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Numerical analysis of the effect of capillary geometry on oxygen transport in the microcirculation by MATLAB

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Abstract: Objective Delivery of oxygen in tissues is limited in the space where oxygen must diffuse between the vascular and the surrounding tissues. Normal capillaries are relatively straight and well spaced, in contrast, the tumor vascular networks usually display more irregularity and the vessel wall shows higher permeability and less elasticity. The purpose of this study was to investigate the effect of capillary elasticity and tortuosity on the oxygen distribution and make further investigation on the mechanism of the formation of hypoxic regions in tumor. **Method** One-dimensional capillary model was coupled with the oxygen diffusion model. Oxygen transport was investigated in a Krogh and tortuous tissue model. The capillary geometry was obtained by the one-dimensional model and transferred to the tissue model. Finite element method was employed in the analysis. **Result** The capillary radii along the flow direction under pressures were obtained for different initial radii and the oxygen distribution in the Krogh cylinder tissue model and the model with a tortuous capillary were computed. **Conclusions** when the capillary radius is small, the effect of vessel elasticity may have not significant effect on the oxygen distribution. However, with the capillary radius increasing, the effect on the oxygen transport becomes obvious. Moreover, with the tortuosity of the capillary increasing, the oxygen distribution becomes more heterogeneous, which is in agreement with the result in available reference. This work will be helpful to the investigation of oxygen transport within tumor.

Key words: Capillary; Oxygen transport; Krogh model; Blood flow; Finite element analysis

基于 MATLAB的微循环数值分析 ——毛细血管几何特性对氧输送特性的影响

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摘要: **目的** 考察毛细血管弹性和血管扭曲度对氧分布的影响,从而进一步考察肿瘤组织内形成乏氧区的机理,为肿瘤的放射线疗法提供理论帮助。**方法** 通过一维毛细血管模型与氧传输模型相结合,考察了 Krogh模型和扭曲血管模型内毛细血管与组织内的氧分压分布。血管截面积尺寸由一维模型获得并传输给组织模型。通过有限元分析计算氧分布。**结果** 获得了在一定血流压力和不同毛细血管初始半径下,血管沿流动方向的尺寸变化,并计算了 Krogh模型和扭曲血管模型中,毛细血管与组织内的氧分压分布。**结论** 当毛细血管较小时,血管弹性对氧分压分布的影响很小;随着管径增大,血管弹性的影响也加大。另外,随着毛细血管扭曲度的增加,组织内氧分压分布的不均一性也增加,计算结果与相关文献的结果一致。该工作将有助于进一步考察肿瘤组织内的氧传输。

关键词: 有限元分析; 毛细血管; 氧传输; Krogh模型; 血液流动
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The microcirculation is the blood circulation between arterioles and venules, which nurtures various tissues by providing oxygen and nutrients, and removing waste products. Hence, the physiology of the microcirculation has profound impact on transport phenomena and nutrient exchange, and consequently on human health and disease.

Blood flow in microcirculation has been studied in detail by Charm and Kurland [1] and an original model was proposed. They regarded the blood flow as one-dimension flow in an elastic capillary. It is considered that in a capillary (its radius is close to red blood cell radius), the influence of red blood cell cannot be neglected. They obtained the relationship between pressure, deformation of red blood cell and flow rate basing on the equations of fluid and solid mechanics, and employed these relationships to calculate the variation of the blood vessel and flow rate.

The tissue oxygen transport is of physiological importance and is closely related to the growth and treatment of tumor. The growth of tumor may consume a large quantity of oxygen. On the other hand, when the tumor cells are in the hypoxic state, they may have more resistance to radiotherapy and chemotherapy. Therefore, a lot of relative researches have been carried out to investigate physical mechanism of oxygen transport and formation of hypoxic regions in tumor[2, 3, 4,].

The Krogh tissue cylinder model[5] of oxygen transport between blood capillaries and tissue has served as the foundation and starting point for many theoretical studies[6]. It has also been broadly used in physiological studies for estimating oxygen distribution in tissue. The essence of Krogh models lie in the assumption that the tissue can be subdivided into circular cylindrical units and the units do not exchange oxygen with each other. Despite the simplifications of the Krogh model, it can provide useful insight into the dependence of tissue hypoxic fraction on blood flow rate and oxygen content, and vascular density.

A Green's function method was later introduced for analysis of oxygen delivery by Secomb[7]. Compared with Krogh Model, this model requires no prior assumptions concerning the extent of the tissue region supplied with oxygen by each vessel segment. A computational efficient Green's function approach was used, in which the tissue oxygen field was expressed in terms of the distribution of source strengths along each segment. This method was introduced to analyze an actual vascular networks based on in vivo observations of vascular geometry and blood flow in the tumor microcirculation. It is found that the estimates of the maximum oxygen consumption rate were substantially lower than those obtained from the Krogh's model, and the heterogeneous structure of tumor microcirculation have a substantial effect on the occurrence of hypoxic micro-regions.

Baish *et al*.[8] constructed a percolation-based model of tumor vascular growth that can predict the effects of network architecture on transport. They found that the number of avascular spaces in tumors scaled with the size of spaces and the tortuosity of the vessels produced locally flow-limited transport and reduced flow through the tumor as a whole. The advantage of this method is that it can reproduce the large variability observed experimentally in tumor networks.

He *et al*[9] investigated the effect of blood perfusion on oxygen transport in the tumor tissue by coupling one-dimensional blood flow model and finite element model of breast. They tried to reveal the relationship between blood flow, temperature, and oxygen transport. Zhang *et al*[10] simulated oxygen transfer in human carotid artery bifurcation with a sinus. They found that the oxygen supply to the arterial wall would be decreased due to the formation of slow eddies in the carotid sinus. They further concluded that this might lead to an atherogenic response of the arterial wall.

MATLAB is well known as its powerful functions in computation and image processing and it has been introduced to analyze blood flow in cerebral artery[11] and the cardiovascular system[12], however, few studies have been

carried out in the microcirculation by using MATLAB.

The objective of the work presented here is to investigate blood flow through a capillary and to analyze oxygen distribution in a vessel and its surrounding tissue by coupling the capillary model and tissue model. All the analysis programs were developed on the platform of MATLAB. It is found that the capillary elasticity and tortuosity can significantly affect the oxygen distribution in the tissue.

Analysis Model

The model for flow through capillaries was employed, which was developed by Charm & Kurland[1]. This model can describe the shape of capillaries under pressures. The deviations of the equations are briefly explained in the following. LaPlace's equation is frequently employed to express the relationship between pressure and radius of a curved surface. It is written as

$$t = P_t R_a \tag{1}$$

Where t is tension force per unit length, P_t is transmural pressure difference. The blood vessels are not simple Hookian material, however, for small stress ranges, they may expressed as Hookie's law:

$$S = E_w e \tag{2}$$

The stress acting in the wall of a thin cylindrical vessel under pressure is

$$S = \frac{t}{T} \tag{3}$$

Where T is the wall thickness. Since the wall thickness varies with the change in circumference, the relationship between the wall thickness and radius is given by

$$\frac{dT}{T} = -\nu\frac{2\pi dR_a}{2\pi R_a} = -\nu\frac{dR_a}{R_a} \tag{4}$$

Where ν is Poisson ratio of vessel wall. For materials of isotropic materials, $\nu = 0.25$. Substituting Eq. (1) and (4) in Eq. (3), and further substituting Eq. (3) in Eq. (2), the relationship between transmural pressure in the vessel and the vessel radius is therefore written as

$$\frac{R_a}{R_0} = \frac{P_t R_0}{E_w T_0}\left(\frac{R_a}{R_0}\right)^{\nu} + 1 \tag{5}$$

Where R_a is radius of vessel at given pressure, R_0 is radius of vessel at rest, E_w is elastic modulus of vessel wall, ν is Poisson ratio of vessel wall, and T_0 is thickness of wall at "rest". It is noted that the equation is suitable for small changes in radius.

The red cell can be considered as a torus encircling a disc membrane. The circumferential stress in the torus is considered to be main stress to cause the radial contraction of the torus. The circumferential strain can be expressed as

$$\frac{\Delta r}{r_c} = \frac{r_c F\cos\theta}{\pi E_c a^2} \tag{6}$$

Where a is the radius of the torus, r_c is the radius of the cell, and F is the force per unit of a circumference exerted on the torus. Because it is know that the red cell deforms in the shape of paraboloid, there is an expression about θ as the following

$$\theta = \frac{P t_c (r_c - \Delta r)}{2LF} \tag{7}$$

Where t_c is the average thickness of cell which is a function of Δr. F can be related to the applied pressure, which is written as

$$F = t_c\left[\frac{E_c (r_c - \Delta r)^2 (P/L)^2}{24(1-\nu_c)}\right]^{1/3} \tag{8}$$

Where Ec is elastic modulus of cell and ν_c is Poisson ratio of cell. Substituting Eq. (7) and Eq. (8) in Eq. (6), we can obtain the change in cell radius

$$\Delta r = \frac{3V_0 r_c^2}{\pi a^2}\left[\frac{P/L}{(r_c-\Delta r)^5 24E_c(1-\nu)^2}\right]^{1/3} \cos\left[\frac{1}{2}\left\{\frac{P}{E_c L}(r_c-\Delta r)[24(1-\nu_c)]\right\}^{1/3}\right] \tag{9}$$

According to Poiseuille equation, the plasma flow rate through a capillary slightly larger than the cell is

$$Q = \frac{\pi\Delta P}{8\mu_p \Delta L}[R_a^4 - (r_c - \Delta r)^4] \tag{10}$$

Where r_c is the radius of cell at rest, Δr is the change in radius of cell due to deformation under pressure, and μ_p is plasma viscosity. Using Eqs. (5), (9), and (10), the capillary geometry under pressure can be determined.

In order to analyse the oxygen transport, the Krogh tissue cylinder model is employed. In Krogh's models, it is assumed that the tissue can be subdivided into circular cylindrical units each of which has a capillary oriented along the axis. The concentration of dissolved free oxygen is proportional to the partial pressure of oxygen, and the partial pressure of oxygen (PO_2) distribution in the tissue cylinder is assumed to be axisymmetric. Thus, the convection and diffusion transfer of oxygen can be expressed as the following[2],

$$\alpha\frac{\partial PO_2}{\partial t} + u\alpha\frac{\partial PO_2}{\partial x} = D_{eff}\alpha\left(\frac{\partial^2 PO_2}{\partial x^2} + \frac{\partial^2 PO_2}{\partial y^2}\right) - M \quad (11)$$

Where α denotes oxygen solubility, D_{eff} denotes effective diffusion coefficient. We assume $\alpha = 3 \times 10^{-5}$ $cm^3O_2\,cm^{-3}\,mmHg^{-1}$ and $D_{eff} = 1.5 \times 10^{-5}$ cm^2/s[3]. M denotes oxygen consumption and is assumed to be constant. u is the blood velocity which is calculated from the capillary model.

Numerical Methods

Eq. (5), (9), and (10) for the capillary can not be solved alone and it should be calculated simultaneously. Supposing that we knew the physical properties through the capillary including entrance pressure, exit pressure, and osmotic pressure difference across the wall, hence, the capillary radius, flow rate and pressure could be solved simultaneously by iterative method. Through adjusting the node pressure difference and computing R_a, Δr and Q iteratively, the radii and pressure drop in different place of capillary could be determined. Fig. 1 gives the flow chart for the computation of capillary parameters. The specific procedures are as the follows.

1. Assume ΔP_1 for the first segment of the capillary and calculate the vessel radius R_a and the radius change of the cell Δr_1 for the same segment according to Eq. (5) and Eq. (9).

2. Compute the hydrostatic and transmural pressures in different segment and calculate R_a and Δr for the corresponded capillary segments.

3. Compare the sum of ΔP_i with the pressure difference P_{in}-P_{out}. If these two values agree, the calculated R and r in different segment are correct. If they do not, a new ΔP_1 will be assumed until the agreement is reached.

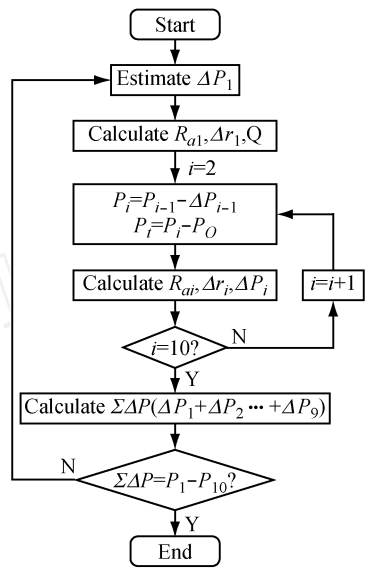


Fig. 1 Flow chart for the computation of the capillary parameters
图 1 计算毛细血管内血液流动和血管参数的流程图

After the blood flow rate and deformation of vascular were obtained, the radii of the vascular and velocity of blood flow might be transferred to the Krogh tissue cylinder model. Therefore, the distribution of oxygen in the capillary and tissue could be calculated numerically by combining Eq. 11 and suitable boundary conditions. Eq. 11 was discretized by Galerkin finite element method. All the work was implemented by MATLAB. Fig. 2 is the schematic diagram of the Krogh model for the analysis of oxygen transport.

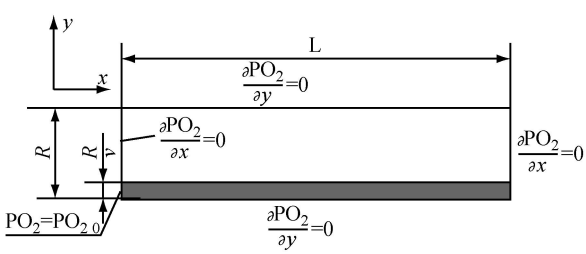
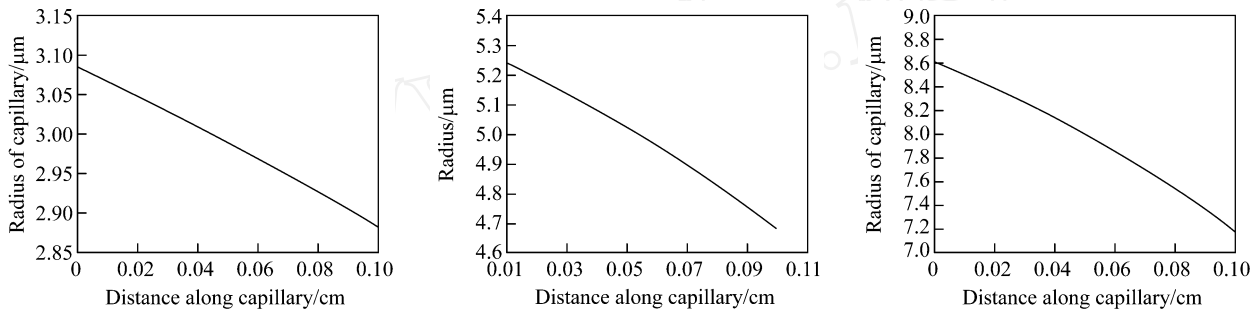


Fig. 2 The analysis model of oxygen transport
图 2 毛细血管及组织内的氧输运分析模型及边界条件

Results and discussion

When blood flows into the capillary, the vessel radii will not remain uniform and it will be tapered under transmural pressures. Figure 3(a)-(c) show the vessel radii

along the flow direction under the constant pressure. The radii of vessel at rest are 3 μm, 5 μm, and 8 μm. It can be seen that the radii decrease along the flow direction non-linearly and the non-linearity becomes greater when the radius at rest state increases. When the initial radius is 3 μm, the capillary radii under pressure decrease gradually and the non-linearity is not obvious (Fig 3a). When the initial radius becomes 8 μm, the shape of the capillary under pressure becomes dif-ferent from that with smaller capillary diameters and the variation rate of the radii becomes greater (fig 3c)



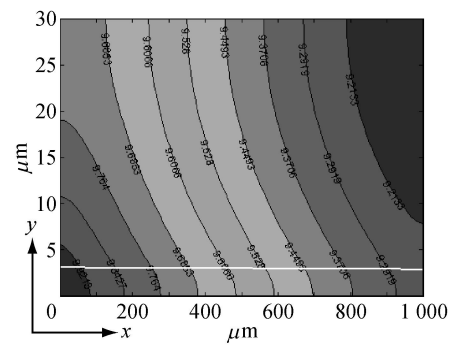
(a) (b) (c)

Fig 3 Variation profiles of capillary radius under pressure for different initial capillary radius (a) R_0 =3 μm, (b) R_0 =5 μm, (c) R_0 =8 μm

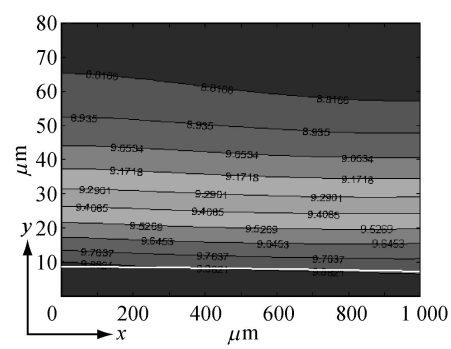
图 3 不同初始血管半径下,血流通过毛细血管时血管半径沿流动方向的变化 R_0 =3 μm, (b) R_0 =5 μm, (c) R_0 =8 μm

After the parameters for the capillary were obtained, the data of capillary radii was transferred to the tissue model for computing the oxygen distribution. Fig 4(a)-4(b) give the oxygen distribution contour in the cylinder tissue model for different capillary radii with the surrounding tissues. The area from the x axis to the white line is referred to the vessel area and other area is referred to the tissue. The number in the solid lines and the color are the partial pressure of the oxygen. It can be seen that for the vessel of 8 μm, the partial pressure of oxygen (oxygen tension) along the flow direction decreases slowly, however it decreases quickly outward from the vessel to tissue. This implies that with the capillary radius increasing, the partial pressure of oxygen far from the vessel will be far less than that near the vessel. The same tendency can also be seen in Fig 5.

Fig 5(a)-(b) give the radial oxygen tension profiles for considering capillary elasticity, where the solid lines denote the profiles without consideration of the deformation of vessel, and the broken lines denote the profiles considering the deformation of vessel.



(a)



(b)

Fig 4 Oxygen distribution for different radii of capillary (a) r = 3 μm, (b) r = 8 μm

图 4 毛细血管半径改变时,血管及组织内的氧分压分布等值线图 (a) r = 3 μm, (b) r = 8 μm

It is seen that there are almost no difference in the oxygen tension profiles for the two conditions when the capillary radius at rest is 5 μm, whereas the oxygen profiles at the entrance and exit appear differ-ence when the initial capillary radius is 8 μm, which reveals that when the capillary radius is small, the effect of vessel elasticity on the oxygen transfer is negligible, however, with the radius increasing, the effect becomes important.

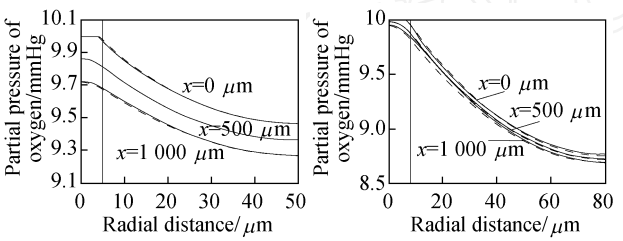


Fig. 5 Radial oxygen profile for considering vessel elasticity (a) $r=5$ μm, (b) $r=8$ μm

图 5 在不同轴向流动位置,考虑血管弹性和不考虑血管弹性时氧分压沿径向方向的变化 (a) $r=5$ μm, (b) $r=8$ μm

The experimental results[13] showed that the tumor vascular is more tortuous than the normal capillary, therefore, the effect of the tortuosity of the vessels on oxygen transport was also investigated. Fig. 6 (a) shows the generated mesh in the computational domain, where the red curved lines are referred to the area of the vessel. The distribution of partial pressure of oxygen with the same size of vessel but with different curvature was computed. Fig. 6 (b) gives the oxygen tension distribution with a less tortuous vessel and Fig. 6 (c) is the oxygen tension distribution with a more tortuous vessel whose curvature is greater. The colors are the scale of oxygen partial pressure and the blue curved lines are referred to the vessel boundaries. It can be seen that, due to the tortuosity of the vessel, the oxygen distribution becomes asymmetrical. In one side, the oxygen tension is higher, and in another side, the oxygen tension is lower. Furthermore, with the tortuosity increasing, the oxygen distribution becomes more heterogeneous.

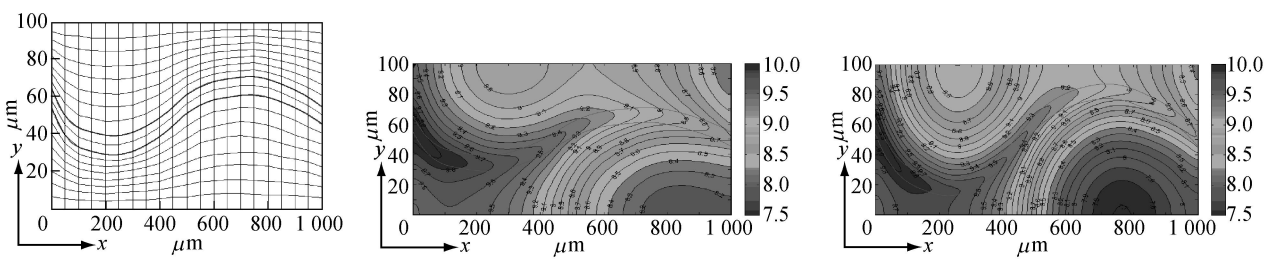


Fig. 6 Oxygen distribution in tissue with tortuous vessels (a) Finite element mesh for computational domain, (b) oxygen distribution for small vessel tortuosity, (c) oxygen distribution for large vessel tortuosity

图 6 扭曲血管组织模型中的氧分压分布等值线图 (a) 计算模型的有限元网格划分, (b) 半径相同,血管扭曲度较小时的氧分压分布等值线图, (c) 半径相同,血管扭曲度较大时的氧分压分布等值线图

Concluding remarks

In this study, a model for blood flow through a capillary is coupled with the tissue model to investigate the effect of capillary on the oxygen transport. The computed results show that with the vessel radius increasing, the oxygen profiles appear different from those when the deformation of the vessel is considered. Moreover, when the vessel is spaced tortuously, the oxygen distribution becomes non-uniform.

In Less's experiment[13] about microvascular architecture in a mammary carcinoma, they found that the mean diameter of the tumor capillary was 10 μm which was greater than that in most normal tissues. Our results show that when the vessel diameter is 8 μm, the partial pressure of oxygen is different from that when the wall elasticity is not considered. These results suggest that the wall elasticity of the tumor capillaries can affect oxygen transfer in tissues. Furthermore, tumors are known to contain many tortuous vessels, which is one reason to form avascular area. The

present study implies that the tortorsity can lead to the formation of hypoxic region, and thus lead to the heterogeneous distribution of oxygen distribution. People wonder why tumor vasculature has a higher resistance than normal vasculature although tumor diameter is greater. Our results may provide an insight into explaining the paradox: Greater diameter can increase the gradient of oxygen partial pressure, however it is not helpful to increase the oxygen partial pressure in tissue. It may be more useful to let the tortuous vessels become regular. The same opinion was given by Baish *et al*[8] who used an invasion percolation-based network model of tumor.

The work may be extended further by including the permeability of capillary vessel and considering the real geometry of tumor vasculature.

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