# Coupled modeling of tumour angiogenesis, tumour growth, and blood perfusion

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(Received 06 April 2011; accepted 14 May 2011; published online 10 July 2011)

**Abstract** This paper proposes a more realistic mathematical simulation method to investigate the dynamic process of tumour angio-genesis by fully coupling the vessel growth, tumour growth and associated blood perfusion. The tumour growth and angiogenesis are coupled by the chemical microenvironment and the cell-matrix interaction. The haemodynamic calculation is carried out on the new vasculature, and an estimation of vessel collapse is made according to the wall shear stress criterion. The results are consistent with physiological observations, and further confirm the application of the coupled model feedback mechanism. The model is available to examine the interactions between angiogenesis and tumour growth, to study the change in the dynamic process of chemical environment and the vessel remodeling. © *2011 The Chinese Society of Theoretical and Applied Mechanics.* [doi:10.1063/2.1104402]

**Keywords** tumour growth, angiogenesis, coupled model, mathematical modeling

Tumour induced angiogenesis is the formation of new blood vessels from the preexisting vasculature for supporting the expansion of the tumour mass by providing a source of oxygen, nutrients and growth factors. According to the dynamic tumour growth process, the local environment can be divided into three basic phenomena such as: (a) tumour microvasculature growth, (b) tumour cell growth and (c) blood perfusion associated with local mass transportation. The three processes are closely coupled and govern the tumour growth. Due to the difficulties of experimental measurement and visualization of the tumour growth, and the complex nature of the tumour local environment, the understanding of the relationship of the three processes is still very poor. Mathematical modeling of tumour induced angiogenesis forms an important part of angiogenesis study in recent years.

The main aim of this study is to propose a more realistic mathematical simulation framework to investigate the dynamic process of tumour angiogenesis by fully coupling the vessel growth, tumour growth and associated blood perfusion. In the simulation process, the tumour growth changes the local vascular endothelial growth factors (VEGF) distribution which will influence the endothelial cells (ECs) migration and angiogenesis. At the same time, the newly formed microvessels change local oxygen supply to influence the tumour growth. The extra-cellular matrix (ECM) is also treated as a haptotaxis factor for both tumour cell (TC) invasion and angiogenesis. We then incorporated the haemodynamic calculation in intravascular and interstitial spaces, and investigated the influence of wall shear stress on vessel collapse and remodeling.

A probabilistic hybrid model is defined on a square lattice, in which 200 × 200 grids for tumour cell proliferation, mitosis, and apoptosis based on the work of Anderson.[1] The 2D9P hybrid discrete-continuum angiogenesis model used here is based on our previous work[2] which assumed the ECs migrating through (1) random motility, with the diffusion coefficient $D_e$; (2) chemotaxis in response to the distribution of VEGF concentration ($c_v$), with chemotaxis coefficient $\phi_c$ and (3) haptotaxis in response to the local ECM concentration ($c_f$), with haptotaxis coefficient $\phi_h$. The equation describing the EC concentration ($e$) is

$$\frac{\partial e}{\partial t} = \underbrace{D_e \nabla^2 e}_{\text{random motility}} - \nabla \cdot \left( \underbrace{\frac{\phi_c}{1+\sigma c_v} e \nabla c_v}_{\text{chemotaxis}} + \underbrace{\phi_h e \nabla c_f}_{\text{haptotaxis}} \right) \tag{1}$$

The mechanism controls the vessel remodeling based on the well recognized fact that microvessels are likely to collapse if they stay in a low wall shear stress for a long term. This principle for tumour vessel remodeling was originally proposed by Bartha and Rieger.[3] The blood perfusion model used in their study, however, only included intravascular flow without the coupling of transcapillary and interstitial flow. A coupled model of blood perfusion in intravascular, transcapillary and interstitial spaces in tumour microvasculature that we developed previously[2] has been adapted in this study.

Figure 1 presents the coupling process of the simulation. The tumour growth and angiogenesis are cou-

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pled by the changes of chemical environment including oxygen, VEGF concentration, and the ECM concentration. It is based on the facts as follows: (a) the tumour growth changes the VEGF distribution which will induce the ECs migration and angiogenesis; (b) at the same time, the newly formed capillaries supply more oxygen for the local tumour growth. The ECM is included in the model to influence the invasions of TCs and angiogenesis to the surrounding tissue. The interactions of the TC-ECM and the EC-ECM are governed by the matrix-degradative enzymes (MDE) equation. The ECM can be degraded by the MDE which is produced by the TCs and ECs. On the other hand, the ECM will influence the EC migration as a haptotaxis factor.

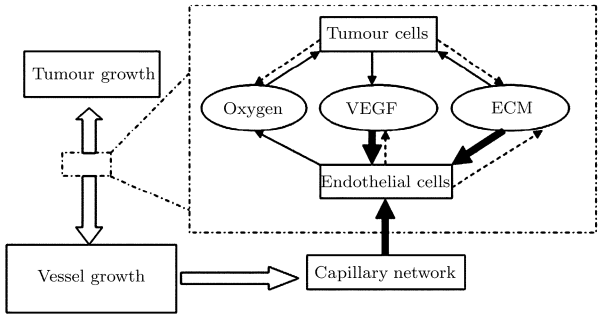


Fig. 1. Schematic diagram of the coupling process of the model. The solid arrow represents the positive effects, while the dotted arrow represents the negative effects. The bold arrows indicate the factors directly influencing angiogenesis.

In the results presented here, the simulation started from the initial tumour and microvascular network and finished at 24 days when the tumour size reached a finishing criteria.

The total number of the micro vessels and tumour cells increase continually in the simulation with time, as shown in Figs. 2(a) and 2(b). However, the proliferating tumour cell numbers reduce at the late period. It is worth mentioning that a rapid increase of necrotic cells appeared in the period of day 8th to day 12th (Fig. 2(b)), due to the inadequate oxygen supply in the tumour region for the time. As a consequence, a rapid angiogenesis phase occurs in the following days (Fig. 2(a)). This result clearly demonstrates the dynamic responses between the tumour and angiogenesis from the model.

The integrated distributions of micro vessel density and TC number from the centre of the tumour to the parent vessel at the final stage are shown in Figs. 2(c) and 2(d). The most dense area of vessels ($x = 0.3$) is more closer to the tumour centre than the maximum TC number region ($x = 0.4$–$0.5$). This implies that the angiogenesis has a time delay on spreading in comparison with the tumour growth.

Figure 3 shows the flow information in the capillary network at three time points. The intravascular pressure $P_v$ drops from the boundary to the centre of the tumour gradually. The higher $P_v$ value was uniformly distributed at the upper and lower boundary of the tumour at the early stage, which is gradually expended to tumour boundary regions with increasing simulation time and eventually becomes heterogenic towards the equator of the tumour. It is also evidenced that the few mature vessels in the centre of the tumour provide important channels on rising the $P_v$ in the tumour central region in the later stage of simulation. The intravascular blood velocity $U_v$ shows that blood flows faster in mature capillaries in the tumour boundary regions while the high $U_v$ region shows a heterogenic distribution. This is consistent with the physiological observation[4] that the abnormal vascular architectures increase the resistance to blood flow in tumours and contribute to intermittent and heterogeneous blood perfusion.

The interstitial pressure $P_i$ and the interstitial fluid velocity $U_i$ are also shown in Fig. 3. A plateau of $P_i$ is formed in the interior of the tumour, and drops dramatically in the margin. As the consequence, $U_i$ is very slow inside the tumour due to the low gradient of $P_i$, and becomes much higher at the periphery area. It is worth mentioning that $U_i$ is 100 times smaller than $U_v$ in value which indicates that intravascular flow plays the most important role in tumour mass transport.

*This work was supported by the National Natural Science Foundation of China (10772051), the State Scholarship Fund of China (2009610108) and the Ninth Innovation Fund for Graduate Students of Fudan University (YAN CAI).*

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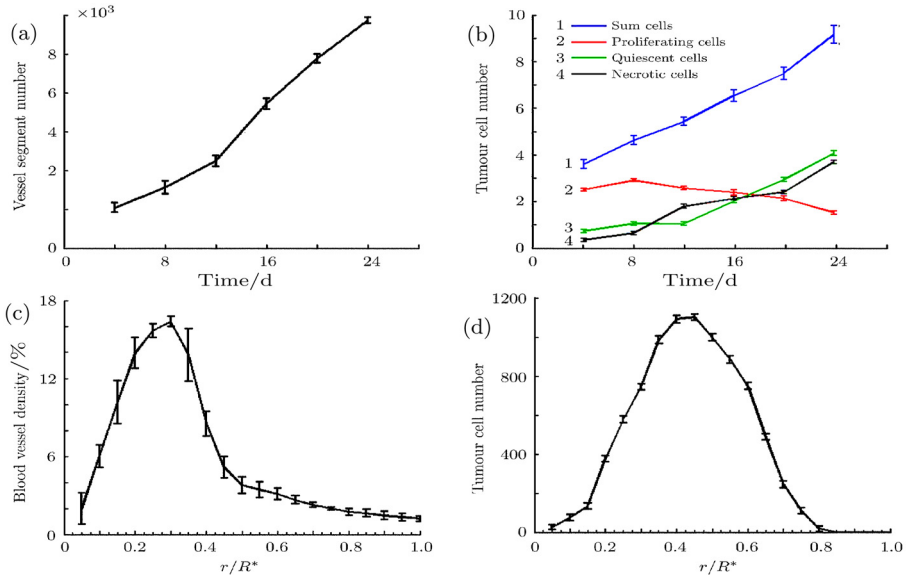


Fig. 2. Vessel and tumour cells growth history (a), (b); spatial integrated distribution of vessel density and tumour cell number at the final stage (c), (d). The $x$-axis is the polar coordinate representation, with the origin at the centre of the whole domain and $x = 1$ is the boundary where the parental vessel located.

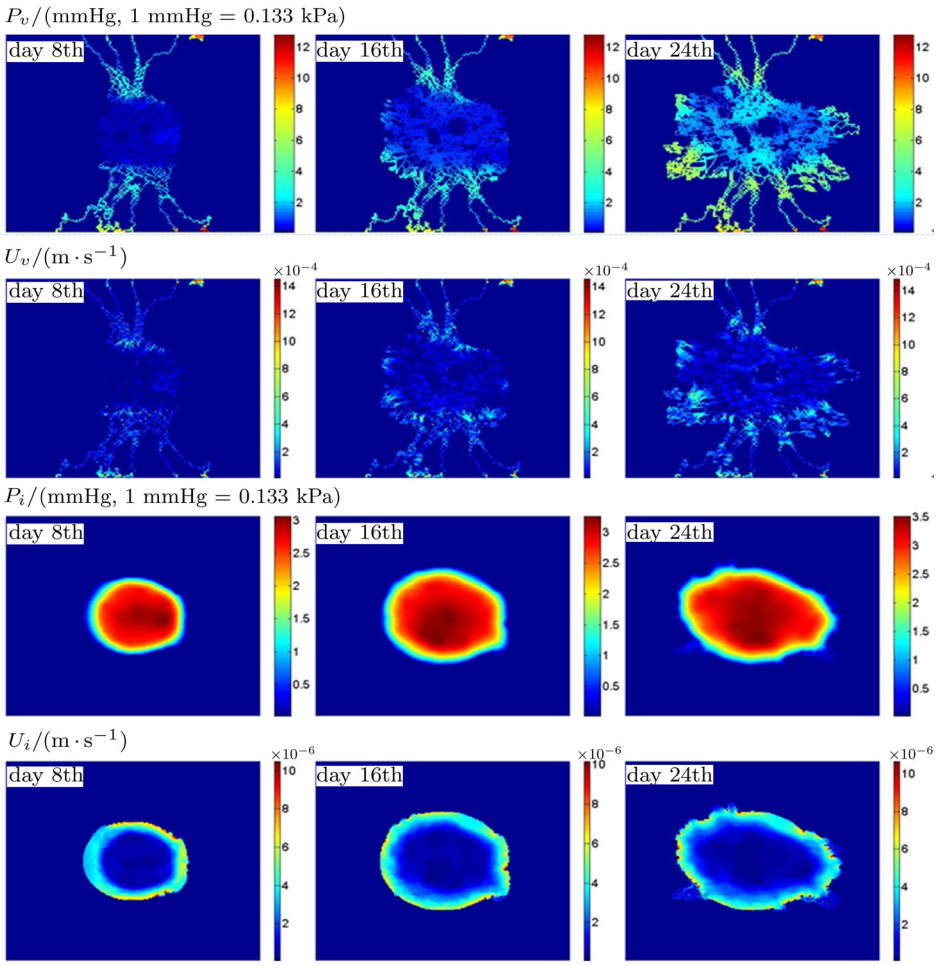


Fig. 3. The heamodynamic information including the intravascular pressure $P_v$, the intravascular blood velocity $U_v$, the interstitial pressure $P_i$ and the interstitial fluid velocity $U_i$, in the capillary network at three time points.