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Convergence of a positive nonlinear Control Volume Finite Element scheme for solving an anisotropic degenerate breast cancer development model

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ABSTRACT

In this paper, a nonlinear control volume finite element (CVFE) scheme for solving an anisotropic degenerate breast cancer development model is introduced and analyzed. This model includes both ordinary differential equations and convection–diffusion–reaction equations modeling the stepwise mutations from a normal breast stem cell to a tumor cell. The diffusion term, which generally involves an anisotropic and heterogeneous diffusion tensor, is discretized on a dual mesh by means of the piecewise linear conforming finite element method and using the Godunov scheme to approximate the diffusion fluxes provided by the conforming finite element reconstruction. The other terms are discretized using a nonclassical upwind finite volume scheme on the dual mesh, where the dual volumes are constructed around the vertices of the original mesh. This technique ensures the positivity and boundedness of discrete solutions without any restriction on the diffusion tensor nor the transmissibility coefficients. The convergence of the scheme is proved, only supposing the shape regularity condition for the original mesh and using *a priori* estimates as well as the Kolmogorov relative compactness theorem. The proposed scheme is robust, locally conservative, efficient, and stable, which is confirmed by numerical experiments over a general mesh.

1. Introduction

According to the World Health Organization, breast cancer is the most common cancer among women worldwide, claiming the lives of hundreds of thousands of women each year and affecting countries at all levels of modernization.

Cancer begins in the cells which are the basic building blocks that make up tissue. Tissue is found in the breast and other parts of the body. Sometimes, the process of cell growth goes wrong (due to some mutations in the gene of the cell) and new cells form when the body does not need them and old or damaged cells do not die as they should. When this occurs, a build up of cells often forms a mass of tissue called a lump, growth, or tumor.

Recent research in breast biology has provided support for the cancer stem-cell hypothesis, stating that breast cancers grow from breast stem cells in the way that healthy organs do [1,2]; accordingly, one makes evidence that mutations of an oncogene or a tumor suppressor gene (TSG) are necessary to model the transformation of normal breast stem cells to tumor cells. The mechanical interactions of tumor cells with healthy tissue have been modeled in several ways, including continuum equations [3–6], multi-phase flow models [7], transport equations [8], and individual based models [9,10]. In

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this paper, we adopt a mathematical model based on the mathematical model proposed by Enderling et al. in [11] which consists of an extension to the original model of the same authors [12]. In [11] and for simplicity, the authors have adapted the approach described in [13], and have assumed that mutations in two TSGs are sufficient to give rise to a tumor.

The mathematical model we consider in this paper consists of four ordinary differential equations describing the stepwise mutations from a healthy breast stem cell (pre-cancerous cell) to a tumor cell [14]. Then, for the dynamics of the tumor cell, the model presents basically a partial differential equation modeling the solid tumor growth and invasion in the sense of examining the invasion of the growing solid tumor and its interaction with its surrounding environment; by releasing matrix degradative enzymes (MDEs). These MDEs degrade the tissue upon contact to make space for the solid tumor to develop and grow into (see e.g. [15]). The partial differential equation modeling the dynamics of the MDEs will constitute the last equation of the mathematical model considered in this paper.

Now, we give an illustrative diagram for the stepwise mutations from a normal breast stem cell to a tumor cell. The two TGSs considered in [11] are labeled TSG_1 and TSG_2, and we denote by $\mathrm{TSG}_1^{+/+}$ and $\mathrm{TSG}_2^{+/+}$ when both alleles are un-mutated. The stepwise mutation pathway is assumed as follows:

$$\mathrm{TSG}_1^{+/+}\mathrm{TSG}_2^{+/+} \xrightarrow{\rho_1} \mathrm{TSG}_1^{+/-}\mathrm{TSG}_2^{+/+} \xrightarrow{\rho_2} \mathrm{TSG}_1^{-/-}\mathrm{TSG}_2^{+/+} \xrightarrow{\rho_3} \mathrm{TSG}_1^{-/-}\mathrm{TSG}_2^{+/-} \xrightarrow{\rho_4} \mathrm{TSG}_1^{-/-}\mathrm{TSG}_2^{-/-},$$

where $\mathrm{TSG}_i^{+/-}$ represents TSG with LOH and $\mathrm{TSG}_i^{-/-}$ represents an inactivated TSG. In the final step of the pathway when both of the TSGs are inactivated, it is assumed the cell to be a cancer cell (see [11] for more details). The superscript ρ_i represents the probability of mutating one allele at every step of the mutation diagram. In this paper, we take the same values for these probabilities as taken in [11] from the studies by Tomlinson et al. [16] and Nowak et al. [17]. The variation of these values would only result in a faster or delayed mutation acquisition.

The intention of this paper is to numerically investigate the early stage of a degenerate anisotropic breast cancer development using a Control Volume Finite Element scheme. From the numerical point of view, the convergence analysis of the finite volume scheme for this type of systems is carried out in [18] for the isotropic case and under the "admissibility" assumption on the mesh used for the space discretization in the sense of satisfying the orthogonality condition (see e.g. [19]). Although its ability to ensure stability, the classical upwind finite volume method does not permit to handle anisotropic diffusion even if the mesh verifies the orthogonality condition. Various "multi-point" schemes, where the approximation of the flux through an edge involves several scalar unknowns, have been proposed in the past decay for anisotropic diffusion problems, see for example [20–25] for a detailed review of modern finite volume methods for diffusion equations. However, nonlinear corrections have been proposed in [26] in order to enforce the monotony, but no complete convergence proof has been provided for such methods yet.

Recently, the authors of [27] proposed and analyzed a nonlinear *Control Volume Finite Element* (CVFE) scheme for solving a degenerate anisotropic Keller–Segel model. This scheme was inspired from the work of Cancès and Guichard [28] where they proposed and analyzed a nonlinear CVFE scheme for solving degenerate anisotropic parabolic diffusion equations modeling flows in porous media. The convergence analysis is carried out without any restriction on the transmissibility coefficients, and the efficiency of the scheme is tested using anisotropic diffusion tensors over an unstructured mesh.

Our aim here, is to elaborate a general approach, inspired from [27–29], to approximate a nonlinear degenerate parabolic system modeling the breast cancer development over a general mesh, with anisotropic and heterogeneous diffusion tensors. The idea consists of discretizing the diffusion terms by means of a conforming piecewise linear finite element method on a primal triangular mesh and using the Godunov scheme to approximate the diffusion fluxes provided by the conforming finite element reconstruction. The other terms are discretized by means of a nonclassical upwind finite volume method on a dual mesh (Donald mesh or Median dual mesh).

The rest of this paper is organized as follows. In Section 2, we introduce the mathematical system modeling the breast cancer progression. This system consists of ordinary differential equations and of degenerate parabolic partial differential equations. We give the main assumptions on this system in order to define a weak solution. In Section 4, we define the space and time discretization of the space. Then, we introduce the nonlinear CVFE scheme and specify the discretization of the degenerate diffusion and convection terms. In Section 4, we derive the discrete properties of the scheme and prove the positivity and boundedness of discrete solutions and show the existence of a discrete solution to our scheme. In Section 5, we give estimates on differences of time and space translates for the approximate solutions. Next, we apply the Kolmogorov relative compactness criterion in order to prove the convergence of a subsequence of discrete solutions towards a limit that we identify in Section 6 as a weak solution to the continuous problem. Finally, in Section 7, some numerical simulations are carried out to investigate and capture the progression of the breast cancer development with an anisotropic and heterogeneous diffusion over a general mesh.

2. The anisotropic degenerate nonlinear breast cancer model

Let Ω be an open bounded polygonal and connected subset of $\mathbb{R}^d$, $d = 2,\ 3$ and let $t_f > 0$ be a fixed finite time. We denote by $Q_{t_f} = \Omega \times (0, t_f)$ and $\Sigma_T = \partial\Omega \times (0, t_f)$. We are interested in a modified degenerate nonlinear system [11] modeling the

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