University of Exeter | Living Systems Institute

Fully funded EPSRC PhD studentship

Engineering and Physical Sciences Research Council

Modelling shape generation by the basement membrane

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Deadline: **6th May 2024**, apply here: https://www.exeter.ac.uk/study/funding/award/?id=5112

Project overview

Morphogenesis is a biophysical process where cellular forces guide complex cellular deformations that shape animal tissues and organs[1]. Understanding the relevant forces and how they act on and deform biological tissues is challenging due to the complex, anisotropic material properties of cells and the extracellular matrix (ECM) surrounding them. The basement membrane (BM), a sheet-like ECM, is essential for guiding epithelial morphology[2,3]. We recently demonstrated that insufficient BM growth results in geometric frustration, accumulation of elastic pre-stresses and tissue deformation[4] (Fig. A). While pre-stress resides in many biological tissues[5–8], the conditions under which pre-stress arises and how they feed back on tissue morphology remain unclear.

This interdisciplinary PhD, spanning physics, mathematics, computing and biology, investigates pre-stress, arising from the mechanical interplay between tissue and BM growth, as a universal mechanism of biological shape generation. In close experimental collaboration, the project will yield a 'data-informed' universal modelling framework paving the road for understanding the biomechanics of shape generation in animal development, disease and synthetic systems.

Main objectives

1. Create a ***novel modelling framework*** to simulate the growth of tissues (via continuum and vertex-modelling) along with their surrounding BM (via continuum and lattice modelling).
2. Incorporate ***growth*** and ***mechanical anisotropies*** to give a sophisticated description of the complex material properties of BMs (see Fig. B).
3. Identify how geometric frustrations arise during growth, leading to ***elastic pre-stress*** that guides complex tissue shapes.
4. Challenge modelling frameworks in different epithelial systems (*Drosophila*, zebrafish and organoids) yielding a ***universal framework*** to predict tissue morphology based on growth dynamics and material parameters.

Approach

Starting from a simplified continuum description of tissue and BM growth, we will design a mathematical model of the growth of tissues. This will involve a vertex model of the cells along with a system of partial differential equations (PDEs) for the BM. These will be solved numerically, based on existing code within the Richards group, using a combination of MATLAB and C++. Material anisotropies and different elastic models (considering strain-stiffening of the BM) will be included to adequately represent the structurally and mechanically anisotropic fibrous BM layer.

Experimental parameter determination (image segmentation, biophysical essays) and model verification (using the *Drosophila* wing disc) will be performed together with SH. Subsequently, the model will be expanded to other growing epithelial tissues including the zebrafish optic cup (with Steffen Scholpp, LSI) and epithelial organoids (with Ge Guo, LSI).

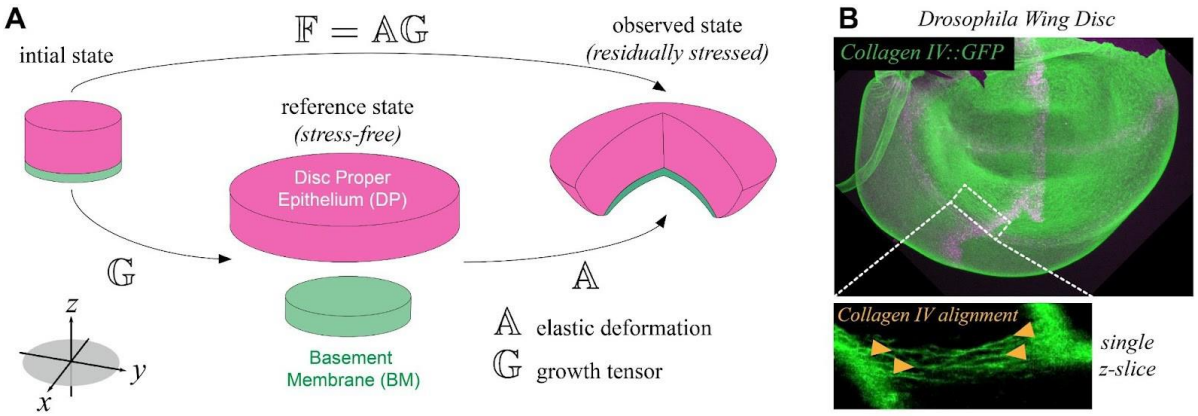

Figure A: Geometric decomposition of the wing disc as a sandwich of growing elastic layers, the tissue layer (magenta) and BM layer (green). The growth tensor G describes growth without stress; different growth rates in the respective layers lead to different sizes of the individual discs. Elastic deformation (described by A) connects the discs into one coherent object, leading to the observed morphology and accumulation of residual stress.
Figure B: Maximum (*top*) and single plain (*bottom*) projections of a *Drosophila* wing disc expressing the major BM protein Collagen IV (green). In the single plain projection, Collagen IV alignment in fibres is indicated by arrowheads.

Broader impact

Shape and function are inherently linked entities as alterations in morphology can lead to malfunction and disease[9,10]. This project will yield unprecedented insight into biological shape generation and the mathematical model will provide a powerful tool to understand animal development and for tissue engineering approaches designing custom tissue shapes.

Application

For more information and discussion of the project please contact Stefan Harmansa (s.harmansa@exeter.ac.uk).

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