

Controlling cell sociology with microrobotics

★ The mechanobiology of cells is an important aspect of medicine. We spoke to **Mahmut Selman Sakar**, Tenure Track Assistant Professor at EPFL in Lausanne, about the work of the ROBOCHIP project in developing microrobotic technologies, research which could open up new perspectives on human physiology and pathology.

The human body is made up of trillions of cells, and the ways that these cells are structurally organised inside various tissues exerts a major influence on the designated function of our organs. Cells are exquisitely sensitive and responsive to their dynamic mechanical environment. Both externally applied forces and the mechanical properties of the extracellular matrix (ECM) have been shown to modulate cell behaviour. As the Principal Investigator of the ROBOCHIP project, Professor Sakar aims to develop a robotic toolkit that could facilitate the investigation of how cells communicate with each other and organize through the ECM. This work centres around developing untethered microscopic machines that can be placed inside engineered three-dimensional (3D) microtissues, where they generate spatiotemporally resolved signals. "We can precisely control the magnitude and duration of the deformation applied by the synthetic microactuators. Using this novel technology, we are studying how mechanical signals propagate within the tissues, how they are sensed and processed by the resident cells, and finally how cells collectively respond to mechanical loading," outlines Professor Sakar.

ROBOCHIP project

The results of this work are expected to provide fundamental new information about the mechanobiology of cells, such as the

quantification of cell behaviour under well-defined static and dynamic loading conditions. "Our group has developed a number of different techniques for powering microactuators wirelessly. They can be powered by magnetic fields, near infrared light, and ultrasound," says Professor Sakar. The methodology also involves engineering the ECM from mechanically characterized fibrous materials and time-lapse imaging. "We track where the cells are and

The **microrobotic toolkit** that we are developing will perfectly complement modern imaging modalities and biochemical manipulation techniques. Together, they will provide a more complete picture on how the resident cells of a particular tissue interrogate and remodel their microenvironment as a community.

what they do in real-time using fluorescent markers so that we can correlate the action of the robotic tools with the biological output," continues Professor Sakar.

The mechanical loading conditions mimic the types of signals that cells are exposed to within the body. The goal then for researchers is to identify what specific factors disrupt homeostasis and what kind of stimulation may facilitate healing. "Do the cells identify the magnitude or the frequency of the mechanical signal? When do they start changing their phenotype and moving beyond physiological limits? What is the contribution of the

architecture of the ECM in these processes?" asks Professor Sakar. As of yet these questions have not been answered.

Cellular communication

The aim here is to essentially uncover the physical rules behind multicellular organization, research that holds wider relevance to our understanding of disease. For example, certain conditions drive the formation of cysts, tumours,

or fibrotic scarring in almost every tissue within the body, and the situation may become much more serious if these masses are allowed to grow and spread unchecked. "The abnormal cell clusters are made of our cells. What are the signals that convince healthy cells to abandon their physiological roles and form non-functional and even destructive tissues? Recent work has shown that fibroblasts and immune cells residing around a tumour may apply forces, which stimulate the cancer cells to spread. This is only one example of how mechanical factors play a key role in the initiation and progression of certain diseases," outlines Professor Sakar.

A deeper understanding of cellular communication could help researchers identify what is wrong with the mechanics of the microenvironment, opening up the possibility of intervening in certain cases to modify cellular behaviour. "For example, with the acquired knowledge, we may be able to design active microscopic implants that can then be mechanically actuated to perform cellular physiotherapy," says Professor Sakar.

The successful execution of the project depends on interdisciplinary efforts, blending techniques from mechanical engineering, nanotechnology, materials science, robotics, and tissue engineering. In the first stage of the project, Professor Sakar and his students designed, manufactured, and calibrated microactuators that could be integrated into engineered tissues. "We are now at the stage where we can deploy untethered microactuators much like cells into fibrous materials, and instruct them to bind to specific moieties on the ECM or membrane proteins," he says. The technology has already enabled collaboration with experts from various domains of the life sciences. "We have teamed up with colleagues from immunology and oncology to develop more comprehensive theories on the mechanobiology of diseases, taking molecular biology and genetics into account," adds Professor Sakar.

The project also holds clear relevance to understanding morphogenesis, the process by which an organism takes its form. In the developing organism, coordinated cell movements and tissue forces crucial for morphogenesis may rely on the same type of mechanical signals that maintain tissue homeostasis or drive the progression of cancer. A deeper understanding of how active and passive mechanics influence cell movement

during morphogenesis could help researchers discover the root causes of developmental disorders. Recent work has shown the feasibility of engineering biomimetic environments that guide stem cells to form microscale organ-like 3D constructs, organoids, through self-assembly. Studying the dynamics of multicellular interactions in their social context at the tissue level may provide detailed instructions of how to control organoid development and close the gap between natural and engineered tissues.

A number of tools are being developed over the course of the project, which will help researchers make quantitative measurements and collect large datasets of cell and ECM mechanics. Considering the complexity of the problem, it is essential to develop a mechanical modelling framework to interpret and suggest experiments. "The continuum models that we have been building provide physical interpretation of empirical data across a range of length and time scales. We are recapitulating the effects of cellular contractility, bulk and surface stresses, ECM plasticity, cell migration and tissue flows, and phase transitions in our models," says Professor Sakar. This is part of the wider objective of essentially hacking cellular communication, and providing a means of controlling multicellular organization. "The final demonstration will involve on-demand construction of layered and compartmentalized tissues from distributed cells with only spatiotemporally controlled mechanical loading. We will also show direct evidence of mechanically-induced transitions on cell states such as migration, proliferation, and contractility, and report quantitative values on thresholds," continues Professor Sakar.

ROBOCHIP

MicroRobotic toolkit to deliver spatiotemporally resolved physicochemical signals and control cell sociology

Project Objectives

The technological objective of this project is the development of a microrobotic toolkit that can apply physiologically relevant mechanochemical signals within three-dimensional multicellular constructs in an automated fashion. The primary scientific objective is the discovery of mesoscale physical principles behind multicellular organization that take place during morphogenesis and regeneration.

Project Funding

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Project Team Members

The ROBOCHIP team consists of four PhD candidates with expertise in different disciplines; Erik Mailand, Raquel Parreira, Fazil Uslu, and Lucio Pancaldi.

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