ORIGINAL ARTICLE

The Effect of Tumor Angiogenesis Agents on Tumor Growth Dynamics: A Mathematical Model

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Received: 15 September 2024 / Accepted: 30 October 2024

Abstract

Purpose: Tumor-induced angiogenesis is a dangerous state of the tumor growth process in which solid tumors have a blood supply. Modeling has been a very important tool in studying tumor growth and angiogenesis. In this paper, we developed a cancer model by introducing tumor angiogenesis agents to better highlight the role of these chemical substances in tumor-induced vascularization. Our model can reconstruct the transition from a pre-angiogenic to a post-angiogenic state.

Materials and Methods: The proposed model comprises five variables: host cells (normal cells), immune cells, tumor cells, endothelial cells, and tumor angiogenesis agents. Chaotic behavior in the production of different populations of cells during vascular growth may confer survival advantages to tumors. Our model has a chaotic regime, which is an indication of tumor-induced angiogenesis dynamics. The fixed points are analyzed biologically, and stability analysis is performed via their eigenvalues. We analyzed the model dynamics via observability and bifurcation analysis.

Results: The numerical simulations illustrate biological and clinical findings about vascular tumors. The results show that the proposed model with the existence of tumor angiogenesis agents could capture both avascular and vascular stages of tumor growth. There is no effect of tumor cell killing rate via immune cells on the system dynamics. However, the increase of inhibitory factors of tumor angiogenesis agents leads to the termination of chaos.

Conclusion: Our results show the ineffectiveness of targeted treatments on the immune system, which has been confirmed by many negative treatment methods in immunotherapies. Tumor-secreted inhibitor factors are essential to regulating the angiogenesis process. However, increasing inhibitor factors via anti-angiogenic drugs would be a more effective therapeutic approach to eradicate metastasis.

Keywords: Chaos; Angiogenesis; Mathematical Model; Vascular Tumor; Tumor Angiogenesis Agents; Numerical Simulation.

DOI: https://doi.org/10.18502/fbt.v12i1.17743

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1. Introduction

A tumor mass results from an uncontrolled cell division. A tumor mass can be benign or malignant. Tumor cells can attack the surrounding tissue. Tumor cells need oxygen and nutrients from neighboring tissue via diffusion and removal of waste products to grow [1]. The need for nutrients in the tumor is proportional to the volume of the tumor; however, its absorption is proportional to its surface. Tumor growth has two stages: avascular growth and vascular growth. Vascular growth is 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 (metastasis). Angiogenesis is the process in which new capillaries are created from the existing blood vessels. This process plays an important role in physiological events such as growth, wound healing, and reproduction [2]. 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 [2]. 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 a real conception of the parameters and may eventually be used as a predicting tool.

In 1971, Folkman published a paper discussing a new theory of angiogenesis [3]. 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 [4]. Because of this, endothelial cells are an ideal target for therapies. The angiogenesis process is extensively modeled by Anderson and Chaplain [5]. 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 branching and blood vessel formation in a process known as anastomosis.

In the past 30 years, several mathematical models have been proposed to describe the various stages of tumor growth. Continuous cell population models 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 [6]. 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 [7, 8]. The following models cover some features of cellular movement and are divided into one of three forms: exposure [9], active penetration [10], or chemotactic [11]. Discrete cell population models could simulate cancer growth on a single-cell scale [12-14]. 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 [15] and the Fokker-Planck method [16, 17].

In 2003, a mathematical cancer model was introduced comprising three variables as normal cells, effector immune cells, and tumor cells [18]. This model was the developed form a model consisting of two cell populations, namely immune cells and tumor cells presented by Kuznetsov et al. [19]. Even for just two cell populations, the model can show rich dynamics and explain important aspects of cancer progression. De Pillis and Radunskaya [18] 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 [20], 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.* [21], who reported turbulence at certain intervals in the control space. The authors introduce symbolic dynamics and Lyapunov's indicators to study chaos in this system. At the same time, Letellier *et al.* [22] performed a topological analysis of the model to show a new trend in understanding interactions between tumor cells. Instead of a single interval, chaos is reported for intervals of 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.* [23] 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 [18] is a chaotic dynamic tumor model. However, this model cannot demonstrate 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 studies the nonlinear dynamics of chaos theory to describe the nature of cancer and metastasis. The main task in understanding this model was Folkman's pioneering work in tumor angiogenesis [2, 24]. Baum *et al.* [25] proposed a mathematical model that describes chaos as working with micrometastatic tumor angiogenesis.

Anderson and Chaplain [26], 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. O'Reilly *et al.* [27] observed in mice models that tumorsalso produced substances like angiostatin as an inhibitor to regulate the formation of neovascularization. In another study by Maggelakis [28], 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.

In recent years some mathematical models with applications in cancer treatment have been introduced. Shafiekhani *et al.* [29] combined distinct treatment modalities in a mathematical model for Pancreatic Ductal Adenocarcinoma (PDAC), including 5-FU chemotherapy and anti-CD25 immunotherapy to improve therapeutic effectiveness. Jung *et al.* [30] developed a model of the mitotic cell cycle. They have used their generalized model to analyze the cancer cell cycle progress under various gene perturbations. Shafiekhani *et al.* [31] developed a mathematical model using a set of ordinary Differential Equations (ODEs) to test the efficiency of anti-PD-L1 and radiotherapy combined treatments. Shafiekhani *et al.* [32] developed a mathematical model that can properly simulate a dynamical complex network of tumor-immune interactions that is appropriate to evaluate different immunology hypotheses. Shafiekhani *et al.* [33] used the Fuzzy Stochastic Petri Net (FSPN) method with uncertain kinetic parameters for Tumor-Immune System modeling.

A 4-dimensional mathematical model including host cell status, immune cells, tumor cells, and endothelial cells was introduced by Viger *et al.* [34]. 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. Letellier *et al.* [35] added a therapy action into Viger's cancer model to study the impact of chemotherapy and antiangiogenic drugs in the cancer model. Starkov [36] studied ultimate dynamics and derived tumor annihilation circumstances by using the localization method for the model proposed by Viger *et al.* [34]. Das *et al.* [37] developed and analyzed a mathematical model of tumor-immune interactions with combined optimal therapy strategies via a formulated optimal control function. Mohseni *et al.*

[38] introduced tumor angiogenesis agents and created a 4-D model for angiogenesis without the existence of host cells.

The modeling of vascular tumor growth by introducing the endothelial cell population has been performed by Viger *et al.* [34]; however, they did not consider the tumor angiogenesis agents in the model which is essential to study the angiogenesis phenomena. The innovation of this paper is to expand their work and explore the effect of tumor angiogenesis agents on tumor vascularization. We introduced a five-dimensional single tumor site model by including tumor angiogenesis agents. We considered five variables including host cells, immune cells, tumor cells, endothelial cells, and tumor angiogenesis agents. TAF and TIF as tumor angiogenesis agents were introduced to the model. Then, we investigated the avascular and vascular stages of tumor growth with the bifurcation analysis of the model dynamics. The next sections of this paper are organized as follows. In section 2 we introduce our 5D cancer model and its parameter values. Section 2.1 comprises the fixed point analysis of the proposed model. The time series, chaotic attractors, and first return map of the model are illustrated in section 3. Observability analysis via differential embedding of each variable is done in section 3.1. To show the impact of the parameter variations on systems dynamics, bifurcation analysis has been performed in section 3.2. In section 4 we discussed our developed model and the results from the numerical simulations. Section 5 is the conclusion part of this paper.

2. Materials and Methods

We proposed a cancer model that 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. Most cancer models do not consider the interactions between angiogenesis and host cells. In metastasis only tumor cells can proliferate through angiogenesis; so, they are more related to the angiogenesis process. The process of neo-vascularization starts via secreting tumor angiogenesis agents via tumor cells. Therefore, tumor cells are more dependent on tumor angiogenesis agents than host cells. On the other hand, 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 Figure 1, our 5D proposed Ordinary Differential Equation (ODE) model is written as (Equation 1):

$$\begin{aligned}
\dot{H} &= \rho_1 H(1-H) - \alpha_{13} HT \\
\dot{I} &= \frac{\rho_2 IT}{1+T} - \alpha_{23} IT - \delta_2 I + \alpha_{24} IE \\
\dot{T} &= \rho_3 T(1-T) - \alpha_{31} HT - \alpha_{32} IT + \frac{\alpha_{34} ET}{1+E} - \alpha_{33} VT \\
\dot{E} &= \frac{\rho_4 VE}{1+V} - \delta_4 E - \alpha_{41} VE \\
\dot{V} &= \frac{\rho_5 TV}{1+T} - \alpha_{51} EV
\end{aligned} \tag{1}$$

where H is the population of host cells, I is the population of effector immune cells, T represents the population of tumor cells, E is the endothelial cell population, and V corresponds with tumor angiogenesis agents secreted by the tumor in the pre-vascular stage:

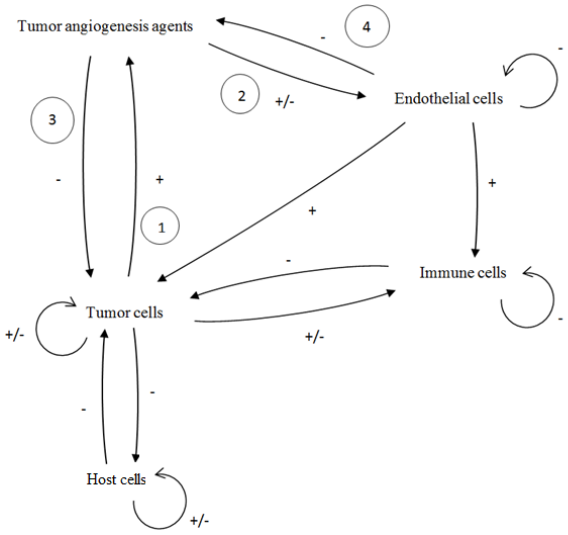


Figure 1. The model flow graph. The interactions are between host cells, immune cells, tumor cells, endothelial cells, and tumor angiogenesis agents

Unlike the presented model by Viger *et al.*, in our model, due to the existence of tumor angiogenesis agents' variable, there is no direct impact on endothelial cell proliferation from tumor in the endothelial cell equation. The tumor cells are producing tumor angiogenesis agents via a hill

function like $\frac{\rho_5 TV}{1+T}$. Instead, the tumor-induced angiogenesis agents have a direct impact on endothelial cell proliferation via the term $\frac{\rho_4 VE}{1+V}$. In the process of vascular tumor growth, tumor cells secrete TAF substances, such as Vascular Endothelial Growth Factors (VEGF), to stimulate vascularization. However, tumor cells also produce smaller amounts of inhibitors which are called TIFs such as angiostatin that can regulate the formation of new blood vessels [27]. When a tumor reaches a critical size, it begins to spread tumor angiogenesis agents with growth rate $\boldsymbol{\rho_5}$ to surrounding tissues, which spread to neighboring blood vessels, creating a chemical gradient. This interaction is shown in arrow 1 on the flow graph (Figure 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 Figure 1. When endothelial cells migrate through the extracellular matrix, the endothelial cells consume tumor angiogenesis agents via the rate of $\boldsymbol{\alpha_{51}}$. The minor negative effect of TIF secreted by tumor cells on endothelial cells is considered by the additional term $\boldsymbol{\alpha_{41} VE}$ to the fourth equation. This minor negative effect is also considered on the tumor cell population with $\boldsymbol{\alpha_{33} VT}$ additional term**.** This interaction corresponds to arrow 3 in Figure 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 [39]. The proliferation rate of the endothelial cell population via tumor angiogenesis agents is considered by $\boldsymbol{\rho_4}$. Then the endothelial cells intake tumor angiogenesis agents while traveling to the tumor site [4]. This interaction corresponds to arrow 4 depicted in the flow graph (Figure 1) and is considered with the term $\boldsymbol{\alpha_{51} EV}$. The endothelial cells' natural death is quantified by the coefficient $\boldsymbol{\delta_4}$. 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 a 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 $\frac{\alpha_{34} ET}{1+E}$. 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 [34]. So, this interaction is considered via parameter $\boldsymbol{\alpha_{24}}$. 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 [40]. 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.

The model assumptions are listed below:

- In the presented model, the positive impact of TAF agents on tumor cell growth is considered by the endothelial cells' indirect impact.
- The impact of tumor cells on endothelial cell growth is indirect and through tumor angiogenesis agents.
- The impact of tumor angiogenesis agents on immune response development is indirect from the endothelial cells.
- In our model, we did not consider the other interactions between immune cells and endothelial cells because they are not relevant in the context of tumor angiogenesis modeling.
- The proposed model is for a single tumor site. So the interaction between cells and tissues and cell migration through diffusion or by circulating over the blood vessels is not considered.
- Both TAF and TIF substances are considered tumor angiogenesis agents' variables. Biologically, it is not unusual for chemical to have both positive and negative impacts on the growth process.
- We do not consider the interactions between angiogenesis and host cells in the context of our

presented model. Because, in metastasis, only tumor cells can proliferate through angiogenesis.

Our 5D model is investigated via parameter values $\boldsymbol{\rho_4}$, $\boldsymbol{\alpha_{41}}$, $\boldsymbol{\rho_5}$, $\boldsymbol{\alpha_{51}}$, and $\boldsymbol{\alpha_{33}}$. The other parameters are equal to the values of the model presented by Viger *et al.* [34]. As in most mathematical models at the tissue level, the biological meaning of the parameter values is not certain [18, 34]. 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 [18, 22, 34, 35]. What is relevant is the impact of the parameter variations on the system's dynamics which will be explored via bifurcation diagrams in section 3.2.

2.1. Fixed Point Stability Analysis

The equilibria are calculated numerically. There are twenty-nine equilibrium points via the mentioned parameter values. Fourteen fixed points have at least one negative coordinate that is biologically irrelevant. Our model is population-based; so, the equilibrium points located in the positive phase space domain must be considered. Two fixed points are duplicated. So, there are thirteen equilibrium points with non-negative coordinates that are not duplicated and correspond to the mentioned parameter values (Table 1) as follows (Equation 2):

- 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 only host cells. For a healthy patient, it must be stable.
- S_2 is associated with a site where tumor angiogenesis agents, endothelial cells, and tumor cells correspond 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_3 corresponds to a site where host cells, tumor cells, endothelial cells, and tumor angiogenesis agents exist without an immune response. Compared with S_2, the existence of host cells in S_3 made the number of tumor cells and endothelial cells less.
- S_4 is inhabited in a site where 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_5, S_6, S_7, and S_8 correspond to a site inhabited by only tumor angiogenesis agents or tumor angiogenesis agents and host cells that have no biological description. A steady state without tumor cells cannot represent the vascular stage of a tumor disease. Most tumor diseases start with avascular growth, i.e. tumor cells are present when the vascular stage starts.
- S_9 represents a domain where 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 for example radiotherapy treatments.
- S_{10} is located in an area with host cells, immune cells, and tumor cells that could correspond to a tumor before

$$S_0=\begin{vmatrix}0\\0\\0\\0\\0\end{vmatrix},\quad S_1=\begin{vmatrix}1\\0\\0\\0\\0\end{vmatrix},\quad S_2=\begin{vmatrix}0\\0\\1.2\\0.39\\0.12\end{vmatrix},\quad S_3=\begin{vmatrix}0.989\\0\\0.003\\0.002\\0.12\end{vmatrix},\quad S_4=\begin{vmatrix}0\\0\\1\\0\\0\end{vmatrix},\quad S_5=\begin{vmatrix}0\\0\\0\\0\\37.37\end{vmatrix},\quad S_6=\begin{vmatrix}1\\0\\0\\0\\37.37\end{vmatrix},\quad S_7=\begin{vmatrix}0\\0\\0\\0\\0.12\end{vmatrix},$$

$$S_8=\begin{vmatrix}1\\0\\0\\0\\0.12\end{vmatrix},\quad S_9=\begin{vmatrix}0\\0.34\\0.13\\0\\0\end{vmatrix},\quad S_{10}=\begin{vmatrix}0.61\\0.1\\0.13\\0\\0\end{vmatrix},\quad S_{11}=\begin{vmatrix}0\\0.36\\0.125\\0.08\\0.12\end{vmatrix},\quad S_{12}=\begin{vmatrix}0.637\\0.114\\0.125\\0.08\\0.12\end{vmatrix}, \tag{2}$$

vascularization. The host cells are dominant at this point; so, if this point is unstable, the tumor cannot increase its size to reach the vascularization state.

- S_{11} inhabited a site where tumor cells, immune cells, endothelial cells, and tumor angiogenesis agents exist. This point can be stable since in this situation metastasis happens due to vascularization produced by tumor angiogenesis agents and endothelial cells.
- S_{12} is associated with a domain in which all five populations exist corresponding to a stage in which angiogenesis already started (the vascular stage of tumor growth).

In all equilibrium points, we can see that the existence of endothelial cells is directly related to tumor angiogenesis agents. There is no state in which endothelial cells exist without tumor angiogenesis agents.

The Jacobin matrix for the stability analysis is achieved as follows (Equation 3):

whose eigenvalues are (Equation 4):

3. Results

We investigated the dynamical behavior of the proposed model (1) by plotting the system's time series and phase portraits and using analysis tools like the first-return map to confirm the chaotic behavior, observability, and bifurcation. The numerical simulations are implemented in Matlab R2013a. The system's time series versus arbitrary time units via mentioned parameter values (Table 1) are shown in Figure 2.

In Figure 2, the time series for five variables associated with initial conditions as $\boldsymbol{H_0 = 1}$, $\boldsymbol{I_0 = 0.01}$, $\boldsymbol{T_0 = 0.04}$, $\boldsymbol{E_0 = 0.1}$, and $\boldsymbol{V_0 = 0.24}$ are depicted. After a little peak, the tumor cells decrease due to being necrotic in the pre-vascular stage. Following, tumor cells release tumor angiogenesis agents to start vascularization and make a high peak to tumor angiogenesis agents. Then the population of endothelial cells grows rapidly to make a second high-peak in the tumor cell population. Then, tumor angiogenesis agents decrease since the endothelial cells intake tumor angiogenesis agents [5]. The tumor cells grow rapidly and decrease the host cells to about

$$J = \begin{pmatrix} \frac{259}{500} - \frac{3T}{2} - \frac{259H}{250} & 0 & -\frac{3H}{2} & 0 & 0 \\ 0 & \frac{3E}{10} - \frac{T}{5} + \frac{9T}{2(T+1)} - \frac{1}{2} & \frac{9I}{2(T+1)} - \frac{I}{5} - \frac{9IT}{2(T+1)^2} & \frac{3I}{10} & 0 \\ -T & -\frac{5T}{2} & \frac{3E}{4(E+1)} - H - 2T - \frac{7V}{100} - \frac{5I}{2} + 1 & \frac{3T}{4(E+1)} - \frac{3TE}{4(E+1)^2} & -\frac{7T}{100} \\ 0 & 0 & 0 & \frac{43V}{50(V+1)} - \frac{V}{50} - 0.09 & \frac{43E}{50(V+1)} - \frac{E}{50} - \frac{43VE}{50(V+1)^2} \\ 0 & 0 & \frac{359V}{500(T+1)} - \frac{359TV}{500(T+1)^2} & -V & \frac{359T}{500(T+1)} - E \end{pmatrix} \quad (3)$$

$$\Lambda_0 = \begin{vmatrix} -0.5 \\ -0.09 \\ 0 \\ 0.518 \\ 1 \end{vmatrix}, \Lambda_1 = \begin{vmatrix} -0.518 \\ -0.5 \\ -0.09 \\ 0 \\ 0 \end{vmatrix}, \Lambda_2 = \begin{vmatrix} 1.834 \\ -0.0013 \pm 0.17i \\ -1.2 \\ -1.28 \end{vmatrix}, \Lambda_3 = \begin{vmatrix} 0.0073 \\ -0.0004 \pm 0.015i \\ -0.48 \\ -0.52 \end{vmatrix},$$

$$\Lambda_4 = \begin{vmatrix} -1 \\ -0.98 \\ -0.09 \\ 0.35 \\ 1.55 \end{vmatrix}, \Lambda_5 = \begin{vmatrix} -0.5 \\ 0 \\ 0.518 \\ -1.6 \\ -1.11e^{-16} \end{vmatrix}, \Lambda_6 = \begin{vmatrix} -0.518 \\ -0.5 \\ 0 \\ 0 \\ -2.61 \end{vmatrix}, \Lambda_7 = \begin{vmatrix} -0.5 \\ 0 \\ 0.518 \\ 0.99 \\ -7.21e^{-16} \end{vmatrix}, \Lambda_8 = \begin{vmatrix} -0.518 \\ -0.5 \\ 0 \\ 0 \\ -0.0084 \end{vmatrix}, \Lambda_9 = \quad (4)$$

$$\begin{vmatrix} -0.09 \\ 0.32 \\ 0.084 \\ -0.066 \pm 0.613i \end{vmatrix}, \Lambda_{10} = \begin{vmatrix} -0.09 \\ 0.084 \\ -0.52 \\ -0.035 \pm 0.25i \end{vmatrix}, \Lambda_{11} = \begin{vmatrix} 0.33 \\ -0.063 \pm 0.619i \\ -0.0004 \pm 0.082i \end{vmatrix}, \Lambda_{12} = \begin{vmatrix} -0.52 \\ 0.031 \pm 0.27i \\ 0.001 \pm 0.082i \end{vmatrix}$$

Table 1. The parameter values of the model

Parameters	Descriptions	Values	References
ρ_1	Host cell growth rate	0.518	[18]
α_{13}	Host cell killing rate by tumor cells	1.5	[18]
ρ_2	Immune cell growth rate	4.5	[20]
α_{23}	Immune cell inhibition rate by tumor cells	0.2	[18]
δ_2	Immune cell natural death rate	0.5	[22]
α_{24}	Immune cell stimulation by endothelial cells	0.3	[34]
ρ_3	Tumor growth rate	1	[18]
α_{31}	Tumor cell killing rate by host cells	1	[18]
α_{32}	Tumor cell killing rate by immune cells	2.5	[22]
α_{33}	Tumor cell inhibition rate via tumor angiogenesis agents	0.07	Estimated
α_{34}	Tumor cell growth rate by endothelial cells	0.75	[34]
ρ_4	Endothelial cell growth rate	0.86	[34]
δ_4	Endothelial cell natural death rate	1/11	[34]
α_{41}	Endothelial cell inhibition rate by tumor angiogenesis agents	0.02	Estimated
ρ_5	Tumor angiogenesis agents' growth rate	0.718	Estimated
α_{51}	Tumor angiogenesis intake rate by endothelial cells	0.9	Estimated

zero. The immune response activates due to a quick reaction against tumor proliferation. We can see the oscillations of all populations in the time series. The evolution of tumor angiogenesis agents followed by endothelial cells increases their population in each oscillation. Then it affects the tumor cells and immune cell dynamics. The endothelial cells are ready to build blood vessels into the tumor. This results in vascular tumor growth thus the metastasis happens during arbitrary time units. Clinically, prediction of metastasis can be done by investigating the ability of a patient to produce endothelial cells via the tumor angiogenesis agents, which is not clinically assessed, and leaving the opinion that the cancer evolution is only qualified by stochastic laws.

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 (Figure 3 and Figure 4). The smooth shape of return maps present the period-doubling cascade that refers to the chaos [41].

3.1. Observability Analysis

For dynamical analysis, we used five differential embedding induced by each variable of the model (1). Assume that a dynamical system is $\dot{\boldsymbol{m}}(\boldsymbol{t}) = \boldsymbol{f}(\boldsymbol{x}(\boldsymbol{t}))$ and the state vector is $\boldsymbol{m} \in \boldsymbol{R^n}$. When $n = 5$ the system can be detailed (Equation 5):

$$\begin{cases} \dot{x} = f_1(x, y, z, w, v) \\ \dot{y} = f_2(x, y, z, w, v) \\ \dot{z} = f_3(x, y, z, w, v) \\ \dot{w} = f_4(x, y, z, w, v) \\ \dot{v} = f_5(x, y, z, w, v) \end{cases} \quad (5)$$

where $x = H(t), y = I(t), z = T(t), w = E(t)$, and $v = V(t)$. The time series (s) is acquired by measurement function c that is $\boldsymbol{s}(\boldsymbol{t}) = \boldsymbol{c}(\boldsymbol{x}(\boldsymbol{t}))$. So the

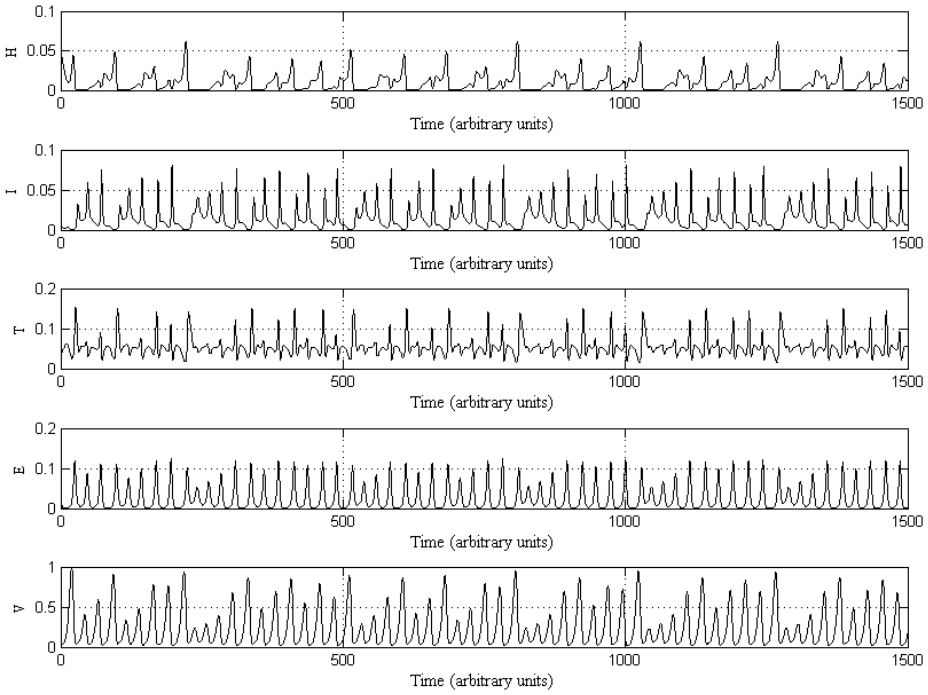
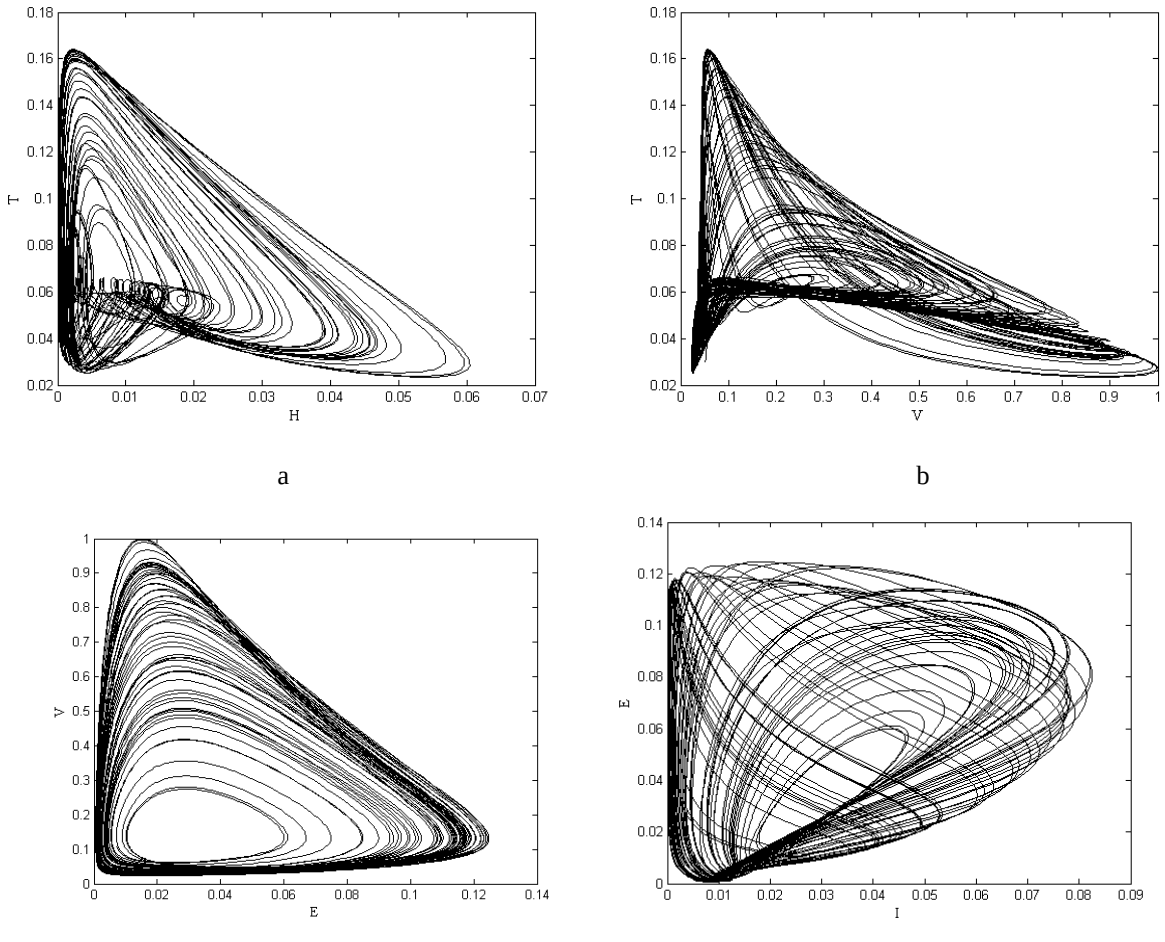


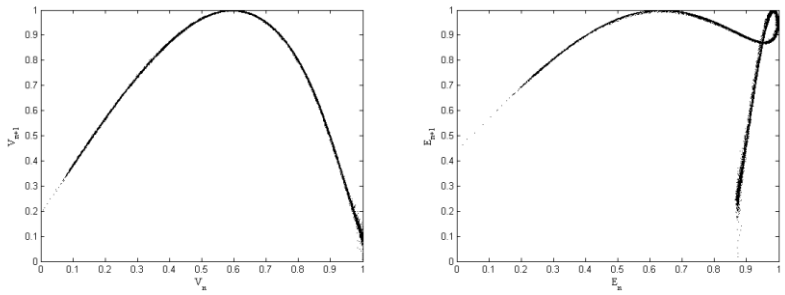
Figure 2. The response of the system with the mentioned parameter values in time series versus arbitrary time units



a b

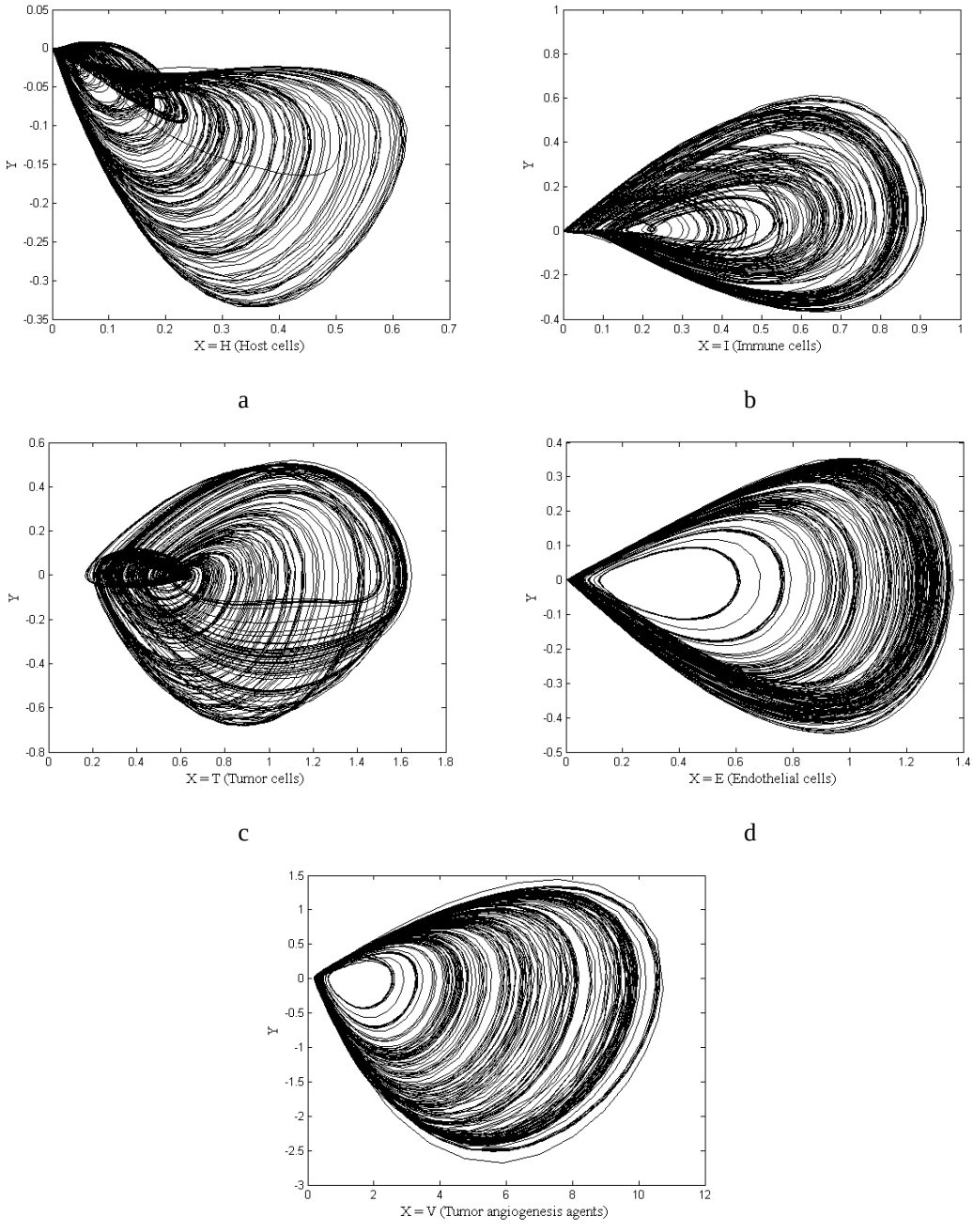
c d

Figure 3. The phase portraits of the proposed model (1). a) Phase portrait of host cells versus tumor cell population. b) Tumor angiogenesis agents versus tumor cells. c) Endothelial cell population versus tumor angiogenesis agents. d) Effector immune cells versus endothelial cells



a b

Figure 4. First-return maps for the model (1) with mentioned parameter values. a) Tumor angiogenesis agents. b) Endothelial cells



a b c d e

Figure 5. Differential embedding reconstructed portraits. a) From host cells. b) From effector immune cells. c) From tumor cells. d) From endothelial cells. e) From tumor angiogenesis agents

reconstruction of the phase portraits can be done by derivative coordinates (Equation 6):

$$\begin{cases} X = s \\ Y = \dot{s} \\ Z = \ddot{s} \\ W = \dddot{s} \\ V = \ddddot{s} \end{cases} \quad (6)$$

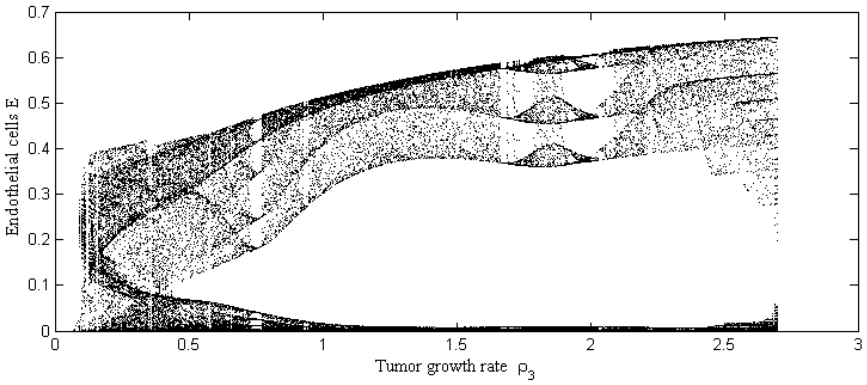
$\emptyset$ is the transformation between the original variables and derivative coordinates, consequently $\emptyset : R^5(x,y,z,w,v) \rightarrow R^5(X,Y,Z,W,V)$.

The 5 X-Y embedding projections shown in Figure 5 correspond to the attractors in Figure 3. The tumor cell has the best observability in our model dynamics because its embedding projection is less squeezed between all variables embedding projections. Therefore, the dynamics of our cancer model are observed with more excellent reliability from the tumor cell population. So we investigated its growth rate $(\boldsymbol{\rho_3})$ variation on the system's 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 Figure 6.

The increase in the tumor growth rate leads to the rise of the tumor angiogenesis agents and endothelial cells in Figure 6. We can observe that the increase in tumor cells' growth rate consequences in an increase in the populations' fluctuations range. When $\boldsymbol{\rho_3 > 2.7}$, the trajectory ejected to infinity. In this case, it can be assumed that the metastasis happens [22, 34]. To explore patient situations, we consider varying the parameter values as $\boldsymbol{\rho_5}$, and $\boldsymbol{\alpha_{33}}$ to study the impact of tumor angiogenesis agents on the system's dynamics. We also investigate the $\boldsymbol{\alpha_{32}}$ 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 [22]. Indeed, the minimal and maximal values at each oscillation of the given variables H, I, T, E, and V were taken to obtain their range of variability versus the mentioned parameters. The bifurcation diagrams



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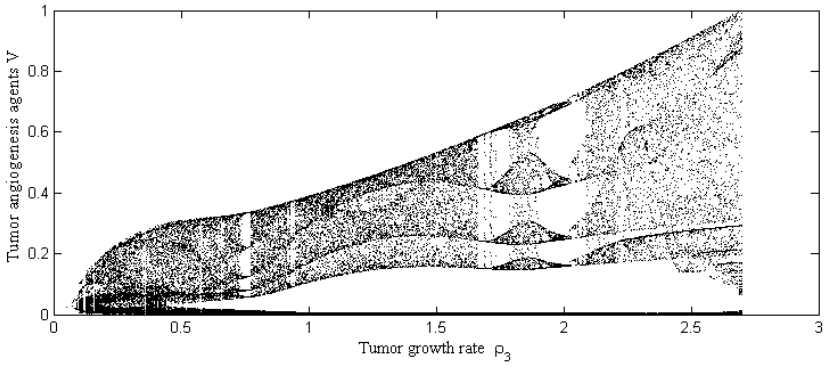

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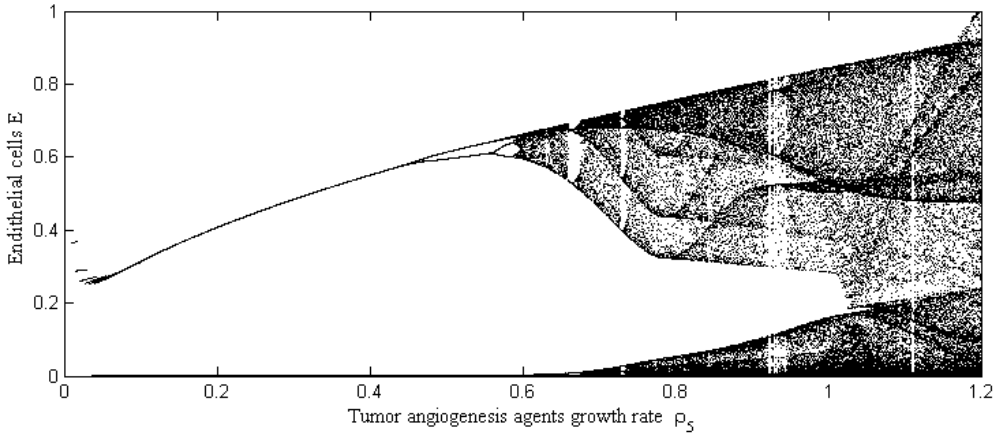
Figure 6. The bifurcation diagrams versus $\boldsymbol{\rho_3}$. a) Exterma of endothelial cells. b) Exterma of tumor angiogenesis agents

versus angiogenesis agents' growth rate ($\boldsymbol{\rho_5}$) are depicted in Figure 7. By increase of $\boldsymbol{\rho_5}$, the population of endothelial cells increases. There is no period-doubling cascade by $\overline{\boldsymbol{\rho_5}} < \mathbf{0.588}$ which means that in this range the tumor growth is non-vascular. When $\boldsymbol{\rho_5} \geq \overline{\boldsymbol{\rho_5}}$, the period-doubling cascade takes place. This shows chaotic behavior representing the vascular phase of tumor growth. The mentioned threshold value depends on the other parameter values that can be varied for other patient conditions. For $\boldsymbol{\rho_5} \geq \mathbf{1.15}$, the neo-vascularization becomes dominant enough. In this case, the endothelial cells proliferate significantly, and the tumor cells saturate the area and migrate to other sites.



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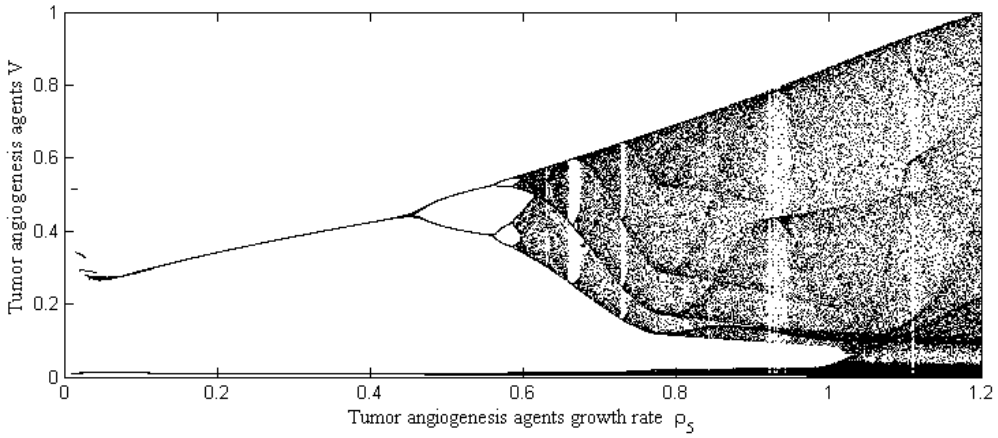

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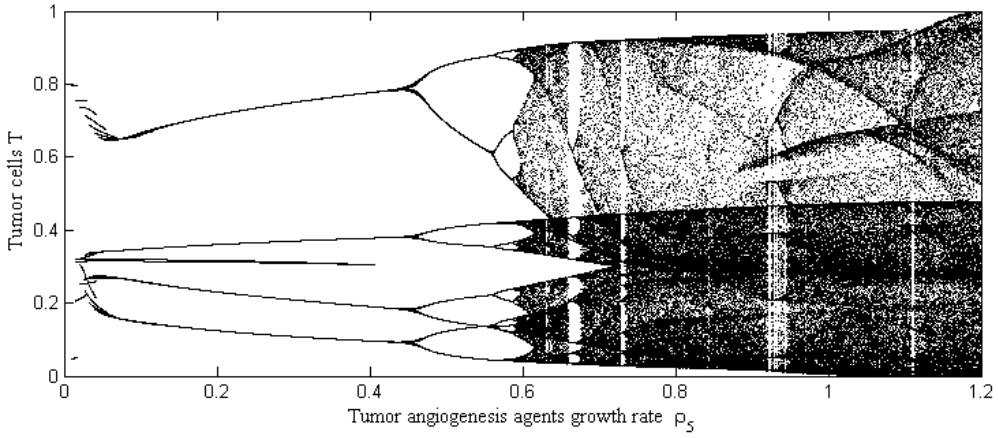

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Figure 7. The bifurcation diagrams versus $\boldsymbol{\rho_5}$. a) Exterma of endothelial cells. b) Exterma of tumor angiogenesis agents. c) Exterma of tumor cells population

There is no bifurcation by variation of parameter $\boldsymbol{\alpha_{32}}$ (Figure 8). Therefore, the tumor cell killing rate by immune cells $\boldsymbol{(\alpha_{32})}$ does not have any impact on the system dynamics. However, this value cannot be zero since the trajectory would be ejected to infinity. This result shows the inefficiency of immune system-targeted therapies [42], [43].

The bifurcation diagram versus tumor cell inhibition rate via tumor angiogenesis agents $\boldsymbol{\alpha_{33}}$ is shown in Figure 9. When $\boldsymbol{\alpha_{33} < 0.037}$, the trajectory goes to infinity. This may correspond to the significance of TIF presence in regulating tumor-induced vascularization. By increasing the parameter $\boldsymbol{\alpha_{33}}$, the amount of tumor angiogenesis agents decreases; so, the population of endothelial cells decreases. When $\boldsymbol{\alpha_{33} \geq 0.096}$, there is no period-doubling cascade. So, the impact of the inhibition factor on angiogenesis can be enough to avoid angiogenesis (Figure 9). Clinically this can be the effect of anti-angiogenic drugs like angiostatin to terminate tumor vascularization.

4. Discussion

In the present work, we proposed a 5D cancer model including tumor angiogenesis agents to study the impact of these substances on vascularization dynamics. The proposed model governs both pre-vascular and vascular tumor growth. 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 [39]. The solid tumor survives via the angiogenesis process. 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 enter the surrounding tissue. While endothelial cells migrate to the tumor site they intake tumor angiogenesis agents [5]. Vascular growth happens when the tumor provides blood vessels that carry nutrients and oxygen directly to the tumor cells [44]. 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 [22, 34].

Previous studies have shown that vascular tumor growth has chaotic dynamics [18, 20, 22, 34]. In this paper, it is theorized that tumors use a diffuse factor called the tumor angiogenesis agent to initiate its vascular growth. It is proved that the tumor also produces a slight amount of substances like angiostatin as Tumor Inhibitor Factors (TIF) to regulate the formation of tumor vascularization [27]. Hence, the effect of tumor angiogenesis agents could be interesting to study their role in tumor-induced angiogenesis. It has been proposed that the presence of endothelial cell population as a key variable for angiogenesis in the cancer model is more effective in studying both avascular and vascular tumor growth [34]. The impact of endothelial cells on tumor vascularization is completely positive. So, they couldn't study the negativities of inhibition factors by just introducing endothelial cells as only a key variable for vascularization in their mathematical model. Inspired by this research, we introduced the generalized cancer model in which tumor angiogenesis agents exist.

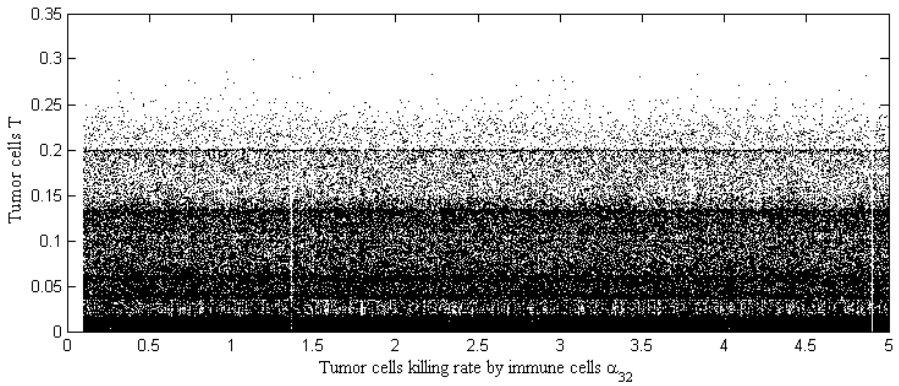
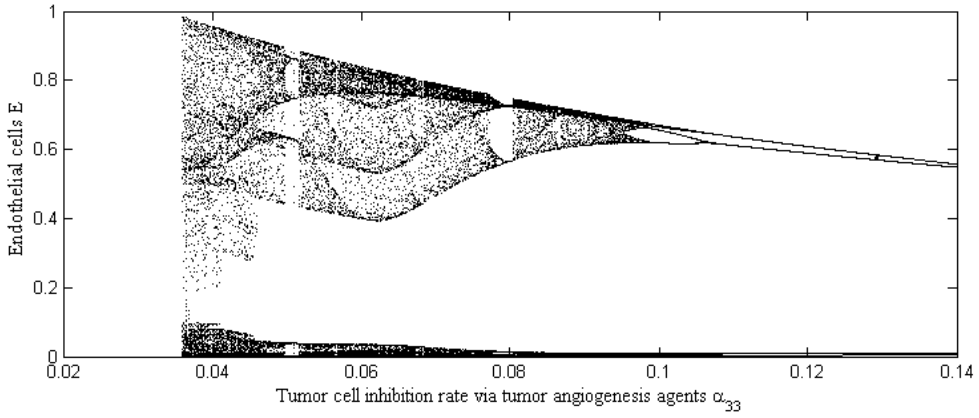


Figure 8. Bifurcation diagram of the tumor cells versus $\boldsymbol{\alpha_{32}}$



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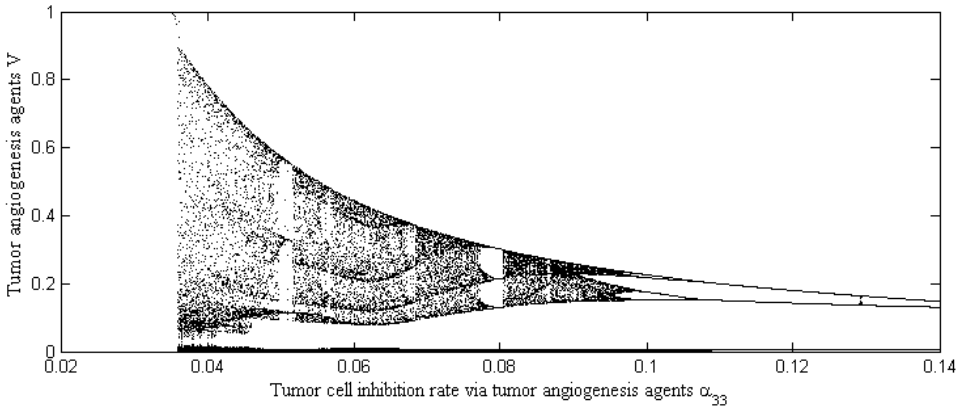

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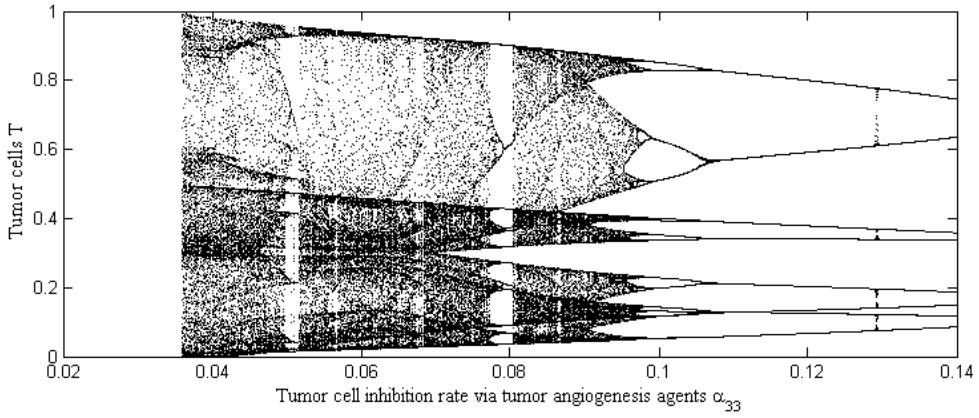

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Figure 9. The bifurcation diagrams versus $\boldsymbol{\alpha_{33}}$. a) Exterma of endothelial cells. b) Exterma of tumor angiogenesis agents. c) Exterma of tumor cells population

For this purpose, we presented a variable as tumor angiogenesis agents that have both stimulant and inhibitor factors on tumor vascularization. The default parameter values of the model are equal to the values of the presented models by Viger *et al.* [34] and Letellier *et al.* [22]. They select the parameter values to achieve a chaotic attractor since the dynamic of their model is studied qualitatively [20, 22, 34]. Our parameter values ($\boldsymbol{\rho_4}, \boldsymbol{\alpha_{41}}, \boldsymbol{\rho_5}, \boldsymbol{\alpha_{51}}$, and $\boldsymbol{\alpha_{33}}$) are chosen to achieve a chaotic attractor solution, too (Figure 3). So, their biological meaning is nonspecific like the studies by [19, 20, 22, 34, 35]. 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 (Figure 4), exactly as observed in the models by [22, 34] with the same parameter values. The variable of the tumor cell population is less clasped in the differential embedding projection portraits (Figure 5). Hence, it is more observable between all model variables. We explored the variation of tumor cell growth rate on the system's dynamics using bifurcation diagrams (Figure 6). Our model also indicates that the increase in the tumor cells' growth rate increases the fluctuations range in endothelial cells and tumor angiogenesis agents' populations.

The presented dynamical model could capture the biological behavior of the tumor-induced angiogenesis process and retain the intrinsic features of its biological process. Based on the time series in Figure 3, when the growth of tumor cells stopped in a range, they secreted tumor angiogenesis agents; so, the population of these agents rose. After that, the TAF overcomes TIF and stimulates the proliferation of the endothelial cells that results in more increase in the tumor cell population to a higher peak. On the other hand, an increase in the tumor cells stimulates the growth of effector immune cells. After, the growth of immune cell populations, they suppress the population of tumor cells (Figure 3). The tumor cells secret the tumor angiogenesis agents to survive being necrotic. So by the increase of this substance, the endothelial cells begin to proliferate from the neighbor vessels and form blood vessels to the tumor gradient. The chaos that occurs due to the increase of $\boldsymbol{\rho_5} \geq \overline{\boldsymbol{\rho_5}}$ would capture this biological process in the system (Figure 7). Naturally, the effect of tumor angiogenesis agents as angiogenesis stimulants (TAF) is much more than their impact as angiogenesis inhibitors (TIF) [28]; 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. The most share of parameter $\boldsymbol{\rho_5}$ is for the stimulant factors since the most share of tumor angiogenesis agents is for TAF. It is not uncommon in biology to observe a chemical species having both a positive and a negative effect on another species or on some process, via the activation of different signaling pathways, therefore this aspect is sometimes captured in models so as to reflect biology. When we talk about TIFs and their slight negative impacts, we point to the negative impact of tumor angiogenesis agents on the system that can be considered biologically as inhibitor factors of tumor angiogenesis agents. We biologically described the TAF and TIF but considered tumor angiogenesis agents, which comprise both, as one variable with a huge positive impact on endothelial cell proliferation and a small negative impact on the inhibition of vascularization which is just for the regulation of the vessel formations. The increase of the negative impact is not happening naturally by the tumor and can be done only via external inhibitors like anti-angiogenic drugs. 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 $\boldsymbol{\rho_5} < \overline{\boldsymbol{\rho_5}}$ 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 $\boldsymbol{\rho_5} \geq \overline{\boldsymbol{\rho_5}}$, the evolution of endothelial cells occurs; thus, the patient has vascular tumor growth. From a dynamical point of view, beyond the threshold amount of tumor angiogenesis agents' growth rate ($\overline{\boldsymbol{\rho_5}}$), the period-doubling cascade in populations begins which leads to chaos. This is clear that the threshold values depend on other parameter values, that would be, other conditions of a patient.

Ecological models include non-linear interactions between tumor cells and their environment; so, their qualitative analysis could be valuable for therapeutic approaches such as non-tumoral-cell-targeted treatments like anti-angiogenic treatments. Therefore, 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 therapeutic ways to encounter cancer. One of them is immune system-targeted therapies. The killing rate of the tumor cells via effector immune cells ($\boldsymbol{\alpha_{32}}$) is not affecting the dynamic of our model (Figure 8). This finding is in line with the biologically/clinically observed lack of efficiency of a large number of therapies targeting the immune system [39, 42, 43]. Another type of cancer therapy is targeting tumor-induced vascularization by injecting anti-angiogenic drugs like angiostatin into the body to prevent vascularization. In the dynamical analysis, our model recommends that angiogenesis-targeted therapies are strongly more effective in the termination of tumor vascularization. Tumor cell inhibition rate via tumor angiogenesis agents is specified by $\boldsymbol{\alpha_{33}}$. This inhibition rate is naturally secreted from tumors in very small doses; however, increasing that with external inhibitor drugs like angiostatin, endostatin, and placket factor 4

(PF4) would be effective in terminating the chaotic behavior of the model (1) that corresponds to the termination of vascularization (Figure 9). Employing anti-angiogenic agents is still a promising therapeutic target; however, further studies are necessary to deliver multi-targeted approaches and combinatorial therapy.

5. Conclusion

The 4D model introduced by Viger *et al.* was developed from the 3D model proposed by de Pillis and Radunskaya. They introduced the endothelial cell population to reproduce the angiogenesis phenomenon. However, the presence of tumor angiogenesis agents is important in investigating their roles in tumor-induced angiogenesis. For this purpose, we expanded their model and introduced the tumor angiogenesis agents in their 4D model to create a new generalized 5D model. We also considered the role of tumor angiogenesis agents in the proliferation of endothelial cells; so, the equation of endothelial cells becomes different from the model presented by Viger *et al.* [34]. Our model can be employed to realize better the tumor vascularization dynamics with tumor angiogenesis agents' interference and qualitatively capture the features of its process. Observability and bifurcation analysis have been performed to study 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 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 does not consider the biological complexity of cancer like genomic instability; however, it considers the term 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 tumor growth. Our model recommends that increasing the inhibition factors of tumor angiogenesis agents can terminate vascularization; however, TIF agents are rarely secreted from the tumor to regulate vascularization. While chemotherapy destroys cancer cells, it also affects host cells. By combining chemotherapy and anti-angiogenic drugs, the treatment will be more successful and reduce side effects. So, introducing the process of chemotherapy to our proposed model by adding a drug variable and applying its effect in the equations can suggest a successful study comparing the use of immune-system-enhancing drugs and anti-angiogenic drugs in the course of chemotherapy.

Acknowledgements

This article was extracted from the thesis prepared by Ali Mohseni to fulfill the requirements for earning the Doctorate degree.

The authors received no financial support for the research, authorship, and/or publication of this article.

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

References

1- Robert M Sutherland, "Cell and environment interactions in tumor microregions: the multicell spheroid model." *Science*, Vol. 240 (No. 4849), pp. 177-84, (1988).

2- Judah Folkman, "Angiogenesis in cancer, vascular, rheumatoid and other disease." *Nature medicine*, Vol. 1 (No. 1), pp. 27-30, (1995).

3- Judah Folkman, "Tumor angiogenesis: therapeutic implications." *N Engl j Med*, Vol. 285 (No. 21), pp. 1182-86, (1971).

4- Anil Bagri, Hosein Kouros-Mehr, Kevin G Leong, and Greg D Plowman, "Use of anti-VEGF adjuvant therapy in cancer: challenges and rationale." *Trends in molecular medicine*, Vol. 16 (No. 3), pp. 122-32, (2010).

5- Alexander RA Anderson and Mark AJ Chaplain, "Continuous and discrete mathematical models of tumor-induced angiogenesis." *Bulletin of mathematical biology*, Vol. 60 (No. 5), pp. 857-99, (1998).

6- Joseph J Casciari, Stratis V Sotirchos, and Robert M Sutherland, "Mathematical modelling of microenvironment and growth in EMT6/Ro multicellular tumour spheroids." *Cell proliferation*, Vol. 25 (No. 1), pp. 1-22, (1992).

7- John A Adam and SA Maggelakis, "Mathematical models of tumor growth. IV. Effects of a necrotic core." *Mathematical biosciences,* Vol. 97 (No. 1), pp. 121-36, (1989).

8- Alan C Burton, "Rate of growth of solid tumours as a problem of diffusion." *Growth,* Vol. 30 (No. 2), pp. 157-76, (1966).

9- HM Byrne and Mark AJ Chaplain, "Free boundary value problems associated with the growth and development of multicellular spheroids." *European Journal of Applied Mathematics,* Vol. 8 (No. 6), pp. 639-58, (1997).

10- Jonathan A Sherratt, "Traveling wave solutions of a mathematical model for tumor encapsulation." *SIAM Journal on Applied Mathematics,* Vol. 60 (No. 2), pp. 392-407, (2000).

11- BP Marchant, J Norbury, and JA Sherratt, "Travelling wave solutions to a haptotaxis-dominated model of malignant invasion." *Nonlinearity,* Vol. 14 (No. 6), p. 1653, (2001).

12- Sabine Dormann and Andreas Deutsch, "Modeling of self-organized avascular tumor growth with a hybrid cellular automaton." *In silico biology,* Vol. 2 (No. 3), pp. 393-406, (2002).

13- W Düchting and Th Vogelsaenger, "Recent progress in modelling and simulation of three-dimensional tumor growth and treatment." *Biosystems,* Vol. 18 (No. 1), pp. 79-91, (1985).

14- Emma L Stott, Nick F Britton, James A Glazier, and Mark Zajac, "Stochastic simulation of benign avascular tumour growth using the Potts model." *Mathematical and Computer Modelling,* Vol. 30 (No. 5-6), pp. 183-98, (1999).

15- Renfrey Burnard Potts, "Some generalized order-disorder transformations." in *Mathematical proceedings of the cambridge philosophical society*, (1952), Vol. 48 (No. 1): *Cambridge University Press*, pp. 106-09.

16- Adriaan Daniël Fokker, "Die mittlere Energie rotierender elektrischer Dipole im Strahlungsfeld." *Annalen der Physik,* Vol. 348 (No. 5), pp. 810-20, (1914).

17- VM Planck, "Über einen Satz der statistischen Dynamik und seine Erweiterung in der Quantentheorie." *Sitzungberichte der,* (1917).

18- Lisette G De Pillis and Ami Radunskaya, "The dynamics of an optimally controlled tumor model: A case study." *Mathematical and Computer Modelling,* Vol. 37 (No. 11), pp. 1221-44, (2003).

19- Vladimir A Kuznetsov, Iliya A Makalkin, Mark A Taylor, and Alan S Perelson, "Nonlinear dynamics of immunogenic tumors: parameter estimation and global bifurcation analysis." *Bulletin of mathematical biology,* Vol. 56 (No. 2), pp. 295-321, (1994).

20- Mehmet Itik and Stephen P Banks, "Chaos in a three-dimensional cancer model." *International Journal of Bifurcation and Chaos,* Vol. 20 (No. 01), pp. 71-79, (2010).

21- Jorge Duarte, Cristina Januario, Carla Rodrigues, and Josep Sardanyes, "Topological complexity and predictability in the dynamics of a tumor growth model with Shilnikov's chaos." *International Journal of Bifurcation and Chaos,* Vol. 23 (No. 07), p. 1350124, (2013).

22- Christophe Letellier, Fabrice Denis, and Luis A Aguirre, "What can be learned from a chaotic cancer model?" *Journal of theoretical biology,* Vol. 322pp. 7-16, (2013).

23- Álvaro G López, Juan Sabuco, Jesús M Seoane, Jorge Duarte, Cristina Januário, and Miguel AF Sanjuán, "Avoiding healthy cells extinction in a cancer model." *Journal of theoretical biology,* Vol. 349pp. 74-81, (2014).

24- Judah Folkman, "Clinical applications of research on angiogenesis." *New England Journal of Medicine,* Vol. 333 (No. 26), pp. 1757-63, (1995).

25- M Baum, MAJ Chaplain, ARA Anderson, M Douek, and JS Vaidya, "Does breast cancer exist in a state of chaos?" *European journal of cancer,* Vol. 35 (No. 6), pp. 886-91, (1999).

26- ARA Anderson, MAJ Chaplain, C Garcia-Reimbert, and CA Vargas, "A gradient-driven mathematical model of antiangiogenesis." *Mathematical and Computer Modelling,* Vol. 32 (No. 10), pp. 1141-52, (2000).

27- Michael S O'Reilly *et al.*, "Angiostatin: a novel angiogenesis inhibitor that mediates the suppression of metastases by a Lewis lung carcinoma." *cell,* Vol. 79 (No. 2), pp. 315-28, (1994).

28- SA Maggelakis, "The effects of tumor angiogenesis factor (TAF) and tumor inhibitor factors (TIFs) on tumor vascularization: A mathematical model." *Mathematical and Computer Modelling,* Vol. 23 (No. 6), pp. 121-33, (1996).

29- Sajad Shafiekhani, Hojat Dehghanbanadaki, Azam Sadat Fatemi, Sara Rahbar, Jamshid Hadjati, and Amir Homayoun Jafari, "Prediction of anti-CD25 and 5-FU treatments efficacy for pancreatic cancer using a mathematical model." *BMC cancer,* Vol. 21pp. 1-21, (2021).

30- Yongwoon Jung, Pavel Kraikivski, Sajad Shafiekhani, Scott S Terhune, and Ranjan K Dash, "Crosstalk between Plk1, p53, cell cycle, and G2/M DNA damage checkpoint regulation in cancer: computational modeling and analysis." *npj Systems Biology and Applications,* Vol. 7 (No. 1), p. 46, (2021).

31- Sajad Shafiekhani, Nematollah Gheibi, and Azam Janati Esfahani, "Combination of anti-PD-L1 and radiotherapy in hepatocellular carcinoma: a mathematical model with uncertain parameters." *Simulation,* Vol. 99 (No. 4), pp. 313-25, (2023).

32- Sadjad Shafiekhani, Sara Rahbar, Fahimeh Akbarian, Jamshid Hadjati, Armin Allahverdy, and Amir Homayoun Jafari, "Providing a Stochastic Petri Net Model for Interactions of the Immune System and B16-F10 Tumor Cells in order to Investigate the Effect of Myeloid-Derived Suppressor Cells (MDSC) on Behavioral States of Tumor."

Frontiers in Biomedical Technologies, Vol. 4 (No. 1-2), pp. 31-37, (2017).

33- Sajad Shafiekhani, Sara Rahbar, Fahimeh Akbarian, and Amir Homayoun Jafari, "Fuzzy stochastic petri net with uncertain kinetic parameters for modeling tumor-immune system." in *2018 25th National and 3rd International Iranian Conference on Biomedical Engineering (ICBME)*, (2018): *IEEE*, pp. 1-5.

34- Louise Viger, Fabrice Denis, Martin Rosalie, and Christophe Letellier, "A cancer model for the angiogenic switch." *Journal of theoretical biology*, Vol. 360pp. 21-33, (2014).

35- Christophe Letellier, Sourav Kumar Sasmal, Clément Draghi, Fabrice Denis, and Dibakar Ghosh, "A chemotherapy combined with an anti-angiogenic drug applied to a cancer model including angiogenesis." *Chaos, Solitons & Fractals*, Vol. 99pp. 297-311, (2017).

36- Konstantin E Starkov, "A cancer model for the angiogenic switch and immunotherapy: Tumor eradication in analysis of ultimate dynamics." *International Journal of Bifurcation and Chaos*, Vol. 30 (No. 10), p. 2050150, (2020).

37- Parthasakha Das, Samhita Das, Pritha Das, Fathalla A Rihan, Muhammet Uzuntarla, and Dibakar Ghosh, "Optimal control strategy for cancer remission using combinatorial therapy: a mathematical model-based approach." *Chaos, Solitons & Fractals*, Vol. 145p. 110789, (2021).

38- A Mohseni, M Pooyan, S Raiesdana, and M. B. Menhaj, "A cancer model including tumor angiogenesis agents." *Power System Technology*, Journal Article Vol. 482, pp. 973-94, (2024).

39- Femke Hillen and Arjan W Griffioen, "Tumour vascularization: sprouting angiogenesis and beyond." *Cancer and Metastasis Reviews*, Vol. 26 (No. 3), pp. 489-502, (2007).

40- Ilaria Brazzoli, Elena De Angelis, and Pierre-Emmanuel Jabin, "A mathematical model of immune competition related to cancer dynamics." *Mathematical Methods in the applied sciences*, Vol. 33 (No. 6), pp. 733-50, (2010).

41- Mitchell J Feigenbaum, "Quantitative universality for a class of nonlinear transformations." *Journal of statistical physics*, Vol. 19 (No. 1), pp. 25-52, (1978).

42- Aniruddha Choudhury, Szilvia Mosolits, Parviz Kokhaei, Lotta Hansson, Marzia Palma, and Håkan Mellstedt, "Clinical results of vaccine therapy for cancer: learning from history for improving the future." *Advances in cancer research*, Vol. 95pp. 147-202, (2006).

43- Ming Chi and Arkadiusz Z Dudek, "Vaccine therapy for metastatic melanoma: systematic review and meta-analysis of clinical trials." *Melanoma research*, Vol. 21 (No. 3), pp. 165-74, (2011).

44- Markus R Owen, Tomás Alarcón, Philip K Maini, and Helen M Byrne, "Angiogenesis and vascular remodelling in normal and cancerous tissues." *Journal of mathematical biology*, Vol. 58pp. 689-721, (2009).