Towards a mathematical model of cell motility.

Dietmar Ölz, Herbert Polzhofer, Stefan Köstler, Christian Schmeiser, J. Victor Small

University of Vienna, Faculty of Mathematics, Wolfgang Pauli Institute and Institute of Molecular Biotechnology of the Austrian Academy of Sciences (IMBA).

Introduction

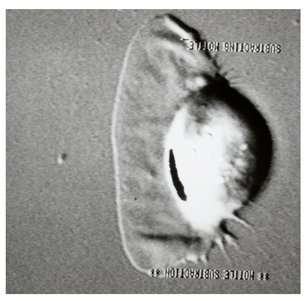
The migration of cells is driven by the directed polimerisation of actin filaments in the region of the cell front termed the lamellipodium.

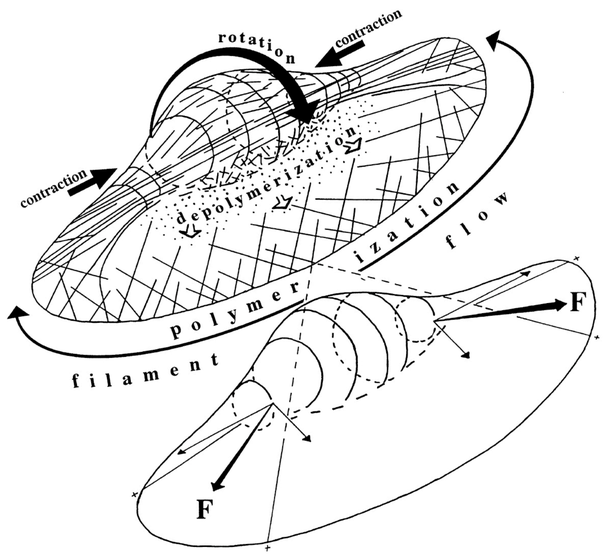
The actin filaments build a meshwork (fig 1) in which the growing ends are at the front and the depolymerising ends are at the rear (fig 2). To maintain stability the filaments are crosslinked by actin binding proteins (ABP). Since there is continuous turnover of the meshwork through treadmilling of actin from the front to the back, there must also be a continuous turnover of the crosslinks.

In this work we model the turnover of the lamellipodium meshwork using basic assumptions about the mechanical consequences of crosslinking interactions.

The biological model

The fastest moving vertebrate cell is the epidermal keratocyte derived from fish or amphibia. These cells exhibit continuous locomotion and a constant shape and therefore are ideal for structural modelling studies.





The diagonal organisation of actin filaments and their continual turnover suggest that there is a lateral flow of filaments across the lamellipodium during cell movement. This lateral flow is intrinsic to the model.

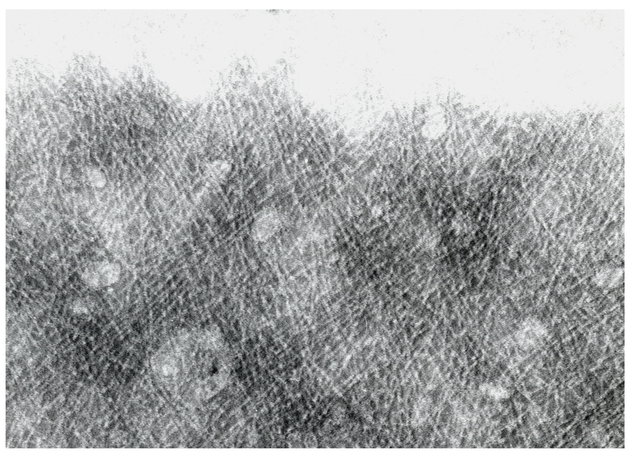
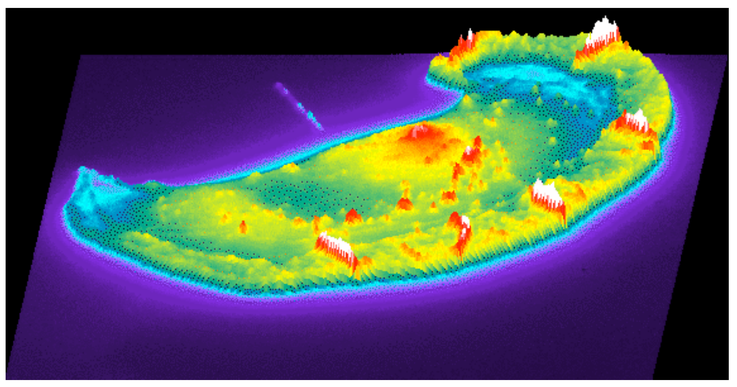


Figure 1: Electron micrograph of a keratocyte lamellipodium showing the diagonal meshwork of actin filaments.



Migrating melanoma cell with actin density highlighted in color code. The lamellipodium is the concave ridge on the right.

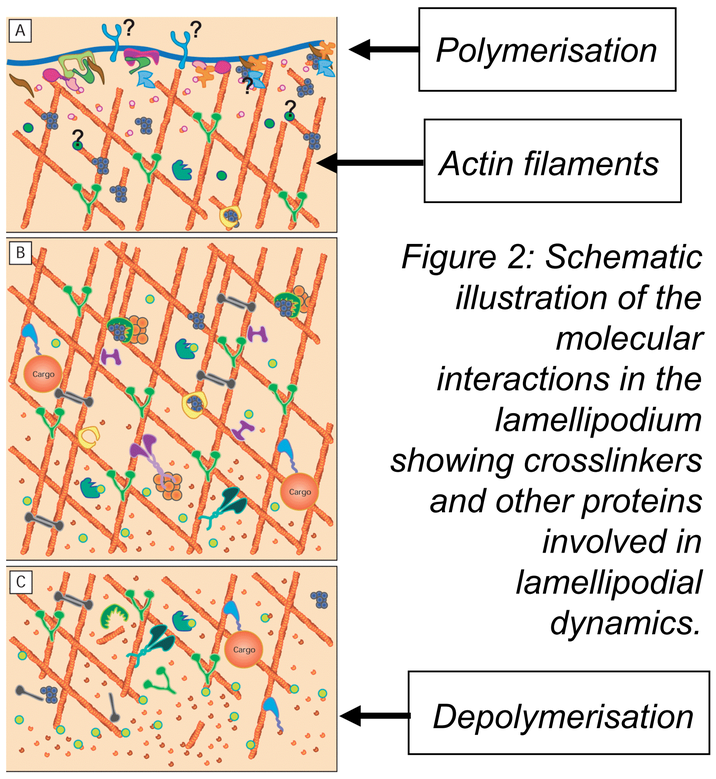
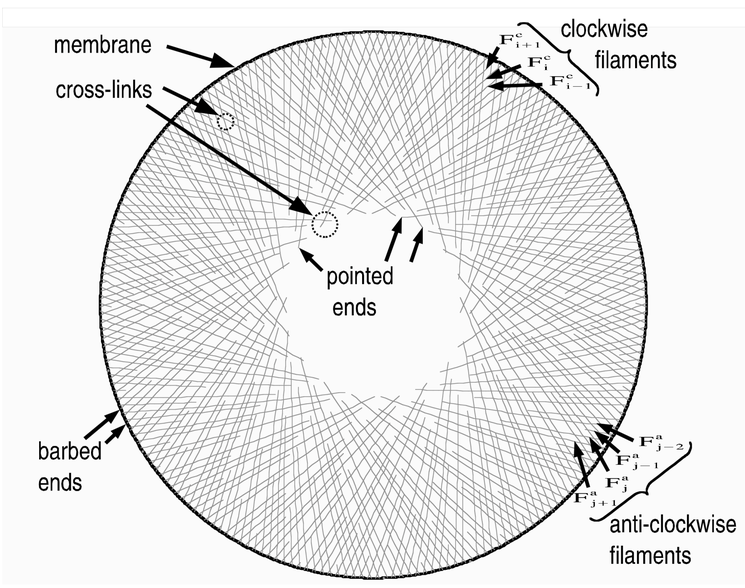


Figure 2: Schematic illustration of the molecular interactions in the lamellipodium showing crosslinkers and other proteins involved in lamellipodial dynamics.

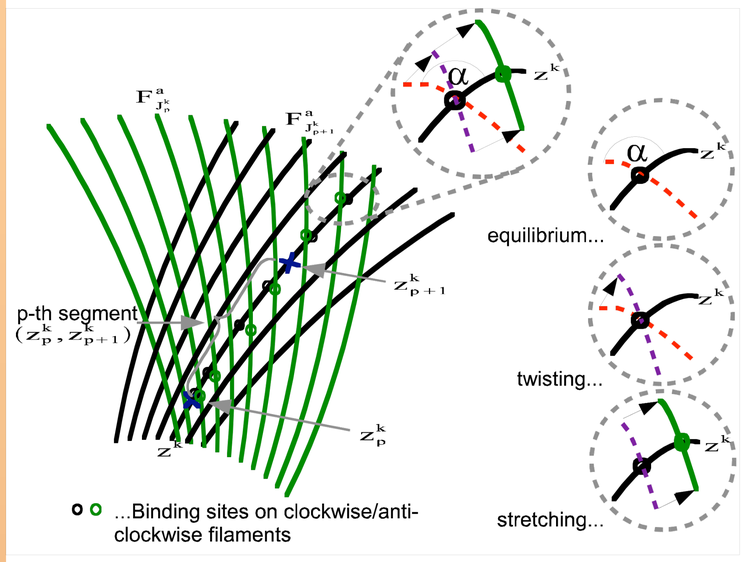
The mathematical model



The mathematical model is based on

- Rotational symmetry as a first approximation.
- Minimising the total potential energy of the network arising from the combined effects of
  - The stretching of the membrane
  - The stiffness of the filaments
  - The twisting and stretching of crosslinks as they move further inwards to a position of smaller radius in the network.
- Graded length of filaments
- Treadmilling
- A dynamic making and breaking of crosslinks according to the changing angle between filaments and the stress in the crosslink.

States of crosslinks.



$z(t,s) \in \mathbb{R}^2$ ... position of a standard filament at time $t \geq 0$

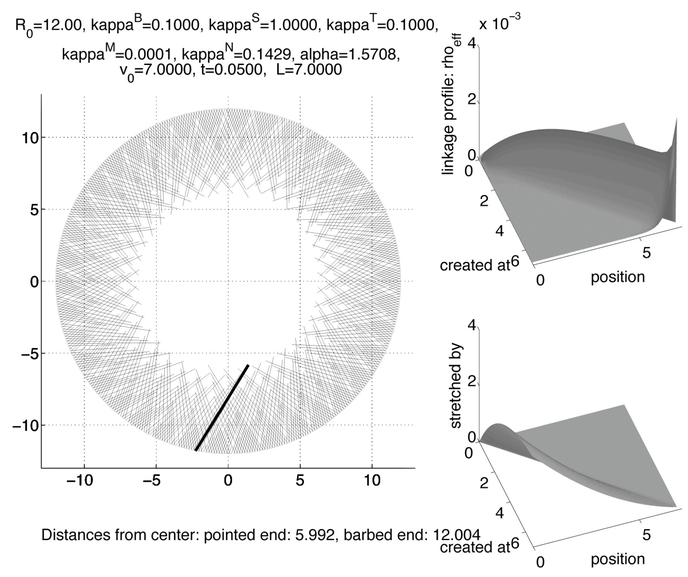
$\rho(t,s,c)$ ... the time dependent density of crosslinks with respect to their position and to their position at the time of nucleation.

potential energy functional...

$$U(t)[z(t,.)] = \int_0^L \left[\frac{\kappa^B}{2}|z''|^2 + \eta \int_s^L \left(\frac{\kappa^S}{2} S^2 + \right. \right.$$
$$\left. \left. + \frac{\kappa^T}{2} T^2 \right) \rho \, dc \right] \eta \, ds + \frac{\kappa^M}{2} \left(2\pi (|z(t,L)| - R_0)_+ \right)^2$$

making and breaking of crosslinks

$$\begin{cases} \rho(t,c,c) = \beta(T(t,c,c))\partial_c \gamma(t,c) \times \\ \qquad \times \left(\frac{1}{v_0} \frac{\kappa^N}{2\pi} - \frac{1}{\eta(t,c)} \int_c^L \frac{\rho_{\text{eff}}(t,\hat{c} - (t - \tau(\hat{c},\gamma(t,c)))v_0,\hat{c})}{\partial_t \gamma(\tau(\hat{c},\gamma(t,c)),\hat{c})} \, d\hat{c} \right), \\ \partial_t \rho(t,s,c) - v_0 \partial_s \rho(t,s,c) = -\zeta(S(t,s,c))\rho(t,s,c) \, . \end{cases}$$



Conclusion and prospects

The basic features of retrograde flow in a symmetrical lamellipodium are explained by the model. Further efforts will be directed at formulating a model for the general, asymmetric case for a moving cell in which there is a transition from polymerising filaments at the front to contracting filaments at the rear.

Acknowledgements

This work was supported by the WWTF and grants from the Austrian Science Fund (FWF) and the Human Frontier Science program (HFSP).