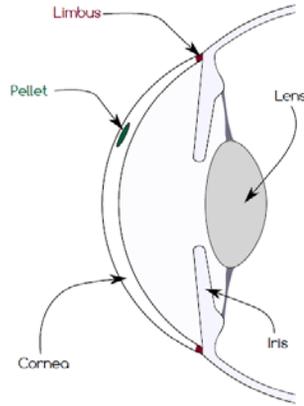


## Introduction

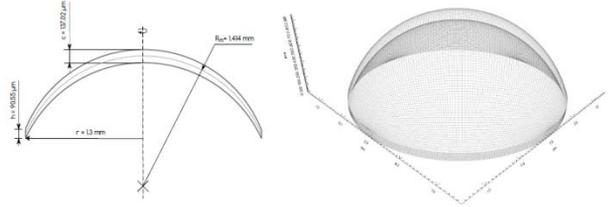
Angiogenesis is defined as the growth of new capillaries from pre-existing ones. Some tumors release a mixture of molecules, called tumor angiogenic factor, that promote angiogenesis. Through this mechanism tumors gain access to nutrients and are able to grow unbounded [1]. An effective antiangiogenic 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. In this work we present a numerical simulation that mimics the aforementioned assay.



## 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).



We used a parametrization which is C1 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 H2.

## Results

We have performed three dimensional simulations using the geometry of the cornea of C57BL/6 mice, but thrice smaller. In Figure 3 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. 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.

## Mathematical model and numerical 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

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

$$\frac{\partial c}{\partial t} = \nabla \cdot (M \nabla (-c + c^3 - \lambda^2 \Delta c)) + B_p(f) c H(c)$$

where  $D$  is the diffusion constant,  $B_u$  is the uptake rate constant,  $H(\cdot)$  is the Heaviside function,  $M$  is the constant mobility,  $\lambda$  is a positive constant proportional to the width of the capillary wall, and  $\beta(\cdot)$  is the proliferative rate function.

The discrete part describes the cells that lead the migration (TEC) which move with a velocity

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

where  $\chi$  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, through the equation

$$c_{TEC} = \frac{4B_p(f(x_{TEC})) R_{TEC}}{3\rho}$$

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.

## 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.

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