**Minisymposium No. 7 : "Mathematical Modeling of Retinal Plasticity and Vascularization"**

**Monday 16th of June: 11:40-15:30**

**Organizers:** *Dr. H. Hatzikirou, Prof. M.A.J. Chaplain and Dr. G. Lolas*

**11:40a.m. – 13:10pm**

**11:40-11:45 a.m.** Welcome and Introduction by *Dr. Haralampos Hatzikirou*

**11:45-12:25 p.m.** Chair*: Prof Mark Chaplain*

**Speaker:** Dr. Muriel Perron (Université Paris-Sud)

Title: "Molecular mechanisms underlying *Xenopus* retinal stem cell proliferation"

Abstract

The amphibian retina contains a reservoir of active neural stem cells in a defined niche, localized at the margin of the retina, that contribute to persistent eye growth throughout life, as well as to regeneration following retinal damage. This system has proved to be very powerful to study *in vivo* the molecular mechanisms underlying neural stem cell behaviour. We focussed our interest on the role of various signalling pathways (Wnt, Hedgehog and Hippo) in the regulation of the proliferative activity of these cells. We investigated in particular their impact on several cellular parameters such as the cell cycle kinetics and the timing of cell cycle exit. Altogether, our data highlight how these signalling pathways interact to regulate retinal stem cell activity and thereby modulate the growth of the post-embryonic retina.

**12:25-12:40 p.m.** Chair: *Prof. Mark Chaplain*

**Speaker**: Dr. Georgios Lolas (cfaed, TU Dreden) Chair: Prof Mark Chaplain

**Title: "**Retinal Plasticity: Mathematical modelling of positional information of sub-apical neurons"

**Abstract**

The coordination between further proliferation, differentiation and cell cycle exit in retina development is a complex and fully coordinated process. More specifically it involves cell cycle exit, migration as well as multiple regulatory pathways which involve transcription factors and cell-cell signaling events. The plethora of retina cell types develop form a common pool of progenitor cells. Pluripotent retinal progenitors produce a varied number of clones of heterogeneous size and cell types. However up until now little is known regarding the involvement of non-apical progenitors in retinal development.

We developed a mathematical model to assess that increasing apical precursors overcrowding leads to non-apical divisions. The model describes a basic lineage relationship between pluripotent progenitors, committed progenitors and neurons located apically and non-apically. We further estimate the maximum transition rate with which an apical progenitor becomes a sub-apically dividing precursor. In addition, we formulate a qualitative mathematical model using a combination of experimentally measured and model selected parameters.

**12:40-13:10p.m.** Chair: *Prof. Mark Chaplain*

**Speaker**: **Dr. Haralampos Hatzikirou** (cfaed, TU Dresden)

**Title:** "On the understanding of avian photoreceptor mosaics development"

**Abstract**

Bird retina development is a great mystery yet to be solved. A central part of the retina is the photoreceptor layer which allows for the sampling of light. However, there is a lack of knowledge concerning the exact developmental mechanisms that dictate photoreceptor mosaic pattern formation. Here, we analyze the spatial correlations of the photoreceptor patterns and we discover a scale invariance of the statistics against variations of the photoreceptor density. In combination with the novel application of fluctuation solution theory in biological problems, we reveal features of photoreceptor mosaics during avian embryonic phase, in terms of photoreceptor interaction range and spatial organization. Interestingly, we conclude that the identified scale invariance contributes to the robustness of the photoreceptor mosaic pattern in terms of functionality and developmental dynamics.

**13:10 – 14:00 LUNCH BREAK**

**14:05 -15:30p.m.**

**14:05 – 14:45p.m.** Chair: *Dr. Georgios Lolas*

**Speaker**: **Dr. Lasse Jensen** (Linkoping University)

**Title**: "Retinal angiogenesis and vascular pathology in response to hypoxia"

**Abstract**:

Retinopathies including age-related macular degeneration, diabetic retinopathy and retinopathy of pre-maturity are the leading causes of blindness and vision-related debilitation affecting millions world-wide and costing billions in Europe alone in health care expenses. These diseases can be viewed as vascular disorders as their progression is driven by deregulated growth of blood vessels (angiogenesis) and/or function (increased leakiness), properties intimately and causally linked to hypoxia in the retina. Understanding of how hypoxia-induced retinal angiogenesis operates in retinopathies is therefore of the outmost importance to understand these diseases as a whole and potentially find improved treatment options. We are attacking this very issue by using zebrafish - the only vertebrate model organism which withstand sufficiently low oxygen concentrations in the environment to allow for such studies.

We have found that hypoxia-induced retinal angiogenesis is a robust, concentration- and time-dependent process, and found that it follows a course closely associated with the clinical cause of angiogenesis in the eye of patients. This include waves of sprouting, vascular growth, anastomosis and maturation which move closer and closer to the center as hypoxia-exposure time increases thus engaging the more critical arterial portion of the vasculature to a higher and higher degree. I will in this talk present our most recent findings including some RNA-seq data indicating which molecules may be involved in this process, and invite the audience to a discussion on how best to model the process - which parameters are important and what further research is needed in order to produce strong mathematical models which could serve as a platform for discovering new important pathways and improving drug design and evaluation in the future.

**14:45 – 15:25 p.m.** Chair: *Dr. Georgios Lolas*

**Speaker: Dr. M. Watson (**Heriot-Watt University)

**Title**: "A Combined Experimental and Numerical Study of Guidance Cues in the Developing Murine Retina"

**Abstract**:

The main focus of the study has been to understand how the various cellular, molecular, and metabolic cues regulate retinal vascular plexus (RVP) growth and form: both in wild-type and transgenic situations. To this end, a number of increasingly intricate mathematical models have been produced, each of which has been closely informed by morphological and molecular data obtained from the related experimental program.

Here, we present an innovative hybrid model that integrates a wide range of key biological mechanisms and provides for the tracking of migrating astrocyte and endothelial tip cells towards the outer retinal boundary throughout retinal development-from embryonic day 15.5 to post-natal day 8. Blood perfusion is included throughout plexus development and the emergent retinal architectures adapt and remodel in response to various biological factors. The resulting in-silico RVP structures have been compared with whole-mounted ex-vivo retinal vasculatures at various stages of development and agreement is found to be. Such quantitative comparisons between experimental and simulated vasculatures represent a particularly rigorous test for the modelling approach.

**15:25-15:30 p.m**. Concluding Remarks.