A model for temporal heterogeneities of tumor blood flow

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Abstract

Tumor blood flow (TBF) plays a fundamental role in tumor growth and treatment, and is characterized by spatial and temporal heterogeneities. Here we show that the interstitial fluid pressure (IFP), which is higher in tumoral tissue than in normal tissue, coupled with the tumor microvascular pressure (MVP) and the higher permeability of tumoral vessels, can explain the sustained oscillatory behavior of TBF, observed in vivo.

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Introduction

Tumor blood flow (TBF) is characterized by spatial and temporal heterogeneities, and can significantly affect tumor growth, metastasis, and therapy (Eskey et al., 1992; Jain, 1988). Moreover, delivery of therapeutic agents and oxygen, a radiation-sensitizer, strongly depends upon TBF distribution. However, despite the important role of TBF in tumor physiopathology and treatment, to date there are no complete explanations for the observed TBF anomalies.

Tumor blood flow, in fact, presents several anomalies if compared to blood flow in a normal tissue. First of all, TBF is characterized by a spatial heterogeneity, i.e., blood is diverted away from the center of the tumor toward a more peripheral path, leaving a scarcely perfused area in the middle of the tumor. This area is thus hypoxic or anoxic, but is also an area where drug delivery is particularly ineffective (Jain, 1994).

Partly responsible of this phenomenon is the high interstitial fluid pressure (IFP), which is a general characteristic of solid tumors. Tumor vessels are leakier than normal vessels due to their abnormal structure, and this in turn leads to high fluid efflux into the body of the tumor and results in interstitial hypertension. This mechanism is also responsible for the observed fluid leakage from the tumor surface (Jain, 1994).

The TBF is also characterized by a temporal heterogeneity. In fact, at a fixed location, the blood flow is not uniform with time, showing an intermittent flow rate and even periodic inversions of the direction of flow (Chaplin and Hill, 1995; Chaplin et al., 1987; Eskey et al., 1992; Intaglietta et al., 1977) (see Fig. 1).

The influence of blood vessel porosity on TBF has already been investigated in Baish et al. (1997) and Netti et al. (1996). In these papers the TBF spatial heterogeneity was explained considering blood flow through a single representative permeable capillary and through a network of permeable capillaries, respectively. In both of these papers, though, the analysis was aimed at finding the steady state (i.e., time independent) solutions of the problem, thus only averaged information on the temporal heterogeneity could be gained.

The purpose of this article is to develop a model capable of describing the temporal heterogeneity observed in tumor blood flow, generalizing the problem considered by Netti et al. (1996). The temporal inhomogeneity has been related by Patan et al. (1996) to the phenomenon of intussusception, i.e., the insertion of interstitial tissue columns, called tissue
pillars or posts, into the vascular lumen and the subsequent growth of these columns, resulting in partitioning of the vessel lumen. Although this mechanism surely contributes to the temporal inhomogeneity, the time scales of intussusception are much greater than the time scales of the observed flow oscillations.

Studies similar to the present one have been performed by various researchers (see for example Hayashi et al., 1998; Kamm and Pedley, 1989; Shapiro, 1977) and applied to several physiological cases, e.g., blood flow in veins which are squeezed by contracting skeletal muscles and air flow in the lungs during forced expiration. None of these studies, though, takes into account the permeability of the vessel, which is particularly relevant for tumorous vessels.

Mathematical modeling

A rough scheme of the problem is depicted in Fig. 2. A representative tumor capillary of length $L$ and of thickness $\delta$ is described as having an equivalent rectangular cross-section with constant width $w$ and variable height $2h$, so that it can be studied as a two-dimensional channel.

The collapse of the vessel occurs through a buckling mechanism (Shapiro, 1977), which is shown qualitatively in Fig. 3. As we can see, the central part of the vessel changes its height greatly, but the width remains almost unchanged. Interestingly, even when the vessel is completely collapsed, there are two small apertures at the vessel sides, which allow some amount of fluid to flow through.

Letting the axial coordinate of the capillary be $x$, the arterial pressure and the venous pressure are denoted by $\pi_a$ and $\pi_v$ respectively. Due to the pressure difference, blood will flow inside the capillary with its pressure $\pi = \pi(x,t)$ varying from $\pi_a$ to $\pi_v$. Let $2h_0$ be the initial uniform height of the capillary, which is also kept constant at the entrance and exit sections, $x = 0$ and $x = L$, respectively.
The vessel is surrounded by the body of the tumor. The interstitial fluid is assumed to be at rest and the IFP is assumed to be uniform and constant and will be represented by \( \pi_c \), thus

\[
p = p(x,t) = \pi(x,t) - \pi_c
\]

is the net pressure acting on the section of the capillary located at \( x \) at time \( t \).

Due to the blood flow, the capillary will deform and this deformation will in turn influence the blood flow. The goal of this study is to determine both the blood flow and the motion of the vessel.

The thickness of the capillary wall \( \delta \) is assumed to be constant and small enough so that membrane theory can be used to describe the deformation of the capillary. Indicating by \( T \) the known constant tension in the capillary walls and by

\[
u = u(x,t) = h(x,t) - h_0
\]

the vertical displacement, the governing equation is:

\[
-\frac{T}{w} \delta^2 \frac{\partial^2 u}{\partial x^2} + \Phi(u) - p + c \frac{\partial u}{\partial t}
+ \rho A \frac{\partial^2 u}{\partial t^2} = 0,
\]

where the last two terms account for the effect of drag on the vessel membrane and of the so-called “virtual mass effect,” respectively (for a discussion on the virtual mass effect see, for example, Birkhoff, 1960). In this respect, \( c \) can be viewed as the drag coefficient, \( \rho \) is the density of the interstitial fluid, and \( H_{abs} \) is the virtual mass coefficient. The virtual mass effect occurs when a solid accelerates within a fluid at rest. The function \( \Phi \) is the capillary stiffness function

\[
\Phi = \begin{cases} 
-\frac{E \delta}{h_0} & \text{for } u \geq 0 \\
-K(1 + \left(1 + \frac{u}{h_0}\right)^{1/2}) & \text{for } u < 0
\end{cases}
\]

in which \( E \) is the Young modulus of the capillary and \( K \) is the bending stiffness. This form for the stiffness function has been introduced by Shapiro (1977), who confirmed its validity through experiments. This relationship is often referred to as “tube law” in the literature and discriminates the cases in which the capillary is being inflated by the internal blood flow or buckles under the external IFP.

For this analysis, we will assume the flow to be one dimensional. We will, therefore, neglect separation effects. We will also treat blood as a Newtonian fluid. Thus, denoting with \( Q = Q(x,t) \) the blood flow rate, we will have

\[
Q = -\frac{2}{3} \frac{w h^3}{\mu} \frac{\partial p}{\partial x}
\]

where \( \mu \) is the viscosity of blood. The equation of conservation of mass for the blood flow then reads

\[
\frac{\partial Q}{\partial x} + V_p + V_w = 0,
\]

where \( V_p \) and \( V_w \) denote the velocity of the fluid perfusing through the porous wall and the velocity of the capillary wall, respectively. The perfusion velocity can be assumed to be given by Darcy’s law as a first approximation:

\[
V_p = -2k \frac{\pi_c - \pi}{\mu \delta},
\]

where \( k \) is the capillary permeability, while the vessel wall velocity is simply given by

\[
V_w = \frac{\partial u}{\partial t}
\]

so that, substituting Eqs. (5), (7), and (8) into (6) we obtain

\[
-\frac{\partial}{\partial x} \left( (h_0 + u) \frac{\partial p}{\partial x} \right) + 3 \frac{k}{w \delta} p + 3 \frac{\mu}{w} \frac{\partial u}{\partial t} = 0.
\]

Equations (3) and (9) constitute a system of coupled nonlinear partial differential equations in the unknowns \( u \) and \( p \):

\[
\begin{align*}
-\frac{T}{w} \delta^2 \frac{\partial^2 u}{\partial x^2} + \Phi(u) - p + c \frac{\partial u}{\partial t}
+ \rho A \frac{\partial^2 u}{\partial t^2} &= 0, \\
-\frac{\partial}{\partial x} \left( (h_0 + u) \frac{\partial p}{\partial x} \right) + 3 \frac{k}{w \delta} p + 3 \frac{\mu}{w} \frac{\partial u}{\partial t} &= 0.
\end{align*}
\]

The proper initial and boundary conditions for the present problem are, respectively:

\[
\begin{align*}
u(0,t) &= 0; & \nu(L,t) &= 0; \\
p(0,t) &= \pi_a - \pi_i; & p(L,t) &= \pi_c - \pi_i
\end{align*}
\]

and

\[
\begin{align*}
u(x,0) &= 0; & \frac{\partial u}{\partial t}(x,0) &= 0; \\
p(x,0) &= \pi_a - \pi_i = \frac{\pi_a - \pi_c}{x} x.
\end{align*}
\]

The system (10) subject to (11) and (12) has been solved with the finite element method.

**Results and discussion**

The results given by the model described in the previous section are shown in Figs. 4 and 5. Figure 4 shows a plot of the shape of the capillary at different times and the corresponding blood pressure distribution. Notice how the capillary deforms showing a diffused stenosis toward the exit section of the capillary, while, at the same time, the pressure increases as the capillary collapses. This pressure increase,
working against the IFP, causes the capillary to open. Once blood starts to flow again in the now reopened capillary, the pressure tends now to decrease, restarting the cycle.

The outcome of this mechanism is evident in Fig. 5, where the arterial flow rate (at the entrance section) $Q_a$ and the venous flow rate (at the exit section) $Q_v$ are plotted.
against time. As we can see, both $Q_a$ and $Q_v$ show a self-sustained periodic oscillatory behavior, with rather irregular amplitudes. Notice that the exit flow rate $Q_v$ is greater than the entrance flow rate $Q_a$: this is mainly due to the negative transmural pressure that pushes fluid into the capillary through the capillary walls. While this can be true for the representative capillary, the same cannot be said for the tumor as a whole, where due to the fluid leakage through the tumor surface, we have to expect that the blood flow exiting the tumor will be actually less than the incoming blood flow (Jain, 1988).

The analysis performed shows that the fluid dynamics of tumor circulation does not necessarily lead to an equilibrium between the average MVP inside the leaky tumor vessels and the IFP outside the vessel, nor to a chronic collapse of the vessel itself. Rather, it is possible in presence of moderate leakiness, that the system evolves toward a sustained oscillatory response, both in the MVP and the blood flow. This temporal heterogeneity is observed in tumors. Tumor blood flow can hence have an unsteady character, that is driven simply by the difference between the arterial and the venous pressure and the closeness of the values of the average MVP and the IFP. This process will not appreciably disturb the macroscopic distribution of the IFP, due to the high ratio of hydraulic permeability between the extracellular matrix and the vessel wall (Boucher et al., 1990).

Even though the model predicts a self-sustained oscillatory behavior, the oscillations have a frequency which is much higher than the frequency observed in vivo, as we can see from Fig. 5. Also, the model is not able to predict the periodic inversion of the direction of the flow, which is observed in vivo. The reasons for this behavior stem from the simplicity of the model. For instance, only one representative straight blood vessel was considered in this analysis; in the case of more vessels, or better, in the case of a vessel network (see for instance Baish et al., 1997), we can think that the interaction of more vessels at oscillating pressure increases the inertial component of the model and hence should yield a lower oscillation frequency and could also lead to the periodic inversions of the direction of the blood flow in some of the network vessels. Vessels growth was also neglected in the model. The inclusion of growth phenomena, such as intussusception (Patan et al., 1996), could contribute to decreasing the characteristic times of the oscillatory behavior.

References