WORKSHOP ON DRIVEN STATES IN SOFT AND BIOLOGICAL MATTER
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Ordered States & Instabilities in Active Polymer Solutions

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The cell cytoskeleton: a novel form of active soft matter.

In vitro filament/motor mixtures as model systems for studying self-organization and rheology

Theoretical modeling of polar filaments, crosslinkers & motor proteins: from single filaments to hydrodynamics

Classification of homogeneous bulk phases

Instabilities and inhomogeneous structures

Rheology → T. Liverpool on Wed., 4/26
**Cell cytoskeleton as active soft material**

Dynamical network of long polar filaments (F-actin, MT, intermediate filaments) and a variety of smaller proteins that can crosslink or cap the filaments.

**Passive crosslinkers**, e.g., α-actinin

**Active crosslinkers** (myosins, kinesins, dyneins) use chemical energy (ATP) to exchange forces among filaments and remodel the network → active behavior

*Svitkina et al. JCB 1997.*

Fish epidermal keratocyte cytoskeleton by fluorescence and electron microscopy.
*In vivo:*

The actin cytoskeleton in a mouse melanoma drives cell migration.

V. Small, IMBA, Vienna.
In vitro: activity drives organization

Cell extracts of stabilized microtubules & motors show self-organization on mesoscopic scales.

Surrey et al., Science 2001: MT & multimeric motors

F. Nedelec, Heidelberg
MT & kinesin
Motor-induced filament sliding


Two labeled actin filament in a dilute solution are made to slide relative to each other by a crosslinking myosin II minifilament (bright spot).
Model systems can be used to address many questions

- How and on which time scale does the structure of the active network change?
- How is the structure related to the mechanical properties?
- How is the structure related to biological function?
- Which behaviors are specific and which generic?
Theoretical modeling of active polymer solutions

Use methods from soft condensed matter and polymer physics to describe the large scale behavior of active matter.

- Numerical simulations (Nedelec et al. 1997; Surrey et al., 2001)
- Hydrodynamic equations, generally written on the basis of symmetry (Lee & Kardar, 2001; Bassetti et al. 2000; Sankararaman et al., 2003; Hatwalne et al., 2004, Kruse et al. 2005; Voituriez et al., 2006; ...)
Our work: bridging between microscopic and hydrodynamics by deriving hydrodynamics from kinetic model → estimate of parameters

How do active and passive crosslinkers change the behavior of polymer solutions?

- Ordered phases & “phase diagram”
- Instabilities and spatial structures
- Mechanical properties and rheology → 4/26

T.B. Liverpool & MCM, PRL 90, 138102 (2003); 93, 159802 (2004).
A. Ahmadi, T.B. Liverpool & MCM, PRE 72, 60901R (2005).
Isotropic - nematic transition

A liquid of long, thin (L>>b) hard rods order in a nematic phase at high density $\rho$ (Onsager 1949)

\[ \rho_N \sim \frac{1}{V_{ex}} \sim \frac{1}{L^2 b} \]

isotropic: orientational symmetry

nematic: broken orientational symmetry

Competition of translational & rotational entropy
Active Polar Rods: model

Rigid polar rods in a quiescent solvent coupled by stationary and mobile crosslinkers

- fixed length $L \gg b$
- excluded volume

$\alpha$-th rod:

$\vec{r}_\alpha$

$\hat{v}_\alpha$

$\vec{r}$

CM

$L$

$b$

stationary crosslinker

motor cluster

- Lee & Kardar 2001
- Kruse & Julicher, 2000 & 2003
- Kruse et al. 2004
- Sankararaman et al. 2004
- ...
Mobile crosslinkers: motor proteins

- kinesins and dyneins on MT
- myosin clusters or minifilaments on F-actin

Active crosslinks that use Adenosine TriPhosphate (ATP) to turn chemical energy into mechanical work and can induce relative sliding of the filaments.

Activity influenced by
- ATP concentration
- processivity

Cartoon from http://www.dentistry.leeds.ac.uk/biochem/
Stationary crosslinkers (e.g., α-actinin)

Can act as torsional springs that induce relative torques at a rate $\gamma \sim \kappa / \zeta$ → “zipping” of filaments

Binding rate may depend weakly on ATP concentration.

- **Polar clusters**: $\gamma_p$ (α-actinin)
- **Non-polar clusters**: $\gamma_{NP}$ (“disordered” myosin clusters)
Smoluchowski equation

Concentration of filaments at $\vec{r}$ along $\hat{v}$: $c(\vec{r}, \hat{v}, t)$

$$\partial_t c + \nabla \cdot J + \mathbf{R} \cdot J^{\text{rot}} = 0$$

$\mathbf{R} = \hat{v} \times \partial_{\hat{v}}$

Translational & rotational currents: competition of diffusion (excl. volume, entanglement), crosslinking & and local driving by motors:

$$\mathbf{J} = \mathbf{J}^{\text{diff}} + \mathbf{J}^{\text{ex}} + \mathbf{J}^{\text{act}}$$

$$\mathbf{J}^{\text{diff}} = \left[ D_{\parallel} \hat{v} \hat{v} + D_{\perp} (1 - \hat{v} \hat{v}) \right] \cdot \nabla c$$

rods: $D_{\perp} < D_{\parallel}$

anisotropic diffusion

$$\mathbf{J}^{R,\text{diff}} = -D_r \mathbf{R} c$$
Active currents

\[
\mathbf{J}^{\text{act}} (\mathbf{r}_1, \mathbf{v}_1) = \int_{\mathcal{S}} \int_{\Omega_{\text{int}}} m(\mathbf{r}_1^{\text{att}}) \mathbf{v}_1(\xi, \mathbf{v}_1, \mathbf{v}_2) c(\mathbf{r}_1, \mathbf{v}_1, t) c(\mathbf{r}_1 + \xi, \mathbf{v}_2, t)
\]

\[
\mathbf{J}^{\text{act}}_{\text{rot}} (\mathbf{r}_1, \mathbf{v}_1) = \int_{\mathcal{S}} \int_{\Omega_{\text{int}}} m(\mathbf{r}_1^{\text{att}}) \mathbf{\omega}_1(\xi, \mathbf{v}_1, \mathbf{v}_2) c(\mathbf{r}_1, \mathbf{v}_1, t) c(\mathbf{r}_1 + \xi, \mathbf{v}_2, t)
\]

motor density \( m \) at attachment point

\[ \mathbf{r}_1^{\text{att}} = \mathbf{r}_1 + \mathbf{v}_1 s_1 \]

below \( m = \text{constant} \)

\[ \xi = \mathbf{r}_2 - \mathbf{r}_1 \approx \mathbf{v}_1 s_1 - \mathbf{v}_2 s_2 \]
Kinematics of filament pair

- overdamped dynamics $\rightarrow$ net force/torque on filaments balanced by fluid friction
- third law: no net force/torque by motor on filament pair

$v_1, v_2$ cm velocities

$\omega_1, \omega_2$ angular velocities

\[
\begin{cases}
\zeta_r \omega_1 = \vec{N} \\
\zeta_r \omega_2 = -\vec{N}
\end{cases}
\quad \rightarrow \quad \omega_1 = -\omega_2
\]

\[
\begin{cases}
\zeta_{ij}(\hat{v}_1)v_{ij} = F_i \\
\zeta_{ij}(\hat{v}_2)v_{2j} = -F_i
\end{cases}
\quad \rightarrow \quad \vec{v}_1 \neq -\vec{v}_2
\]

Anisotropy of rod diffusion allows for a net velocity of the pair
Motor cluster dynamics

Each cluster is modeled as a rigid object made up of two heads attached at \( \mathbf{r}^m_{\alpha} = \mathbf{r}_\alpha + \mathbf{v}_\alpha s_\alpha \). Each head:

- steps at a inhomogeneous rate \( u(s) \) along the fil.
- rotates at rate \( \sim \kappa \) about the motor axis, \( \perp \) plane of the filaments: \( \zeta \dot{\theta} = \kappa \sin \theta \approx \kappa \theta \)

\[
\ddot{\mathbf{V}}_\alpha = \frac{d\mathbf{r}^m_{\alpha}}{dt} = \mathbf{v}_\alpha + \dot{\mathbf{v}}_\alpha u(s_\alpha) + s_\alpha \dot{\omega}_\alpha \times \mathbf{v}_\alpha
\]

\[
\dot{\omega}_\alpha = \omega_\alpha + (-1)^\alpha \dot{\theta}(\mathbf{v}_1 \times \mathbf{v}_2)
\]

Motors in cluster rigidly connected:

\[
\mathbf{V}_1^m = \mathbf{V}_2^m \quad \mathbf{\omega}_1^m = \mathbf{\omega}_2^m
\]
⇒ Active velocities

\[ \vec{v}_1 - \vec{v}_2 = \beta(\hat{v}_2 - \hat{v}_1) + \alpha \xi \]
\[ \vec{v}_1 + \vec{v}_2 = \frac{\xi_\perp - \xi_\parallel}{\xi_\perp + \xi_\parallel} \left[ -\beta(\hat{v}_2 + \hat{v}_1) + \alpha(\hat{v}_1 s_1 + \hat{v}_2 s_2) \right] \]
\[ \vec{\omega}_1 - \vec{\omega}_2 = \left[ \gamma_\text{P} + \gamma_\text{NP} (\hat{v}_1 \cdot \hat{v}_2) \right] (\hat{v}_1 \times \hat{v}_2) \]

CM separation:
\[ \xi = \vec{r}_2 - \vec{r}_1 \]
\[ \approx \hat{v}_1 s_1 - \hat{v}_2 s_2 \]

sorting of opposite-polarity filaments

bundling of same-polarity filaments

rotation

\[ \beta = \langle u \rangle_L \]
\[ \alpha = L \left\langle \frac{du}{ds} \right\rangle_L \]
\[ \gamma = \kappa / \xi \]
From Smoluchowski to Hydrodynamics

Hydrodynamics: description of phases and dynamics of systems of many interacting degrees of freedom in terms of a few coarse-grained fields:

- Conserved densities
- Broken symmetry variables in states with spatial order

Two routes:

**Phenomenology:**
Write free energy or hydrodynamics on the basis of symmetry \(\Rightarrow\) unknown parameters

**Microscopic approach:**
Derive hydrodynamics by coarse-graining microscopic dynamics
Order parameters & broken symmetry variables

Polarized state

Polarization:
\[ \tilde{P} = \left\langle \sum_\alpha \hat{v}_\alpha \delta(\vec{r} - \vec{r}_\alpha) \right\rangle \]
\[ \tilde{P} = \rho \, P_0 \hat{P} \]

\[ P_0 \neq 0 \rightarrow S \neq 0 \]
\[ \mathbf{p} \neq -\mathbf{p} \]

Nematic state

Alignment tensor:
\[ Q_{ij} = \left\langle \sum_\alpha (\hat{v}_{\alpha i} \hat{v}_{\alpha j} - \tfrac{1}{d} \delta_{ij}) \delta(\vec{r} - \vec{r}_\alpha) \right\rangle \]
\[ Q_{ij} = \rho \, S \left( n_i n_j - \tfrac{1}{d} \delta_{ij} \right) \]

S \neq 0 \quad P_0 = 0

\[ \mathbf{n} \leftrightarrow -\mathbf{n} \]

Hydrodynamic fields:

- Filament density \( \rho \)
- Director \( \mathbf{p} \)

- Filament density \( \rho \)
- Director \( \mathbf{n} \)
Coarse-graining the Smoluchowski eqn.

Dynamics on length scales \( \gg L \rightarrow \) gradient expansion:

\[
c(\vec{r}_1 + \vec{\xi}, \vec{v}_2) = c(\vec{r}_1, \vec{v}_2) + \xi_i \partial_i c + \frac{1}{2} \xi_i \xi_j \partial_i \partial_j c + \ldots \quad \vec{\xi} = \vec{r}_2 - \vec{r}_1
\]

Moment expansion of concentration + truncation:

\[
\begin{align*}
\rho(\vec{r},t) &= \int c(\vec{v},\vec{r},t) \quad \text{density - conserved density} \\
\bar{P}(\vec{r},t) &= \int \vec{v} c(\vec{v},\vec{r},t) \quad \text{polarization} \\
Q_{ij}(\vec{r},t) &= \int (\vec{v}_i \vec{v}_j - \frac{1}{d} \delta_{ij}) c(\vec{v},\vec{r},t) \quad \text{alignment tensor}
\end{align*}
\]

\{ \text{possible broken symmetries} \}
Homogeneous states

\[ \partial_t \rho = 0 \]

\[ \partial_t P_i = -[D_r - \gamma_P m \rho]P_i + [D_r \frac{1}{\rho_N} - \gamma m]Q_{ij} P_j \]

\[ \partial_t Q_{ij} = -[D_r (1 - \frac{\rho}{\rho_N}) - \gamma_{NP} m \rho]Q_{ij} + 2\gamma_P m (P_i P_j - \frac{1}{2} \delta_{ij} P^2) \]

\( m=0: \) Isotropic \( \rightarrow \) Nematic at \( \rho > \rho_N = 3\pi/2L^2 \)

\( \gamma_P, \gamma_{NP} \sim \frac{\kappa}{\zeta} \) rates of rotation from Polar & NonPolar crosslinks

Competition of diffusion, excluded volume & “zipping”
"Phase Diagrams" of bulk states

$g < 1/4$

\[
\begin{align*}
\rho & = \gamma_P / \gamma_{NP} \\
\tilde{m} & = \frac{\rho_N m y_{NP}}{D_r}
\end{align*}
\]

\[
\rho_{IN} (\tilde{m}) = \frac{\rho_N}{1 + \tilde{m}/4}
\]

\[
\rho_{NP} (\tilde{m}) = \frac{\rho_N}{\tilde{m}}
\]

critical density $\tilde{m}_x = \frac{1}{g - 1/4}$

using $D_r \sim \gamma_P$

\[
\begin{align*}
L & \sim 10 \mu M \\
\tilde{m}_x & \sim 1 \rightarrow m_x \sim 0.5 \mu M
\end{align*}
\]

$0.5 \mu M$

$10 \mu M$

$10 nm$
Numerical simulation of 2d rigid filaments interacting with motors grafted to a substrate

Hydrodynamics of polarized phase

\[ \begin{align*}
\mathbf{u}(s) & \rightarrow \text{stepsize } \times R_{\text{ATP}} \\
\mu & \sim m \times R_{\text{ATP}} \\
(\partial_t - \beta \mu \hat{p} \cdot \nabla) \delta \rho &= \beta' \mu \nabla \cdot \hat{p} + (D - \alpha \mu \rho) \nabla^2 \delta \rho \\
(\partial_t + \tilde{\beta} \mu \hat{p} \cdot \nabla) \hat{p} &= \tilde{\beta}' \mu \nabla \delta \rho + (K + \gamma_p \mu \rho - \alpha \mu \rho) \nabla^2 \hat{p} + (K' - \alpha' \mu) \nabla \left( \nabla \cdot \hat{p} \right)
\end{align*} \]

Filament advection along \( \hat{p} \)

Simha & Ramaswamy, PRL 2002

Coupling between splay and density fluctuations allowed in a polar fluid

Kruse et al., 2004; Voituriez et al. 2006; Kung et al. 2006

\[ \begin{align*}
\bar{P} &= \rho p_0 \hat{p} \\
p_0 &= \text{const.}, \quad |\hat{p}| = 1 \\
\rho &= \rho_0 + \delta \rho
\end{align*} \]

Filament bundling \( \alpha \) renormalizes diffusion, bend and splay \( \Rightarrow \) instability
Inhomogeneous Structures

Hydrodynamic modes:
\[
\delta \rho_{\tilde{k}}(t) = \sum_{v} a_{v k}^{\rho} e^{-\lambda_{v}(k) t}
\]
\[
\delta p_{\tilde{k}}(t) = \sum_{v} a_{v k}^{p} e^{-\lambda_{v}(k) t}
\]

Re\[\lambda_{v}(k)\] < 0
→ unstable growth of fluctuations for
\[
\rho > \rho_{B} \sim \frac{D}{\alpha \rho \mu}
\]
Active mechanisms & parameters

Activity $\mu \sim$ motor density $\times$ $R_{ATP}$: driving force that maintains the system out of equilibrium

Rotations $\rightarrow$ Polar and NP “zipping” rates $\gamma_p, \gamma_{NP} \sim \kappa / \zeta$: control homogeneous states and build up polarization & nematic order (may be independent of $R_{ATP}$)

Uniform stepping of motors $\rightarrow$ polarization sorting rate $\beta$ $\sim$ mean motor speed $\langle u(s) \rangle_L$: yields filament drift & vortices

Inhomogeneities in motor speed $\rightarrow$ bundling rate $\alpha$: softens all elastic constants and is the main pattern-forming mechanism
Numerical estimates

\[ \gamma \sim \frac{\kappa}{\zeta} = \frac{\kappa D_r}{k_B T} \]

\[ \kappa_{\text{kinesin}} \sim 10^{-22} \text{nm/rad} \]

\[ \beta \sim u_0 \sim \frac{\text{nm}}{\text{msec}} \]

\[ \alpha = L \left< \frac{du}{ds} \right>_L \sim u_0 \frac{b}{L} \]

\[ m \rho \alpha / L \sim D / L^2 \]

Competition of:
- diffusion
- driving by motors

<table>
<thead>
<tr>
<th>( D_r \sim 10^{-2} / s )</th>
<th>( \gamma \sim 10^{-1} / s )</th>
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<tbody>
<tr>
<td>( D / L^2 \sim 10^{-2} / s )</td>
<td>( \alpha / L \sim 10^{-4} / s )</td>
</tr>
<tr>
<td>( \beta \sim 10^{-6} \text{m/s} )</td>
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\[ m_{\text{kinesin}} = 1.2 \mu M \]
\[ \rho_{\text{tubulin}} = 26 \mu M \]
\[ L = 10 \mu m \]
\[ b = 10 \text{nm} \]
\[ \text{sample thickness} = 1 \mu m \]

\[ \rightarrow m \rho \alpha / L \sim 10^{-2} f \]
Conclusions

- Active filament solutions are significantly different from passive ones
- Non-equilibrium analogues of bulk phase transitions driven by crosslink-induced rotations
- Inhomogeneous states with mesoscopic structures driven by motor activity. Type of defect structures depend on homogeneous states.
- Bundling - the main pattern-forming mechanism - is due to spatial inhomogeneities in the motor velocity
- Next: include flow of solvent.