Project title: Energy and Metabolism Models of the Aging Outer Retina

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Background: Visual processing begins in the outer retina (OR), where photoreceptor cells convert light into electrical signals. These cells are supported by adjacent retinal pigment epithelial cells, which play essential roles in maintaining retinal homeostasis. The retina is among the most energy-demanding tissues in the body. In our recent work, we generated energy balance sheets for the OR, detailing energy supply and demand across its constituent cell types (1, 2).

With aging, the OR undergoes significant metabolic and structural changes. Energy imbalance is a hallmark of age-related retinal degeneration, yet it remains unclear how energy production and use are coordinated across cell types, or how this coordination fails with age. Understanding these dynamics is crucial for identifying points of intervention that could help restore or preserve vision.

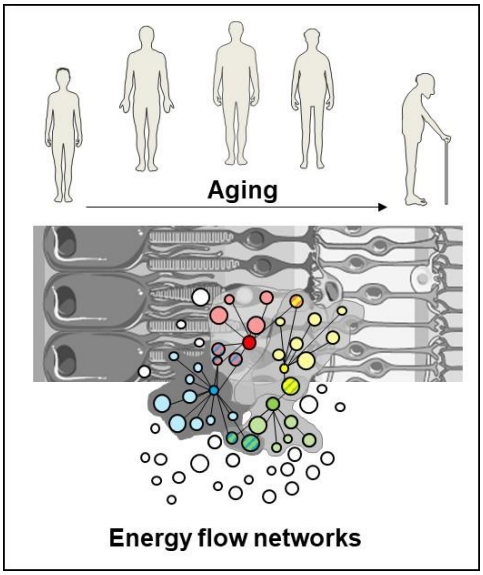
The PhD project will address the following questions:

• How is available energy distributed along energy-demanding (homeostatic) processes?

• How does energy supply and demand change in the aging OR?

• Can we identify targets for network-and energy-centric steering that shift energy priorities towards restoration?

Research Approach: The project will develop integrative, mechanistic computational network model of the OR. These models will focus on core production and consumption pathways, and will be informed by gene and protein expression data (bulk and single-cell datasets) across different age groups. Anatomical changes associated with aging will also be incorporated to simulate how structural remodelling alters intercellular metabolic dependencies and network topology. Models will be used to simulate perturbations or therapeutic interventions that could re-prioritize energy allocation in favour of protective or reparative functions, hence offering new insights into the systems-level biology of retinal aging.



Techniques: Computational model development using ODE-based frameworks (e.g. MATLAB, Python, COPASE); translation of cellular and tissue-level processes into formalized computational rules; protein-protein-interaction network modeling (e.g.

Cytoscape, CellDesigner); integration and analysis of transcriptomic and proteomic data (bulk, tissue, and single-cell; R programming language; statistical and systems biology approaches to infer regulatory mechanisms and prioritize candidate targets.

References

(1) Prins S, Kiel C, Foss AJE, Zouache MA, Luthert PJ. Energetics of the outer retina I: Estimates of nutrient exchange and ATP generation. PLoS One. 2024 Dec 31;19(12):e0312260.

(2) Kiel C, Prins S, Foss AJE, Luthert PJ. Energetics of the outer retina II: Calculation of a spatio-temporal energy budget in retinal pigment epithelium and photoreceptor cells based on quantification of cellular processes. PLoS One. 2025 Jan 27;20(1):e0311169.