

CURRENT AND PAST RESEARCH PROJECTS

THE BIGGER PICTURE

An improved understanding of how mechanical cues affect cellular behavior is key to developing novel therapeutic strategies. This ranges from artificially engineered constructs to replace diseased tissues to new drugs that directly influence cell behavior. Due to the multiscale nature of the system, ranging from molecules to cells to tissues, studies at different length and time scales are required to gain insight into the underlying mechanisms of mechanobiology.

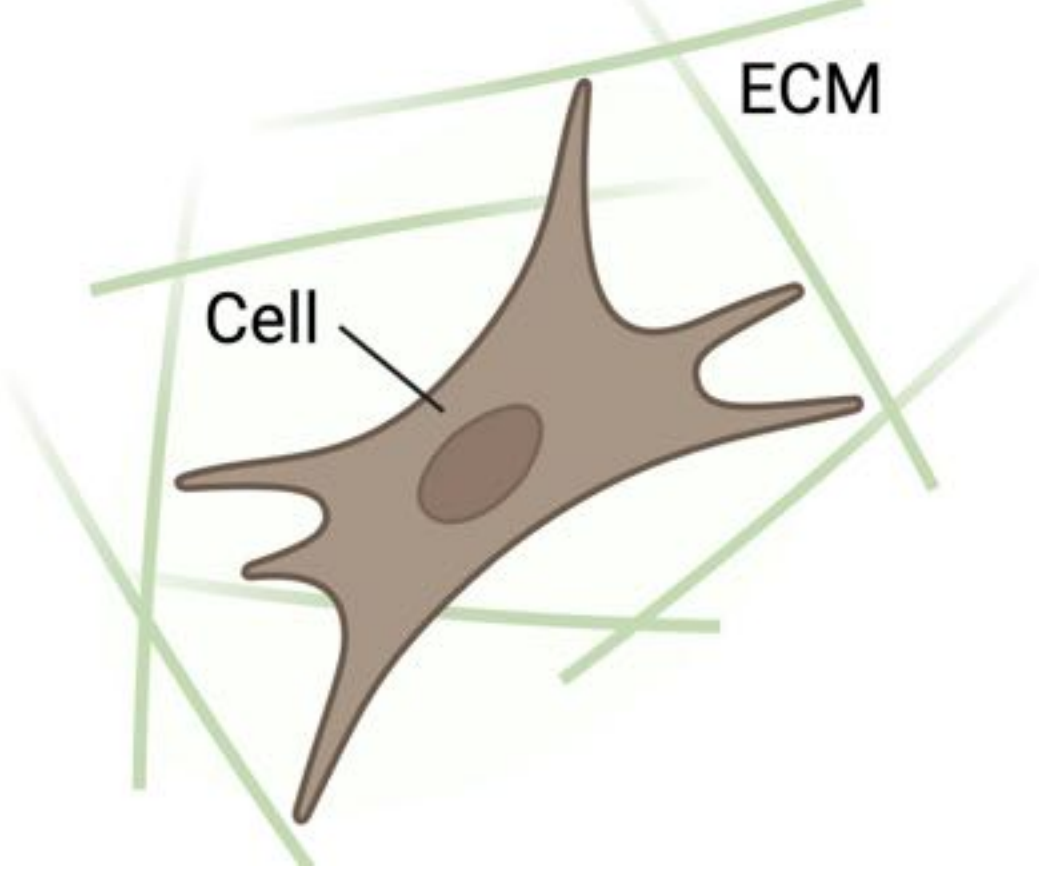
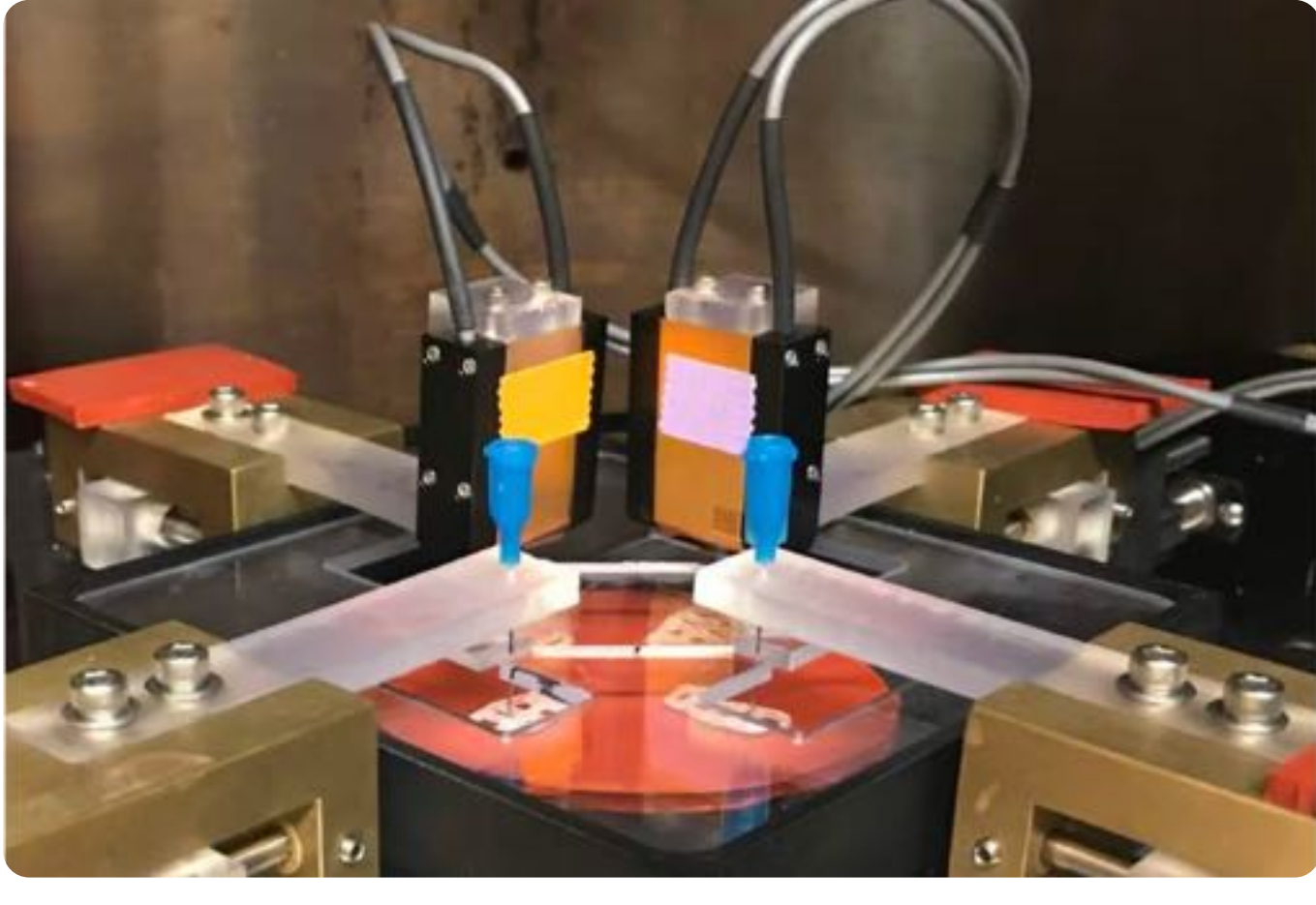
MECHANOBIOLOGY – the influence of mechanics on biological processes

HOMEOSTASIS – the tendency of a system to maintain a preferred state

PROJECT 1 | A BIAXIAL BIOREACTOR FOR MECHANICAL TESTING OF CELL-SEEDED TISSUE EQUIVALENTS

MOTIVATION

Soft biological tissues consist of cells and an extracellular matrix (ECM) – a fibrous network of different proteins. The cells can actively sense their surrounding ECM and regulate its mechanical state to maintain a preferred – also called homeostatic – state. Researchers use cell-seeded collagen gels to study these interactions, but there is limited quantitative data on the stresses or forces cells generate in these gels, which are mostly derived from uniaxial experiments despite tissues experiencing multiaxial loading in the body.



METHODS

To bridge the gap between current data and in-vivo conditions, we developed a computer-controlled bioreactor that reliably measures cell-generated forces in tissue equivalents under biaxial loads. Typical forces are in the range of 0.1 to 1 millinewtons (mN) – approximately equivalent to the weight of a postage stamp. This device enables studies on how cells establish and maintain a preferred mechanical state and how various factors, like the number of cells, growth factors, and different loading conditions, affect these processes.

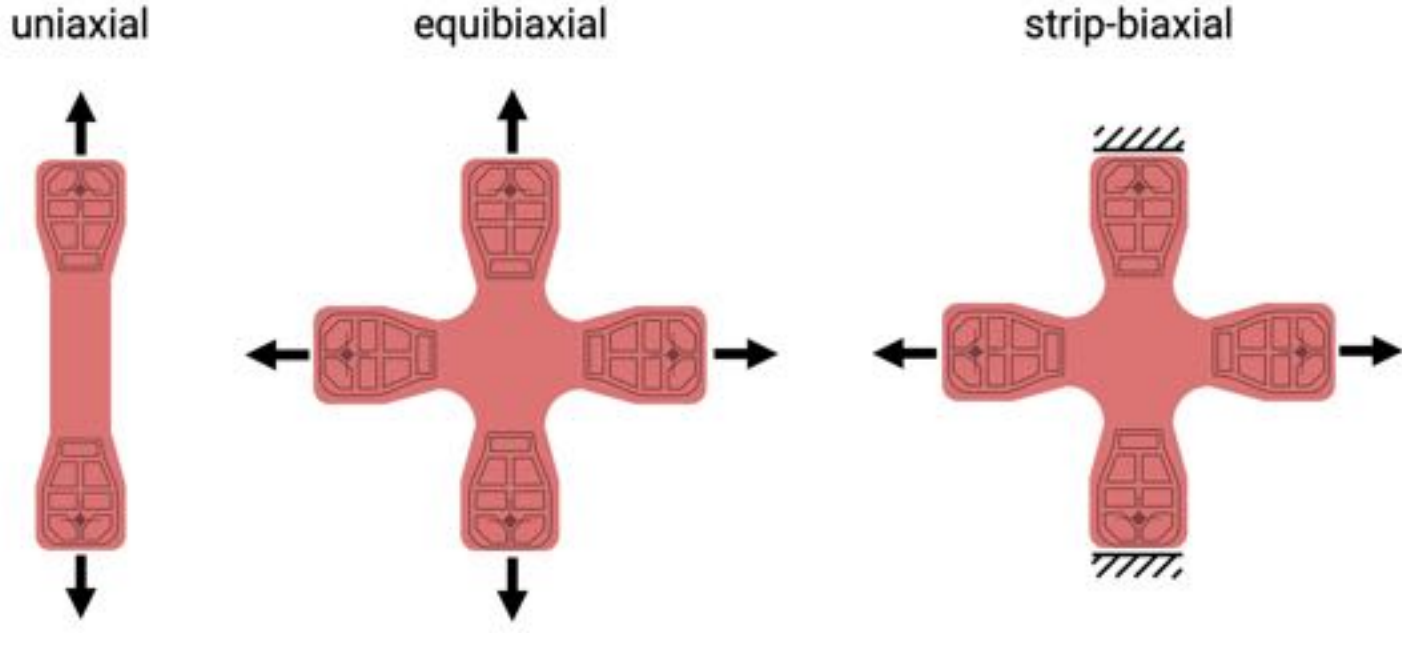
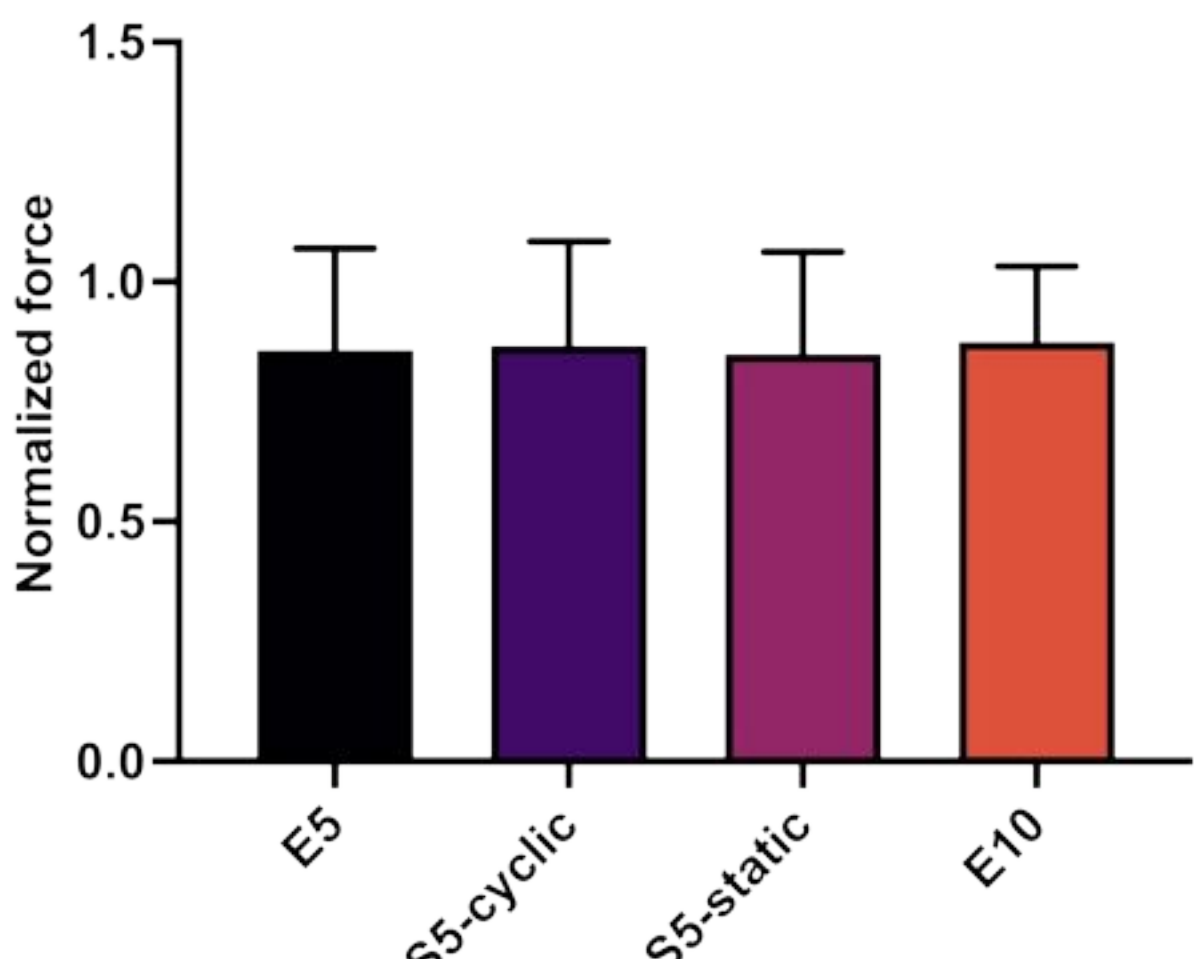
RESULTS

To test and validate the device, we show that fibroblasts – a common cell type in connective tissue – establish a homeostatic mechanical state that depends on cell density and collagen concentration. Following perturbations from this homeostatic state, the cells were able to restore a mechanical state similar to the one prior to the perturbation. Depending on the applied loads, however, they were not always able to fully maintain that state.

PROJECT 2 | VASCULAR SMOOTH MUSCLE CELL ADAPTATION TO PHYSIOLOGICALLY RELEVANT MECHANICAL STIMULI

MOTIVATION

Smooth muscle cells (SMCs) are essential in maintaining proper function of the aorta and are constantly subjected to dynamic multiaxial loading of various magnitudes. For example, loads can temporarily increase during exercise or permanently during disease, such as hypertension. However, only a few quantitative studies report the forces the SMCs establish and maintain in collagen-based tissue equivalents under dynamic biaxial loading.



METHODS

To begin to close this gap, we use the previously developed biaxial bioreactor to subject collagen gels seeded with aortic SMCs to different biaxial loading conditions. First, the effects of increased biaxial loads were examined using cyclic equibiaxial loading of different amplitudes (5% (E5) vs. 10% (E10) strain). Second, the effects of cyclic equibiaxial versus cyclic strip-biaxial loading were examined while keeping the amplitude of the stretching the same (E5 vs. S5-cyclic vs. S5-static). Note that a strip biaxial test holds the sample at a constant overall stretch along one axis (S5-static) while cyclically stretching in the orthogonal axis (S5-cyclic), which resembles mechanical constraints experienced by SMCs over a cardiac cycle in the aorta.

RESULTS

Irrespective of loading amplitude and boundary condition, similar mean steady-state forces emerged across all tests. Additionally, the stiffness-force relationships – the stiffness at a given force – of the gels were remarkably similar. Taken together, this suggests that vascular SMCs mechano-adapt to maintain a preferred force or stress.

PROJECT 3 | A MULTISCALE FINITE ELEMENT MODEL OF SOFT TISSUE GROWTH AND REMODELING

MOTIVATION

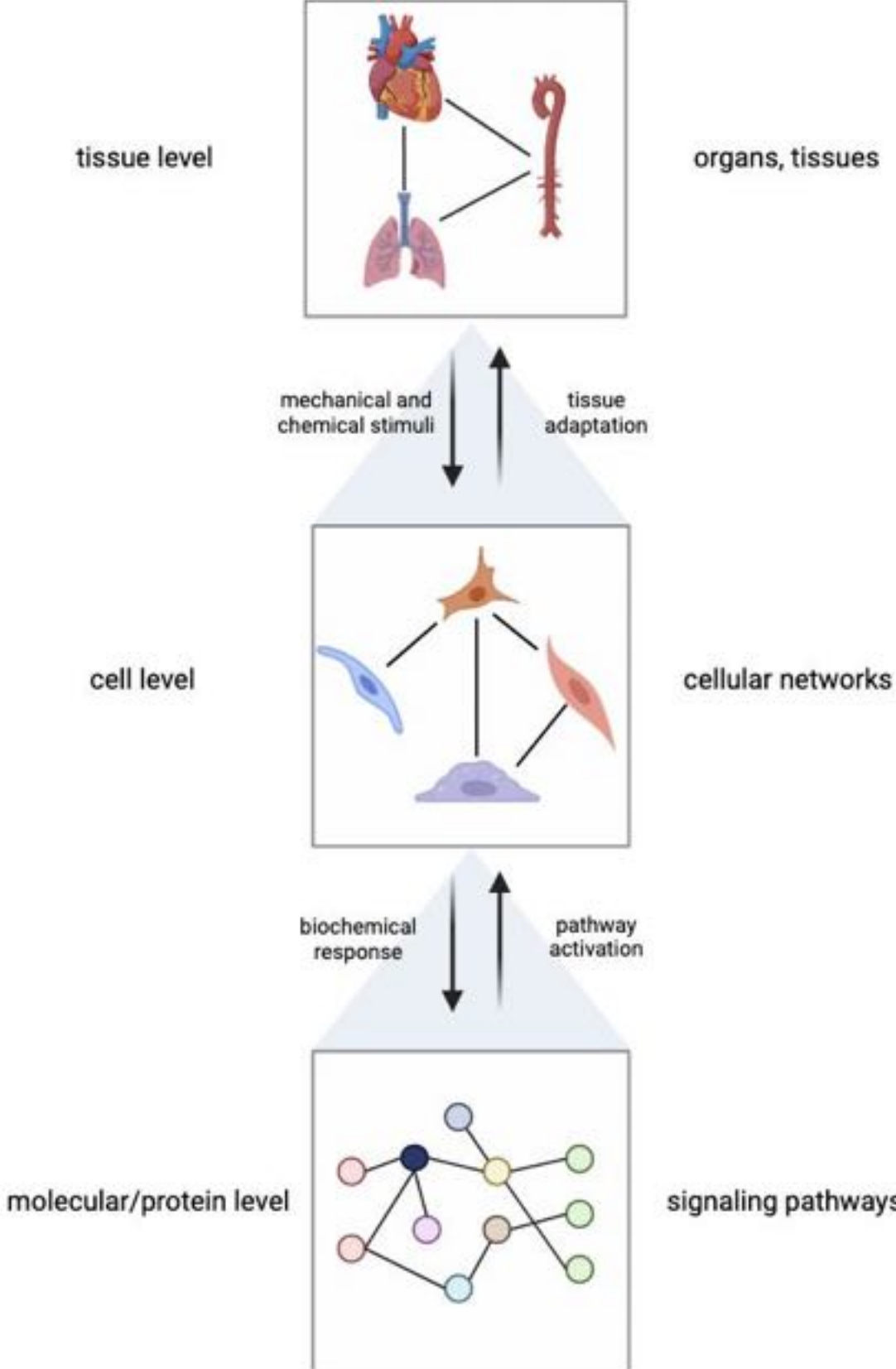
Soft tissue has a remarkable ability to adapt to changes in mechanical loading. For example, it has been observed that the aorta tends to thicken in response to elevated blood pressure to reduce the increased load of the vessel wall. While this adaptation can be directly observed on the tissue scale, the mediators are the tissue-resident cells. In this project, we focused on developing a computational model that includes cellular signal processing to address the multiscale nature of mechanobiology.

METHODS

We model cellular signal processing as a coupled system of ordinary differential equations and capture long-range biochemical interactions between cells via diffusion-reaction equations. The mechanical behavior of soft tissue is described using standard nonlinear continuum mechanics. The multiscale model is implemented in a finite element code based on several open-source libraries.

RESULTS

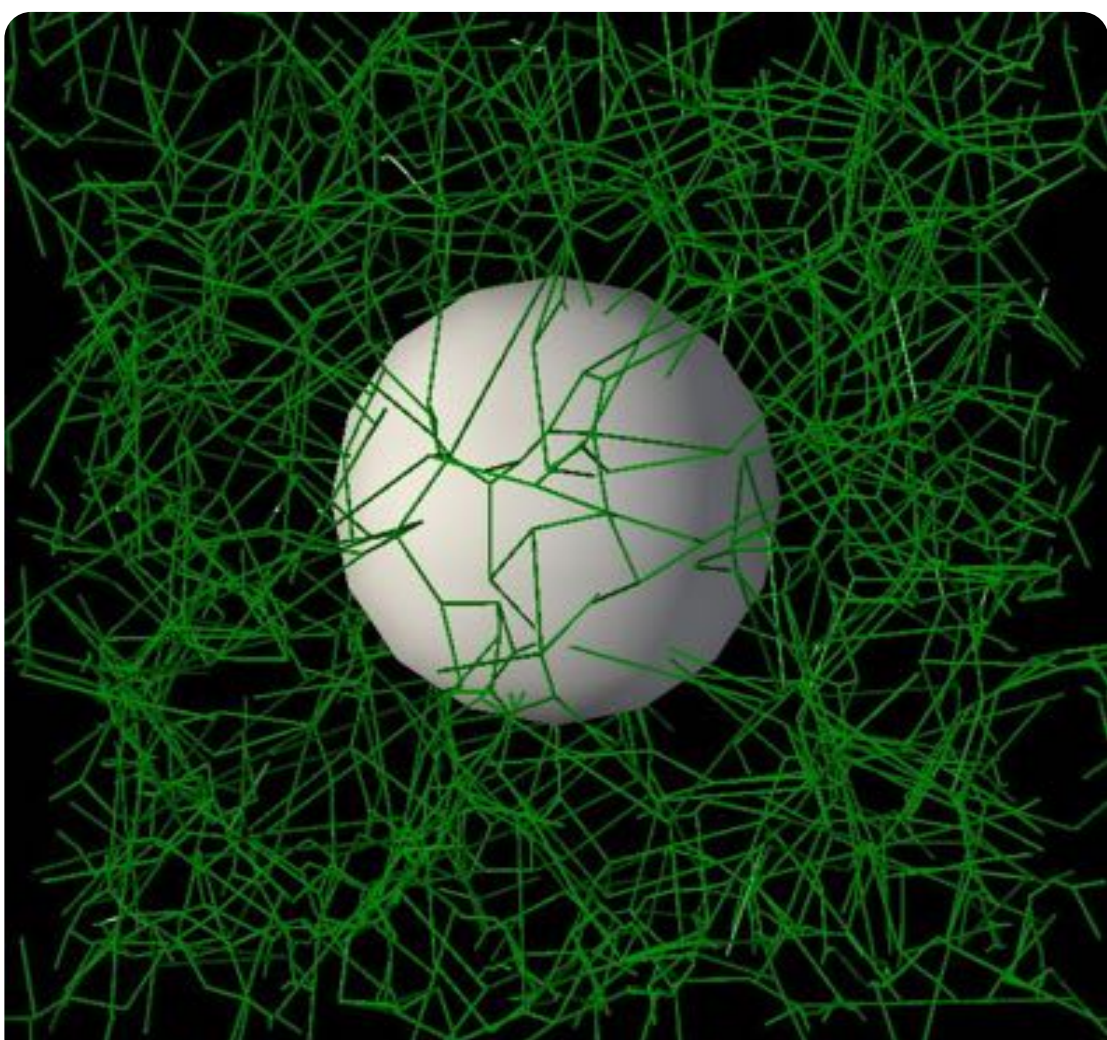
The model can successfully reproduce previously observed experimental and computational results. In addition, it allows us to study how genetic defects (on the molecular/protein level) might translate to maladaptive tissue responses (on the tissue level) and how different cell types communicate to maintain tissue form and function.



PROJECT 4 | CELL MIGRATION IN THREE-DIMENSIONAL FIBER NETWORKS

MOTIVATION

Cell migration is crucial for processes like development, wound healing, and cancer. However, the key mechanisms behind cell migration in three-dimensional fiber networks are not well understood. This is mainly due to limitations in experimental studies, which make it challenging to control individual parameters, thereby hindering hypothesis validation.



METHODS

To overcome this limitation of experimental studies, we developed a computational model where cells and extracellular matrix fibers are represented by discrete mechanical objects on the micrometer scale. In doing so, we have exact control of the mechanisms by which cells and matrix fibers interact with each other.

RESULTS

We identified two key mechanisms for cell migration: a specific type of bond between cells and extracellular matrix and active cellular contraction. These two mechanisms are sufficient to reproduce experimentally observed cell migration patterns including a biphasic relation between migration efficiency and matrix stiffness and durotaxis – the cell's preference to migrate towards stiffer regions.