Bio-inspired Chemo-mechanical Nanocomposites for Biomedical Applications

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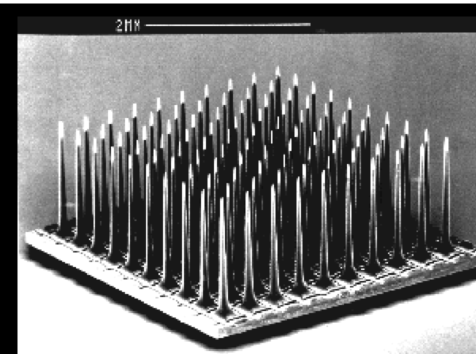
Introduction

The Brain Computer Interface

Intracortical microelectrode - penetrating electrodes implanted into the cortex of the brain



http://www.bioen.utah.edu/cni/projects/blindness.htm#overview

Improve the quality of life of persons that have sustained central nervous system disability resulting from spinal cord injury, head trauma, stroke, Parkinson's disease, ALS, and other neurological disorders.

Offers the potential to:

– Record electrical pulses of individual neurons

– Restore communication to damaged neural pathways used to control organs and limbs

Limited clinical implementations

– Kennedy et al. = limited horizontal control of cursor
– Hochberg et al. = both horizontal and vertical control of cursor, email, and simple computer games.

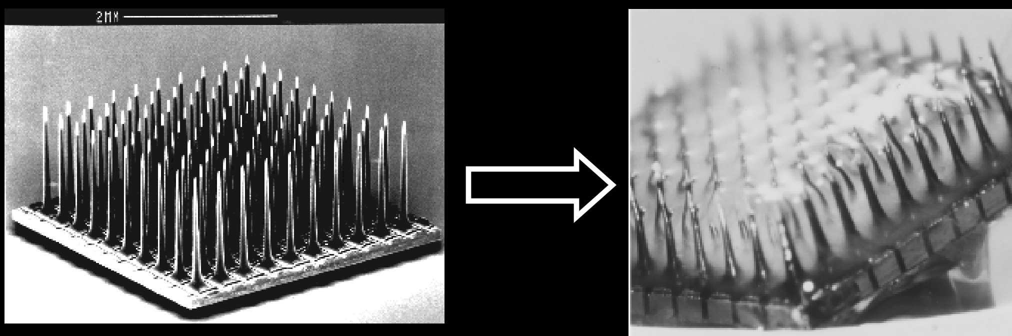
Kennedy, et al., *IEEE Trans, Rehabil. Eng.,* 2000. Hochberg, et al., *Nature*, 2006. Taylor, et al. *Science*, 2002. Santhanam, et. al., *Nature*, 2006. Nicolelis, et al. Proc Natl Acad Sci USA, 2003, New York Times 2008.

The Brain Computer Interface

- **Major Roadblock: Stop Working, why?**

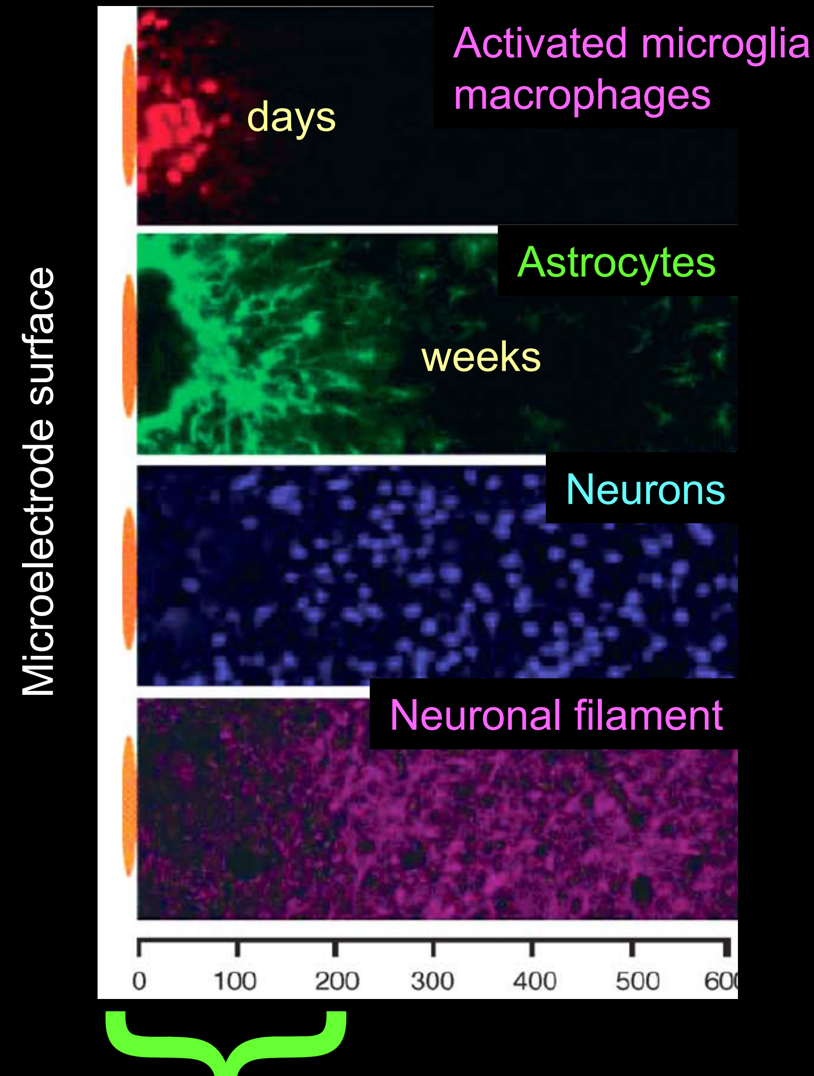
➢ **Tissue Response:** Formation of Glial scar

➢ **Reduces lifetime of the probe**
– rapid signal decay 60 days to 18 months post-implant



10 month explant –

Gliosis: a dense fibrous network of neuroglia (supporting cells)



"Dead zone" = >100 μm (4 weeks);
Recording site must be <20 μm from cell body to determine between neurons

Leading hypothesis attributes this effect to the mechanical mismatch between the brain and electrode materials

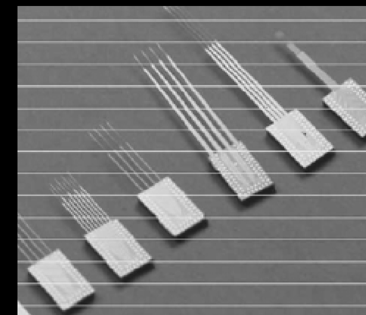
Introduction

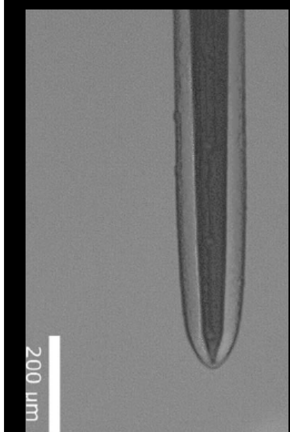
Main Classes of Intracortical Electrodes

Microwire or Silicon – e.g. Tungsten, Stainless steel, or other biocompatible metal

Advantages: Insertion, easily arrayed, fabricated

Disadvantages: **Gliosis forms,** signal loss for 1/2 units, month for good units





Polymer coatings to traditional probes – Hydrogel coating polymer.

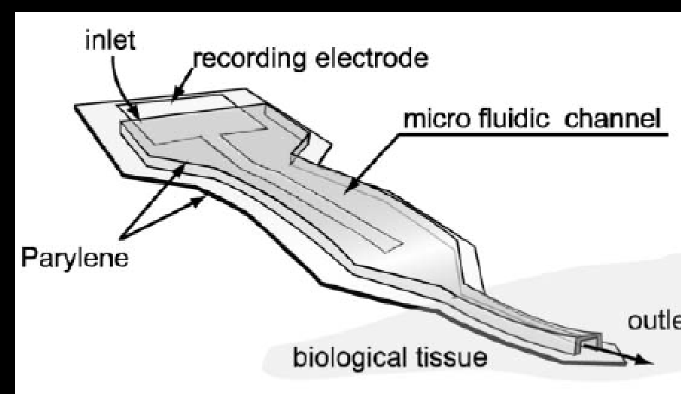
Advantages: Reduce mechanical stiffness encountered by brain, elute bioactive molecules

Disadvantages: **Neurons farther from recording sites – decreased signal quality**, swelling (> 100 x), long term performance of hydrogel, effective silicon stiffness

Polymer substrates – polyimide, PDMS, parylene

Advantages: Fabrication, multiple configurations, built in circuitry, DRUG elution

Disadvantages: **Gliosis forms,** difficult to insert (pia piercing), water uptake, limited data



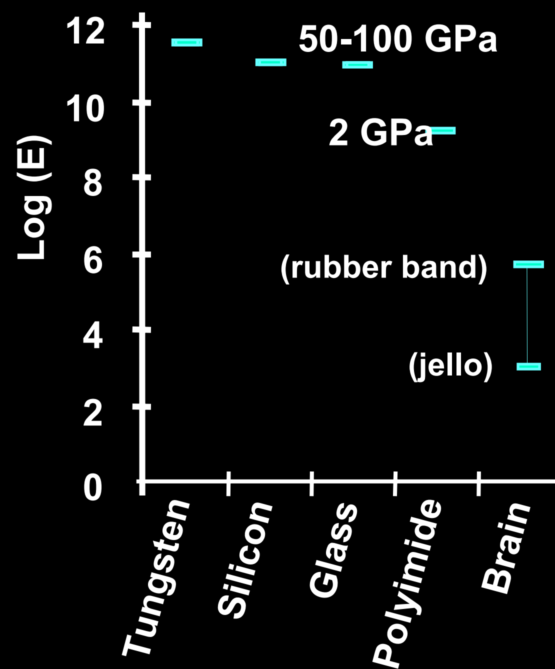
Jensen, et. al., *IEEE Trans Biomed Eng*, 2006. Moxon, K.A., et al., *IEEE Trans Biomed Eng*, 2004. Kim, D.H. and D.C. Martin, *Biomaterials*, 2006. Rousche, P.J., et al., *IEEE Trans Biomed Eng*, 2001. Takeuchi, S., et al., *Lab Chip*, 2005.

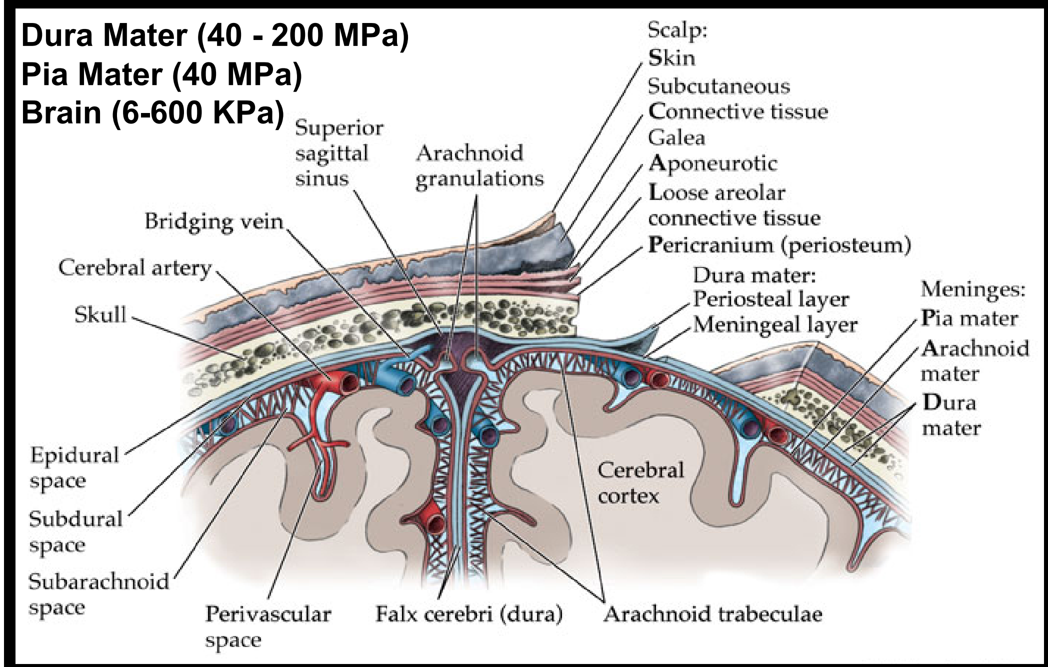
Objective / Hypothesis

Mechanically Adjustable Cortical Implants

Goal: Design cortical electrodes that exhibit reduced tissue response to allow for a longer useful lifetime.

Tissue Response: Formation of Glial scar, reduces lifetime and S/N ratio of electrode
-Cellular Response to Implanted Material
-Mechanical Mismatch between the brain and electrode, Micromotion

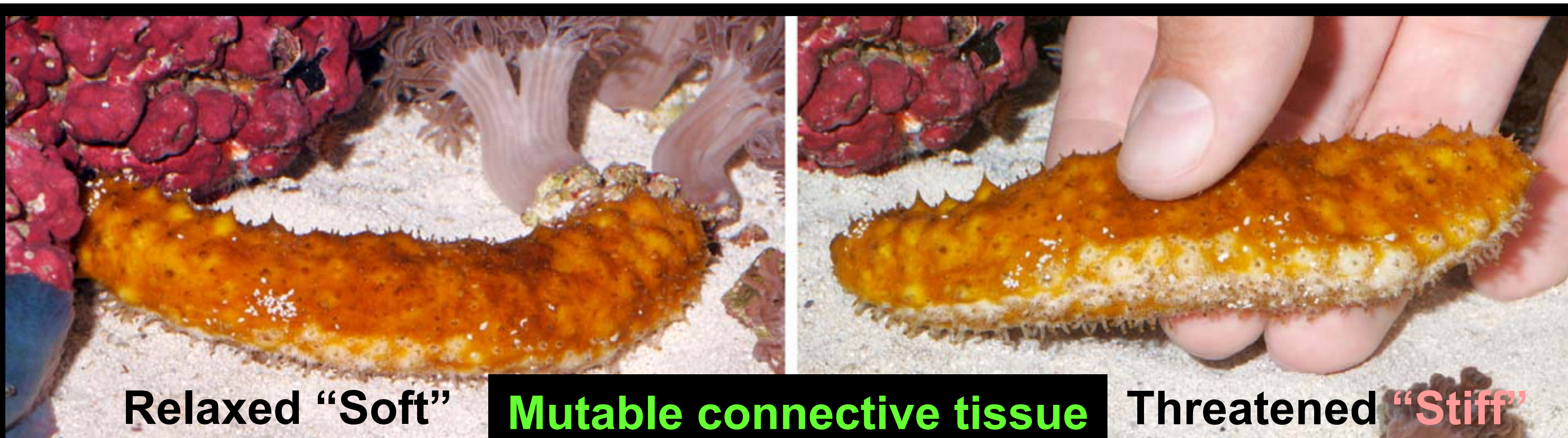




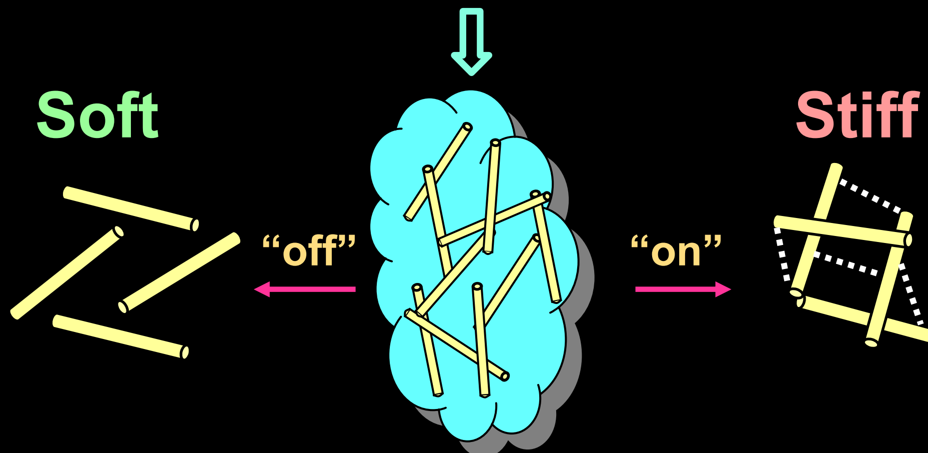
Hypothesis

An electrode should be stiff enough to allow insertion into the cortex but become compliant (soft) after implantation to match the stiffness of cortical tissue.

The Sea Cucumber's Dermis A Chemo-mechanical Nanocomposite



Low modulus matrix (collagen, fibrillin, H_2O)



High modulus micro-fibers (collagen)

Peptide "cross-linkers" (Tensilin)

Stiffening through secretion of protein (tensilin)

Effect is reversed through proteinases

In vitro: 5 to 50 MPa in microseconds

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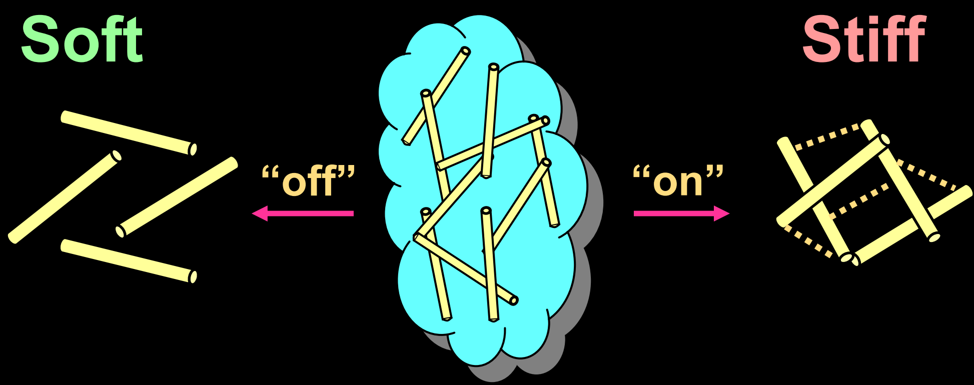
Wilke *J. Exp. Biol.* **2002**. Szulgit, Shadwick *J. Exp. Biol.* **2000**. Trotter et. al. *J. Exp. Biol.* **1999**. Trotter, Heuer et. *al. Biochem. Soc. Trans.* **2000**.

Model System

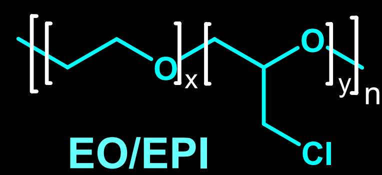
Mimic the functionality and structural design of the sea cucumber dermis



Control of Filler-Filler interactions via stimulus (chemical, electrical,…)

Soft state – matrix polymer

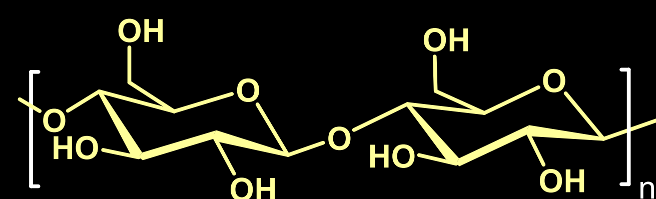
- Young's modulus = 0.5 – 3.0 MPa
- Ethylene oxide copolymer
- Model system, processable



EO/EPI

Rigid state – "stiff" nanofiller

- High-aspect-ratio high-stiffness filler
- Microcrystalline cellulose
- Young's modulus = 120 – 150 GPa



Cellulose

Natural whisker-whisker (Hydrogen Bonding) interactions

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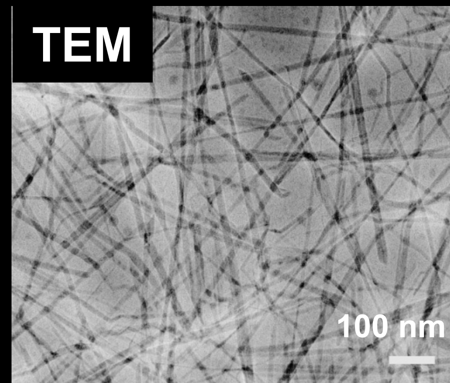
Cellulose Whiskers

High-Aspect Ratio Cellulose Nanofibers

1. Base

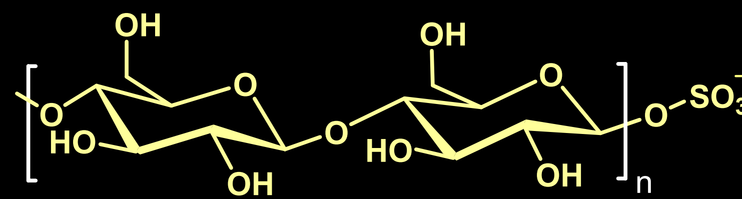
2. Acid (H_2SO_4)



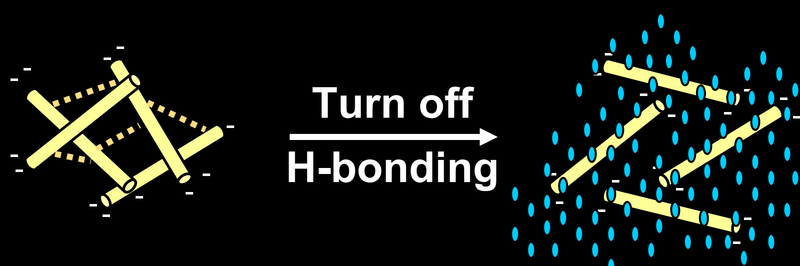
High aspect ratio cellulose fibers

l = 2.20 +/- 0.20 μm

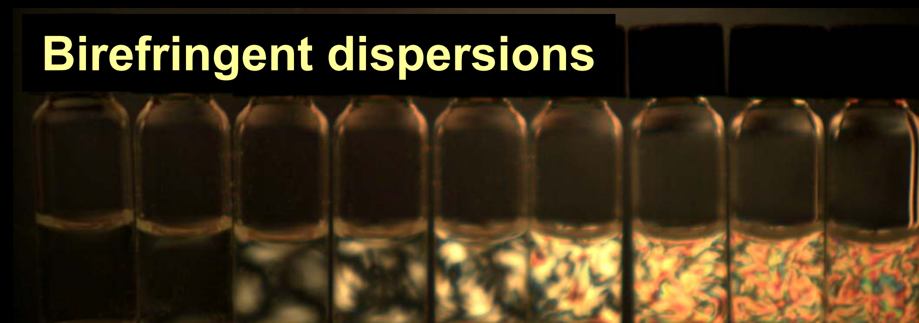
d = 20.0 +/- 3.0 nm



Sulfuric acid hydrolysis introduces sulfate surface groups, which impart dispersibility in water



Birefringent dispersions



0.1 0.5 1.0 2.0 3.0 4.0 5.0 6.0 7.0

mg/mL H_2O.

Solution cast

Whisker film

E′ = 3.9 GPa

Marchessault et al. *Nature* **1959**, *184*, 632. Favier, Chanzy, Cavaillé *Macromolecules* **1995**, *28, 6365.* van den Berg, Capadona, Weder *Biomacromolecules* 2007, 8(4): 1353-1357.

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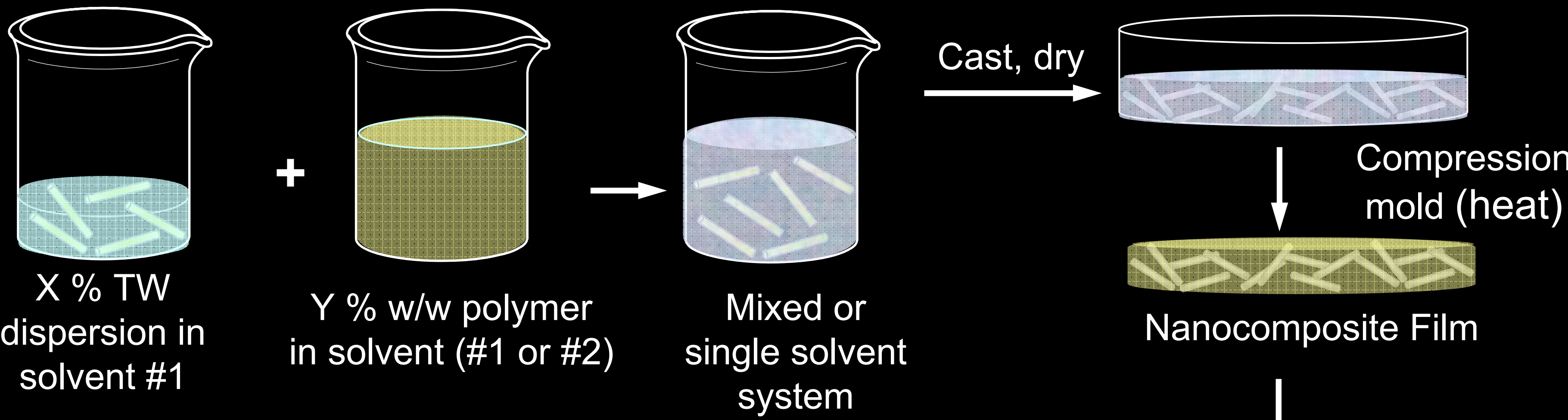
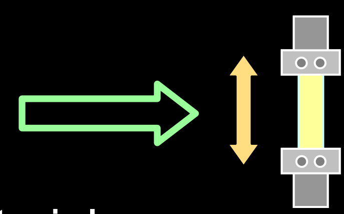
TW Nanocomposites

Traditional Processing



Weight fraction TW: 0, 1, 5, 10, 15, 20 %

Apply oscillatory stress and measure strain to determine the Young's modulus of the material



Young's modulus is a measure of the stiffness of a material

Gel	10-100 KPa
Rubber	10-100 MPa
Polyethylene (LDPE)	200 MPa
Polypropylene	1-2 GPa
Nylon	3-7 GPa
Glass	65-90 GPa
Kevlar	130-180 GPa
Carbon Nanotube (single)	>1000 GPa

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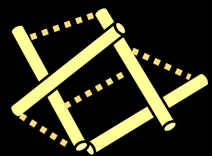
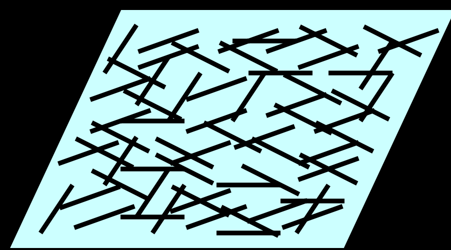
TW Nanocomposites

Classical Data Fits

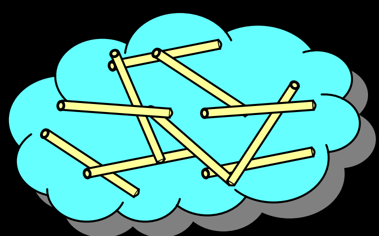


"percolation / ON"

1) Percolation model



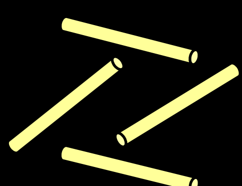
"complete interconnected network of fillers within the matrix, in which ALL fillers are connected to each other through a filler-filler interactions to complete a series"

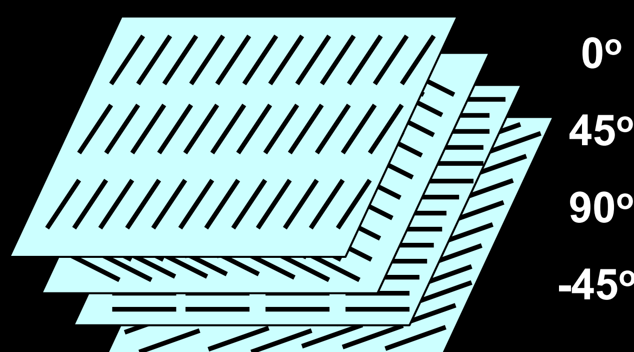


Polymer Composites, 1996, v17, p 604-611; *Polymer Eng & Sci* 1997, v37, p1732-39 ; *Acta mater*, 1997 v45, p1557-65; *Polymer Eng & Sci* **1997**, v37, p1732-39

2) Halpin-Kardos / Halpin-Tsai: Mean field approach

"mean field or percolation OFF"





"fibers are assumed to be smeared into a matrix to form a homogeneous continuum with no interactions between filler taken into account"

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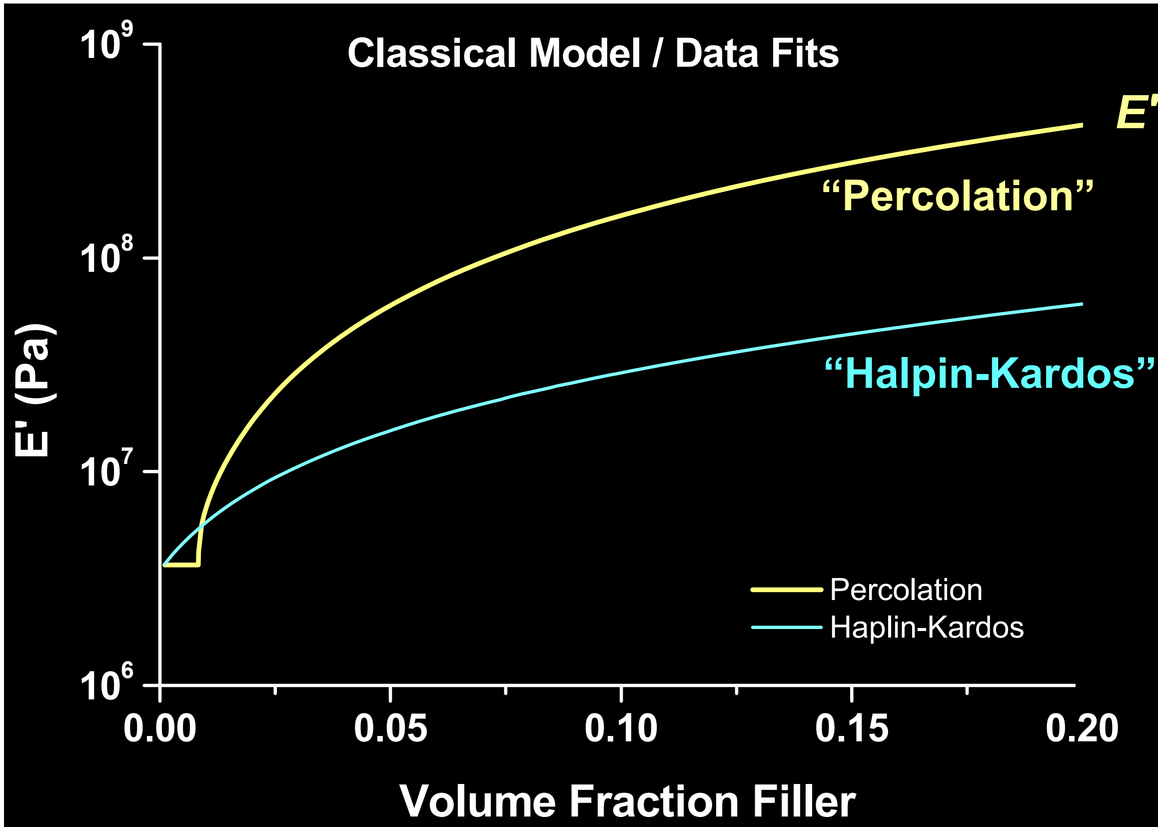
EO-EPI/TW Nanocomposites

Classical Data Fits



$$E' = \frac{(1 - 2\psi X_r)E_sE_r + (1 - X_r)\,\psi E_r^2}{(1 - X_r)E_r + (X_r - \psi)E_s}$$

$$\psi = X_r\left(\frac{X_r - X_c}{1 - X_c}\right)^{0.4}$$

$$E'_C = 4U_5(U_1 - U_5)/U_1$$

$U_1 = 1/8(3Q_{11} + 3Q_{22} + 2Q_{12} + 4Q_{66})$

$U_5 = 1/8(Q_{11} + Q_{22} - 2Q_{12} + 4Q_{66})$

$Q_{11} = E_L/(1 - \nu_{12} * \nu_{21})$

$Q_{22} = E_T/(1 - \nu_{12} * \nu_{21})$

$Q_{12} = \nu_{12} * Q_{22} = \nu_{21} * Q_{11}$

$Q_{66} = G_{12}$

$\nu_{12} = \phi_f * \nu_f + \phi_m * \nu_m$

$G_{12} = G_m(1 + \eta * \phi_f)/(1 - \nu * X_f)$

$\eta = (G_f/G_m - 1)/(G_f/G_m + 1)$

$E_T = E_m(1 + 2 * \eta_T * \phi_f)/(1 - \eta_T * \phi_f)$

$\eta_T = ((E_{tf}/E_m) - 1)/(E_{tf}/E_m) + 2)$

$E_L = E_m(1 + 2(L/D)\,\eta_L * \phi_f)/(1 - \eta_L * \phi_f)$

$\eta_L = ((E_{lf}/E_m) - 1)/((E_{lf}/E_m) + 2(L/D))$

Significant increase in mechanical reinforcement with whisker-whisker interactions

Takayanagi, Uemura, Minami *J. Polym. Sci. C* 5, 113 (1964); Hajji, Cavaille, Favier, Gauthier, Vigier *Polym. Comp.* V 17, 612 (1996)

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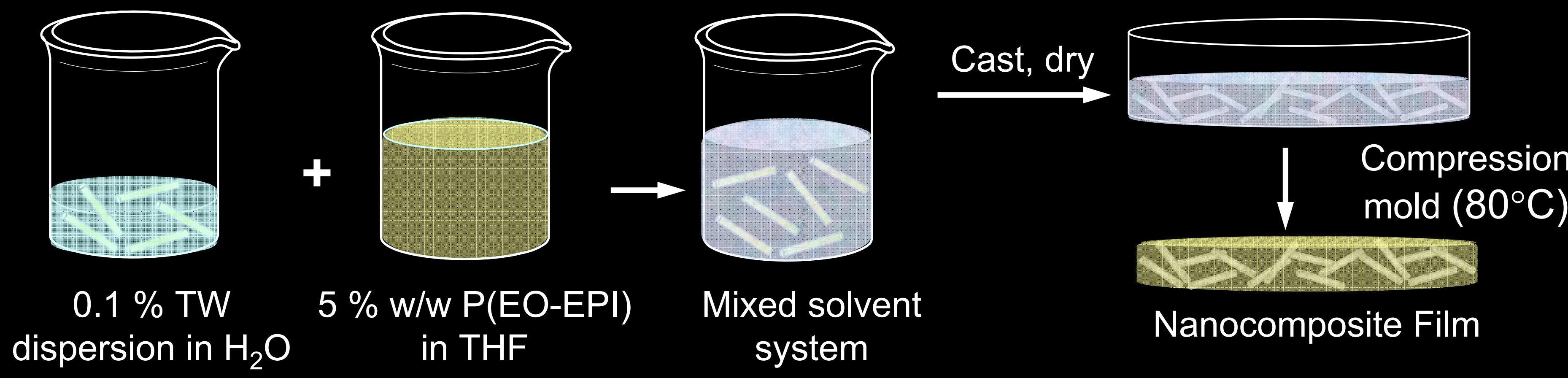
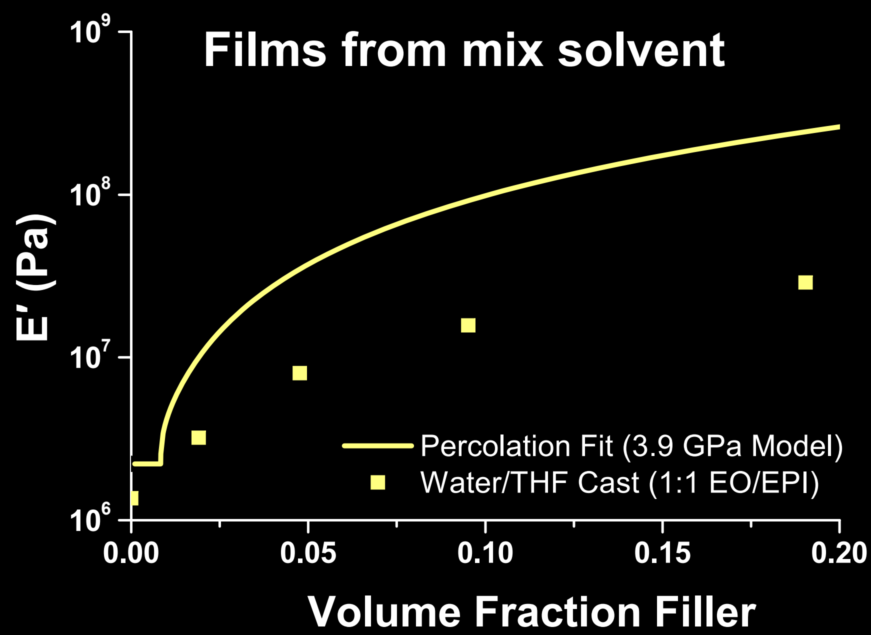
Solution Casting -Processing

Dual Solvent Systems





Data from DMTA of dry nanocomposites @ RT

Falls short of predicted reinforcement, does not mimic the “threatened” sea cucumber

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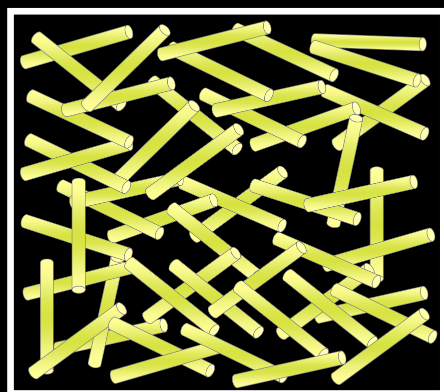
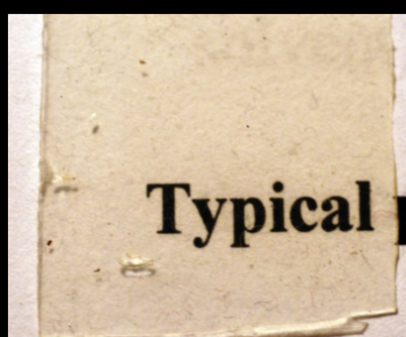
TW Nanocomposites

Traditional Processing

Single solvent system

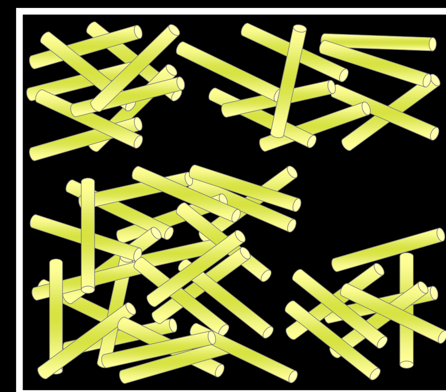
Evenly Dispersed
Percolating Whisker Network





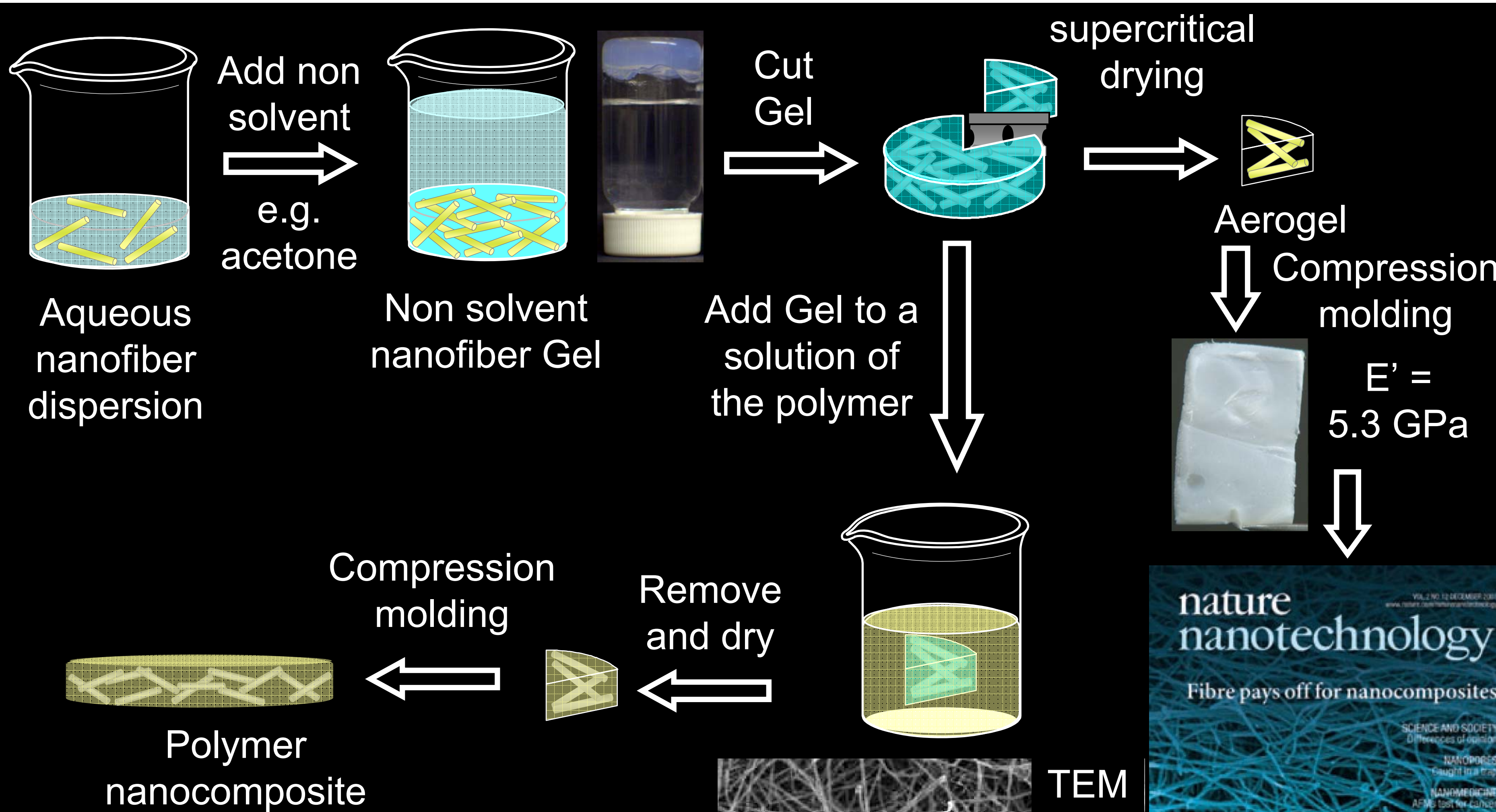
Dual solvent system

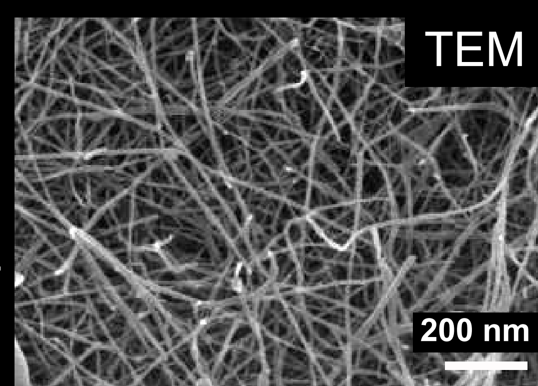
Phase Segregated
Non-Percolating Whisker Network



Novel Nanocomposite Fabrication Scheme

Gel Approach





Capadona, et al. *Nat. Nanotech.* 2007 2(12); 765-769.

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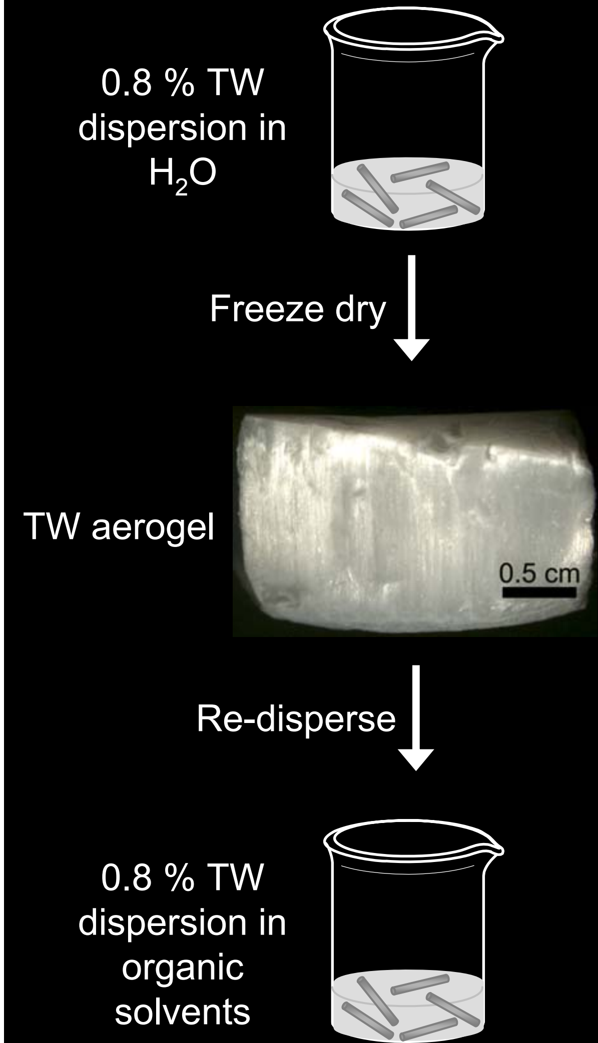
Cellulose Whiskers

Solution Casting -Processing



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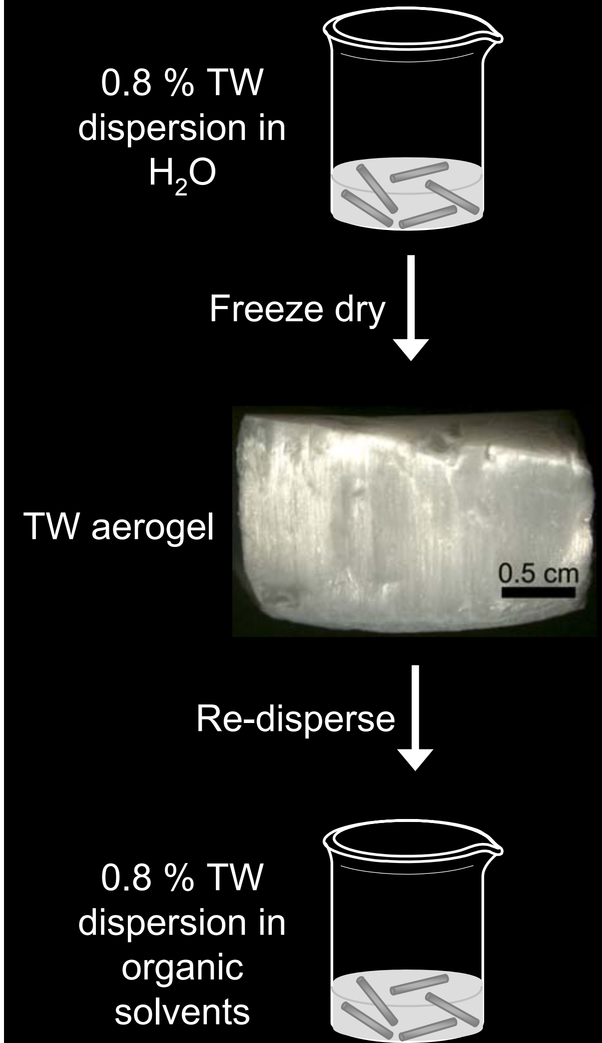
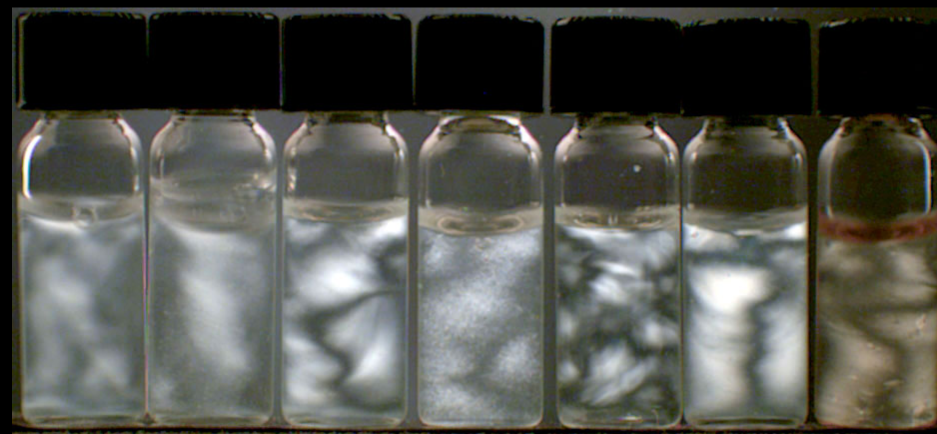
Cellulose Whiskers

Solution Casting -Processing



Dispersions of freeze-dried, re-dispersed TWs (5 mg/mL)



"New" solvents broaden processing options!

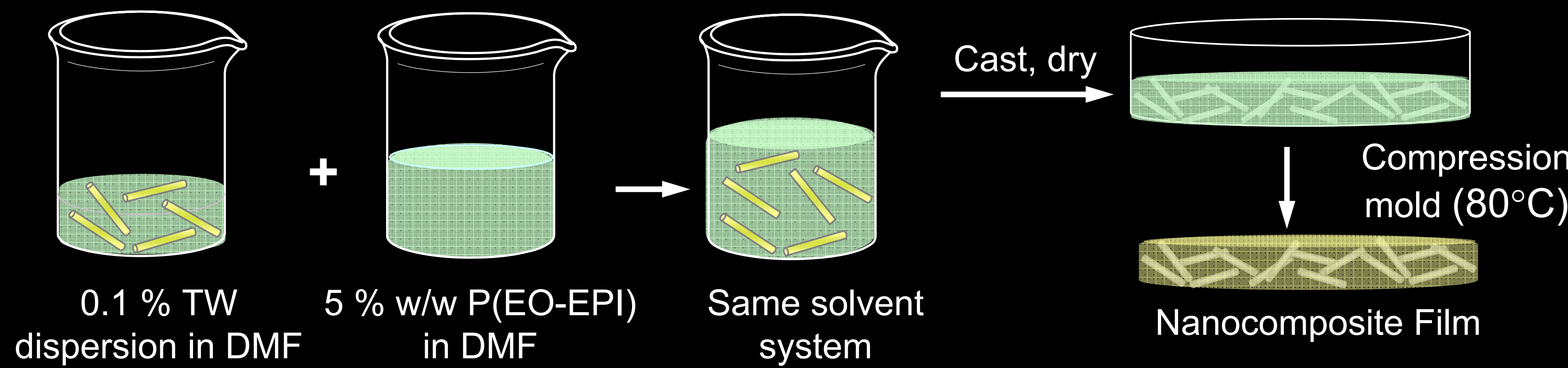
van den Berg, Capadona, Weder *Biomacromolecules* **2007, 8(4): 1353-1357**.

Azizi et al. *Macromolecules* **2004**, *37*, 1386.
Marcovich et al. *J. Mater. Res.* **2006**, *21*, 870.

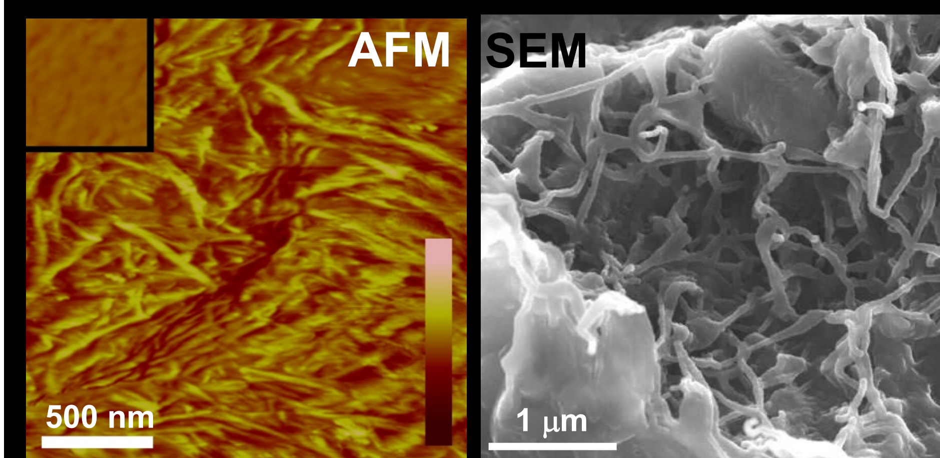
Tubak, A.; Snyder, F.; Sandberg, K. *US Patent 4378381* (**1983**).

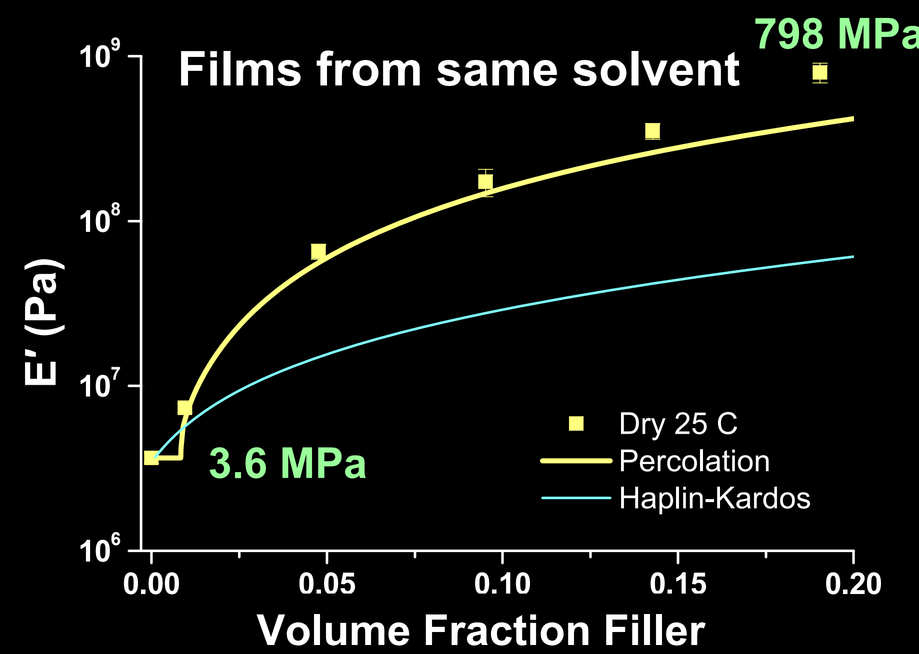
Solution Casting -Processing

Single Solvent Systems



10 % w/w TW nanocomposite





Data now fit percolation model demonstrating reinforced nanocomposites in the "ON" state

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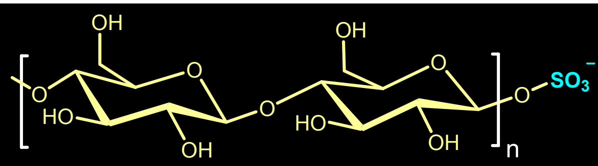
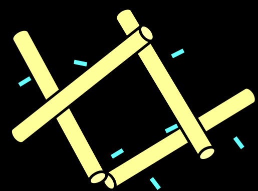
Capadona, et. al. *Science* 2008.

Mechanical "Switching"

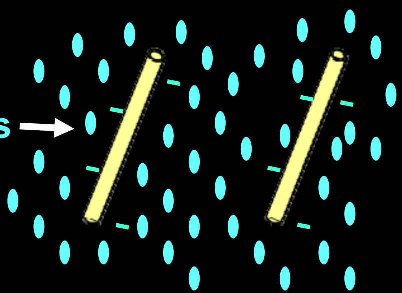


6% of sugar residues charged



Hydrogen bonding between whiskers yields percolating networks → Gel

water molecules

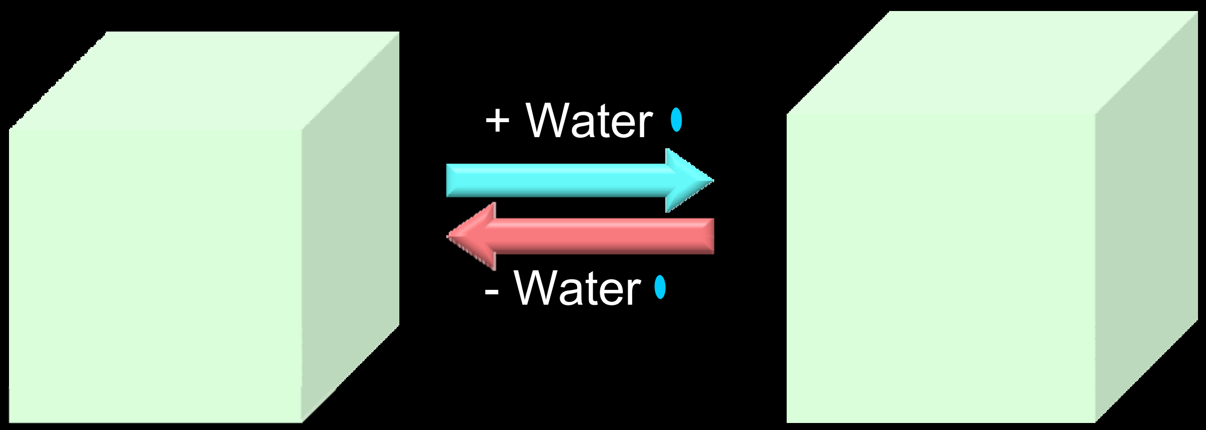


Hydration of fibers along with negative charge minimizes whisker interactions

→ Dispersed Solutions

Chemo-responsive Nanocomposites?

Stiff Film



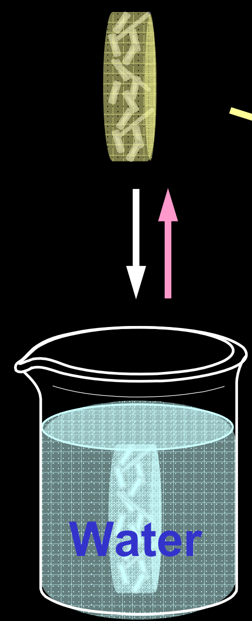
Soft Film

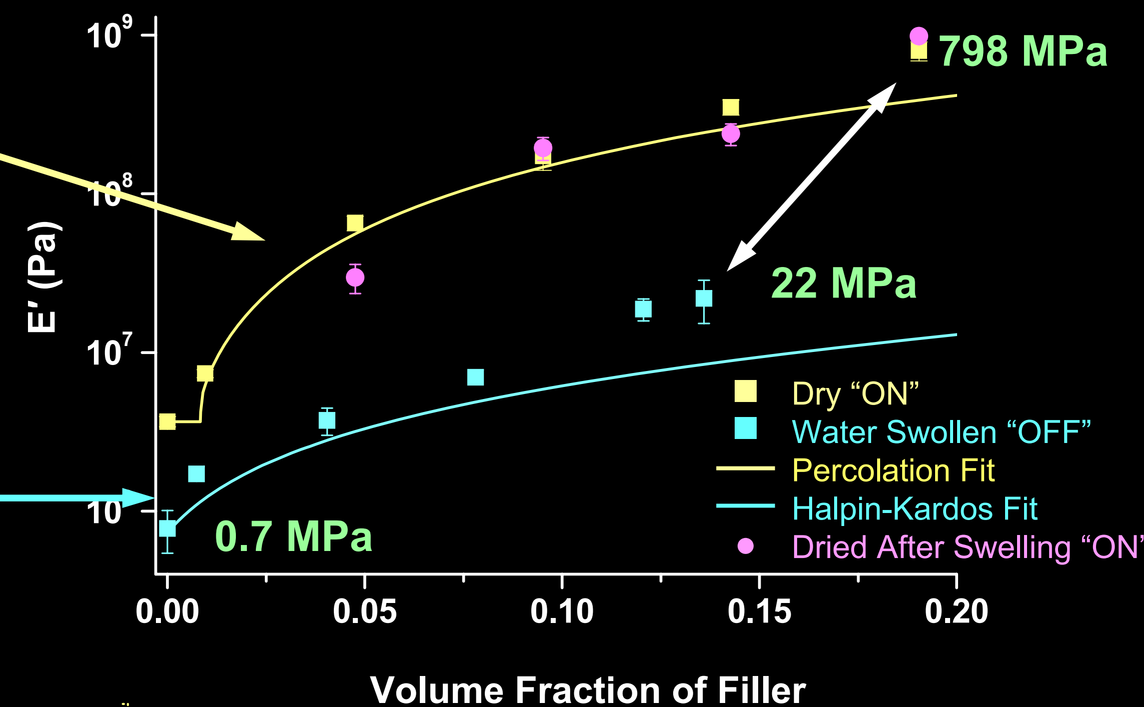
Whisker interaction "on"

Whisker interaction "off"

Mechanical "Switching"

By Hydration





Submerged in water films swells ~ 26% at equilibrium

Hydrated composites no longer fit percolation ("ON") model, but fall just above the Halpin – Kardos ("OFF")

System is Reversible

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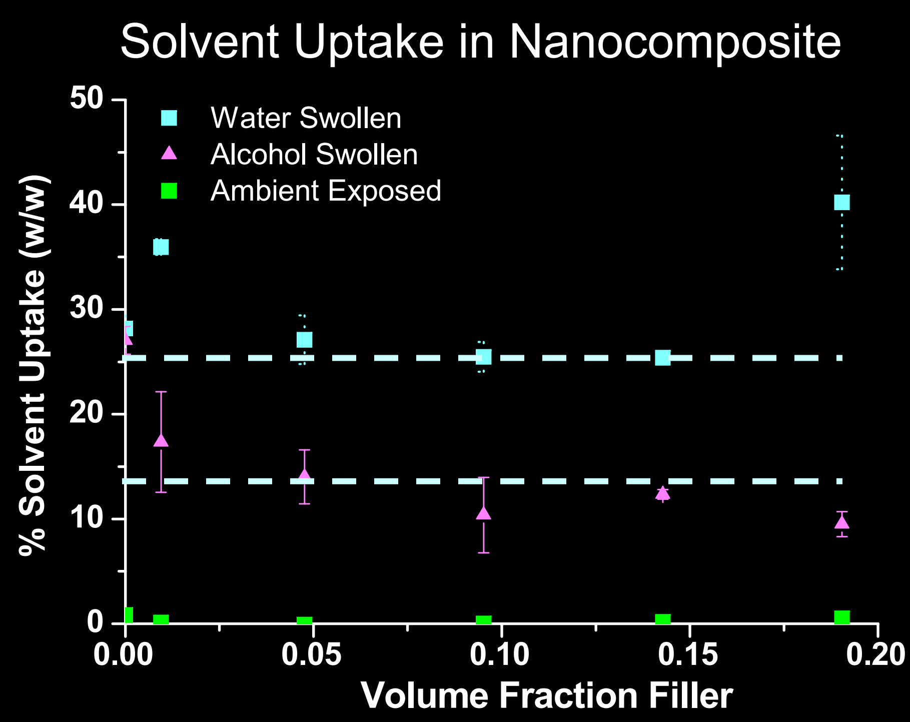
Capadona, et. al. *Science* 2008, 319(5869); 1370-1374.

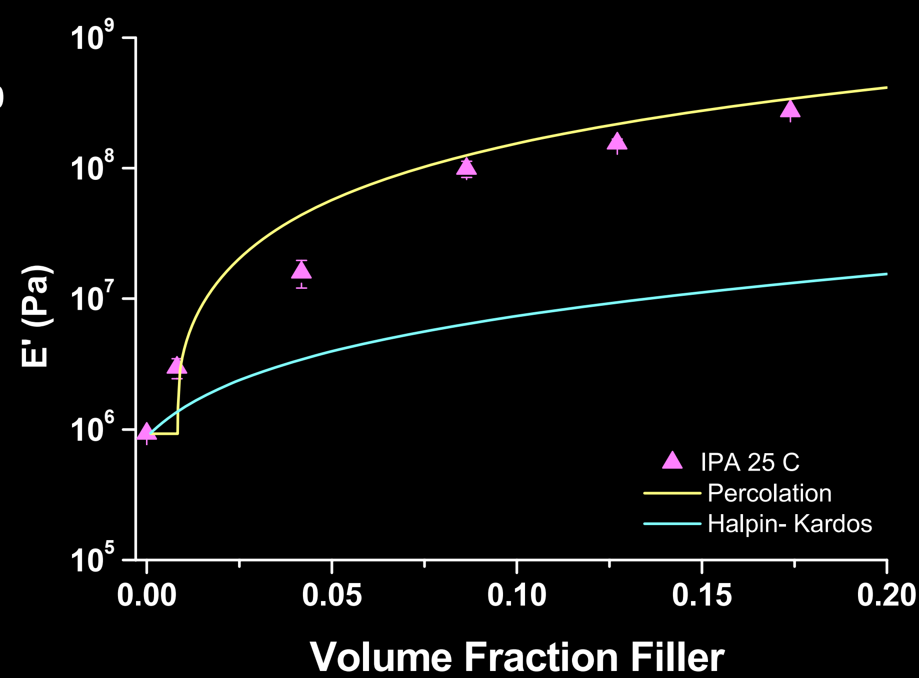
Is the Mechanical Switching Caused by….. Simple Swelling?



Submerged in solvent until at swollen equilibrium;

Water ~ 26%,

Isopropanol ~ 14%



Alcohol swollen nanocomposites do not "switch off" the whisker percolation

⇩

Response is chemoselective

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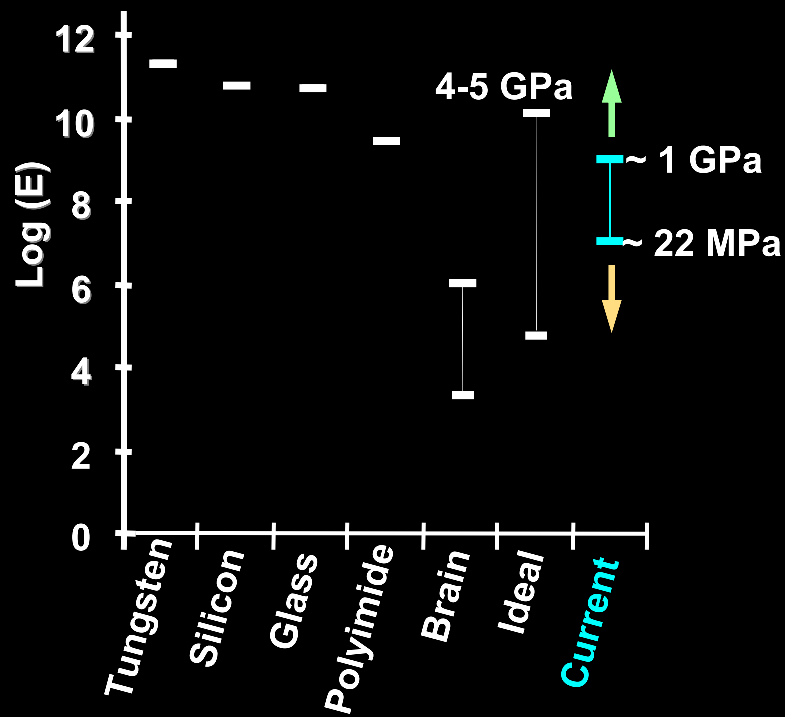
Capadona, et. al. *Science* 2008, 319(5869); 1370-1374.

Summary So Far and Next Steps



Over all goal of mechanical switching over 4 to 6 orders of magnitude, demonstrated 2 orders.

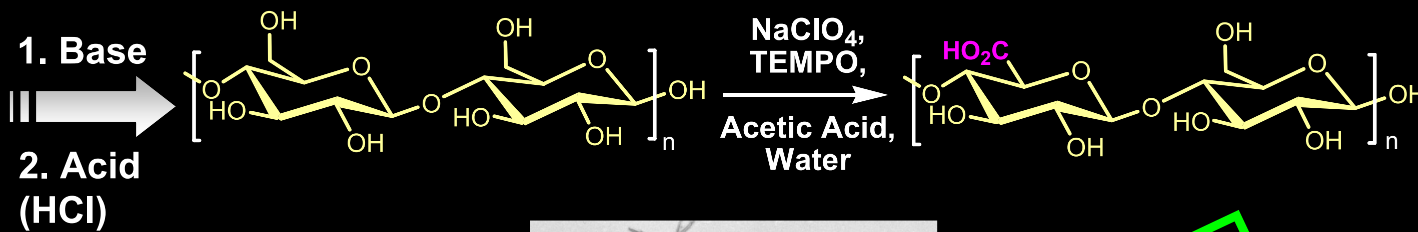
Need to decrease modulus in “OFF” state, and increase modulus in “ON” state.

Decrease → complete the dissociation of whisker – whisker interactions

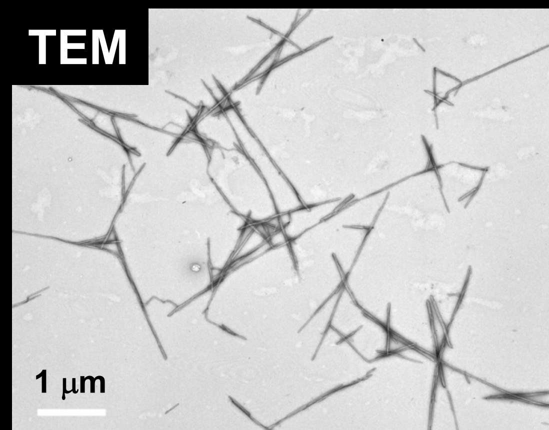
Increase → use synergistic effects to increase overall modulus

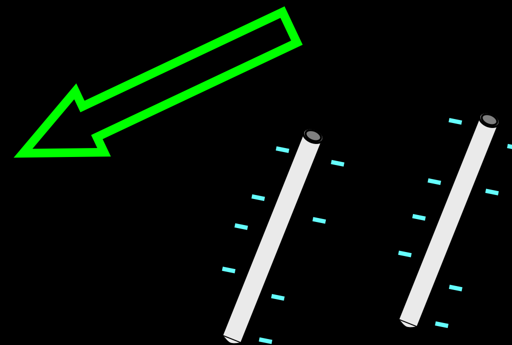
Surface Modifications to Cellulose

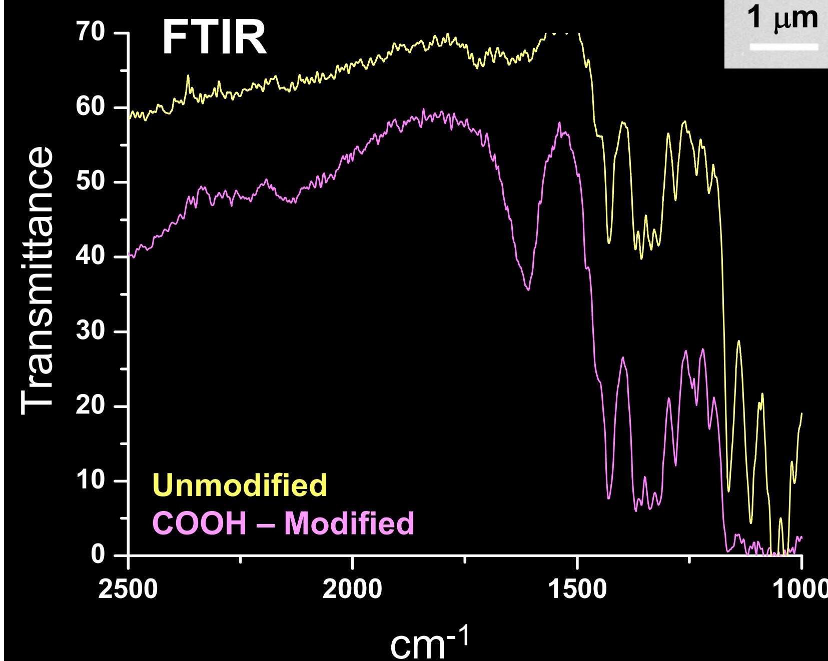
Methods

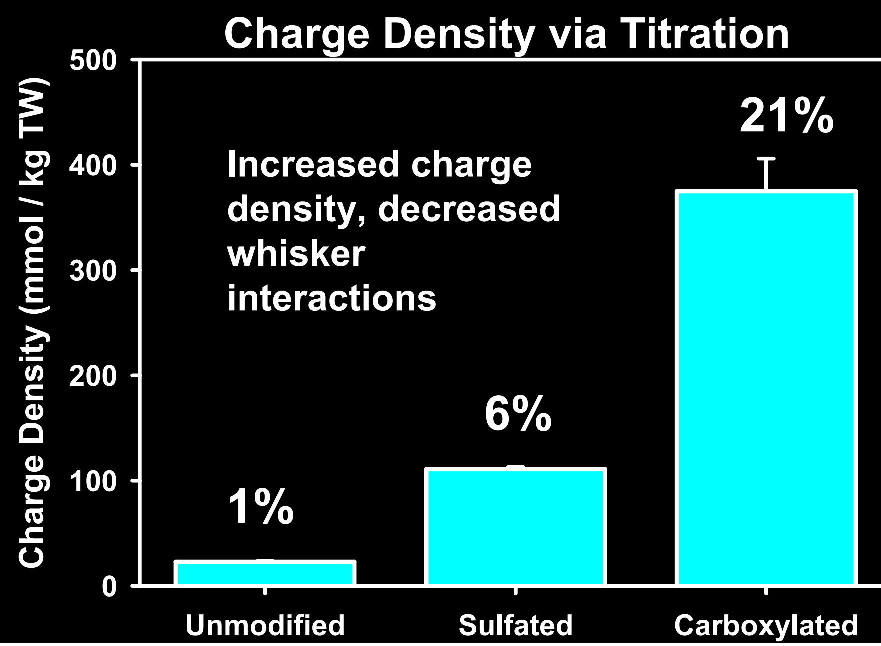


L = 735 nm +/- 573 nm
d = 10 nm +/- 3.4 nm
Aspect ratio = 75









Decreasing the Modulus of the "OFF" State

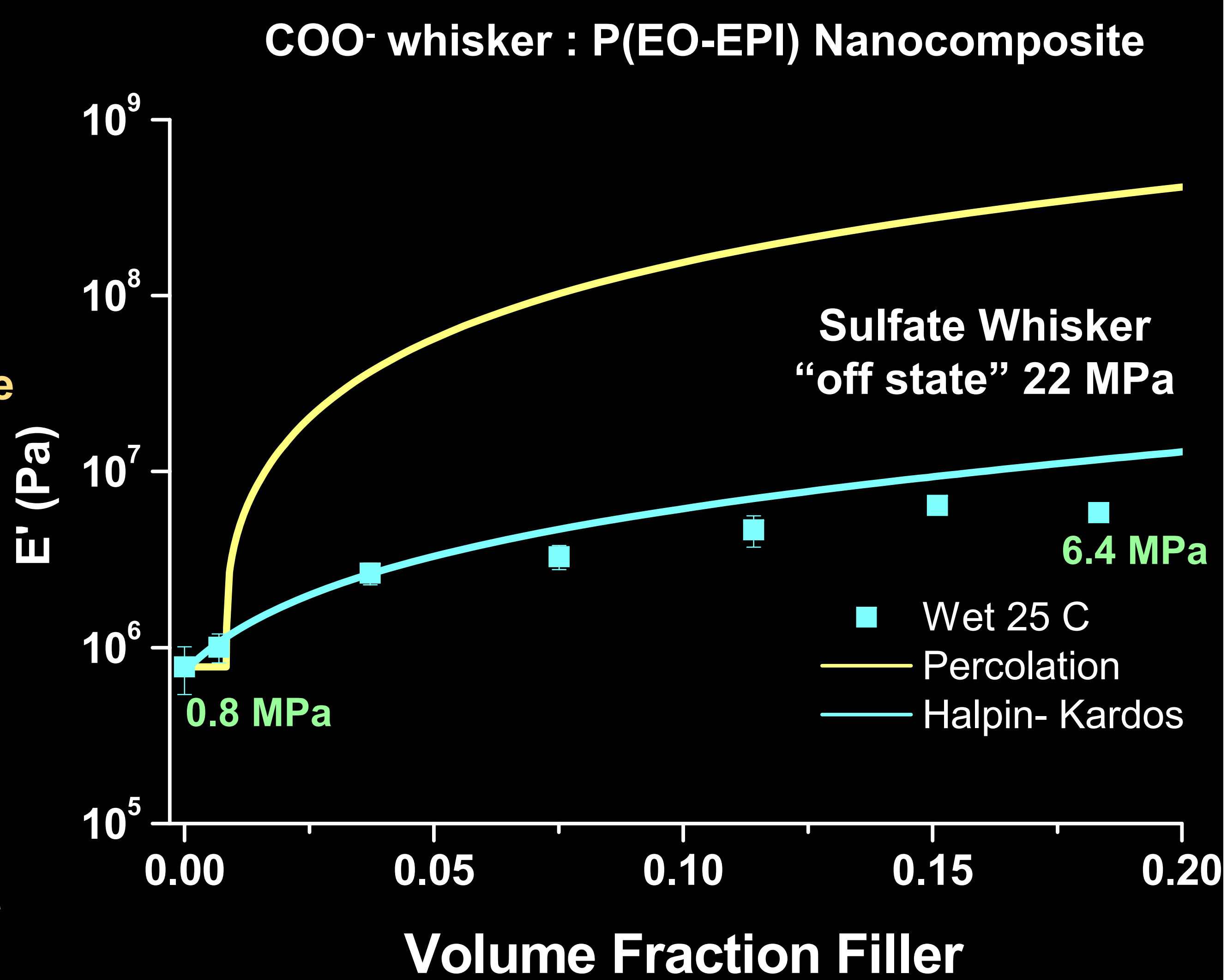
Tune "OFF" state through chemical modifications of the whiskers.

⇩

Suggests more complete dissociation of the whisker – whisker interactions.

⇩

6.4 MPa is within range of current goals for soft – compliant materials for cortical probes.



Increased contrast by 1 order of magnitude!!

Synergistic Mechanical Strengthening

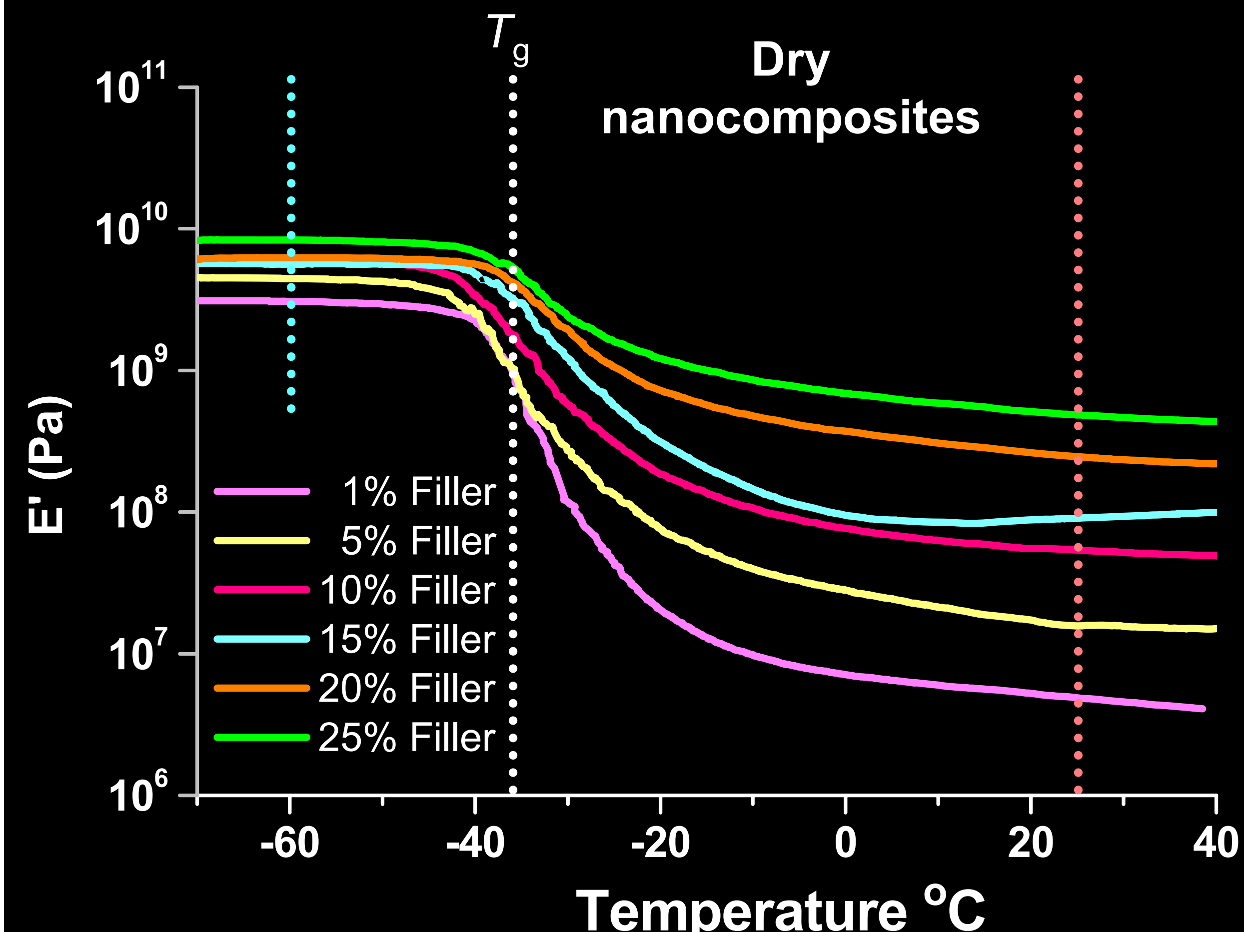
- **Systems evaluated** thus far have only exploited **reinforcement properties within the rubbery state** of the matrix polymer

- Utilize thermal induced transitions within the matrix polymer
  - Glass transition temperature (T_g)
    - Often accompanied by a significant mechanical change

Synergistic Mechanism

Using T_g to Increase the "ON" Modulus

COO^- whisker : P(EO-EPI) Nanocomposite - Full Temperature Sweep



Nanocomposites with dramatic 1000 fold modulus contrast from "Stiff" to "Soft" states.

⇩

Temperature range not applicable to cortical probes (biomaterials)

Filler (15%)	Dry - 60°C	Dry 25°C
SO_4^--TW	10.7 GPa	798 MPa
CO_2^--TW	6.3 GPa	235 MPa

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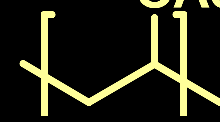
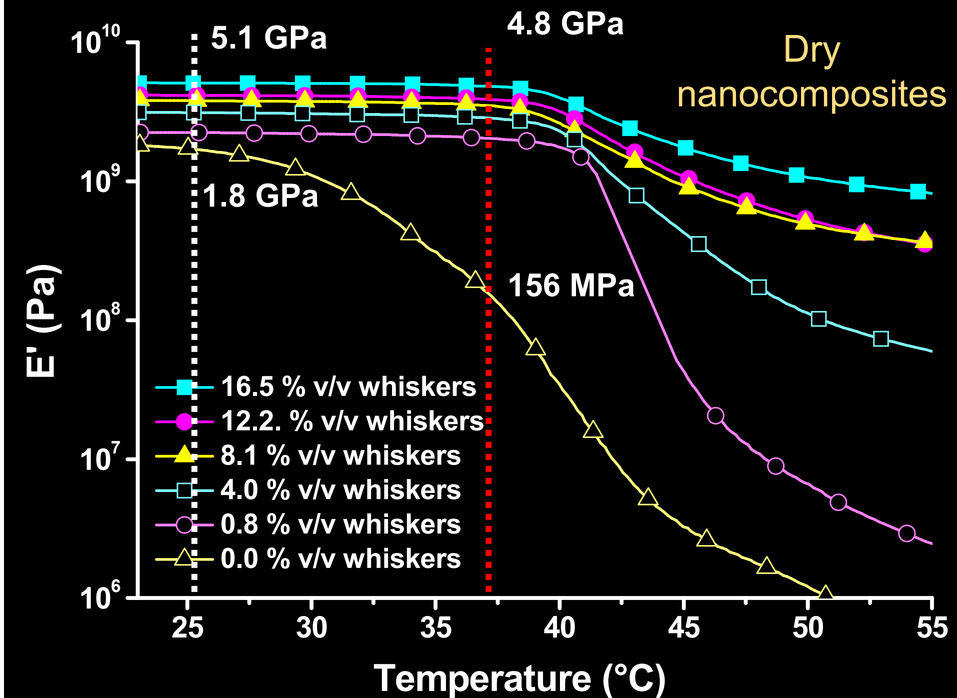
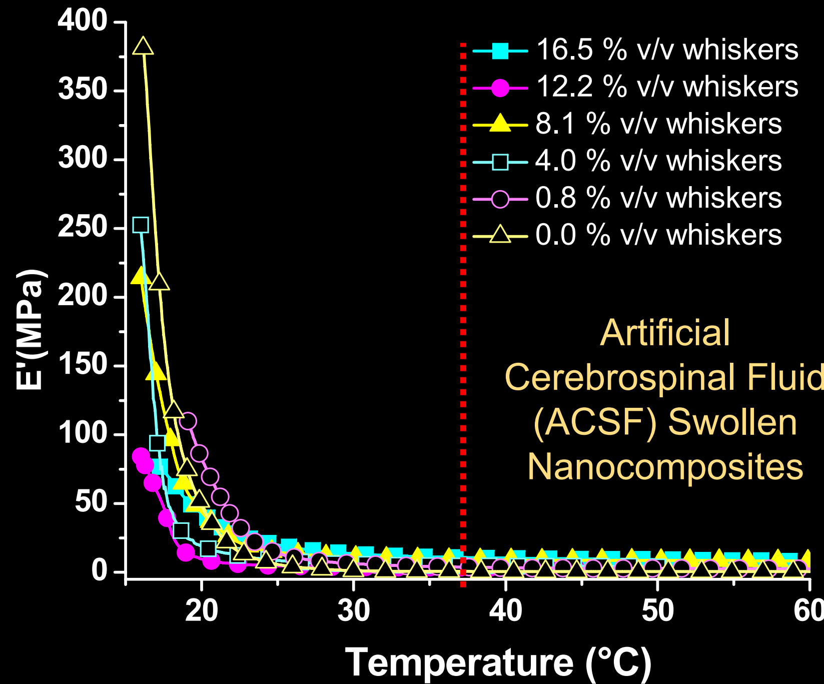
Second Generation Materials   Poly(vinyl acetate) nanocomposites

Poly(vinyl acetate) nanocomposites

T_g (~42°C) above room temperature and physiological temperature
Minimal aqueous swelling (4.5%) allows for synergistic switching mechanisms







Demonstrated significant reinforcement with increased filler density above and below T_g

T_g shifted to higher temperatures with the introduction of cellulose fillers

Aqueous swelling plasticizes nanocomposites, lowering T_g to below physiological

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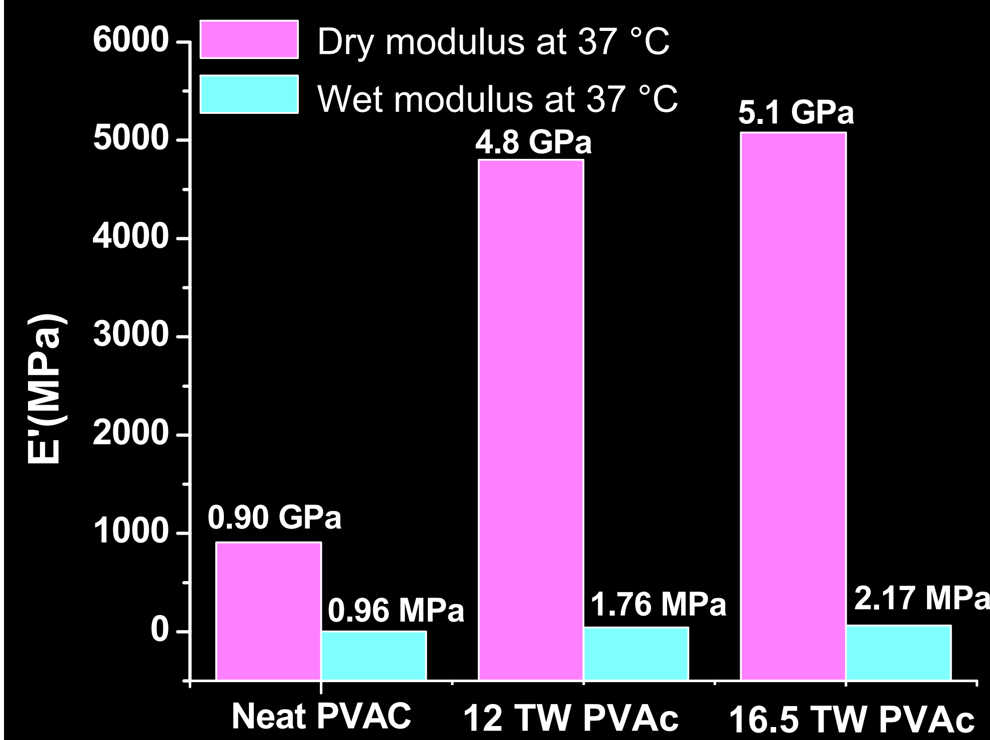
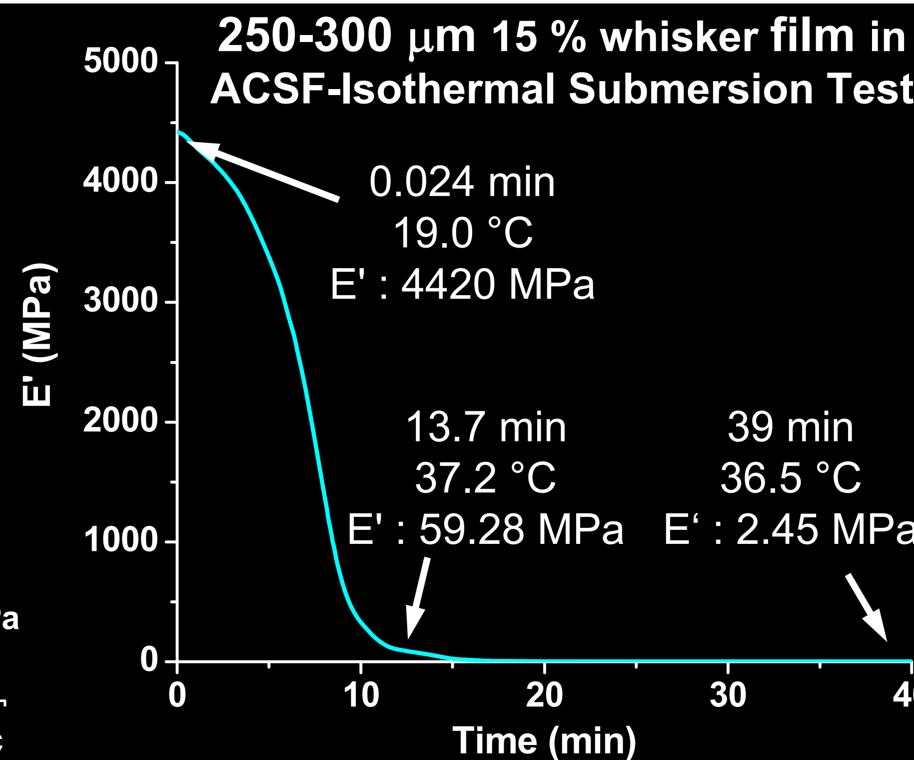
Capadona, et. al. *Science* 2008, 319(5869); 1370-1374.

"Switching" of the PVAc Nanocomposites

Application Relevant





Relatively fast mechanical switching from GPa to MPa range

Initial degradation studies show no loss of mass or mechanical integrity after 3 months

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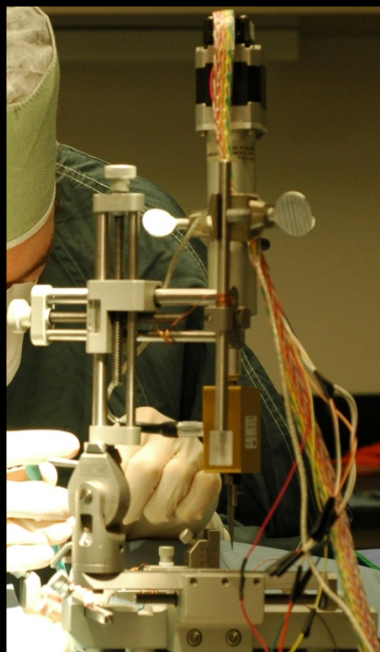
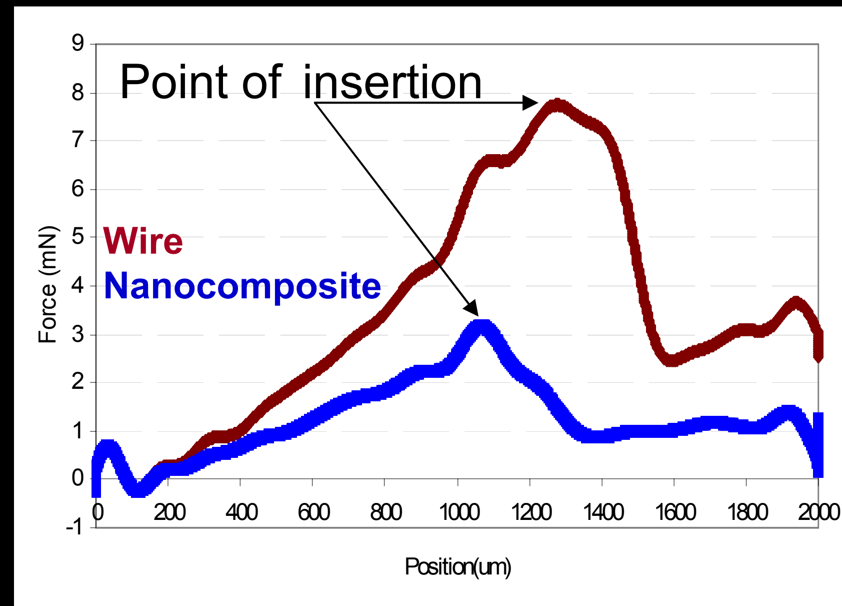
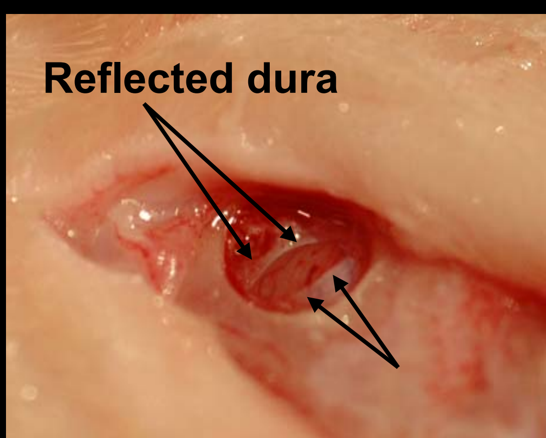
Capadona, et. al. *Science* 2008, 319(5869); 1370-1374.

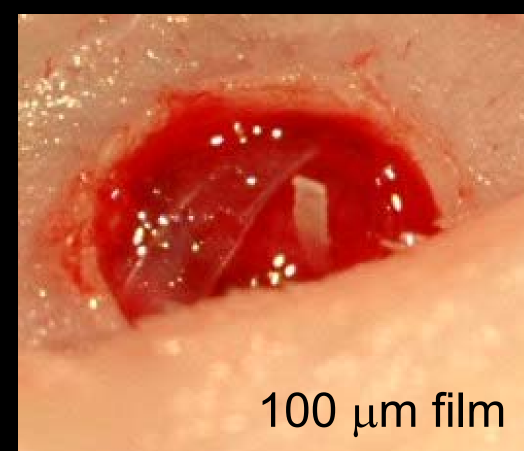
Nanocomposites As Cortical Implants



Inserter mounted to a stereotaxic frame to measure the insertion force



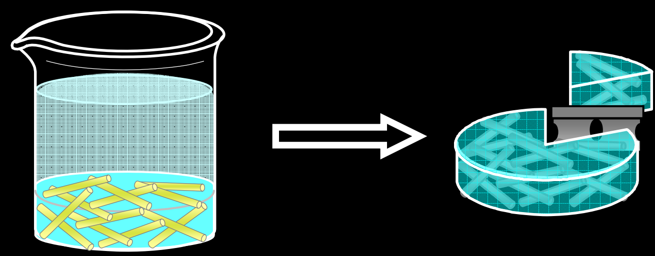




- **Preliminary *in vivo* experiments demonstrate improved tissue response**
  - **Hand cut crude shaped materials**
- **EECS – laser guided fabrication of electrodes**
  - **Acute recordings of action potentials from single neurons within the cockroach**
  - **Large chronic tissue response currently underway (~30 rats)**

Conclusions

- **Established robust processing methods to access percolating nanocomposites with nearly ANY matrix polymer**
  - **tailored for specific applications**



- **Developed mechanically-dynamic materials modeled after the sea cucumber's defense mechanism**
  - **contrast in modulus of over 1000 fold through control of supramolecular interactions**

- **Preliminary results suggest that the dynamic nanocomposite cortical electrodes will increase the longevity of the electrodes, and could lead to more clinical application of the technology.**

Acknowledgements

Thank you – Questions???

- Contributors / Collaborators
  - Dr. Christoph Weder & Lab – Materials development
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