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Simulation of tumor induced angiogenesis using an analytical adaptive modeling including dynamic sprouting and blood flow modeling

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ABSTRACT

In this paper, an adaptive model for tumor induced angiogenesis is developed that integrates generation and diffusion of a growth factor originated from hypoxic cells, adaptive sprouting from a parent vessel, blood flow and structural adaptation. The proposed adaptive sprout spacing model (ASS) determines position, time and number of sprouts which are activated from a parent vessel and also the developed vascular network is modified by a novel sprout branching prediction algorithm. This algorithm couples local vascular endothelial growth factor (VEGF) concentrations, stresses due to the blood flow and stochastic branching to the structural reactions of each vessel segment in response to mechanical and biochemical stimuli. The results provide predictions for the time-dependent development of the network structure, including the position and diameters of each segment and the resulting distributions of blood flow and VEGF. Considering time delays between sprout progressions and number of sprouts activated at different time durations provides information about micro-vessel density in the network. Resulting insights could be useful for motivating experimental investigations of vascular pattern in tumor induced angiogenesis and development of therapies targeting angiogenesis.

Introduction

One solid tumor is a dense mass of cells with the common feature of uncontrolled cellular growth. If these cells be able to form a new capillary network to supply oxygen and nutrients and to remove waste products, cancer will happen. Tumor angiogenesis, the process by which new blood vessels are formed from pre-existing ones through migration and proliferation mechanisms (Figg and Folkman, 2008 and Vilanova et al., 2013), is a crucial component in continuous cancerous tumor growth (Mantzaris et al., 2004).

Tumor angiogenesis is dynamically regulated by several pro- and anti-angiogenic molecules produced by a variety of sources including tumor cells, endothelium, extracellular matrix, pericytes, and plasma clotting products (Mantzaris et al., 2004; Araujo and McElwain, 2004 and Jain, 2005). Among a variety of pro-angiogenic growth factors, a number of chemicals, collectively known as tumor angiogenic factors (TAF) (Folkman and Klagsbrun, 1987) have a predominant role. Also, it has been shown that some anti-angiogenic factors are produced in the vicinity of blood vessels underlying angiogenesis including tumstatin, arrestin, and canstatin, and most notably, angiostatin and endostatin (Addison-Smith et al., 2008 and Anderson et al., 2000a). Angiostatin, a 38 kDa protein cleaved from the serum protein plasminogen by the action of factors such as tissue plasminogen activator (tPA) and several of the matrix metalloproteases (MMPs) (Jurasz et al., 2003), and endostatin, an 18–22 kDa fragment of collagens in the vascular and epithelial basement membrane (Saarela et al., 1998), inhibit endothelial cell (EC) growth, proliferation and migration and tumor-induced angiogenesis, with the possible mechanism being disruption of cell–matrix interactions.

When a cancerous tumor reaches to its maximum size in the avascular growth state, secretes TAF into the surrounding tissue (Folkman and Klagsbrun, 1987) and upon reaching to the neighboring blood vessels, it increases permeability in nearby blood vessels (Dvorak, 2003). As a result, blood plasma leaks in the surrounding extracellular matrix (ECM) before angiogenesis sprouting is initiated. This plasma contains both factors of plasminogen activators (PAs) and matrix metalloproteases (MMPs) (Addison-Smith et al., 2008). In both of these enzyme systems (PAs/MMPs), several endogenous inhibitors exist (Kleiner and Stetler-Stevenson, 1993; Beattie and Smyth, 1998). These enzymes are often secreted as inactive precursors which must themselves be partially degraded to reach full activity. These factors may also be present in the ECM through production by endothelial cells or may be released by tumor cells during angiogenesis (Addison-Smith et al., 2008).

Interaction between pro- and anti- angiogenic molecules results formation of new sprouts from an existing parent vessel. Anti-angiogenic

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factors act like a feedback control mechanism to inhibit the sprout formation. The formed sprouts then start to migrate towards the tumor in response to angiogenic factors. The initial response of ECs to these angiogenic factors is a chemotactic one at the tip of the sprouts (Sholley et al., 1984; Terranova et al., 1985; Paweletz and Knierim, 1989; Stokes et al., 1990). There are also some interactions between ECs and ECM that directly affect the cell migration. Fibronectin as a major component of ECM enhances the cell adhesion to the matrix and so promotes ECs migration. This response of ECs to a gradient of adhesiveness of fibronectin, termed haptotaxis response (Anderson and Chaplain, 1998b). Every sprout initiated from the parent vessel migrates towards the tumor, interacting with TAF and fibronectin and after a specific distance may form some branches and anastomosis. As ECs form capillary tube-like structures, blood flows through the structure and the tumor can growth further. Blood consists of forming elements and plasma which make blood flow as a non-Newtonian fluid flow, that its properties, most commonly the viscosity, are dependent on the shear rate (Purves et al., 2004).

Angiogenesis is the formation of new blood vessels in order to deliver blood flow to the tumors. A proper theoretical modeling of this process can be very useful to find effective tumor spreading parameters and the ways of treatment. In the past three decades, several mathematical models have been developed to simulate some of the important features of angiogenesis process. These models can be divided into four main groups; models describe: (1) the avascular tumor growth and invasion (Anderson et al., 2000b; Ramis-Conde et al., 2008; Anderson et al., 2000a and Frieboes et al., 2010; Hosseini and Naghavi, 2015), (2) the sprout spacing process (Addison-Smith et al., 2008; Orme and Chaplain, 1996; Levine et al., 2001; Hosseini and Naghavi, 2016), (3) the sprout progression in response to chemical stimulus and formation of capillary networks (Anderson and Chaplain, 1998b; Hao et al., 2006; Sun et al., 2005; Capasso and Morale, 2009; Travasso et al., 2011) and (4) the blood flow into the hollow capillary structures and network remodeling (McDougall et al., 2002; Stéphanou et al., 2006; Wu et al., 2008; Macklin et al., 2009 and Cai et al., 2011). These models are useful to provide information about the angiogenesis and capillary network specifications such as micro-vessel number (MVN) and network expansion rates, but they rarely coupled all these different parts together.

The numerical procedure of blood flow modeling in a known angiogenesis network is similar in many previous researches. McDougall et al. (2002) introduced a mathematical blood flow in 2D vascular networks. Their blood flow formulation in the vessel was based on the simple fluid mechanics relations. They considered vessels as cylindrical rigid bodies and numerically calculated the blood pressure at each node of the network based on the mass conservation law. Stephanou et al. (2005) used a similar technique for flow modeling through vascular networks in a 2D and 3D network. Afterward Stéphanou et al. (2006) applied the value of the pressure to obtain stresses that induced by fluid flow in the vessels. General relationship between the intravascular pressure and stresses can be seen in some studies (Stéphanou et al., 2006 and Wu et al., 2008).

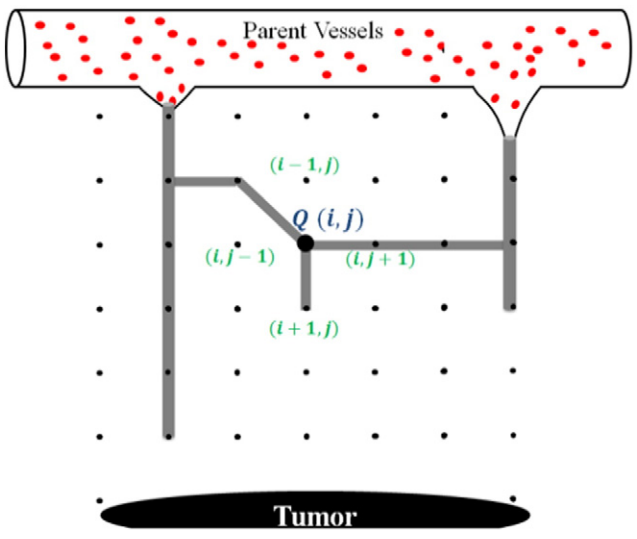

Fig. 1. A Schematic diagram of grid adjoining nodes used in the blood flow modeling.

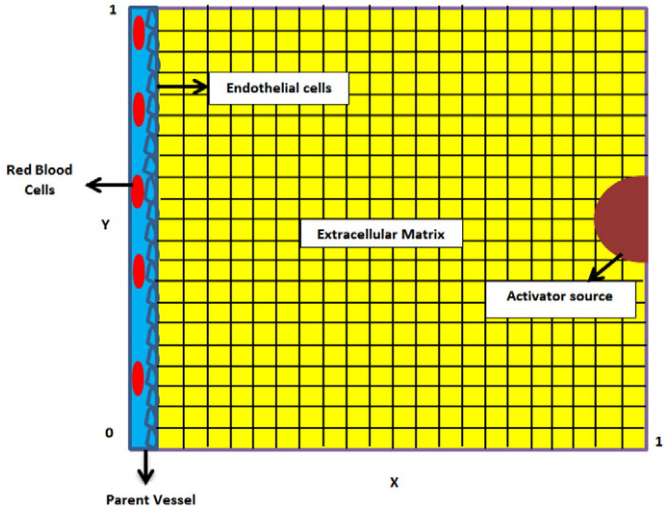

Fig. 2. A schematic diagram of the model domain includes a parent blood vessel, endothelial cells lining the blood vessel and hypoxic cells of the tumor as the source of activator. Discretization of the simulation domain is also illustrated.

In this paper, blood is considered as a non-Newtonian fluid that flows as an incompressible flow and vessels are cylindrical solid rigid boundaries. This structure is coupled with the generation and diffusion of a growth factor originated from hypoxic cells (TAF: VEGF), adaptive sprout spacing along the parent blood vessel at the beginning of the angiogenesis process, and structural adaptation during vascular patterning. Moreover, progression of these sprouts in ECM and their penetration into the tumor as well as penetration of blood flow through the capillary structure is presented. Both sprout (tip) and vessel branching process are considered. Also a time adaptation algorithm is utilized to estimate whether a newly created vessel body has the probability of branching in the future time duration. This time duration, enables us to produce a more realistic capillary structure with considering different time steps.

The main contributions of this work are: 1) development of an analytical model for adaptive sprout spacing process to estimate the time, position and number of sprouts created along the parent vessel; 2) modifying the rules of branching for both sprouts (tips) and body of the newly created vessels as a time adaptation algorithm and 3) coupling of three steps of angiogenesis process including the adaptive sprout spacing, sprout progression, blood flow and network remodeling.

Table 1
Sprout tip branching probabilities as a function of the local TAF concentration and magnitude of the wall shear stress (Stéphanou et al., 2006).

[WSS] [TAF]	≤0.4	]0.4–0.6]	]0.6–0.8]	0.8
≤0.3	0	0	0	0
]0.3–0.5]	0	0	0.1	0.3
]0.5–0.7]	0	0	0.3	0.5
]0.7–0.8]	0	0.1	0.4	0.6
0.8	0	0.5	0.8	1.0

[TAF: Tumor Angiogenic Factor], [WSS: Wall Shear Stress].