Touching the surface—how cells determine the mechanical properties of their environment and respond—a mathematical model

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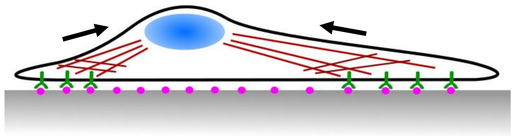
Cells behave differently in different stiffness environments

- When grown in a soft environment stem cells become more brain-like, while in stiff environments they develop into more bone-like cell types. This change in behaviour can occur without the input of external chemical cues [1].
- Cancerous cells are more malignant in stiffer environments and more likely to invade healthy tissue [2].
- Recent results link the ageing of stem cells in the central nervous system with the stiffening of their microenvironment [3].
- Understanding mechanical cellular behaviour is crucial for tissue engineering applications and disease control.

Cells stick to their environment and contract

- Cells bind to their environment – the extra cellular matrix (ECM).
- These adhesions are linked to the actin cytoskeleton by focal adhesion complexes (FAs), which tend to form at the cell periphery.
- Myosin motors shorten the actin fibres, causing the cell to contract.
- These contractile forces are transmitted to the ECM through the adhesions.
- The cell experiences a resistance from the substrate, this allows it to mechanically 'sense' its environment.



Sketch of an adhered cell cross-section, arrows show direction of contraction

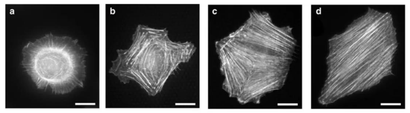
Experimentally measuring cellular contractile forces

- In the most common biological experiments to measure cellular contractile forces cells are seeded onto a designed substrate with known physical properties.
- In traction force microscopy (TFM) the substrate is a gel with embedded fluorescent marker beads. Arrays of micropillars with fluorescent tips are also commonly used.
- When cells come into contact with such surfaces they spread out, adhere and contract.
- The force applied by the cell deforms the substrate.
- Displacement of the fluorescent marker beads or pillar tips can be measured and used to infer the force applied by the cell.

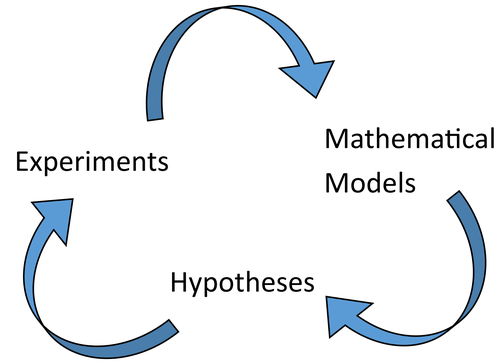
Biological observations of cellular stiffness response

- Cells tend to appear smaller and rounder on softer substrates.
- On stiffer substrates they appear larger and more angular.
- On stiffer substrates cells tend to have more and larger focal adhesions and greater forces are measured.

Images of the cell cytoskeleton on different stiffness substrates (cells are all from the same cell line and stiffness increases from a to d) [4]



My objective is to predict the observed cellular adaptations to changes in the mechanical properties of the underlying substrate.



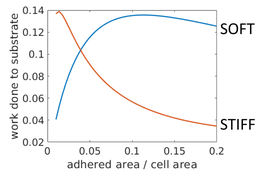
Key results

The pattern of adhesion between the cell and substrate affects the resistance it experiences.

- Cells with a larger adhered area experience more resistance and so effectively experience a stiffer substrate.
- Large gaps between adhesions cause localised regions of high deformation, making the substrate effectively appear softer.
- Elongated adhesions may make the substrate appear softer than round adhesions.

On stiff substrates it is energetically favourable for the cell to elongate adhesions.

- On stiff substrates, larger adhesions reduce the work done to the substrate.
- On soft substrates different dynamics are displayed which may result in larger adhesions increasing the work done to the substrate.



If energy output is conserved, cellular contractility increases on stiffer substrates.

- The work done to the substrate can be considered the energy output of the cell. Recent experimental findings suggest this may be a conserved quantity for cells of the same type and size. In order to achieve this, cells must become more contractile on stiffer substrates.

Modelling cellular contractility

- We have made a mathematical model balancing the force exerted by a cell on a substrate (a gel or array of micropillars) and the resistance from the substrate.

Force from the cell = substrate resistance

$$\nabla \cdot \sigma = \begin{cases} K\mathbf{u}, & \text{adhesion} \\ \mathbf{0} & \text{no adhesion} \end{cases}$$

The stress, σ (force per area) in the cell is described in two parts:

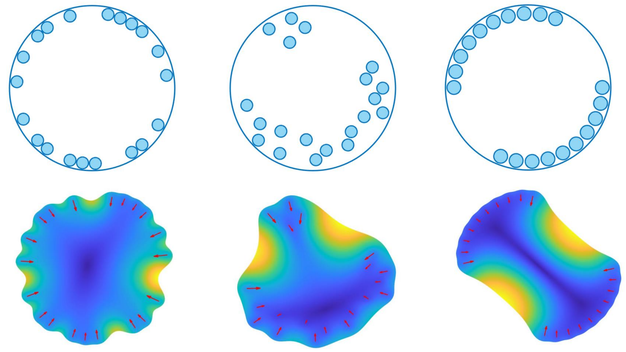
$$\sigma = \sigma^P + \sigma^A$$

σ^P is a passive term expressing the resistance of the main cell body to deformations,

σ^A is an active contractile pressure pulling the cell inwards.

K describes the substrate stiffness; $\mathbf{u}$ is the deformation.

- We solve the model to find the cell deformation using both analytical techniques (pen and paper) and Finite Element Methods (implemented on a computer).
- Guided by biological observations, we change the distribution of adhesion throughout a cell so that it is only adhered in a ring around the cell edge, or at particular 'spots'.



Deformation of cells with different distributions of adhesive spots: schematic diagrams show spot distributions pre-contraction; heat map shows cellular deformation, red arrows spot deformation.

Conclusions

- Our results highlight the importance of considering the placement of adhesion between the cell and its environment to the apparent mechanical response it experiences [5].
- Energy considerations are shown to have significant implications for the optimisation of cell adhesion.
- These results suggest possible explanations for the mechanical responses of cells to different stiffness environments.

Acknowledgements

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References [1] Engler et al. 2006 *Cell*; [2] Paszek et al. 2005 *Cancer Cell*; [3] Segel et al. 2019 *Nature*; [4] Gupta et al. 2015 *Nat. Commun.*; [5] Solowiej-Wedderburn & Dunlop (*in preparation*)