Effect of Wall Compliance and Permeability on Blood-Flow Rate in Counter-Current Microvessels Formed From Anastomosis During Tumor-Induced Angiogenesis

Peng Guo^{1,2}

e-mail: pguo@ccny.cuny.edu

Bingmei M. Fu¹

e-mail: fu@ccny.cuny.edu

Department of Biomedical Engineering,
The City College of the City
University of New York,
160 Convent Avenue,
New York, NY 10031

Tumor blood-flow is inhomogeneous because of heterogeneity in tumor vasculature, vessel-wall leakiness, and compliance. Experimental studies have shown that normalization of tumor vasculature by antiangiogenic therapy can improve tumor microcirculation and enhance the delivery of therapeutic agents to tumors. To elucidate the quantitative relationship between the vessel-wall compliance and permeability and the blood-flow rate in the microvessels of the tumor tissue, the tumor tissue with the normalized vasculature, and the normal tissue, we developed a transport model to simultaneously predict the interstitial fluid pressure (IFP), interstitial fluid velocity (IFV) and the blood-flow rate in a counter-current microvessel loop, which occurs from anastomosis in tumor-induced angiogenesis during tumor growth. Our model predicts that although the vessel-wall leakiness greatly affects the IFP and IFV, it has a negligible effect on the intravascular driving force (pressure gradient) for both rigid and compliant vessels, and thus a negligible effect on the blood-flow rate if the vessel wall is rigid. In contrast, the wall compliance contributes moderately to the IFP and IFV, but significantly to the vessel radius and to the blood-flow rate. However, the combined effects of vessel leakiness and compliance can increase IFP, which leads to a partial collapse in the blood vessels and an increase in the flow resistance. Furthermore, our model predictions speculate a new approach for enhancing drug delivery to tumor by modulating the vessel-wall compliance in addition to reducing the vessel-wall leakiness and normalizing the vessel density. [DOI: 10.1115/1.4006338]

Keywords: vessel-wall compliance, permeability, blood-flow rate, interstitial fluid pressure, interstitial fluid velocity

1 Introduction

Tumor blood flow controls tumor growth by delivering nutrients and oxygen to tumors and carrying metabolic waste away from tumors. Insufficient delivery of oxygen leads to hypoxic and acidic regions in solid tumors [1]. It also affects the efficacy of treatment by delivering blood-borne therapeutic agents to tumors. Inability of delivering a sufficient amount to all tumor cells results in residual tumor cells leading to tumor regrowth and development of resistant cells [2–5]. Hence, investigation of the blood flow in tumor vasculature may lead to a better understanding of tumor pathology and development of new treatment methods.

Compared to the blood flow in normal tissues, tumor blood flow is inhomogeneous because of heterogeneity in tumor vasculature, vessel-wall leakiness, and compliance. In general, it is reduced and thus hinders delivery of nutrients, oxygen, as well as therapeutic drugs [5–12]. Blood flow in a microvessel, if approximated by the Hagen-Poiseuille's law, is determined by the driving

force, the difference between arterial and venous pressures, and by the resistance controlled by the blood viscosity, blood vessel size, and geometry. In the central region of a tumor, the arteriole–venule pressure difference is reduced compared to the surrounding normal tissues and the tumor vasculature is also more tortuous [5,13,14]. These factors can partially explain the reduced tumor blood flow compared to that in the surrounding normal tissue [13,14].

In addition, other well-documented tumor characteristics, such as tumor vessel leakiness, elevated interstitial fluid pressure (IFP), the coupling between intravascular, and interstitial fluid exchange, might also contribute to the reduced tumor blood flow [8,15–17]. Evidence for tumor vessel leakiness or increased vessel permeability has come from the observation of extravasation of soluble tracers and blood-borne particles by scanning electron microscopy and magnetic resonance imaging [18]. Highly active but less regulated angiogenesis and microvascular remodeling are believed to attribute to tumor vessel leakiness and increased permeability. Elevated IFP is derived from the accumulated water caused by tumor vessel leakiness and the lack of functional lymphatic vessels [5,10]. The IFP can affect the vessel radius if the vessel is compliant, and, as a consequence, affect the tumor blood flow.

Much effort has been made to elucidate the relationship among tumor vessel leakiness, the IFP, the interstitial fluid velocity (IFV), and the drug delivery to tumor using both experimental and theoretical approaches [16,17,19–26]. Jain and his co-workers

¹P. Guo and B. M. Fu contributed equally to this work.

²Corresponding author.

Contributed by the Bioengineering Division of ASME for publication in the JOURNAL OF BIOMECHANICAL ENGINEERING. Manuscript received June 30, 2011; final manuscript received February 22, 2012; accepted manuscript posted March 15, 2012; published online April 5, 2012. Assoc. Editor: Hai-Chao Han.

developed a series of mathematical models to predict the elevated IFP and study the effect of tumor vessel leakiness and compliance on the pressure–flow relation and pressure profiles in solid tumors or along a vessel. Pertinent to this study, Netti et al. [16] and Baish et al. [17] modeled the tumor vasculature as one or a pair of equivalent permeable and compliant vessels embedded in an isotropic porous medium. Other researchers primarily focused on the interactions between intravascular, transmural, and interstitial fluid flow in a complex tumor vessel network formed by tumor-induced angiogenesis [22,24,25]. However, few investigated the combined effects of vessel-wall compliance and permeability on the blood-flow rate in the tumor vessels, and the normalized tumor vessels after anti-angiogenic therapy [27,28]. The normalized vasculature is characterized by the reduced vessel wall permeability, normalized vessel diameter, and normalized vessel density and organization [29–31].

Therefore, to elucidate the quantitative relationship between the vessel-wall compliance and permeability and the blood-flow rate in the microvessels in the tumor tissue, in the tumor tissue with the normalized vasculature, as well as in the normal tissue, we developed a transport model to simultaneously predict the IFP, the IFV, and the blood-flow rate in a counter-current microvessel loop, which frequently occurs from anastomosis during tumor-induced angiogenesis [32,33] [see Fig. 1(a)]. Tumor angiogenesis is a very complicated and poorly regulated process including sprout formation from parental vessels, sprout extension and branching, anastomosis, tube formation, and vessel maturation [34]. The resulting vasculature forms a complex network and is structurally and functionally abnormal: tumor vessels are very leaky and tortuous; the vessel–vessel interconnections are quite random and irregular [32,34]. The simplified counter-current microvessel loop shown in Fig. 1(a) represents anastomosis in the formation of tumor vessel network during tumor angiogenesis [33,35]. Figure 1(a) also shows the vessel sprouts from the parent vessels, branches, and four counter-current microvessel loops during anastomosis. For this simplified geometry, three analytical solutions were obtained for the rigid or compliant impermeable vessel, and the rigid permeable vessel. These analytical solutions served to validate the numerical simulation for the compliant and permeable vessel.

Our model has the ability to simultaneously predict the effects of vessel-wall compliance and leakiness on the intravascular pressure distribution, the IFP, the IFV, and the blood-flow rate. Therefore, it can be used to explain the experimental observations for

the microcirculation in a variety of tumor tissues and that in the tissue after treatments [27,28,36,37]. More importantly, it can be used to suggest new treatment and drug delivery strategies by targeting both the wall compliance and permeability of tumor vessels.

2 Model Description

2.1 Model Geometry and Mathematical Formulation.

Figure 1(b) shows our model geometry for a basic unit, the shaded region in Fig. 1(a) during anastomosis. This basic cylinder-shaped tissue unit has a length L and a radius R_t containing a pair of counter-current microvessels connected at one end. The blood flow in the vessel is driven by the pressure difference between P_{a0} and P_{v0} , the intravascular pressure in the entrance branch and in the exit branch at $X=0$, respectively. In addition to the pressure difference, the flow rates, Q_a in the entrance branch and Q_v in the exit branch, depend on the vessel radius, the interstitial fluid pressure (IFP) P_i , as well as the vessel compliance and leakiness. For the blood flow in this size of the microvessels, the non-Newtonian effect is small [38], and we thus assumed that the blood is a Newtonian fluid in our model. We have introduced the Krogh cylinder to describe the radius R_t for the basic cylinder-shaped tissue unit in our model [17]. R_t is required to satisfy the measured vascular surface area per unit tissue volume S/V , $(2\pi R_0 \times 2L/\pi R_t^2 L) = S/V$. R_0 is the vessel radius for a rigid vessel or for a deformable vessel when the transmural pressure is 0. Hence, $R_t = [4R_0/(S/V)]^{1/2}$.

The same as in Baish et al. [17], the flow rate Q_a in the entrance branch was approximated by the Hagen-Poiseuille's law,

$$Q_a = -\frac{\pi R_a^4}{8\mu} \frac{dP_a}{dX} \quad (1)$$

Here, R_a is the vessel radius and P_a is the hydrodynamic pressure in the entrance branch. For a permeable vessel, Q_a is required to satisfy the mass conservation equation,

$$\frac{dQ_a}{dX} = -2\pi R_a L p (P_a - P_i) \quad (2)$$

Here Lp is the hydraulic conductivity of the vessel wall and P_i is the IFP in the tissue. Transvascular flow velocity $Lp(P_a - P_i)$, is described by the Starling's equation. Because of large pore size in

Fig. 1 Simplified model geometry. (a) Schematic of counter-current microvessels (shaded regions) in anastomosis during tumor-induced angiogenesis. Three processes are plotted: sprouting from the parental vessels, sprout branching, and anastomosis. (b) Model geometry: enlarged shaded region in (a) comprises counter-current microvessels that are connected at $X = L$. The Krogh cylinder of radius R_t represents the tumor tissue surrounding the counter-current vessels. Blood flow is driven by the intravascular pressure at $X = 0$ in the entrance branch P_{a0} and that in the exit branch P_{v0} . $X = 0$ represents the outer edge of the tumor tissue, which is the interface between the tumor and normal tissues. The drawing is not to scale.

tumor vessels and the negligible oncotic pressure difference across the vessel wall [39,40], the contribution of the oncotic pressures to transvascular flow velocity is neglected for the tumor vessel [37].

Similarly, the flow rate Q_v in the exit branch is given by

$$Q_v = \frac{\pi R_v^4}{8\mu} \frac{dP_v}{dX} \quad (3)$$

Here, R_v is the vessel radius and P_v is the hydrodynamic pressure in the exit branch. The mass conservation for Q_v requires

$$\frac{dQ_v}{dX} = 2\pi R_v L p (P_v - P_i) \quad (4)$$

We assumed that Lp is the same for both branches.

The interstitial flow is governed by the Darcy's Law,

$$u_i = K \frac{dP_i}{dX} \quad (5)$$

Here, u_i is the interstitial flow velocity (IFV) and K is the hydraulic permeability of the tissue. For simplicity, we assumed that u_i only changes along the longitudinal direction X and parallel to the axis of the tissue cylinder [see Fig. 1(b)] but not along the radial direction. We required that u_i satisfy the following mass conservation equation,

$$-\pi R_t^2 \cdot \frac{du_i}{dX} = 2\pi R_a L p (P_a - P_i) + 2\pi R_v L p (P_v - P_i) \quad (6)$$

We also assumed there is no volume exchange across the cylindrical surface at R_t .

The microvessel wall can be rigid or compliant. If compliant, its deformation is described by a viscoelastic model [41,42].

$$\Delta P + \frac{\kappa}{\lambda_1} \frac{\partial \Delta P}{\partial t} = \lambda_2 E + \kappa \left[1 + \frac{\lambda_2}{\lambda_1} \right] \frac{\partial E}{\partial t} \quad (7)$$

Here, $\Delta P = P_a - P_i$ or $P_v - P_i$ is the transmural pressure. Because the amplitude of blood-flow pulsatility is small in microvessels, we can thus neglect the unsteady term in Eq. (7),

$$\Delta P = \lambda_2 E$$

E is the diameter strain given by

$$E = \frac{1}{2} \left[\left(\frac{R_i}{R_0} \right)^2 - 1 \right], \quad i = a, v \quad (8)$$

λ_1 , λ_2 , and κ are material coefficients of the vessel, which were assumed to be the same for both branches.

2.2 Dimensionless Equations and Boundary Conditions. After introducing characteristic length L ($x = X/L$), characteristic pressure P_{a0} , characteristic vessel radius R_0 , characteristic intravascular flow rate $[(P_{a0} - P_{v0})/L](\pi R_0^4/8\mu)$, characteristic interstitial fluid velocity $K P_{a0}/L$, and characteristic transvascular flow velocity $L p P_{a0}$, the above equations can be expressed into the following dimensionless forms. All the variables hereafter are dimensionless:

$$\frac{dP_i}{dx} = u_i \quad (9a)$$

$$\frac{du_i}{dx} = -\frac{\alpha^2}{2} [R_a (P_a - P_i) + R_v (P_v - P_i)] \quad (9b)$$

$$\frac{dQ_a}{dx} = -\beta R_a (P_a - P_i) \quad (9c)$$

$$\frac{dP_a}{dx} = -(1 - \gamma) \frac{Q_a}{R_a^4} \quad (9d)$$

$$P_a - P_i = \delta [R_a^2 - 1] \quad (9e)$$

$$\frac{dQ_v}{dx} = \beta R_v (P_v - P_i) \quad (9f)$$

$$\frac{dP_v}{dx} = (1 - \gamma) \frac{Q_v}{R_v^4} \quad (9g)$$

$$P_v - P_i = \delta [R_v^2 - 1] \quad (9h)$$

Four dimensionless parameters appear in the above equations (1) $\alpha = L[(L p/K)(S/V)]^{1/2}$ describes the ratio of the resistance of the interstitial flow to that of the transvascular flow. It is also the ratio of the cylinder length L to a characteristic length determined by $[K/L p (S/V)]^{1/2}$. The latter describes the length of the region where IFP and IFV changes precipitously. (2)

$$\beta = \frac{16 L p \mu L^2}{\left(1 - \frac{P_{v0}}{P_{a0}}\right) R_0^3}$$

describes the ratio of the resistance to flow along the vessels to that through the vessel wall. It is also the ratio of the characteristic total flux filtered through the vessel wall to the characteristic intravascular flux. (3) $\gamma = P_{v0}/P_{a0}$ is the ratio of the exit pressure to the entrance pressure at $x = 0$. It is the dimensionless driving force for the blood flow. (4) $\delta = \lambda_2/2P_{a0}$ describes the relative compliance of the vessel wall. The smaller the δ , the more compliant the vessel is.

Equations (9a–9h) are a set of nonlinear equations with eight unknowns. Therefore, eight boundary conditions are required for this problem.

$$\text{At } x = 0, P_{a0} = 1, P_{v0} = \gamma, \text{ and } P_i = 0 \quad (10a)$$

$P_i = 0$ because $x = 0$ is the outer edge of the tumor tissue, which is the interface between the tumor and normal tissues. The interstitial pressure is low in the normal tissue.

$$R_a \text{ and } R_v \text{ at } x = 0 \text{ are determined by Eqs. (9e) and (9h)} \quad (10b)$$

$$\text{At } x = 1, P_a = P_v, Q_a = Q_v, \text{ and } u_i = 0 \quad (10c)$$

Equation (10c) requires that the intravascular pressure and flow rate be continuous at $x = 1.0$, whereas there is no fluid exchange between the basic cylindrical tissue region and the surroundings.

2.3 Analytical and Numerical Solutions

Case 1: Rigid and Impermeable Vessel—Analytical Solution. In this case, $Lp = 0$ and $\alpha = \beta = 0$. Integrating Eq. (9b) and applying (10c), we had $u_i = 0$; further, integrating (9a) and applying (10a), we got $P_i = 0$; then, integrating Eqs. (9c) and (9f) and applying (10c), $Q_a = Q_v = Q$ is constant. λ_2 and δ are infinite, and $R_a = R_v = 1$; integrating (9d) and (9g), we obtained $P_a = 1 - (1 - \gamma) \cdot Q \cdot x$ and $P_v = \gamma + (1 - \gamma) \cdot Q \cdot x$. Applying boundary condition (10c), we got $Q = 0.5$. In fact, it is exactly the solution described by the Hagen-Poiseuille's law.

Case 2: Compliant and Impermeable Vessel—Analytical Solution. In this case, $Lp=0$ and $\alpha=\beta=0$; again $u_i=0$, $P_i=0$, and $Q_a=Q_v=Q$ is constant. Thus, the governing equations turn into

$$\frac{dP_a}{dx} = -(1-\gamma)\frac{Q}{R_a^4} \text{ and } P_a = \delta[R_a^2 - 1] \quad (11a)$$

$$\frac{dP_v}{dx} = (1-\gamma)\frac{Q}{R_v^4} \text{ and } P_v = \delta[R_v^2 - 1] \quad (11b)$$

After elimination of P_a and P_v , its analytical solution can be found:

$$R_a(x) = \left[R_a^6(0) - \frac{3(1-\gamma)}{\delta} \cdot Q \cdot x \right]^{1/6} \quad (12a)$$

$$R_v(x) = \left[R_v^6(0) + \frac{3(1-\gamma)}{\delta} \cdot Q \cdot x \right]^{1/6} \quad (12b)$$

Once R_a and R_v are obtained, P_a and P_v can be obtained. Apply (10c) and we can find Q :

$$Q = \frac{\delta}{6(1-\gamma)} [R_a(0)^6 - R_v(0)^6] \quad (12c)$$

(12c) is the dimensionless form of the result in Ref. [42]. Replace $R_a(0)^6$ and $R_v(0)^6$ with P_a and P_v and we find

$$Q = \frac{\delta}{6(1-\gamma)} \left[\left(\frac{1}{\delta} + 1 \right)^3 - \left(\frac{\gamma}{\delta} + 1 \right)^3 \right] \\ = \frac{1}{6(1-\gamma)} \left[3(1-\gamma) + \frac{3(1-\gamma^2)}{\delta} + \frac{(1-\gamma^3)}{\delta^2} \right] \quad (12d)$$

In the limit $\delta=\infty$ as in a rigid vessel, Eq. (12d) becomes $Q=0.5$, the same result as obtained in Case 1.

Case 3: Rigid and Permeable Wall—Analytical Solution. In this case, λ_2 and $\delta=\infty$, and $R_a=R_v=1$. The governing equations turn into

$$\frac{dP_i}{dx} = u_i \text{ and } \frac{du_i}{dx} = -\frac{\alpha^2}{2} [(P_a - P_i) + (P_v - P_i)] \quad (13a)$$

$$\frac{dP_a}{dx} = -(1-\gamma)Q_a \text{ and } \frac{dQ_a}{dx} = -\beta(P_a - P_i) \quad (13b)$$

$$\frac{dP_v}{dx} = (1-\gamma)Q_v \text{ and } \frac{dQ_v}{dx} = \beta(P_v - P_i) \quad (13c)$$

By first eliminating u_i , Q_a , and Q_v and then applying boundary conditions (10a) and (10c), the analytic solutions for P_a , P_v , P_i , and u_i can be obtained:

$$P_a - P_i = \frac{1+\gamma}{2} \cosh(\sigma x) - \frac{1+\gamma}{2} \frac{\sinh(\sigma)}{\cosh(\sigma)} \sinh(\sigma x) \\ + \frac{1-\gamma}{2} \cosh(\tau x) - \frac{1-\gamma}{2} \frac{\cosh(\tau)}{\sinh(\tau)} \sinh(\tau x) \quad (14a)$$

$$P_v - P_i = \frac{1+\gamma}{2} \cosh(\sigma x) - \frac{1+\gamma}{2} \frac{\sinh(\sigma)}{\cosh(\sigma)} \sinh(\sigma x) \\ - \frac{1-\gamma}{2} \cosh(\tau x) + \frac{1-\gamma}{2} \frac{\cosh(\tau)}{\sinh(\tau)} \sinh(\tau x) \quad (14b)$$

$$P_i = -\frac{\alpha^2}{\sigma^2} \frac{1+\gamma}{2} (\cosh(\sigma x) - 1) + \frac{\alpha^2}{\sigma^2} \frac{1+\gamma}{2} \frac{\sinh(\sigma)}{\cosh(\sigma)} \sinh(\sigma x) \quad (14c)$$

$$u_i = -\frac{\alpha^2}{\sigma} \frac{1+\gamma}{2} \sinh(\sigma x) + \frac{\alpha^2}{\sigma} \frac{1+\gamma}{2} \frac{\sinh(\sigma)}{\cosh(\sigma)} \cosh(\sigma x) \quad (14d)$$

Here, $\sigma^2 = \alpha^2 + (1-\gamma)\beta$ and $\tau^2 = (1-\gamma)\beta$.

Finally, at $x=1.0$

$$Q_a = Q_v = \frac{\tau \cosh^2(\tau) - \sinh^2(\tau)}{2 \sinh(\tau)} \quad (15)$$

Case 4: Compliant and Permeable Vessel—Numerical Solution. For this case, there is no analytical solution for the problem described by Eqs. (9) and (10). It can be numerically solved via iteration for each set of parameter values. First, initial guesses for the pressures were used to calculate the vessel radius; second, the intravascular flow rates and IFV were obtained and used to adjust the pressures in the lumen and in the tissue. The process was iterated until the flow rates and the vessel radii converged. The numerical method was first tested and validated by comparing to the analytical solutions in the above three cases.

2.4 Parameter Values. Table 1 summarizes the parameter values used in the model. They were obtained from the literature. L was chosen to be 1 mm, which is sufficiently long to capture the region where tumor IFP dropped sharply in tumor periphery [36]. Vessel radius R_0 is 6 μm , the measured value of perfused functional microvessels [28,43,44]. Blood viscosity μ is dependent on temperature, hematocrit, and tube diameter [45,46]; it was chosen to be 0.004 PaS in the microvessels considered in the current study [17]. Although, because of vessel leakiness and diameter change, μ may change slightly along the axial direction. But this change is negligible in our study (see the discussion below).

The surface area of the vessel wall per unit volume of the tissue S/V generally falls in the range of 50 to 250 cm^2/cm^3 for the normal and tumor tissues [37]. In this analysis, a typical value of 200 cm^2/cm^3 was chosen for the tumor tissue [17,47], and 50 cm^2/cm^3 for the normal tissue [37]. Because the measured data for S/V in the normalized tumor tissue was not available, and it was believed to be between the measured value for the normal tissue and that for a typical tumor tissue [37], we thus assumed the S/V value for the normalized tumor tissue to be 100 cm^2/cm^3 . Therefore, the cylindrical tissue radius $R_t = [4R_0/(S/V)]^{1/2}$ [see Fig. 1(b)], is 35, 49, and 69 μm , respectively, for the tumor tissue, the tumor tissue with the normalized vasculature, and the normal tissue.

Both K and Lp vary among tissue types, tumor types, as well as within individual tumors. In this study, we chose K of 1.7×10^{-7} $\text{cm}^2/\text{mmHg/s}$, a reported value for human colon adenocarcinoma LS174T tumor xenograft and other solid tumors [48–50]. We also used the same value for the normal tissue and the tumor tissue with the normalized vasculature because Jain et al. [37] estimated that there was negligible difference in K among these tissues. We used a value of 1.86×10^{-6} cm/s/mmHg for the hydraulic conductivity (Lp) of the tumor microvessel from the measurement in human colon adenocarcinoma LS174T tumor xenograft [48]. Lp of the microvessels in the normal tissue is much smaller than that of the microvessels in the tumor tissue. We chose 3.6×10^{-8} cm/s/mmHg [37] for the microvessel Lp in the normal tissue. The normalization of the tumor vasculature by antiangiogenic therapy reduced Lp . We thus used 3.7×10^{-7} cm/s/mmHg for the Lp of the normalized vessels in tumor tissue [37].

Intravascular pressures in the microvessels generally vary from 5.5 to 34 mmHg [37]. For simplicity, we chose a typical value of 16 mmHg for P_{a0} and 8 mmHg for P_{v0} [17]. For comparison, we assume P_{a0} and P_{v0} are the same for the normal tissue and the tumor tissue with the normalized vasculature. For vessel-wall compliance, we chose $\lambda_2=64$ –300 mmHg as calculated from the relationship between the transmural pressure and the vessel radius measured in normal and tumor microvessels [16,17,51]. Based on the above measured values from the literature, the dimensionless

Table 1 Measured and estimated parameters in the model

Parameters	Tumor	Normalized	Normal
L (cm)	0.1 [35]	0.1	0.1
μ (PaS)	0.004 [17]	0.004	0.004
R_0 (μm)	6 [42,43]	6	6
S/V (cm^2/cm^3)	200 [17,44]	100	50 [36]
K ($\text{cm}^2/\text{s}/\text{mmHg}$)	1.7×10^{-7} [45]	1.7×10^{-7} [36]	1.7×10^{-7} [36]
L_P ($\text{cm}/\text{s}/\text{mmHg}$)	1.86×10^{-6} [36]	3.7×10^{-7} [36]	3.6×10^{-8} [36]
P_{a0} (mmHg)	16 [17]	16 [17]	16 [17]
P_{v0} (mmHg)	8 [17]	8 [17]	8 [17]
λ_2 (mmHg)	64–300 [16,17,49]	64–300	64–300 [49]
$R_t = \sqrt{4R_0/(\frac{S}{V})}$ (μm)	35	49	69
$\alpha = L\sqrt{L_P \frac{S}{V}/K}$	4.7	1.5	0.33
$\beta = \frac{16L_P\mu L^2}{\left(1 - \frac{P_{v0}}{P_{a0}}\right)R_0^3}$	0.083	0.016	0.0016
$\delta = \frac{\lambda_2}{2P_{a0}}$	2–9.3	2–9.3	2–9.3
$\gamma = \frac{P_{v0}}{P_{a0}}$	0.5	0.5	0.5

parameters α , β , δ , and γ were estimated. The estimated values are summarized in Table 1.

3 Results

3.1 Effect of Wall Compliance on the Blood-Flow Rate in Microvessels With the Impermeable Wall. For the vessels with the compliant and impermeable wall, the blood-flow rates in the entrance and exit branches are the same, which are given by an analytical solution in Eq. (12d). In Fig. 2, we plotted the flow rate versus the vessel wall stiffness δ when the driving force $\gamma = P_{v0}/P_{a0}$ is fixed as 0.5. Figure 2 indicates that the flow rate increases with the vessel-wall compliance (when δ decreases). This is because of a reduced intravascular flow resistance caused by an increase in the vessel radius caused by the intravascular pressure. To validate our numerical simulation method for the compliant and permeable vessel, in Fig. 2, we also compared the analytical solution (the line) with that through the numerical simulation (symbols) for the blood-flow rate. In the numerical simulation, the parameters related to the wall permeability, α and β , were chosen to be very small to approximate the impermeable condition for the analytical solution. We can see that the agreement between numerical and an-

Fig. 2 Effect of the vessel-wall compliance on the blood-flow rate in an impermeable vessel. The line is the analytical solution; symbols are the results from the numerical computation. For a rigid vessel, $\delta = \infty$.

alytical solutions is remarkable with the difference less than 0.3% for the range of δ under our consideration. When $\delta > 500$, the dimensionless flow rate converges to the analytical solution described by the Hagen-Poiseuille's equation for a rigid and impermeable vessel, which equals 0.5.

As observed from the various experiments in the normal and tumor tissues, as well as in the tumor tissue with the normalized vasculature after antiangiogenic therapy [37], the different vessel-wall compliance and permeability, and the surface area of vessel wall per unit tissue volume would affect intravascular pressures, interstitial fluid pressure (IFP), interstitial flow velocity (IFV), and vessel radius. As a consequence, they would affect the blood-flow rate in the vessels. In the following sections, we used the validated numerical simulation to quantify the relation between vessel-wall compliance and these variables in the tumor tissue, the tumor tissue with the normalized vasculature, and the normal tissue. The corresponding parameters used in the simulation are summarized in Table 1. For a compliant vessel, we chose $\delta = 2$, which was one of the smallest values estimated from the literature for the microvessel wall [16,17]. For a rigid vessel, $\delta = \infty$ and an analytical solution was obtained as in Eqs. (14a–14d) and Ref. [15].

3.2 Effect of Wall Compliance on the Intravascular Pressures in Microvessels of Tumor Tissue, Tumor Tissue With Normalized Vasculature, and Normal Tissue. Figure 3 demonstrates the intravascular pressures P_a and P_v change with the location from the peripheral ($x=0$) toward the center of the tissue when the vessel wall is rigid [Fig. 3(a)] or compliant [Fig. 3(b)]. We compared the results for P_a and P_v in the microvessels of the tumor tissue (indicated by T in the figure), the tumor tissue with the normalized vasculature (indicated by N.V. in the figure) and the normal tissue (indicated by N in the figure) in both rigid and compliant vessels. Although α increases by ~ 14 -fold, β by ~ 52 -fold from the normal to tumor tissues, there are negligible changes in P_a and P_v in the microvessels of these distinctive tissues no matter the vessel wall is rigid or compliant. Therefore, the driving force (the pressure gradient) for the blood flow is not compromised by the vessel leakiness and the compliance in the tumor tissue compared with that in the normal tissue.

3.3 Effect of Wall Compliance on the Interstitial Fluid Pressure (IFP) in Microvessels of Tumor Tissue, Tumor Tissue With Normalized Vasculature, and Normal Tissue. In Fig. 4, we compared the IFP distribution from the peripheral toward the center of the tissue for the tumor tissue, the tumor tissue with

(A)

(B)

Fig. 3 Effect of the vessel-wall compliance on intravascular pressures. The intravascular pressure in the entrance branch P_a and that in the exit branch P_v in the microvessels of the tumor tissue (T), the tumor tissue with the normalized vessels (N.V.), and the normal tissue (N): (a) rigid vessels, and (b) compliant vessels. Axis x is the normalized position defined by X/L .

the normalized vasculature, and the normal tissue when the vessel wall is rigid [Fig. 4(a)] or compliant [Fig. 4(b)]. In contrast to the intravascular pressures, the IFP is greatly affected by the vessel permeability (leakiness) L_p and the surface area of vessel wall per unit tissue volume (S/V). IFP in the tumor tissue with the larger L_p and S/V is much higher than that in the normal tissue. It increases sharply from the peripheral, plateaus at about half way to the end of the anastomosis, whereas IFP in the normal tissue increases slightly in a linear manner from the peripheral toward the center of the tissue. The maximum IFP at the end of the anastomosis ($x=1$) in the tumor tissue is ~ 19 -fold of that in the normal tissue. Vascular normalization by antiangiogenic therapy decreases the IFP in the tumor tissue as expected. Whereas the vessel wall hydraulic conductivity L_p and S/V contribute significantly to the IFP, changing the vessel-wall compliance from $\delta=\infty$ (rigid) to 2 only increases IFP by $\sim 4\%$, 8% , and 20% in the tumor tissue, the tumor tissue with the normalized vasculature and the normal tissue, respectively.

3.4 Effect of Wall Compliance on the Interstitial Fluid Velocity (IFV) in Microvessels of Tumor Tissue, Tumor Tissue With Normalized Vasculature, and Normal Tissue. Figure 5 shows IFV distribution in the tissue region when the vessel wall is

(A)

(B)

Fig. 4 Effect of the vessel-wall compliance on interstitial fluid pressure (IFP). IFP in the tumor tissue (T), in the tumor tissue with the normalized vessels (N.V.), and in the normal tissue (N): (a) rigid vessels, and (b) compliant vessels. Axis x is the normalized position defined by X/L .

rigid [Fig. 5(a)] or compliant [Fig. 5(b)]. Because of nearly the same intravascular pressures P_a and P_v for different types of tissues (Fig. 3), and the precipitous increase in IFP (P_i) in the tumor tissue (Fig. 4) from the peripheral ($x=0$) toward the center of the tumor tissue [Fig. 1(a)], IFV (u_i) is much higher in the peripheral region of the tumor tissue than that in the normal tissue, ~ 46 -fold at $x=0$ because K is the same for both tumor tissue and normal tissue. IFV sharply drops from the peripheral toward the center of the tumor tissue, whereas it decreases slowly in the normal tissue. Reducing L_p and S/V by the vascular normalization significantly decreases the IFV in the tumor tissue. In contrast, increasing the vessel-wall compliance from $\delta=\infty$ (rigid) to 2 only increases IFV by $\sim 9\%$, 10% , and 19% in the tumor tissue, the tumor tissue with the normalized vasculature, and the normal tissue, respectively.

3.5 Effect of Wall Compliance on the Vessel Radius in Microvessels of Tumor Tissue, the Tumor Tissue With Normalized Vasculature, and Normal Tissue. In Fig. 6, we plotted the vessel radius as a function of location in the tumor tissue, the tumor tissue with the normalized vasculature, and the normal tissue when the vessel wall is rigid [Fig. 6(a)] or compliant [Fig. 6(b)]. As

Fig. 5 Effect of the vessel-wall compliance on interstitial fluid velocity (IFV). IFV in the tumor tissue (T), in the tumor tissue with the normalized vessels (N.V.), and in the normal tissue (N): (a) rigid vessels, and (b) compliant vessels. Axis x is the normalized position defined by x/L .

Fig. 6 Effect of the vessel-wall compliance on vessel radius. Vessel radius in the entrance branch R_a and that in the exit branch R_v in the microvessels of the tumor tissue (T), the tumor tissue with the normalized vessels (N.V.), and the normal tissue (N): (a) rigid vessels, and (b) compliant vessels. Axis x is the normalized position defined by x/L .

shown above, the vessel wall hydraulic conductivity Lp and S/V only affect IFP significantly but not intravascular pressures P_a and P_v , the resulting transmural pressure $\Delta P = P_n - \text{IFP}$ ($n=a, v$) would change the vessel radius if the vessel wall is compliant. As shown in Fig. 6(b), the microvessel radius in the tumor tissue experiences the largest change because of the changes in IFP and thus varies the most from the peripheral toward the center of the tissue. Because of the highest IFP at the end of the anastomosis, the vessel radius is the minimum at that location. When $\delta = 2$, the dimensionless vessel radius (compared to the radius of a rigid vessel) at the end of the anastomosis is 1.004, 1.076, and 1.168 for the microvessel in the tumor tissue, the tumor tissue with the normalized vasculature, and the normal tissue, respectively. The radius of the vessel in the normal tissue and that in the tumor tissue with the normalized vasculature is $\sim 16\%$ and 7.2% , larger than that of the vessel in the tumor tissue, respectively.

3.6 Effect of Wall Compliance on the Blood-Flow Rate in Microvessels of Tumor Tissue, Tumor Tissue With Normalized Vasculature, and Normal Tissue. Finally, in Fig. 7, we plotted the blood-flow rates in the microvessels Q_a and Q_v as a

function of location in the tumor tissue, the tumor tissue with the normalized vasculature, and the normal tissue when the vessel wall is rigid [Fig. 7(a)] or compliant [Fig. 7(b)]. For a rigid vessel, despite the large difference in the vessel wall hydraulic conductivity Lp and S/V (α ranges from 0.33 to 4.7, β from 0.0016 to 0.083), there is a negligible change in the blood-flow rate in the microvessels in the tumor tissue, the tumor tissue with the normalized vasculature, and the normal tissue. The blood-flow rate in a rigid vessel almost satisfies the Hagen-Poiseuille equation because of the much smaller fluid loss from the vessel wall. However, for a compliant vessel, the increased vessel radius can reduce the intravascular resistance and result in an increase in the blood-flow rate. Compared to a rigid vessel, the compliant vessel with $\delta = 2$ can increase the blood-flow rate by $\sim 13\%$, 47% , and 85% , respectively, in the microvessel of the tumor tissue, the tumor tissue with the normalized vasculature, and the normal tissue.

To further explore the vessel compliance on the blood-flow rate, in Fig. 8, we compared the blood-flow rate when the vessel compliance $\delta = 2, 4$, and 9 and ∞ in the microvessels of the tumor

Fig. 7 Blood-flow rate in rigid and compliant vessels. Blood-flow rate in the entrance branch Q_a and that in the exit branch Q_v in the microvessels of the tumor tissue (T), the tumor tissue with the normalized vessels (N.V.), and the normal tissue (N): (a) rigid vessels, and (b) compliant vessels. Axis x is the normalized position defined by X/L .

tissue [Fig. 8(a)], the tumor tissue with the normalized vasculature [Fig. 8(b)] and the normal tissue [Fig. 8(c)]. For a microvessel in the tumor tissue, increasing its compliance from $\delta = 4$ to 2, from 9 to 4, and from ∞ to 9 would increase the blood-flow rate by $\sim 5\%$, 4% , and 3% , respectively. For the same step decreases in δ , the blood-flow rate in a microvessel of the tumor tissue with the normalized vasculature would increase by $\sim 19\%$, 12% , and 10% ; and that in a microvessel of the normal tissue would increase by $\sim 33\%$, 20% , and 16% , respectively. For the same δ , vascular normalization in the tumor tissue would increase the blood-flow rate by $\sim 32\%$, 16% , 7% , and 0.6% when $\delta = 2, 4, 9$, and ∞ .

4 Discussion

In this study, we developed a transport model to investigate the effect of vessel-wall compliance and permeability on the blood-flow rate in a pair of counter-current microvessels connected at one end. This vessel geometry represents anastomosis during tumor-induced angiogenesis [33,35]. This vessel geometry is different from that in Baish et al. [17] in which a pair of counter-current tumor vessels penetrate the entire tumor. The counter-

Fig. 8 Effect of the vessel-wall compliance on the blood-flow rate. Blood-flow rate in the entrance branch Q_a and that in the exit branch Q_v in the microvessels of (a) the tumor tissue, (b) the tumor tissue with the normalized vessels, and (c) the normal tissue. Axis x is the normalized position defined by X/L .

current vessels in our study are connected at one end and have lengths in the range of 1 mm, which is an order of magnitude smaller than that in Baish et al. [17].

Our model predictions indicate that the vessel-wall compliance and leakiness has a negligible influence on the intravascular pressure distribution (the driving force for the blood flow) regardless of the vessel-wall compliance (Fig. 3). However, the vessel-wall compliance contributes to the IFP and IFV, although its contribution is much less than that of the wall leakiness (Figs. 4 and 5). Figures 4 and 5 demonstrate that because of the increased microvessel permeability in the tumor, the IFP is greatly enhanced in the center region of the tumor tissue, whereas the IFV is enhanced near the peripheral region. These predictions are consistent with the experimental observations in a variety of tumors [36] and also consistent with the model predictions from others under different geometries for the tumor vasculature [37,47]. Because the tumor vessels are very leaky, the combined effects of vessel compliance and hyperpermeability can greatly increase the IFP, which leads to a partial collapse of the blood vessel and an increase in flow resistance, resulting a reduction in the blood-flow rate compared to the normal vessels [Fig. 6(b)].

Because of the volume loss through leaky tumor vessels and the vessel diameter change, the viscosity may be varied in compliant permeable vessels. We thus estimate the viscosity changes based on the empirical equations in Refs. [45] and [46]. In our case, the volume loss from the vessel into tumor is described by β , whose maximal value is 0.083 for the leakiest tumor vessels. It means that 8.3% of the volume in the vessel will be lost into tumor interstitium. Using 8.3% volume loss and 45% hematocrit at $x=0$ in the entrance branch, the hematocrit will increase to $\sim 49\%$ [$=0.45/(1.0 - 0.083)$] at the exit branch. In Fig. 6(b), we can see that more than 70% of a tumor microvessel has a relative diameter increase of less than 10%. If 10% is used as the average of the relative diameter increase, combined with the increase in hematocrit because of volume loss through the leaky tumor vessels, the increase in viscosity in the tumor vessel is $\sim 2.7\%$ based on the empirical equations summarized in [45,46]. Therefore, we used a constant viscosity in our model.

The empirical equations in [45,46] are for viscosity change in a single vessel. In our case, the viscosity change in a vessel because of the diameter change and the volume loss can be neglected as calculated using the empirical formula. Our simplified counter-current geometry simulates anastomosis, which is one pattern induced by tumor angiogenesis [33]. To use this simplified and local geometry ($\sim 0.1 \text{ mm} \times 1 \text{ mm}$), we can explicitly find the relationship between the vessel compliance and permeability and the IFP, IFV, and the blood-flow rate in the tumor microvessels. To simulate entire region of tumor angiogenesis ($\sim 1 \text{ cm}^2$ or larger) and its 3D network structure, much more effort will be made to include the heterogeneity in the viscosity, permeability, and compliance in different types of microvessels.

Recently, an antiangiogenic therapy by a short-term anti-VEGFR treatment on melanomas grown in dorsal skinfold chambers of hamsters was found to increase microvascular blood flows as well as microvessel diameters [28]. Treatment by other antiangiogenic agents also leads to multiple changes in tumor vessels and tumor vasculature, the process called normalization of tumor vasculature. The normalization results in reduced microvessel permeability, reduced IFP and IFV, normalized vessel density, and enhanced blood flows [27,28,30,31]. The predictions from our model successfully reflect the normalization process by antiangiogenic therapies. Because of the reduced microvessel permeability, L_p and normalized vessel density (reduced S/V), our model predicts that the IFP and IFV greatly decrease in the tumor tissue with the normalized vasculature (Figs. 4 and 5) in both rigid and compliant vessels. However, the increased vessel radius (Fig. 6) and therefore the increased blood-flow rate (Fig. 7) in the normalized vessel can only occur in a compliant vessel. This implicates that the tumor vascular normalization by antiangiogenic therapies may also normalize the vessel-wall compliance.

As shown in Neal and Michel [51], the compliance of a microvessel wall is determined by the basement membrane surrounding the endothelial cells lining the luminal surface of a microvessel. It was found that the basement membrane in the tumor vasculature is either absent or too thick [29]. This may be responsible for the heterogeneity in the tumor microvessel compliance and result in the heterogeneity in the tumor blood flow according to our model predictions (Figs. 7 and 8). As predicted in Figs. 7 and 8, increasing vessel compliance can further enhance the tumor blood flow in addition to the reduced microvessel permeability L_p and normalized vessel density. Basement membrane surrounding the microvessel wall consists of collagen type IV, heparin sulfate proteoglycans, laminin, fibronectin, and other extracellular matrix (ECM) proteins [52,53]. Further investigations for how to modulate the basement membrane composition and structure to increase its compliance should be conducted in the future. However, modulation of the tumor vessel compliance implies another approach to enhance the tumor blood flow for the oxygen and drug delivery to the tumor to improve the treatment efficacy.

For our simplified geometry, three analytical solutions were obtained for the rigid permeable and impermeable vessels, and compliant impermeable vessels. They serve to validate our numerical simulation for the compliant permeable vessels. For more complicated geometry, the chance to find three analytical solutions is small and thus impossible to validate the numerical simulation and impossible to elucidate the insight between the vessel compliance, vessel permeability and the IFP, IFV, and blood-flow rate. Therefore, our simplified geometry can serve to validate the numerical simulations for compliant permeable vessels in more complicated geometries. However, the successful predictions of our model for the elevated IFP and reduced blood-flow rate in the tumor vasculature and for the reduced IFP and enhanced blood-flow rate in the normalized tumor vasculature after antiangiogenic therapies also validate our simplified geometry. Although we anticipate that the relationship between the vessel compliance, vessel permeability, and the IFP, IFV, and blood-flow rate is similar for a more complicated geometry, detailed numerical calculation should be performed in the future.

In conclusion, we developed a transport model to elucidate the quantitative relationship between the vessel-wall compliance and permeability and the blood-flow rate in the microvessels of the tumor tissue, the tumor tissue with the normalized vasculature and the normal tissue. Our model predicts that the vessel-wall compliance contributes significantly to the tumor blood flow; It also predicts the increase in both vessel diameter and blood-flow rate in surviving and normalized tumor microvessels after antiangiogenic therapy, which was observed in Czabanka et al. [28]. This phenomenon is observed only in recent years and yet no other existing models can be available to explain it. Based on the model predictions, we propose that tumor compliance and leakiness can be simultaneously targeted to increase drug delivery in tumor tissue. This proposal is of clinical significance and is not well investigated yet.

Acknowledgment

This work is supported by NIH/NCI CA153325-01 and NSF CBET-0754158.

Nomenclature

E = diameter strain of the vessel
 K = hydraulic permeability of the tissue
 L = length of the tissue region in our model
 L_p = hydraulic conductivity of the vessel wall
 P_a = intravascular pressure in the entrance branch
 P_i = interstitial fluid pressure (IFP)
 P_v = intravascular pressure in the exit branch
 ΔP_n = transmural pressure ($n = a$ or v) $\Delta P_a = P_a - P_i$;
 $\Delta P_v = P_v - P_i$
 Q_a = blood-flow rate in the entrance branch

Q_v = blood-flow rate in the exit branch
 R = radial position in tumor tissue
 R_0 = vessel radius when the transmural pressure is zero or the rigid vessel
 R_a = vessel radius of the entrance branch
 R_t = radius of tissue cylinder
 R_v = vessel radius of the exit branch
 S/V = the surface area of the vessel wall per unit volume of the surrounding tissue
 u_i = interstitial fluid velocity (IFV)
 X = position along the vessel axis
 x = dimensionless position along the vessel axis: $x = X/L$

Greek Symbols

α = ratio of the interstitial flow resistance to the transvascular flow resistance
 β = ratio of the resistance to flow along the vessel to that through the vessel wall
 δ = the relative stiffness of the vessel wall
 γ = ratio of the exit pressure to the entrance pressure at $X = 0$
 λ_i = material coefficient of the vessel wall ($i = 1, 2$)
 κ = material coefficient of the vessel wall
 μ = blood viscosity
 $\sigma = \sigma^2 = \alpha^2 + (1 - \gamma)\beta$
 $\tau = \tau^2 = (1 - \gamma)\beta$

References

- Gillies, R. J., Schomack, P. A., Secomb, T. W., and Raghunand, N., 1999, "Causes and Effects of Heterogeneous Perfusion in Tumors," *Neoplasia*, **1**(3), pp. 197–207.
- Baguley, B. C., and Finlay, G. J., 1995, "Pharmacokinetic/Cytokinetic Principles in the Chemotherapy of Solid Tumours," *Clin. Exp. Pharmacol. Physiol.*, **22**(11), pp. 825–828.
- Durand, R. E., 1990, "Slow Penetration of Anthracyclines Into Spheroids and Tumors: A Therapeutic Advantage?," *Cancer Chemother. Pharmacol.*, **26**(3), pp. 198–204.
- Erlanson, M., Daniel-Szolgay, E., and Carlsson, J., 1992, "Relations Between the Penetration, Binding and Average Concentration of Cytostatic Drugs in Human Tumour Spheroids," *Cancer Chemother. Pharmacol.*, **29**(5), pp. 343–353.
- Jang, S. H., Wientjes, M. G., Lu, D., and Au, J. L., 2003, "Drug Delivery and Transport to Solid Tumors," *Pharm. Res.*, **20**(9), pp. 1337–1350.
- Jain, R. K., 1987, "Transport of Molecules Across Tumor Vasculature," *Cancer Metastasis Rev.*, **6**(4), pp. 559–593.
- Jain, R. K., 1988, "Transvascular and Interstitial Transport in Tumors," *Adv. Exp. Med. Biol.*, **242**, pp. 215–220.
- Jain, R. K., 1988, "Determinants of Tumor Blood Flow: A Review," *Cancer Res.*, **48**(10), pp. 2641–2658.
- Jain, R. K., 1991, "Haemodynamic and Transport Barriers to the Treatment of Solid Tumours," *Int. J. Radiat. Biol.*, **60**(1–2), pp. 85–100.
- Jain, R. K., 1998, "Delivery of Molecular and Cellular Medicine to Solid Tumors," *J. Control Release*, **53**(1–3), pp. 49–67.
- Jain, R. K., 1999, "Transport of Molecules, Particles, and Cells in Solid Tumors," *Annu. Rev. Biomed. Eng.*, **1**, pp. 241–263.
- Jain, R. K., and Stylianopoulos, T., 2010, "Delivering Nanomedicine to Solid Tumors," *Nat. Rev. Clin. Oncol.*, **7**(11), pp. 653–664.
- Hori, K., Suzuki, M., Tanda, S., and Saito, S., 1990, "in vivo Analysis of Tumor Vascularization in the Rat," *Jpn. J. Cancer Res.*, **81**(3), pp. 279–288.
- Hori, K., Suzuki, M., Tanda, S., and Saito, S., 1991, "Characterization of Heterogeneous Distribution of Tumor Blood Flow in the Rat," *Jpn. J. Cancer Res.*, **82**(1), pp. 109–117.
- Sevick, E. M., and Jain, R. K., 1991, "Effect of Red Blood Cell Rigidity on Tumor Blood Flow: Increase in Viscous Resistance During Hyperglycemia," *Cancer Res.*, **51**(10), pp. 2727–2730.
- Netti, P. A., Roberge, S., Boucher, Y., Baxter, L. T., and Jain, R. K., 1996, "Effect of Transvascular Fluid Exchange on Pressure-Flow Relationship in Tumors: A Proposed Mechanism for Tumor Blood Flow Heterogeneity," *Microvasc. Res.*, **52**(1), pp. 27–46.
- Baish, J. W., Netti, P. A., and Jain, R. K., 1997, "Transmural Coupling of Fluid Flow in Microcirculatory Network and Interstitium in Tumors," *Microvasc. Res.*, **53**(2), pp. 128–141.
- Hashizume, H., Baluk, P., Morikawa, S., McLean, J. W., Thurston, G., Roberge, S., Jain, R. K., and McDonald, D. M., 2000, "Openings Between Defective Endothelial Cells Explain Tumor Vessel Leakiness," *Am. J. Pathol.*, **156**(4), pp. 1363–1380.
- Mollica, F., Jain, R. K., and Netti, P. A., 2003, "A Model for Temporal Heterogeneities of Tumor Blood Flow," *Microvasc. Res.*, **65**(1), pp. 56–60.
- Netti, P. A., Baxter, L. T., Boucher, Y., Skalak, R., and Jain, R. K., 1995, "Time-Dependent Behavior of Interstitial Fluid Pressure in Solid Tumors: Implications for Drug Delivery," *Cancer Res.*, **55**(22), pp. 5451–5458.
- Netti, P. A., Hamberg, L. M., Babich, J. W., Kierstead, D., Graham, W., Hunter, G. J., Wolf, G. L., Fischman, A., Boucher, Y., and Jain, R. K., 1999, "Enhancement of Fluid Filtration Across Tumor Vessels: Implication for Delivery of Macromolecules," *Proc. Natl. Acad. Sci. USA*, **96**(6), pp. 3137–3142.
- Pozrikidis, C., 2010, "Numerical Simulation of Blood and Interstitial Flow Through a Solid Tumor," *J. Math. Biol.*, **60**(1), pp. 75–94.
- Pozrikidis, C., and Farrow, D. A., 2003, "A Model of Fluid Flow in Solid Tumors," *Ann. Biomed. Eng.*, **31**(2), pp. 181–194.
- Wu, J., Long, Q., Xu, S., and Padhani, A. R., 2009, "Study of Tumor Blood Perfusion and Its Variation due to Vascular Normalization by Anti-Angiogenic Therapy Based on 3D Angiogenic Microvasculature," *J. Biomech.*, **42**(6), pp. 712–721.
- Wu, J., Xu, S., Long, Q., Collins, M. W., Konig, C. S., Zhao, G., Jiang, Y., and Padhani, A. R., 2008, "Coupled Modeling of Blood Perfusion in Intravascular, Interstitial Spaces in Tumor Microvasculature," *J. Biomech.*, **41**(5), pp. 996–1004.
- Milosevic, M. F., Fyles, A. W., and Hill, R. P., 1999, "The Relationship Between Elevated Interstitial Fluid Pressure and Blood Flow in Tumors: A Bioengineering Analysis," *Int. J. Radiat. Oncol. Biol. Phys.*, **43**(5), pp. 1111–1123.
- Czabanka, M., Vinci, M., Heppner, F., Ullrich, A., and Vajkoczy, P., 2009, "Effects of Sunitinib on Tumor Hemodynamics and Delivery of Chemotherapy," *Int. J. Cancer*, **124**(6), pp. 1293–1300.
- Eichhorn, M. E., Strieth, S., Luedemann, S., Kleespies, A., Noth, U., Passon, A., Brix, G., Jauch, K. W., Bruns, C. J., and Dellian, M., 2008, "Contrast Enhanced MRI and Intravital Fluorescence Microscopy Indicate Improved Tumor Microcirculation in Highly Vascularized Melanomas Upon Short-Term Anti-VEGFR Treatment," *Cancer Biol. Ther.*, **7**(7), pp. 1006–1013.
- Jain, R. K., 2005, "Normalization of Tumor Vasculature: An Emerging Concept in Antiangiogenic Therapy," *Science*, **307**(5706), pp. 58–62.
- Jain, R. K., 2008, "Lessons from Multidisciplinary Translational Trials on Anti-Angiogenic Therapy of Cancer," *Nat. Rev. Cancer*, **8**(4), pp. 309–316.
- Willett, C. G., Boucher, Y., di Tomaso, E., Duda, D. G., Munn, L. L., Tong, R. T., Chung, D. C., Sahani, D. V., Kalva, S. P., Kozin, S. V., Mino, M., Cohen, K. S., Scadden, D. T., Hartford, A. C., Fischman, A. J., Clark, J. W., Ryan, D. P., Zhu, A. X., Blaszkowsky, L. S., Chen, H. X., Shellito, P. C., Lauwers, G. Y., and Jain, R. K., 2004, "Direct Evidence That the VEGF-Specific Antibody Bevacizumab Has Antivascular Effects in Human Rectal Cancer," *Nat. Med.*, **10**(2), pp. 145–147.
- Chaplain, M. A., McDougall, S. R., and Anderson, A. R., 2006, "Mathematical Modeling of Tumor-Induced Angiogenesis," *Annu. Rev. Biomed. Eng.*, **8**, pp. 233–257.
- Helfand, S. C., 2008, "Canine Hemangiosarcoma: A Tumor of Contemporary Interest," *Cancer Ther.*, **6**, pp. 457–462.
- Mantzaris, N. V., Webb, S., and Othmer, H. G., 2004, "Mathematical Modeling of Tumor-Induced Angiogenesis," *J. Math. Biol.*, **49**(2), pp. 111–187.
- Boucher, Y., Leunig, M., and Jain, R. K., 1996, "Tumor Angiogenesis and Interstitial Hypertension," *Cancer Res.*, **56**(18), pp. 4264–4266.
- Boucher, Y., Baxter, L. T., and Jain, R. K., 1990, "Interstitial Pressure Gradients in Tissue-Isolated and Subcutaneous Tumors: Implications for Therapy," *Cancer Res.*, **50**(15), pp. 4478–4484.
- Jain, R. K., Tong, R. T., and Munn, L. L., 2007, "Effect of Vascular Normalization by Antiangiogenic Therapy on Interstitial Hypertension, Peritumor Edema, and Lymphatic Metastasis: Insights From a Mathematical Model," *Cancer Res.*, **67**(6), pp. 2729–2735.
- Liu, Q., Mirc, D., and Fu, B. M., 2008, "Mechanical Mechanisms of Thrombosis in Intact Bent Microvessels of Rat Mesentery," *J. Biomech.*, **41**(12), pp. 2726–2734.
- Yuan, F., Dellian, M., Fukumura, D., Leunig, M., Berk, D. A., Torchilin, V. P., and Jain, R. K., 1995, "Vascular Permeability in a Human Tumor Xenograft: Molecular Size Dependence and Cutoff Size," *Cancer Res.*, **55**(17), pp. 3752–3756.
- Stohrer, M., Boucher, Y., Stangassinger, M., and Jain, R. K., 2000, "Oncotic Pressure in Solid Tumors Is Elevated," *Cancer Res.*, **60**(15), pp. 4251–4255.
- Skalak, T. C., and Schmid-Schonbein, G. W., 1986, "The Microvasculature in Skeletal Muscle. IV. A Model of the Capillary Network," *Microvasc. Res.*, **32**(3), pp. 333–347.
- Schmid-Schonbein, G. W., 1988, "A Theory of Blood Flow in Skeletal Muscle," *J. Biomech. Eng.*, **110**(1), pp. 20–26.
- Lu, D., Wientjes, M. G., Lu, Z., and Au, J. L., 2007, "Tumor Priming Enhances Delivery and Efficacy of Nanomedicines," *J. Pharmacol. Exp. Ther.*, **322**(1), pp. 80–88.
- Leunig, M., Yuan, F., Menger, M. D., Boucher, Y., Goetz, A. E., Messmer, K., and Jain, R. K., 1992, "Angiogenesis, Microvascular Architecture, Microhemodynamics, and Interstitial Fluid Pressure During Early Growth of Human Adenocarcinoma LS174T in SCID Mice," *Cancer Res.*, **52**(23), pp. 6553–6560.
- Pries, A. R., Neuhaus, D., and Gaetgens, P., 1992, "Blood Viscosity in Tube Flow: Dependence on Diameter and Hematocrit," *Am. J. Physiol.*, **263**(6, Pt 2), pp. H1770–H1778.
- Sugihara-Seki, M., and Fu, B. M. M., 2005, "Blood Flow and Permeability in Microvessels," *Fluid dynamics research*, **37**, pp. 82–132.
- Baxter, L. T., and Jain, R. K., 1989, "Transport of Fluid and Macromolecules in Tumors. I. Role of Interstitial Pressure and Convection," *Microvasc. Res.*, **37**(1), pp. 77–104.

- [48] Boucher, Y., Brekken, C., Netti, P. A., Baxter, L. T., and Jain, R. K., 1998, "Intratumoral Infusion of Fluid: Estimation of Hydraulic Conductivity and Implications for the Delivery of Therapeutic Agents," *Br. J. Cancer*, **78**(11), pp. 1442–1448.
- [49] Netti, P. A., Berk, D. A., Swartz, M. A., Grodzinsky, A. J., and Jain, R. K., 2000, "Role of Extracellular Matrix Assembly in Interstitial Transport in Solid Tumors," *Cancer Res.*, **60**(9), pp. 2497–2503.
- [50] Griffon-Etienne, G., Boucher, Y., Brekken, C., Suit, H. D., and Jain, R. K., 1999, "Taxane-Induced Apoptosis Decompresses Blood Vessels and Lowers Interstitial Fluid Pressure in Solid Tumors: Clinical Implications," *Cancer Res.*, **59**(15), pp. 3776–3782.
- [51] Neal, C. R., and Michel, C. C., 2000, "Effects of Temperature on the Wall Strength and Compliance of Frog Mesenteric Microvessels," *J. Physiol.*, **526** (Pt 3), pp. 613–622.
- [52] Paulsson, M., 1992, "Basement Membrane Proteins: Structure, Assembly, and Cellular Interactions," *Crit. Rev. Biochem. Mol. Biol.*, **27**(1–2), pp. 93–127.
- [53] Ribatti, D., Nico, B., Crivellato, E., and Vacca, A., 2007, "The Structure of the Vascular Network of Tumors," *Cancer Lett.*, **248**(1), pp. 18–23.