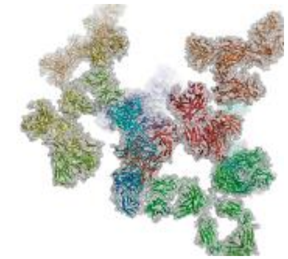
Keith Johnston Research Group

Nanomaterials Chemistry/Colloid and Interface Science/Polymer Science

kpj@che.utexas.edu



Protein stability and drug delivery

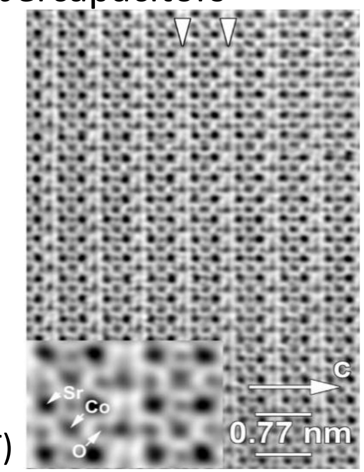
Morphology and protein-protein interactions

Rheology: subcutaneous injection

Adv. Fxn'l Nanomaterials (metals, metal oxides, polymers))

Electrocatalysis = f (morphology) electronic properties, mechanistic pathways

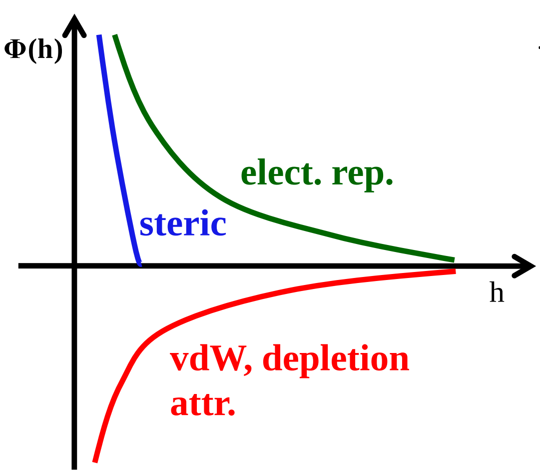
O_2 reduction and evolution reactions for water splitting and metal air batteries, supercapacitors
Biodegradable photonic Au nanoclusters for cancer imaging



Nanoparticle Interact. with Liq. and Solid Interfaces

Oil/water and gas/water interfaces (emulsions and foams)

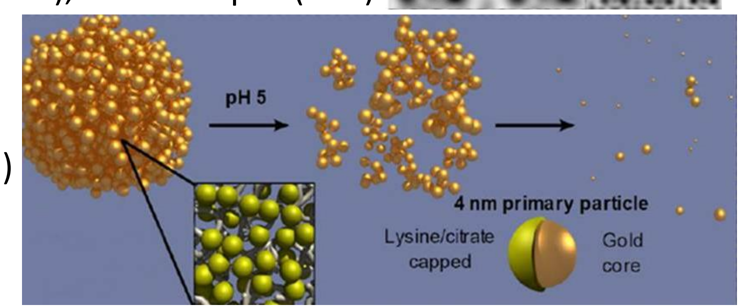
Solid surfaces (adsorption and transport in porous media)



Collaborators
Tom Truskett, Nate Lynd, Kurt Pennell

Keith Stevenson (Skoltech), Sheng Dai (ORNL), Alexie Kolpak (MIT)
Kostia Sokolov, (M.D. Anderson)

Masha Prodanovic, David DiCarlo
George Hirasaki, Quoc Nguyen (Petr. Eng.)

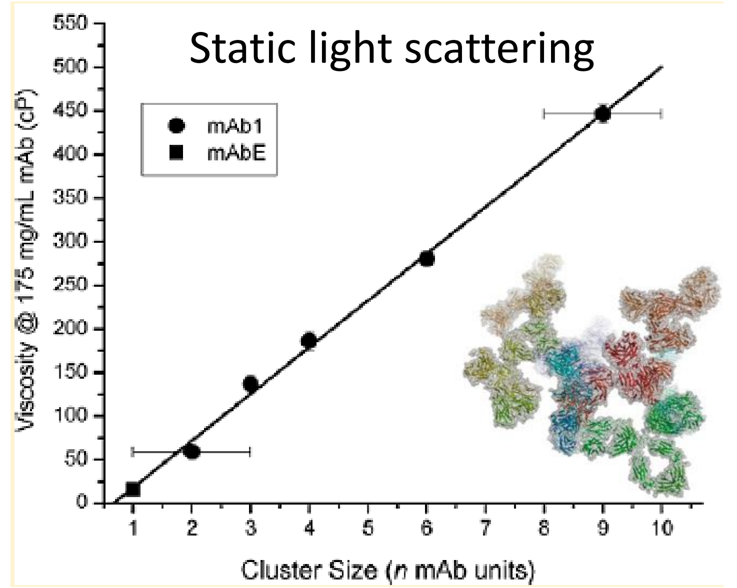


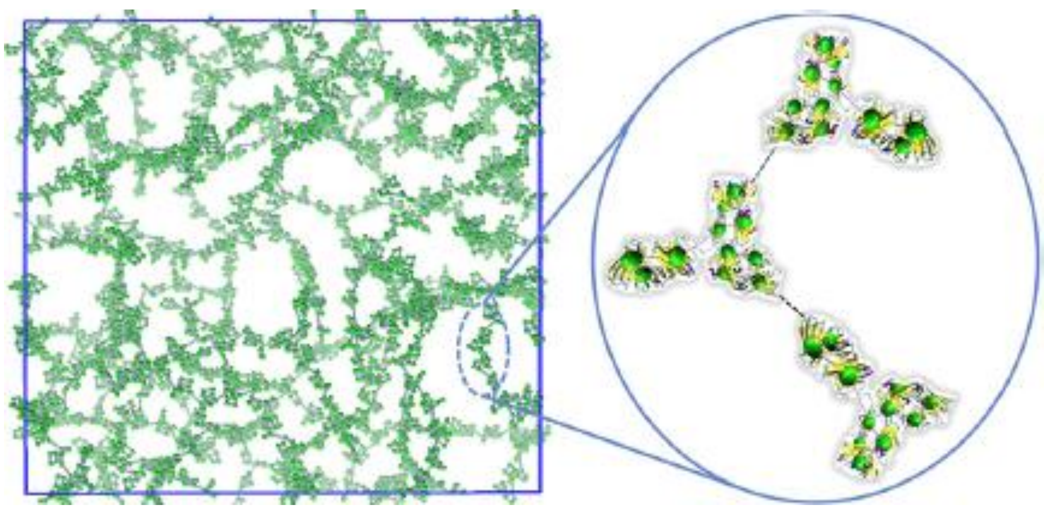
Subcutaneous injection (SC) of concentrated monoclonal antibodies at 300 mg/ml is a major drug delivery challenge

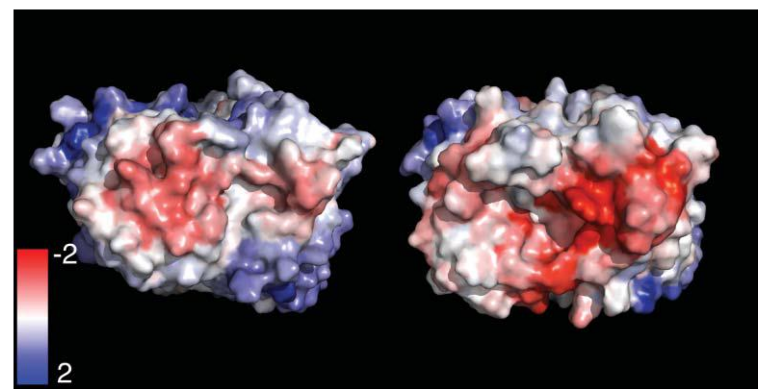
- >20% of all biopharmaceuticals in clinical trials are mAbs
- cancer, allergies, asthma, inflammatory diseases, cardiovascular diseases, infectious diseases, etc.

Name	Indication	Company	Conc.
ACTEMRA	RA, juvenile arthritis	Genetech	180mg/mL
Herceptin	Breast and gastric cancer	Roche	120 mg/mL

- At high conc. spacings are small – specific short-ranged attraction cause association and high viscosity
  - Hydrogen bonds, anisotropic elect. attraction
  - Hydrophobic interactions







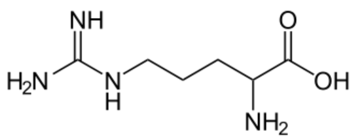
Fv domains: light chain on left side
Red: exposed negative patches

Agrawal et al, mAbs (16)

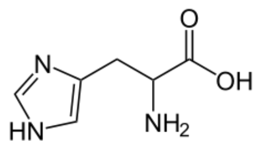
Fukuda et al., *Pharm Res* (2015), Lilyestrom et al., *JPCB* (2013), Buck, et al., *Mol Pharm* (2012)

Use co-solutes to mitigate attractive interactions to lower viscosity up to 10 x

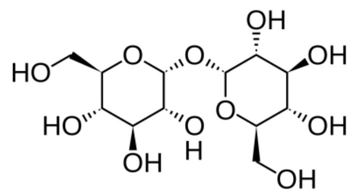
- Local anisotropic electrostatic attraction
- Hydrophobic interactions
- Depletion attraction



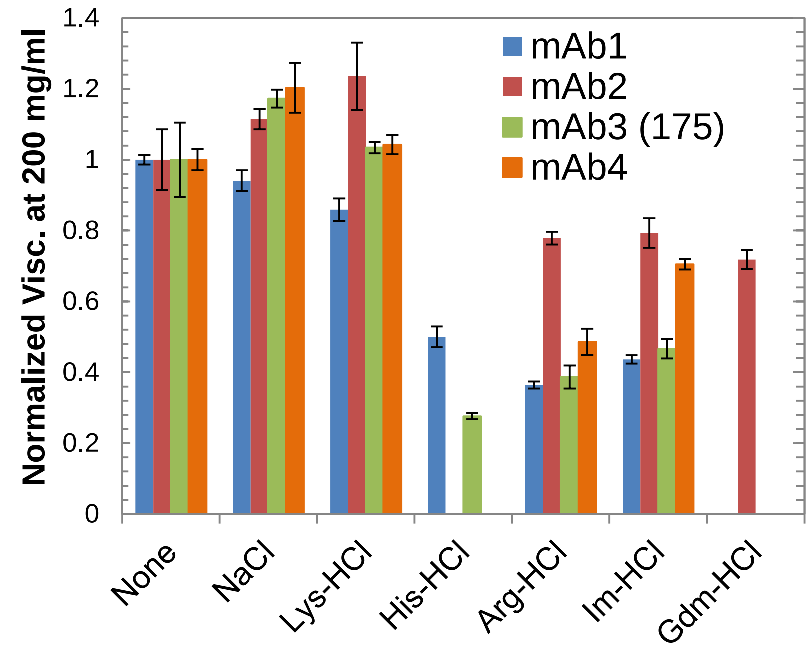
Arginine



Histidine

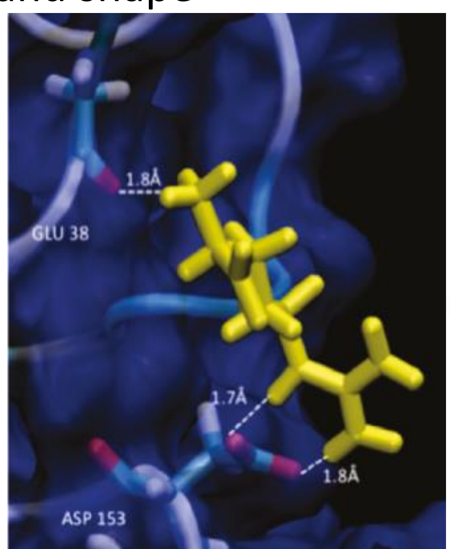


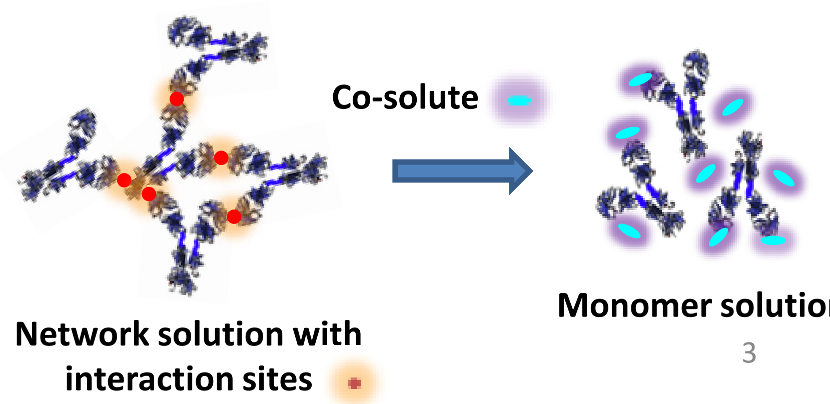
Trehalose



$$\frac{\eta}{\eta_0} = exp\left(\frac{c[\eta]}{1-c[\eta](k/\nu)}\right)$$ Ross-Minton

- k/ν is ratio of crowding and shape factors
- $\eta_{inh} \equiv \frac{ln(\eta/\eta_0)}{c}$





Chari et. al., *Pharm. Res.* (2009), Shukla et al., *JPCB* (2011), Hung et al., *J Membr. Sci.* (2016)

Research Goals

- **Understand co-solute effects on protein viscosity/stability as function of interactions with proteins- break networks**
- **Characterize protein morphology, protein-protein interactions and network structure for 200-250+ mg/mL mAb**
  - Static structure: SAXS, DLS, SLS,
  - Dynamic structure: DLS, shear rheology
  - Conformational stability: DSC/DSF, intrinsic fluorescence, CD
- **Relate viscosity/stability to protein morphology and interactions**
  - Effect of mAb structure, pH, and ionic strength
  - Develop design rules for cosolutes to achieve low viscosity (10 – 20 cP) and high stability

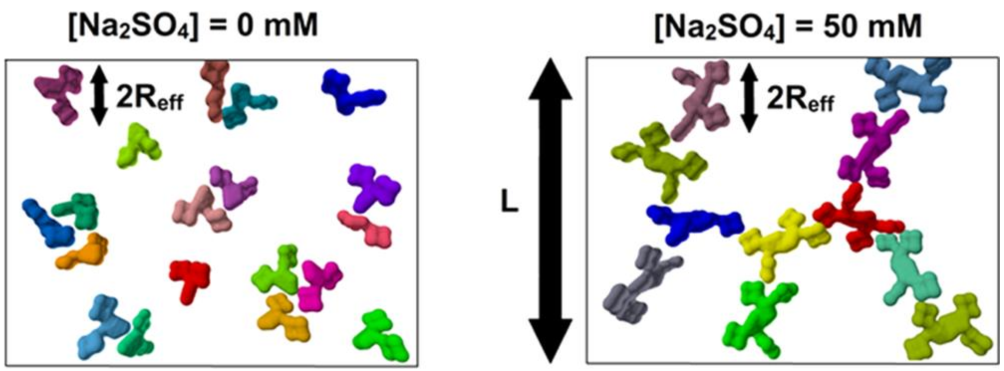
- **Sponsors: NSF Inspire, Abbvie, Pfizer, Merck**

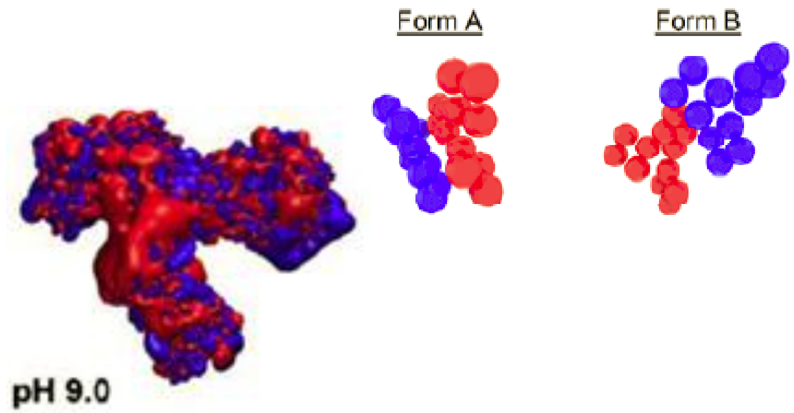
Proposed: SAXS- Determine interactions from structure factor S(q) using 12 bead model for form factor P(q)

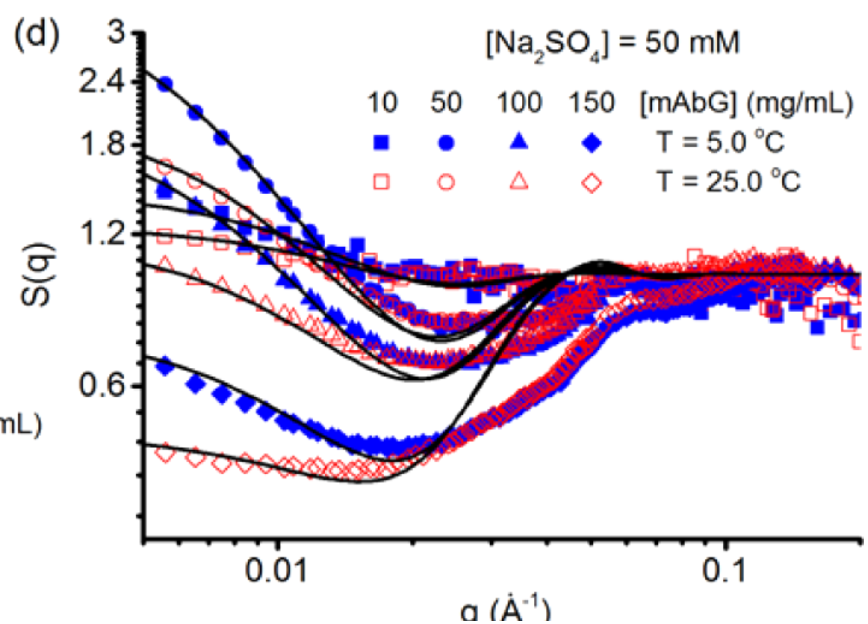
- Viscosity incr. by network formation of dimers w/ added salt.

$$I(q) = c * (\Delta\rho)^2 * P(q) * S(q)$$

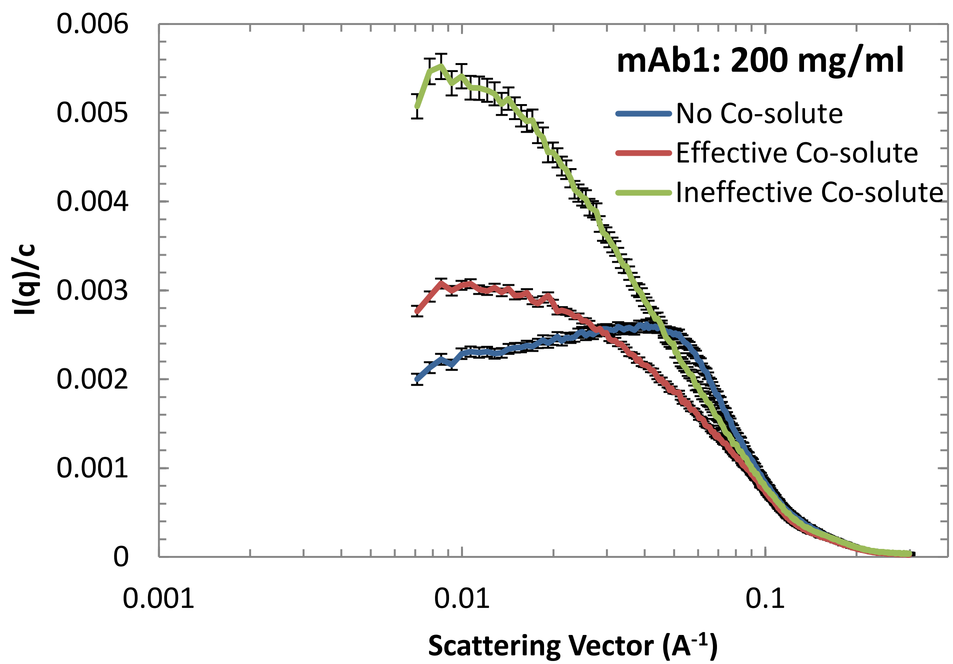
Dimer Conformations







Godfrin, et al., *JPCB* (2016)

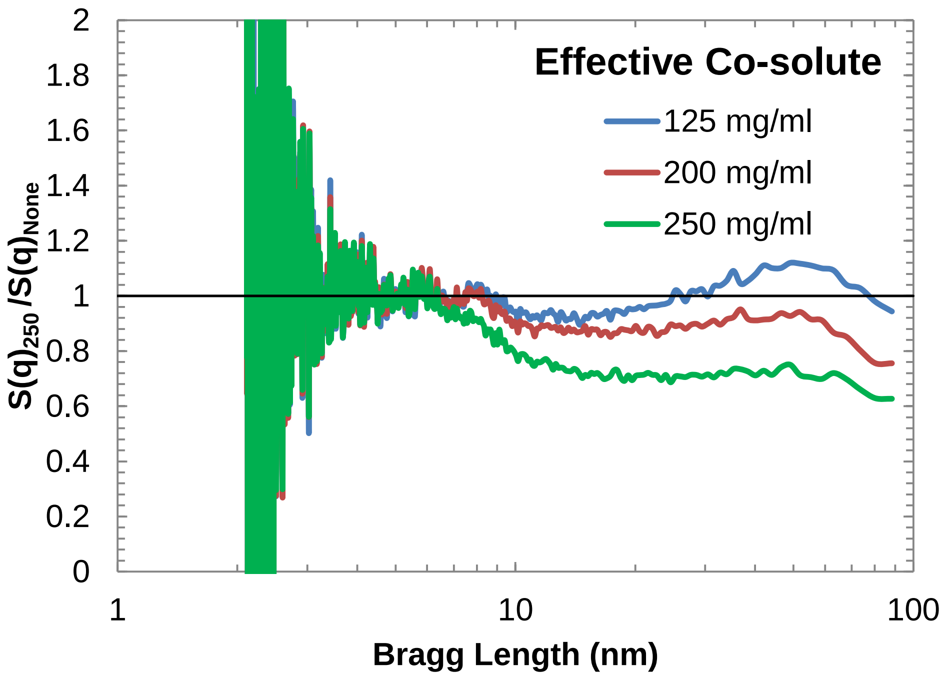


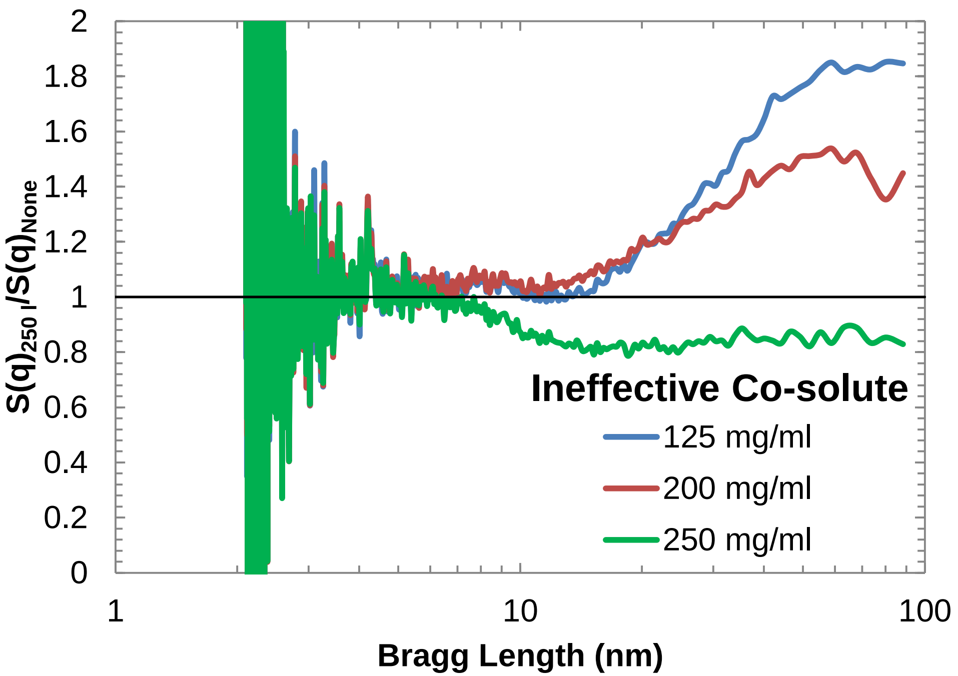
SAXS: Co-solutes cause lower $S(q)_{eff}$ at higher conc

- Dividing $S(q)_{co\text{-}solute}$ over $S(q)_{none}$ shows the relative attraction/repulsion between samples with co-solute compared to those without co-solute for each q value
- Each q can be converted into a length scale

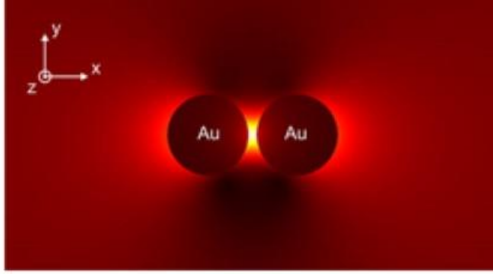
$$l_{Bragg} = \frac{2\pi}{q}$$

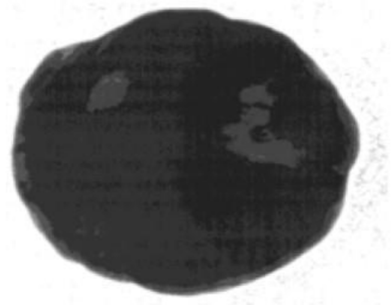
- As protein conc↑ and protein average spacing↓ the net effect of co-solutes is to increase net repulsion/decrease net attraction
- Eff causes more repulsion than Ineff for all concentrations





NIR Photoacoustic Imaging /Therapy: Cancer Theranostics

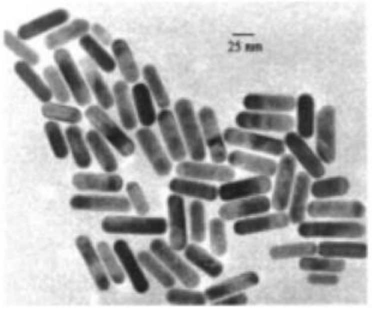




Nanoshells

d = 130 nm

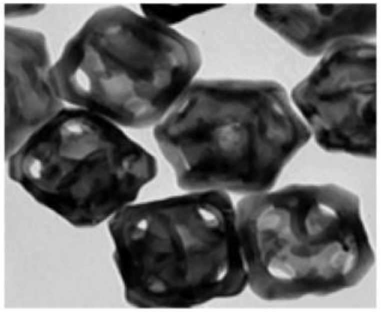
Hirsch et al. (2003) *PNAS*



Nanorods

15 nm x 50 nm

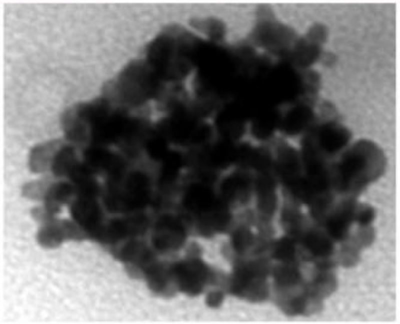
Link et al. (1999) J Phys Chem B



Nanocages

x = 50 nm

Skrabalak et al. (2007) Adv. Mater.

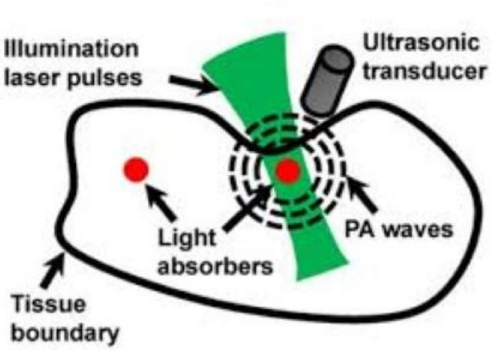


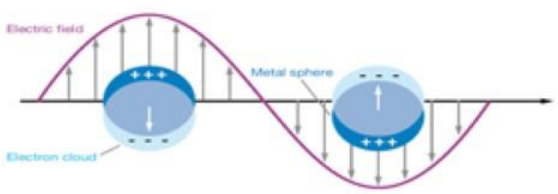
Nanoclusters

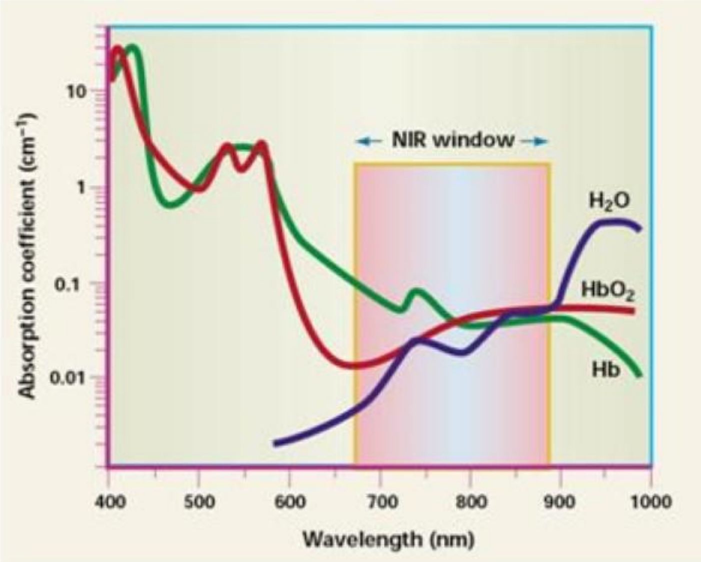
d = 30-80 nm

Tam, KPJ ACS Nano(13), Langmuir (10)

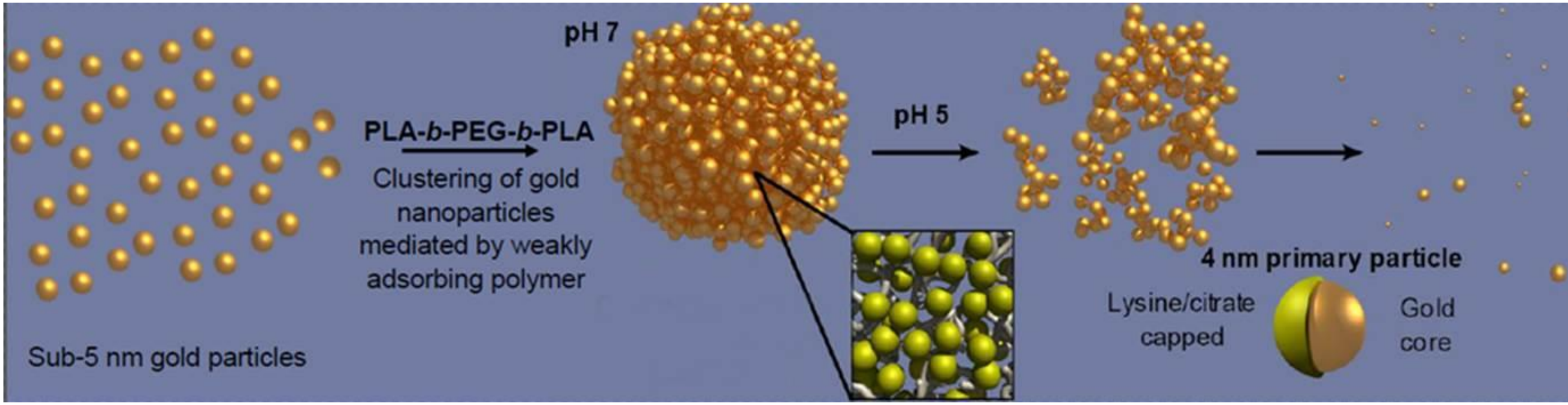
- **Asymmetry shifts SPR from 532 nm to NIR- dipoles/multipoles**
- **Challenging to achieve NIR for particles < 5nm**
- **Clearance possible for biodegradable nanoclusters**

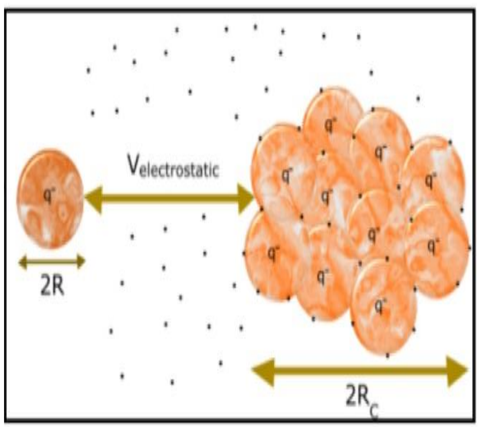


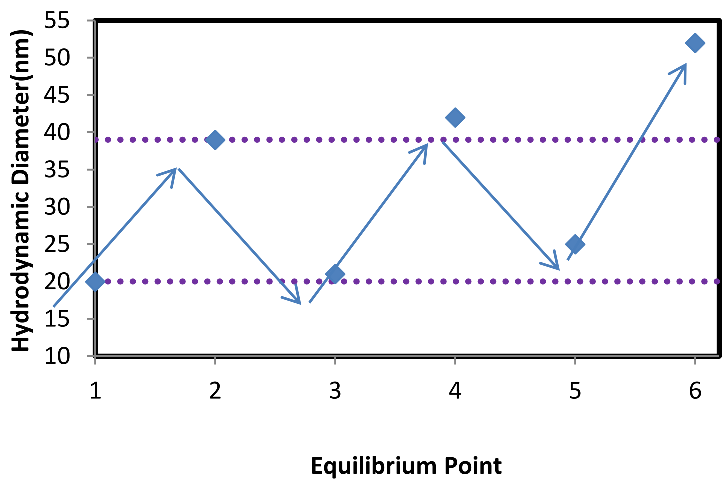


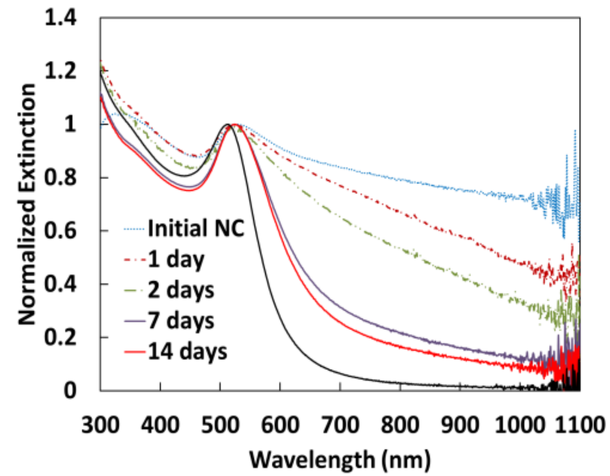


Reversible Gold Nanoclusters for Imaging/Therapy





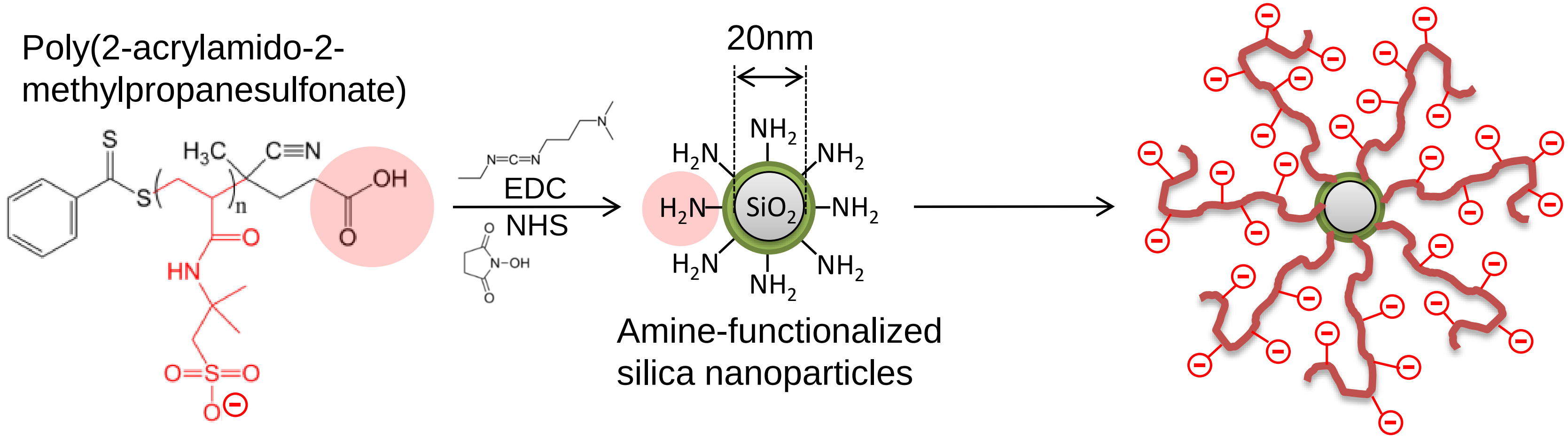


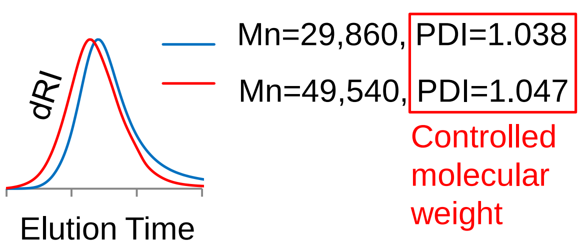


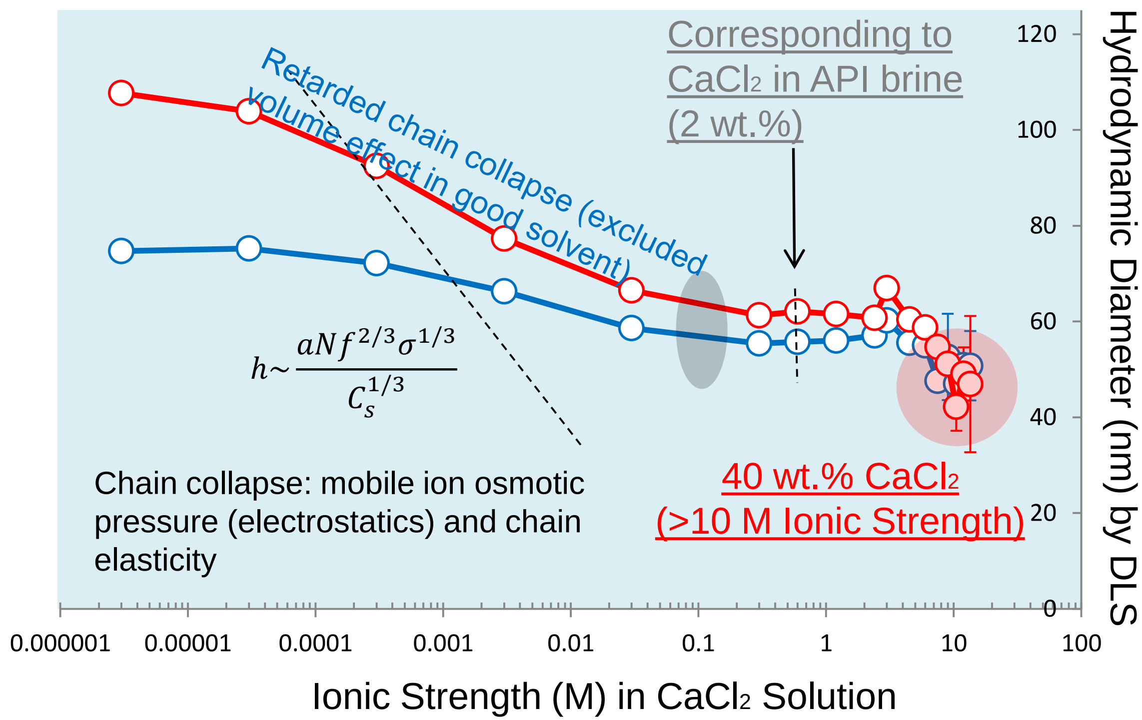
- **Reversible equilibrium control of cluster size: self-limited growth**
- **NIR active nanoclusters with small particle spacing**
- **Design reversibility and lack of protein adsorption for clearance**

Johnston, Sokolov, Truskett, Stover, Moaseri: ACS Nano (13), JACS (13), JPChem (14), Langmuir (16)

Chain Extension of Polyelectrolyte Brushes Grafted to Colloidal Silica Nanoparticles in High Salinity Brines

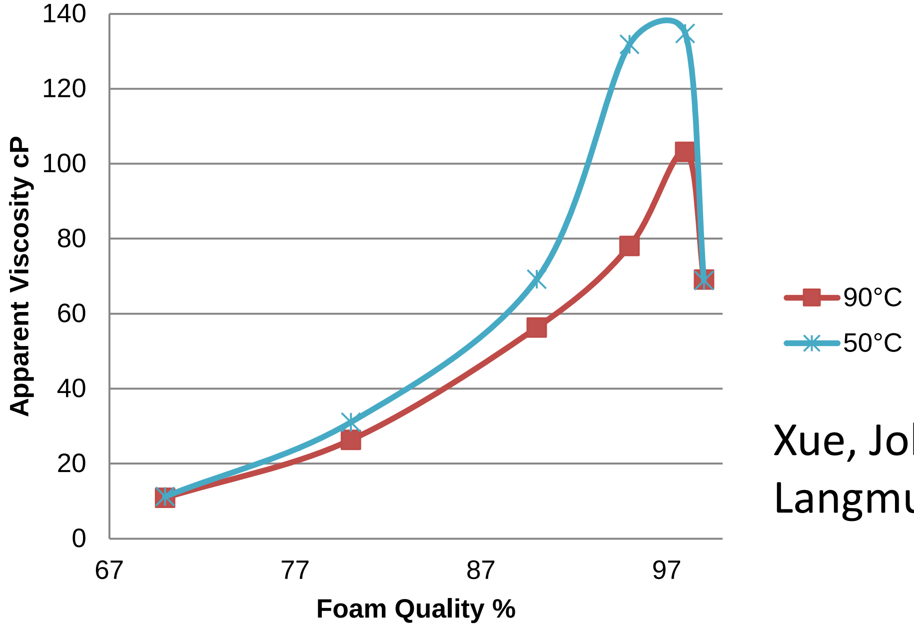






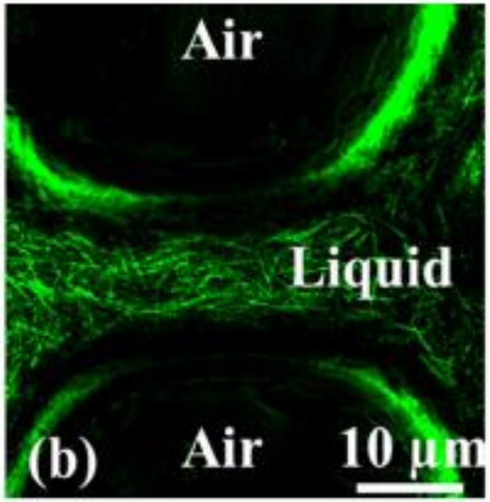
- Lack of aggregation even at 40 wt.% $CaCl_2$ (>10 M Ionic str.)
- Greater solvation than polystyrene sulfonate
- Little change in hyd. diam. to 90 C
- Iqbal and Johnston, KP (17), Bagaria and Johnston, KP (13)

Wormlike Micelles Impart Viscoelasticity for Ultra Dry Foams



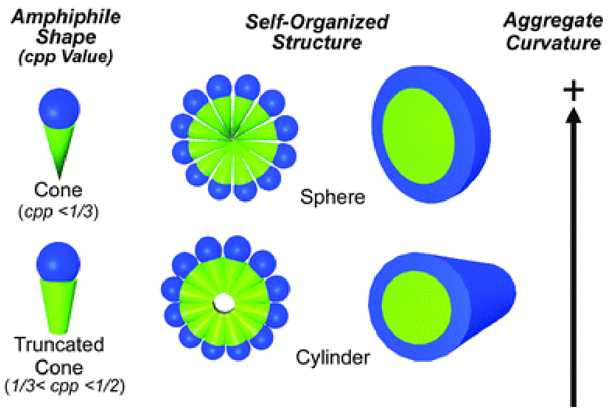
- 208 trillion m^3 of CH_4 in shale (world)
- 2~5 million gallons of water/well for disposal

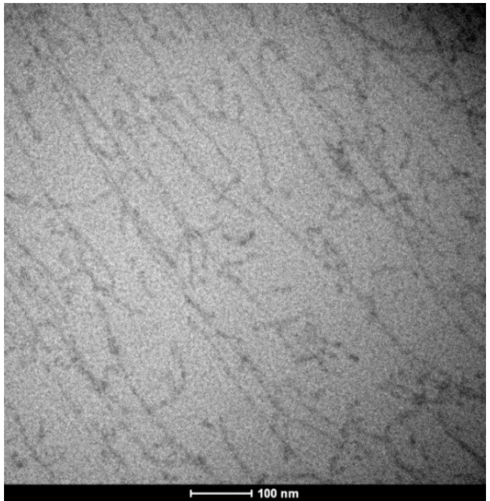
Xue, Johnston, KP, Langmuir (16)

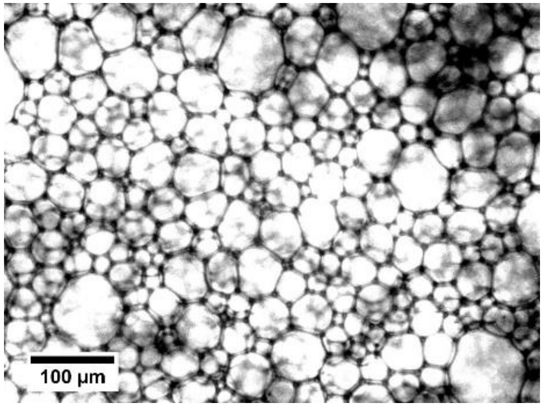


Stable foams at only 2% water:
low drainage of viscoelastic lamellae
thicker lamellae resist Ostwald ripening and coalescence

Catanionic micelles:
Jamming: slow drainage maintains thick lamellae
Fameau et al., Ang. Chem. (11)



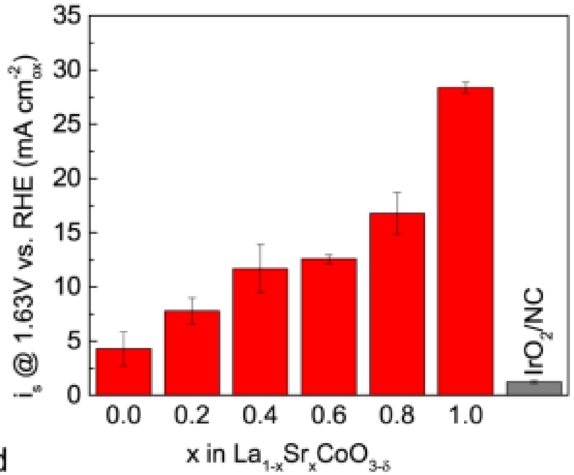




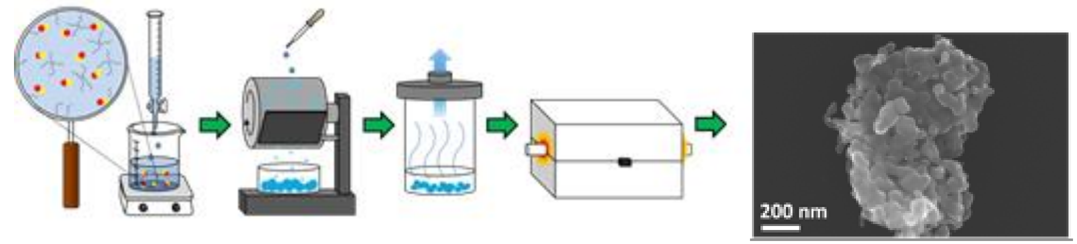
Nanostructured Perovskite Oxides for Electrocatalysis: batteries, supercapacitors, water splitting

Oxygen Evolution Reaction (OER)

$$4OH^- \rightarrow 2H_2O + 4e^- + O_2$$



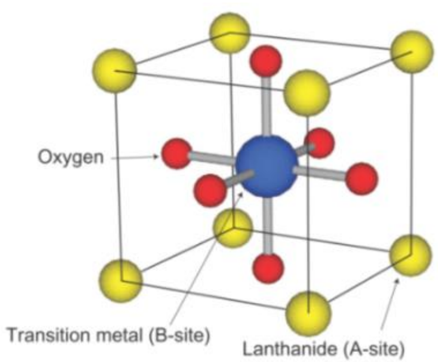
High Surface Area to raise activity

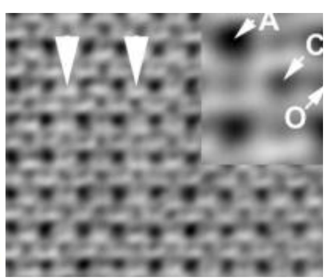


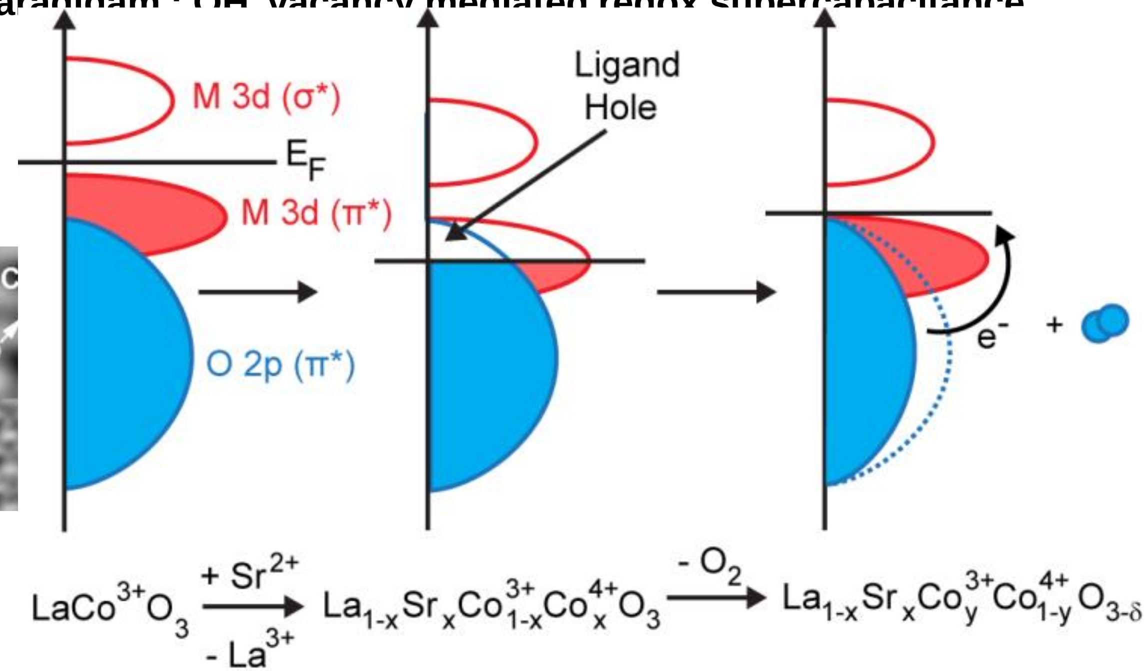
Subst. of Sr^{2+} for La^{3+} creates O vacancies: high covalency of Co-O bond

OER rate correlated to O vacancy conc.

Novel paradigam : OH- vacancy mediated redox supercapacitance







Hardin, **Johnston**, K.P. et al. ; Highly Active $LaNiO_3$, *J. Phys. Chem. Let.* **2013,** Mefford, Hardin, **Johnston**, K.P. et al. ; $LaMnO_3$ Pseudocapacitor, *Nature Mater.* **2014**

Hardin, Mefford, **Johnston**, K.P. et al. ; Perovskite Active Site Variation, *Chem. Mater.* **2014,** *Nature Comm.* **2016**

Destination of PhD Students

Gupta	Auburn
Balbuena	Texas A + M
Meredith	Ga. Tech.
Yates	U. Rochester
Da Rocha	Virginia Tech.
Lee	U. S. California
Ziegler	U. Florida
Lu	Nat. Univ. Singapore
Elhag	Petroleum Inst. (Abu Dhabi)

Shah	Pfizer
Pham	Sematech
Chen	Abbott
Dickson	Exxon-Mobil
Smith	Exxon-Mobil
Overhoff	Schering-Plough
Engstrom	Bristol-Meyers-Squibb
Matteucci	Dow
Gupta	Exxon-Mobil
Tam	Bristol-Meyers-Squibb
Patel	Lam Research
Ma	Dupont
Miller	Medimmune
Slanac	Dupont
Murthy	Roche
Chen	Dow
Xue	Ecolab
Borwankar	Bristol-Meyers-Squibb
Worthen	Exponent

Protein therapeutics
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Gold imaging nanoclusters
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Subsurface nanotechnology
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Energy storage (electrochemistry)
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Caleb Alexander
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NSF Inspire Program
DOE CFSES, DOE NETL
Advanced Energy Consortium, AbbVie, Pfizer, Merck

Welch Foundation
Abu Dhabi Nat. Oil. Co.
GOMRI, NSF CBET,
NIH

Growth of 16 nm Magnetic Nanoparticles with High Crystallinity to Yield Magnetic Susceptibility of 4!

Precise control over particle nucleation/growth to control particle size and crystallinity

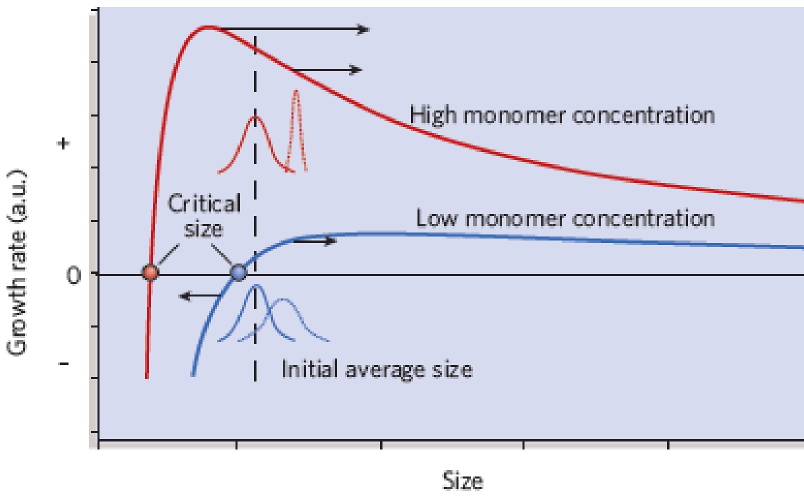
$Fe(CH_3COO)_2$ dissociates rapidly at 210 C: high supersat. for focused size distribution

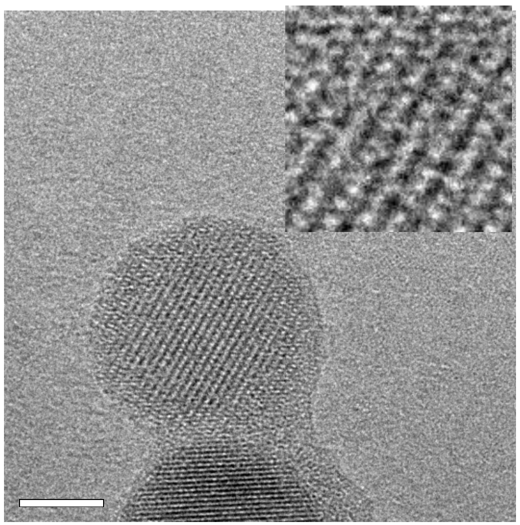
crit. size is small for high monomer conc.

small particles grow faster than large ones

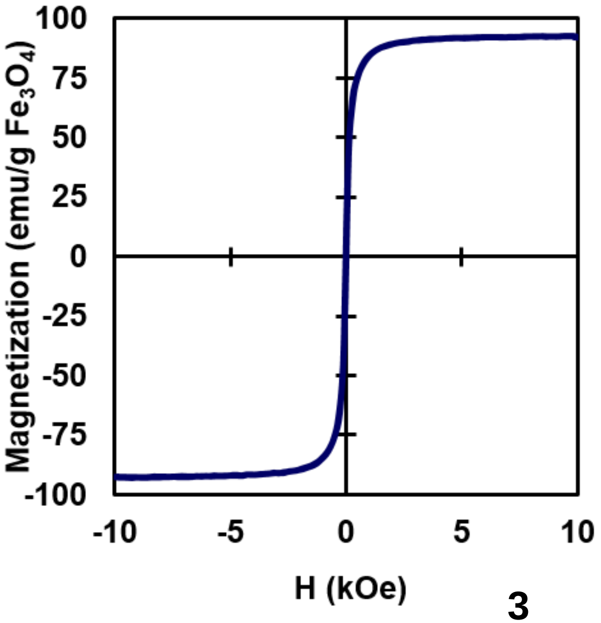
arrest growth in focusing region

Applications: imaging- subsurface and biomedical, magnetic separations, sensors





$$\chi_i = \frac{M}{H} = \frac{\epsilon \mu_0 \pi M_d^2 D_p^3}{18 k_B T}$$



Characterization: XRD (cryst. Structure), TEM: part. size, Mossbauer spectroscopy (Fe valence)