth rate;	**4.5**
α_{41}	Immune cell inhibition rate by tumor cells;	**0.2**
δ_2	Immune cell natural death rate;	**0.5**
α_{42}	Immune cell stimulation by endothelial cells;	**0.3**

Our model is investigated with parameter values $\rho_1, \alpha_{11}, \rho_2, \alpha_{22},$ and α_{33} and the other parameters are equal to the values of the model by Viger et al. (2014). As in most of the mathematical models at the tissue level, the biological meaning of the parameter values is not certain (Letellier et al., 2013; Viger et al., 2014). These parameter values are considered to achieve a chaotic attractor solution. We use them to analyze the qualitative dynamics of tumor growth as performed in (De Pillis and Radunskaya, 2003; Letellier et al., 2013; Letellier et al., 2017; Viger et al., 2014). What is relevant is the impact of the parameter value changes on the system's dynamics.

2.1. Fixed point analysis

There are seven fixed points with at least one negative coordinate that are biologically irrelevant. We must consider the fixed points located in the positive domain of phase space since our model is population-based and the population should be positive. The equilibria are calculated numerically.

There are seven equilibrium points with non-negative coordinates that correspond to the mentioned parameter values (Table.1) as follows:

$$S_0 = \begin{vmatrix}0\\0\\0\\0\end{vmatrix}, S_1 = \begin{vmatrix}0.39\\0.11\\1.20\\0\end{vmatrix}, S_2 = \begin{vmatrix}0\\0\\1\\0\end{vmatrix}, S_3 = \begin{vmatrix}0\\39.38\\0\\0\end{vmatrix}, S_4 = \begin{vmatrix}0\\0.12\\0\\0\end{vmatrix}, S_5 = \begin{vmatrix}0\\0\\0.13\\0.34\end{vmatrix}, S_6 = \begin{vmatrix}0.07\\0.11\\0.125\\0.36\end{vmatrix}$$

- The equilibrium point S_0 is located at the origin of the phase space that shows no population existence. This point must be unstable because it is an empty site and has no biological meaning.
- S_1 is associated with a site occupied by endothelial cells, tumor angiogenesis agents, and tumor cells corresponding to vascular tumor growth without an immune response. This shouldn't be stable since the immune response will engage in the vascular tumor growth process.
- S_2 is associated with a site in which only tumor cells exist. This corresponds to a pathological state in which tumor cells are in a hypoxic condition and should be unstable by definition.
- S_3 and S_4 correspond to a site inhabited by only tumor angiogenesis agents that has no biological description. A steady state without tumor cells cannot represent the vascular stage of a tumor

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disease. Most tumor diseases start with avascular growth, i.e. tumor cells are present when the vascular stage starts.

- S_5 represents a domain in which the tumor cells and effector immune cells exist that are associated with the avascular stage of tumor growth. So, metastasis does not occur, and the patient could be treated completely by radiotherapy treatments (Viger et al., 2014).
- S_6 is associated with a domain in which all four populations exist corresponding to a stage in which angiogenesis happens (the vascular stage of tumor growth).

The jacobian matrix for the stability analysis is achieved as follows:

$$J=\begin{pmatrix} \frac{23c}{25(c+1)}-\frac{c}{50}-0.09 & \frac{23n}{25(c+1)}-\frac{n}{50}-\frac{23cn}{25(c+1)^2} & 0 & 0 \\ -c & \frac{359*T}{500*(T+1)}-n & \frac{359c}{500(T+1)}-\frac{359Tc}{500(T+1)^2} & 0 \\ \frac{3T}{4(n+1)}-\frac{3Tn}{4(n+1)^2} & -0.07T & \frac{3n}{4(n+1)}-2T-0.07c-\frac{5I}{2}+1 & -\frac{5T}{2} \\ 0.3I & 0 & \frac{9I}{2(T+1)}-\frac{I}{5}-\frac{9IT}{2(T+1)^2} & 0.3n-\frac{T}{5}+\frac{9T}{2(T+1)}-\frac{1}{2} \end{pmatrix}$$

whose eigenvalues are:

$$\Lambda_0=\begin{vmatrix}-0.5\\-0.09\\0\\1\end{vmatrix},\Lambda_1=\begin{vmatrix}1.83\\-0.001\pm0.17i\\-1.37\end{vmatrix},\Lambda_2=\begin{vmatrix}-1\\-0.09\\0.35\\1.55\end{vmatrix},\Lambda_3=\begin{vmatrix}-0.5\\0\\0\\-1.6\end{vmatrix},$$

$$\Lambda_4=\begin{vmatrix}-0.5\\0\\0\\0.99\end{vmatrix},\Lambda_5=\begin{vmatrix}-0.09\\0.08\\-0.06\pm0.61i\end{vmatrix},\Lambda_6=\begin{vmatrix}0.02\pm0.33i\\-0.27\pm0.77i\end{vmatrix}$$

The stability of the equilibria is evaluated via their eigenvalues numerically. S_0 is a saddle point; so, it is unstable. S_1 is a saddle focus with a 1-dimensional unstable manifold. S_2 is a saddle unstable node. Point S_3 does not have a specific situation (it is located on two eigenvectors): two eigenvalues are null. S_4 also has no situation and is located on two eigenvectors due to having two null eigenvalues. S_5 is a saddle focus (SF_) with a 1D unstable manifold. S_6 is a saddle focus with two complex conjugated eigenvalues spanning the 2D unstable manifold.

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3. Results

We investigate the dynamical behavior of the proposed model (1) by plotting the system's time series and phase portraits and using the analysis tools like the first-return map and bifurcation diagram. The numerical simulations are implemented in Matlab R2013a. The system's time series versus arbitrary units of time with considered parameter values (Table.1) are depicted in Fig.2.

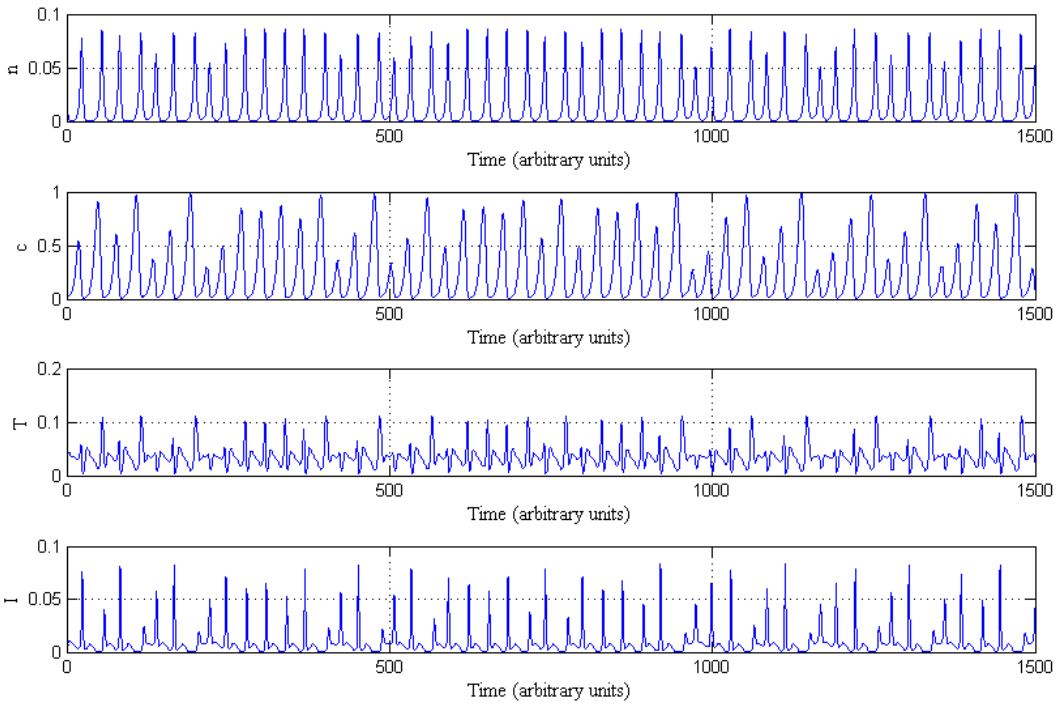

Fig.2. The time series of the populations of the proposed model (1) with mentioned parameter values. The initial conditions are $\boldsymbol{n_0} = \mathbf{0.36}$, $\boldsymbol{c_0} = \mathbf{0.24}$, $\boldsymbol{T_0} = \mathbf{0.29}$, and $\boldsymbol{I_0} = \mathbf{0.12}$.

In Fig.2, the time series for four populations associated with initial conditions as $\boldsymbol{n_0} = \mathbf{0.36}$, $\boldsymbol{c_0} = \mathbf{0.24}$, $\boldsymbol{T_0} = \mathbf{0.29}$, and $\boldsymbol{I_0} = \mathbf{0.12}$ are depicted. From a biological point of view, when a tumor grows, it secrets tumor angiogenesis agents to release endothelial cells for vascularization. This process can be seen in the time series when the population of tumor cells (T) goes to the small peak, and after a bit of time, the tumor angiogenesis agents (c) grow. This is indicating that the tumor reaches a specific size and for being rescued from necrotic, it releases tumor angiogenesis agents. After, endothelial cells (n) grow since the angiogenesis agents can proliferate them from the neighboring vessels and c decreases since the endothelial cells intake tumor angiogenesis agents when migrating to the tumor site (Anderson and Chaplain, 1998). Following the proliferation of the endothelial cells, the tumor cells grow up to higher peaks due to vascular growth. The increase of tumor cells results in the growth of effector immune cells. The increase in immune cells makes the tumor cell population decrease. With the mentioned parameter values (Table.1) the chaotic attractor solution characterized by the first return maps built from the maxima of the model variables can be observed (Fig.3 and

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Fig.4). The smooth shape of return maps present the period-doubling cascade that refers to the chaos (Feigenbaum, 1978).

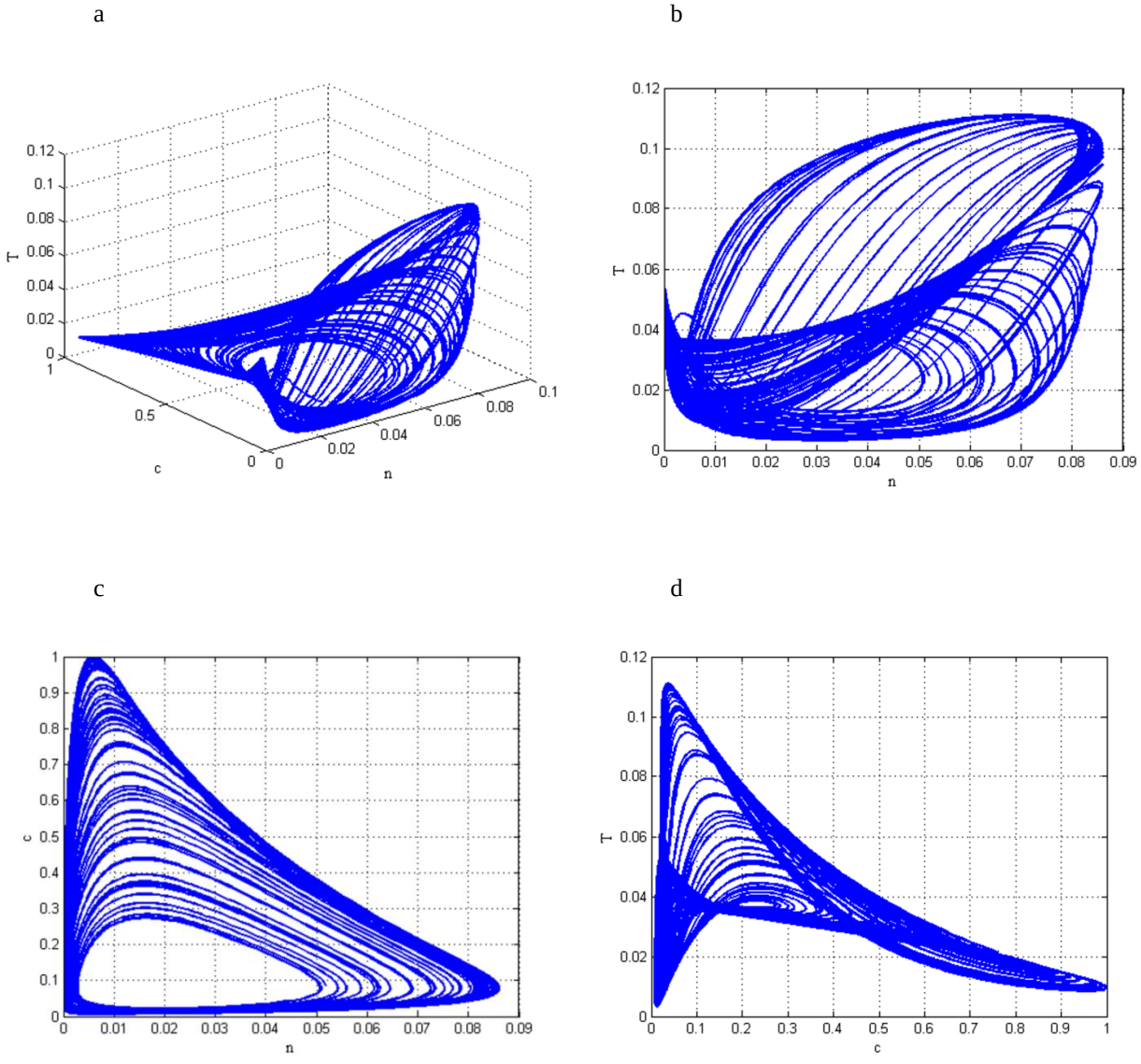

Fig.3. The phase portraits of the proposed model (1). a) 3-dimentional phase portrait of tumor cells versus tumor angiogenesis agents versus endothelial cell population. b) Tumor cells versus endothelial cells. c) Tumor angiogenesis agents versus endothelial cell population. d) Tumor cells versus tumor angiogenesis agents. The initial conditions are $\boldsymbol{n_0 = 0.36}$, $\boldsymbol{c_0 = 0.24}$, $\boldsymbol{T_0 = 0.29}$, and $\boldsymbol{I_0 = 0.12}$.

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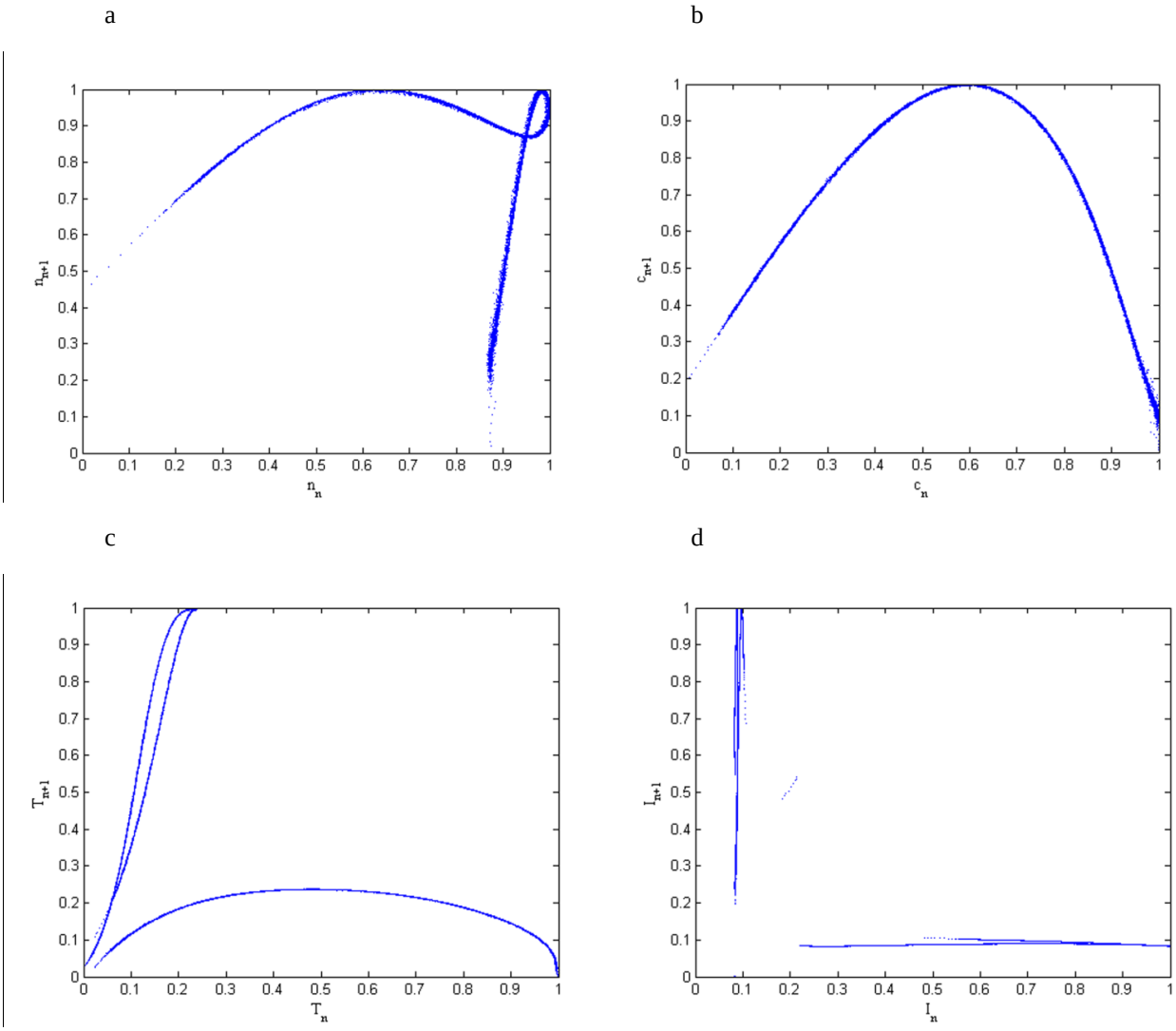

Fig.4. First-return maps to a Poincare´ section for the model (1). a) Endothelial cells. b) Tumor angiogenesis agents. c) Tumor cells. d) Effector immune cell population.

3.1. Observability analysis

Assume that a dynamical system is $\dot{\boldsymbol{x}}(\boldsymbol{t}) = \boldsymbol{f}(\boldsymbol{x}(\boldsymbol{t}))$ and the state vector is $x \in R^m$. When m=4 the system can be detailed:

$$\begin{cases} \dot{x} = f_1(x) \\ \dot{y} = f_2(x) \\ \dot{z} = f_3(x) \\ \dot{w} = f_4(x) \end{cases} \quad (2)$$

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where $x = n(t), y = c(t), z = (T(t), and\ w = I(t)$. The time series (s) is obtained by measurement function h that is $s(t) = h(x(t))$. So the reconstruction of the phase portraits can be done by derivative coordinates:

$$\begin{cases} X = s \\ Y = \dot{s} \\ Z = \ddot{s} \\ W = \dddot{s} \end{cases} \tag{3}$$

$\emptyset$ is the transformation between the original variables and derivative coordinates, consequently $\emptyset: R^4(x, y, z, w) \rightarrow R^4(X, Y, Z, W)$.

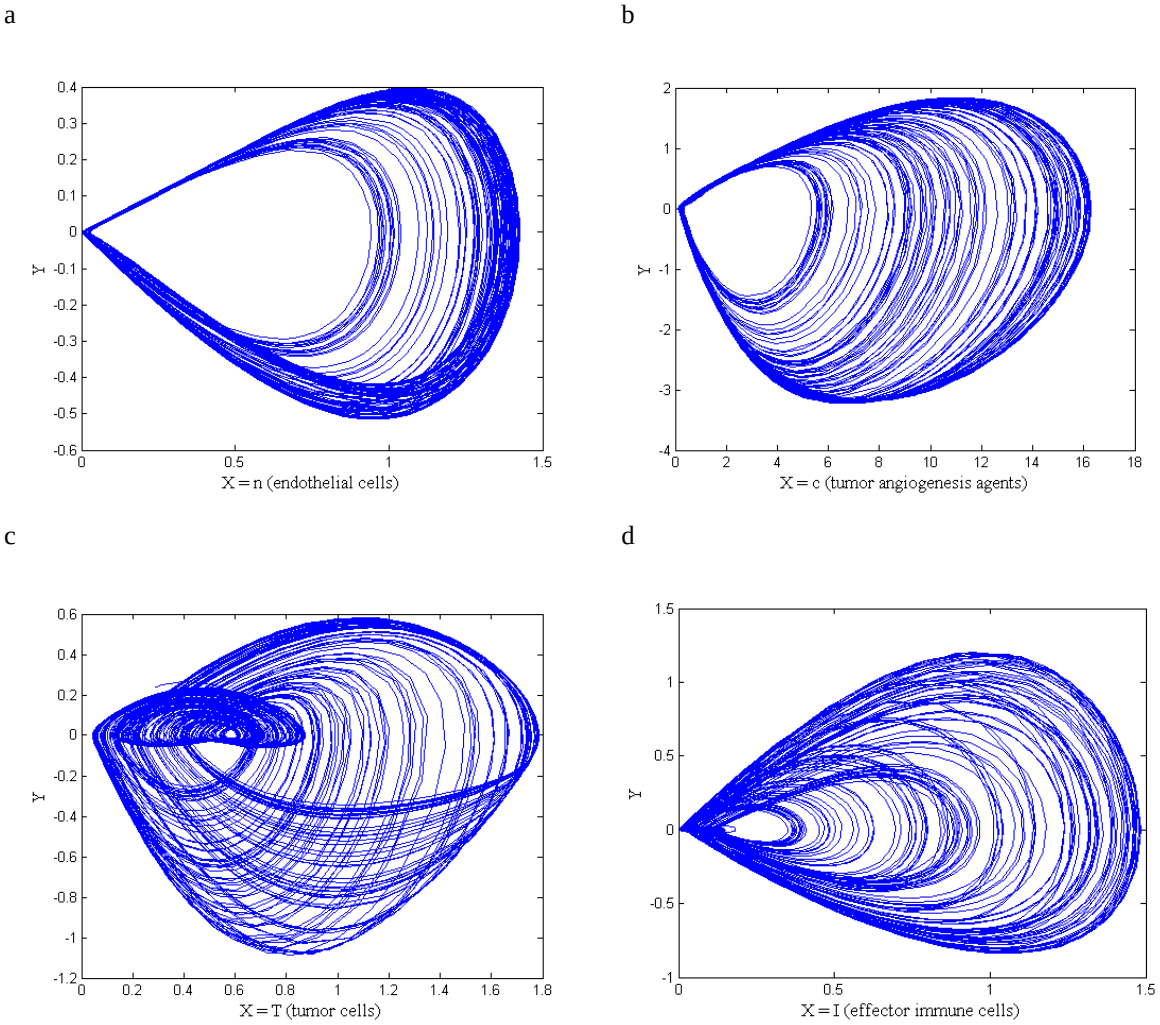

Fig.5. Differential embedding induced by variables of model (1). a) From endothelial cells. b) From tumor angiogenesis agents. 3) From tumor cells. d) From effector immune cells.

The embedding projections shown in Fig.5 are corresponding to the chaotic attractors in Fig.3. The tumor cell population has the best observability in our model dynamics because its embedding projection is less squeezed between all variables projections. So we investigated its growth rate ($\boldsymbol{\rho_3}$) variation on the system's

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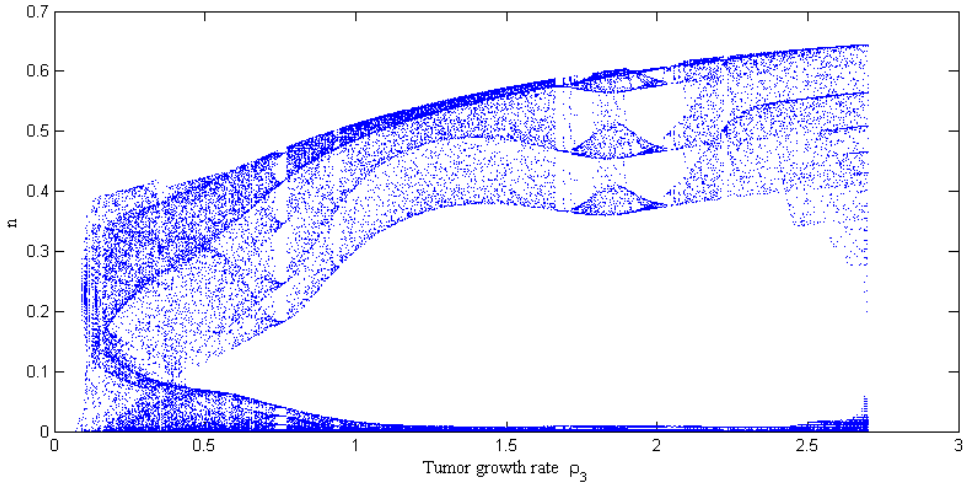
dynamics. Immune cells have very poor observability of our system's dynamics. Therefore, to investigate the system's dynamics, measuring only the population of effector immune cells is not efficient.

3.2. Bifurcation analysis

The bifurcation diagrams of the endothelial cell and tumor angiogenesis agents versus tumor growth rate $\boldsymbol{\rho_3}$ are depicted in Fig.6.

a



b

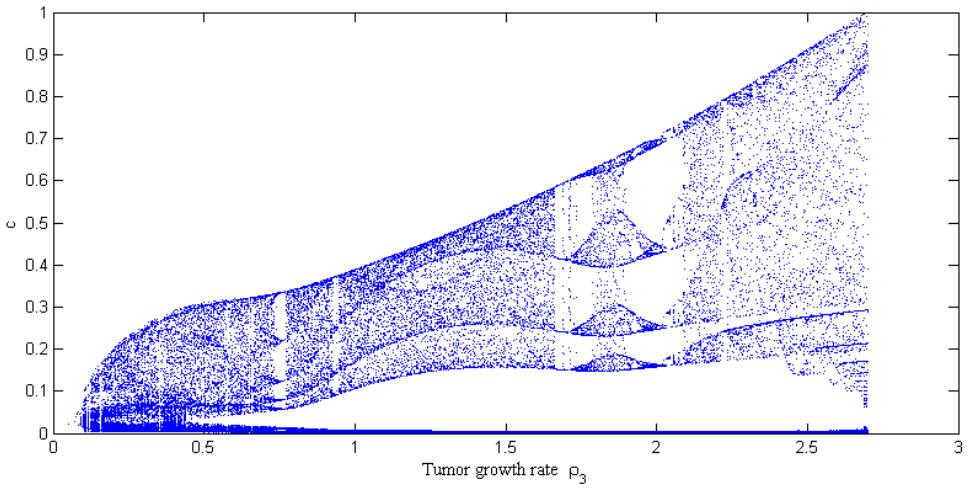


Fig.6. The bifurcation diagrams versus tumor growth rate $\boldsymbol{\rho_3}$. a) Exterma of endothelial cells. b) Exterma of tumor angiogenesis agents.

The increase in the tumor growth rate resulted in the increase of the tumor angiogenesis agents and endothelial cells in Fig.6 which is clinically true and described in the introduction and first paragraph of the result section. We can observe that the increase in tumor cells' growth rate results in an increase in the

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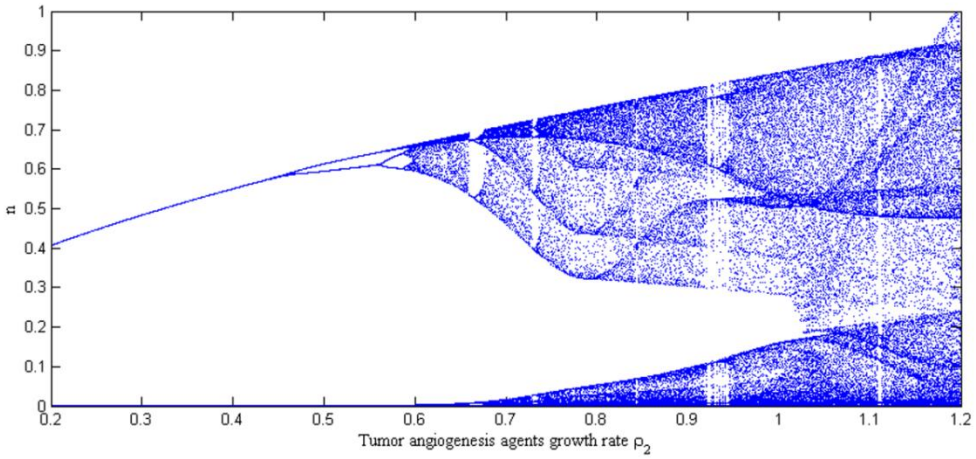
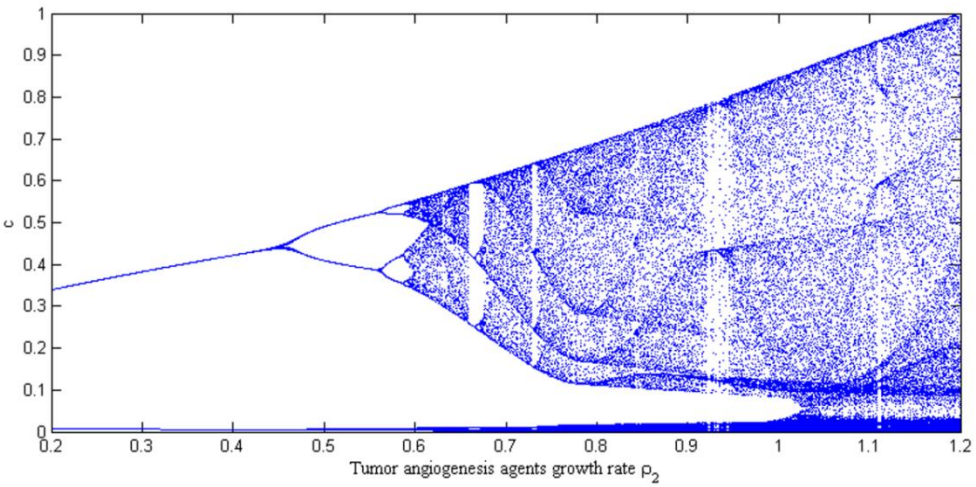
populations' fluctuations range too. When $\boldsymbol{\rho_3 > 2.7}$, the trajectory ejected to infinity. In this case, it can be said that the metastasis happens (Viger et al., 2014; Letellier et al., 2017). To investigate patient situations, we consider varying the parameter values as $\boldsymbol{\rho_2}$, and $\boldsymbol{\alpha_{33}}$ to study the impact of tumor angiogenesis agents on the behavior of the system's dynamics. We also investigate the $\boldsymbol{\alpha_{31}}$ variation to evaluate the impact of the killing rate of the tumor cells via effector immune cells' impacts on the model dynamics. Our model is population based; so, the bifurcation diagram should be computed as a modified version as described in (Letellier et al., 2013). Indeed, the minimal and maximal values at each oscillation of the given variables n, c, T, and I were taken to obtain their range of variability versus the mentioned parameters. The bifurcation diagrams versus angiogenesis agents' growth rate ($\boldsymbol{\rho_2}$) are depicted in Fig.7. By increase of $\boldsymbol{\rho_2}$, the population of endothelial cells increases. There is no period-doubling cascade by $\boldsymbol{\overline{\rho_2} < 0.588}$ which means that in this range the tumor growth is nonvascular and nonmetastatic. When $\boldsymbol{\rho_2 \geq \overline{\rho_2}}$, the period-doubling cascade occurs. This presents chaotic behavior representing the vascular phase of tumor growth. The mentioned threshold value depends on the other parameter values that can be considered for other patient conditions.

a



b



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c

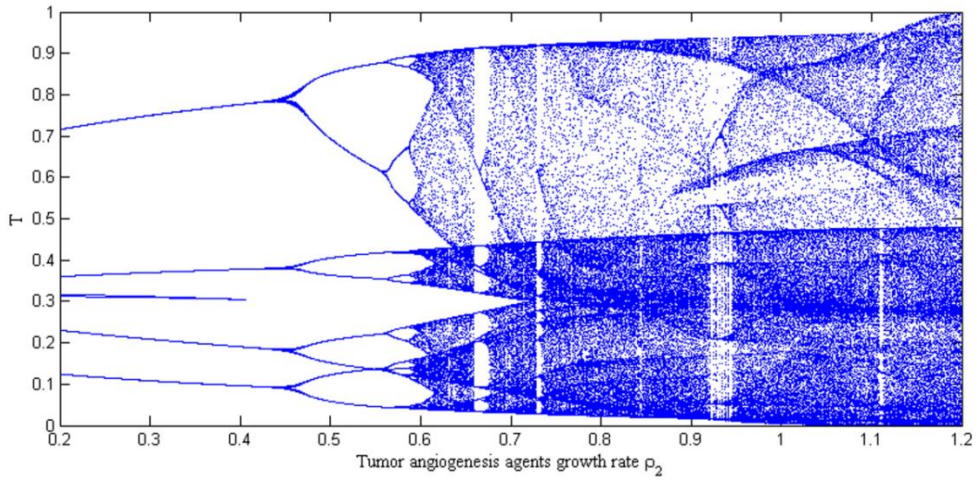
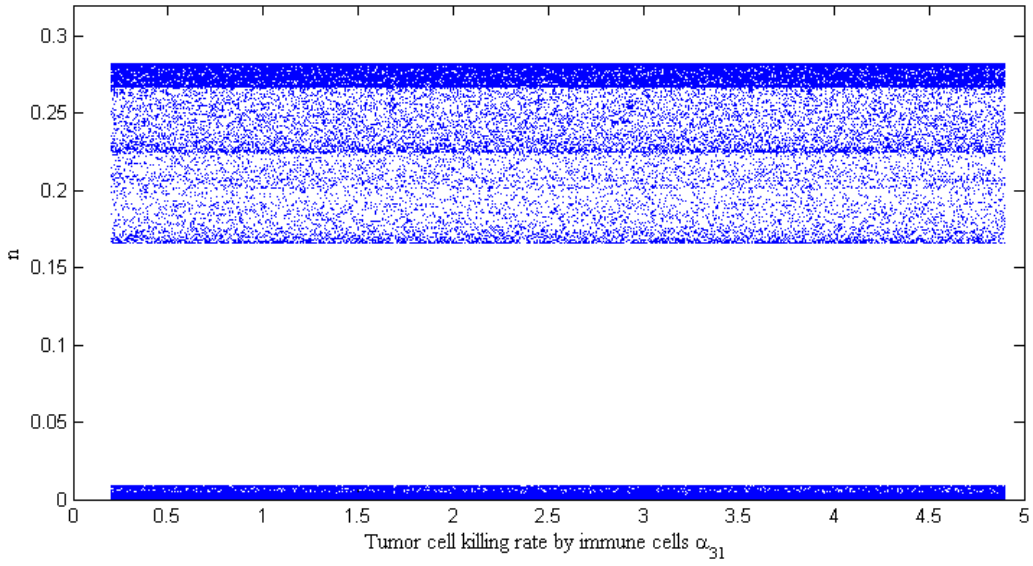


Fig.7. The bifurcation diagrams versus tumor angiogenesis agents' growth rate $\boldsymbol{\rho_2}$. a) Exterma of endothelial cells. b) Exterma of tumor angiogenesis agents. c) Exterma of tumor cells population.

There is no bifurcation versus $\boldsymbol{\alpha_{31}}$; thus, There is no impact of the tumor cell killing rate by immune cells $\boldsymbol{(\alpha_{31})}$ on the system dynamics (Fig.8). This value cannot be zero since the trajectory would be ejected to infinity. This parameter value just requires being non-zero because the chaotic attractor exists when $\boldsymbol{\alpha_{31} > 0}$; however, it doesn't depend on this parameter value variation. This result shows the inefficiency of immune system-targeted therapies (Choudhury et al., 2006; Chi and Dudek, 2011).

a



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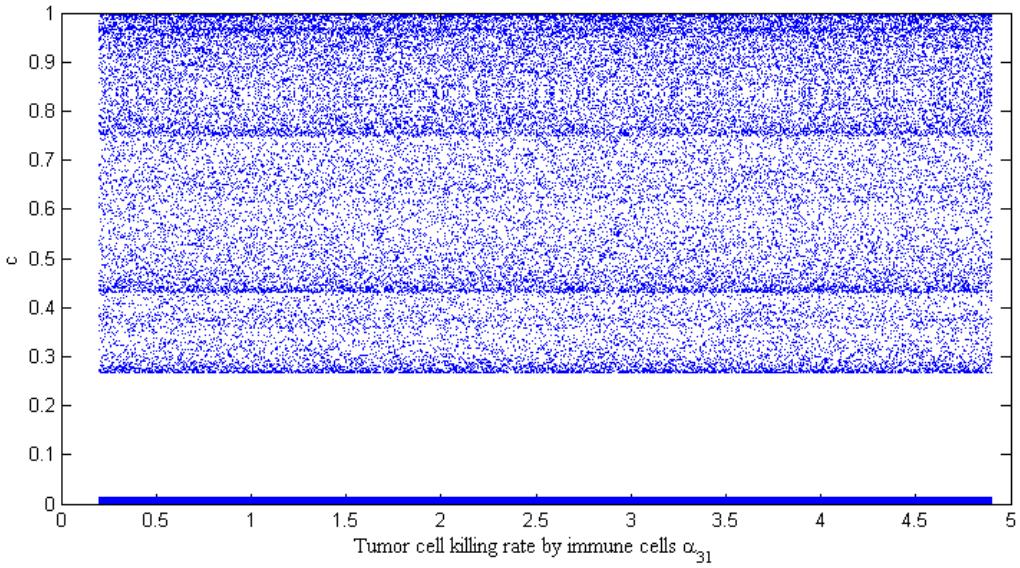
b



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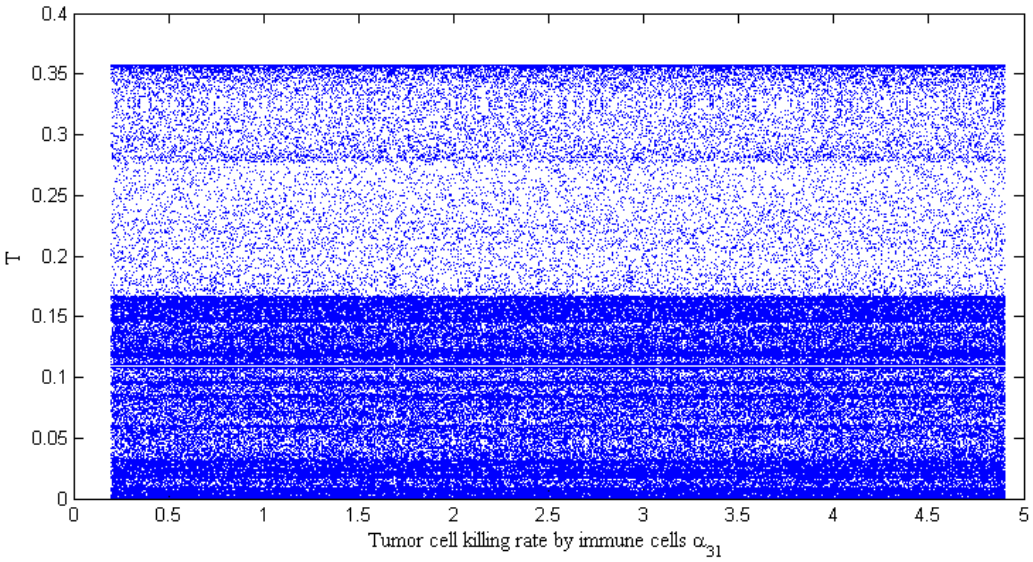

Fig.8. Bifurcation diagrams versus tumor cell killing rate by immune cells ($\boldsymbol{\alpha_{31}}$). a) Exterma of endothelial cells. b) Exterma of tumor angiogenesis agents. c) Exterma of tumor cells population.

The inhibition factor of tumor angiogenesis agents $\boldsymbol{\alpha_{33}}$ on tumor cells is depicted in Fig.8. With $\boldsymbol{\alpha_{33} < 0.037}$ the trajectory tends to infinity. This may correspond to the importance of TIF existence to the regulation of tumor vascularization. By increasing the parameter $\boldsymbol{\alpha_{33}}$, the amount of tumor angiogenesis agents decreases.

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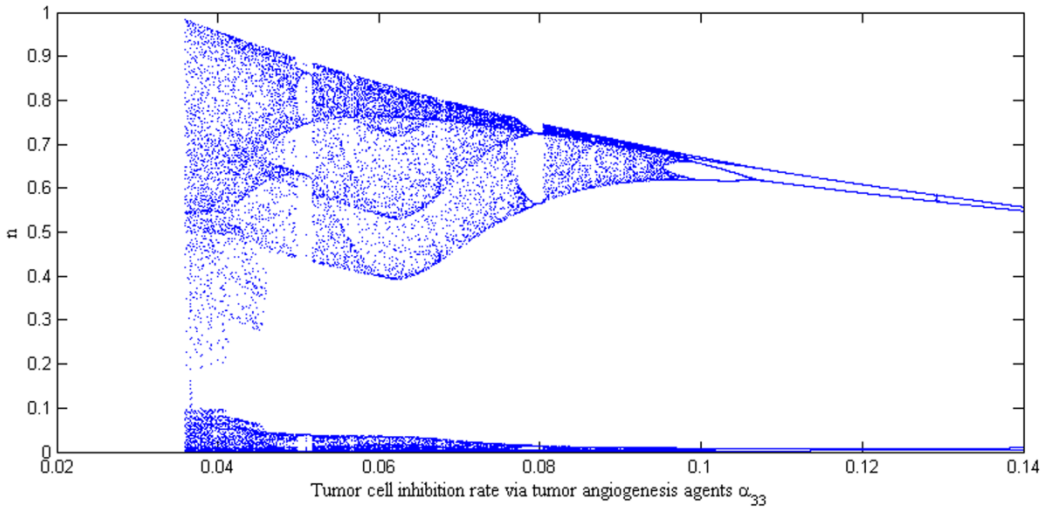
So the population of endothelial cells decreases. When $\boldsymbol{\alpha_{33} \geq 0.096}$, the dynamic of the system becomes periodic; so, the impact of inhibition factor on angiogenesis can be enough to avoid vascularization (Fig.9). Clinically this can be the impact of anti-angiogenic drugs like angiostatin to terminate tumor-induced vascularization.

a



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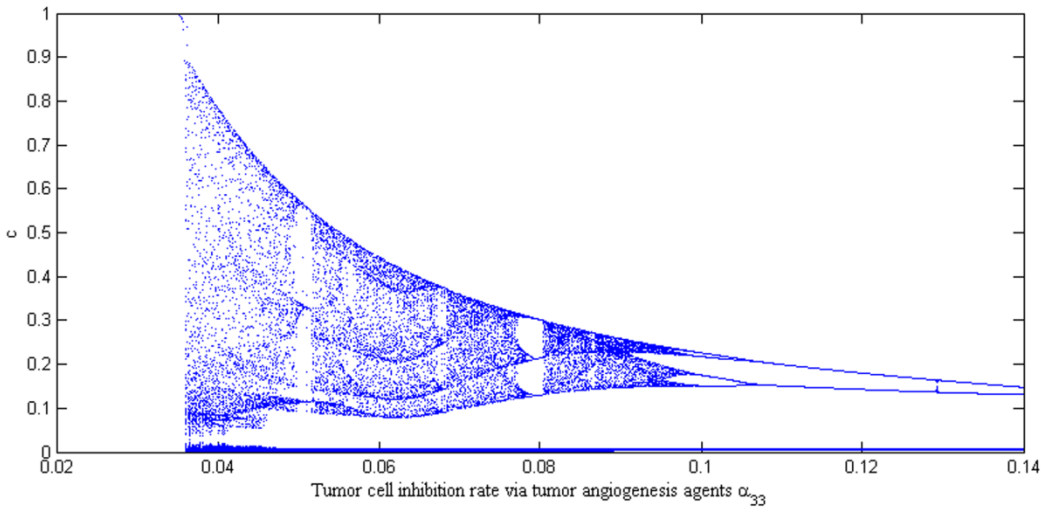

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c

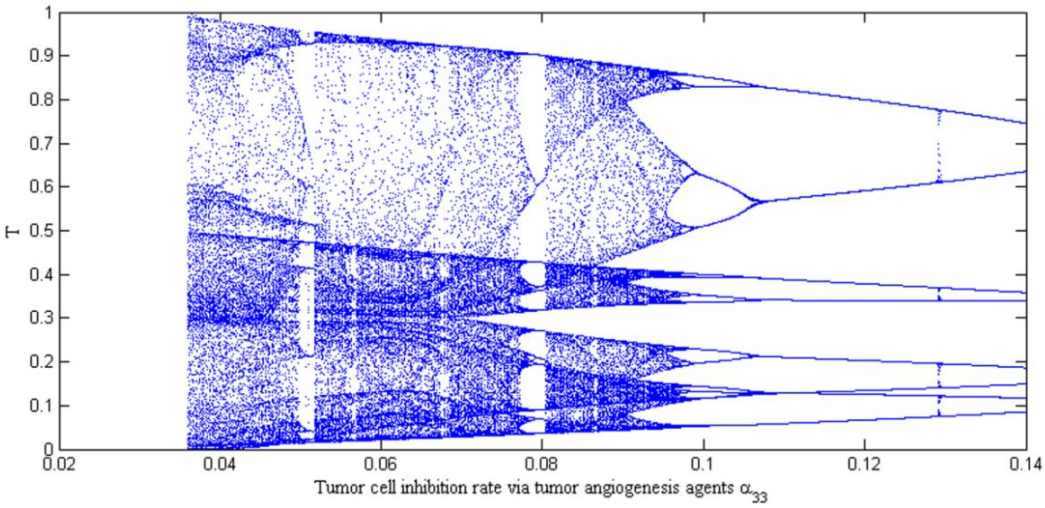

Fig.9. Bifurcation diagrams versus tumor angiogenesis agents' inhibition rate on tumor cells $\boldsymbol{\alpha_{33}}$. a) Exterma of endothelial cells. b) Exterma of tumor angiogenesis agents. c) Exterma of tumor cells population.

4. Discussion

In the present work, we proposed a 4-D cancer model including tumor angiogenesis agents governing both pre-vascular and vascular tumor growth stages to study the impact of tumor angiogenesis agents on vascularization dynamics. Avascular growth results when the tumor does not have its blood supply; so, instead relies on the diffusion of nutrients and oxygen through the surrounding tissue across the tumor surface for growth. When the demand for nutrients and oxygen exceeds the amount of supply and thus becomes stable (appears to be approximately 1-3 mm in diameter), the stage of avascular growth ends (Hillen and Griffioen, 2007). The solid tumor survives via the angiogenesis process. In this process, blood vessels form around it. To obtain the tumor angiogenesis agents' equation, we first consider the primary event of tumor-induced angiogenesis. When the tumor angiogenesis agents are secreted from the tumor, they penetrate the surrounding tissue and extracellular matrix. As endothelial cells migrate through the extracellular matrix, the endothelial cells intake tumor angiogenesis agents (Anderson and Chaplain, 1998). Vascular growth occurs when the tumor provides one or more blood vessels that carry oxygen directly to the tumor cells (Owen et al., 2009). This formation of blood capillaries to the tumor is known as angiogenesis. Angiogenesis is an example of a pathological state in tumor growth that results in metastasis. One of the most interesting phenomena in characterizing the vascular phase of tumor growth is chaos (Letellier et al., 2017; Viger et al., 2014).

Previous studies have shown that chaotic dynamics exist in vascular tumor growth (De Pillis and Radunskaya, 2003; Itik and Banks, 2010; Letellier et al., 2013; Viger et al., 2014). In this paper, it is theorized that tumors have new blood vessels that use a diffuse factor called the Tumor Angiogenesis Factor (TAF), a

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factor that stimulates angiogenesis in the tumor. It is proved that the tumor is also producing a slight amount of substances like angiostatin as Tumor Inhibitor Factors (TIF) to regulate the formation of neovascularization (O'Reilly et al., 1994). Therefore, the impact of tumor angiogenesis agents (TAF and TIF) that are very important in vascularization could be interesting to study their role in angiogenesis. It has been suggested that the existence of endothelial cell population as a key variable for vascularization in the cancer model is more effective to study both avascular and vascular stages of tumor growth (Viger et al., 2014). Inspired by this research, we introduced the generalized cancer model in which tumor angiogenesis agents exist. For this purpose, we considered a variable as tumor angiogenesis agents that have both stimulant and inhibitor factors on vascularization and tumor growth. The default parameter values of the model are equal to the values of the presented models by (Letellier et al., 2013; Viger et al., 2014). They had chosen their parameter values to attain a chaotic attractor since the dynamic of their model is studied qualitatively (Itik and Banks, 2010; Letellier et al., 2013; Viger et al., 2014). The values of our introduced parameters ($\boldsymbol{\rho_1}$, $\boldsymbol{\alpha_{11}}$, $\boldsymbol{\rho_2}$, $\boldsymbol{\alpha_{22}}$, and $\boldsymbol{\alpha_{33}}$) are selected to achieve a chaotic attractor solution (Fig.3). Therefore, the biological meaning of the parameter values is nonspecific like the studies by (Kuznetsov et al., 1994; Itik and Banks, 2010; Letellier et al., 2013; Letellier et al., 2017; Viger et al., 2014). What is relevant is investigating the impact of parameter variations on the system's dynamics. For this purpose, we used some bifurcation diagrams. The smooth character of the return maps built from the variables' maxima is the route to the existence of chaos in our model (Fig.4), exactly as observed in the models by (Letellier et al., 2013; Viger et al., 2014) with the same parameter values. The tumor cell population is less squeezed in the differential embedding projection portraits (Fig.5). Therefore, it is more observable between all model variables. We investigated its growth rate variation on the system's dynamics via bifurcation analysis (Fig.6). Our model also indicates that the tumor cells' growth rate infers a high range of fluctuations in all the populations.

The presented dynamical model could capture the angiogenic switch and biological behavior of the tumor growth process and retains intrinsic features of the biological process. Based on the time series in Fig.3, when the growth of tumor cells stopped in a range, they secreted tumor angiogenesis agents; so, their population increased. After that, the TAF overcomes TIF and stimulates the proliferation of the endothelial cell population which results in more increase in the tumor cell population. On the other hand, an increase in the tumor cells stimulates the growth of effector immune cells. After, the rise of immune cell populations, they suppress the population of tumor cells (Fig.3). The tumor cells secret the tumor angiogenesis agents to survive from being necrotic. So by the increase of this substance, the endothelial cells begin to form blood vessels. The chaos that occurs due to the increase of $\boldsymbol{\rho_2} \geq \overline{\boldsymbol{\rho_2}}$ would capture this biological process in the system (Fig.7). Naturally, the impact of tumor angiogenesis agents as angiogenesis stimulants (TAF) is much more than their impact as angiogenesis inhibitors (TIF) (Maggelakis, 1996); however, the increase of their TIF agents can result in the termination of the chaos in the system's dynamics and vascularization on the patient's tumor. Clinically, different conditions of a patient can be assumed based on the model (1) parameter values. First, we can assume the patient with tumor angiogenesis agents' growth rate $\boldsymbol{\rho_2} < \overline{\boldsymbol{\rho_2}}$ and keep the other parameter values as mentioned previously. In this case, the patient has few tumor cells without any metastasis as long as his parameter values do not change. When the parameter $\boldsymbol{\rho_2} \geq \overline{\boldsymbol{\rho_2}}$, the evolution of endothelial cells occurs; thus, patient has vascular tumor growth. From a dynamical point of view, beyond the threshold amount of tumor angiogenesis agents' growth rate ($\overline{\boldsymbol{\rho_2}}$), the period-doubling cascade in populations begins which leads to chaos.

Ecological models take into account the non-linear interactions between tumor cells and their environment and their qualitative analysis could be useful for therapeutic approaches such as non-tumoral-cell-targeted treatments like anti-angiogenic treatments. Hence, the contribution of non-tumor cells in cancer dynamics appears to be very important in the global behavior of the system. There are a few paths to encountering cancer. One of them is immune system-targeted therapies. The killing rate of the tumor cells via effector immune cells ($\boldsymbol{\alpha_{31}}$) is not affecting the dynamic of our model (Fig.8). This finding is in line with the biologically/clinically observed lack of efficiency of a large number of therapies targeting the immune system (Hillen and Griffioen,

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2007; Choudhury et al., 2006; Chi and Dudek, 2011). Another type of cancer therapy is targeting tumor-induced angiogenesis via injecting anti-angiogenic agents like angiostatin into the body to prevent vascularization. In the dynamical analysis, our model suggests that the angiogenesis-targeted therapies are strongly more effective than immune system-targeted therapies. Tumor cell inhibition rate via tumor angiogenesis agents is indicated by $\boldsymbol{\alpha_{33}}$. This inhibition rate is naturally very small; however, increasing that via external inhibitor drugs like angiostatin would be effective to terminate the chaotic behavior of the model (1) that corresponds to the termination of vascularization (Fig.9).

5. Conclusion

The 4-D model introduced by Viger et al. was the developed model from the 3-D model proposed by de Pillis and Radunskaya. They introduced the endothelial cell population to reproduce the angiogenesis phenomenon. However, the existence of tumor angiogenesis agents is crucial to investigate their role in neo-vascularization. For this purpose, we introduced the tumor angiogenesis agents in their 4-D model and created a new 4-D model. This model can be employed to better realize the tumor vascularization dynamics with tumor angiogenesis agents' interference and capture the features of its process qualitatively. Bifurcation and observability analysis have been done to investigate the model dynamics. Angiogenesis is a complex biological phenomenon involving several types of cells, agents, and interacting fields at different scales. Moreover, it comprises various migration mechanisms and transport processes. Spatial dynamics and heterogeneity are thus essential to adequately describe angiogenesis and its relation to tumor growth. Our 4-D model reproduces the dynamical transfer between pre-vascular and vascular stages of tumor growth which is very important in metastasis and tissue invasion. So, it should be employed before considering a tumor spatial model. In conclusion, the existence of tumor angiogenesis agents is crucial for the beginning of neo-vascularization. Our model is not considering the biological complexity of a cancer like genomic instability; however, it takes into account the expression of a given inhibition factor like TIF agents. Our model focuses on the interactions between different cell populations. Therefore it allows reproducing situations observed in vivo or in clinics like non-vascular and vascular phases of the tumor growth.

Contributions

M.P. designed the study; A.M. performed the research and simulations; A.M. wrote the manuscript; All authors reviewed the manuscript.

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Conflict of Interest Statement

The authors have no conflicts to disclose.

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Financial interests

The authors declare they have no financial interests.

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