Patient-specific Phase-Field modeling and simulation of Retinal Hemangioblastoma provides new perspectives on the role of anti-VEGF therapy

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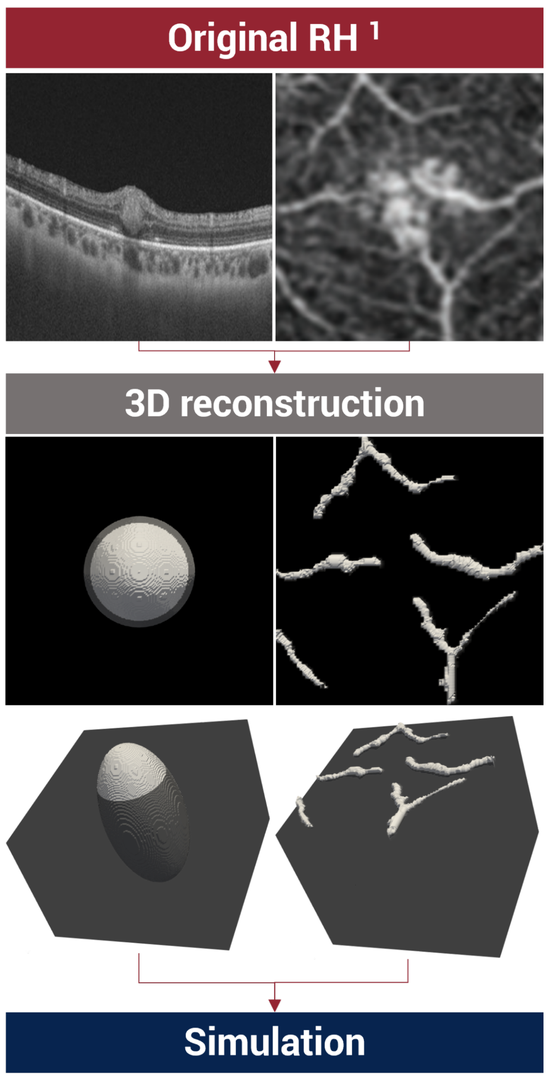
INTRODUCTION

Retinal Hemangioblastoma (RH) is the most frequent and the earliest manifestation of the von Hippel-Lindau disease (VHL). It usually presents as a slowly-growing, vascular benign tumor but can lead to severe visual impairment. Its pathology is well known, but the absence of an animal model limits the study of its development in time. On the other hand, its dimension and the availability of high-precision imaging tools such as Optical Coherence Tomography Angiography (OCTA) make RH a perfect case study with computational approaches. Thus, we developed a mathematical model to explore RH growth and RH-driven angiogenesis in a patient-specific way, using OCTA evidence as a validation source.

METHODS

We selected an OCTA case report of an early-stage RH[1], for which the tumor borders and blood vessels were visible. We used the images to 3D reconstruct a putative initial condition, and we simulated RH development and RH-driven angiogenesis in time. For our simulations, we used the FEniCS computational platform and our recently released Python package, Mocafe.

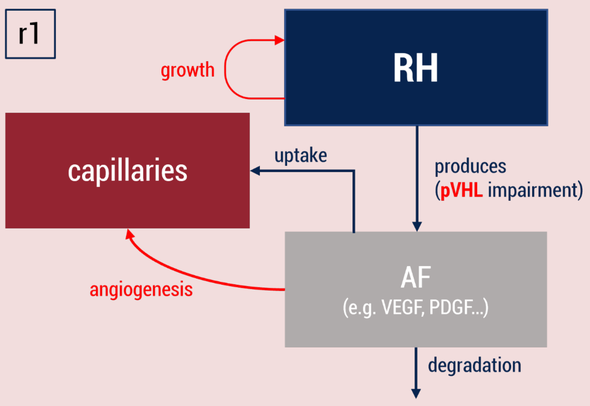


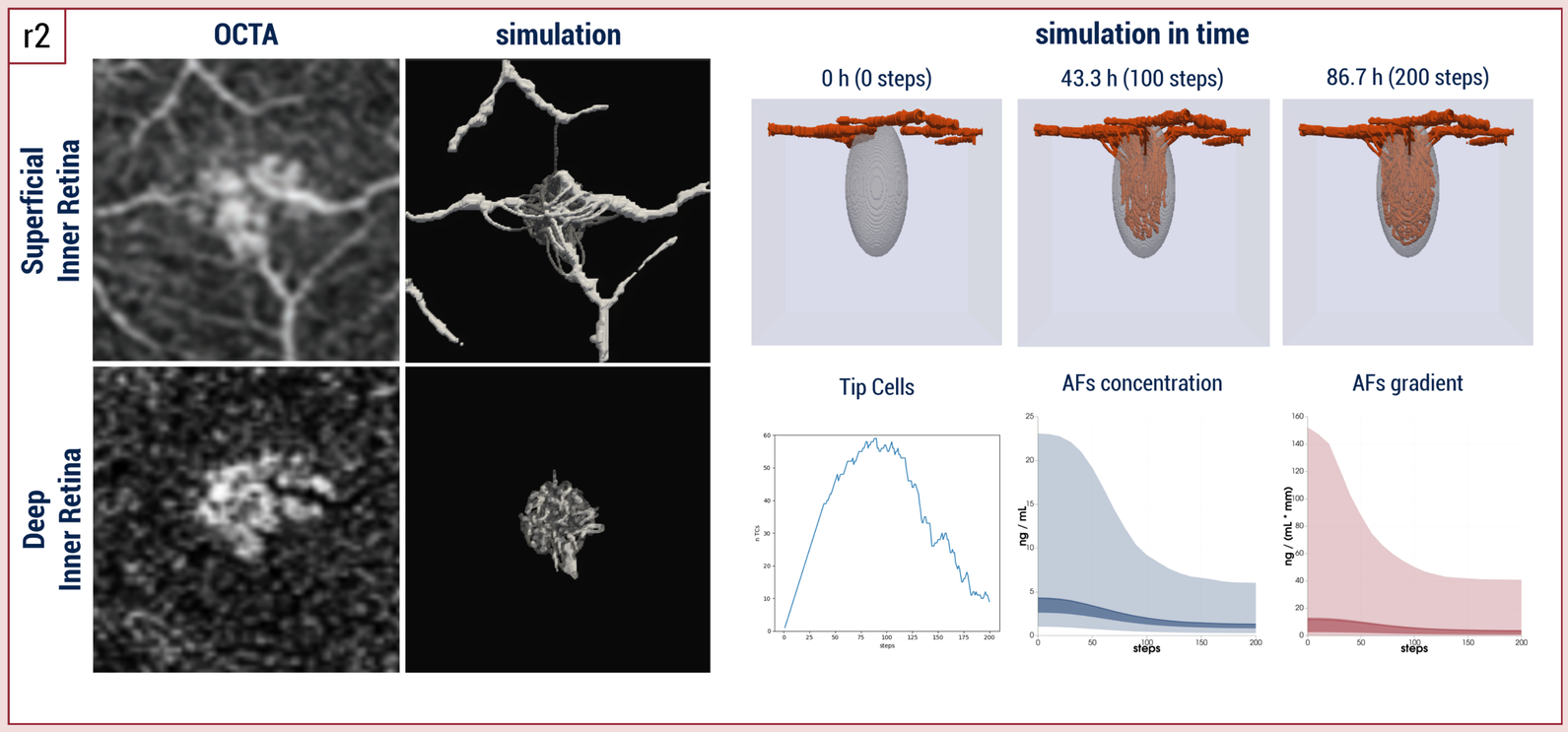
CONCLUSION

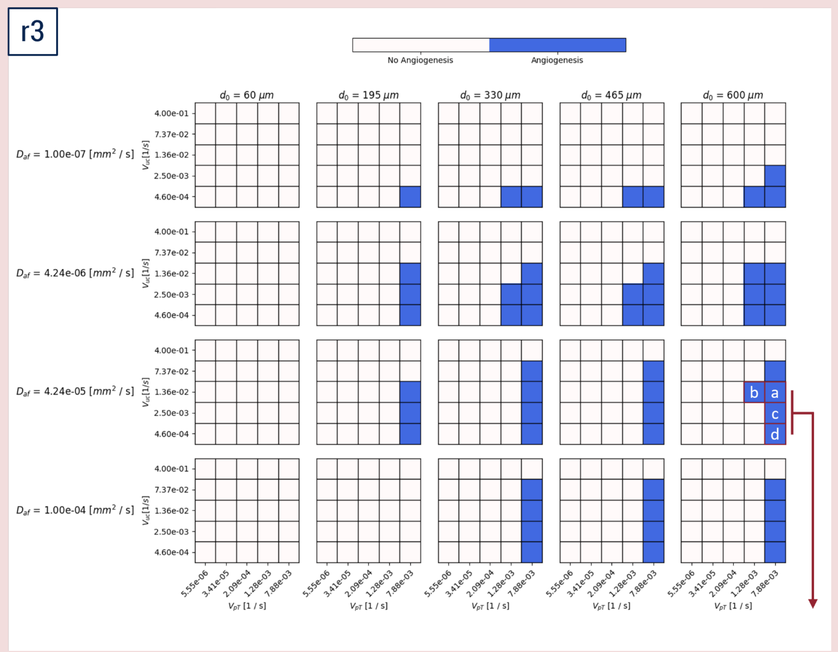
Our model can reproduce RH development and angiogenesis in a patient-specific way. Even though further validation is necessary, it can serve as the basis for an application for research and predictive medicine in RH. Furthermore, our model allowed the exploration of RH in real time, suggesting that time plays a critical role in antiangiogenic therapy.

RESULTS

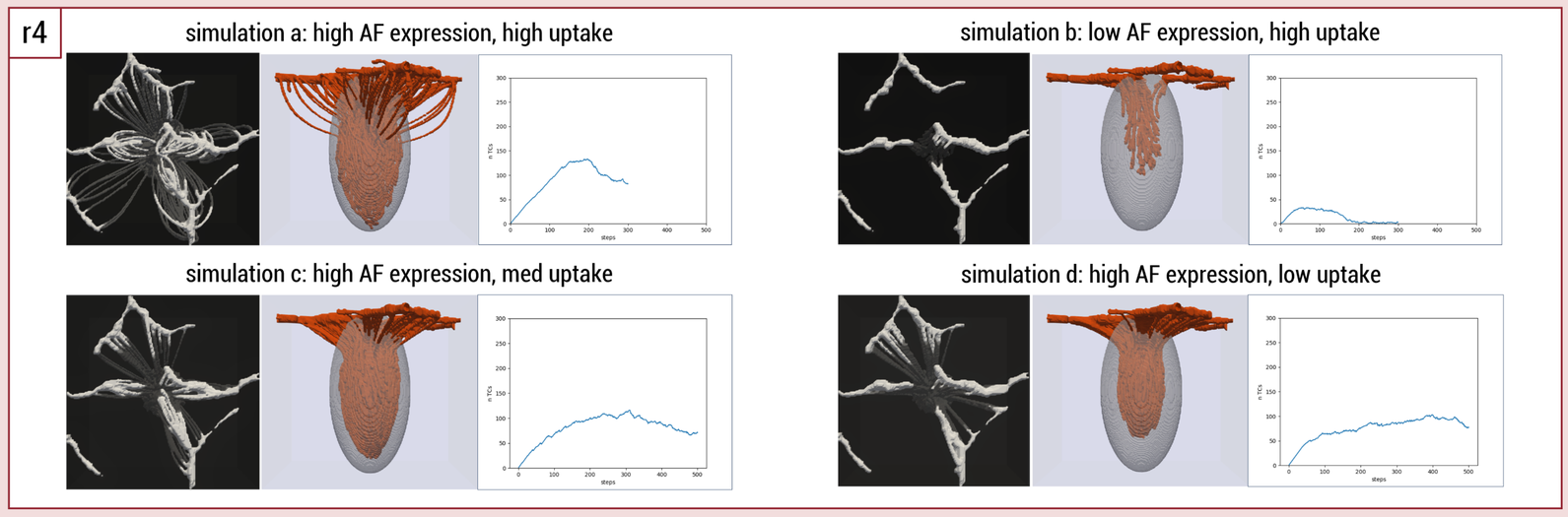
We developed a simple but well-grounded mathematical model of RH development (Figure r1). The model is based on partial differential equations (PDE) and employs an angiogenesis mathematical model already presented in the literature.
The simulations obtained with our model closely match the OCTA images presented for the patient[1]. Moreover, the angiogenic factors (AFs) concentration is in the same range reported for VHL-related tumors (Figure r2).
These results suggest that our model could be used to predict RH development for other patients, but additional experiments are necessary to assess the model's predictive capability.
We also observe that angiogenesis occurs rapidly, leading to full tumor invasion in about 87 hours (Figure r2).







Changing the parameters' values, we notice that the simulated RH triggers angiogenesis only under specific conditions (Figure r3). First, the tumor cannot be too small (< 195 μm); otherwise, the produced AFs are not enough to trigger angiogenesis. Second, the AFs production rate must be sustained. Since the tested range for AF production derives from experimental evidence, this further validates our model. Indeed, it makes sense that RH, as a VHL-related tumor, must overexpress AFs to produce its observed phenotype.
Third, we observed that angiogenesis occurs rapidly for different parameter choices. Even considering the tumor at its maximum extent, there are cases where capillaries fully invade the tumor in less than ten days (Figure r4a, r4c). Moreover, there are cases where the angiogeneis ends before full tumor invasion (Figure r4b). This opens a new perspective on the critical role of time in antiangiogenic therapy for RH. If angiogenesis is quick as predicted, there is no surprise that this therapy led to disappointing results. It might be that when RH is diagnosed, most of the capillaries are already mature.



[1]For the original case report see Goswami, A. *et al.* (2021) Optical Coherence Tomography Angiography of Early Stage 1a Retinal Hemangioblastoma in Von-Hippel-Lindau. *J. Kidney Cancer VHL*, **8**, 15–18.
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