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Phenomenological model of interstitial fluid pressure in a solid tumor

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Abstract

Tumor interstitial fluid pressure (TIFP) has the potential to predict tumor response to nonsurgical cancer treatments, including radiation therapy. At present the only quantitative measures available are of limited use, since they are invasive and yield only point measurements. We present the mathematical framework for a quantitative, noninvasive measure of TIFP. The model describes the distribution of interstitial fluid pressure in three distinct tumor regions: vascularized tumor rim, central tumor region, and normal tissue. A relationship between the TIFP and the fluid flow velocity at the periphery of a tumor is presented. This model suggests that a measure of fluid flow rate from a tumor into normal tissue reflects TIFP. We demonstrate that the acquisition of serial images of a tumor after the injection of a contrast agent can provide a noninvasive and potentially quantitative measure of TIFP.

I. INTRODUCTION

Tumor interstitial fluid pressure (TIFP) is an important parameter in tumor prognosis, tumor treatment, drug delivery, tumor therapy, and tumor metastasis [1–6]. Rofstad *et al.* [4] showed that radiation resistance may be associated with high TIFP. Ferretti *et al.* [1] observed the relationship between TIFP and the response to chemotherapy. It is established that TIFP originates mainly in fluid accumulation because of the increase in the capillary permeability and impaired lymphatic drainage in the tumor area. The interstitial fluid pressure (IFP) is elevated in tumors due to the abnormal structure and function of blood and lymphatic vessels [7]. A high IFP results from leaky vessels in tumors that lack permselectivity and are unable to sustain the hydrostatic and oncotic pressure gradients across the vessel wall. Baxter and Jain [8] presented a model to express the transportation of fluid and the distribution of tumor pressure based on Starling's law [8], which is adopted to explain the effect of capillary-capillary interaction, and Darcy's law [8], which reflects the porous tissue condition. Boucher *et al.* [9] measured TIFP distribution in tissue-isolated and subcutaneous tumors to support this model. Jain *et al.* [7] applied this model to study the “effect of vascular normalization by antiangiogenic therapy on interstitial hypertension, peritumor edema, and lymphatic metastasis.” Experiments and theoretical analysis [7–12] report that IFP is uniform throughout the central area of the tumor. There is a steep gradient of IFP in the peripheral area. Baxter and Jain [8] studied two cases: (1) an isolated tumor, where the enhanced TIFP is tumor limited, and (2) an embedded tumor. In the special case of an isolated tumor, the TIFP at the periphery rapidly decreases to zero (atmospheric level) or the pressure of the environment. In the more common situation of an embedded tumor (enclosed by normal tissue), the raised TIFP extends beyond the tumor radius into the

normal tissues before equilibrating to zero (relative to atmosphere), or the pressure of the environment. The schematic is shown in Fig. 1. Here, R represents the radius of a tumor, p_0 is the tumor IFP (TIFP) in the central area, and p_∞ is the pressure of the environment (the IFP of normal tissue).

The factors that lead to an elevated TIFP are known. Although it is recruited from normal vasculature by tumor proangiogenic factors, tumor vasculature is abnormal. Tumor microvasculature generally lacks pericytes, often associated with a damaged basal lamina. Its morphology is usually tortuous, dilated, and saccular. Tumor microvessels are longer, larger in diameter, and denser than normal microvessels. Importantly, tumor microvessels are generally much more permeable to blood proteins, with all of the mechanisms for transvascular leakage of blood proteins being in evidence, including enlarged fenestrae at the endothelial junctions, and increased vesicular transport. A leakage of proteins, with its corollary decrease in osmotic pressure, an increased blood supply with its potential for increased vascular pressure, and the general lack of a competent lymphatic system all have been thought to contribute to an increased TIFP. Microvascular pressure is the main driving force of IFP [13] and proliferating cancer cells cause interstitial hypertension and the collapse of tumor vessels [14]. These effects lead to flow that, despite the proliferation of blood vessels, is limited by the TIFP via the Starling effect. As the tumor grows, these factors limit the flow of metabolites to the tumor center, resulting eventually in a necrotic core surrounded by a perfused and growing rim with an elevated interstitial pressure that drops sharply past the boundary of the tumor. However, in the boundary region, the increased interstitial fluid leads to a local ischemia, and a consequent release of vascular endothelial growth factor (VEGF), recruitment of additional blood supply to the tumor, increased vascular permeability, and so on.

The foregoing demonstrates that the distribution and evolution of tumor-associated vasculature influence TIFP distribution and evolution directly and vitally. Extending the single-tube model of Pozrikidis and Farrow [15], Pozrikidis [16] developed a network model that assumes the tumor vasculature is like a branching tree consisting of a cascade of straight bifurcating capillary segments. However, when this model is applied to the spherical symmetric case, it is incompatible with Baxter and Jain's model [8] which considered more factors. Additionally, the solution of the Pozrikidis model for TIFP may not possess the properties shown in Figs. 1 and 3. Baish and Jain [17] attributed the chaotic, poorly regulated growth of a tumor to "fractal" geometry. Chaplain *et al.* [18] modeled the angiogenesis of a solid tumor. Dreher *et al.* [19] investigated tumor vascular permeability, accumulation, and penetration of macromolecular drug carriers. Karshafian *et al.* [20] modeled transit time kinetics in ordered and disordered vascular trees using simple rules of branching and fractal geometry in two dimensions. Pindera *et al.* [21] simulated the angiogenesis using a convected element method. Since angiogenesis of tumor is time dependent, the TIFP should be related to the stages of tumor growth. However, no existing TIFP model considered time dependence. Both Pozrikidis and Karshafian *et al.* view the vasculature system as a treelike branching structure. Normal tissues have an ordered treelike branching pattern, but the tumor vascular network has a chaotic and random nature as shown in Fig. 2 [16,20].

Since the density (denseness) of vascular networks from the central region to the peripheral area is completely different, the activity of cells may be different in various locations. For convenience, we model a tumor as a spherical structure. Later, we will explain why it is not necessarily limited to a spherical case. Considering the difference of vascular network distribution and cell activity in various regions, especially the change of TIFP, we divide a tumor into three regions: a necrotic central core where most cells are dead and there are no small functional vessels, a vascularized region which is composed of some quiescent tumor cells with a few abnormal vessels and a peripheral well vascularized rim with active tumor

cells, as well as an intermediary region. We will describe these three regions in detail later. The schematic is shown in Fig. 3.

Baxter and Jain's model [8] explains the spatial distribution of TIFP. Boucher *et al.* [9] measured the spatial distribution of TIFP and the results in some cases seem not to be exactly the same as they predicted. The experimental results for ovarian tissue-isolated (Fig. 6) and subcutaneously grown (Fig. 3(b)) mammary adenocarcinoma R3230AC tumors in Ref. [9] were reported to indicate that the TIFP reached a maximum value at a depth of less than 1 mm from the tumor surface, and then the IFP stayed steady and uniform in the central region of the tumor. The best fit through the data suggests otherwise as shown in Fig. 4. Figure 3(b) of Ref. [9] is typical and we introduce it here in Fig. 4. We draw the best fit curve, which is shown in blue (upper curve) on Fig. 4, for the black dot data points since they are the most completed ones in the entire experimental region. Similarly, we can draw the best fit curves for other data. Considering the clear nature of the graph, we do not depict them in Fig. 4. We also draw the best fit curve for all of the data and show it in red (lower curve). Obviously, TIFP in the central area is steady and uniform with a smaller value relative to the maximum at ~1 mm below the surface of the tumor.

II. THE MODEL

A simple model is proposed to explore the relationship between tumor pressure and fluid flow. Tumor regions are divided into three areas: (1) inside the blood vessel area—necrotic core ($r < r_n$); (2) intermediary region ($r > R$); (3) the well perfused periphery ($r_n < r < R$). It is assumed that there are no functional lymphatics within the tumor but some enlarged lymphatics exist near the periphery. In the necrotic core, there are some dead cells but almost no functional exchange vessels. The existence of so-called super capillaries in tumors is inefficient at best with respect to nutritional delivery and waste removal. Therefore, there is no source or drain in the necrotic core region. In the blood vessel area, there is fluid source but not an efficient drainage system. We assume that the drain exists near the edge of the tumor. Outside the tumor (in the normal tissue), there are drains due to the functional lymphatics in the normal tissue. In the well vascularized area, blood vessels or capillaries are very abundant (much more plentiful than that in the normal tissue). They form a chaotic vascular network. This network may maintain a pressure distribution in the tumor.

Usually, tumor tissues can be divided into three subcompartments: vascular, interstitial, and cellular. The interstitial space is mainly composed of collagens and elastic fiber networks [22]. It can be divided into two compartments: the interstitial fluid and the structural molecules of the interstitial or the extracellular matrix [23]. The fluid that leaks out from blood vessels is inevitably met by resistance from the surroundings.

Let us now show how the pressure forms in detail. According to Starling's law, the net fluid flux J_s (m^3/s) across the wall of a blood vessel is expressed as [8,10]

$$J_s = LA [p_v - p - \sigma(\pi_v - \pi)], \quad (1)$$

where L is the hydraulic conductivity of the blood vessel ($\text{m}^2 \text{ s/kg}$), A the surface area of the blood vessel (m^2), p_v the vascular fluid pressure (the pressure in the blood vessel), p represents the tumor IFP, σ the osmotic reflection coefficient, π_v osmotic pressure of the plasma, and π represents the osmotic pressure of interstitial fluid. In a tumor, L and A are much greater than that in the normal tissue. Equation (1) describes the source of TIFP. The detailed distribution of TIFP depends on the drain (sink) and the outflow flux condition. We discuss them respectively.

A. The IFP of vascularized spherical shell

In our model, blood vessels are mainly distributed in the periphery region. There must be a fluid resistance or pressure barrier which makes the leaked fluid contribute to the elevated pressure in the central region. At first, let us imagine that the vascularized region is isolated. Suppose that there is no necrotic core in the tumor's central area (only a vascularized spherical shell). If both outer and inner spherical surfaces of the vascularized region are closed and no fluid can flow out, then the IFP at steady state is $p_m = p_V - \sigma(\pi_V - \pi)$. When the TIFP reaches this value, no fluid flows out from blood vessels. When there are openings on each spherical surface, the pressure will be modified from the two surfaces to the central area of the vascularized region. With the openings increasing, the pressure decreases, as shown in Fig. 5. Therefore, it forms a pressure barrier in the leaking (vascularized) region. In the maximum pressure region, the fluid stays still [velocity $u(r) = 0$ because there is no pressure difference]. The maximum pressure region becomes narrower when the openings become larger. The flow rate on these two surfaces correspondingly becomes larger. Gradually, the maximum pressure region is narrowed down to a point when the openings widen to a critical value. If the openings continue to increase, then the highest pressure p_0 becomes smaller than p_m . The bigger the openings are, the smaller the p_0 . The maximum value of IFP at steady state is between 0 and p_m ($0 < p_0 \leq p_m$). Considering the fact that more functional blood vessels are distributed in the periphery region, we draw the highest pressure point closer to the tumor periphery. The exact value p_0 depends on the conditions, such as the pressure p_V inside the blood vessels, the lymphatic drainage ability and fluid flow rate from the openings. The pressure at r_n depends on the pressure in the necrotic core p_n , and the pressure at R depends on the conditions of the environment. We will discuss them in detail later. Though the p_0 is higher when there is more fluid accumulated, it is noteworthy that this pressure is not caused by gravity of the collected fluid. In fact, it is from the resistance of the collagen and elastic fiber network, as well as their interactions. Though we focus on the case of a tumor with a necrotic core, the results may also be applied to the case of nonnecrotic core, $r_n = 0$.

B. TIFP in the central area

In our model, there is a pressure barrier p_0 in the vascularized region as shown in Fig. 5. At the beginning, the pressure in the necrotic core area is smaller than the pressure p_0 . The leaked fluid flows to this area. Since there is no drain (sink) (lymphatics), more and more fluid accumulates in this area. The pressure in this region gradually increases. It reaches p_0 after the fluid fills up this area. Afterwards, no more fluid can flow into it. It maintains a constant pressure p_0 —the pressure is as high as that of the pressure barrier. Then, all leaked fluids flow to the outside. We assume that the radius that corresponds to the pressure barrier p_0 is r_0 and fluid flows into the necrotic core with velocity u_{in} across the core radius r_n . Figure 6 shows the structure schematic.

We may take the vascularized region as a porous medium and use Darcy's law to describe the flow in this region since the cells are alive. However, we may not take the necrotic core as a porous media since there are dead cells. We take it as a uniform homogeneity. If we ignore the gravity, we have the relation

$$u(r) = -K \frac{dp(r)}{dr}, \quad (2)$$

where K is the hydraulic conductivity of the interstitium. The pressure in the necrotic core should be the same as that at the surface $r = r_n$ where the fluid flows in. The more fluid accumulates in this region, the higher the pressure will be. Correspondingly, the pressure difference between $p_0(r_0)$ and $p(r_n)$ becomes smaller and smaller. Therefore, the fluid

velocity across the surface ($r = r_n$) of the necrotic core will also be smaller. When $p(r_n) = p_0$, the pressure difference is zero so no more fluid flows in. Then the whole region inside $r = r_0$ reaches the pressure p_0 . In fact, at $r = r_0$, pressure p_0 is at the maximum, so $dp/dr|_{r_0} = 0$, $u(r_0) = 0$. This is consistent with our view that we discussed previously. The increased pressure in the necrotic core ($r < r_n$) should be proportional to the amount of the fluid inflow, so

$$p_{in}(t) - p_{in}(0) = \gamma 4\pi r_n^2 \int_0^t u_{in}(t) dt. \quad (3)$$

Here γ is a coefficient of proportionality. Its unit is mm Hg/cm³. Equation (3) can be rewritten as

$$\frac{dp_{in}(t)}{dt} = \gamma 4\pi r_n^2 u_{in}(t). \quad (3')$$

For Eq. (2), when $r_0 - r_n$ is small (blood vessels are distributed in a narrow spherical shell), K can be taken as a constant and the pressure varies with radius linearly. Thus,

$$\bar{u} = \frac{u(r_0) + u(r_n)}{2} = \frac{u_{in}(t)}{2} = K \frac{p_0 - p_{in}(t)}{r_0 - r_n}. \quad (4)$$

Combining Eq. (3') with Eq. (4), we have

$$p_{in}(t) = p_0 - [p_0 - p_{in}(0)] e^{-\alpha t} \quad (r < r_n), \quad (5)$$

where

$$\alpha = 8\pi\gamma K \frac{r_n^2}{r_0 - r_n}.$$

Equation (5) shows that the IFP $p_{in}(t)$ in the necrotic core may be close to p_0 asymptotically. The actual situation depends on the initial pressure $p_{in}(0)$ of this region and time constant α . At a steady state, the pressure is p_0 . The pressure p_0 in the leaky area is the maximum. This corresponds to the experiment results which are given in Ref. [9]. Letting $p_0 = 15$ mm Hg, we can obtain the $p_{in}(t) - p_{in}(0) \sim t$ graph for different values of factor α as shown in Fig. 7, which includes the result given in Ref. [10]. Equation (5) may also be applied to the contrast agent if one is used.

The region inside r_0 is a fluid reservoir. We assume the fluid is incompressible. Before the pressure reaches p_0 in this region, some of the fluid flows into this region until the pressure is balanced (at a steady state). Then all the fluids flow outside. If more fluid flows outside, the flow rate at the tumor's periphery will increase. This causes the fluid velocity to increase. Correspondingly, p_0 may be elevated. This causes TIFP in the entire tumor area to increase and then Starling's law adjusts the leaky source until a new balance (steady state) is reached. Then $r_0 = r_n$ before p_0 reaches p_m since there is no fluid source inside r_n . Whether p_0 can reach p_m or not depends on the drainage ability of the tumor. Once p_0 reaches p_m , the radius r_0 is between r_n and R ($r_n < r_0 < R$), only the blood vessels beyond r_0 can leak out fluid. All blood vessels within r_0 may not leak fluid due to the elevated IFP p since they all satisfy the equation $J_s(r \leq r_0) = LA(r \leq r_0)(p_m - p) = 0$. Thus, at steady state, the total fluid flux leaking from the blood vessels should be the same (balanced) as the flow rate of outflow fluid from the tumor. The weaker the drainage ability of the tumor periphery, the bigger the

r_0 is. The fluid source and drain can become balanced this way. The schematic of the IFP in the central area ($r < r_0$) with different drainage abilities at tumor periphery is shown in Fig. 8.

C. TIFP in the periphery

With the pressure in the necrotic core becoming higher and higher, less and less fluid flows in, and more and more fluid flows out. When the pressure in the necrotic core reaches the pressure barrier value p_0 , no fluid flows inward; instead, it flows outward. During this process, if the lymphatics at the periphery are capable of draining the fluid away in time, the pressure $p(R)$ at the tumor periphery may remain zero or at the pressure of the environment; otherwise, it may cause $p(R)$ to increase. The p_0 is likely enhanced. Note that once p_0 is changed, Starling's law will adjust the fluid flux to make the fluid source and sink (drain) be balanced. Then a new steady state is formed. The fluid flux can still be described by Eq. (2). When $R - r_0$ is small, we can use an approximate equation, which is similar to Eq. (4), to express

$$u(R) = 2K \frac{p_0 - p(R)}{R - r_0} \quad \text{or} \quad p(R) = p_0 - \frac{(R - r_0) u(R)}{2K}. \quad (6)$$

Equation (6) connects p_0 , $p(R)$, and $u(R)$ together. Therefore, we can estimate the value of p_0 by measuring $p(R)$ and $u(R)$. Velocity $u(R)$ has been measured in the past invasively. There is potential to measure $u(R)$ noninvasively using any contrast enhanced imaging modality including computed tomography (CT), magnetic resonance imaging (MRI), or ultrasound (US) [24,25]. MRI has particularly high potential because it has the best spatial resolution, however, it does suffer from poor temporal resolution and the signal intensity is not linearly proportional to the amount of contrast agent in tissue.

If $u(R)$ increases, the difference of $p_0 - p(R)$ also increases. If $p(R) = 0$, $u(R) = 2Kp_0/(R - r_0)$. Therefore, if $u(R) \geq 2Kp_0/(R - r_0)$, $p(R) = 0$; if $u(R) < 2Kp_0/(R - r_0)$, $p(R) > 0$. We call it the critical fluid velocity: $u_c(R) = 2Kp_0/(R - r_0)$. For instance, let $p_0 = 15$ mm Hg, $K = 4.13 \times 10^{-8}$ cm²/mm Hg s [8,12], $r_0 = 0.9$ cm, $R = 1.0$ cm. We have $u_c(R) = 0.124$ μ m/s or 0.5 mm/h which corresponds to the results for isolated tumors [8]. Butler *et al.* [26] measured the flow rate of some solid tumors. Based on the data, Baxter and Jain [8] estimated that the fluid velocity at the periphery of isolated tumors is 0.13–0.2 μ m/s. For Gd-DTPA, a widely used MR contrast agent, we would expect fluid flow in tumor on the order of millimeters per second. For iodinated contrast agents widely used in CT we expect fluid flow in tumors to be on the same order depending on to what the iodide is bound.

According to this discussion, we may conclude that the TIFP $p(R)$ at the periphery is zero if the lymphatic drainage's ability is large enough to ensure the maximum drainage Q_m is greater than the critical flow rate Q_c : $Q_m \geq Q_c = 4\pi R^2 u_c(R) = 8K\pi R^2 p_0 / (R - r_0)$. For a tumor with $R = 1.0$ cm, $Q_c = 1.56 \times 10^{-4}$ ml/s. Therefore, if $Q_m < Q_c$, the drainage ability is small so that TIFP at the periphery will be high. When the TIFP at the periphery is too high, the tumor must find a way to release the pressure by creating channels that connect with normal tissue. The cost is that it may break the normal structure at the interface or make it complicated. Q_c may be a factor for determining whether it is an isolated or embedded tumor. In this case, the fluid flux Q at a tumor edge meets $Q_m < Q = 4\pi R^2 u(R) < Q_c$. Some fluid crosses over the edge ($r = R$) and flows into the normal tissue. Lymphatics are plentiful and functional in normal tissue, so some fluid is drained away. Similar to Starling's law, the net fluid flux drained from the lymphatics may be expressed as [8] $J_L = L_L A_L (r_m)(p - p_L)$. L_L is the hydraulic conductivity of lymphatics, p_L is the pressure in lymphatics, and r_m is the maximum radius that the fluid from the tumor can spread. It corresponds to the radius from

which the pressure becomes the same as the pressure of the normal tissue. When balanced, the pressure p_L in lymphatics should be the same as the environment p_∞ . $A_L(r_m)$ is the total surface area of the lymphatics within radius r_m . At steady state, the radius is a fixed value; therefore, the $A_L(r_m)$ is fixed. Since no fluid collects outside the tumor, the total fluid flux across the tumor edge should be conserved. Thus, at the surface of radius r , the velocity $u(r)$ satisfies

$$Q = 4\pi R^2 u(R) = Q_m + 4\pi r^2 u(r) + L_L A_L(r_m)(p - p_L) \quad (R < r \leq r_m). \quad (7)$$

We also take this area as a porous medium and Eq. (2) can be used. Combining Eqs. (2) and (7), we have

$$p(r) = p_L + \frac{Q - Q_m}{L_L A_L(r_m)} - \left[\frac{Q - Q_m}{L_L A_L(r_m)} - p(R) + p_L \right] \times e^{\frac{L_L A_L(r_m)}{4\pi k R}} \left(1 - \frac{R}{r} \right), \quad (R < r \leq r_m). \quad (8)$$

Here, $p(R)$ and $u(R)$ are related by Eq. (6). Usually, p_0 is determined by the distribution of the capillaries and their permeability. Therefore, if we know the velocity or the pressure at the tumor edge $r = R$, we may find the pressure distribution in the interface area between tumor and normal tissue. Consequently, any noninvasive measure of the fluid flow velocity may be able to provide a measure of the TIFP.

Now let us determine the TIFP distribution in region $r_0 < r < R$ more accurately. We may not obtain the exact pressure distribution in this region since we do not know the pressure gradient. Also, the fluid flux is not conserved. However, we know values at surfaces $r = r_0$ and $r = R$ and their tangent values. We can use the continuity condition to get the TIFP function, which can reflect the main features of the real TIFP of a tumor. Since this region is narrow, this approach should be good enough for describing real situations.

1. The drainage ability Q_m is greater than the critical flow rate Q_c : $Q_m \geq Q_c$. In this condition, $p(r_0) = p_0$, $dp(r_0)/dr = 0$ and $p(R) = 0$. We can use a quadratic function to express the values and get

$$p(r) = -\frac{p_0}{(R - r_0)^2} \left[r^2 - 2r_0 r + R(2r_0 - R) \right], \quad (r_0 < r < R). \quad (9)$$

2. The drainage ability Q_m is smaller than the critical flow rate Q_c , but greater than the fluid flux Q at the periphery: $Q \leq Q_m < Q_c$. Now, $p(r_0) = p_0$, $dp(r_0)/dr = 0$ and $p(R) = p_\infty = 0$. We have

$$p(r) = -\frac{1}{(R - r_0)^2} \left[(p_0 - p_\infty) r^2 - 2r_0 (p_0 - p_\infty) r - R^2 p_0 + 2Rr_0 p_0 - r_0^2 p_\infty \right], \quad (r_0 < r < R). \quad (9')$$

3. The drainage ability Q_m is smaller than the fluid flux Q : $Q_m < Q < Q_c$. Under this condition, $p(r_0) = p_0$, $dp(r_0)/dr = 0$, $p(R) = p_\infty$, and $dp(R^-)/dr = dp(R^+)/dr$. After we apply a cubic fit and combine it with Eq. (8), we get $p(r) = ar^3 + br^2 + cr + d$, where

$$\begin{aligned}
A &= \frac{Q - Q_m}{4\pi R^2 K} \\
&\quad - \frac{L_L A_L(r_m) [p(R) - p_L]}{4\pi K R^2}; \quad a \\
&= \frac{2[p_0 - p(R)] - (R - r_0)A}{(R - r_0)^3}; \quad b \\
&= \frac{(R + 2r_0)(R - r_0)A - 3(R + r_0)[p_0 - p(R)]}{(R - r_0)^3}; \quad c \\
&= \frac{6Rr_0[p_0 - p(R)] - r_0(R - r_0)(2R + r_0)A}{(R - r_0)^3}; \quad d \\
&= \frac{R^3 p_0 - r_0^3 p(R) - 3R^2 r_0 p_0 + 3R_0^2 p(R) + Rr_0^2 (R - r_0)A}{(R - r_0)^3}.
\end{aligned}$$

If the drainage of the lymphatics is small, $L_L A_L(r_m) \ll 1$, $A = \frac{Q - Q_m}{4\pi R^2 K}$. Also, Eq. (8) reduces to

$$p(r) = p(R) - \frac{4\pi R^2 u(R) - Q_m}{4\pi K} \left(\frac{1}{R} - \frac{1}{r} \right), \quad (r > R). \quad (8')$$

Let $p_0 = 15$ mm Hg, $K = 4.13 \times 10^{-8}$ cm²/mm Hg s [8,17], $r_0 = 0.9$ cm, $R = 1.0$ cm, so $u_c(R) = 0.124$ μ m/s or $Q_c = 1.56 \times 10^{-4}$ ml/s. Figure 9 shows the TIFP for different cases of flow rate: (a) $Q_m \geq Q_c$; (b) $Q = 5.19 \times 10^{-5}$ ml/s $\leq Q_m < Q_c$; (c) $Q_m < Q < Q_c$. The slope of the IFP outside the tumor is dependent on the flow rate across the surface $Q(R)$ and the drainage ability at the periphery of the tumor.

D. Time dependent TIFP

For an incompressible fluid, the increased rate of its volume equals that of the fluid source plus the inflow rate minus the fluid sink (drain) and outflow rate (here we ignore the diffusion):

$$\frac{\partial V_F}{\partial t} = J_s + \oint \vec{u}_1 \cdot d\vec{S}_1 - J_d - \oint \vec{u}_2 \cdot d\vec{S}_2. \quad (10)$$

Here, V_F is the total fluid volume in the tumor area, J_s is the fluid source, and J_d is the fluid drain (sink). There is no lymphatic drainage in the tumor, so $J_d = 0$. Lymphatic drainage exists at the periphery. We take it as a constant Q_m . The second term on the right side of Eq. (1) represents the inflow rate of the fluid and the fourth term represents the outflow rate. Since no fluid flows into the tumor from outside, Eq. (1) can be simplified as

$$\frac{\partial V_F}{\partial t} = J_s(t) - J_d(t) - \oint \vec{u}_{\text{drain}} \cdot d\vec{S}. \quad (11)$$

In the normal tissues, the blood vessels grow harmoniously with the tissue and lymphatics are functional, so the interstitial fluid is balanced. We assume that all capillaries have the same L , σ , pressure difference $p_V - p$ and osmotic pressure difference $\pi_V - \pi$. However, in the tumor tissue, the capillaries are deformed because of the fast growing tumor tissue. Different capillaries may have varying deformities. Therefore, they may have different L , σ ,

and $\pi_V - \pi$ though the p_V may stay the same. Also, the pressure p may be spatial dependent. The total fluid flux at time t can be expressed as

$$J_s(t) = \sum_i J_i(t) = \sum_i L_i(t) A_i(t) [p_V - p_i(t) - \sigma_i \Delta \pi_i(t)], \quad (12)$$

where $\Delta \pi_i$ is the osmotic pressure difference. The faster a tumor grows, the more deformed the capillaries are. This causes the value of the hydraulic conductivity to increase; therefore, the permeability of the capillaries increases. The thinner the capillaries, the smaller the osmotic pressure difference. When the capillary is broken (or there is a big hole in the capillary), the osmotic pressure $\Delta \pi_i$ becomes zero. Most capillaries are concentrated near the edge and the conductivity of the capillaries in this area is greater than that of the capillaries in the central region. Also, the osmotic pressure difference is smaller in this area. The total fluid flux near the edge should be much greater than that in the central area. We use the total fluid flux near the edge to represent the total fluid flux of the tumor. In this narrow area, the value of all different parameters (L , σ , and $\Delta \pi$) should not change much. We take them as invariables and use the average value to represent. Thus,

$$\begin{aligned} J_s(t) &= \bar{L}(t) \left[p_V - \bar{p}(t) - \bar{\sigma} \Delta \bar{\pi}(t) \right] \\ \sum_i A_i(t) &= \bar{L}(t) A(t) \left[p_V - \bar{p}(t) - \bar{\sigma} \Delta \bar{\pi}(t) \right], \end{aligned} \quad (13)$$

where $A(t)$ is the total surface area of blood vessels at time t . Putting Eq. (13) into Eq. (11), we have

$$\frac{\partial V_F(t)}{\partial t} = \bar{L}(t) A(t) \left[p_V - \bar{p}(t) - \bar{\sigma} \Delta \bar{\pi}(t) \right] - J_d(t) - \oint \vec{u}_{\text{drain}} \cdot d\vec{S}. \quad (14)$$

The IFP of the tumor should be related to the accumulated amount of fluid in a tumor. As we know, the more fluid is accumulated, the higher the pressure. Reference [27] experimentally showed that the TIFP is linearly related to tumor water content. We assume that tumor water content is proportional to the amount of accumulated fluid. The fluid's effect should be relative to the size of a tumor. If the tumor size is big, the pressure may not be high despite the large quantity of accumulated fluid. In contrast, if the tumor size is small, a slight amount of accumulated fluid may cause high pressure. We assume that the average pressure $\bar{p}(t)$ has a linear relationship with the ratio of the amount of accumulated fluid to the size (volume) of the tumor. $\bar{p}(t) = \gamma V / V_{\text{tumor}}$. Thus,

$$\frac{\partial \bar{p}(t)}{\partial t} = \gamma \frac{C m_c}{m(t)} \left\{ \bar{L}(t) A(t) \left[p_V - \bar{p}(t) - \bar{\sigma} \Delta \bar{\pi}(t) \right] - J_d(t) - \oint \vec{u}_{\text{drain}} \cdot d\vec{S} \right\}, \quad (15)$$

where γ is a coefficient and m_c is the mass of a tumor cell. Angiogenesis is an important property of tumors. Therefore, $A(t)$ is different at various stages of tumor growth. Usually, it increases. When a tumor grows at a fast rate, its size (m) increases quickly, and the state of the blood vessels changes rapidly. This may cause $\bar{L}(t)$ to increase and $\Delta \bar{\pi}(t)$ to decrease promptly. At the fast growth stage, it is difficult to determine the parameters. However, when a tumor is almost mature ($m \approx M$), all parameters tend to be steady. So,

$$\frac{\partial \bar{p}(t)}{\partial t} = \gamma \frac{C m_c}{M} \left\{ \bar{L} A \left[p_V - \bar{p}(t) - \bar{\sigma} \Delta \bar{\pi} \right] - J_d(t) - \oint \vec{u}_{\text{drain}} \cdot d\vec{S} \right\}. \quad (16)$$

The solution for Eq. (16) depends on the boundary conditions and initial conditions. It is difficult to get a general analytic solution. We are interested in the spatial distribution of pressure in a tumor. Here we consider the stable situation, $p(r, t)/t = 0$, and have the equation

$$\bar{L} A \left[p_v - \bar{p}(r) - \bar{\sigma} \Delta \bar{\pi} \right] - J_d - \oint \vec{u}_{\text{drain}} \cdot d\vec{S} = 0. \quad (17)$$

Here we consider the spherical symmetry case and take the tumor as a porous medium. Based on the discussions in Secs. II A–II C, we divide the domain into three regions: $r < r_0$, $r_0 < r < R$, and $r > R$. In the central region ($r < r_0$), fluid does not flow at a steady state and $u_{\text{drain}} = 0$. The TIFP is uniform. Thus Eq. (17) gives

$$p(r) = p_0 = p_v - \bar{\sigma} \Delta \bar{\pi} - \frac{J_d}{\bar{L} A}, \quad (r < r_0). \quad (18)$$

It provides a constant solution. If $J_d = 0$, it presents $p(r) = p_0 = p_m = p_v - \bar{\sigma} \Delta \bar{\pi}$. The results correspond with the cases that were discussed in Secs. II A and II B. Since the outflow velocity u_{drain} is unknown in the region $r_0 < r < R$, we cannot use Eq. (17) to get its pressure distribution. In the region $r < R$ at steady state, the fluid leaked from the capillaries should be equal to the total fluid flux across the edge ($r = R$):

$$\bar{L} A \left[p_v - \bar{p}(r) - \bar{\sigma} \Delta \bar{\pi} \right] = 4\pi R^2 u(R). \quad (19)$$

Considering the drainage of lymphatics, we can also derive Eq. (7) from Eqs. (17) and (19). The results in Sec. II C can be applied. It is consistent with the situations that were discussed in this paper.

III. DISCUSSION

According to the present model, p_0 and r_0 are the most important parameters. They represent the IFP of the central area in a tumor at steady state. When $r_0 > r_n$ (it includes the case of no necrotic core, $m = 0$), $p_0 = p_m = p_v - \sigma(\pi_v - \pi)$. In this case, the TIFP in the central region is determined by the conditions of the vascular vessels in the tumor. When $r_0 = r_m$, the situation is complicated and p_0 is between 0 and p_m ($0 < p_0 < p_m$). The value can be estimated using Eq. (6) as we discussed in Sec. II C. It is quite possible to estimate the values of r_0 and r_n by noninvasive means such as MRI and CT. Lee *et al.* [27] found that the tumor water content correlated significantly with TIFP. They actually showed that TIFP has a linear relationship with tumor water content. The best fit line indicated that water content increased from 79% to 85% when TIFP increased from ~2 to ~14 mm of Hg for tumors ($< 500 \text{ mm}^3$). Leunig *et al.* [28] also found that TIFP still correlated with tumor water content after they applied photodynamic therapy (PDT) to an amelanotic melanoma in a hamster. Some MRI images also suggest that the IFP is related to tumor water content [29–32]. The image contrast of MRI in the central region is distinct from that of the outer region. These results strongly imply that the tumor central region contains more water (protons), which coincides with the present model in the steady state. Lyng *et al.* [33] suggested that there was no correlation between the TIFP and T_1 or T_2 . Haider *et al.* [32] studied the correlations between, Dynamic Contrast Enhanced Magnetic Resonance Imaging, DCE-MRI and IFP of cervical cancer *in vivo* and found that there is a moderate negative correlation between the initial area under the enhancement curve (relative to muscle) at 60 minutes, the permeability

(rk_{trans}), and IFP. Hassid *et al.* [30,31] suggested that the distribution of steady-state tissue GdDTPA concentration reflected the distribution IFP inside the tumor. Gulliksrud *et al.* [29] concluded that DCE-MRI may be developed to be a useful noninvasive method for assessing IFP in tumors without necrosis through the relation between EF and IFP (where E is the initial extraction fraction of GdDTPA and F is blood perfusion). It is noteworthy that the water content can only relatively reflect the IFP in a tumor since MRI is based on the density of water (protons). It shows only the variation of IFP in the same tumor. Two different tumors may not have the same IFP even though they have the same water content. This is due to the difference between their sizes and fluid compositions. For example, if some other incompressible matter such as collagens has occupied the volume in the central region of a tumor, water may not enter this region. Even so, it does not mean that the pressure is lower there. Even in the same tumor, the distribution of water in the central region may not be even. Less water density in a small local region might not mean a low IFP there. It may be more reliable to determine the r_0 and r_n noninvasively and then estimate the IFP. Though we use a spherical model to describe the distribution of interstitial fluid and the pressure for the sake of convenience, it is not necessarily limited as a spherical structure. We may use the distribution difference of water content or the features of the tumor structure to determine r_n , or more generally, the necrotic region, and use the velocity property to determine r_0 or the uniform IFP p_0 region. Before reaching steady state, the contrast agent flows inwards in the region $r < r_0$ but outwards in the region $r > r_0$. After reaching the steady state, the contrast agent stays still in the region $r < r_0$ but flows outwards in the region $r > r_0$. Once we know r_0 and the pressure or velocity at R (also the value of R), we can get the distribution of TIFP in the area from r_0 to R based on Eq. (9') or (9'). But now there is not a general formula for TIFP distribution and we have to calculate the values of different points or different gradient directions.

IV. CONCLUSION

The present work illustrates the relationship between TIFP and fluid flow. A dynamic measure of contrast agent streaming away from a central mass may provide a measure of fluid flow and consequently TIFP. This formulation may become a practicable method for determining a quantitative noninvasive measure of TIFP. Since TIFP is a critical predictor of tumor response to nonsurgical cancer treatments, the methods proposed have strong practical clinical potential.

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FIG. 1.
Schematic of tumor interstitial fluid pressure distribution.

FIG. 2.
(Color online) Tree branching structure model for tumor vasculature: (a) Generated tumor vascular tree model [20]; (b) tumor vascular network model [16]. Figures used with permission.

FIG. 3.
(Color online) Schematic of tumor structure.

FIG. 4.

(Color online) Experimental result of TIFP distribution in a s.c. tumor [9] (surface is 0).

Blue and red curves are lines of best fit of circle and x symbols, respectively. Figures used with permission.

FIG. 5. Schematic of pressure modification for different boundary conditions in the vascularized region.

FIG. 6.
(Color online) Schematic of TIFP.

FIG. 7.
(Color online) TIFP of the necrotic core ($r \leq r_n$) vs time.

FIG. 8.
Schematic of IFP in the central area ($r < r_0$).

FIG. 9.
(Color online) Tumor interstitial fluid pressure vs tumor radius.