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Full-scale, three-dimensional simulation of early-stage tumor growth: The onset of malignancy

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Highlights

- A 3D model to predict vascular tumor growth at the onset of malignancy is proposed.
- We propose a suitable computational method based on isogeometric analysis.
- We present numerical simulations that aim at reproducing in vitro and in vivo setups.
- We use the geometry of a colon histopathological image in macroscopic simulations.

Abstract

Malignant tumors have the ability to trigger the growth of new vasculature towards them through a complex process called tumor angiogenesis. These new blood vessels provide cancerous cells with sufficient nutrients for growth and a means to escape the primary tumor and invade other tissues. This paper proposes a three-dimensional model that aims at predicting how the tumor and its associated vasculature grow during the onset of malignancy. The cellular growth equations of our model are derived using the phase-field method. We use standard reaction–diffusion equations to model the transport of chemicals. The model resolves the tumor-induced vasculature explicitly, considering capillaries with a diameter of up to $\sim$25 μm. We propose a suitable computational method based on isogeometric analysis. We present several numerical examples to test the model, including a macroscopic simulation ($\sim$1 cm^3) on a geometry taken from a histopathological image of a human colon. The proposed model naturally predicts the angiogenic switch. Our computations show realistic patterns of tumor and vascular growth.

Keywords: Vascular tumor growth; Angiogenesis; Phase-field modeling; Isogeometric analysis

1. Introduction

Healthy cells produce signals to control their division process. Cancer cells, however, reproduce without the normal restraints. Abnormal cells that proliferate out of control may give rise to a tumor [1,2]. In most cases, tumors grow rapidly consuming the nutrient and oxygen delivered by pre-existing blood vessels. However, when the cancerous

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mass reaches approximately 2–3 mm^3 [3], the absence of blood vessels inside the tumor arrests the growth of the lesion. Simplifying significantly the actual biological process, we could say that those cells located at the outermost rim may still obtain nutrients and oxygen from the circulatory system through diffusion mechanisms and continue their proliferation. On the contrary, cells in deep layers of the tumor do not have access to any source of nutrients and die from starvation forming a necrotic core. There is a transition layer between the proliferating rim and the necrotic core, called hypoxic region. The level of oxygen in such region is low due to an imbalance between the oxygen consumption and supply [4,5]. Under hypoxic conditions, cancer cells enter a temporary, dormant state. Growth at the proliferating rim and death at the necrotic core balances the global growth of the tumor. This situation may persist for years without presenting a threat to the life of the individual.

Hypoxic tumor cells may be able to promote the growth of new capillaries towards them through a process known as tumor-induced angiogenesis. These cells have gained the ability to release a series of chemical substances to the extracellular matrix, generally termed tumor angiogenic factors or TAFs. Some of the most potent TAFs include vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), integrins, placenta growth factor (PLGF), or thrombospondin-1 (TSP-1) [6–9]. TAFs diffuse from the tumor until they bind to the membranes of the cells that line the blood vessels, that is, endothelial cells. At this point tumor-induced angiogenesis starts and may be briefly described as follows (for a detailed explanation the reader is referred to [10–12]). Initially, TAFs alter the quiescent phenotype of endothelial cells either to a migratory or to a proliferative phenotype [13,14]. The former, the tip endothelial cells or TECs, will lead the capillary growth, while the latter, the stalk endothelial cells or SECs, will elongate the sprout through continuous cell division. The selection between TECs or SECs is based on the lateral inhibition mechanism [15]. The first cells reached by TAFs become TECs and subsequently express a protein called delta-like ligand 4 or Dll4. This protein binds to the nearby endothelial cell Notch receptors. Notch-activated endothelial cells become stalk cells instead of tip cells when TAFs reach them. As a result, an incipient sprout starts to develop from the parent vessels. Once liberated from the vascular membrane that envelops the parent vessel, TECs spearhead the migration following gradients of TAF. To enhance the survey of their microenvironment they extend forward membrane protrusions called filopodia [16]. Behind, the capillary grows as SECs multiply rapidly. The process continues until the leading cell fuses with another vessel (anastomosis) or until the driving stimuli end. The outcome of tumor-induced angiogenesis is a new, although pathologically defective, vascular network that partially satisfies the metabolic demands of the highly-proliferative cancer cells. As a consequence, the previously small, growth-restrained tumor can now grow unbounded becoming malignant. Tumor angiogenesis plays a key role in the onset of malignancy in several solid cancers. In particular, it is critical in the growth of colorectal cancer, in which we focus in this work.

Colorectal cancer is the third most common type of cancer globally and the third leading cause of death in United States [17,18]. Usually, this disease develops slowly, often showing no symptoms, which makes its detection difficult. Colorectal cancer incidence and death rates have decreased due to the increase of screening frequency through colonoscopy and improvement of treatments. Due to the crucial role of angiogenesis, a number treatments that target the growth of capillaries have been developed, such as bevacizumab, regorafenib, or aflibercept [19]. Moreover, colorectal cancer develops through a series of differentiated stages, as shown next, being angiogenesis an important predictor for early-stage colorectal cancer [20].

The colon and the rectum form part of the lower digestive system. Their main functions are to absorb water and nutrients from digested food, to form and store waste and to move waste out of the body. As shown in Fig. 1, the colon is made up of distinct tissue layers, which from innermost to outermost are: mucosa, submucosa, *muscularis propria* and serosa. The mucosa layer lines the lumen of the colon and is composed by a thin layer of epithelial cells, a layer of connective tissue and a thin layer of muscle. The submucosa is a connective tissue that envelops the mucosa in which blood and lymph vessels, nerves and mucous glands are embedded. The submucosa is in turn surrounded by a thick layer of muscles, the *muscularis propria*, that powers the movement of the stool through the colon. Finally, the serosa layer enwraps the colon. The main blood and lymph vessels that supply and drain wastes from the colon are located outside these layers in the mesentery. The rectum also presents concentric layered tissues analogous to those of the colon. Due to the ordered colon and rectum layered microstructure, colorectal cancer staging is commonly defined using the TNM staging system [21], where T stands for the size of the primary tumor, N for its spread to regional lymph nodes and M for the presence of distant metastases. In this system, each letter is followed by a number, such that the higher the number, the more advanced the cancer stage. Thus, in colorectal cancer, at the earliest stage of cancer, that is Tis or carcinoma *in situ*, the tumor is at the beginning of its development, appears as a budding shape