Study of capillary network directionality and irrigation of hypoxic tissue in an angiogenesis lattice model

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HIGHLIGHTS

- We propose a simplified lattice model for capillary network formation.
- Hypoxic tissue and a growing capillary network can produce growth factors.
- We consider an inhibition mechanism due to irrigation of hypoxic tissue.
- Directionality of the network is more evident when local growth factors are absent.
- A better irrigation is achieved when the inhibition mechanism is considered.

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ABSTRACT

To shed light on the understanding of the angiogenesis process, we study a simplified lattice model for the capillary network formation between an existing blood vessel and an initially hypoxic tissue. We consider that the cells of the tissue surface can release growth factors that will diffuse, leading to the formation of new capillaries that ultimately arrive at the tissue. Additionally, we consider the local production of growth factors by the growing capillary network. We also propose the existence of an inhibition mechanism at the hypoxic surface, i.e., a fixed number of neighboring sites of an already irrigated site of the hypoxic tissue stop releasing growth factors due to the arrival of nutrients. Particularly, the goal of this work is to study the effect of the release of local growth factors and the inhibition mechanism on properties such as the directionality of the growing network and the irrigation of the hypoxic tissue. Therefore we propose the quantification of these two relevant features for angiogenesis modeling. We establish a relationship between the model behavior without the release of local growth factors in the presence of the inhibition mechanism and a normal angiogenesis process. In this situation, the model gives a directional capillary network and a good irrigation of the hypoxic tissue. On the other hand, for a large number of released local growth factors in the absence of the inhibition mechanism, the model could be appropriate for the description of tumor angiogenesis. In this case, the model provides a rather small directionality for the growing structure, with a worse degree of irrigation of the hypoxic tissue, as well as a more tortuous capillary network with many closed branches and loops.

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1. Introduction

Angiogenesis is the complex physiological process that results in the growth of new blood vessels from preexisting ones. It involves the growth, the branching, and the extension of these blood vessels (capillaries) until the hypoxic tissue. Under

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normal circumstances, angiogenesis not only supports the growth and development of tissues, but also helps repair and heal injured ones. This is a complex process governed by a balance of several pro-angiogenic and anti-angiogenic factors. Among the identified substances that promote angiogenesis, the so-called vascular endothelial growth factor (VEGF) and the basic fibroblast growth factor (bFCF) seem to be the most prevalent [1–3]. On the other hand, substances such as thrombospodin, angiostatin, endostatin, etc., are the best known inhibitors of the angiogenesis process [4].

Nearly 40 years ago, cancer researchers started to focus their attention on angiogenic factors when it was established that dormant tumors might release this kind of substance in order to foster their own growth. In fact, in his pioneer work, J. Folkman [5] argues that some tumors, unable to grow beyond 2–3 mm^3 in size due to the lack of enough nutrients, can produce and release angiogenic growth factors that, after diffusion toward vascular endothelial cells, may induce the formation of new vessels and the subsequent vascularization of the tumor [6]. Nowadays it is well known that the disruption of the delicate balance between pro- and anti-angiogenic factors is related to a large number of diseases. In fact, many human diseases are driven by persistently up-regulated angiogenesis, which generates an over-irrigation [7]. In some nonmalignant processes, such as keloid formation, angiogenesis is prolonged but still self-limited [8], whereas in tumor angiogenesis this process continues indefinitely without control [9]. Therefore, the control of the angiogenic switch has an enormous potential for the generation of new therapies [9–13].

Under these circumstances, the study and understanding of angiogenesis have become the focus of growing activity. Apart from well-established experimental methods, more recently the mathematical modeling and simulation of angiogenesis have received increasing attention [14]. In fact, by using this alternative approach one can gain an insight into the underlying mechanisms involved in these complex biological processes and contribute to a more comprehensive description. An overview of recent work on the mathematical modeling of angiogenesis reveals that several strategies have already been used. The continuous approach assumes that the relevant ingredients of the process, such as the density of new capillaries, the concentration of angiogenic factors, etc., can be described by means of a set of coupled partial differential equations [15–17]. In this case, one deals with continuous quantities treated in a mean-field fashion. On the other hand, discrete models at the mesoscopic scale have also been proposed. Usually, these models are based on a set of simple rules inspired by biological mechanisms and often containing stochastic ingredients at the level of individual cells and molecules [17–19]. Besides, hybrid models, which include the discrete approach at the cellular level and continuous equations for the diffusion at the extracellular level, have been reported to describe angiogenesis [20–29].

Within this broad context, the aim of this paper is to study the capillary network obtained from a simplified lattice model by means of Monte Carlo computer simulations. Our model is based on an early work by Gazit et al. [18] who proposed to study the scale-invariant behavior of normal and tumor capillary network formation through simplified models. They consider that growth begins at a single central seed and that growth factors diffuse from points at a certain distance from the structure, in a circular geometry in $d = 2$ dimensions [18]. In order to obtain a compact structure, observed experimentally in a normal subcutaneous capillary network [30], Gazit et al. compare two hypotheses for network formation. As one possibility, they consider that the main source of growth factors is the growing structure itself, that is, besides the release of growth factors from points distant from the structure, there is a release of local growth factors. As an alternative scenario, they also consider a low interaction probability between growth factors and the growing structure. The authors show that both mechanisms can lead to the formation of the compact capillary network observed experimentally [18]. It is worth noting that the model proposed by Gazit et al. derives from the classic diffusion limited aggregation model (DLA) [31].

In this paper we study a model for the formation of new capillaries between an hypoxic tissue and a neighboring blood vessel [18]. The growing of the capillary network is induced by growth factors released by the hypoxic tissue, as well as, by a local amplification of this signal. We made an extension of the model proposed by Gazit et al. [18]. In this way, we include an inhibition mechanism, i.e., a fixed number of neighboring sites of an already irrigated site of the hypoxic tissue stop releasing growth factors due to the arrival of nutrients. Besides, we propose a geometry that allows the study of the directionality of the growing network. Particularly, our task in this paper is to study the effect of the release of local growth factors and the inhibition mechanism on properties such as the directionality of the growing network and the degree of irrigation of the hypoxic tissue, in order to obtain a better description and understanding of the angiogenesis process.

The manuscript consists of the description of the model and the simulation method (Section 2), the presentation and discussion of the results (Section 3), and the statement of the conclusions (Section 4).

2. Description of the model and the simulation method

Simulations are performed in a two-dimensional square lattice by considering samples of width L (horizontal axis) and length M (vertical axis). The first column on the leftmost-hand side of the sample is assumed to be taken by an existing blood vessel (see Fig. 2), composed of endothelial cells. Also, a fraction of the last column at the rightmost-hand side of the sample, having a length m, is assumed to be taken by the part of the tissue that is initially hypoxic (see Fig. 2). Hereafter, we use $m \sim M/3$ because in this work we are interested in studying how the capillary network grows toward a hypoxic tissue of length smaller than that of the vessel. The sites between the blood vessel and the tissue surface are considered as extracellular matrix.

The closest distance between the hypoxic tissue and the vessel is the sample width L, while the structure of the bulk of tissue, which is irrelevant for the purpose of the present work, is no longer considered. Despite the great complexity of angiogenesis, we consider that the cells of the hypoxic tissue can release only the vascular endothelial growth factor