BIG IDEAS in 'mechanobio'

For High School Teachers and Students

This document was created summer 2017 by CEMB master teachers Mark Hayden, Richard Staniec, and Catherine Khella to help connect science and technology concepts in mechanobiology to guide the Research Experience for Teachers program.

1. Scientists across STEM disciplines are now collaborating to study living cells in 2D and 3D dynamic environments that mimic physiological conditions. This is a shift away from examining non-living, stained cells in petri dishes.

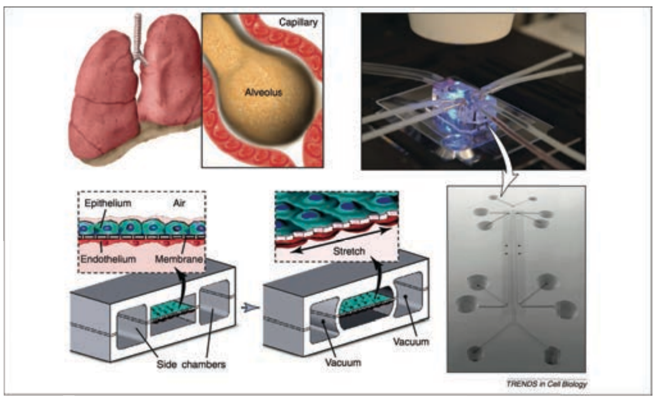

Figure 1. One type of microfluidic device created by the Huh Lab is a human breathing lung-on-a-chip. (Huh, D. et al. 2010)

Huh Lab
Bioengineering
University of Pennsylvania

The Huh lab creates bioengineered systems modeled after biological systems to study and improve human health and promote environmental sustainability. They create channels and chambers in biocompatible gel then use these systems to grow layers of cells. These designs are able to mimic the 3D dynamic systems that represent processes in the human body.

http://tiny.cc/CEMB-huhlab

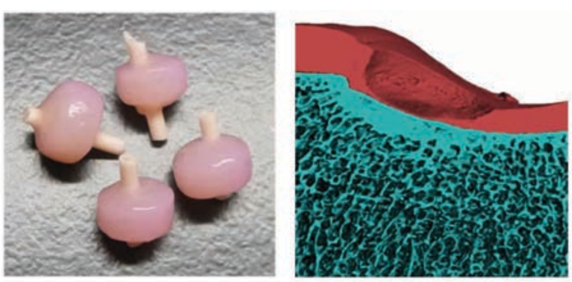

Figure 2. Engineered cartilage constructs (left). Focal defect in minipig cartilage imaged by microCT (right). (Burdick and Mauck 2017)

Mauck Lab
Orthopaedic Surgery
University of Pennsylvania

The Mauck lab studies the characteristics of connective tissue, in particular articular cartilage, in order better understand both healthy and diseased tissue. They uses the characteristics of native tissue to create 3D constructs to study these systems and guide progress towards functional tissue replacements.

http://tiny.cc/CEMB-maucklab

Video explaining organ on a chip: http://tiny.cc/organonachip

2. The extracellular matrix (ECM) is the biological molecules that make up a cell's 3D environment. ECM-Cell and ECM-ECM interactions play a critical role in cell function, movement, signaling, sensing, adhesion, and transport.

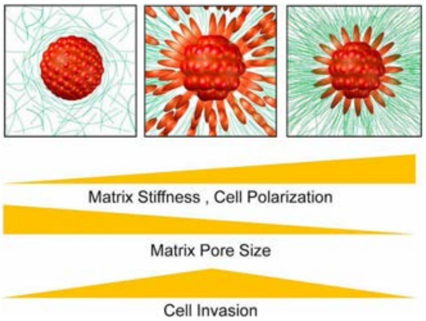

Figure 3. The stiffness of the ECM can determine how likely it is that a cancer cell will proliferate and migrate. (Hossein Ahmadzadeh et al 2017)

<u>Shenoy Lab</u>
Materials Science and Engineering
University of Pennsylvania

The Shenoy lab works to better understand the forces and interactions between cells and the ECM then creates mathematical models and simulations of these interactions. These models will help predict the behavior of cells and single molecules within biological systems at very small scales. The work of this lab occurs at the intersection of biology, physics, chemistry, material science, and applied mathematics.

http://tiny.cc/CEMB-shenoylab

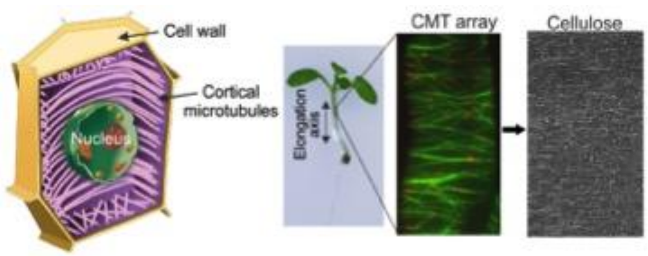

Figure 4. Organization of structures within plants that connect the interior structure of plants to the cell wall and extracellular space (Dixit, 2017)

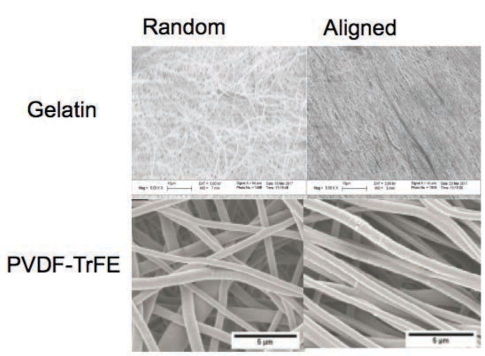

Figure 5. Exploring possible materials to create plants on a chip (Arinzeh,2017)

<u>Dean/Dixit/Arinzeh</u>

Dean Lab
Biomedical Engineering
Alabama State University

Arinzeh Lab
Biomedical Engineering
New Jersey Institute of Technology

Dixit Lab
Biology
Washington University in St. Louis

These labs collaborate to study how plants respond to physical and chemical stimuli in their environment. They are developing 3D scaffolds that can be manipulated to allow these tissues to be subjected to various forces as well as the ability capture data using high-resolution live cell imaging techniques and are in the process of developing plant on a chip model devices.

http://tiny.cc/CEMB-deanlab

http://tiny.cc/CEMB-dixitlab

http://tiny.cc/CEMB-arinzehlab

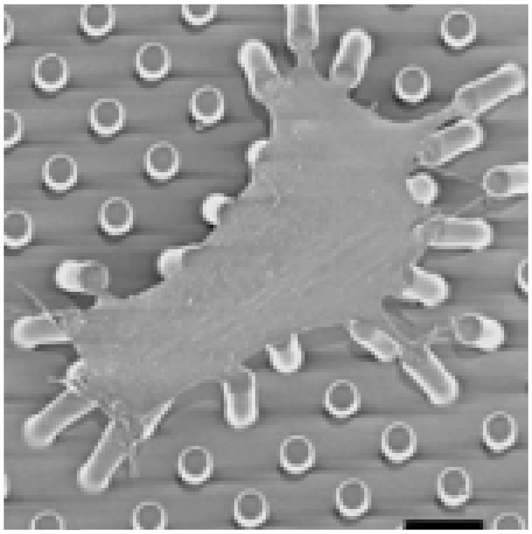

Figure 6. Cells grown on micropillars to measure the forces that cells are applying to their environment (Chen, 2017)

Chen Lab
Biomedical Engineering
Boston University

The Chen Lab seeks to understand how cells interact with their environment. They study the interaction between mechanical forces and biochemical signaling in dynamic 3D environments that match the native environment of cells. In order to do this work the Chen Lab develops unique nanofabrication tools to control and measure the mechanical environment of cells. These tools and techniques allows them to better understand how the mechanical environment around and within a cell impacts cell function.

http://tiny.cc/CEMB-chenlab

Chris Chen and William Pollacheck provide a visual outlining the various methods for measuring cellular forces:
http://tiny.cc/measuringcellforce

Brief animation of cell spreading on a micropillar device:
http://tiny.cc/micropillaranimation

3. Protein polymers, especially of tubulin and actin present in a cell's cytoskeleton, facilitate a connection to ECM, playing an instrumental role in function, movement, signaling, sensing, adhesion, and transport.

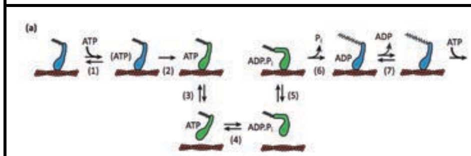

Figure 7. Diversity of unloaded kinetics in the myosin-I family. ATPase mechanochemical cycle followed by all myosin isoforms. (Greenberg MJ, Ostap EM, 2012)

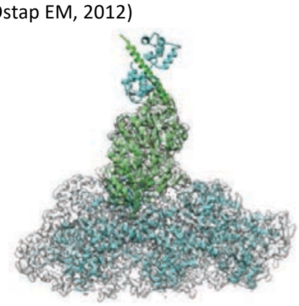

Figure 8. Model from ongoing research related to the structural mechanism of force sensing by mysoin-1. (Ostap EM, 2017)

Ostap Lab
Physiology
University of Pennsylvania

Molecular motors are biological machines that facilitate movement in living systems. The Ostap Lab is involved in researching how motors found in the cytoskeleton of cells sense force. Some of the many applications of this work include cell and tissue development, cell transport, and immune/disease function.

http://tiny.cc/CEMB-ostaplab

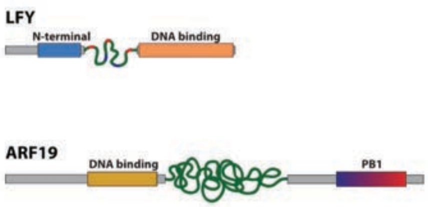

Figure 9. LFY and ARF19, intrinsically disordered proteins.
(Strader, Rhoades, Pappu, and Wagner, 2017)

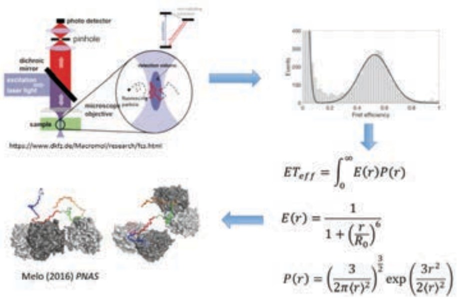

Figure 10. A graphic representation of single molecule FRET, a technique used to study intrinsically disordered proteins. Laser light absorbed/emitted by fluorescently labeled proteins is detected. FRET efficiency data is produced and run through computer models to generate protein structures.
(Rhoades 2017)

Strader and Rhoades Labs

Strader Lab
Biology
Washington University in St. Louis

Rhoades Lab
Chemistry
University of Pennsylvania

Both the Strader Lab and the Rhoades lab are focused on intrinsically disordered proteins (IDPs). These proteins have regions which are not stable under physiological conditions, which makes traditional techniques for identifying structure (i.e. x-ray crystallography, NMR, etc.) insufficient. After identifying amino acid residues via fluorescence labeling, these researchers use single molecule spectroscopy (FRET) to study IDPs.

http://tiny.cc/CEMB-straderlab

http://tiny.cc/CEMB-rhoadeslab

The Vale Lab (University of California at San Francisco- Cellular and Molecular Pharmacology) has compiled various images and movies that relate to organization, signaling, and movement within cells. This media can be used for educational purposes:
http://tiny.cc/valelab-media

4. Cells can sense their environment through various mechanical and chemical pathways and can transduce that information to other cells, resulting in changes to cell function and behavior.

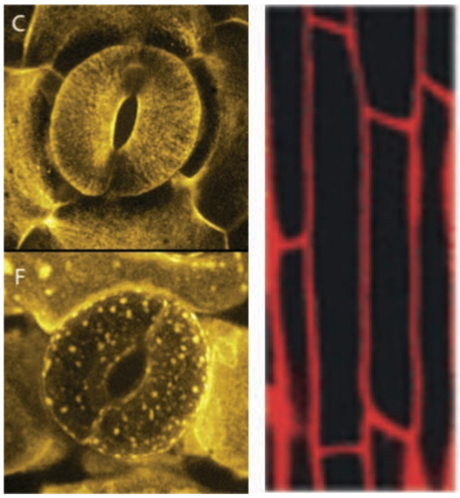

Figure 11 . These fluorescent microscopy images show Auxin, a plant hormone. Auxin levels determine whether a plant chooses to grow tall or become bushy. It also is a factor in "phototropism", the process of growing towards the light— it promotes elongation on the dark side. (Strader & Genin 2017)

<u>Genin Lab</u>
Mechanical Engineering & Materials Science
Washington University in St. Louis

The Genin Lab studies interfaces and adhesions, points of attachment in human and plant systems. Their work focuses on interfaces between tissues at the attachment of tendon to bone, between cells in cardiac fibrosis, and between protein structures at the periphery of plant and animal cells. (From Genin page on WUSTL School of Engineering and Applied Science website)

http://tiny.cc/CEMB-geninlab

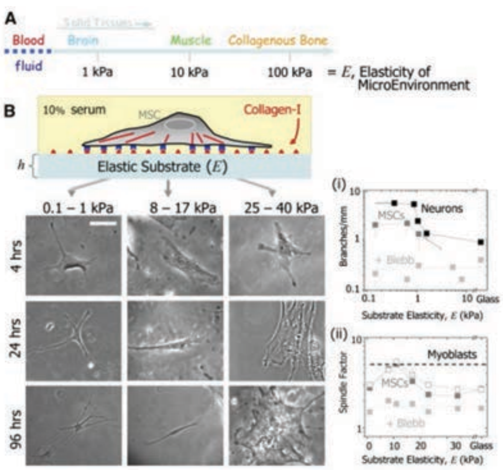

Figure 12. Stem cell differentiation is directed by the stiffness of the substrate in groundbreaking research done by the Discher Lab (Engler et al., *Cell* 2006)

<u>Discher Lab</u>
Chemical and Biomolecular Engineering
University of Pennsylvania

Stem cells are undifferentiated cells that have the potential to develop into a variety of specialized cells. In a very well-known and often-cited paper, the Discher Lab demonstrated a high sensitivity toward elasticity in stem cells. Cells developed into soft tissue on soft substrates and stiff tissue on stiff substrates. The Discher Lab studies mechanobiology of stem cells and cancer, as well related phenomena in the nucleus, ECM, and cell membranes.

http://tiny.cc/CEMB-discherlab

Video with basic information about stem cells and how they differentiate:
http://tiny.cc/stemcellsoverview

5. By measuring forces exerted by and on cells, scientists calculate many biomechanically important quantities such as stress, strain, stiffness, etc. Stiffness is particularly relevant in pathology (i.e. fibrosis, cirrhosis, cardiovascular disease, progeria, etc.)

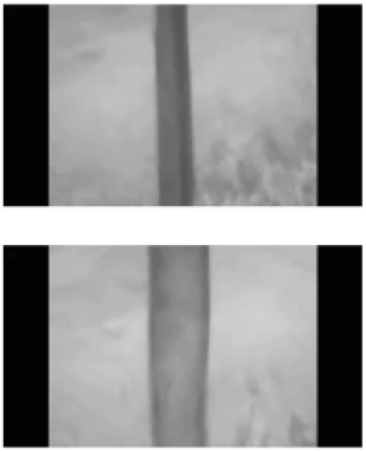

Figure 13. Arterial stiffness with age and disease (Assoian, 2017).

Assoian Lab
Pharmacology and Translational Therapeutics
University of Pennsylvania

The Assoian lab studies how cells sense changes in the physical properties of their microenvironment and how they convert this information into chemical signals, behavior and function. Qualities like stress, strain, and stiffness are measured via pressure myography, atomic force microscopy, and other tools. Ultimately, by better understanding vascular stiffness and how muscle cells sense and respond to stiffness, researchers may be able to develop new cholesterol-independent treatments for cardiovascular disease (from Assoian lab homepage).

http://tiny.cc/CEMB-assoianlab

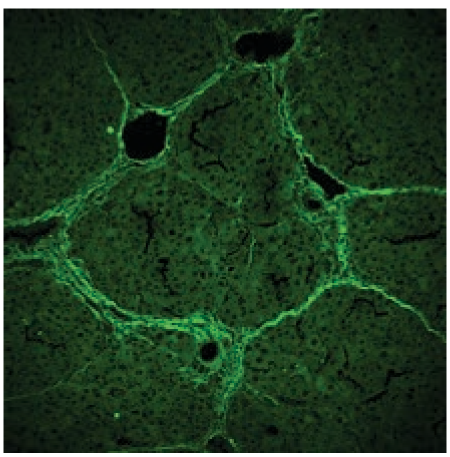

Figure 14. Rat liver with cirrhosis. The green bands are collagen imaged by a special microscopy technique (second harmonics generation), and show that this liver has cirrhosis (collagen bands completely enclosing cells) (Wells, 2017).

Wells Lab
Pharmacology and Cell & Molecular Biology
University of Pennsylvania

Liver fibrosis and bile-duct fibrosis result from the deposition of excess, abnormal extracellular matrix (ECM) in the context of chronic liver injury. It has previously been thought that stiffness was an effect of disease but now it may be a cause, adding evidence for the idea that stiffness and disease work in a cycle rather than in a linear, unidirectional progression. The Wells lab investigates the mechanisms of fibrosis and is applying the results of experiments with isolated cells to whole animal models and to the study of human diseases, including hepatocellular carcinoma and biliary fibrosis.

http://tiny.cc/CEMB-wellslab

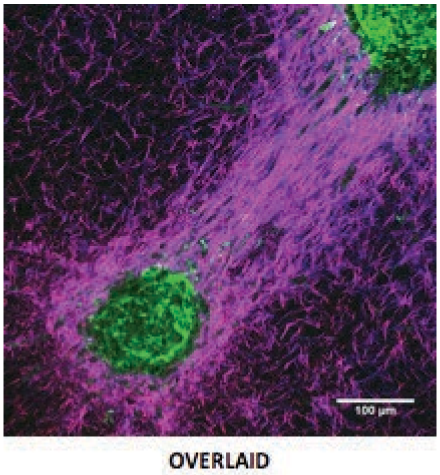

Figure 15. Two spheroids of cells on a collagen gel. Cells show up as green, collagen as pink. This shows that the cell clusters reorganize the collagen in between them. The Wells lab believes this mimics what is occurring in the liver, as shown in **figure 14** (Wells, 2017).

Detailed protocols for isolation of aortas from mouse and measurement of their elastic modulus using atomic force microscopy:
http://tiny.cc/aortastiffness

6. Both traditional and state-of-the-art instruments and techniques are required for data collection, imaging, characterization, fabrication, and modeling during research related to biological molecules and cells.

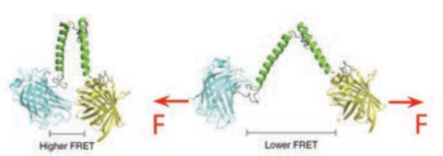

Figure 16. Conformational changes of a protein molecule are measured using FRET sensors (Goldman, 2017).

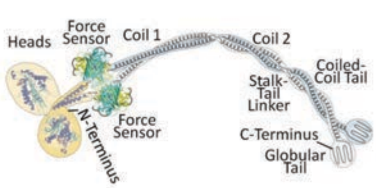

Figure 17. Placement of force sensors is shown on a kinesin protein motor molecule (Goldman, 2017).

<u>Goldman Lab</u>
Physiology
University of Pennsylvania

The Goldman lab is using groundbreaking tools and techniques to study the molecular forces exerted in cells. These novel biophysical techniques include nanometer tracking of single fluorescent molecules, bifunctional fluorescent probes and infrared optical traps (laser tweezers). Specifically, the Goldman lab is interested in relating the structural changes of proteins to enzymatic reactions and mechanical steps of energy transduction.

http://tiny.cc/CEMB-goldmanlab

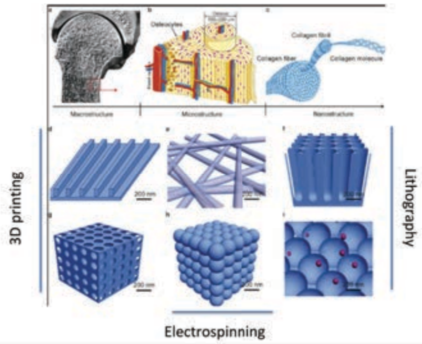

Figure 18. Nano to macroscale engineering (Burdick, 2017).

<u>Burdick Lab</u>
Bioengineering
University of Pennsylvania

The Burdick Lab is focused on both fundamental and applied studies for the development of polymer networks that can be used for understanding stem cell behavior, tissue regeneration, and drug delivery. For example, the lab uses the technique of electrospinning to create fibrous networks that mimic the ECM in order to study the behavior of cells within and on top of these networks. Additionally, they have found that the chemical structure of the material can dictate the differentiation (or lack of) of an entrapped stem cell. Researchers can control material structure and properties spatially to control stem cell differentiation in patterns.

http://tiny.cc/CEMB-burdicklab

Fluorescently labeled myosin XI walking along actin filaments:
http://tiny.cc/walkingmyosin

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