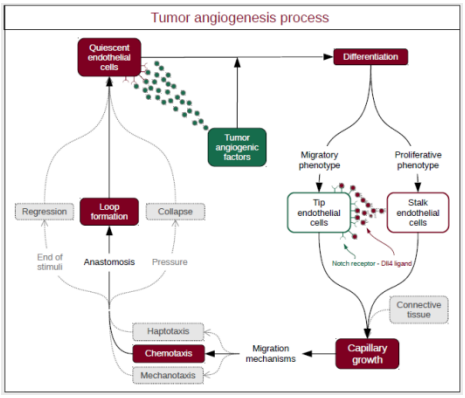
An isogeometric-analysis based numerical method for tumor angiogenesis

Introduction

Angiogenesis plays a critical role in tumorigenesis triggering the vascular phase of solid tumor growth [1]. It is a complex biological phenomenon (schematically described in Fig. 1), that activates endothelial cells and promotes capillary growth.



Many researches have developed in silico models using discrete, continuous, hybrid or composite approaches [2]. Specifically, the hybrid description is able to track individual cells, whilst it considers continuous phases.

Mathematical model

The proposed numerical simulation uses a model for tumor angiogenesis posed by Travasso et al. in [3]. It is essentially a multiscale, hybrid model and it is composed by a continuous and a discrete part, merged through an equation. Firstly, the continuous description is a non-conservative, phase-field model (Eq. 1), where c is the phase. It is coupled with a diffusion equation (Eq. 2) for the tumor angiogenic factor, represented by T, and both describe the proliferation of the stalk endothelial cells,

$$\frac{\partial c}{\partial t} = M\Delta(-c + c^3 - \lambda\Delta c) + \alpha_p(T)cH(c) \qquad \frac{\partial T}{\partial t} = \nabla\cdot(D\nabla T) - \alpha_T T c H(c)$$

where M is the constant mobility; λ is proportional to the width of the capillary wall; $\alpha_p(T)$ is the proliferation rate function; $H(c)$ is the Heaviside function; D is the diffusion constant and α_T is the uptake rate. On the other hand, the discrete part is an agent-based model (Eq. 3) that describes the migration of the tip endothelial cells (TECs) towards the gradient of angiogenic factor,

$$v_{TEC} = \chi\nabla T\mathcal{L}(\nabla T)$$

where v_{TEC} is the velocity of the TEC, is the proliferation coefficient and $\mathcal{L}$ is a limiting function.

Numerical method

The proposed numerical method uses isogeometric analysis (IGA) [4] as the main tool to solve the model. IGA is a computational methodology based on finite element analysis which uses NURBS (Non-Uniform Rational B-Splines) as basis functions. The advantages of using IGA rely in its capacity to accurately integrate high-order derivatives guarantying C^1 and higher order continuity. The isogeometric analysis is complemented with the generalized- method as a time integration scheme, an adaptive time-step scheme and a parallel code.

Results

The simulations show how the tip endothelial cells are activated and migrate by chemotaxis followed by a set of proliferating stalk endothelial cells (see Fig. 3). As the capillary grows, new branches are formed resulting in a vascular network.

Whenever a capillary is near a source of tumor angiogenic factor, the source stops emitting the factors, as it has nourishment and oxygen coming from the new capillary. Finally, a parametric study (Fig. 4) explained the influence of the most biologically relevant parameters of the model: the chemotactic versus the proliferation constants.

Conclusions

- We have developed a new methodology, based on isogeometric analysis, to simulate a tumor angiogenesis model. The methodology produces accurate results and allows the performance of a parametric study.
- Our simulations provide insights into the dynamics of the governing equations and may help understand fundamental processes behind tumor angiogenesis.
- The chemotactic and proliferation constants are key parameters to the development of the new vasculature in the model, as it occurs in tumor angiogenesis.

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European Research Council
Established by the European Commission
GOBIERNO DE ESPAÑA MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD
XUNTA DE GALICIA