Journal of Computational Physics 230 (2011) 1335–1358

Contents lists available at ScienceDirect

Journal of Computational Physics

journal homepage: www.elsevier.com/locate/jcp

# Fictitious domains and level sets for moving boundary problems. Applications to the numerical simulation of tumor growth ☆

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ARTICLE INFO

*Article history:*
Received 11 June 2010
Received in revised form 28 October 2010
Accepted 2 November 2010
Available online 17 November 2010

*Keywords:*
Tumor growth
Fictitious domain method
Level set method

ABSTRACT

In this work we present a new strategy for solving numerically a (relatively simple) model of tumor growth. In principle, this is devoted to describe avascular growth although, by choosing the parameters appropriately, it also permits to give an idea of the behavior after vascularization. The numerical methods rely on fictitious domain and level set techniques, with a combination of quadratic finite elements and finite differences approximations. We present a collection of numerical results that essentially coincide with others, previously obtained with other techniques.



## 1. Introduction

In the battle against cancer many strategies, experimental techniques and theoretical approaches have emerged throughout the last centuries. Nevertheless, like in the case of many other scientific areas, we have the possibility to appeal to the mathematical modeling to interpret and understand the experimental results. Thus, the mathematical study of tumors growth is a topic of present time for several years. The first contributions in this field were made at the beginning of the twentieth century.

In accordance with [4], in order to develop effective treatments, it is important to identify the mechanisms controlling cancer growth, how they interact and how they can most easily be manipulated to eradicate (or manage) the disease. To carry out such purposes, it becomes necessary to make a great number of experiments, together with a considerable dedication of time. In this context, applied mathematics has the potential of elucidating new results (through virtual experiments, relying on numerical methods) and also the capability of validating or confirming the results of real experiments and measurements.

A primary tumor can grow up to a typical size of 1 mm without requiring new supply of nutrients; during this stage the tumor is said to be avascular. During this avascular growth, tumors receive nutrients via diffusion through the host tissue. As the tumor grows, less nutrient reaches the center of the tumor. Interior cells become hypoxic, begin to die (necrose), and are broken down by enzymes. In order to continue to grow, the tumor requires new sources of nutrients. To this end, it secretes the so called *tumor angiogenic factors*, that which stimulate the formation of new blood vessels, attracting them and leading them towards the tumor cells. This process is called *angiogenesis*; usually, a tumor which has evolved beyond this stage is said to be *vascularized*.

☆ Partially supported by DGES-Spain under Grant MTM2006-07932 and Junta de Andalucía (Spain), under Grant EXC/2005/FQM-520.

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0021-9991/$ - see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.jcp.2010.11.005

In general, models that simulate the avascular phase are free boundary problems for which it is interesting to study how the shape of the tumor evolves as time changes.

Our work will be mainly focused on the growth of a solid tumor (carcinoma) in the avascular phase. We have use a model resulting from the reformulation of several previous systems [15,2,3,6,1,7,16,22,18]. However, it is known that the solution of models of this kind, with an appropriate choice of the parameters, also give some ideas on the behavior of some tumors in vascular phase.

The tumor will be treated as an incompressible fluid where tissue elasticity is neglected. Cell-to-cell adhesive forces are modelled by a surface tension at the tumor–tissue interface. On the other hand, the growth of the mass of the tumor is governed by a balance between cell *mitosis* and *apoptosis* (programmed cell death). The rate of mitosis depends on the nutrient density inside the tumor, where the concentration of capillaries is assumed to be uniform.

We will consider necrotic and non-necrotic tumors. The latter can be viewed as preliminary models for small size tumors and also concern the case in which the nutrient concentration levels in the blood and in the external tissues are high. Nevertheless, the model that we use can also serve to predict the behavior in other situations; see [7].

The outline of this paper is as follows. In Section 2, we deduce the model under consideration. The numerical analysis of the problem will be discussed in Section 3; we study fictitious domains and level set methods that serve to solve the problem numerically. Finally, Section 4 deals with numerical results for non-necrotic and necrotic tumors.

## 2. Mathematical formulation

We will denote by $\omega(t) \subset \mathbb{R}^d$ $(d = 2,3)$ the region occupied by the tumor at time $t$, and by $\gamma(t)$ its boundary.

The variable $\sigma = \sigma(\mathbf{x},t)$ represents the concentration of nutrient inside the tumor. Let $\sigma_N > 0$ be given and let us introduce the set

$$\omega_N(t) = \{\mathbf{x} \in \omega(t) : \sigma(\mathbf{x},t) < \sigma_N\}$$

and its boundary $\gamma(t) = \partial\omega(t)$. By definition, $\omega_N(t)$ is the necrotic core at time $t$. In practice, $\sigma_N$ is chosen from real experiments; see below, in Section 4.

We will assume that the cells within the tumor are alive while $\sigma(\mathbf{x},t) \geqslant \sigma_N$ and they are proliferating. Let $\omega_P(t)$ be the proliferating region (see Fig. 1). Then we can write

$$\omega(t) = \omega_P(t) \cup \omega_N(t) \cup \gamma_N(t).$$

Obviously, if $\sigma(\cdot,t)$ is continuous (which seems to be a reasonable assumption), one has

$$\omega_P(t) = \{\mathbf{x} \in \omega(t) : \sigma(\mathbf{x},t) > \sigma_N\}.$$

Based on the assumption that the time scale necessary for the tumor to undergo significant changes in volume ($\backsim$ days) is typically much larger than the nutrient diffusion time scale ($\backsim$ minutes), the nutrient diffusion inside the tumor is considered quasi-steady. Thus, the nutrient satisfies the following diffusion equation:

$$0 = \nabla \cdot (D\nabla\sigma) + \lambda_B(\sigma_B - \sigma) - \lambda_U\sigma, \tag{1}$$

where $D$ is the diffusion coefficient (constant), $\lambda_B(\sigma_B - \sigma)$ describes the source of nutrient from the vasculature while $\lambda_U\sigma$ describes the nutrient uptake by cells. Here, $\lambda_B$ is the blood–tissue transfer rate of nutrient and $\lambda_U$ is the rate of consumption of nutrient by the tumor cell.

Notice that, in the necrotic region, the tumor cells do not consume nutrients. However, when cells necrose they release their cellular contents which are oxygen reactive and thus this effect on the nutrient concentration can be modelled through

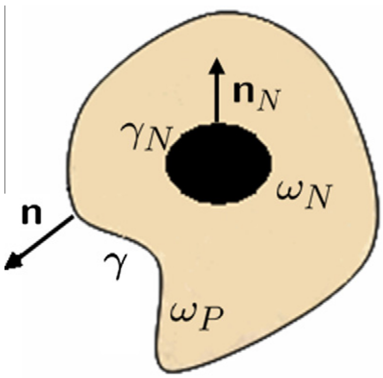


**Fig. 1.** Diagram of a necrotic tumor.