Christian Schmeiser La Habana, February 19, 2010

Nonlinear friction in the cytoskeleton as a macroscopic limit of the activity of cytoskeletal proteins

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Joint work with **Dietmar Ölz**
Also involved in this subject: **Nikolaos Sfakianakis**, **Christoph Winkler** (Univ. Vienna), and the group of **Vic Small** (IMBA)

Friction from building and breaking elastic connections

Consider a sailing ship equipped with a large number N of anchors on elastic ropes, which break loose at random times and are re-attached, again at random times.
The wind exerts a force F(t).

How does the ship move, if the stretching of the anchor ropes is always in equilibrium?

Friction from building and breaking elastic connections (ctd.)

Position of the ship at time t: $x(t)$

Stretching at time t of an anchor of age a:
$x(t) - x(t-a)$

Probability distribution with respect to age of an anchor being active at time t: $\rho(t,a)$

$$\int_0^\infty \rho(t,a)da \le 1$$

Expected age distribution of active anchors: $N\rho$

Friction from building and breaking elastic connections (ctd.)

Age structured population model for the anchor distribution:

$$\partial_t \rho + \partial_a \rho = -\zeta \rho$$

$$\rho(t,0) = \beta \left(1 - \int_0^\infty \rho(t,a)da \right)$$

Time scales for ρ: ζ^{-1}, β^{-1}

Friction from building and breaking elastic connections (ctd.)

Quasistationary force balance:

$$F(t) = Nk \int_0^\infty (x(t) - x(t-a))\rho(t,a)\,da$$

k ... spring constant of an anchor rope

Volterra integral equation for $x(t)$

Friction from building and breaking elastic connections (ctd.)

Nondimensionalization:

$$\varepsilon\partial_t\rho + \partial_a\rho = -\zeta\rho$$

$$\rho(t,0) = \beta\left(1 - \int_0^\infty \rho(t,a)da\right)$$

$$F(t) = \int_0^\infty \frac{x(t) - x(t-\varepsilon a)}{\varepsilon}\rho(t,a)da$$

with $\varepsilon = \bar{a}/\bar{t} \ll 1$, the ratio of microscopic (anchor) to macroscopic (ship) time scales

Friction from building and breaking elastic connections (ctd.)

Variational formulation: potential energy

$$U(t)[z] = \frac{1}{2\varepsilon}\int_0^\infty (z - x(t-\varepsilon a))^2 \rho(t,a)\,da - F(t)z$$

$$x(t) = argmin_z\, U(t)[z]$$

Friction from building and breaking elastic connections (ctd.)

The macroscopic limit $\varepsilon \to 0$:

$$\rho(t,a) = \frac{\beta\zeta}{\beta+\zeta} e^{-\zeta a}, \qquad F(t) = \kappa \dot{x}(t)$$

with friction coefficient

$$\kappa = \int_0^\infty a\rho(a)\,da = \frac{\beta}{\zeta(\beta+\zeta)}$$

Friction from building and breaking elastic connections (ctd.)

Stretching dependent breaking coefficient:

$$\zeta = \zeta\left(\frac{x(t) - x(t-\varepsilon a)}{\varepsilon}\right) \to \zeta(a\dot{x}(t))$$

Example: $\zeta = a\dot{x} \quad \Rightarrow$

$$\kappa = \kappa(\dot{x}) = \frac{\beta\sqrt{2\dot{x}/\pi}}{\dot{x}(\beta + \sqrt{2\dot{x}/\pi})}, \quad \dot{x} = \frac{\pi}{2}\left(\frac{\beta F}{\beta - F}\right)^2$$

Examples of crawling cells

Melanoma cell

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benötigt.

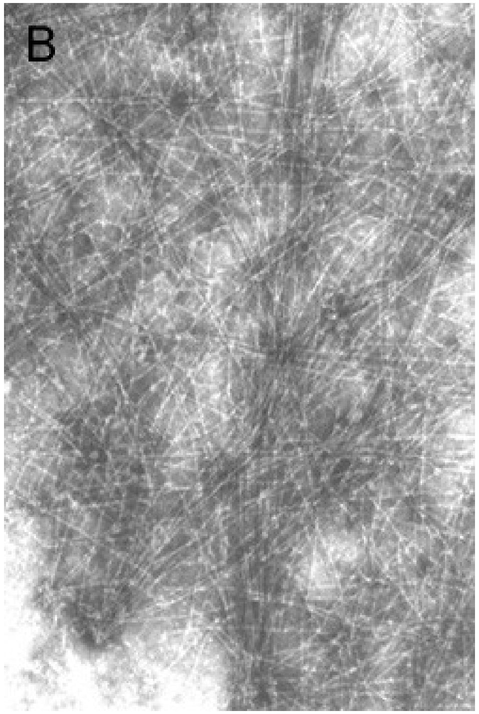
Fibroblast

Fish keratocyte

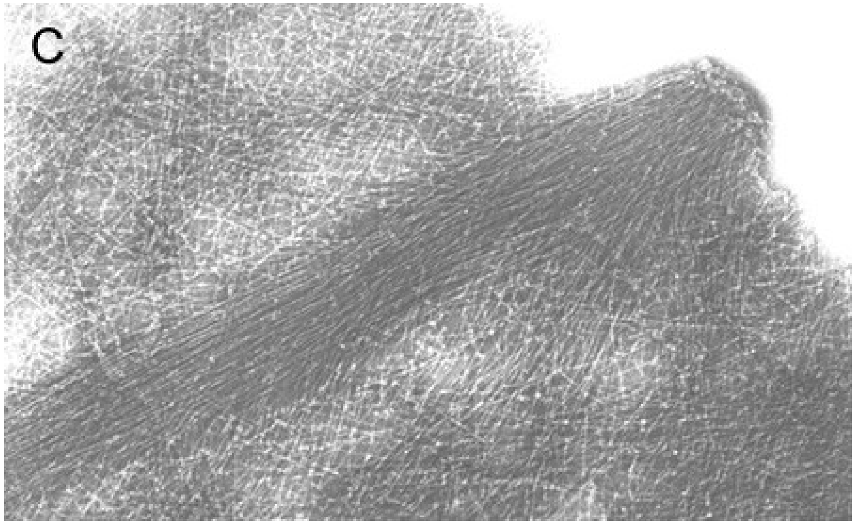
cellix.imolbio.
oeaw.ac.at

Actin network in the lamellipodium

(through the light microscope)

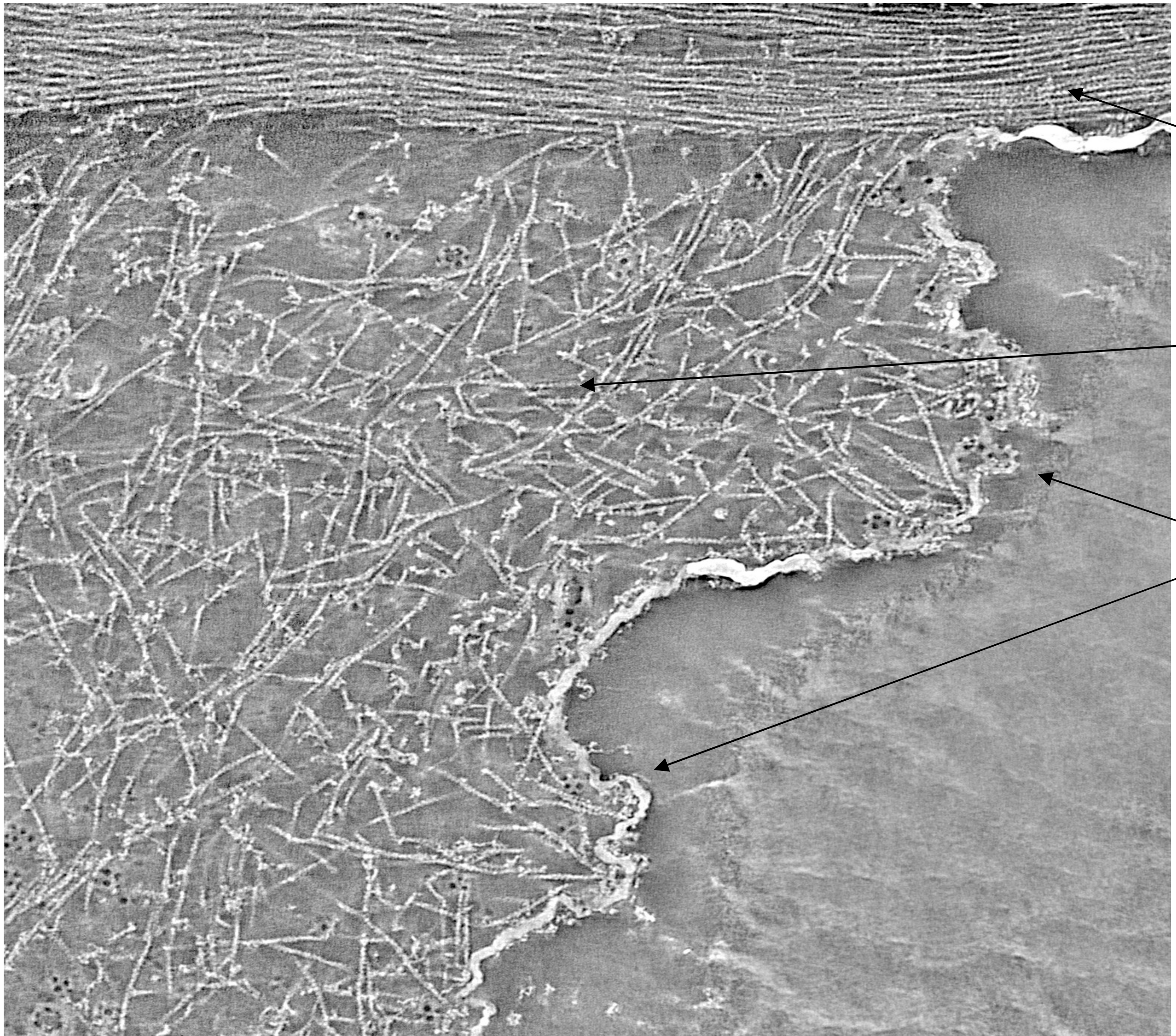


Keratocyte



Fibroblast

Electron microscopy (fibroblast)



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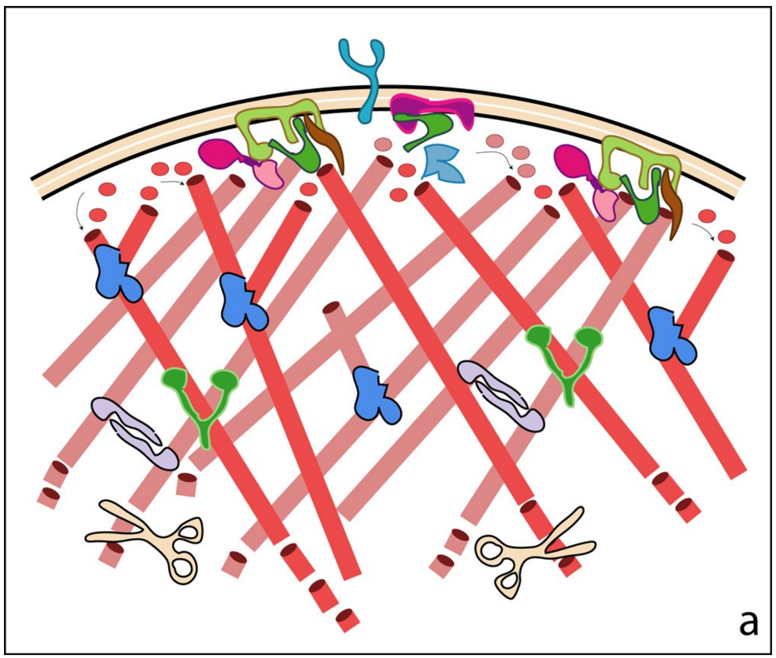
Cytoskeleton dynamics: treadmilling, cross-linking, adhesion



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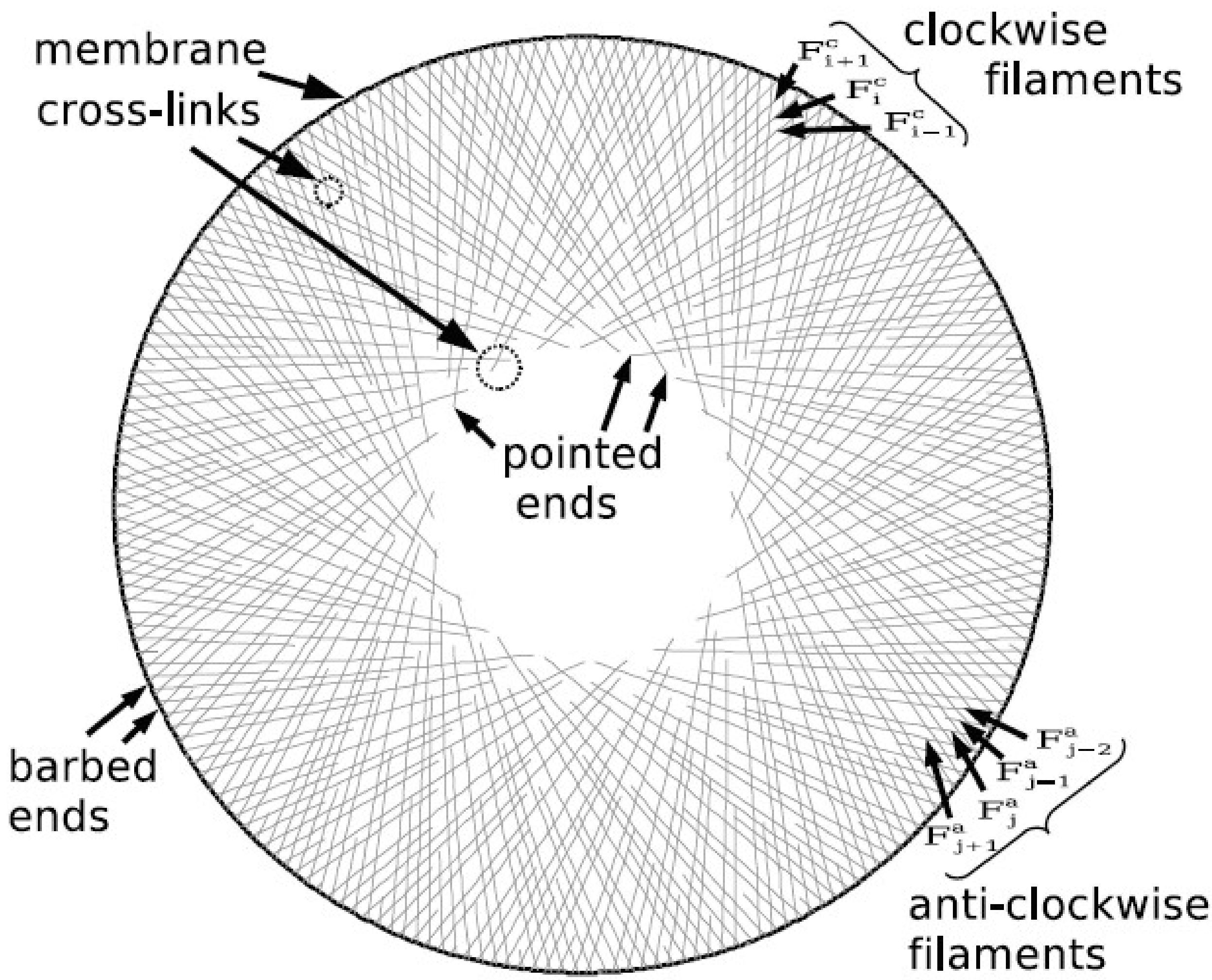
Mathematical model (D. Ölz): assumptions



- 2D
- 2 directions (2-phase model)
- Barbed ends attached to the leading edge
- Stochastic (de)polymerization
- Stochastic building and breaking of cross-links and substrate adhesions
- Quasistationary force balance: bending, membrane, stretching and twisting adhesions and cross-links

Mathematical model: variables and parameters

$F^{\pm}(t, \alpha^{\pm}, s) \in R^2$: filament position with filament label $\alpha^{\pm}$, arclength s

$\rho(t, \alpha^+, \alpha^-, a)$: age (a) dependent cross-link probability density

$S(t, \alpha^+, \alpha^-, a)$, $T(t, \alpha^+, \alpha^-, a)$: stretching and twisting of cross-links

$\rho_{\mathrm{adh}}^{\pm}(t, \alpha^{\pm}, s, a)$: age dependent adhesion density

$\eta^{\pm}(t, \alpha^{\pm}, s)$: length distribution of filaments (given)

Cross-link dynamics

Age structured population model (nondimensionalized):

$$\varepsilon\partial_t\rho + \partial_a\rho = -\zeta(S,T)\rho$$

$$\rho(a=0) = \beta(T_0)\left(1 - \int_0^\infty \rho\, da\right)$$

$$\rho(t,\alpha^+,\alpha^-,a) = 0 \quad \text{for } (\alpha^+,\alpha^-) \in \partial\mathcal{C}(t-\varepsilon a)_+$$

$$\rho(t=0) = \rho_I$$

$$\varepsilon \ll 1: \text{ scaled lifetime}$$

Analogous for **adhesions**

Potential energy contributions

$$U_{\rm membrane}[F^\pm] = \kappa^M \left(\frac{C^+[F^+] + C^-[F^-]}{2} - C_0 \right)_+^2$$

$$U^\pm_{\rm bending}(t)[F^\pm] = \frac{1}{2} \int_B |\partial_s^2 F^\pm|^2 \eta^\pm \, d(\alpha, s)$$

$$U_{\rm scl}(t)[F^+, F^-] = \frac{\kappa^S}{2\varepsilon} \int_0^\infty \int_{\mathcal{C}(t-\varepsilon a)} |S|^2 \rho_{\rm eff} \, d(\alpha^+, \alpha^-) \, da$$

$$U_{\rm tcl}(t)[F^+, F^-] = \frac{\kappa^T}{2} \int_0^\infty \int_{\mathcal{C}(t-\varepsilon a)} T^2 \rho_{\rm eff} \, d(\alpha^+, \alpha^-) \, da$$

$$U^\pm_{\rm adh}(t)[F^\pm] = \frac{\kappa^F}{2\varepsilon} \int_0^\infty \int_B \left| F^\pm - F^{\pm *} \right|^2 \rho^\pm_{\rm adh} \eta^\pm \, d(\alpha, s) \, da$$

The complete problem

Minimize the total potential energy under the constraints

1) Filament inextensibility:

$$|\partial_s F^{\pm}| = 1$$

1) Barbed ends attached to the leading edge:

$$\{F^+(t,\alpha^+,s=0):\ \alpha^+\} = \{F^-(t,\alpha^-,s=0):\ \alpha^-\}$$

This is a mixed 2D-3D problem with delay.
Very expensive to compute with!

Instantaneous cross-link and adhesion turnover

After the limit $\varepsilon \to 0$ the problems for cross-link and adhesion densities (both 3D) can be solved explicitly. The problem for the filaments (2D) becomes local in time.
Resistance against stretching of adhesions and cross-links turns into **friction**.

The Euler-Lagrange equations in the limit:

$$\partial_s^2(\eta^\pm \partial_s^2 F^\pm) - \partial_s(\eta^\pm \lambda^\pm \partial_s F^\pm) + \eta^\pm \; \mu^A \; D_t^\pm F^\pm$$
$$\pm \partial_s \left(\eta^+ \eta^- \; \mu_\pm^T(T) T \, \partial_s F^{\pm\perp}\right)$$
$$\pm \eta^+ \eta^- \mu_\pm^S(T) \left(D_t^+ F^+ - D_t^- F^-\right) = 0$$

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Unsymmetric pushed lamellipodial fragment

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