2023-12-19

International PhD Program IC-PhD

PhD thesis project

2024 Call for application

Electrohydraulic properties of cells and tissues

General information

Call	2024
Reference	2024-03-DUCLUT_RISLER
Keyword(s)	Biophysics; active gels; tissue hydraulics; tissue bioelectricity; tissue mechanics.

Director(s) and team

Thesis director(s)	Charlie Duclut & Thomas Risler
Research team	Physical Approach of Biological Problems
Research department	UMR 168 – Physical Chemistry Curie

Description of the PhD thesis project

Abstract

Harnessing ion transport is a primitive and essential ability of all living cells, allowing them to create an electric potential difference across their membrane, and to tightly regulate their volume via water flux driven by osmotic pressure differences. Despite this ubiquity, the study of endogenous electric fields has been focused on their role in excitable cells such as neurons, while physicists interested in tissues and development have been more concentrated on the interplay between mechanics and morphogen expression, hence leaving electric fields and water transport as a blind spot in today's biophysics.

Identifying timescales and mechanisms which are relevant for these processes, and constructing novel models that bring together active mechanical, electrical and hydraulic properties of cells and tissues are the challenges set by this proposal. We will tackle these challenges by constructing a numerical, cell-based model for tissues, that include fluid and ion transport. By putting electrohydraulics to the foreground, this project will explore the role of endogenous or external electric fields as cues for growth control, tissue patterning, and morphogenesis.

Background

The cell lipid bilayer membrane is presumably a critical structure for the origin and evolution of life. This membrane, by permitting the existence of a voltage difference with the outside, probably facilitated early and rudimentary cell bioenergetics. However, how such fundamental cell properties come together in complex multicellular structures is still poorly understood. Although certain collective properties of tissues, such as the transepithelial potential or wound current, have been measured for decades, their biological role remains elusive, and their theoretical modelling are even scarcer. In fact, even the role of water transport – driven by the osmotic pressure difference induced by ion transport – has long been overlooked.

Recent experiments have however shown that tissues are not only chemically and mechanically active devices, but they also employ electricity and hydraulics to perform various biological functions. One example is the hydraulic size control of mammalian embryo. Another is the role of external electric fields to inflate and pattern *in vitro* epithelial monolayers. Bioelectricity is also suspected to play a role in proliferation and morphogenesis.
In this context, the gap between experimental results and theoretical understanding is becoming increasingly blatant, and a comprehensive framework that unites active mechanical, hydraulic and electric properties of tissue behaviour is conspicuously absent.

Objectives
The main objectives of this project are:

- **exploring the role of electrohydraulics in wound healing and regeneration.** The project will delve into the different time scales of wound healing, recognizing the central role that electric or hydraulic tissue properties likely play at each step. For example, in zebrafish, the wound cut creates a transepithelial voltage short-circuit that is suspected to play a role in the initiation of the healing process. At the regeneration timescales (hours to days), it is likely that electric signalling continues to play a role, since disruption of electric currents in amputated salamander and newt limbs leads to delayed or abnormal regeneration.
- **exploring the role of electrohydraulics in tissue patterning and morphogenesis.** Initially, the focus of the project will be to unravel the interplay between fluid pumping and mechanics which leads to the breaking of symmetry in spherical lumens. This understanding is essential to comprehend embryogenesis, organogenesis and organoid development. In addition, by exploring the relationship between bioelectricity and proliferation, this project aims to challenge the existing paradigm for tissue patterning, where gradients of morphogens (with sometimes a hint of mechanics) are central, to rather show that ion flows and electric field could also generate large-scale patterning cues and be pivotal in morphogenesis.

Experimental approaches
This project will focus on developing a cell-based description of tissues that emphasizes fluid and ion transport as core elements. This will be achieved by reevaluating one of the cornerstones of contemporary tissue biophysics: the vertex model (VM). Despite its success, the VM predicts cell shape and dynamics by minimizing a phenomenological and non-physical “energy functional”. To address this limitation, the project will introduce a cell-based electrohydraulic vertex model (EHVM). In this model, the degrees of freedom are the positions of the cell vertices, together with the ion concentrations within each cell. Ionic concentrations are set by cell-cell transport and exchange with the outer medium, building both an electric potential difference and an osmotic pressure difference. The osmotic and hydrostatic pressure differences then impose cell volume through water transport. Cell volume constraints and active mechanics at cellular junctions finally determines the vertices position. Backflows through the interstitial clefts between cells and due to transepithelial pressure differences and electroosmotic transport will also be described.
This model not only resolves the issue of the unphysical functional but also provides a framework to study the interplay between ion and water transport and tissue mechanics.

International, interdisciplinary & intersectoral aspects of the project

Interaction and collaboration with experimentalists will be pivotal throughout the project, enabling the identification of key factors and the validation of theoretical models using data from various tissue models at different scales. The project will thrive on a collaboration with Rita Mateus' group (Max Planck Institute for Cell Biology, Dresden, Germany), which focuses on investigating bioelectric phenomena, ranging from wound healing assays to fin growth during development, in zebrafish. In addition, a collaboration with Thuan

Beng Saw's team (Westlake University, Hangzhou, China), known for pioneering the application of external electric fields to MDCK cell monolayers, will also be fostered during the project.

This project is intrinsically at the frontier between biology and physics. Exchanges between biologists will be pivotal to construct a realistic model, and to compare our theoretical and numerical results to experiments.

Recent publications

1. Active T1 transitions in cellular networks, **C. Duclut**, J. Paijmans, M. M. Inamdar, C. D. Modes, and F. Jülicher, *Eur. Phys. J. E* **45**, 29 (2022)

2. Stochastic dynamics of chemotactic colonies with logistic growth, R. Ben Alì Zinati, **C. Duclut**, S. Mahdisoltani, A. Gambassi, and R. Golestanian, *EPL* **136**, 50003 (2022)

3. Nonlinear rheology of cellular networks, **C. Duclut**, J. Paijmans, M. M. Inamdar, C. D. Modes, and F. Jülicher, *Cells & Development* **168**, 203746 (2021)

4. Hydraulic and electric control of cell spheroids, **C. Duclut**, J. Prost, and F. Jülicher, *Proc. Natl. Acad. Sci. U.S.A.* **118**, e2021972118 (2021)

5. Fluid pumping and active flexoelectricity can promote lumen nucleation in cell assemblies, **C. Duclut**, N. Sarkar, J. Prost, and F. Jülicher, *Proc. Natl. Acad. Sci. U.S.A.* **116**, 19264 (2019)

Expected profile of the candidate

Candidates should have a master's degree in physics or applied mathematics and a strong interest in soft matter/active matter/biophysics and theoretical modeling. Knowledge and/or interest in numerical modeling and simulations is expected.