Collective properties of myosin motors and actin filaments

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Outline

1. Molecular motors
   - Molecular motors in cells
   - Two-states models of molecular motors

Outline

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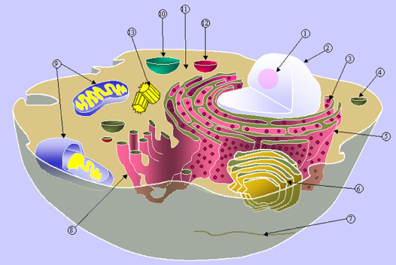
1. Molecular motors
   - Molecular motors in cells
   - Two-states models of molecular motors
2. Collective properties of molecular motors
   - Spontaneous oscillations of molecular motors
   - Soft Motor model
   - Bidirectional motion of motor assemblies
3. Active gel theory
   - Constitutive equations of active polar gels
   - Instabilities of active gels
   - Other types of active gels

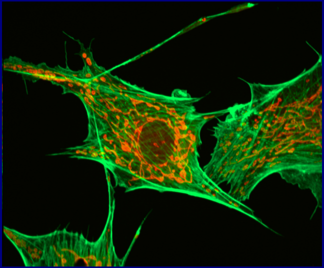
Outline

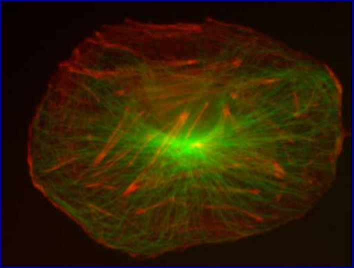
Outline

Outline

Organelles and Cytoskeleton







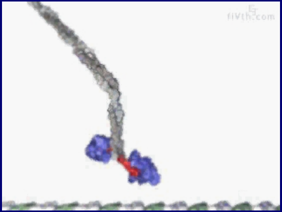
Molecular motor functions

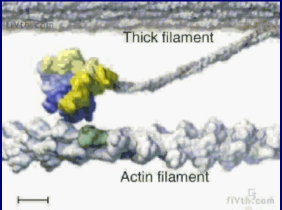
Motor proteins

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

- Polar filament
- ATP Consumption 25kT

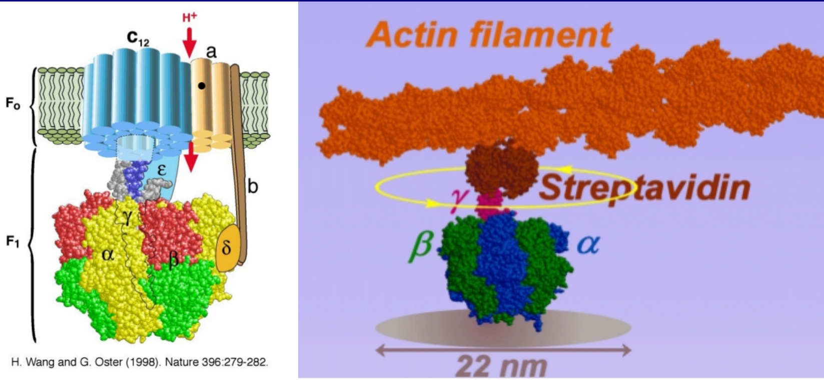
Motor structure





Vale

ATP synthase



- Kinosita
- Molecular machine regenerating ADP into ATP

Molecular motor functions

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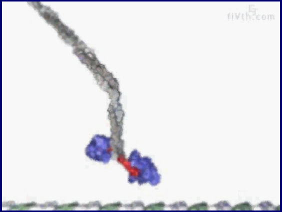
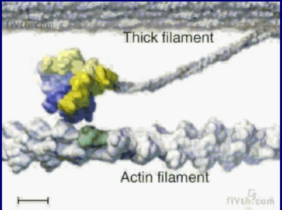
Motor structure

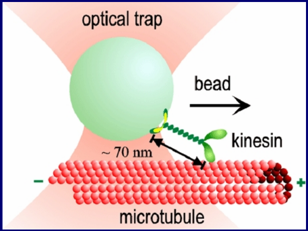




Vale

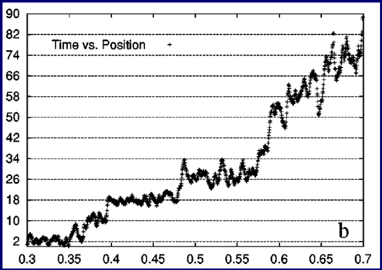
Single molecule experiments

Processive motors, Bead assays



- Motor unbinding
  Processivity length $\sim 1\mu m$
- Stall force $6pN$ Block
- Velocity $1\mu m/s$

Motor steps

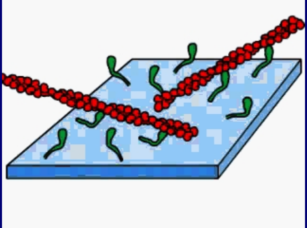


Cappello

- Steps at the period of microtubule
- Existence of backward steps
- Processivity 200 steps

Processivity and motility assays

Motility assay

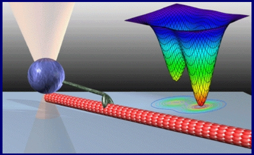


Processivity

- On and off rates $t_{on} = k_{off}^{-1}$, $t_{off} = k_{on}^{-1}$
- Duty ratio $r = \frac{t_{on}}{t_{on}+t_{off}} = \frac{k_{on}}{k_{on}+k_{off}}$
- Fraction of bound motors r, $1/r$ motors required on the filament
- Myosin are non-processive $r = 0.02$. Myosin filaments

Thermodynamics of molecular motors

Linear flux-force relation



- External forces on the motor
  - Mechanical force (optical trap) f
  - Chemical force $\Delta\mu = \mu_{ATP} - \mu_{ADP} - \mu_{Pi}$
- Flux-force relation

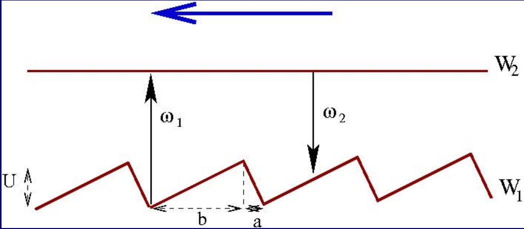
$$
\begin{aligned}
v &= \lambda_{11} f + \lambda_{12}\Delta\mu \\
r &= \lambda_{21} f + \lambda_{22}\Delta\mu
\end{aligned}
$$

- Works as a motor if $f < 0, \Delta\mu > 0$
- Onsager symmetry relations $\lambda_{21} = \lambda_{12}$
- Stall force $f_s = -\lambda_{12}\Delta\mu/\lambda_{11}$
- Yield $\eta = -fv/r\Delta\mu$, does not satisfy Carnot's law

Outline

Thermal ratchet motion

Periodic potential



Qualitative study

- Efficient motor $a \sim (2D/\omega_2)^{1/2}$
- Gliding velocity $v_g = \frac{1}{\zeta}(\frac{U}{b} - f)$
- Average velocity $v = p\frac{a+b}{\omega_2^{-1}+b/v_g}$
- Stall force $U = fb$ or $p \sim 0$

Fokker Planck equation

Probability conservation

$$\frac{\partial P_1}{\partial t} + \frac{\partial j_1}{\partial x} = -\omega_1(x)P_1 + \omega_2 P_2$$
$$\frac{\partial P_2}{\partial t} + \frac{\partial j_2}{\partial x} = -\omega_2 P_2 + \omega_1(x)P_1$$

Probability fluxes $j_i = -D\left(\frac{\partial P_i}{\partial x} + \frac{P_i}{kT}\frac{\partial W_i}{\partial x} - \frac{P_i}{kT}f\right)$

- No motion at thermal equilibrium
- Non-equilibrium transitions due to ATP consumption
- Advancing velocity
  $v = \left(\int_0^\ell (P_1 + P_2)dx\right)^{-1} \int_0^\ell (j_1 + j_2)dx$

Outline

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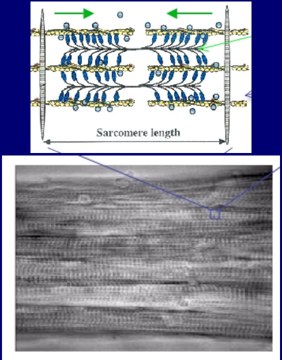
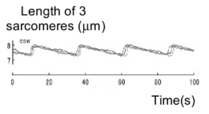
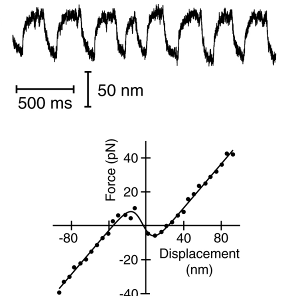
Oscillations of molecular motors

Heart muscle fiber oscillations Sasaki



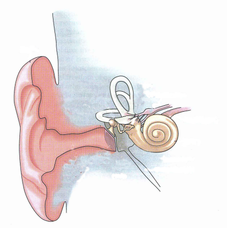


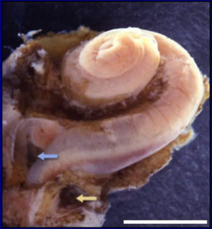
Hair cell oscillations Martin



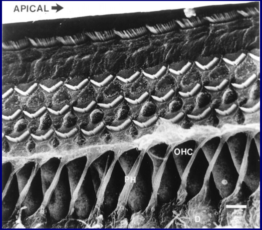
Cochlea

Inner ear and Cochlea



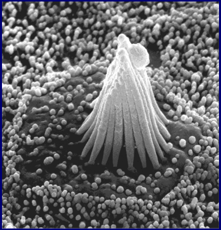


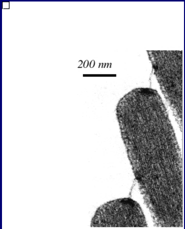
Organ of Corti and hair cells



Hair cells

Stereocilia and tiplinks



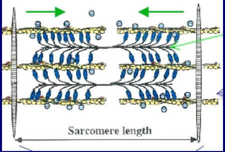


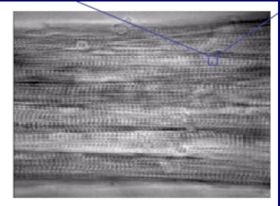
Ciliated cells of the inner ear

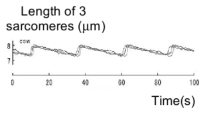
- Bundle of actin cilia
  - Graded sizes in a bundle
  - Connections via tip-links Hudspeth, Martin
  - Bundles of varying sizes
- Shape and size regulation

Oscillations of molecular motors

Heart muscle fiber oscillations Sasaki







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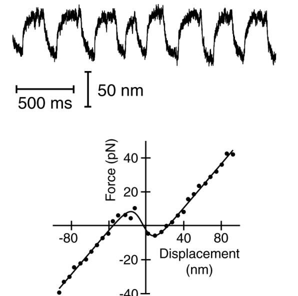
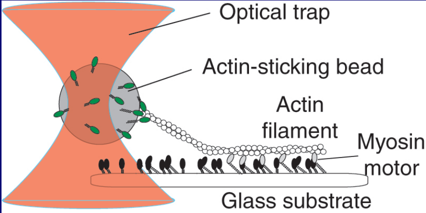


Biomimetic system

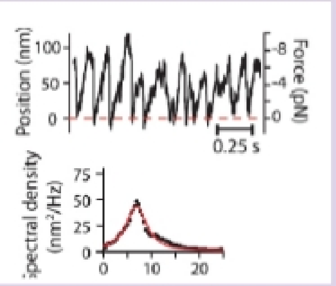
Motility Assay



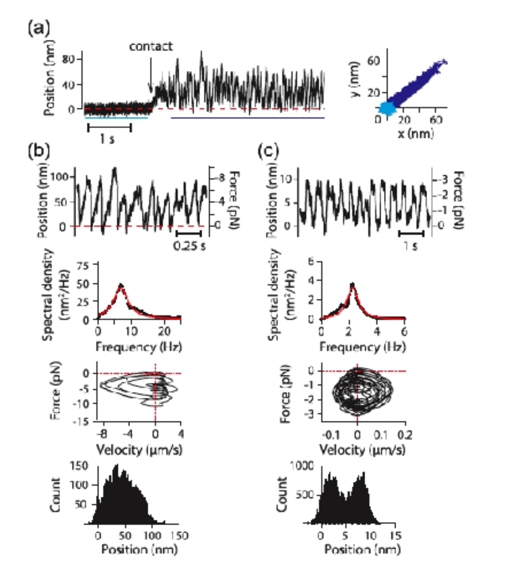
Plaçais et al.

Oscillations

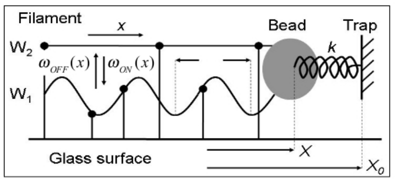
Fixed optical trap



Spontaneous oscillations



Two-state model of rigidly bound motors
Julicher and Prost



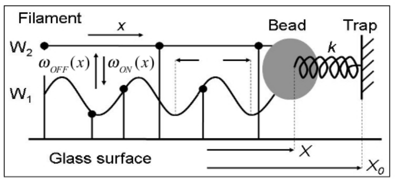
- Trap position X_0 bead position X
- Fokker Planck Equation (no thermal noise)

$$\frac{\partial P_1}{\partial t} - \frac{dX}{dt}\frac{\partial P_1}{\partial x} = -\omega_{off}(x)P_1 + \omega_{on}(x)P_2$$

$$\frac{\partial P_2}{\partial t} - \frac{dX}{dt}\frac{\partial P_2}{\partial x} = -\omega_{on}P_2 + \omega_{off}P_1$$

- Random distribution of motors $P_1 + P_2 = 1/\ell$

Rigid two-state model



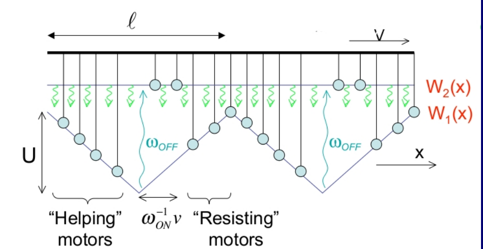
Force Balance

$$\xi \frac{dX}{dt} = -k(X - X_0) + N \int_0^\ell dx \left(P_1 \frac{\partial W_1}{\partial x} + P_2 \frac{\partial W_2}{\partial x}\right) + J(t)$$

- Friction force
- Optical trap elastic force
- Motor force
- White noise

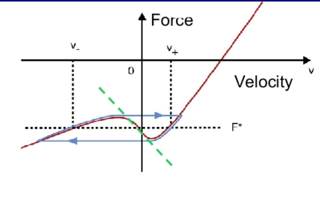
Active friction

Negative friction



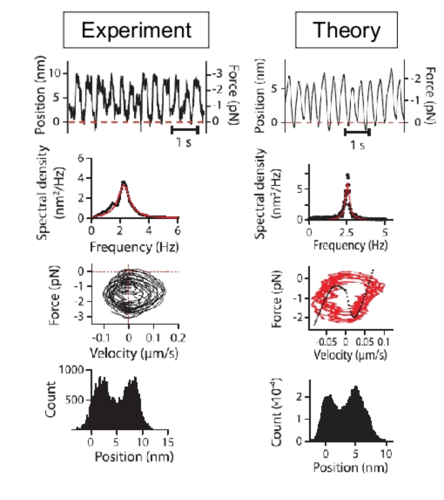
- Motion at constant velocity v
- Motor force $F = N\frac{U}{\ell}\frac{v}{\omega_{on}\ell} \sim -\xi_{ac} v$

Force-velocity relation



- Negative slope at stall force ($v = 0$) if $-\xi_{ac} > \xi$
- Oscillations

Spontaneous oscillations

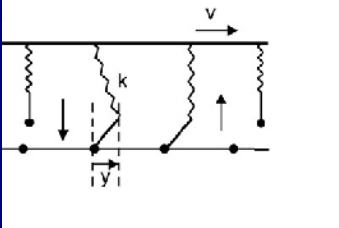


Oscillations

- Oscillations if $-\xi_{ac} - \xi \geq k/\omega_{on}$
- Oscillation pulsation at threshold $\Omega = (\omega_{on} k/\xi]^{1/2}$
- Bimodal symmetric oscillations if
  - Weak Noise
  - Close to threshold
- Relaxation oscillations

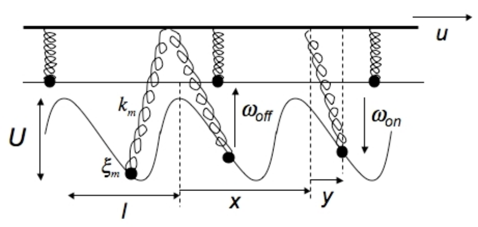
Outline

Crossbridge models Huxley, Duke, Vilfan



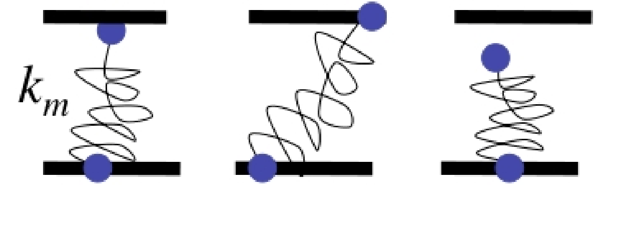
- No specific adsorption site
- Powerstroke just after attachment
- Load dependent detachment rate
- Oscillations

Soft motor model



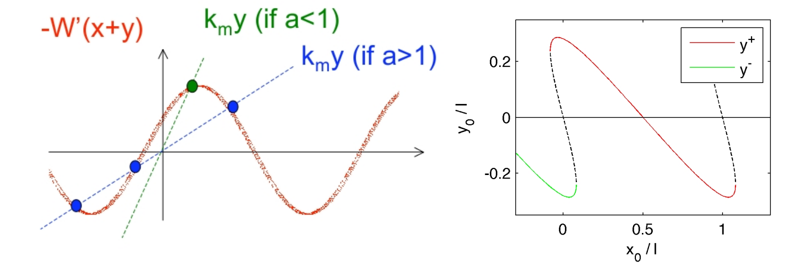
- Elongation of a motor at time t at position x attached for a time τ, $y(x,\tau,t)$
- Force balance
  $\zeta_m\left(\partial_t y + \partial_\tau y + u(t)(\partial_x y + 1)\right) = -k_m y - W'(x+y)$
- Probability $p(x,\tau,t)$, $n_d(x,t) + \int_0^\infty d\tau\; p(x,\tau,t) = 1/\ell$
- Probability conservation
  $\partial_t p + \partial_\tau p + u(t)\partial_x p = -\omega_{off}(x+y,y)p + \omega_{on}(x)\delta(\tau)n_d$
- Motor force $F_m = N\, k_m \int_0^\infty d\tau \int_0^\ell dx\; y(x,\tau,t)\; p(x,\tau,t)$

Protein friction Sekimoto



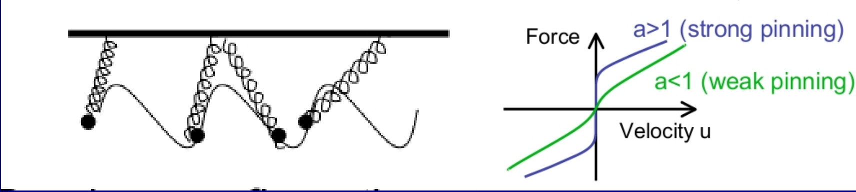
- Dissipation of spring elastic energy upon detachment
- Protein friction $\xi_p = N_{bound} k_m / \omega_{off}$
- Number of bond motors $N_{bound} = N\omega_{on}/(\omega_{on} + \omega_{off})$
- Much larger than hydrodynamic friction
- Dominant effect if $\epsilon = \zeta_m / t_m k_m \gg 1$, motor time $t_m \sim \omega^{-1}$
- No dynamic instability if $\epsilon \gg 1$

Equilibrium positions of motors in the potential



- Equilibrium positions $0 = -k_m y - W'(x+y)$
- Pinning parameter $a = |\min(W''(x)/k_m)| \sim U/(k_m \ell^2)$
- $a < 1$ one equilibrium position
- $a > 1$ two equilibrium positions

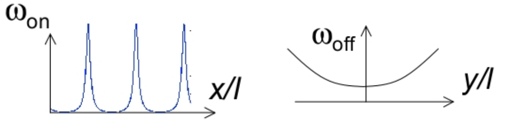
Tomlinson model of solid friction



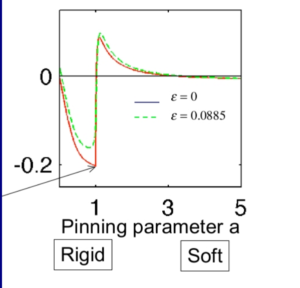
- Continuous force-velocity relation of $a < 1$
- Discontinuity at $u = 0$ if $a > 1$ associated to jumps between equilibrium positions
- Solid friction
- No solid friction for the two state model

Adiabatic approximation

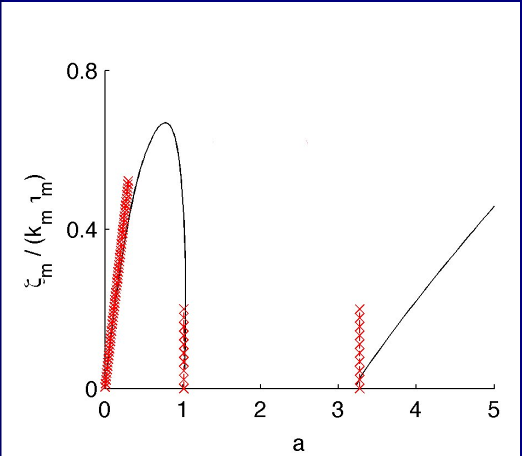
- Limit of low friction $\epsilon \ll 0$
- Steady state for the elongation y
- Effective friction coefficient $\xi_{eff} = -\frac{\partial F_m}{\partial u}(u = 0)$



- Effective friction coefficient



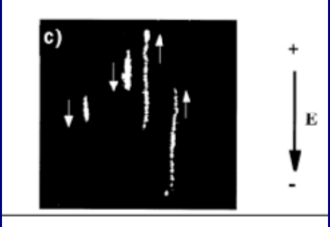
Stability diagram



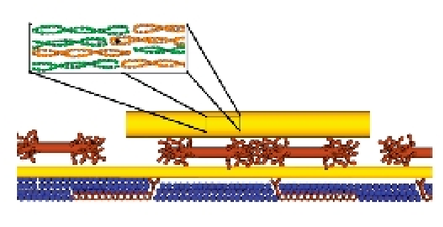
- Two instability regions
- Rigid motors
- Soft motors: similar to powerstroke model Vilfan, Duke
- Load dependent detachment rate
- Myosins are soft motors

Outline

Bidirectional motion

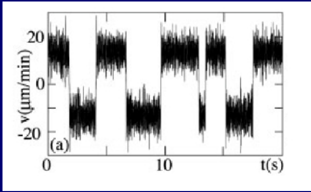


Riveline et al



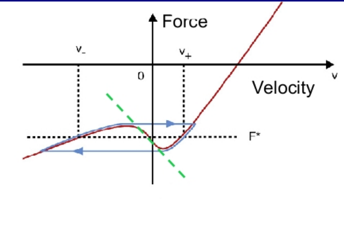
Gilboa et al

Numerical simulations
Badoual et al.



- Symmetric filament
- Reversal time proportional to $\exp(N/N_0)$

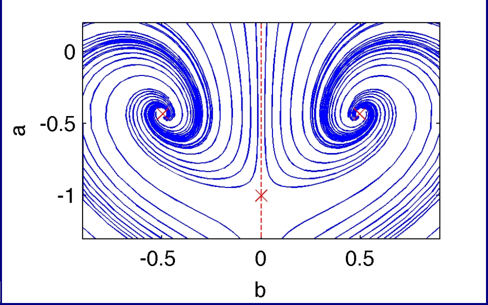
Rigid two-state model



- Symmetry breaking: two possible velocities for $N \to \infty$
- Motion reversal for N finite due to noise
- rates $\omega_{on} + \omega_{off} = \omega$, $\omega_{on} = \omega(\eta - \alpha \cos \frac{2\pi x}{\ell})$
- η= average fraction of bound motors
- Potential $W(x) = \frac{U}{2}(1 - \cos \frac{2\pi x}{\ell})$
- Dynamical phase transition if $\gamma = \frac{\alpha U}{\xi \omega \ell^2} = 1$

First passage time calculation

- Density of attached motors
  $\rho(x) = \eta/\ell + a\cos\frac{2\pi x}{\ell} + b\sin\frac{2\pi x}{\ell}$
- Other Fourier components have negligible contribution
- Fokker Planck Equation $\frac{\partial P}{\partial t} = -\nabla\cdot(\vec{u}P) + \frac{D}{2N}\nabla^2 P$
- Velocity field $u_a = -(a + 1 - \gamma b^2)$, $u_b = -(b + \gamma ab)$
- Diffusion constant $D = 4\eta(1-\eta)/\alpha^2$
- Flow field

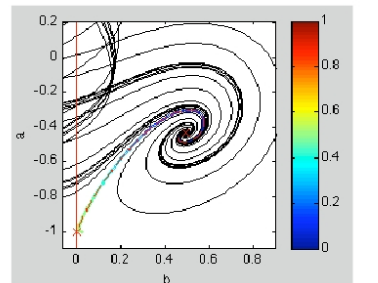


Mechanical analogy Maier and Stein

- No well defined potential (Kramers)
- WKB Approximation

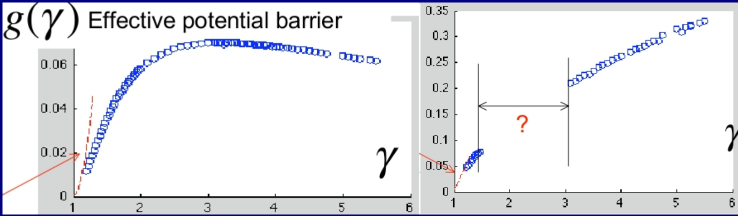
$$P(a,b,t) = \exp - NS(a,b,t) \quad 0 = \vec{u} \cdot \nabla S + \frac{D}{2} \nabla S^2$$

- S can be considered as an action with the Hamiltonian $H = \vec{u} \cdot \vec{p} + \frac{D}{2} \vec{p}^2$
- Most likely paths are classical trajectories of the Hamiltonian minimizing S



Reversal time calculation

- Reversal time calculated as the first passage time between the two fixed points
- $t_{rev} = \frac{1}{\omega h(\gamma)} \exp \frac{N\alpha^2}{4\eta(1-\eta)} g(\gamma)$



- Bidirectional motions $t_{rev} \sim \exp \frac{N}{N_0} \gg \omega$, $N > N_0 \sim 60$

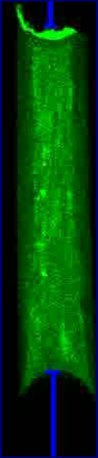
Outline

1. Molecular motors
   - Molecular motors in cells
   - Two-states models of molecular motors
2. Collective properties of molecular motors
   - Spontaneous oscillations of molecular motors
   - Soft Motor model
   - Bidirectional motion of motor assemblies
3. Active gel theory
   - Constitutive equations of active polar gels
   - Instabilities of active gels
   - Other types of active gels
4. Cortical actin and dynamics of Cytokinesis
   - Acto-Myosin Cortex
   - Dynamics of cytokinesis

Outline

In vitro active gels, G.Koenderink

Actin Myosin gel



Build-up of contractile stress

- Actin-myosin gel in a 400μm diameter capillary
- Accelerated 180 times
- ATP introduced at time $t = 0$. Tensile stress increases with time

Actin gel properties

Actin polarization

- Polarization vector
  - Local unitary vector $\mathbf{n}$ Unitary vector $\mathbf{p} = < \mathbf{n} >$
  - Nematic or polar ordering
- Conjugate field
  - Free energy change $d\mathcal{F} = -\mathbf{h} d\mathbf{p}$
  - Torque aligning the director $h_\perp = K\nabla^2\phi$
  - Longitudinal field

Maxwell viscoelasticity

- Elastic at short time, viscous at long time
- Single relaxation time τ $\eta = E\tau$
- Constitutive equation

$$\tau \frac{\partial \sigma_{\alpha\beta}}{\partial t} + \sigma_{\alpha\beta} = 2\eta v_{\alpha\beta}$$

- Elastic and viscous stress

Hydrodynamic Theory

- One component effective gel, incompressible

Hydrodynamic Theory

- One component effective gel, incompressible
- Linear relations between fluxes and forces

Hydrodynamic Theory

- One component effective gel, incompressible
- Linear relations between fluxes and forces
- Description based only on symmetries
  - Polar symmetry: vector **p**, tensor $q_{\alpha\beta} = p_\alpha p_\beta - \frac{1}{3}p^2\delta_{\alpha\beta}$
  - Time reversal symmetry
    reactive and dissipative components
  - Active effects (motors) described in terms of ATP consumption $\Delta\mu = \mu_{ATP} - \mu_{ADP} - \mu_P$

Dissipative and reactive fluxes for polar active liquids

Dissipative fluxes

Onsager relations: crossed terms are equal

$$\begin{aligned}
\sigma^d_{\alpha\beta} &= 2\eta v_{\alpha\beta} \\
P^d_\alpha &= \frac{h_\alpha}{\gamma_1} + \lambda_1 p_\alpha \Delta\mu \\
r^d &= \Lambda\Delta\mu + \lambda_1 p_\alpha h_\alpha
\end{aligned}$$

Reactive fluxes

Opposite crossed terms. Antisymmetric stress

$$\begin{aligned}
\sigma^r_{\alpha\beta} &= -\zeta\Delta\mu q_{\alpha\beta} + \frac{\nu_1}{2}(p_\alpha h_\beta + p_\beta h_\alpha - \frac{2}{3} h_\gamma p_\gamma \delta_{\alpha\beta}) \\
P^r_\alpha &= -\nu_1 v_{\alpha\beta} p_\beta \\
r^r &= \zeta q_{\alpha\beta} v_{\alpha\beta}
\end{aligned}$$

Mechanical stress

Stress equation

Symmetric stress
$$2\eta v_{\alpha\beta} = \left(1 + \tau \frac{D}{Dt}\right)$$
$$\left\{\sigma_{\alpha\beta} + \zeta \Delta\mu q_{\alpha\beta} + \tau A_{\alpha\beta} - \frac{\nu_1}{2}(p_\alpha h_\beta + p_\beta h_\alpha - \frac{2}{3} h_\gamma p_\gamma \delta_{\alpha\beta})\right\}$$

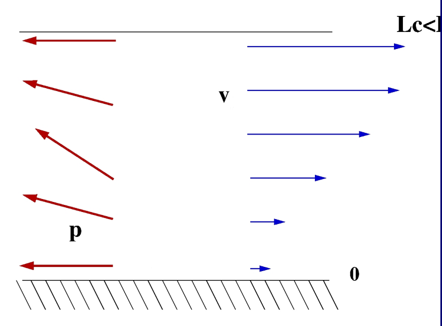
Antisymmetric stress
$$\sigma^a_{\alpha\beta} = \frac{1}{2}(p_\alpha h_\beta - p_\beta h_\alpha)$$

- Convected Maxwell model
- Coupling between stress and polarization
- Active stress
  - myosin coupling to filaments
  - normal stress difference
  - activity coefficient $\zeta < 0$

Outline

Spontaneous Frederiks transition

Parallel anchoring conditions



Flow bifurcation

R.Voituriez

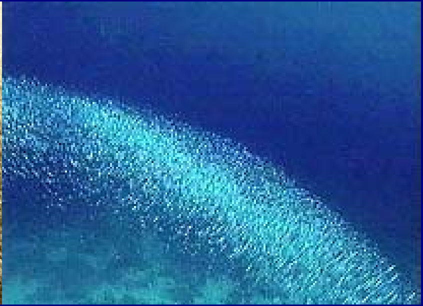
- Same anchoring condition on both surfaces
- Active stress equivalent to an external magnetic field along x axis
- Instability for a finite thickness

$$L_c = \left(- \frac{\pi^2 K \left(\frac{4\eta}{\gamma_1} + (\nu_1 + 1)^2 \right)}{2\tilde{\zeta}\Delta\mu(\nu_1 + 1)} \right)^{1/2}$$

Outline

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

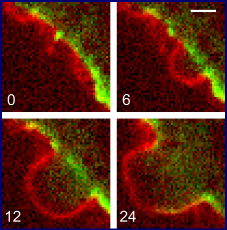


Outline

Outline

Cell Cortex

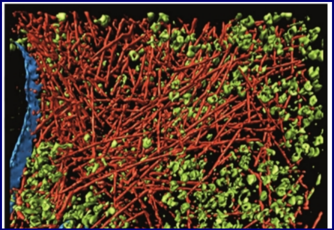
Optical Imaging



Charras

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

Electron microscopy

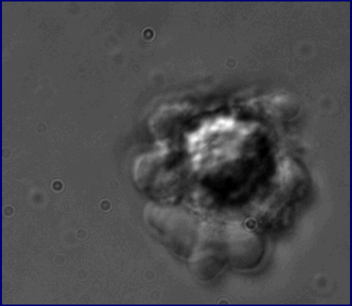


Medalia

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

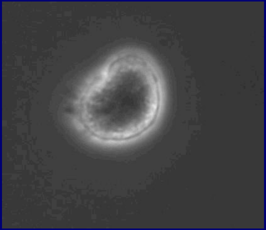
Cell instabilities associated to cortical layer

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)

Multicomponent active gels Callan-Jones and Julicher

- Random polarization parallel to the membrane
- Two component system: actin and cytoplasm
- Actin conservation law

$$\partial_t \rho_{\mathrm{g}} + \partial_\alpha \rho_{\mathrm{g}} v_{\mathrm{g},\alpha} = -k_d \rho_{\mathrm{g}}$$

- Boundary condition $\rho_{\mathrm{g}} v_{\mathrm{g},z}\big|_{z=0} = v_p \rho_0$
- Constitutive equation, relative flux

$$\begin{aligned} \rho_{\mathrm{g}} \left(v_\alpha - v_{\mathrm{g},\alpha} \right) &= \chi \left(\partial_\beta \sigma^{\mathrm{g}}_{\alpha\beta} - \partial_\alpha \Pi \right) \\ 0 &= 2\eta \partial_\beta v_{\mathrm{g},\alpha\beta} - \partial_\alpha \Pi \quad . \end{aligned}$$

- Effective pressure includes contractile stress of molecular motors $\Pi(\rho) = P(\rho) - \zeta \Delta\mu$
- Neglect permeation

Active prewetting

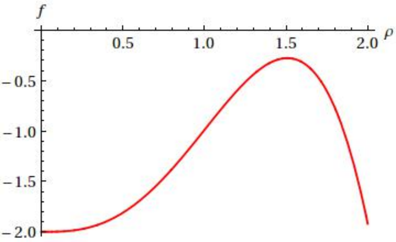
- One-dimensional geometry

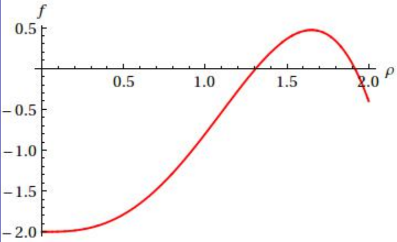
Dynamic equations

$$\partial_t \rho + \partial_z \rho v = -k_d \rho$$

$$\eta \partial_z v - \Pi(\rho) = 0$$

- Actin velocity $\eta v = \left(\frac{\partial \rho}{\partial z}\right)^{-1} \rho f(\rho)$ $\quad f(\rho) = -k_d \eta - \Pi(\rho)$

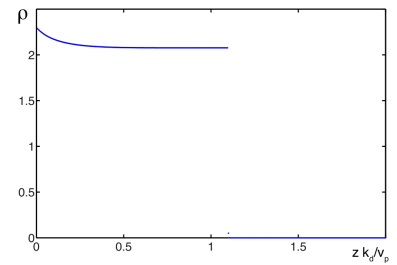




- No Flux at infinity
- 3 possible fixed points

Concentration profile in actin layer

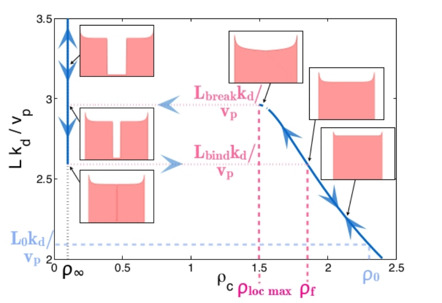
- Small activity (Myosin concentration): exponential decay of cencentration
- Large activity: formation of an active prewetting layer



- Actin cortical layer viewed as a wetting layer
- Almost constant concentration
- Thickness $e \sim v_p/k_d$

Interactions between two cortical layers: capillary condensation

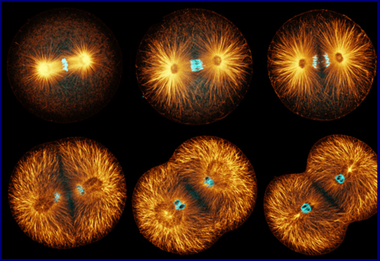
- Two layers in close contact
- Existence of metastable states
- Hysteretic phenomena
- Active capillary condensation
- Lamellipodium structure



Outline

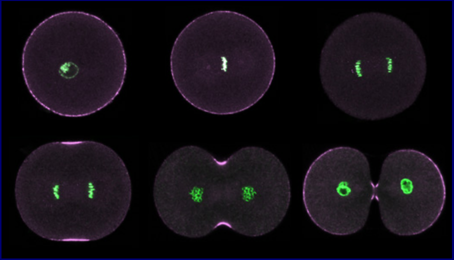
Final stages of cell division von Dassow

Final stage of cell division



- Separation between daughter cells
- See urchin

Myosin contractility

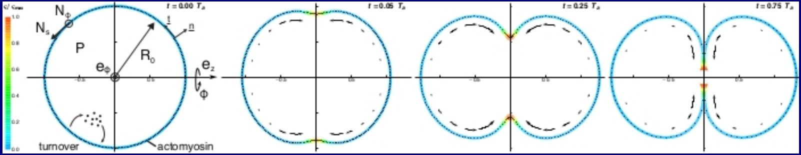


- Ring closure due to actin contractility
- Local enhancement of myosin activity due to astral microtubules

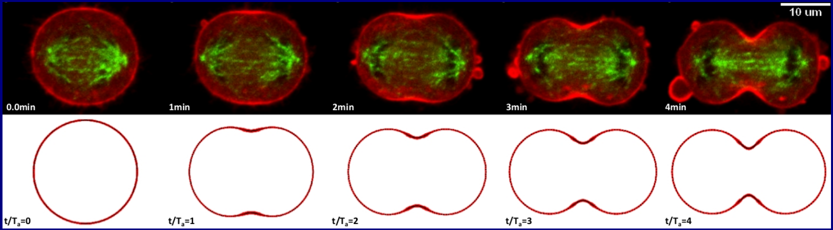
Active gel theory of Cytokinesis

- Cytokinesis driven by myosin contractility in the actin cortical layer: cortical flow
- 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
- Numerical solution of active gel equations, using Lagrangian coordinates
- Impose cylindrical symmetry of the cell

Dynamics of Cytokinesis

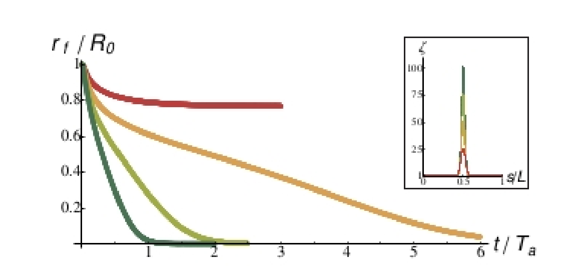


- Critical value of activity for cytokinesis completion
- Low activity of the ring: cytokinesis failure
- Large activity of the ring: cytokinesis success

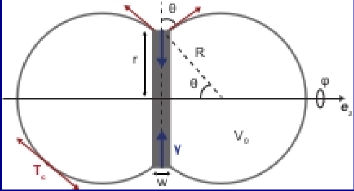


Kinetics of ring closure

- 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 independent of R_0
- Good agreement with experiments

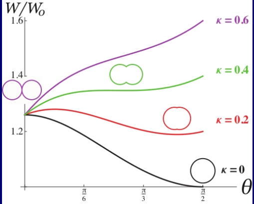


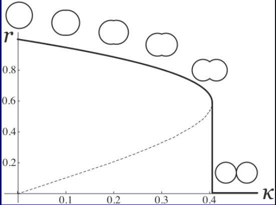
Qualitative interpretation



- 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

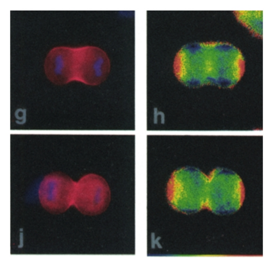




- Linear constriction if dissipation dominated by cortical flow

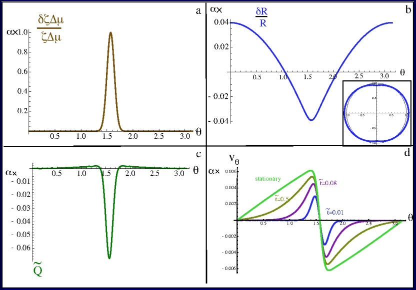
Furrow formation during cytokinesis G.Salbreux

Cleavage furrow Y. Wang et al.



- Enhanced myosin activity at the equator
- Actin flow
- Flow alignment coupling

Active gel theory



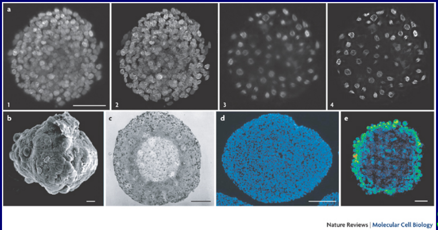
- C.Elegans embryos S.Grill

Summary

- Molecular motors
  - Myosin 1b: a non-processive catch-bond motor A. Mamane
  - Myosin 1b can pull tubes P. Bassereau
  - Fast oscillations of molecular motors
  - Other mechanisms of dissipation: Channel clatter P. Martin
- Active gels
  - Non-equilibrium effects: fluctuation-dissipation theorem
  - Mitotic spindle as an active liquid drop C. Erlenkaemper
  - Tissues: polarized liquid-like systems consuming energy M. Delarue
- Cytokinesis
  - Actin polarization
  - Blebs
  - Cell oscillations
  - Asymmetric cell division

Liquid like behavior of tissues Steinberg

Isotropic Surface tension of tissues



Stelzer

Stress relaxation by Cell division

- Elastic behavior at short times
- Internal stress due to cell division and apoptosis
- Coupling between cell division and local stress Piel, Bornens
- Tissue viscosity $\eta \sim E/k_d$

Cell division and Homeostatic pressure

Cell division and apoptosis

- Division rate $k_d(\rho, \text{biochemical state})$
- Apoptosis rate k_a

$$\frac{\partial \rho}{\partial t} + \partial_\alpha(\rho v_\alpha) = (k_d(\rho) - k_a(\rho))\rho$$

Tissue Pressure

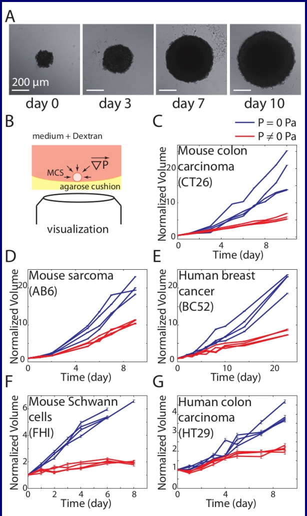
- Pressure exerted by the cells
- Division rate k_d decreases with pressure
- Apoptosis rate k_a increases with pressure

Homeostatic pressure

- Steady state pressure of a tissue P_h
- $k_d - k_a(P_h) = 0$

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

Collective properties of myosin motors and actin filaments

Marbach, Joanny, Kruse, Audoly, Turlier, Ramaswamy, Prost

Molecular motors

Molecular motors in cells

Two-states models of molecular motors

Collective properties of molecular motors

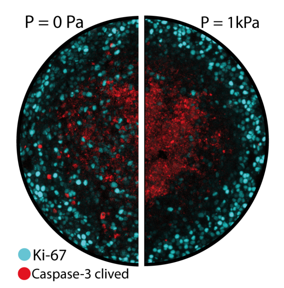
Spontaneous oscillations of molecular motors

Soft Motor model

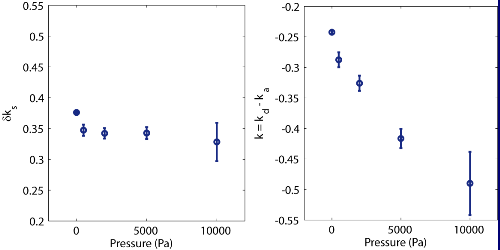
Bidirectional motion of motor assemblies

Active gel theory

Surface growth



Pressure dependence

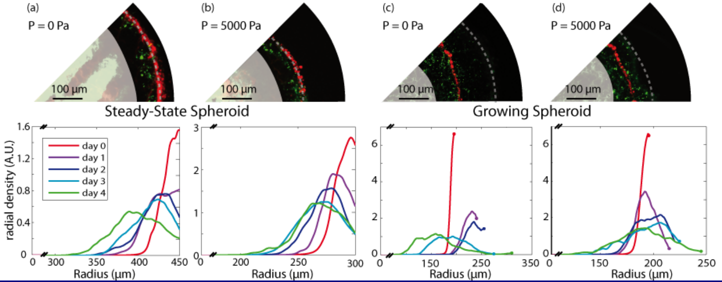


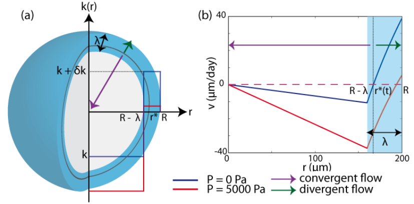
$$\partial_t V = (k_d - k_a) V + 4\pi \left(\frac{3}{4\pi}\right)^{2/3} \delta k_s \lambda V^{2/3}$$

- Nutrient effect
- Crowding effect
- Negative homeostatic pressure Elgeti

Cell flow

- Injection of fluorescent nano-particles

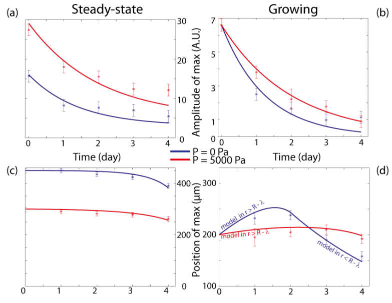




- Incompressible fluid
- Velocity field $\nabla \cdot \mathbf{v} = k(r)$

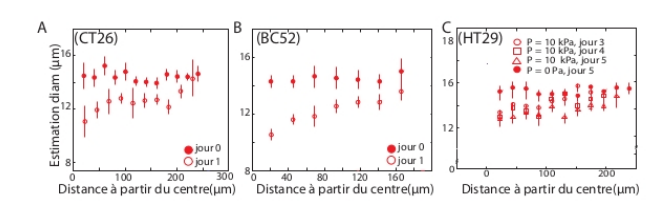
Particle distribution

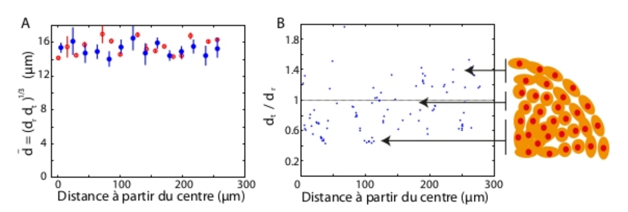
- Transport by cell flow $\partial_t \rho + \nabla v \rho = 0$
- Negligible diffusion
- Density $\rho(r,t) = \rho_0(\tilde{r},0)\, e^{-(k+\delta k)t}$ if $r > R - \lambda$
- $\tilde{r}^3 = e^{-(k+\delta k)t}\, r^3 + \int_0^t \delta k (R(t') - \lambda)^3\, e^{-(k+\delta k)t'}\, dt'$



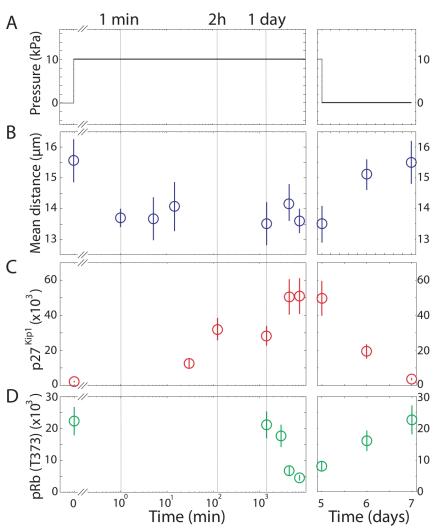
Volume change after a pressure step

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





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

Volume Change after a pressure step

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
- Alternative: Anisotropic elastic modulus

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