Towards patient-specific simulations and validation of a tumor angiogenesis model using isogeometric analysis

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Introduction

Angiogenesis is defined as the growth of new capillaries from pre-existing ones. Some tumors release a mixture of molecules, called tumor angiogenic factor, that promote angiogenesis. Through this mechanism tumors gain access to nutrients and are able to grow unbounded [1].

An effective antiangiogenic therapy has been long pursued and insights in new therapies are usually obtained through *in vivo* and *in vitro* experimentation. One of the most widely known *in vivo* experiments is the mouse corneal micropocket angiogenesis assay. In this experiment, a pellet that releases angiogenic factor is implanted in a micropocket in the cornea (Figure 1). The cornea is an avascular tissue, thus angiogenesis does not start until the factor reaches the capillaries on the edge of the cornea (limbus). The transparency of the cornea facilitates the observation of angiogenesis.

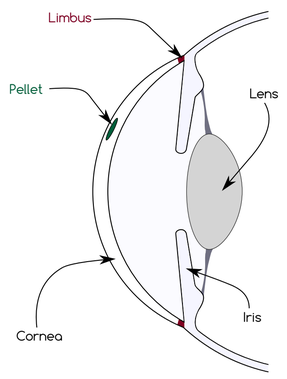


Figure 1. Schematic plot of the anterior eye.

In this work we present a numerical simulation that mimics the aforementioned assay. The computational method used to solve the mathematical model is based on Isogeometric Analysis.

Model and method

The mathematical model was proposed by Travasso et al. [2] and further extended by Vilanova et al. [3,4]. It is a multi-scale hybrid model consisting of two continuous equations and autonomous agents governed by a set of discrete rules.

The model considers two continuous variables. The first one, f, represents a tumor angiogenic factor released by cancer cells that promote the growth of capillaries. The second, c, is a phase field defining the location of the capillaries. Both variables are governed by the equations

$$\frac{\partial f}{\partial t} = \nabla \cdot (D \nabla f) - B_u f c \mathcal{H}(c)$$

$$\frac{\partial c}{\partial t} = \nabla \cdot \left(M \nabla \left(-c + c^3 - \lambda^2 \Delta c \right) \right) + \mathcal{B}_p(f)\, c \mathcal{H}(c)$$

where D is the diffusion constant, B_u is the uptake rate constant, $\mathcal{H}(\cdot)$ is the Heaviside function, M is the constant mobility, λ is a positive constant proportional to the width of the capillary wall, and $\mathcal{B}_p(\cdot)$ is the proliferative rate function.
The discrete part describes the cells that lead the migration (TEC) which move with a velocity

$$\mathbf{v}_{\mathrm{TEC}} = \chi \nabla f \mathcal{L}(\|\nabla f\|)$$

where χ is the proliferation coefficient and $\mathcal{L}(\cdot)$ is a limiting function. The continuum-discrete coupling is performed assigning a value of the phase field to the TEC (centered in $\mathbf{x}_{\mathrm{TEC}}$ with radius R_{TEC}) through the equation

$$c_{\mathrm{TEC}} = \frac{4 \mathcal{B}_p(f(\mathbf{x}_{\mathrm{TEC}}))\, R_{\mathrm{TEC}}}{3\rho}$$

We developed a mathematical framework and a computational method based on Isogeometric Analysis [5] that deals with the high order terms and the coupling between the discrete and the continuous equations.

Geometry

The geometry of the cornea of a mouse is defined by two spherical caps with different radius. Using the values provided in [6] we created this geometry using NURBS (Figure 2).

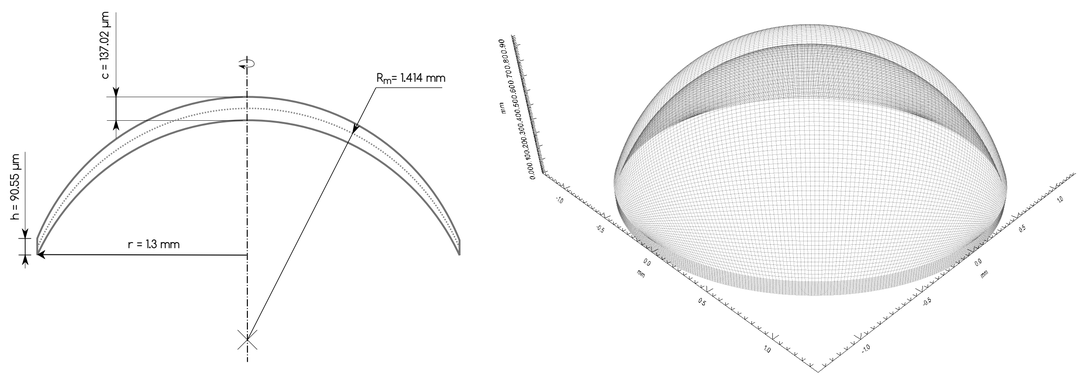


Figure 2. Left: Definition of the geometry of a C57BL/6 mouse cornea [6]. Right: The exact geometry is defined by NURBS and used in the simualtions.

We used a parametrization which is C^1 globally continuous as required by the fourth order term. In addition, we defined the parametrization such that the unavoidable singular points lie in the contours of the geometry where the limbus of the cornea is located (Figure 2). There we are forced to impose Dirichlet boundary conditions for physiological reasons, hence, the parametrization is H^2 regular and the integrals exists in the whole computed domain.

Results and validation

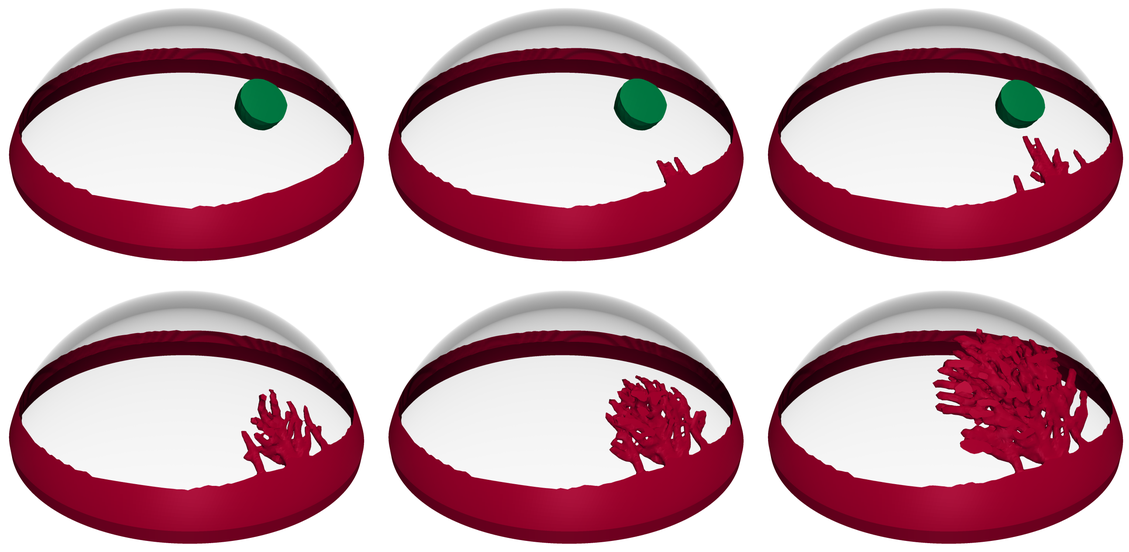


Figure 3. Evolution of a vascular network. The pellet (green) releases tumor angiogenic factor that promotes the growth of new capillaries (red).

We have performed three dimensional simulations using the geometry of the cornea of C57BL/6 mice, but thrice smaller. In Figure 3 and Central Panel we show snapshots of the evolution of angiogenesis. Initially, there is a capillary at the limbus of the cornea (red) and a pellet immersed in the cornea. The tumor angiogenic factor released by the pellet (green) diffuses until it reaches the limbus. At this point several capillaries start to grow towards the pellet forming new vasculature. The capillaries form a three dimensional network more complex than those obtained in two dimensional simulations (see Figure 4 for an example).

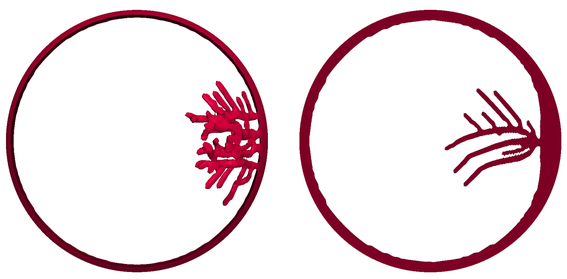
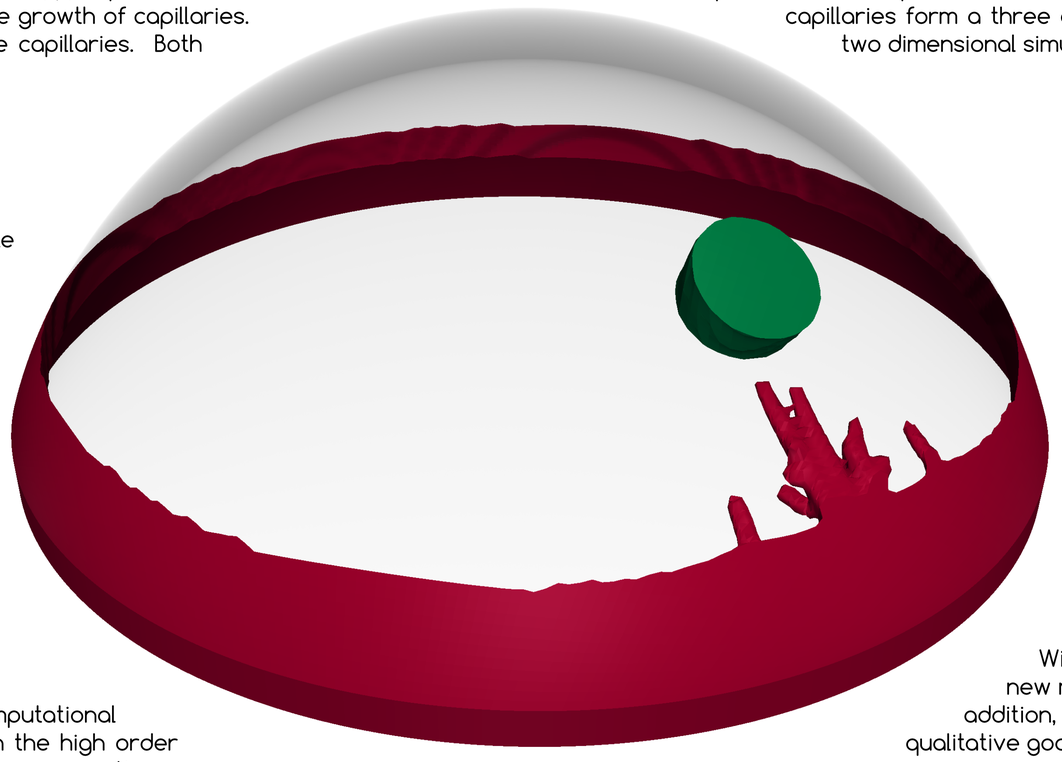


Figure 4. Comparison of the final network between a 3D (left) and a 2D (right) simulation.

The configuration of the simulation is the same as that in the mouse corneal micropocket angiogenesis assay. One of the highlights of the assay is the easy observation of the growing capillaries, for the cornea is transparent. Consequently, the validation of the mathematical model is not anymore hindered by the complexities of the visualization techniques.

With this new *in silico* experiment ready we are developing a new method of quantitative validation based on graph theory. In addition, by means of simple visual inspection our results show a qualitative good agreement with the *in vivo* assays.



Central Panel. Development of a vascular network in a mouse cornea induced by tumor angiogenic factor.

Conclusions

- We present a three-dimensional simulation of a tumor angiogenesis model based on an efficient and robust computational method and performed in a cornea of a C57BL/6 mouse.
- To the best knowledge of the authors, this is the first tumor angiogenesis simulation that includes complex and real geometries.
- The simulation shows how the computational method based on Isogeometric Analysis has the potential to enable calculations on patient-specific anatomies.
- Our *in silico* configuration mimics the *in vivo* mouse corneal micropocket angiogenesis assay, hence it allows to assess the ability of potential antiangiogenic therapies using an innocuous procedure.

Further information

If you are interested in a video of the simulation you are invited to scan the QR code or to type http://caminos.udc.es/gmni/gente/gvilanovac/media.html in your web browser.

References:

[1] J Folkman, New Engl J Med 285, 1182-1186 (1971).
[2] RDM Travasso et al., PLoS ONE 6, e19989 (2011).
[3] G Vilanova et al., Int J Numer Methods Biomed Eng 29, 1015–1160 (2013).
[4] G Vilanova et al., Comput Mech, doi: 10.1007/s00466-013-0958-0.
[5] TJR Hughes et al., Comput Methods Appl Mech Eng 194, 4135–4195 (2005).
[6] JT Henriksson et al., Invest Ophthalmol Vis Sci 50, 3648-3654 (2009).

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