Mechanotransduction in organoid development

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Organoids and the force

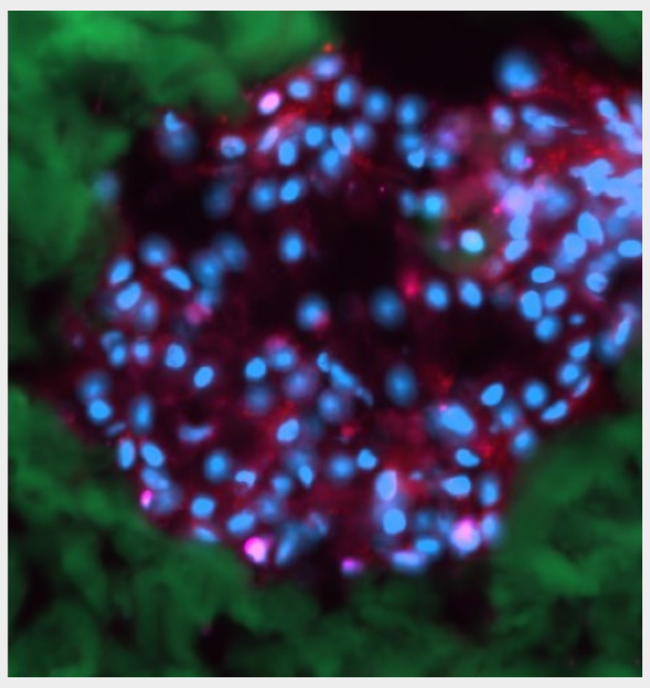
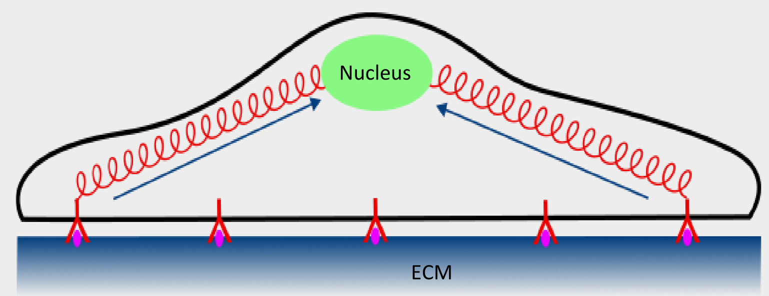


Image credit: Isabel Uwagboe (Imperial College London). Normal Human Bronchial Epithelial Cell (NHBE) organoid.

- **What are organoids?**
  Organoids are mini, simplified tissues derived from tissue fragments or stem cells, grown in a hydrogel scaffold for further investigation.
- **Why are organoids important?**
  Organoids mimic in-vivo tissues making them ideal test beds for experiments [1]. Since organoids are more specific to individual patients, they allow for targeted therapies (personalised medicine). They allow for broader screening for drugs and reduce the need for animal testing in line with the NC3Rs mission.
- **What is mechanotransduction?**
  Cells and tissues respond differently when in different stiffness environments, stem cells placed on stiffer substrates differentiate to stiffer cell types and vice versa [2], suggesting that the mechanical environment impacts development of cells and tissues.
- **Mathematical modelling can help us understand the behaviour of such complex systems, and with the role that mechanical forces can play, continuum mechanics models are needed [3]**

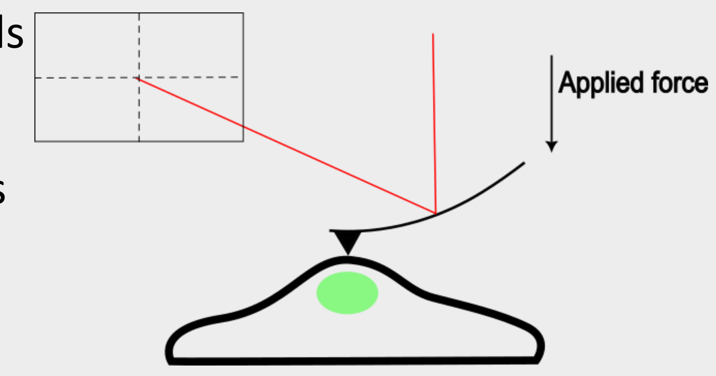
The contractile network



- Cells have an internal network (the cytoskeleton) that allows them to exert forces on their environments
- Cells can adhere to and pull on their neighbours and environment generating stresses
- These adhesions link the surrounding material to the internal structure of the cell

Material characterisation

- To better understand the role mechanics plays in biological processes, we need to know the mechanical properties of cells and tissues
- One way to determine these properties is via *Atomic Force Microscopy* (AFM)
- However, tissues are active and can undergo remodeling, changing their mechanical structure and properties



Aim: develop a continuum model to understand the role of contractility in organoid development

Modelling framework

- Adopt an active stress decomposition in the framework of linear elasticity theory
- Assume the tissue and gel are in mechanical equilibrium (no net force)

$$\nabla \cdot \sigma = 0$$

- The tissue stress, σ, is decomposed into passive and active components, analogous to *thermoelasticity and thermal cooling*

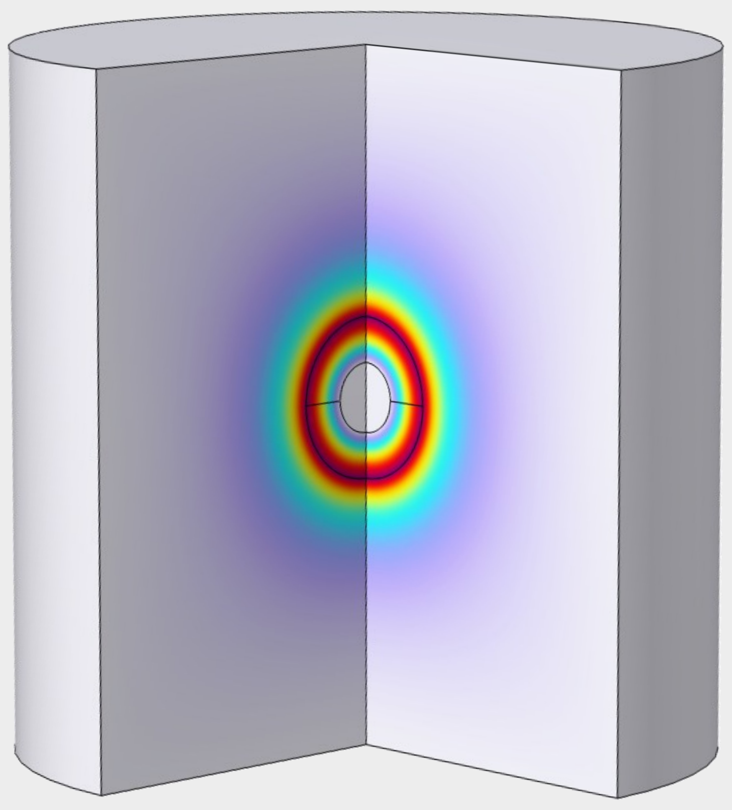
$$\sigma = \sigma^P + \sigma^A$$

- The active stress captures to contribution to the stress due to the contractile nature of the tissue
- The stress for the isotropic contractile tissue is given, in terms of the strain, by

$$\sigma_{ik} = \frac{E}{1+\nu}\left(\epsilon_{ik} + \frac{\nu}{1-2\nu}\epsilon_{ll}\delta_{ik}\right) - \frac{E}{3(1-2\nu)}c\delta_{ik}$$

Active stress contribution

- We introduce the contractile response function, *c*, which we assume is known. Initially, we consider a constant contractile pressure/pull, $c = -c_0$, with *c* a `target strain' or `target contraction'
- Here, we consider a contractile tissue, with a rigid core, surrounded by an elastic gel scaffold

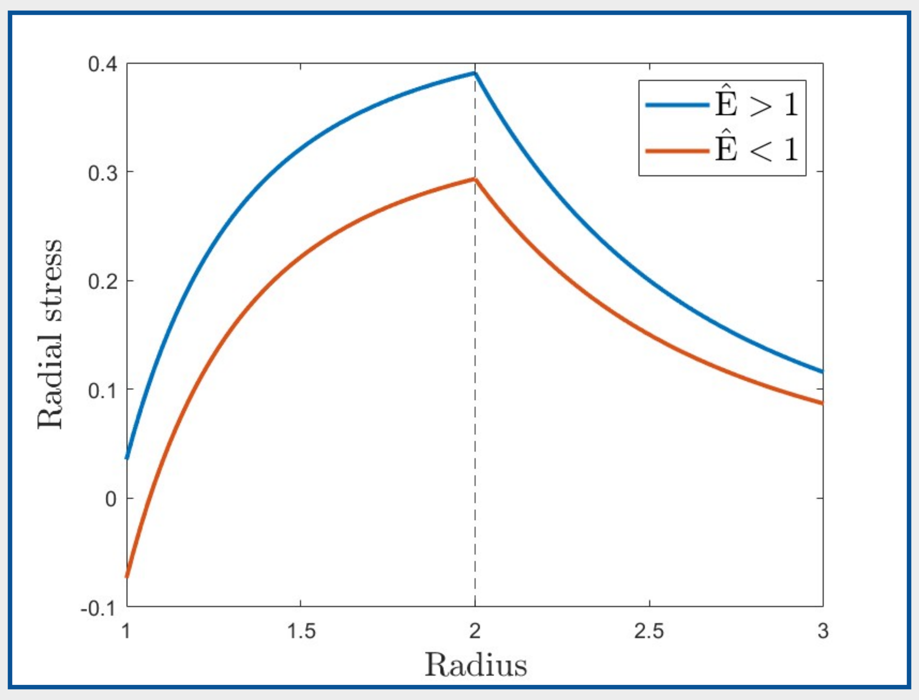


Result 1: Stiffness ratio

$$\hat{E} = \frac{\text{Stiffness of gel}}{\text{Stiffness of tissue}}$$

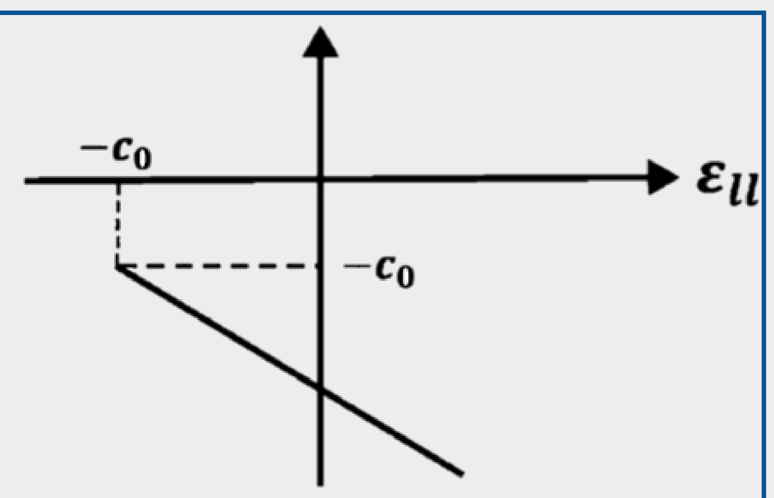
Stiffness ratio

- Focus on the interface between the rigid core and the tissue
- Compression switches to tension based on the value of $\hat{E}$: mechanical signal that could elicit a biological response
- **Stiffness ratio key in stress-based mechanisms for mechanotransduction**



Result 2: Effective stiffness

- Cells can alter their contractility in response to mechanical cues
- We now include a *strain-based feedback mechanism* in the contractile response of the tissue



$$c = -c_0 + \alpha(\epsilon_{ll} + c_0)$$

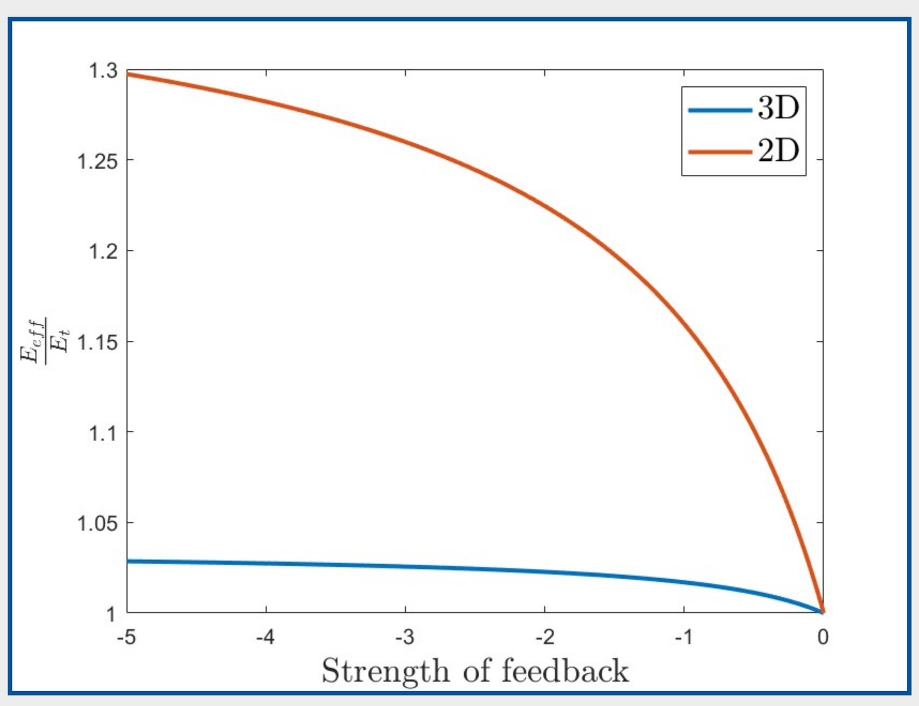
- We find that the mechanical deformations are the same as those for a passive tissue with stiffness, E_{eff}, from which we see that feedback stiffens tissues

$$E_{eff} = \frac{3E_t(1-\alpha)}{3-2\alpha(1+\nu_t)}$$

- **Tissue characterization can only measure effective stiffness, not its true value**
- **Mechanism for active remodeling**

Result 3: The third dimension

- Tissues in 3D are seen to behave differently than in 2D, that same behaviour is seen here
- The same feedback model can be repeated in a 2D setting
- Effective stiffness in 2D increases a lot more in comparison to 3D
- **Cells undergo greater remodeling in 2D environments**
- **We need 3D experiments to accurately model tissue development**



References and Acknowledgements

[1] Kim, J., Koo, B. K. & Knoblich, J. A. Human organoids: model systems for human biology and medicine. Nature Reviews Molecular Cell Biology vol. 21 571–584 (2020).

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[3] Littlejohns, E. & Dunlop, C. M. Mechanotransduction mechanisms in growing spherically structured tissues. New J Phys **20**, 043041 (2018).

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