Modelling active cell processes in multicellular sheets

Timothy Newman College of Life Sciences University of Dundee

Multicellular modelling Subcellular Element Model Calibration Active processes Primitive streak formation

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Collaborators:Funding:Cornelis Weijer, University of DundeeNSFSebastian Sandersius, Arizona State University/CaltechHFSPMembers of the PSOC NetworkNIH PSOC

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Special focus on physical oncology



University of Dundee, College of Life Sciences

postdoc positions available <u>t.newman@dundee.ac.uk</u>

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



Laws of physics hold in biology

Optimist	Pessimist
"Let's get to work"	Yes, but
Write down Newton's laws of motion	Cell is not a mechanical device
Stress/strain relationships for tissues	Tissue/tumour is an assembly of cells
Energy of a tissue, energy of a tumour,	Therefore tissue is not a mechanical entity
Free energy, if fluctuations are not small	Colle de potivet "recet" te forços (receive)
Minimize, diagonalize,	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



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 T. J. Newman, Mathematical Biosciences and Engineering **2**, 611 (2005)

Modeling cell rheology with the Subcellular Element Model S.A. Sandersius and T.J. Newman, Physical Biology **5**, #015002 (2008) 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', (in-phase) and viscous, G'', (out-of-phase) moduli.

Magnetic bead cytometry

An external magnetic field applies a stress to a magnetic bead. The bead is position tracked 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 and is interpreted 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.





Viscoelastic "Complex" Modulus

$$G^{*}(\omega) = G'(\omega) + iG''(\omega)$$

$$\uparrow$$
elasticity viscosity
(storage modulus) (loss modulus)

From: K.E. Kasza, A.C. Rowat, J. Liu, T.E. Angelini, C.P. Brangwynne, G.H. Koenderink, D.A. Weitz. 2007. Curr Opin Cell Biol. **19**(1):101-107.

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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 <u>behaviour</u> of cells scales with a weak power law."

Uhde J, Ter-Oganessian N, Pink DA, Sackmann E, Boulbitch A. 2005. Phys. Rev. E **72**, 061916. Deng L, Trepat X, Butler JP, Millet E, Morgan KG, Weitz DA, Fredberg JJ. 2006. Nat Mater. **5**(8):597-598. Alcaraz J, Buscemi L, Grabulosa M, Trepat X, Fabry B, Farre R, Navajas D. 2003. Biophys J. **84**(3): 2071–2079.

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Micro-rheology of a single cell using the ScEM



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 10⁴ 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 S A Sandersius, C J Weijer, T J Newman 2011 Physical Biology **8** 045007.

Streaming morphologies in tissue invasion



Primitive streak formation in the developing avian embryo



Movement patterns during streak formation the enduring search for a mechanism

Chuai M, Zeng W, Yang X, Boychenko V, Glazier JA, Weijer CJ 2006 Developmental Biology **296** 137-149 *Cell movement during primitive streak formation*

Voiculescu O, Bertocchini F, Wolpert L, Keller RE, Stern CD 2007 Nature **449** 1049-1052 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

Movement patterns during avian gastrulation the "chemotactic dipole"

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 $~v \sim \nabla \phi$ 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

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)

S A Sandersius, M Chuai, C J Weijer, T J Newman 2011 Physical Biology **8** 045008. "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