Modelling active cell processes in multicellular sheets

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Multicellular modelling
Subcellular Element Model
Calibration
Active processes
Primitive streak formation
Modelling active cell processes in multicellular sheets

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postdoc positions available

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physics and biology

length and time scales
independence of scales
feedback between scales
equilibrium
demographics
emergence of complexity
active dynamics
that which is optimised
heterogeneity

T.J. Newman, Physical Biology 2011 8 010201
Life and death in biophysics
Regulation and emergence

Cold $\text{H}_2\text{O}$

Warm $\text{H}_2\text{O}$
### Laws of physics hold in biology

#### Optimist

- “Let’s get to work”
- Write down Newton’s laws of motion
- Stress/strain relationships for tissues
- Energy of a tissue, energy of a tumour, …
- Free energy, if fluctuations are not small
- Minimize, diagonalize, …

#### Pessimist

- Yes, but …
- Cell is **not** a mechanical device
- Tissue/tumour is an assembly of cells
- Therefore tissue is not a mechanical entity
  - i.e. it is not a “material”
- Cells do not just “react” to forces (**passive**)
  - they “behave” in response to forces (**active**)

#### Pragmatist

- It depends on time scales: short times (< 1-10s) **cells react**, longer times (> 10s) **cell behave**
- The challenge in both experiments and theory is to extend physics tools to describe **behaviour**
- Biologists call the corresponding biological challenge “**systems biology**”
  - understanding interaction of gene/signalling networks which drive cell behaviour
Length scales in modelling multicellular systems

- **Computationally inaccessible >10^6 variables**
  - Cell-based models
  - Density models

- **Biologically meaningless**
  - Vesicle
  - Microtubule

- **Protein complexes**

- **Next generation models**
  - Cell

- **ScEM**

- **Early tissue/region**

- **Cell sub-cellular region**

- **Tissue region**

- **Early tissue/embryo**

- **Tissue “patch” of cytoskeleton**

- **Tissue “patch” of cells**
Computation - Subcellular Element Model

Each cell represented as a cluster of viscoelastically coupled nodes

Overdamped dynamics described by set of Langevin equations

Couplings are defined by short-range potentials

Algorithms are grid-free, and intrinsically three-dimensional
Computation - Subcellular Element Model

Modeling multicellular systems using subcellular elements

Modeling cell rheology with the Subcellular Element Model
ScEM - single cell
ScEM - cell growth and successive divisions
ScEM - growth and division leads to large 3D cell mass
ScEM - cross-sectional view shows adaptive cell shapes
Biophysical calibration

**A simple guide to understanding common physical methods to probe mechanical properties of cells**

- **Bulk rheology**: A material is sheared between two plates using an oscillatory stress to probe the shear elastic, \( G'(\omega) \), and viscous, \( G''(\omega) \), moduli.

- **Magnetic bead cytometry**: An external magnetic field applies a stress to a magnetic bead. The bead is positioned to determine the response.

- **Traction force microscopy**: Cell contractions deform a flexible substrate. Forces are estimated from bead displacements.

- **Atomic force microscopy**: A cantilever applies stress to the cell. The cantilever deflection is measured by laser reflection.

- **Microrheology**: The motion of probe particles is measured using either video or laser tracking techniques. Particle motion is either driven externally or thermally induced to yield the viscoelastic modulus.

- **Whole cell stretching**: A cell is attached to two surfaces. A force is applied to one surface and the plate separation is measured.

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**Viscoelastic “Complex” Modulus**

\[
G^*(\omega) = G'(\omega) + iG''(\omega)
\]

- elasticity (storage modulus)
- viscosity (loss modulus)

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“Rheology of actin networks is governed by the entropic dynamics of their semiflexible polymer chains. In living cells this behaviour is observed only over short time scales (<0.01s), whereas mechanical cellular functions operate at much longer time scales. Over longer time scales, rheological behaviour of cells scales with a weak power law.”

Micro-rheology of a single cell using the ScEM

Creep response

fixes dissipation scale

Modelling cell rheology with the Subcellular Element Model
S A Sandersius, T J Newman 2008 Physical Biology 5 015002

Storage and loss moduli

fixes energy scale
Active processes in cell and tissues

Examples:

active cytoskeletal rearrangement to survive large shear forces and drive gross morphological changes - at cell scale

effective tissue viscosity (relevant to embryonic tissue)

generation of pseudopodia for migration through connective tissue, or even epithelial-like tissue (leading to interesting movement patterns)

We incorporate active processes into the ScEM by “fading in” and “fading out” subcellular elements.

This is essentially a phenomenological model of cytoskeletal construction and deconstruction. We use biologically plausible time scales for this process (~10 cubic microns/sec).
Slow cell stretching and cytoskeletal adaptation
“Tissue viscosity”

Forcing a 60 micron bead through planar tissue enables a measurement of effective tissue viscosity

We find effective viscosity of order $10^4$ Pa s which is in line with measurements on various embryonic systems

Gordon et al 1972 (chick heart)
Rieu et al 2002 (Hydra)
Schoetz et al 2007 (zebrafish)

Micron-scale calibration producing millimetre scale prediction of material properties of tissue

Emergent cell and tissue dynamics from subcellular modelling of active biomechanical processes
Streaming morphologies in tissue invasion
Primitive streak formation in the developing avian embryo

from Wolpert et al (OUP)
Movement patterns during streak formation
the enduring search for a mechanism

Cell movement during primitive streak formation

The amniote primitive streak is defined by epithelial cell intercalation before gastrulation

Zamir EA, Rongish BJ, Little CD 2008 PLoS Biology 6 2163-2171
The ECM moves during primitive streak formation - computation of ECM versus cellular motion

Newman TJ 2008 Current Topics in Developmental Biology 81 157-182
Grid-free models of multicellular systems, with an application to large-scale vortices accompanying primitive streak formation
In the steady-state, the equation governing the diffusion of chemical signals is:

$$D \nabla^2 \varphi - \lambda \varphi = \delta^2 (x - x_i)$$

This is mathematically analogous to Poisson’s equation of electrostatics

The chemotactic velocity $\mathbf{v} \sim \nabla \varphi$

is analogous to the electric field

Sources of chemoattractant (repellent) are analogous to negative (positive) charges

This analogy allows the simple construction of a “chemotactic dipole” which gives flow patterns similar to those observed in the chick embryo.
Movement patterns during avian gastrulation

*primitive simulations using elastic spheres*

![Diagram showing movement patterns](image)

**strong chemotaxis**  
**weak chemotaxis**

Produces encouraging movement patterns, but cell flow almost non-existent - due to jamming
Movement patterns during avian gastrulation

ScEM simulation of streak formation

Simulations are performed on a scaled-down system of 1200 cells.

Simulation parameters (both for mechanotaxis and chemotaxis) are calibrated at the cell scale (1-10 microns, 1-10 seconds).

Anterior of streak moves ~300 microns in 2 hours, which is consistent with experiment (~1200 microns in 8 hours).

Model, calibrated at the cell scale, provides results at the tissue scale, in qualitative and quantitative agreement with experiment.

But, dipole mechanism is only robust to ~10% deviation in chemoattractant/repellent parameters (if dipole comprises ~200 cells).


“Chemotactic dipole” mechanism for large-scale vortex motion during primitive streak formation in the chick embryo.
Summary

Contrasted physics and biology

Presented Subcellular Element Model (ScEM)

Calibration of model from biophysical data

Discussed need for models to incorporate active processes

Examples given:
  slow cell stretching
  tissue fluidity
  invasion morphologies
  primitive streak formation