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Adjoint method for a tumor invasion PDE-constrained optimization problem in 2D using adaptive finite element method

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ABSTRACT

In this paper we present a method for estimating an unknown parameter that appears in a two dimensional non-linear reaction–diffusion model of cancer invasion. This model considers that tumor-induced alteration of micro-environmental pH provides a mechanism for cancer invasion. A coupled system reaction–diffusion describing this model is given by three partial differential equations for the 2D non-dimensional spatial distribution and temporal evolution of the density of normal tissue, the neoplastic tissue growth and the excess H^+ ion concentration. Each of the model parameters has a corresponding biological interpretation, for instance, the growth rate of neoplastic tissue, the diffusion coefficient, the re-absorption rate and the destructive influence of H^+ ions in the healthy tissue.

The parameter is estimated by solving a minimization problem, in which the objective function is defined in order to compare both the real data and the numerical solution of the cancer invasion model. The real data can be obtained by, for example, fluorescence ratio imaging microscopy.

We apply a splitting strategy joint with the adaptive finite element method to numerically solve the model. The minimization problem (the inverse problem) is solved by using a gradient-based optimization method, in which the functional derivative is provided through an adjoint approach.

1. Introduction

Cancer is one of the diseases causing the most deaths in the world, despite the best efforts of medicine. Human and financial resources are devoted for cancer research, and on several occasions these efforts are successful [1–6].

Some comments on the importance of mathematical modeling in cancer can be found in the literature. In the work [4] the authors say "Cancer modelling has, over the years, grown immensely as one of the challenging topics involving applied mathematicians working with researchers active in the biological sciences. The motivation is not only scientific as in the industrial nations cancer has now moved from seventh to second place in the league table of fatal diseases, being surpassed only by cardiovascular diseases."

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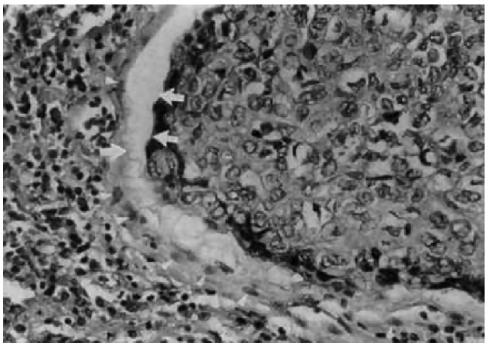

Fig. 1. Loss of normal cell layers in the tumor–host interface that facilitates tumor invasion [7, Fig. 4a].

We use the analysis proposed by Gatenby and Gawlinski in [7], which supports the acid-mediated invasion hypothesis. Therefore, it can be represented mathematically as a reaction–diffusion system which describes the spatial and temporal evolution of the tumor tissue, normal tissue, and excess H^+ ion concentration.

The model simulates a pH gradient extending from the tumor–host interface. The effect of biological parameters that control this transition is supported by experimental and clinical observations [8].

Some authors [7] model tumor invasion in order to find an underlying mechanism by which primary and metastatic cancers invade and destroy normal tissues. They do not attempt to model the genetic changes that lead to the transformation and seek to understand the causes of these changes. Likewise, they do not attempt to model the large-scale morphological aspects of tumor necrosis such as central necrosis. Instead, they concentrate on the interactions of microscopic scale populations that occur at the tumor–host interface, arguing that these processes influence the clinically significant manifestations of invasive cancer.

Moreover, in [7], the authors suppose that transformation-induced reversion of neoplastic tissue to primitive glycolytic metabolic pathways, with resultant increased acid production and the diffusion of that acid into surrounding healthy tissue, creates a peritumoral micro-environment in which the tumor cells survive and proliferate, while normal cells may not remain viable. The following temporal sequence would derive: (a) a high concentration of H^+ ions in tumors will diffuse chemically as a gradient to adjacent normal tissue, exposing these normal cells to an interstitial pH like in the tumor, (b) normal cells, immediately adjacent to the edge of the tumor, are unable to survive in this chronically acid environment, and (c) progressive loss of normal cell layers in the tumor–host interface facilitates tumor invasion, see Fig. 1. Key elements of this mechanism of tumor invasion include low pH due to primitive metabolism and reduced viability of normal tissue in an acidic environment.

This model depends only on a small number of cellular and sub-cellular parameters. The analysis of the equations shows that the model simulates a crossover from a benign tumor to a malignant invasive tumor when some combination of parameters turn over some threshold value.

We follow the PDE-based model by Gatenby and Gawlinski [7] (a coupled nonlinear system of partial differential equations), in a two-dimensional tissue and estimate one of its model parameters: the destructive influence of H^+ ions in the healthy tissue.

In this paper we propose a method to estimate the mentioned parameter via a PDE-constrained optimization problem. The objective function is defined as the difference between the real data and the numerical solution of the model in the Lebesgue measure. It is possible to get data of excess H^+ ion concentration [8] via fluorescence ratio imaging microscopy.

We solve the minimization problem using the trust-region-reflective method where the functional derivative is computed using the adjoint method.

The numerical solution of the model is obtained with a splitting strategy to divide the original problems in two simpler ones: (a) the first problem, consisting in a system of ordinary differential equations, corresponding to the reaction process, and (b) the second problem, consisting in a system of PDEs representing the diffusion process. This strategy allows a parallelization of the reaction problem. The PDE system is solved by the adaptive finite element method (AFEM).

This kind of minimization problem constitutes a particular application of the so-called inverse problems, which are being increasingly used in a broad number of fields in applied sciences. For instance, problems referred to structured population dynamics [9], computerized tomography and image reconstruction in medical imaging [10,11], and more specifically tumor growth [12–14], among many others.

This work follows the ideas in [15] where the space variable was in a one dimensional space. The extension of the model to two dimensional space allows us to approach the results to more realistic biological hypotheses. The differences of this work with respect to [15] are: (a) we take advantage of a more complex geometry in 2D instead of 1D, for the implementation of the finite element method (FEM); (b) we compute the *a posteriori* error estimation in order to use the adaptivity technique; (c) we use the splitting method to transform the original problem into two simpler problems, one of these is a linear problem, and the other one is nonlinear but parallelizable.

Regarding the novelty with existing literature, we cite two papers. Namely, Hogea et al. [13] model gliomas growth and their mechanical impact on the surrounding brain tissue. The model is a reaction–diffusion equation where the unknown is the local density of tumor cells. In our paper we have a coupled system of reaction–diffusion equations that considers competition terms.