Self-organization of Active Polar Rods:
Self-Assembly of Microtubules and Molecular Motors

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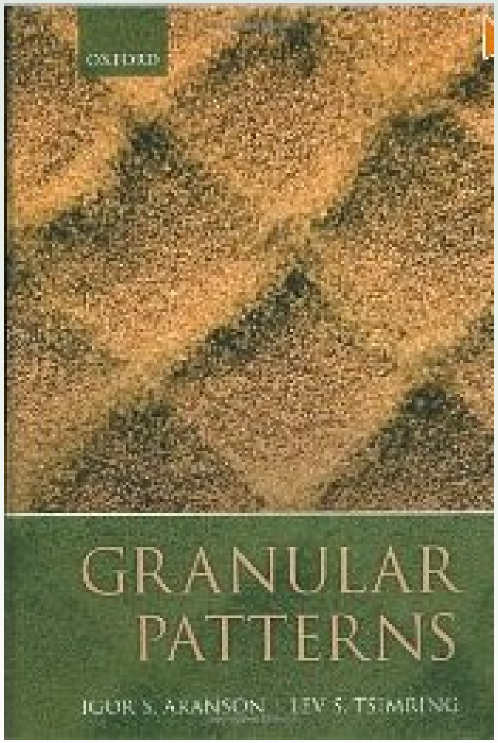
Review papers

*I. Aranson and Lev Tsimring, **Patterns and collective behavior in granular media: Theoretical concepts**, Rev Mod Phys, 78, 641 (2006)*

I. Aranson and Lev Tsimring,
***Granular Patterns**,*
Oxford Univ Press, 2009



Outline

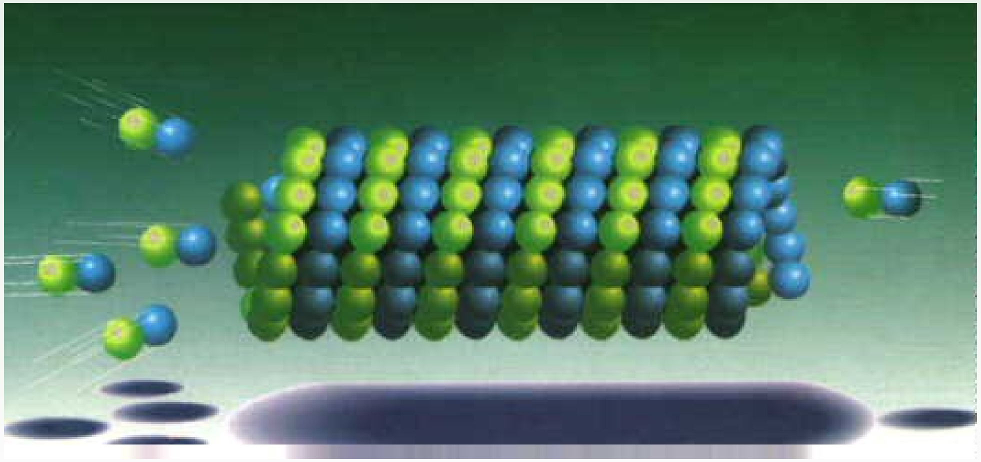
in-vitro experiments
Micromechanical calculations
Maxwell model for polar rods and granular analogy
Asters and vortices

Microtubules

Very long rigid polar hollow rods (length – 5-20 microns, diameter -40 nm, Persistent length – few mm)

Length varies in time due to polymerization/depolymerization of tubulin

Multiple function in the cell machinery: cytoskeleton formation, cell division, cell functioning



Molecular motors-Associated Proteins

- **Linear motors** (kinesin, dynein, myosin) cytosceleton formation, transport
- **Rotary motors:** (flagellar motor, F-ATPase) flagella rotation
- **Nucleic acid motors:** (helicase, topoisomerase) – DNA unwinding/translocation

Linear motors clusters:

Have one head and one tail, but may cluster

One attached to MT

Other attached to vesicles, granules, or another MT

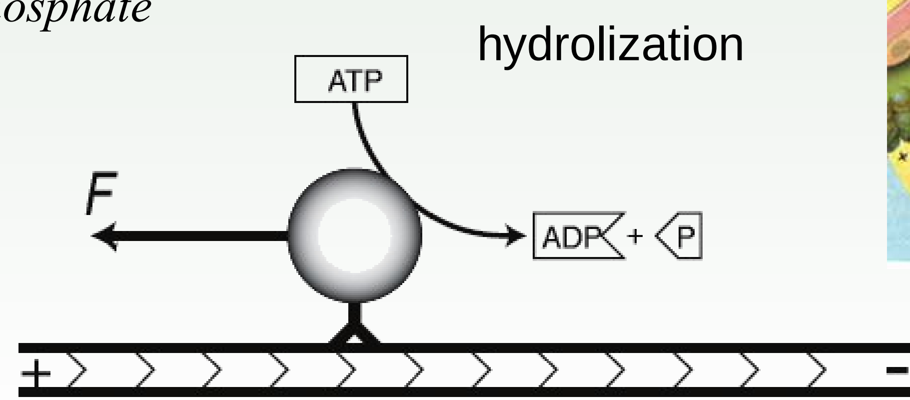
Take energy from hydrolysis of ATP

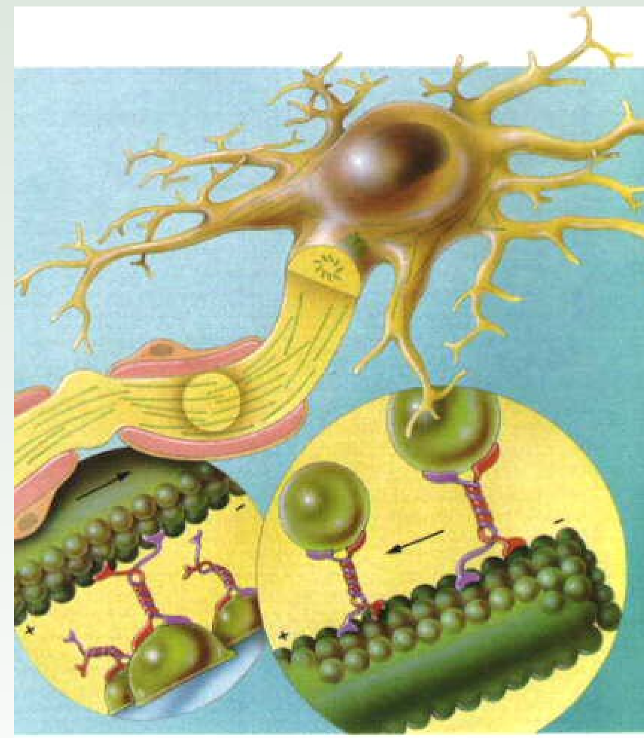
Speed ~1μm/s, step length 8 nm, run length ~1μm

Exert force about 6 pN

ATP – Adenosine triphosfate

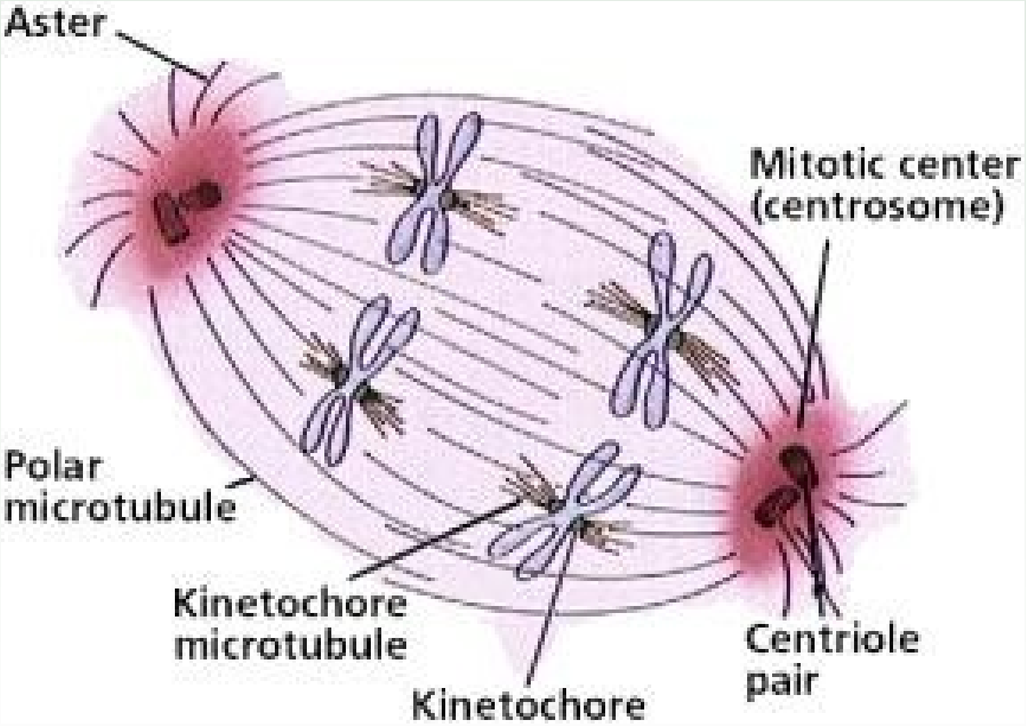
ADP- Adenosine diphosphate



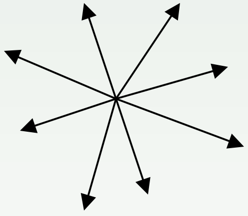


Dividing Cells and Mitotic Spindles

MT form cytoskeleton of dividing cells
Separate chromosomes
Asters: ray-like arrays of MT located around centrioles

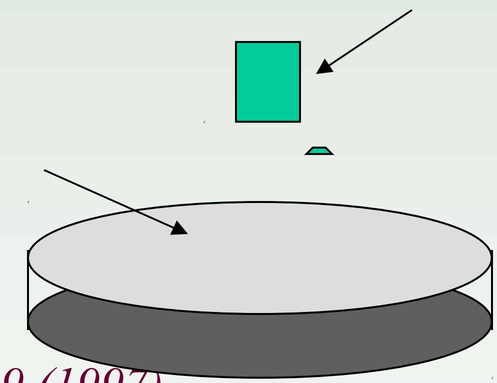


Aster



in-vitro Self-Assembly of MT and MM

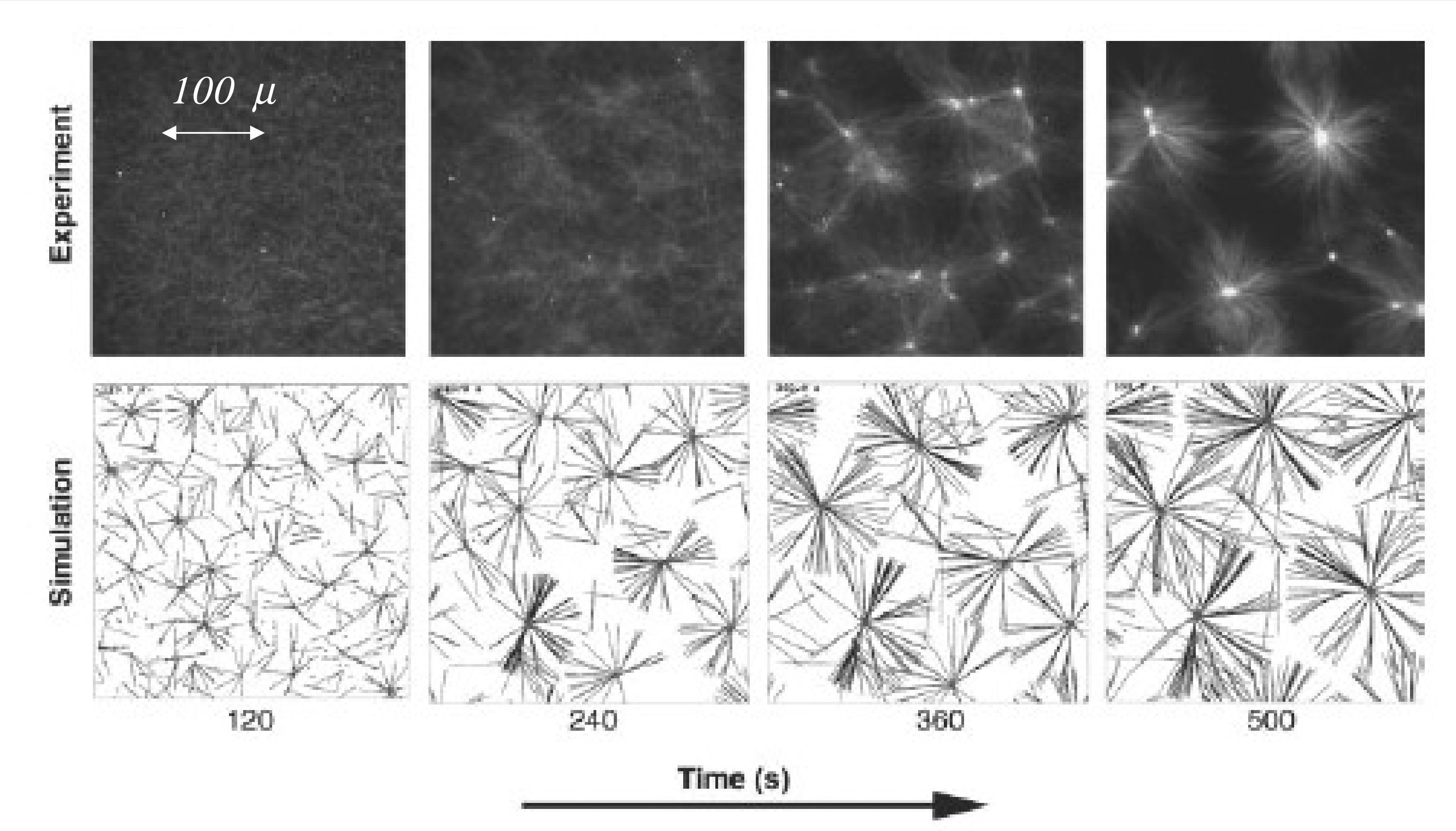
- *Simplified system with only few purified components*
- *Experiments performed in 2D glass container: diameter 100 μm, height 5μm*
- *Controlled tubulin/motor concentrations and fixed temperature*
- *MT have fixed length 5μm due to fixation by taxol*



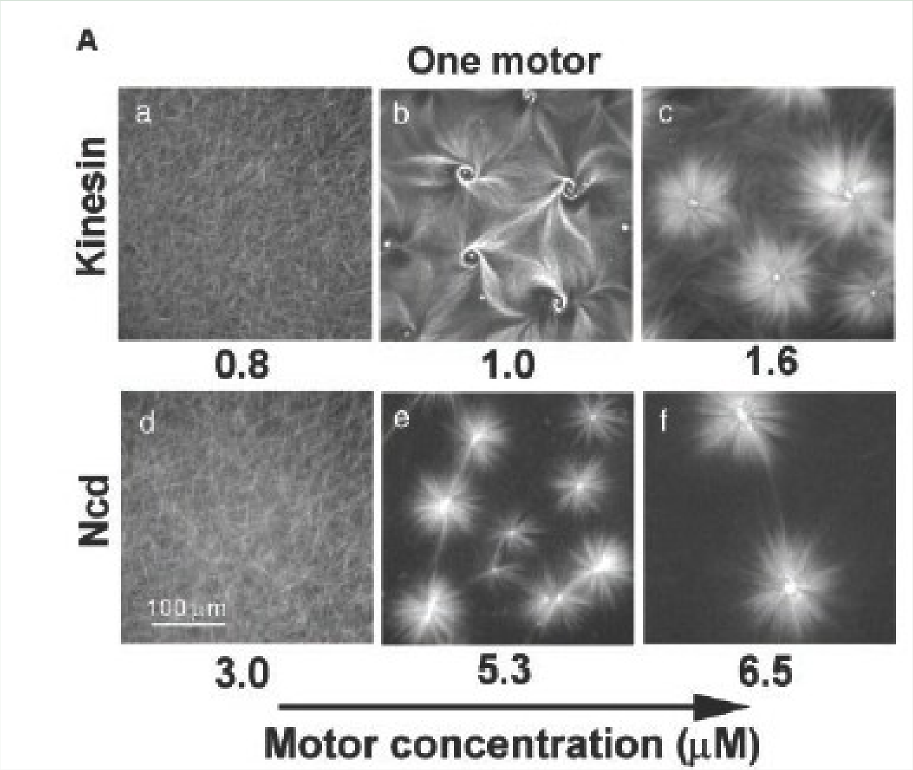
F. Nedelec, T. Surrey, A. Maggs, S. Leibler,
Self-Organization of Microtubules and Motors, Nature, 389 (1997)
T. Surray, F. Nedelec, S. Leibler & E. Karsenti,
Physical Properties Determining Self-Organization of Motors & Microtubules, Science, 292 (2001)

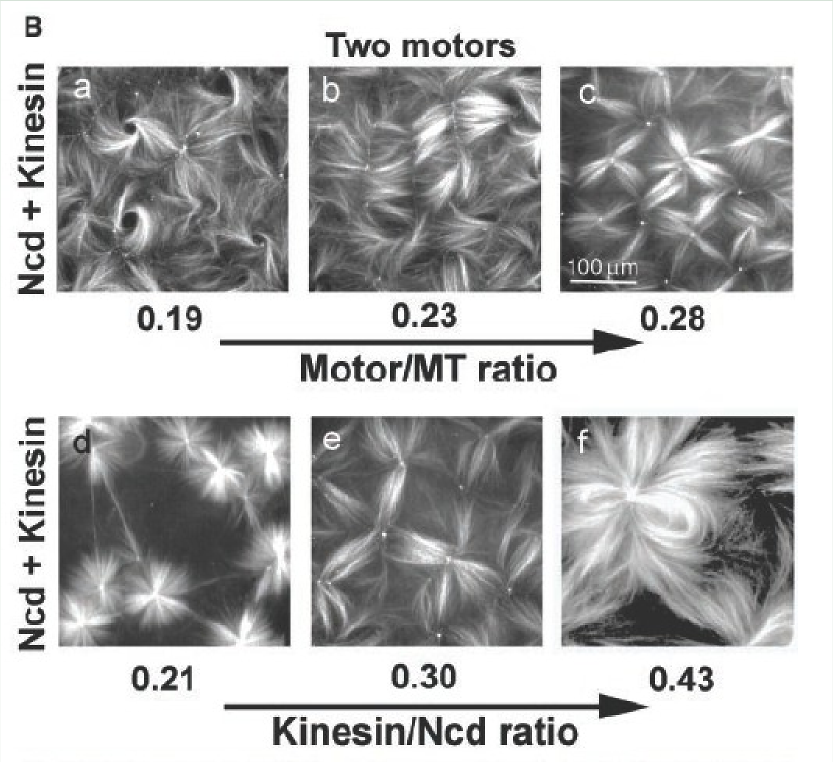
Patterns in MM-MT mixtures

Formation of asters, large kinesin concentration (scale 100 μ)



Vortex – Aster Transitions





Ncd – gluththione-S-transferase-nonclaret disjunctional fusion protein
Ncd walks in opposite direction to kinesin

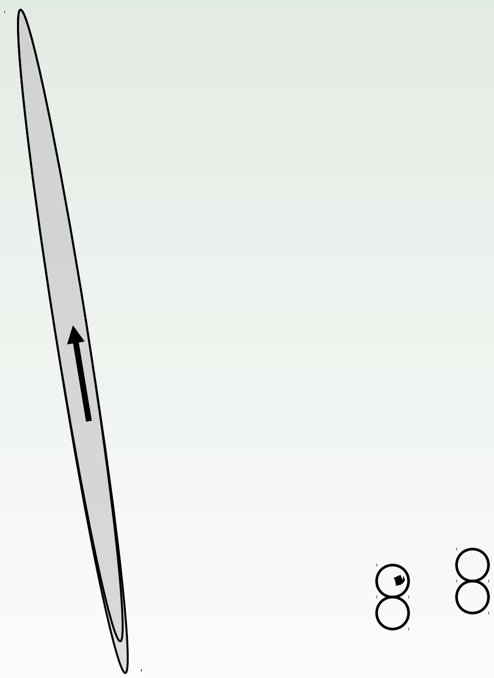
Summary of Experimental Results

Kinesin: vortices   for low density of MM and asters for higher density
Ncd: asters are observed for all MM densities
Bundles for very high MM density, asters disappear

Possible difference between kinesin and NCD: kinesin falls off the end of MT, NCD sticks and dwells

Mechanism of Self-Organization

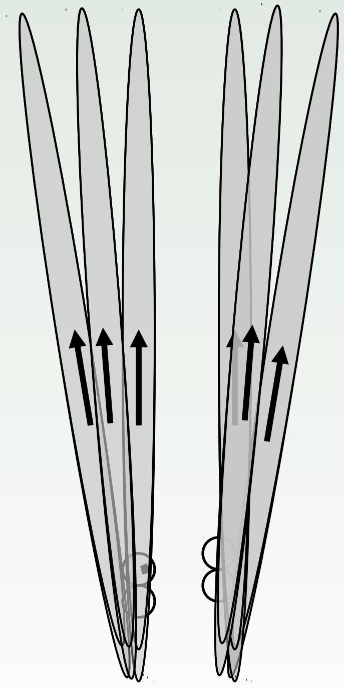
Motor binding to 1 MT – no effect



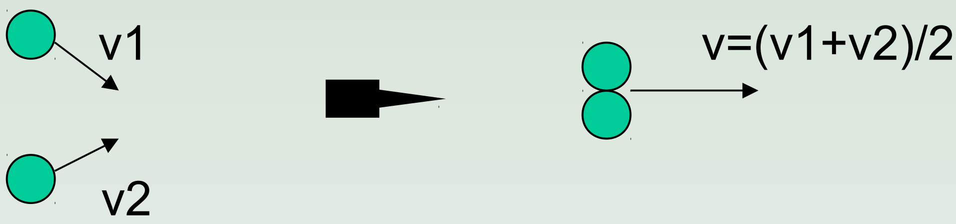
Motor binding to 2 MT –

mutual orientation after interaction

Zipper effect or inelastic collision



Collisions of Inelastic Grains



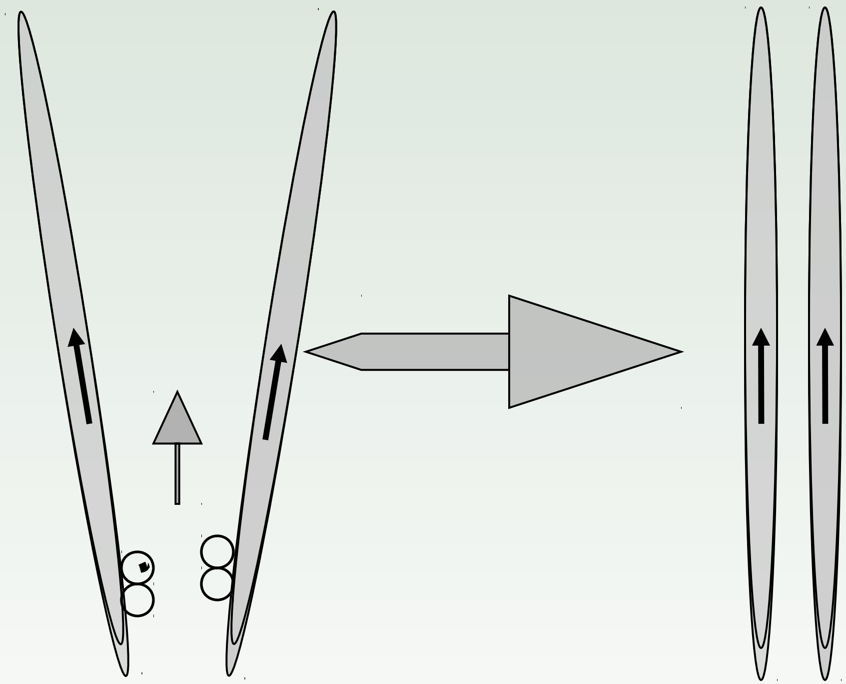
va & vb velocities after/before collision

γ=0 – elastic collisions

γ=1/2 – fully inelastic collision

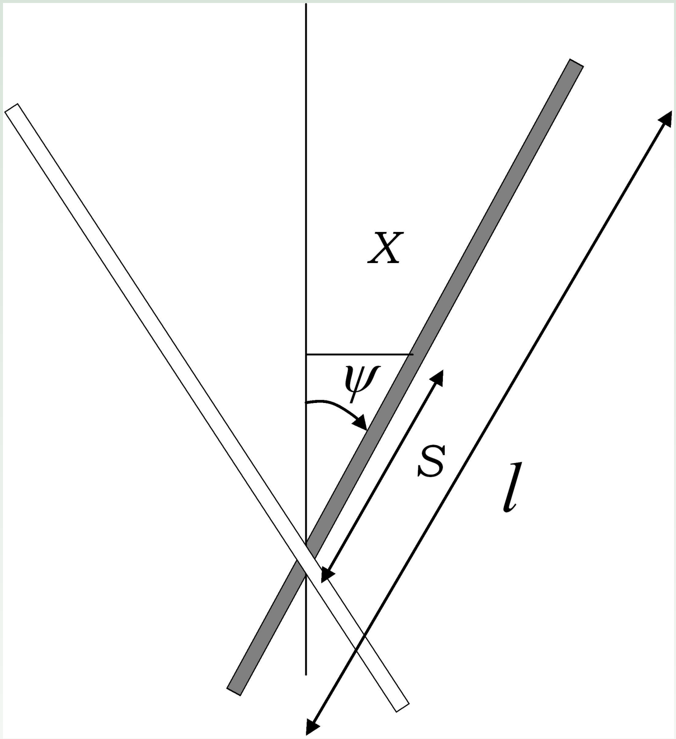
$\gamma=1$ – no interaction

Inelastic Collision of Polar Rods



Fully Inelastic Collision!!!

Interaction of Two Microtubules



- *Point-wise motor at the intersection point*
- *Rigid rods*
- *Symmetric motor attachment*
- *Motor moves with constant speed V*
- *Exerts force F(V)*

$$\begin{aligned} \partial_t \psi &= \xi_r^{-1} S \cos\psi F \\ \partial_t X &= \xi_{\|}^{-1} F, \\ \partial_t Y &= 0. \end{aligned}$$

I.A. & L Tsimring, PRE 2006

Solution for two rods

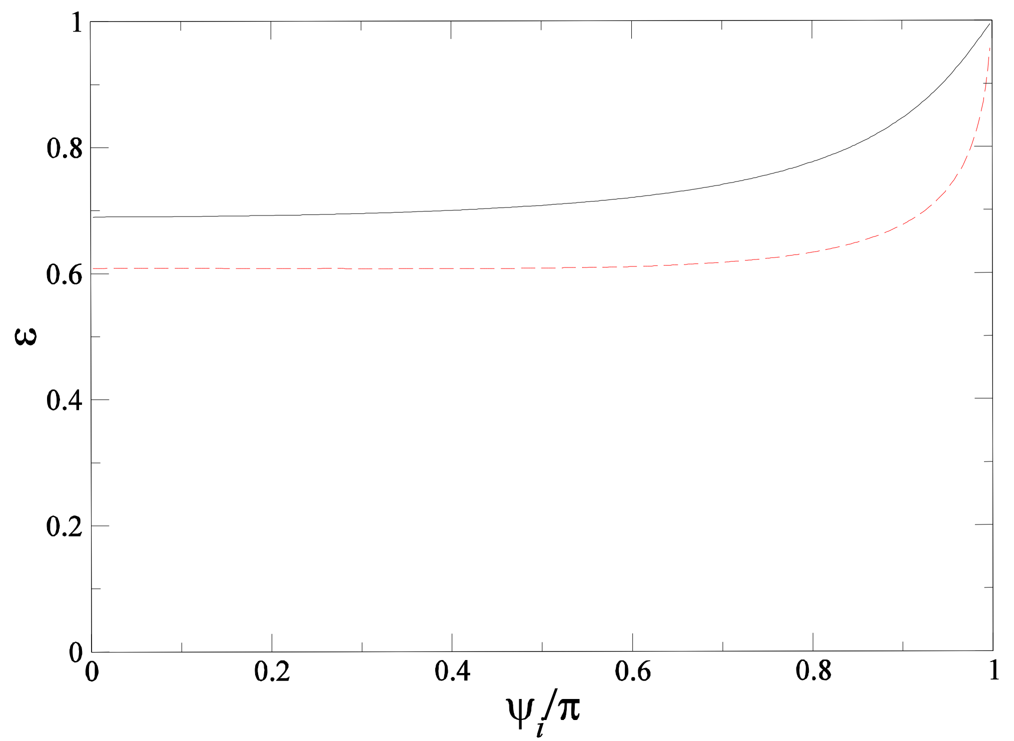
Motor attachment condition

Evolution of the angle

Exact solution (C=const is determined by i.c.)

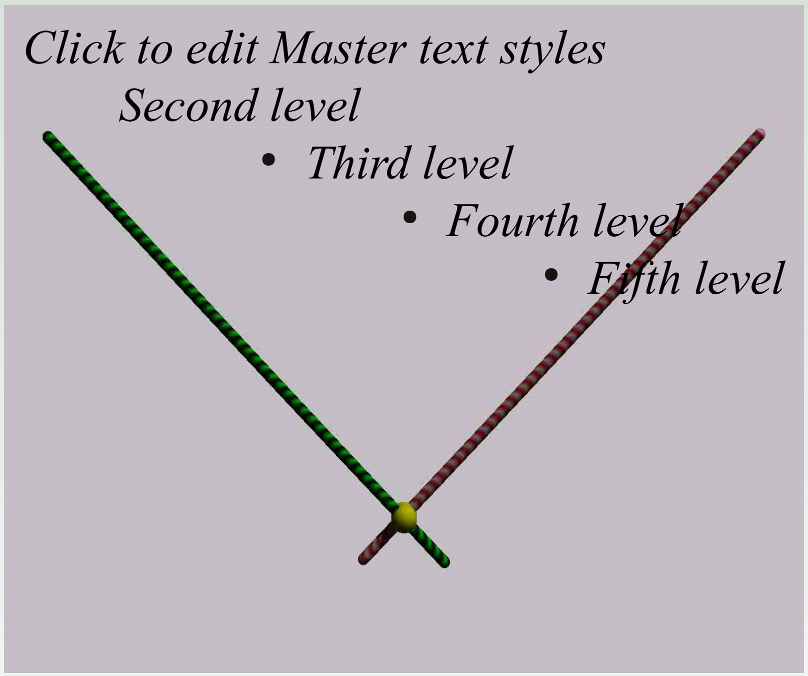
Averaged angle after interaction

Inelasticity factor for two rigid rods

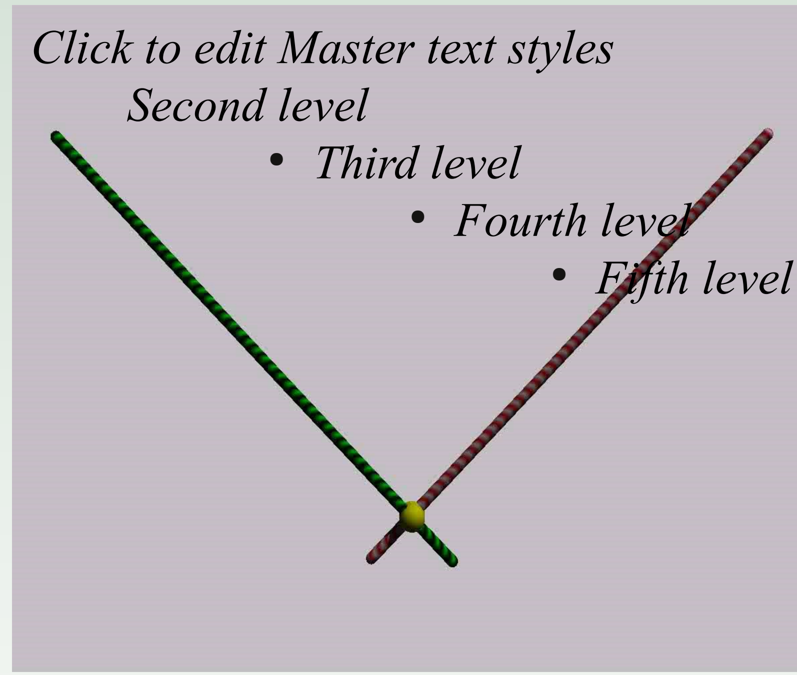


Inelasticity enhanced by flexibility

Motor released from the end

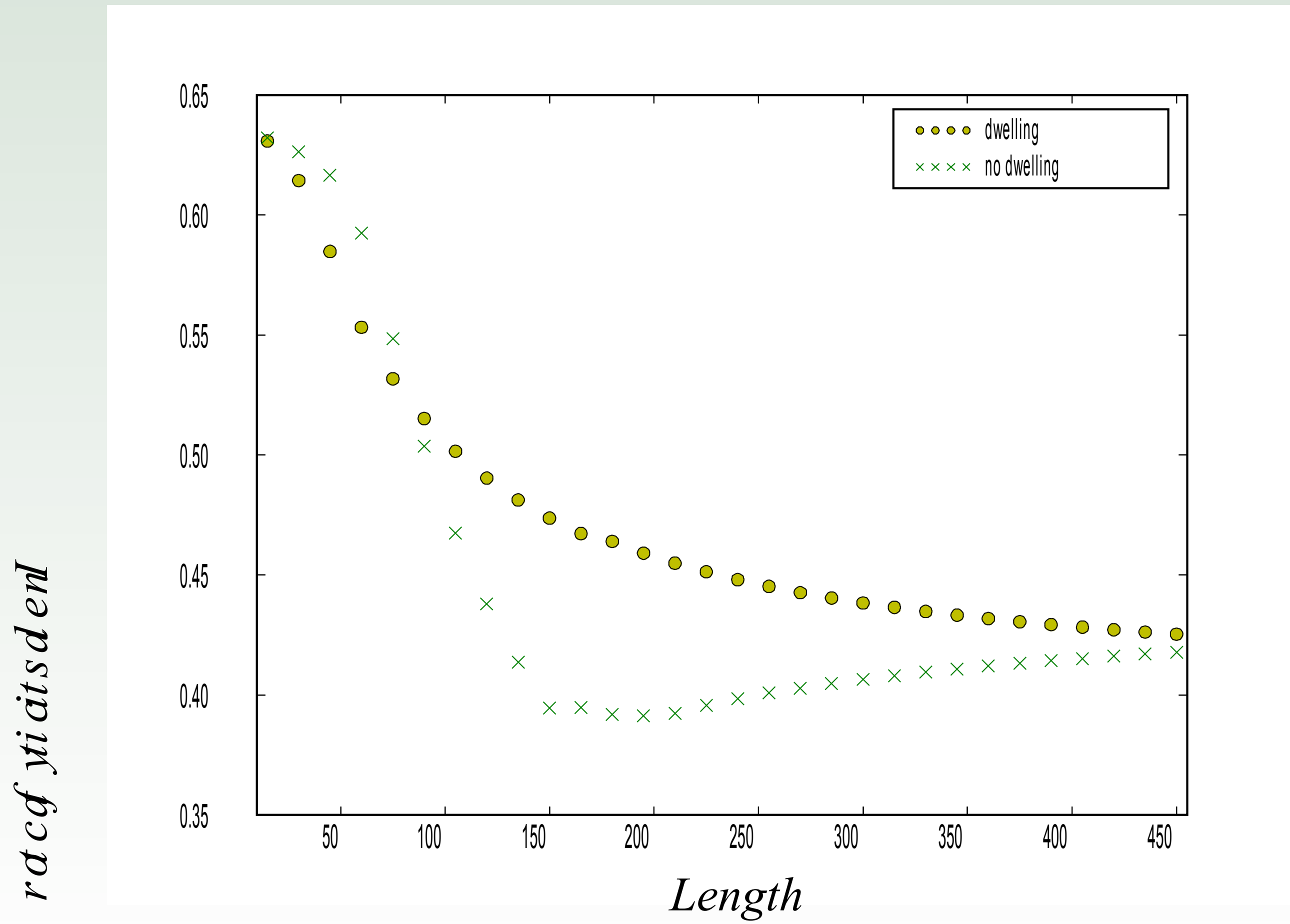


Motor dwells at the end



Inelasticity vs flexibility and length

Effective stiffness



Molecular Dynamics Simulations of Stiff Inelastic Rods

Simple rules

-rigid rods of equal length

-no explicit motors

-fully inelastic collisions

- rods diffuse anisotropically in 2 dim, Dparallel=2 Dperpendic

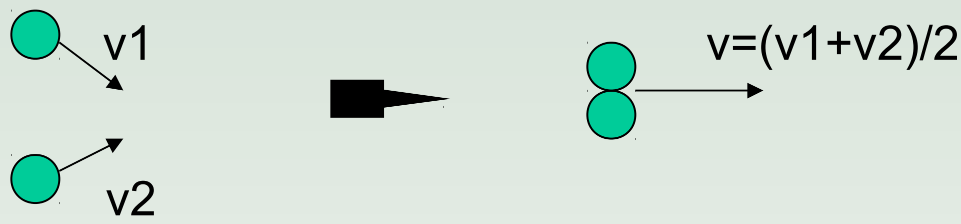
-reorient upon collision with some probability Pon

-probability of interaction depends on proximity to the end (dwelling)

Jia, Bates, Karpeev, I.A. PRE 2008

Maxwell Model for Inelastic Particles

inelastic grains



va & vb velocities after/before collision

γ=0 – elastic collisions

γ=1/2 – fully inelastic collision

$\gamma=1$ – no interaction

Probability distributions *P(v)*

Collision rate g does not depend on relative velocity (Maxwell molecules)
No spatial dependence
D- thermal diffusion, D ~T, T – temperature of heat bath
Binary uncorrelated collisions

Distribution function for $\gamma = 1/2$

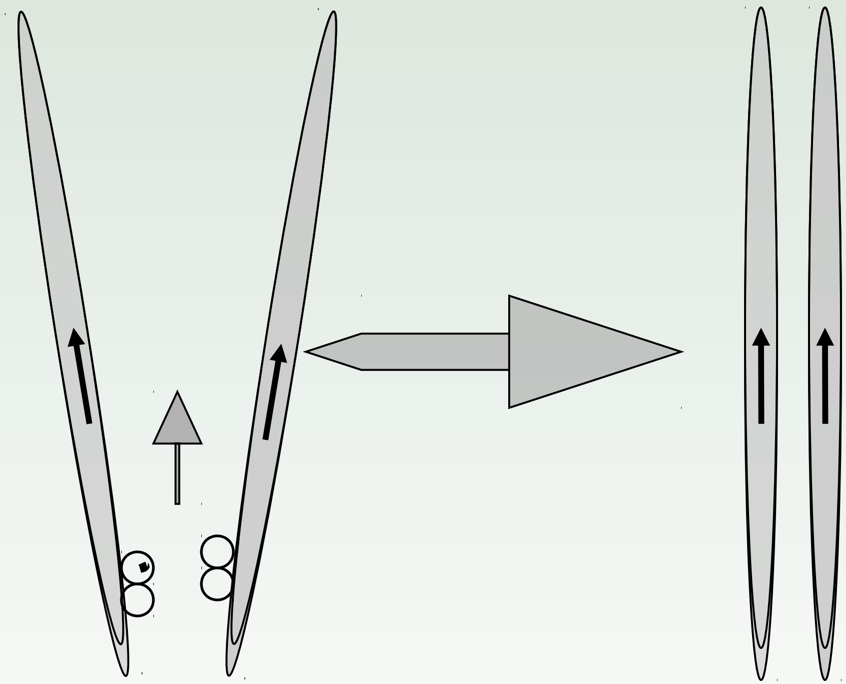
source term

sink term

heat bath

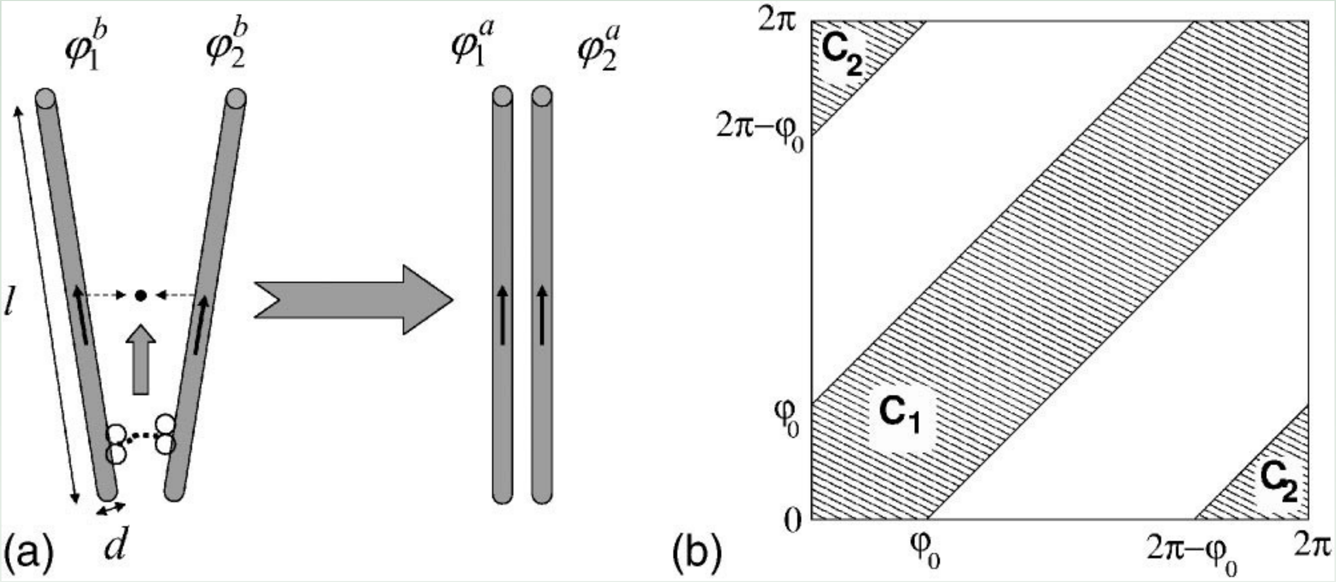
Ben-Naim & Krapivsky, PRE 2000

Inelastic Collision of Polar Rods



Fully Inelastic Collision!!!

Collision Integral



Collision Integral

- *Dr - thermal rotational diffusion*
- *g – collision efficiency (~ concentration of motors)*

since diffusion of motors >> diffusion of microtubules

assume g=const

Kinetic Equation for *$P(\varphi)$*

For simplicity $\phi 0 = \pi$
Main difference – integration over a finite interval due to 2π periodicity of the angle
Phase transition with the increase of g!!!

Stability of isotropic state

No preferred orientation: $P(\varphi)=P0=1/2\pi$
Small perturbations: $P(\varphi)=1/2\pi+ \xi n e \lambda t+in\varphi+c.c.$
λ *– growth-rate of linear perturbations*

For $g>Dr/(4/\pi-1)\approx 3.662\ Dr$ *- disoriented state loses stability*
Orientation phase transition above critical motor density !!!

Macroscopic Variables

Density of MT

Average orientation $\boldsymbol{\tau}=(\tau x, \tau y)$

"Complex orientation"

Fourier Expansion

Relation to observables

Asymptotic expansion for *Pn* $(\gamma=1/2)$

Scaling of variables

Diffusion -Drk2 forces rapid decay higher harmonics

Linear growth rates λn

$\lambda 0=0$

$\lambda n<0 \;\; \text{for} \; |n|\geq 2$ *Neglect higher harmonics*

Asymptotic Landau Equation

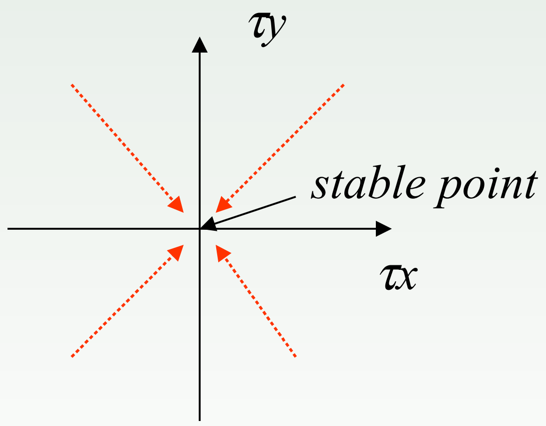
Truncation of series for $|n|>2$

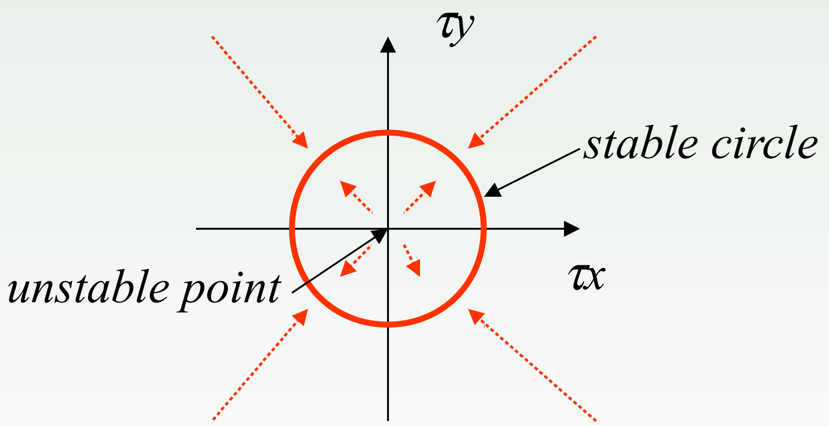
Second order phase transition for $\rho>\rho c = 1/0.273 \approx 3.662$

Second order phase transition for ρ>ρc

ρ< ρc – no preferred orientation
*|**τ**|→ 0, stable point **τ**=0*

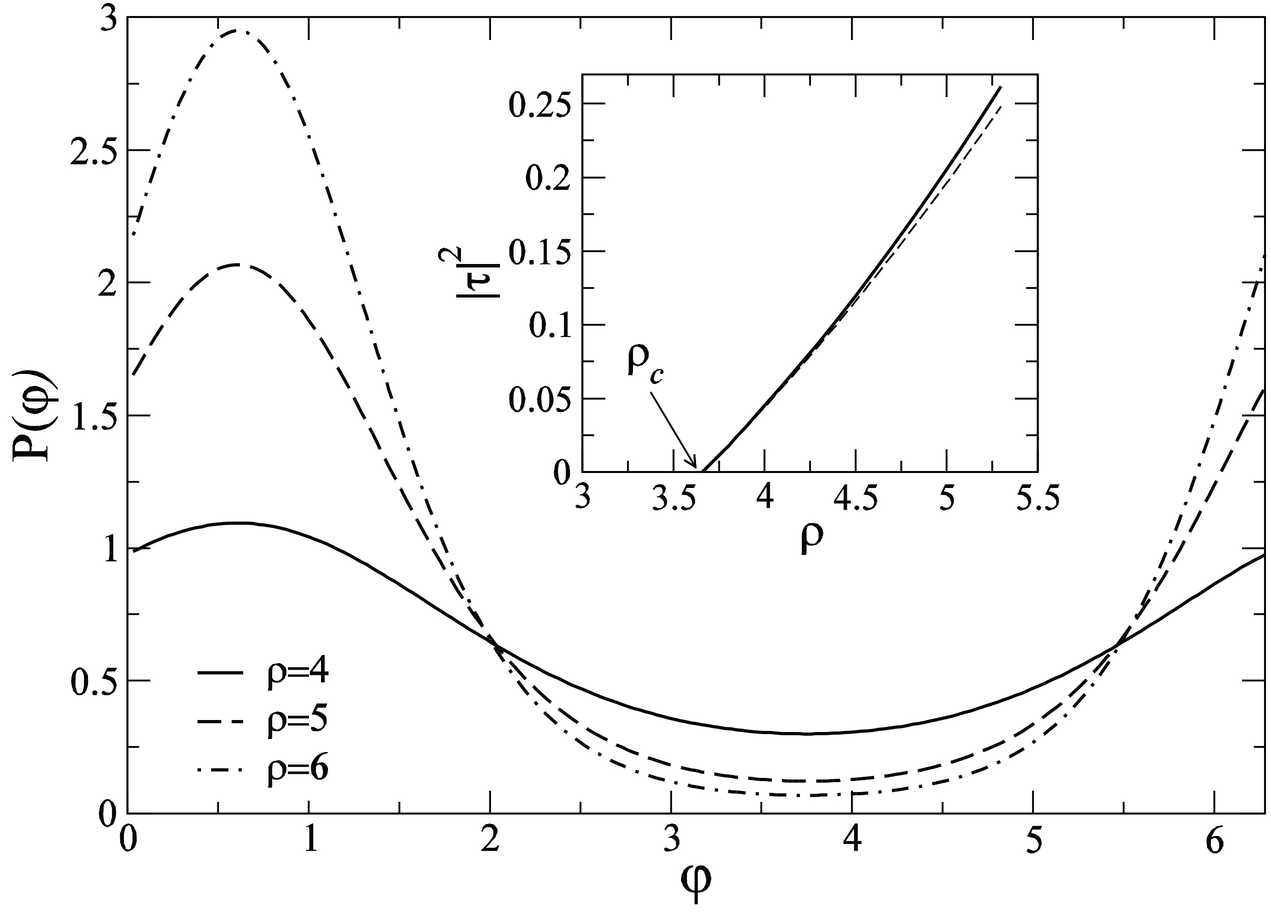
ρ>ρc – onset of preferred orientation
*|**τ**|→ const, direction is determined by initial distribution, stable limit circle*





Compare with Hopf Bifurcation Scenario

Stationary Angular Distributions Comparison with Numerical Solution



Spatial Localization of Interaction

Interaction between rods decay with the distance
Translational and rotational diffusion of rods

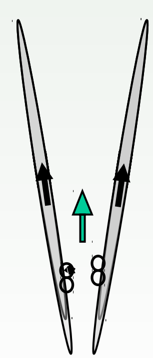
The Diffusion Matrix in Kirkwood Approximation

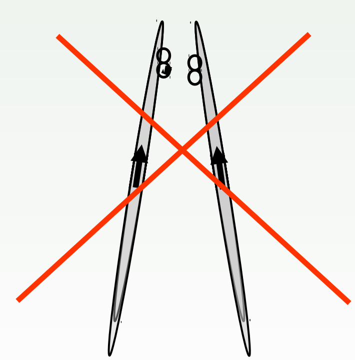
l – length of the rod, d- diameter, ηs – viscosity of solvent

Collision Integral

Interaction Kernel

Decays with distance between rods
Depends on relative angle between rods
Symmetric with respect permutation of rods





β *small for kinesin*
β *large for NCD*

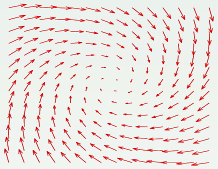
Continuum Equations

Term prohibited by the momentum conservation

Asters and Vortices

For HB2 <<1 equations split and become independent

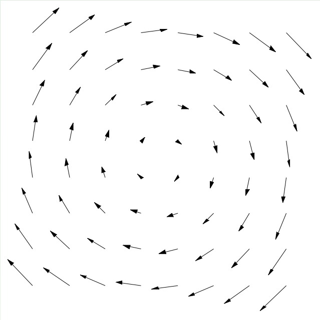
Without blue and red terms Eq possesses "Abrikosov Vortex Solution"



Vortices

For H=0 (no red terms) the only stable solutions $\varphi = \pm\pi/2$

-Vortex: MT circle around the center



- Liquid crystals analogy: Frank Free Energy

splay ***bend***

Term penalizes splay deformations → vortices

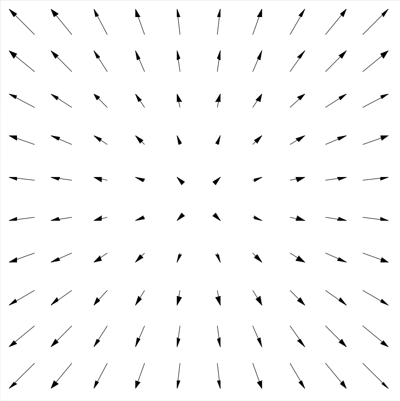
Aranson & Tsimring, PRE 2003

Asters

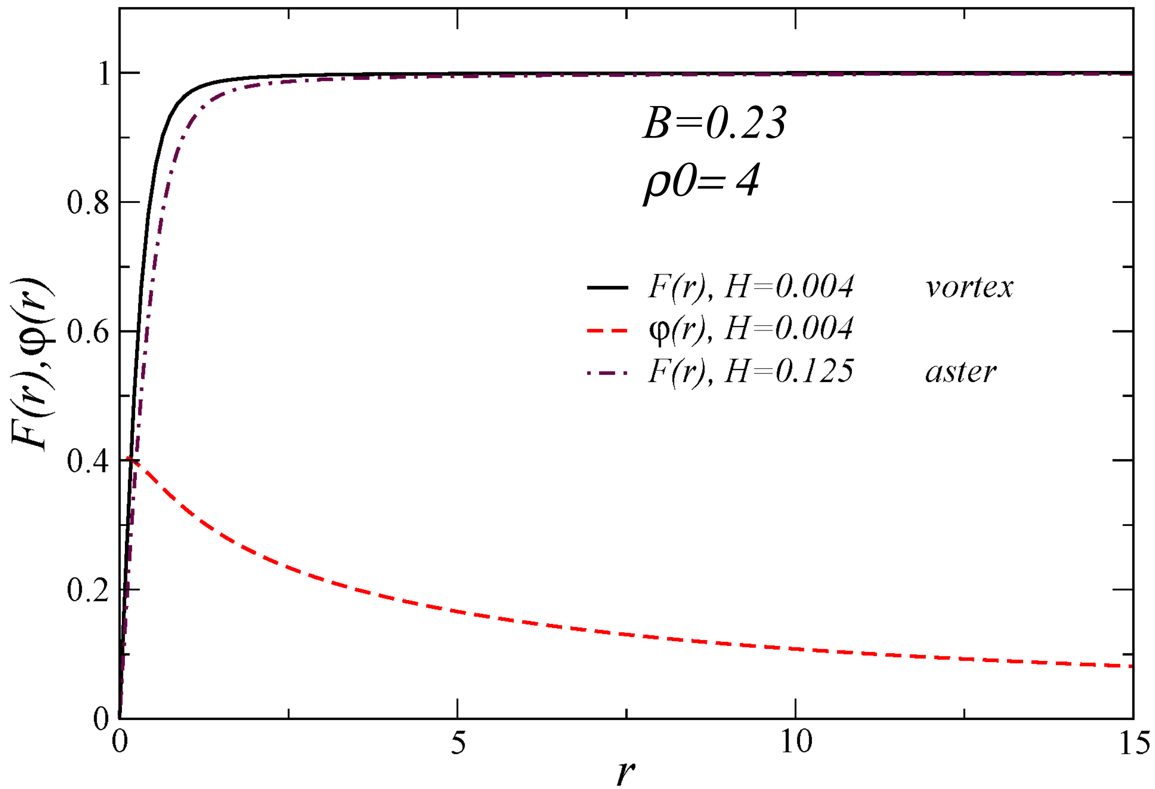
For H≠0 (no blue terms) the only stable solution $\varphi = 0$

No phase degeneracy:

Aster: MT directed towards the center



Vortex/Aster Solutions



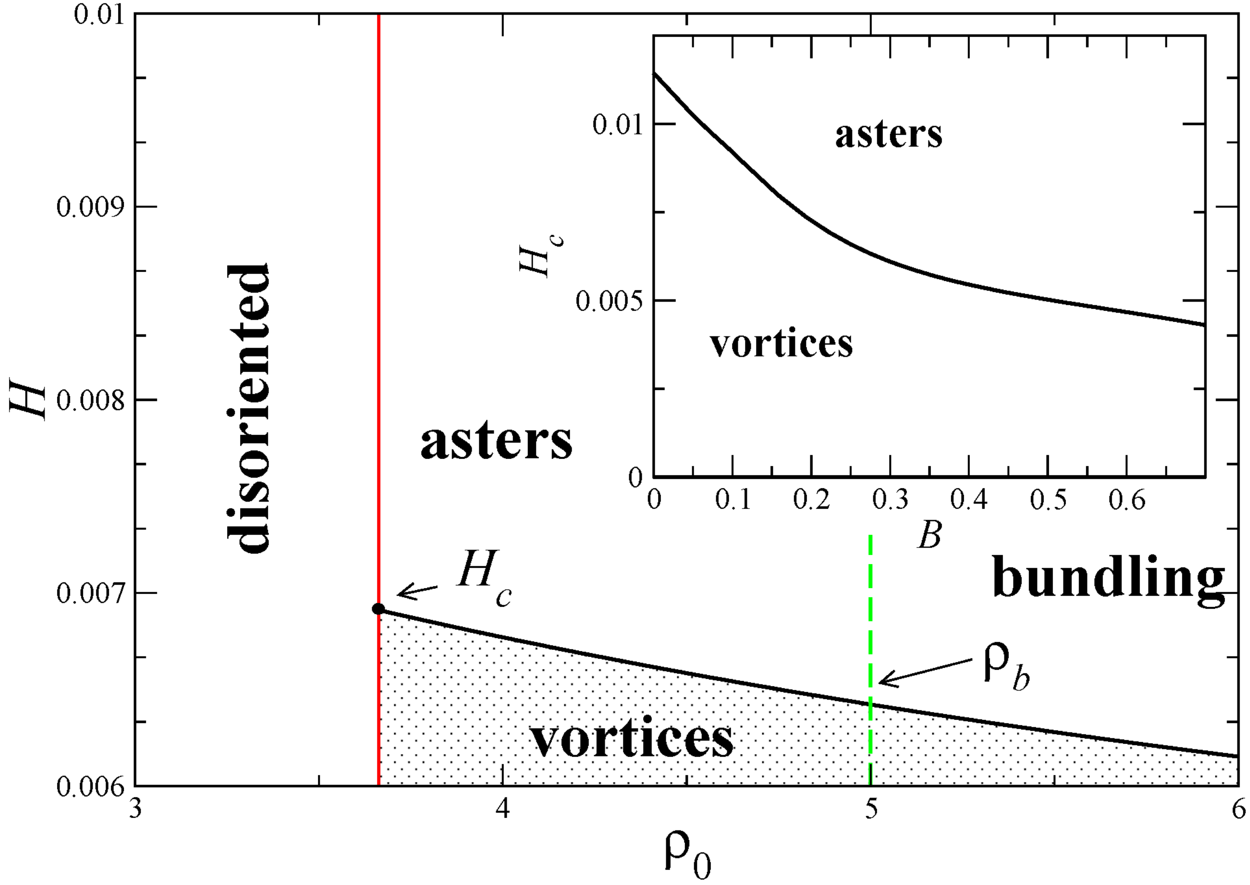
For H≠0 far away from the core the distinction between vortex and aster disappears

Linear Instability of Aster

Linearized Equation for Aster

Equations solved numerically by shooting-matching method with Newton iterations

Phase Diagram



Implications of Analysis

Asters stable for large MM density
Vortices stable only for low MM density
No stable vortices for H>Hc for all MM density
(in experiments no vortices in Ncd for all densities)

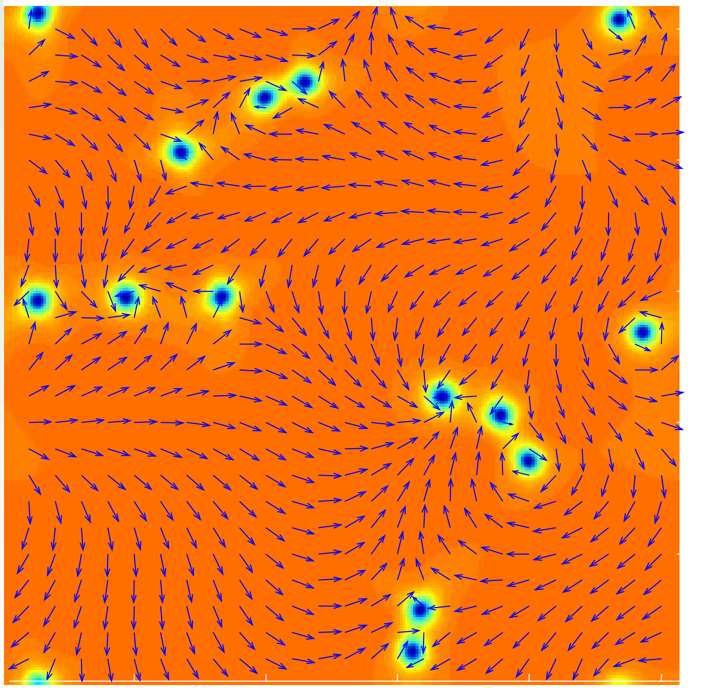
Experiment

- 2D mixture of MM & MT exhibits pattern formation
- In kinesin vortices are formed for low density of MM and asters are formed for higher density
- In Ncd only asters are observed for all MM densities
- For very high MM density asters disappear and bundles formed

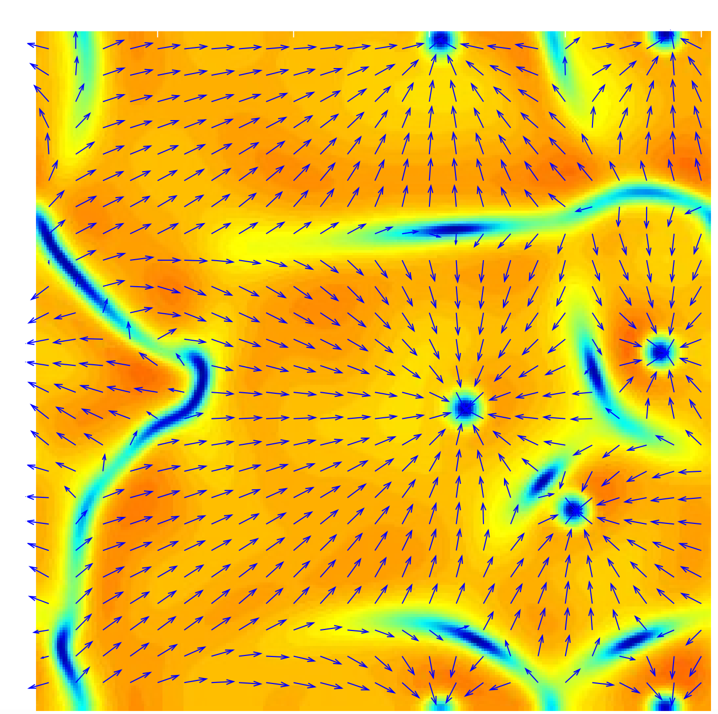
Numerical Solution

Quasispectral Method ; 256x256 FFT harmonics
Periodic boundary conditions
Spontaneous creation of vortices and asters

H=0.004

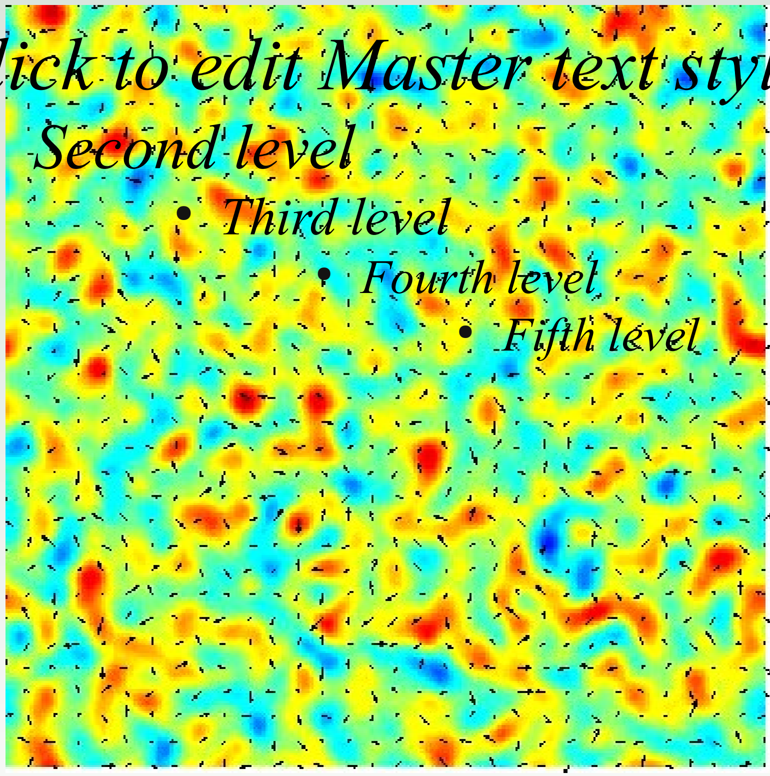


H=0.125

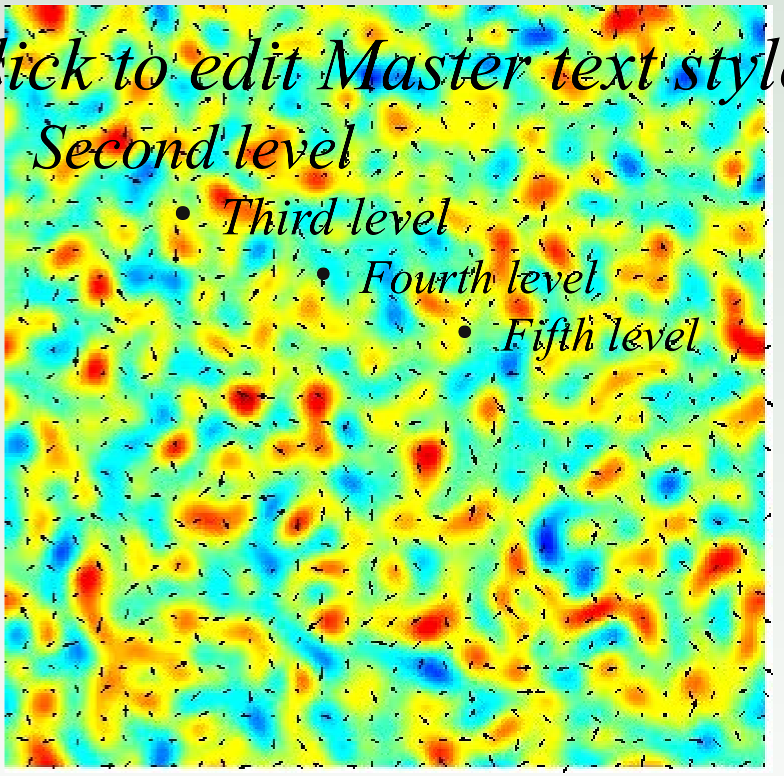


Evolution of Vortices and Asters

Large anisotropy H



Small anisotropy H



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Second level

- *Third level*
  - *Fourth level*
    - *Fifth level*

Click to edit Master text styles

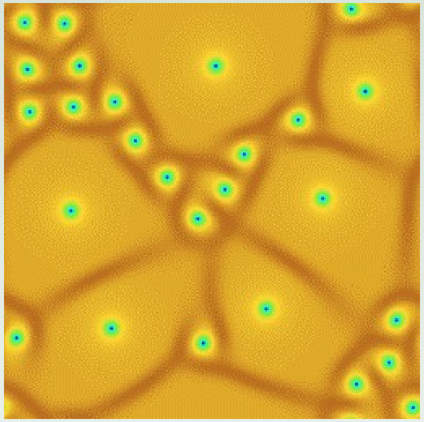
Second level

- *Third level*
  - *Fourth level*
    - *Fifth level*

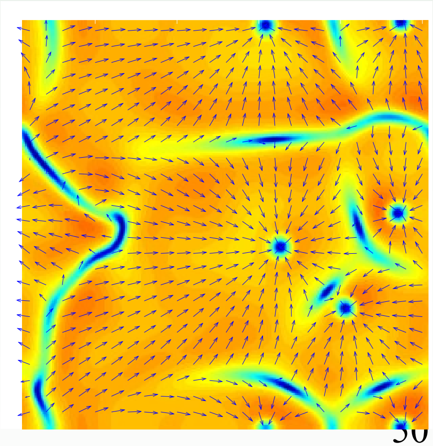
Complex Ginzburg-Landau Equation Analogy

*I.A. L. Kramer, The World of the Ginzburg-Landau Equation, Rev Mod Phys, **72**, 99 (2002)*

Vortex Glass State



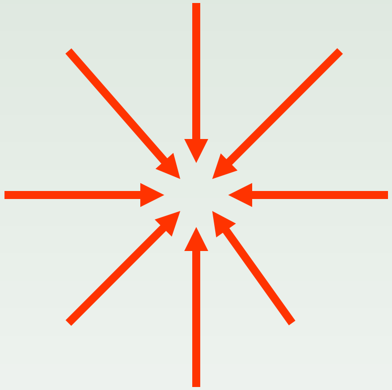
Aster Lattice



Generalizations
Inhomogeneous Motor Distribution *m(x,y,t)*

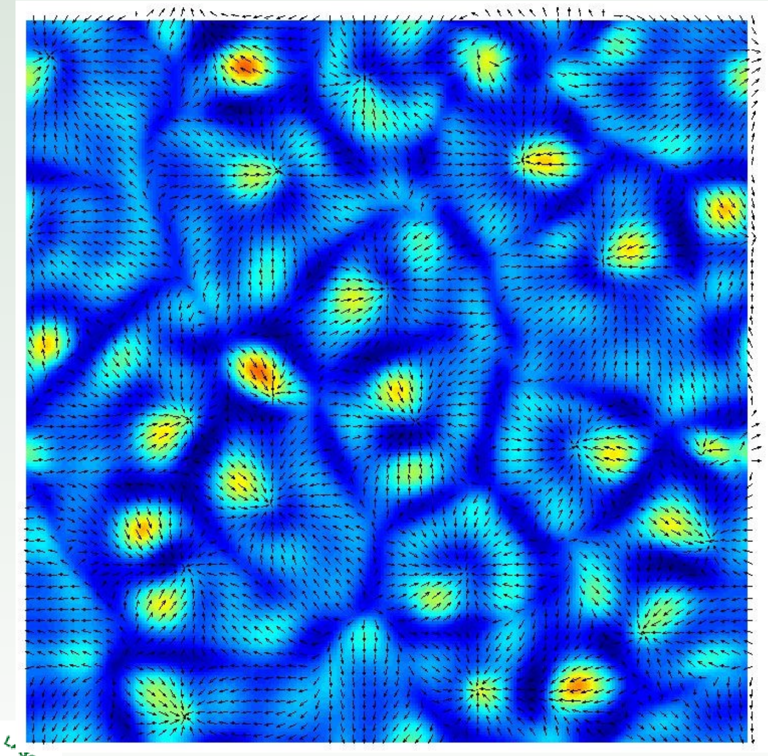
Motors move along MT and accumulate in the centers of asters and vortices
$g \sim m \neq const$

additional diffusion-advection equation for motors m(x,y,t)

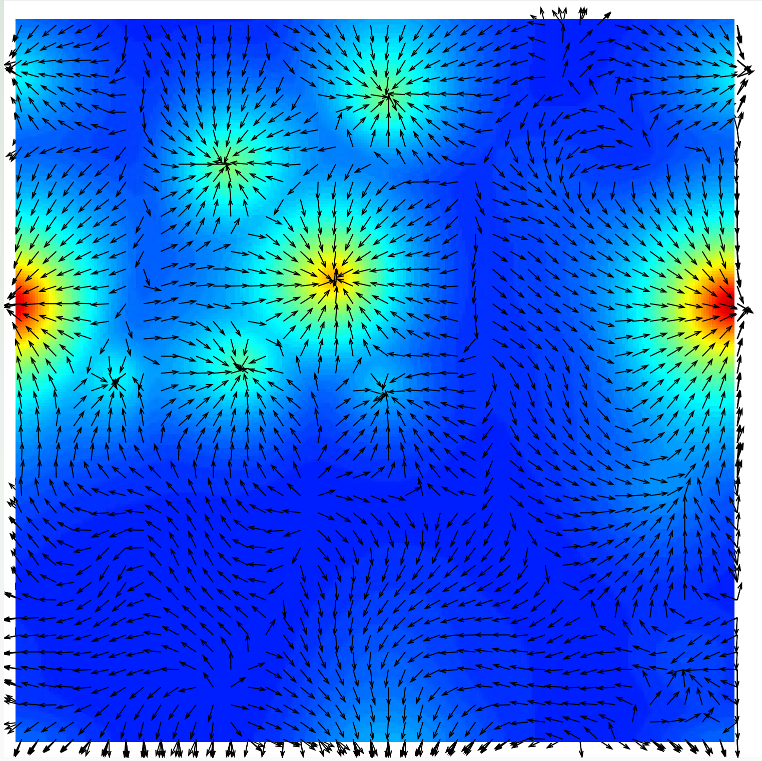


Generalizations

Bundling instability: high MM density



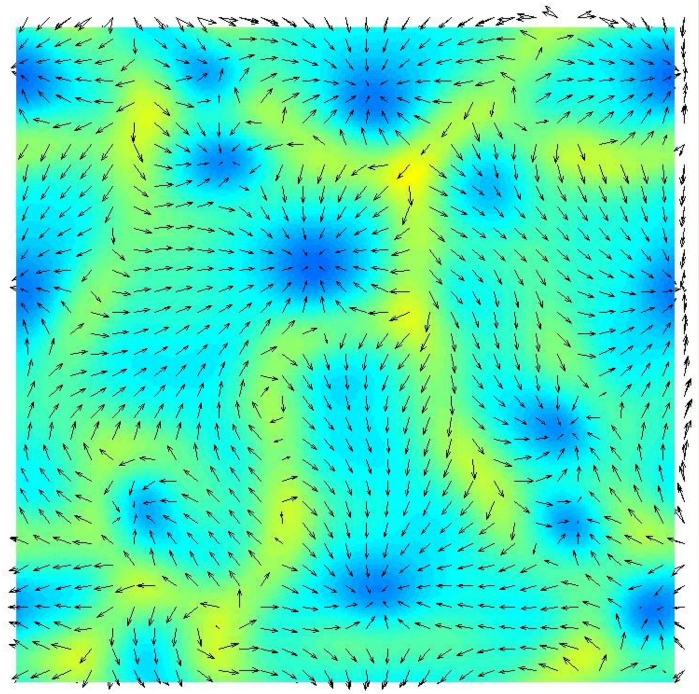
Variable MM dynamics:
Accumulation of MM at asters centers



Motors Attached to Substrate

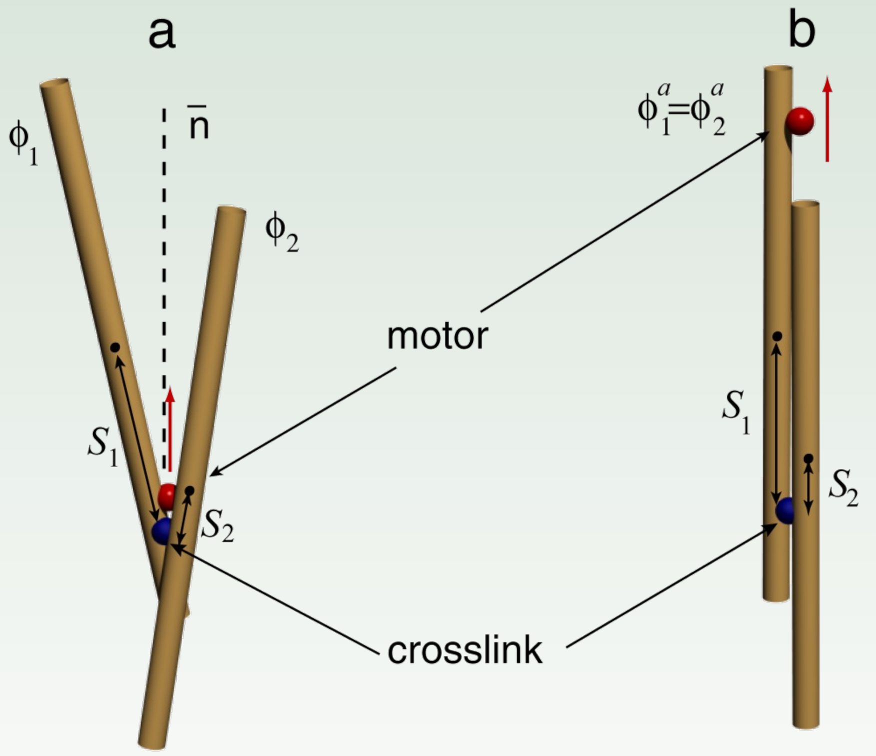
Connection to self-propelled particles, Bertin, Droz, and Gregoire, PRE 2006
Shaller et al, Nature, 2010

·*Rotation of vortices/Drifting domains*
·*Density depressions in center of vortices and asters*



Crosslinks and formation of bundles

·*Crosslinks result in a fast and complete alignment*
·*Suppress relative sliding of filaments*



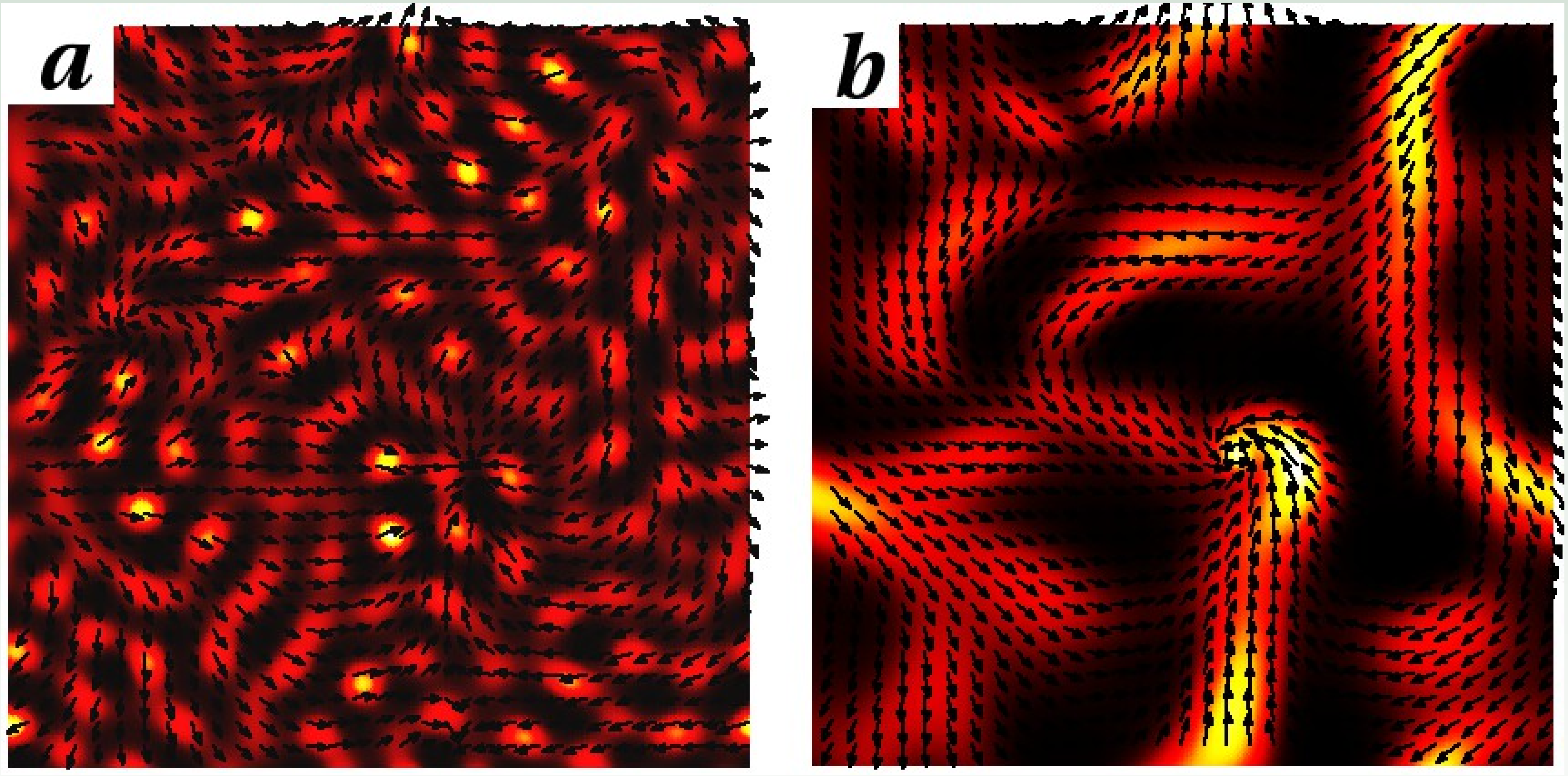
F Ziebert, I.A., L Tsimring, NJP 2008

Modification of density equation due to crosslinks

- *Isotropic instability without crosslinks (η=0)*
- *Enhancement of density instability perp orientation of microtubules with crosslinks – bundles formation*

No crosslinks η=0:
No density/orientation correlation

With crosslinks η=1:
Polar bundles



Comparison with experiment

Model with crooslinks

Microtubules with
2 motor types
Surrey et al, Science 2001

Actin- myosin mixture
(Smith et al, Biophys J, 2007
Kas group)