

A theoretical investigation of oxygen transport and the growth of avascular solid tumor in the micro-environment

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論 文 名 : A theoretical investigation of oxygen transport and the growth of avascular solid tumor in the micro-environment
(微小循環における酸素輸送と無血管期の腫瘍の成長に関する理論研究)

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論 文 内 容 の 要 旨

The present dissertation begins with an investigation of a very significant and fundamental topic involved in the microcirculation, namely, the study of the distribution of oxygen concentration at the most detailed level. For this, we numerically calculated the entire process of oxygen transport, by developing a 3D porous media model with coupled solid deformation--fluid seepage--convection and diffusion. The principal novelty of the model is that it takes into account the volumetric deformation of both capillaries and tissue resulting from capillary fluctuations. The model couples the deformations with seepage, and then the coupled deformation and seepage impacts on the convection-diffusion of oxygen. Specifically, we quantitatively examined how solid deformation, fluid seepage, and convection-diffusion combine to affect the transport of oxygen. We obtained the following important findings:

1. Solid deformation is more significant in the middle of a capillary, where the maximum value of volumetric deformation reaches about 0.5%;
2. Though solid deformation has a small impact on seepage, it can exert a positive influence on the tissue fluid so that it flows more uniformly; it can also cause the oxygen to be transported more uniformly, which eventually impacts on the distribution oxygen concentration by 0.1%~0.5%.
3. The change in pore pressure distribution within the tissue near the arteriole end and near the venule end of a capillary is several times larger than within the tissue surrounding the middle of the capillary.
4. Convection-diffusion given by coupled deformation and seepage has a 16% maximum, and a 3% average, increase in oxygen concentration, compared to pure diffusion. Its more significant role is to allow oxygen to be transported more evenly, especially away from the capillary.
5. Convection-diffusion has a greater effect in the middle of a capillary than near the ends of a capillary. Also, larger values of the permeability coefficient, or smaller values of the diffusion coefficient, produce a more obvious effect on oxygen transport.

Thus, the numerical results from this more comprehensive theoretical model indicate that the convection-diffusion of oxygen transport should be taken into consideration in relevant studies; the importance of the role lies in the fact that it allows oxygen to be transported more uniformly. This property should be given more attention and studied in more detail.

Then, building on this mathematical coupled model for oxygen transport, we developed a coupled mathematical model of avascular tumor growth based on porous media mechanics. This comprises of the migration of tumor cells (TCs), the degradation of extracellular matrix (ECM), the transport of matrix-degrading enzymes (MDEs), the seepage of tissue fluid, and the supplement and consumption of oxygen. The simulation of a solid tumor grows in the micro-environment composed of the pre-existing capillaries and the surrounding tissues. The specific property of changing porosity with the growth of TCs in a tumor micro-environment is taken into account. We proposed functional coefficients for fluid seepage and oxygen diffusion, and incorporated the convection-diffusion of oxygen and the convection of MDEs. From this modified model the main findings included: first, a solid tumor originating in the inlet region undergoes necrosis in the outlet region because of a low supply of oxygen, while a solid tumor originating in the outlet region undergoes necrosis at the primary site because of overconsumption of oxygen; second, tumors further from capillaries grow faster than tumors close to adjacent capillaries; third, the pre-existing capillaries greatly impact on the transport of those chemical factors involved in tumor growth, further impacting on tumor migration and necrosis.

In addition, many previous studies have predicted the importance of MDEs for the diagnosis of certain cancers, for increased MDEs (matrix-degrading enzymes) are experimentally examined in early stages of solid tumors, i. e. avascular tumors. However, no quantitative standard exists for MDEs as diagnostic bio-markers. To quantify MDE transport during the avascular stage of solid tumors, a mathematical model based on diffusion-advection models is proposed, coupling MDE convection and diffusion, the amoeboid-like migration of TCs (tumor cells), fluid seepage, ECM (extracellular matrix) degradation, and oxygen convection and diffusion. The data are presented in the fourth chapter. A specific capillary-tissue micro-environment for avascular tumors with changing porosity for the porous medium is incorporated. The numerical results indicated that TCs enter the blood long before cell necrosis; however, MDEs diffuse much further than the TC migration, and enter the blood circulation much earlier than TCs; when a solid tumor originates at the inlet end, MDEs enter the blood 12 cell cycles earlier than TCs; when a tumor originates at the outlet end, MDEs enter the blood 15 cell cycles earlier than TCs. These results theoretically demonstrate the diagnostic significance of MDEs for early cancers, quantitatively provide a basis to determine the tumor stage when MDEs can be detected in blood, and estimate solid tumor size by measuring MDE concentrations in blood.