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Multiscale modeling of ocular physiology

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1 Background and Purpose

Our purpose is to devise mathematical models that can serve as synergistic complements to experimental and clinical studies and deepen the current knowledge of ocular physiology in health and disease. One of the main challenges in developing a mathematical description of ocular physiology stems from the inherent multiscale nature of life in time and space. For example, the time scales of cellular biochemical reactions, cardiac cycle, circadian rhythm and aging differ by several orders of magnitude and yet they all matter when studying diseases such as glaucoma. Similarly, the length scales of ion channels, cells, tissues and organs span from nanometers to centimeters and yet they all interact to determine our body functions.

In this article, we highlight two recent contributions towards the multiscale modeling of ocular physiology that our group presented at the 2017 Annual Meeting of the Association for Research in Vision and Ophthalmology (7-11 May, 2017, Baltimore, MD, USA). The first contribution presents a mathematical virtual simulator, henceforth indicated as *model M1*, to simulate the biomechanics and the tissue perfusion of the lamina cribrosa (LC) [5]. Model M1 may serve as a computational tool to visualize hemodynamic and biomechanic parameters in the LC such as LC displacement, blood flow velocity and pressure, and predict their spatial and temporal variability. The aim of model M1 is to leverage partial data available on some parts of the eye (e.g. blood velocity in the central retinal vessels and ocular geometry) to provide further information on other parts of the eye that are very important from a clinical

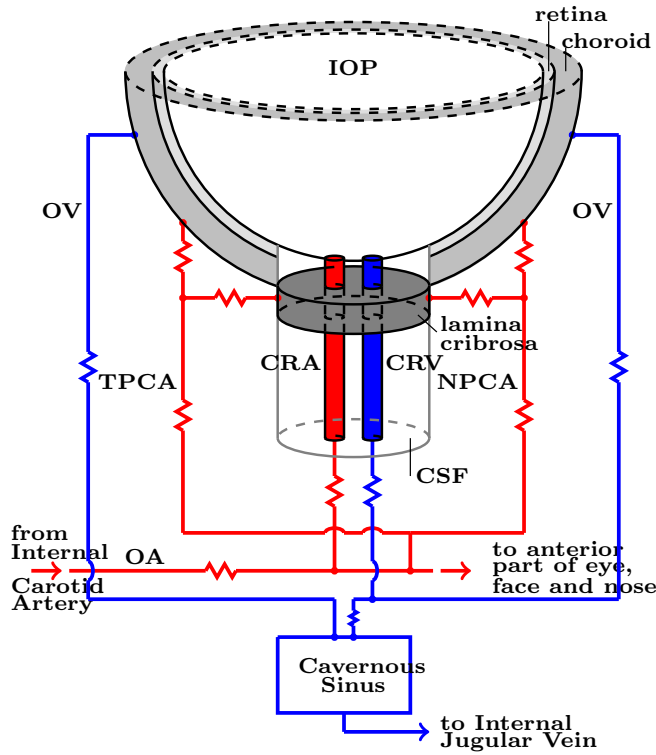


Figure 1: Mathematical virtual simulator multiscale scheme. Schematic representation of the ocular blood supply.

viewpoint but that may not be easily accessible with standard investigation instruments.

The second contribution presents a mathematical model, henceforth indicated as *model M2*, to theoretically investigate the role of neural nitric oxide (nNO), jointly with 20-hydroxyeicosatetraenoic acid (20-HETE) and epoxyeicosatrienoic acid (EET), in the regulation of retinal neurovascular coupling [4]. The analysis is motivated by experimental data of flicker light-induced functional hyperemia in humans indicating that increased nitric oxide levels mediated by 20-HETE reduce vasodilation [3]. The aim of model M2 is to provide quantitative predictions of the effect of increased levels of nNO on the vasodilation of retinal arterioles to theoretically investigate the conjecture that increased nitric oxide levels may be responsible for suppressing flicker-evoked vasodilation in diabetic retinopathy [3].

2 Methods

In both models M1 and M2, a deterministic multiscale approach is adopted, in which equations are derived by general physical principles, such as balance of mass and linear momentum. In addition, both models M1 and M2 are designed so that their input data include quantities that can be determined in a clinical setting, such as systolic and diastolic blood pressure (SBP and DBP), intraocular pressure (IOP) and ocular geometry. Model M1 employs a system of partial differential equations to provide a detailed spatial and temporal characterization of the physical variables within the LC, combining a three-dimensional porous-media model for LC perfusion with a circuit-based model for blood flow in the retrobulbar and ocular posterior segments (Fig. 1). The whole coupled system is solved using advanced computational and visualization methods [6]. Model M2 employs a system of ordinary differential equations to provide a systemic view of retinal hemodynamics, combining an equivalent electrical circuit of resistive and capacitive compartments for the retinal vasculature (Fig. 2b) with a cellular scale chemomechanical description of neurovascular coupling as the resulting interaction between vasoactive agents synthesized by active neurons, astrocytes and smooth muscle cell contraction/dilation (Fig. 2a). Kirchhoff current law is solved at each node of the equivalent electrical circuit to determine the time evolution of nodal blood pressures and compartment diameters [2].

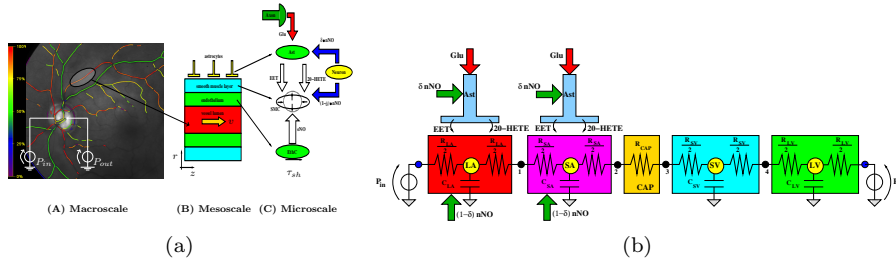


Figure 2: (a) Multiscale description of neurovascular coupling in the retina. The model inputs at the *Macroscale* (A) are the blood pressures at the inlet and outlet of the retinal circulation, P_{in} and P_{out} . The *Mesoscale* (B) focuses arterioles, whose walls comprise endothelium and smooth muscle cells. The *Microscale* (C) entails the biochemistry at the cellular level that governs the change in smooth muscle shape. (b) Macroscale, Mesoscale and Microscale are effectively combined in a single model by means of appropriate equivalent resistances.

3 Results

Fig. 3a reports the M1 visualization of ocular geometry. Simulations performed using the mathematical virtual simulator show that (i) LC displacement (Fig. 3f)

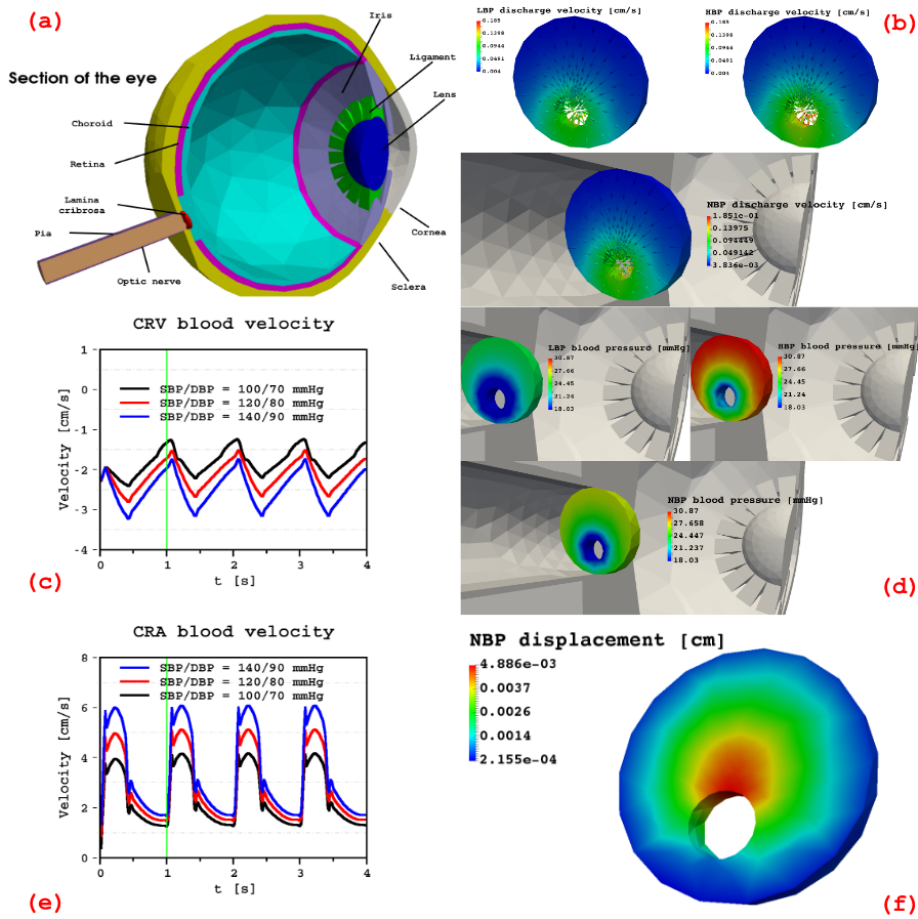


Figure 3: Lamina cribrosa perfusion simulated using the mathematical virtual simulator in the case of low, normal and high blood pressure, denoted by LBP, NBP and HBP, respectively. (a) Digitalized geometry of the eye. (b) Simulated discharge velocity. (c) Simulated blood velocity in the central retinal vein (CRV). (d) Simulated pressure distribution. (e) Simulated blood velocity in the central retinal artery (CRA). (f) Simulated lamina displacement. Only NBP displacement is shown because simulations in LBP and HBP conditions yield similar results.

is not highly influenced by the presence of the CRA/CRV opening[7] and the values are comparable to those reported in experimental studies[9], (ii) LC blood pressure distribution (Fig. 3d) is highly influenced by the values of SBP/DBP imposed at the inlet of the circuit model and attains realistic values[1], in particular on the lateral boundary, (iii) LC perfusion (Fig. 3b) increases with SBP/DBP, particularly near the nasal area and (iv) CRA and CRV blood veloc-

ities (Figs. 3c and 3e, respectively) are comparable to those obtained via direct imaging modalities[8].

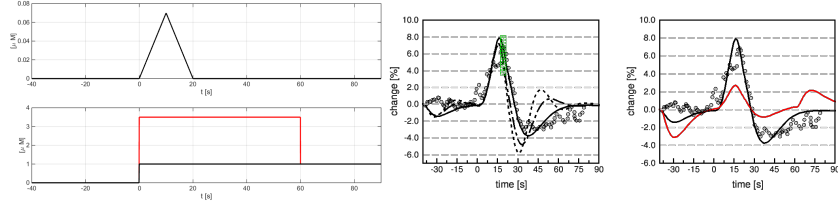


Figure 4: Neurovascular coupling simulations. (Top Left) Glutamate stimulus. (Bottom Left) Baseline (black) and elevated (red) levels of nNO. (Center) Simulated % change in MAD. Black circles: experimental data of[3]; green rectangle: data variation at the end of the GLU stimulus; dashed line: only one LA is NVA; dash-dotted line: network where only LA are NVA; solid black line: network where both LA and SA are NVA. (Right) Simulated % change in MAD. Black circles: experimental data of[3]; solid black line: network where both LA and SA are NVA, $nNO=nNO_b$; red black line: network where both LA and SA are NVA, $nNO=nNO^+$.

Fig. 4 shows the results of model M2 in the simulation of functional hyperemia (FH) in humans under flicker light stimulation (FLS)[3]. In the left panel FLS is modeled by a triangular glutamate (GLU) input signal of $0.07 \mu\text{M}$ for 20 seconds. Simulations are performed for two different nNO levels (baseline value, nNO_b , black line; increased value, $nNO^+ > nNO_b$, red line). In the central panel FH in humans is simulated with the triangular GLU signal, $nNO=nNO_b$ and different neurovascularly active (NVA) segments. The y-axis is the % change in mean arterial diameter (MAD). Black circles indicate the experimental data of[3]; the green rectangle highlights data variation at the end of the GLU stimulus; the dashed line shows model prediction using only one large arteriole (LA); the dash-dotted line is model prediction using the network of Fig. 2(b)b where only LA are assumed to be NVA; the solid black line shows model prediction using the network of Fig. 2(b)b where both LA and small arterioles (SA) are assumed to be NVA. Results indicate that FH is correctly represented only if both LA and SA are assumed to be NVA. In the right panel we illustrate the simulated effect on vasodilation due to the GLU signal and a 60s stimulus of $nNO=nNO^+$. Results indicate that elevated nNO may reduce vasodilation by a factor of 4.

4 Conclusions

Multiscale mathematical models may provide new ways to recover information on ocular physiology in health and disease. In particular, model M1 may serve as an instrument to illustrate and estimate LC perfusion parameters whereas model M2 may serve as a virtual lab where hypothesized neurovascular coupling

mechanisms can be tested and compared. The importance of the two proposed mathematical models is that, starting from general physical laws commonly adopted in academic and industrial contexts, they may be able to describe various aspects of ocular physiology. Moreover, after a severe validation process against experimental data, they can also be used as valid predictive instruments in a virtual laboratory serving as a complementary approach to experimental and clinical investigation in Ophthalmology.

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