Numerical Study of Tumor Growth : Tumor Development, Tumor Cells Movement and Cell–Matrix Interactions

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ABSTRACT

In this paper we present a mathematical model of the tumor development, tumor cells movement and cell–matrix interactions. This model is considered tumor cells, concentration of oxygen, concentration of nutrient, changes in their microenvironment (tumor angiogenic factors (TAF), extracellular matrices (ECM)) and their matrix of blood vessels, expressed by a chain of discrete tips. With this mathematical model and the results of numerical simulation, the cell properties are closely individual-based cell interactions, can affecting the tumor shape, the tumor's final structure and also discussed which of these interactions is perhaps tumor cells are discrete. Also we described the procedure of tumor development and the changes in microenvironment from avascular to vascular phase, indicating that the matrix of blood vessels develops step by step as the tumor grows.

KEYWORDS: *mathematical model, tumor angiogenic factors, extracellular matrices, concentration of oxygen, concentration of nutrient.*

INTRODUCTION

Many previous models represent these as discrete layers, separated by moving boundaries. Here, we developed a new model, formulated in terms of densities of tumor cells, concentration of ECM, concentration of oxygen, concentration of nutrient, together with a nutrient and oxygen concentration.

Tumors can be regarded as one of the most significant causes of death among the human beings particularly that of malignant tumors, this Mathematical Oncology was tackled by

Anderson *et al.* [1], branch dealing with the research of tumor has gained consideration. Tumor growth is an intricate progression that involves synergy between the extracellular matrices and tumor cells with the inclusive of cell-cell interactions, & ultimately the proliferations and death of the tumor cells. A broadly used model amid the mathematical models dealing with tumor growth is termed as hybrid mathematical model that merges the concepts of discrete and continuous models. That deals with the chemical changes seen in tumors microenvironment on the basis reaction-diffusion equation was proposed by Jie Lyu *et al.* [2]. Since there are abundant of quantitative modeling methods, a surge in the successful implementation through theoretical tactics for cancer biology has been initiated subsequently by the last two decades was studied by Heiko Enderling *et al.* [3]. Other efforts in modeling angiogenesis include hybrid models that combine continuum and discrete approaches proposed by Vilanova G. *et al.* [4].

A particular enzyme by the name of matrix degrading enzymes (MDEs) is secreted by the tumor – cancer cells that help in making the ECM infective by degrading its functionality was studied by Linan Zhang *et al,* [5]. In regards of the hybrid model specific cell properties are taken into consideration at an individual level by the help of equation to help govern the cell migration, which is the discretized form of the partial differential equation. The parameters examined it the successful making of this model are production/degradation at the individual cell level, cell–cell adhesion, proliferation, death and mutation of cell at individual level while keeping the chemicals/ ECM at continuous levels was studied by Anderson *et al.* [6]. But we need to note that a few cell processes like that of cell–cell adhesion can be tough to model to that of the continuum level. To further more shed a light on angiogenesis, it is a process being carried out by the stimulus given external chemicals resulting in the formation of capillary sprout formation and a subsequent proliferation of cells near the tips of these sprout eventually completing the process. The focus to create such model is to scrutinize the corresponding influence of haptotaxis in ensuring the migration of endothelial cells, with also keeping in the mind to examine the formation of capillary network with or without the influence of endothelial cell, eventually creating a theoretical capillary network structure that's forms a model on the basis of sound physiological principles that are in line with the realistic parameter values as seen in vivo was studied by Anderson *et al.* [7]. In the other parts of the tumor there can be seen a variation in the cellular components of Tumor Microenvironment (TME) was studied by Quail *et al.* [8], also can be noticed in between tumors of a single person and in fact even in between patients was studied by Ansell *et al.* [9].
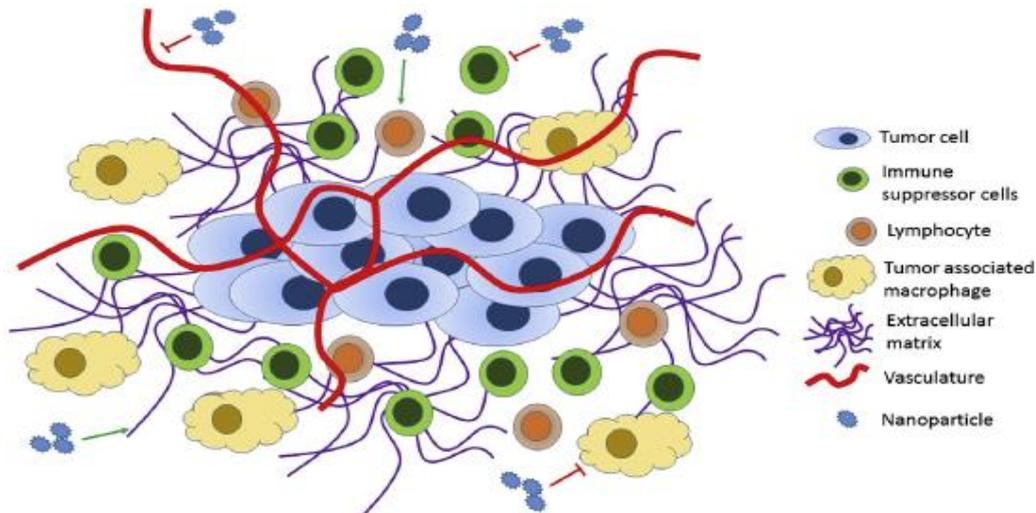
Figure 1: The Tumor Microenvironment (TME). In the microenvironment of TME there can be found the extracellular matrix (ECM), a variety of types of cells (stromal including immune and cancer cells) and myriad molecules like that of microRNAs, chemokines, cytokines and factors of growth as presented by Elizabeth L. Siegler *et al* [10].

Components of Tumor Microenvironment (TME) are shown in figure 1, aspects including vasculature, ECM, and immune cells, with a focus on modulating the immune response was described by Elizabeth L. Siegler *et al.* [10]. The idea in developing a mathematical model for tumor growth was inspired by the dependence of events taking place at different scales, and also to understand the interrelations among the cellular, subcellular, and tissue scales was studied by Deisboeck TS *et al.* [11]. Caleb M. Phillips, *et al.,* studied the growth and angiogenesis hybrid model to tumor growth [12]. The effects of tumor inhibitor factors (TIFs) on tumor angiogenesis and tumor angiogenesis factor (TAF) with also predicting its initiation of vascularization, a mathematical tool was presented by Maggelakis [13]. Anderson and Chaplain explained for the suppression of secondary tumors caused by the primary tumor put forward a one-dimensional mathematical model which in turn explains the angiogenic response of endothelial cells (ECs) on to a secondary tumor [14].

MATHEMATICAL MODEL OF TUMOR VASCULATURE GROWTH

We aim to showcase the in depth model to show the development needed to include the effects presented by the blood flow for vasculature tumor within its capillaries, also in line with the effects of oxygen concentration and nutrients. Based on Anderson and Chaplain' model [7], Heiko Enderling and M. A.J. Chaplain' model [3] and Jie Lyu's model [2], we modified and improved their model in five aspects i.e. density of tumor cells, concentration of extracellular matrix, nutrient concentration, oxygen concentration and concentration of tumor angiogenesis factor. This also aims to show the eventual increase in the number of blood

vessels and tumor cells with time, respectively. The discrete points have been shown for the simulation results. It must be noted that a number of random factors have been taken into account to the model although keeping into consideration the number of blood points and tumor cells follow are persistent.

The logistic model is summarized the example of a per capita growth rate of tumor that is reliant on the tumor size which is relative to the host carry capacity was studied by McAneney H. *et al.* [15]. The balance of cell death and cell proliferation is actually a result of diffusion of nutrients and oxygen in the interior of the tumor at the time of vascular dormancy is presented by Holmgren L. *et al.* [16]. In context to this mathematical model to focus merely on the role of cancer cell migration in invasion, the cell proliferation studied by Anderson ARA *et al.* [17] in the later stages cancer cell proliferation was inducted into the separate version of model. Apart from this various other continumm were put forwarded studied by Chaplain and Lolas *et al.* [18] and Andasari *et al.* [19]. Scrutinizing in-depth detailed effects of degrading enzyems specially that of the urokinase plasminogen system is studied by Frieboes *et al.* [20]. Gerisch *et al.* has presented a Mathematical model of cancer cell invasion of tissue for Local and non-local models and the effect of adhesion [21].

In the system of partial differential equations being used to model for density of tumor cells $n(x,t)$, concentration of extracellular matrix $f(x,t)$, concentration of nutrients $u(x,t)$, oxygen concentration $c(x,t)$ and concentration of TAF $a(x,t)$ is as follows:

$$\frac{\partial n}{\partial t} = \underbrace{D_n \nabla^2 n}_{\text{Random Motility}} - \underbrace{\rho \nabla \cdot (n \nabla f)}_{\text{Haptotaxis}} + \underbrace{\lambda n(1-n)}_{\text{Logistic Growth}} \tag{1}$$

$$\frac{\partial f}{\partial t} = \underbrace{-\mu u f}_{\text{Degradation}} + \underbrace{f(1-f)}_{\text{Logistic Growth}} \tag{2}$$

$$\frac{\partial u}{\partial t} = \underbrace{D_u \nabla^2 u}_{\text{Diffusion}} - \underbrace{\sigma u}_{\text{Decay}} \tag{3}$$

$$\frac{\partial c}{\partial t} = \underbrace{D_c \nabla^2 c}_{\text{Diffusion}} - \underbrace{\omega n}_{\text{Uptake}} - \underbrace{\emptyset c}_{\text{Decay}} \tag{4}$$

$$\frac{\partial a}{\partial t} \;=\; \underbrace{D_a \nabla^2 a}_{\text{Diffusion}} + \underbrace{\beta_{428} n}_{\text{Production}} - \underbrace{\varphi a}_{\text{Decay}} \qquad\qquad (5)$$

Where $D_n = 5 \times 10^{-6}$ is the tumor cell diffusion coefficient (constant random motility coefficient), $D_u = 5 \times 10^{-6}$ is the nutrient diffusion coefficient (constant), $D_c = 2.5 \times 10^{-4}$ is the oxygen diffusion coefficient (constant), $D_a = 5 \times 10^{-6}$ is the TAF diffusion coefficient (constant), $\rho = (3c + 0.7)\rho_{std}$, $\rho_{std} = 10^{-4}$, $\omega = (3c + 0.7)\,\omega_{std}$, $\omega_{std} = 0.6$, constant $\mu = 50$, $\lambda = 0.05$ is the tumor cell proliferation rate.

To approximate a row of tumor cells we also considered from Anderson' model [7], Jie Lyu, *et al.* [2] and Heiko Enderling [3] an initial TAF concentration field of the form, $a(x, y, 0) = e^{-(1-x)^2/\epsilon_1}, (x, y) \in [0,1] \times [0,1]$. The initial data is given by the distribution in Figure 2, which has three discrete peaks of the form $n(x, y, 0) = e^{-x^2/\epsilon_3} sin^2, (x, y) \in [0,1] \times [0,1]$ with the positive parameter $\epsilon_3 = 0.001$. We take the initial concentration profile of fibronectin is given by the distribution in Figure 3 in the extracellular matrix to have the form, $f(x, y, 0) = ke^{-x^2/\epsilon_2}, (x, y) \in [0,1] \times [0,1]$.
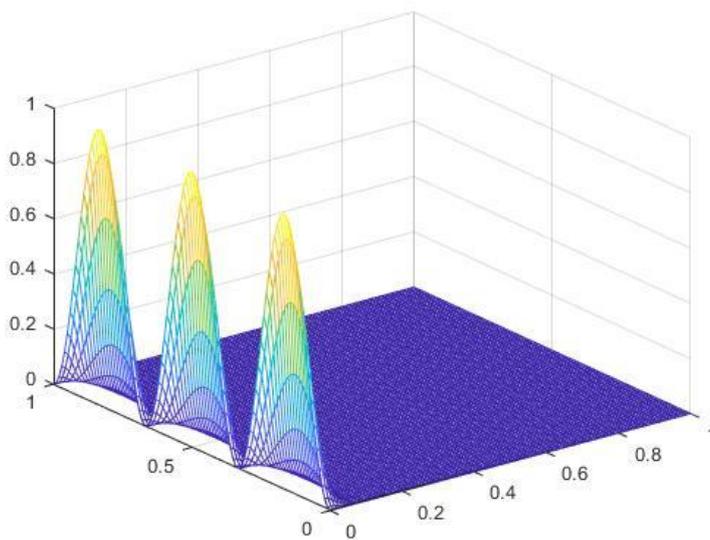

Figure 2. distribution of initial endothelial-cell density for the two-dimensional simulations representing the three initial regions of capillary sprout outgrowth $\epsilon_3 = 0.001$.
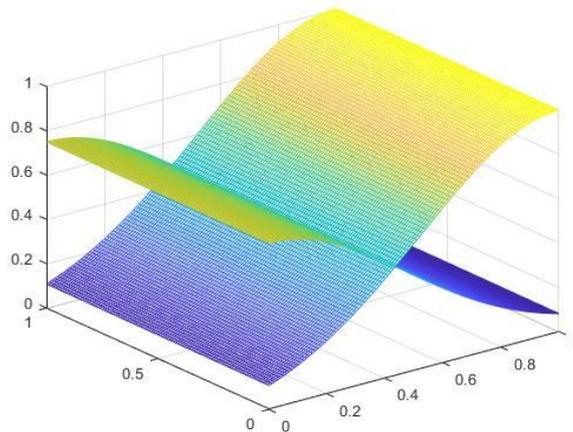
Figure 3. Initial fibronectin concentration and initial TAF concentration profiles for the two-dimensional simulations; The fibronectin initial concentration is highest near the parent vessel at $x = 0$.

To enable not just a qualitative but also quantitative comparison with *in vivo* experimental results a novel mathematical model will be developed that will be discrete model of tumor induced angiogenesis. The assumptions taken into consideration for the model will be based around the movement of an individual endothelial cell found at the tip of capillary sprouts which governs the motion of the entire sprout. The following discrete models can be taken as considered particular illustrations of a wider class of models that are referred broadly as cellular automata models, which in turn have been applicable to a widespread of problems in the various areas of applied mathematics.

Using the Euler finite difference approximation (Mitchell and Griffiths, 1980) [24], we discretize the equations (1) to (5)

$$\frac{\partial n}{\partial t} = \frac{n_{i,j}^{k+1} - n_{i,j}^{k}}{\Delta t}$$

$$D_n \nabla^2 n = D_n \left[\frac{n_{i+1,j}^{k} - 2n_{i,j}^{k} + n_{i-1,j}^{k}}{h^2} + \frac{n_{i,j+1}^{k} - 2n_{i,j}^{k} + n_{i,j-1}^{k}}{k^2} \right]$$

$$\nabla.(n\nabla f) = \frac{n_{i+1,j}^{k}}{4h^2} \left(f_{i+1,j}^{k} - f_{i-1,j}^{k} \right) - \frac{n_{i-1,j}^{k}}{4h^2} \left(f_{i+1,j}^{k} - f_{i-1,j}^{k} \right) + \frac{n_{i,j+1}^{k}}{4h^2} \left(f_{i,j+1}^{k} - f_{i,j-1}^{k} \right)$$

$$- \frac{n_{i,j-1}^{k}}{4h^2} \left(f_{i,j+1}^{k} - f_{i,j-1}^{k} \right) + \frac{n_{i,j}^{k}}{h^2} \left(f_{i+1,j}^{k} + f_{i-1,j}^{k} - 4f_{i,j}^{k} + f_{i,j+1}^{k} + f_{i,j-1}^{k} \right)$$

$$n_{i,j}^{k+1} = \left(n_{i,j}^k\right)^2(-\lambda\Delta t) \quad + \quad n_{i,j}^k\left[1 + \lambda\,\Delta t - \frac{4D_n\Delta t}{h^2}\right.$$
$$-\frac{\rho\Delta t}{h^2}\left(f_{i+1,j}^k + f_{i-1,j}^k + f_{i,j+1}^k + f_{i,j-1}^k - 4f_{i,j}^k\right)\Big]$$
$$+ n_{i+1,j}^k\left[\frac{D_n\Delta t}{h^2} - \frac{\rho\Delta t}{4h^2}\left(f_{i+1,j}^k - f_{i-1,j}^k\right)\right] + n_{i-1,j}^k\left[\frac{D_n\Delta t}{h^2} + \frac{\rho\Delta t}{4h^2}\left(f_{i+1,j}^k - f_{i-1,j}^k\right)\right]$$
$$+ n_{i,j+1}^k\left[\frac{D_n\Delta t}{h^2} - \frac{\rho\Delta t}{4h^2}\left(f_{i,j+1}^k - f_{i,j-1}^k\right)\right] + n_{i,j-1}^k\left[\frac{D_n\Delta t}{h^2} + \frac{\rho\Delta t}{4h^2}\left(f_{i,j+1}^k - f_{i,j-1}^k\right)\right]$$

The full discretized system is

$$n_{i,j}^{k+1} = \left(n_{i,j}^k\right)^2(-\lambda\,\Delta t) \;+\; n_{i,j}^k P_0 + n_{i+1,j}^k P_1 + n_{i-1,j}^k P_2 + n_{i,j+1}^k P_3 + n_{i,j-1}^k P_4$$

Where the coefficient P_0, which is proportional to the probability of no movement, has the form

$$P_0 = 1 + \lambda\Delta t - \frac{4D_n\Delta t}{h^2} - \frac{\rho\Delta t}{h^2}\left(f_{i+1,j}^k + f_{i-1,j}^k + f_{i,j+1}^k + f_{i,j-1}^k - 4f_{i,j}^k\right)$$

and the coefficients P_1, P_2, P_3 and P_4 which are proportional to the probabilities of moving left, right, down and up, respectively, have the forms

$$P_1 = \frac{D_n\Delta t}{h^2} - \frac{\rho\Delta t}{4h^2}\left(f_{i+1,j}^k - f_{i-1,j}^k\right)$$

$$P_2 = \frac{D_n\Delta t}{h^2} + \frac{\rho\Delta t}{4h^2}\left(f_{i+1,j}^k - f_{i-1,j}^k\right)$$

$$P_3 = \frac{D_n\Delta t}{h^2} - \frac{\rho\Delta t}{4h^2}\left(f_{i,j+1}^k - f_{i,j-1}^k\right)$$

$$P_4 = \frac{D_n\Delta t}{h^2} + \frac{\rho\Delta t}{4h^2}\left(f_{i,j+1}^k - f_{i,j-1}^k\right)$$

$$f_{i,j}^{k+1} \quad = \quad f_{i,j}^k \quad - \quad \mu u_{i,j}^k f_{i,j}^k \Delta t \quad + \quad f_{i,j}^k\left(1 - f_{i,j}^k\right)$$

$$u_{i,j}^{k+1} = u_{i,j}^k\left[1 - \sigma\,\Delta t - \frac{4D_u\Delta t}{h^2}\right] + u_{i+1,j}^k\left[\frac{D_u\Delta t}{h^2}\right] + u_{i-1,j}^k\left[\frac{D_u\Delta t}{h^2}\right] + n_{i,j+1}^k\left[\frac{D_u\Delta t}{h^2}\right] + n_{i,j-1}^k\left[\frac{D_u\Delta t}{h^2}\right]$$

$$c_{i,j}^{k+1} \quad = \quad c_{i,j}^k \quad + \quad \frac{D_c\Delta t}{h^2}\left(c_{i+1,j}^k + c_{i-1,j}^k - 2c_{i,j}^k\right) + \frac{D_c\Delta t}{h^2}\left(c_{i,j-1}^k + c_{i,j+1}^k - 2c_{i,j}^k\right)$$
$$- \left(\omega_{i,j}^k n_{i,j}^k + \emptyset c_{i,j}^k\right)\Delta t$$

$$a_{i,j}^{k+1} \quad = \quad a_{i,j}^k \quad + \quad \frac{D_a\Delta t}{h^2}\left(a_{i+1,j}^k + a_{i-1,j}^k + a_{i,j+1}^k + a_{i,j-1}^k - 4a_{i,j}^k\right) + \Delta t\left(\beta n_{i,j}^k - \varphi\,a_{i,j}^k\right)$$

Where the subscripts and the superscripts specify the location and time steps respectively, i.e. the positive parameters are $x = ih$, $y = jh$ and $t = qk$, where i , j , k, q and h are positive parameters. For the discrete technique the chief assumption is that of the five coefficients

being P_0 to P_4 are in proportion with the probability of tumor cell being static (P_0), or moving up (P_4), down (P_3), right (P_2) or left (P_1). Which shows us that in any one direction the tumor cell is not biased and is less (more) expected to be immobile approximating a random unbiased walk. It must be noted that as the interaction with other tumor cells, the motion will be get altered. The parameter values have been adopted from Anderson and Chaplain [7]. The domain is a square with length as 1 (non-dimensional).

With the yield of new cell, each of the cell is handed out an exclusive identification number (or also can be assigned in the beginning for the opening 50 cells). At each time step in the simulation primarily updating of all the positions of cells (by their identification number, i.e. larger the number will be, later will it be updated) and once this is done the updating of the individual-based process for all cells is done, e.g. mutation, death and proliferation. As a cause of this the cells do not get simultaneously updated or in a top-to-bottom, left-right manner but as per their identification number. For the update in migration part, the cells with smaller numbers are given a priority in the identification method (i.e. they get to move primarily) but since there is a widespread distribution of the cells over the tumor this method shall not produce any visible bias. The moment the cells have moved, the process of updating the individual-based process gets under way and done again for per cell identification number, but only now the cells get updated immediately after process occurs, e.g., proliferation, this shall evade any conflicts for space.

SIMULATION RESULTS FOR THE DISCRETE MODEL

Figure 4 shows the tumor growth process during the time of simulation, where the proliferative cells are denoted by the blue area, where as yellow for quiescent cells and eventually for the dead cells its inside blue. Figure 5 intensifies the vascular network synchronization as the growth of tumor takes place. Figure 6 and 7 show the oxygen and TAF concentration at individual moment respectively.

The oxygen can be seen as sufficient within the simulated area during the early stages of the tumor growth, the tumor cells are small in number and cells have ample room for tumor proliferation. As a result of which proliferation cells are found in abundance than the others. Meanwhile TAF is secreted by the hypoxic cells, which includes the blood vessel point surrounding the tumor. Since there is limited distribution and concentration of TAF in the simulation area is at this point is depressed, to improve the oxygen environment the blood

vessel points appear but only in the center of the tumor. Due to the lack of blood vessels at center of the tumor, diffusion of oxygen from the external area can barely make it inside. Concentration of TAF distribution is opposite to that of oxygen.
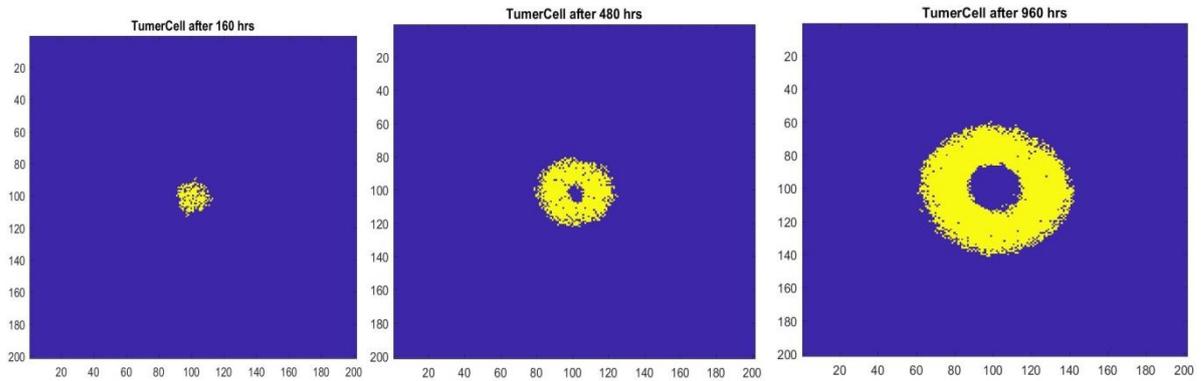

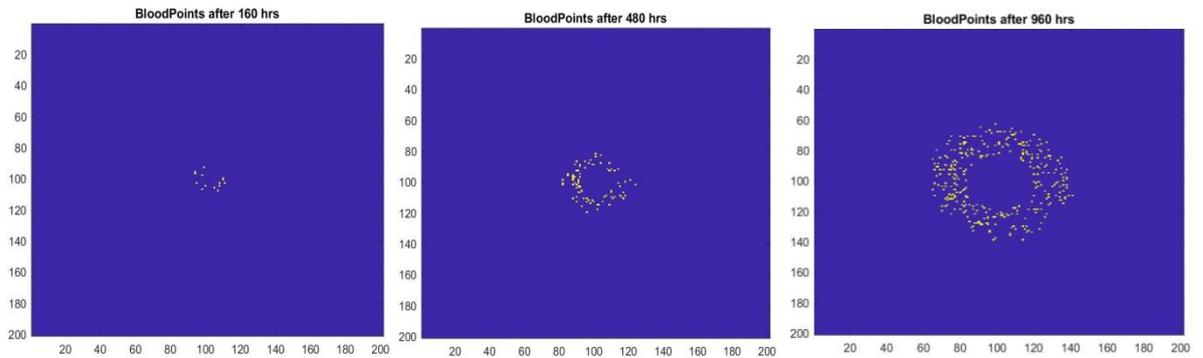Fig 4. Process of tumor growth during the simulation.

Fig 5. Development of blood vessel network during the simulation.
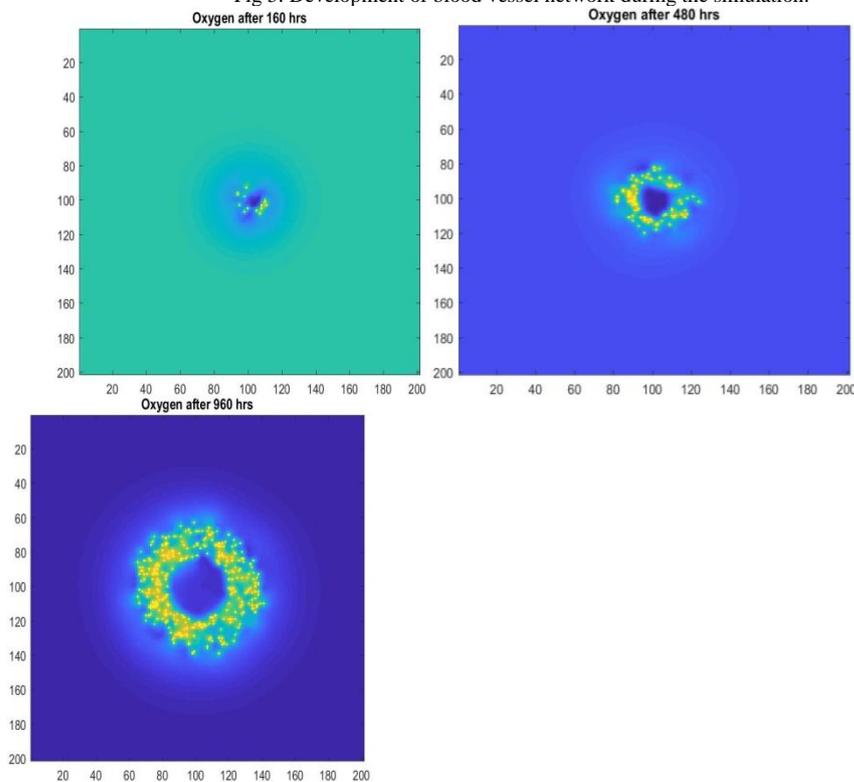

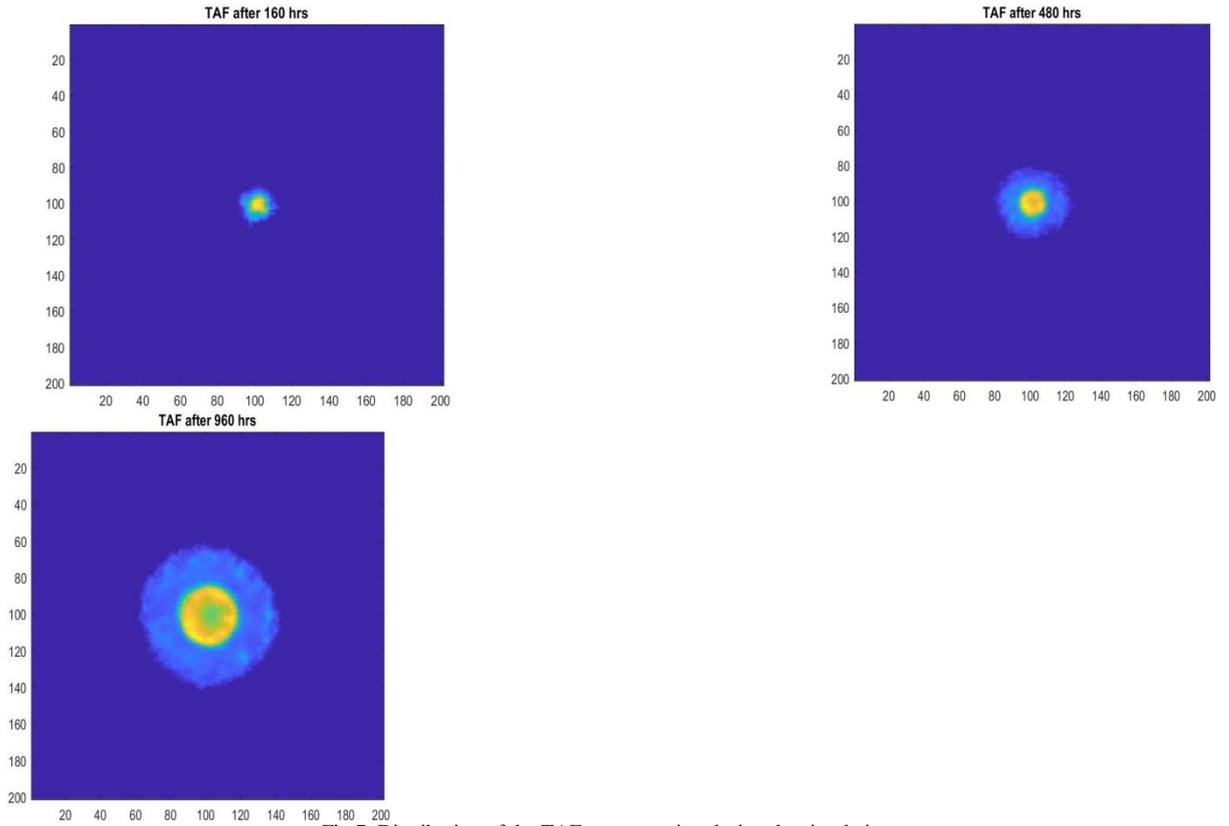Fig 6. Distribution of the oxygen concentration during the simulation.

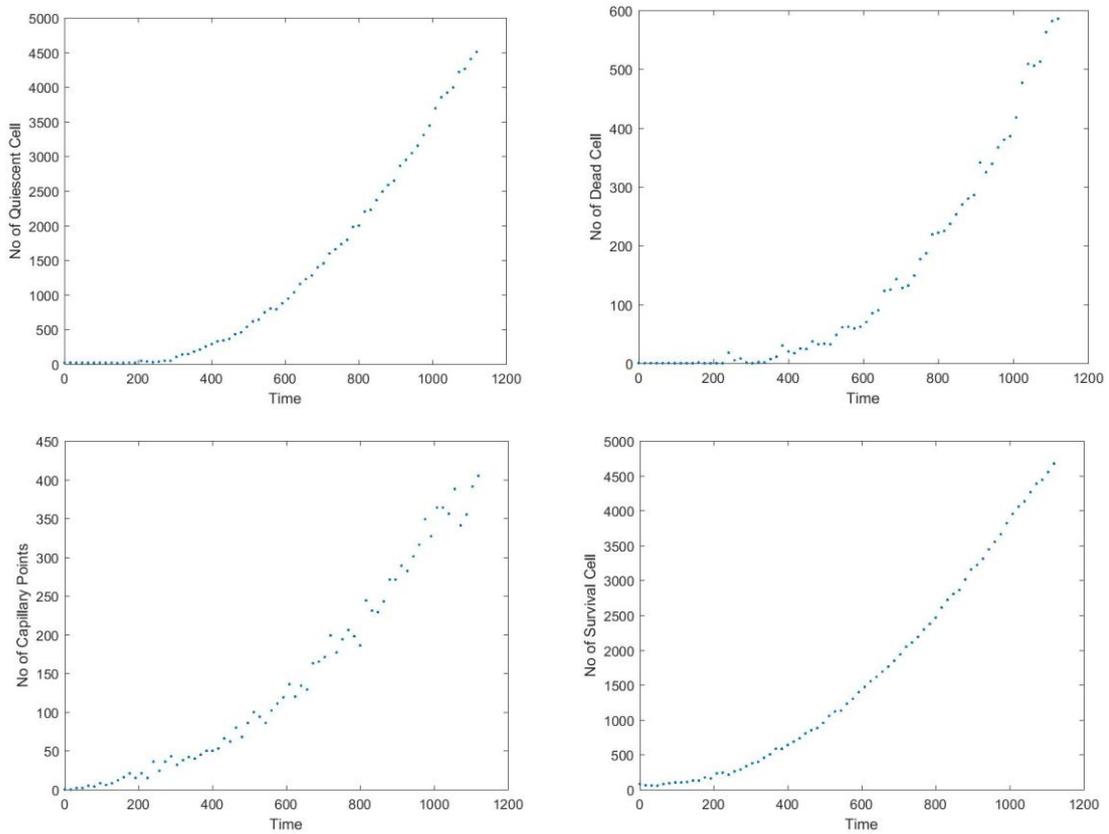Fig 7. Distribution of the TAF concentration during the simulation.

Fig 8. Numbers of tumor cells vs. time (4 simulations).

Without changing the model parameters, we repeated the numerical simulation four times Figure 8 show the increase in number of tumor cells and blood vessels with time, respectively.
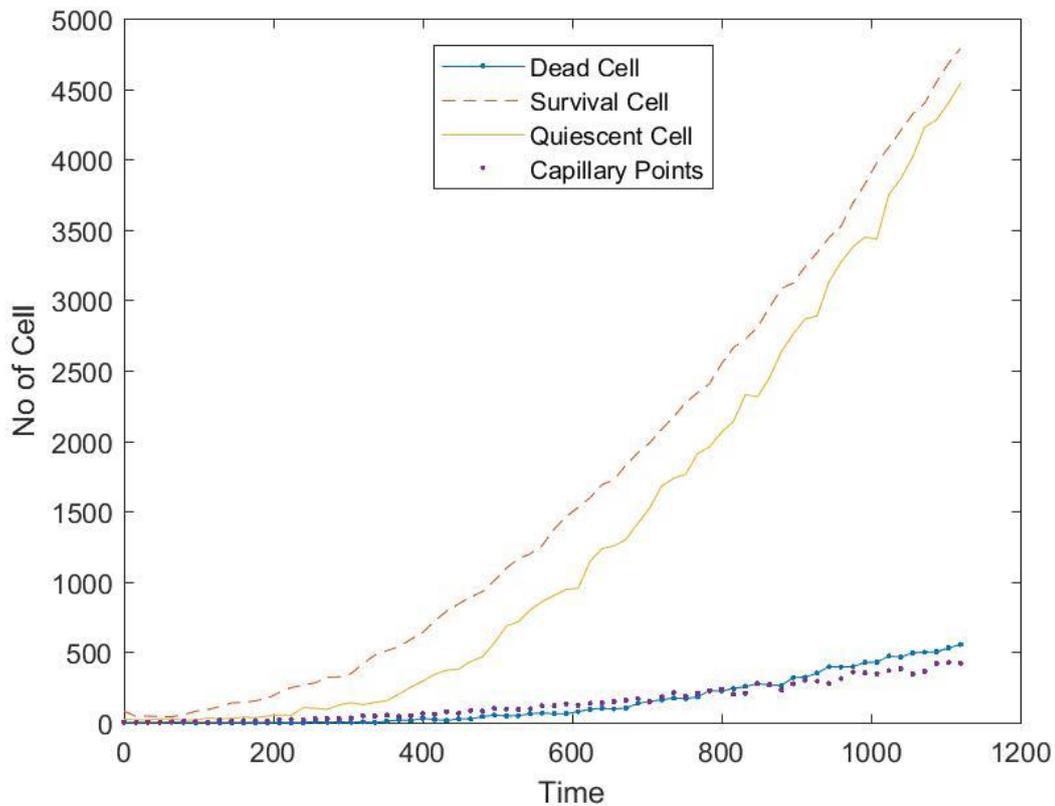

Fig 9. Numbers of tumor cells and blood vessel points vs. time.

The mathematical model also shows the numbers of tumor cells and blood vessel points vs. time, respectively in figure 9.

DISCUSSION

Upon the growing of an invading tumor, the effects of cell-matrix and cell-cell interaction have been examined here especially by taking into consideration the five partial different equations of density of tumor cells, concentration of extracellular matrix, nutrient concentration, oxygen concentration and concentration of tumor angiogenesis factor. A heterogeneous tumor cell population was taken into consideration for the examination of cell-cell adhesion, that comprised of any four picked phenotypes each with its unique levels of cell-cell adhesion with variable levels of adhesion. For the initial four selected phenotypes, a linear mutation sequence is taken into use where all the cells are phenotype I to begin with (highest cell-cell adhesion with least aggression type) and by mutations become more aggressive as move from type II, III and eventually IV (zero cell-cell adhesion, maximum aggressions).

This study has added more linking features focusing on the early stage of tumor growth by taking the basis of coupled model of tumor growth, tumor angiogenesis and blood perfusion in preceding work.

CONCLUSIONS

The mathematical model has been developed complete interfacial framework for tumor cells movements, cell–matrix interactions and tumor vasculature growth. Subsequently this study introduces a new mathematical model and numerical simulation to visualize the changes in the tumor microenvironment, distribution of oxygen concentration, distribution of nutrient concentration, growth of blood vessels, concentration of extra cellular matrix (ECM) and concentration of tumor angiogenesis factor (TAF) during tumor growth. Additionally, numerical simulation provides simplification for tumor cells migration by secreting matrix-degrading enzymes which degrade the extra cellular matrix. Also this discretized form of the partial differential equations demonstrates the significance of interactions between extracellular matrix and endothelial cells. The presence of fibronectin in the extra cellular matrix and a haptotactic response from the endothelial cells arbitrates a vast variation of cellular interactions with the extracellular matrix and takes key role in cell movements, cell-matrix interaction and tumor vasculature growth. These results would create the impression to appear better haptotactic response for the formation of enough effectively-connected growth in tumor vasculature.

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