

Computational energy supply and demand model of the aging human outer retina

PI: Christina Kiel; co-PI/collaborator: Philip J. Luthert (UCL Ophthalmology, UK)

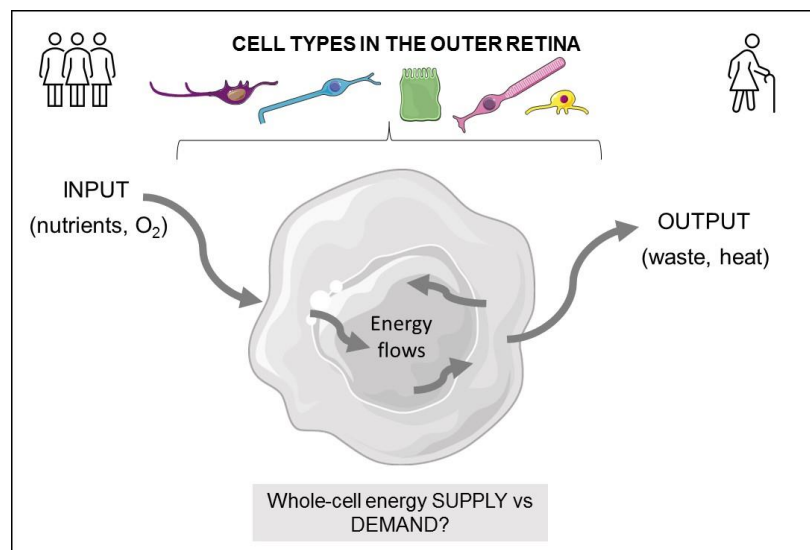
Research Theme/Topic: Systems Biology

Background: Visual processing starts in the outer retina (OR), where photoreceptor (PR) cells sense photons that trigger electrical responses. Retinal pigment epithelial (RPE) cells are located external to the photoreceptor layer and have critical functions in supporting cell and tissue homeostasis and thus sustaining a healthy retina. The visual system is highly energy demanding. It is suggested that with progressive ageing or in the context of risk factors that promote age-related blinding diseases, RPE cells are increasingly unable to execute all tasks at an optimum level. Therefore, RPE cells may compromise their own vital functions and/or stop supporting the PR cells, which either way ultimately results in PR cell death and vision loss. It remains enigmatic how RPE cells integrate and prioritize different interlinked processes, and the associated energy demands of the whole (OR and choroid) system. Whole-cell and -tissue simulation of the human OR is a pivotal approach to understanding aging and linked age-related complex disease and is critical for developing novel restorative interventions.

The PhD project will address the following questions:

- How does aging impact the ability to generate energy in the OR?
- How is available energy distributed along energy-demanding (repair) processes?
- Are there specific networks, processes, and energy properties common to larger groups of individuals/patients?
- Can we identify targets for network- and energy-centric steering that are likely to shift energy priorities in the OR towards restoration (if applicable, in personalized approach)?

The approach is to develop an integrative computational model of the OR that has at its centre energy supply and demand. Building on our recently developed model for different cancer cells, we will generate metabolic models to predict the ability to generate energy in different cell types in the OR. Models will be constrained by incorporation of gene (and protein) expression levels based on bulk data and individuals from different age-groups. On the demand side, will extend our recently developed energy-centric database (EnerSysGO) to generate detailed quantitative energy centric network models for energy requiring cellular processes. This will result in an “energy budget” for all OR cell types. Information about gene, protein, and anatomical changes during aging, will enable us to generate energy supply and demand models for different age groups. The generated models will be exploited to predict how alterations of networks and associated energy-requiring processes steer the systems towards favouring homeostasis and restoration processes.



Techniques: Computational methods to model building and analysis (Matlab, Python, COBRA toolbox); translate cell and tissue processes from publications into computer-readable language and rules; protein-protein-interaction network analyses (network representation using Cytoscape and Cell Designer); bioinformatics databases; statistical analysis of gene and protein expression data in single cells and bulk/ tissue samples; non-equilibrium thermodynamics.