Mathematical modeling of intraocular fluids to study glaucoma

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Introduction and purpose

• Intraocular pressure (IOP) is the pressure created by the fluids within the eye. Elevated IOP is a major risk factor for glaucoma.
• However, clinical studies report disease despite reduced IOP and vision loss despite normal IOP. Therefore, understanding what is the relative contribution of each risk factor is of major importance.

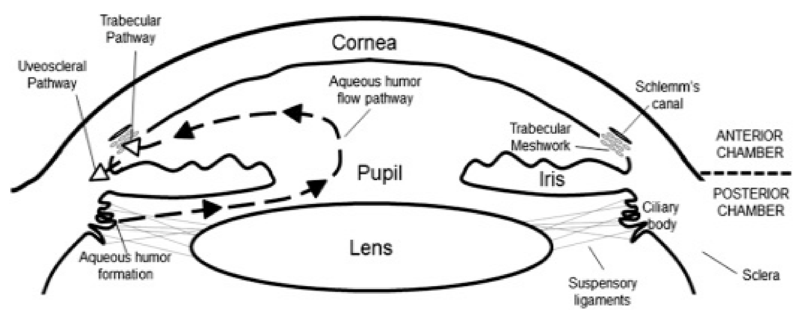

Figure 1:Anatomy of the eye

Mathematical models

To model IOP, we use the analogy between electrical circuits and fluid networks. The flow is the equivalent of the intensity and difference of pressure the equivalent of voltage.
Steady model: [4] (fig 2 in blue) results from the equilibrium between production (ultrafiltration J_{uf}, active secretion J_s) and drainage (trabecular meshwork pathway J_{tm}, uveoscleral pathway J_{uv}) of aqueous humor (AH) $\Rightarrow$ nonlinear equation to solve.
Unsteady model: [3] (fig 2 in red). We take into account blood pressure variations (through J_{ch} and P_{ext}) which induce changes in ocular blood volume $\Rightarrow$ non-linear differential equation to solve.

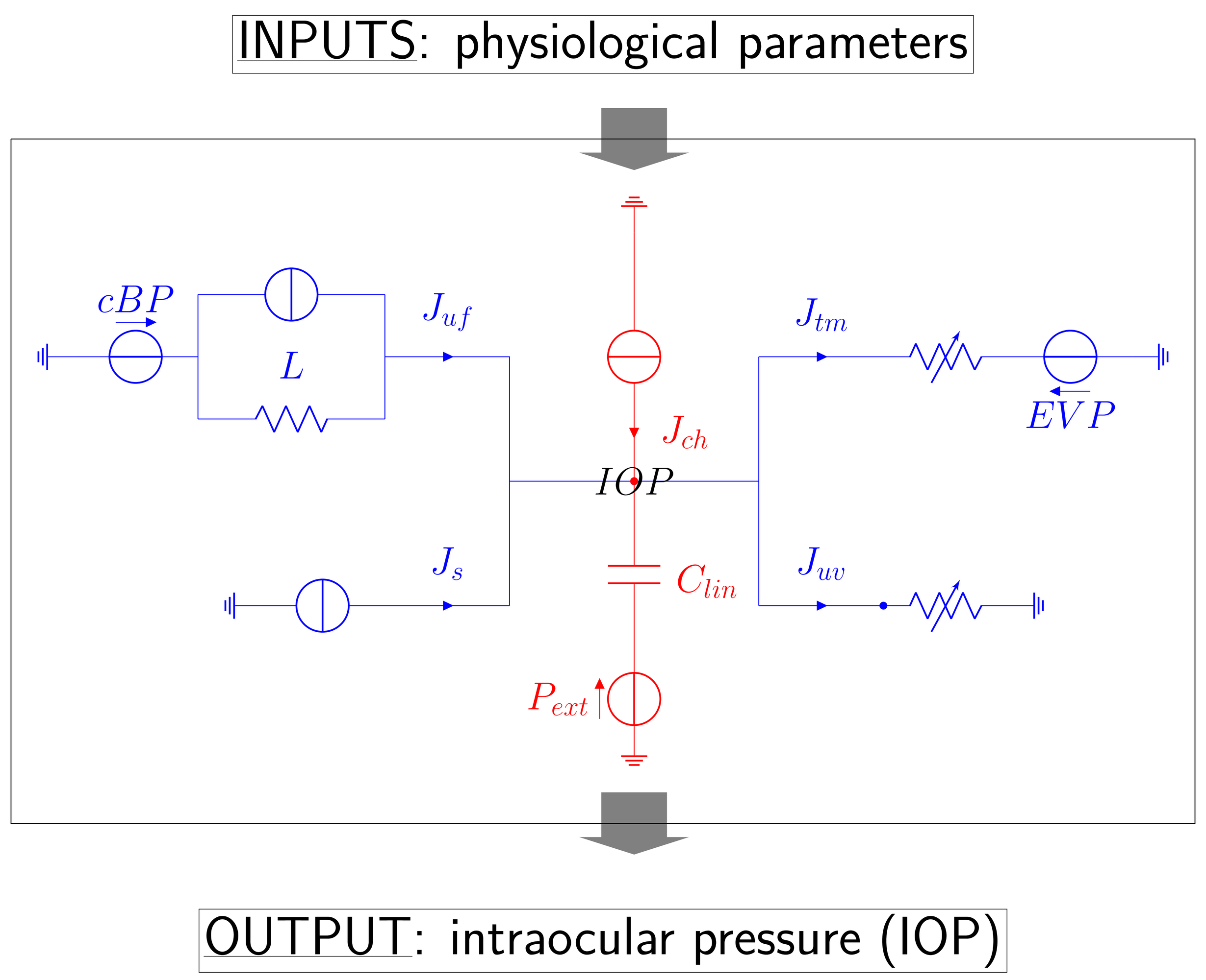

Figure 2:The circuit

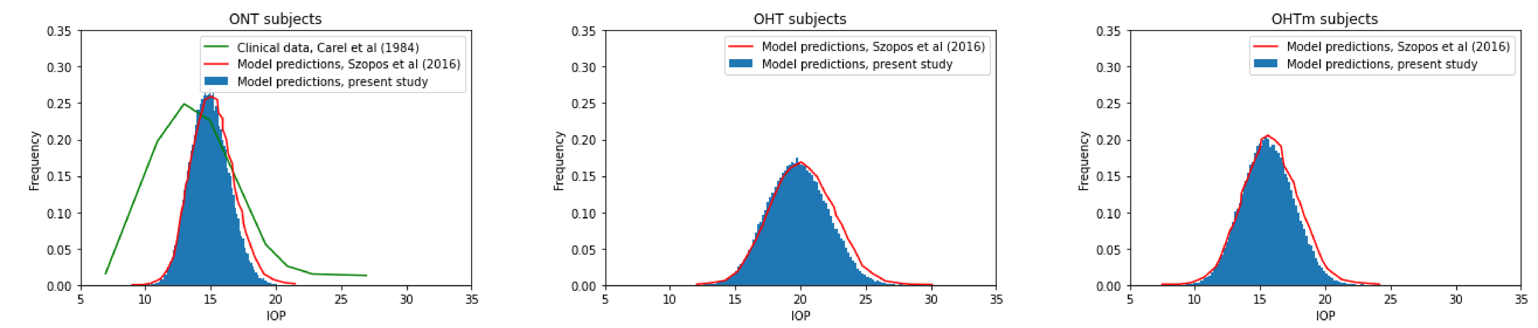

Figure 3:Probability density functions of IOP: ocular normotensive (ONT), ocular hypertensive (OHT), ocular hypertensive subjects with IOP-lowering medication (OHTm).

	Model, present study
L (total inflow facility)	0.071054
CBP (capilary blood pressure)	0.401432
$\Delta\pi_s$ (blood/AH osmotic pressure difference)	0.302130
EVP (episcleral veinous pressure)	0.071274
R (trabecular outflow resistance)	0.098163
k_1 (maximum uveoscleral flow rate)	0.000651

Figure 4:Sobol indices.

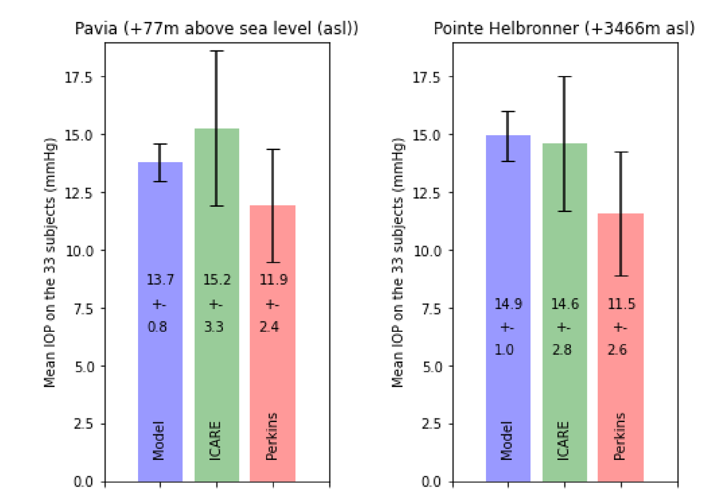

Figure 5:Mont Blanc study.

Numerical results: steady model

Probability density functions: We computed IOP for 3 populations each with 100,000 samples (figure 3). To do so, we increased R to simulate hypertension and decreased $\Delta\pi_s$ to mimic medication. Results are in accordance with a clinical study of $\sim 12,000$ subjects. Moreover, the changes in IOP follow the literature: higher IOP for OHT and IOP back to ONT values for OHTm patients.
Sensitivity analysis: The Sobol indices are values between 0 and 1 which give the importance of a parameter on the model result. They show that Blood Pressure (cBP) and active secretion ($\Delta\pi_s$) are the two most important factors that impact the resulting IOP.
Mont Blanc study: [1] The IOP and blood pressure ($cBP = \alpha \cdot MAP$) of 33 participants were measured in different altitudes with two tonometers. Thanks to MAP, we computed IOP. In Pavia, the theoretical IOP is between the two sensors. But the measured and theoretical IOP don't follow the same trend with altitude : indication that the other important factor ($\Delta\pi_s$) may play a role.

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Data from The Indianapolis Glaucoma Progression Study: Prof. Alon Harris and collaborators, Icahn School of Medicine at Mount Sinai, New York, USA.

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Numerical results: unsteady model

First observations: The output of the unsteady model is a sinusoidal signal (fig 6) with mean coherent to steady model. The ranges of IOP and OPA are coherent with the clinical literature [2] (fig 7).
Indianapolis Glaucoma progression study: We see in fig 8 that the OPA vs PD trend is supposed to be increasing. The model is too simplified to reproduce such a result.

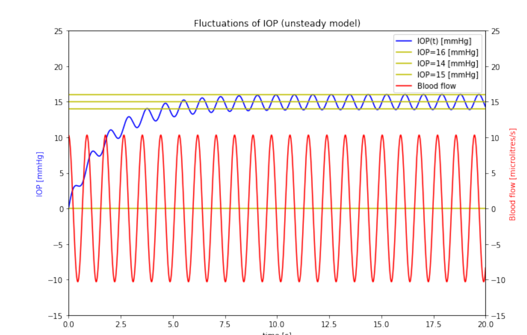

Figure 6:Shapes of IOP and blood flow

	Model	Clinical data
IOP (mean ± sd)	14.92 ± 1.47 (mmHg)	14.27 ± 2.81 (mmHg)
OPA (mean ± sd)	3.18 ± 0.23 (mmHg)	2.56 ± 1.18 (mmHg)

Figure 7:Comparison of IOP and OPA (ocular pulse amplitude = amplitudes of IOP) with data

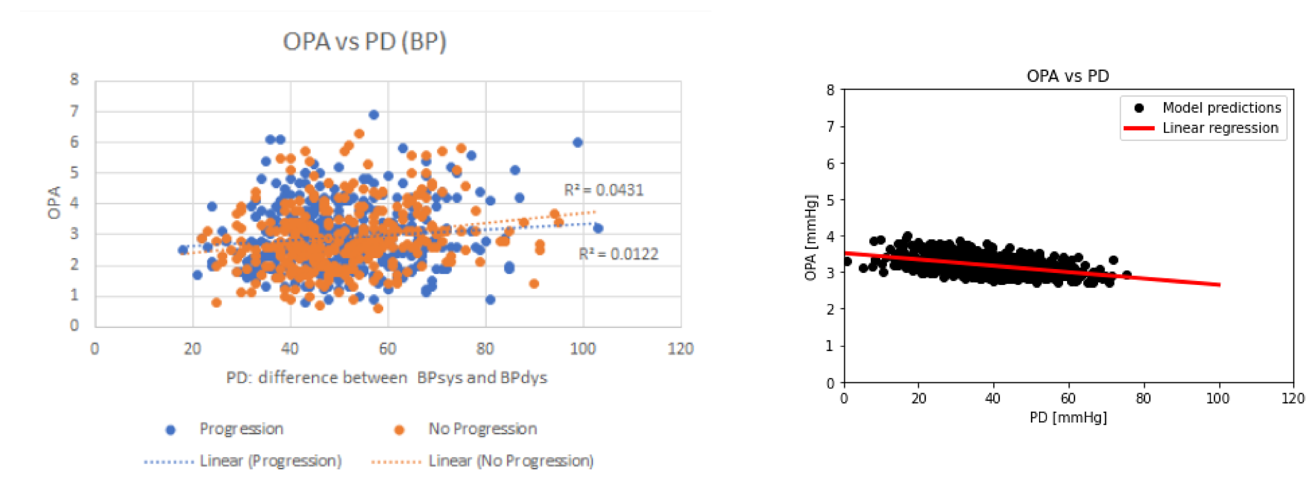

Figure 8:OPA vs PD (= SystolicBP - DiastolicBP), data and model

Conclusions and perspectives

• The sensitivity analysis allowed us to highlight the driving factors that impact IOP (cBP and $\Delta\pi_s$). Moreover, we saw that our model is able to simulate sickness and medication.
• Some improvements may come from a better account of the active secretion (steady model) to explain the differences occured in the Mont Blanc study. In the unsteady model, we think that a more precise blood flow could lead to results closer from data.

[1] Bruttini C. et al. "The Mont Blanc Study: The effect of altitude on intra ocular pressure and central corneal thickness". In: *Plos One* (2020).
[2] Cheng et al. "Ocular pulse amplitude in different types of glaucoma using dynamic contour tonometry: Diagnosis and follow-up of glaucoma". In: *Experimental and therapeutic medicine* (2018).
[3] Stefanoni et al. "Clinical assessment of intraocular pressure: a whole-eye dynamic model". In: *Journal for Modeling in Ophthalmology* (2018).
[4] Szopos et al. "Mathematical modeling of aqueous humor flow and intraocular pressure under uncertainty: towards individualized glaucoma management". In: *Journal for Modeling in Ophthalmology* (2016).