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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Special focus on physical oncology

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postdoc positions available

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*p*hysics and *b*iology

length and time scales

independence of scales

feedback between scales

equilibrium

demographics

emergence of complexity

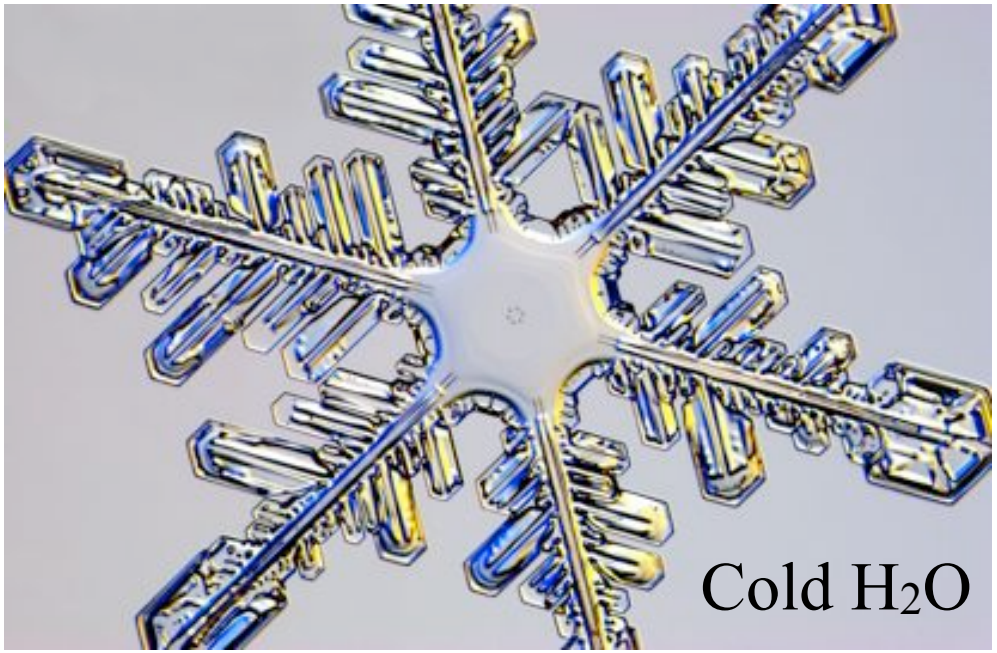
active dynamics

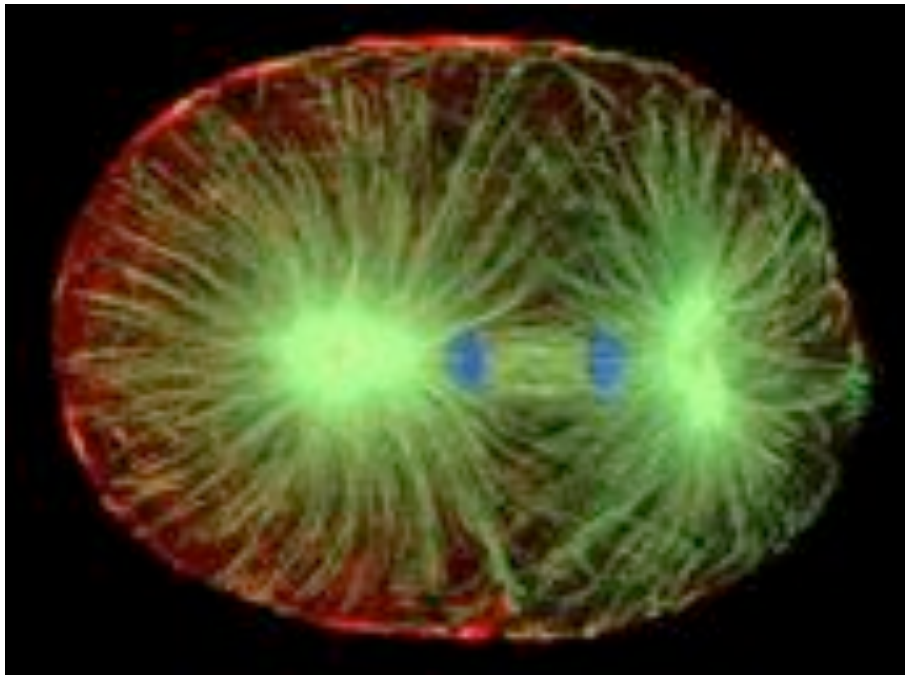
that which is optimised

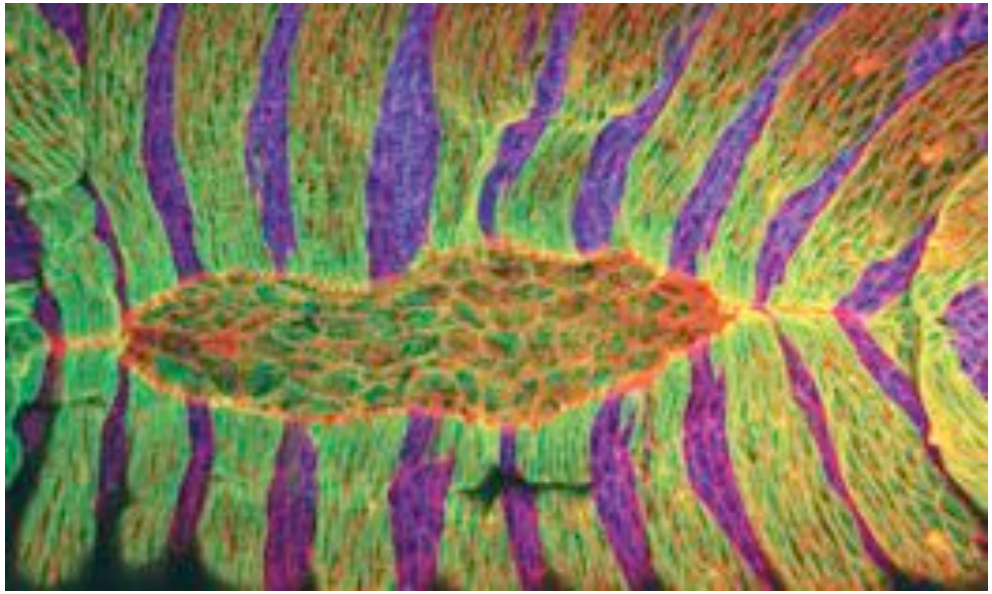
heterogeneity

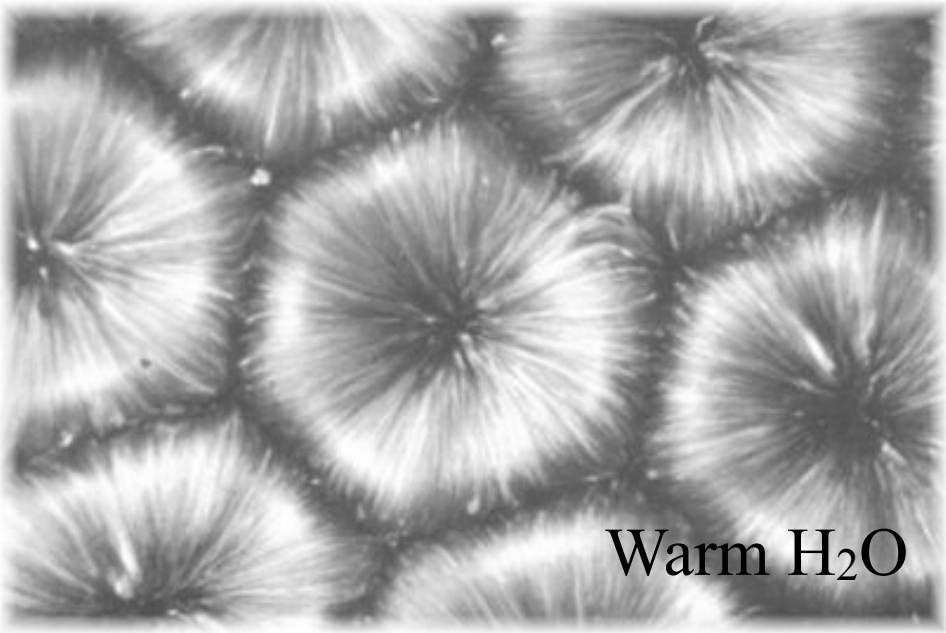
T. J. Newman, Physical Biology 2011 **8** 010201
Life and death in biophysics

Regulation and emergence









Laws of physics hold in biology

Optimist

"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**)

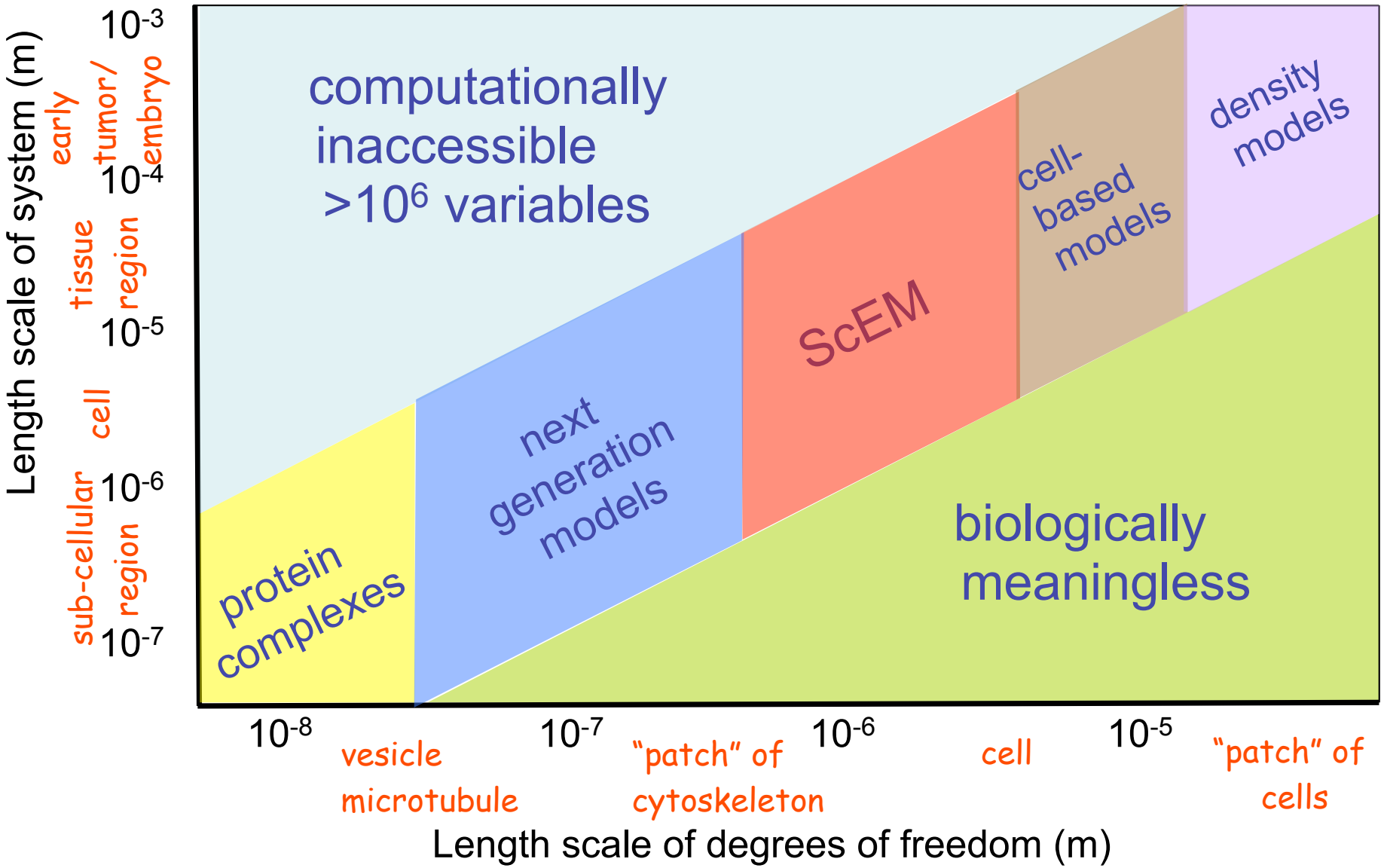
Pragmatist

It depends on time scales: short times (< 1-10s) *cells react*, longer times (> 10s) *cell behave*

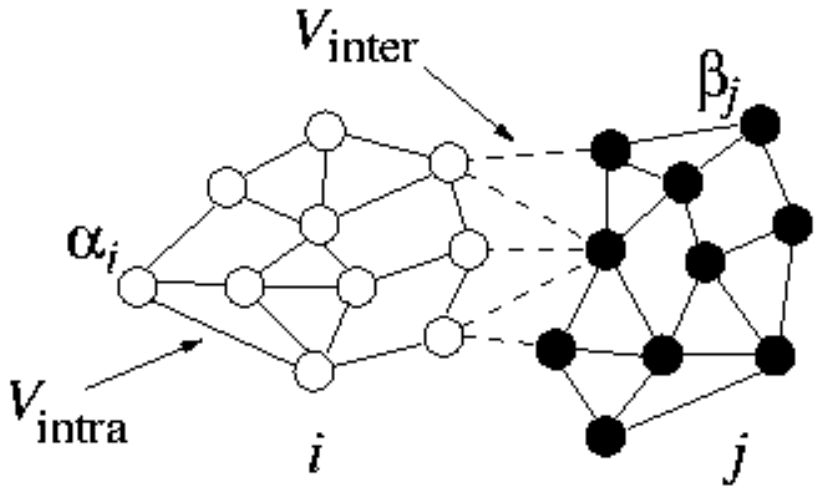
The challenge in both experiments and theory is to extend physics tools to describe **behaviour**

Biologists call the corresponding biological challenge **"systems biology"**
understanding interaction of gene/signalling networks which drive cell behaviour

Length scales in modelling multicellular systems



Computation - Subcellular Element Model



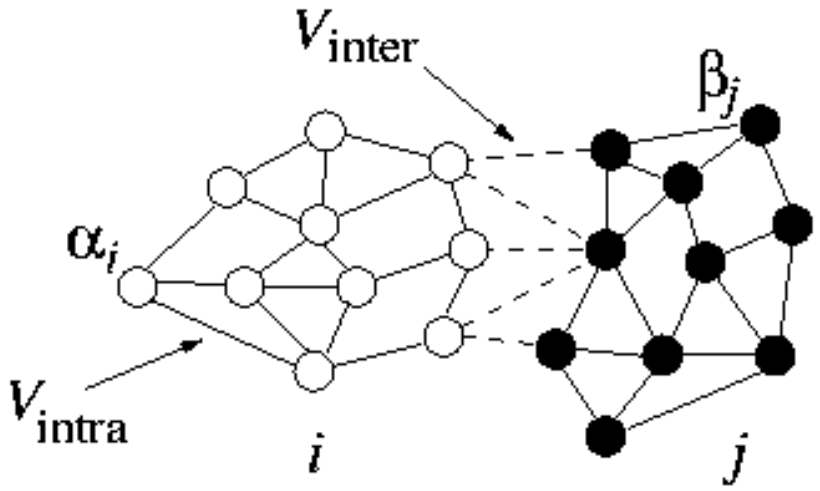
Each cell represented as a cluster of viscoelastically coupled nodes

Overdamped dynamics described by set of Langevin equations

Couplings are defined by short-range potentials

Algorithms are grid-free, and intrinsically three-dimensional

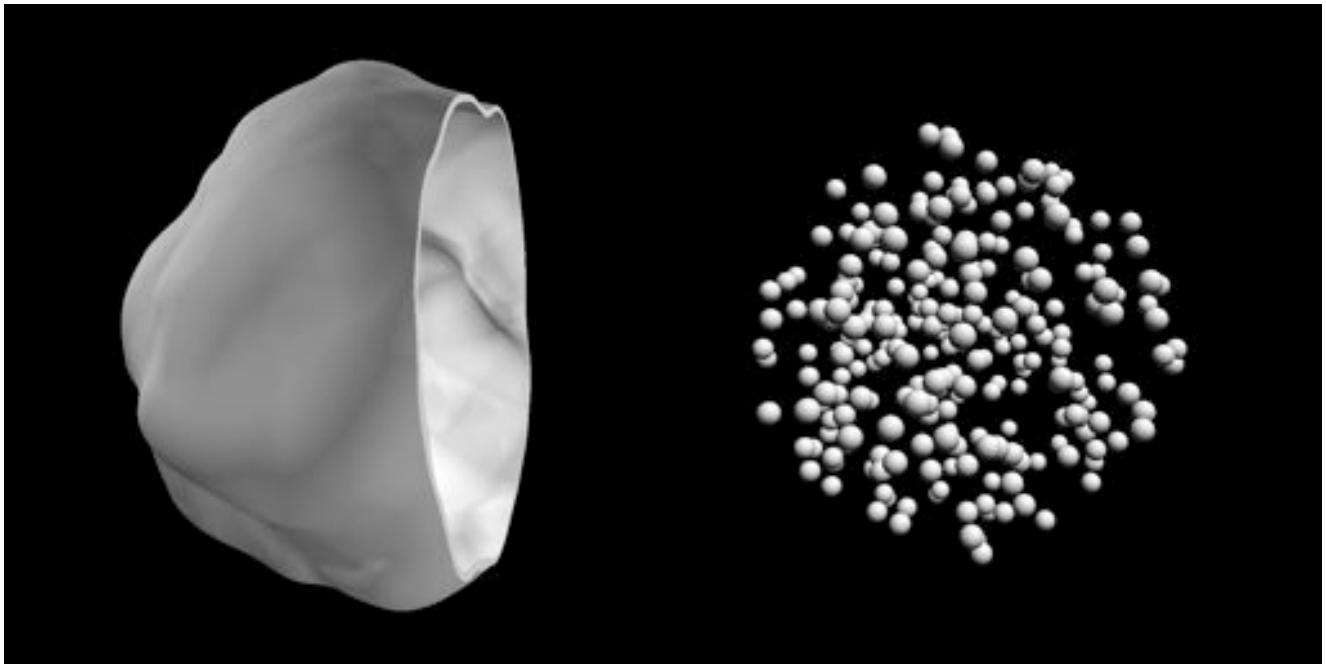
Computation - Subcellular Element Model



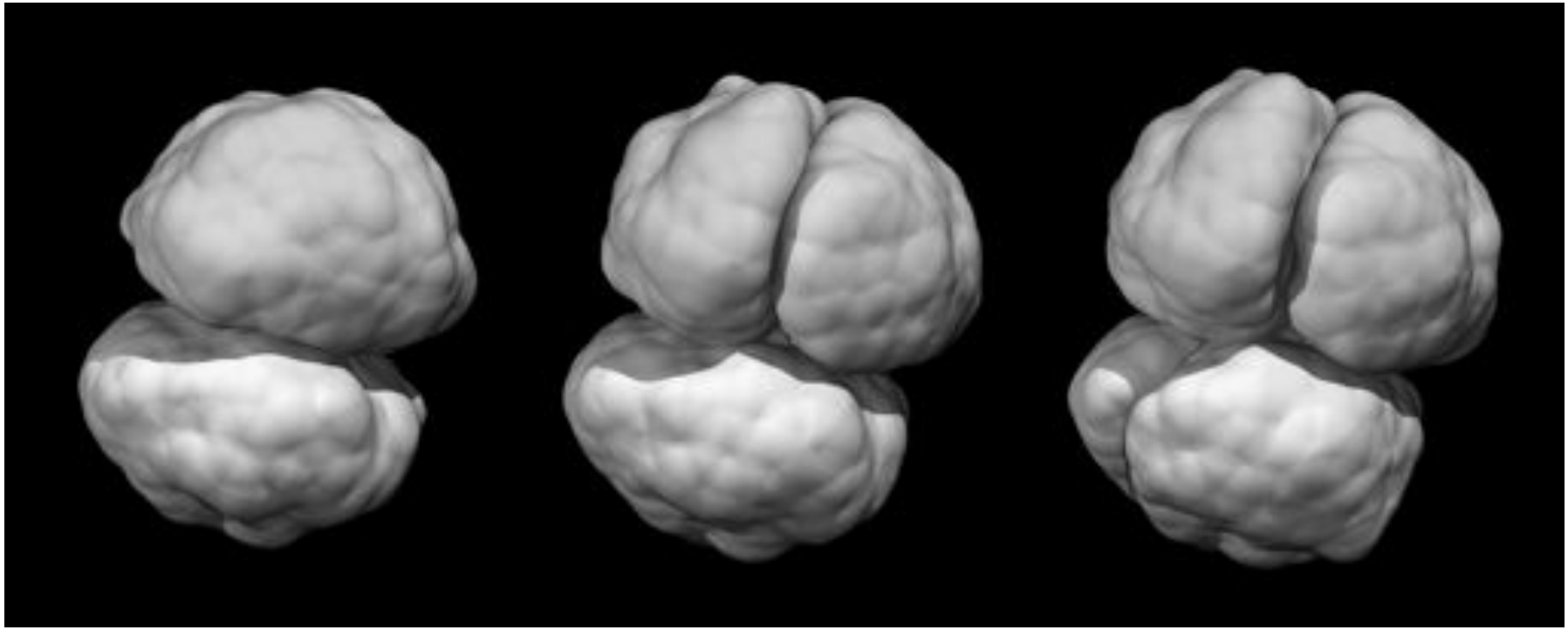
Modeling multicellular systems using subcellular elements
T. J. Newman, Mathematical Biosciences and Engineering **2**, 611 (2005)

Modeling cell rheology with the Subcellular Element Model
S. A. Sandersius and T. J. Newman, Physical Biology **5**, #015002 (2008)

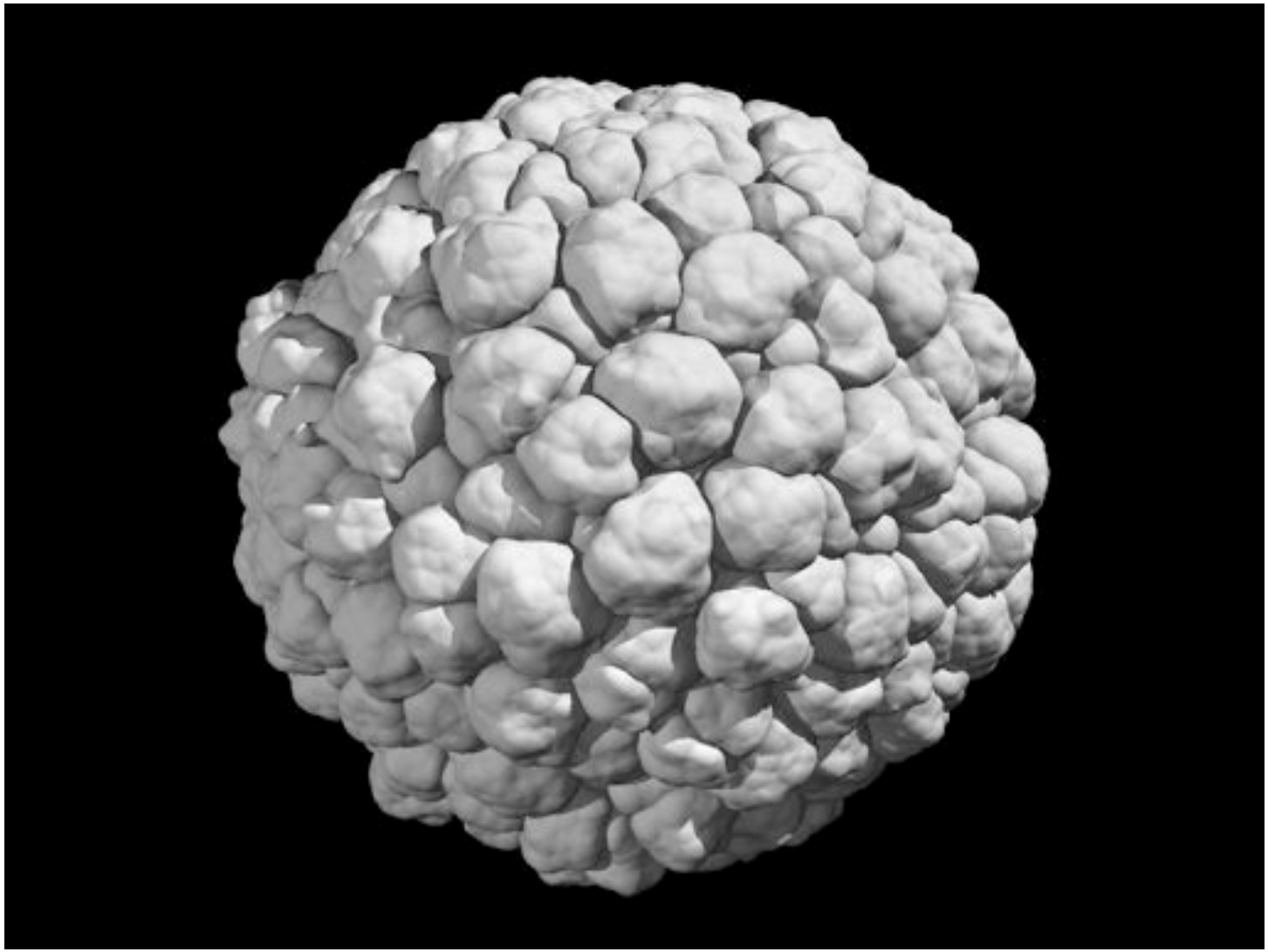
ScEM - single cell



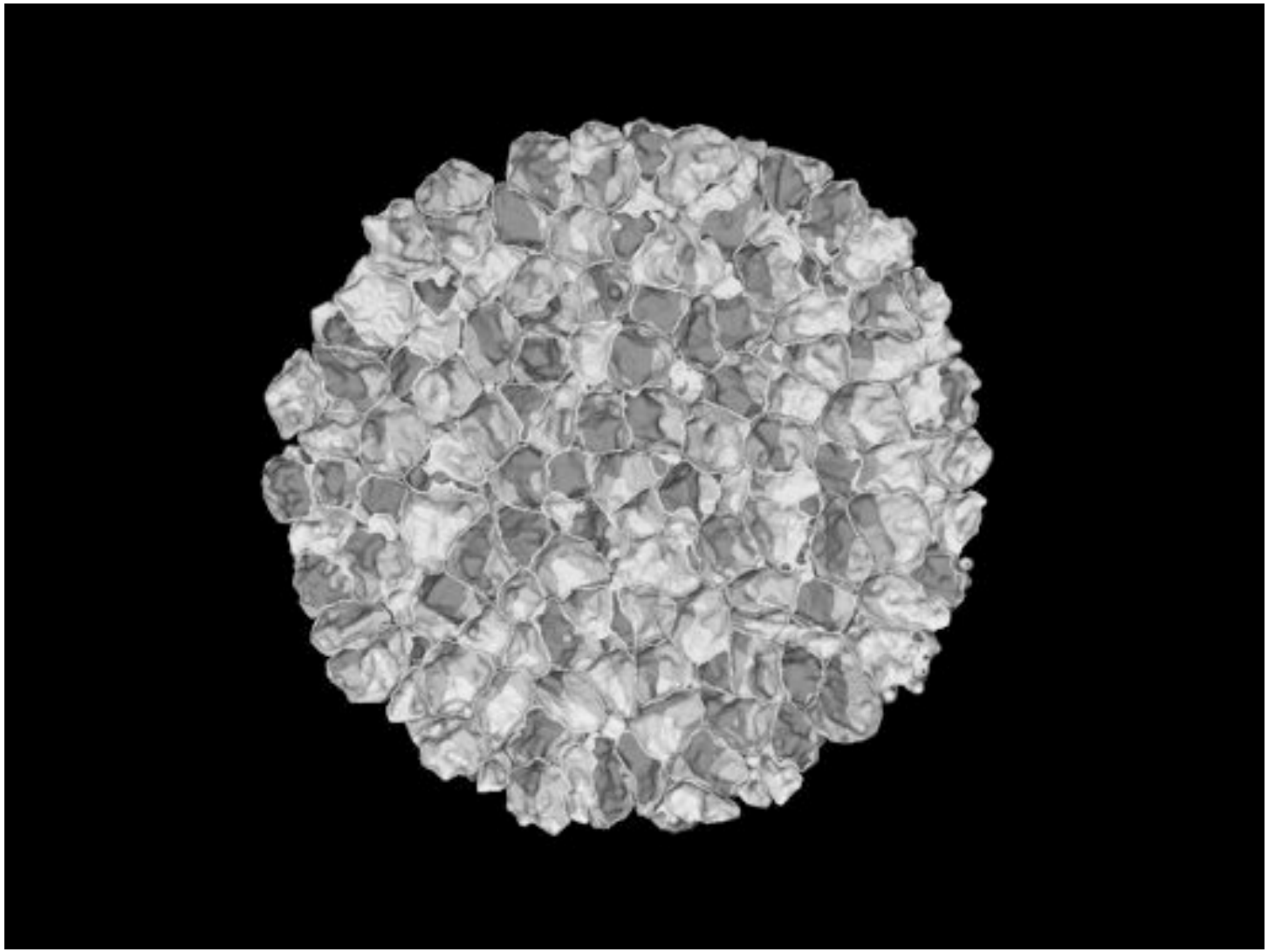
ScEM - cell growth and successive divisions



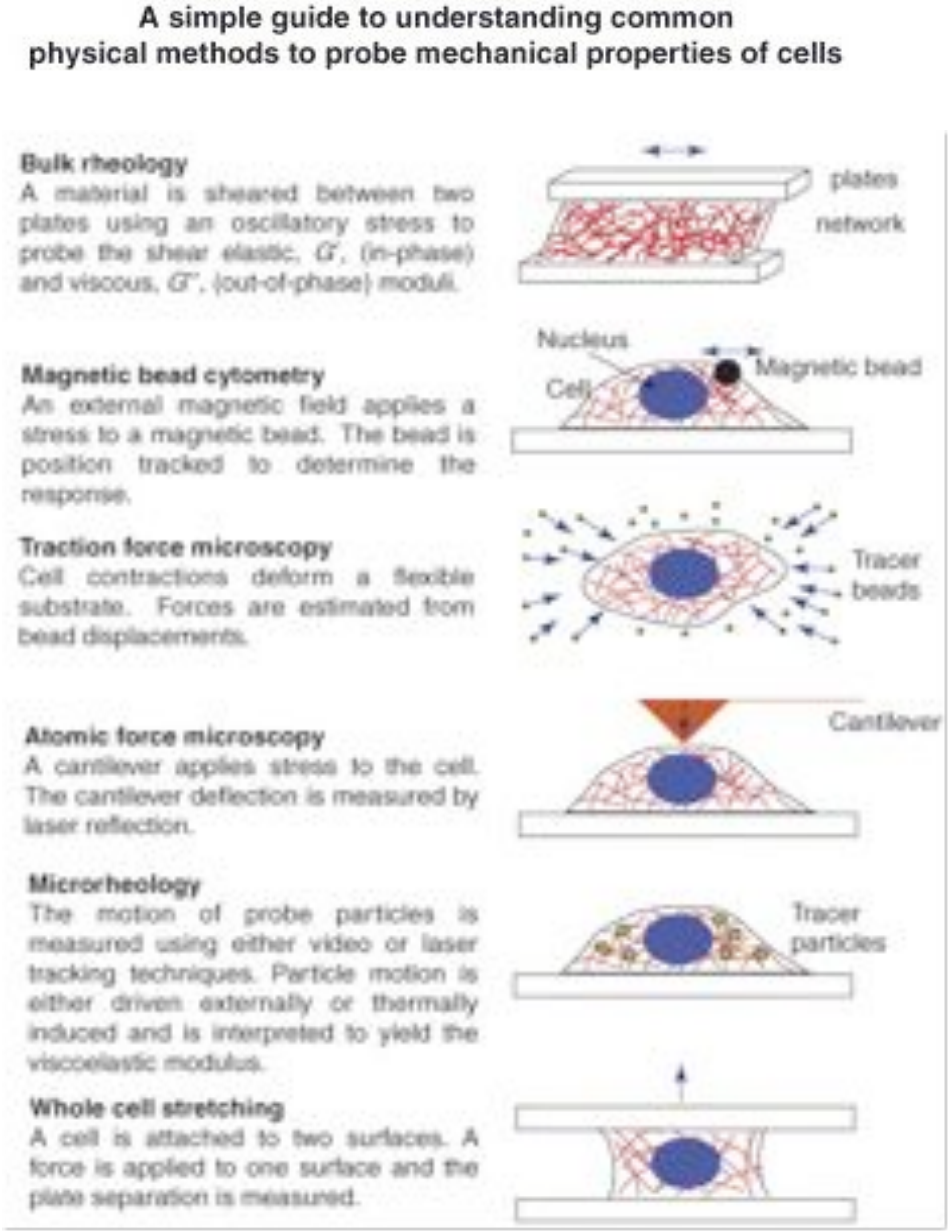
ScEM - growth and division leads to large 3D cell mass

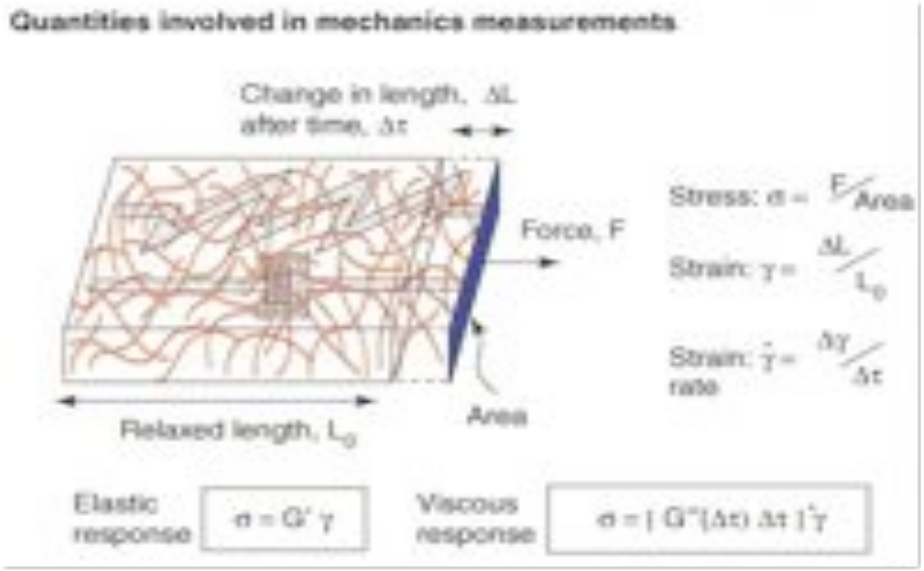


ScEM - cross-sectional view shows adaptive cell shapes



Biophysical calibration





Viscoelastic "Complex" Modulus

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

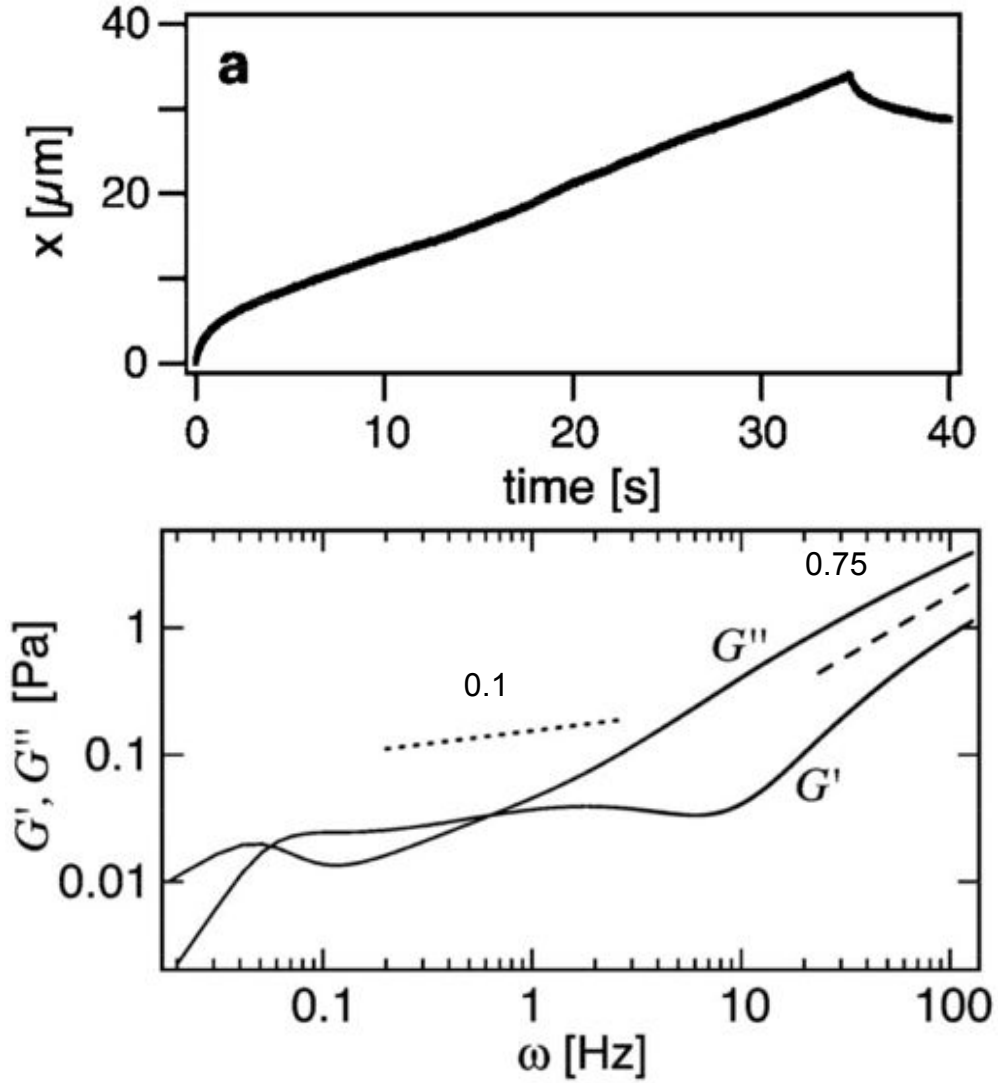
elasticity (storage modulus)

viscosity (loss modulus)

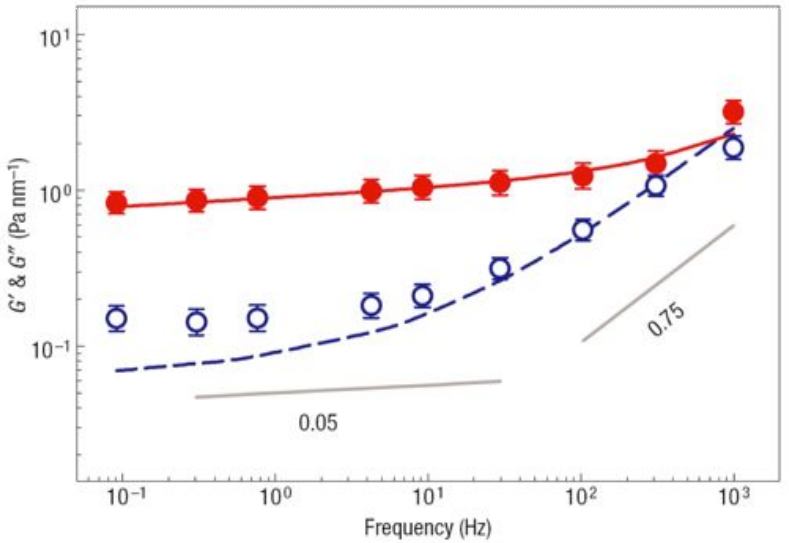
From: K.E. Kasza, A.C. Rowat, J. Liu, T.E. Angelini, C.P. Brangwynne, G.H. Koenderink, D.A. Weitz. 2007. Curr Opin Cell Biol. **19**(1):101-107.

Local (micro) rheology

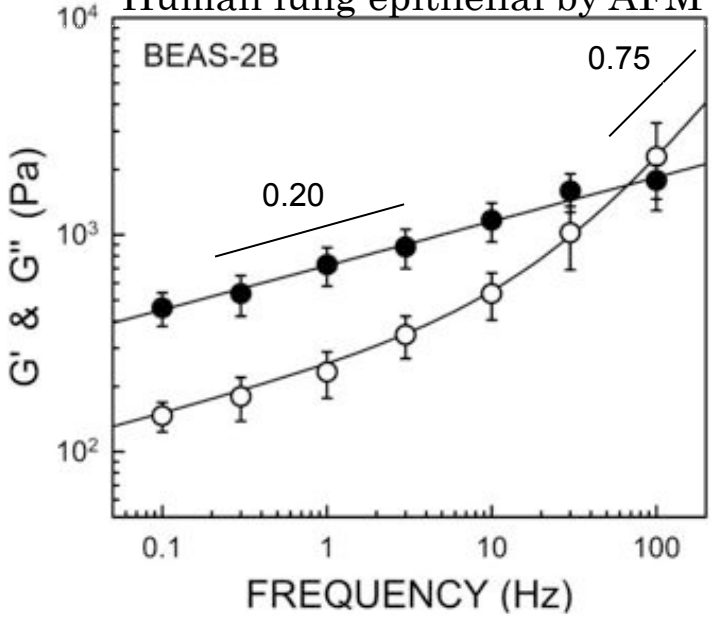
Entangled F-actin solutions, no associated proteins



Bovine smooth muscle by bead cytometry



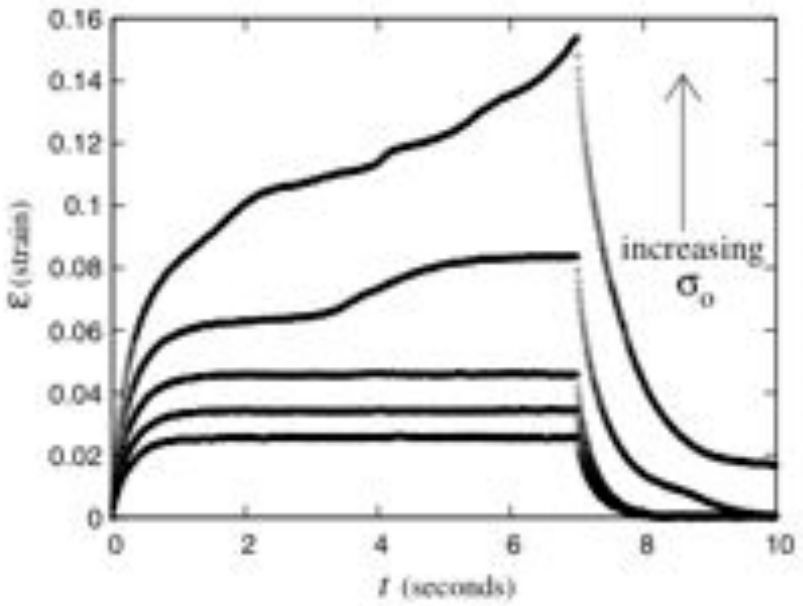
Human lung epithelial by AFM

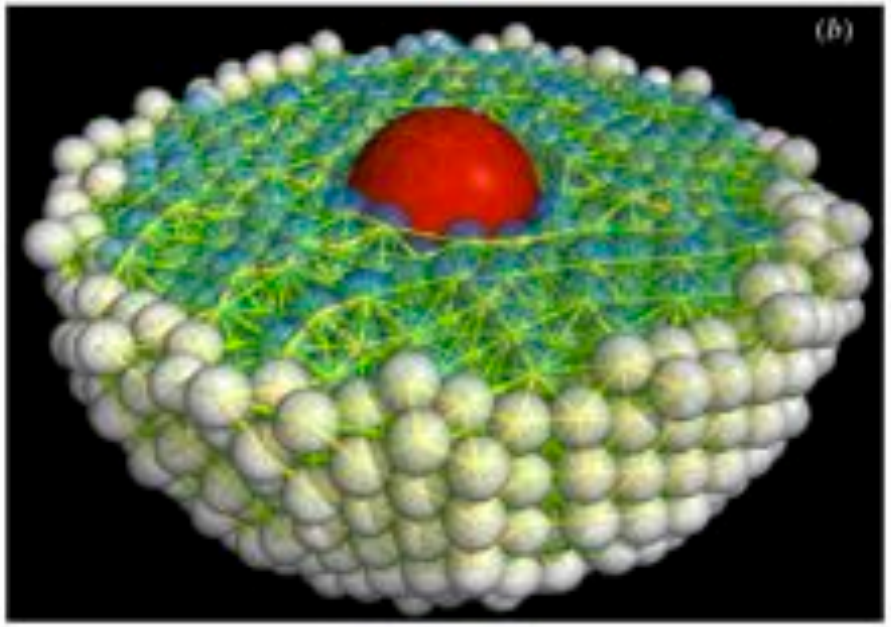


"Rheology of actin networks is governed by the entropic dynamics of their semiflexible polymer chains. In living cells this behaviour is observed only over short time scales (<0.01s), whereas mechanical cellular functions operate at much longer time scales. Over longer time scales, rheological behaviour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

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.

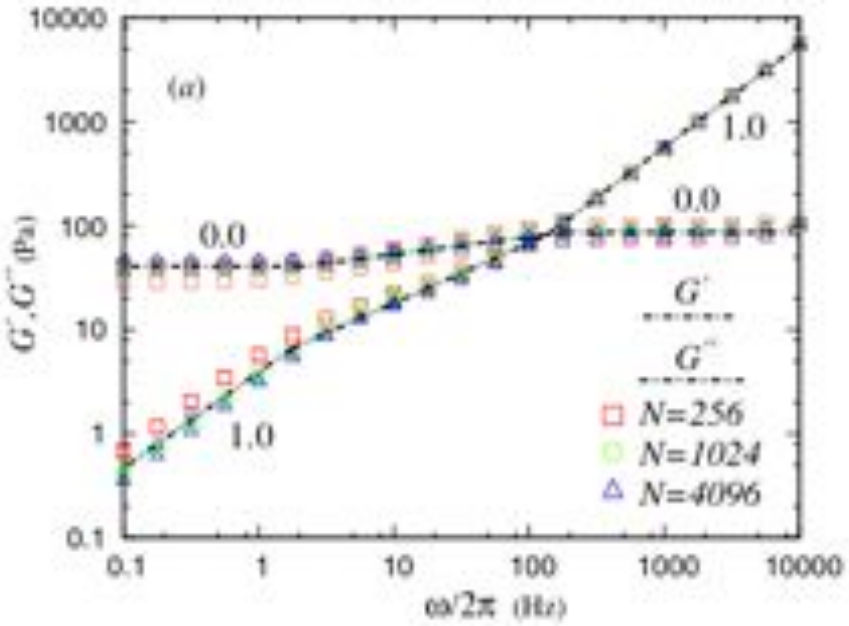
Micro-rheology of a single cell using the ScEM





Creep response

fixes dissipation scale



Storage and loss moduli

fixes energy scale

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

Active processes in cell and tissues

Examples:

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

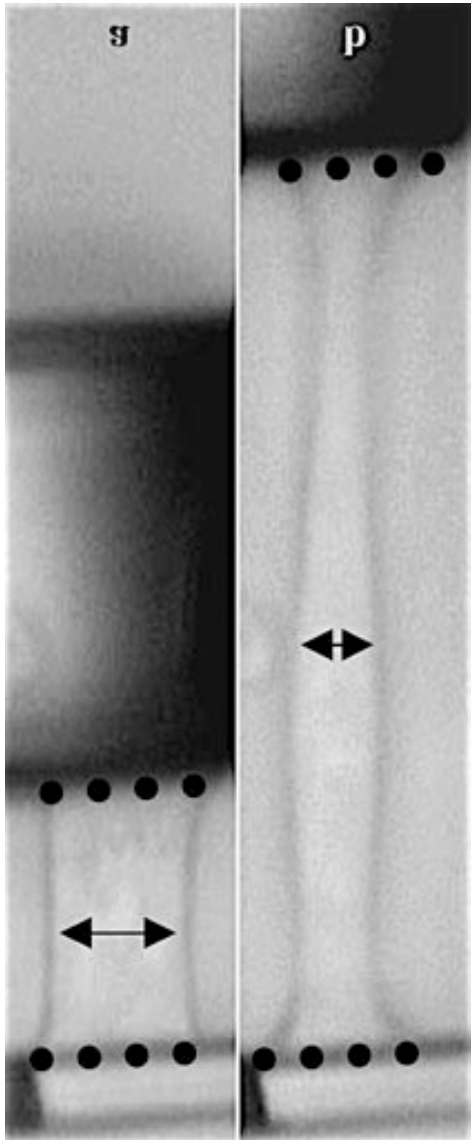
effective tissue viscosity (relevant to embryonic tissue)

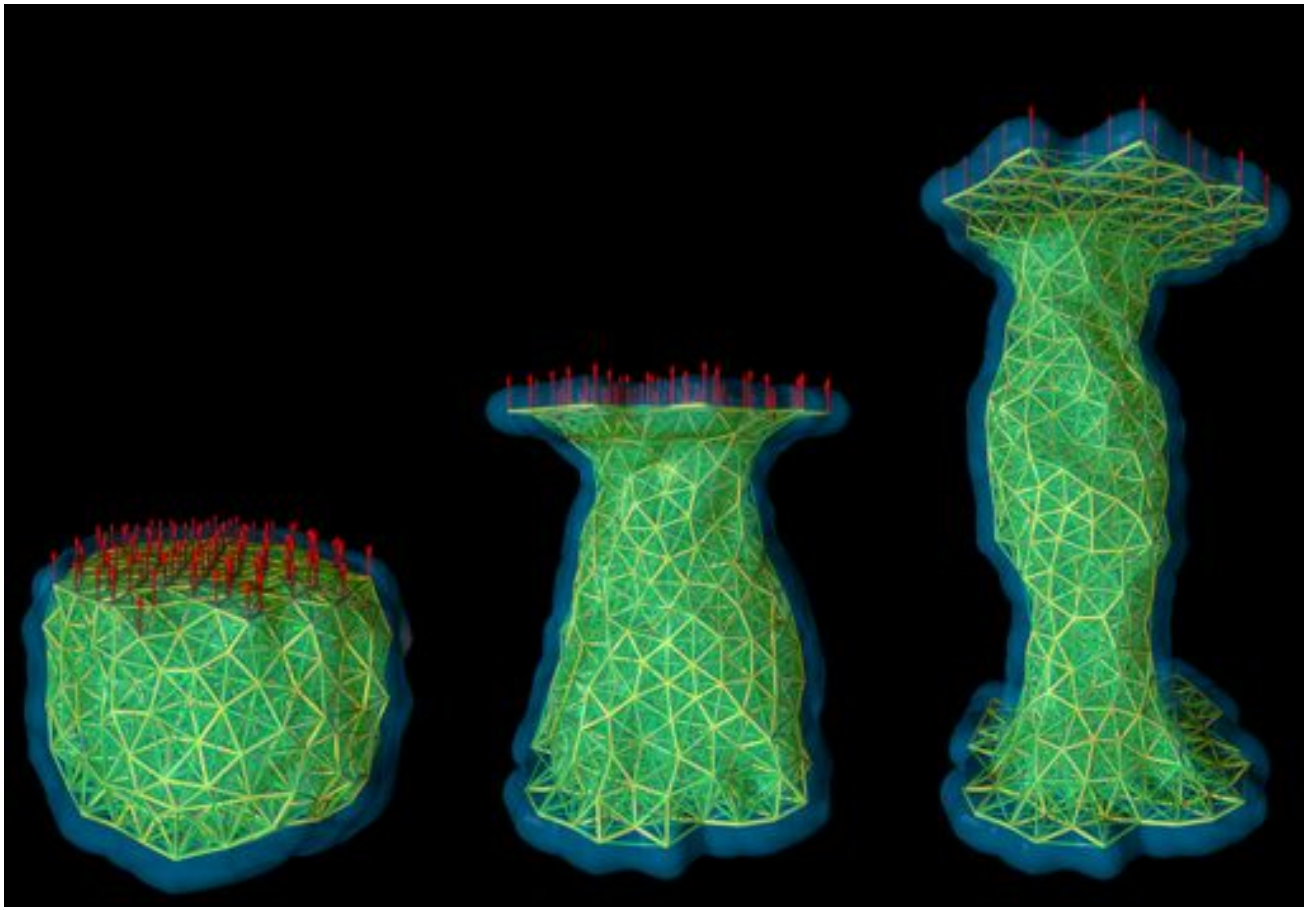
generation of pseudopodia for migration through connective tissue, or even epithelial-like tissue
(leading to interesting movement patterns)

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).

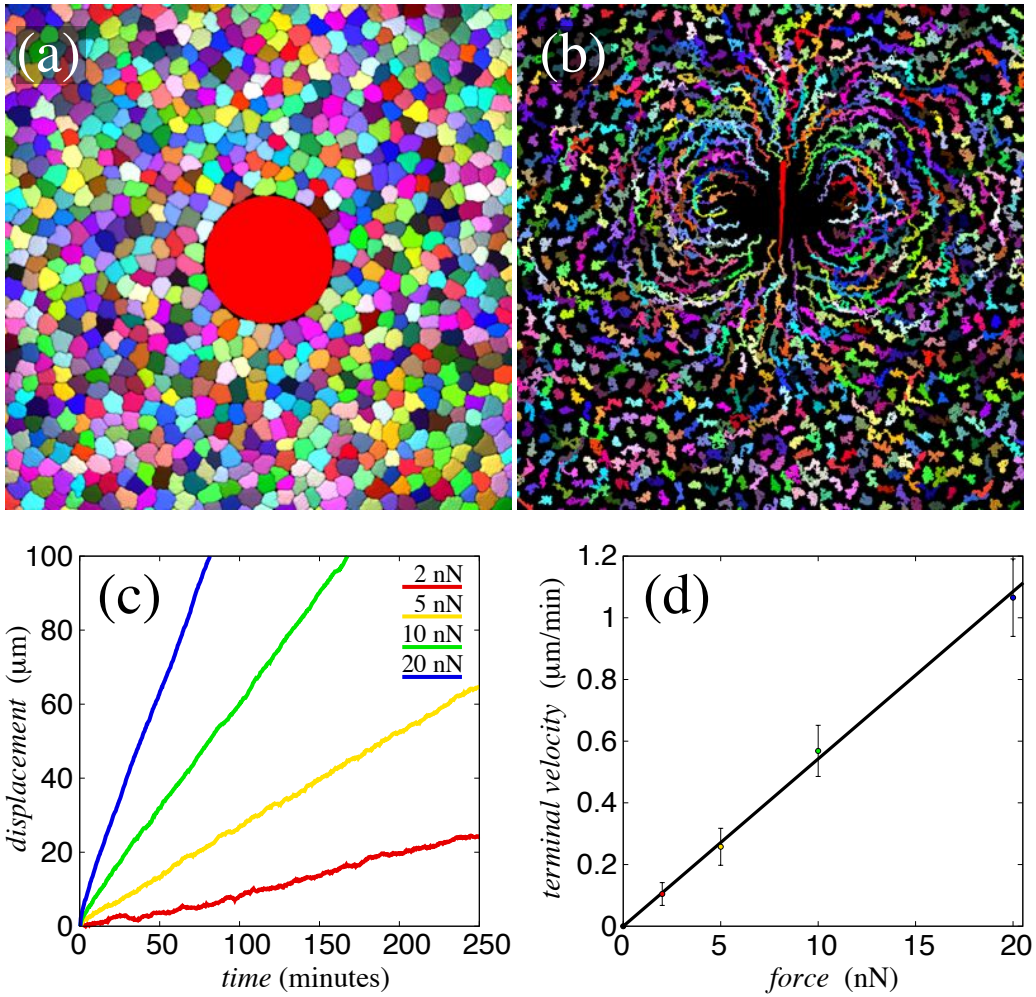
Slow cell stretching and cytoskeletal adaptation





"Tissue viscosity"

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



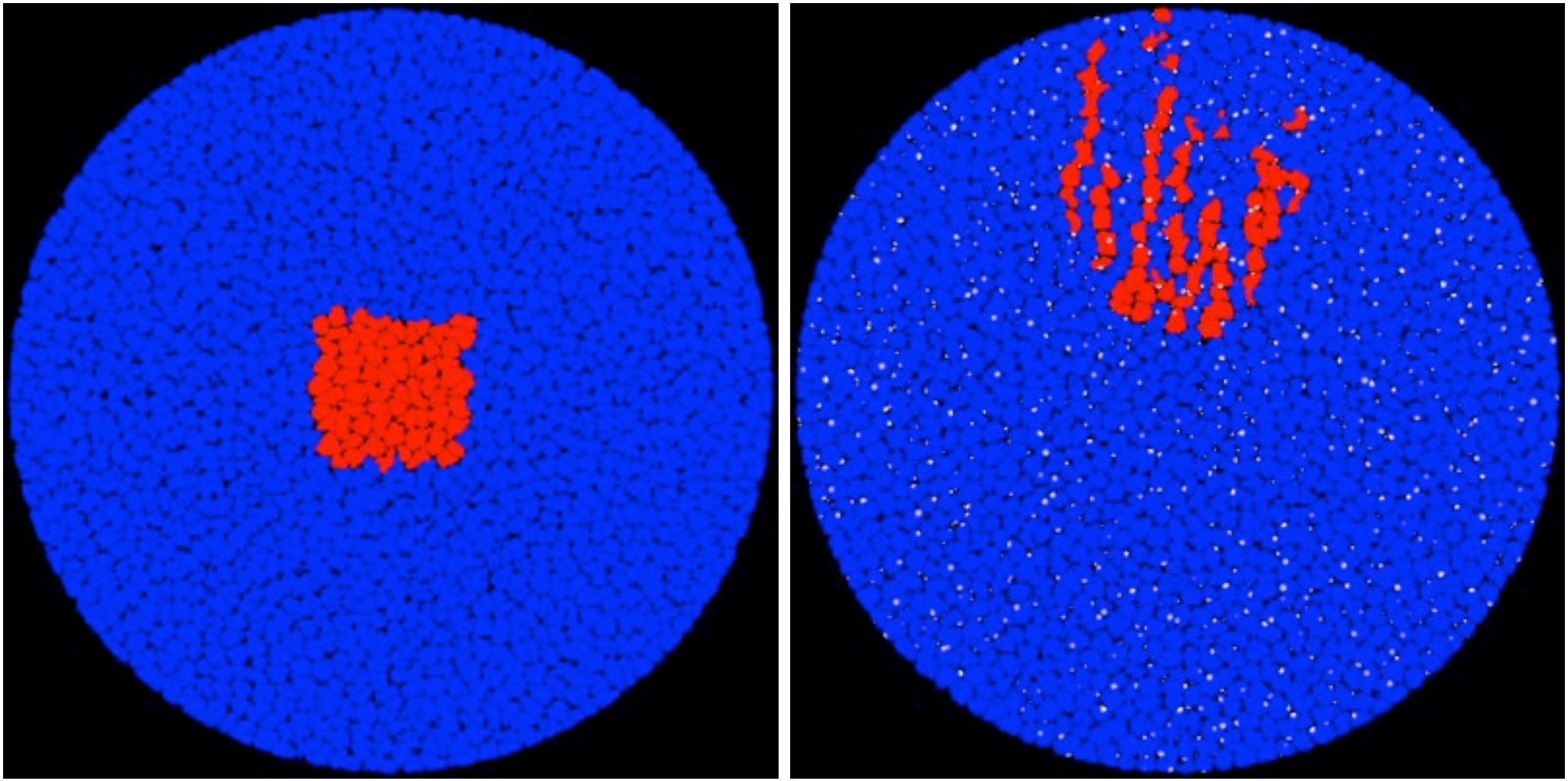
We find effective viscosity of order 10^4 Pa s which is in line with measurements on various embryonic systems

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

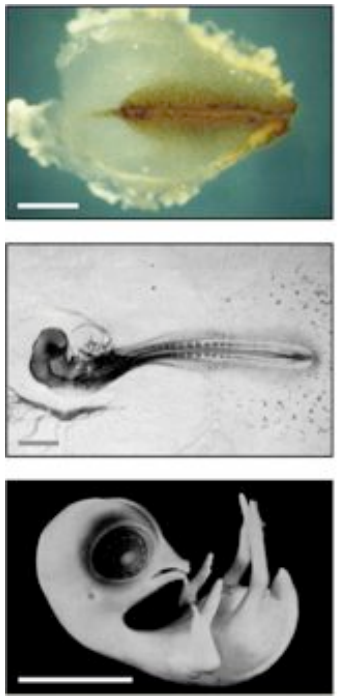
Micron-scale calibration producing millimetre scale prediction of material properties of tissue

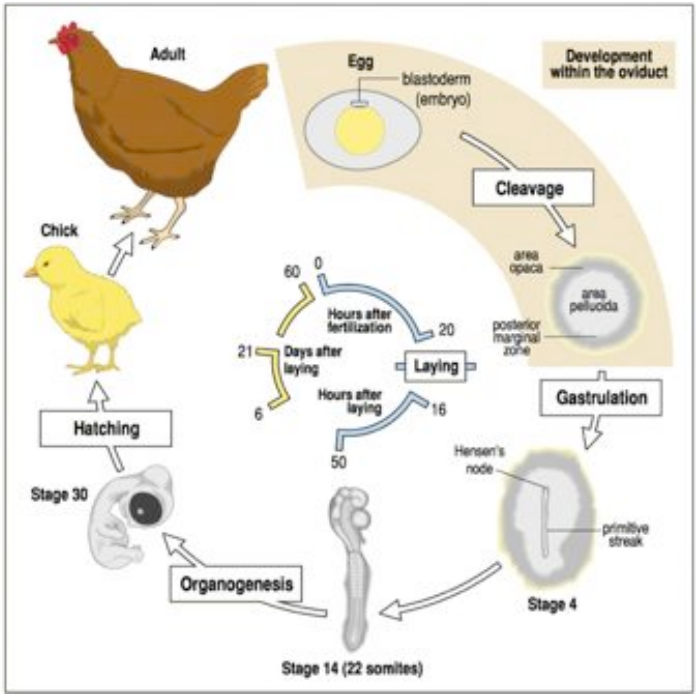
Emergent cell and tissue dynamics from subcellular modelling of active biomechanical processes
S A Sandersius, C J Weijer, T J Newman 2011 Physical Biology **8** 045007.

Streaming morphologies in tissue invasion

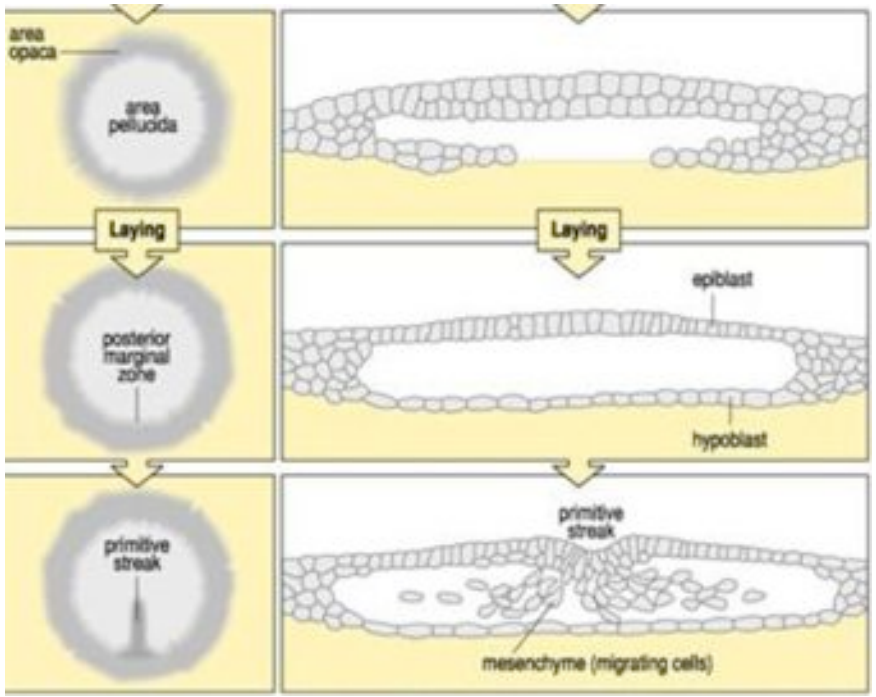


Primitive streak formation in the developing avian embryo

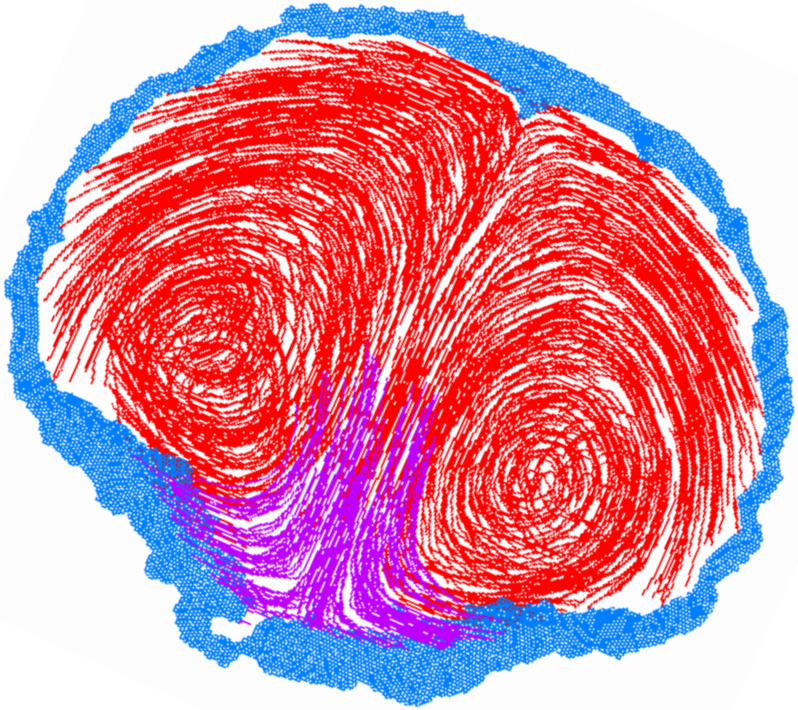


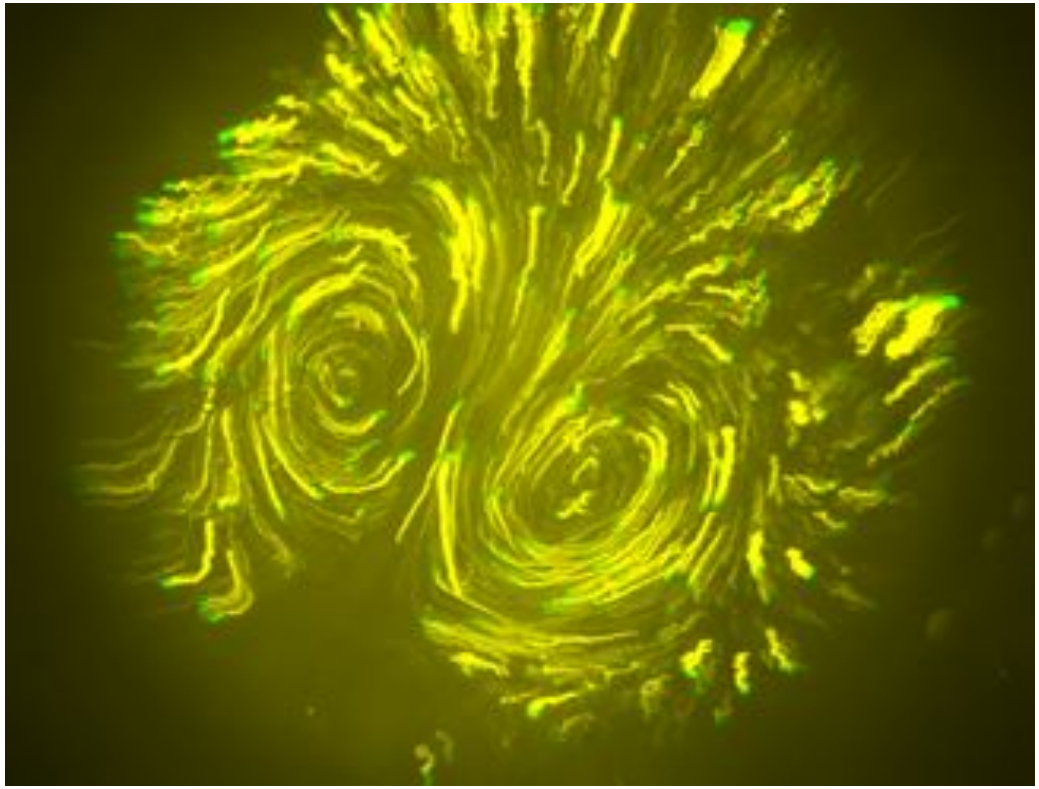


from Wolpert et al (OUP)



Movement patterns during streak formation
the enduring search for a mechanism





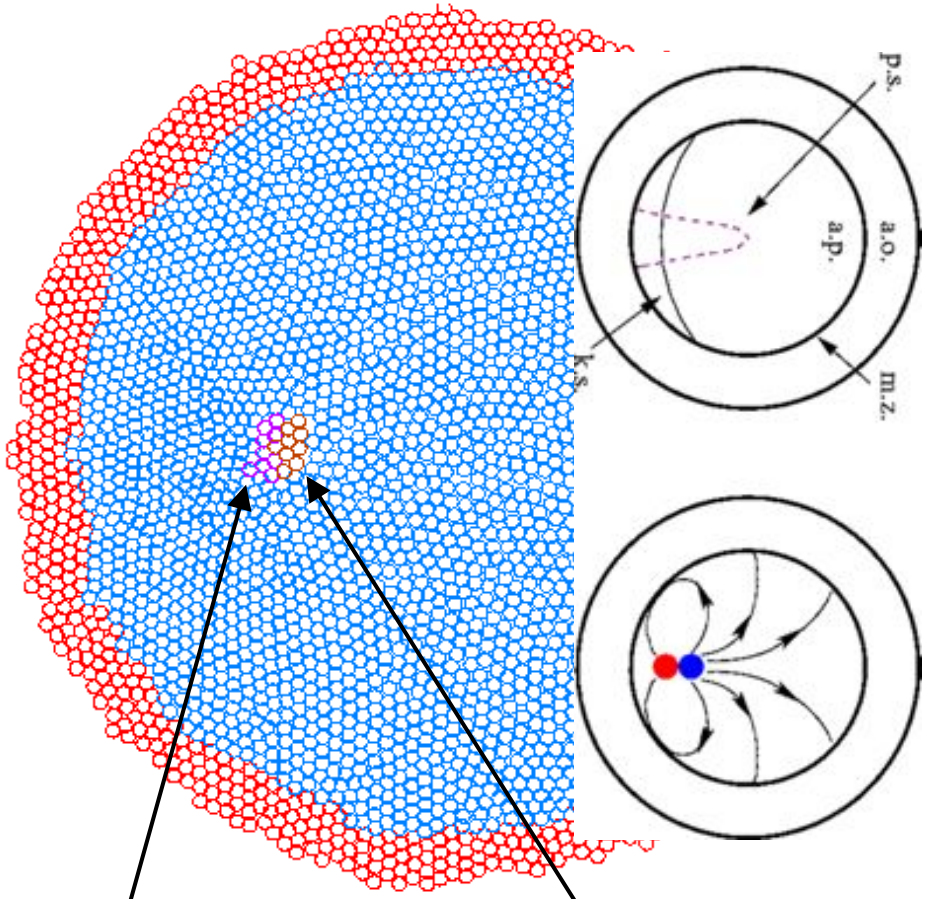
Chuai M, Zeng W, Yang X, Boychenko V, Glazier JA, Weijer CJ 2006 Developmental Biology **296** 137-149
Cell movement during primitive streak formation

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

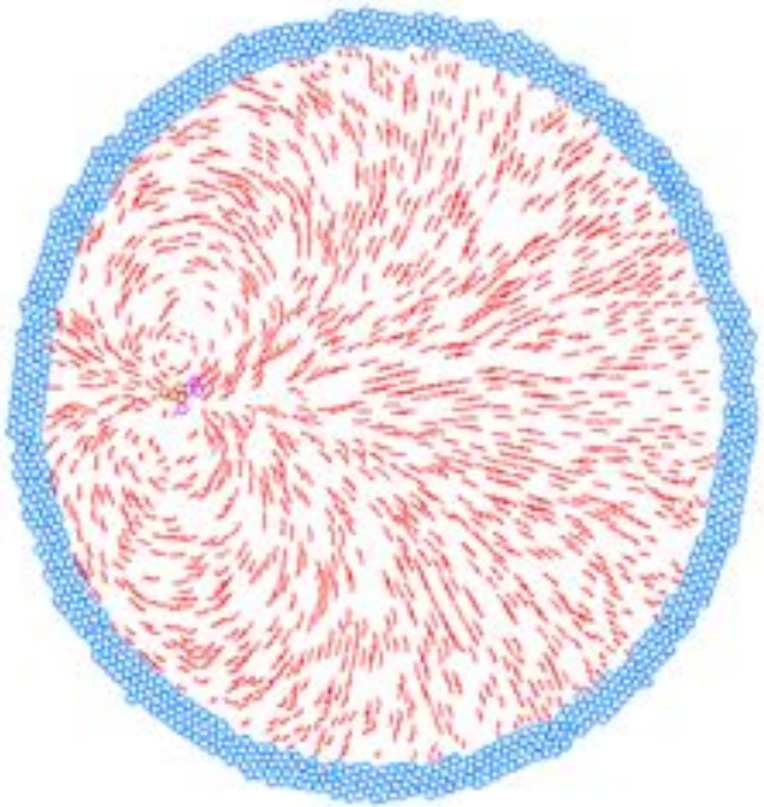
The chemotactic velocity $\mathbf{v} \sim \nabla\varphi$ is analogous to the electric field

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

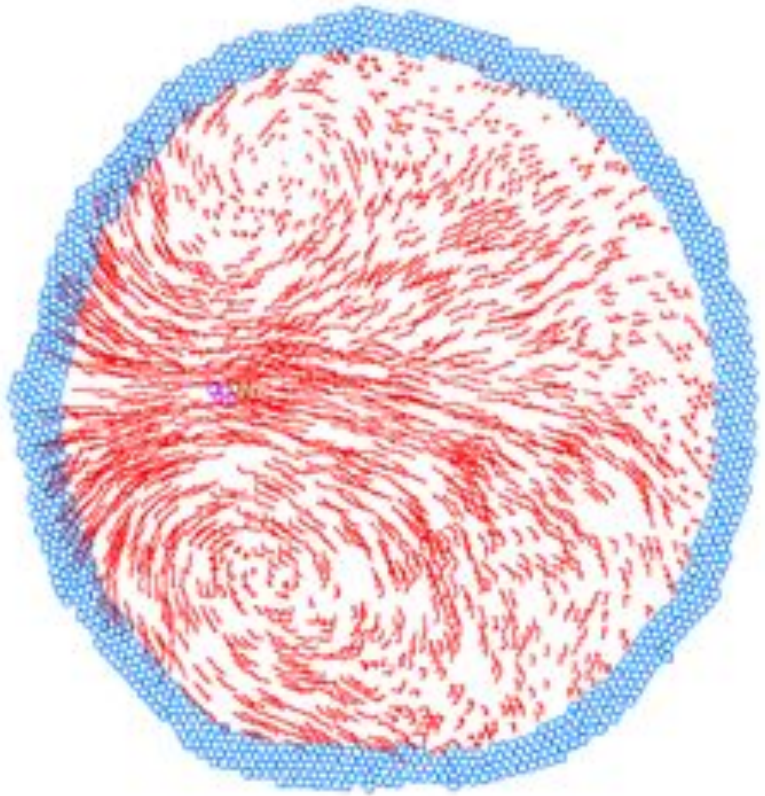
This analogy allows the simple construction of a "chemotactic dipole" which gives flow patterns similar to those observed in the chick embryo.

Movement patterns during avian gastrulation

primitive simulations using elastic spheres



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

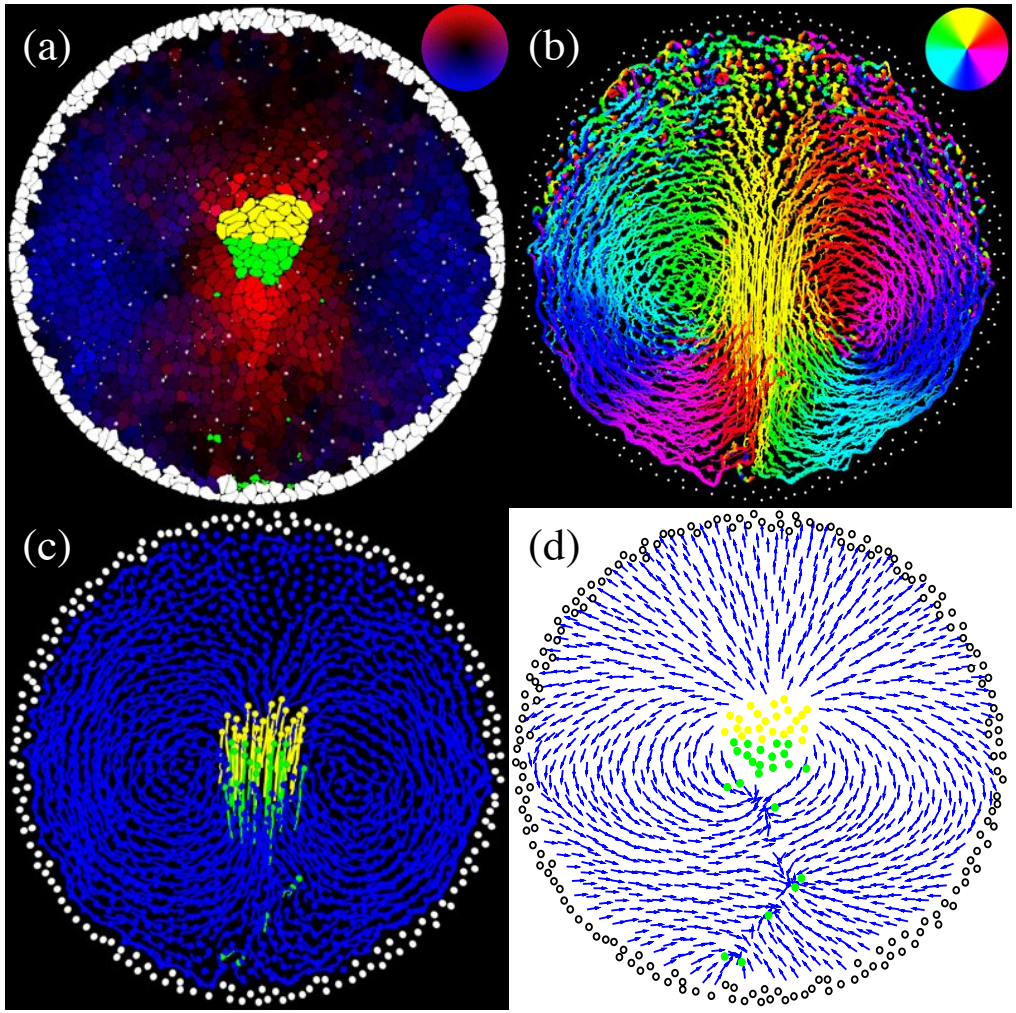
Simulations are performed on a scaled-down system of 1200 cells

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