A Continuum Model and Numerical Simulation for Avascular Tumor Growth

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Abstract. A spatio-temporal continuum model is developed for avascular tumor growth in two dimensions using fractional advection-diffusion equation as the transportation in biological systems is heterogeneous and anomalous in nature (non-Fickian). The model handles skewness with a suitable parameter. We study the behavior of this model with a set of parameters, and suitable initial and boundary conditions. It is found that the fractional advection-diffusion equation based model is more realistic as it provides more insightful information for tumor growth at the macroscopic level.

Keywords: Avascular tumor growth · Anomalous diffusion · Fractional advection-diffusion equation

1 Introduction

Initially, tumor growth does not have any direct vascular support. It takes necessary oxygen and nutrients for sustainable unbounded growth from the surrounding micro-environment through passive diffusion [1, 2]. The metabolic consumption of an avascular tumor nodule also grows with its volume proportionally, but actually it absorbs oxygen and nutrients proportionate to its surface area [3]. So, after a certain time, due to the deprivation of oxygen and nutrients tumor growth will be stagnant (1–2 mm in radius approx.).

Oxygen and nutrients deficiency gradually increase among the tumor cells with distance from the outer layer of the tumor towards its center. At the center of the tumor deficiency level will be the maximum. The deficiency of oxygen and nutrient within tumor cells divides the tumor into three different layers; though these layers are not clearly separated [4]. The outer layer mostly consists of proliferative cells and the inner most contains only the dead cells (necrotic core). The layer in between them is called the quiescent layer (collection of hypoxic cells) which are alive but do not divide. In this study, we consider quiescent cells consume less oxygen and nutrients compared to the proliferative cells.

Mathematicians have immensely studied avascular tumor growth since 1950's and developed various models from different perspectives. Greenspan [5] developed first

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ever tumor growth model with proliferative, quiescent, and necrotic cell zones. Later researchers have adapted this framework and tried different modifications, like Ward and King [6] have developed tumor growth models in terms of dead and live cells densities and also considered that the cell population is space filling with new cells through cell divisions. Later, they [7] have extended their work and included cell motility into tumor spheroid. Sherratt and Chaplain [8] have developed a spatio-temporal model which considered different types of cells in tumor spheroid (which are not sharply divided into layers) and the tumor growth is driven by the cell movements under the influence of nutrients concentration.

In this study, we consider that the avascular tumor (only for epithelium tissue) is *in vivo* and disk shaped. Oxygen and nutrients synthesize the structural support of the tumor cells. Diffusion and convection processes in biological systems are very complex as most of the transportations pass through cellular membranes which are nonhomogeneous in nature. From the studies of the past few decades, it has been shown that entity concentrations passing through heterogeneous media are anomalous or non-Fickian in nature with a long leading or trailing edges [9, 10]. Within the cellular membrane, diffusion coefficient (constant) alone cannot describe the diffusion process. It changes with the spatial coordinates as the structural complexity varies close to the membrane surface [10].

The aim of this research work is to develop a mathematical model based on coupled fractional advection-diffusion equations (FADE) from phenomenological point of view. Initially, we develop a two dimensional (in Polar coordinate system) spatio-temporal model based on simple advection-diffusion equation, assuming less sharp demarcations between different cell layers. Afterwards we modify the basic model based on FADE. We include memory based diffusion process [10] to handle the non-Fickian nature of the process and also include a suitable parameter to express skewness in diffusion. Though, memory formalism in FADE is not adequate enough to model such a complex system like tumor microenvironment in the microscopic level, as several molecular activities are involved. But at the macroscopic level, FADE based model offers more realistic description of the overall system.

This paper is organized as follows: Sect. 2 describes the two dimensional model based on simple advection-diffusion equation in polar coordinate system; modification of the model with respect to anomalous diffusion is presented in Sect. 3, Sect. 4 is concerned with parameter estimation and model evaluation, and Sect. 5 concludes the paper.

2 Simple Advection-Diffusion Based Model

We consider that the tumor is disk shaped. Considering the radial symmetry, we assume that $p(r, t)$, $q(r, t)$, and $n(r, t)$ denote proliferative, quiescent, and necrotic cell concentrations respectively. Here, r denotes the spatial domain in polar coordinate system, and t indicates time. The tumor grows due to diffusive and convective force. The movement of extracellular matrix (ECM) surrounding the tumor is responsible for convection. In this model v_e denotes the velocity of ECM. While, the distinctions between these three layers are not sharp, but the presence of one layer restricts the

movement of the other layers. We assume that necrotic cells cannot migrate, divide or do not consume oxygen or nutrients. Hence, no cell flux is required for necrotic core as they are collection of dead cells. In this study we also include parameters (a_p, a_q) to handle the death rates due to apoptosis in the proliferative as well as quiescent cells. We assume that the values of a_p and a_q are the same.

We further assume that oxygen ($c_o(r, t)$) and nutrient ($c_n(r, t)$) concentrations are different entities. The tumor cell divisions, proliferation, transformation into quiescent or necrotic cells are controlled by concentration levels of oxygen and nutrients. Hence, all the parameters: proliferation rate, proliferative to quiescent and quiescent to necrotic transformation rates should be accompanied by c_o and c_n or some function of c_o and c_n. Under these assumptions we develop the following system Eq. (1),

$$\begin{aligned}
\frac{\partial p}{\partial t} &= \frac{\partial}{\partial r}\left(D_p \frac{\partial p}{\partial r} - v_e p\right) + \frac{1}{r}\left(D_p \frac{\partial p}{\partial r} - v_e p\right) + \alpha h_1(c_o, c_n)p - \beta h_2(c_o, c_n)p - a_p p \\
\frac{\partial q}{\partial t} &= \frac{\partial}{\partial r}\left(D_q \frac{\partial q}{\partial r} - v_e q\right) + \frac{1}{r}\left(D_q \frac{\partial q}{\partial r} - v_e q\right) + \beta h_2(c_o, c_n)p - \gamma h_3(c_o, c_n)q - a_q q \\
\frac{\partial n}{\partial t} &= \gamma h_3(c_o, c_n)q \\
\frac{\partial c_o}{\partial t} &= \frac{\partial}{\partial r}\left(D_o \frac{\partial c_o}{\partial r} - v_e c_o\right) + \frac{1}{r}\left(D_o \frac{\partial c_o}{\partial r} - v_e c_o\right) + \mu_o c_o - k_1 c_o - k_2 p c_o - k_3 q c_o \\
\frac{\partial c_n}{\partial t} &= \frac{\partial}{\partial r}\left(D_n \frac{\partial c_n}{\partial r} - v_e c_n\right) + \frac{1}{r}\left(D_n \frac{\partial c_n}{\partial r} - v_e c_n\right) + \mu_n c_n - w_1 c_n - w_2 p c_n - w_3 q c_n
\end{aligned} \tag{1}$$

Were, D_p, D_q, D_o, and D_n are the diffusion coefficients of proliferative, quiescent, oxygen, and nutrients concentrations respectively; α, β, and γ are the rates of proliferations, proliferative to quiescent, and quiescent to necrotic transformations; μ_o and μ_n are scalars controlling the levels of oxygen and nutrients at any point in the domain of interest; whereas, k_1, k_2, k_3 and w_1, w_2, w_3 express the losses due to consumption by proliferative and quiescent cells. The system of Eq. (1) contains three functions h_1, h_2, and h_3. We consider,

$$\begin{aligned}
&h_1(c_o, c_n) = 1 + 0.1(c_o.c_n);\ h_2(c_o, c_n) = exp(-c_o/s_1)/(1 + exp(-c_n/s_1)); \\
&h_3(c_o, c_n) = exp(-c_o/s_2)/(1 + exp(-c_n/s_2)),\ \text{where } 0 < s_1, s_2 < 1.
\end{aligned} \tag{2}$$

3 Model Based on Fractional Advection Diffusion

Generally, biological processes pass through cell membranes which are porous media and heterogeneous in nature. In this work, the profile concentration of the diffusing tumor cells, oxygen and nutrients inside an organ/tissue has been calculated on the basis of the FADE by introducing memory formalism (diffusion with memory). Diffusion with memory indicates the past behaviour of the function itself [10]. This approach generalizes the classical diffusion models to more complex systems, where diffusion coefficients are the function of c_o, c_n as both of them are varied with spatial domain. Skewness in diffusion may also be considered through a suitable parameter (φ). FADE with fixed order have shown certain advantages to model anomalous (non-Fickian) diffusion to some extent [11, 12]. In this phase, we modify model (1) and

include FADE based model using the Caputo definition of fractional derivative. We use an unconditionally stable finite element method (FEM) [13] to solve FADE.

As the medium of convection-diffusion in biological system is porous, it is also assumed that diffusion coefficient and convective velocity are related as:

$$(\textit{Diffusion coefficients}) \propto (\textit{convection velocity})^{\rho}, \text{ where, } 1 \leq \rho \leq 2. \tag{3}$$

We consider, $v_e(c_o, c_n) = v_{e0}h(c_o, c_n)$. According to (3),

$$\begin{aligned} &D_p(c_o, c_n) = D_{p0}h^{\rho}(c_o, c_n); D_q(c_o, c_n) = D_{q0}h^{\rho}(c_o, c_n); D_o(c_o, c_n) = D_{o0}h^{\rho}(c_o, c_n); \\ &D_n(c_o, c_n) = D_{n0}h^{\rho}(c_o, c_n), \text{ where, } v_{e0}, D_{p0}, D_{q0}, D_{o0}, \text{ and } D_{n0} \text{ are the diffusivity constants.} \end{aligned} \tag{4}$$

By combining (1) and (4), we get the following,

$$\begin{aligned} \frac{\partial p}{\partial t} = {} & D_{p0}h^{\rho}\frac{\partial^2 p}{\partial r^2} - v_{e0}h\frac{\partial p}{\partial r} + \frac{1}{r}\left(D_{p0}h^{\rho}\frac{\partial p}{\partial r} - v_{e0}hp\right) + D_{p0}\left(\frac{\partial h^{\rho}}{\partial c_o}\frac{\partial c_o}{\partial r} + \frac{\partial h^{\rho}}{\partial c_n}\frac{\partial c_n}{\partial r}\right)\frac{\partial p}{\partial r} \\ & - v_{e0}\left(\frac{\partial h}{\partial c_o}\frac{\partial c_o}{\partial r} + \frac{\partial h}{\partial c_n}\frac{\partial c_n}{\partial r}\right)p + \alpha h_1(c_o, c_n)p - \beta h_2(c_o, c_n)p - a_p p \end{aligned} \tag{5}$$

Here, we have used h instead of $h(c_o, c_n)$, and h^{ρ} instead of $h^{\rho}(c_o, c_n)$ for the purpose of clarity. $\partial q/\partial t$, $\partial n/\partial t$, $\partial c_o/\partial t$, and $\partial c_n/\partial t$ also look similar to $\partial p/\partial t$.

We consider,

$$h(c_o, c_n) = exp(\theta - c_o c_n), \theta \text{ is a constant}, \theta > 0 \tag{6}$$

We assume that the minimum distance from the tumor center ($r = 0$) to its nearest blood vessel is d. Therefore, we consider a circular domain of radius d in which the tumor has grown. Here, r is the radial direction from the center ($r = 0$) towards the boundary ($r = d$) of the disk shaped domain. Now, we non-dimensionalize the system of Eq. (5) by rescaling distance d with time $\tau = d^2/D_{o0}$. Proliferative cell, quiescent cell, necrotic cell, oxygen, and nutrients concentrations are also rescaled with p_0, q_0, n_0, c_1, and c_2 respectively (where p_0, q_0, n_0, c_1, and c_2 are the appropriate reference variables). Therefore, $p^* = p/p_0$; $q^* = q/q_0$; $n^* = n/n_0$; $c_o^* = c_o/c_1$; $c_n^* = c_n/c_2$; $t^* = t/\tau$. The new system of equations becomes (by dropping the stars),

$$\begin{aligned} \frac{\partial p}{\partial t} = {} & D_1 h^{\rho}\frac{\partial^2 p}{\partial r^2} - vh\frac{\partial p}{\partial r} + \frac{1}{r}D_1 h^{\rho}\frac{\partial p}{\partial r} - \frac{1}{r}vhp + D_1\left(\frac{\partial h^{p}}{\partial c_o}\frac{\partial c_o}{\partial r} + \frac{\partial h^{p}}{\partial c_n}\frac{\partial c_n}{\partial r}\right)\frac{\partial p}{\partial r} \\ & - v\left(\frac{\partial h}{\partial c_o}\frac{\partial c_o}{\partial r} + \frac{\partial h}{\partial c_n}\frac{\partial c_n}{\partial r}\right)p + \alpha h_1(c_o, c_n)p - \beta h_2(c_o, c_n)p - a_p p \end{aligned} \tag{7}$$

The rest of the equations ($\partial q/\partial t$, $\partial n/\partial t$, $\partial c_o/\partial t$, and $\partial c_n/\partial t$) also look similar to $\partial p/\partial t$ where, $\alpha^* = \alpha d^2/D_{o0}$; $\beta^* = \beta d^2/D_{o0}$; $a_p^* = a_p d^2/D_{o0}$; $\eta^* = \beta d^2/D_{o0}q_0$; $a_q* = a_q d^2/D_{o0}$;

$\gamma^* = \gamma d^2/D_{o0}$; $\omega^* = \gamma d^2/D_{o0} n_0$; $\mu_o^* = \mu_o d^2/D_{o0}$; $\mu_n^* = \mu_n d^2/D_{o0}$; $k_1^* = k_1 d^2/D_{o0}$; $k_2^* = k_2 d^2/D_{o0}$; $k_3^* = k_3 d^2/D_{o0}$; $w_1^* = w_1 d^2/D_{o0}$; $w_2^* = w_2 d^2/D_{o0}$; $w_3^* = w_3 d^2/D_{o0}$; $v^* = v_e d/D_{o0}$; $D_1^* = D_{p0}/D_{o0}$; $D_2^* = D_{q0}/D_{o0}$; $D_3^* = D_{n0}/D_{o0}$.

Now, the space fractional derivative is included in the model. From [14], we have,

$$\frac{\partial^\phi p}{\partial r \phi} \approx \left(\left(\frac{1+\varphi}{2} \right) \mathcal{D}_L^\phi(p) + \left(\frac{1-\varphi}{2} \right) \mathcal{D}_R^\phi(p) \right), 1 < \Phi \leq 2 \tag{8}$$

where, ϕ is the fractional order, and φ ($-1 \leq \varphi \leq 1$) is the skewness parameter. $\mathcal{D}_L^\phi$ and $\mathcal{D}_R^\phi$ are the left- and right-handed fractional derivatives respectively. L ($L = 1$) and R ($R = 2$) are the corresponding lower and upper bounds of ϕ. The definitions of left- and right-hand derivatives are,

$$\mathcal{D}_L^\phi = \frac{\partial^\phi}{\partial (r)^\phi} \quad \text{and} \quad \mathcal{D}_R^\phi = \frac{\partial^\phi}{\partial (-r)^\phi} \tag{9}$$

and

$$\frac{\partial^\xi p}{\partial r^\xi} \approx \left(\left(\frac{1+\psi}{2} \right) \mathcal{D}_L^\xi(p) - \left(\frac{1-\psi}{2} \right) \mathcal{D}_R^\xi(p) \right), \ 0 < \zeta \leq 1 \tag{10}$$

where, $\zeta\ (= \Phi - 1)$ is the fractional order. $\mathcal{D}_L^\xi$ and $\mathcal{D}_R^\xi$ are the left- and right-handed fractional derivative respectively. L ($L = 0$) and R ($R = 1$) are the corresponding lower and upper bounds of ξ. The definitions of left- and right-hand limits are,

$$\mathcal{D}_L^\xi = \frac{\partial^\xi}{\partial (r)^\xi} \quad \text{and} \quad \mathcal{D}_R^\xi = \frac{\partial^\xi}{\partial (-r)^\xi} \tag{11}$$

For $\phi = 2$ and $\varphi = 0$, it indicates no skewness in the diffusion (Fick's diffusion). Approximation sign ($\approx$) may be replaced by equality ($=$) sign. If $\varphi < 0$, the dispersion is skewed backward: a slow evolving contaminant plume followed by a heavy tail. For $\varphi > 0$, it shows a forward dispersion: a fast evolving contaminant plume followed by a light tail. We replace all the second-order derivatives with (8) and first-order derivatives with (10) in (7), except the derivatives with respect to time. We assume, $t_k = k \times \Delta t$, $0 \leq t_k \leq T$, where $k = 0, 1, 2, \ldots, n_t$ and $r_i = i\Delta r$, $0 \leq r_i \leq d$, where $i = 0, 1, 2, \ldots, n_r$.

The FEM of the fractional order derivatives according to Grünwald definition for the left-handed as well as the right-handed derivatives [15] are,

$$\frac{\partial^\phi p}{\partial r^\phi} = \frac{1}{\kappa^\phi} \sum\nolimits_{\chi=0}^{i+1} g_\chi p_{i-\chi+1} \text{ and } \frac{\partial^\phi p}{\partial (-r)^\phi} = \frac{1}{\kappa^\phi} \sum\nolimits_{\chi=0}^{\chi-i+1} g_\chi p_{i+\chi-1} \tag{12}$$

$$\frac{\partial^\xi p}{\partial r^\xi} = \frac{1}{\kappa^\xi} \sum\nolimits_{\chi=0}^{i+1} g_\chi p_{i-\chi+1} \text{ and } \frac{\partial^\xi p}{\partial (-r)^\xi} = \frac{1}{\kappa^\xi} \sum\nolimits_{\chi=0}^{\chi-i+1} g_\chi p_{i+\chi-1} \tag{13}$$

where, $g_\chi = \frac{\Gamma(\phi+1)}{\Gamma(\chi+1)\Gamma(\phi-\chi+1)}$.

$\Gamma(.)$ is the Euler gamma function, and x is the uniform size of the intervals into which the spatial axis is divided. We have applied the fractional derivative on spatial domain only. Now, the system of Eq. (7) is solved by combining (8), (9), (10), (11), (12), and (13) with the following initial condition and boundary conditions.

Initial conditions: $p(r,\ 0) = 0.01 * exp(-0.1 * r)$, $q(r,\ 0) = 0$, $n(r,\ 0) = 0$, $c_o(r,\ 0) = 1$, and $c_n(r,\ 0) = 1$ and the boundary conditions: $p(0,\ t) = p(d,\ t) = 0$, $q(0,\ t) = q(d,\ t) = 0$, $c_o(0,\ t) = c_o(d,\ t) = 1$, and $c_n(0,\ t) = c_n(d,\ t) = 1$ (no boundary condition is needed for n).

4 Parameter Estimation and Simulation

In this study we have used referred or previously estimated values from the experimental data, if possible. All the experiments are done in 10^{-2} mm scale. As we have mentioned before that at the avascular stage a tumor can grow at most 1–2 mm in radius, so, we consider the value of $d = 2.50$ mm (250 mm^{-2}). As, our study is concentrated on the tumor in epithelium tissue, it is considered that the diffusivity constants of proliferative and quiescent cells are the same as the epithelium cells. For this study we have taken $D_{p0} = D_{q0} = 3.5 \times 10^{-11}$ cm^2s^{-1} [16]. We further consider that the diffusivity of nutrients (D_{n0}) is 1.1×10^{-6} cm^2s^{-1} [17] and oxygen (D_{o0}) as 1.82×10^{-6} cm^2s^{-1}(estimated).

For simulation purpose we use proliferation rate (α) = 1.1 d^{-1} [18], $\gamma = 3.8 \times 10^{-6}$ s^{-1} [19], and apoptosis rates $a_p = a_q = 4 \times 10^{-10}$ s^{-1} [19]. We could not find any reference for β, hence, the value is taken (1.7×10^{-4} s^{-1}). We also use $v_{e0} = 2.4$ 10^{-10} cms^{-1}, $s_1 = 0.25$, $s_2 = 0.30$; $\mu_o = \mu_n = 1.0$ d^{-1}, and the consumption rates $k_1 = w_1 = 1.0$ d^{-1}, $k_2 = w_2 = 0.8$ d^{-1}, and $k_3 = w_3 = 0.3$ d^{-1}. It is considered that the temporal as well as the spatial step sizes for our simulation are $\Delta t = 0.004$ and $\Delta r =$ $= 1$ respectively. We simulate our model with $p_0 = 1$, $q_0 = 2.25$, $n_0 = 1.5$, $c_1 = 1$, $c_2 = 1$. We assume $\theta = 1$, and $\varphi = 0.5$ in this study.

4.1 Simulation and Discussion

According to [20], an avascular tumor in epithelial tissue takes approximately 10 years to grow 1–2 mm in radius. In this experiment, we assume that an iteration of the simulation represents one day. So we have iterated the simulation process for 3500 times (3500 days $\approx$ 10 years) collected the result at the interval of 500 days. All the simulation is done in MATLAB R2017a for this study.

Initially, the microenvironment is full of nutrients and oxygen. So tumor cell absorb these nutrients and oxygen and proliferate. Proliferative cells are concentrated near the tumor centre up to 500 days (Fig. 1 (a)). After that it gradually move forward and at the end of the simulation it reaches 2 mm (approx.). Figure 1(b) shows that after 1000 days the hypoxic cells gradually increase due to the steady fall of oxygen (Fig. 2(b)) and nutrient (Fig. 2(c)) concentrations within the tumor cells nearer to the centre. After 1500 days, oxygen and nutrients levels decrease further near to the centre of the tumor

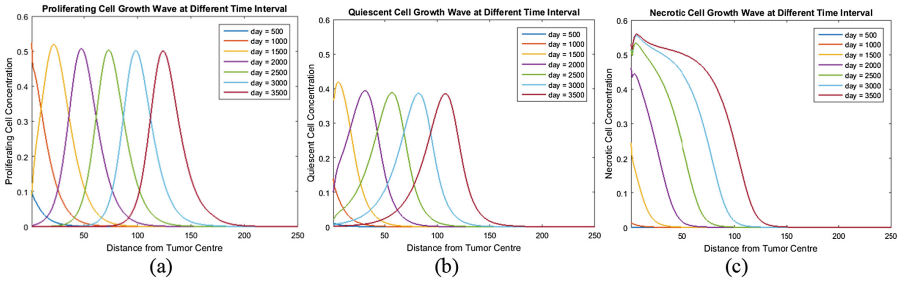

Fig. 1. (a) Proliferative (p/p_0), (b) quiescent (q/q_0), and (c) necrotic (n/n_0) cell concentration waves at different time intervals with respect to the distance (d) from tumor center.

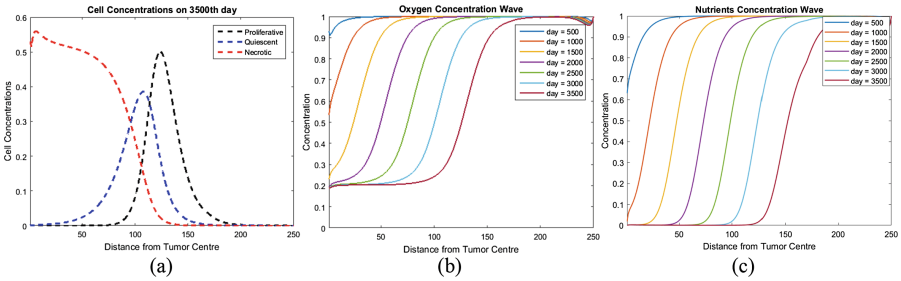

Fig. 2. (a) Represents proliferative, quiescent, and necrotic cell concentrations at 3500th day; (b) oxygen (c_o/c_1), and (c) nutrients (c_n/c_2) concentrations in different time intervals.

and quiescent cells (hypoxic) residing at that place are transformed into necrotic cells. With time the necrotic core increases rapidly and reaches approximately 1.4 mm (Fig. 1(c)) in radius, whereas hypoxic cells grow approximately 1.65 mm from the tumor centre (Fig. 1(b)). This means that necrotic core acquires approximately more than 70 percent area whereas, proliferative cells contain 17.5% and quiescent cells contain only 12.5% area in an avascular tumor. The outer surface of the tumor always contains proliferative cells with higher concentration. The overlapping areas between the proliferative and quiescent, and quiescent and necrotic cells in Fig. 2(a) indicate

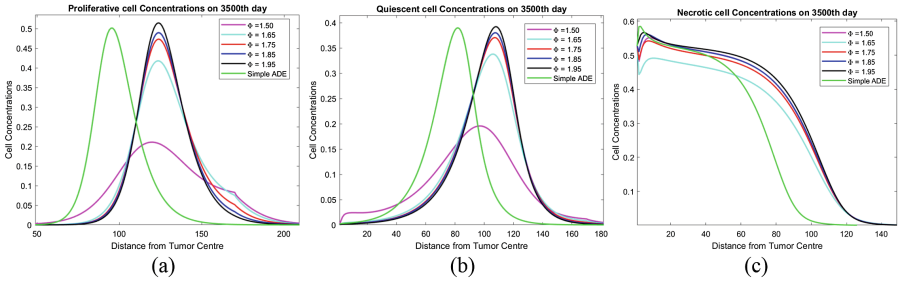

Fig. 3. (a) Proliferative (p/p_0), (b) quiescent (q/q_0) and (c) necrotic (n/n_0) cell concentration waves at different order FADE for 3500th day (φ = 0.5 and ϕ varying from 1.5 to 1.95).

that at any time, boundary between the two layers is not clear. Tumor regression cannot be seen in its life time. The above simulation has done with $\phi = 1.85$.

FADE model is also tested with different orders ϕ = 1.5, 1.65, 1.75, 1.85, and 1.95. It can be seen (Fig. 3(a)–(c)) that varying order does not affect proliferative, quiescent, and necrotic cell concentrations much excepting when $\phi = 1.5$ in terms of intensity. It is also clear that simple ADE always underestimate the radius of tumor than FADE based model with the same set of parameters. This means that tumor grows faster in FADE based model than in simple ADE based model. Not only tumor radius but also the quiescent and necrotic cell concentrations increase and the necrotic cells acquire almost 3/5 portion of the tumor spheroid. In FADE we have also considered porosity and dynamic behaviour of cell membranes. FADE-based model tries to represent tumor growth more realistically than the simple ADE based model.

5 Conclusion

Transport processes through cell membranes are anomalous; hence we propose a memory based FADE model to explain avascular tumor growth *in vivo*. We solve the models numerically with a set of parameters with suitable initial and boundary conditions using FEM. We also compute the result with different values of ϕ. It is found that changing the order (ϕ) results in very small changes in the variables: proliferative, quiescent, and necrotic concentrations. But simple ADE based model always underestimate tumor growth than the FADE-based model. From the phenomenological point of view, FADE-based model provides more realistic description at the macroscopic level.

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