Forces and symmetries in cells and tissues

Eckert, J.

Forces and Symmetries in Cells and Tissues

Julia Eckert

Forces and Symmetries in Cells and Tissues

Proefschrift

ter verkrijging van
de graad van doctor aan de Universiteit Leiden,
op gezag van rector magnificus prof.dr.ir. H. Bijl,
volgens besluit van het college voor promoties
te verdeding op dinsdag 6 december 2022
klokke 10.00 uur

door

Julia Eckert

geboren te Dresden, Duitsland
in 1991

Promotor:	Prof. dr. T. Schmidt
Promotiecommissie:	Dr. M. Gloerich (UMC Utrecht) Dr. B. Ladoux (DR CNRS, Institut Jacques Monod) Prof. dr. J. Aarts Prof. dr. ir. S.J.T. van Noort Prof. dr. B.E. Snaar-Jagalska

Cover: Polygonal shape of cells in a monolayer. The front cover shows the nematic director field as rods superimposed to the apical part of cells, forming two topological defects represented as dots. After moving the focus through all pages of this thesis, the back cover ends with the basal part of the monolayer in which actin stress fibers are connected to micropillars.

Casimir PhD Series, Delft-Leiden, 2022-28
ISBN 978-90-8593-536-0
An electronic version of this thesis can be found at
https://openaccess.leidenuniv.nl

The only source of knowledge is experience.

- Albert Einstein -

Contents

Outline of this thesis

The way organisms develop from the initial single-cellular state to a complex final assembly like the human body, and how the final body is maintained throughout life, is one of the greatest mysteries and it's understanding one of the biggest scientific challenges. What has been surprising in the last decade is that the initial assembly and also later maintenance of integrity is not only determined by intricate biochemical communication networks, but in part by physical forces that cells, their neighbors, and their environment apply in a bidirectional manner. The resulting collectivity of cells determines the development of organisms and are crucial to the health and disease state of the organism.

In this thesis, we develop and utilize concepts from physics to quantitatively understand forces that develop between cells and their environment and neighboring cells, and how the interplay between these forces regulates the arrangement, shape, and topology of tissue. These topics range from the development of novel experimental methods to the combination of experimental observations with theoretical descriptions. Thus, this thesis is at the interface of physics and biology, for which we collaborated with groups from both fields. Our results contribute to a better understanding of cell and tissue integrity.

Chapter 1 reviews the current knowledge about cell-cell adhesion from the molecular and cellular level to tissue and organs. The central focus is set on finding a common base for understanding the biological and physical principles of cell-cell adhesion. This chapter covers a description of the molecular interaction between cells and describes the role of intracellular signaling processes. The chapter appeared as a scientific review article written in a collaboration with the Heisenberg lab in Klosterneuburg (ISTA, Austria).

In **Chapter 2**, we compare the mechanics of single endothelial and fibroblast cells. Using elastic micropillar arrays, we study differences in traction forces of both cell lines. Comparing the morphology-dependent force distribution, we find that endothelial cells exert less traction forces

on substrates and tend to be more circular in their morphology with a broader force distribution when compared to fibroblasts. This study is conducted in collaboration with the Mashaghi lab in Leiden (LACDR, Leiden University).

In **Chapter 3**, we develop a novel methodology to measure the maximum intercellular adhesion force between two cells adhered to a substrate. We name our design the Cell-Cell Separation Device (CC-SD). The CC-SD makes it possible to separate cells in doublet configurations while simultaneously measuring the traction forces, and hence the modulation of intercellular forces. It allows us to get information about the maximum resistance against detachment of cells in tissues. For this project, we collaborate with Stefan Partel and his team in Dornbirn (FHV, Austria).

In **Chapter 4**, we describe the methodology to study the symmetry of tissues by combining *in vitro* experiments with numerical simulations. By detecting the orientational order of cells in monolayers, we identify that the nematic and hexatic order in epithelial monolayers coexist at different length scales. Cells are hexatic at small length scales, changing to nematic at larger length scales. This novel description creates the basis for a correct identification of topological defects, which were identified as location of biological functionality. The project is performed in collaboration with the Giomi group in Leiden (LION, Leiden University).

In **Chapter 5**, we study the hexatic and nematic symmetry of epithelial monolayers as a function of the cell-cell adhesion, monolayer density, and the influence of the underlying substrate stiffness. We find that the crossover from the dominant hexatic order at short length scales to the nematic one at larger length scales strongly depends on the monolayer density and is affected by the cell-cell adhesion. Our results indicate that the length scale of the crossover is controlled by the interplay of the cell-matrix and cell-cell adhesion in confluent monolayers. The work resulted from a collaborative project with Ladoux - Mège lab in Paris (Institut Jacques-Monod, France) and Luca Giomi in Leiden (LION, Leiden University).