An isogeometric-analysis based numerical method for tumor angiogenesis

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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.

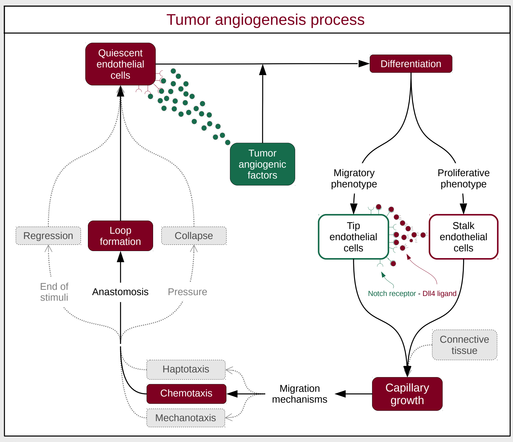

Figure 1: This flowchart is a scheme of the tumor angiogenesis process, from the quiescent endothelial cells in the pre-existing capillaries to the loop formation after the newly formed blood vessels. The phenomena plotted in light gray are those not included in the numerical simulation.

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.

The tumor angiogenesis 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,

$$\frac{\partial c}{\partial t} = \nabla \cdot (M \nabla (\mu(c) - \lambda \Delta c)) + \alpha_p(T)\, c\mathcal{H}(c) \tag{1}$$

$$\frac{\partial T}{\partial t} = \nabla \cdot (D \nabla T) - \alpha_T T c \mathcal{H}(c) \tag{2}$$

where M is the constant mobility; $\mu(c) = c^3 - c$ is the chemical potential ; $\sqrt{\lambda}$ is proportional to the width of the capillary wall; $\alpha_p(T)$ is the proliferation rate function; $\mathcal{H}(\cdot)$ 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,

$$v_{TEC} = \chi \nabla T \mathcal{L}(|\nabla T|) \tag{3}$$

where v_{TEC} is the velocity of the TEC, χ is the proliferation coefficient and $\mathcal{L}$ is a limiting function.
Finally, the following equation merges the two parts of the model and assigns a value of the phase-field c_{TEC} to the tip endothelial cell:

$$c_{TEC} = \frac{\alpha_p(T)\, \pi R_{TEC}}{2\,|v_{TEC}|} \tag{4}$$

where R_{TEC} is the tip endothelial cell radius.

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 $\mathscr{C}^1$ and higher order continuity.
The isogeometric analysis is complemented with the generalized-α method as a time integration scheme, an adaptive time-step scheme and a parallel code.

Results and Discussion

We employ periodic boundary conditions in the horizontal direction, free flux in the vertical and the initial conditions represented in Fig. 2.

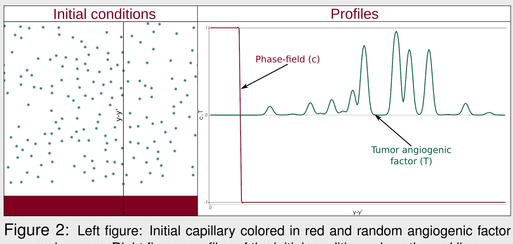

Figure 2: Left figure: Initial capillary colored in red and random angiogenic factor sources in green. Right figure: profiles of the initial conditions along the y-y' line.

Results and Discussion

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.

Figure 3: This picture is one of the simulations using the new methodology. It shows the growing capillaries guided by the tip endothelial cells towards the gradient of angiogenic factor. It is noteworthy the anastomosis occurring at the center of the picture.

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 (χ) versus the proliferation (α_p) constants.

Figure 4: Nine simulations using different values of the chemotactic and proliferation constants. The morphology changes which each pair of parameter values.

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.

Further information

If you are interested in a video of the simulation captured in Fig. 3 you are invited to scan the QR code with your electronic device or to type http://caminos.udc.es/gmni/gente/gvilanovac/ in your browser.

References:

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[4] T.J.R. Hughes, J.A. Cottrell, Y. Bazilevs, Isogeometric analysis: CAD, finite elements, NURBS, exact geometry and mesh refinement, Comp. Meth. App. M. 194 (2005), 4135-4195.

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