Contrat doctoral – ED Galilée

Titre du sujet : Mathematical Modeling and Analysis of Angiogenesis Patterns in Neurodegenerative Diseases

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- Domaine de recherche : Mathématiques pour la biologie et la médecine
- Mots clés : maladies neurodégénératives, modélisation, EDP

Sujet décrit page suivante.

Mathematical Modeling and Analysis of Angiogenesis Patterns in Neurodegenerative Diseases

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May 7, 2025

Thesis Proposal

Neurodegenerative diseases (ND) constitute a major health burden worldwide, with an estimated number of more than 3 billion people currently living with neurological conditions ([Ste24]) and dementia projected to affect 152 million people by 2050 [ea22]. Cerebral blood flow dysregulation has been recognized as a significant cause of many cases of dementia [WE24, OPM+24, TERT+24, ZNB+22]. To tackle ND issues, it is crucial to better understand the microvasculature of the brain in healthy and diseased environments. In this context, an effective approach is to use in vitro pluripotent induced stem cells (iPSC) to derivate brain microvascular endothelial cells (BMEC), and to investigate their characteristics in control versus diseased environment. Network formation of blood vessels has been observed in vitro for many years, see for example [Goo07], but the advent of computational methods to be applied to large sets of biological data has opened the path for discovery of related molecular markers, and allows to search for correlation between such patterns and various omics data in brain. In the context of applied mathematics, pattern formation is a classical field of study. The most widespread class of models used in this context are Reaction-Diffusion (RD) equations. Spatial and spatio-temporal patterns arise quite commonly in RD equations, trough for example Turing or Hopf bifurcations, lock-phased periodic solutions, chaos, etc; see for example [Mur10, Tur52, AAA12, AAA16]. For in vitro cell patterns, a celebrated mathematical model is the Keller-Segel (KS) equation [KS71], which in addition to diffusive terms, contain also terms to model chemotaxis. Recently, in [ASPGE25], a KS type model has been successfully used to reproduce experimentally observed angiogenesis patterns ([Ela23]) and classify control versus diseased patterns. In their original contribution [KS71], Keller and Segel model relied on observations of Escherichia coli placed in an environment with oxygen and an energy source, to propose a PDE to describe the appearance of bands in the bacterial concentration traveling at constant speed in plates. Since then, numerous variants of the model have been studied numerically and theoretically. For example, a growth term was added and discussed in [MT96]. We refer to [MT96, DP04, CPZ04, KOST12] and references therein cited for relevant mathematical and numerical studies. In [ASPGE25] the following modified KS type equation was considered,

$$\begin{cases} u_t &= f(u) - b\nabla\cdot(u\nabla v) + d_u\Delta u \\ v_t &= cu - ev + d_v\Delta v \end{cases} \tag{1}$$

on a bounded domain Ω with Neuman Boundary Conditions (NBC), and with

$$f(u) = au(1-u)(u-\gamma).$$

Equation 1 can be used to reproduce patterns analog to those observed in angiogenesis experiments, see Figure 1. In this figure, the panel on the left represents the image of the well with BMEC after 8 hours (Courtesy of our partner, the Elahi Lab at Mount Sinai). The center image represents the same image after a filtering by the angiotool software [Ang, ZGKV11]. The figure in the right panel represents the solution of (1) at a fixed time.

The aim of the proposed thesis is to investigate more in depth the ability of the model to reproduce the exact biological data and to identify the parameters that are relevant to characterize diseased

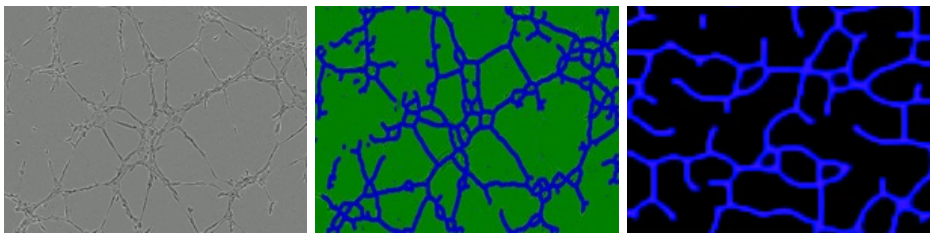

Figure 1: Left: Image of endothelial provided by microscopy after 8 hours of evolution. Middle: transformed image provided by the free software angiotool. Right: solution of the discretized modified KS model (1) at a fixed time.

environments. Rooted in the theory of Dynamical Systems, our plan is to use also complex systems, advanced statistical and machine learning methods beyond the state of the art to test the efficiency of the models to reproduce and predict biological data. A strong collaboration with the Elahi Lab at the ICAHN School of Medicine at Mount Sinai, is in the essence of the proposal.

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