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"Statistical Biological Physics: From Single Molecule to Cell (ONLINE)"  
7-18 December 2020

# Fluctuations and pattern formation in active membranes

Nir Gov



מכון ויצמן למדע  
WEIZMANN INSTITUTE OF SCIENCE

Department of  
CHEMICAL &  
BIOLOGICAL PHYSICS



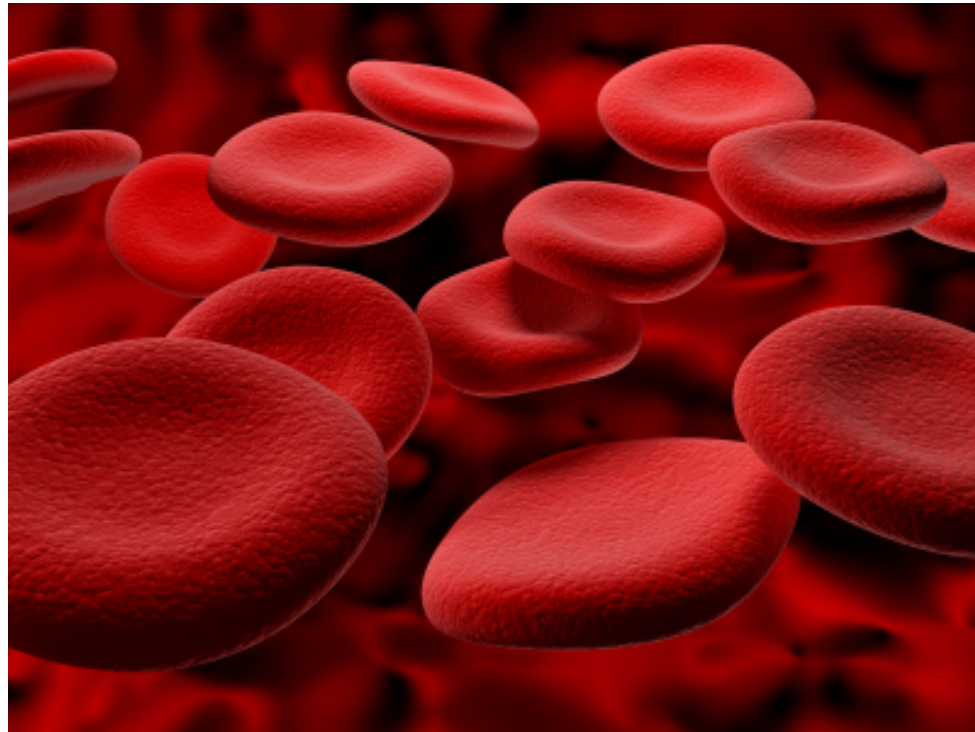
# Outline

- Random active (non-equilibrium) forces acting on cell membranes: active noise

- Directed active (non-equilibrium) forces acting on cell membranes: pattern formation

**We start with the random forces  
acting on a cell membrane**

**The simplest example:  
the Red-Blood Cell**



The “flickering” of the RBC membrane was first observed 45 years ago.

However, only in the past 20 years it was realized that these are not purely thermal fluctuations:



Park, YongKeun, Catherine A. Best, Thorsten Auth, Nir S. Gov, Samuel A. Safran, Gabriel Popescu, Subra Suresh, and Michael S. Feld. "Metabolic remodeling of the human red blood cell membrane." *PNAS* 107, no. 4 (2010): 1289-1294.

# The simplest model: independent motors

PRL **93**, 268104 (2004)

PHYSICAL REVIEW LETTERS

week ending  
31 DECEMBER 2004

## **Membrane Undulations Driven by Force Fluctuations of Active Proteins**

N. Gov

*Department of Chemical Physics, The Weizmann Institute of Science, P.O.B. 26, Rehovot, Israel 76100*  
(Received 2 August 2004; published 20 December 2004)

Biophysical Journal Volume 88 March 2005 1859–1874

1859

## **Red Blood Cell Membrane Fluctuations and Shape Controlled by ATP-Induced Cytoskeletal Defects**

N. S. Gov\* and S. A. Safran<sup>†</sup>

PRL **106**, 238103 (2011)

PHYSICAL REVIEW LETTERS

week ending  
10 JUNE 2011

## **Effective Temperature of Red-Blood-Cell Membrane Fluctuations**

Eyal Ben-Isaac,<sup>1</sup> YongKeun Park,<sup>2</sup> Gabriel Popescu,<sup>3</sup> Frank L. H. Brown,<sup>4</sup> Nir S. Gov,<sup>1,\*</sup> and Yair Shokef<sup>5,†</sup>

Lets remember the continuum model for the bending energy of a membrane:

Helfrich-Canham-Evans free energy

$$G_{\text{bend}} = \frac{\kappa}{2} \int dA \underbrace{(\kappa_1(x, y) + \kappa_2(x, y))}_{2\bar{\kappa}}^2$$

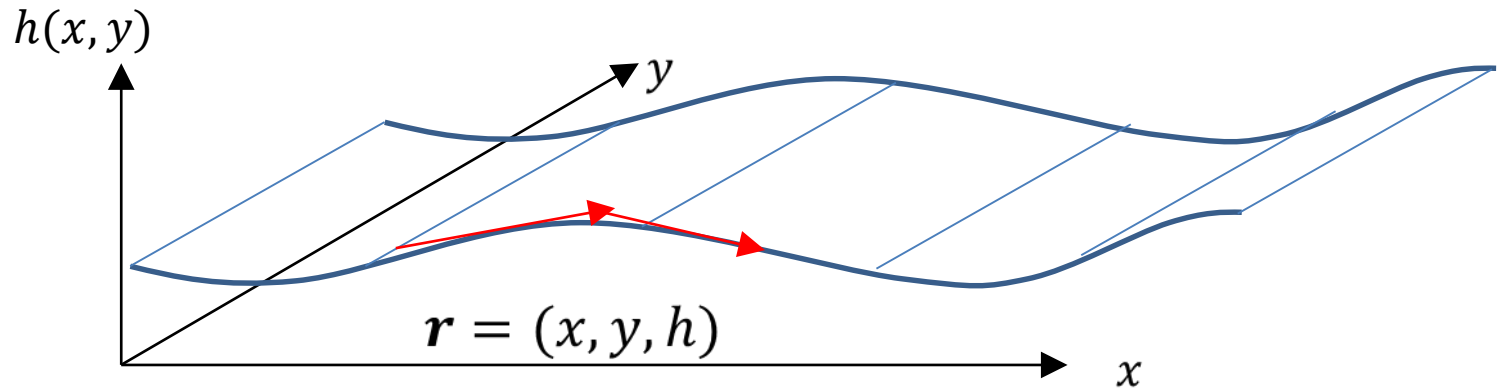
Where the mean curvature is the mean of the two principle curvatures:

$$\bar{\kappa} = \frac{\kappa_1 + \kappa_2}{2}$$

The bending modulus:

$$\kappa \sim 10 - 100 k_B T$$

Consider the Monge-gauge (small deformations), along one dimension only:



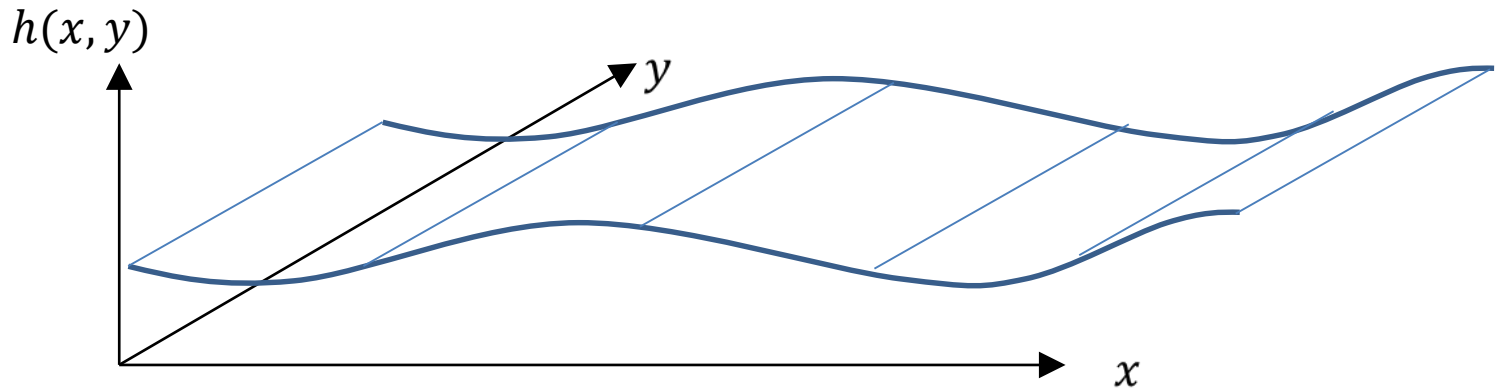
The local tangent is given by:

$$\mathbf{t} = \frac{\partial \mathbf{r}}{\partial x} = (1, 0, \partial h / \partial x)$$

The local curvature is given by:

$$\kappa = \left| \frac{\partial \mathbf{t}}{\partial x} \right| \sim \frac{\partial^2 h}{\partial x^2}$$

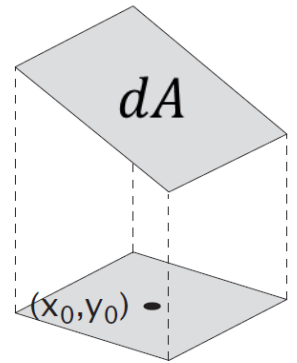
## Bending and membrane tension:



$$G_{tot} = \frac{\kappa}{2} \int \left( \frac{\partial^2 h}{\partial x^2} \right)^2 dA + \sigma \int dA$$

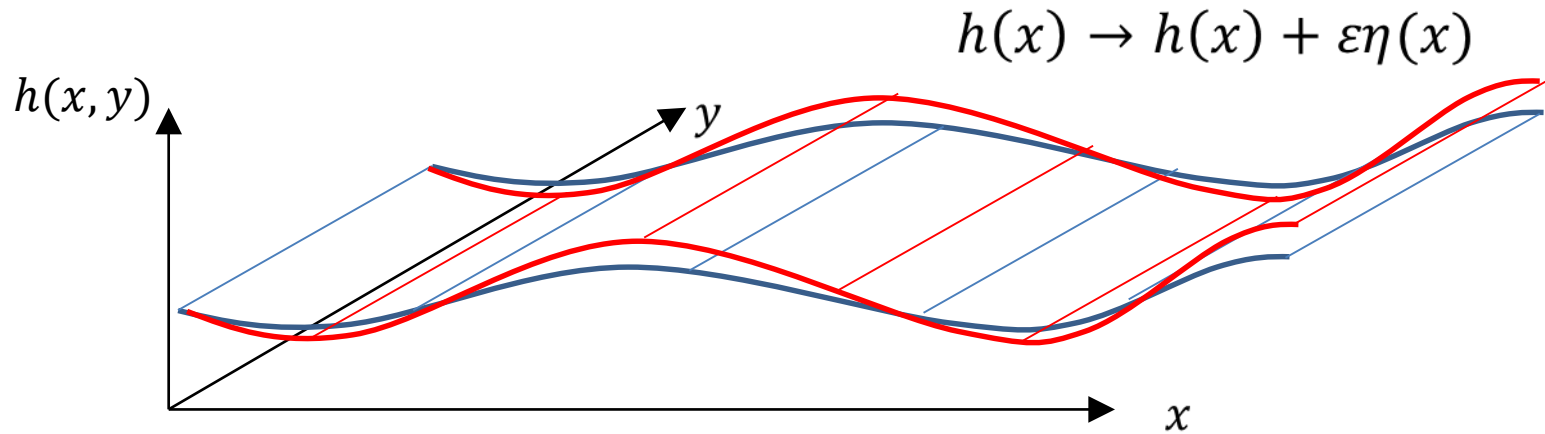
The area element is given by:

$$dA = dx \sqrt{1 + \left( \frac{\partial h}{\partial x} \right)^2} \approx dx \left( 1 + \frac{1}{2} \left( \frac{\partial h}{\partial x} \right)^2 \right)$$





To find the membrane shape we need to minimize the energy, using variation of the shape:



The energy up to second order terms:

$$G_{tot} = \frac{\kappa}{2} \int \left( \frac{\partial^2 h}{\partial x^2} \right)^2 dA + \frac{\sigma}{2} \int \left( \frac{\partial h}{\partial x} \right)^2 dA$$

$$\Rightarrow \frac{\delta G_{tot}}{\delta h(x)} = \kappa h'''' - \sigma h''$$

The equation of motion of the membrane can be written as:

$$\frac{\partial h(r)}{\partial t} = \int \mathcal{O}(r - r') \left( -\frac{\delta G_{tot}}{\delta h(r')} + \xi(r') \right) dr'$$

Where  $\mathcal{O}$  is the hydrodynamic friction of the membrane with the surrounding fluid, and  $\xi$  are the thermal random forces.

Note: we need to write equations of motion and calculate the dynamics, in order to include non-equilibrium forces.

In equilibrium, we could use thermodynamics

$$\frac{\partial h(r)}{\partial t} = \int \mathcal{O}(r - r') \left( -\frac{\delta G_{tot}}{\delta h(r')} + \xi(r') \right) dr'$$

Fourier-transform the equation of motion in space:

$$\dot{h}_q = -\lambda_q h_q + \mathcal{O}_q [F_T(q, t) + F_A(q, t)]$$

$$\lambda_q = \mathcal{O}_q (\bar{\kappa} q^4 + \sigma q^2)$$

$$\mathcal{O}_q = (4\eta q)^{-1} \quad \text{Oseen hydrodynamic interaction kernel.}$$

Thermal forces are given by:

$$\langle F_T(q, t) F_T(-q, t') \rangle = 2T_B \mathcal{O}_q^{-1} \delta(t - t') \quad \langle F_T(q, t) \rangle = 0$$

So that the thermal modes obey the Fluctuation-Dissipation theorem:

The mean-square fluctuations:  $\langle |h_q^2| \rangle(\omega) = \frac{T \mathcal{O}_q}{\omega^2 + \lambda_q^2}$

The response function (to external drive):

$$\dot{h}_q = -\lambda_q h_q + \mathcal{O}_q F_{ext} e^{i\omega t}$$

Where the response is defined as:

$$h_q(t) = \chi_q(t) F_{ext} e^{i\omega t}$$

The response function (after Fourier):  $\chi_q(\omega) = \frac{\mathcal{O}_q}{-i\omega + \lambda_q}$

Fluctuation-Dissipation theorem:

$$T = \frac{\langle |h_q^2| \rangle}{2\text{Im}[\chi_q]}$$

The overall amplitude of the fluctuations: do not depend on dynamical variables, such as viscosity.

$$\langle |h_q^2| \rangle = 2\pi \int \langle |h_q^2| \rangle(\omega) d\omega = \frac{T\mathcal{O}_q}{\lambda_q} = \frac{T}{\kappa q^4 + \sigma q^2}$$

The active forces have typical amplitude and time-scale:

$$\langle \xi(0)\xi(t) \rangle(q) = \left( \frac{F}{4\eta q} \right)^2 \frac{n}{2} e^{-|t|/\tau} \quad \langle \xi(q, t) \rangle = 0$$

With areal density of active motors  $n$ .

We can consider “direct” force motors, or “bending” motors that couple to the local curvature:  $F^2 \rightarrow F_r^2 (qr)^4$

So that the mean-square fluctuations become:

$$\langle |h_q^2| \rangle(\omega) = \frac{(F\mathcal{O}_q)^2}{\omega^2 + \lambda_q^2} \frac{n\tau}{1 + (\tau\omega)^2}$$

Direct motor

$$\langle |h_q^2| \rangle(\omega) = \frac{(F\mathcal{O}_q(qr)^2)^2}{\omega^2 + \lambda_q^2} \frac{n\tau}{1 + (\tau\omega)^2}$$

Bending motor

We will assume that the thermal and active fluctuations are uncorrelated

The response function remains the same:

$$\chi_q(\omega) = \frac{\mathcal{O}_q}{-i\omega + \lambda_q}$$

Generalized Fluctuation-Dissipation theorem:

$$\frac{\langle |h_q^2| \rangle}{2\text{Im}[\chi_q]} = T + \mathcal{O}_q \frac{n\tau F^2}{1 + (\tau\omega)^2}$$

However, experimental verification took a long time...

# Some experimental work pointed the way:

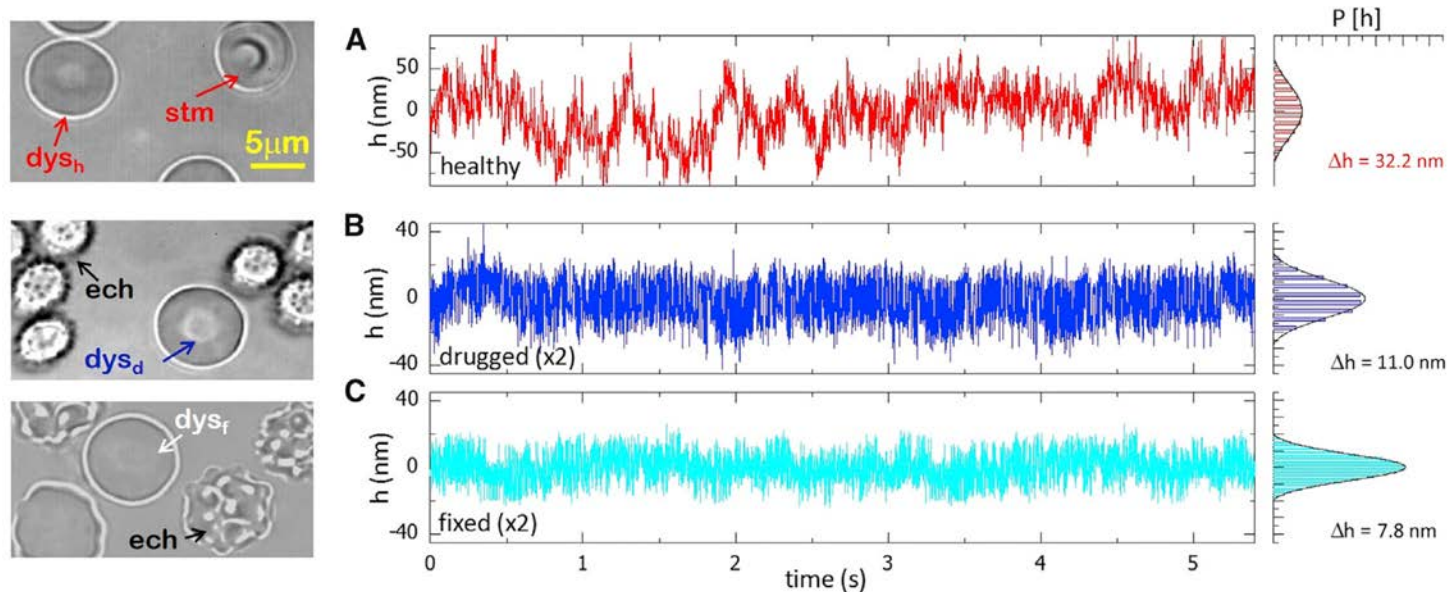
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Biophysical Journal Volume 108 June 2015 2794–2806

## Article

### Direct Cytoskeleton Forces Cause Membrane Softening in Red Blood Cells

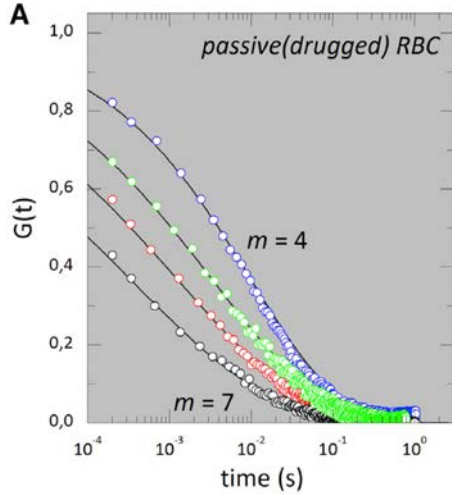
Ruddi Rodríguez-García,<sup>1</sup> Iván López-Montero,<sup>1,2</sup> Michael Mell,<sup>1,2</sup> Gustavo Egea,<sup>3</sup> Nir S. Gov,<sup>4</sup>  
and Francisco Monroy<sup>1,2,\*</sup>



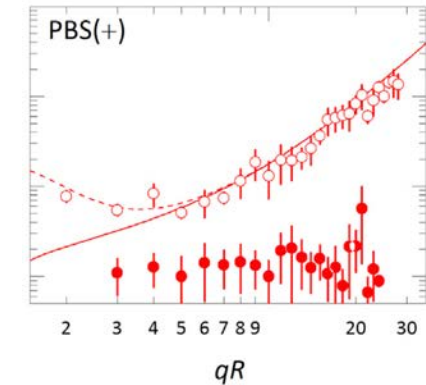
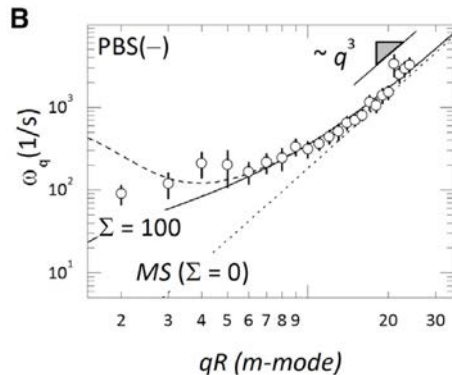
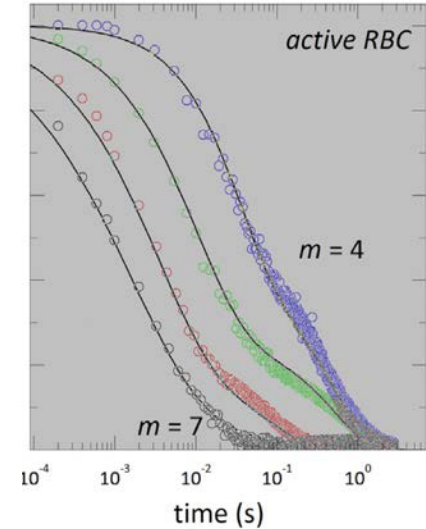
But the overall amplitude is not enough: ATP modifies also the elastic moduli of the cell



The time-dependent displacement-displacement correlation function is obtained, for each deformation mode:

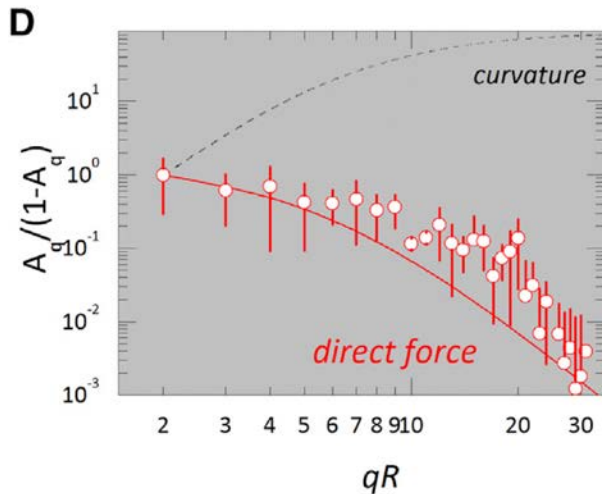
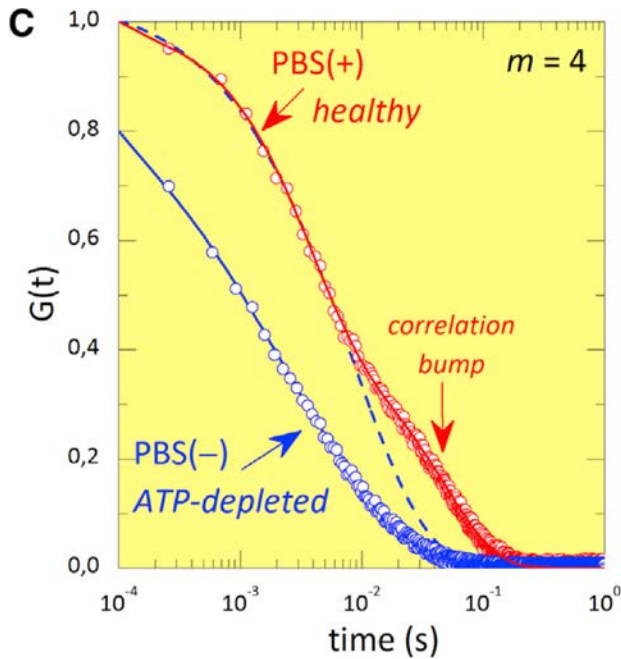


$$\langle |h_q^2| \rangle(t) = \frac{T}{\kappa q^4 + \sigma q^2} e^{-\lambda_q t}$$



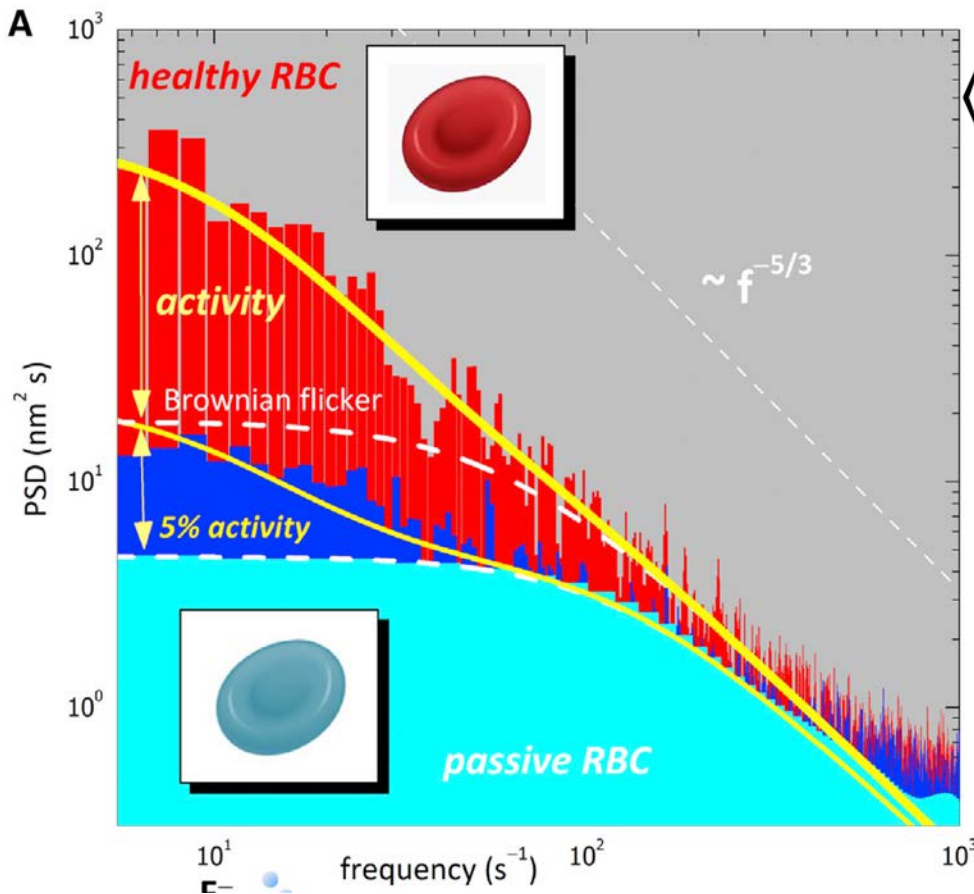
$$\langle |h_q^2| \rangle(\omega) = \frac{n(F\mathcal{O}_q)^2}{\lambda_q^2 - \tau^{-2}} \left( e^{-t/\tau} + \frac{1}{\lambda_q \tau} e^{-\lambda_q t} \right)$$

The activity appears as a qualitatively new mode:



The ratio of the two modes is predicted by the model, and allows to distinguish between the “direct” and “curvature” motors.

The power-spectrum fits the model, using the parameters fitted to the correlation function:



$$\langle |h^2| \rangle(\omega) = \frac{1}{(2\pi)^2} \int \langle |h_q^2| \rangle(\omega) d^2q$$

The problem with these measurements is that ATP depletion affects both the elastic moduli ( $\kappa, \sigma$ ), as well as active forces.

What was still missing was a direct measure of breakdown of thermal equilibrium: FDT

nature  
physics

ARTICLES

PUBLISHED ONLINE: 18 JANUARY 2016 | DOI: 10.1038/NPHYS3621

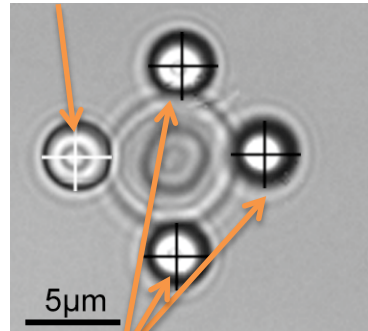
## Equilibrium physics breakdown reveals the active nature of red blood cell flickering

H. Turlier<sup>1,2,3</sup>, D. A. Fedosov<sup>4</sup>, B. Audoly<sup>3,5</sup>, T. Auth<sup>4</sup>, N. S. Gov<sup>6</sup>, C. Sykes<sup>2</sup>, J.-F. Joanny<sup>2,3,7</sup>,  
G. Gompper<sup>4</sup> and T. Betz<sup>2,8\*</sup>

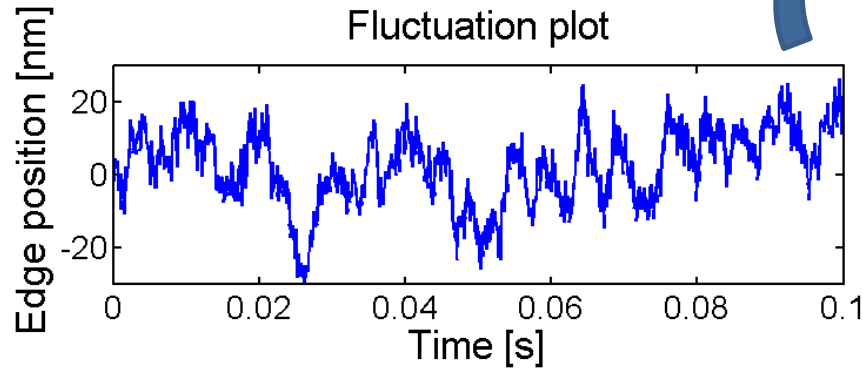
# Experimental tour-de-force:

## Measurement of free fluctuations:

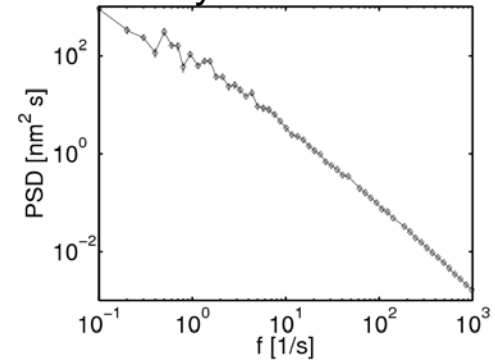
Weak trap 50 $\mu$ W



Stiff traps 15mW



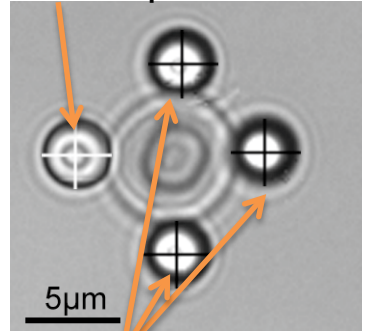
Power-spectral-density



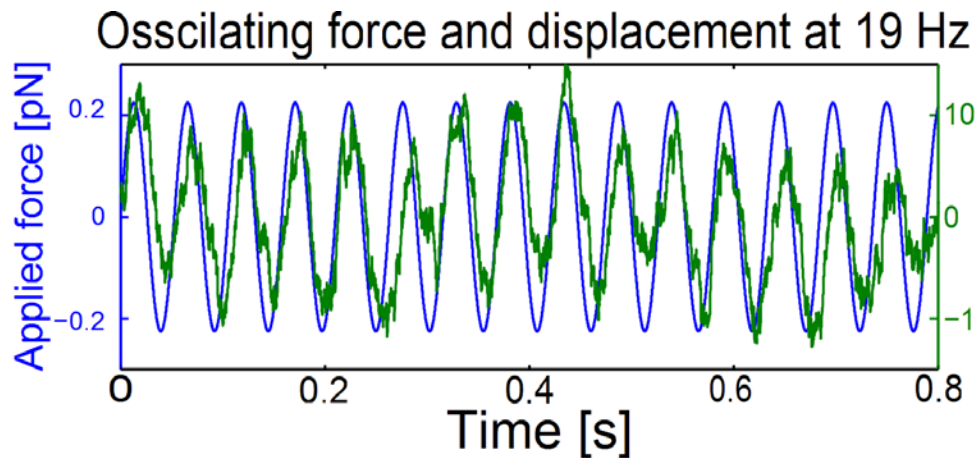
## Measurement of response function (applied for 80 frequencies between 0.1 - 1000

Hz):

Stiff trap 15mW



Stiff traps 15mW



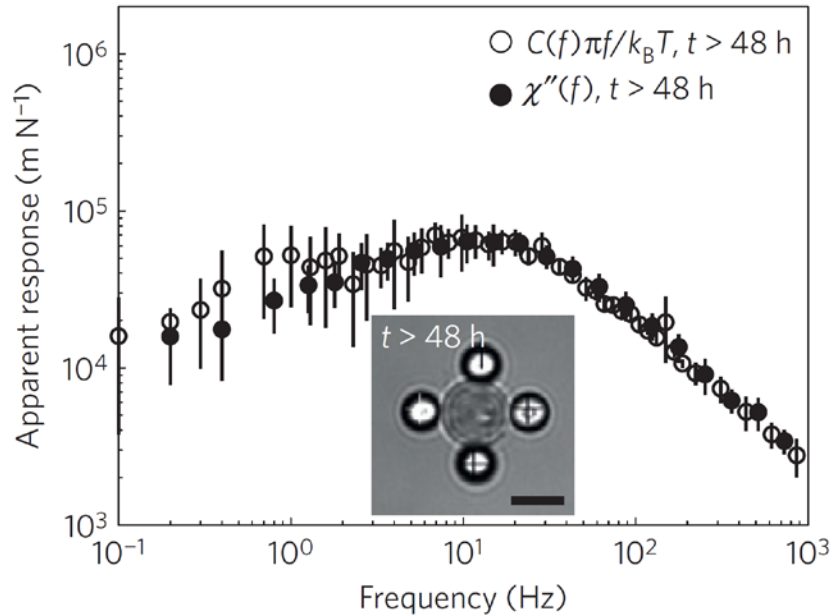
**Response function:**

In phase deformation:  
elastic response

Out of phase  
deformation: dissipative  
response

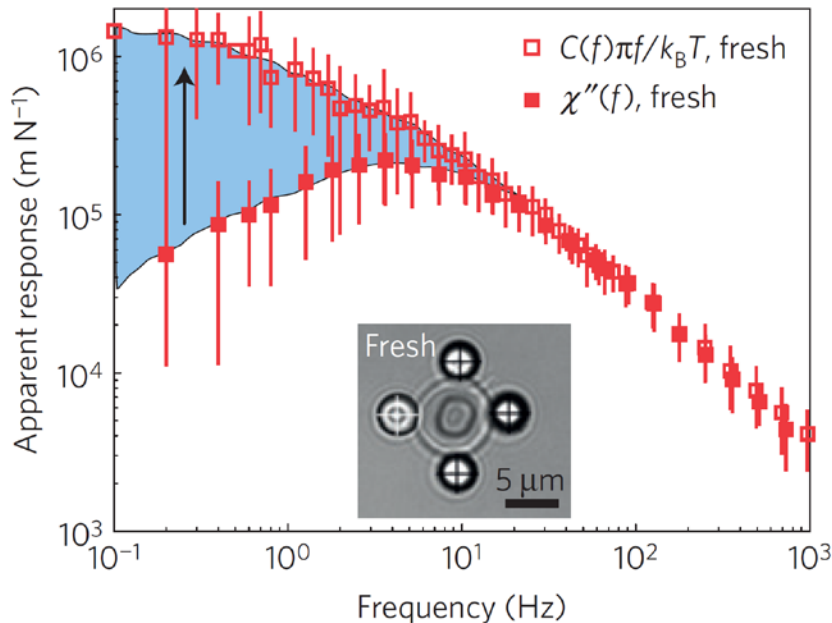
$$\text{Im}[\chi_q]$$

# ATP-depleted cells exhibit agreement with FDT:



$$\frac{\langle |h_q^2| \rangle}{2\text{Im}[\chi_q]} = T$$

# But normal cells do not:



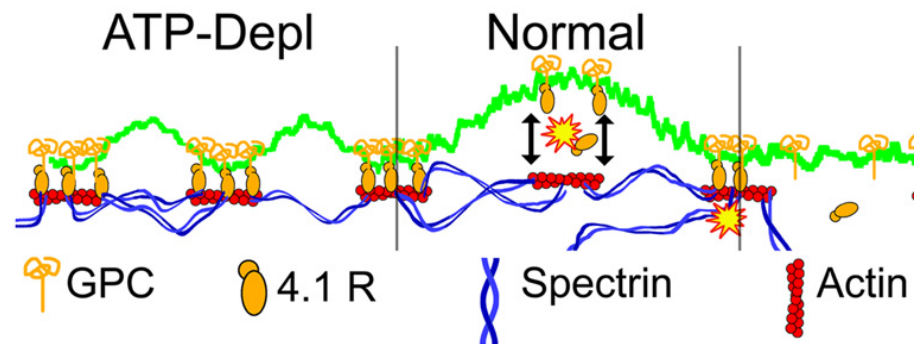
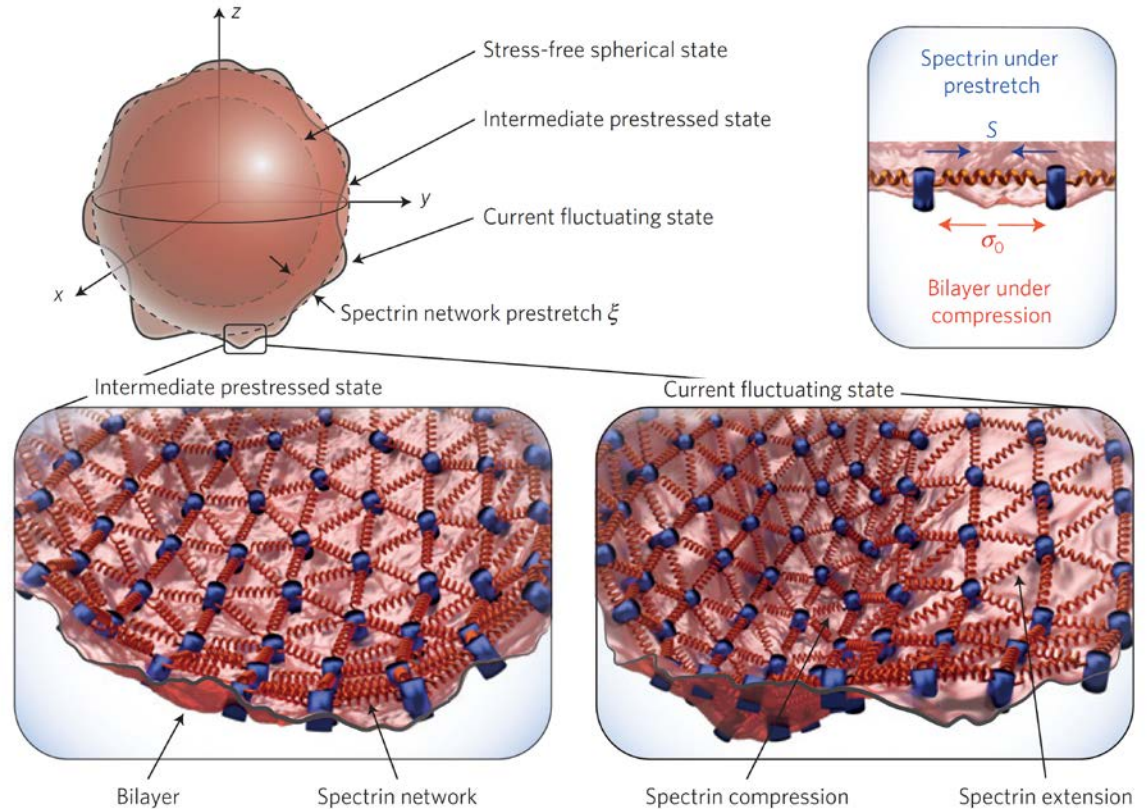
The model predicts:

$$\frac{\langle |h_q^2| \rangle}{2\text{Im}[\chi_q]} = T + \mathcal{O}_q \frac{n\tau F^2}{1 + (\tau\omega)^2}$$

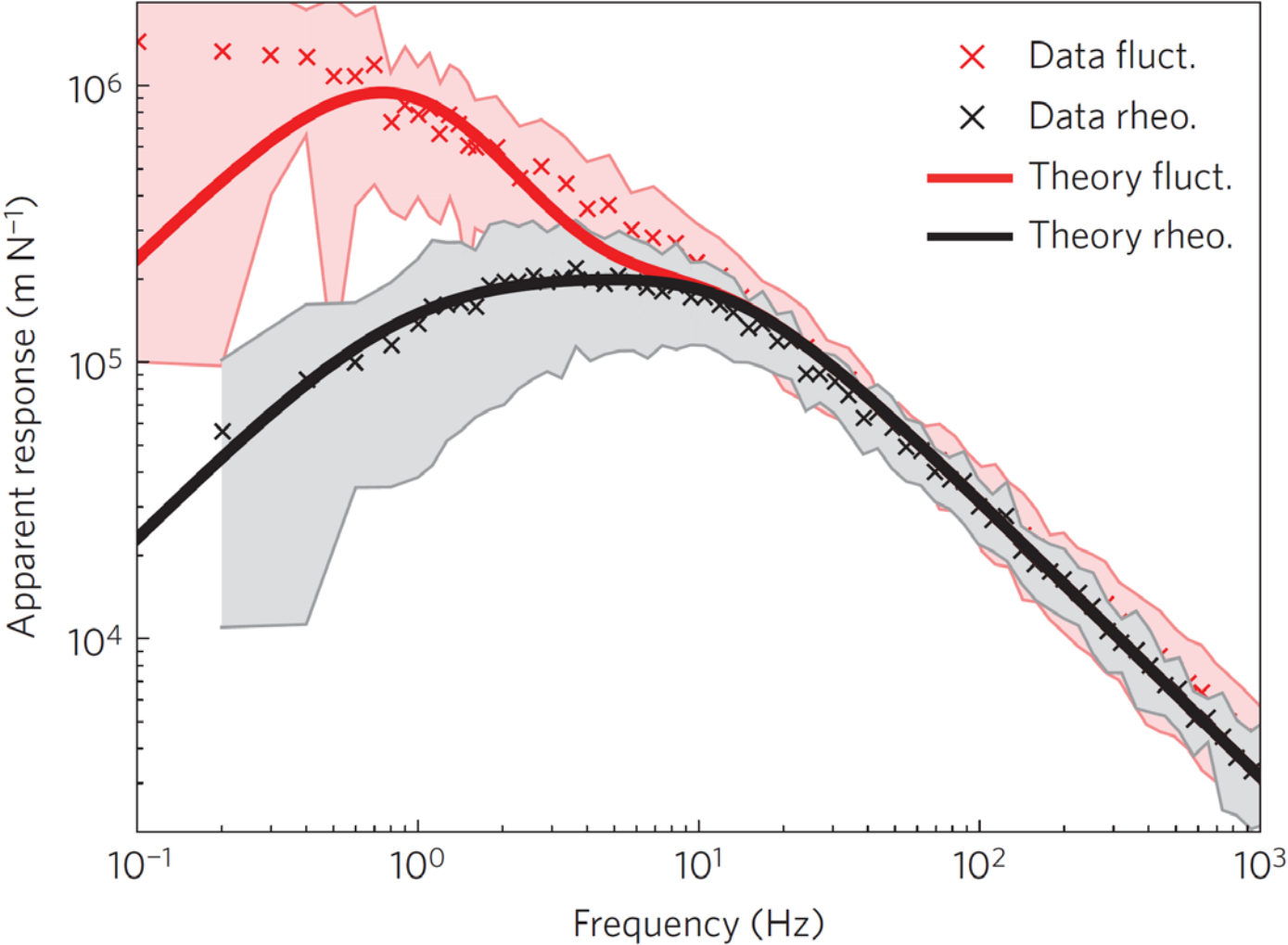
This is independent of the elastic parameters !

# What are the “motors” in the RBC membrane ?

- The spectrin filaments are stretched when connected.
- ATP-induced detachments/unfolding releases the stress.
- At curved regions, this release of in-plane stress converts to normal force component.
- These same active processes also control the cell’s overall stiffness, and shape. The fluctuations may be a side-effect.



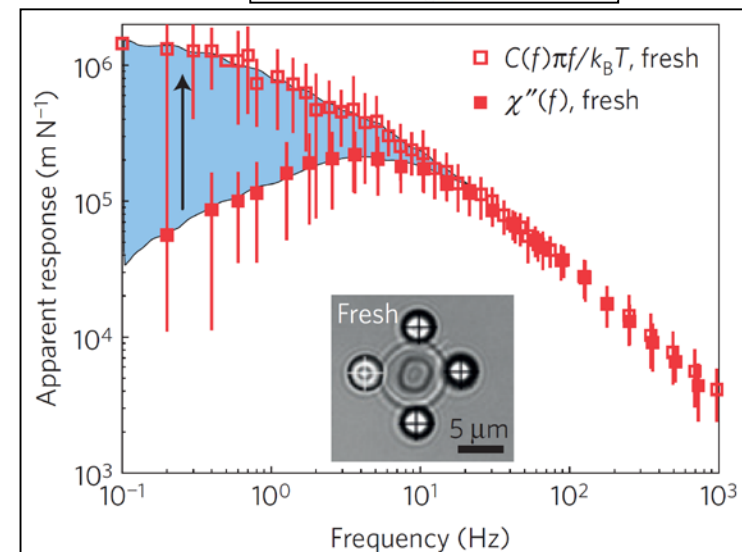
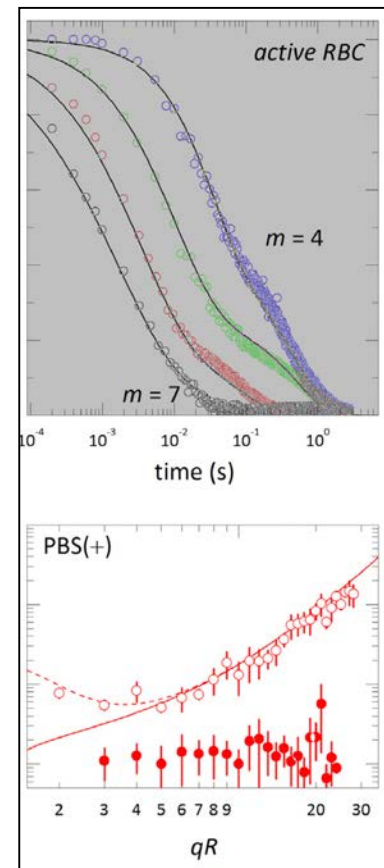
The analytic model, with randomly softening tangential stress, reproduced the experimental results:





# Conclusions

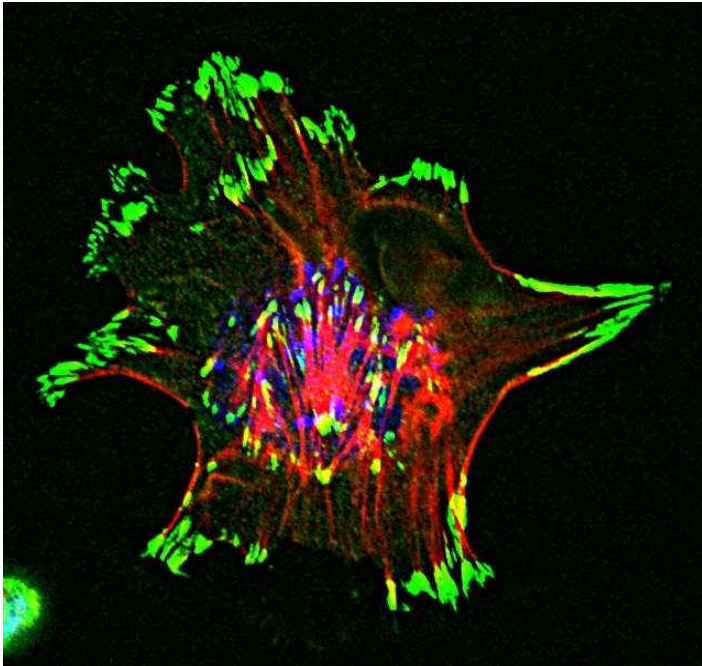
- Active noise is qualitatively different from thermal noise
- Gives rise to new dynamical features and breakdown of FDT
- Simple models allow to predict many specific features and general properties



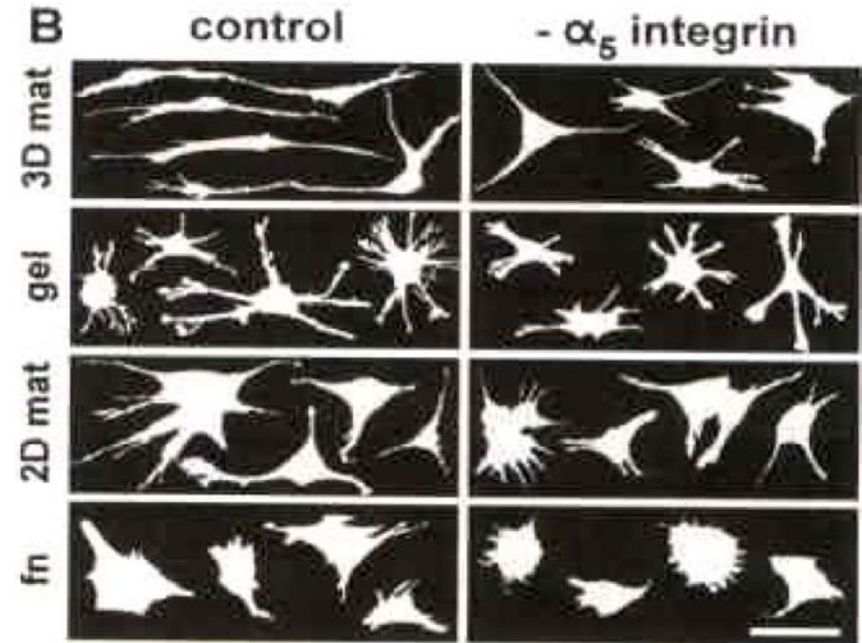
**So far we saw membranes with a uniform distribution of random active forces (“active noise”)**

**Now we’ll look at membranes with a non-uniform distribution of non-random active forces**

# Cells come in a variety of shapes: What mechanisms can produce them ?



[www.mshri.on.ca](http://www.mshri.on.ca)

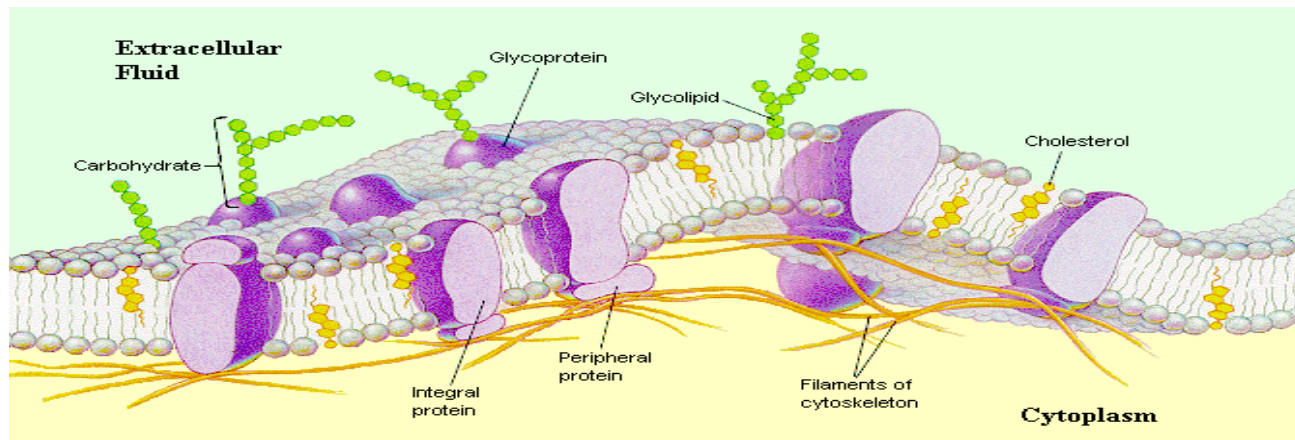


The cytoskeleton !

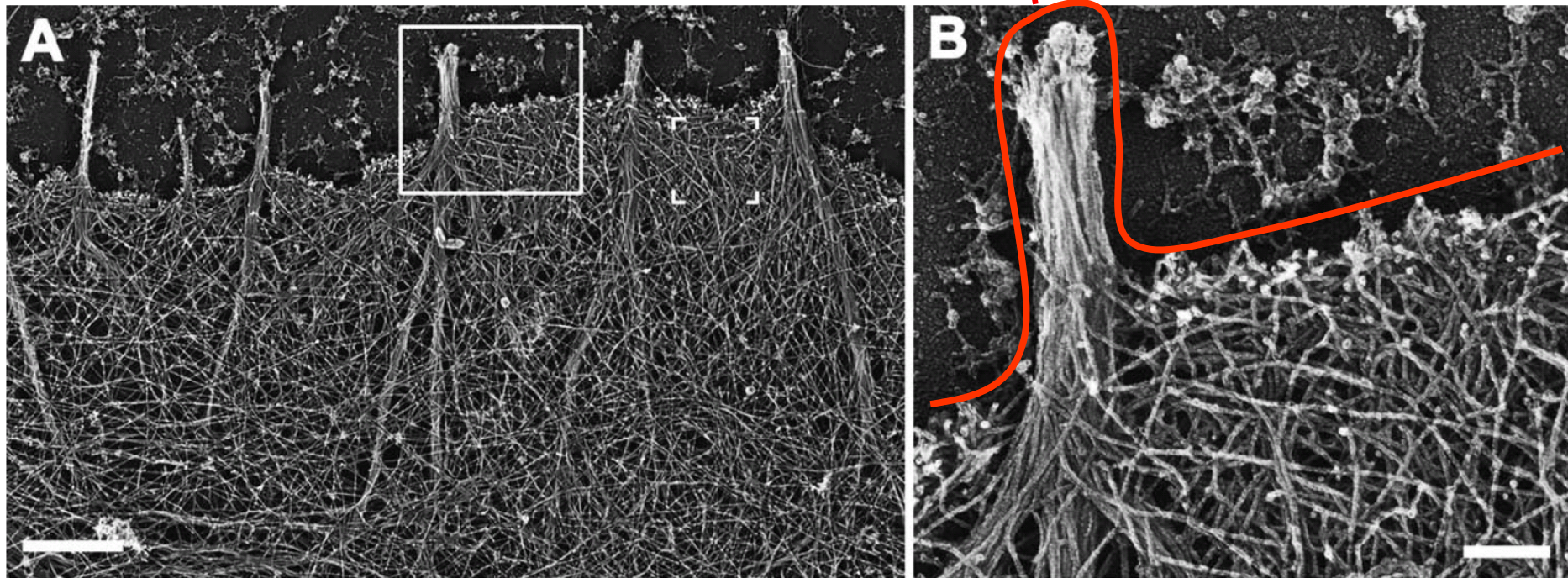
Engler, Bacakova, Newman, Hategan, Griffin & Discher, *Biophys J.*, 2004;  
Discher, Janmey & Wang, *Science*, 2005.

# 3 components

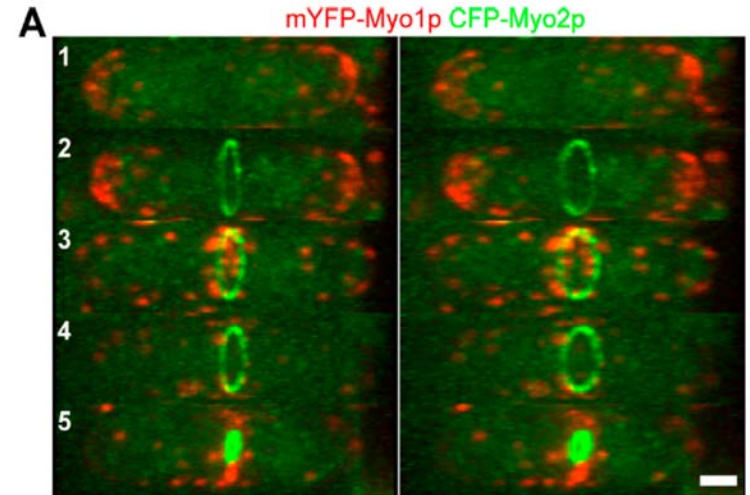
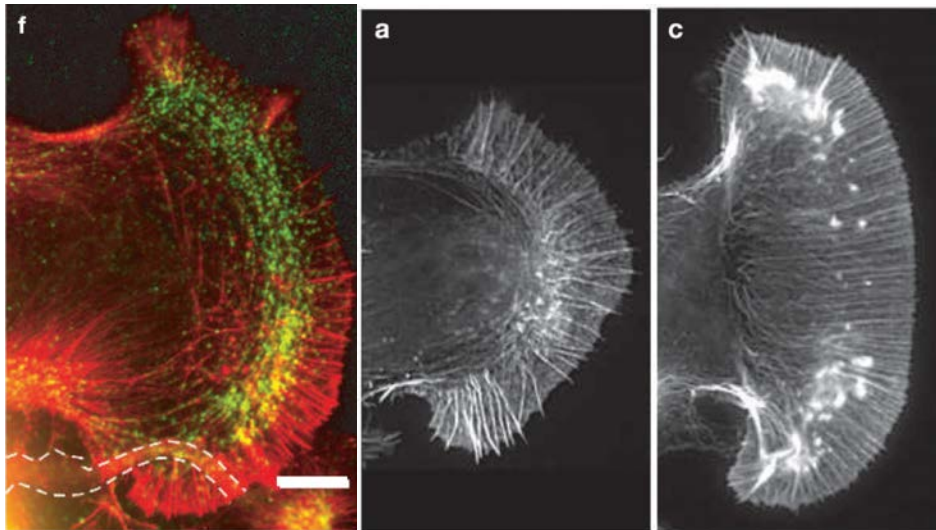
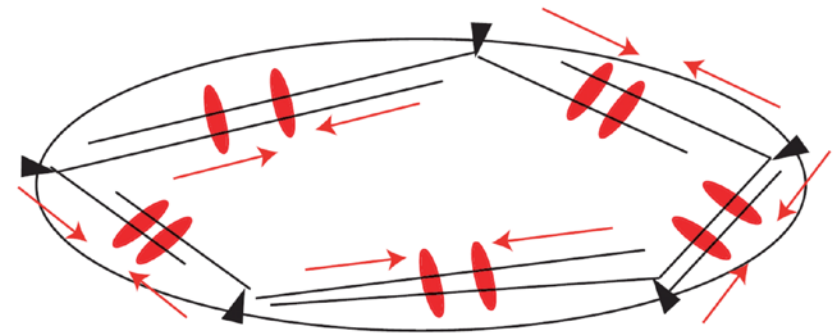
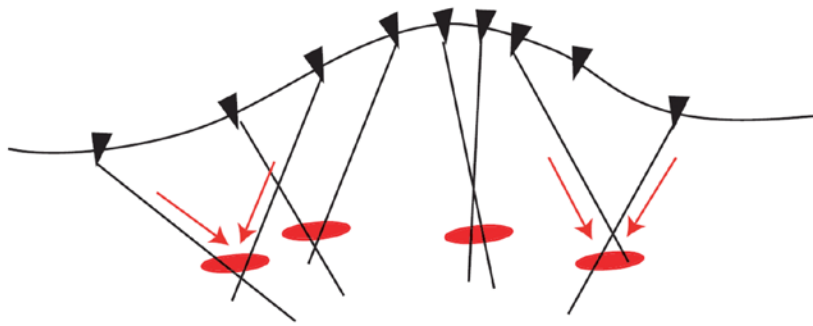
Fluid membrane, with bending and effective tension elasticity



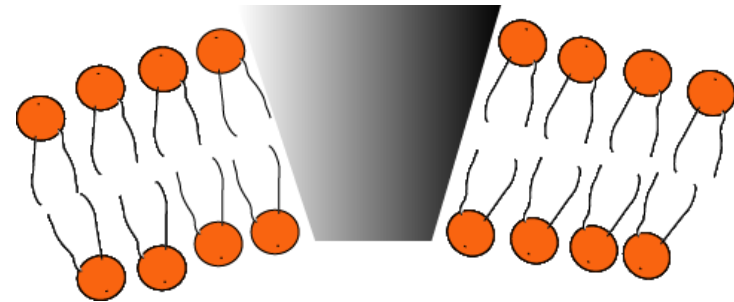
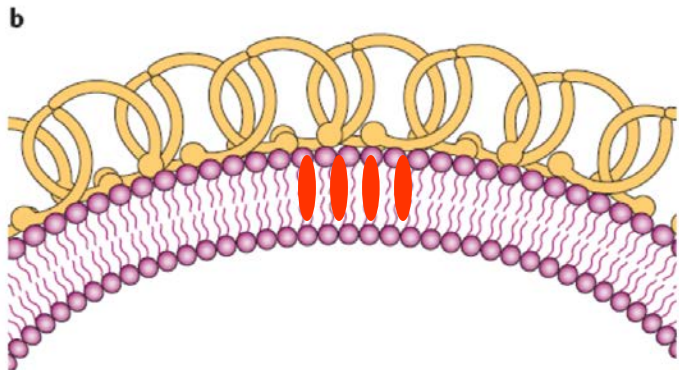
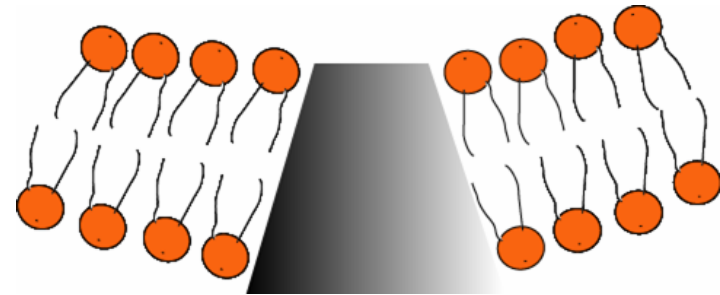
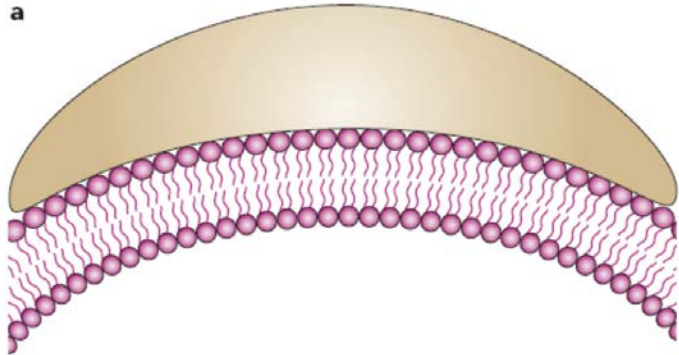
# Protrusive force due to actin polymerization near the membrane:



Contractile forces result from myosin motors pulling on anti-parallel actin filaments in opposite directions:



# Spontaneous curvature



*Joshua Zimmerberg\* and Michael M. Kozlov*  
*Nature Reviews Molecular Cell Biology* | AOP, published online 15 November 2005

**Note: any adsorption to the membrane breaks the symmetry and induces some curvature !**

# Self-organization → feedback between the 3 components

Cell membrane deformation



Active forces due to the cytoskeleton

Curved membrane activators of the cytoskeleton respond to the membrane shape.

PHILOSOPHICAL  
TRANSACTIONS B

[rstb.royalsocietypublishing.org](http://rstb.royalsocietypublishing.org)

Guided by curvature: shaping cells by  
coupling curved membrane proteins  
and cytoskeletal forces

N. S. Gov

*Phil. Trans. R. Soc. B* **373**: 20170115.



It all started over 10 years ago...



Ajay Gopinathan

What are the dynamics of membrane that have on them curved proteins that recruit actin polymerization ?

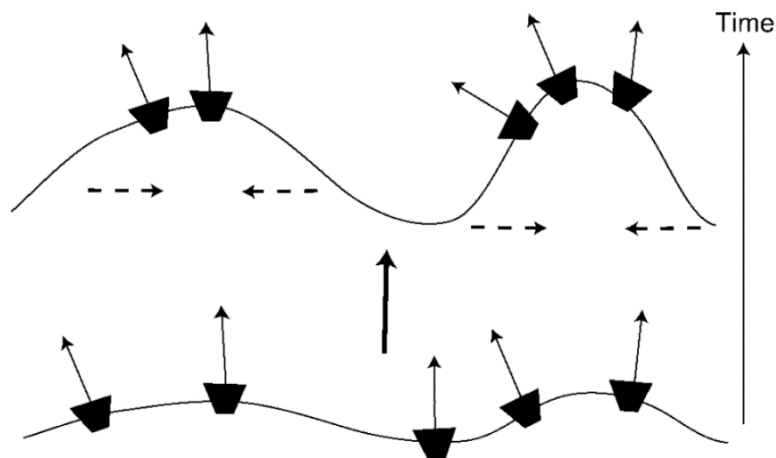
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Biophysical Journal Volume 90 January 2006 454-469

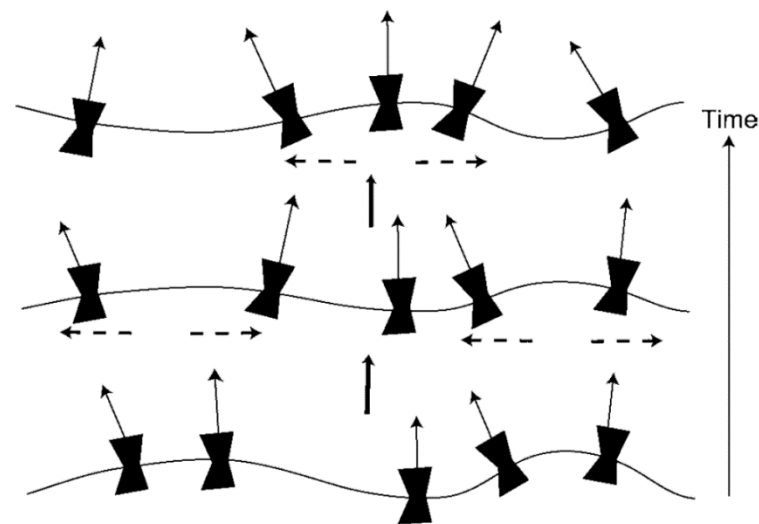
### Dynamics of Membranes Driven by Actin Polymerization

Nir S. Gov\* and Ajay Gopinathan†

\*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



Convex + actin protrusive force  
→ Instability, protrusions

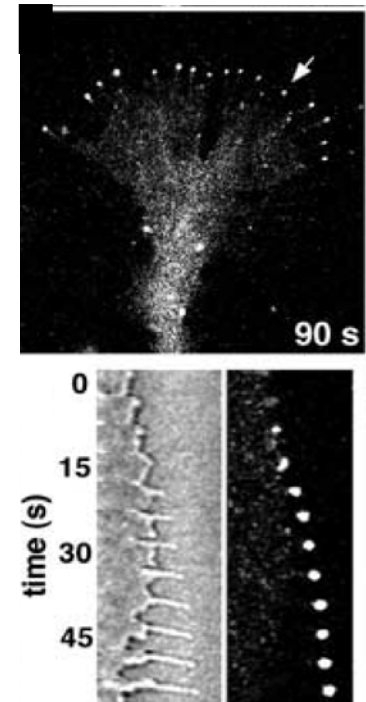
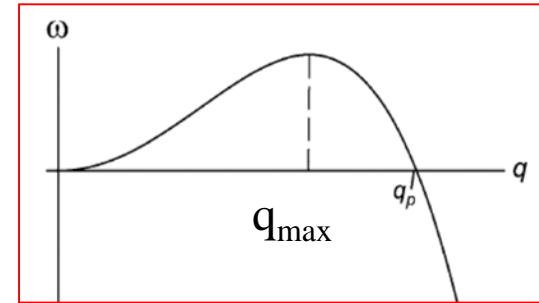
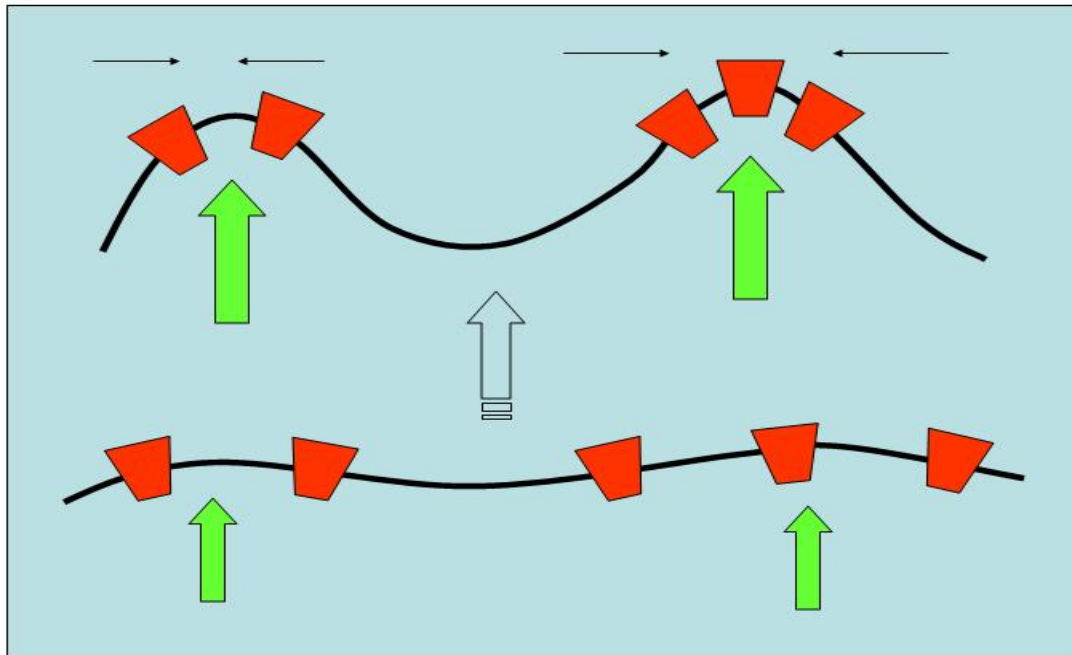


Concave + actin protrusive force  
→ Damped waves

# Convex protein curvature can drive spontaneous initiation of protrusions

“Turing” instability:  
→ Regularly spaced, static fingers

$$\lambda = 2\pi/q$$



## The model:

The free energy, now with density of curved membrane proteins (MP),  $\phi$ :

$$F = \int_S \left( \frac{1}{2} \sigma (\nabla h)^2 + \frac{\kappa}{2} \left( \nabla^2 h + \frac{\phi}{R} \right)^2 + \frac{T}{a^2} (\phi \ln \phi + (1 - \phi) \ln (1 - \phi)) + \frac{J}{2a^2} \phi (1 - \phi) + \frac{J}{4} (\nabla \phi)^2 \right) d^2 r$$

where  $S$  is the membrane area,  $a$  is the lateral size of a MP,  $\kappa$  is the bending modulus,  $\sigma$  is the membrane tension coefficient,  $J$  is the binding interaction between the MP, and  $T$  is the temperature (including the factor of  $k_B$ ).

The equation of motion for the membrane deformation:

$$\frac{\partial h(\vec{r}, t)}{\partial t} = \frac{d}{8\eta} \left( -\frac{\delta F}{\delta h(\vec{r}, t)} + f(\phi(\vec{r}, t) - \phi_0) \right)$$

Where:  $f(\phi(\vec{r}, t) - \phi_0)$  describes the protrusive force due to actin polymerization. We also assume local hydrodynamics for simplicity.

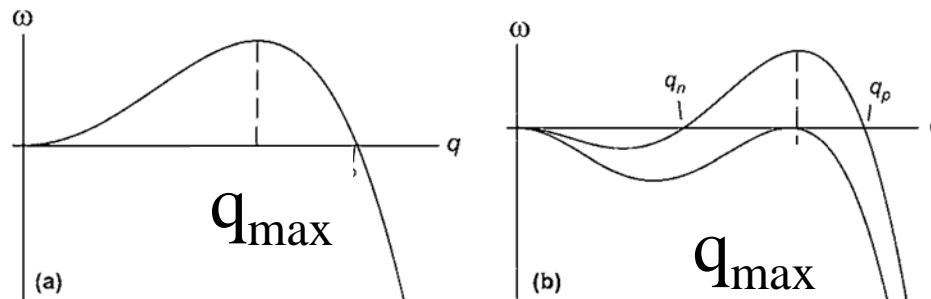
## The model:

The equation of motion for the density field of the curved MP,  $\phi$ , is given by the mass-conservation equation:

$$\frac{\partial \phi(\vec{r}, t)}{\partial t} = \frac{D a^2}{T} \nabla \left( \phi(\vec{r}, t) \nabla \frac{\delta F}{\delta \phi(\vec{r}, t)} \right)$$

where  $D$  is the diffusion coefficient.

The equations of motion are then expanded up to linear order, Fourier transformed, and linear stability analysis is performed (per mode).



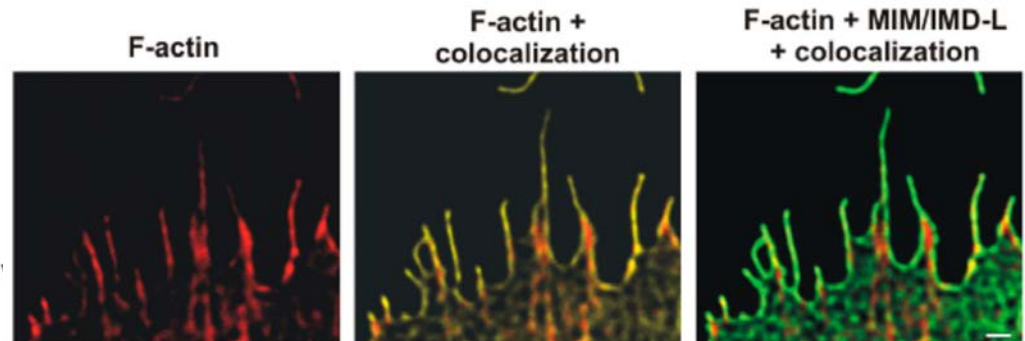
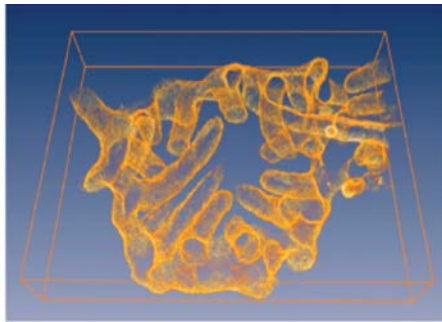
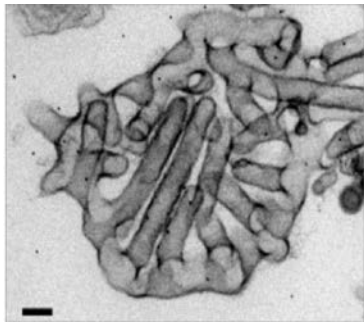
At the time of our paper there we no known convex proteins that recruit actin, that can serve to initiate protrusions according to our mechanism.

Review

Cell  
PRESS

# IRSp53: crossing the road of membrane and actin dynamics in the formation of membrane protrusions

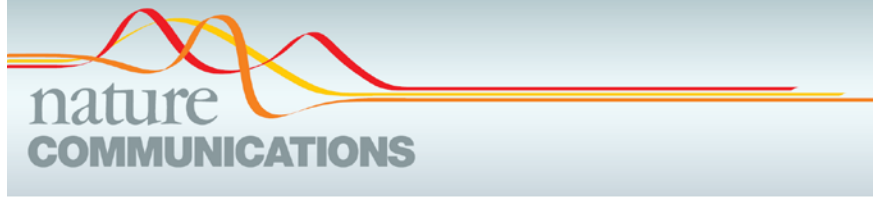
Giorgio Scita<sup>1,2</sup>, Stefano Confalonieri<sup>1</sup>, Pekka Lappalainen<sup>3</sup> and Shiro Suetsugu<sup>4</sup>



Pieta K. Mattila, Anette Pykäläinen, Juha Saarikangas,  
and Pekka Lappalainen

The Journal of Cell Biology, Vol. 176, No. 7, March 26, 2007 953–964

# Recent studies of the convex proteins:



## ARTICLE

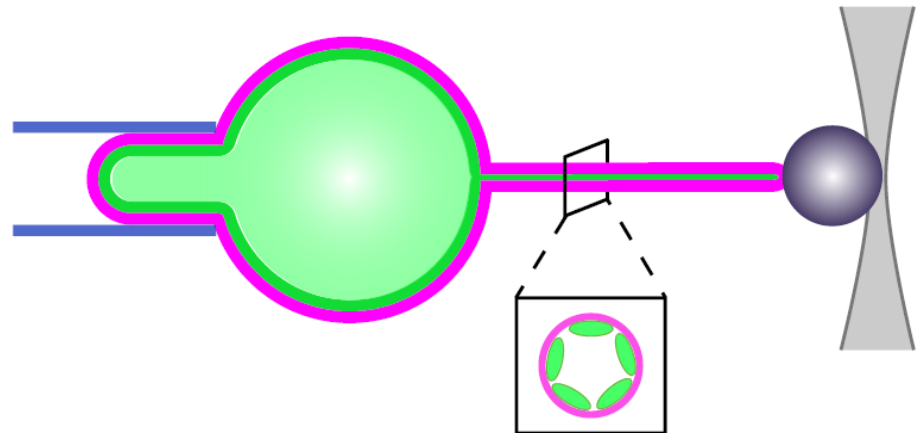
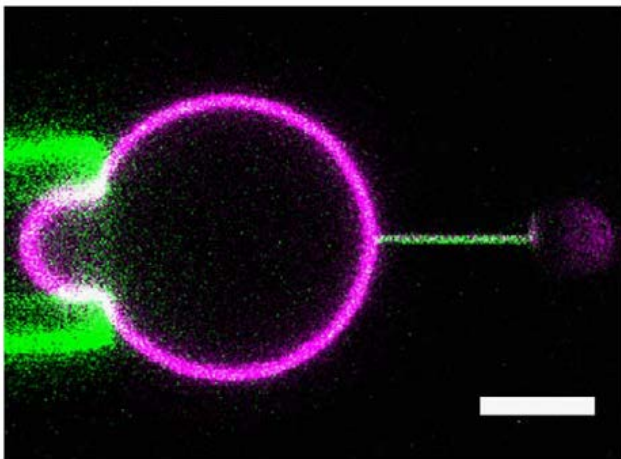
Received 26 Feb 2015 | Accepted 30 Aug 2015 | Published 15 Oct 2015

DOI: [10.1038/ncomms9529](https://doi.org/10.1038/ncomms9529)

OPEN

# IRSp53 senses negative membrane curvature and phase separates along membrane tubules

Coline Prévost<sup>1,2,3,4</sup>, Hongxia Zhao<sup>5</sup>, John Manzi<sup>1,2,3</sup>, Emmanuel Lemichez<sup>6</sup>, Pekka Lappalainen<sup>5</sup>, Andrew Callan-Jones<sup>7,4,\*</sup> & Patricia Bassereau<sup>1,2,3,\*</sup>



# More recent findings support this mechanism:

The EMBO Journal (2013) 32, 2735–2750  
www.embojournal.org



THE  
EMBO  
JOURNAL

## CDC42 switches IRSp53 from inhibition of actin growth to elongation by clustering of VASP

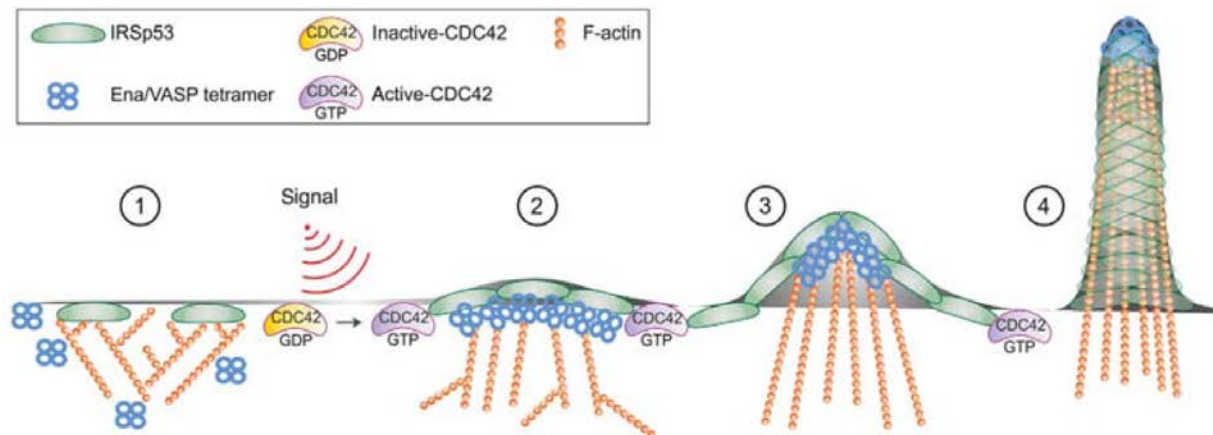
Andrea Dianza<sup>1,8</sup>, Sara Bisi<sup>1,8</sup>,  
Moritz Winterhoff<sup>2</sup>, Francesca Milanese<sup>1,9</sup>,  
Dmitry S Ushakov<sup>2,10</sup>,  
David Kast<sup>3</sup>, Paola Marighetti<sup>1</sup>,  
Guillaume Romet-Lemonne<sup>4</sup>,  
Hans-Michael Müller<sup>5</sup>, Walter Nickel<sup>5</sup>,  
Joern Linkner<sup>2</sup>, Davy Waterschoot<sup>6</sup>,  
Christophe Ampère<sup>6</sup>, Salvatore Cortellino<sup>1</sup>,  
Andrea Palamidessi<sup>1</sup>, Roberto Dominguez<sup>3</sup>,  
Marie-France Carlier<sup>4</sup>, Jan Faix<sup>2,\*</sup> and  
Giorgio Scita<sup>1,7,\*</sup>

activity and promotes IRSp53-dependent recruitment and clustering of VASP to drive actin assembly. These events result in spatial restriction of VASP filament elongation for initiation of filopodia during cell migration, invasion, and tissue repair.

*The EMBO Journal* (2013) 32, 2735–2750. doi:10.1038/emboj.2013.208; Published online 27 September 2013

*Subject Categories:* cell & tissue architecture

*Keywords:* actin dynamics; cell migration; CDC42; filopodia; IRSp53



# Recent findings support this mechanism:

## ARTICLE

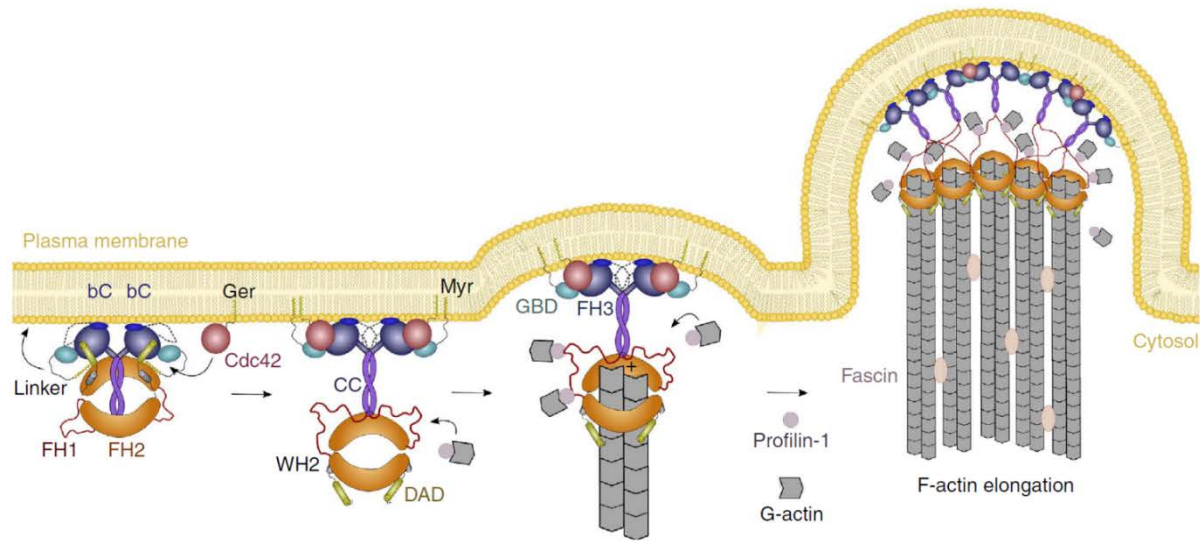
Received 24 Oct 2014 | Accepted 31 Mar 2015 | Published 12 May 2015

DOI: [10.1038/ncomms8088](https://doi.org/10.1038/ncomms8088)

OPEN

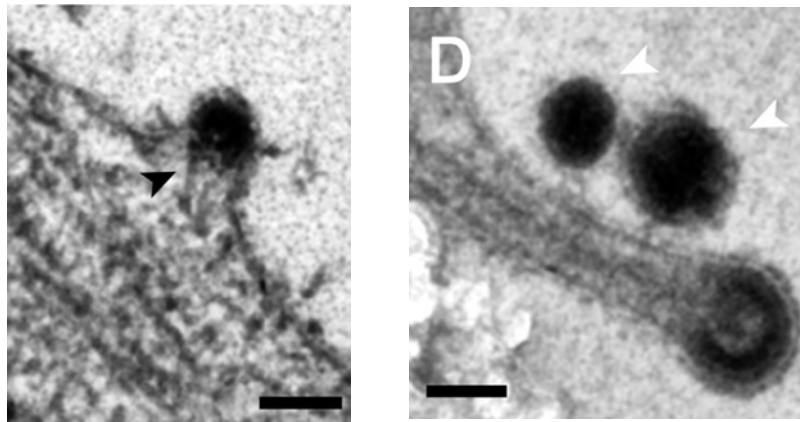
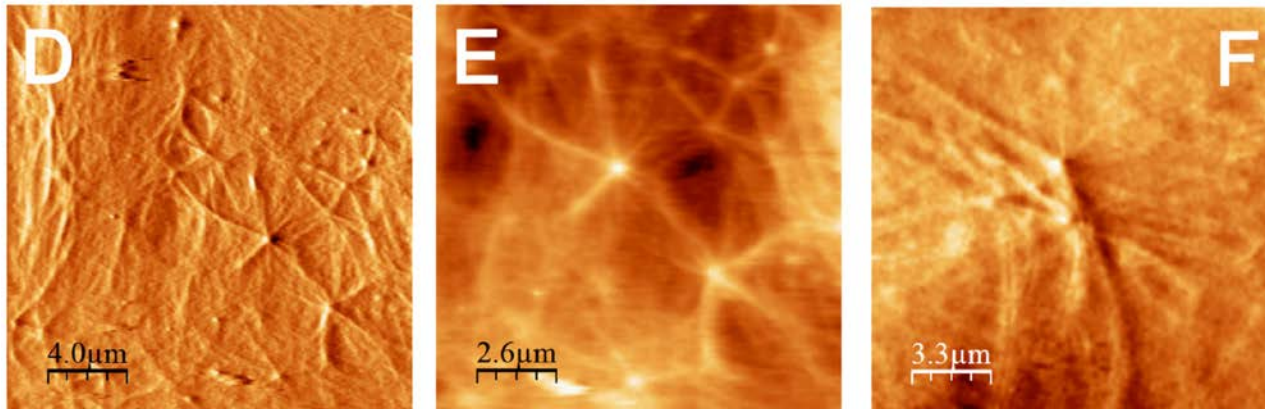
# The structure of FMNL2-Cdc42 yields insights into the mechanism of lamellipodia and filopodia formation

Sonja Kühn<sup>1,2</sup>, Constanze Erdmann<sup>1,2</sup>, Frieda Kage<sup>3,4</sup>, Jennifer Block<sup>3</sup>, Lisa Schwenkmezger<sup>3</sup>, Anika Steffen<sup>3,5</sup>, Klemens Rottner<sup>3,4,5</sup> & Matthias Geyer<sup>1,2,6</sup>



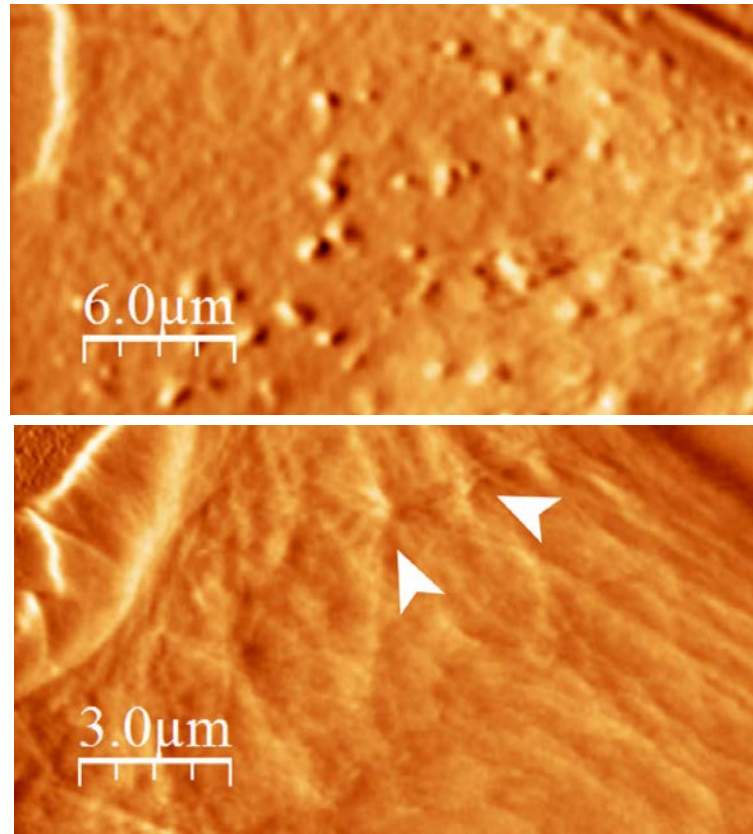


## HIV budding: driven by actin



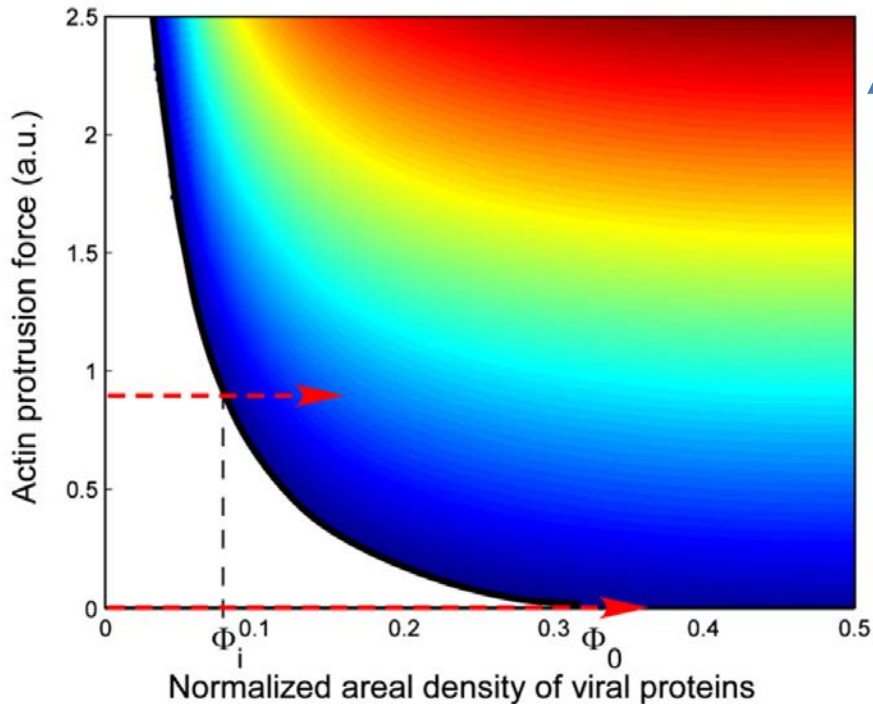
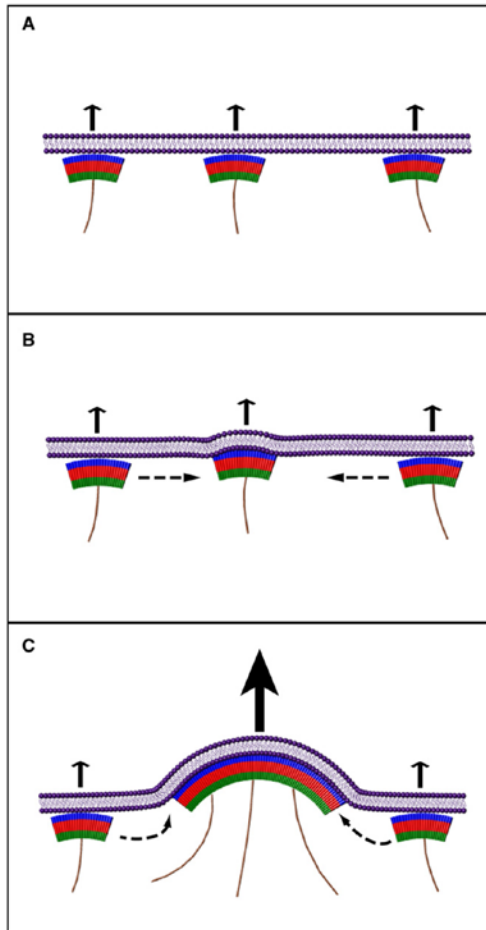
Gladnikoff, Micha, et al. "Retroviral assembly and budding occur through an actin-driven mechanism." *Biophysical journal* 97.9 (2009): 2419-2428.

Without actin's help, budding at high membrane concentration of coat proteins



Gladnikoff, Micha, et al. "Retroviral assembly and budding occur through an actin-driven mechanism." *Biophysical journal* 97.9 (2009): 2419-2428.

# The actin-curvature feedback explains this:



Color shows increasing rate of growth of the unstable mode

Gladnikoff, Micha, et al. "Retroviral assembly and budding occur through an actin-driven mechanism." *Biophysical journal* 97.9 (2009): 2419-2428.

# What about highly non-linear shapes ?



Aleš Iglič



Miha Fošnarič



Mitja Drab



Veronika Iglič



Samo Penič

Univerza v Ljubljani



*Laboratory of Biophysics*

*Faculty of Electrical Engineering*

*University of Ljubljana*

# Recently published:



## Soft Matter

PAPER



Cite this: *Soft Matter*, 2019,  
15, 5319

### Theoretical study of vesicle shapes driven by coupling curved proteins and active cytoskeletal forces†

Miha Fošnarič, <sup>a</sup> Samo Penič, <sup>b</sup> Aleš Iglič, <sup>b</sup> Veronika Kralj-Iglič,<sup>a</sup>  
Mitja Drab<sup>b</sup> and Nir S. Gov\*<sup>c</sup>

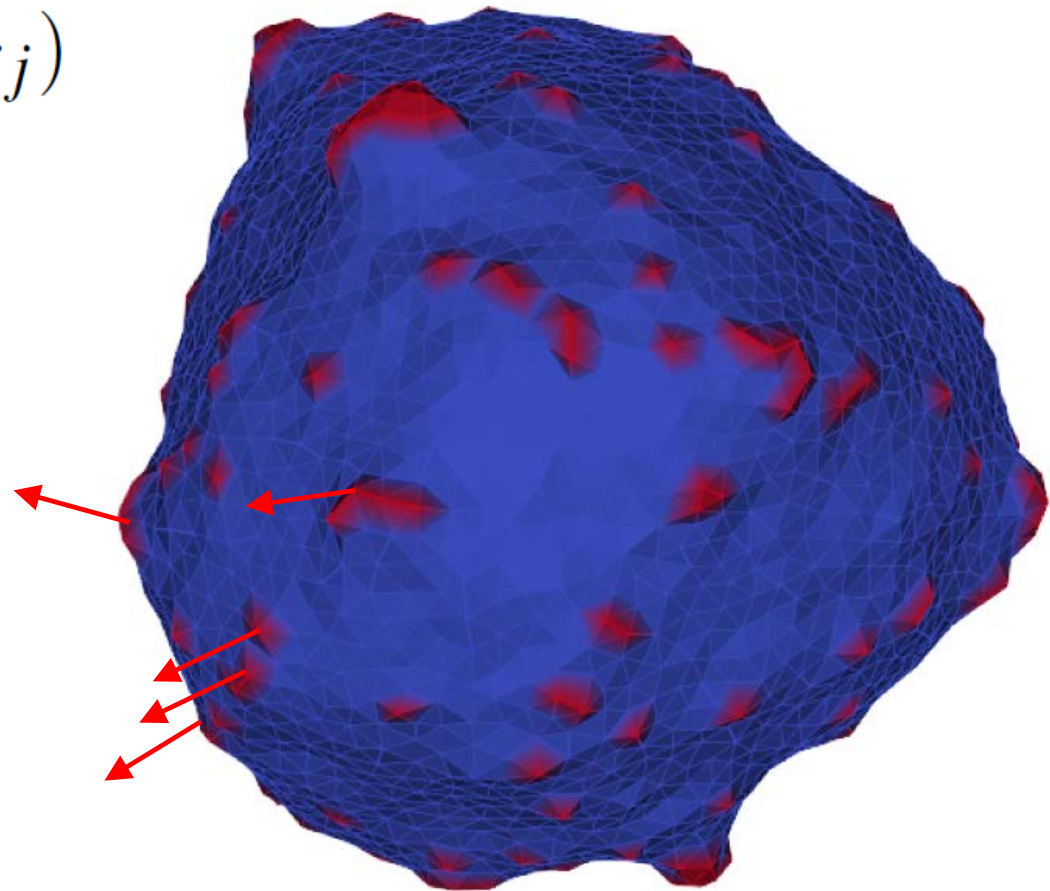
# MC simulations

$$W_b = \frac{\kappa}{2} \int_A (C_1 + C_2 - C_0)^2 dA$$

$$W_d = -w \sum_{i < j} \mathcal{H}(r_0 - r_{ij})$$

Active proteins:  
protrusive normal force

$$W_F = -F \sum_i \hat{n}_i \cdot \vec{x}_i$$



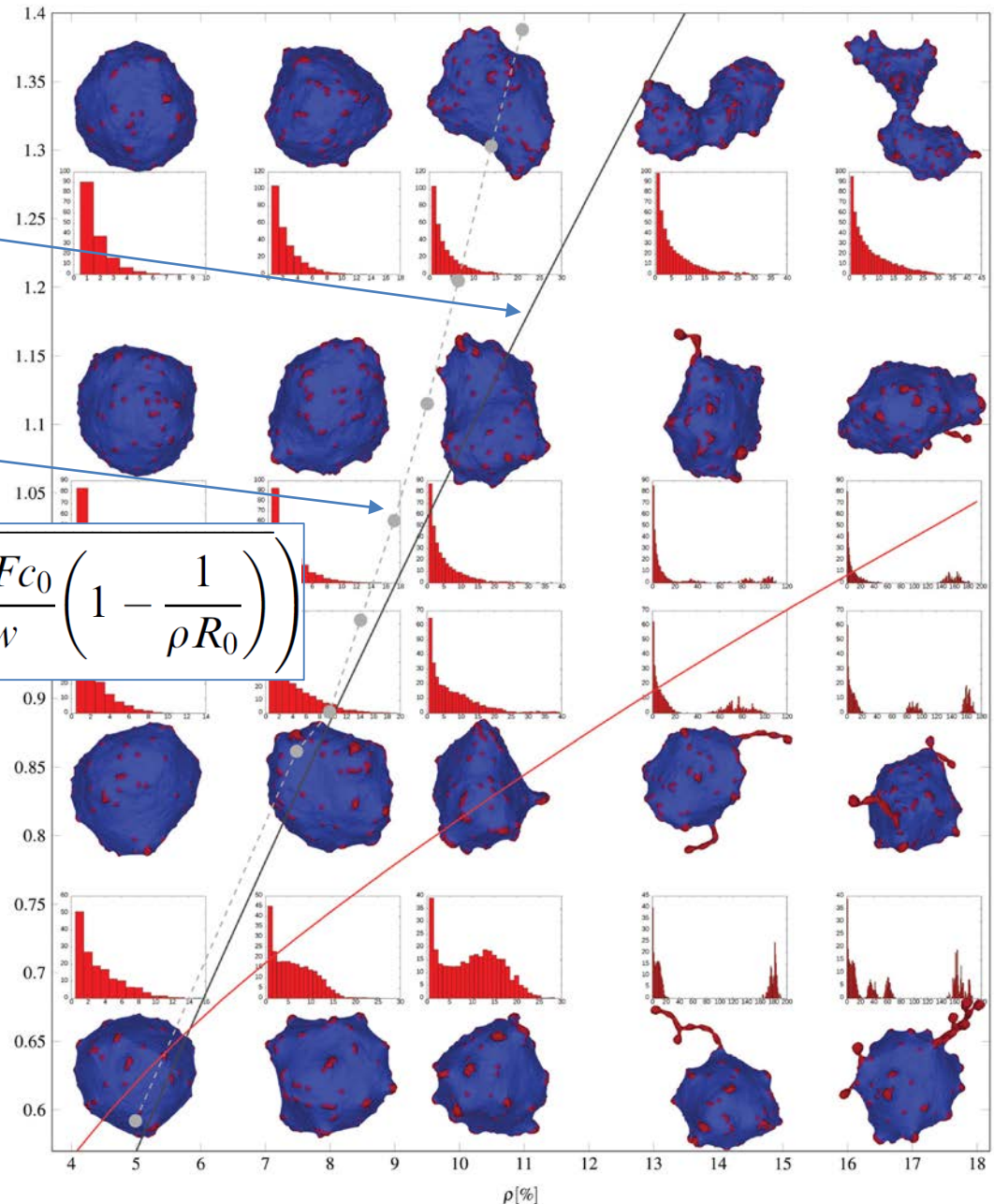
# Passive curved proteins: phase-separation

Linear-stability critical temperature (spinodla) for budding.

Simulation line for:  $\langle N_{cl} \rangle \sim 2$

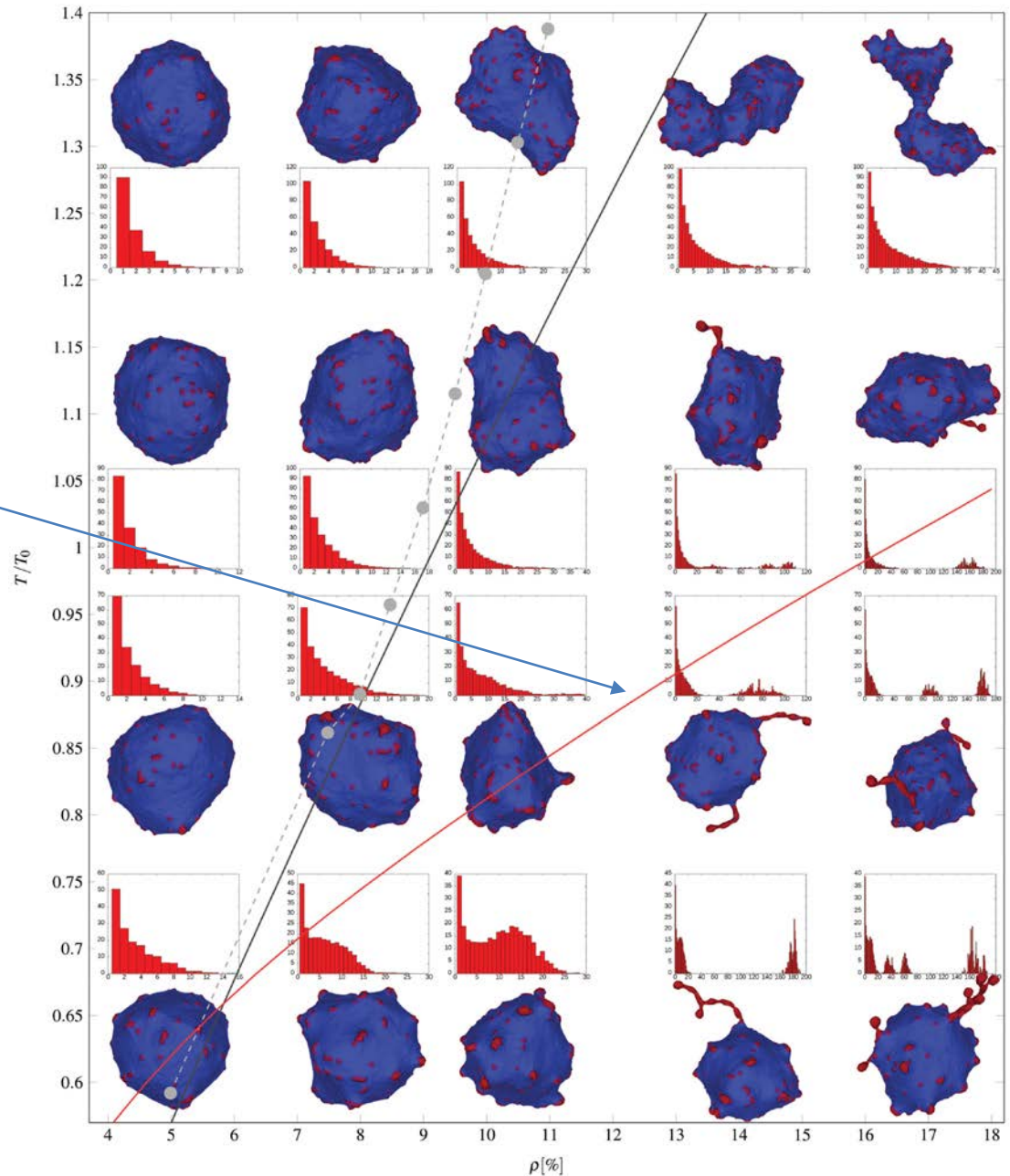
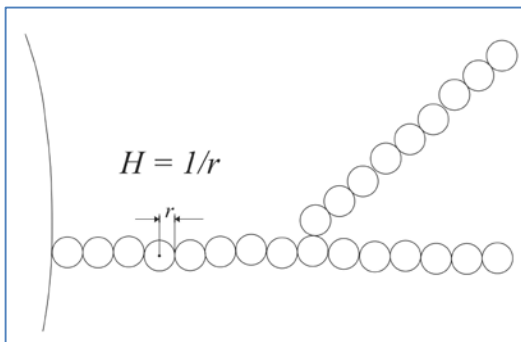
$$kT^{(c)} = 12w(1 - \rho)\rho \left( 1 + \sqrt{\frac{l_{\min}^2 F c_0}{12w} \left( 1 - \frac{1}{\rho R_0} \right)} \right)$$

The budding transition depends on the force, and spontaneous curvature of the curved active proteins.



# Passive curved proteins: phase-separation

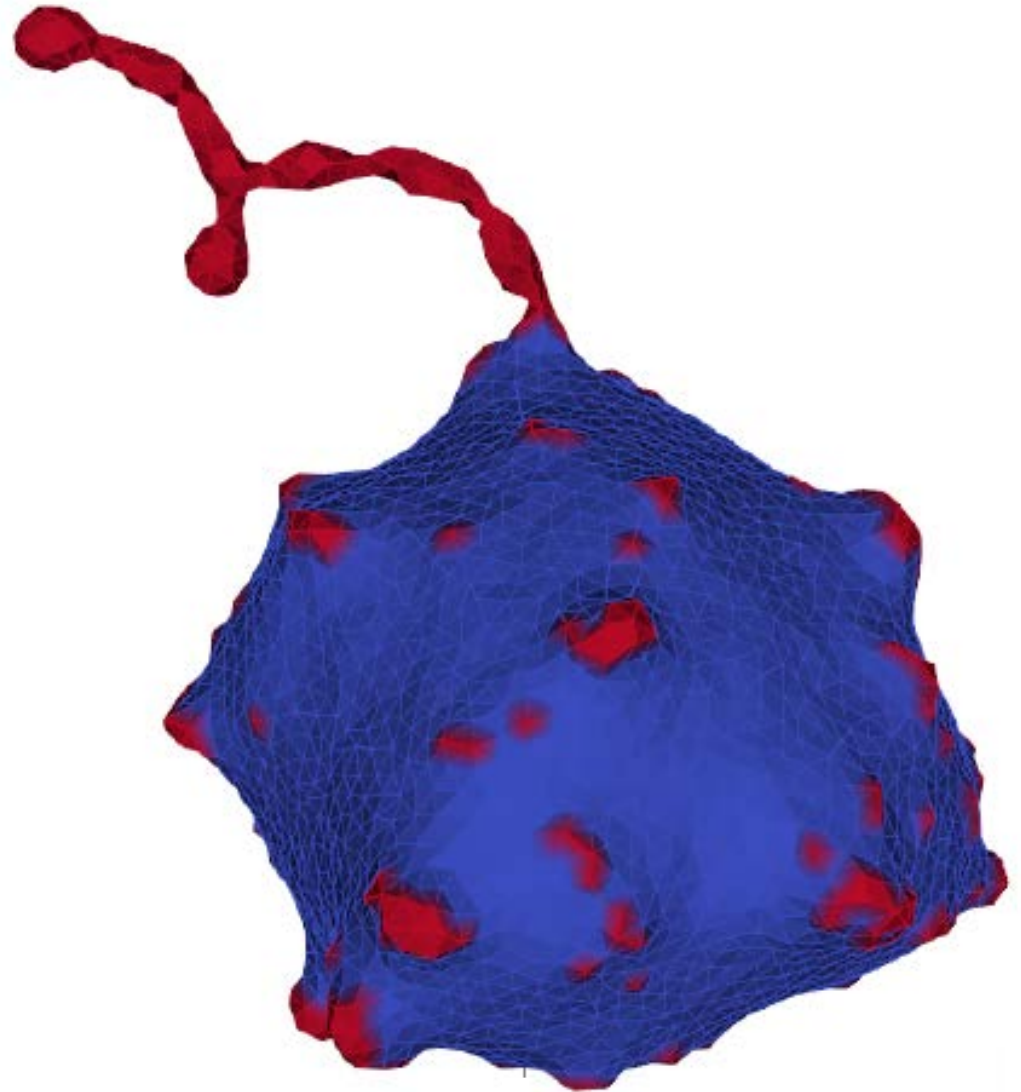
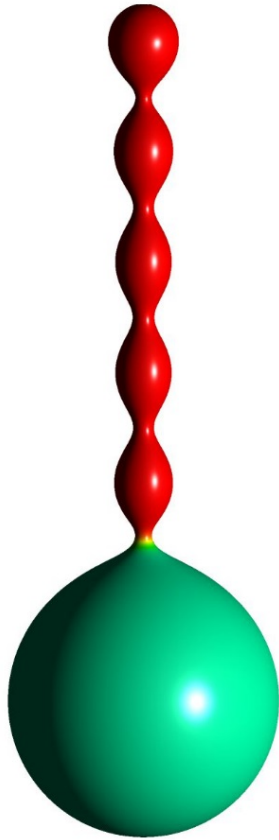
Critical temperature (spinodal) for a mean-field model of pearled-chains aggregation.



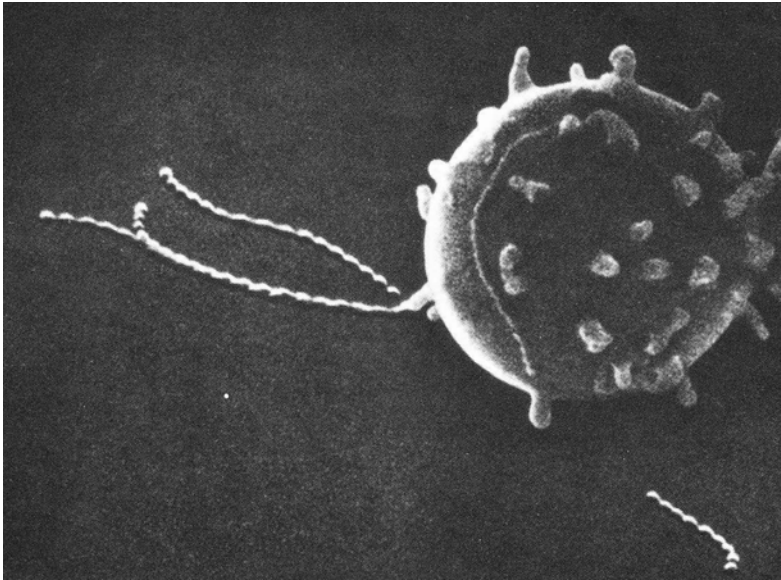


# Some funny shapes:

Which were predicted  
using analytic theory:



And may even exist in cells:

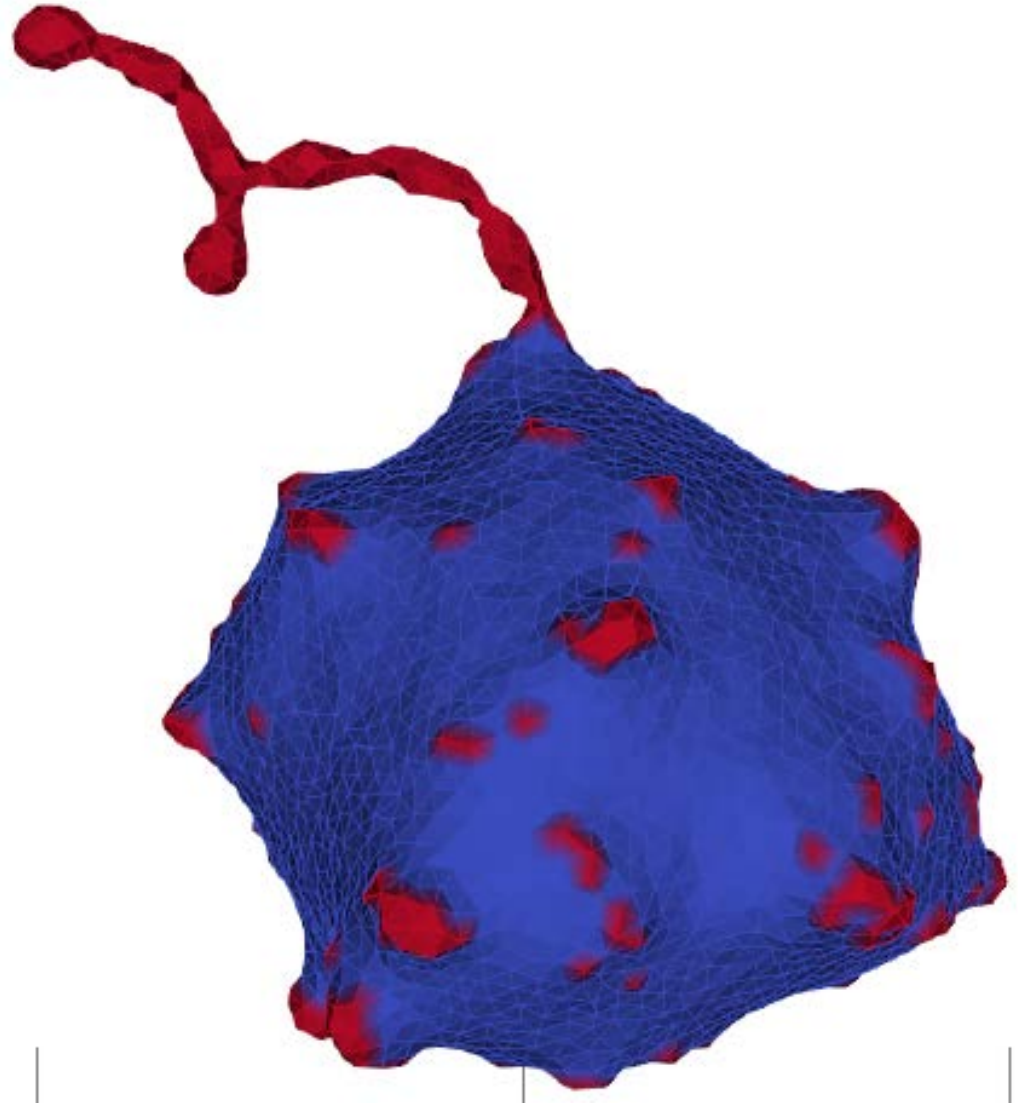


Blood Cells 3, 713–720 (1977)

Blood Cells  
© Springer-Verlag 1977

### A Theoretical Explanation for the Myelin Shapes of Red Blood Cells

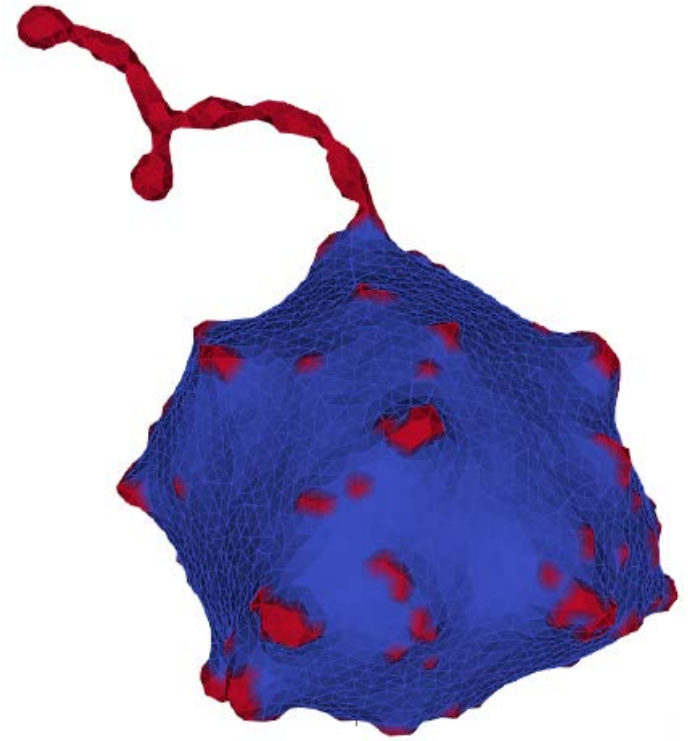
H.J. DEULING and W. HELFRICH



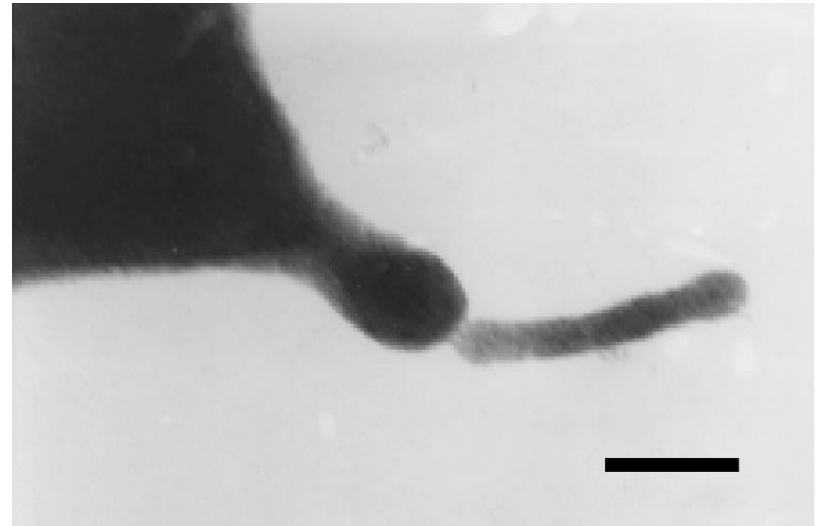
And seen in  
experiments:  
Artificial vesicles



Veronika Kralj-Iglič  
et al., *J. Phys. A:  
Math. Gen.* **35**  
(2002) 1533–1549

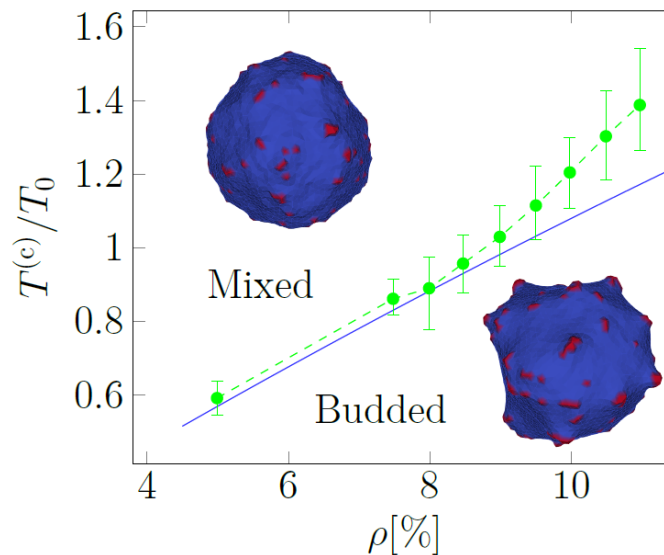
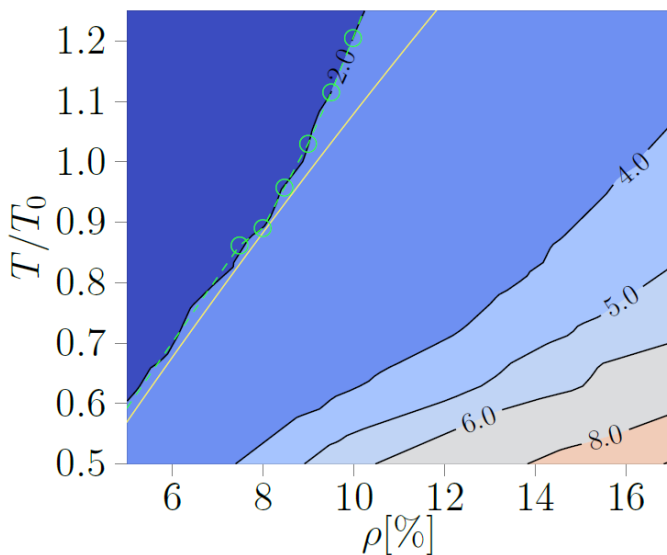


And RBC's:

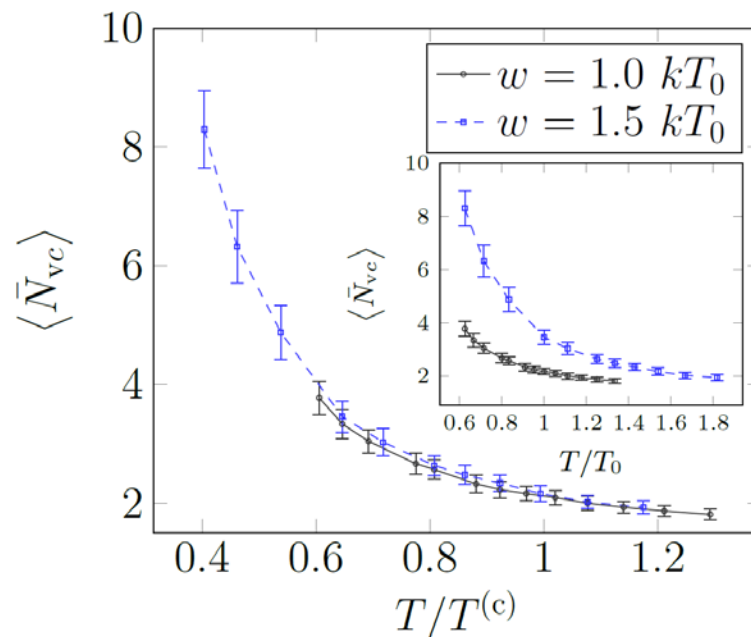
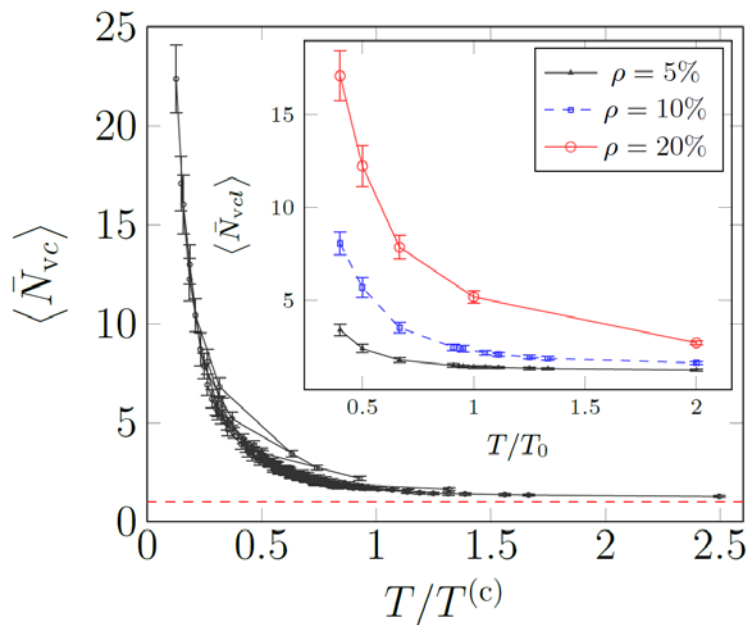


Kralj-Iglič, V., et al.  
*Physical Review  
E* 61.4 (2000): 4230.

# Passive case: only one transition temperature

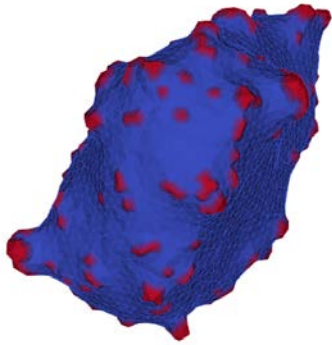


## Data collapse using the critical temperature scale:

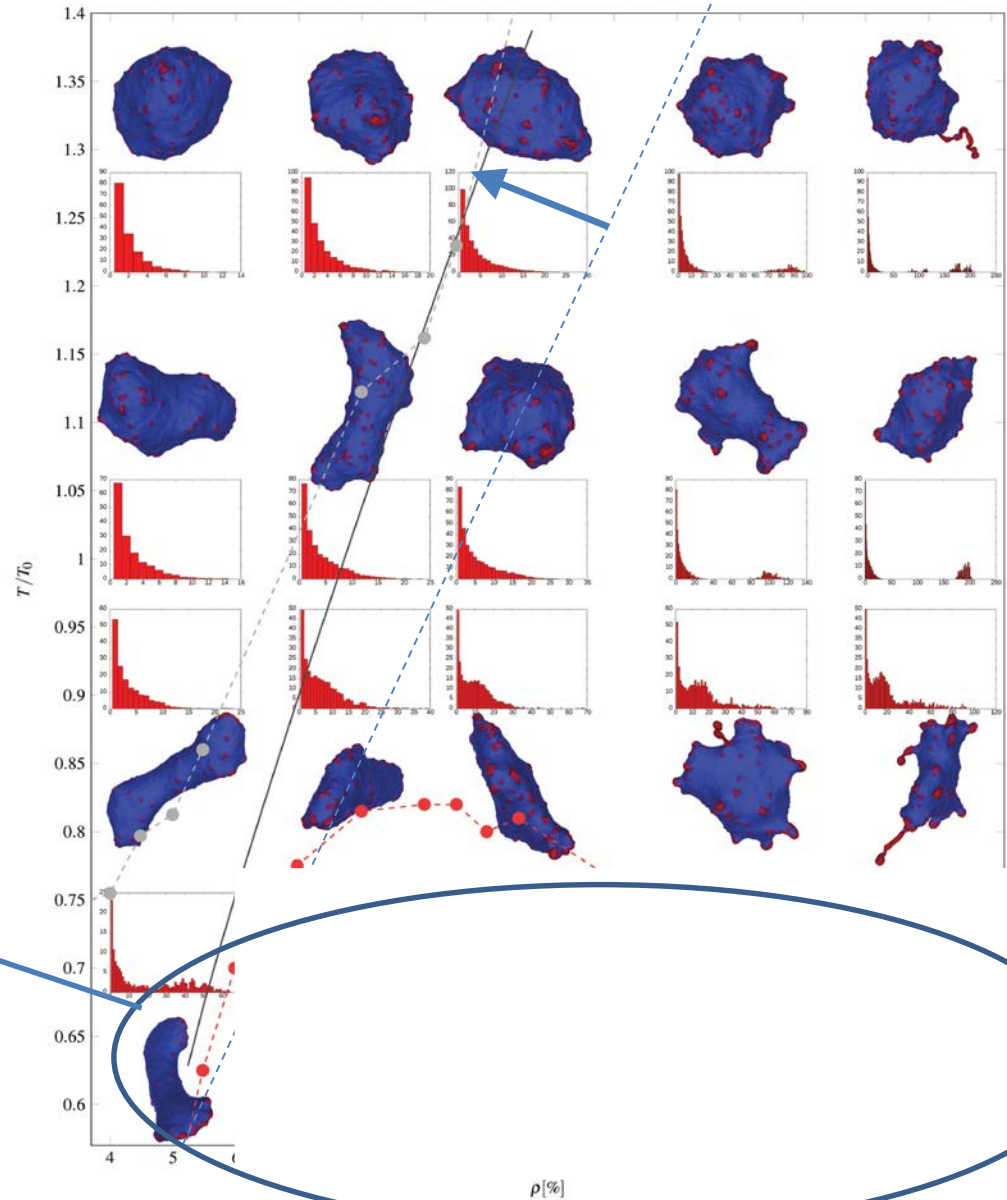


# With activity:

Phase separation at higher  $T$  and lower  $\rho$   
(HIV budding...)

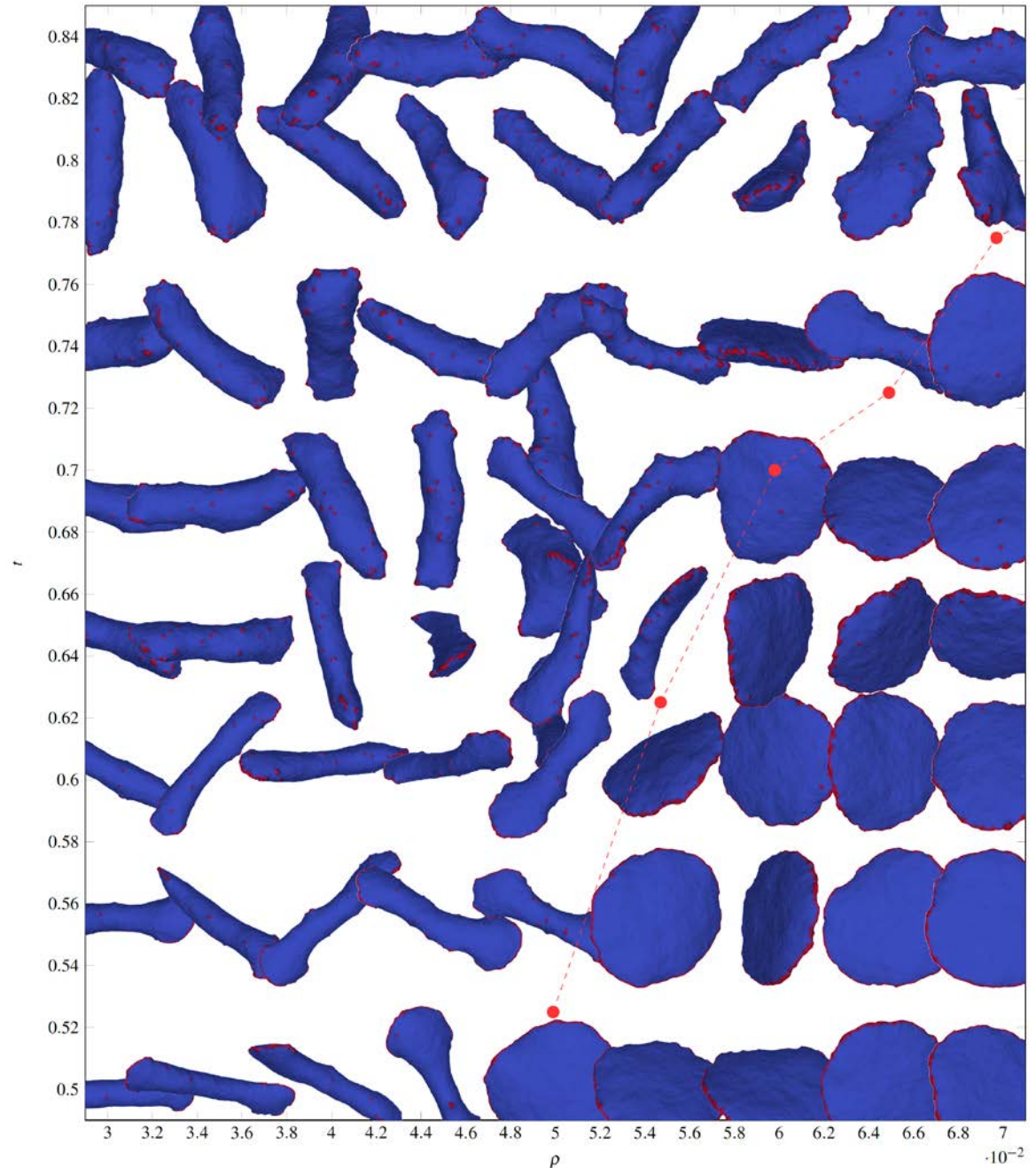


A new, unexpected,  
pancake-like phase:

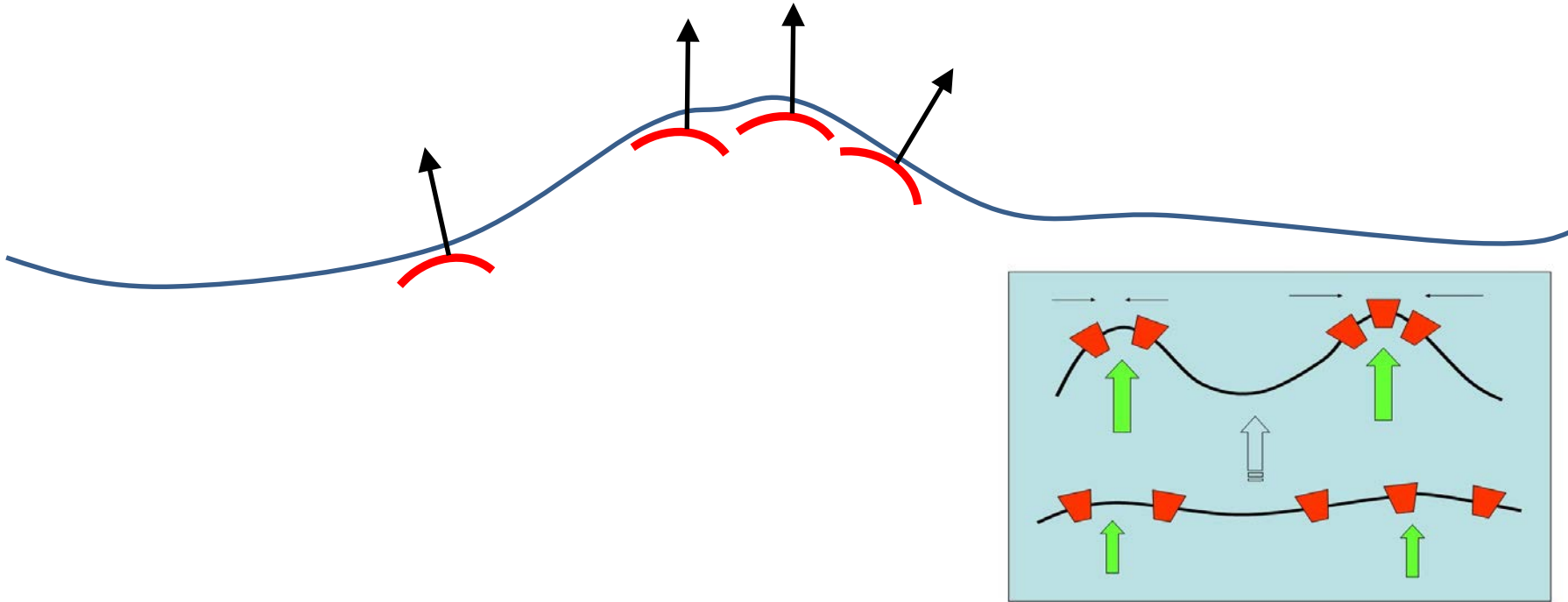


It's a sharp transition

What is the mechanism driving this new transition ?

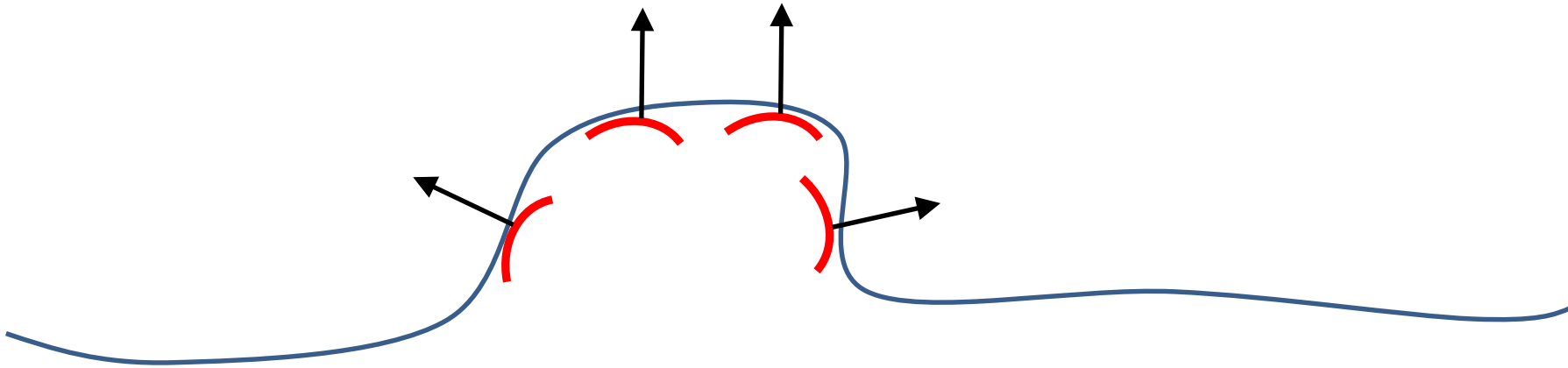


For almost flat membrane, the active force acts to push outwards, with respect to the spherical vesicle:



This deforms the membrane in a similar way as the curved proteins, driving their faster aggregation and budding.

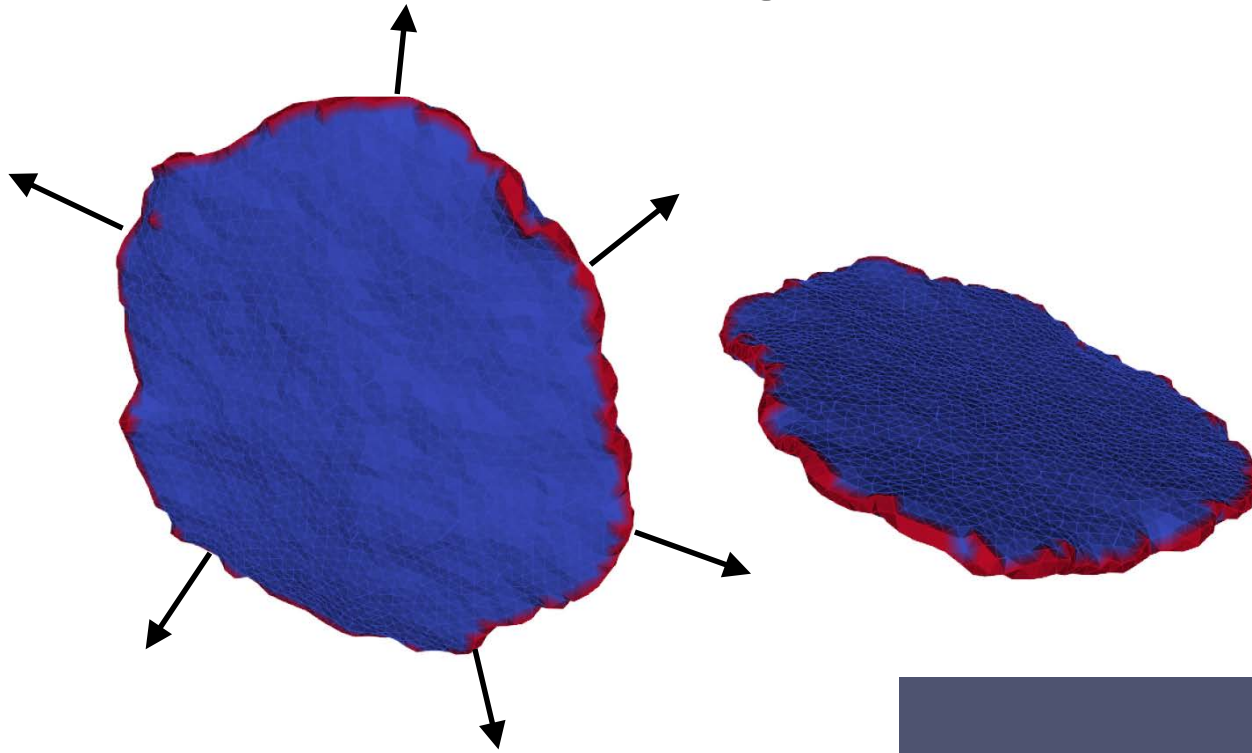
However, when the aggregates are highly budded out, the active force acts to destabilize them:



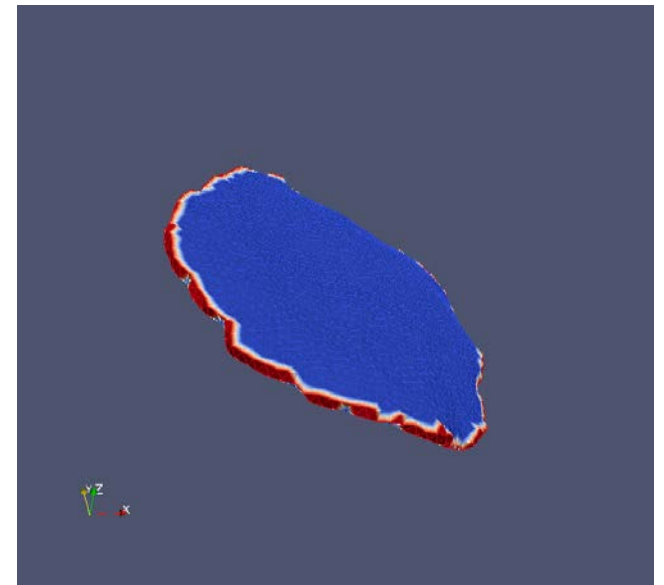
At a critical aggregate size, the side-ways force is too large and the isolated aggregates are **destabilized**.



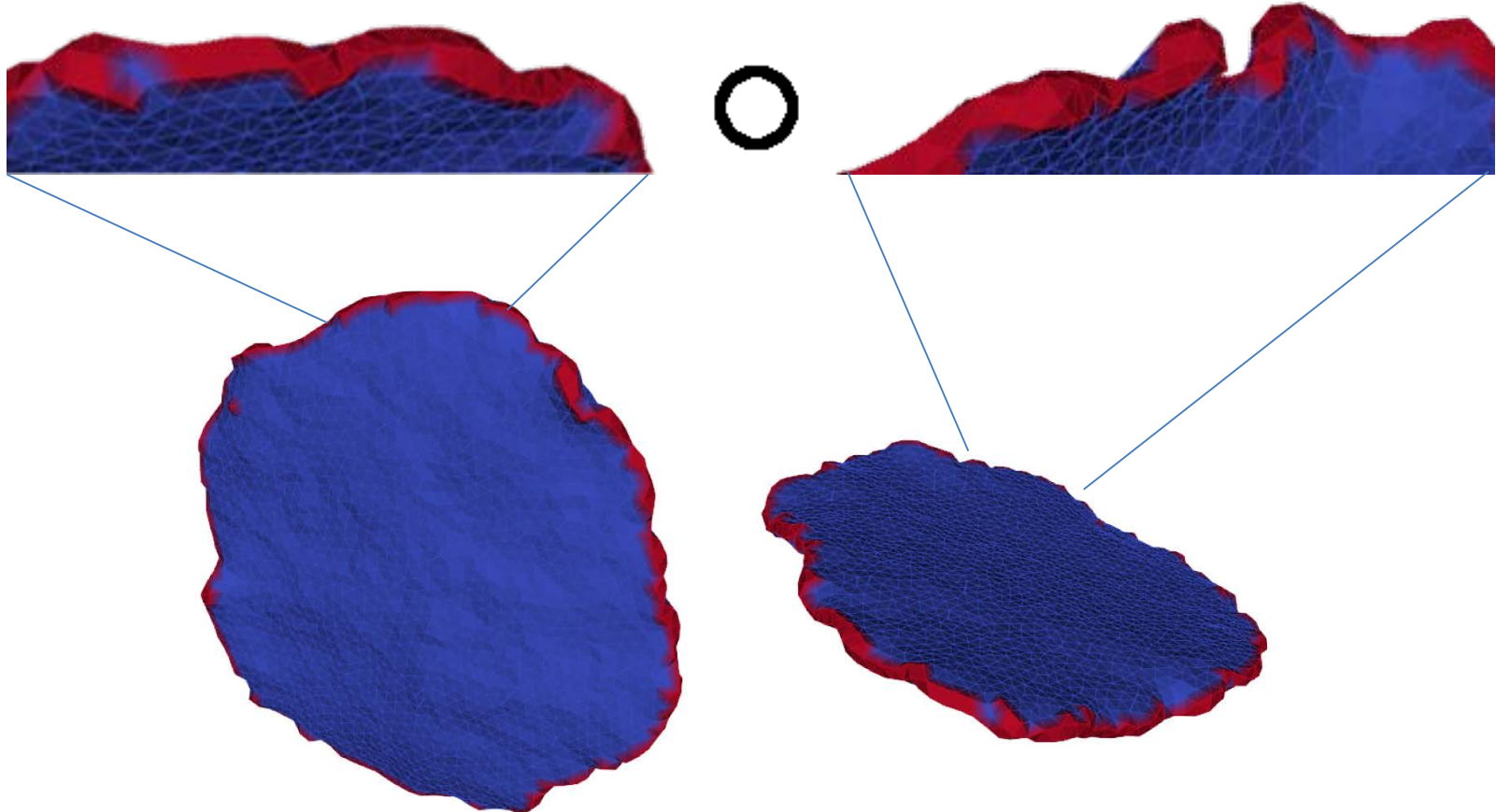
And a new stable configuration is found:



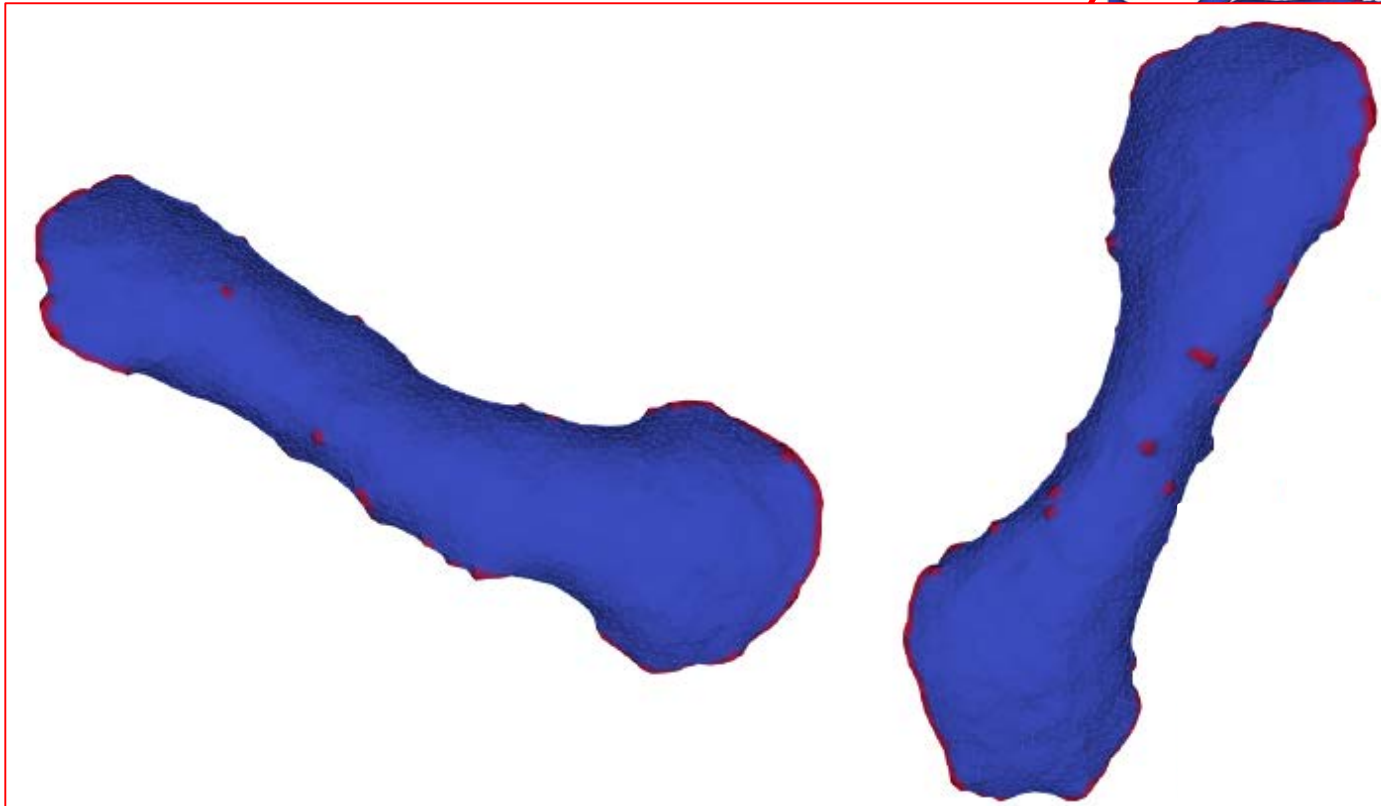
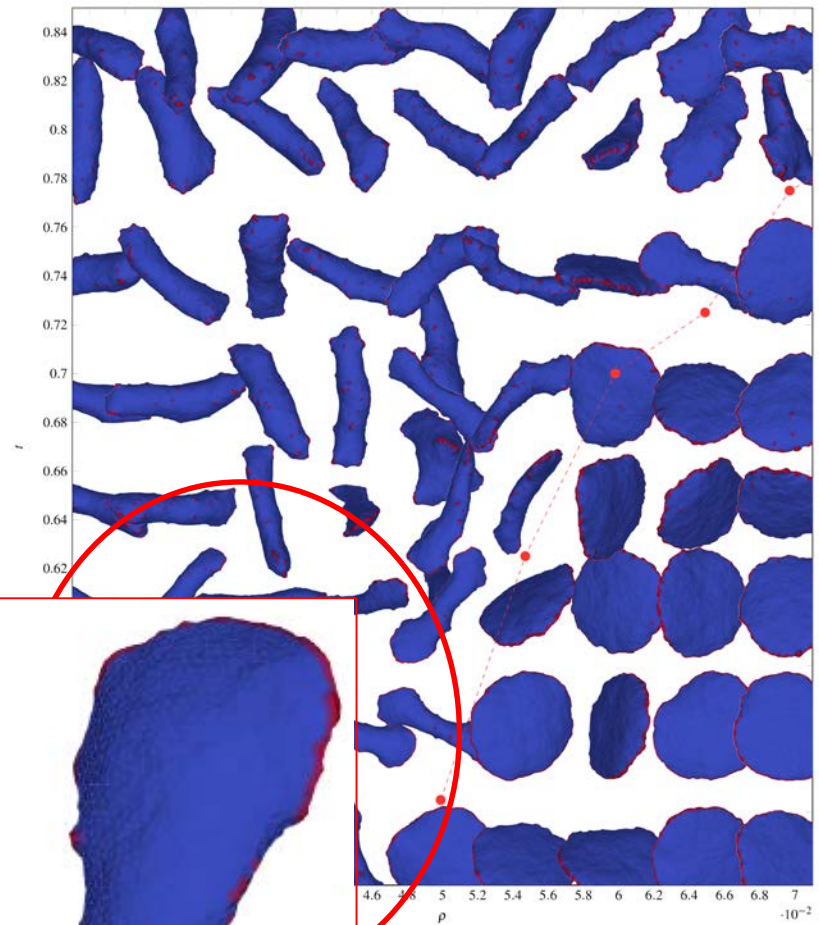
In this way all the active forces act to maintain the shape, and the proteins form a stable rim-localized aggregate.



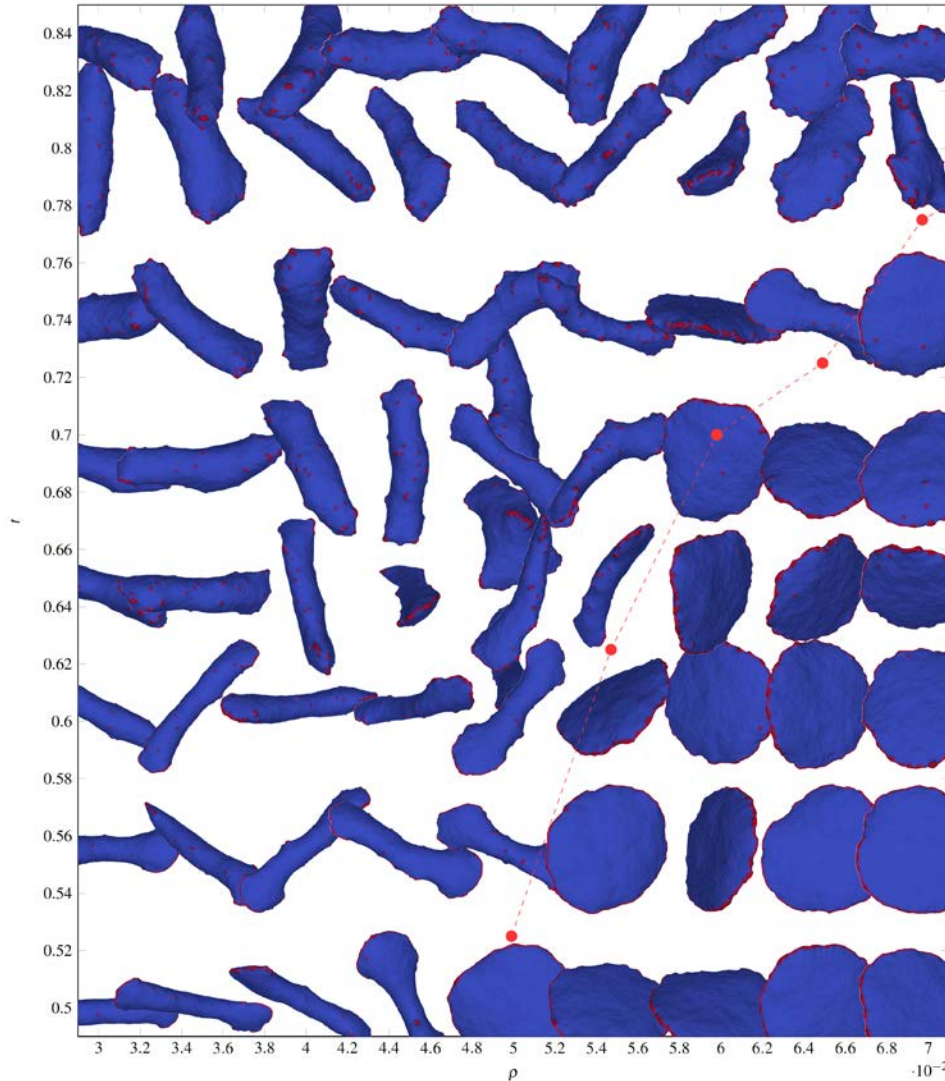
Due to the high spontaneous curvature of the proteins, the rim forms small-scale undulations:



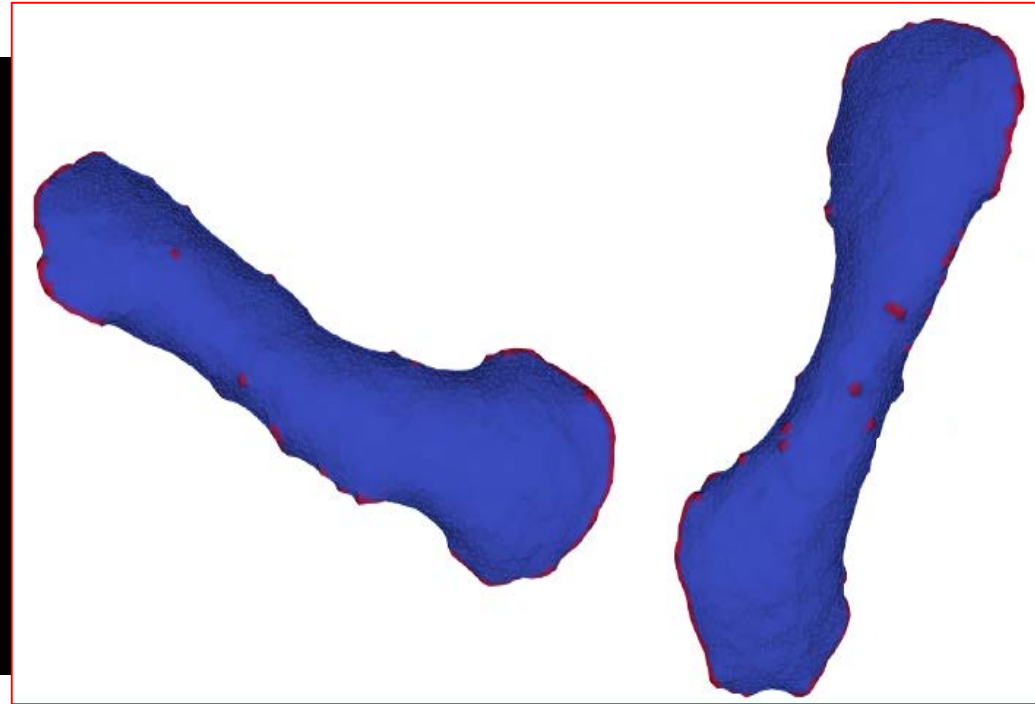
Below a critical amount of proteins, there are not enough to form a closed rim: Two flat aggregates form, connected by a ~cylindrical part.



Could this be the mechanism maintaining the flat lamellipodia ?

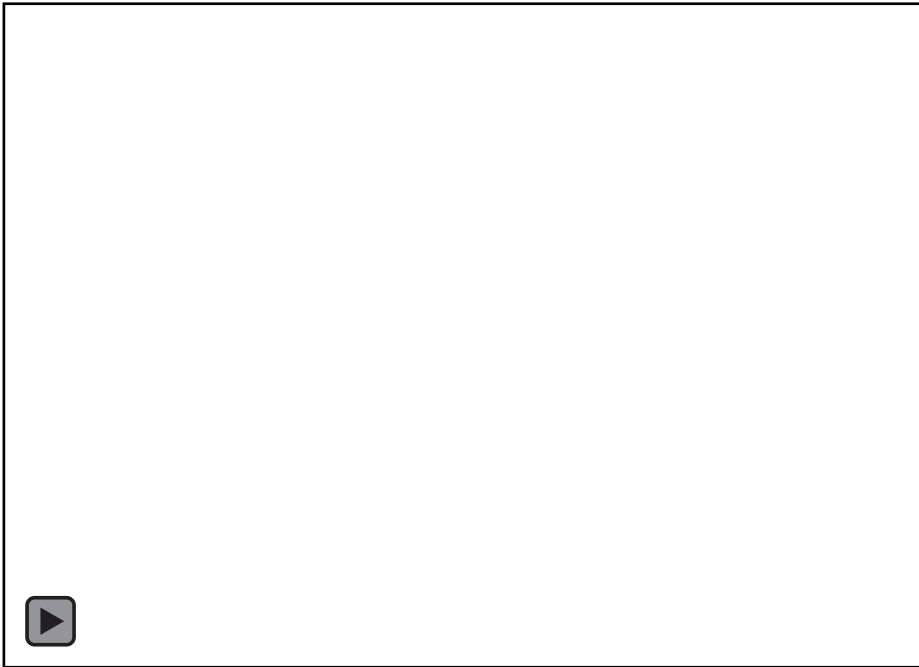


# Could this be the mechanism maintaining the flat lamellipodia ?

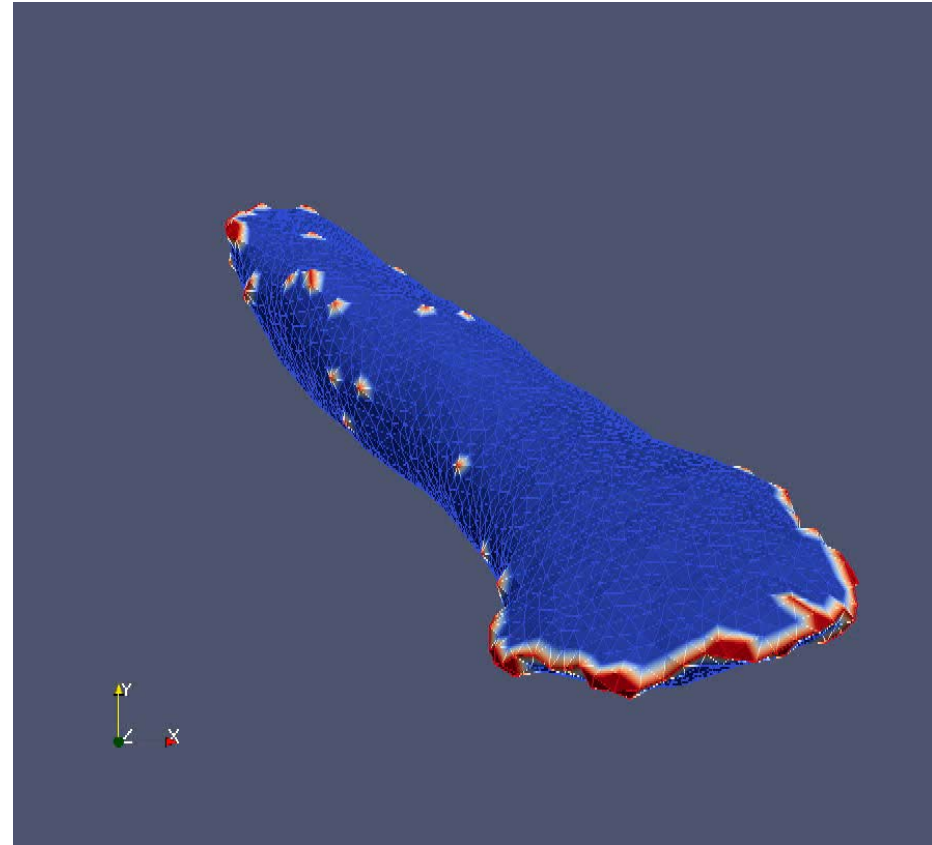


Fritz-Laylin, Lillian K., et al. "Actin-based protrusions of migrating neutrophils are intrinsically lamellar and facilitate direction changes." *Elife* 6 (2017): e26990.

# Could this be the mechanism maintaining the flat lamellipodia ?



**Example of 'rosette' pseudopods built by cells crawling through polymerized collagen networks.**



Fritz-Laylin, Lillian K., et al. "Actin-based protrusions of migrating neutrophils are intrinsically lamellar and facilitate direction changes." *Elife* 6 (2017): e26990.

Could this be the mechanism maintaining  
the flat lamellipodia ?

Are there convex complexes that activate  
actin at the lamellipodia edge ?

Begemann, I., et al.

"Mechanochemical self-organization determines search pattern in migratory cells."  
*Nature Physics*(2019): 1.



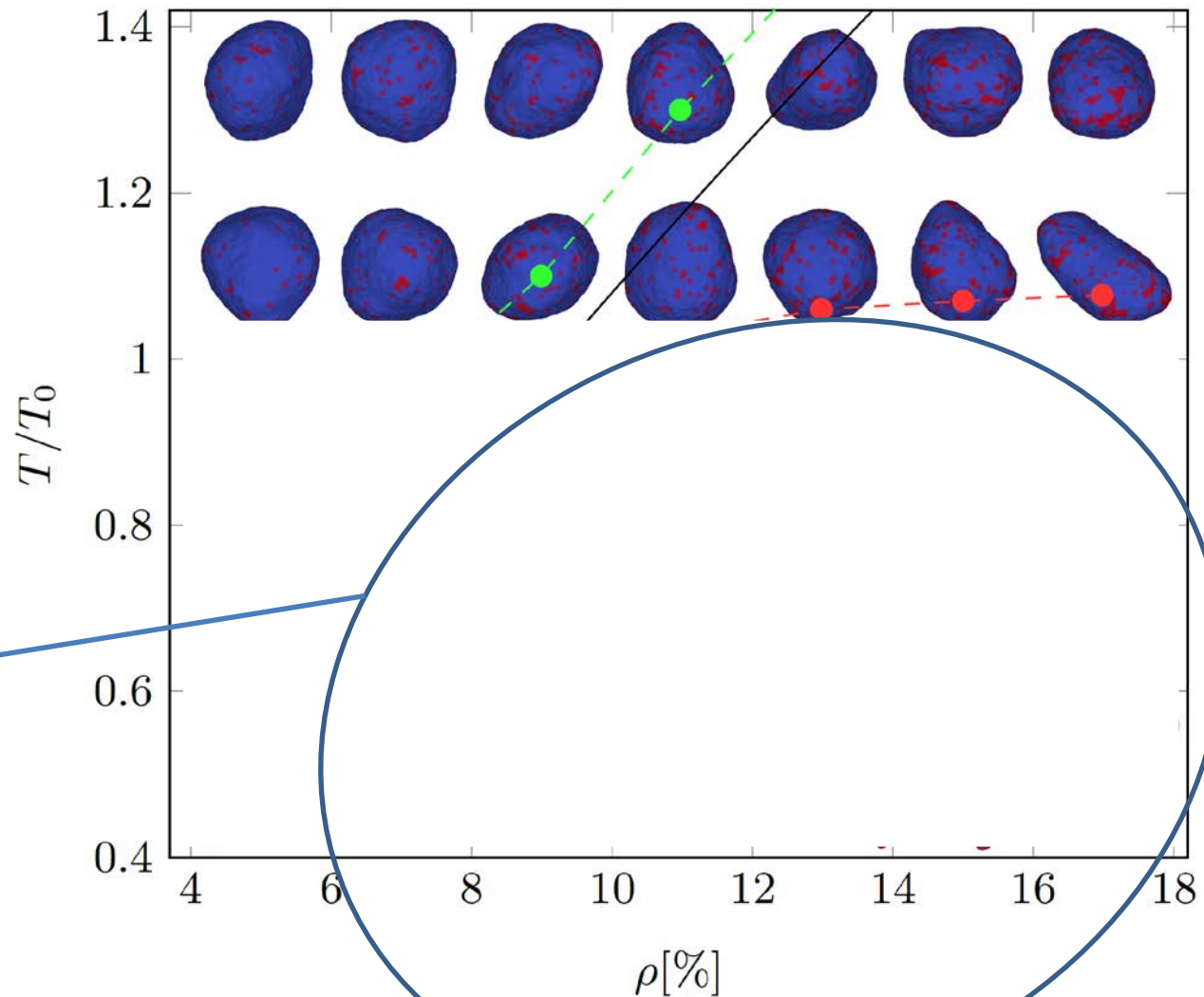
Milos  
Galic  
(Munster)

Recent work reports the role of I-BAR  
proteins at the lamellipodia edge, and  
shows that they are essential to initiate the  
protrusive activity of the lamellipodia.

# Is the activity alone driving the flat shape ?

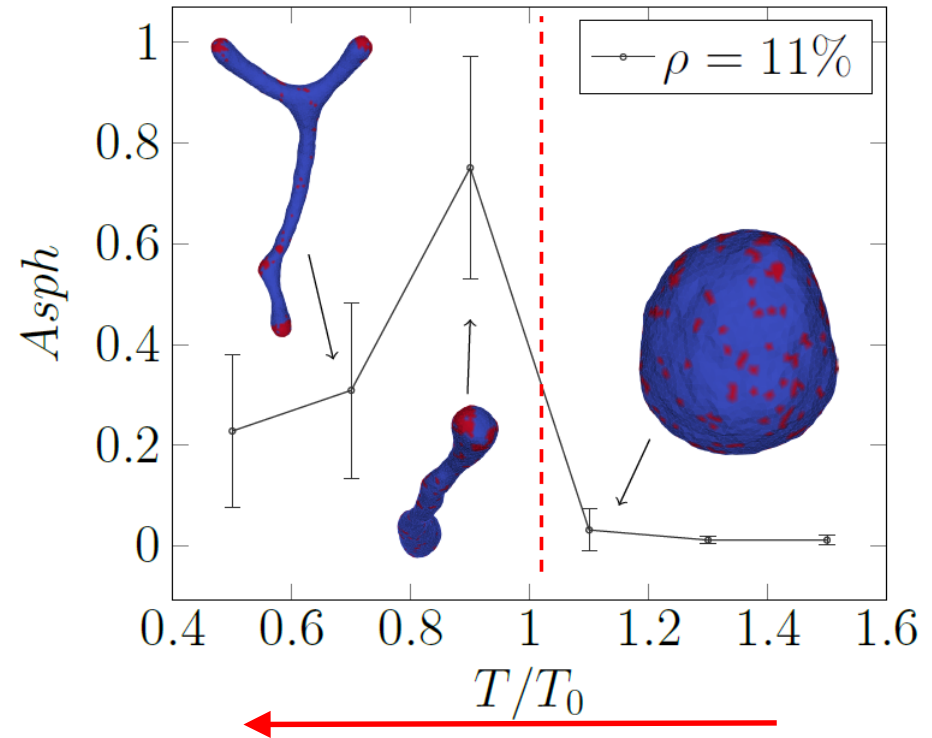
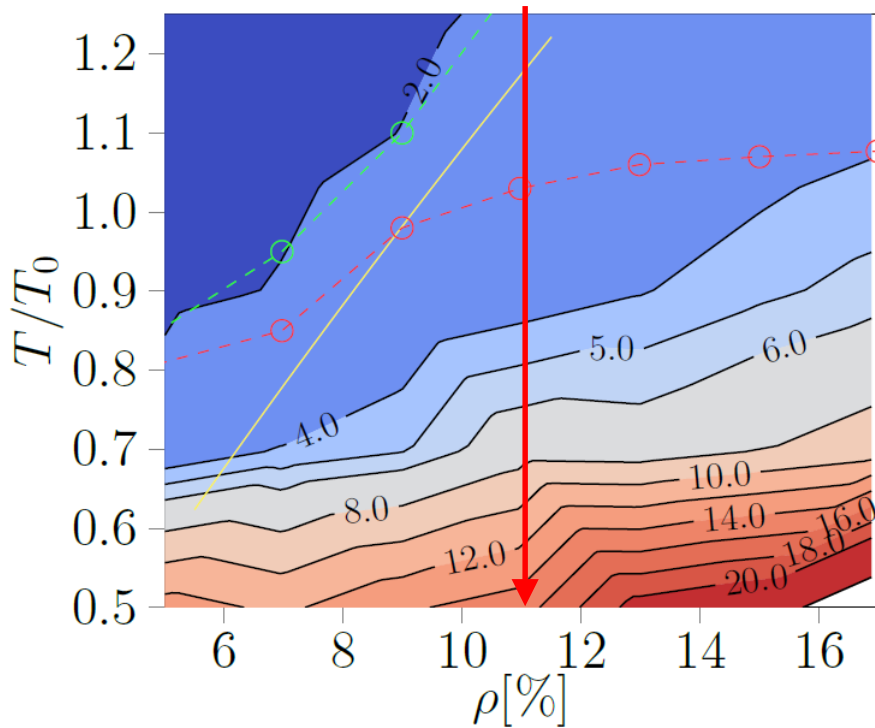
Flat active proteins:

No, another phase, characterized by long tether-like shapes appears:

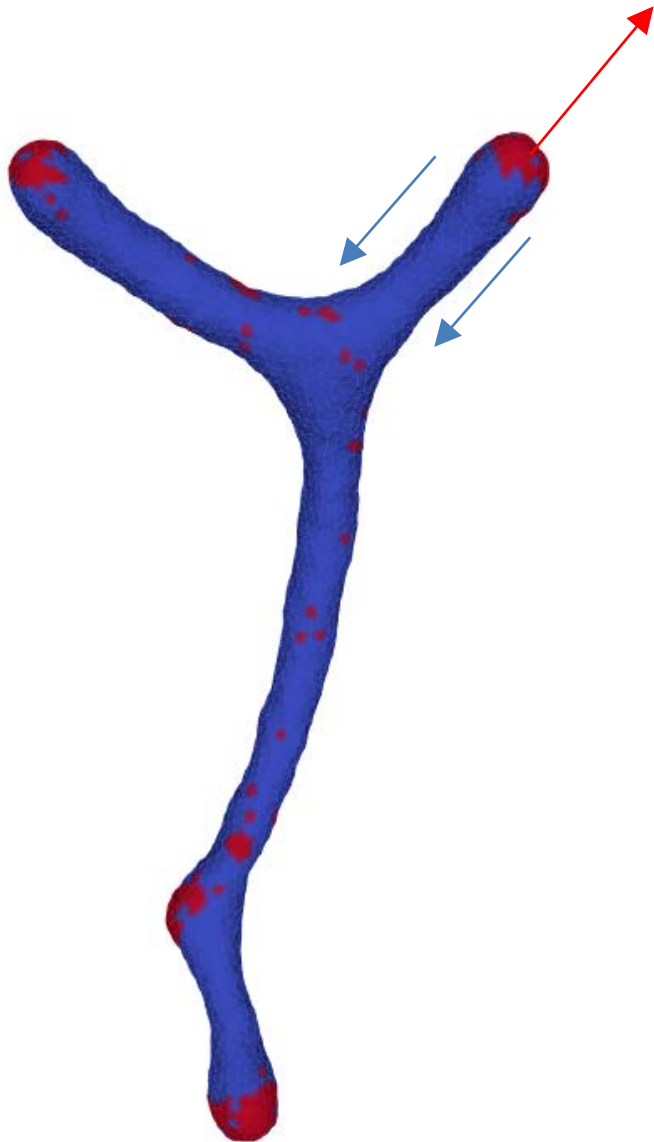




Above a critical aggregate size, the active force is able to pull “tethers”



The radius of the protrusions is given by force balance:



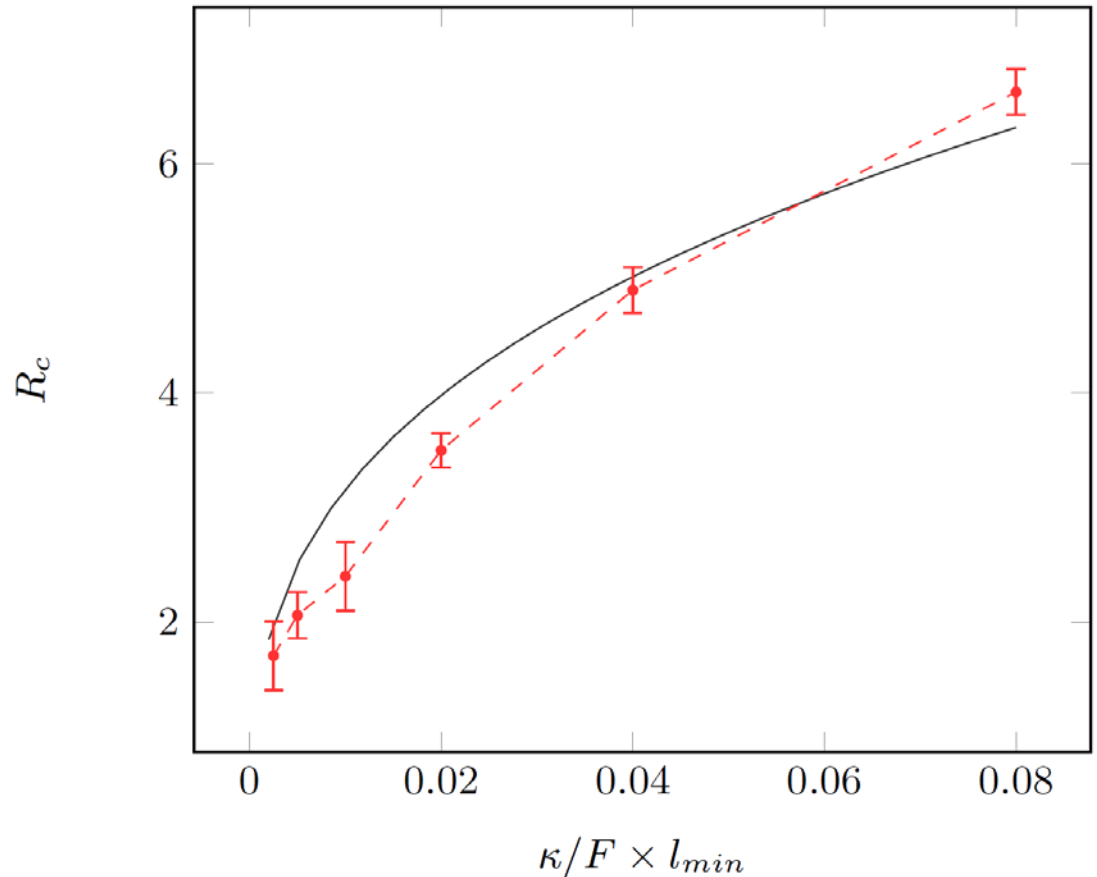
$$F_a = F \frac{\pi R^2}{a}$$

$$F_b = \kappa \frac{2\pi}{R}$$

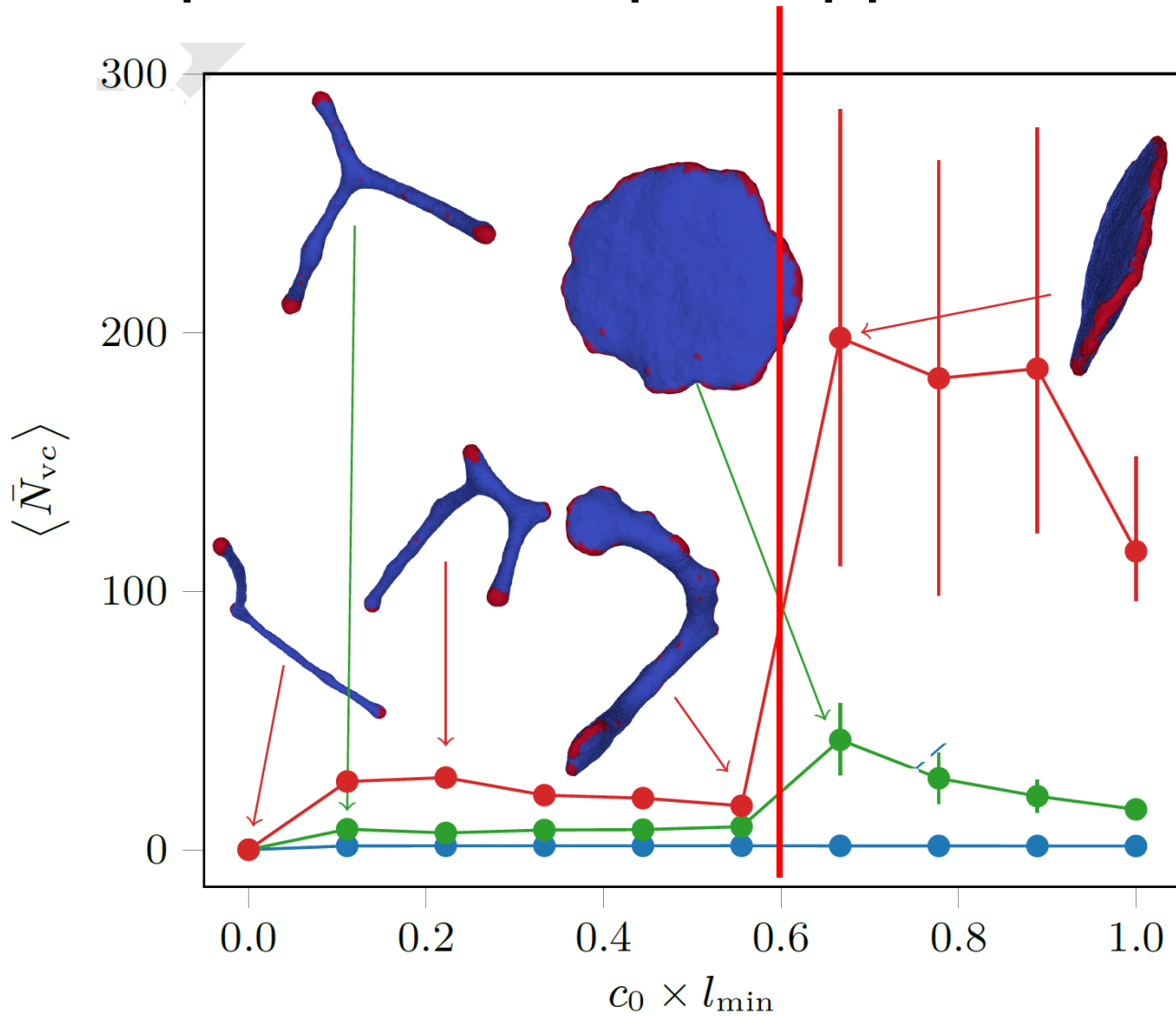
$$R_c = \left( \frac{2\kappa a}{F} \right)^{1/3}$$

The radius of the protrusions is given by force balance:

$$R_c = \left( \frac{2\kappa a}{F} \right)^{1/3}$$

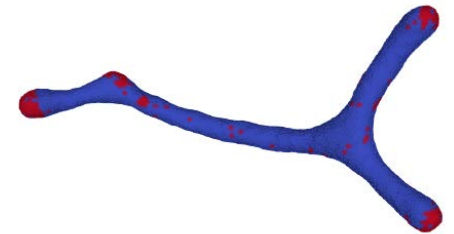
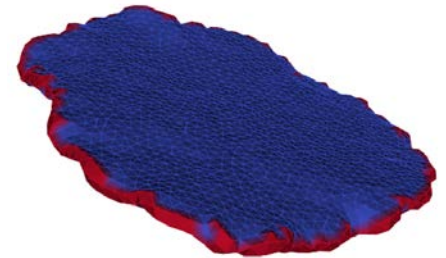
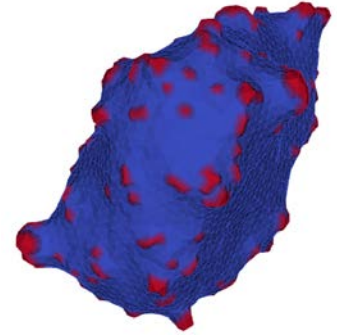


Above a critical spontaneous curvature, the pancake shapes appear



# Conclusions

- Protrusive activity + convex curvature drives faster budding (HIV).
- Above a critical cluster size, they can drive ruffle and lamellipodia-looking structures.
- Flat complexes that recruit protrusive activity can drive tether (or filopodia)-like structures.





Thank you !