Multiscale modeling of ocular and cardiovascular systems

organized by
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Workshop Summary

Overview.

The Eye2Heart workshop was born from the AIM SQuaRE project *Modeling the relationship between cardiovascular function and ballistocardiogram* and the recently accepted article on the Eye2Heart model in Mathematical Biosciences and Engineering [sala2025eye2heart]. The eye provides a unique, noninvasive window into systemic physiology. Many cardiovascular, inflammatory, and aging-related processes manifest simultaneously in the eye and in the systemic circulation. The goal of this workshop was to explore mathematical and computational models that link ocular measurements to whole-body hemodynamics, while identifying multiscale mechanisms that couple microvascular, macrovascular, and systemic processes.

Participants came from mathematics, statistics, engineering, physiology, and clinical research, representing institutions in the United States and Europe. Each morning began with introductory lectures highlighting current research directions, followed by collaborative problem-solving sessions in the afternoons. Over the course of the week, seven groups were formed and made meaningful progress, whether in model development, data analysis, literature reviews, or conceptual framing. These efforts have laid a strong foundation for new, long-term collaborations.

The problems addressed in the working groups reflected the breadth of the field, including sex-specific cardiovascular modeling, pregnancy-driven hemodynamic changes, waveform-based inference of cardiac function, and construction of a data-informed digital twin for sepsis.

Summary of Talks.

The morning lectures provided a broad overview of current advances in cardiovascular and ocular modeling, spanning patient-specific hemodynamics, mechanisms of circulatory failure, electrophysiology and arrhythmogenesis, ocular biomechanics, and the emerging field of digital twins for both the eye and the cardiovascular system. Several talks highlighted recent progress in the Eye2Heart framework and in linking retinal measurements to systemic circulation. Together, the lectures established the scientific context for the workshop and

motivated the formation of the afternoon problem groups, many of which were built directly on the themes introduced during these sessions.

Afternoon Problem Sessions

After an open discussion on the first day, participants divided into seven groups. Each group included members with complementary expertise, and most groups continued their work throughout the week. Their main findings and progress are summarized below.

Group 1: A Data-Informed Digital Twin for Sepsis.

This group explored how acute systemic inflammation affects cardiovascular function, with the long-term goal of developing a real-time digital twin for sepsis. The group:

- assembled and explored large Intensive Care Unit (ICU) datasets capturing early sepsis trajectories;
- translated clinical markers into model inputs;
- developed a compact mechanistic model linking inflammation to vasodilation and arterial pressure collapse;
- began documenting the literature on digital twins in critical care.

Future work will focus on cohort-level calibration, validation of predictions, and potential connections between retinal vascular responses and sepsis severity.

Group 2: Three Time Scales for Modeling Aging.

This group proposed a conceptual model of aging dynamics based on three interacting time scales:

(1) **Fast time scale:** stochastic harmful events modeled via shot-noise or Hawkes processes;
(2) **Intermediate time scale:** cumulative transitions between gradually shifting physiological equilibria;
(3) **Slow time scale:** irreversible decline beyond functional thresholds.

The resulting framework distinguishes transient perturbations from long-term degeneration and may be associated with measurable ocular or cardiovascular biomarkers. Future steps include formal mathematical analysis and potential integration with clinical aging measurements.

Group 3: Reconstructing Cardiovascular Parameters from Ocular Waveforms.

This group investigated the feasibility of inferring cardiac mechanics from the central retinal artery (CRA) waveforms and mean arterial pressure (MAP). The group:

- decomposed CRA waveforms into physiologically meaningful features;
- used stroke volume, MAP, and waveform features as predictors;
- trained a multitask Gaussian Process model (Matérn kernel) to predict end-systolic and end-diastolic elastance;
- achieved good predictions for elastance parameters, while reconstruction of the unloaded volume requires additional features.

This work suggests that noninvasive reconstruction of pressure-volume loops characteristics from ocular measurements may be possible.

Group 4: Sex-Specific Extensions of the Eye2Heart Model.

This group created a first sex-specific extension of the Eye2Heart model [sala2025eye2heart]. Taking as a starting point the baseline male configuration, they:

- adjusted heart rate, cardiac elastance, vessel geometry, resistance, and inertance according to reported sex differences;
- propagated changes consistently through systemic and ocular circulations;
- compiled a literature review of sex-specific physiological data;
- established a shared GitHub repository for reproducible simulations.

Future work includes validation with clinical datasets, incorporation of nonlinear ocular resistances, and comparative simulations to quantify sex-specific differences in ocular and systemic hemodynamics.

Group 5: Modeling Pregnancy-Induced Cardiovascular Adaptation.

This group extended the Eye2Heart [sala2025eye2heart] framework to incorporate pregnancy-related hemodynamic changes. The work included:

- a comprehensive literature review of cardiovascular changes across trimesters and postpartum;
- introduction of new ordinary differential equations (ODE) components to represent uterine circulation;
- initial parameter calibration of a pregnancy-specific cardiovascular model.

Future plans include the refinement of trimester-specific models, the completion of parameter estimation, and modeling pathological conditions such as preeclampsia.

Group 6: Cross-Species Translation and Meaningful Measurements.

This group studied how rodent ocular measurements can be interpreted in the context of human physiology. They:

- identified key anatomical and hemodynamic differences between human and rodent ocular circulation;
- used sensitivity analysis to determine which parameters scale consistently across species;
- outlined a mapping strategy for translating rodent measurements into human-relevant model components.

This work provides a foundation for principled cross-species scaling and for determining which measurements are most informative for validating ocular circulation models.

Group 7: Extending the Eye2Heart Model [sala2025eye2heart.]

This group expanded the arterial network in the Eye2Heart model by:

- adding both eyes and their asymmetric arterial branching patterns;
- introducing R–C–R and R–C–L circuit elements for realistic pulsatile flow;

- ensuring pressure continuity and mass balance within the enlarged arterial tree.

The group also reviewed vitreous humor biomechanics, noting that existing models either assume Newtonian behavior or lack age-dependent effects. The group identified vitreous liquefaction and its impact on retinal dynamics as promising future modeling directions.

Concluding Remarks

The workshop successfully fostered rich interdisciplinary collaborations and produced meaningful progress in several directions, from sex-specific and pregnancy-specific modeling to cross-species scaling, ocular waveform analysis, and sepsis modeling. The complementary expertise of the participating groups has helped push forward the boundaries of research in mathematics applied to biology and medicine. Several groups plan to continue their work beyond the workshop through joint manuscripts, shared repositories, and student-led projects.

We warmly thank AIM for supporting this workshop and for providing an environment conducive to deep mathematical discussion, collaborative problem-solving, and creative interdisciplinary exchange.

Bibliography

[sala2025eye2heart] L. Sala, M. Zaid, F. Hughes, M. Szopos, V. H. Huxley, A. Harris, G. Guidoboni, and S. Lapin. *Eye2Heart: a reduced mathematical model bridging cardiovascular and ocular hemodynamics.* To appear in *Mathematical Biosciences and Engineering*, 2025.