Mechanical properties of cells and tissues

J.F. Joanny

Physico-Chimie Curie
Institut Curie

Boulder Summer school, July 2015

Outline

1. Cell Mechanics
   - Acto-myosin cytoskeleton
   - Dynamics of cytokinesis

Outline

1. Cell Mechanics
   - Acto-myosin cytoskeleton
   - Dynamics of cytokinesis
2. Mechanics and growth of tissues
   - Macroscopic theory of tissues
   - Fluidization by cell division and apoptosis

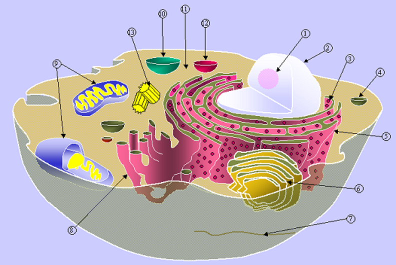
Outline

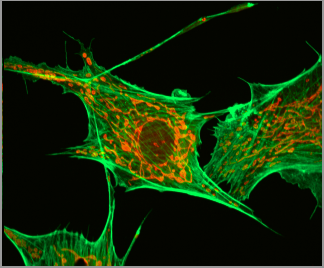
1. Cell Mechanics
   - Acto-myosin cytoskeleton
   - Dynamics of cytokinesis
2. Mechanics and growth of tissues
   - Macroscopic theory of tissues
   - Fluidization by cell division and apoptosis
3. Multicellular spheroids
   - Tissue surface tension
   - Spheroid growth

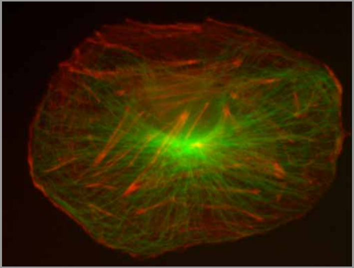
Outline

Outline

Organelles and Cytoskeleton





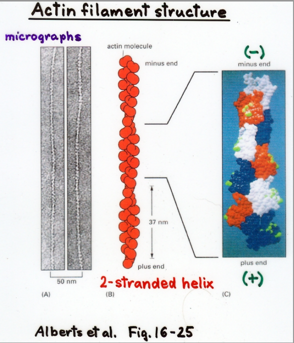


Actin polymerization

Actin monomers

- molecular weight 45kDa
- size $\delta = 5.5$nm
- ATP binding pocket
- polar monomer

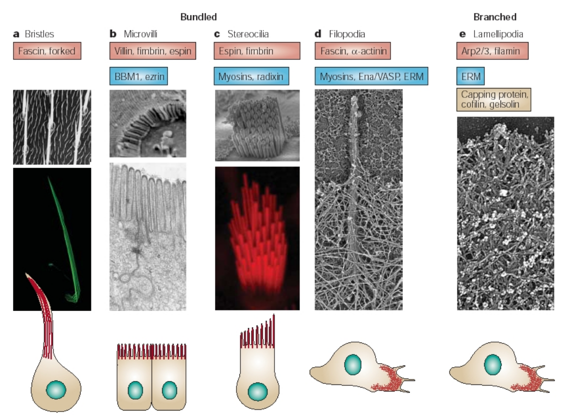
Actin polymers



- 2 protofilaments
- right-handed helix, 72nm pitch, 24 monomers per turn

Actin in vivo

Actin interacting proteins



Revenu et al.

Molecular motors

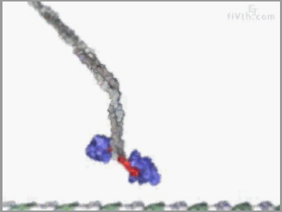
Motor proteins

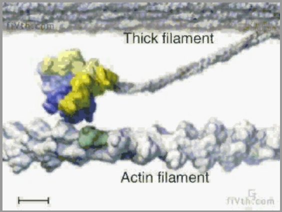
- Muscle contraction (myosin II)
- Cilia and axonemes (Dynein)
- Mitosis
- Intracellular transport
- Inner ear hair cells (Myosin 1c)
- Rotating motors

General properties

- Motors consume ATP
- Processive and non-processive motors

Motor structure

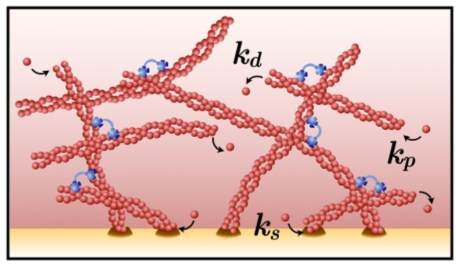




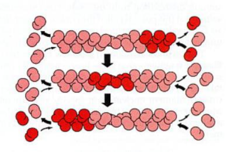
Vale

Cytoskeleton mechanics

Actomyosin gel



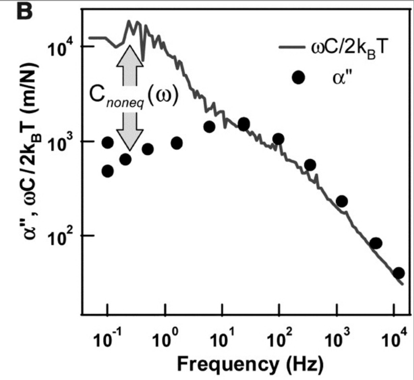
Treadmilling



Polar filament with + and − end

Violation of the fluctuation dissipation theorem

Fluctuations of acto-myosin networks

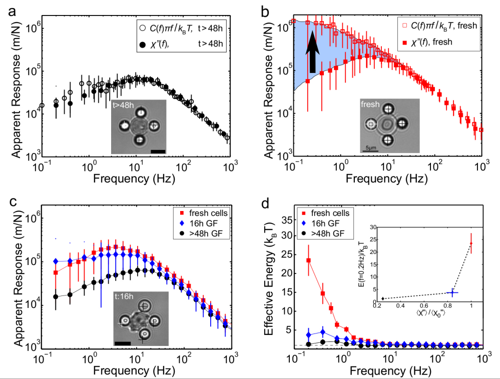


Mizuno et al.

- Microrheology experiment: active and passive
- Similar experiment with cells

Red blood cells

Fluctuations of red blood cells



Betz et al.

- Spectrin network needs to be prestressed
- Non-equilibrium reaction: binding and unbinding of spectrins to the membrane

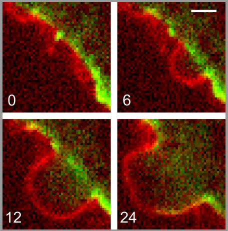
Active Systems

- Tissues
- Bacterial colonies Kessler, Goldstein
- Vibrated granular materials Menon et al.
- Active colloids, Active nematics Ramaswamy et al.
- Bird flocks, Fish shoals Vicsek, Toner, Chaté, Carere

- Marchetti et al, Rev.Mod.Phys. 2013

Cell Cortex

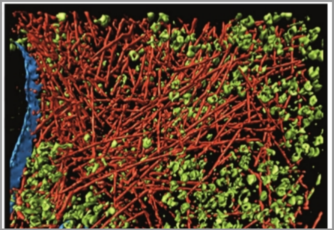
Optical Imaging



Charras

- Actomyosin layer
- Polymerization from the surface (formins)
- Treadmilling time $\sim$ 30s
- Cortex tension

Electron microscopy

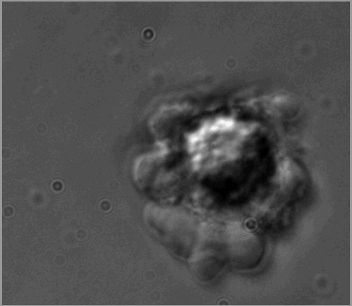


Medalia

- Dense actin layer
- Thickness $\sim 1\mu$m
- Filaments parallel to the cell surface

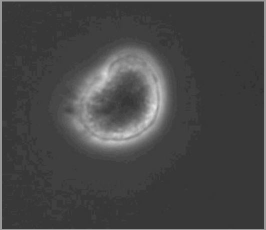
Cell instabilities associated to cortical layer

Blebs Paluch



- Detachments of the membrane form the cortical layer
- Bleb lifetime 30s

Cell oscillations Pullarkat



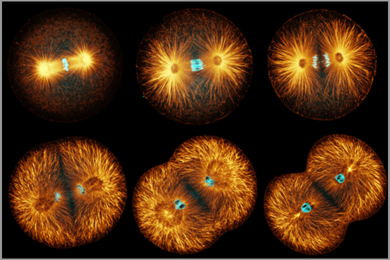
- Oscillations depend on actin contractility
- Oscillations depend on calcium (threshold density)

Outline

1. Cell Mechanics
   - Acto-myosin cytoskeleton
   - Dynamics of cytokinesis
2. Mechanics and growth of tissues
   - Macroscopic theory of tissues
   - Fluidization by cell division and apoptosis
3. Multicellular spheroids
   - Tissue surface tension
   - Spheroid growth

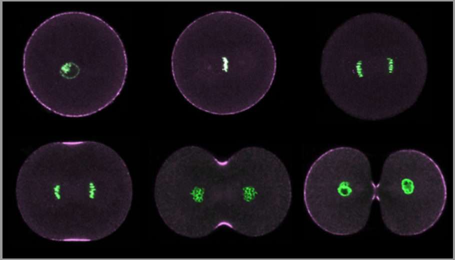
Final stages of cell division von Dassow

Final stage of cell division



- Separation between daughter cells
- See urchin

Myosin contractility

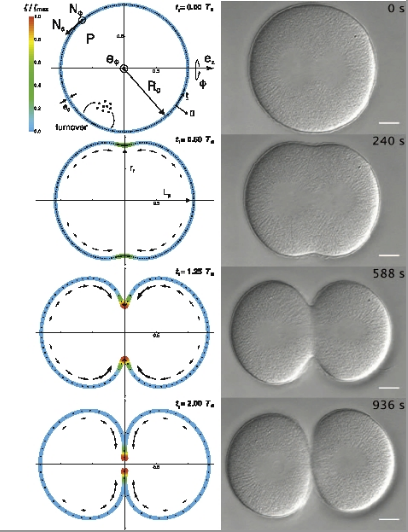


- Ring closure due to actin contractility
- Local enhancement of myosin activity due to astral microtubules

Active gel theory of Cytokinesis

- Cytokinesis driven by myosin contractility in the actin cortical layer
- Excess of contractility at the equator of the cell.
- Actin cortical layer described by active gel theory
  - Constant density in cortical layer
  - Ignore polarization effects
  - Viscoelastic actin layer
  - Active stress $\zeta\Delta\mu$ non homogeneous, increases at the equator
- Cortical flow due to active stress gradient
- Numerical solution of active gel equations, using Lagrangian coordinates
- Impose cylindrical symmetry of the cell

Dynamics of Cytokinesis

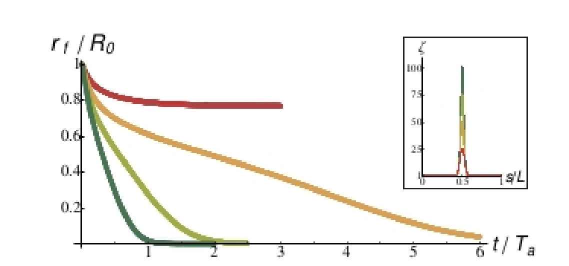


Cytokinesis completion

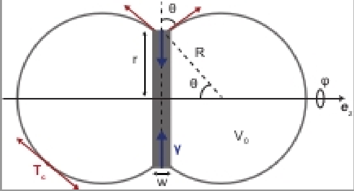
- Critical value of activity for cytokinesis completion
- Low activity of the ring: cytokinesis failure
- Large activity of the ring: cytokinesis success

Kinetics of ring closure

- Quasi-linear furrow constriction
- Rate of constriction increases with amplitude and width of input signal
- If $w \sim R_0 \frac{dR}{dt} \sim R_0$, Closure time $T_c \sim \eta/\zeta\Delta\mu$ independent of R_0
- Good agreement with experiments

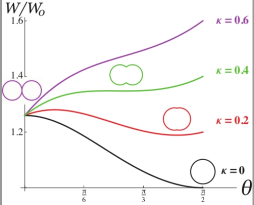


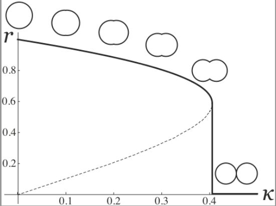
Qualitative interpretation



- Cell tension $T = \frac{e\zeta\Delta\mu}{2}$
- Line tension $\lambda = \int ds(T(s) - T_p) \sim w\delta T$
- Dimensionless number $\kappa \sim \lambda/(2T_pR_0)$

Discontinuous closure transition





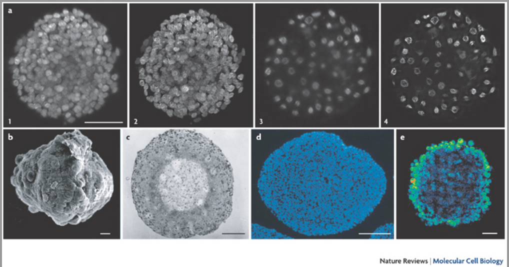
- Linear constriction if dissipation dominated by cortical flow

Outline

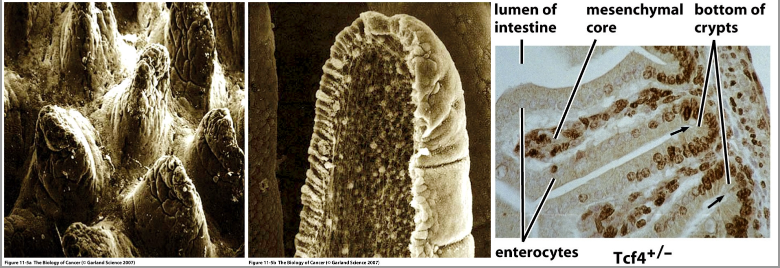
1. Cell Mechanics
   - Acto-myosin cytoskeleton
   - Dynamics of cytokinesis
2. Mechanics and growth of tissues
   - Macroscopic theory of tissues
   - Fluidization by cell division and apoptosis
3. Multicellular spheroids
   - Tissue surface tension
   - Spheroid growth

Outline

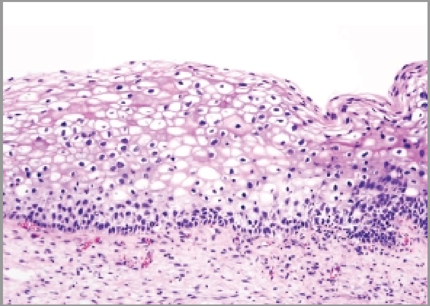
Multicellular spheroids



Intestinal epithelia



Epithelial tissues



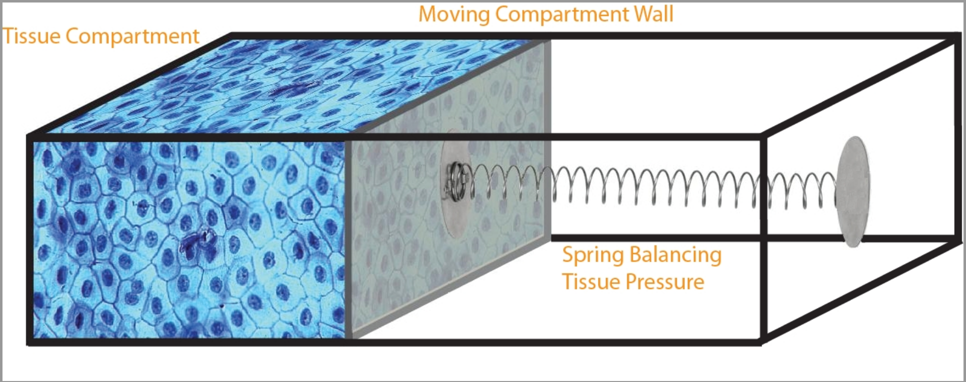
Epithelial structure

- Dividing cells
- Differentiated cells
- Apoptotic cells

Tissue mechanics

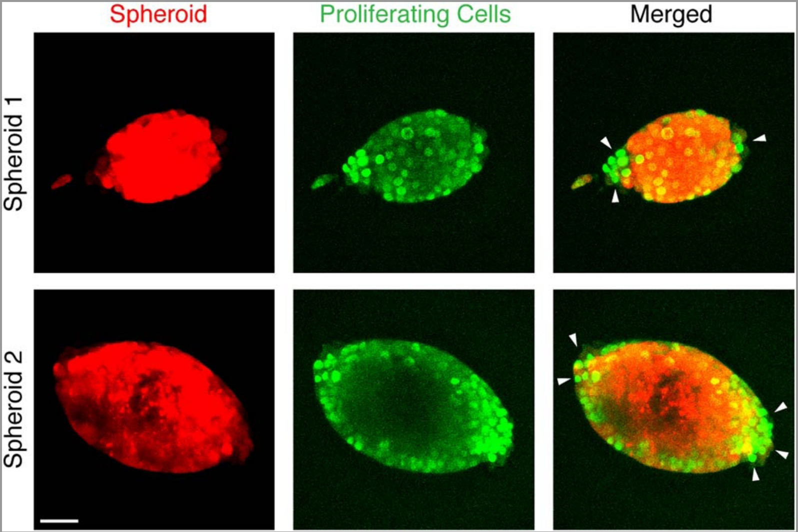
- Solid-like behavior
- Liquid-like behavior
- Viscoelastic liquid, relaxation time T
- Plastic behavior

Homeostatic pressure

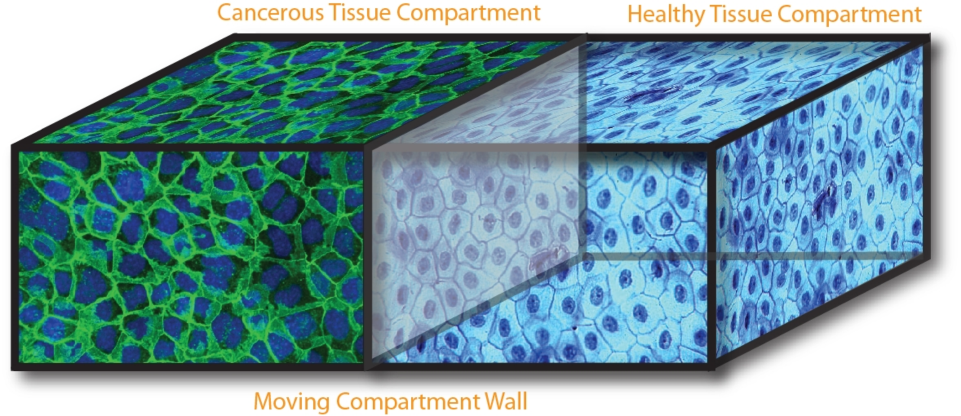


- Membrane permeable to interstitial fluid
- Steady State ($k_d = k_a$) defines homeostatic density
- Homeostatic pressure

Cell proliferation and stress Cheng et al.



Competition between two tissues



- Tissue with larger homeostatic pressure invades the other one
- Final state: homeostatic density
- Numerical simulation of tissue invasion

Outline

Stress relaxation in a tissue Ranft, Julicher

Force dipoles induced by division and apoptosis

- Dividing or apoptotic cells exert a force dipole $f_\alpha d_\beta$
- Force dipole density $Q_{\alpha\beta} = \sum d^i_{\alpha\beta}\delta(\mathbf{r} - \mathbf{r}_i)$
- Force balance $\partial_\beta \sigma^{el}_{\alpha\beta} + \sum f^i_\alpha \delta(\mathbf{r} - \mathbf{r}_i) = 0$
- Total stress $\sigma_{\alpha\beta} = \sigma^{el}_{\alpha\beta} - Q_{\alpha\beta}$ so that $\partial_\beta \sigma_{\alpha\beta} = 0$

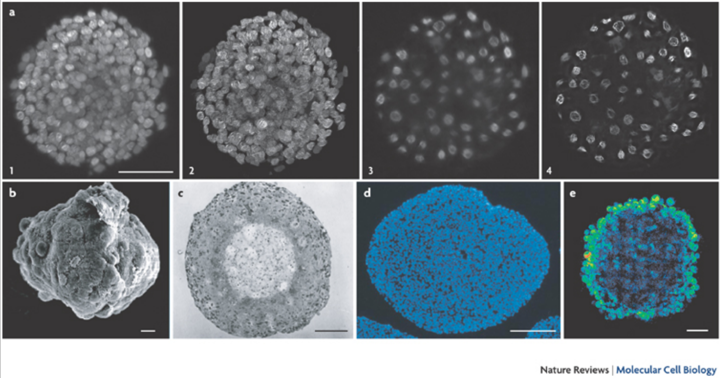
Internal stress in a tissue $\sigma^{in}_{\alpha\beta} = -Q_{\alpha\beta}$

- Change in internal stress due to division and apoptosis
- Cell division coupled to stress Fink, Cuvelier

$$
\begin{aligned}
\frac{d}{dt}\sigma^{\text{int}} &= -\rho p_d k_d - \rho p_a k_a \\
\frac{d}{dt}\tilde{\sigma}^{\text{int}}_{\alpha\beta} &= -\rho \tilde{p}_d k_d < n_\alpha n_\beta - \frac{1}{3}\delta_{\alpha\beta} >= -\frac{1}{\tau_a}\tilde{\sigma}_{\alpha\beta}
\end{aligned}
$$

Outline

Multicellular spheroids

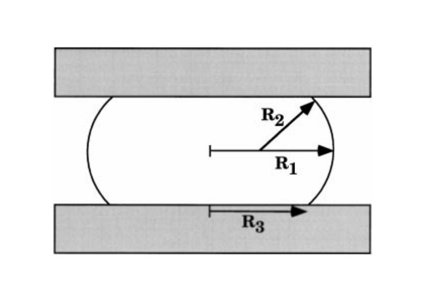


Tissue spheroids in micropipettes Guevorkian,Brochard

Outline

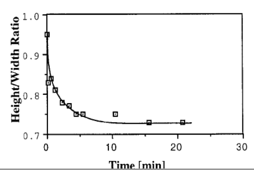
Surface tension of Tissues

Relaxation measurements
Steinberg et al., F. Montel



Relaxation measurements
Steinberg et al.

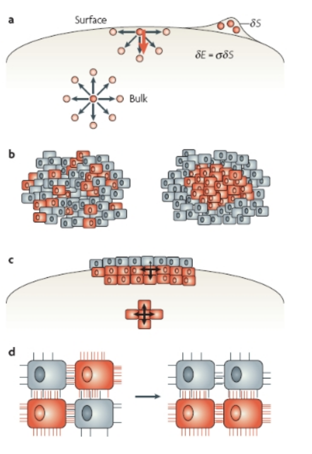
Neural Retina relaxation



Interfacial tension

Interfacial tension between tissues

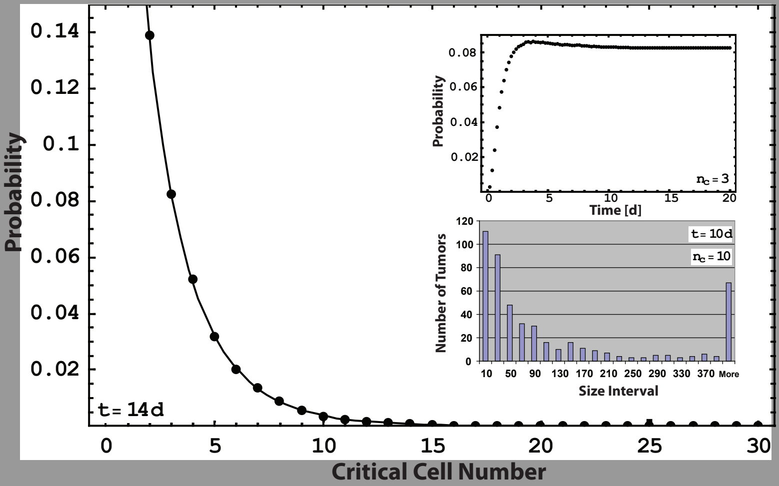
Steinberg



Adhesion between cells

- Interfacial tension depends on adhesion molecules Steinberg
- depends on actomyosin cytoskeleton and contractility
- Laplace law $P_h^c - P_h^h = \frac{2\gamma}{r}$

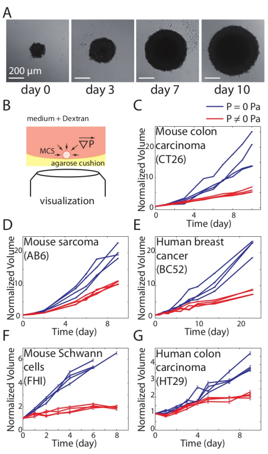
Metastatic Inefficiency



Outline

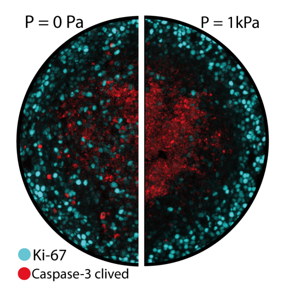
Spheroid growth F.Montel, M.Delarue

Growth experiments

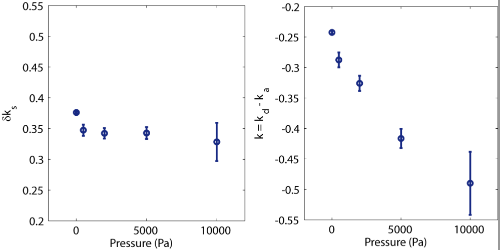


- Indirect experiments
  - Dialysis bag
  - Pressure exerted by dextran
- Direct experiments
  - Spheroid in contact with dextran solutions
  - No penetration of dextran in spheroid

Surface growth



Pressure dependence

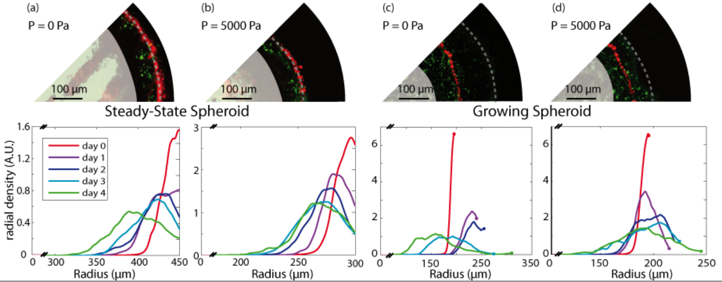


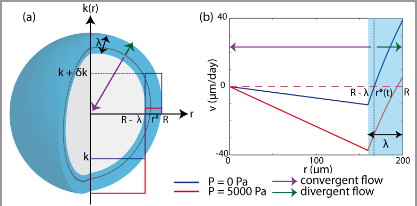
$$\partial_t V = (k_d - k_a)V + 4\pi\left(\frac{3}{4\pi}\right)^{2/3} \delta k_s \lambda V^{2/3}$$

- Nutrient effect
- Crowding effect
- Negative homeostatic pressure Elgeti

Cell flow

- Injection of fluorescent nano-particles

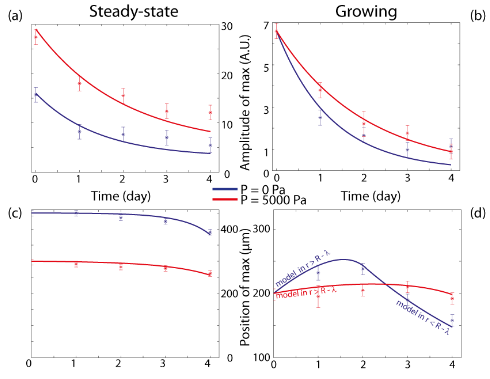




- Incompressible fluid
- Velocity field $\nabla \cdot \mathbf{v} = k(r)$

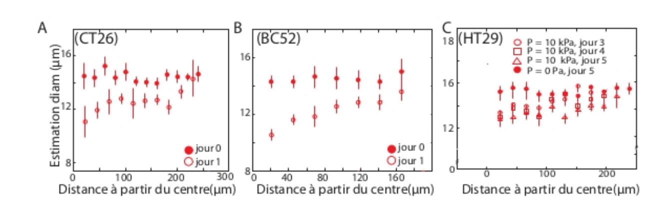
Particle distribution

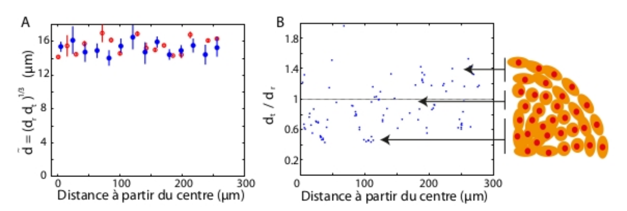
- Transport by cell flow $\partial_t \rho + \nabla \, v\rho = 0$
- Negligible diffusion



Volume change after a pressure step

- Growing spheroid with no applied pressure
- Pressure step 5000 Pa after 4 days
- Volume and anisotropy from correlations between nuclei position





Hydrodynamic calculation

Isotropic liquid Spheroid

- Constant pressure both in outer dividing layer and in inner layer
- Pressure jump, larger pressure in the outer layer
- Upon pressure jump, cell contraction in the outer layer

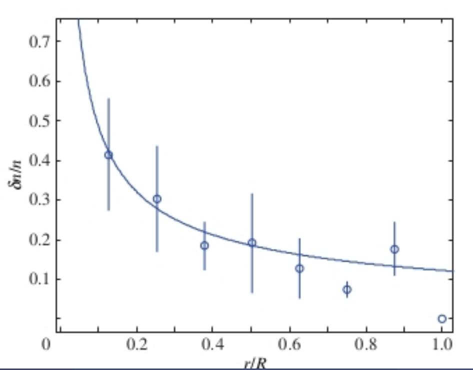
Cell orientation

- Viscoelastic spheroid. Elastic short time response
- Active stress because of cell orientation $\sigma^a_{\alpha\beta} = \zeta\Delta\mu p_\alpha p_\beta$
- Active stress depends on pressure

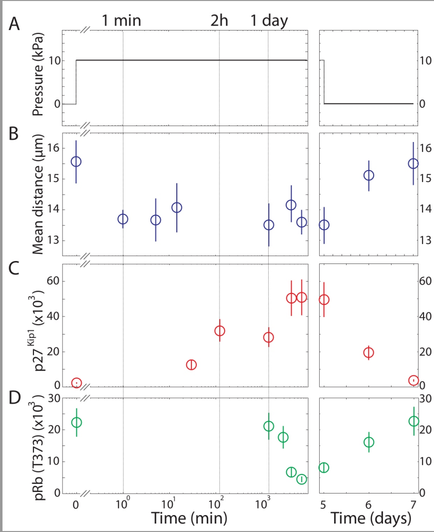
Active hydrodynamics of tissues

- Radially polarized cell cells
- Active gel hydrodynamics with active stress depending on pressure
- Power law decay of density $\frac{\delta n}{n} = \frac{\Delta P(3+\beta_e)}{3K}\left(\frac{r}{R_0}\right)^{\beta_e}$

$\beta_e = -0.6$



Volume decrease and cell division



- Decrease in cell division rate, no change in apoptosis
  - Decrease in cell diameter at center after 5 min.
  - P27 Overexpression after 1 day
  - Decrease in cell division after 4 days
  - Cell proliferation arrest in G1 phase

Curie Theory Group

Thomas Risler

Philippe Marcq

Morgan Delarue

Pierre Recho

Jonas Ranft

C. Erlenkamper

Edouard Hannezo

Hervé Turlier

Alexandre Mamane