Mathematical Modeling of Coupled Cardiovascular-Ocular Hemodynamics

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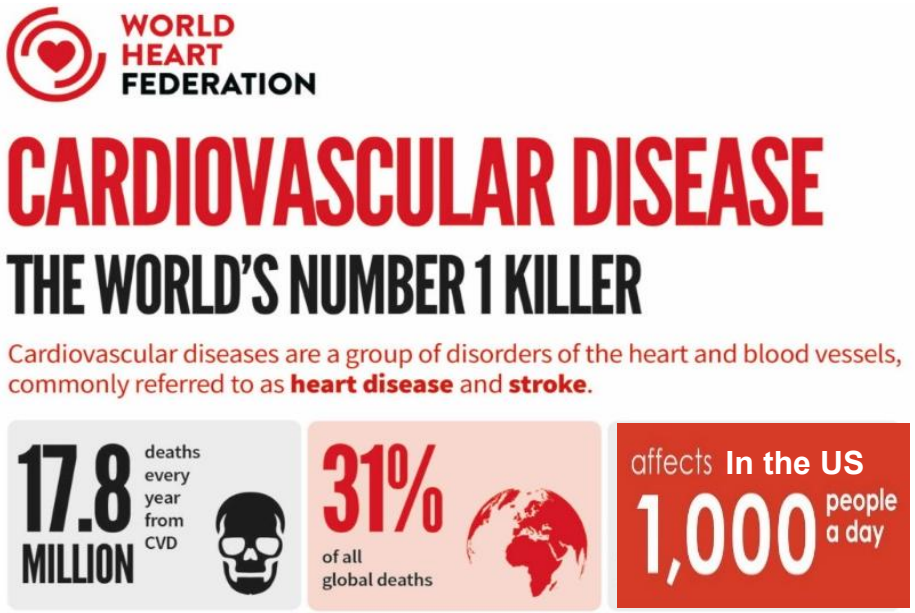
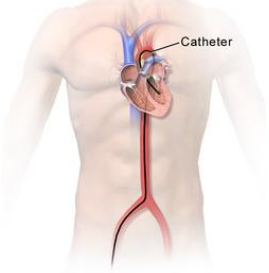
Clinical background

Cardiovascular diseases remain the leading cause of death worldwide — early detection is critical.



The development of precise non-invasive diagnostic methods remains challenging due to the heart's inaccessibility

Highly invasive



Heart catheterization

Radiation exposure

CT/MRI Scan

To early diagnose and treat cardiac dysfunctions is essential to identify novel non invasive biomarkers of cardiac contractility.

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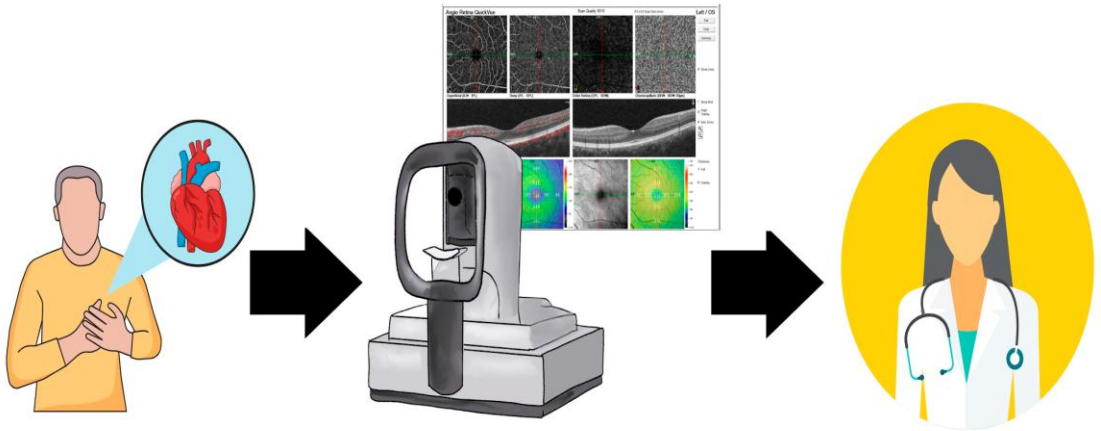
Q: Can ocular imaging provide a window to evaluate heart functions?

- Cardiovascular signals influence ocular hemodynamics, thus retinal waveforms may encode systemic status.
- Retinal vascular features are established biomarkers for hypertension, diabetes, and cardiovascular risk.
- Retinal biomarkers could enable screening for hypertension, heart failure, and vascular dysfunction.

The eye's microvascular offers a unique non-invasive window to the heart



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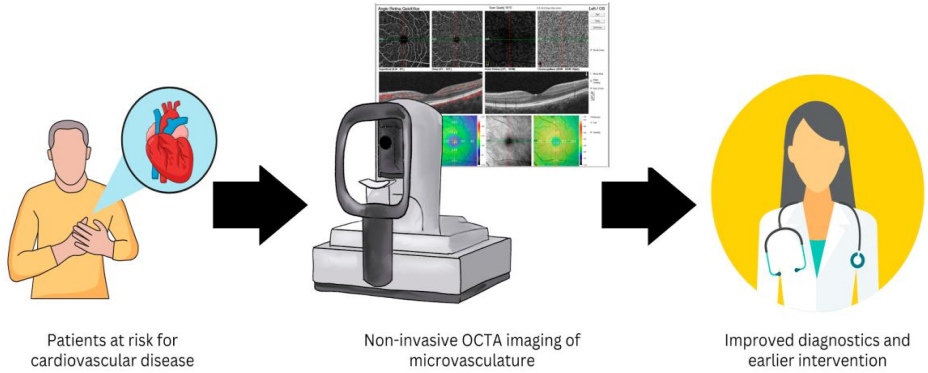

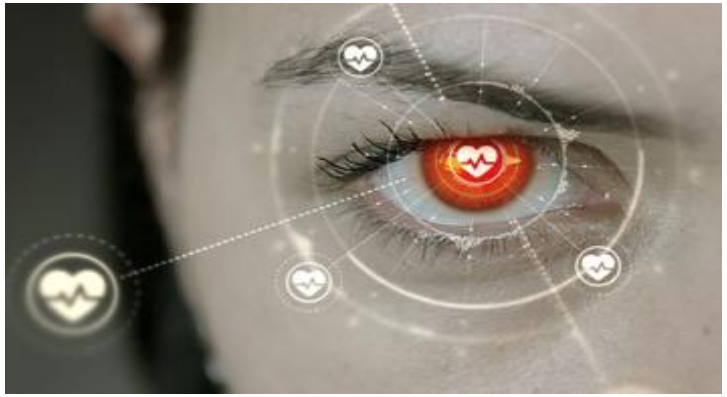

Oculomics, an emerging field that leverages ocular imaging to uncover systemic health conditions, particularly cardiovascular diseases

From medicine to mathematics …

… and back!

Medicine needs:

- **quantitative methods** to **detect** and grade abnormalities and **identify** underlying pathogenic mechanisms;
- some **patient-specific** information obtained in a **non-invasive** way.

Math modeling can:

- help **visualize** and **estimate** quantities of interest for the disease process that cannot be measured directly *in vivo*;
- help **isolate** the effect of single risk factors and **quantify** their influence on the disease process.

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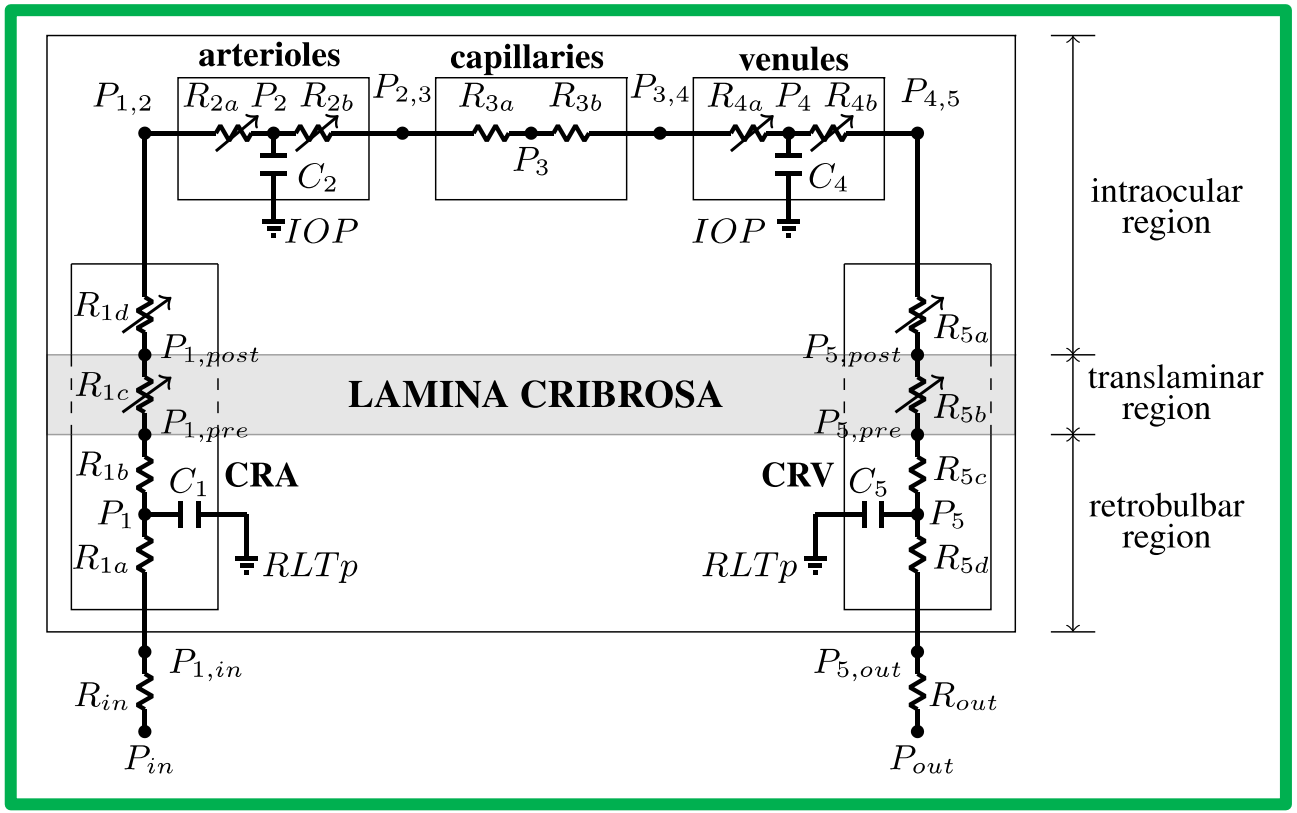
Motivation

- Integrated modeling helps interpret ocular biomarkers as proxies for central hemodynamics.
- Prior studies often rely on empirical associations or imaging-based machine learning models.
- Existing ocular hemodynamic models are mostly open-loop (eye isolated from systemic circulation).
- There is a need for an integrated, physics-based model that captures bidirectional coupling.

Develop and validate a closed-loop eye-heart model to test clinically relevant scenarios.

Eye-heart multiscale coupling in a closed-loop model

Guidoboni et al., “Intraocular Pressure, Blood Pressure, and Retinal Blood Flow Autoregulation: A Mathematical Model to Clarify Their Relationship and Clinical Relevance”. *Investigative Ophthalmology & Visual Science*. 2014



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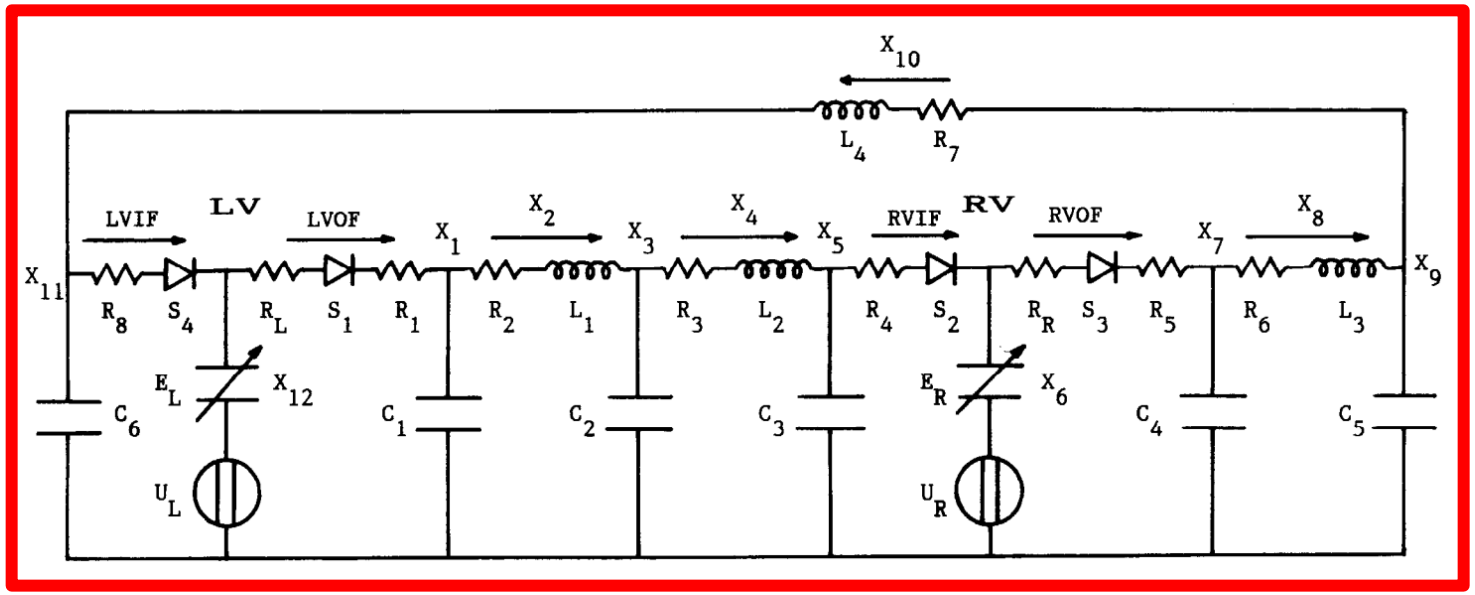

Avanzolini et al., “CADCS simulation of the closed-loop cardiovascular system”. *International journal of biomedical computing.* 1988

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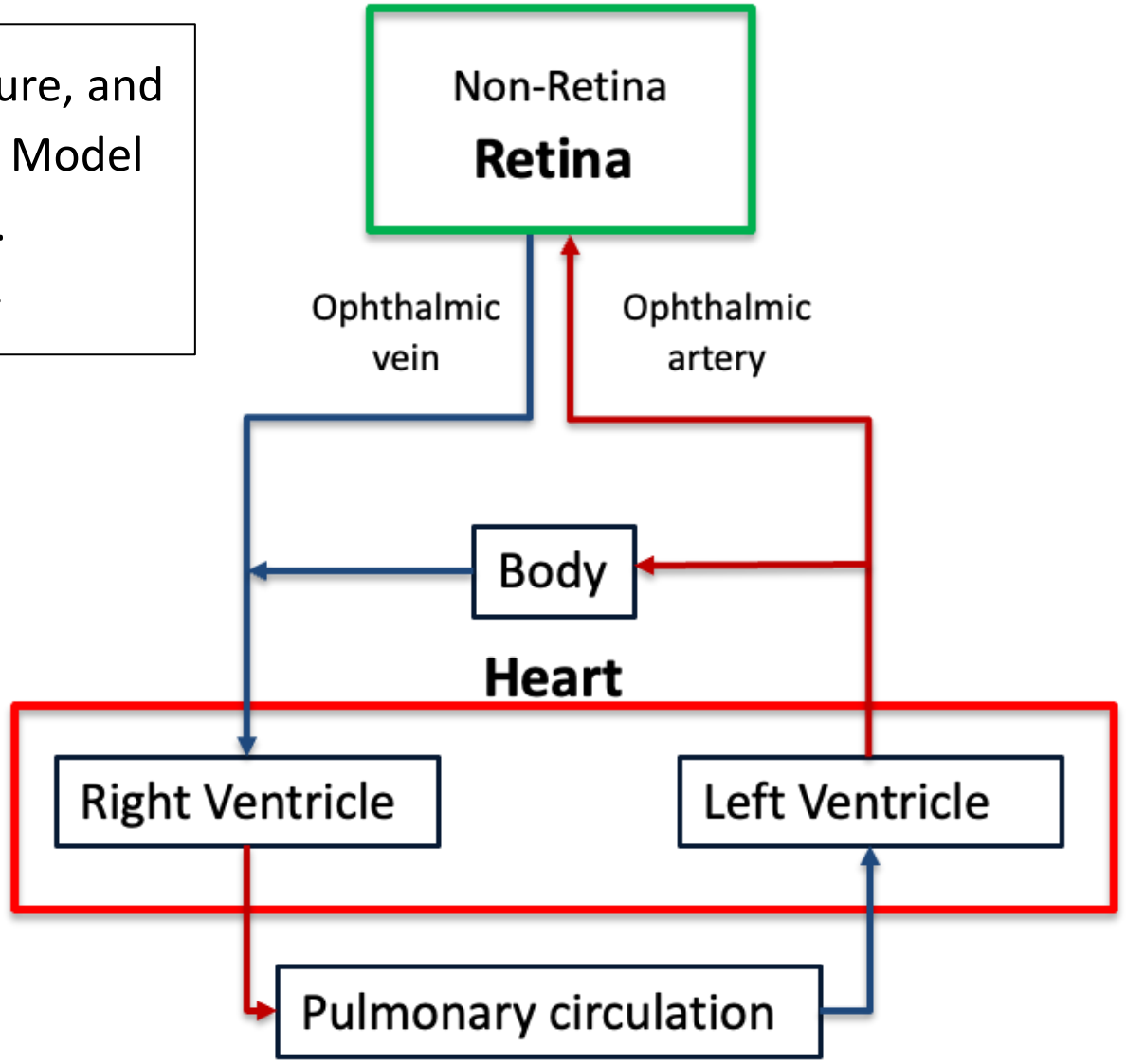
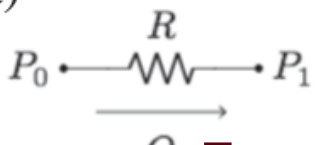


Eye2Heart model

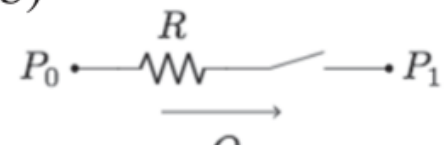
Exploit electric analogy to fluid flow

(a)



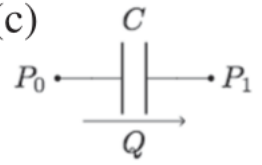
$$Q = \frac{(P_0 - P_1)}{R},$$

(b)



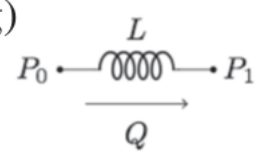
$$Q = \sigma_{P_0 - P_1} \frac{(P_0 - P_1)}{R},$$

(c)

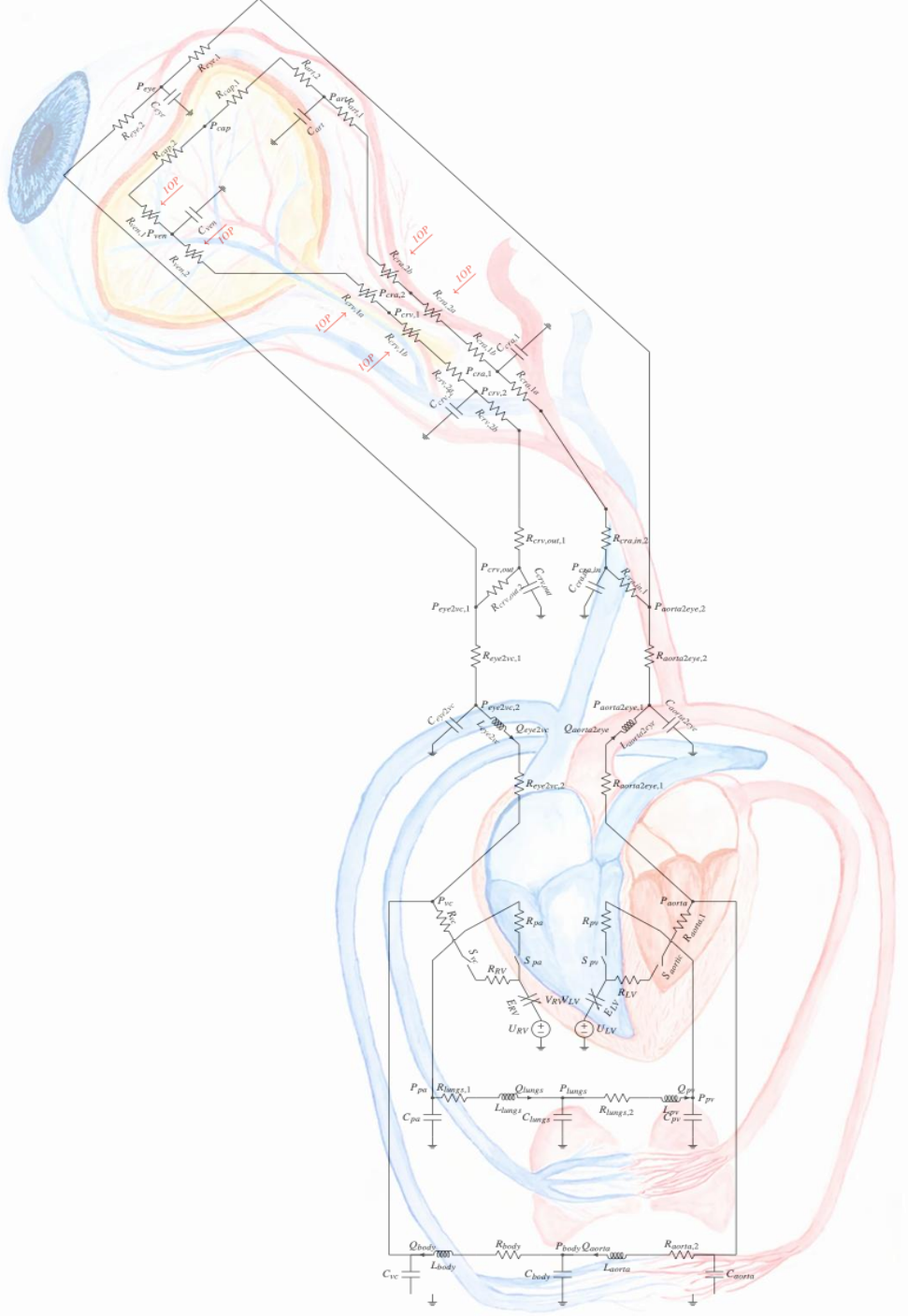


$$\frac{dV}{dt} = Q. \quad V = C(P_0 - P_1)$$

(g)



$$L\frac{dQ}{dt} = P_0 - P_1$$



Ocular vasculature

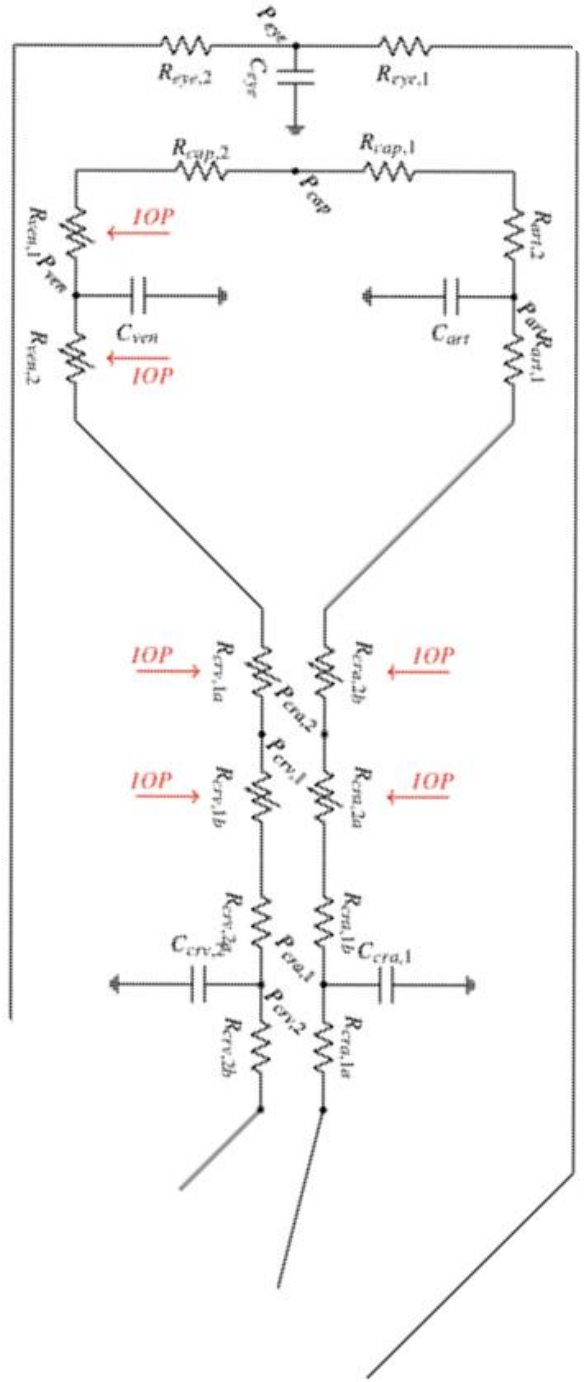
Ocular circulation modeled with retinal vasculature and the rest of the eye hemodynamics.
Retina is composed by five compartments: CRA, arterioles, capillaries, venules, CRV.

$$\Delta P_{cra} = P_{cra,2} - \mathrm{IOP}$$

$$R_{\mathrm{cra},i} = \frac{1}{k_{0_{\mathrm{cra},i}}} \left(1 + \frac{\Delta P_{\mathrm{cra}}}{K_{p_{\mathrm{cra},i}}\, K_{l_{\mathrm{cra},i}}}\right)^{-4}, \quad i \in \{2a, 2b\}.$$

$$\Delta P_{\mathrm{ven}} = P_{\mathrm{ven}} - \mathrm{IOP}, \qquad \Delta P_{\mathrm{crv}} = P_{\mathrm{crv},1} - \mathrm{IOP}.$$

$$R_{\mathrm{crv},i} = \begin{cases} \dfrac{1}{k_{0_{\mathrm{crv},i}}} \left(1 + \dfrac{\Delta P_{\mathrm{crv}}}{K_{p_{\mathrm{crv,i}}}\, K_{l_{\mathrm{crv,i}}}}\right)^{-4}, & \text{if } \Delta P_{\mathrm{crv}} \geq 0, \\ \dfrac{1}{k_{0_{\mathrm{crv},i}}} \left(1 - \dfrac{\Delta P_{\mathrm{crv}}}{K_{p_{\mathrm{crv,i}}}}\right)^{4/3}, & \text{if } \Delta P_{\mathrm{crv}} < 0. \end{cases}$$



Cardiovascular sytem

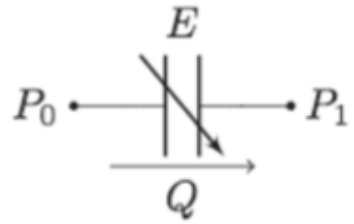
2 chamber heart model: time-varying elastances for the ventricles.
Valve states determined by pressure gradients.

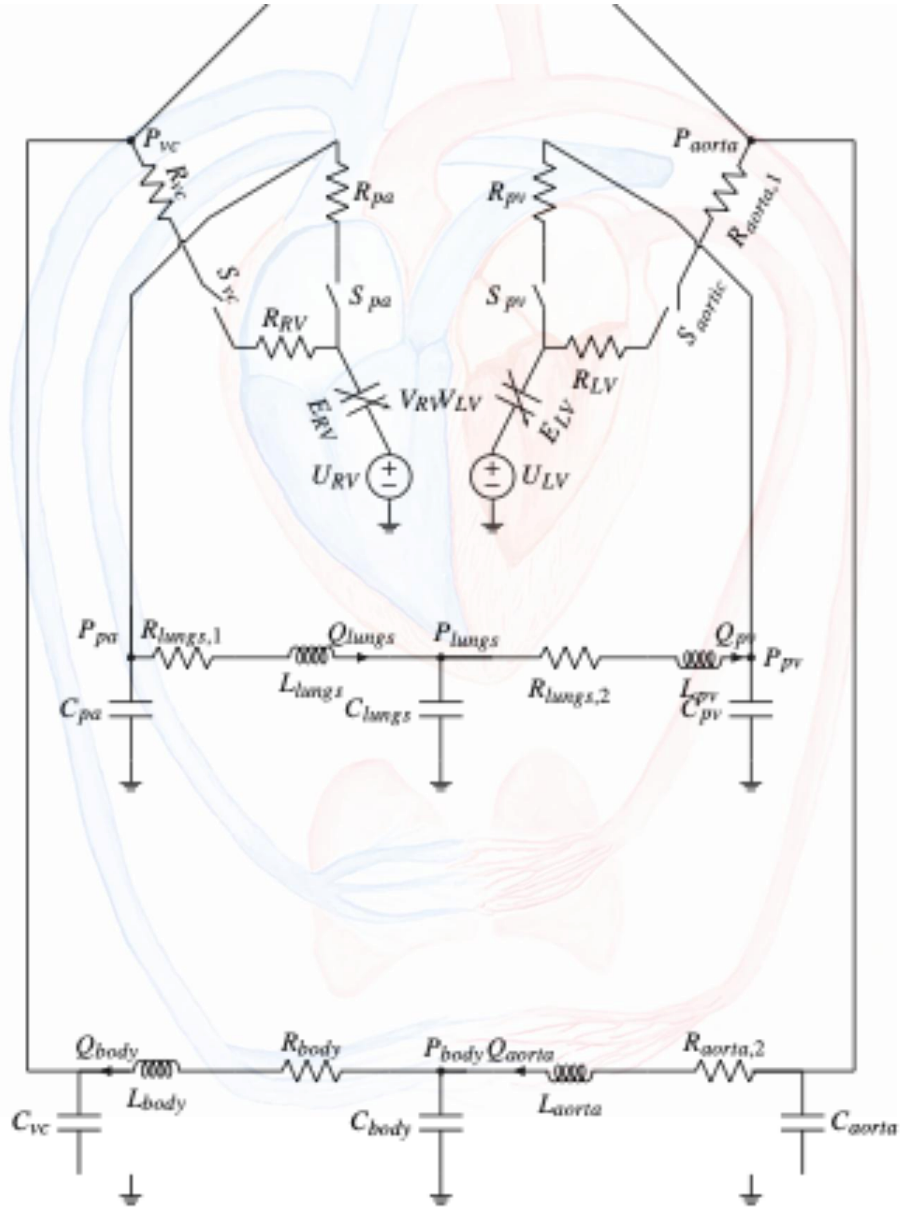
$$T_c = \frac{60}{\mathrm{HR}}, \qquad T_s = 0.16 + 0.3\, T_c$$

$$a(t) = \begin{cases} \frac{1}{2}\left(1 - \cos\left(2\pi \frac{t \bmod T_c}{T_s}\right)\right), & \text{if } t \bmod T_c < T_s \\ 0, & \text{otherwise} \end{cases}$$

$$U_L(t) = U_{L0}\, a(t), \qquad E_L(t) = E_{LD} + E_{LS}\, a(t),$$
$$U_R(t) = U_{R0}\, a(t), \qquad E_R(t) = E_{RD} + E_{RS}\, a(t).$$

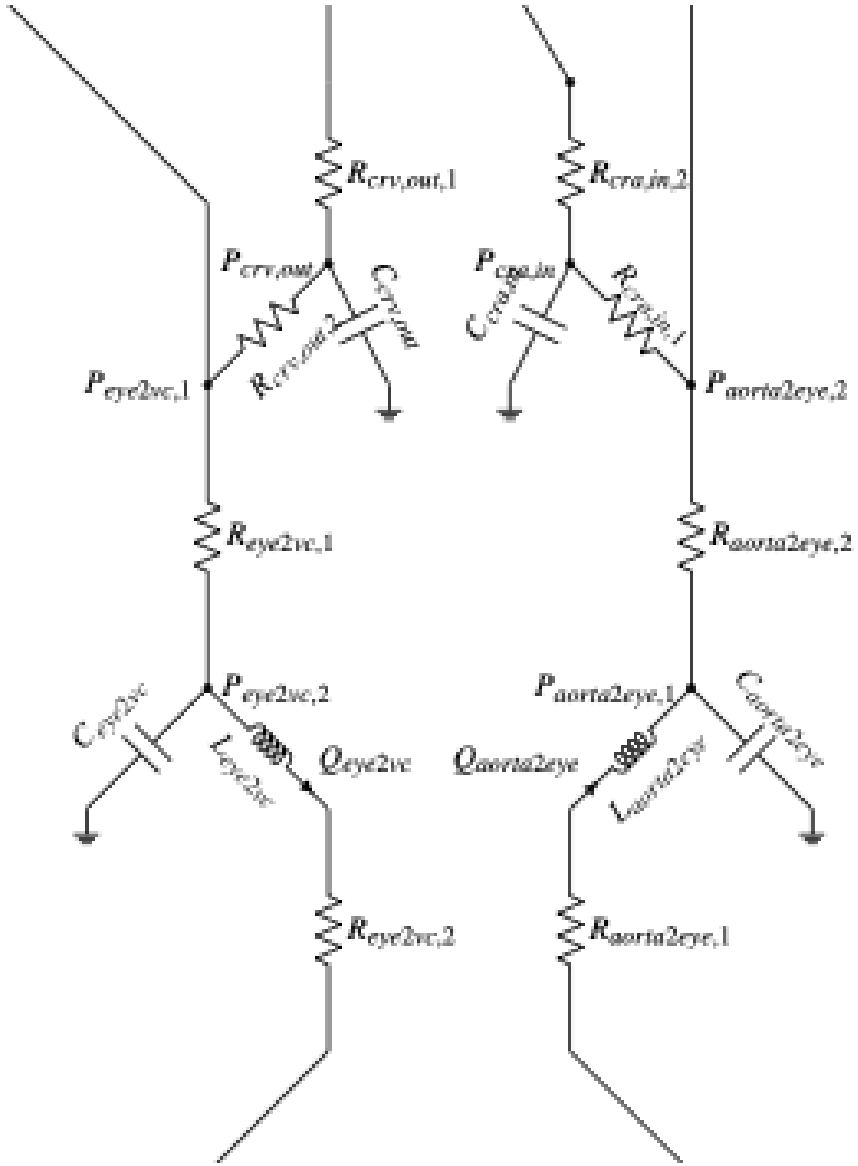
$$P_{\mathrm{LV}}(t) = U_L(t) + E_L(t)\, V_{\mathrm{LV}}(t)$$
$$P_{\mathrm{RV}}(t) = U_R(t) + E_R(t)\, V_{\mathrm{RV}}(t)$$





Coupling eye - heart

- Peripheral resistance adjusted to maintain correct mean arterial pressure with added flow path
- Not real vessel, just « effective connection » between aorta and CRA (CRV and vena cava, respectively)
- Aortic pressure drives CRA inflow
- Calibration strategy of new parameters based on steady state physiological targets. Specifically, we used literature data on retinal flows reported by Dorner et al. as reference values. To calibrate the coupling parameters, we considered the reduced circuit with resistive components only and applied Kirchhoff's laws to compute parameter values offline.



Model equations

$$\frac{dP_{aorta}}{dt} = \frac{1}{C_{aorta}}\left(\frac{(P_{LV} - P_{aorta})S_{aorta}}{R_{LV} - R_{aorta,1}} - Q_{aorta2eye} - Q_{aorta}\right) \tag{C.1}$$

$$\frac{dQ_{aorta}}{dt} = \frac{1}{L_{aorta}}(P_{aorta} - P_{body} - R_{aorta,2}Q_{aorta}) \tag{C.2}$$

$$\frac{dP_{body}}{dt} = \frac{1}{C_{body}}(Q_{aorta} - Q_{body}) \tag{C.3}$$

$$\frac{dQ_{body}}{dt} = \frac{1}{L_{body}}(P_{body} - P_{VC} - R_{body}Q_{body}) \tag{C.4}$$

$$\frac{dP_{VC}}{dt} = \frac{1}{C_{VC}}\left((Q_{body} + Q_{eye2VC}) - \frac{(P_{VC} - P_{RV})S_{VC}}{R_{VC}}\right) \tag{C.5}$$

$$\frac{dV_{RV}}{dt} = \frac{(P_{VC} - P_{PA})S_{VC}}{R_{VC}} - \frac{(P_{RV} - P_{PA})S_{PA}}{R_{RV} + R_{PA}} \tag{C.6}$$

$$\frac{dP_{PA}}{dt} = \frac{1}{C_{PA}}\left(\frac{(P_{RV} - P_{PA})S_{PA}}{R_{RV} + R_{PA}} - Q_{lungs}\right) \tag{C.7}$$

$$\frac{dQ_{lungs}}{dt} = \frac{1}{L_{lungs}}(P_{pa} - P_{lungs} - R_{lungs,1}Q_{lungs}) \tag{C.8}$$

$$\frac{dP_{lungs}}{dt} = \frac{1}{C_{PA}}(Q_{lungs} - Q_{PV}) \tag{C.9}$$

$$\frac{dQ_{PV}}{dt} = \frac{1}{L_{PV}}(P_{lungs} - P_{PV} - R_{lungs}Q_{PV}) \tag{C.10}$$

Model equations

$$\frac{dP_{PV}}{dt} = \frac{1}{C_{PV}}\left(\frac{(P_{PV} - P_{LV})S_{PV}}{R_{PV}} - Q_{PV}\right) \tag{C.11}$$

$$\frac{dV_{LV}}{dt} = \frac{(P_{PV} - P_{LV})S_{PV}}{R_{PV}} - \frac{(P_{LV} - P_{aorta})S_{aorta}}{R_{LV} + R_{aorta,1}} \tag{C.12}$$

$$\frac{dQ_{aorta2eye}}{dt} = \frac{1}{L_{aorta2eye}}(P_{aorta} - P_{aorta2eye} - R_{aorta2eye,1}Q_{aorta2eye}) \tag{C.13}$$

$$\frac{dP_{aorta2eye,1}}{dt} = \frac{1}{C_{aorta2eye}}\left(Q_{aorta2eye} - \frac{P_{aorta2eye,1} - P_{aorta2eye,2}}{R_{aorta2eye,2}}\right) \tag{C.14}$$

$$\frac{dP_{eye}}{dt} = \frac{1}{C_{eye}}\left(\frac{P_{aorta2eye,2} - P_{eye}}{R_{eye,1}} - \frac{P_{eye} - P_{eye2VC}}{R_{eye,2}}\right) \tag{C.15}$$

$$\frac{dP_{CRAin}}{dt} = \frac{1}{C_{CRAin}}\left(\frac{P_{aorta2eye,2} - P_{CRAin}}{R_{CRAin,1}} - \frac{P_{CRAin} - P_{CRA,1}}{R_{CRAin,2} + R_{CRA,1a}}\right) \tag{C.16}$$

$$\frac{dP_{CRA,1}}{dt} = \frac{1}{C_{CRA,1}}\left(\frac{P_{CRAin} - P_{CRA,1}}{R_{CRAin,2} + R_{CRA,1a}} - \frac{P_{CRA,1} - P_{art}}{R_{CRA,1b} + R_{CRA,2a} + R_{CRA,2b} + R_{art,1}}\right) \tag{C.17}$$

$$\frac{dP_{art}}{dt} = \frac{1}{C_{art}}\left(\frac{P_{CRA,1} - P_{art}}{R_{CRA,1b} + R_{CRA,2a} + R_{CRA,2b} + R_{art,1}} - \frac{P_{art} - P_{ven}}{R_{art,2} + R_{cap,1} + R_{cap,2} + R_{ven,1}}\right) \tag{C.18}$$

$$\frac{dP_{ven}}{dt} = \frac{1}{C_{ven}}\left(\frac{P_{art} - P_{ven}}{R_{art,1} + R_{cap,1} + R_{cap,2} + R_{ven,1}} - \frac{P_{ven} - P_{CRV,2}}{R_{ven,2} + R_{CRV,1a} + R_{CRV,1b} + R_{CRV,2a}}\right) \tag{C.19}$$

Model equations

$$\frac{dP_{CRV,2}}{dt} = \frac{1}{C_{CRV,1}}\left(\frac{P_{ven} - P_{CRV,2}}{R_{ven,2} + R_{CRV,1a} + R_{CRV,1b} + R_{CRV,2a}} - \frac{P_{CRV,2} - P_{CRVout}}{R_{CRV,2b} + R_{CRVout,1}}\right) \tag{C.20}$$

$$\frac{dP_{CRVout}}{dt} = \frac{1}{C_{CRVout}}\left(\frac{P_{CRV,2} - P_{CRVout}}{R_{CRV,2b} + R_{CRVout,1}} - \frac{P_{CRVout} - P_{eye2VC,1}}{R_{CRVout,2}}\right) \tag{C.21}$$

$$\frac{dP_{eye2VC}}{dt} = \frac{1}{C_{eye2VC}}\left(\frac{P_{eye2VC,1} - P_{eye2VC,2}}{R_{eye2VC,1}} - Q_{eye2VC}\right) \tag{C.22}$$

$$\frac{dQ_{eye2VC}}{dt} = \frac{1}{L_{eye2VC}}(P_{eye2VC,2} - P_{vc} - R_{eye2VC,2}Q_{eye2VC}) \tag{C.23}$$

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Numerical methods

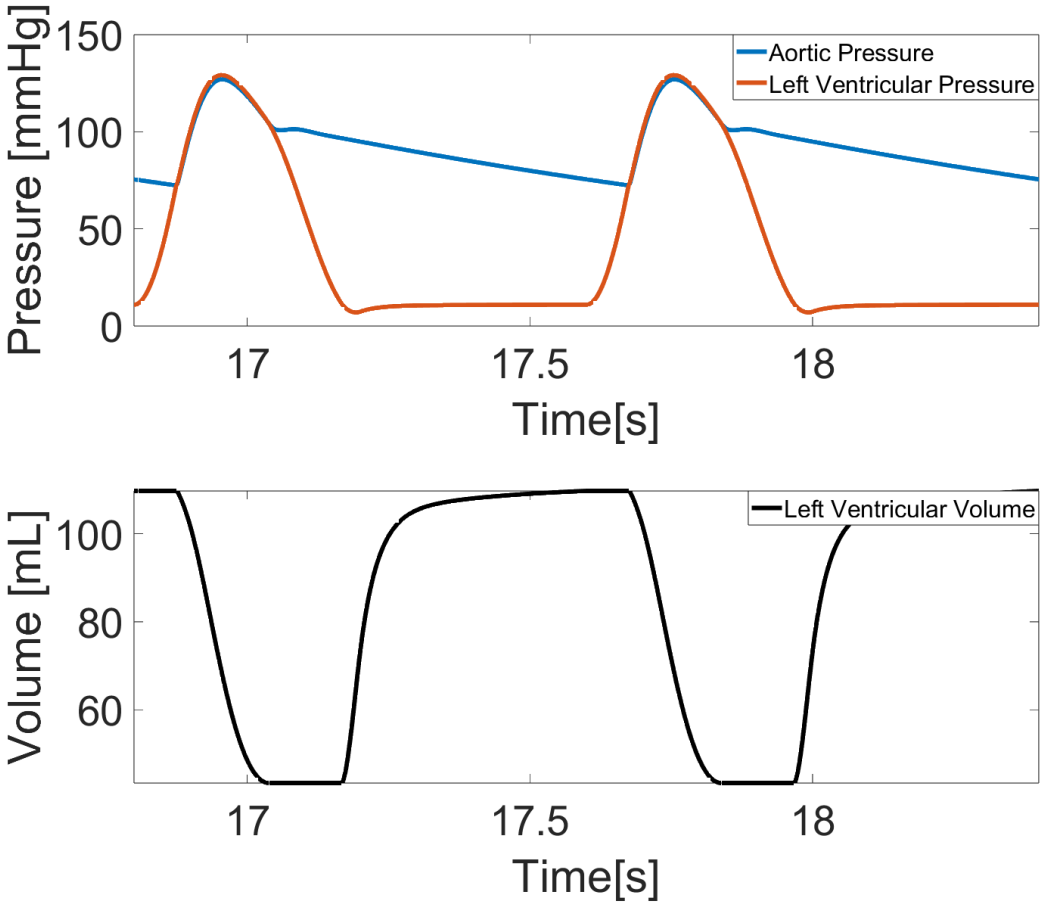
- 23 nonlinear ODEs
- Integrate over ≥10 heartbeats until periodic solution
- Current model available in two versions:
  Matlab and Python
- *ODE15S* for Matlab
- *solve_ivp* with LSODA for Python

Variable	Description	Initial condition	Units
Cardiovascular			
P_{aorta}	aortic pressure	90.1	mmHg
P_{body}	body pressure	70.5	mmHg
P_{VC}	vena cava pressure	3.32	mmHg
P_{PA}	pulmonary artery pressure	13.4	mmHg
P_{lungs}	lungs pressure	13.3	mmHg
P_{PV}	pulmonary vein pressure	11.2	mmHg
Q_{aorta}	aortic flow rate	8.89	ml/s
Q_{body}	body flow rate	67.3	ml/s
Q_{lungs}	lungs flow rate	0.78	ml/s
Q_{PV}	pulmonary vein flow rate	23.8	ml/s
V_{RV}	vena cava volume	105	ml
V_{LV}	left ventricle volume	112	ml
Eye-Heart Coupling			
$P_{aorta2eye,1}$	aorta-to-eye pressure	80.25	mmHg
P_{CRAin}	pre-laminar CRA pressure	70.2	mmHg
P_{CRVout}	post-laminar CRV pressure	8.57	mmHg
P_{eye}	eye pressure	65.5	mmHg
$P_{eye2vc,2}$	eye-to-vena cava pressure	4.52	mmHg
Q_{eye2vc}	eye-to-vena-cava flow rate	0.15	ml/s
$Q_{aorta2eye}$	aorta-to-eye flow rate	0.15	ml/s
Ocular Circulation			
$P_{CRA,1}$	CRA pressure	43.5	mmHg
P_{art}	arteriole pressure	35.5	mmHg
P_{ven}	venule pressure	21.8	mmHg
$P_{CRV,2}$	CRV pressure	18.9	mmHg

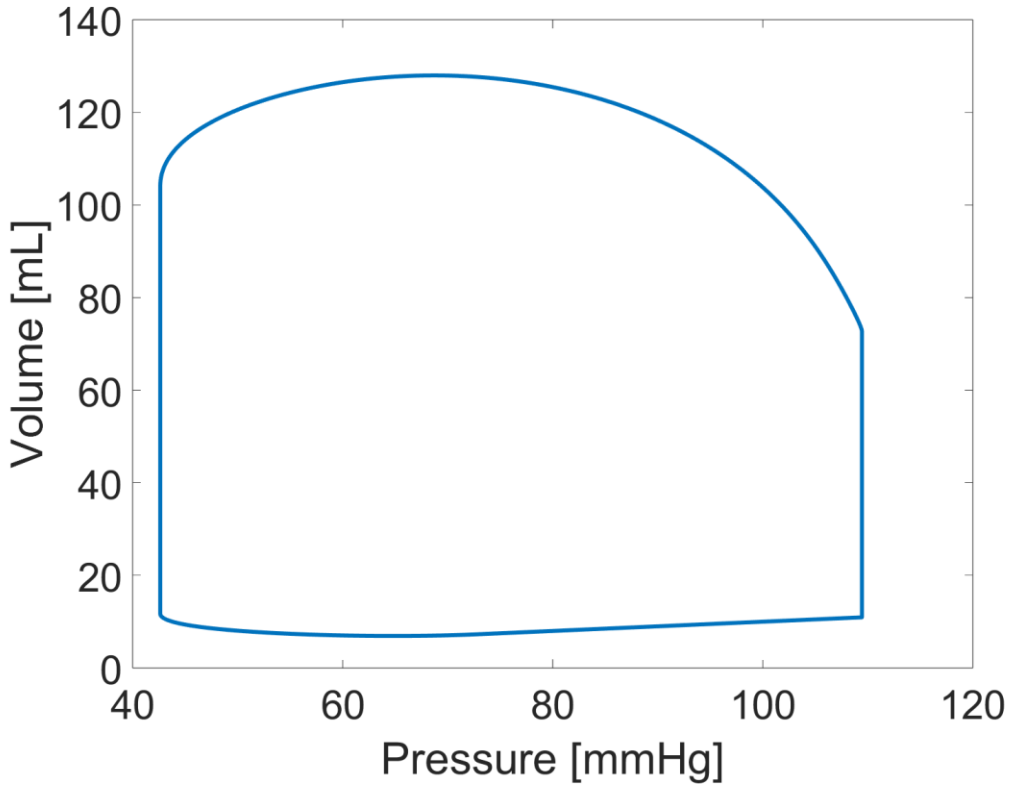
Baseline simulation results

Parameter	Unit	Clinical Ranges from literature		Present work	
		Left Ventricle	*Right Ventricle*	*Left Ventricle*	*Right Ventricle*
End-Systolic Volume (ESV)	[ml]	47 (27,68) [27] 35 ±13 [36] 30 ± 12 [28]	50 (22,78) [26] 43 ± 19 [36] 50-100 [24]	42.59	43.81
End-Diastolic Volume (EDV)	[ml]	142 (102,183) [27] 108 ±27 [36] 109 ± 27 [28]	144 (98,190) [26] 115 ± 31 [36] 100 - 160 [24]	112.76	115.25
Stroke Volume (SV)	[ml/beat]	95 (67, 123) [27] 60 - 100 [24] 81 ± 18 [6] 78 ± 20 [28]	94 (64, 124) [26] 60-100 [24]	70.18	71.45
Cardiac Output (CO)	[l/min]	4-8 [24] 5.524 ± 1.488 [6] 4.8 ± 1.3 [28]	4-8 [24]	5.26	5.36
Ejection Fraction (EF)	[%]	67 (58, 76) [27] 72 ± 7 [28]	66 (54, 78) [26] 40 - 60 [24]	62.32	61.99
End-Systolic Elastance (E_{es})	[mmHg/ml]	1.74 [33]	0.7 ± 0.2 [39]	1.03	0.32
Arterial Elastance (E_a)	[mmHg/ml]	1.2 [33]	0.5 ± 0.2 [39]	1.65	0.52
Central Systolic Pressure (SP)	[mmHg]	124.1 ± 11.1 [37]		125.7	
Central Diastolic Pressure (DP)	[mmHg]	77.5 ± 7.1 [37]		72.7	
Right Atrial Pressure (P_{ra})	[mmHg]	3 ± 2 [25]		3.78	

Baseline simulation results: systemic biomarkers

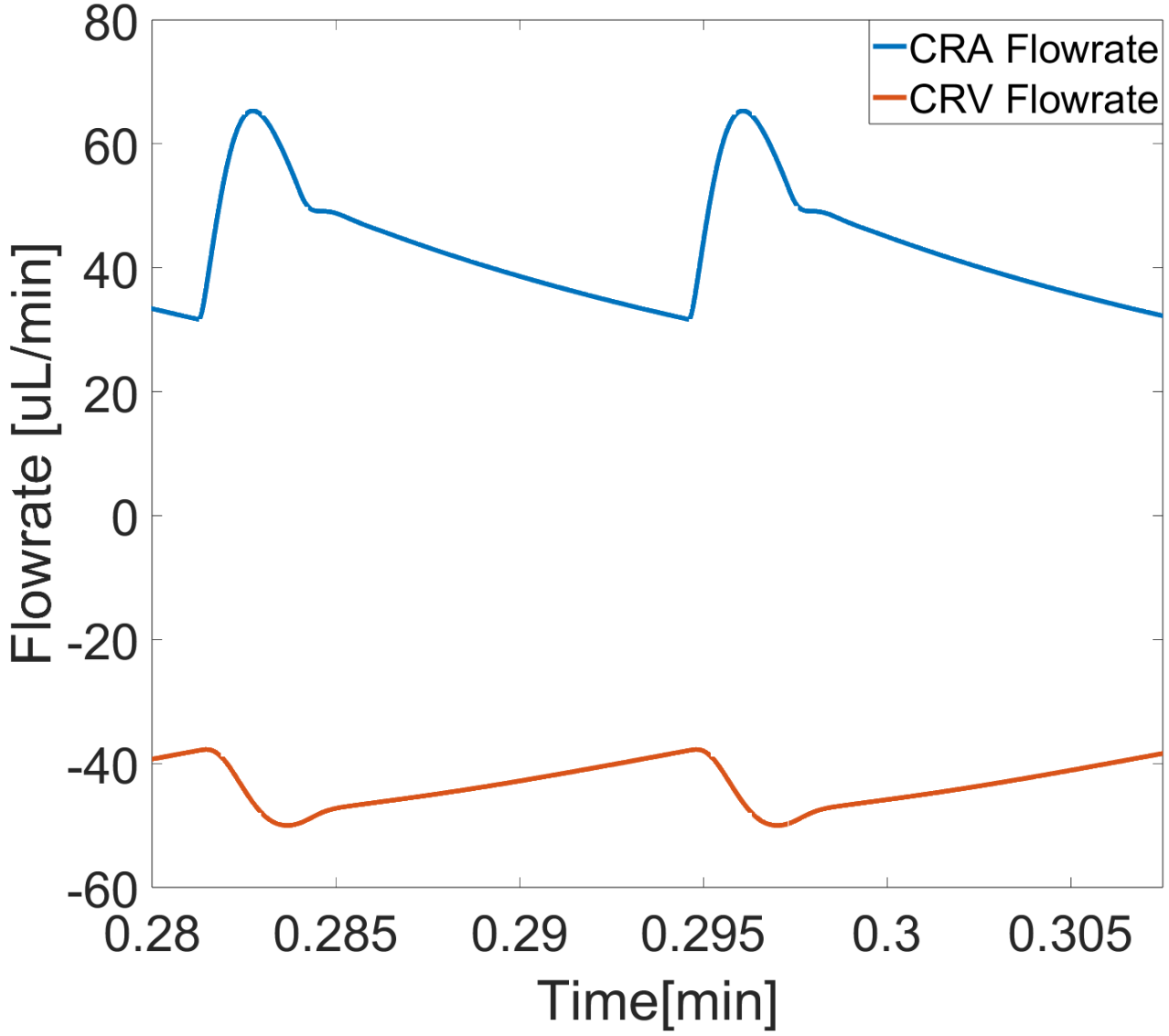


Wiggers' diagram



Left Ventricle PV loop

Baseline simulation results: CRA and CRV



Predictive scenario: IOP elevation

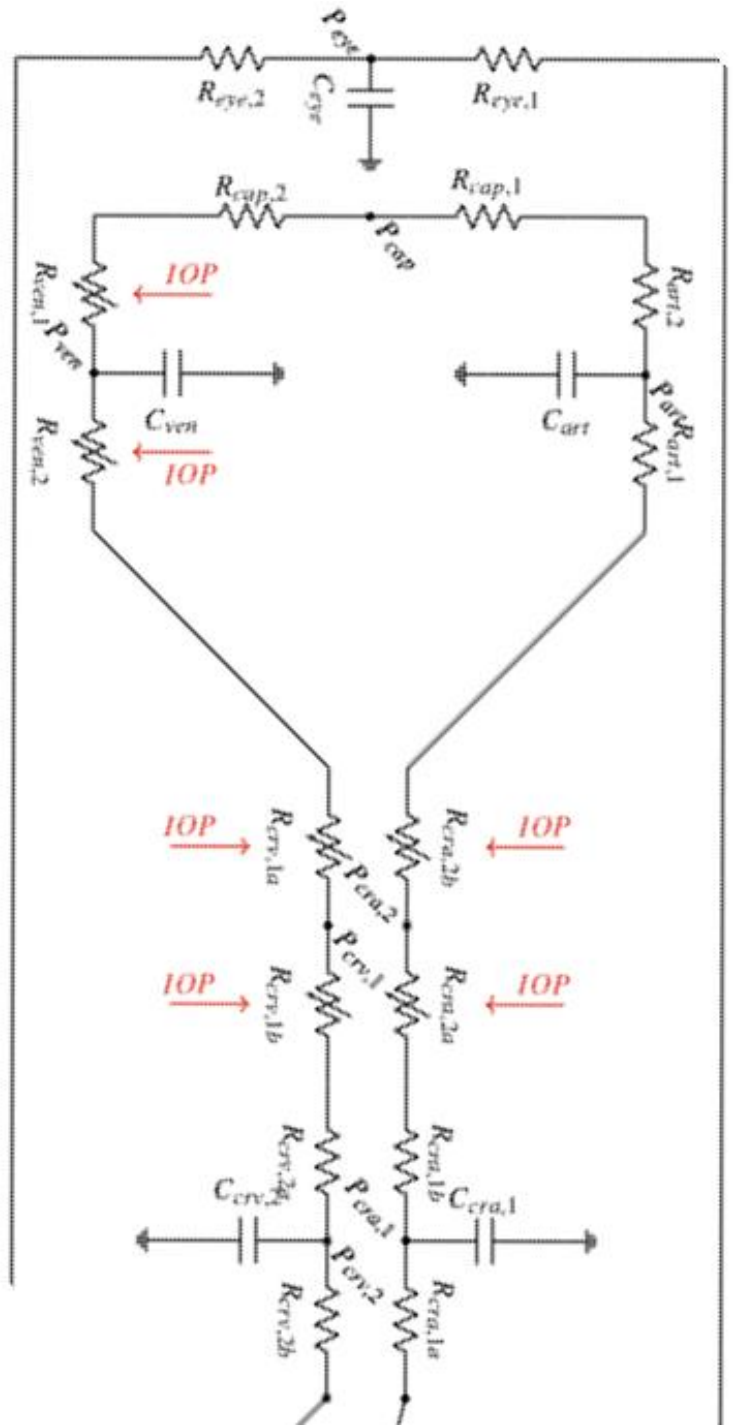
Increase IOP from 15 mmHg to 30 mmHg

$$\Delta P_{cra} = P_{cra,2} - \mathrm{IOP}$$

$$R_{\mathrm{cra},i} = \frac{1}{k_{0_{\mathrm{cra},i}}} \left(1 + \frac{\Delta P_{\mathrm{cra}}}{K_{p_{\mathrm{cra},i}}\, K_{l_{\mathrm{cra},i}}}\right)^{-4}, \quad i \in \{2a, 2b\}.$$

$$\Delta P_{\mathrm{ven}} = P_{\mathrm{ven}} - \mathrm{IOP}, \qquad \Delta P_{\mathrm{crv}} = P_{\mathrm{crv},1} - \mathrm{IOP}.$$

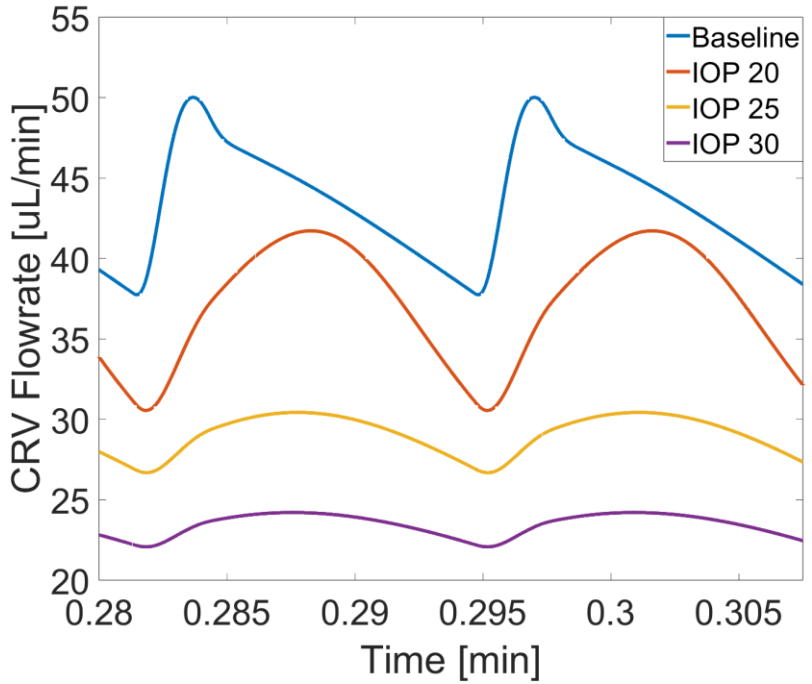
$$R_{\mathrm{crv},i} = \begin{cases} \dfrac{1}{k_{0_{\mathrm{crv},i}}} \left(1 + \dfrac{\Delta P_{\mathrm{crv}}}{K_{p_{\mathrm{crv,i}}}\, K_{l_{\mathrm{crv,i}}}}\right)^{-4}, & \text{if } \Delta P_{\mathrm{crv}} \geq 0, \\ \dfrac{1}{k_{0_{\mathrm{crv},i}}} \left(1 - \dfrac{\Delta P_{\mathrm{crv}}}{K_{p_{\mathrm{crv,i}}}}\right)^{4/3}, & \text{if } \Delta P_{\mathrm{crv}} < 0. \end{cases}$$



Predictive scenario: IOP elevation

Output	Unit	IOP = 15 mmHg	IOP = 20 mmHg	IOP = 25 mmHg	IOP = 30 mmHg
SP / DP	[mmHg]	128/69	127/69	127/69	127/69
EDV / ESV	[ml]	113/43	113/43	113/43	113/43
CO	[l/min]	5.26	5.26	5.26	5.26
CRA mean BF	[$\mu l/min$]	46.6	43.6	36.3	30.8
CRV mean BF	[$\mu l/min$]	43.5	40.5	29.1	23.3

- Systemic MAP and CO remain nearly unchanged
- CRA mean flow decreases.
- CRV mean flow drops with high IOP
- Capillary pressure drops ⇒ reduced ocular perfusion pressure.



Predictive scenario: LV Compliance Reduction

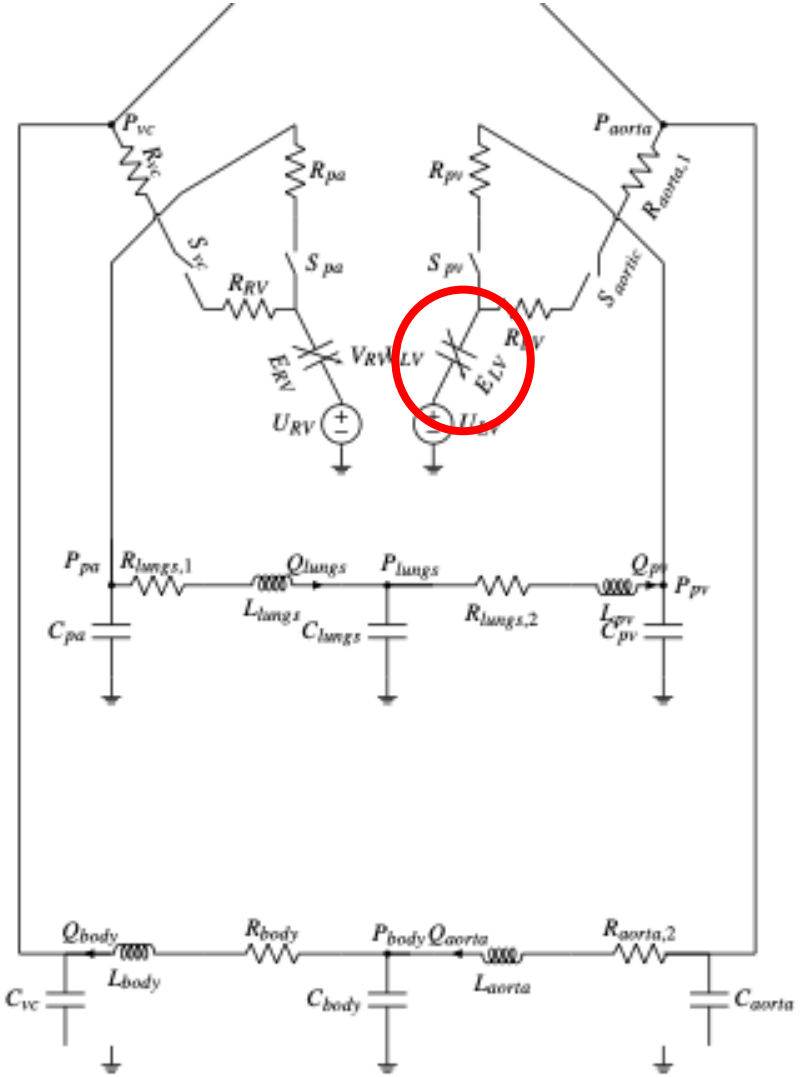
LVc is a proxy for left ventricular contractility and is closely linked, in our modelling, to ELS.

Variations in LVc may reflect pathological changes such as those seen in systolic heart failure, where reduced contractility leads to impaired systemic perfusion.

$$E_L(t) = E_{LD} + E_{LS}\ a(t),$$

$$P_{\mathrm{LV}}(t) = U_L(t) + E_L(t)\ V_{\mathrm{LV}}(t)$$

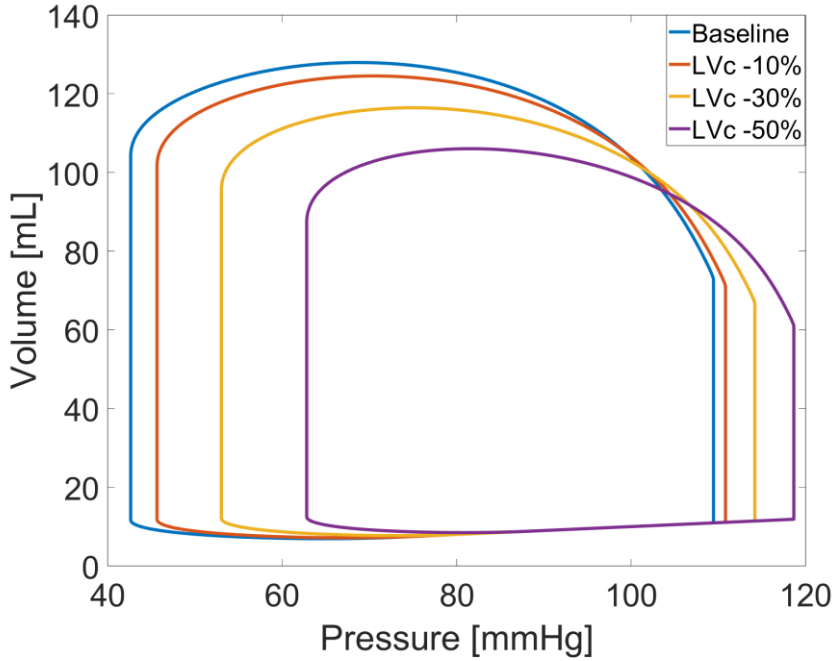
$$P_{\mathrm{RV}}(t) = U_R(t) + E_R(t)\ V_{\mathrm{RV}}(t)$$



Predictive scenario: LV Compliance Reduction

Output	Unit	LVc: Baseline	LVc: -10%	LVc: -30%	LVc: -50%
SP / DP	[mmHg]	128/69	123/69	116/67	107/61
EDV / ESV	[*ml*]	113/43	113/46	114/53	119/62
CO	[l/min]	5.26	5.03	4.59	4.24
CRA mean BF	[$\mu l/min$]	46.6	45.6	43.0	38.1
CRV mean BF	[$\mu l/min$]	43.5	43.3	41.1	35.2

- CO and MAP decrease



Predictive scenario: LV Compliance Reduction

Output	Unit	LVc: Baseline	LVc: -10%	LVc: -30%	LVc: -50%
SP / DP	[mmHg]	128/69	123/69	116/67	107/61
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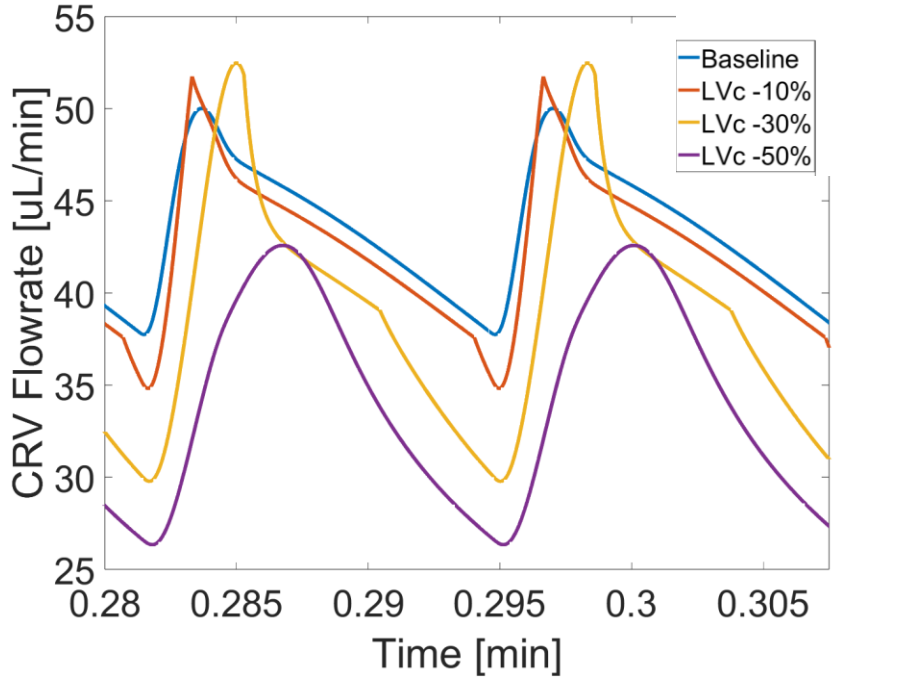
CRV mean BF	[$\mu l/min$]	43.5	43.3	41.1	35.2

- CO and MAP decrease
- CRA / CRV flows decrease



Predictive scenario: IOP elevation and reduced LVc

SP/DP [mmHg]	IOP = 15 mmHg	IOP = 20 mmHg	IOP = 25 mmHg	IOP = 30 mmHg
LVc: Baseline	128/69	127/69	127/69	127/69
LVc: -10%	123/69	123/69	123/69	123/69
LVc: -30%	116/67	116/67	116/67	116/67
LVc: -50%	107/61	107/61	107/61	107/61
EDV/ESV [ml]	IOP = 15 mmHg	IOP = 20 mmHg	IOP = 25 mmHg	IOP = 30 mmHg
LVc: Baseline	112.8/42.6	112.8/42.6	112.8/42.6	112.8/42.6
LVc: -10%	112.76/45.7	112.8/45.7	112.8/45.7	112.8/45.7
LVc: -30%	114.2/52.9	114.2/52.9	114.2/52.9	114.2/52.9
LVc: -50%	118.6/62.1	118.6/62.1	118.6/62.1	118.6/62.1
CO [l/min]	IOP = 15 mmHg	IOP = 20 mmHg	IOP = 25 mmHg	IOP = 30 mmHg
LVc: Baseline	5.26	5.26	5.26	5.26
LVc: -10%	5.03	5.03	5.03	5.03
LVc: -30%	4.59	4.59	4.59	4.59
LVc: -50%	4.24	4.24	4.24	4.24

Predictive scenario: IOP elevation and reduced LVc

CRA MEAN BF [$\mu l/min$]	IOP = 15 mmHg	IOP = 20 mmHg	IOP = 25 mmHg	IOP = 30 mmHg
LVc: BASELINE	46.6	43.6	36.3	30.8
LVc: -10%	45.6	42.0	35.0	29.6
LVc: -30%	43.0	38.3	31.8	26.8
LVc: -50%	38.1	33.6	27.8	23.1

CRV MEAN BF [$\mu l/min$]	IOP = 15 mmHg	IOP = 20 mmHg	IOP = 25 mmHg	IOP = 30 mmHg
LVc: BASELINE	43.5	40.5	29.1	23.3
LVc: -10%	43.3	38.8	28.5	23.1
LVc: -30%	41.1	35.0	27.4	22.4
LVc: -50%	35.2	31.7	26.2	21.2

Limitations

- 0D lumped model
- 2-heart chamber
- Single-eye representation and simplified ocular branch
- No systemic feedbacks (baroreflex) or ocular autoregulation included.
- Limited calibration due to lack of combined cardiovascular–ocular datasets.

Conclusions

- Eye2Heart as tested against clinical data closed-loop model linking cardiovascular and ocular hemodynamics
  - Replicates key systemic (EDV, ESV, CO, EF) and ocular (CRA/CRV flows) parameters.
  - Simulates physiologic and pathologic scenarios (e.g., IOP elevation, LV compliance changes).
  - Enables in-silico experimentation to test “what-if” scenarios and quantify effects on retinal perfusion
- It provides a mechanistic framework to interpret ocular biomarkers within the context of systemic physiology, thereby contributing to the emerging field of oculomics

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Perspectives

- Improve model details (ocular branches; heart model)
- Perform sensitivity and uncertainty analyses to identify key drivers and ensure robustness.
- Include biomechanics
- Refine parameter calibration and incorporate individual variability
- Enable patient-specific simulations to support oculomics and precision medicine → digital twin

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Thanks for your attention

Any questions ?