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SMR 1746 - 2

WORKSHOP ON DRIVEN STATES IN SOFT AND BIOLOGICAL MATTER
18 - 28 April 2006

Active Thermodynamics of Cell Membranes

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Workshop on Driven States in Soft and Biological Matter

ICTP, April 18-28, 2006

Active thermodynamics of cell membranes

Nir Gov

Department of Chemical Physics

מכון ויצמן למדע

WEIZMANN INSTITUTE OF SCIENCE

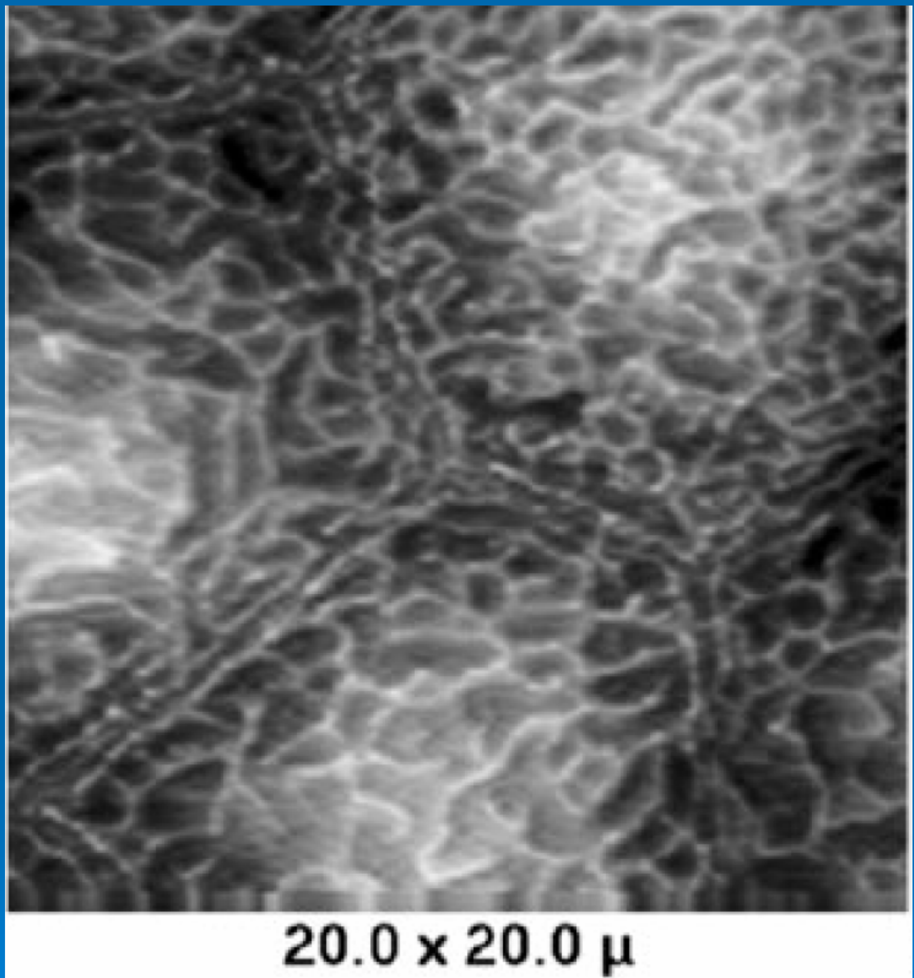
FACULTY OF CHEMISTRY

CHEMICAL PHYSICS Department

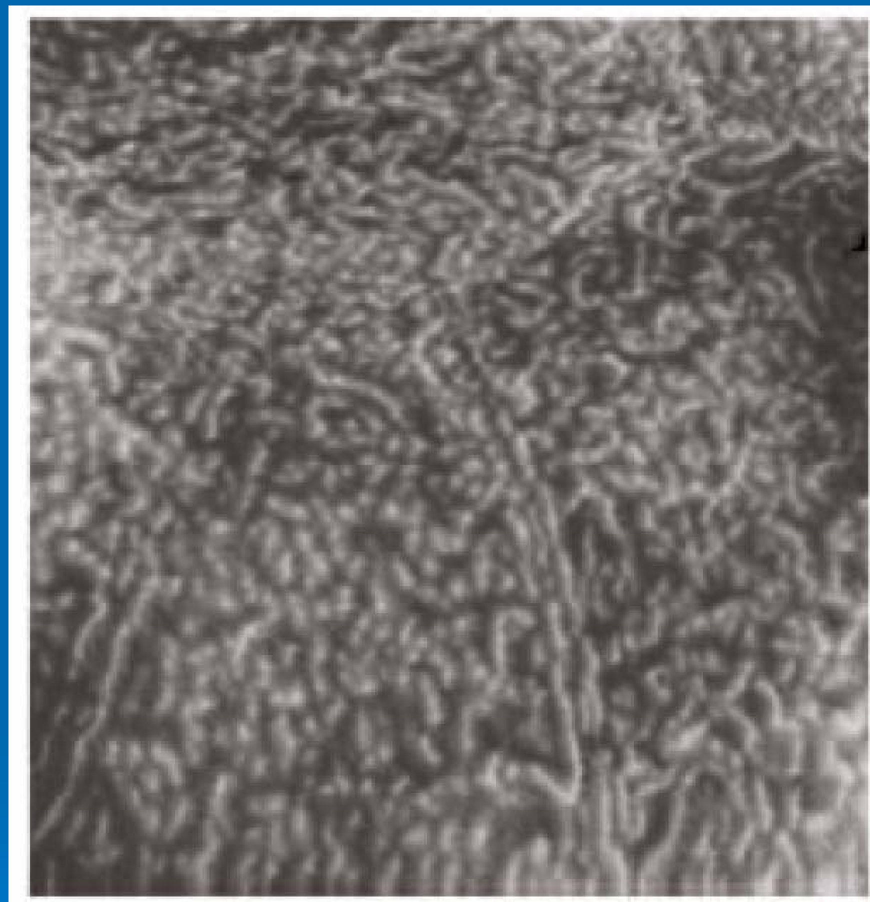
Plan

- Introduction: Microvilli
- Microvilli height distribution
- Microvilli organization and morphology
- Conclusions and future directions: **Neurons**

Introduction: Microvilli

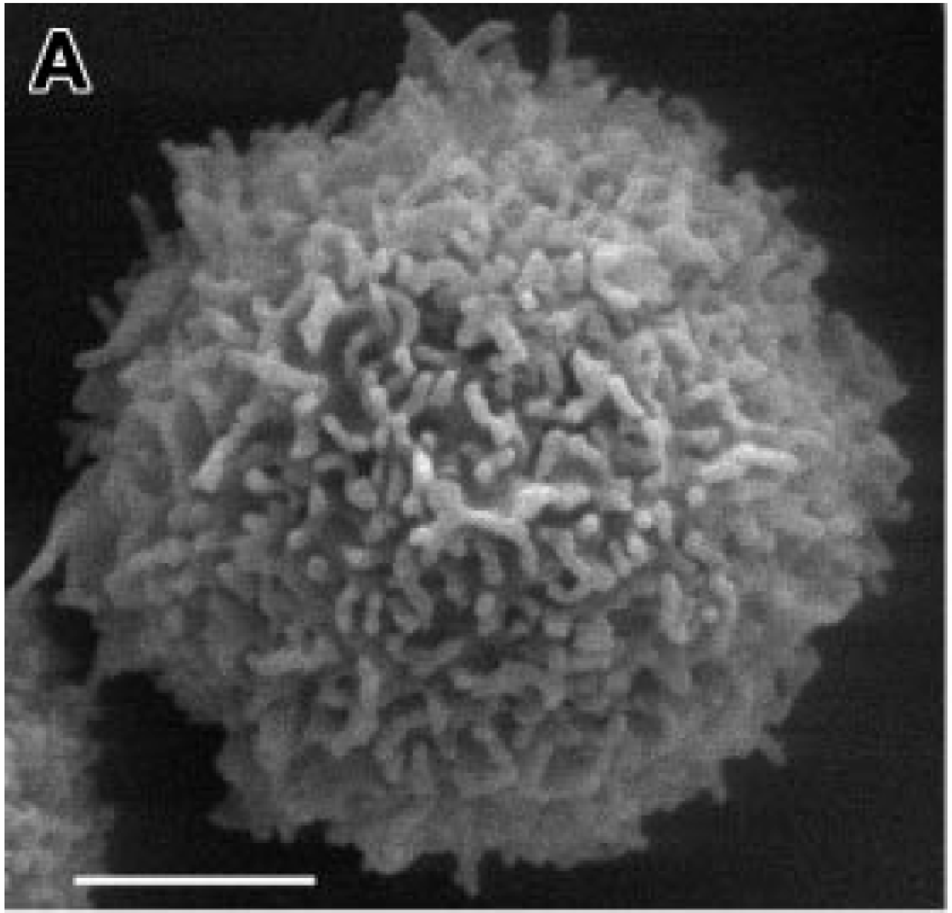


living epithelial cell (A6 cell line)

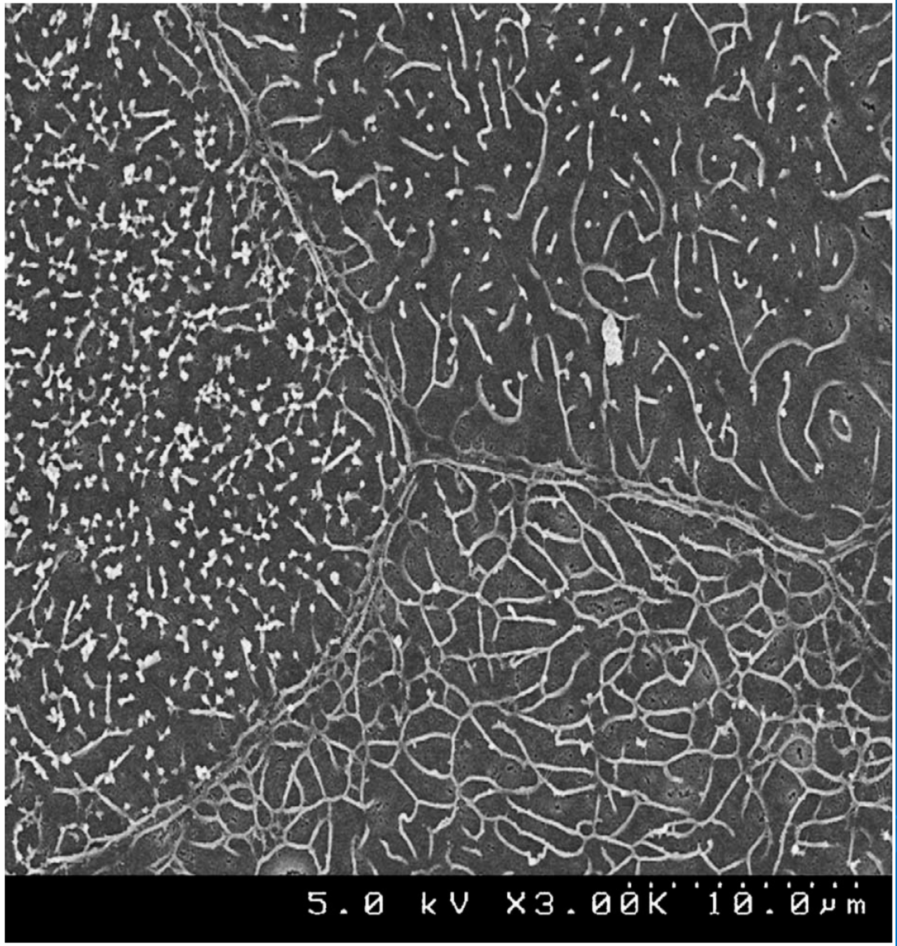


J. Gorelik *et. al.* ; PNAS 100, 5819–5822 (2003)

Introduction: Microvilli



human blood lymphocyte

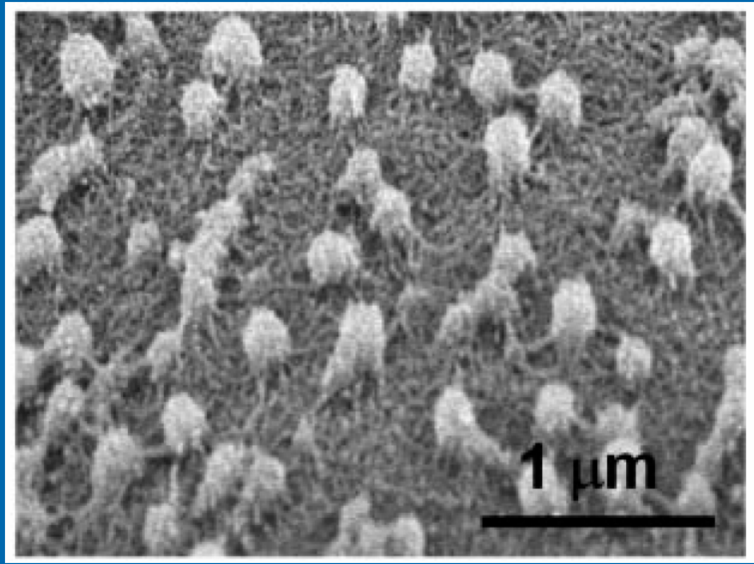


S. Majstoravich *et. al.* ;
BLOOD (2004) 104, 1396.

J. Gorelik *et. al.* ;
Mol. Cell. Endo. 217 (2004) 101

Introduction: Microvilli

Actin bundles:

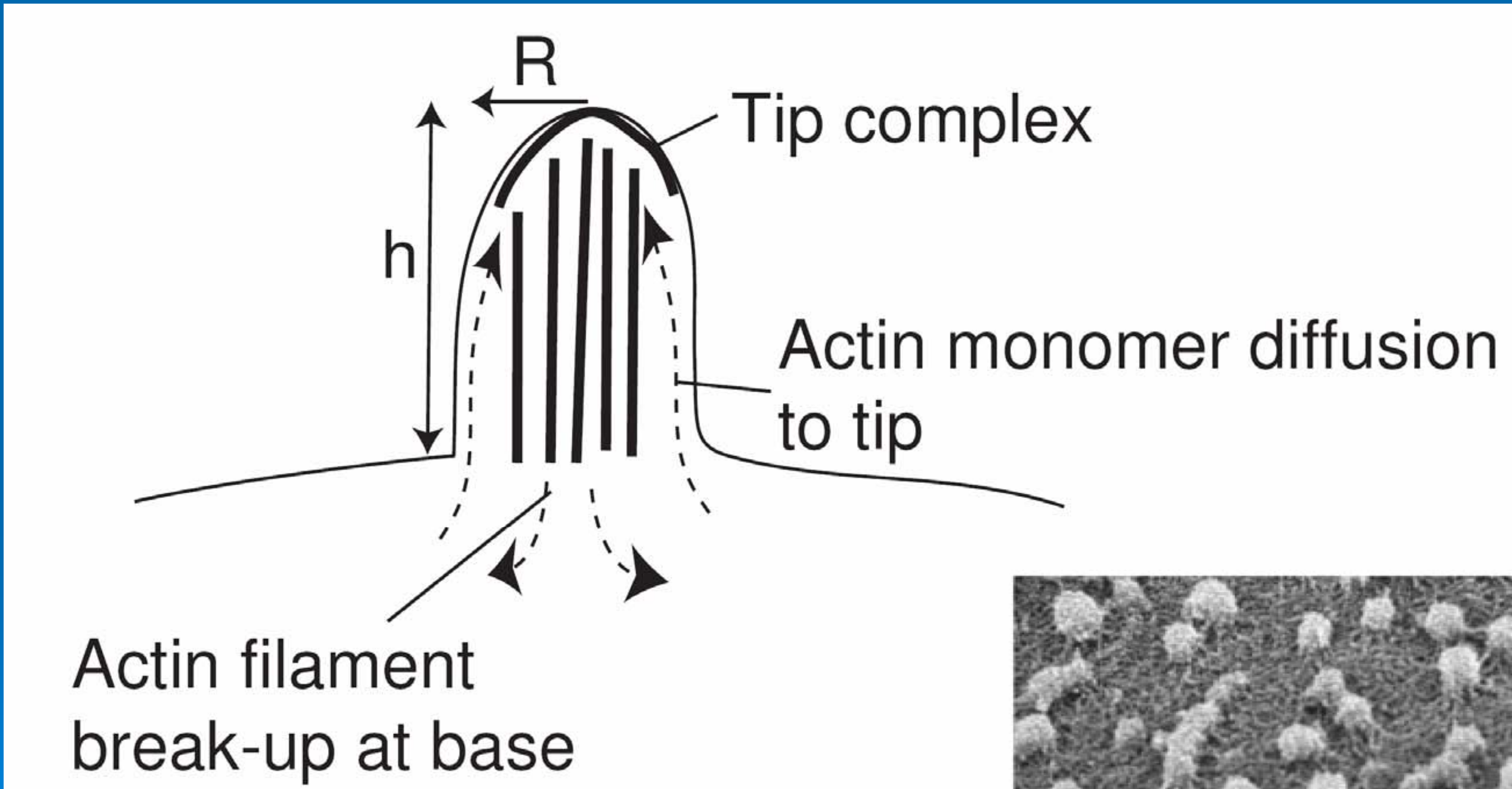


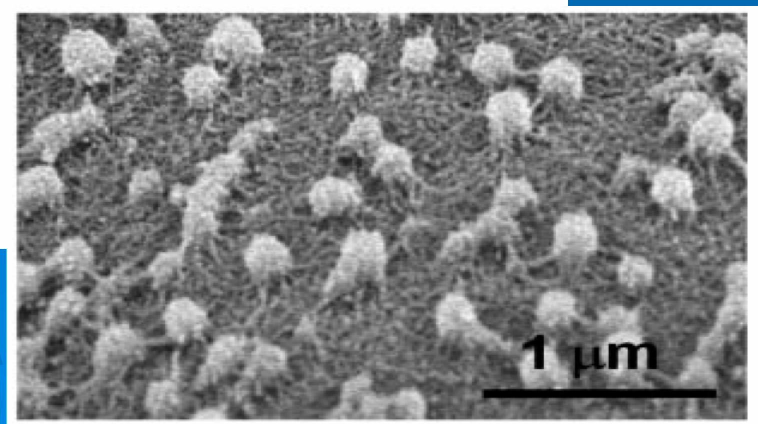
Dynamic:

J. Gorelik *et. al.* ; PNAS 100, 5819–5822 (2003)

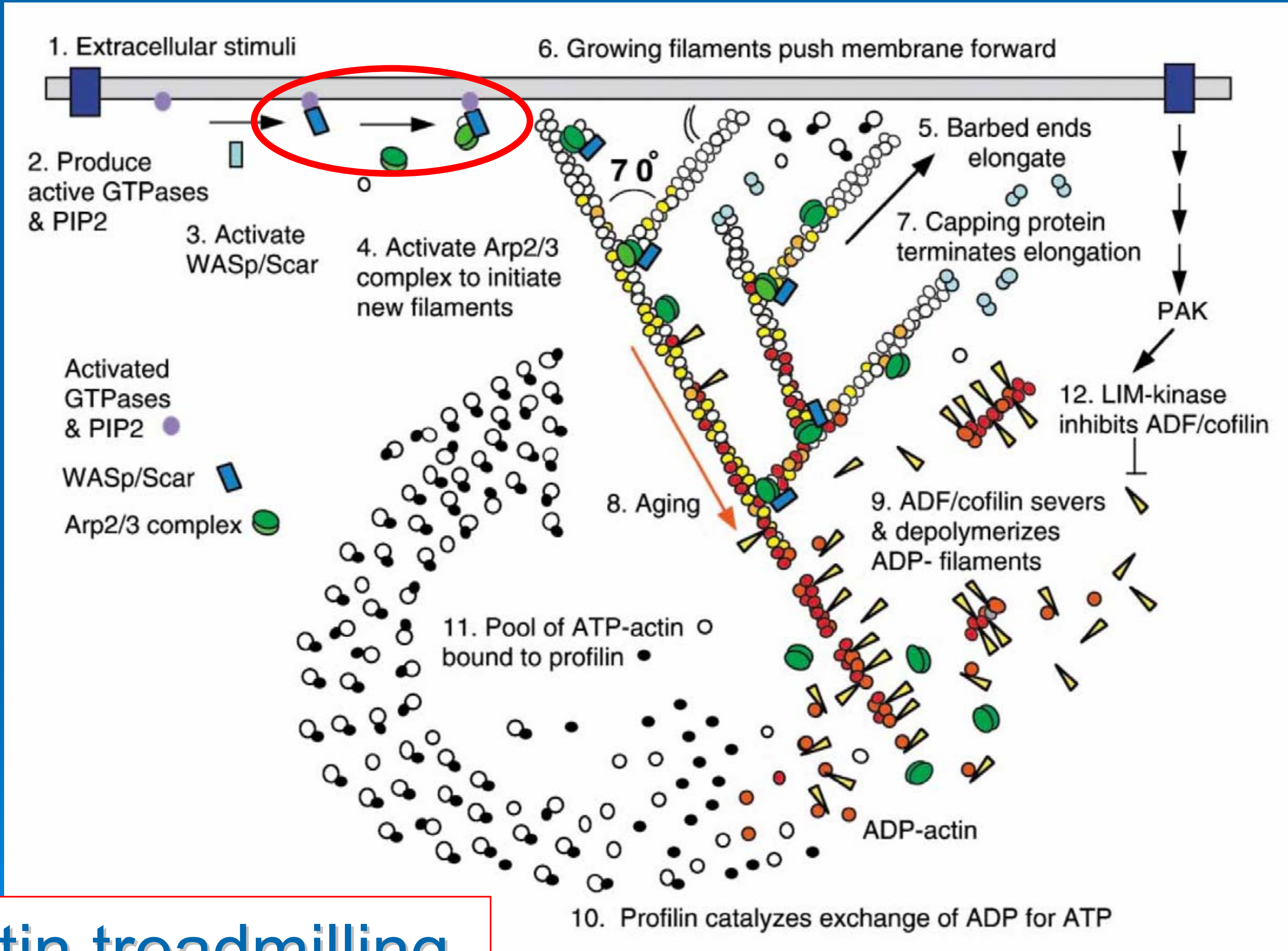
Microvilli

Schematic picture:





Actin polymerization driven motion

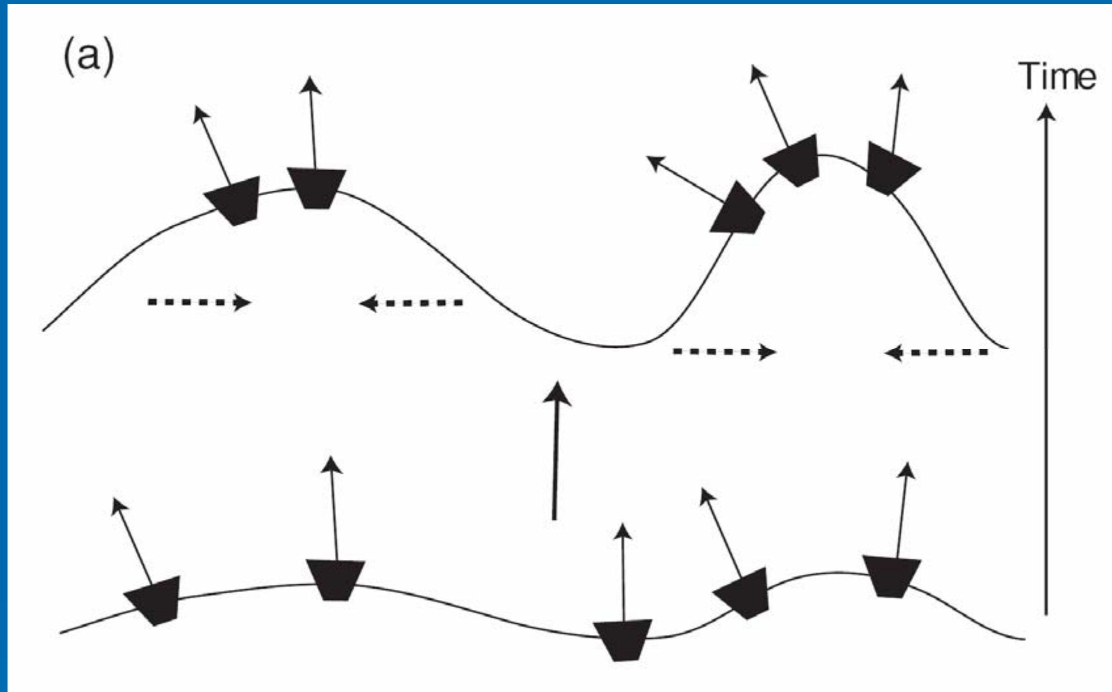


Actin treadmilling

Our model: link actin polymerization with membrane curvature

Instability

$\rightarrow$ Filopodia



454 Biophysical Journal Volume 90 January 2006 454–469

Dynamics of Membranes Driven by Actin Polymerization

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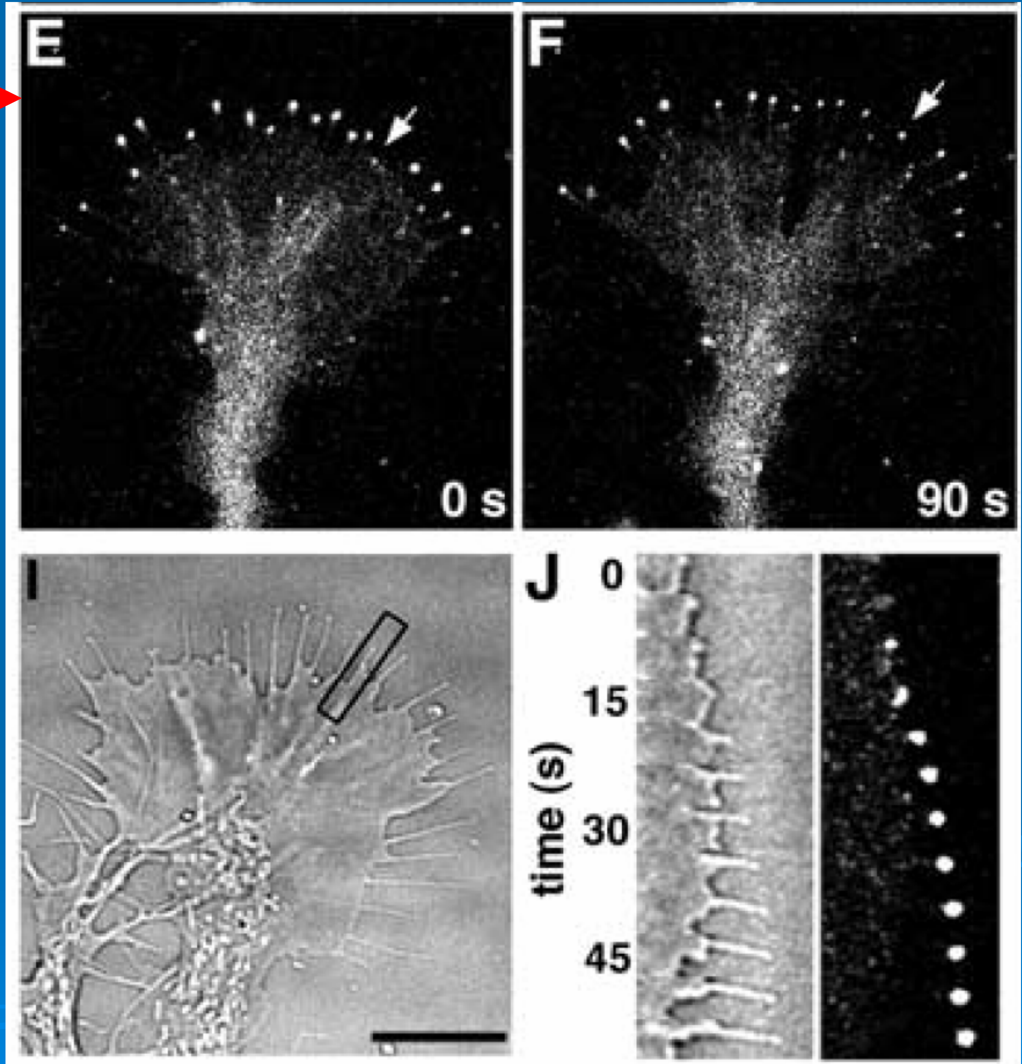
*Department of Chemical Physics, The Weizmann Institute of Science, Rehovot, Israel 76100; and †Department of Physics and Materials Research Laboratory, University of California, Santa Barbara, California 93106-9530 USA

Filopodia: Membrane proteins at the tip

Phospho-tyrosine (PY), Cdc42, Src etc.

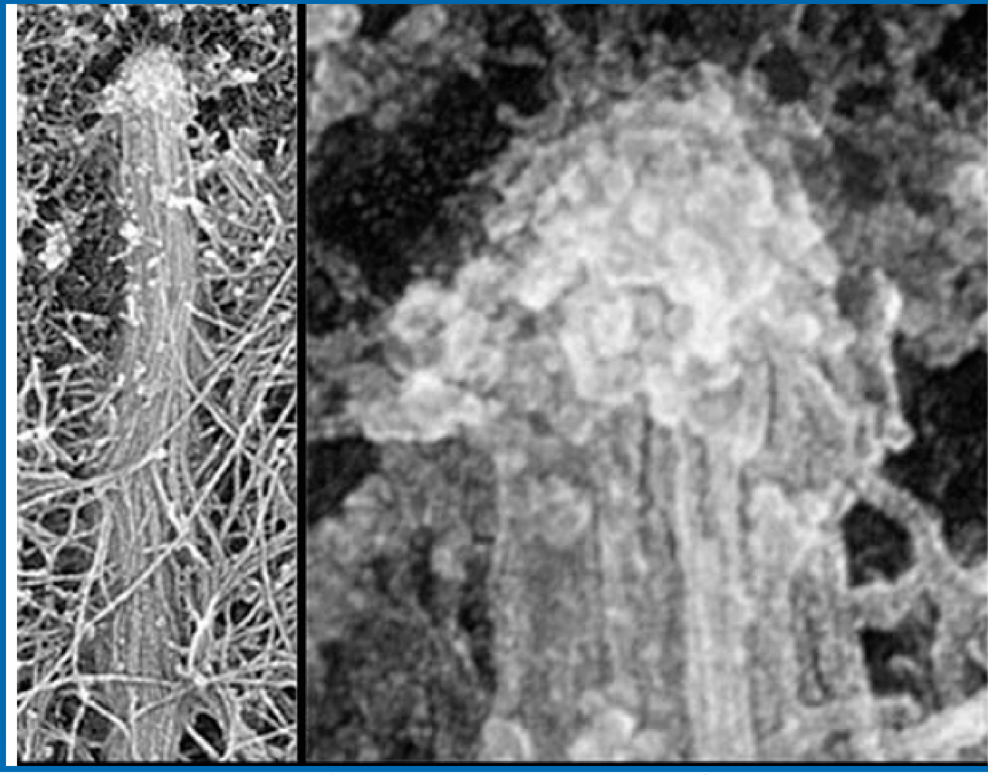
Do these active proteins have a positive spontaneous curvature ?



Estuardo Robles, Stephanie Woo, and Timothy M. Gomez
The Journal of Neuroscience, August 17, 2005 • 25(33):7669–7681

Filopodial tip complex

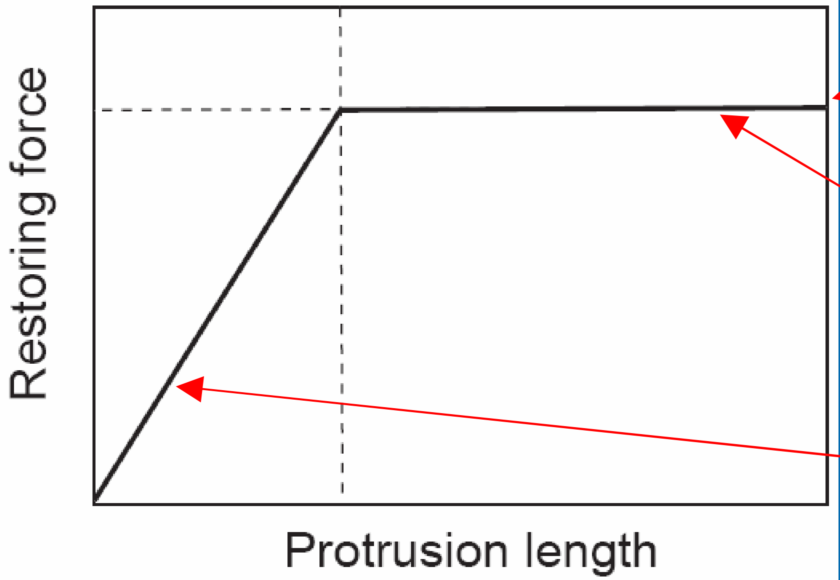
- Also important are bundling proteins such as Fascin
- Tip contains formins, protecting actin from capping



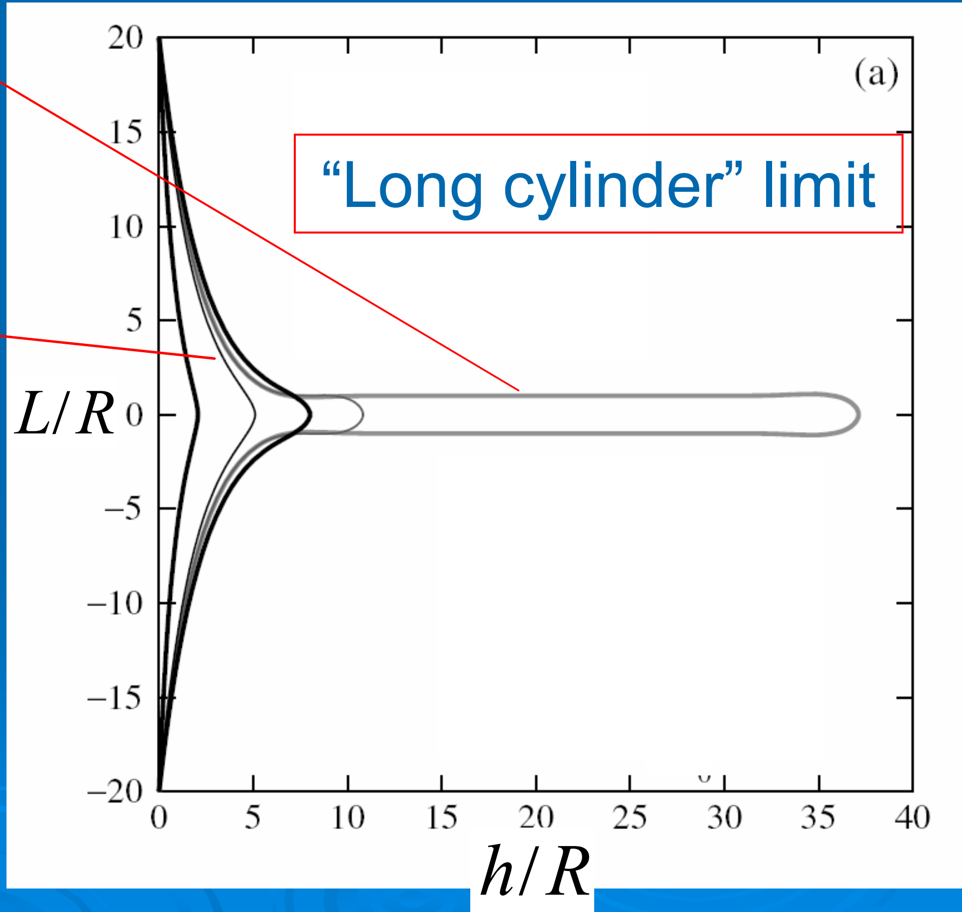
Tatyana M. Svitkina,[1] Elena A. Bulanova,[2] Oleg Y. Chaga, Danijela M. Vignjevic,[1] Shin-ichiro Kojima, Jury M. Vasiliev,[2] and Gary G. Borisy
The Journal of Cell Biology, Volume 160, Number 3, February 3, 2003 409–421

Restoring force: saturation

$h_c \propto L$



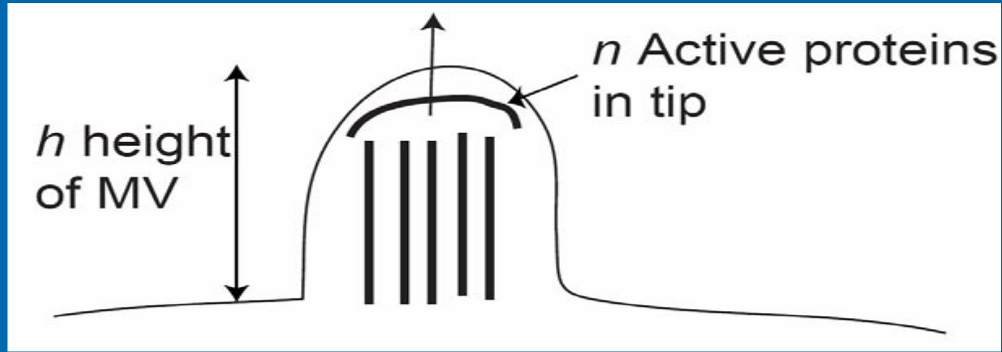
$F_0 \approx \kappa / R$



I. Derényi, F. Jülicher and J. Prost, *Phys. Rev. Lett.* **88** (2002) 238101.

Equation of motion

$$\frac{\partial h}{\partial t} = -\omega h + An$$



Where:

$$\omega \propto F_0 / h_c$$

Restoring force

$$v_0 = A\langle n \rangle$$

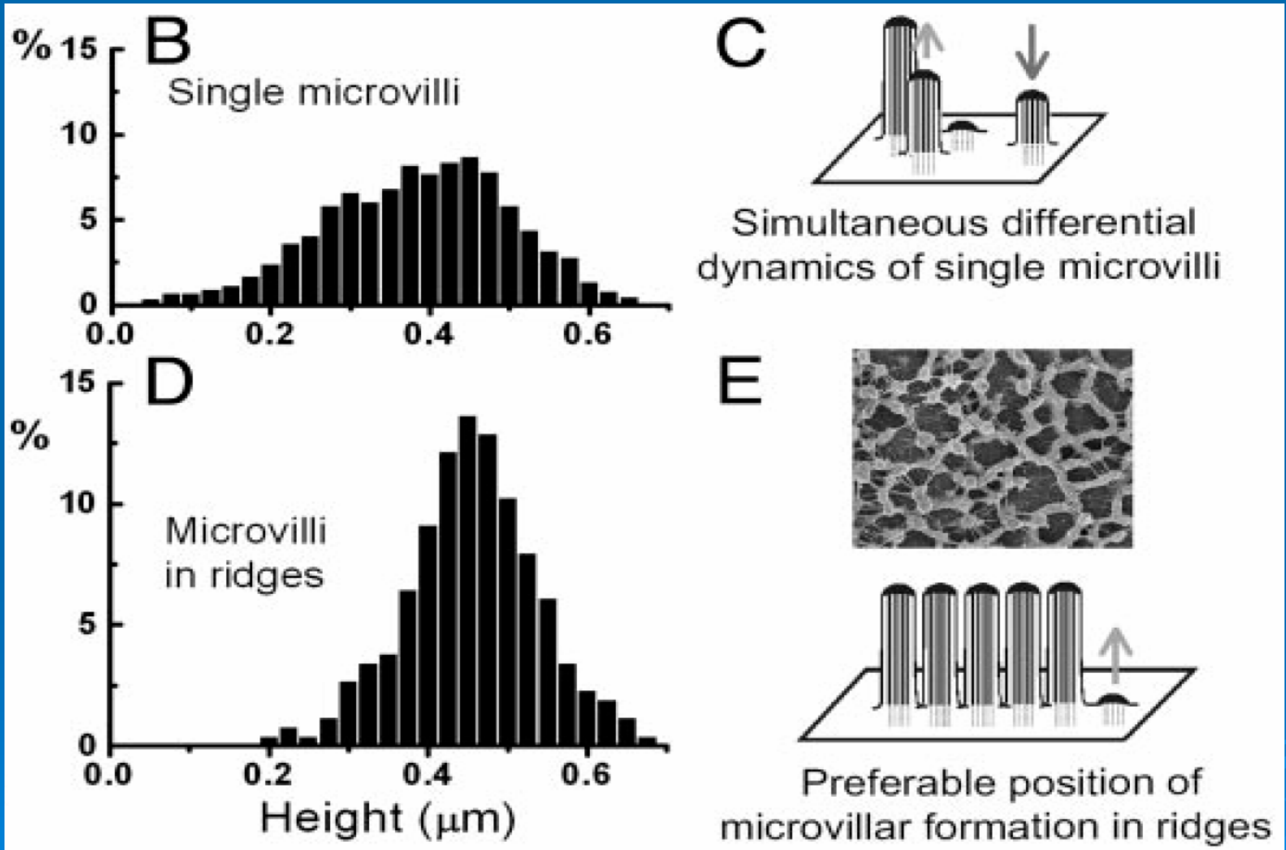
Growth velocity

And a noise term:

$$\left\langle \left(n - \langle n \rangle\right)^2 \right\rangle \neq 0$$

Microvilli: Height distribution

Observations:



J. Gorelik *et. al.* ; PNAS 100, 5819–5822 (2003)

Microvilli: Height probability distribution

From the equation of motion

→ Fokker-Planck equ.:

$$\frac{\partial P}{\partial t} = \frac{\partial}{\partial h}(\omega h P) + \frac{1}{2}\frac{\partial^2 P}{\partial h^2}\frac{A}{\omega}\langle n^2\rangle - \frac{\partial P}{\partial h}A\langle n\rangle$$

At steady-state we get: $\partial P / \partial t = 0$

$$\Rightarrow P(h) = R_n e^{2hv_0/D_h} e^{-h^2\omega/D_h}$$

where:

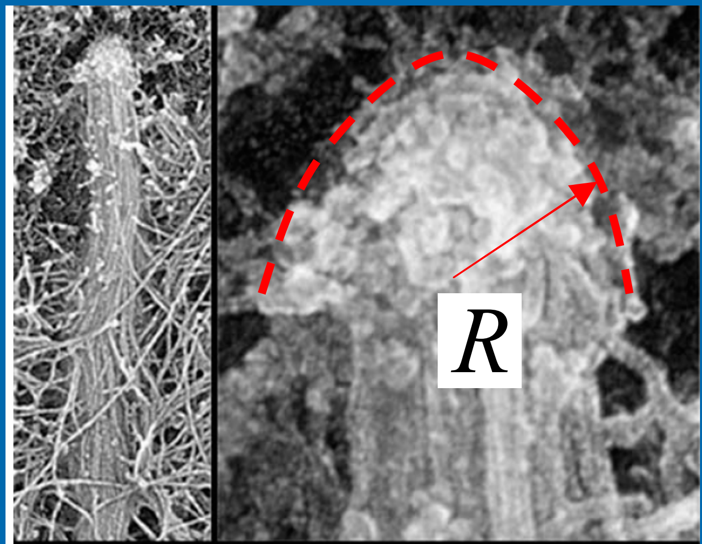
$$D_h = A^2\langle n^2\rangle/\omega = (\Delta n/n_0)^2 v_0^2/\omega$$

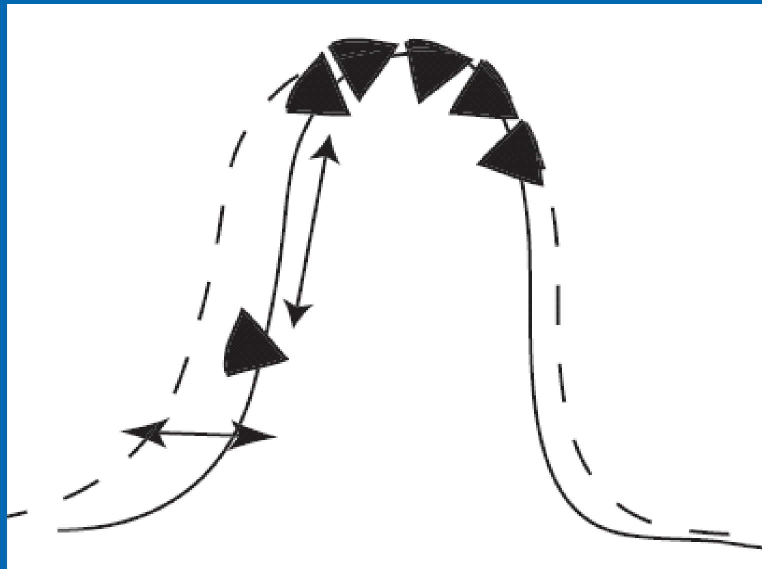
Describes the distribution of tip activity

Fluctuations in the size of the MV tip

Aggregation driven by spontaneous curvature:

$$n \propto R^2$$



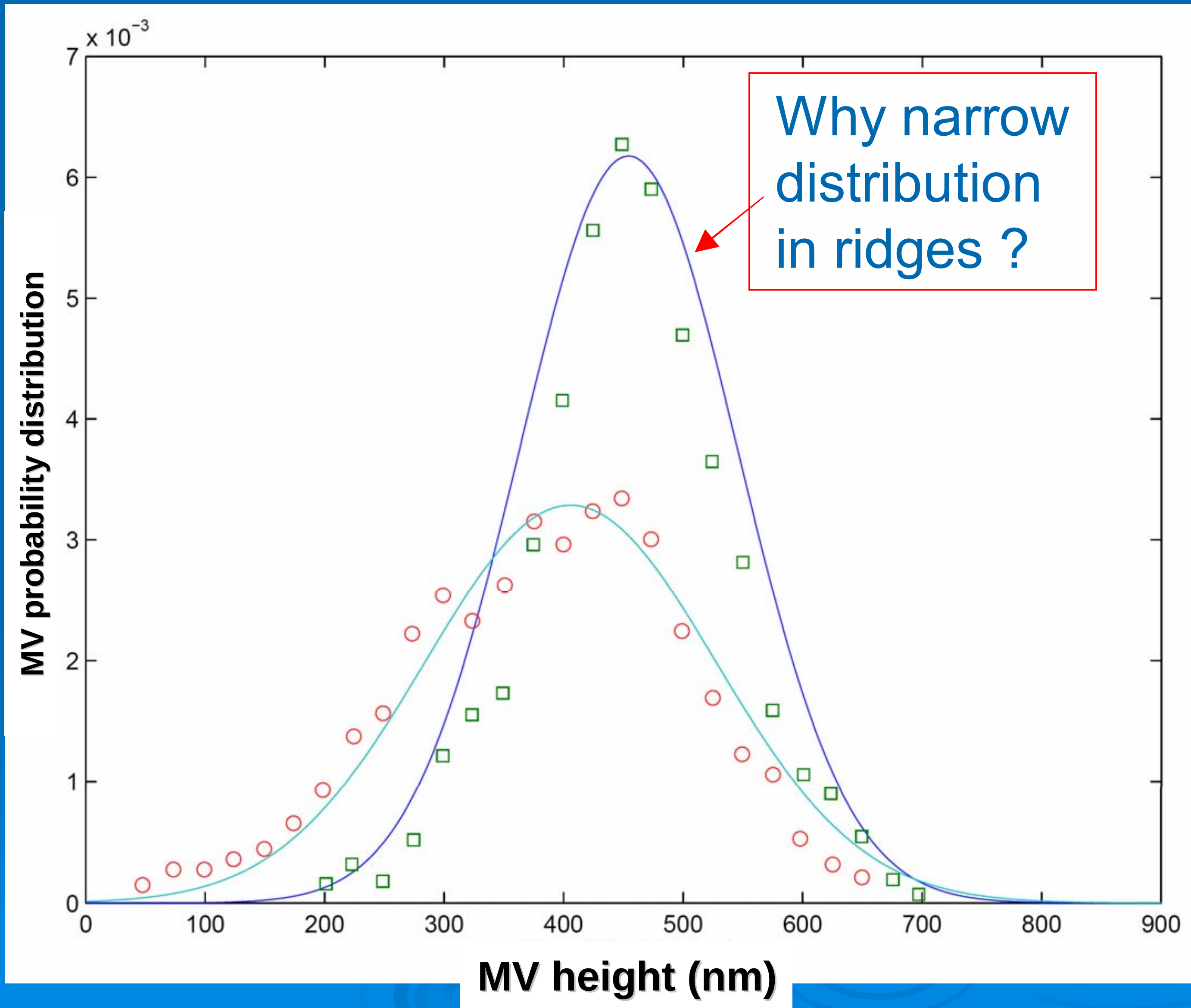


$$\langle n^2 \rangle = \frac{k_B T}{\partial^2 E_n / \partial n^2} \approx n_0^2 \frac{k_B T}{\kappa} \Rightarrow \left(\frac{\Delta n}{n_0} \right)^2 \approx \frac{k_B T}{\kappa}$$

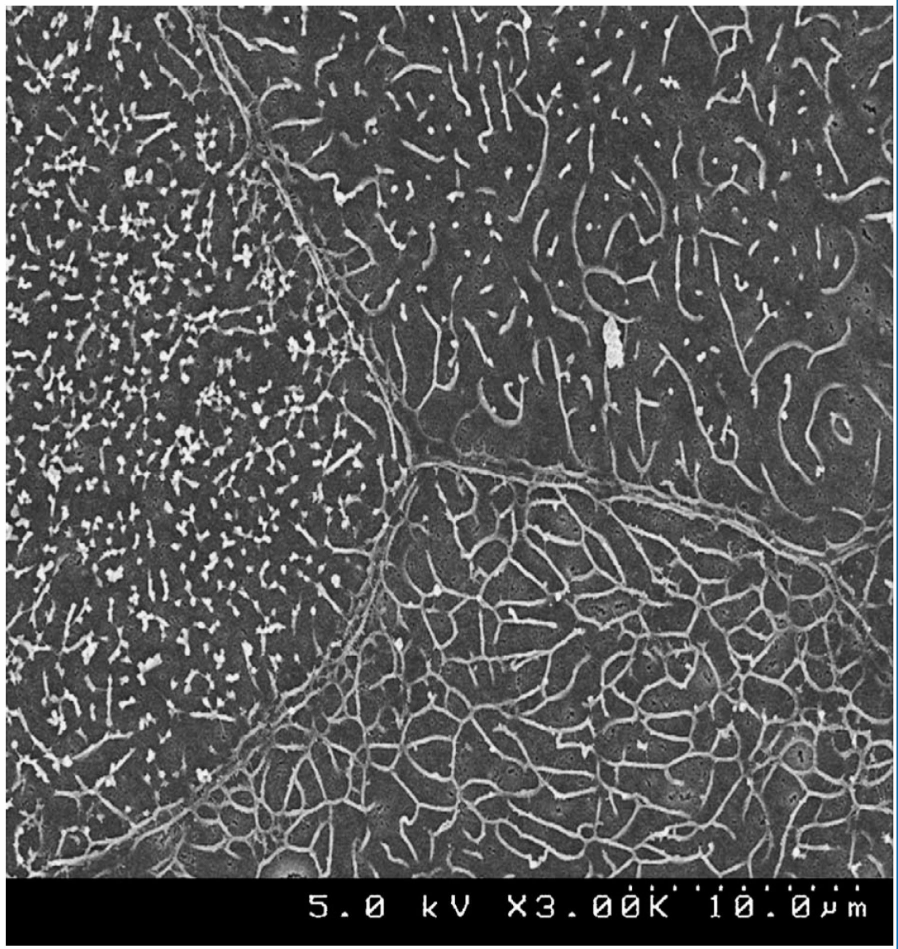
Thermal noise !

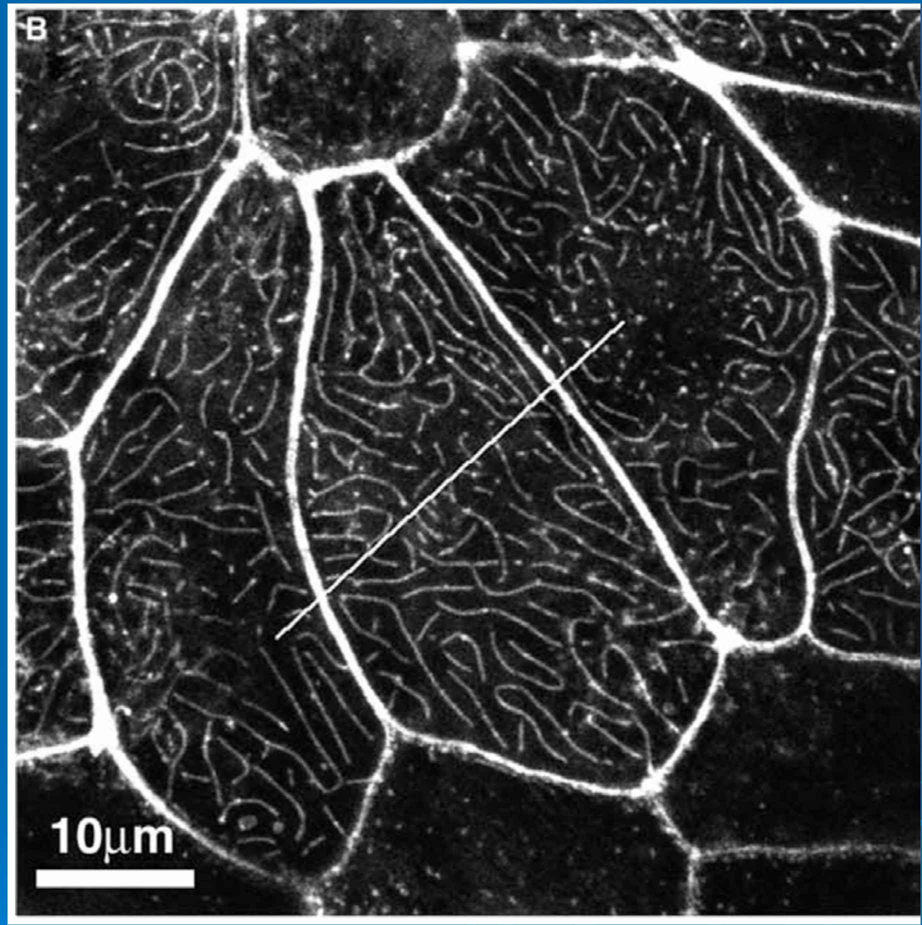
Typically κ~5-20 $k_B T$

Microvilli: Height probability distribution



Microvilli: Spatial distribution/patterns



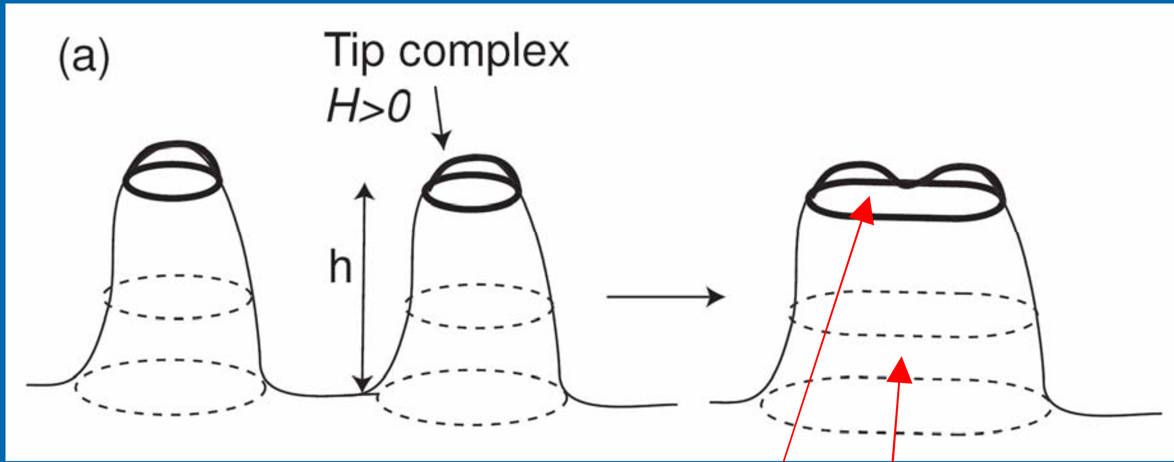


J. Gorelik *et. al.* ;
Mol. Cell. Endo. 217 (2004) 101

A. Sharma *et. al.* ;
FEBS Letters 579 (2005) 2001

Microvilli: Spatial distribution/patterns

MV-MV attractive interactions:



Reduced membrane curvature energy between the MV:

$$E_{curv} \approx \frac{\kappa h}{R}$$

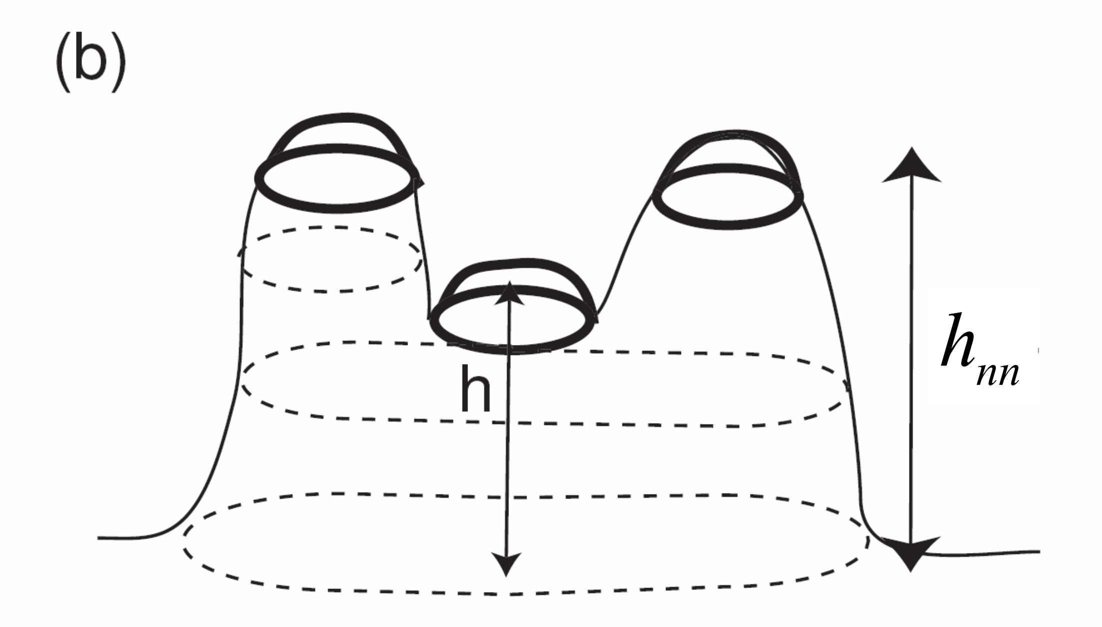
Increased curvature energy of flattened tip:

$$E_{bend} \approx \frac{\pi\kappa}{8}$$

Min. height for ridge:

$$E_{curv} \geq E_{bend} \Rightarrow h_{ridge} \approx \frac{\pi}{8} R$$

Microvilli: ridges & height distribution



MV of unequal heights attract each other less then MV of equal heights

$\Rightarrow$ Additional restoring force: $-\omega\left(h-h_{nn}\right)$

MV in ridges: Height prob. distribution

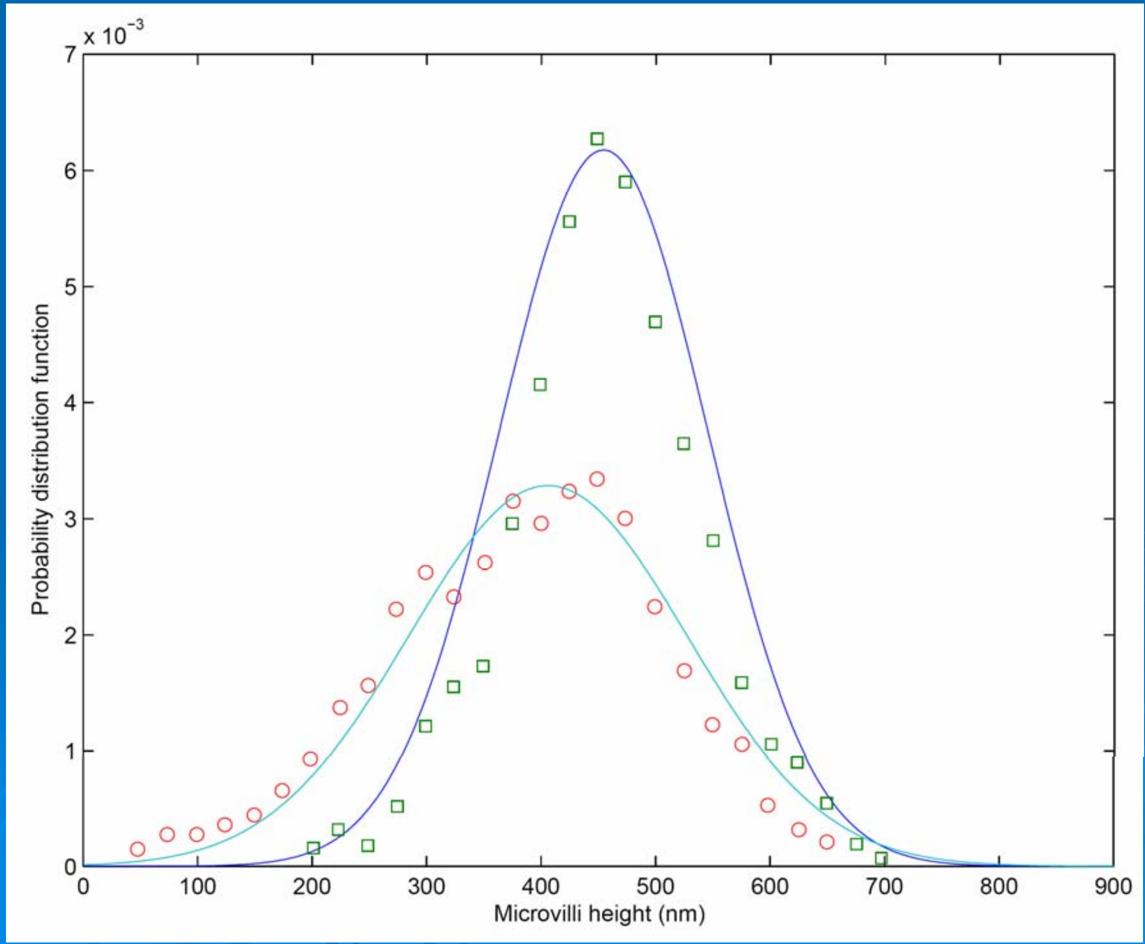
Ridge height equation of motion:

$$\frac{\partial h}{\partial t} = -\omega h + An_0 - \omega\left(h - h_{nn}\right)$$

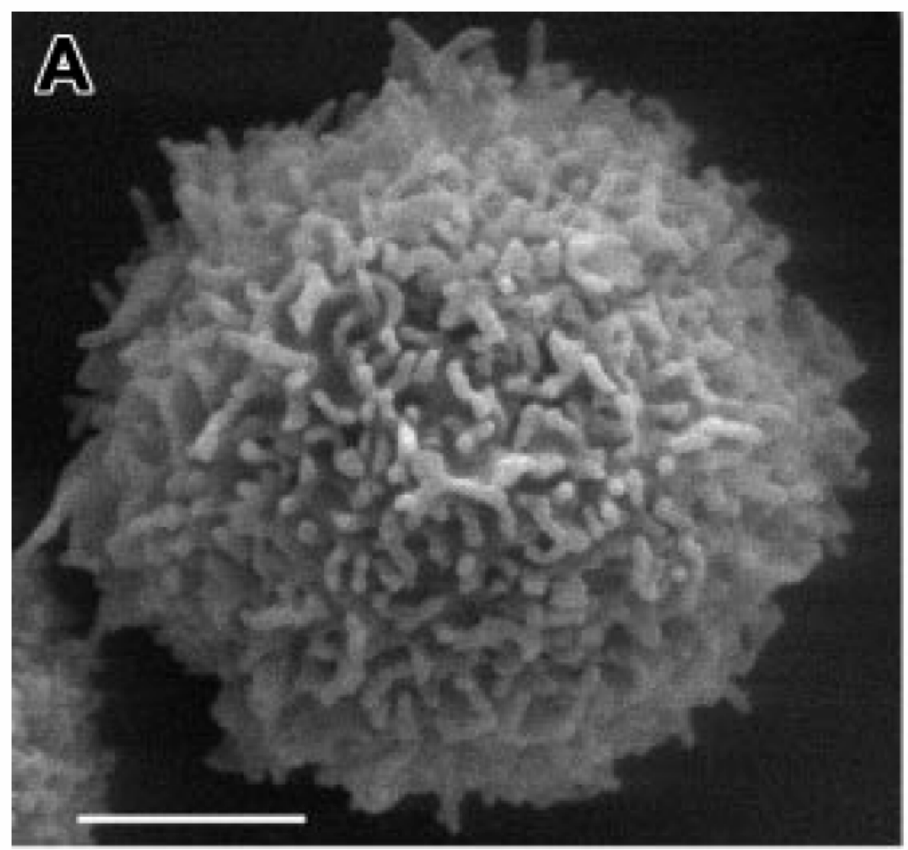
Mean-field:

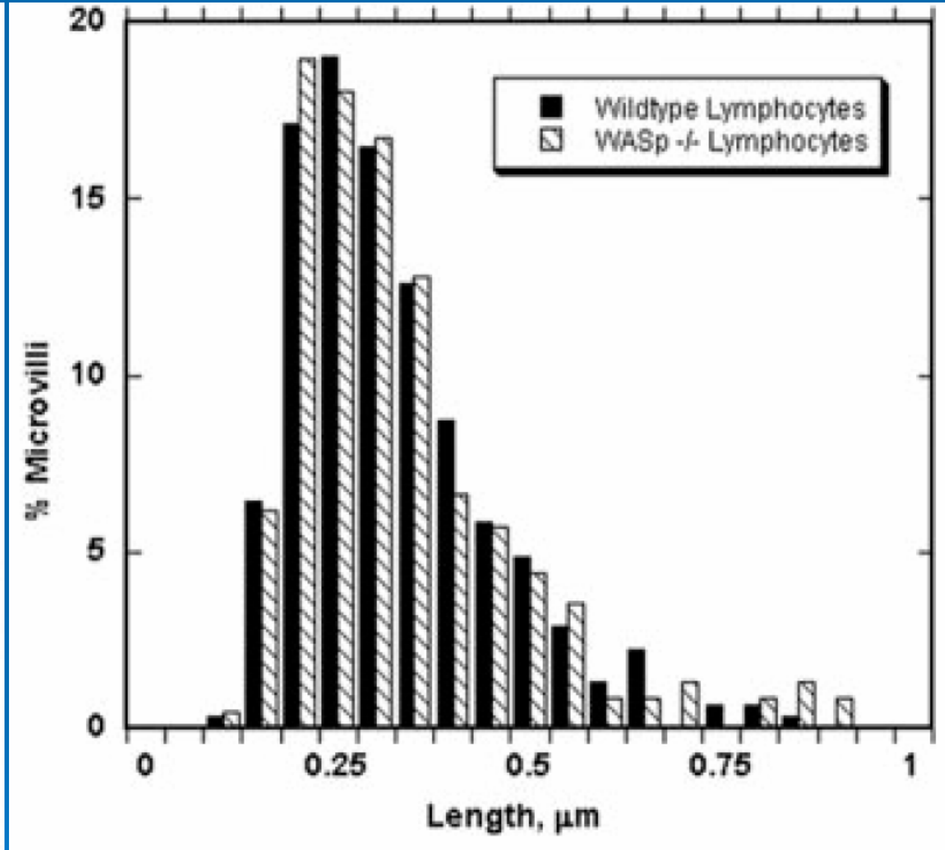
$$h_{nn} \approx \langle h \rangle$$

$\Rightarrow$



Exponential tails: due to force saturation

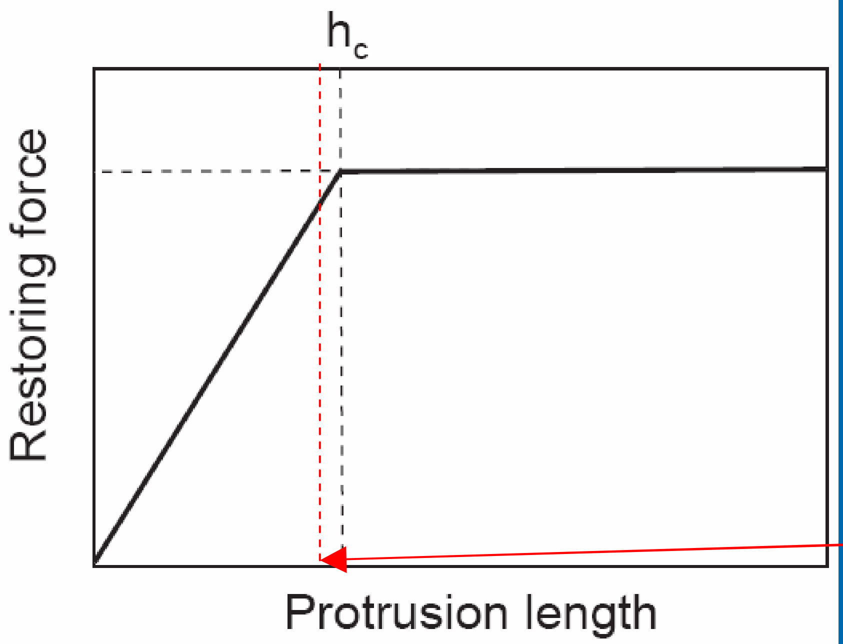




human blood lymphocyte

S. Majstoravich *et. al.* ; BLOOD (2004) 104, 1396.

Long Microvilli: Force saturation



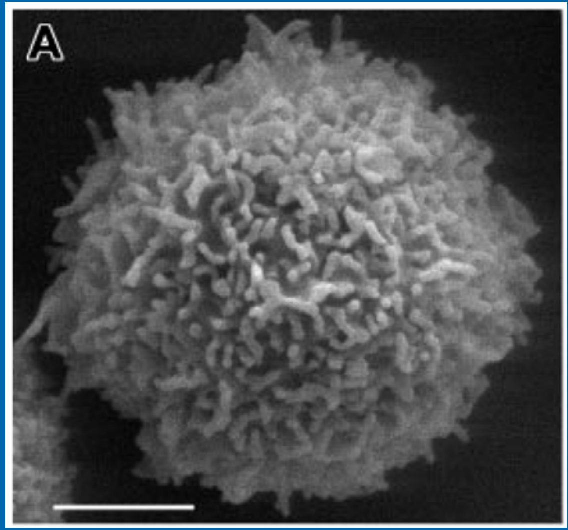
$$\Rightarrow \frac{\partial h}{\partial t} = \begin{cases} -\omega h + An & h < h_c \\ -\omega h_c + An & h > h_c \end{cases}$$

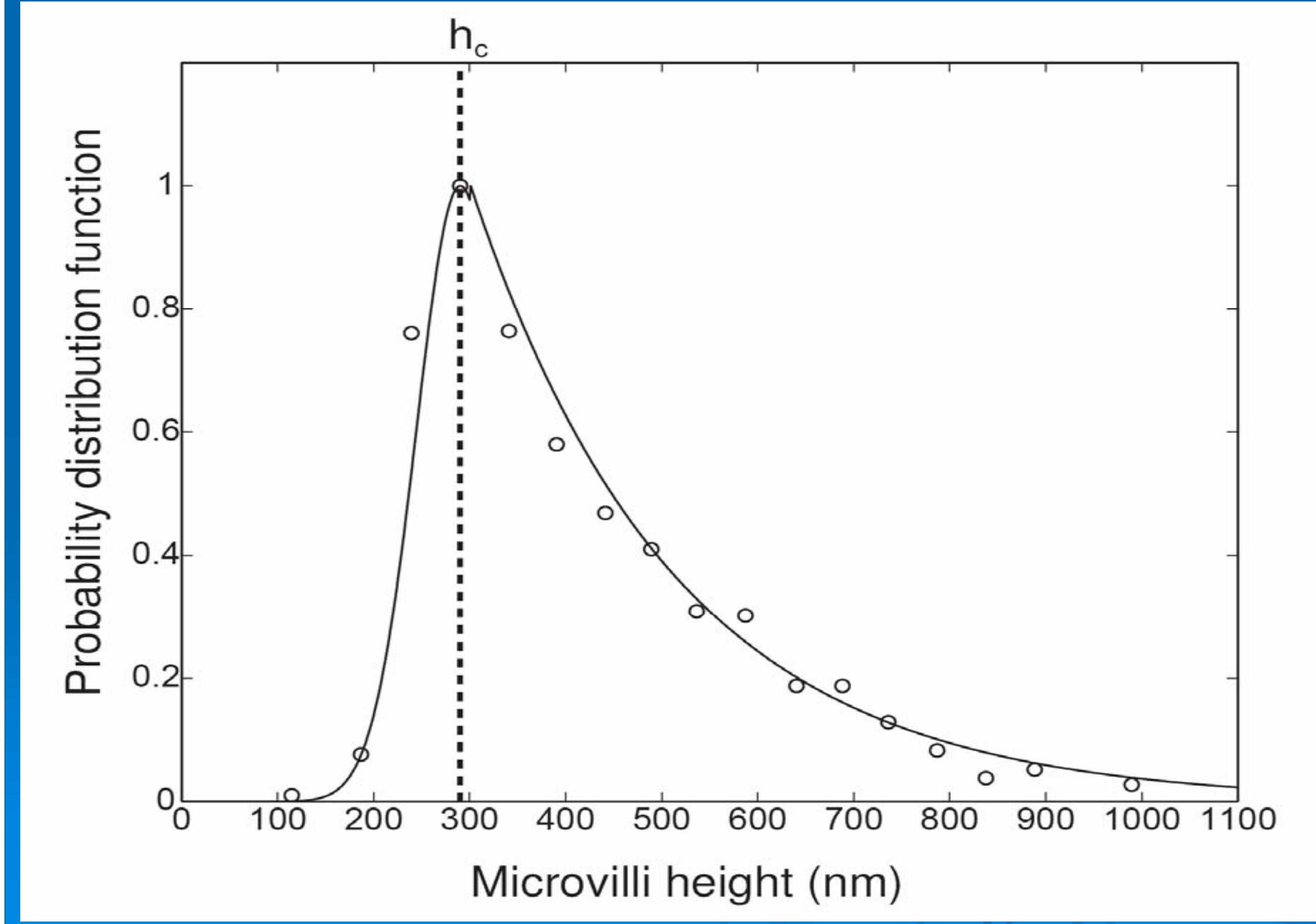
$$\langle h \rangle \approx A\langle n \rangle / \omega < h_c$$

$$P(h) = \begin{cases} R_n e^{2hv_0/D_h} e^{-h^2\omega/D_h} & h < h_c \\ R_n' e^{2h(-\omega h_c + A\langle n \rangle)/D_h} & h > h_c \end{cases}$$

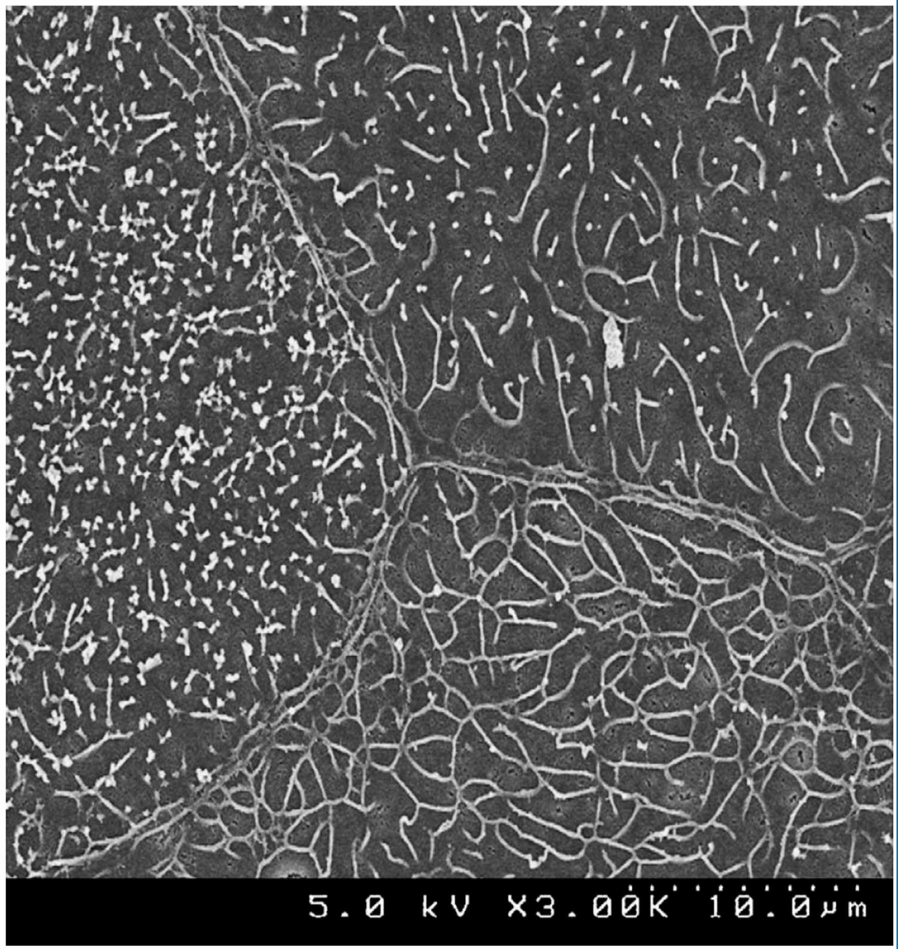
Gaussian replaced by long exponential tail

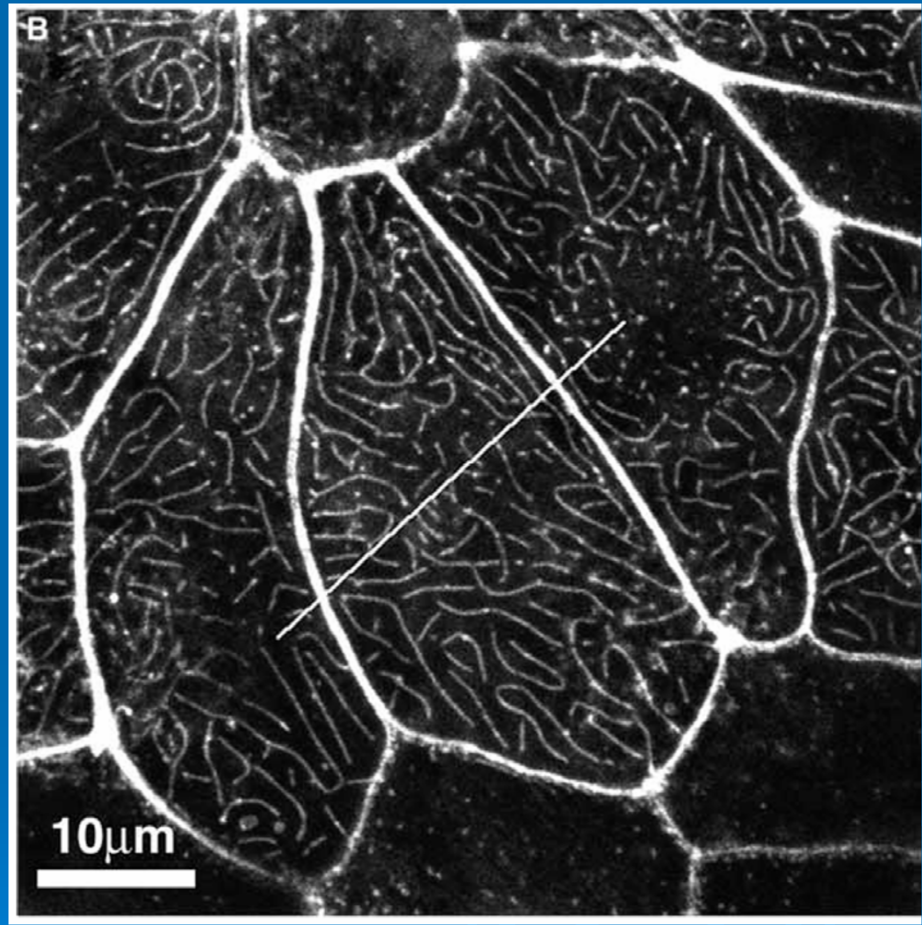
Long MV: Height probability distribution





Microvilli: Spatial distribution/patterns



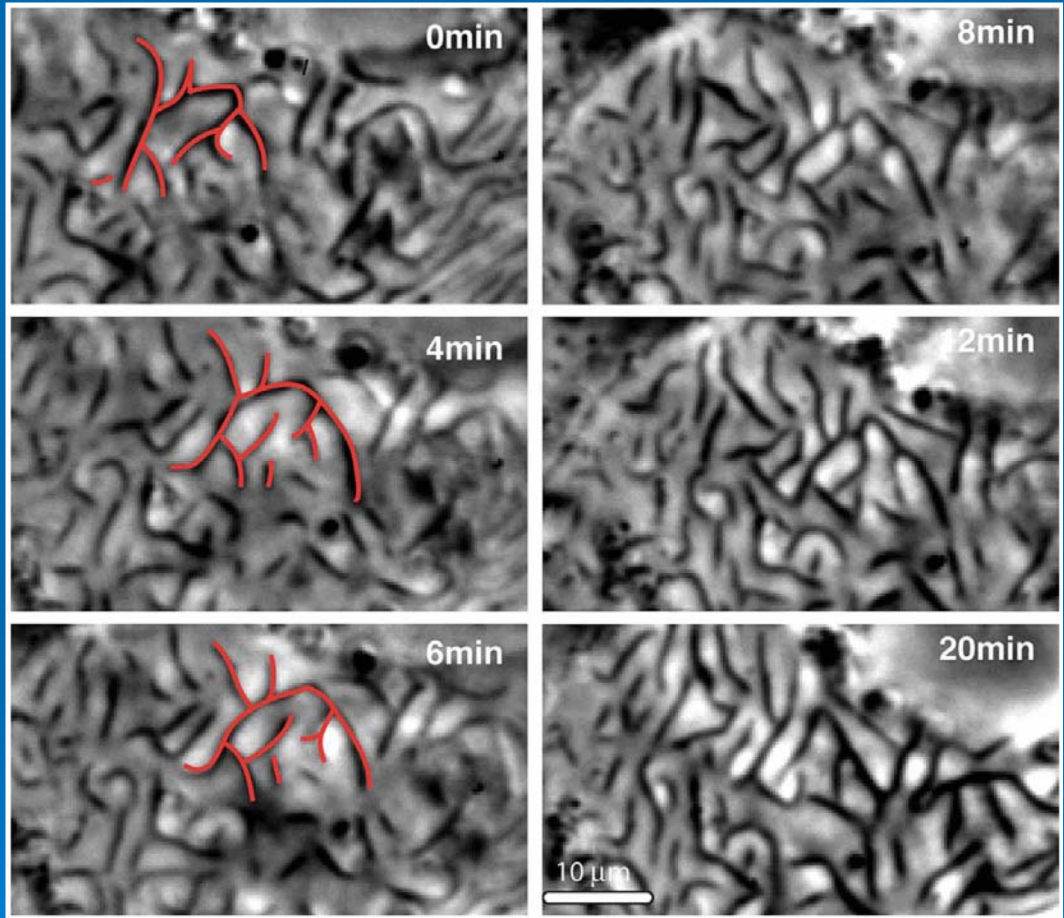


J. Gorelik *et. al.* ;
Mol. Cell. Endo. 217 (2004) 101

A. Sharma *et. al.* ;
FEBS Letters 579 (2005) 2001

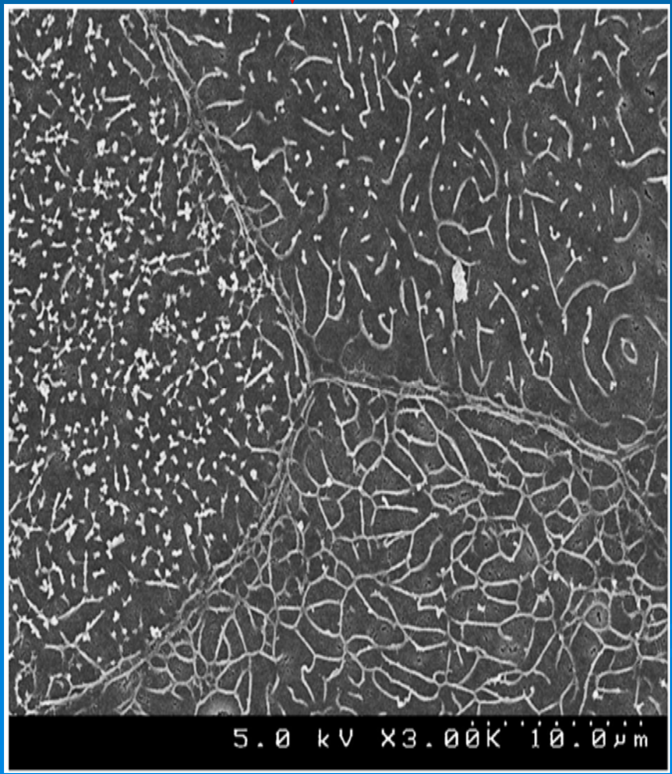
Microvilli: Spatial distribution/patterns

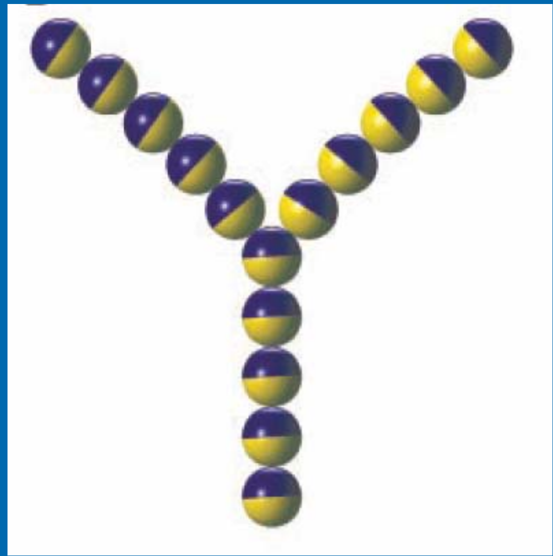
- Dynamic → T_{eff}
- “Thermodynamic” phase diagram



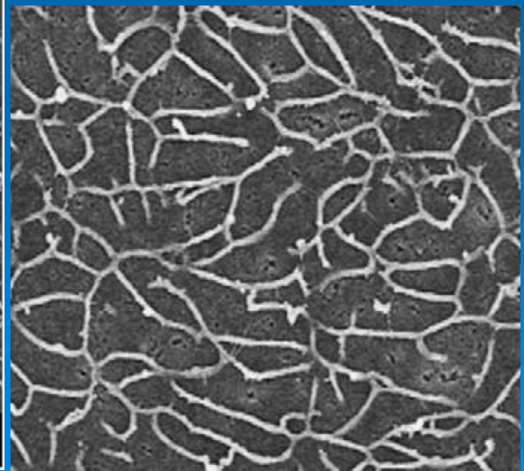
Microvilli: Spatial distribution/patterns

• Linear aggregates due to positive spontaneous curvature of tip complex





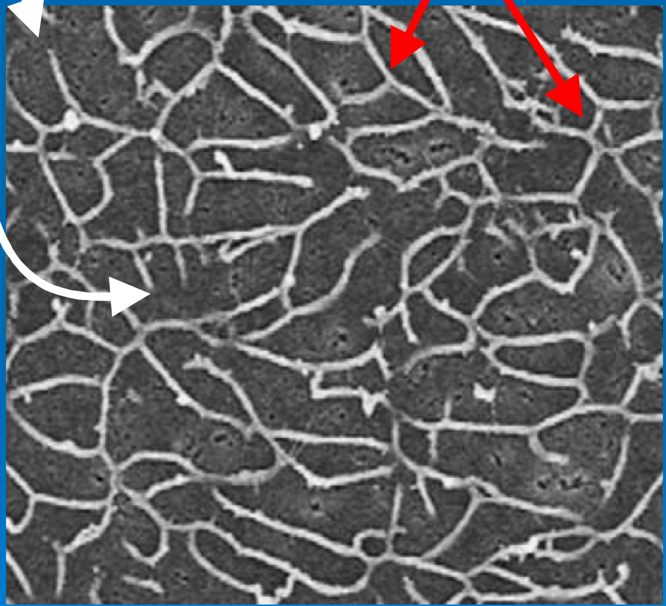
T. Tlusty & S. Safran; Science 290 (2000) 1328



2D dipolar fluid, network of worm-like micelles etc.

Microvilli: Spatial distribution/patterns

- Assume single height of MV: <h>
- Excluded volume interactions
- Defects: free ends and 3-fold junctions



Based on:
Zilman, A; Safran, S.A.; Sottmann, T.; Strey, R.; *Langmuir*, **20** 2199 (2004).

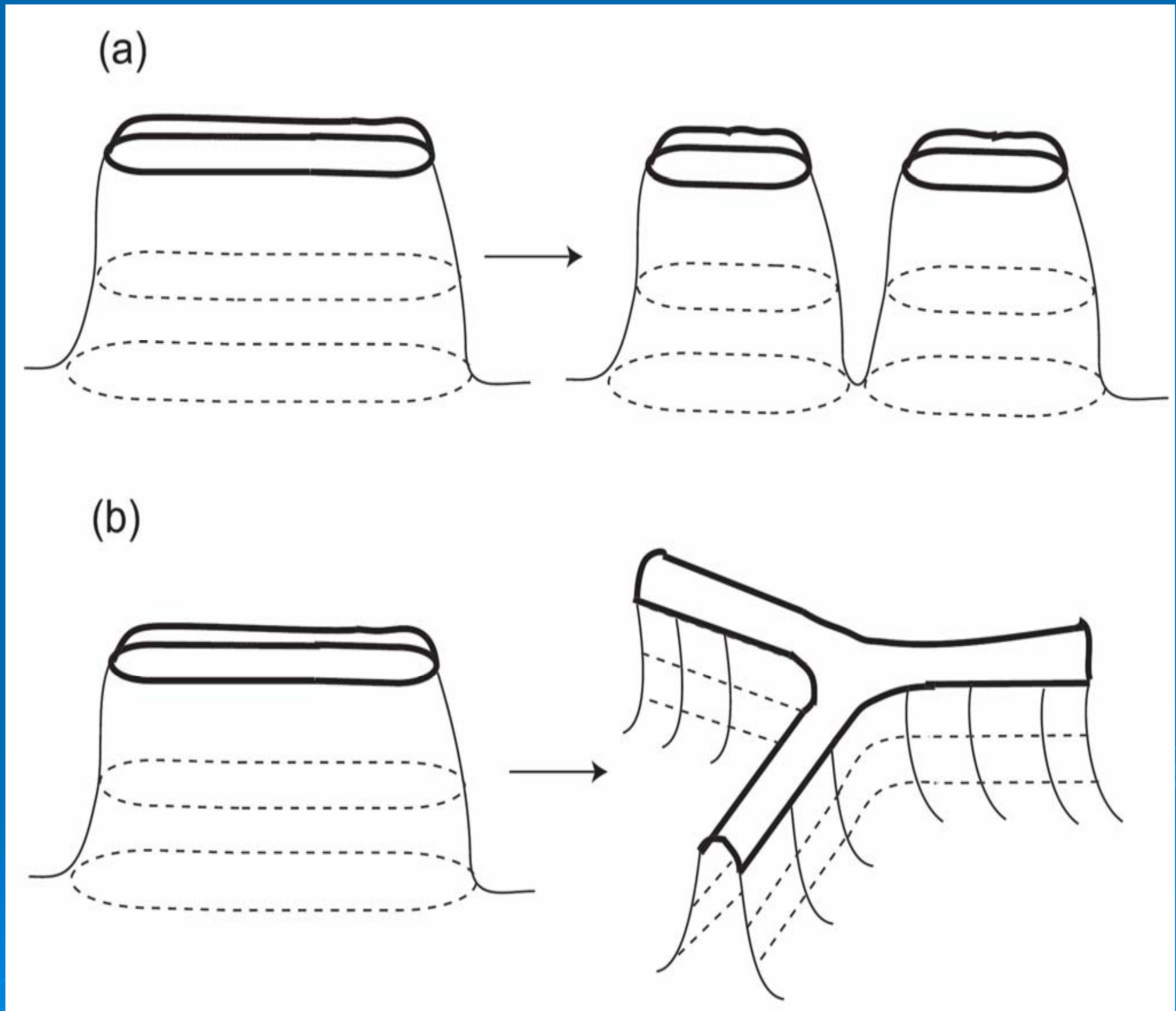
Microvilli: Energy of defects

$$E_{end} \approx \frac{2\pi\kappa h}{R} - \frac{\pi\kappa}{8}$$

Increases with *h*

$$E_{junct} \approx \frac{\pi\kappa h}{6R} + \frac{2\pi\kappa}{15}$$

Increases more slowly with *h*



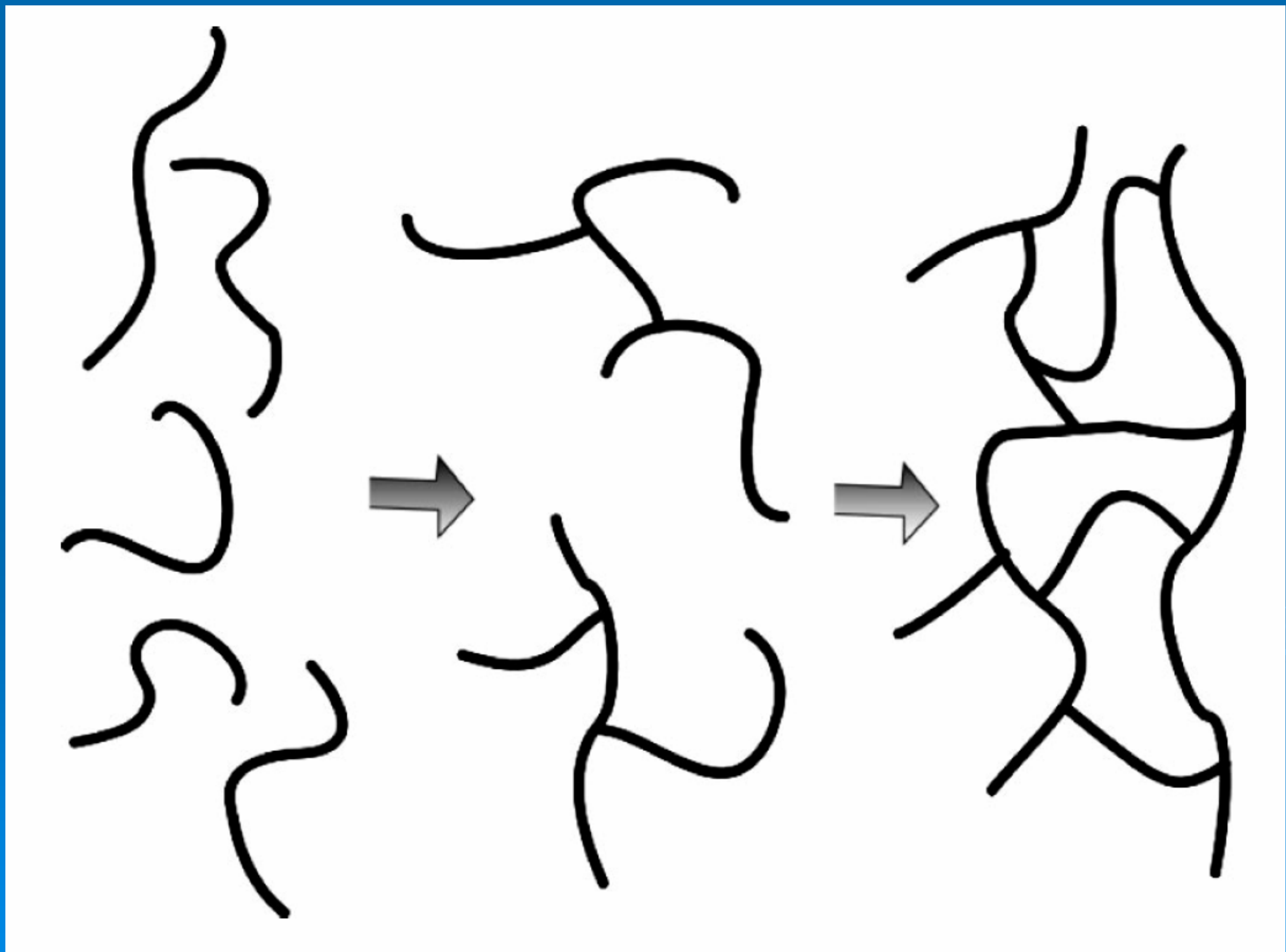
Formation of networks

If the MV height increases, junctions multiply over ends:

Phase transition to a connected network:

$$\partial^2 F/\partial\phi^2 = 0$$

Spinodal



Free energy of gas of defects

$$F(\phi)/k_BT = (1-\phi)\ln(1-\phi) + \phi_e(\ln\phi_e - 1) + \phi_j(\ln\phi_j - 1) + \phi_e\epsilon_e + \phi_j\epsilon_j - \frac{1}{2}\phi_e\ln\phi - \frac{3}{2}\phi_j\ln\phi$$

Φ is the area fraction of the MV

Φ_e & Φ_j is the area fraction of the ends and 3-fold junctions respectively

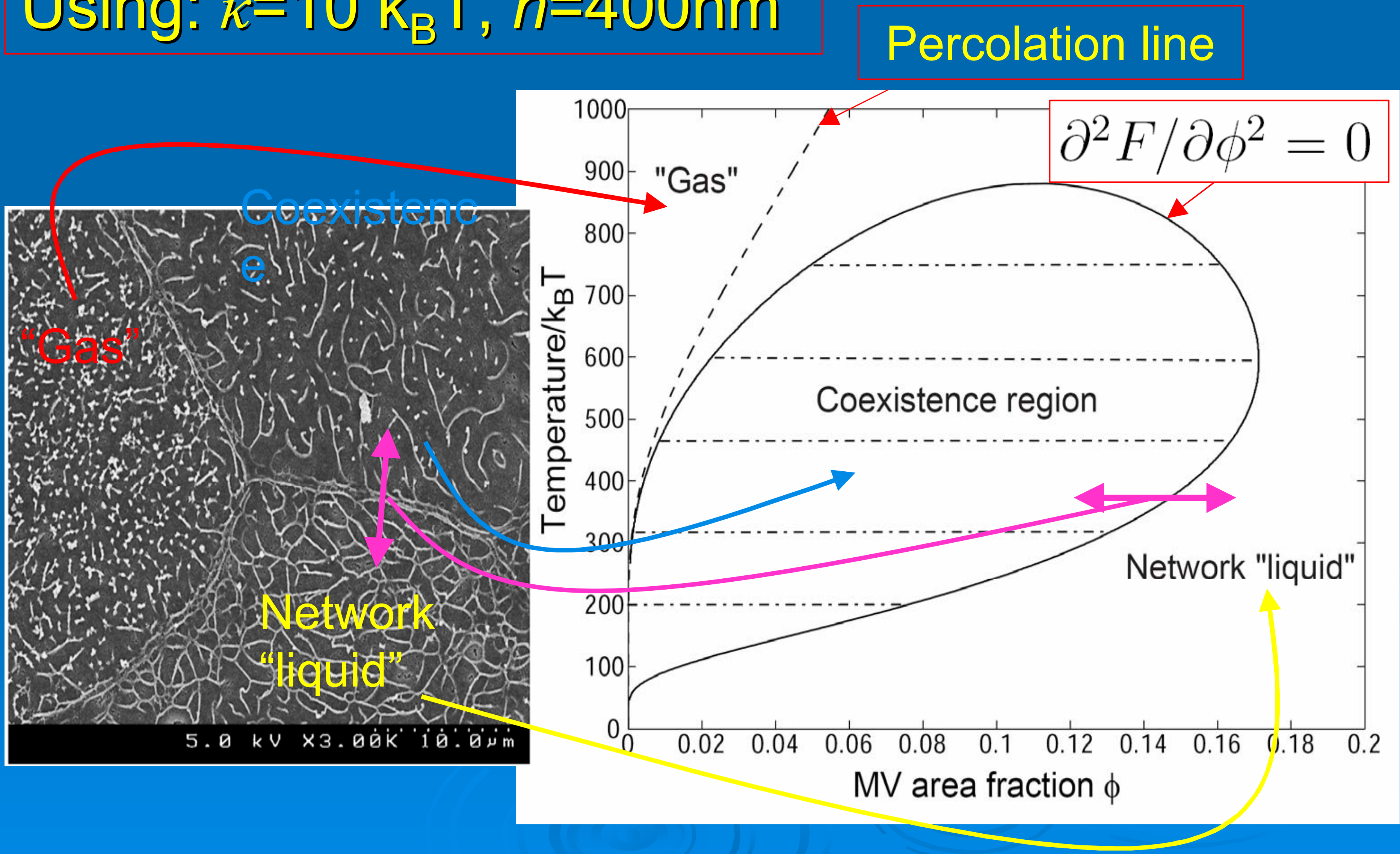
Minimize with respect to independent defects' concentrations:

$$\phi_j = \phi^{3/2}e^{-\epsilon_j}$$

$$\phi_e = \phi^{1/2}e^{-\epsilon_e}$$

Microvilli: Spatial distribution/patterns

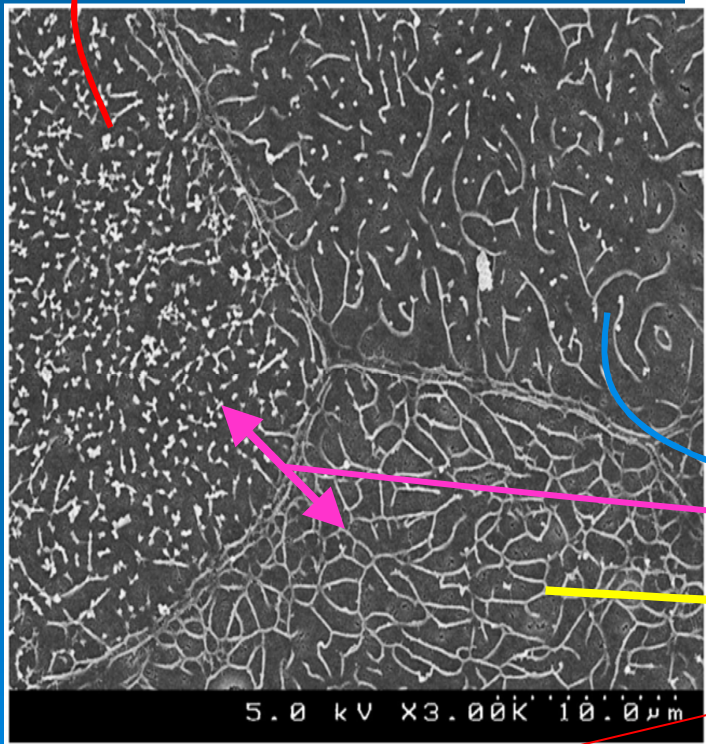
Using: κ=10 k_BT, h=400nm

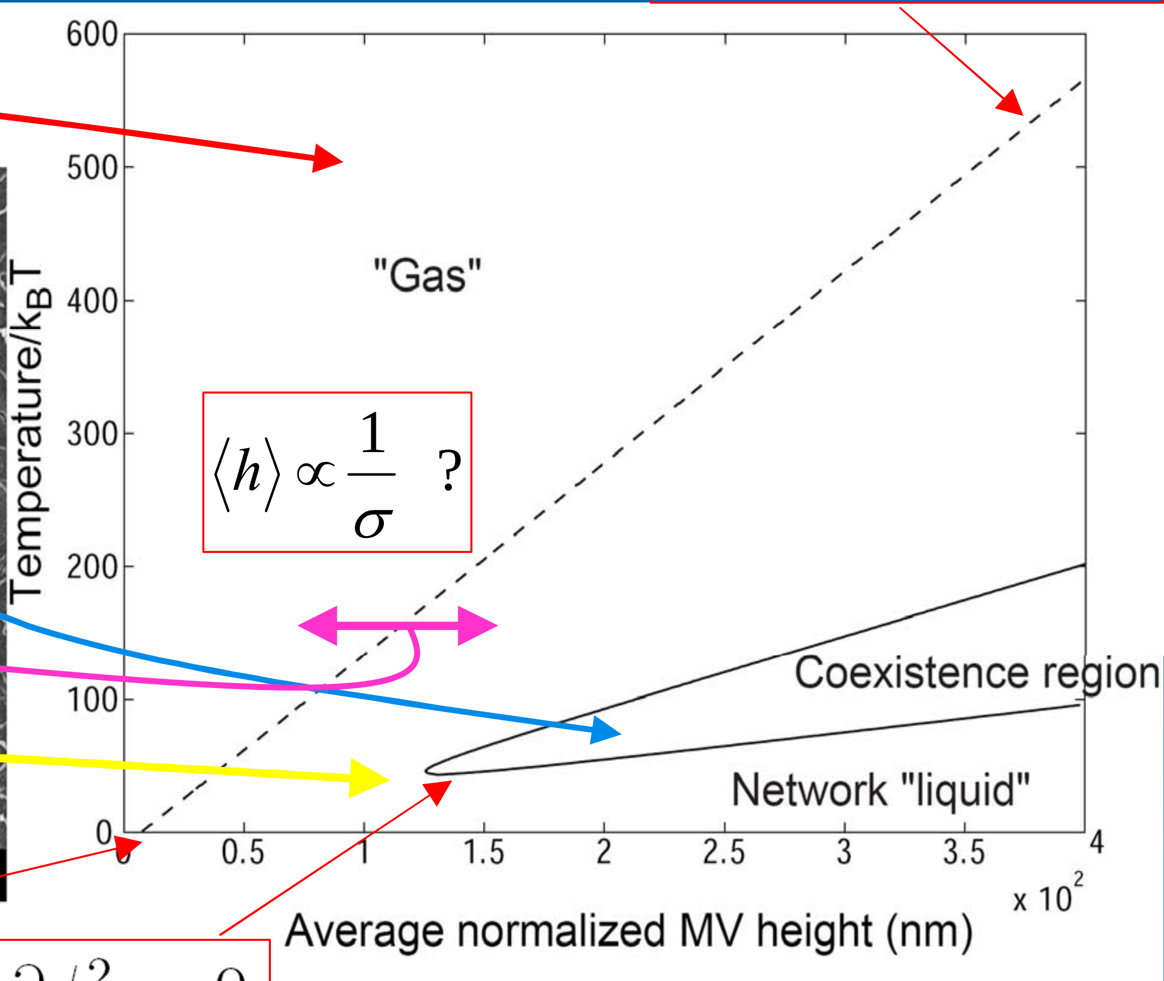


Note: Large “effective” temperature

Using: κ=10 k_BT, Φ=0.05

Percolation line



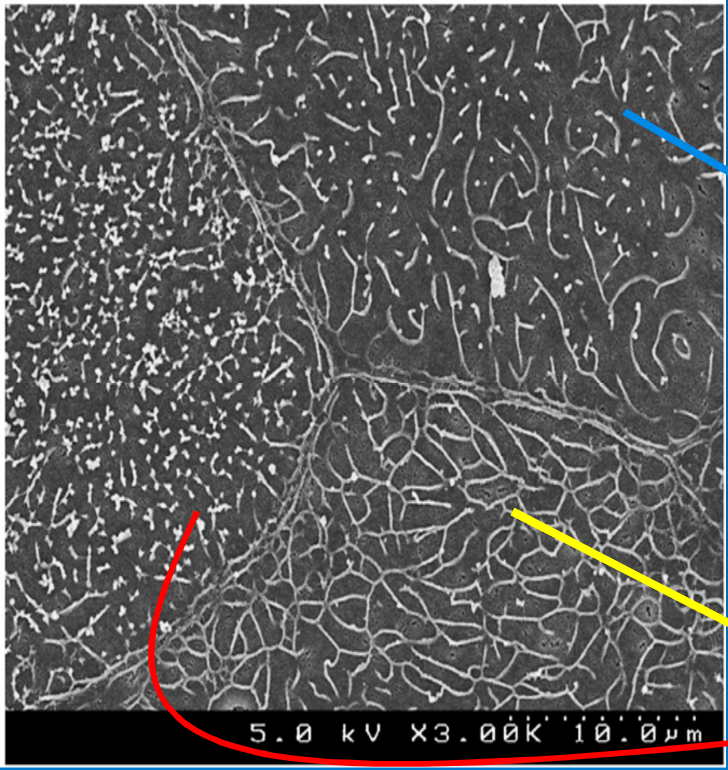


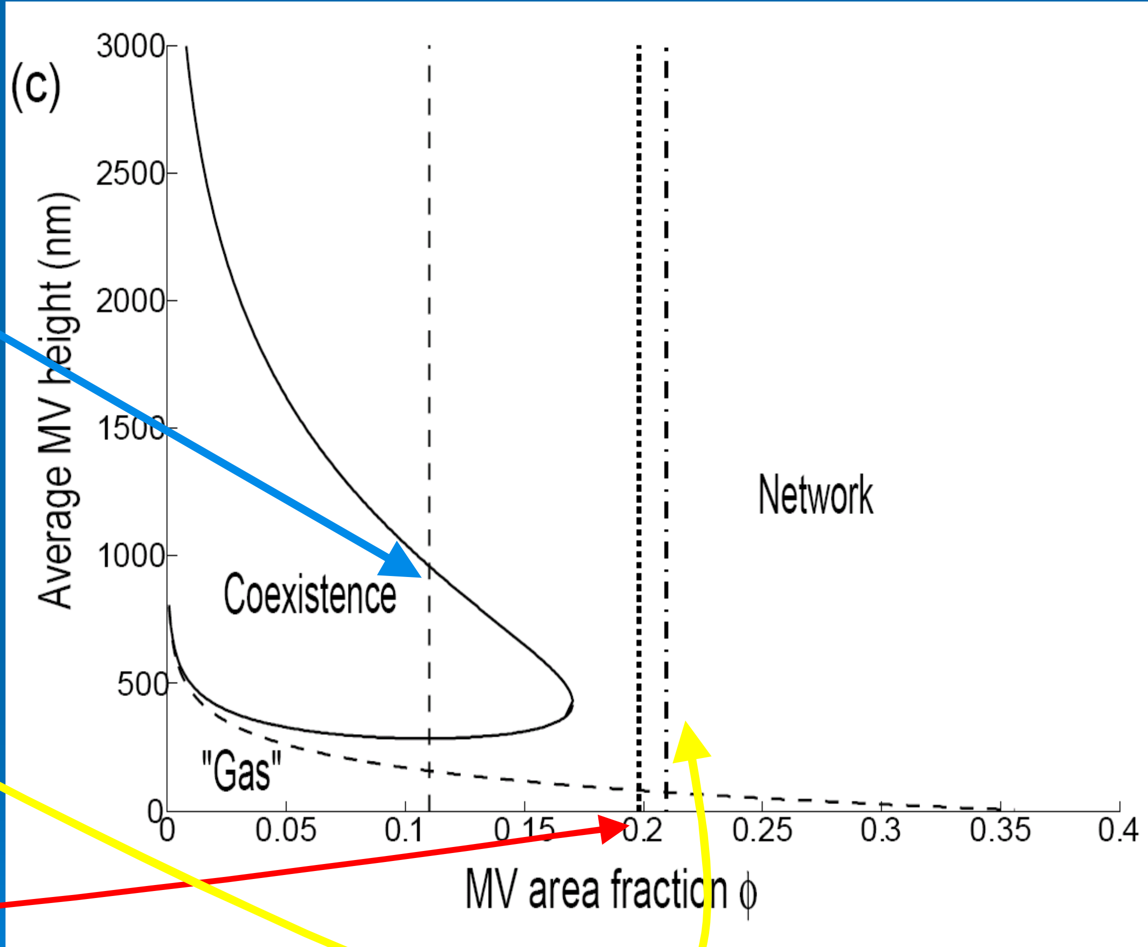
$$\langle h \rangle \propto \frac{1}{\sigma} \quad ?$$

$$h_{ridge} \approx \frac{\pi}{8} R$$

$$\partial^2 F / \partial \phi^2 = 0$$

height-density phase diagram





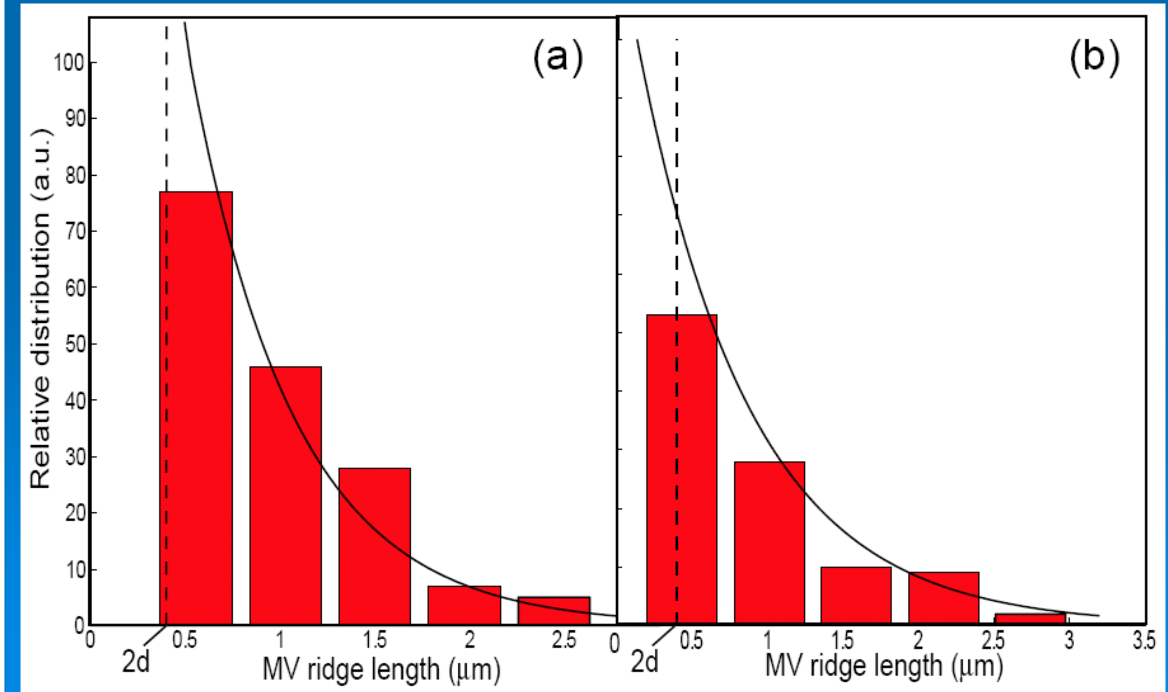
Using a fixed T_{eff}

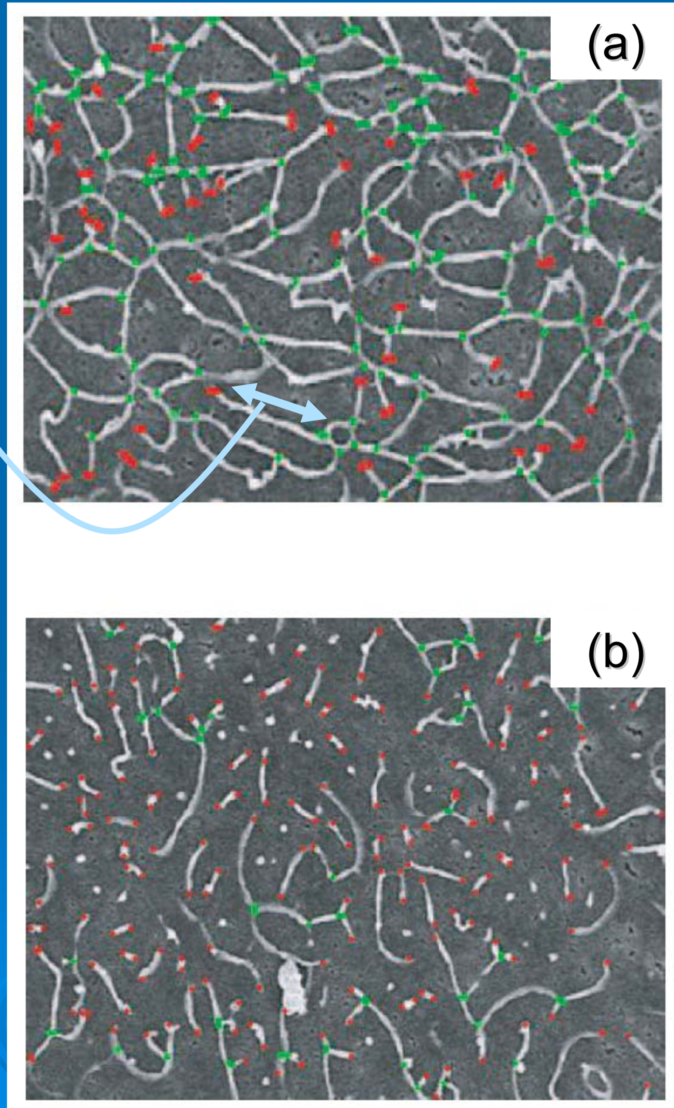
Does it really behave as "active"-thermodynamics ?

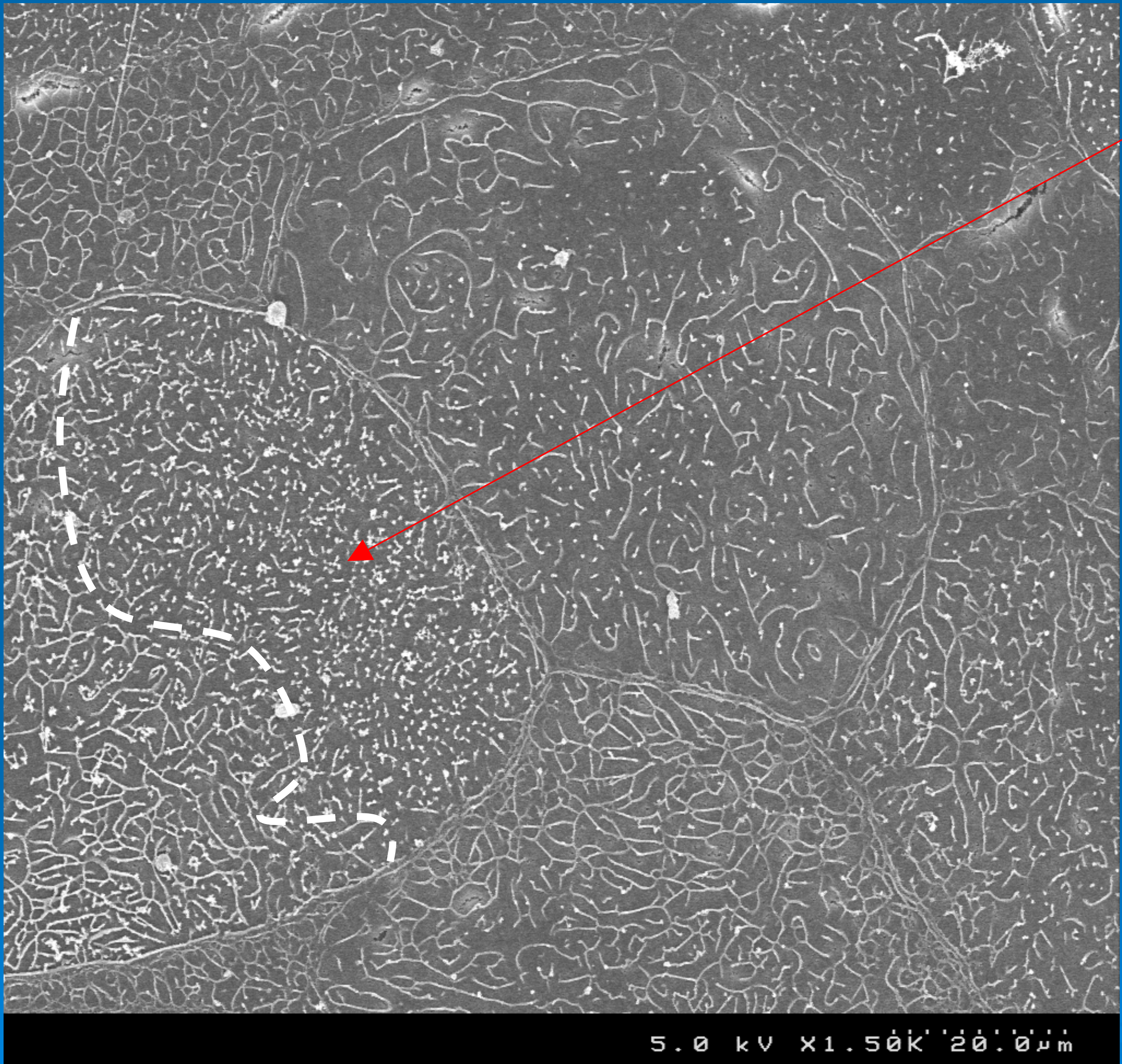
Predictions of thermodynamic theory:

$$P(l) \sim \bar{e}^{l/\bar{l}}, \text{where}: \ \bar{l} = \frac{\phi}{\phi_e/2 + 3\phi_j/2}$$

l







- Phase separation ?
- What changes between cells ?
- Equilibrium between systems in contact ?

J. Gorelik *et. al.*

Conclusions

- Spontaneous curvature of membrane proteins that activate actin polymerization drives Microvilli dynamics and morphology.
- Coupling of active and thermal fluctuations on different length and time scales: “Active-Thermodynamics”

Acknowledgements

Theory

Ajay Gopinathan (UCSB)

Sam Safran (WIS)

Jacques Prost (Curie)

Experiment

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Ronen Alon (WIS)

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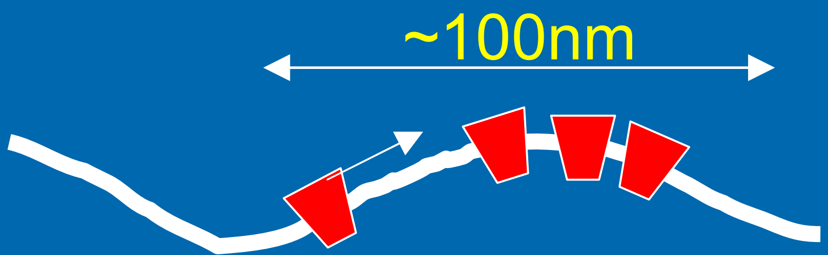
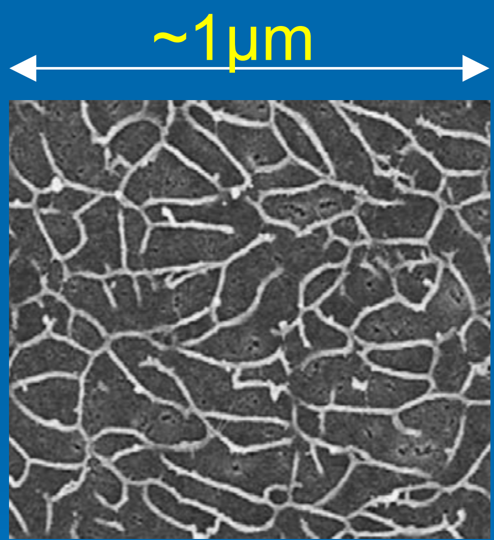
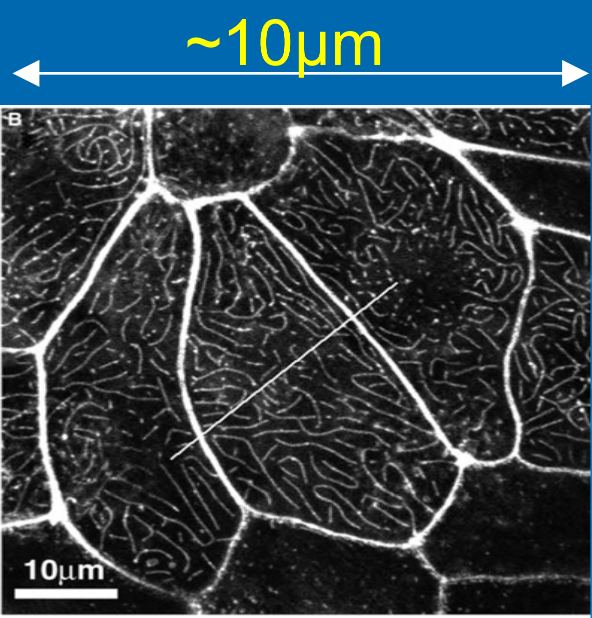
Multi-scale Modeling



Thermal & actin-driven aggregation → Tip formation



Thermal & actin-driven aggregation of MV → Network formation



Cell-wide morphology and shape

Experimental challenge:

We need to characterize the physical parameters of the protein aggregates at the membrane:

- **What is the spontaneous curvature ?**