Morphogenesis

and

Random Cytoskeletal Networks

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EMBL

A simple physical model
of
The early mouse embryo

Jean-Léon Maître

Hervé Turlier

Ritsuya Niwayama

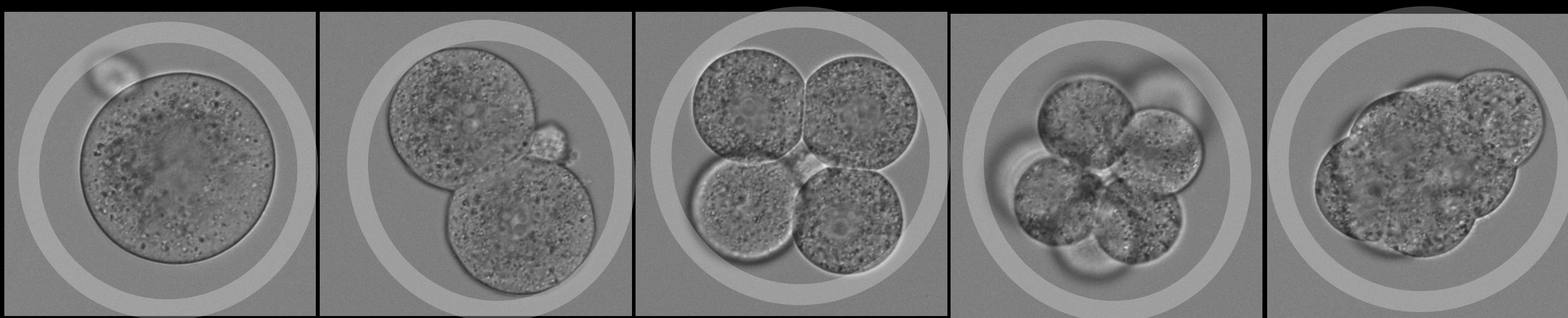
Takashi Hiiragi

EMBL

Early Mammalian Development

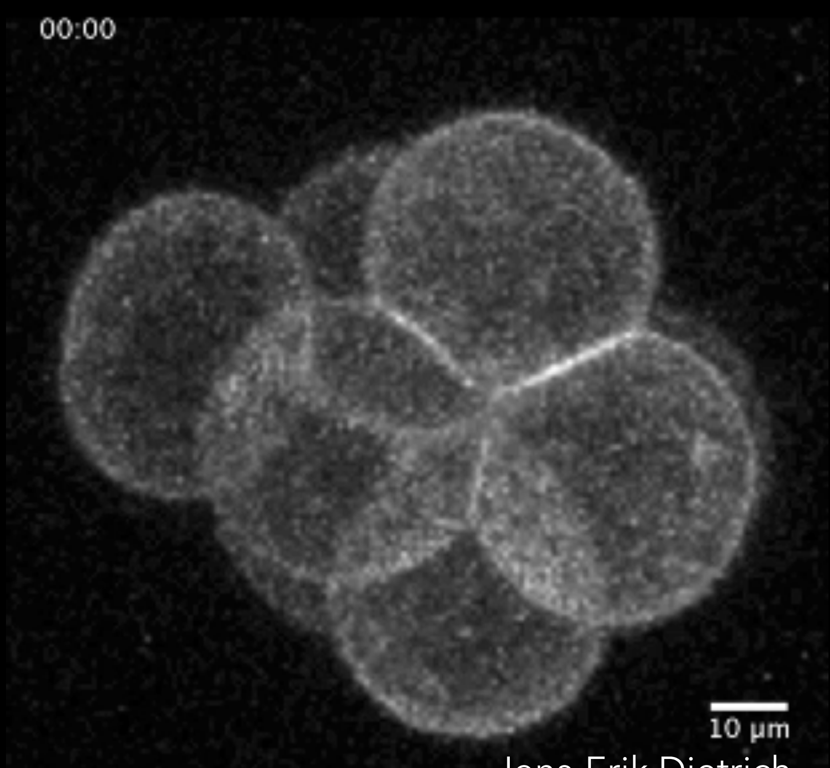
Mouse embryo

fertilization | 1 day | 1.5 days | 2 days | 13.5 days

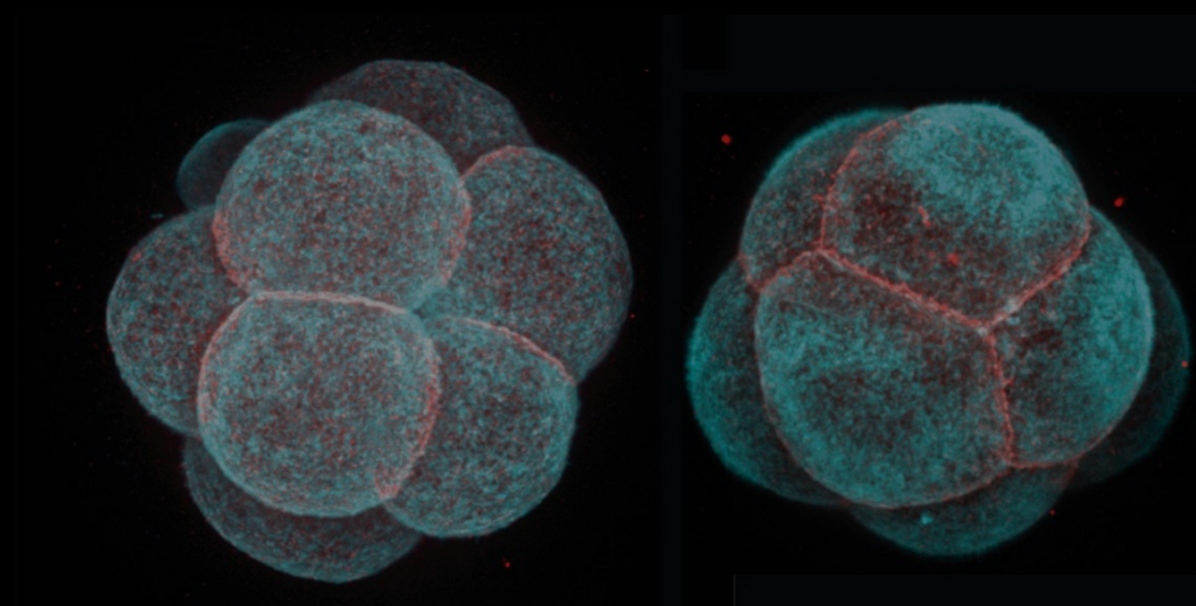


1 cell | 2 cells | 4 cells | 8 cells | 8 cells

A. Inoue and S. Yamaguchi



Jens-Erik Dietrich

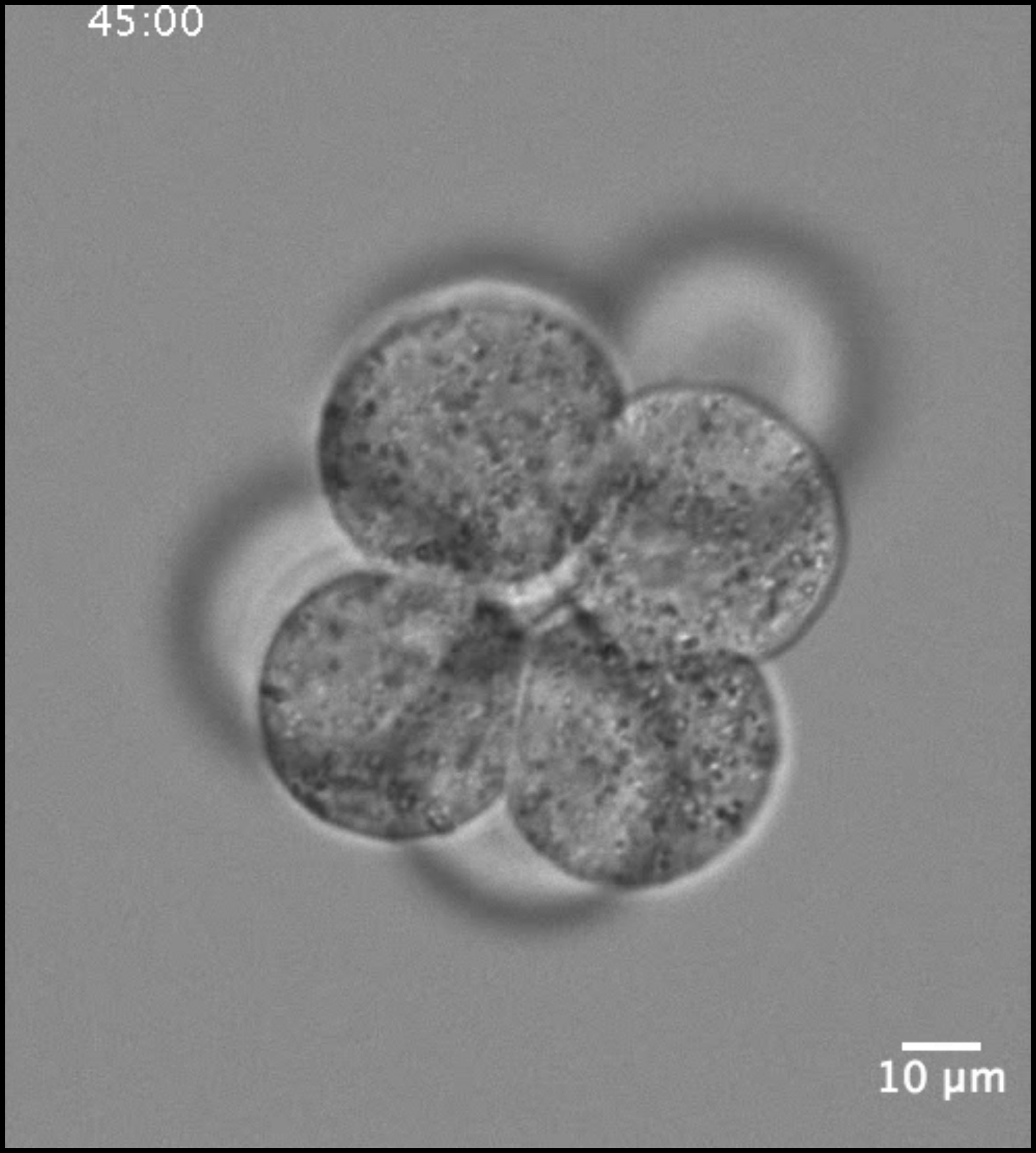


Compaction

Maître et al. Nature Cell Biology 2015
Maître et al. Nature 2016

Jean-Léon Maître, Takashi Hiiragi Group

Early Mammalian Development



JL Maître

Very slow process ~ 9h

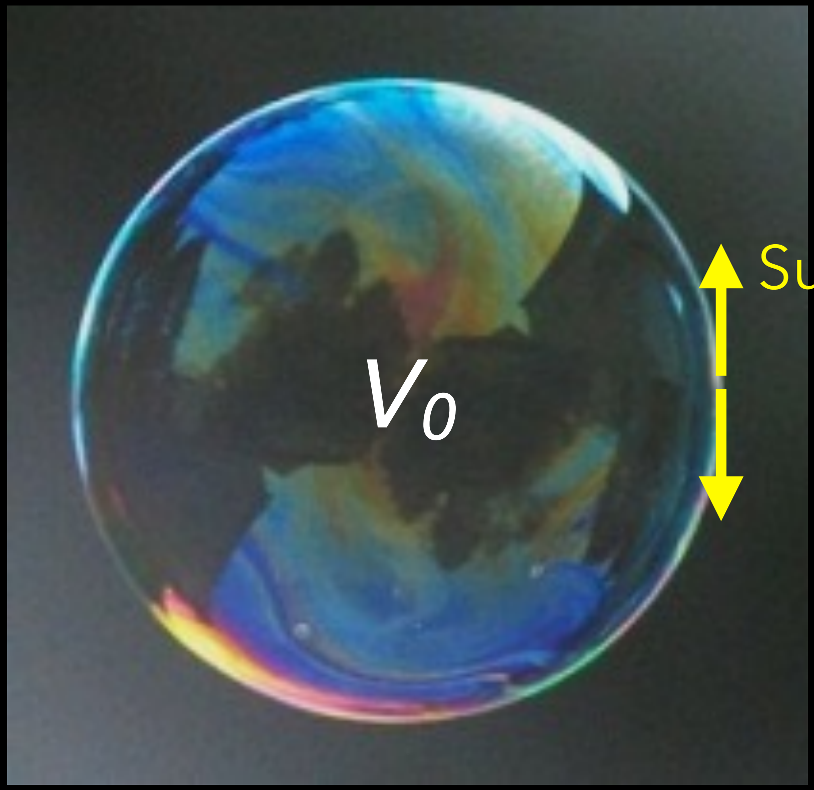
Quasistatic

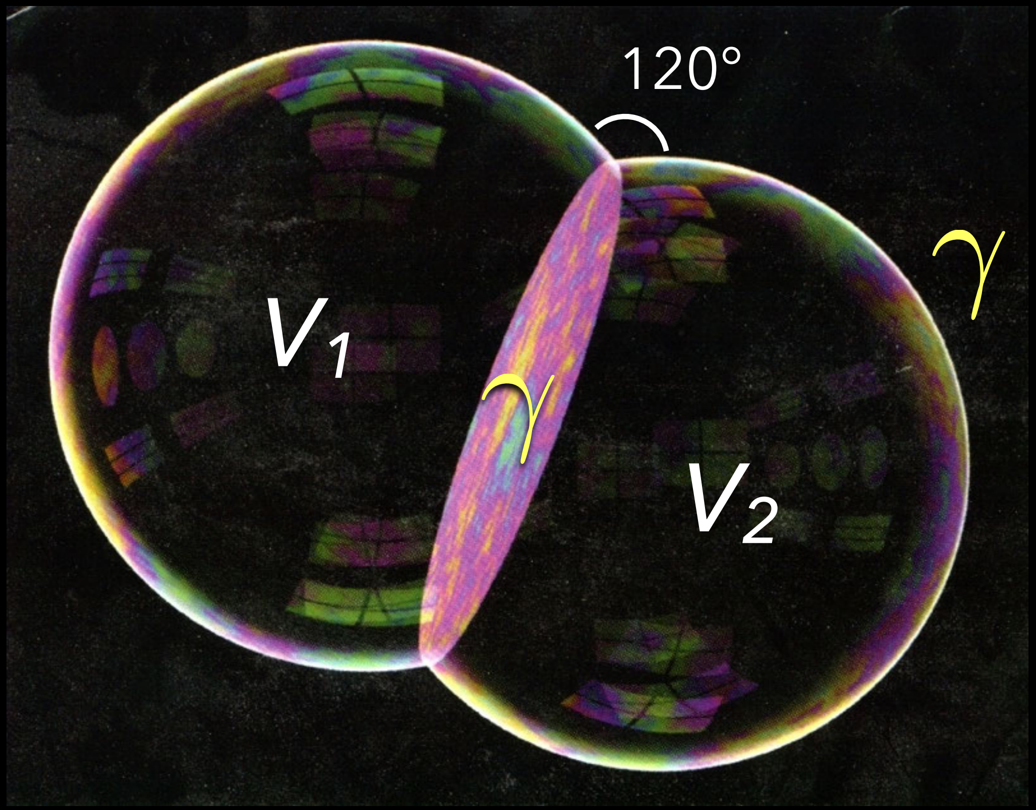
Flat Contacts

Symmetric cell-cell contacts
(all cells identical)

The Physics of Soap Bubbles

Joseph Plateau (1801 – 1883)

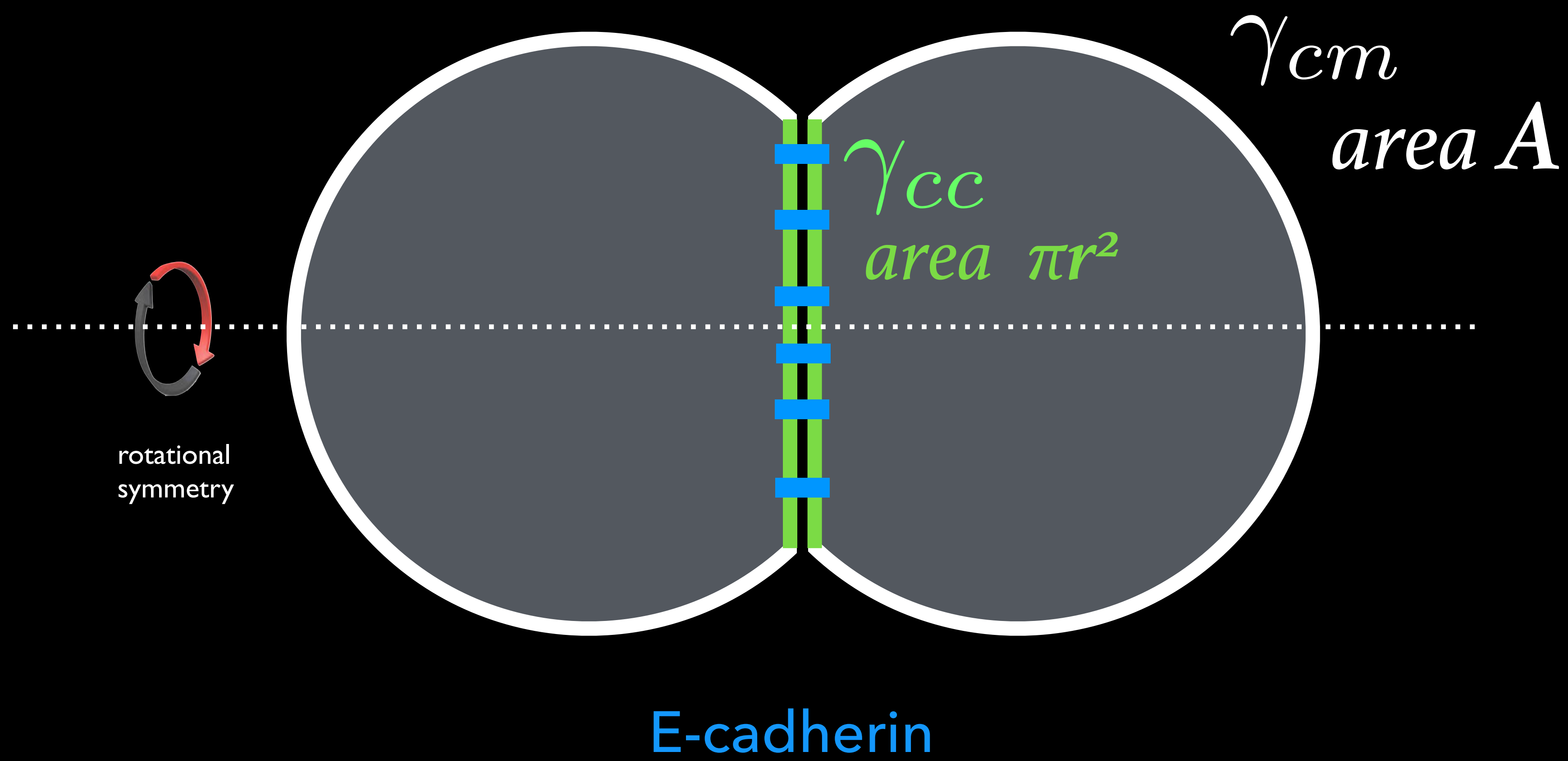




Surfaces of minimal energy: $\mathcal{E} = \gamma \sum_i A_i$

… given that volumes $\boldsymbol{V_i}$ are conserved.

Shape of a Symmetric Cell Doublet



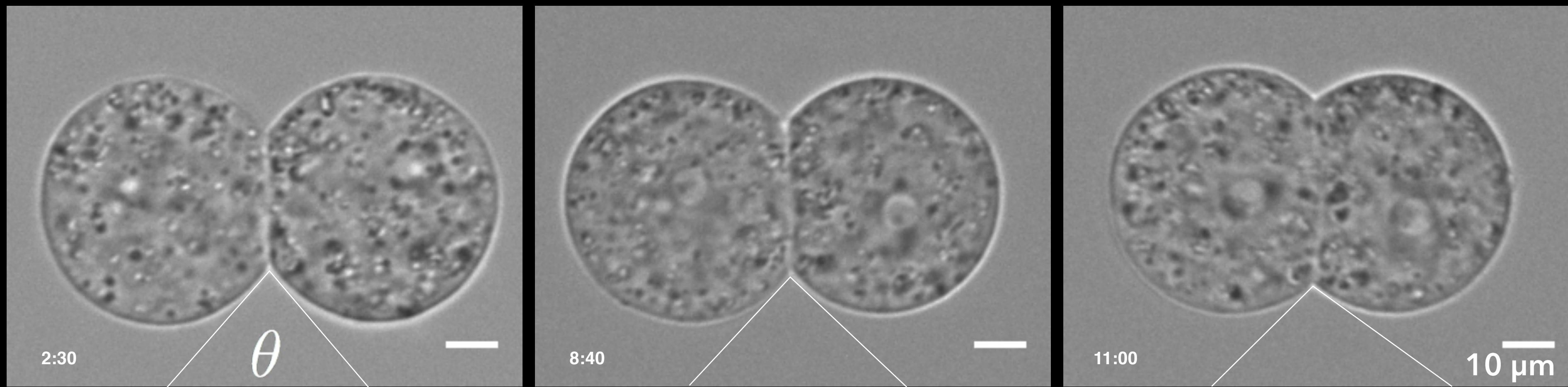
Minimize surface energy:

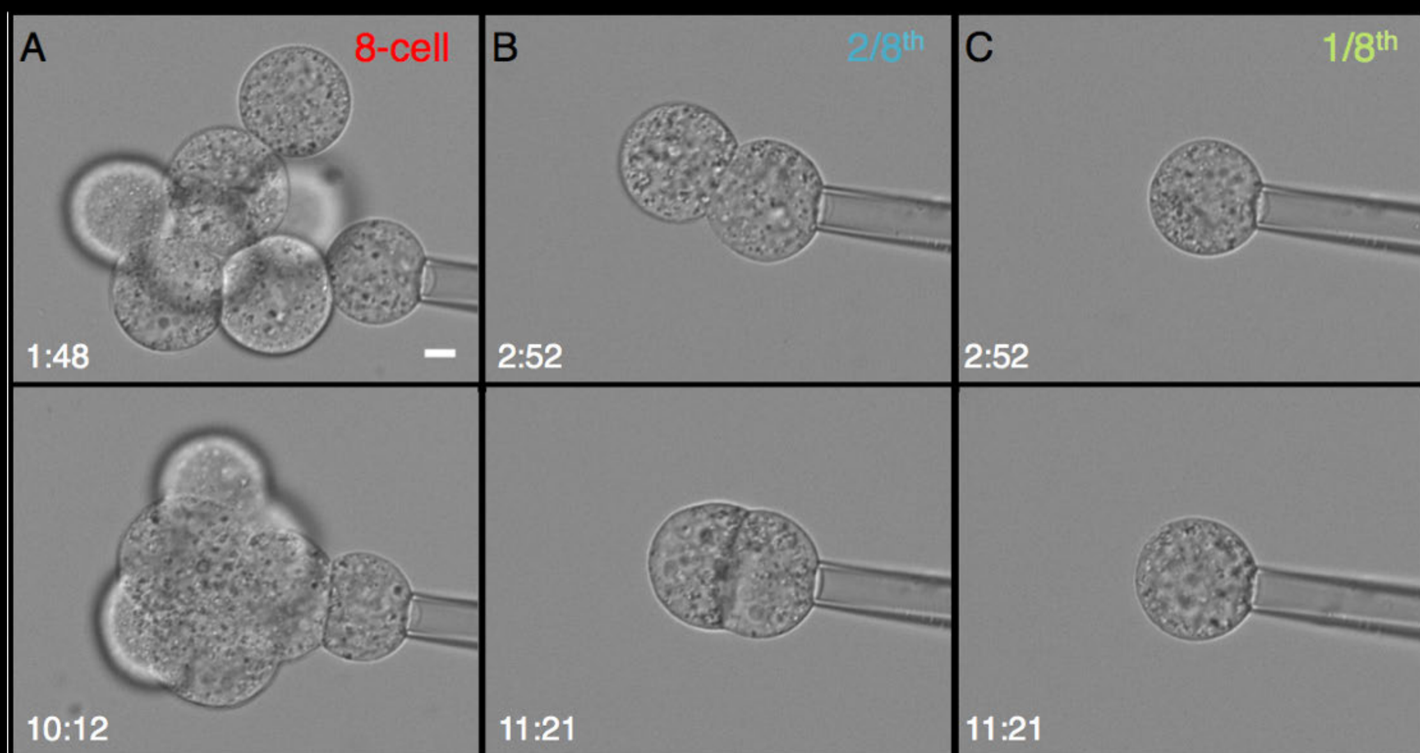
$$\mathcal{E} = 2A\,\gamma_{cm} + \pi r^2\,\gamma_{cc}$$

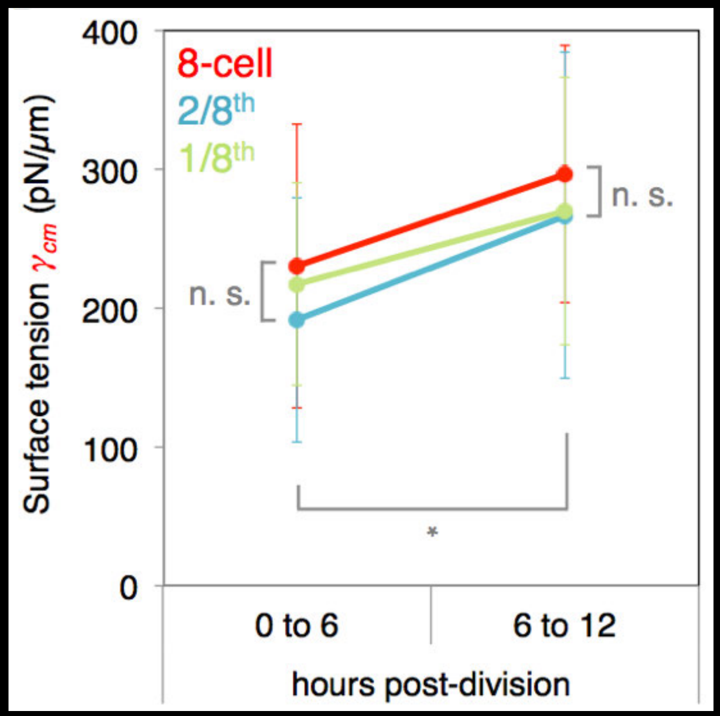
…assuming that volumes are conserved

Turlier et al. Biophysical Journal 2014

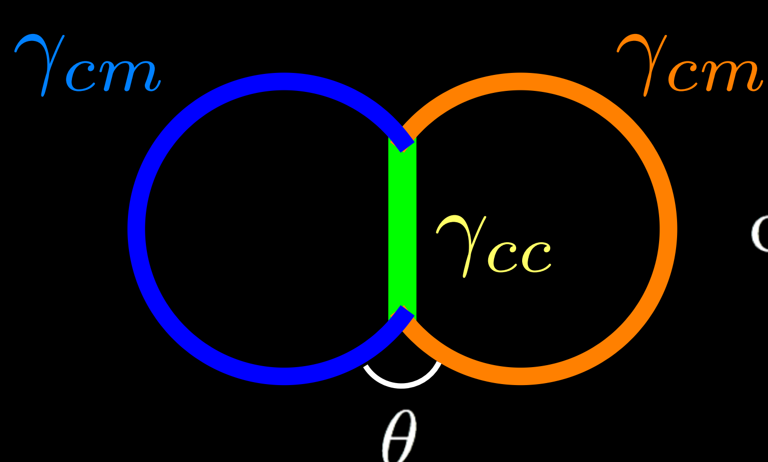
Compaction of blastomere doublet







Jean-Léon Maître, Takashi Hiiragi Group



$$\cos\frac{\theta}{2} = \frac{\gamma_{cc}}{2\gamma_{cm}}$$

γ_{cm} increasing

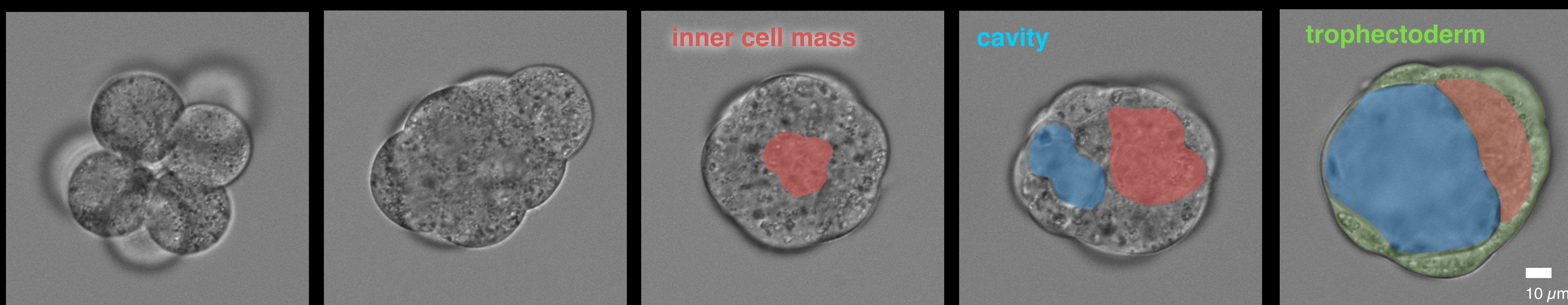
by contraction of the cortex

Maître et al. Nature Cell Biology 2015

Early Mammalian Development

Mouse embryo

8 cells | compacted 8 cells | 16 cells | 32 cells | blastocyst



Compaction → Internalization → Cavitation

Cells have inhomogeneous properties

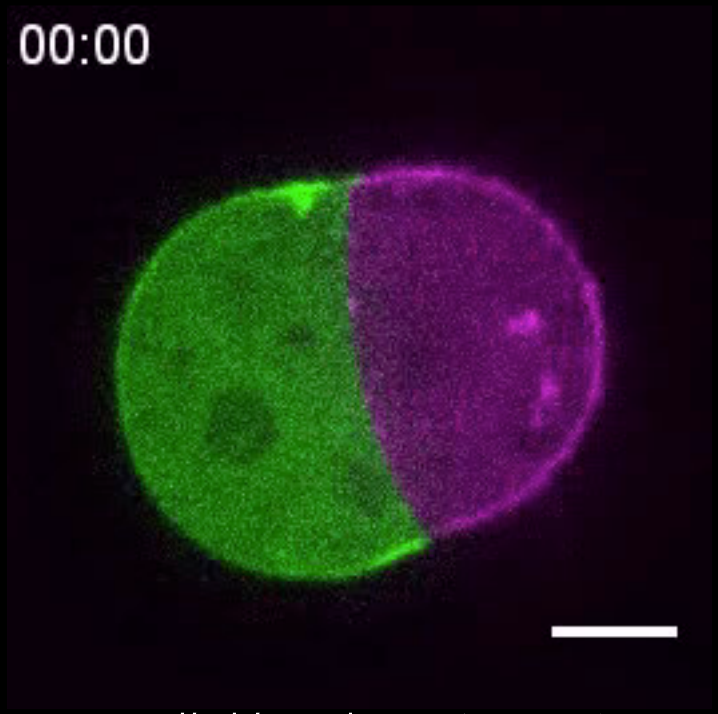
V γ_{cm} γ_{cc}

Cells become different

V' γ'_{cm}

Cavity

Asymmetric Cell Doublet



R. Illukkumbura (EMBL)

$$\mathcal{E} = \sum_i \gamma_i A_i$$

→ Different surface tensions

3 surface tensions & 2 volumes

Compaction parameter

$$\alpha = \frac{\gamma_{cc}}{2\gamma_{cm}}$$

Tension asymmetry

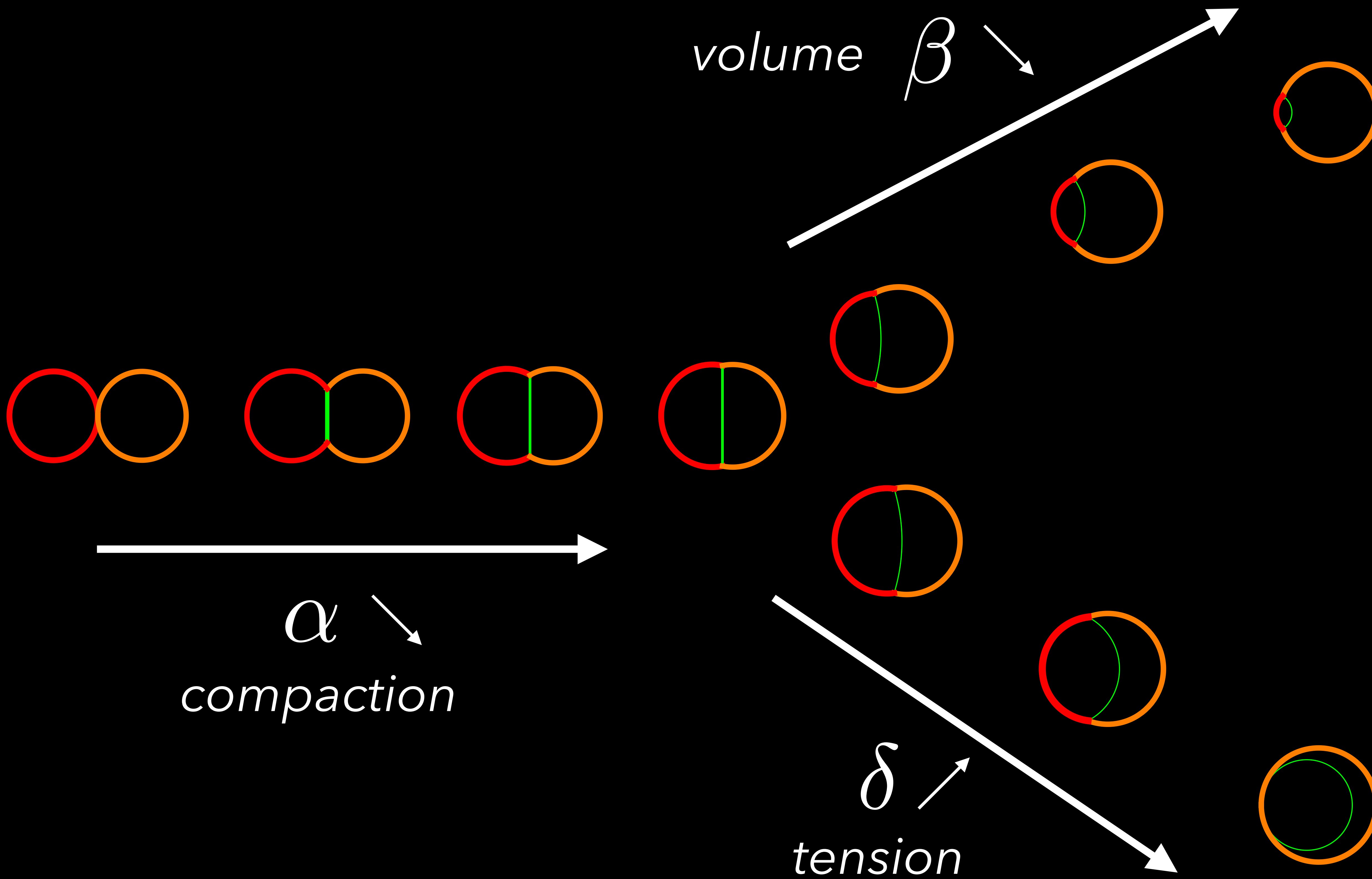
$$\delta = \frac{\gamma'_{cm}}{\gamma_{cm}}$$

Volume asymmetry

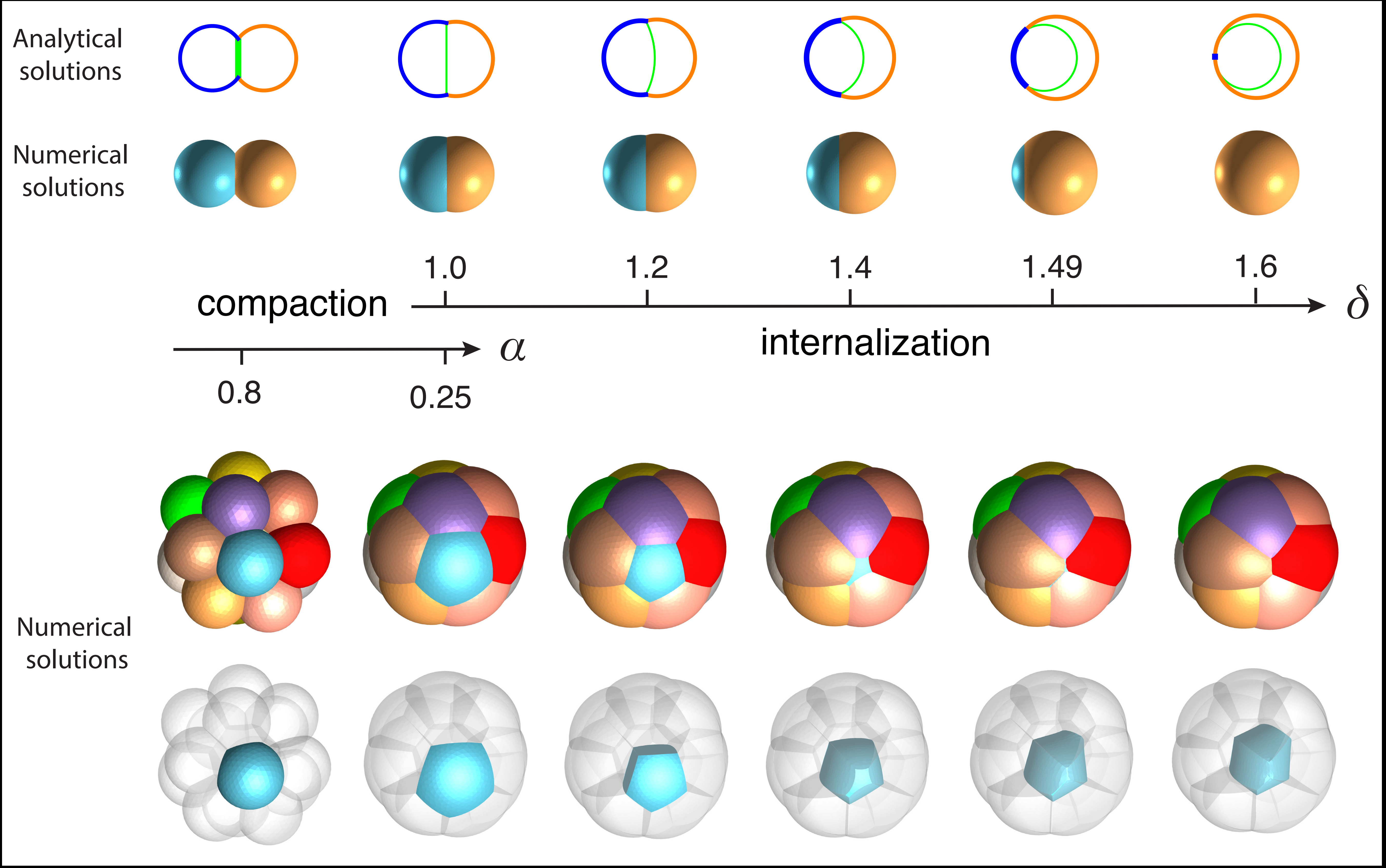
$$\beta = \frac{V'}{V}$$

Maître et al. Nature 2016

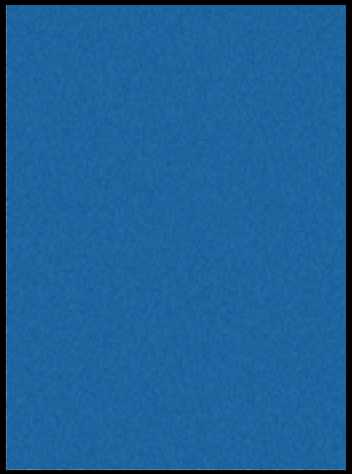
Predictions for an Asymmetric Cell Doublet



From Doublet to 16-cell Embryo



Theory Predicting
Contraction/Expansion of Cytoskeletal Networks

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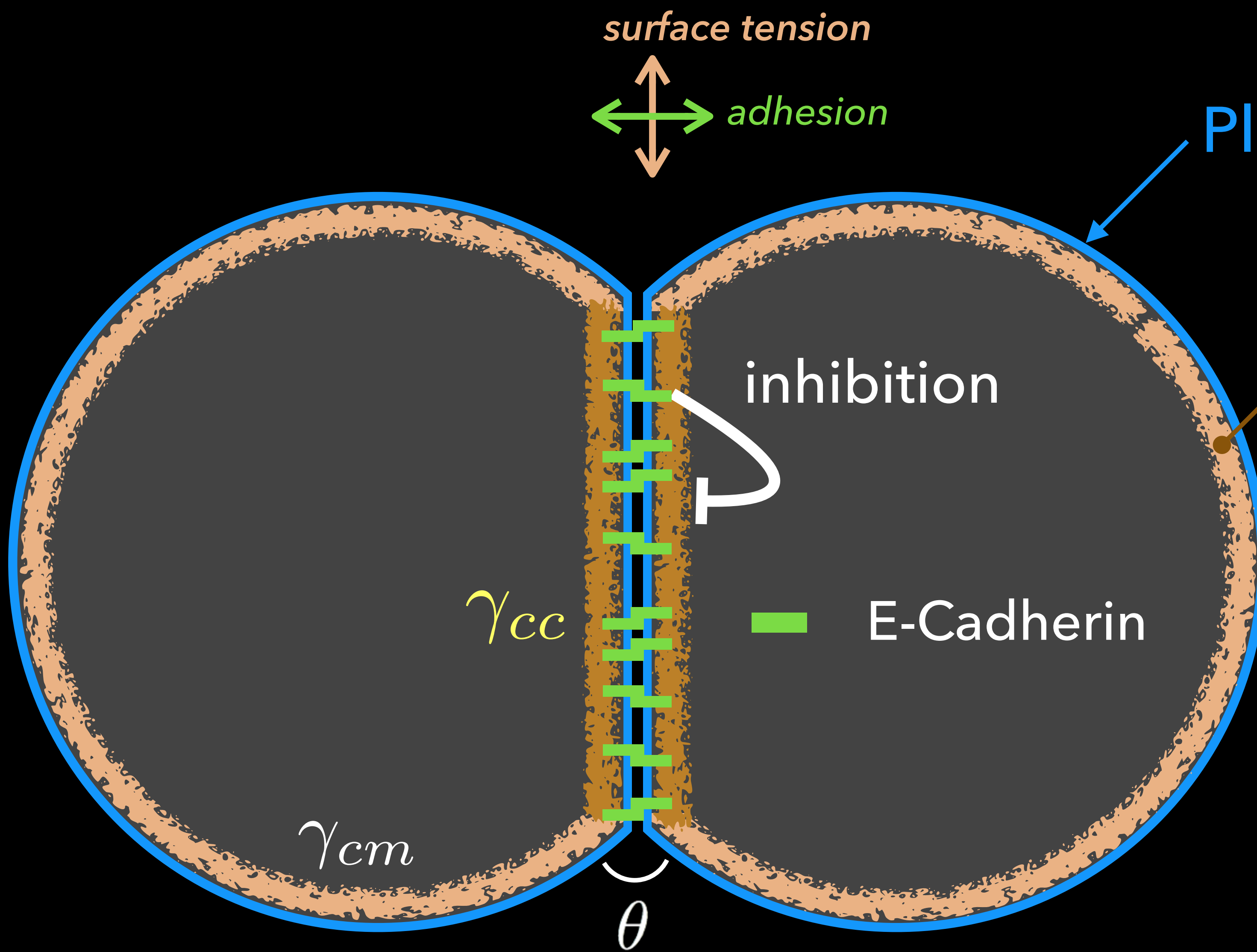
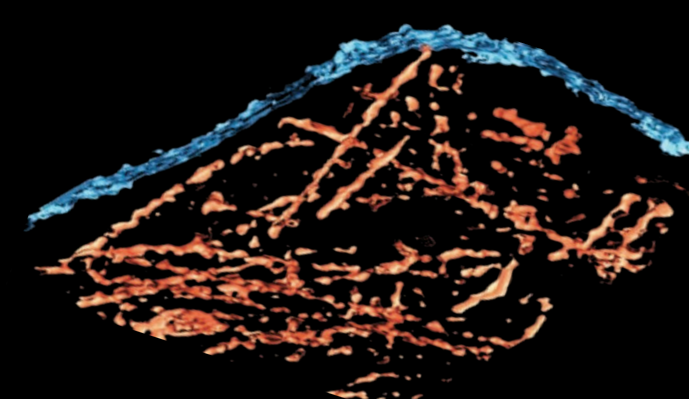
Cortical Tensions Shape Animal Cells



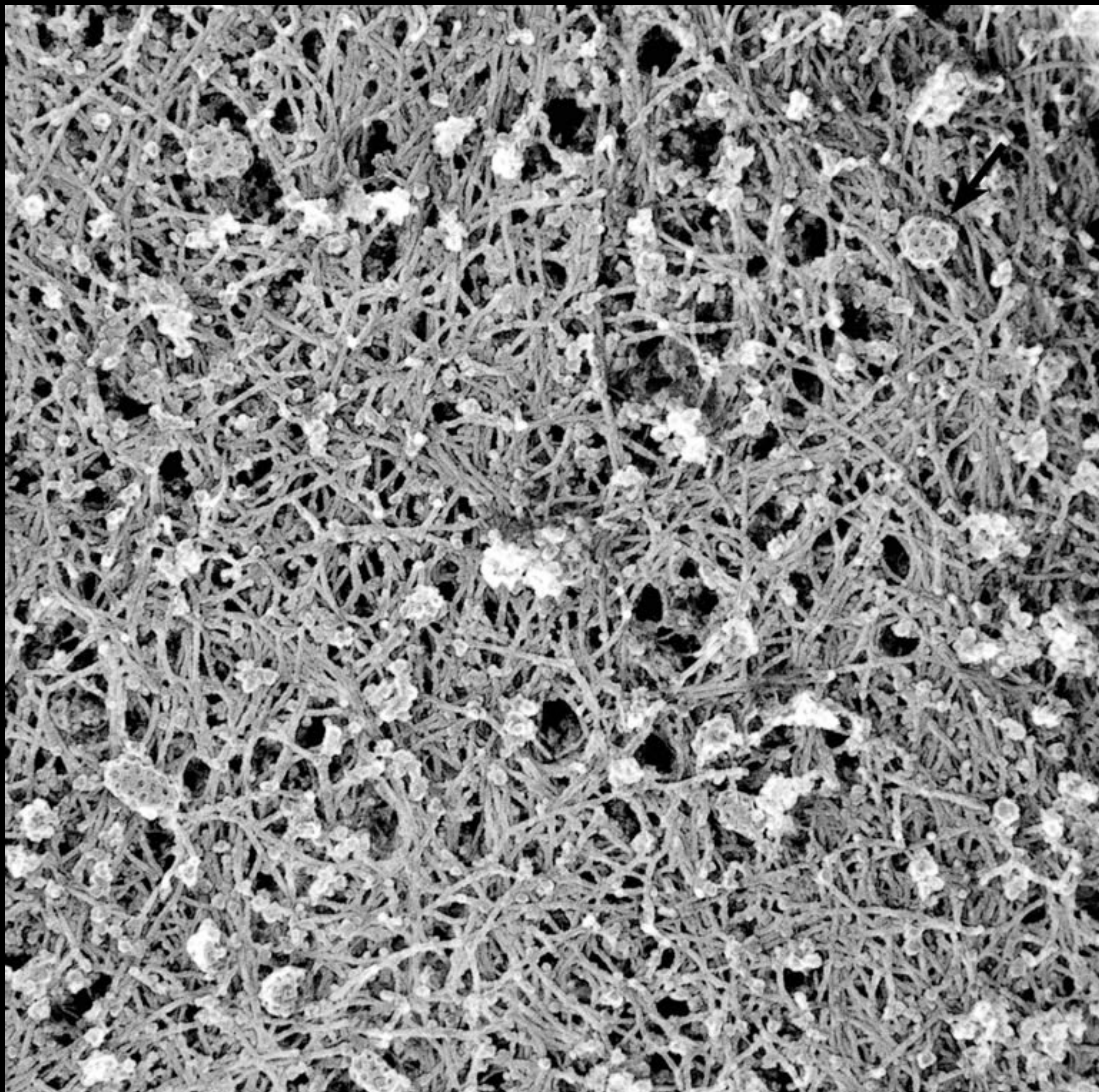


Electron Microscopy
Medalia et al. Science 2002

$$\cos\frac{\theta}{2} = \frac{\gamma_{cc}}{2\gamma_{cm}}$$

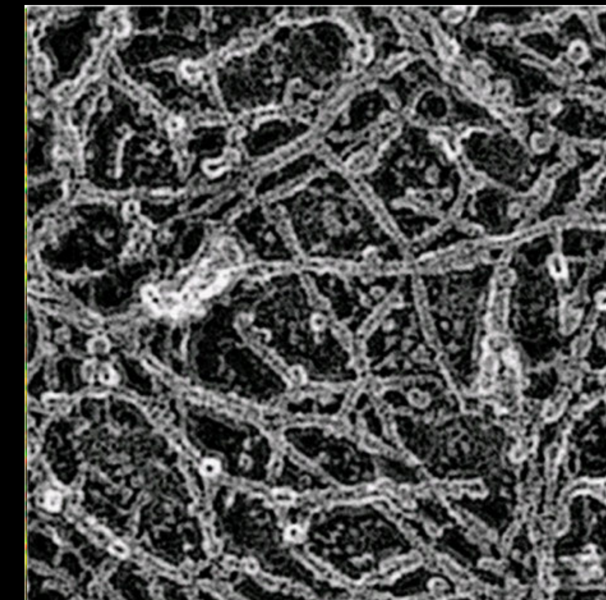
Hervé Turlier
Maître et al. Nature Cell Biology 2015
Maître et al. Nature 2016

Stewart et al. Nature 2011
Salbreux et al. 2012
Fischer-Friedrich Biophysical J. 2016



~100nm

Platinum replica of the cortical actin cytoskeleton of a CD36-positive hematopoetic cell.
NIH Christopher Bleck



100nm

Morone et al. JCB 2006

F-actin:

Persistence Length = 17 μm

average Length = 0.5 – 3 μm

Mesh size ~ 30 nm

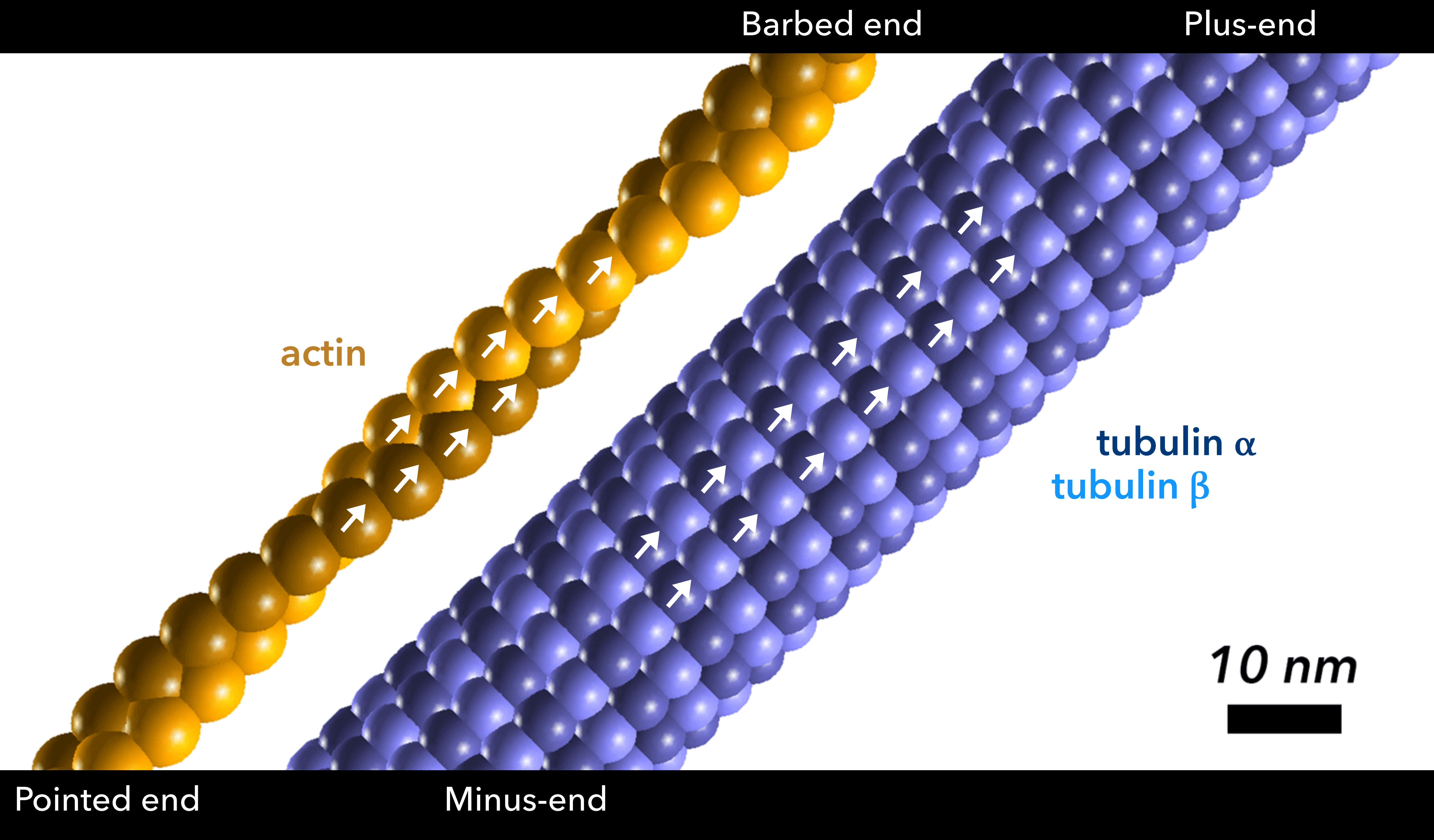
Fritzsche et al. 2016

Saha et al. 2016

Polar Cytoskeletal Filaments

Actin filament
bending elasticity ~ 0.05 pN.μm^2

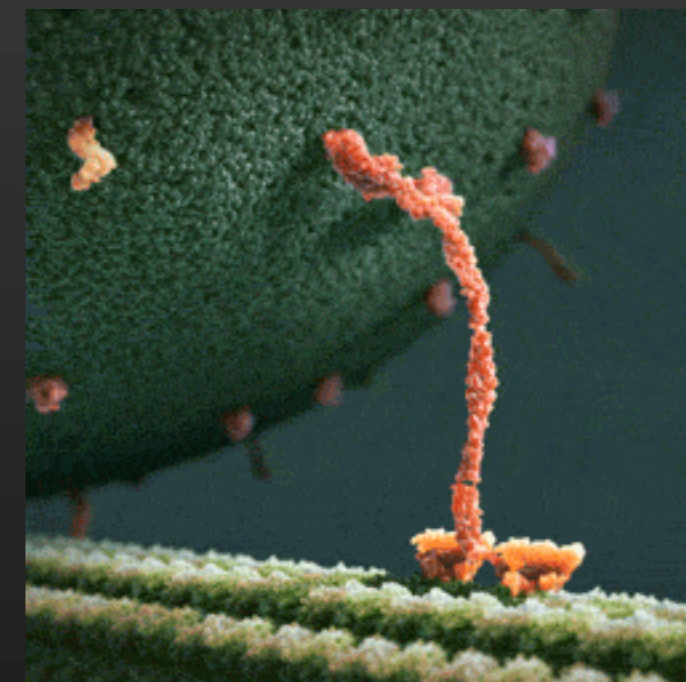
Microtubule
bending elasticity ~ 20 pN.μm^2



Molecular Motors

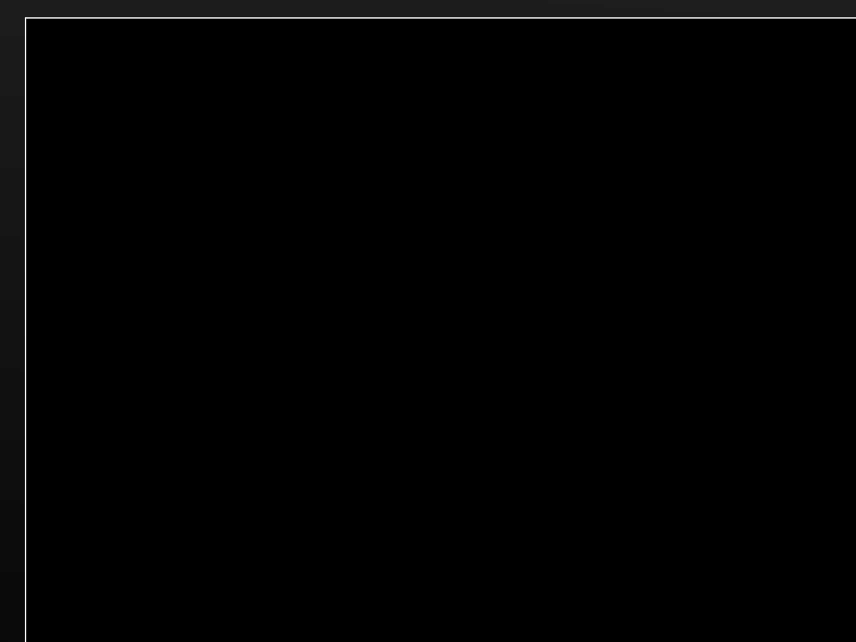
Microtubule: Kinesin, Dynein
Actin: Myosin

Ron Vale, 1985



***Kinesin** – The Inner Life of the Cell*

- plus-end or minus-end directed
- active walkers, consume ATP
- speed ≈ 1 μm/s
- force ≈ 5 pN

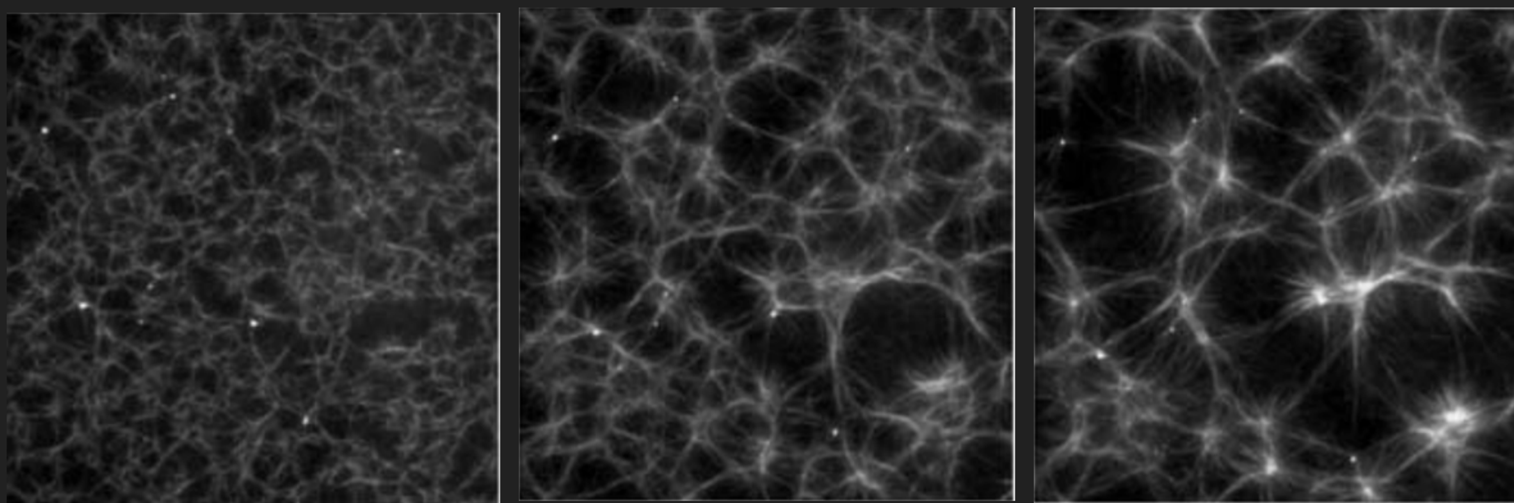


***Myosin** – Vale & Milligan 2000*

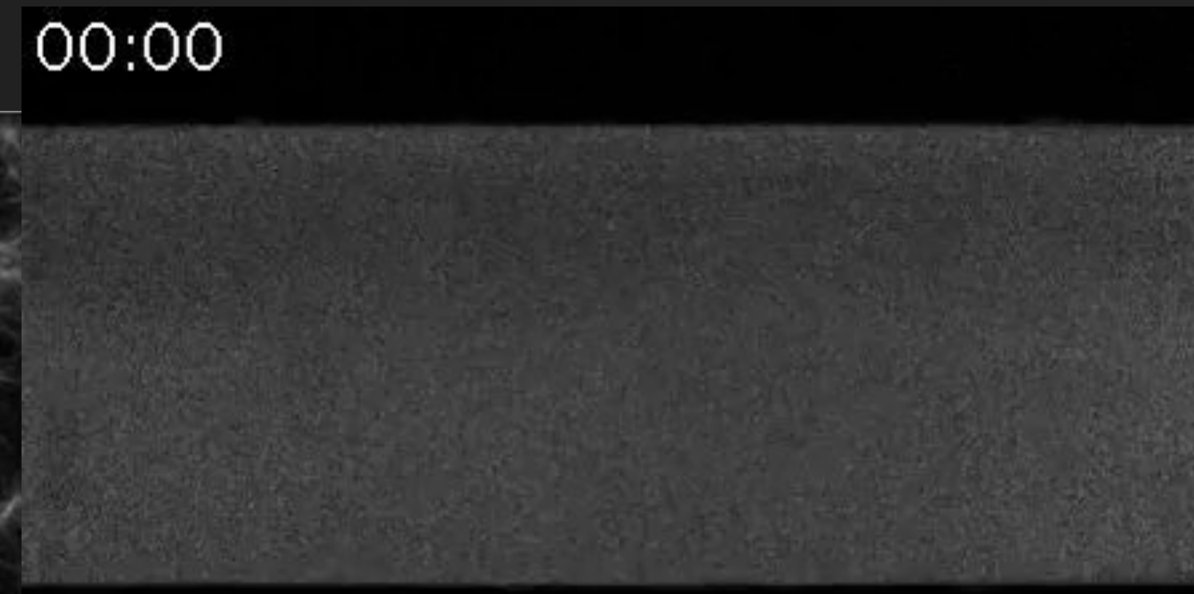
Networks with filaments of fixed length contract *in vitro*

work by Surrey, Bernheim-Groswasser, Sykes, Gardell, Koenderink, Needlemann, schwille, Dogic …

Microtubules

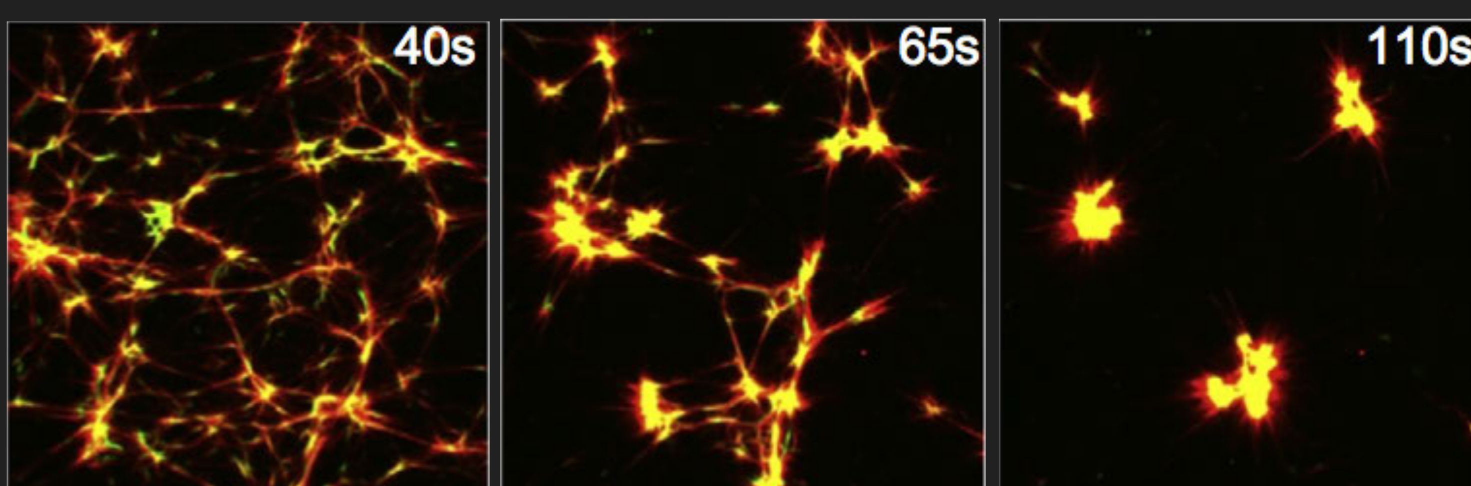


Dynamics of microtubule aster formation by motor complexes
Nedelec, Surrey et al. CRAS 2001

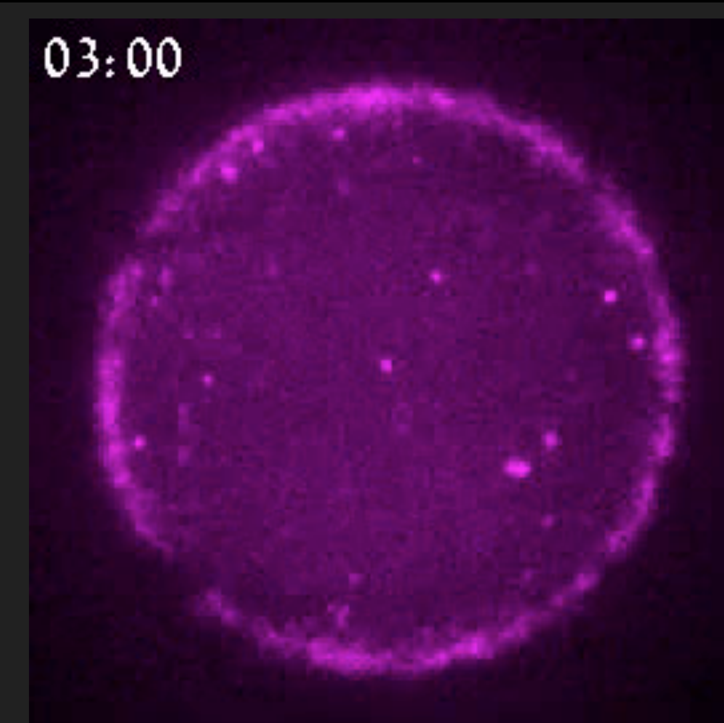


Active contraction of microtubule networks
Foster et al. eLife 2016

Actin filaments



Reconstitution of Contractily in Actomyosin Arrays
Murrell et al. Meth. Enz. 2014



Abu Shah and Keren. eLife 2014

Open Questions

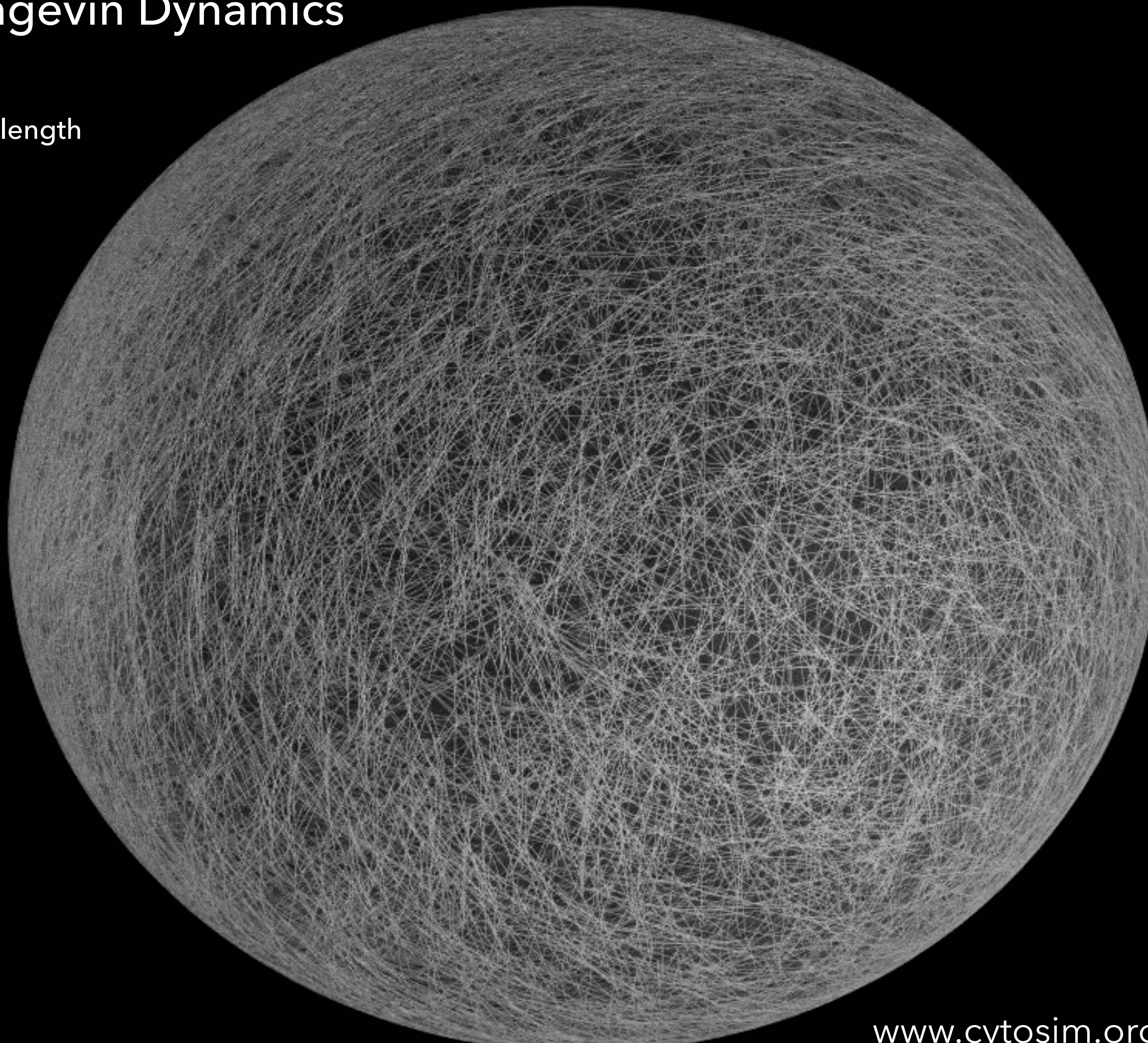
- Why active networks contract?
    - Several mechanisms
- Can we predict the contraction rate?
- Can a network expand?
    - not driven by polymerization
    - Active networks of microtubules+motors

Kruse, MacKintosh, Carlsson, Liverpool, Lenz, Salbreux, Needleman, Gardell, Murrell, etc.

Overdamped Langevin Dynamics

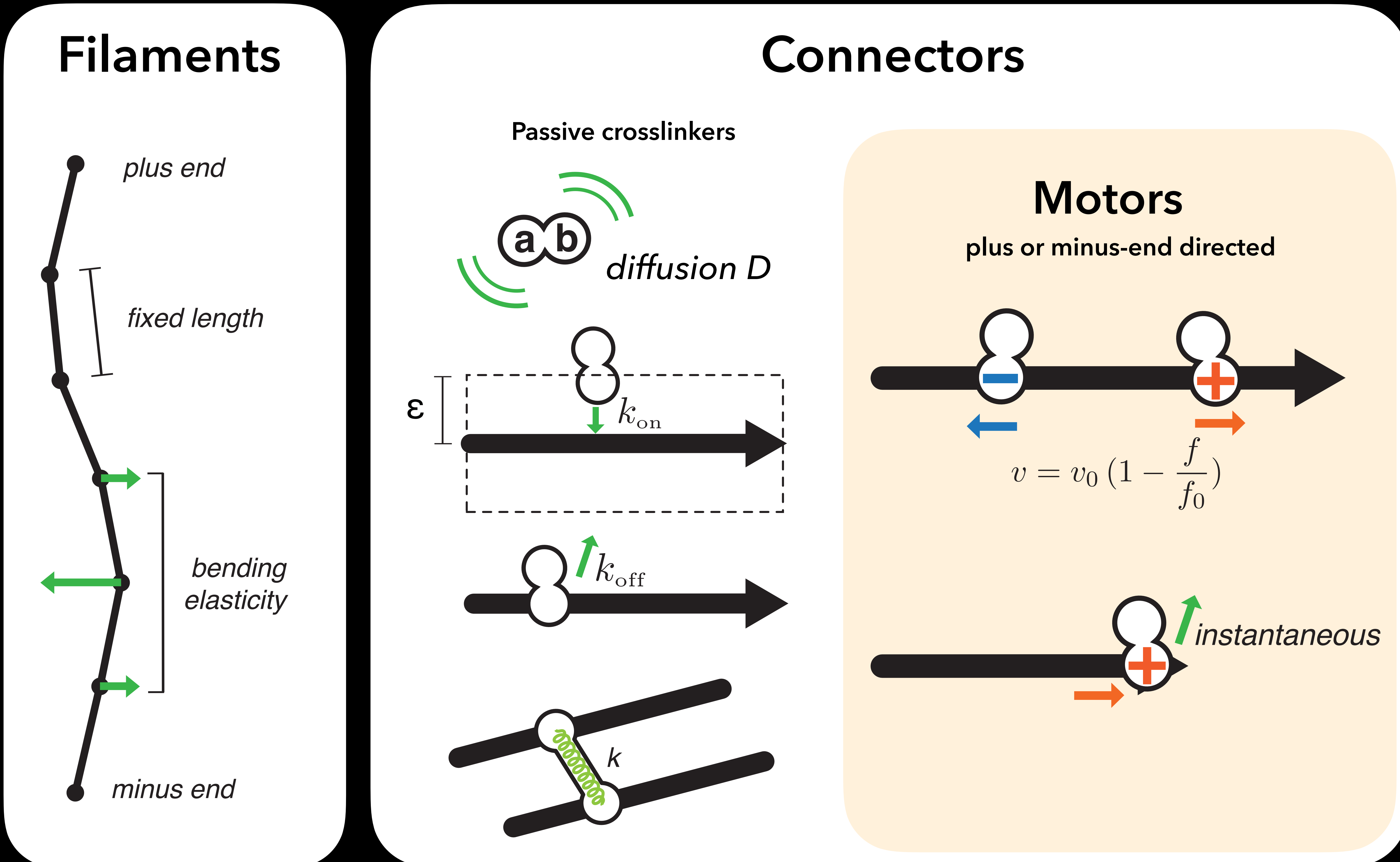
16 000 filaments of constant length
500 000 connectors:
- bi-functional motors
- passive crosslinkers

~10^6 degrees of freedom
Computation ~ 1 day
(sequential)



www.cytosim.org
github.com/nedelec/cytosim

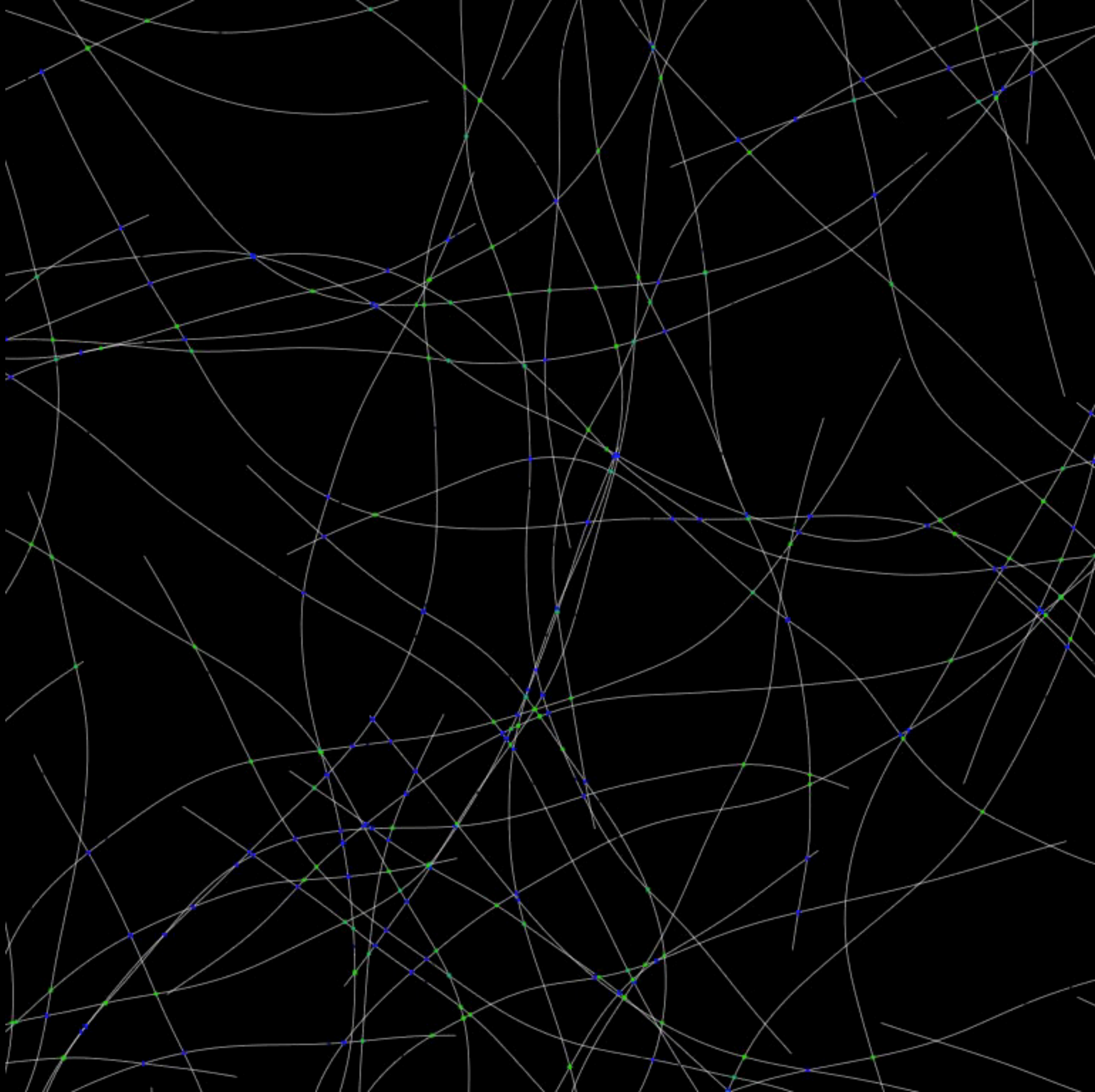
Physical/Computational Model



Nedelec and Foethke — New Journal of Physics 2007

Crosslinkers

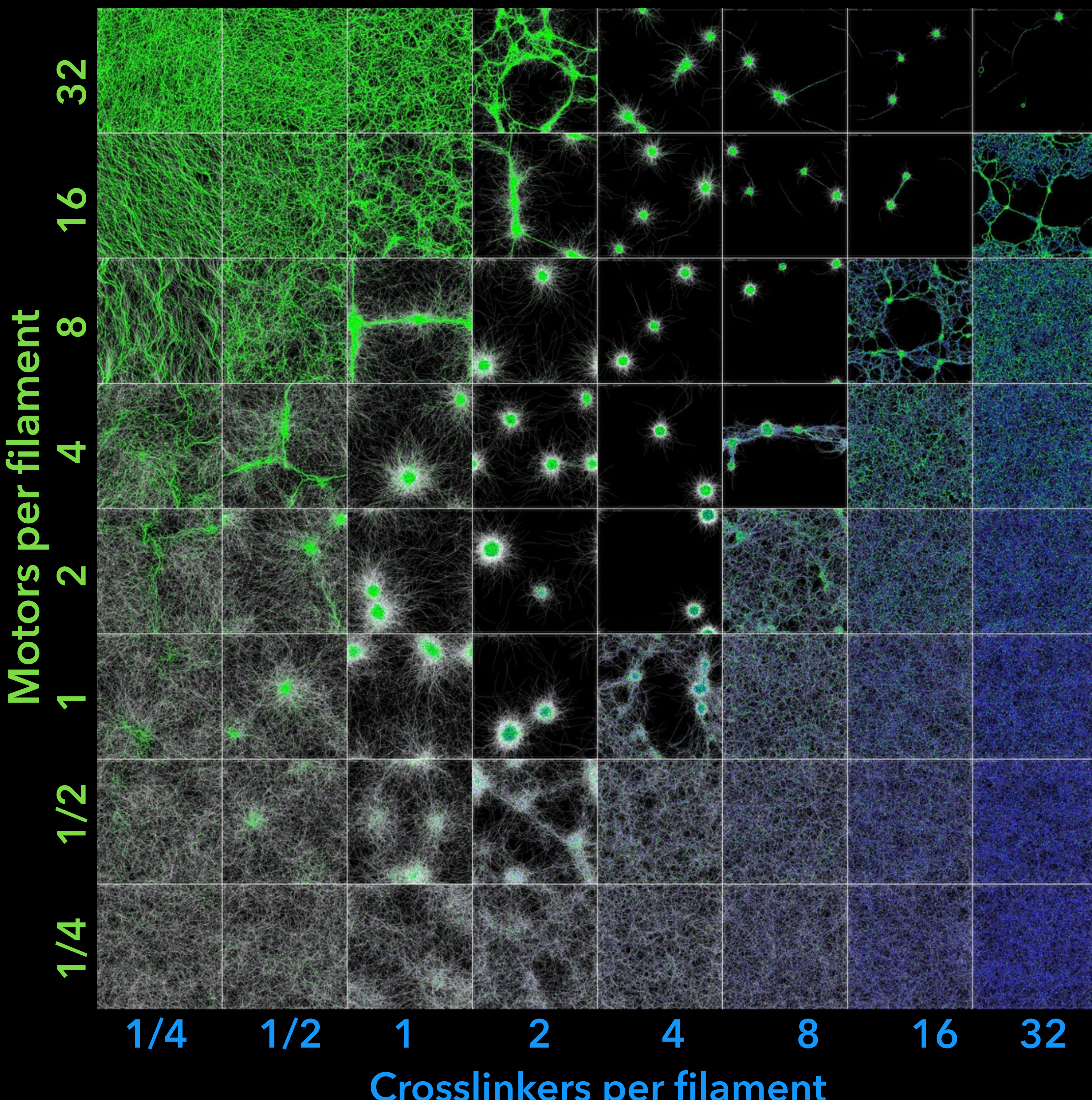
Motors

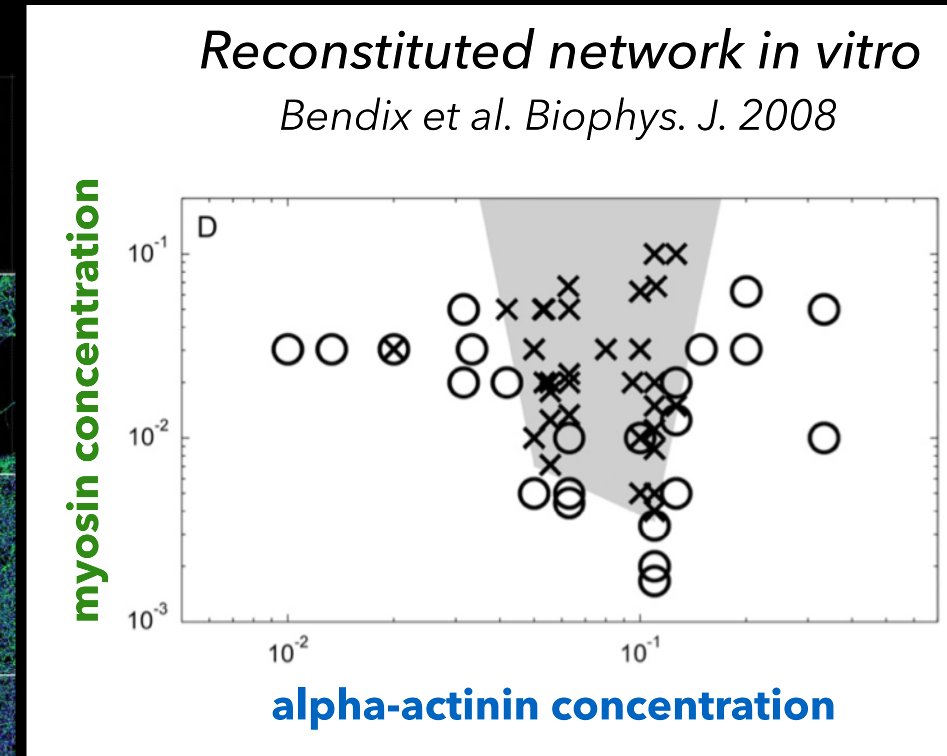


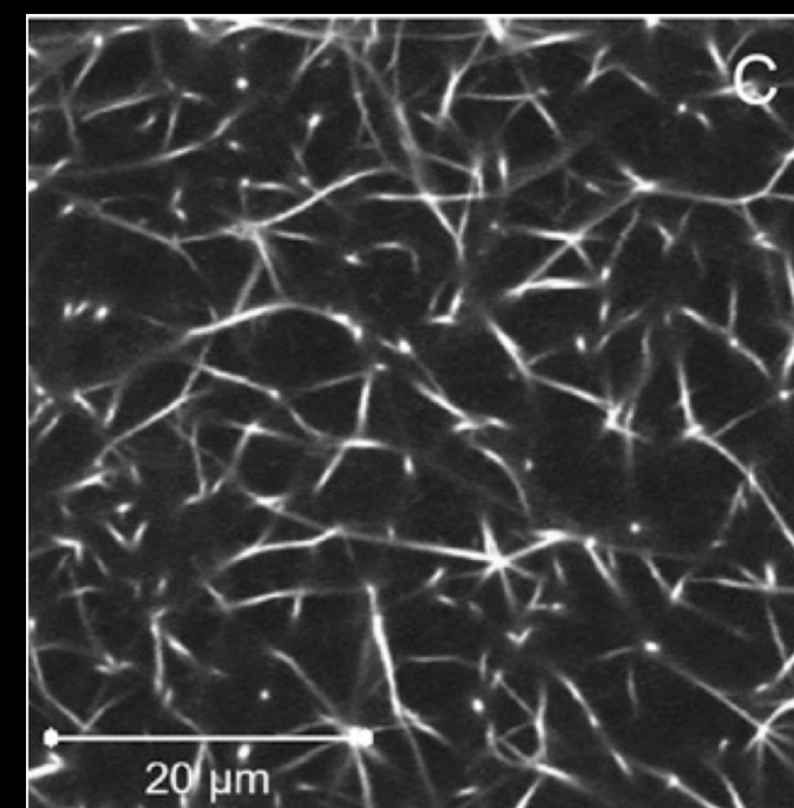
www.cytosim.org

github.com/nedelec/cytosim

with periodic boundaries

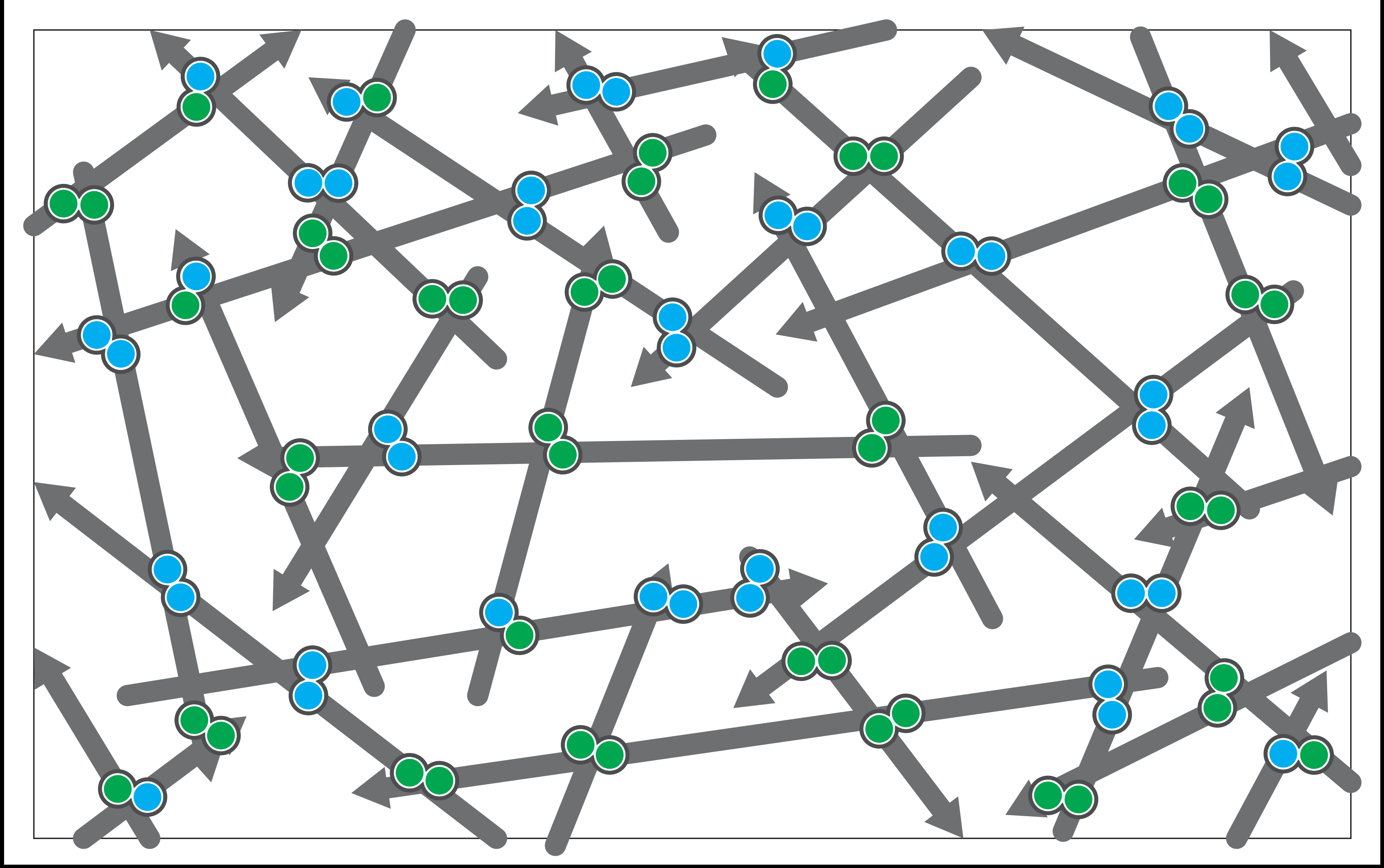






Given a disorganized network:

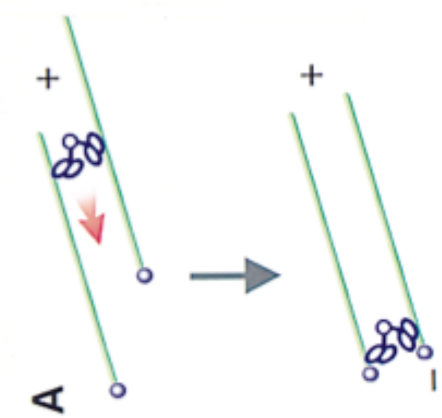
- Filaments are polar & flexible
- Filaments oriented randomly, equally in all directions
- The network is well connected: number of connections per filament ≥ 2



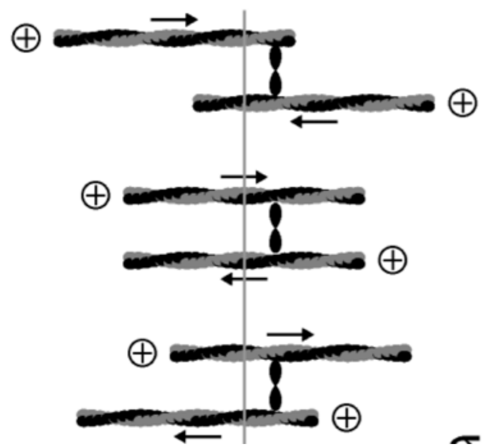
Given you know what and do:

Will this network contract or expand?

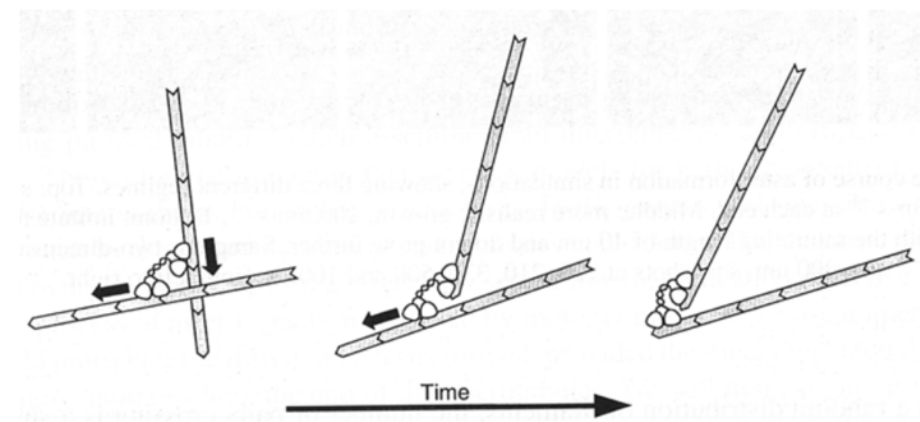
Hyman, Cell 1996



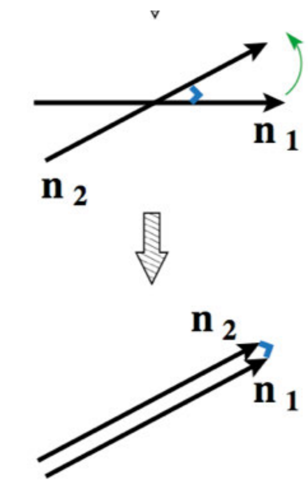
Kruse, PRL 2000



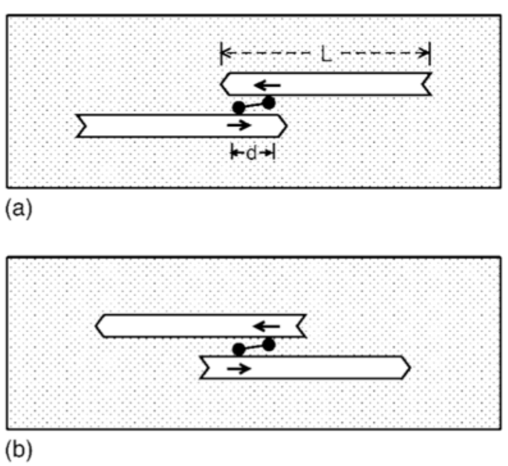
Nedelec, CRAS 2001



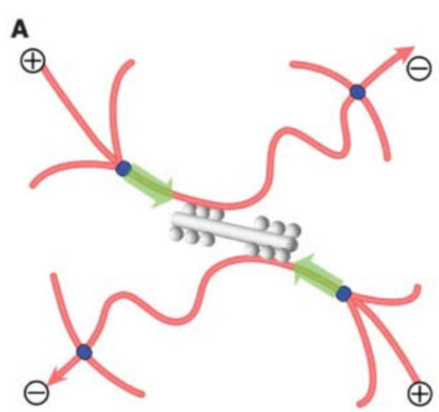
Liverpool, PRE 2003



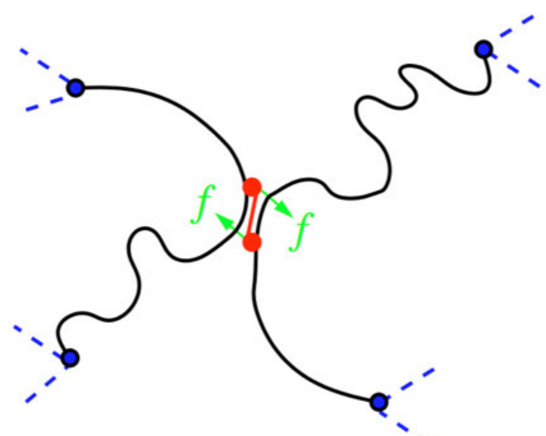
Carlsson, PRE 2006



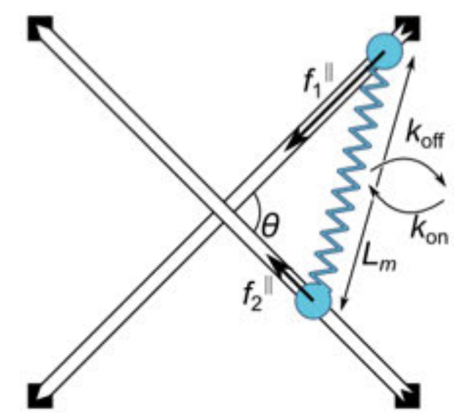
Mizuno, Science 2007



Liverpool, EPL 2009



Lenz, PRX 2014

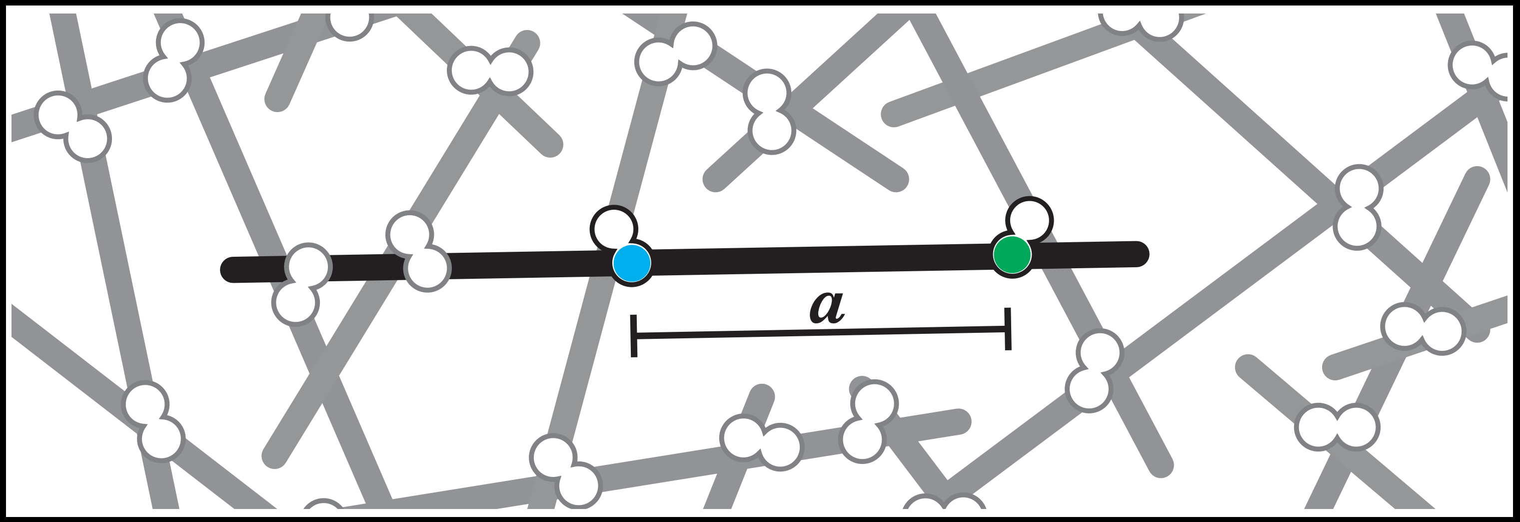


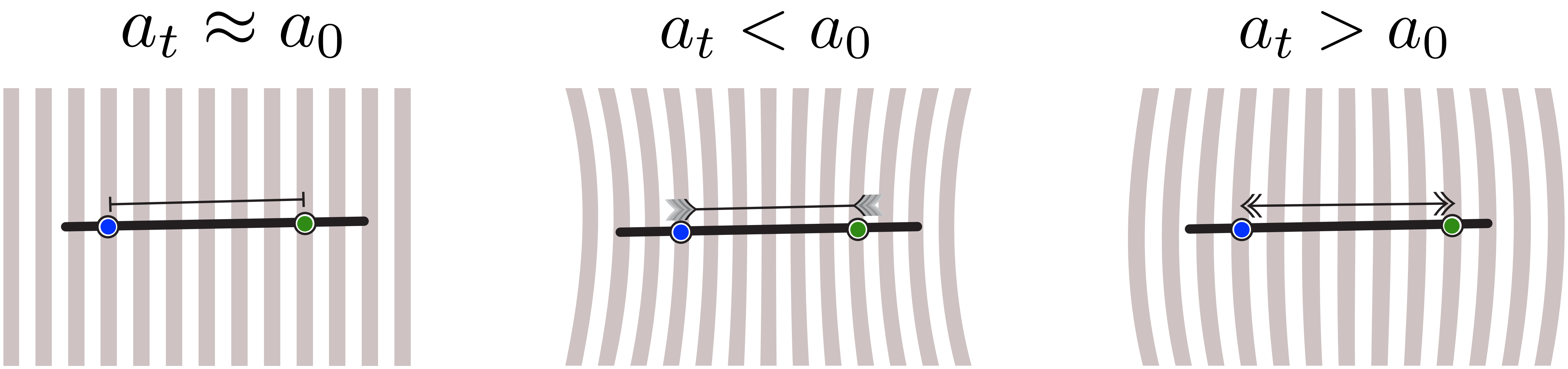
➜ Better suited for loosely connected networks; with few motors

➜ Motors and Crosslinkers are treated differently

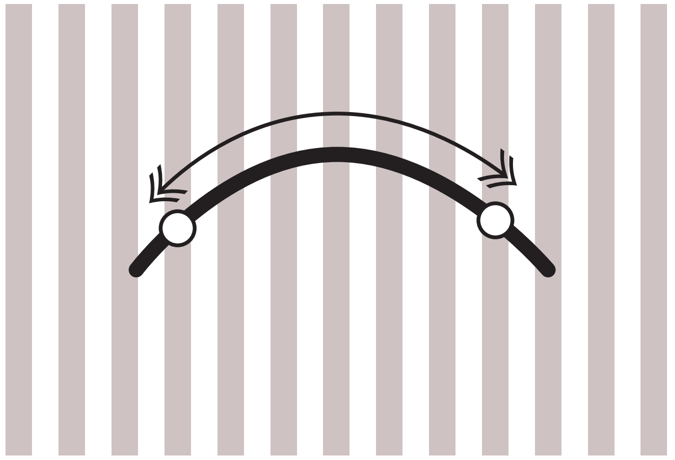
Kruse, MacKintosh, Carlsson, Liverpool, Lenz, Salbreux, Needleman, Gardell, Murrell, etc.

Consider **one filament** and a **pair of connectors**





with flexible filament:



Predicting Contraction/Extension

List all possible configurations:

$$\begin{cases} \textbf{length} & a_i \\ \textbf{speed} & v_i = \dfrac{da_i}{dt} \\ \textbf{probability} & p_i \end{cases}$$

Sum over all configurations:

$$\chi = \frac{\sum_i \Phi(a_i, v_i) p_i v_i}{\sum_i p_i a_i}$$

rigid filaments: $\Phi = 1$

semi-flexible filaments: $\Phi = \begin{cases} 0 & \text{if } v_i > 0 \text{ and } a_i > b \\ 1 & \text{otherwise} \end{cases}$

flexible filaments: $\Phi = \begin{cases} 0 & \text{if } v_i > 0 \\ 1 & \text{otherwise} \end{cases}$

Prediction

1D system of length L

$$\frac{1}{L}\frac{dL}{dt} \approx \chi$$

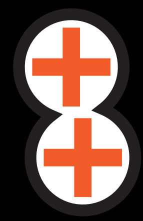
2D system of surface S

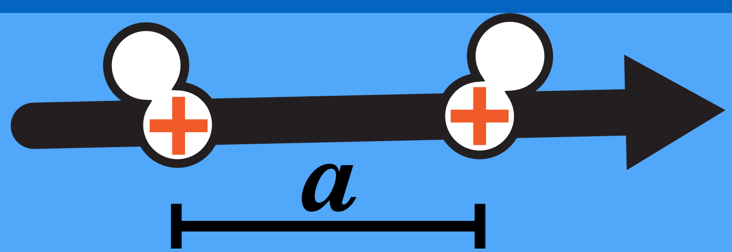
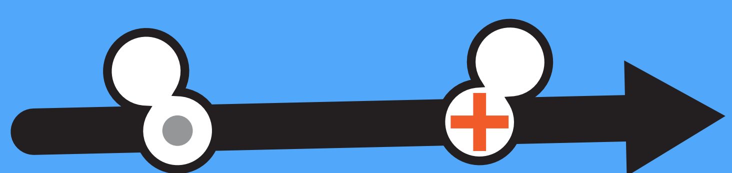
$$\frac{1}{S}\frac{dS}{dt} \approx 2\,\chi$$

3D system of volume V

$$\frac{1}{V}\frac{dV}{dt} \approx 3\chi$$

Simple Symmetric Composition

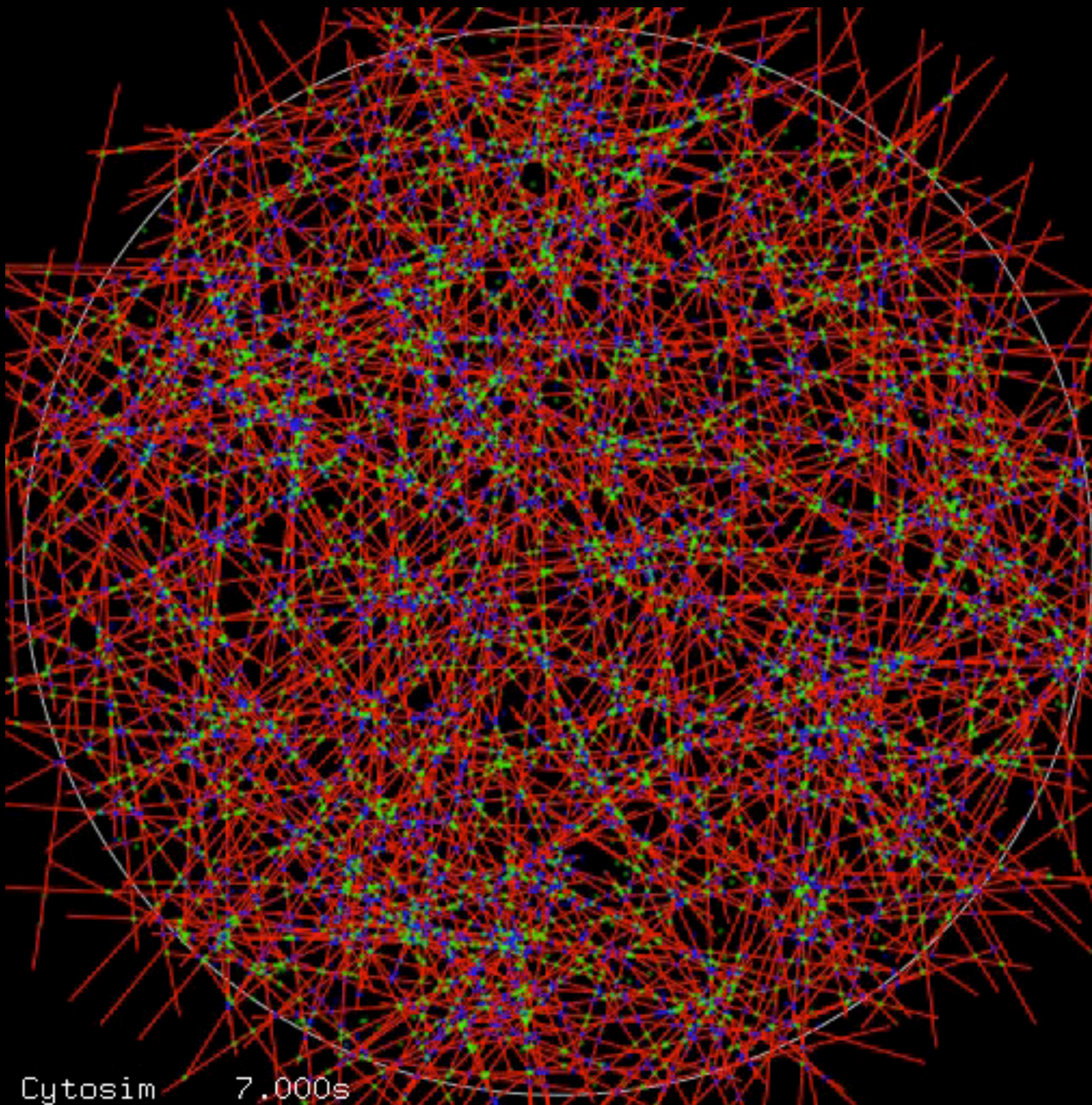
50%  *50%*  *Same binding/unbinding rates*

Configuration	da/dt		
	*0*		
	*-v*		
	*+v*		
	*0*		

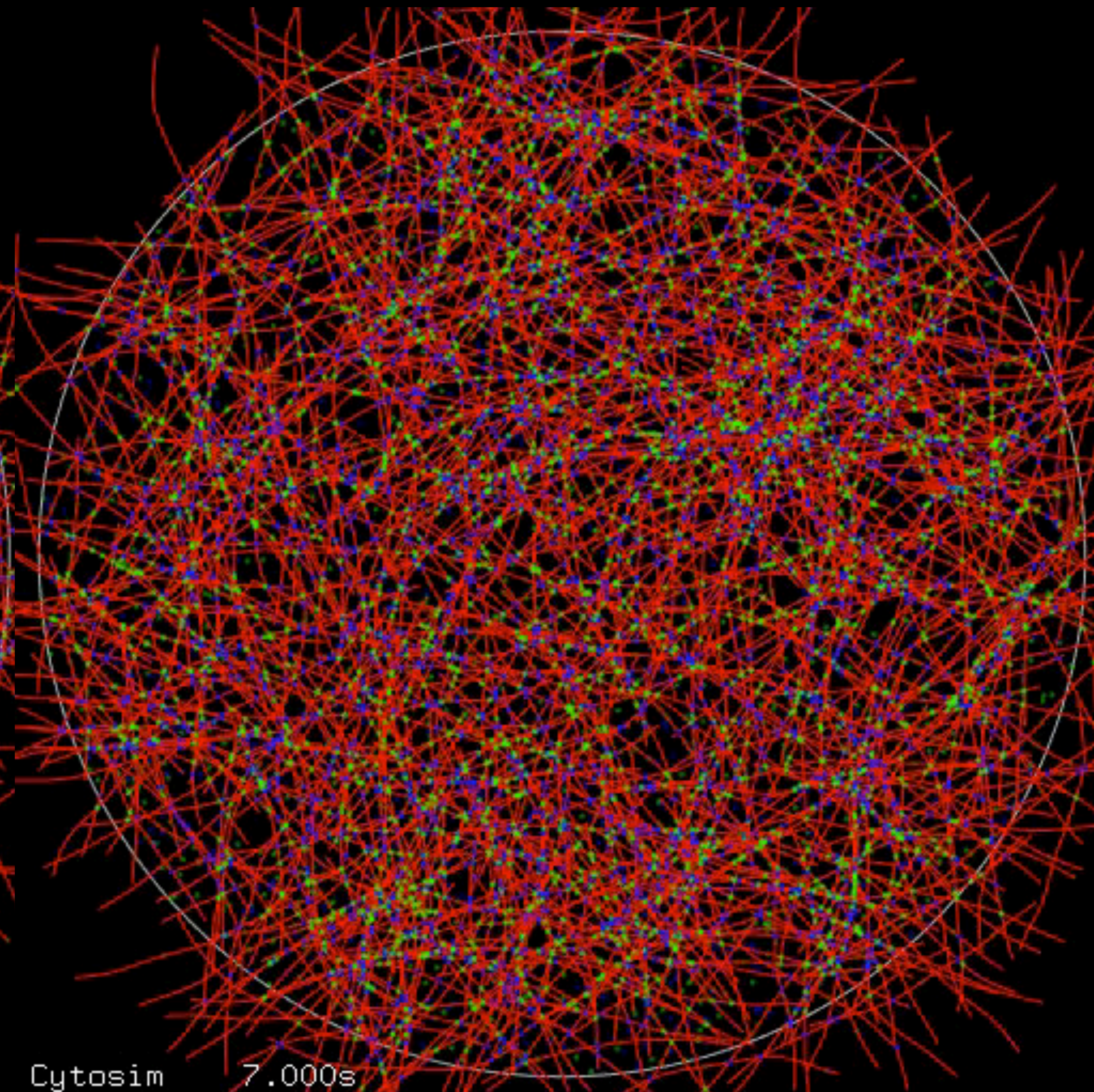
→ not contractile →contractile

1000 filaments, L = 2.5μm 8000 Motors 8393 Crosslinkers

Rigid $K = 30\ \mu m^2.pN$
(microtubules)



Flexible $K = 0.05\ \mu m^2.pN$
(actin)

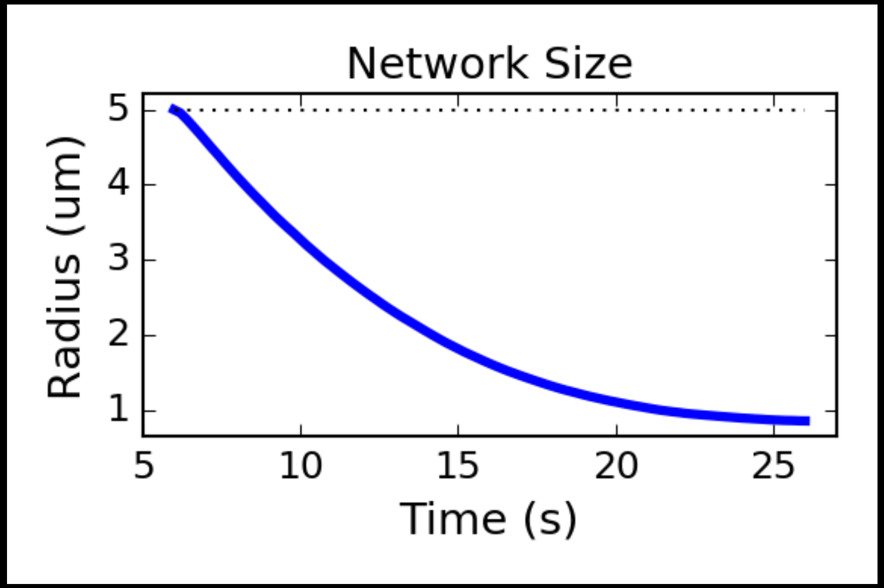


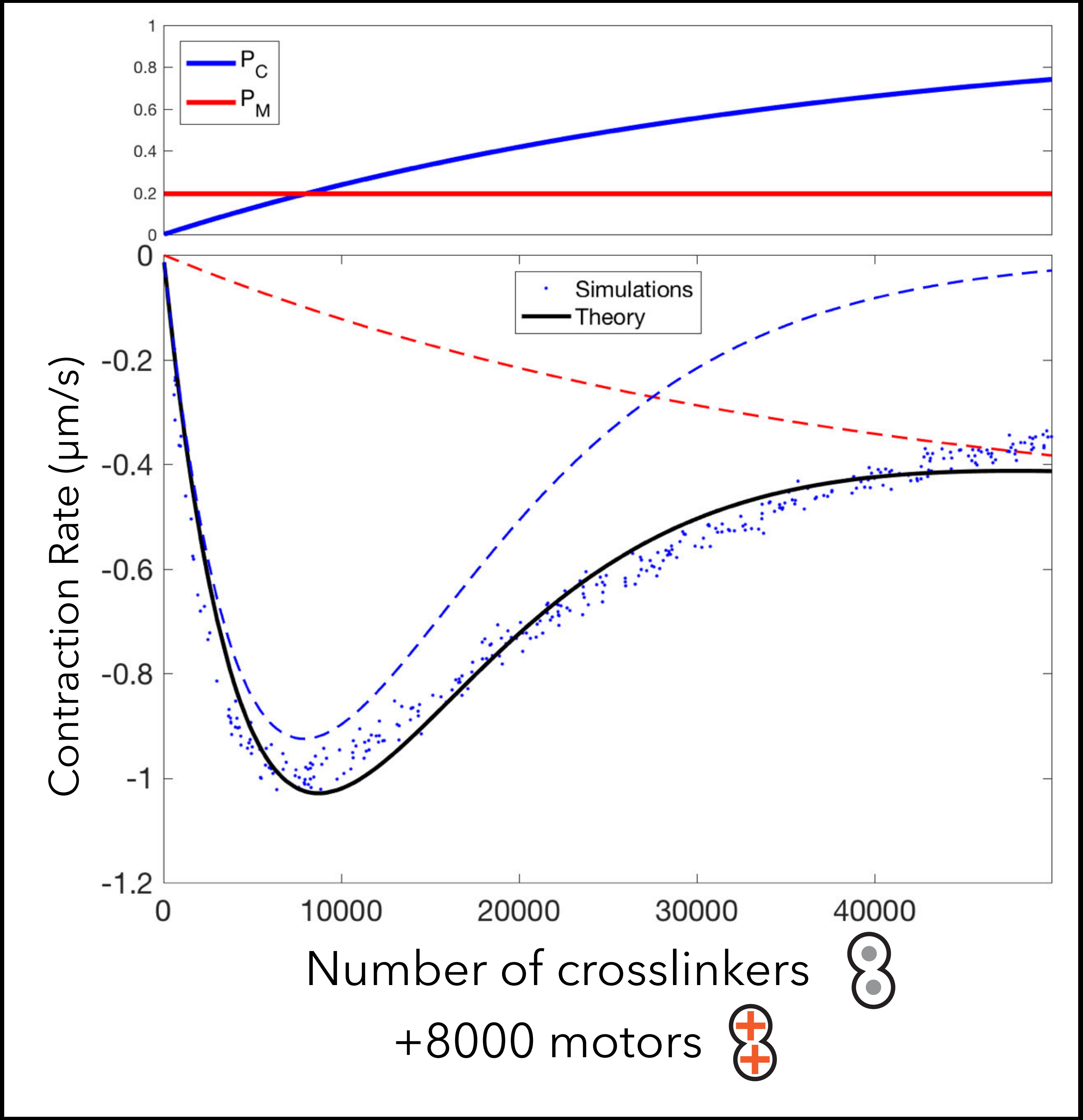
Semi-flexible Filaments

unconstrained circular networks

3.2 filaments / μm^2

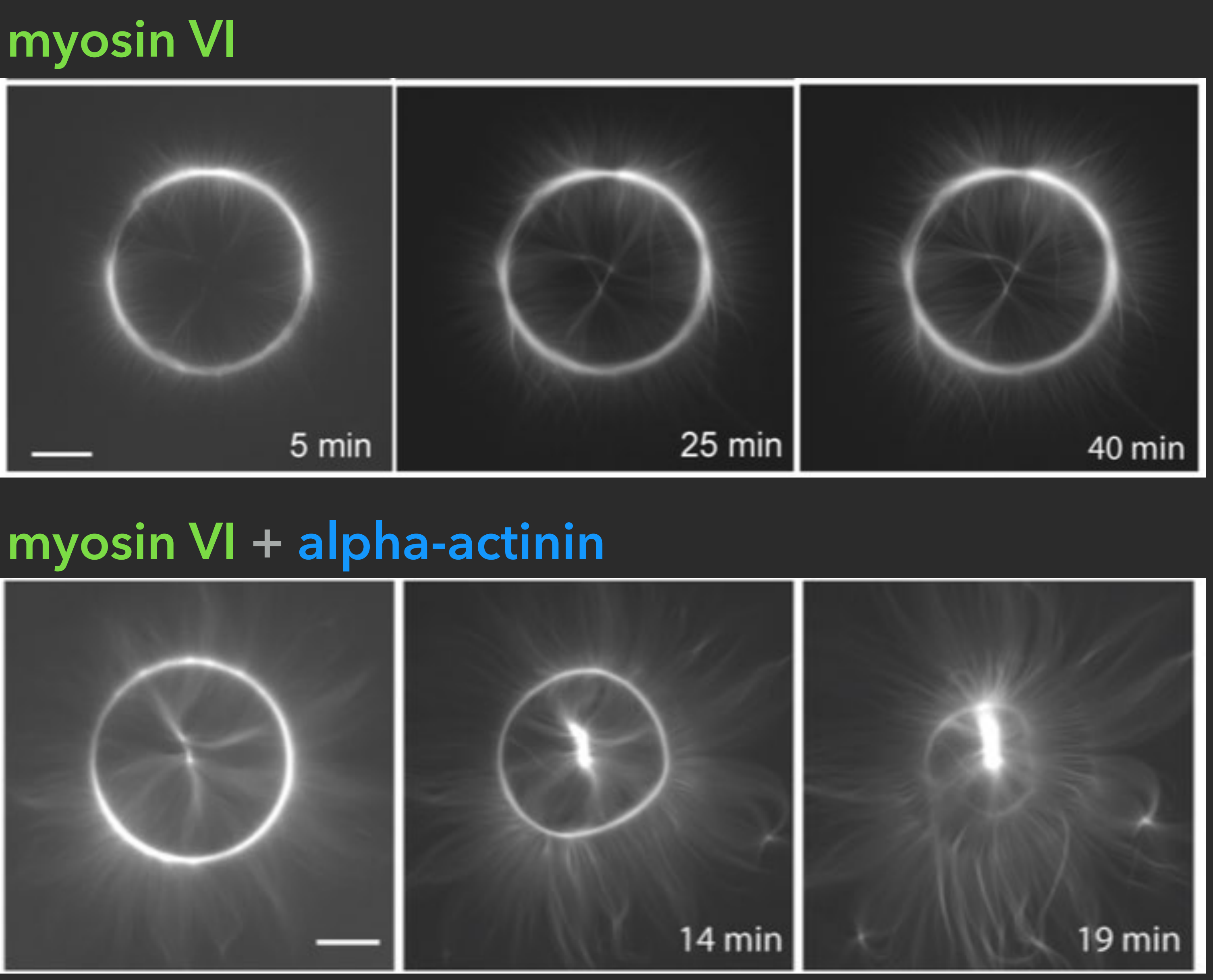
$L_{filament} = 5\ \mu m$

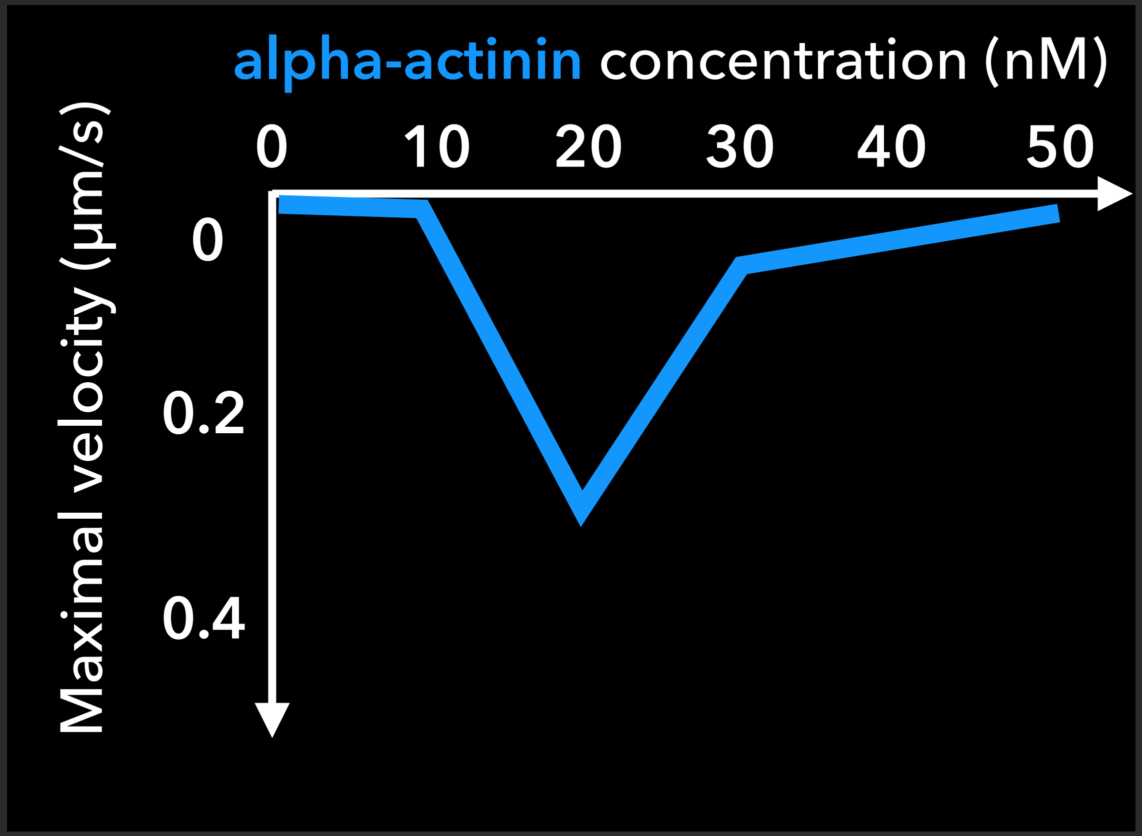




Disordered Actomyosin Ring

in vitro

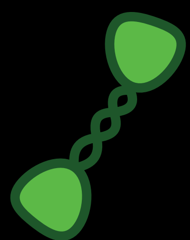




H. Ennomani et al. Curr. Bio. 2015 — Laurent Blanchoin and Manuel Thery
W. J. Ding et al. JCB, Vol 216 (4) 2017 — Ronen Zaidel-Bar

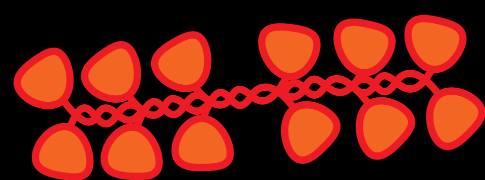
Actin-Related Proteins

Crosslink



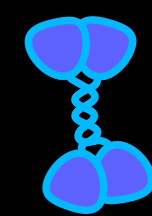
2 binders
parallel / anti-parallel

Myosin 2



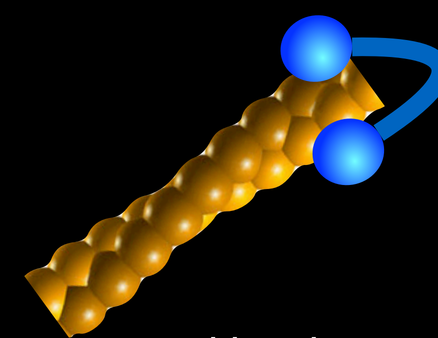
Plus-end directed
minifilaments

Myosin 6



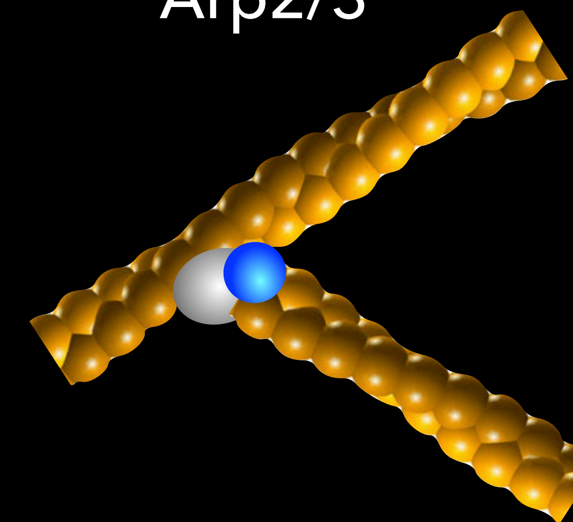
Minus-end directed
small oligomers

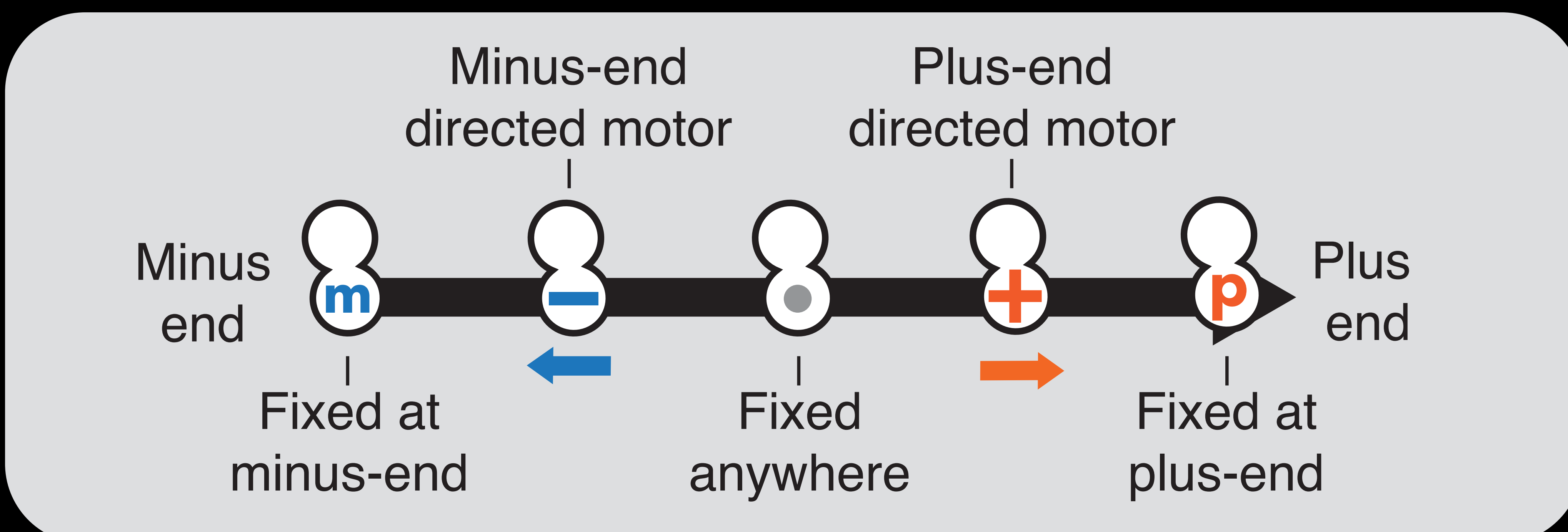
Formin



end binder
track ends?

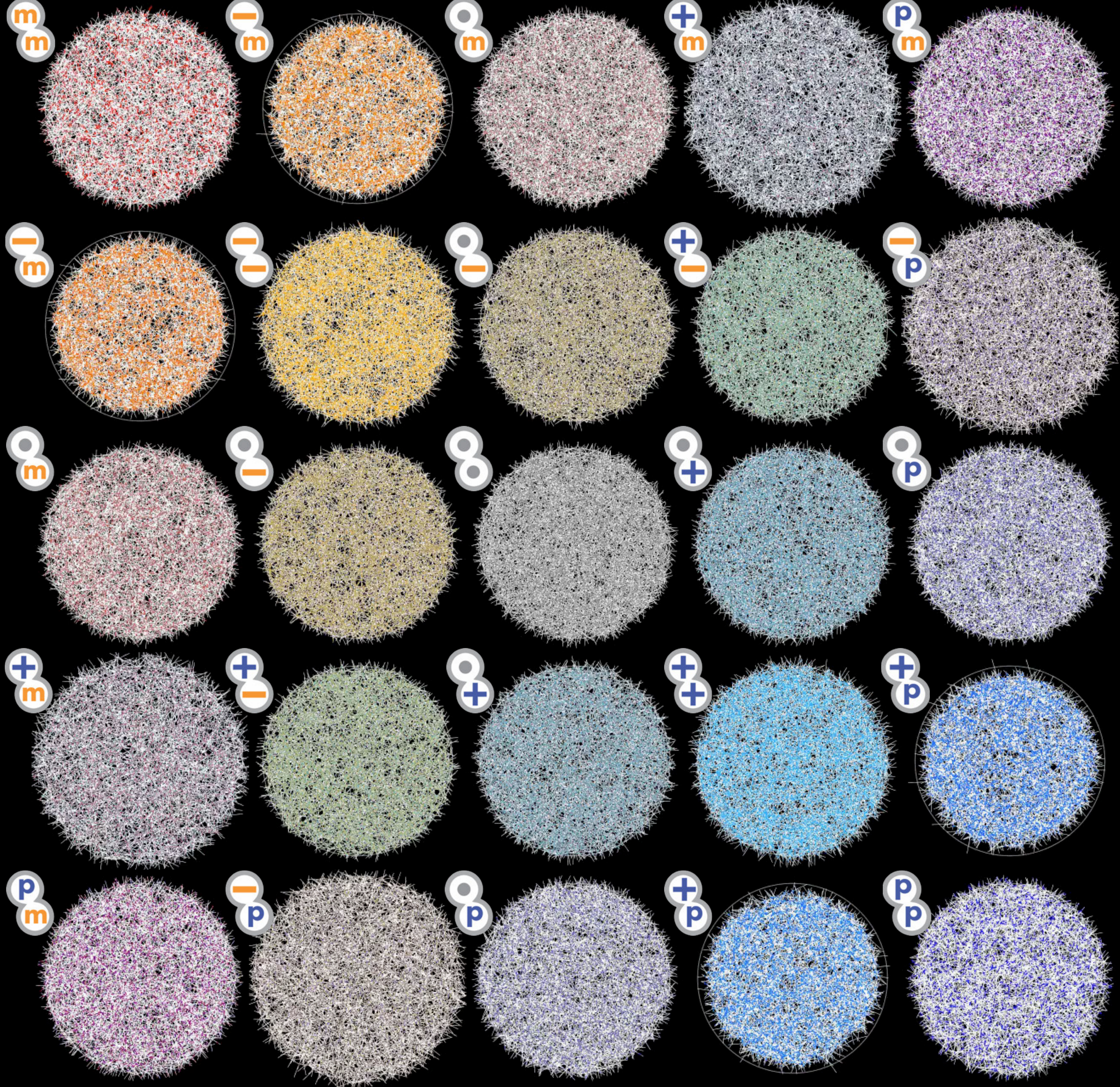
Arp2/3



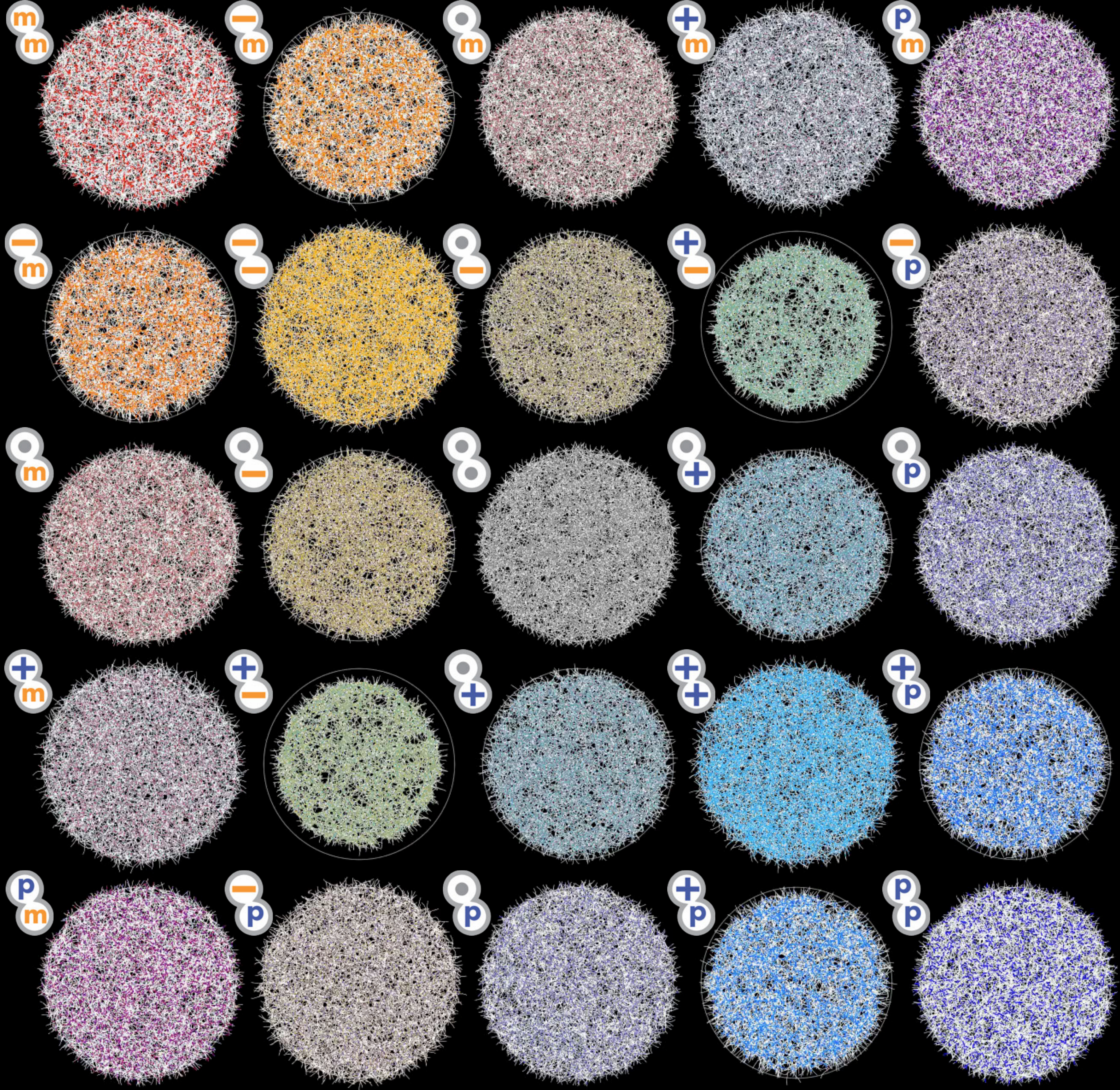


➡15 possible connectors

Rigid filaments

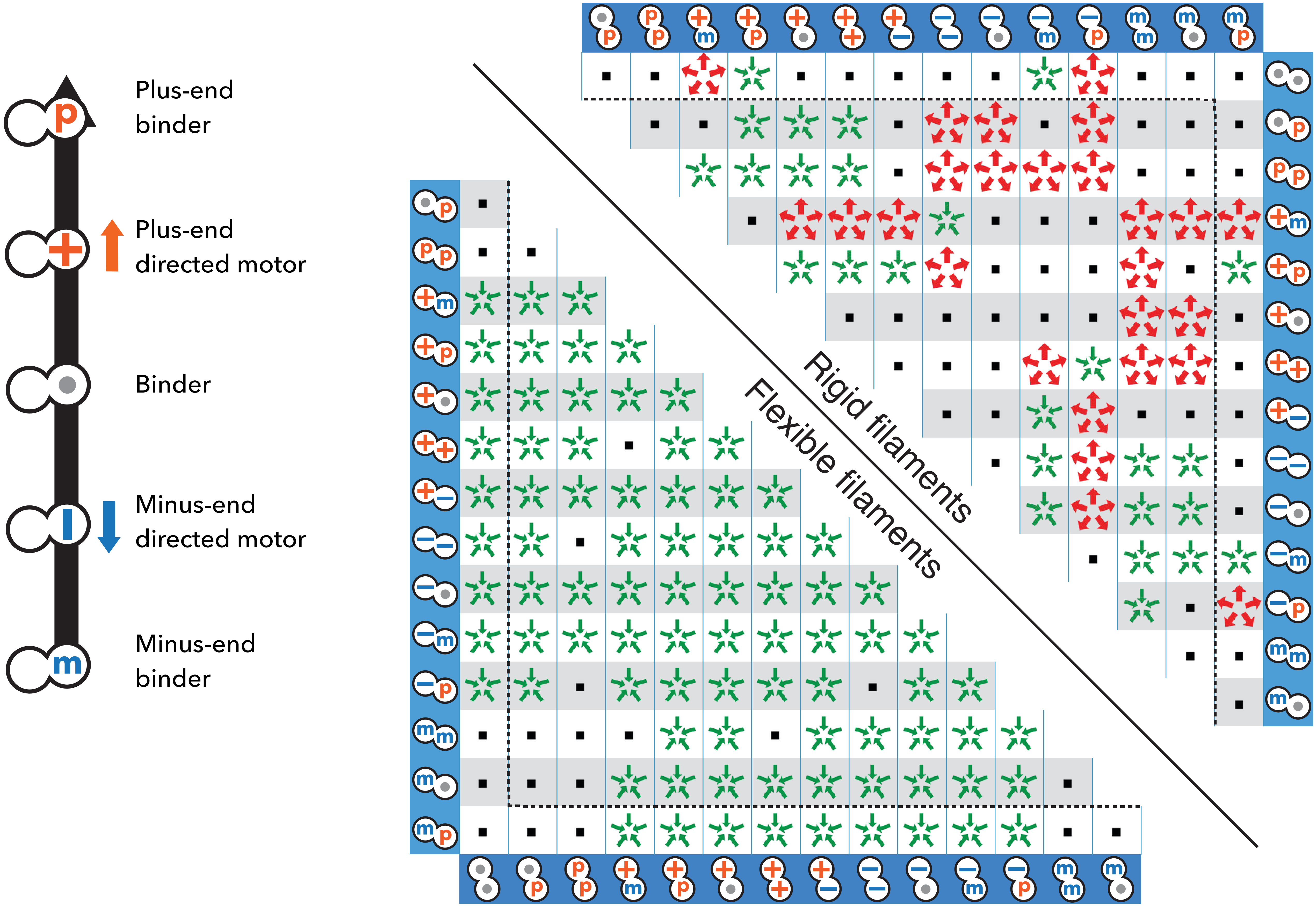


Flexible filaments



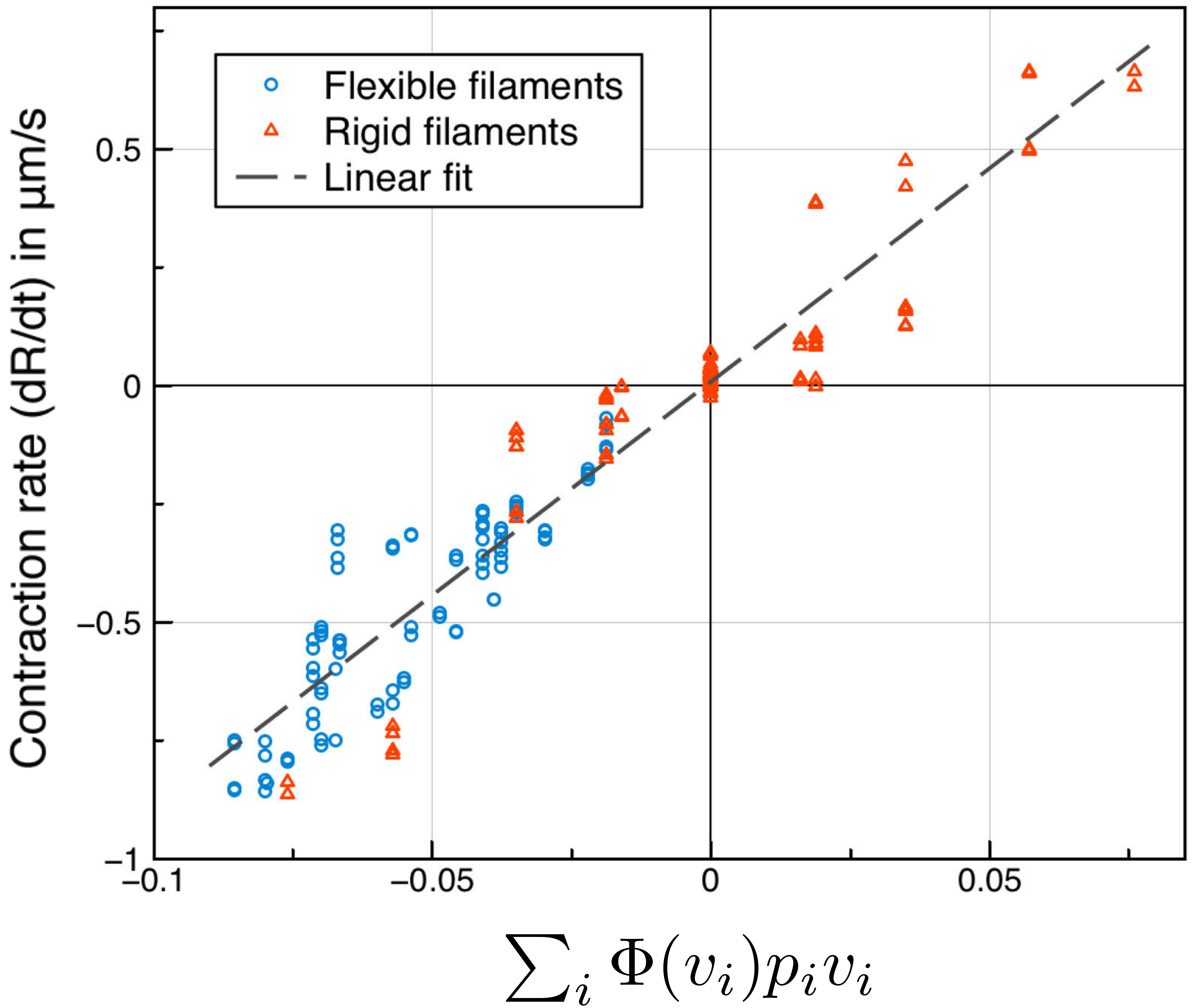
Predictions for Systems with 2 Types of Connectors

(in equal number, with equal rates)



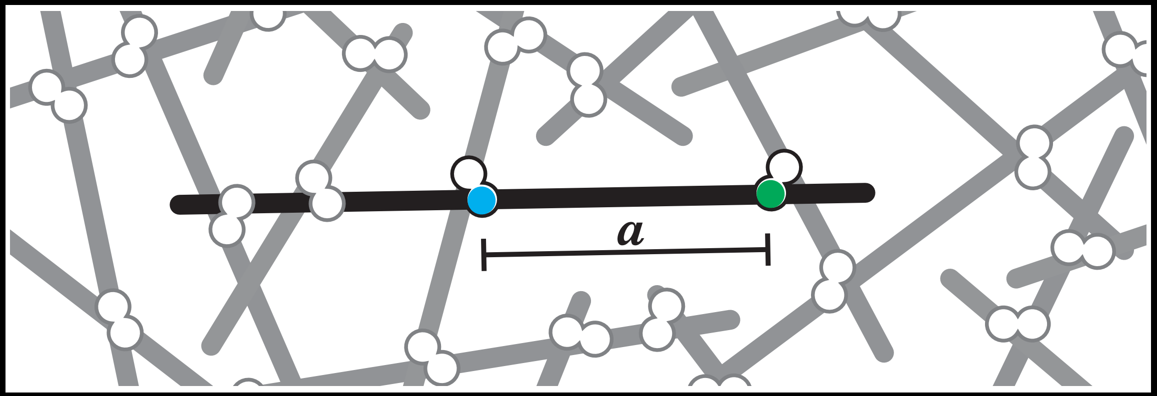
Predictions for Systems with 2 Types of Connectors

(in equal number, with equal rates)



Summary

- Consider elementary configurations in the network:



$$\frac{1}{\bar{a}}\frac{d\bar{a}}{dt}$$

  - validated by:
    - simulations with rigid, flexible and semi-flexible filaments
    - experiments with motors+crosslinkers (Enomani et al. 2016)

- Unifies previously proposed mechanisms of contraction
  - different mechanisms for actin and microtubules networks

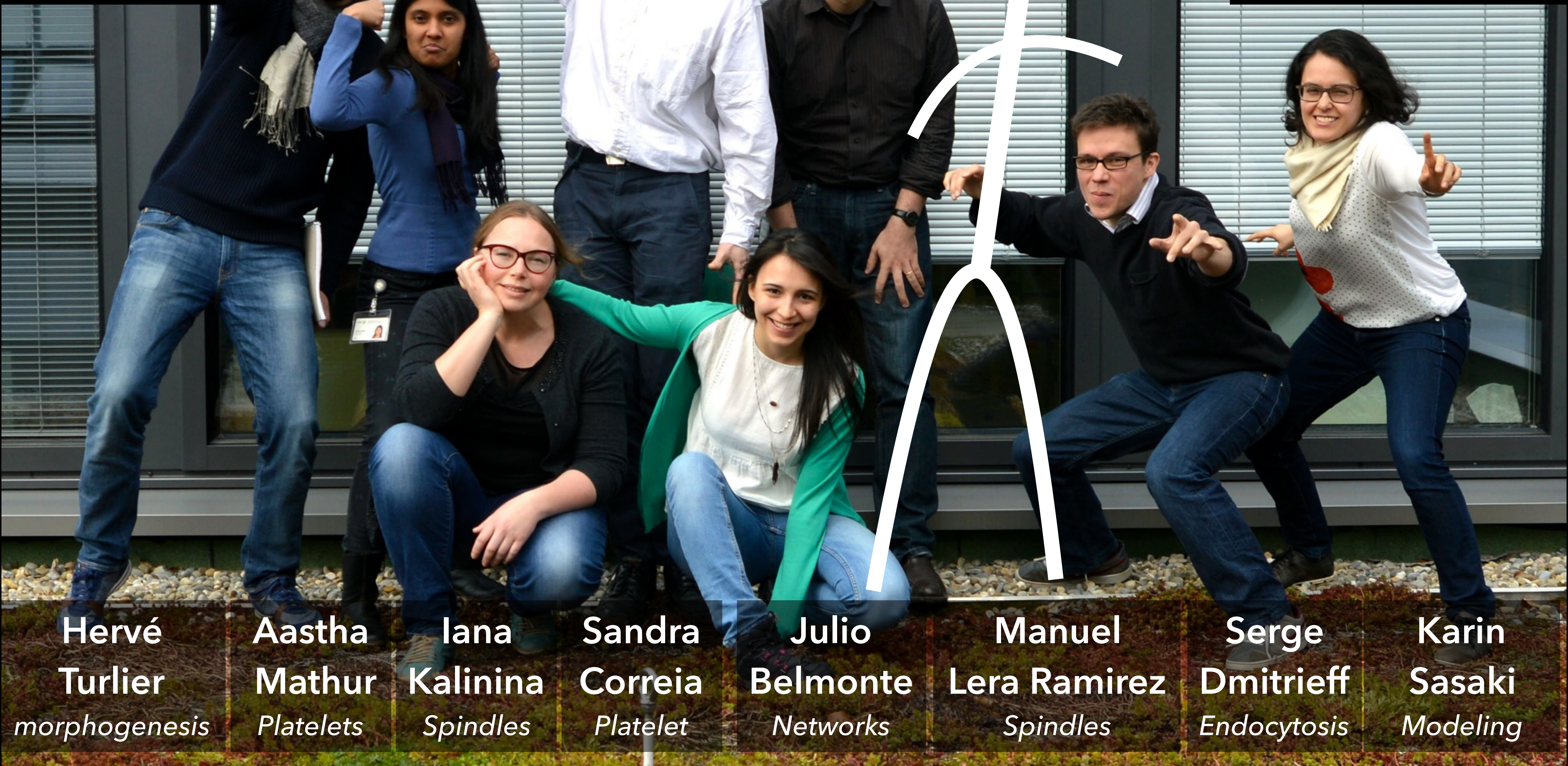
- Predicts network contraction/expansion rate as a function of:
  - motor/crosslinker properties and concentrations
  - density, length of filaments

Cellular Architecture Group

Maria Leptin

EMBL

BioMS
EU FP7
DivIDE



Talk

Poster #

Poster #94