Supplement

Details of the mathematical model

The mathematical model aims to examine the overall interstitial fluid pressure and interstitial fluid velocity profile throughout the entire tumor (1). The tumor is considered spherical. The length scales of the pressure and concentration profiles are assumed to be on the order of the tumor radius. Detailed structures of blood vessels, cells, and the interstitial matrix are not considered explicitly. The model assumes a continuous, spatially distributed source throughout the tumor. It also assumes that the tumor growth rate is slow compared to transport rates, and thus all transport parameters are independent of time.

First, the transport of fluid in the tumor interstitium is described by Darcy's law.

$$u_i = -K\frac{dP_i}{dr} \tag{1}$$

where K is the hydraulic permeability of the interstitium (cm^2/mmHg/s) and u_i is the fluid velocity (cm/s). This equation is then combined with the continuity equation for steady-state incompressible flow:

$$\underline{\nabla} \cdot \underline{u_i} = \phi_v(r) \tag{2}$$

where $\phi_v(r)$ is the fluid source term (s^{-1}) given by the Starling's Law:

$$\phi_v(r) = \frac{J_v S}{V} = L_p \frac{S}{V}(P_v - P_i - \sigma(\pi_v - \pi_i)) \tag{3}$$

where J_v is the fluid flux across the vascular wall (cm/s), S/V is the surface area of vessel wall per unit volume of tissue (cm^{-1}), L_p is the hydraulic permeability of the vessel wall (cm/mmHg/s). P_v is the microvascular pressure (MVP), and P_i is the interstitial fluid pressure (IFP). The hydrostatic pressure gradient (P_v - P_i) is countered by the oncotic pressure gradient (the difference between π_v, plasma oncotic pressure and π_i, interstitial oncotic pressure), and the reflection coefficient, σ, determines the effectiveness of the oncotic pressure gradient to induce water convection. L_p and σ depend on the properties of solute (i.e. size, charge, configuration)

and physiological properties of the vascular wall (pore size, charge). P_v, P_i, and the two oncotic pressures also depend on the properties of the tissue, blood and lymphatic vasculature.

This equation implies that the fluid source term is uniformly distributed throughout the tumors. This model assumes that there is no functional lymphatic vasculature inside the tumor to drain interstitial fluid (2, 3).

The equation for Darcy's Law is then combined with the continuity equation to give:

$$-\underline{\nabla} \cdot K\underline{\nabla} P_i = \phi_v(r) \tag{4}$$

Assuming all parameters except for P_i are constant, the equation can be simplified to:

$$\nabla^2 P_i = -\frac{\alpha^2}{R^2}\left[P_v - P_i - \sigma(\pi_v - \pi_i)\right], \tag{5}$$

where $\alpha = R\sqrt{\frac{L_p S}{KV}}$.

There is a no flux boundary condition at the center of the tumor due to symmetry:

$$\nabla P_i\big|_{r=0} = 0$$

At the surface of the tumor, two boundary conditions were used for this analysis. For tumors embedded in a fluid, referred to as isolated tumor case here (Case I), the boundary condition is:

$$P_i\big|_{r=R} = 0$$

When the tumor is embedded in tissue (Case II), i.e. the continuity of pressure and interstitial velocity hold:

$$P_i\big|_{r=R^-} = P_i\big|_{r=R^+} \quad \text{and} \quad -K_T \frac{dP_i}{dr}\bigg|_{r=R^-} = -K_N \frac{dP_i}{dr}\bigg|_{r=R^+} \tag{6}$$

where R^- and R^+ represent the tumor-host boundary at the tumor and host side, respectively. K_T and K_N are the hydraulic conductivities of tumor and normal tissue, respectively. The remaining

boundary condition for Case II is that P_i becomes 0 as R approaches infinity, assuming that blood vessels and lymphatic vessels in normal tissue eventually drain all excess interstitial fluid.

Analytical Solutions

The differential equations using the appropriate boundary conditions, pressure and interstitial velocity profiles can be solved analytically for tumors growing as an isolated mass in a body cavity (Case I) or embedded in a host organ (Case II, Figure 1). Equation (5) is arranged into the form of a Bessel equation for each tissue (designated by the subscript *j*); the solution is then a sum of modified Bessel functions:

$$P = r^{1/2} I_{-1/2}\left(\alpha_j \frac{r}{R}\right) + r^{-1/2} I_{1/2}\left(\alpha_j \frac{r}{R}\right). \qquad (7)$$

However, Bessel functions of an order which is half of an odd integer may be transformed into elementary functions. In the present case, $I_{-1/2}(x) = \sqrt{\frac{2}{\pi x}}\cosh(x)$ and $I_{1/2}(x) = \sqrt{\frac{2}{\pi x}}\sinh(x)$. Further details of the derivation can be found in reference (4). The relative interstitial fluid pressure ($\hat{P}$) and relative interstitial fluid velocity ($\hat{u}_i$) as a function of relative radial position ($\hat{r}$) are then given in terms of a single parameter α:

Case I: Tumor surrounded by bodily fluid:

$$\hat{P} = \frac{P_i}{P_v - \sigma(\pi_v - \pi_i)} = 1 - \frac{1}{\hat{r}}\frac{\sinh(\alpha\hat{r})}{\sinh(\alpha)} \qquad (8)$$

$$\hat{u}_i = \frac{u_i R}{K_T(P_e)} = \frac{1}{\hat{r}^2}\left[\frac{\alpha\hat{r}\cosh(\alpha\hat{r}) - \sinh(\alpha\hat{r})}{\sinh(\alpha)}\right] \qquad (9)$$

Here, $\hat{P}$ is the interstitial pressure relative to the "effective pressure" P_e defined as $P_e = P_v - \sigma(\pi_v - \pi_i)$. In tumors, $\pi_v \approx \pi_i$ so that P_e is approximately the same as P_v and therefore, $\hat{P}$ is the interstitial pressure relative to the vascular pressure. $\hat{r}$, the relative radius, is simply r/R, and the relative interstitial velocity, $\hat{u}_i$, is the local velocity relative to an effective, or average, bulk velocity at the margin, calculated as though the IFP were uniform throughout the tumor:

$\frac{K(P_e - P_\infty)}{R}$ (here we assume that P_∞, the pressure far from the tumor, is equal to zero). α is defined as $R\sqrt{\frac{L_p S}{KV}}$, where L_p and K are the hydraulic conductivities of the vessel wall and tumor interstitium, respectively, S/V is the ratio of vessel surface area to tumor volume and R is the tumor radius.

Case II: Tumor surrounded by normal tissue:

For a tumor embedded within normal tissue, the relative IFP is given by

$$\hat{P} = 1 - \frac{(1+\alpha_N)}{\hat{r}} \frac{\sinh(\alpha_T \hat{r})}{(\phi+\theta)}; \qquad \hat{r} \le 1 \qquad (10)$$

$$\hat{P} = \frac{\theta \cdot e^{\alpha_N(1-\hat{r})}}{\hat{r}(\phi+\theta)}; \qquad \hat{r} > 1 \qquad (11)$$

where, $\theta = \hat{K}[\alpha_T \cdot \cosh(\alpha_T) - \sinh(\alpha_T)]$ and $\phi = (1+\alpha_N) \cdot \sinh(\alpha_T)$; The relative hydraulic permeability, $\hat{K}$ is given by K_T/K_N. Where the subscripts T and N refer to tumor and normal tissue, respectively.

The relative velocity of the fluid through the interstitium is

$$\hat{u}_i = \frac{(1+\alpha_N)\left[\hat{r}\alpha_T \cosh(\alpha_T \hat{r}) - \sinh(\alpha_T \hat{r})\right]}{(\phi+\theta)\hat{r}^2} \qquad \hat{r} \le 1 \qquad (12)$$

$$\hat{u}_i = \frac{\theta(1+\hat{r}\alpha_N)e^{\alpha_N(1-\hat{r})}}{(\phi+\theta)\hat{r}^2} \qquad \hat{r} > 1 \qquad (13)$$

Therefore, at the tumor boundary ($\hat{r} = 1$),

$$\hat{P} = \frac{\theta}{\phi + \theta} \tag{14}$$

$$\hat{u}_i = \frac{(1+\alpha_N)\theta}{(\phi + \theta)} \tag{15}$$

Limitations of the Current Model:

While the model used here provides considerable insight into the mechanism of the reduction of IFP, it has certain assumptions and limitations. First of all, the tumor is considered to be homogeneous. In reality, a tumor is highly heterogeneous, and there can be avascular and necrotic regions. A tumor can also have a variable growth rate and interstitial components. These can lead to variable transport properties throughout the tumor. The absence of functional blood vessels in necrotic regions also provide a less uniform fluid source, thus affecting the shape of interstitial fluid pressure and velocity profiles.

The pressure distribution around individual blood vessels is also not considered in this model. This may lead to an overestimation of fluid filtration because vessel-vessel interaction can lead to lower pressure gradients around the vessels due to the opposing filtration driving force.

Several of these assumptions were relaxed in subsequent models by Baxter and Jain (5-7), but did not change the overall conclusions. Hence we have not explicitly relaxed these assumptions in this study.

Supplement References

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3. Padera TP, Kadambi A, di Tomaso E et al. Lymphatic metastasis in the absence of functional intratumor lymphatics. Science 2002;296:1883-6.

4. Baxter LT Transport of fluid and macromolecules in normal and neoplastic tissue. Chemical Engineering, Vol. Ph.D., pp. 448. Pittsburgh, PA: Carnegie Mellon University, 1990.

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