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# Simple PDE Model of Ductal Carcinoma in situ and Vascularisation of Nutrient

**Deepak Kumar**

*Department of Mathematics, FET,*
*Manav Rachna International University, Faridabad (India)*
*deepakman12@gmail.com*

**Abstract:**

Multiscale approaches to modeling biological phenomena are going rapidly. We present here, some recent results on the tumor growth in a rigid walled cylindrical duct. The model takes tumor cell concentration, dead cells and water (lumen). In this work we explore cell carrying capacity of nutrient in tumor cell because tumor growth depends on the supply of nutrient. We find that the nutrient concentration in the tumor cell in different variations of cell carrying capacity of nutrient in the tumor.

**Key words:** solid tumor, mathematical model, anti-angiogenic, nutrient, neovascularisation.

**AMS (1991) subject classification number:** 92C50 / 92C35

## Introduction:

In last few years research on tumor growth has made a considerable progress and is receiving more and more attention. This study addresses the most common cause of cancer death, the breast cancer. The diameter of the duct in a healthy breast is *0.2*mm and surround by stroma. Tumors induce blood vessel growth (angiogenesis) by secreting various growth factors (e.g. Vascular Endothelial Growth Factor or VEGF). Growth factors, such as such as BFGF (basic fibroblast growth factor) VEGF can

induce capillary growth into the tumor, by supplying required nutrients and allowing for tumor expansion. Thus angiogenesis is a necessary and required step for transition of a small harmless cluster of cells, to a large tumor. Angiogenesis is also required for the spread of a tumor, or metastasis. Evidences now suggest that the blood vessel in a given solid tumor may in fact be mosaic vessels, comprised of endothelial cells and tumor cells. This mosaicity allows for substantial shedding of tumor cells into the vasculature. The subsequent growth of such metastases will also require a supply of nutrients and oxygen.

Tumor cells in general are well known to have high glycolytic activity. This is of course partly, because of tumor cells progress through multiple steps of carcinogenesis exposed to insufficient oxygen supply, because of excessive oxygen demand and thereby insufficient vascularization. Even after the tumor increases in size, the immediate environment of cancer cells often becomes heterogeneous. In addition, some regions of large tumors often have microenvironmental niches, displaying a significant gradient of critical metabolites including oxygen, glucose, other nutrients, and growth factors. Therefore, angiogenesis is regarded as a key step in tumor growth, and antiangiogenesis is the most promising cancer therapy, with extensive by studied to prevent tumor angiogenesis.

***Jain (2005)*** **worked on** solid tumors reported that it require blood vessels for growth, and many new cancer therapies are directly against the tumor vasculature (formation of blood vessels). The widely held view is that these antiangiogenic therapies should destroy the tumor vasculature, thereby depriving the tumor of oxygen and nutrients. Here, his review emerging evidence supporting an alternative hypothesis that certain antiangiogenic agents can also transiently normalize the abnormal structure and function of tumor vasculature to make it more efficient for oxygen and drug delivery. Drugs that induce vascular normalization can relieve oxygen and increase the efficacy of conventional therapies if both are carefully scheduled. A better understanding of the molecular and cellular underpinnings of vascular normalization may ultimately lead to more effective therapies, not only for cancer but also for diseases with abnormal vasculature, as well as regenerative medicine, in which the goal is to create and maintain a functionally normal vasculature.

*Gastl et.al.(1997)* worked on angiogenesis and observed that it is a key step towards tumor treatment, invasion and metastasis. Thus, antiangiogenic therapy was postulated to be an attractive approach for antitumor treatment. On the basis of recent information, some strategies for inhibition of angiogenesis are feasible (1) inhibition of release of angiogenic factors from tumor cells and/or neutralization of angiogenic molecules that have already been released (2) inhibition of vascular endothelial cell proliferation and migration, and (3) inhibition of the synthesis and turnover of vessel

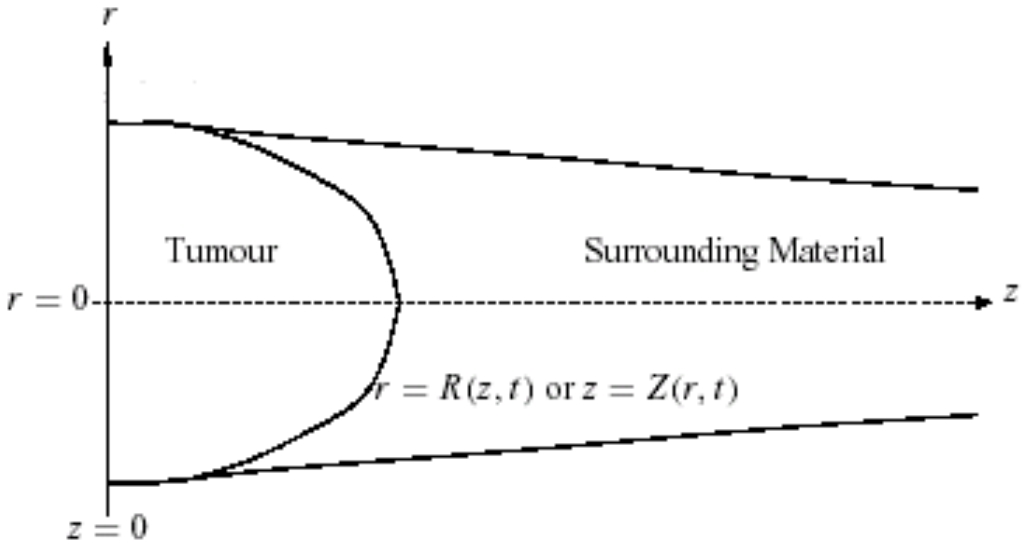
basement membrane. In animal models, treatment with angiogenesis inhibitors has proven antitumor effects. Early medical researches experience with angiogenic inhibitors that indicates optimal antiangiogenic therapy in the future is likely to be based on the long-term administration to cancer patients in adjunct to surgery, radiotherapy and conventional chemotherapy. The tumors, it seemed, had found a way to circumvent even this most ingenious of treatment approaches.

Here we are interested to have mathematical study of ductal carcinoma *in situ* (DCIS) of the breast. The duct is made up of a central region of lumen water (extra cellular fluid) lined by a thin layer of epithelial cells, a layer of myo-epithelial cells and an outer basement membrane (the duct wall) comprising a meshwork of proteins. We consider the tumors growth using a nutrient-limited model. The birth and death rate of cells is dependent upon the concentration of a nutrient while immune response providing suppression. We consider a cylindrically symmetric geometry of the breast duct, which is a rigid walled cylinder, and that growth occurs only in the axial direction. In this work, we assume that the duct is an in compressible cylindrical compliant membrane and tumor growth and resulting membrane deformations are axisymmetric. *Franks et. al. (2003)* worked in this directions considering a model for the early growth of ductal carcinoma and observed the tumor's growth is described using a nutrient-limited model in which the birth and death of cells is dependent upon the concentration of a nutrient which is supplied by diffusion from the surroundings (either outside of the duct or from the fluid within the duct).

Angiogenesis performs a critical role in the development of tumor. Solid tumor is smaller than 2 cubic millimeters are not vascularized. To spread, they need to be supplied by blood vessels that bring oxygen and nutrients and remove metabolic wastes. Beyond the critical volume of 2 cubic millimeters, oxygen and nutrients have difficulty in diffusing to the cells in the center of the tumor, causing a state of cellular hypoxia that marks the onset of tumor angiogenesis. New blood vessel development is an important process in tumor progression. It favors the transition from hyperplasia to neoplasia i.e. the passage from a state of cellular multiplication to a state of uncontrolled proliferation characteristic of tumor cells. Neovascularization also influences the dissemination of tumor cells throughout the entire body eventually leading to metastasis formation.

The main focus of this study is that the tumors need nutrients and oxygen which is supplied by blood vessels in order to grow. They also use blood vessels to spread to other parts of the body. This process, known as metastasis, is the most lethal stage of cancer and the leading cause of cancer-related death. Fighting cancer by starving tumors of life-giving blood vessels has generated great interest in recent years. In this work result suggests that mechanisms which inhibit angiogenesis will have potential as cancer therapeutics.

**Mathematical Model:**




This model is based on the research work of *Franks et. al. (2003).* Since we are modeling for a *neovascularisation,* we consider a term for cell carrying of nutrient in tumor cells. The tumor's growth depends upon a generic nutrient, the cells divining and growing at a dependent upon its concentration. The nutrient diffuses through the basement membrane from the vessels surrounding the duct. We formulate the growth of a tumor in a rigid walled cylindrical duct which is examined in order to model the initial stages of a tumor cell expansion in ductal carcinoma *in situ* of the breast. We denote the concentrations of tumor cell, dead cell and water (lumen) by $n(x,t)$, $m(x,t)$ and $\rho(x,t)$ respectively. The internal velocity field is represented by $v(x,t)$, which is created by birth and death rate of cells, where $v=(u(x,t),w(x,t))$ and the pressure by $p(x,t)$ where $x=(r,z)$, $r$ and $z$ being the distances in the radial and axial directions, respectively while $t$ is the time. The diffusion coefficients of tumor cell, dead cell and water (lumen) represent respectively by $D_n$, $D_m$ and $D_\rho$. The proliferation rate and death rate and death rate of cells represents by $\lambda$ and $\delta$ respectively. The term *k* represents the cell carrying capacity, regarded as a variable in its own right, proportional to the amount of neovascularization. The tumor is assumed so large that neovascularization dominates the availability of nutrients. We write

$$\frac{\partial n}{\partial t}+\nabla.(nv)=\lambda n(1-\frac{n}{k})-\delta n+D_n\nabla^2 n \tag{1}$$

$$\frac{\partial m}{\partial t}+\nabla.(mv)=\delta n+D_m\nabla^2 m \tag{2}$$

$$\frac{\partial \rho}{\partial t}+\nabla.(\rho v)=D_\rho\nabla^2\rho \tag{3}$$

Let $\lambda = Ac$ and $\delta = B(1-\sigma c)$, where $A$ and $B$ are positive constant and $0 \le \sigma < c_I^{-1}$, so that $\delta > 0$ for all $c$, to account for cell death.

The nutrient is very much necessary to growth of solid tumor. The concentration of nutrient is denoted by $c(x,t)$, $\phi$ is represents the rate of nutrient consumption during proliferation and $D_c$ which is representing diffusion coefficient constant.

$$\frac{\partial c}{\partial t} + \nabla.(cv) = D_c \nabla^2 c - \phi\lambda n(1-\frac{n}{k}) \tag{4}$$

We suppose that concentration of each cell is in the form of an incompressible, continuous fluid and the tumor consists exclusively of these three constituents, therefore we set

$$n + m + \rho = 1 \tag{5}$$

Adding (1)-(3) and using (5) we get the velocity field. Let

$$\nabla v = \lambda n(1-\frac{n}{k}) \tag{6}$$

Since the system is multi-dimensional, equation (6) is not sufficient to determine the velocity field fully because we require a constitute law for material deformation. In order to describe the multi-dimensional system within the tumor, we adopt Stokes law (with a volumetric source due to proliferation) which shows slow viscous flow and relates the stress, experienced by the cells to their of strain and appears more appropriate in the this context. When stating the constitutive law for the stress tensors $\sigma_{ij}$, the tumor cell pressure $p = -\frac{1}{3}\sigma_{kk}$, the rate of strain tensor $e_{ij}$ and the viscosity $\mu$, we have the following relations

$$\sigma_{ij} = -p\delta_{ij} + 2\mu(e_{ij} - \frac{1}{3}\Delta\delta_{ij})$$

where $p = -\frac{1}{3}\sigma_{kk}$ and $\Delta$ is the dilation. The rate of strain tensor and dilation defined as

$$e_{ij} = \frac{1}{2}(\frac{\partial u_i}{\partial x_j} + \frac{\partial u_j}{\partial x_i}), \qquad \Delta = e_{kk}$$

The solid tumor contained only tumor cell and dead cell $(n+m=1, \rho=0)$ and of the outside, it has only water $(n+m=0, \rho=1)$. The viscosity depends solely on the type of cells, so as the viscosity $\mu = \mu(n+m)$ *i.e.* $\mu(1)$ is the tumor and $\mu(0)$ the water. In this context the viscosity represents the resistance to motion experienced by the cells this being related to the strength of the bonds that hold them together which is, in turn, likely to be determined by the degree of differentiation of the tumor cells.

We suppose that there are momentum is with neglecting inertia, we have

$$\frac{\partial \sigma_{ij}}{\partial x_j} = 0$$

Now substituting of $\sigma_{ij}$ into the momentum equation, gives the Stokes equations.

$$\nabla p = \mu(\nabla^2 + \frac{1}{3}\nabla(\nabla.v)) \tag{7}$$

We suppose that the tumor is containing only uninfected tumor cell and infected tumor cells, while the water is at the surface of tumor. Here $t = 0$ to be the time at which the nutrient is first administrated, therefore we take the following as initial conditions

$$n(x,0) = \begin{cases} 1 & 0 < x < r \\ 0 & x > r \end{cases} \quad c(x,0) = c_I \tag{8}$$

We also impose the following boundary condition.

$$\begin{aligned}
&\text{on } z = 0 && \frac{\partial n}{\partial z} = 0,\ \frac{\partial p}{\partial z} = 0,\ \frac{\partial u}{\partial z} = 0,\ v = 0,\ \frac{\partial c}{\partial z} = 0, \\
&\text{as } z \to \infty && n = 0,\ u = 0,\ \frac{\partial v}{\partial z} = 0,\ \frac{\partial n}{\partial z} = 0\ c = c_I, \\
&\text{on } r = 0 && \frac{\partial n}{\partial r} = 0,\ \frac{\partial p}{\partial r} = 0,\ u = 0,\ \frac{\partial v}{\partial r} = 0,\ \frac{\partial c}{\partial r} = 0 \\
&\text{as } r = 1 && \frac{\partial n}{\partial r} = 0,\ u = 0,\ \mu\frac{\partial v}{\partial r} = -\varphi v,\ c = c_I
\end{aligned} \tag{9}$$

Initially, we suppose that tumor is symmetric about $z = 0$ and $r = 0$ so that zero flux conditions hold and cellular material has zero axial velocity and radial velocity, respectively. As $z \to \infty$ along the duct, the concentration of tumor cells tends to zero and the nutrient concentration takes some constant value $c = c_I$. On the rigid wall, $r = 1$ the nutrient concentration is also constant, the radial velocity is zero and the axial velocity satisfies a slip condition so that the shear stress is equal to product of the coefficient of slip $\varphi$ and tangential velocity. The coefficient of slip provides a measure of how much the cells adhere to the wall of the duct, so when $\varphi = 0$ the tumor surface is flat and the movement of the cells one-dimensional in $z$.

***Non-dimensionalization of variables:***

Denoting dimensionless variables by carets ($\wedge$) and taking the rate of cell proliferation to set the timescale, we introduce the following rescaling.

$$t = \frac{\hat{t}}{A}, \qquad c = c_I\hat{c},\ n = \hat{n},\ r = \hat{r},$$

$$p = p_I\hat{p},\ z = \hat{z},\ u = A\hat{u} \text{ and } v = A\hat{v}$$

In terms of new variables, the system (1)-(6) takes the following dimensionless forms:

$$\frac{\partial \hat{n}}{\partial t} + \nabla.(\hat{n}\hat{v}) = \hat{\lambda}\hat{n}(1-\frac{\hat{n}}{\hat{k}}) - \hat{\delta}\hat{n} + \hat{D}_n\hat{\nabla}^2\hat{n} \tag{11}$$

$$\nabla\hat{v} = \hat{\lambda}\hat{n}(1-\frac{\hat{n}}{\hat{k}}) \tag{12}$$

$$\hat{\nabla}\hat{p} = \hat{\mu}(\hat{\nabla}^2 + \frac{1}{3}\hat{\nabla}(\hat{\nabla}\hat{v})) \tag{13}$$

$$\nabla^2\hat{c} = \hat{\phi}\hat{\lambda}\hat{n}(1-\frac{\hat{n}}{\hat{k}}) \tag{14}$$

We have used quasi-steady form in the equation (14) for the nutrient concentration as we find dimensionless form that the left hand side of equation (4) is negligible in comparison to right hand side. Concerns the research work of *Frank et. al. (2003)*, this kind of condition implies that diffusion, rather than convection is the dominant mechanism for the redistribution of nutrient within the tumor. The non-dimensional parameters are

$$\hat{\lambda} = c, \qquad \hat{\delta} = \hat{B}(1-\sigma c),\ \hat{B} = \frac{B}{A}\ \ \hat{D}_n = \frac{D_n}{A}$$

$$\hat{\phi} = \frac{\phi A}{D}\ \ \hat{\mu} = \frac{\mu A}{p_I}\ \ \hat{\varphi} = \frac{\varphi A}{p_I}\ \ \hat{k} = k(c)$$

The boundary conditions for the dimensionless system are given

$$\begin{aligned}
&\text{on } \hat{z}=0 && \frac{\partial\hat{n}}{\partial\hat{z}}=0,\ \frac{\partial\hat{p}}{\partial\hat{z}}=0,\ \frac{\partial\hat{u}}{\partial\hat{z}}=0,\ \hat{v}=0,\ \frac{\partial\hat{c}}{\partial\hat{z}}=0,\\
&\text{as } \hat{z}\to\infty && \hat{n}=0,\ \hat{u}=0,\ \frac{\partial\hat{v}}{\partial\hat{z}}=0,\ \frac{\partial\hat{n}}{\partial\hat{z}}=0\ \hat{c}=1,\\
&\text{on } \hat{r}=0 && \frac{\partial\hat{n}}{\partial\hat{r}}=0,\ \frac{\partial\hat{p}}{\partial\hat{r}}=0,\ \hat{u}=0,\ \frac{\partial\hat{v}}{\partial\hat{r}}=0,\ \frac{\partial\hat{c}}{\partial\hat{r}}=0\\
&\text{as } \hat{r}=1 && \frac{\partial\hat{n}}{\partial\hat{r}}=0,\ \hat{u}=0,\ \hat{\mu}\frac{\partial\hat{v}}{\partial\hat{r}}=-\hat{\varphi}\hat{v},\ \hat{c}=1
\end{aligned} \tag{16}$$

Generally, the viscosity is variant this model comprises system of five coupled equations (11)-(14). However, if we assume that the viscosity has the same value inside and outside of the tumor, the pressure, velocity and nutrient concentration can be found in terms of the tumor cell concentration only and hence the system simplifies significantly.

## Numerical Results:

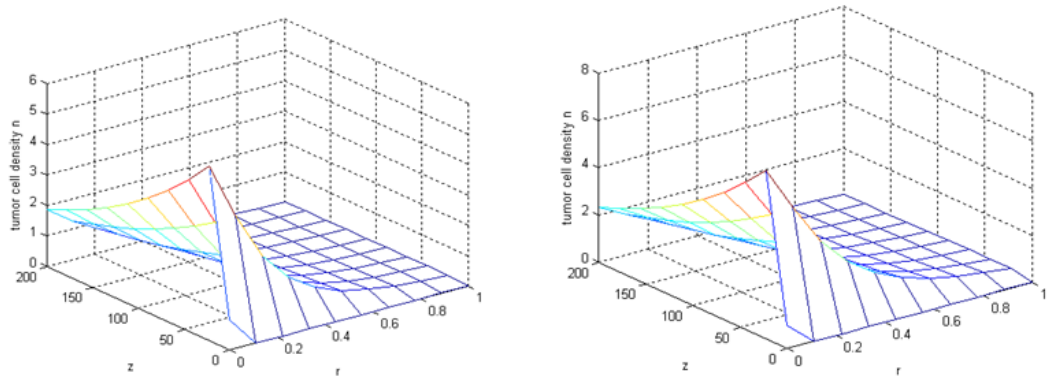
The numerical procedure used to approximate the system partial differential equations (11)-(16), being approximated using the MATLAB 6.0, to solve the partial differential

equation. All the simulation describes in this section use the same parameters values adopted in the simulation described in the section (2.3.2) of *Frank et. al. (2003)*. We take the viscosity inside and outside the tumor to be uniform and consider the tumor surface flat whereas for larger values of coefficient of the slip $\varphi = 5$.

$$B = 1, \qquad \sigma = 0.9,\ \phi = 0.1,\ \mu = 1,\ \varphi = 5,\ D_n = 10^{-5}$$

Figure represents the evolution of tumor cell concentration with the radial *(r =0 to 1)* and the axial *(z =0 to 200)* directions. We see that in the figure *1* (a) the tumor cell concentration is a *1.9* (approx.) when cell carrying capacity of nutrient is less than the tumor cell concentration. In the figure *1* (b) the tumor cell concentration is a *2.1* (approx.) when cell carrying capacity of nutrient is greater than the tumor cell concentration. In these figures, we shows that the growth of tumor cell concentration is depend on the nutrient because tumor cell proliferation rate and death rate are the functions of nutrient.

Figure shows the evolution of nutrient concentration in solid tumor with the radial *(r =0 to 1)* and the axial *(z =0 to 200)* directions. We see that in the figure *2* (a) the nutrient concentration is 1 (approx.) initially and it's going down up to *0.1* (approx.), when cell carrying capacity of nutrient is very low in the tumor cell concentration. In the figure *2* (b) the nutrient concentrations is a *1* (approx.) initially and it's going down up to *12.5* (approx.), when cell carrying capacity of nutrient is very high in the tumor cell concentration. In these figures we show the nutrient concentration is high in the tumor cell concentration, when the cell carrying capacity of nutrient is high.




(a) (b)

**Fig1.** Evolution of the tumor cell concentration (a) when cell carrying capacity of nutrient is very low (b) when cell carrying capacity of nutrient is very high

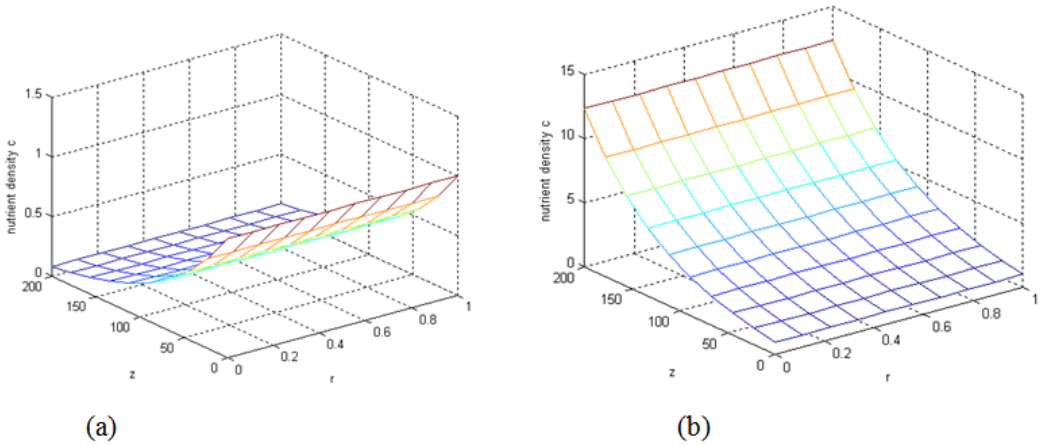



**Fig2.** Evolution of the nutrient concentration (a) when cell carrying capacity of nutrient is very low (b) when cell carrying capacity of nutrient is very high

## Discussion:

The mathematical modeling of *in vitro* nutrient testing studies are limited but remarkably worthwhile, since results can be derived by a relatively simple extension of an existing model. In this work we have accordingly work on an earlier model of *Franks et. al. (2003)* to investigate the effect of a nutrient on the tumor cell concentration. In particular we studied the cell carrying capacity of the nutrient in solid tumor. Good qualitative agreement with experiments has been obtained in terms of the dependence of cell survival on the nutrient in the tumor. The numerical simulations mainly involved the study of the cell carrying capacity of nutrient in solid tumor. The simulation emphasize that cell-carrying capacity of nutrient is a crucial factor in the determining tumor growth effectiveness.

In this work, we have introduced cell carrying of nutrient in the tumor cell because the solid tumor growth depends on nutrient it work as a fuel for the growth of tumor. We have observed for the different values of the cell carrying capacity of nutrient in the tumor cell. The figure 2 shows if the cell carrying capacity of nutrient is high then nutrient concentration in the tumor cell is high. In the figure 1 we see that if nutrient concentration is high in tumor cell then tumor cell concentration is high. The numerical simulation mainly involved the study of the nutrient concentration in the tumor cell in different variations of cell carrying capacity of nutrient in the tumor. This is result is in the support of the work of ***Jain (2005).*** If we can apply the anti-angiogenic therapy of the nutrient vascularization of the solid tumor then growth of the solid tumor will remove.

Perhaps the most important feature missing in the current model is a mechanism for delay in the recovery of hypoxic cells to a proliferating on renewal of an adequate nutrient supply. In this model, we are describing the growth of an avascular tumor in rigid cylindrical duct. We observed that for tumor cell concentration with the cell carrying capacity of nutrient in tumor, suggesting that this may be a mechanism that

causes the duct wall to deform. Further considerations, such as the role of blood and mathematical models, will also form the focus of future studies.

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