Multi-scale Modeling of Biomimetic Systems: Designing Synthetic Leukocytes and Artificial Cilia

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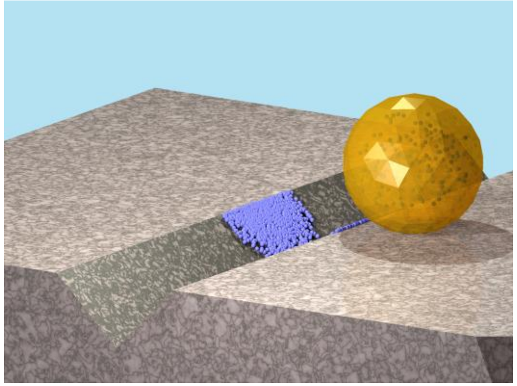
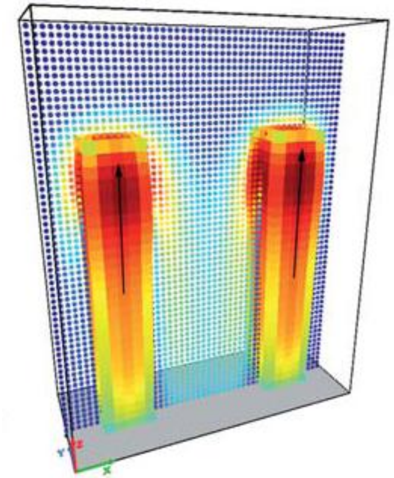
Olga Kuksenok, German Kolmakov





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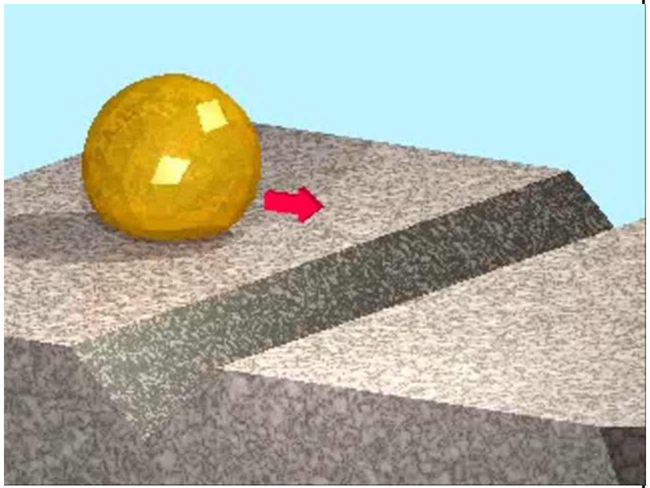
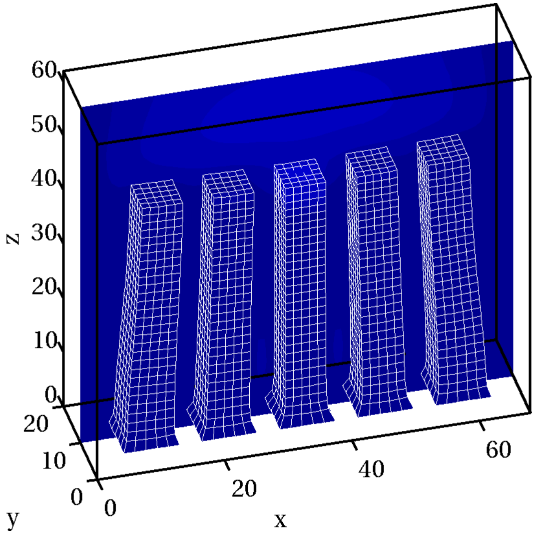
Design Challenges



- **Integrate interactions among all species**
  - Micron and millimeter-sized soft elements
  - Nanoparticles
  - Fluids
- **Capture dynamic behavior of all species**
  - Motion of microscopic compliant objects
  - Diffusion of sub-micron species
  - Fluid flow
- **Provide useful guidelines for experiments**
  - Determining ideal materials to observe predicted behavior



Example 1: Design "Leukocytes" to Heal Synthetic Systems

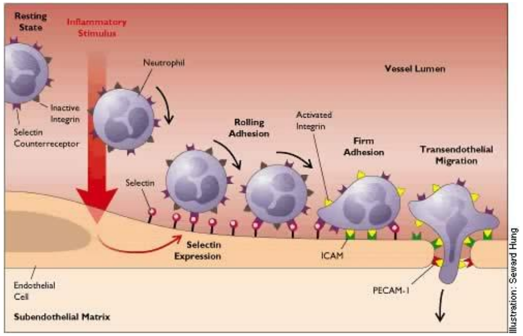
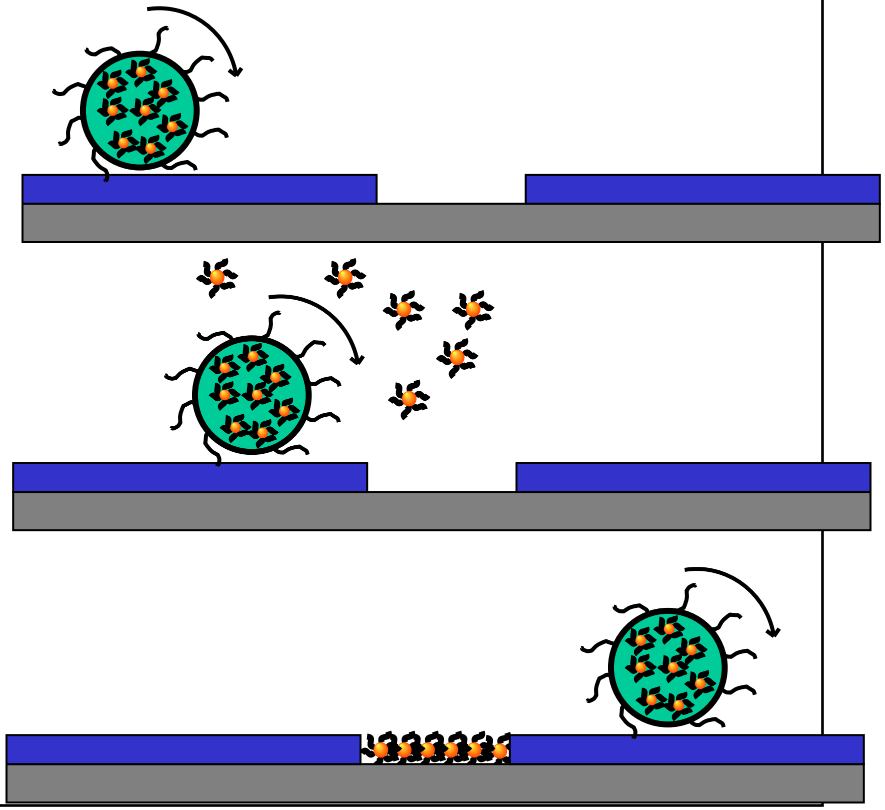


Illustration: Seward Hung

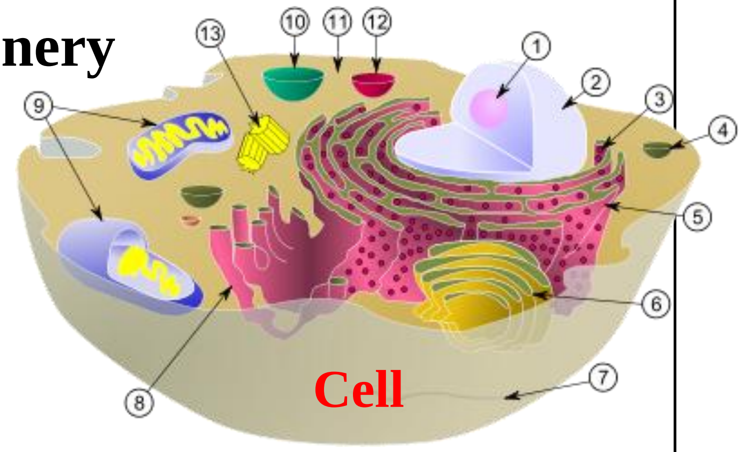
- ❑ **Create synthetic cells with similar features**
  - ☞ Can sense & respond to damage
  - ☞ Extend lifetime & sustainability of system
- ❑ **"Cell": nanoparticle-filled microcapsule**

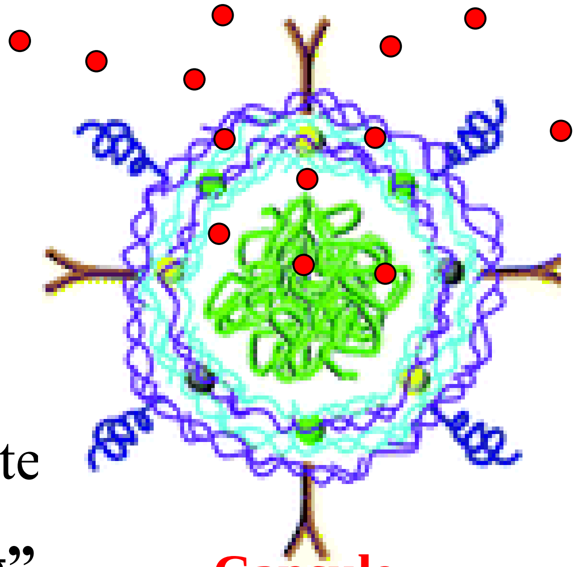


- ❑ **Drive capsules to move along damaged surface**
  - ☞ Contains nano- or micro-crack
- ❑ **Localize at crack**
- ❑ **Trigger release of particles**
- ❑ **Move on to next crack**
  - ☞ Create "repair and go"

Design Synthetic “Cells” with Biomimetic Functionality

- **Cells utilize complex biochemical machinery**
  - Multiple, interacting components
- **Goal: achieve biomimetic functionality using purely synthetic components**
- **Focus on microcapsules**
  - Same size as cells
- **Can encapsulate various species**
  - Species diffuse out of porous capsule
    - Set up communication with exterior
- **Can functionalize outer surface of capsule**
  - Capsules can “sense” properties of substrate
- **Function of interest: response to “wounding”**

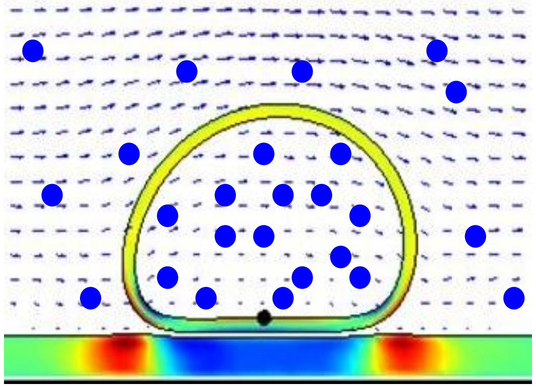




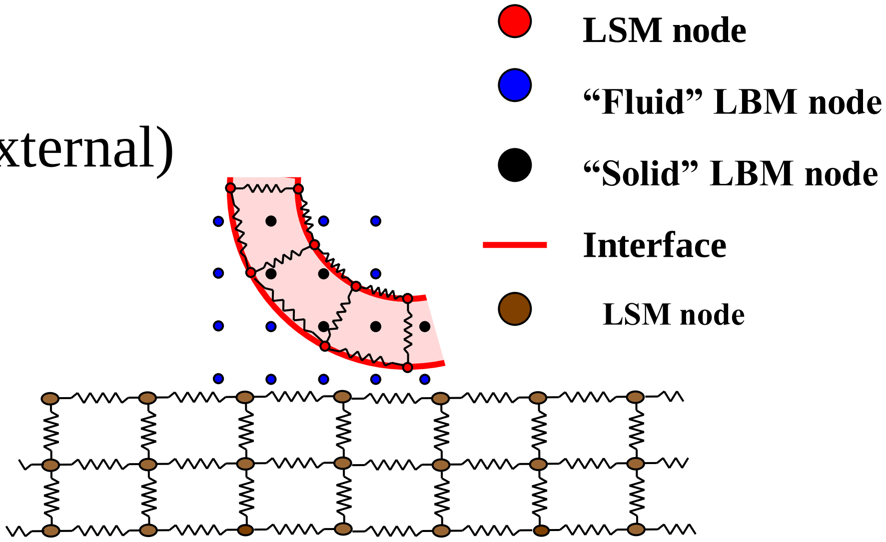
Capsule

Model: Hybrid Computational Approach

- **Microcapsule: fluid-filled elastic shell**
- **Serves as model for**
  - Biological cells (leukocytes)
  - Polymeric microcapsules
- **Encapsulates nanoparticles**

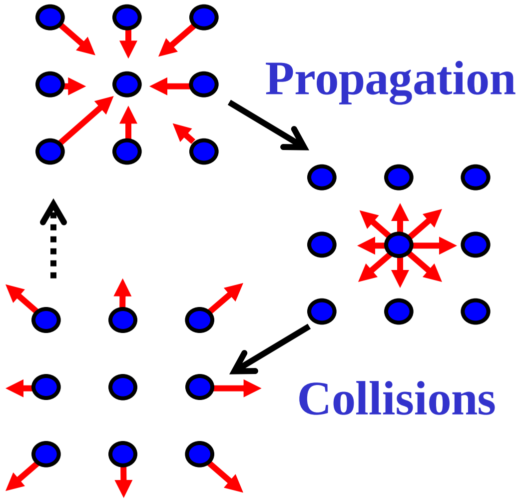


- **Develop hybrid approach for capturing following interactions:**
  - Capsule-substrate
    - Lattice Spring model
  - Shell-fluid (encapsulated & external)
    - Lattice Boltzmann model
  - Particle-fluid & particle-solid
    - Tracer particles
    - Brownian dynamics

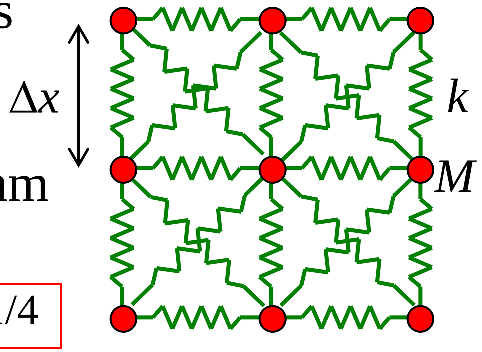


Model for Elastic Shell in Fluid

- **Lattice Boltzmann model (LBM) – solver for Navier-Stokes equations**
  - Fluid particles move along lattice
  - Collisions allow particles to reach equilibrium
  - Hydrodynamic fields obtained from velocity moments of the distribution function



- **Lattice spring model (LSM) – solver for continuum elasticity equations**
  - Network of harmonic springs connecting mass points
  - 3D: 18 springs connecting nodes on a regular lattice
  - Integrate Newton equation of motion: Verlet algorithm



- **Coupling of LB and LSM**
  - At the fluid-solid boundaries

Poisson ratio = 1/4

Young's modulus $E = \frac{5k}{2\Delta x}$

Solid density $\rho_s = \frac{M}{(\Delta x)^3}$

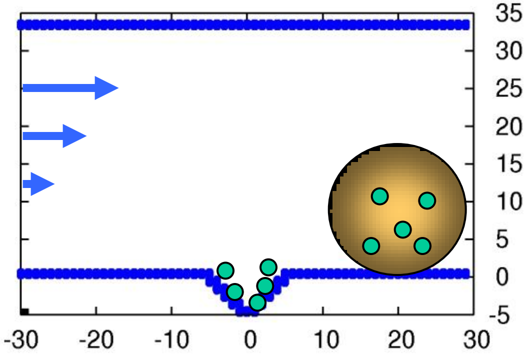
A. Alexeev *et al.*, *Macro.* **38**, 10244 (2005)

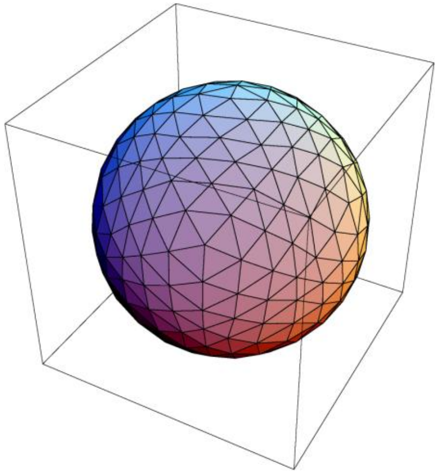
Repair-and-Go System

- **Amphiphilic microcapsules**
  - ☞ Hydrophilic exterior
  - ☞ Hydrophobic interior
- **Adhesion between capsule and substrate**
  - ☞ Modeled via Morse potential

$$U(r) = \varepsilon_0 \left(1 - \exp\left(-\frac{r-a}{r^*}\right)\right)^2$$

- **Capsules encase hydrophobic nanoparticles**
  - ☞ Dispersed in oil phase
- **Capsule driven by imposed shear flow**
  - ☞ Move over hydrophilic, cracked surface
- **Interior surface of crack hydrophobic**





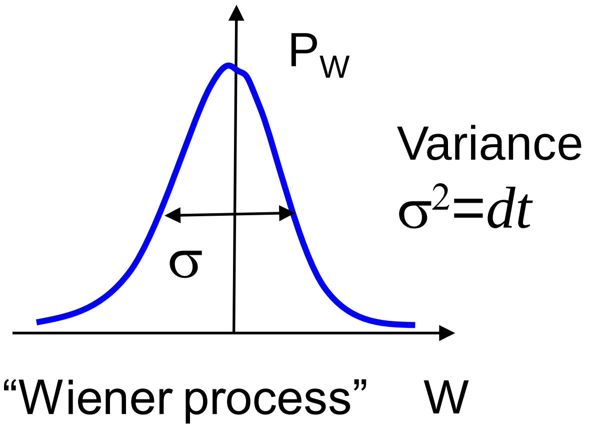
N = 2 layers *x* 122

D=10Δx, Δx ≈ 1.5

r^*=D/10

Crack width = D

Nanoparticle Dynamics



- **Dynamics within capsule**

$$d\mathbf{r} = \mathbf{u}\,dt + \sqrt{2D}\,d\mathbf{W}(t)$$

  - ☞ Equivalent to convection-diffusion for NP density

$$\frac{\partial n}{\partial t} = (\mathbf{u}\nabla)n + D\Delta n$$

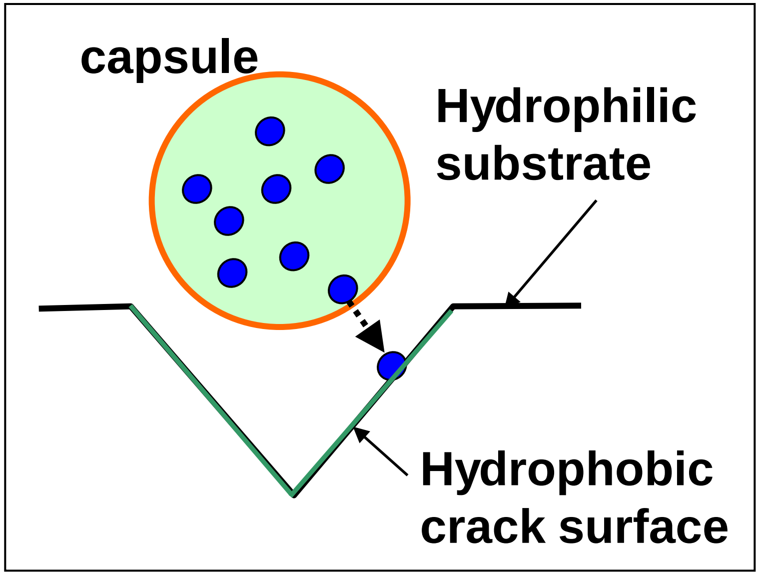
- **"Tunneling" toward crack wall**

$$k = t_{tun}^{-1} e^{-r/r_{tun}}$$

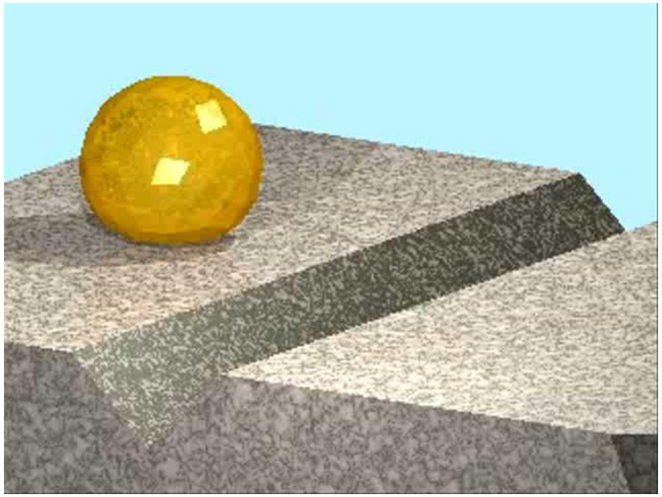
$$w_{tun} = 1 - e^{-k\Delta t}$$

r_{tun}~R*; R* = range of adhesion force

- **If particle tunnels through**
  - ☞ Becomes stuck at crack walls

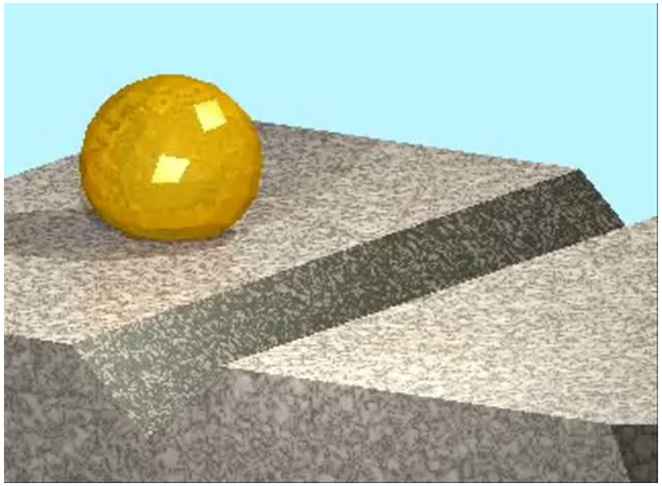


Motion of Capsules

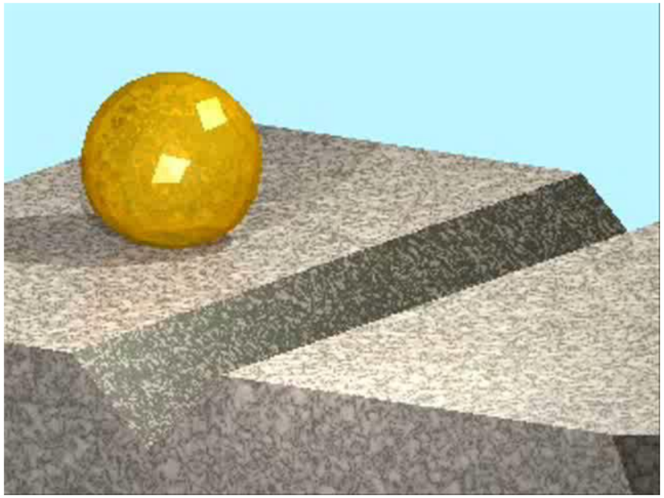


(1)

- ☐ **Effect of imposed shear flow**
- ☐ **Low shear:**
  - ☞ Captured in crack—(1)
- ☐ **Moderate shear:**
  - ☞ Move along substrate—(2)
- ☐ **High shear:**
  - ☞ Fly away due to lift force—(3)



(2)



(3)

Phase Map for Capsule Motion

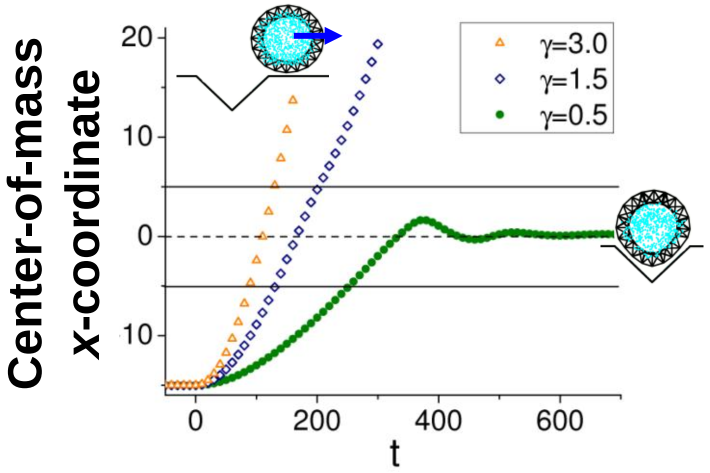
- **Dimensionless capsule-surface adhesion strength**

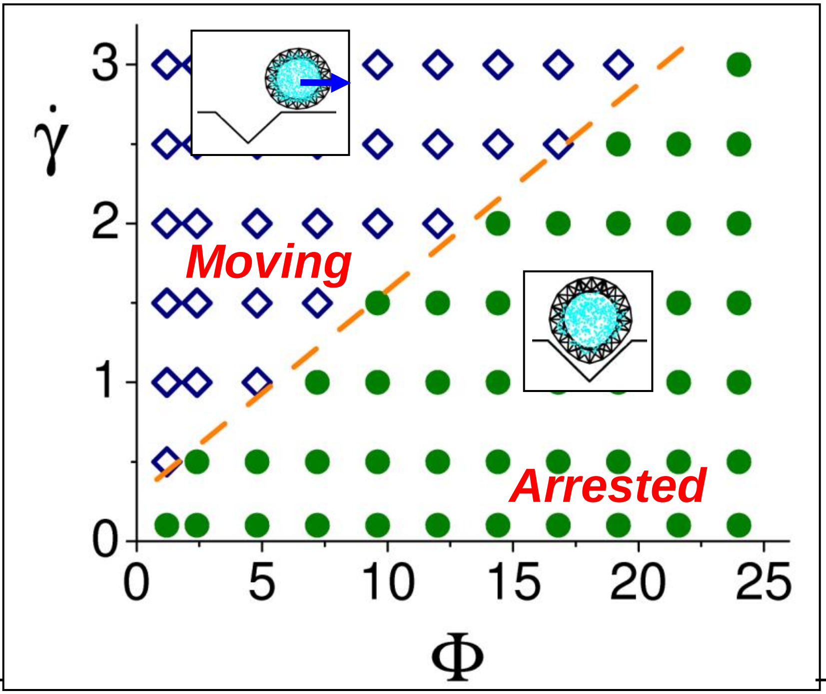
$$\Phi = \frac{attraction \quad strength}{capsule \quad stiffness} = \frac{\varepsilon_0 N}{ERr^{*2}}$$

- ☞ E – Young’s modulus
- ☞ R – capsule radius
- ☞ ε_0 – capsule-surface interaction
- ☞ r^* – interaction cut-off length
- ☞ N – number of gel nodes

G. Kolmakov et al

ACS Nano, 4 (2010) 1115-1123





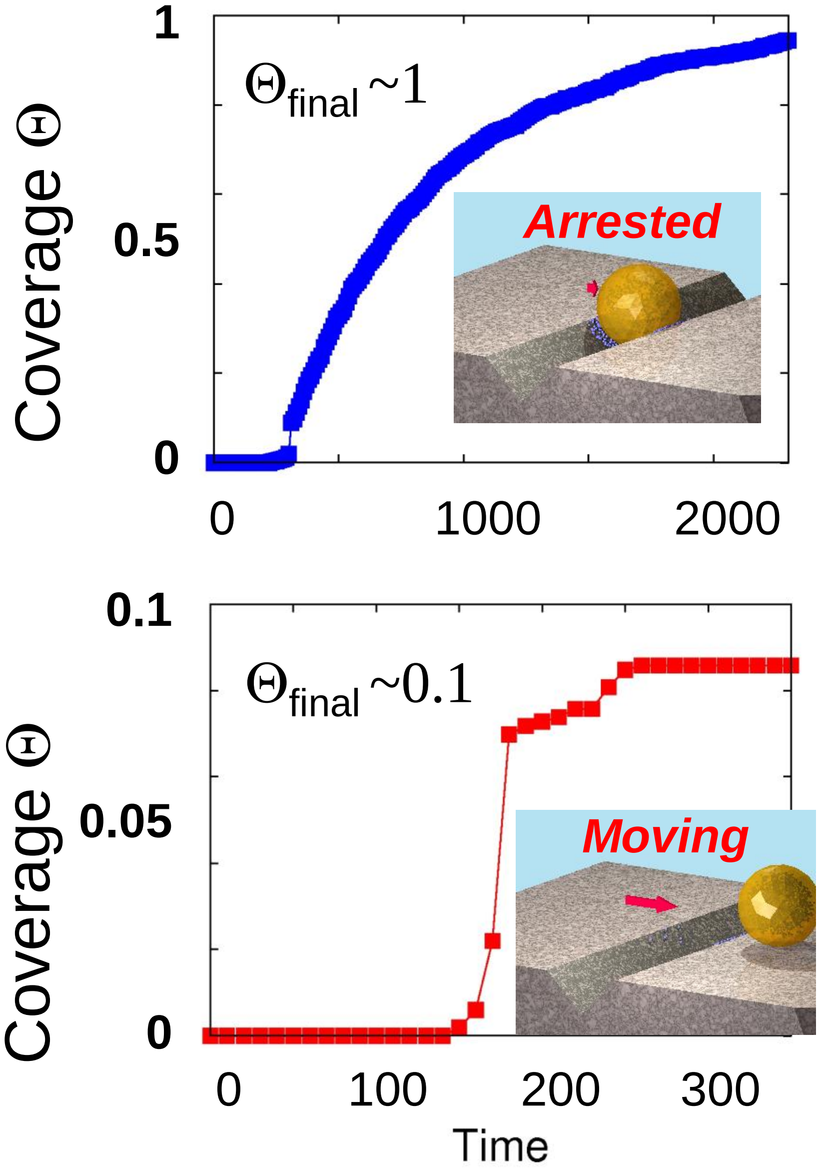
Deposition of Nanoparticles

- **Capsule releases NPs on crack surface**
- **At low shears and strong adhesion:**
  - Arrested capsule
  - Virtually full coverage of crack surface by NPs

$$\Theta_{\text{final}} = N_{NP}/N_{NP}^{(\max)} \sim 1$$

- **At high shear and weak adhesion:**
  - Moving capsule
  - Partial coverage

$$\Theta_{\text{final}} \sim 0.1$$



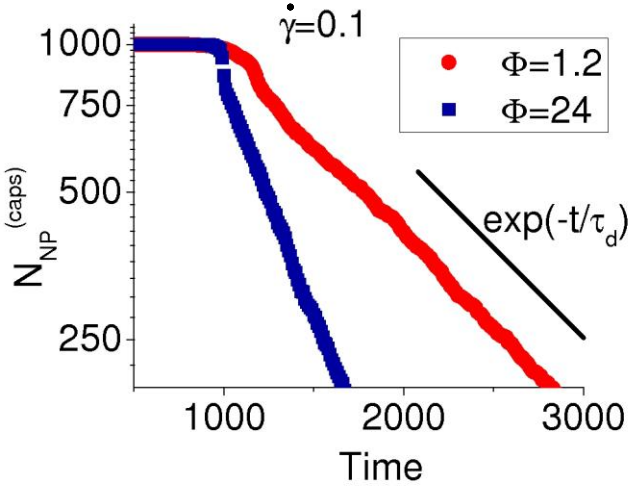
Arrested Capsule

- **Deposition of NPs on crack surface**

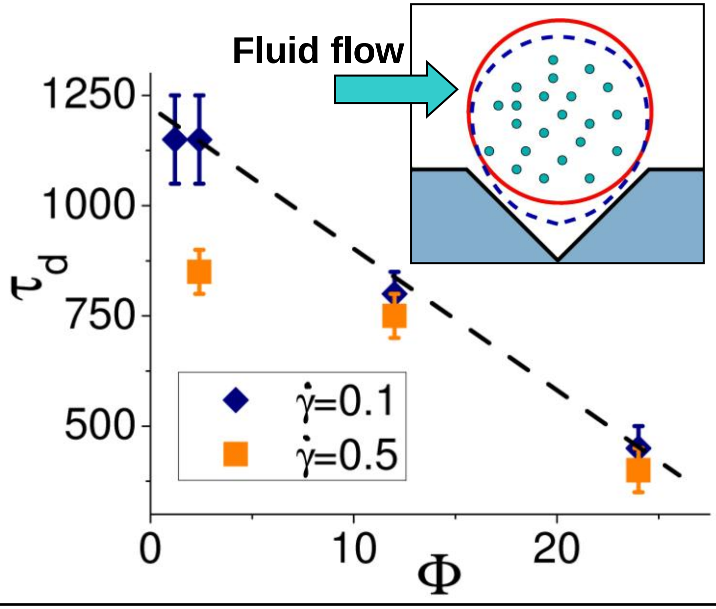
$$N_{NP}^{(caps)}(t) = N_{NP}^{(caps)}(0)\ \exp(-t/\tau_d)$$

  - τ_d – characteristic deposition time
  - Coverage at $t \gg \tau_d$

$$\Theta = 1 - \exp(-t/\tau_d) \rightarrow 1$$

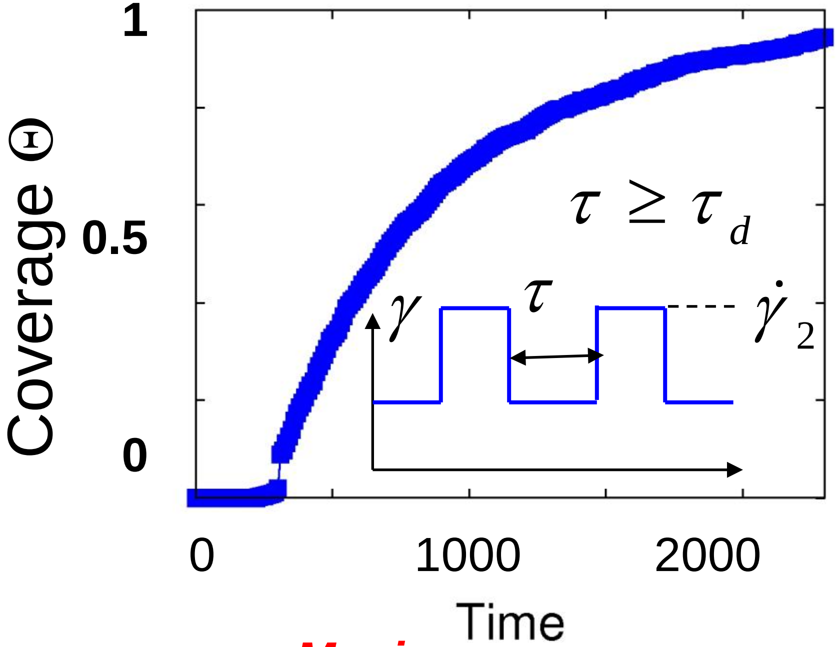


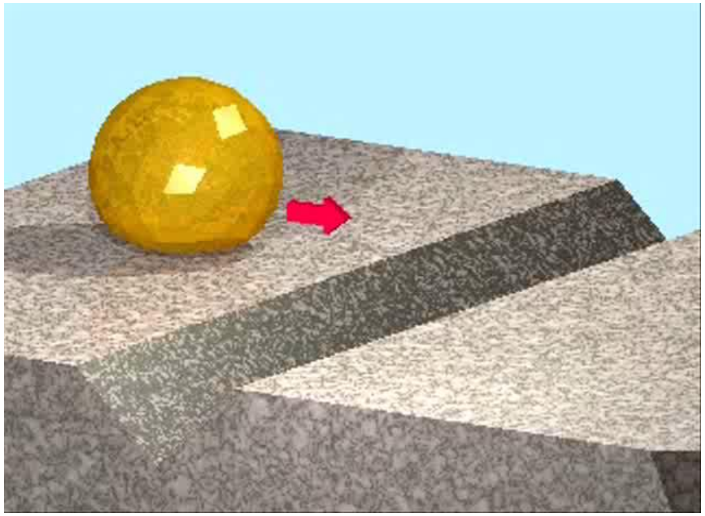
- **Value of τ_d depends on**
  - Adhesion strength
    - Deform capsule by adhesion
  - Shear rate at weak adhesion
    - Deform capsule by fluid flow
- **But want repair and go**
  - Need capsule to leave crack

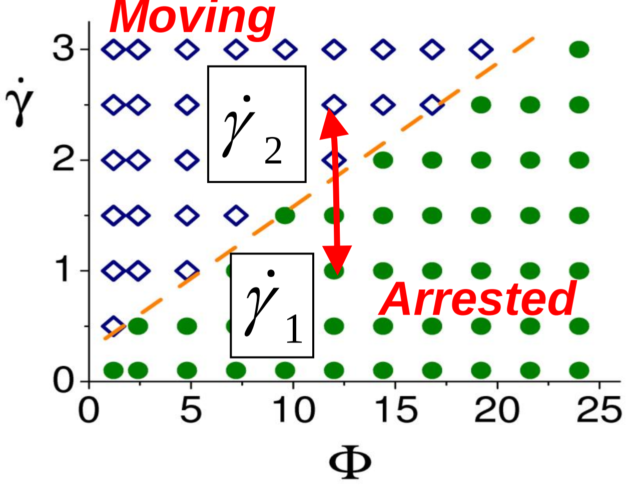


Possible Solution: Capsule in Pulsatile Flow

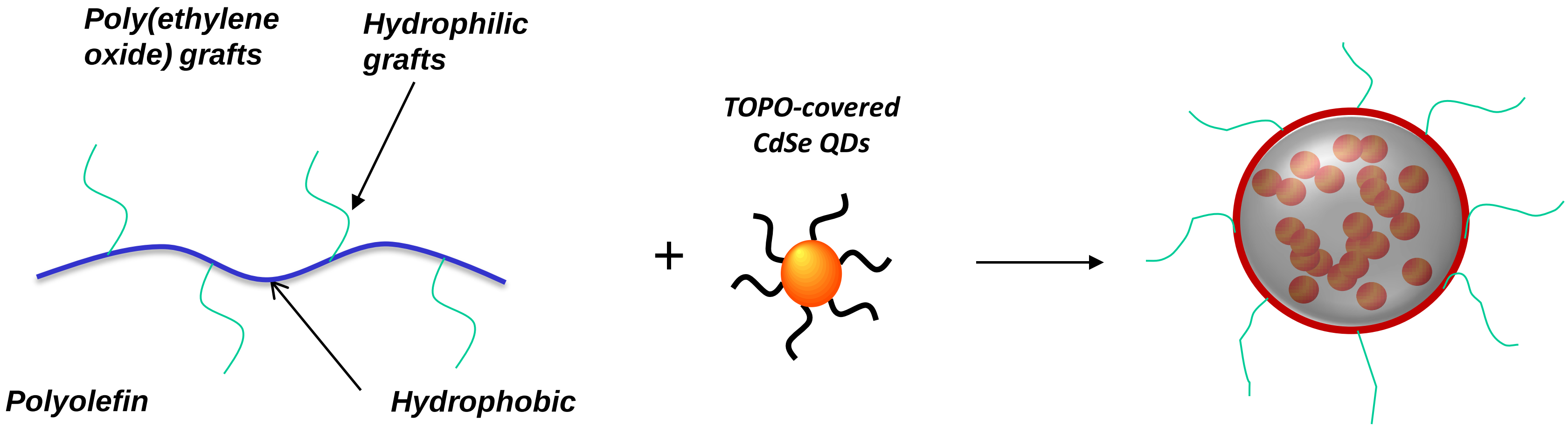
- **Motion of capsule**
  - Arrested at low shear period
    - Releases NPs
  - Leaves crack at high shear period
    - Moves toward next crack
- **Resultant coverage Θ~1**





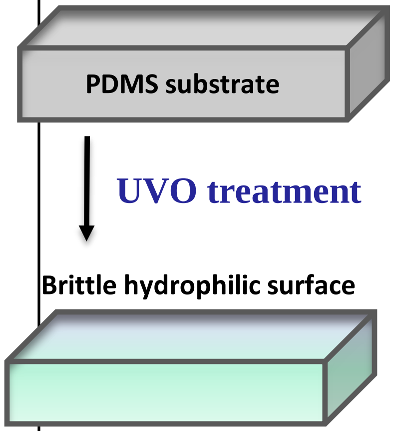


Experiments: A. Crosby, T. Emrick, T. Russell, UMass



- **Microcapsule: formed from amphiphilic comb copolymer**
  - Hydrophilic teeth, hydrophobic backbone
- **Nanoparticles: quantum dots with hydrophobic coating**
- **In oil/water mixtures: form nanoparticle-loaded capsules**
  - Nanoparticles localized in encapsulated oil phase
    - Forms in one step
  - Capsule stable in water—hydrophilic teeth

Crack Repair with Nanoparticle-loaded Capsules

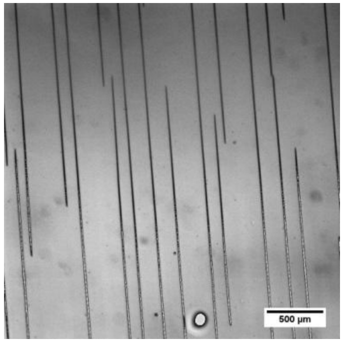


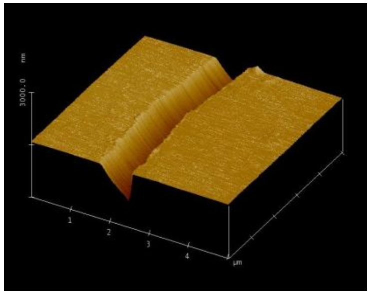
PDMS substrate

UVO treatment

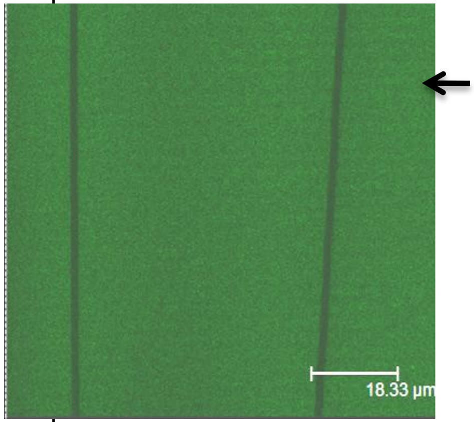
Brittle hydrophilic surface

uniaxial stretching

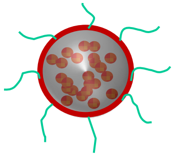




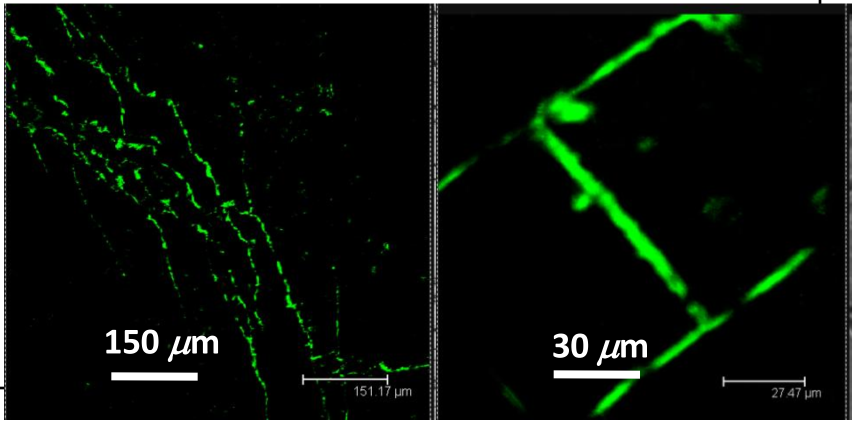
15 mL/min; ~15 psi back pressure,
Pulsed intervals: flow and rest



control experiment with PEGylated q-dots (unencapsulated)



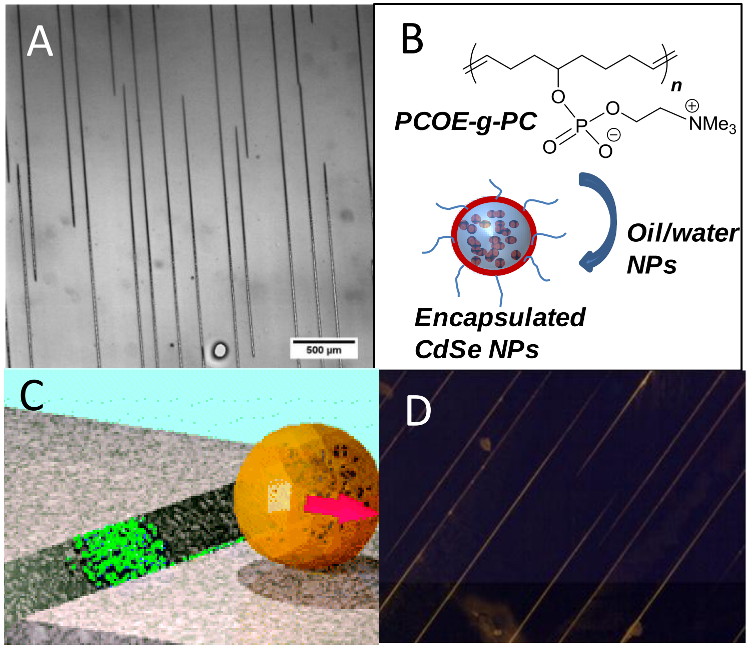
repair-and-go

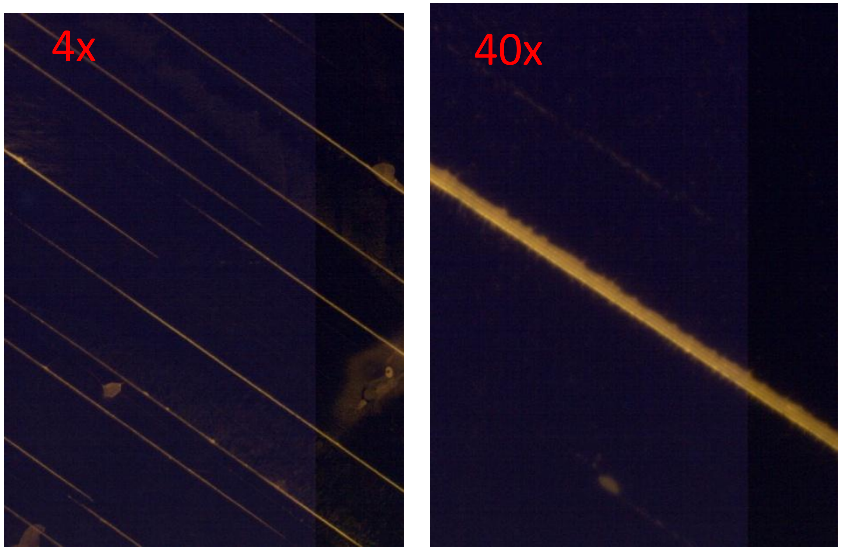


Crosby, Emrick, Russell

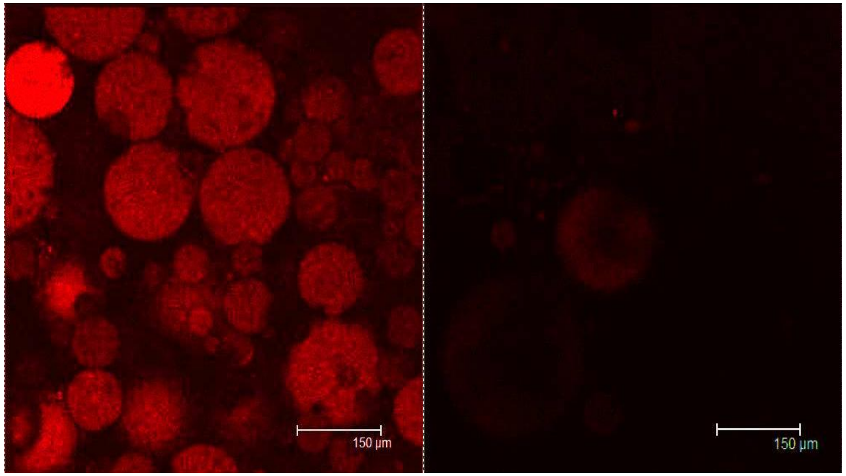
Site-specific Nanoparticle Deposition

Repair-and-go with PC-polyolefin microcapsules





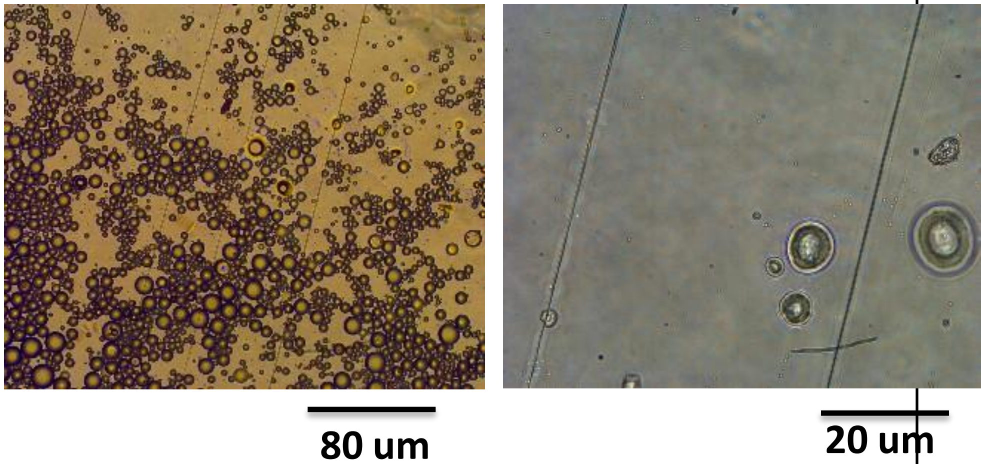
K. Kratz et al. Nature Nanotechnology, **7 (2012) 87-90**



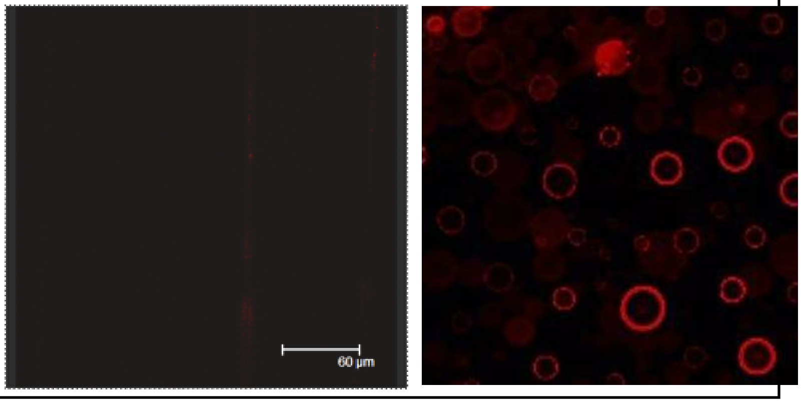
- ❑ **Bottom image**
  - ☞ Left—capsule before exp.
  - ☞ Right—capsule after exp.
    - ☞ Nanoparticles remain in crack

Control Experiments

- **No nanoparticles in capsules**
  - ☞ No localization of capules into cracks
    - ☞ Capsules labeled with rhodamine

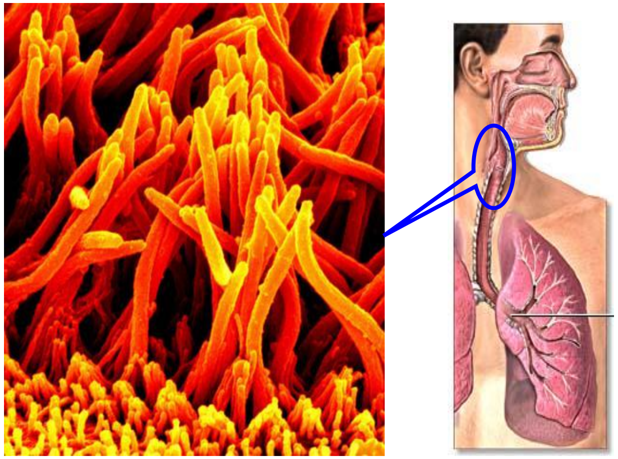


- **No capsules—free particles**
  - ☞ In water and PEG-coating, particles bound everywhere on surface
  - ☞ In toluene and hydrophobic coating, non-selective deposition
- **No difference in surface energies**
  - ☞ Oxidation of surface after cracking
    - ☞ No hydrophobic domains
  - ☞ No surface deposition of particles
    - ☞ Remain in capsules

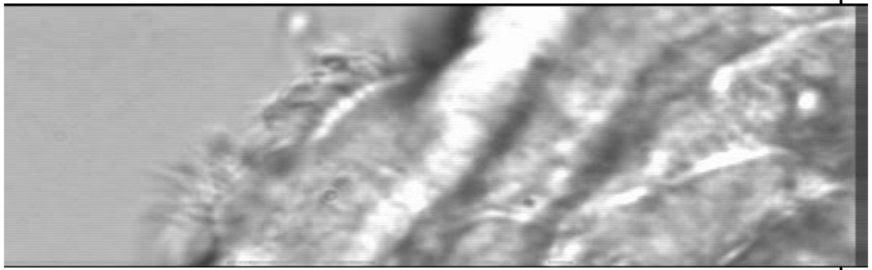


Example 2: Design Artificial Chemo-responsive Cilia

- **Cilia in respiratory system**
  - Exhibit collective motion
    - Metachronal waves
  - Can expel particulates
- **Design artificial cilia**
  - System undergoes collective motion
- **Devise BZ cilia**
  - Control collective behavior using light
    - Regulate transport of particles in microfluidic devices



Shah *et al* *Science* 2009, **325**, 1131

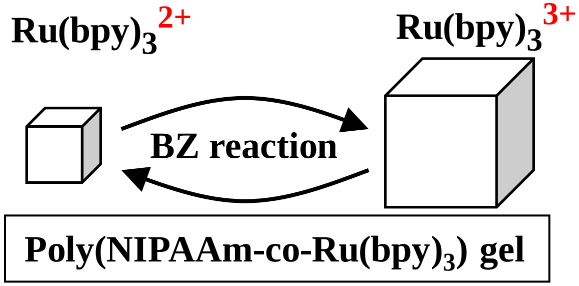


users.umassmed.edu/michael.sanderson/

Enabling Material—BZ Polymer Gels

- ☐ **BZ reaction in solution**
  - ☞ Exhibits rich dynamical behavior

- ☐ **BZ in gel causes periodic, *autonomous* swelling/deswelling**
  - ☞ Catalyst grafted to polymer:

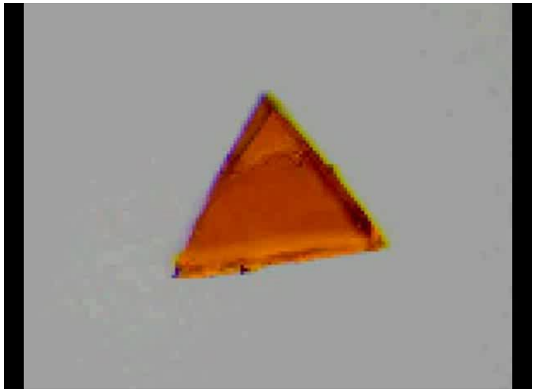


$Ru(bpy)_3^{2+}$ **$Ru(bpy)_3^{3+}$**

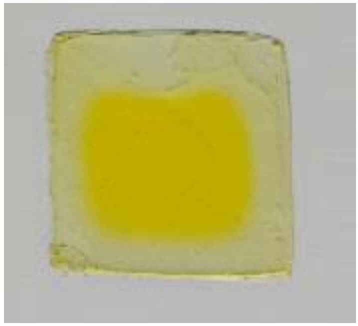
BZ reaction

Poly(NIPAAm-co-$Ru(bpy)_3$) gel

R. Yoshida *et al*, *JACS*, 1996, **118**, 5134.



☞ Small sample (~ 1 *mm*)

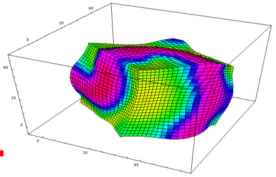


☞ Larger: 3 x 3 *mm*

- ☞ Yellow: swollen polymer
- ☞ Orange: contracted polymer

I. Chen et al,
Soft Matter, 2011, **7**, 3141

Model for Chemo-responsive Gels in 3D



❑ Evolution equations:

*V.V.Yashin et al, JCP, 2007, **126**, 124707*

O. Kuksenok et al. PRE (2008)

$$\frac{\partial \phi}{\partial t} = -\nabla \cdot (\phi \mathbf{v}^{p})$$

$$\frac{\partial v}{\partial t} = -\nabla \cdot (v \mathbf{v}^{p}) + \varepsilon G$$

$$\frac{\partial u}{\partial t} = -\nabla \cdot (u \mathbf{v}^{s}) - \nabla \mathbf{j}^{s} + F$$

$\phi, \mathbf{v}^{p}$ volume fraction & velocity of polymer

v concentration of oxidized catalyst

$u, \mathbf{v}^{s}$ concentration & velocity of activator

$\mathbf{j}^{s} = -(1-\phi)\nabla \dfrac{u}{1-\phi}$ diffusion of u in system

☞ Reaction kinetics : modified Oregonator model

$$F = (1-\phi)^{2} u - u^{2} - f\, v (1-\phi) \frac{u - q(1-\phi)^{2}}{u + q(1-\phi)^{2}}; \qquad G = (1-\phi)^{2} u - (1-\phi) v$$

☞ Relaxational dynamics:

$$\nabla \cdot \hat{\boldsymbol{\sigma}} \sim \zeta(\phi)(\mathbf{v}^{p} - \mathbf{v}^{s})$$

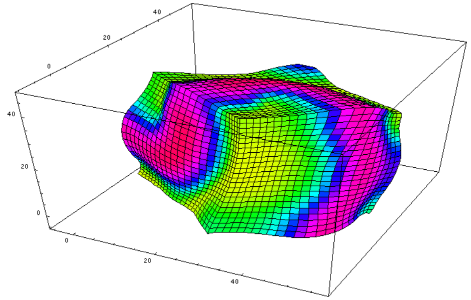
$\hat{\sigma}$ stress tensor

$\zeta(\phi)$ friction coeff.

☞ Neglect total velocity

$$\phi\, \mathbf{v}^{p} + (1-\phi)\, \mathbf{v}^{s} \equiv 0$$

Model for Chemo-responsive Gels in 3D



❑ Define energy density of deformed gel

- $\boxed{U = U_{el}(I_1, I_3) + U_{FH}(I_3)}$
  - Elastic energy $U_{el} = \frac{c_0 v_0}{2}\left(I_1 - 3 - \ln I_3^{1/2}\right)$
  - Interaction energy $U_{FH} = \sqrt{I_3}\left[(1-\phi)\ln(1-\phi) + \chi_{FH}(\phi)\phi(1-\phi) - \chi^* v(1-\phi)\right]$
  - c_0 is crosslink density, $\boxed{\chi^* > 0}$: hydrating effect of oxidized catalyst

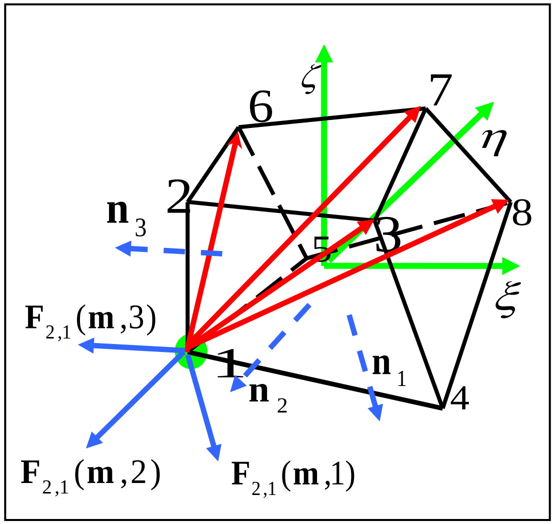
❑ Use 3D gLSM model

- Calculate velocities of node **n** of element **m**

$$\boxed{\frac{d\mathbf{r}_n(\mathbf{m},t)}{dt} = M_n(\mathbf{m},t)\left[F_{1,n}(\mathbf{m},t) + F_{2,n}(\mathbf{m},t)\right]}$$

Spring-like

From pressure

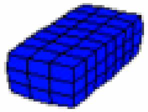


- Update $v(\mathbf{m},t)$ and $u(\mathbf{m},t)$
  - Combination of finite elements & finite difference techniques

O. Kuksenok et al. PRE (2008)

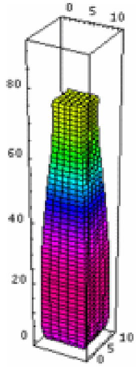
3D gLSM: Compare Simulations and Experiment

❑ Small cubic samples



- ☞ Oscillations uniform though the sample
- ☞ In-phase synchronization of chemical & mechanical oscillations
  - ☞ Similar to experiments *R. Yoshida et al, J.Phys.Chem, 104, 2000*

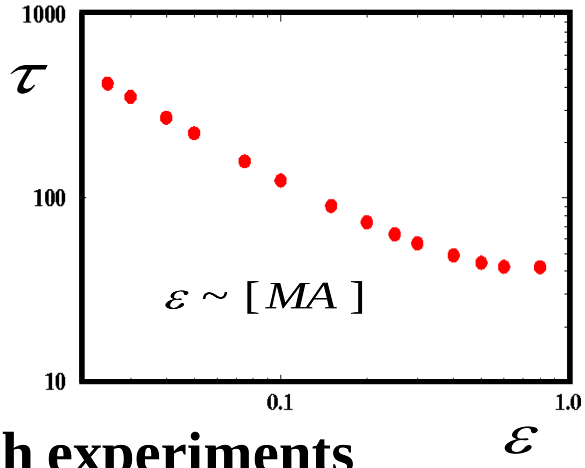
❑ Long rectangular samples attached to wall



- ☞ Traveling wave propagates from wall towards free end
  - ☞ Similar to experiments *R. Yoshida et al, Chaos, 9,1999,*

❑ Effect of $\varepsilon \sim [MA]$ on period of oscillations

- ☞ Increase in [MA] decreases period
- ☞ At higher ε transition to steady-state
  - ☞ Similar to experiments *D. Suzuki at al, J.Phys.Chem. B **112**, 2008*



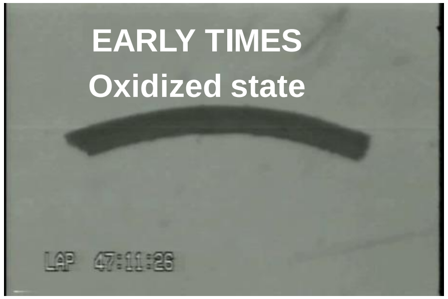
❑ Simulations are in qualitative agreement with experiments

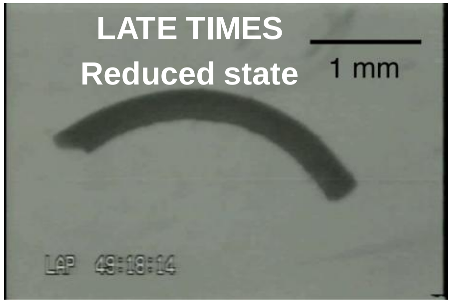
Gels with Gradient in Crosslink Density

- ☐ **What can we learn from experiments?**

Images are provided by R. Yoshida et. al.

Kuksenok, Yoshida, Balazs
J Mat. Chem.
21 (2011) 8360

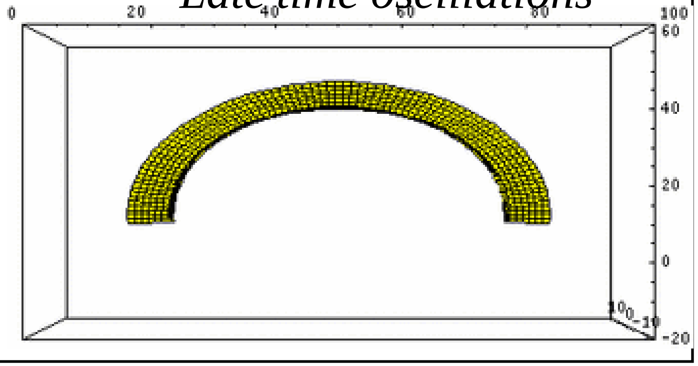




- ☞ Bending is smaller at early times and increases with reaction time
- ☞ Amplitude of motion of gel’s ends increases with reaction time
- ☞ Sample seen to slowly move “up”

- ☐ **Simulations show qualitative agreement with experiments**

Late time oscillations



Modify gLSM: Introduce Diffusion/Reaction in Solution

- **Activator (*u*) produced inside the gel only**
  - Diffuses to/from gel's surfaces
  - Concentration in outer solution decays
    - Due to disproportionation reaction

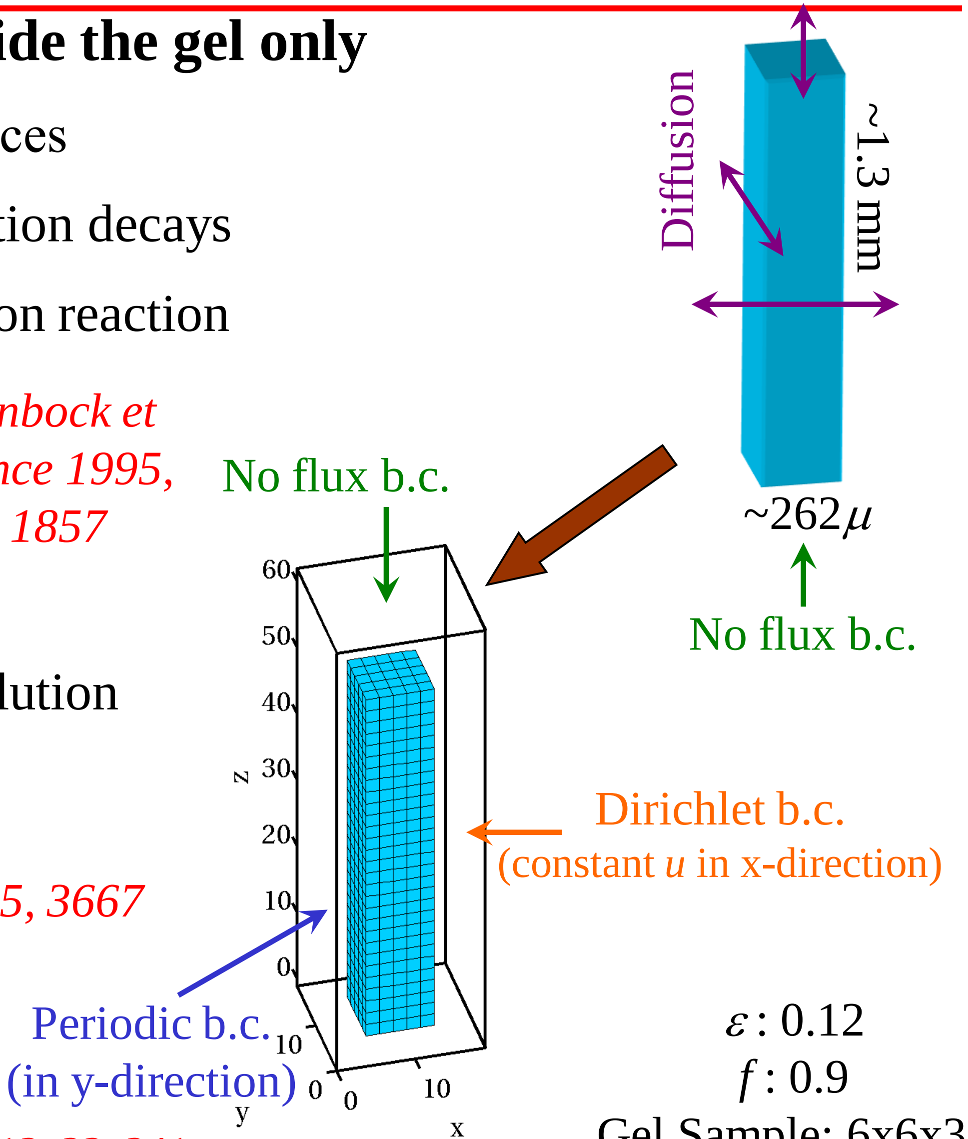
$$\frac{du}{dt} = \nabla^2 u - u^2$$

O. Steinbock et al, Science 1995, 269, 1857

- **Diffusivity of *u*:**
  - Equal in solvent & outer solution
    - $D = 2\text{x}10^{-9} \text{m}^2/\text{s}$

      R. Yoshida et al,
      J. Phys. Chem. A 2001, 105, 3667
  - Unit of length: ~25μ
  - Unit of time: ~0.3 s

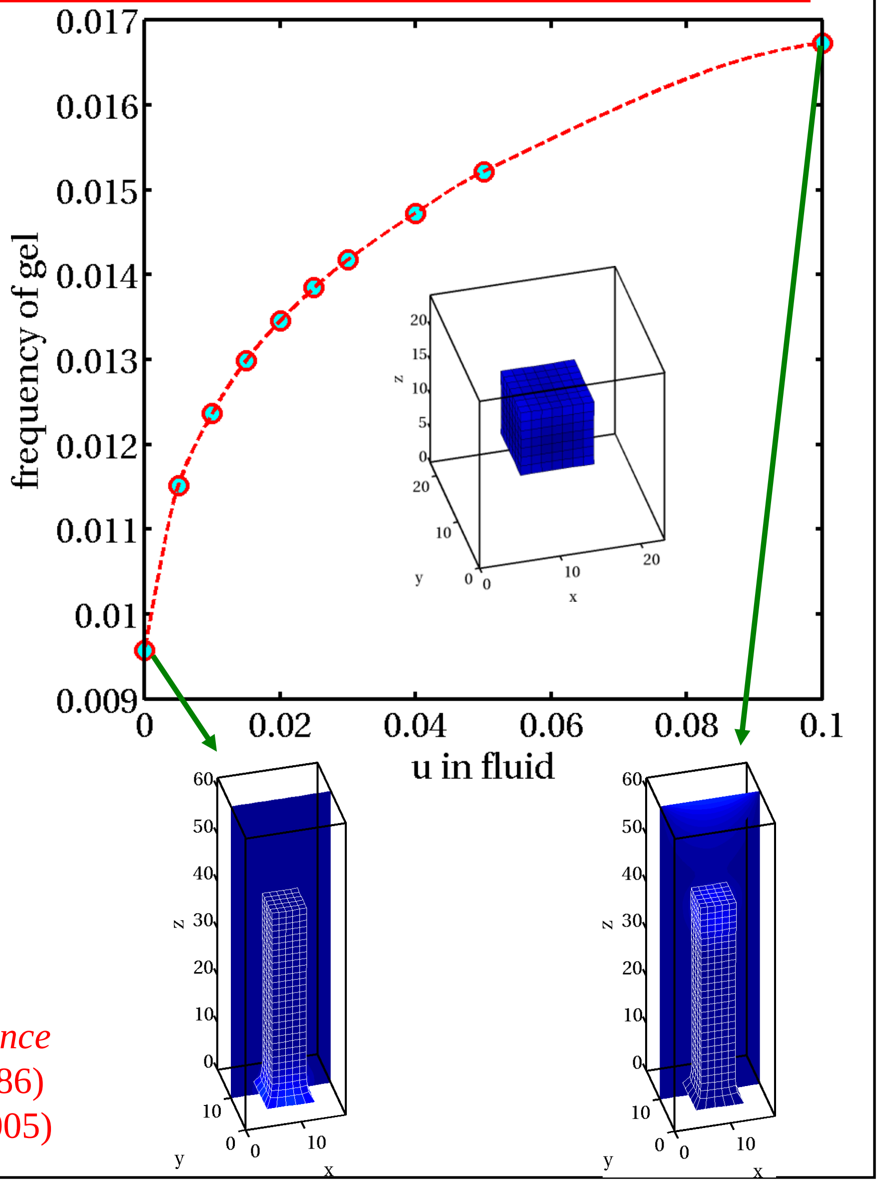
P. Dayal et al, J. Mater. Chem. 2012, 22, 241



ε : 0.12
f : 0.9
Gel Sample: 6x6x30

Dependence of Frequency of Oscillations on *u*

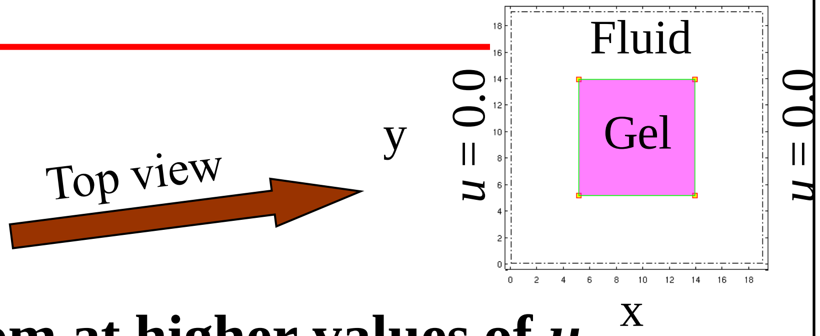
- ❑ **Frequency increases with increase in *u* at fluid boundaries**
  - ☞ Sample size: 8x8x8
  - ☞ Frequency ~0.032-0.055 Hz
- ❑ **For longer samples**
  - ☞ Each node is an oscillator
- ❑ **Area of higher frequency dominates**
  - ☞ Sets directionality of wave propagation
    - ☞ From higher *u* to lower *u*



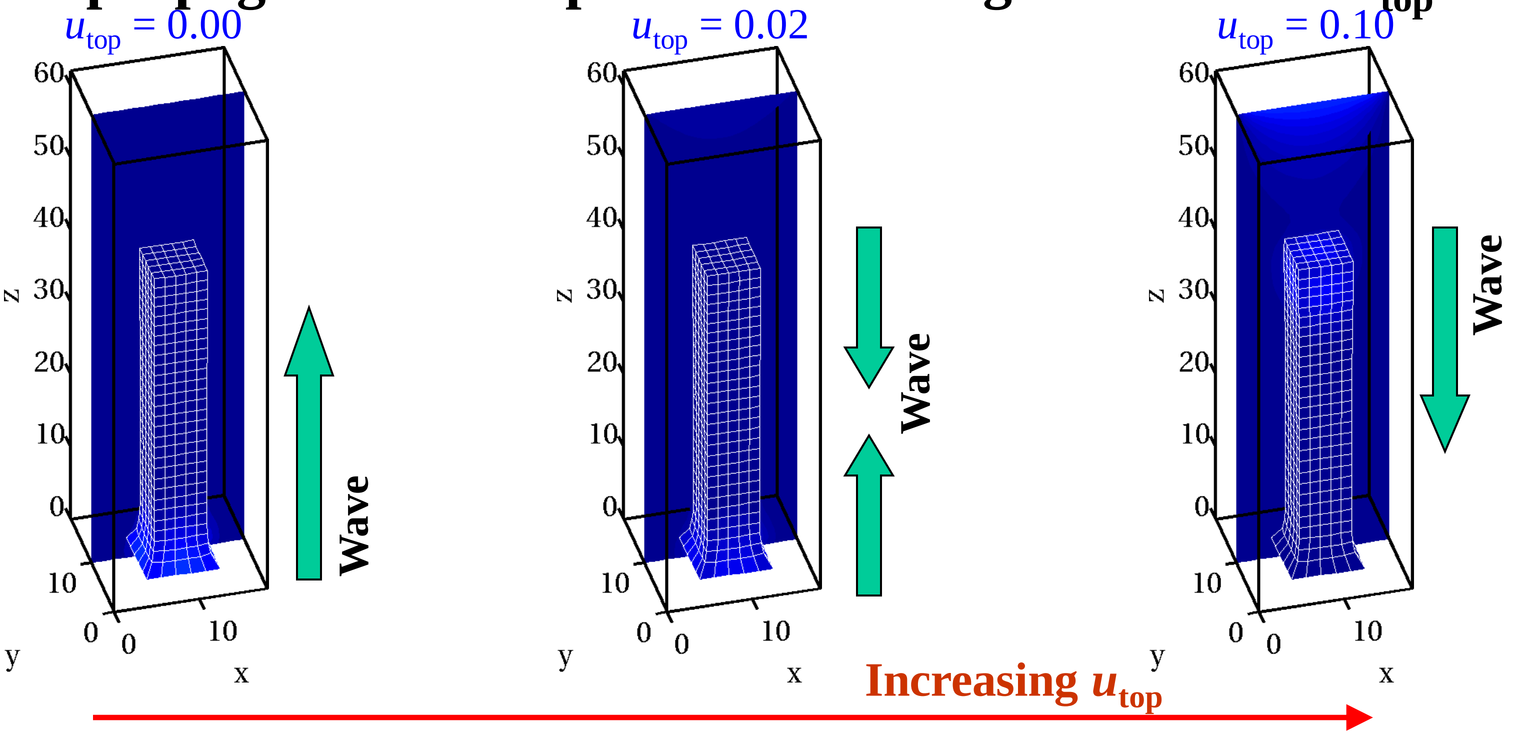
Y. Kuramoto, *Chemical Oscillations, Waves, and Turbulence*
A. S. Mikhailov and A. Engel, Phys. Lett. A 117, 257 (1986)
B. Blasius and R. Tonjes, Phys. Rev. Lett. 95, 084101 (2005)

Wave Propagation in Single Cilium: Effect of Activator *u*

- **Boundary conditions**
  - ☞ $u = 0.0$ at $x = 0$, L
  - ☞ $u = u_{top}$ at top of the fluid box



- **Wave propagates from top to bottom at higher values of u_{top}**



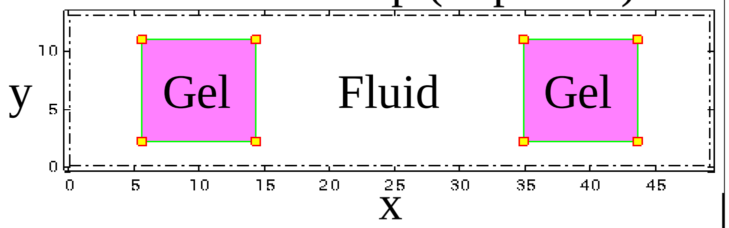
P. Dayal et al, J. Mater. Chem. 2012, 22, 241

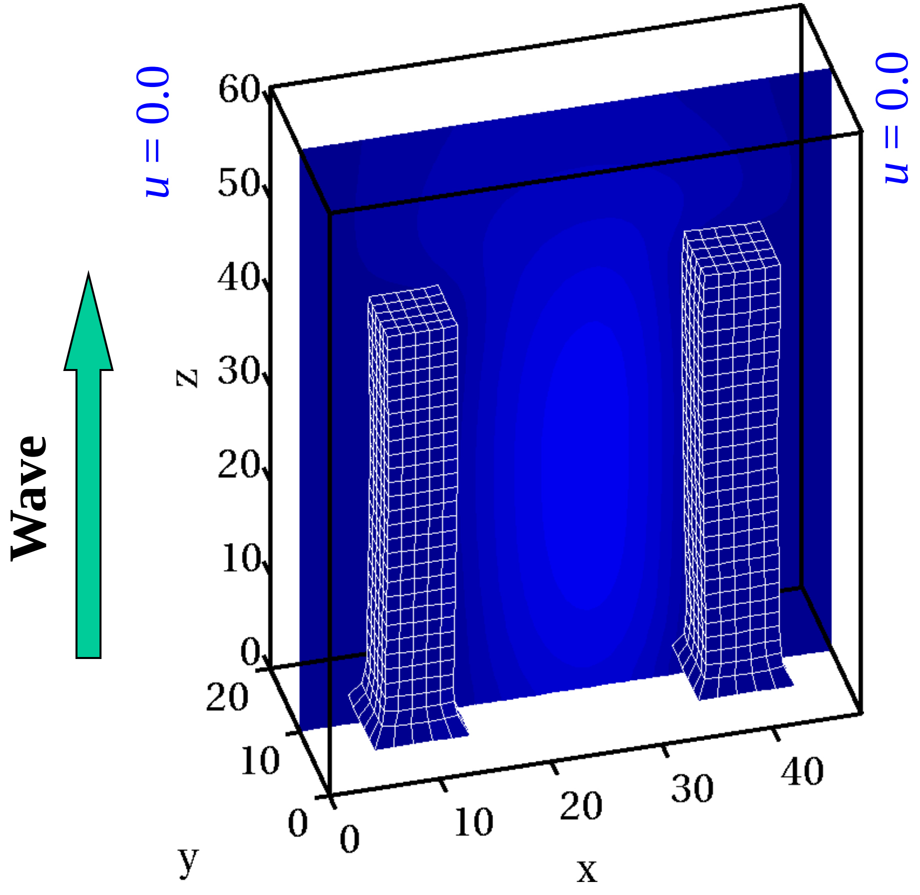
- **Activator concentration changes direction of wave propagation**

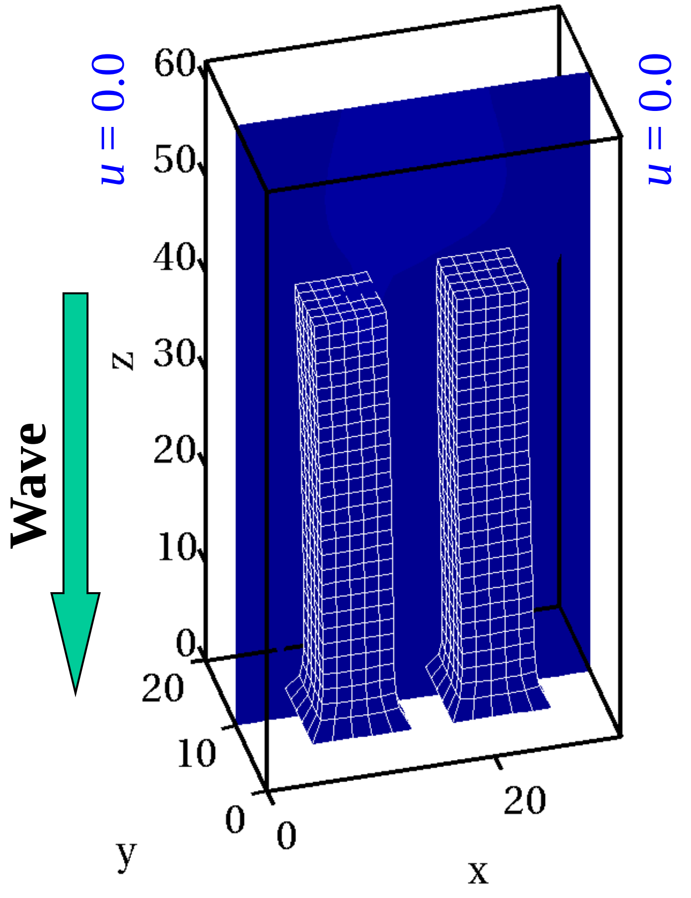
Two Cilia: Effect of Spacing

- **Decrease spacing between cilia**
  - Change direction of wave propagation

Initial Setup (Top view)

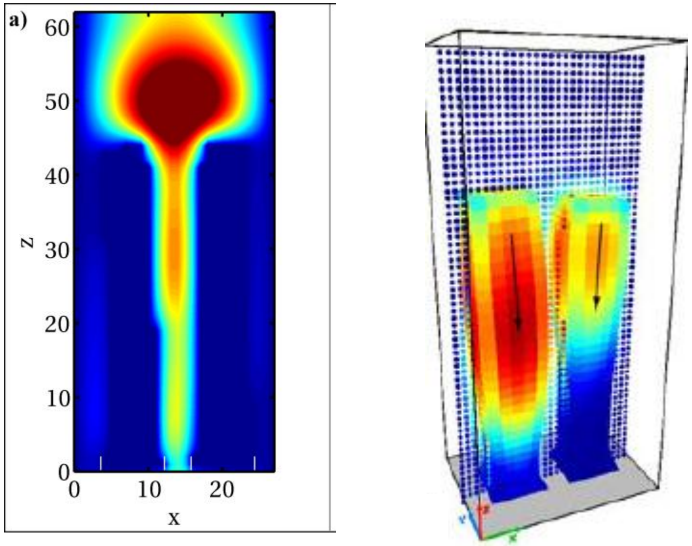


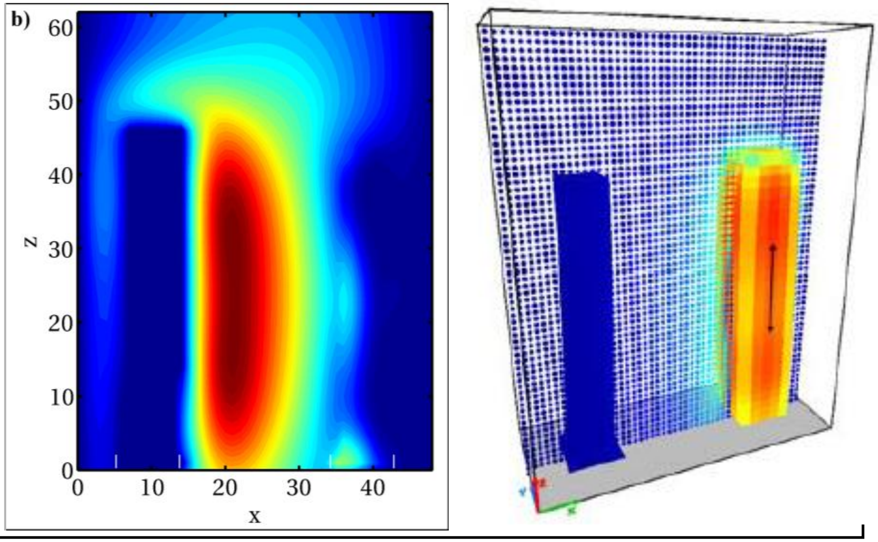




Two Cilia: Distribution of Activator *u*

- ❑ **Directionality of wave propagation**
  - ☞ Determined by local distribution of *u*
- ❑ **Cilia spaced close together**
  - ☞ Highest *u* concentration above cilia
    - ☞ Wave propagates top-down
- ❑ **Cilia spaced further apart**
  - ☞ Highest *u* concentration between cilia at midpoint of each gel
    - ☞ Wave propagates from center of each cilium
- ❑ **Control directionality of wave propagation**
  - ☞ By varying spacing

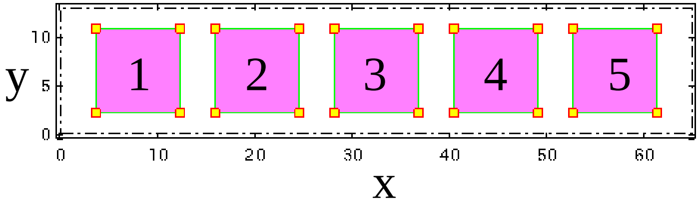


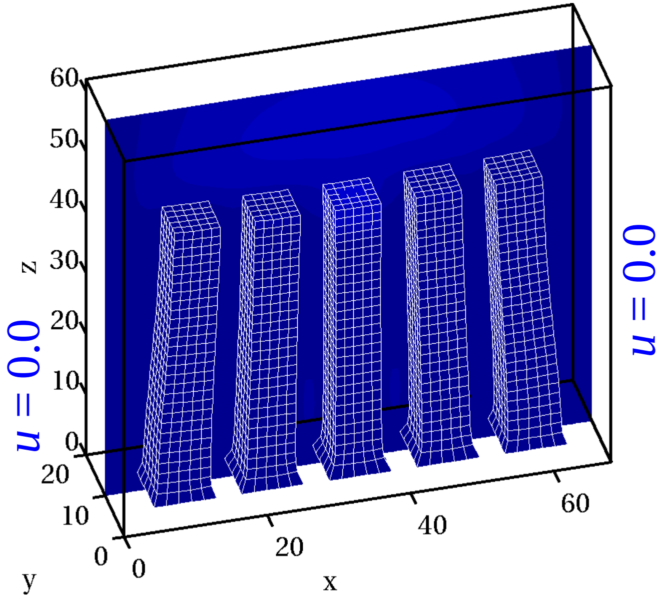


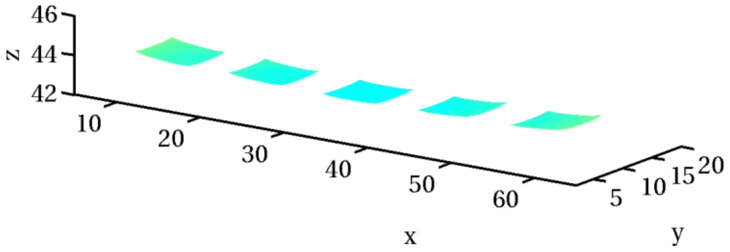
Communication Between Five Cilia

- **Boundary conditions**
  - $u = 0.0$ at $x = 0$, x = L
- **At early times**
  - Wave travels from bottom to top
- **At late times**
  - Wave travels from top to bottom
  - Cilia bends towards center
    - Highest concentration of u
- **Multiple cilia exhibit collective behavior**
  - Wave in cilium 3 leads
    - Higher concentration of u
  - Oscillations are synchronized

Initial Setup (Top view)







P. Dayal et al, J. Mater. Chem. 2012, 22, 241

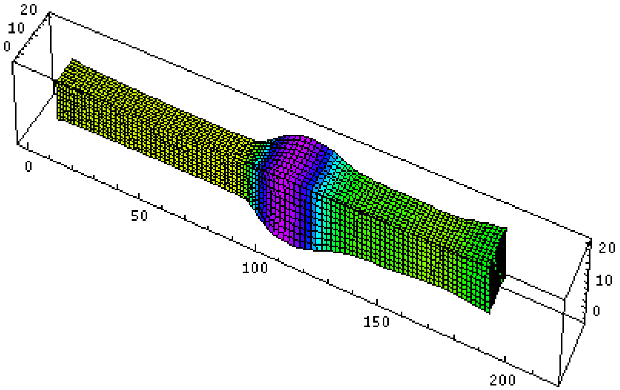
Exploit Photosensitivity of BZ Reaction

- **Ruthenium-catalyzed BZ reaction photosensitive**
- **Introduce external light source of specific wavelength (~ 450 nm)**
  - Increases production of bromide ions
  - Suppresses oscillations

Krug, H.-J.; Pohlmann, L.; Kuhnert, L. *J. Phys. Chem.* 1990, *94*, 4862-4866.

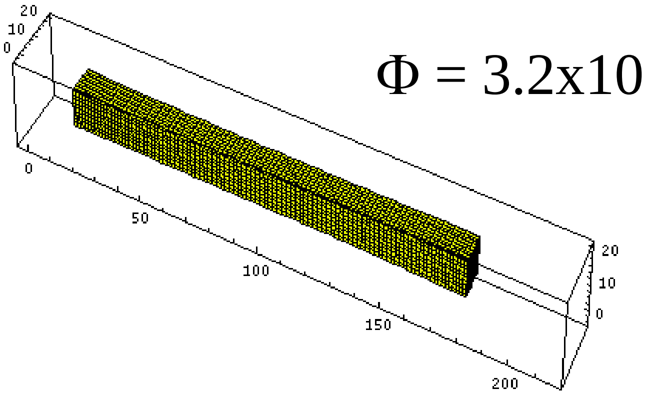
$$F(u,v,\phi) = (1-\phi)^2 u - u^2 - (1-\phi)[fv + \Phi]\frac{u - q(1-\phi)^2}{u + q(1-\phi)^2}$$

- Without external light source



- With external light source

$\Phi = 3.2\text{x}10^{-4}$



- Similar results seen experimentally

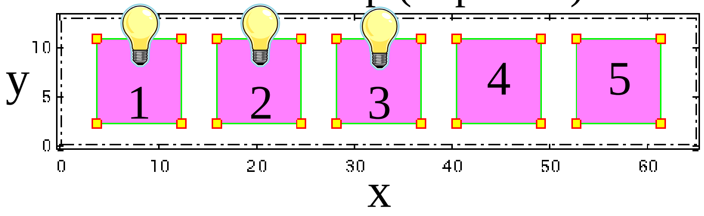
Shinohara *et al*, Angew. Chem. Int. Ed. 2008, 47, 9039

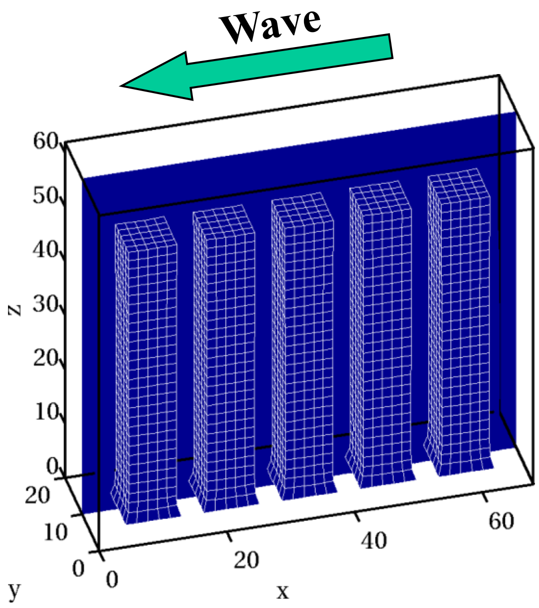
Multiple Cilia: Effect of Light

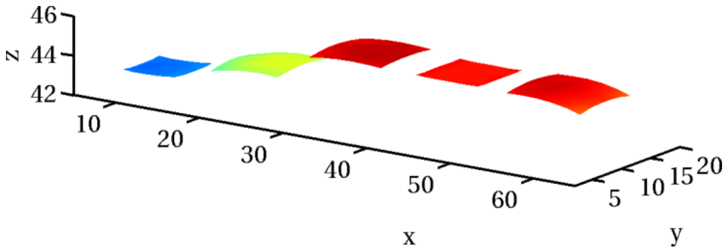
- **Use light to alter dynamics**
  - ☞ Illuminate cilia 1-3
    - ☞ $\Phi = 6\text{x}10^{-4}$: Suppresses oscillations in isolated sample
- **Communication between cilia through fluid**
  - ☞ Light does not suppress oscillations in cilia 1-3
    - ☞ Due to diffusion of *u* in fluid
  - ☞ Wave originates in dark region
- **"Play" cilia like piano keyboard**
  - ☞ Address individual cilium
    - ☞ Control collective behavior

P. Dayal et al, J. Mater. Chem. 2012, 22, 241

Initial Setup (Top view)



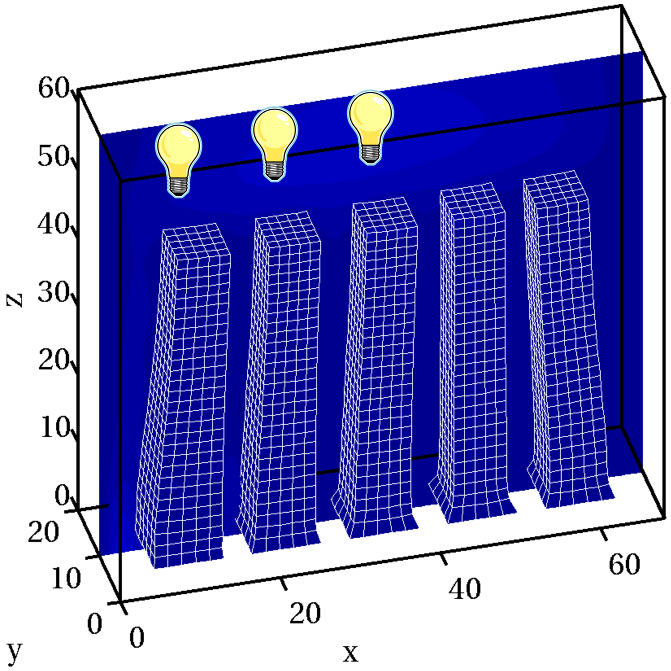


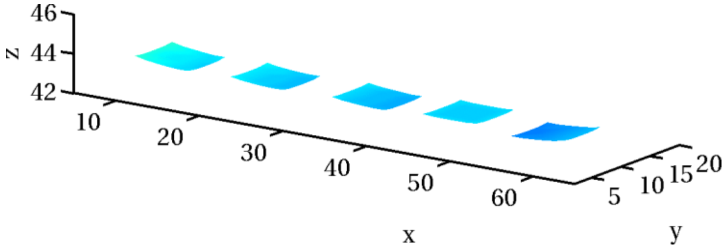


Summary

- **Multiple cilia exhibit collective behavior**
  - Oscillations synchronized
  - Degree of bending determined by gradient in *u*
    - Cilium bends towards higher *u*
  - Direction of wave propagation is controlled by distribution of *u*
- **Effect of light**
  - Provides means for remote and non-invasive control
  - Changes frequency of oscillations
    - Dynamics can be controlled by non-uniform illumination

Late times





Experimental Evidence for *u*-mediated Communication

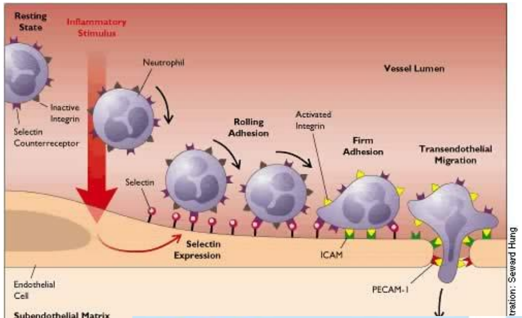
- **BZ gels mechano-responsive**
  - Can drive non-oscillatory sample into oscillatory phase

    Kuksenok et al, *Soft Matter*, 5 (2009) 1835;
    Soft Matter, 3 (2007) 1138; Chen, I.C., Van Vliet. K.J., *et al*
    Adv. Func. Mat, 2012 (DOI:10.1002/adfm.201103036).
- **Exploit mechanical force as stimulus**
- **All pieces initially non-oscillatory**
- **Push on smile (through cover slip)**
  - Driven to pulsate
  - Releases *u* into surrounding solution
- ***u* diffuses to eyes**
  - Initiates oscillations in eyes
- **If eyes too far away**
  - Do not sense *u*
    - Do not wink

http://www.newscientist.com/blogs/nstv/2012/03

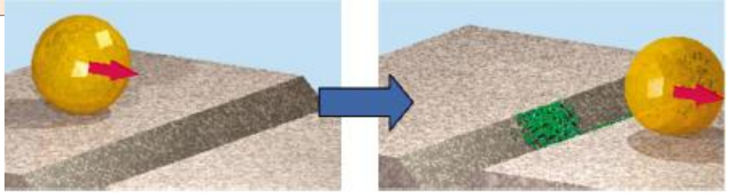
Conclusions: Used Modeling to Design Biomimetic Systems

- ☐ **Leukocytes**
  - ☞ Sense damage
  - ☞ Migrate to damaged site
  - ☞ Initiate repair



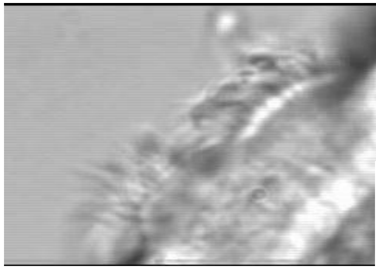
Leukocytes

- ☐ **Synthetic leukocytes**
  - ☞ Heal nanoscale cracks in substrates



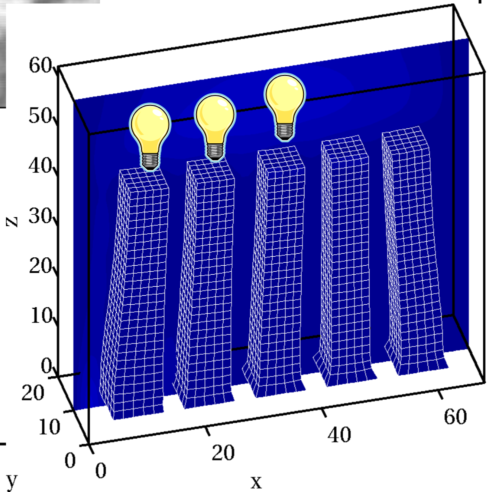
K. Kratz et al. Nature Nano., 7 (2012) 87

- ☐ **Cilia**
  - ☞ Exhibit collective dynamics



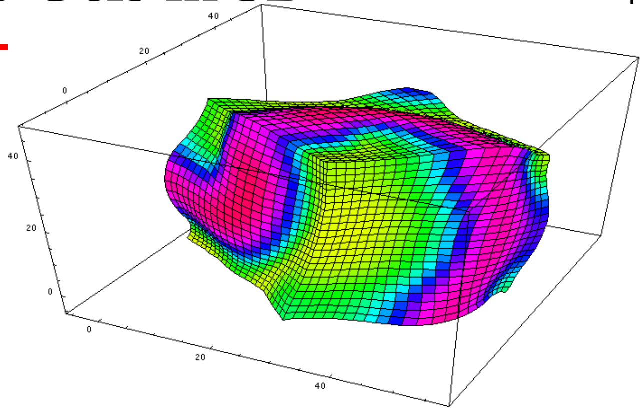
Cilia

- ☐ **Artificial cilia**
  - ☞ Communicate via diffusion of *u*
  - ☞ Can be controlled by light
    - ☞ Regulate transport in microfluidic devices



P. Dayal et al, J. Mater. Chem. 22 (2012) 241

Model for Chemo-responsive Gels in 3D



☐ Define energy density of deformed gel

- $\boxed{U = U_{el}(I_1, I_3) + U_{FH}(I_3)}$
    - Elastic energy $U_{el} = \frac{c_0 v_0}{2}\left(I_1 - 3 - \ln I_3^{1/2}\right)$
    - Interaction energy $U_{FH} = \sqrt{I_3}\left[(1-\phi)\ln(1-\phi) + \chi_{FH}(\phi)\phi(1-\phi) - \chi^* v(1-\phi)\right]$
    - c_0 is crosslink density, $\boxed{\chi^* > 0}$: hydrating effect of oxidized catalyst

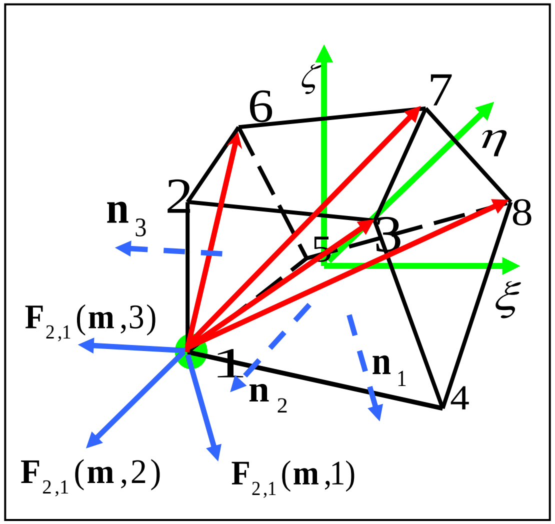
☐ Use 3D gLSM model

- Calculate velocities of node **n** of element **m**

$$\boxed{\frac{d\mathbf{r}_n(\mathbf{m},t)}{dt} = M_n(\mathbf{m},t)\left[F_{1,n}(\mathbf{m},t) + F_{2,n}(\mathbf{m},t)\right]}$$

Spring-like

From pressure



- Update $v(\mathbf{m},t)$ and $u(\mathbf{m},t)$
    - Combination of finite elements & finite difference techniques

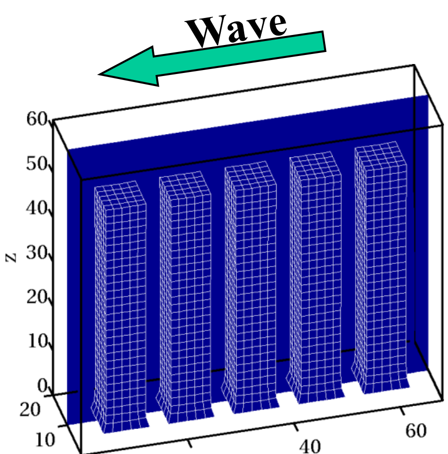
O. Kuksenok et al. PRE (2008)

Introduce Light

❑ Focus on array of BZ gels attached to substrate

- ☞ Cilia communicate via diffusion of reagents
- ☞ Motion can be controlled by light

P. Dayal et al, J. Mater. Chem. 2012, 22, 241

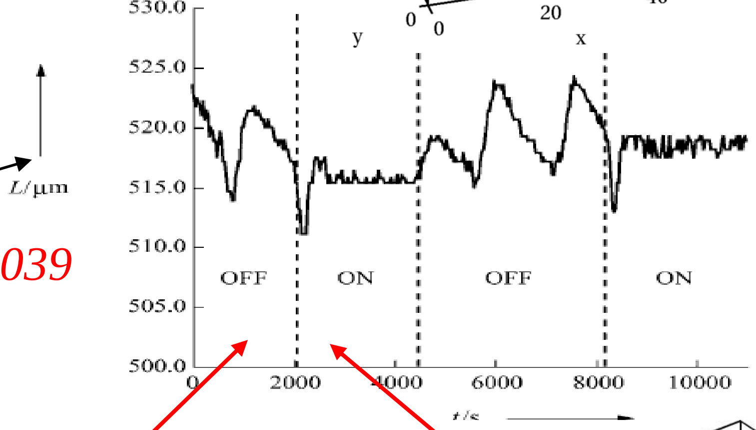


❑ Effect of visible light on BZ gels

- ☞ Enhances production of bromide ions
  - ☞ Inhibits oscillations

$$I = 6.45\,mW\;;\lambda = 436\,nm$$

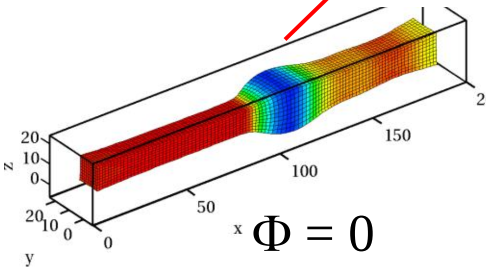
S. Shinohara et al, Angew. Chem. 2008, 47, 9039



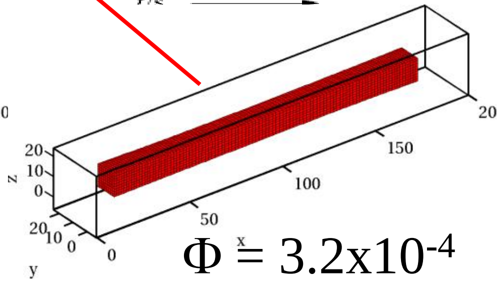
❑ Modify reactive term in gLSM

- ☞ Additional flux of bromide ions

$$(\Phi \propto I)$$



$\Phi = 0$



$\Phi = 3.2x10^{-4}$