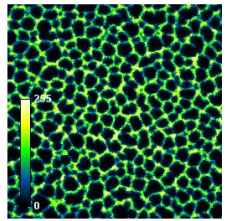
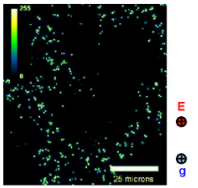
Cluster Phases

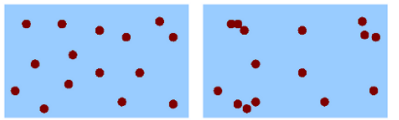
in colloidal suspensions

and protein solutions

Anand Yethiraj

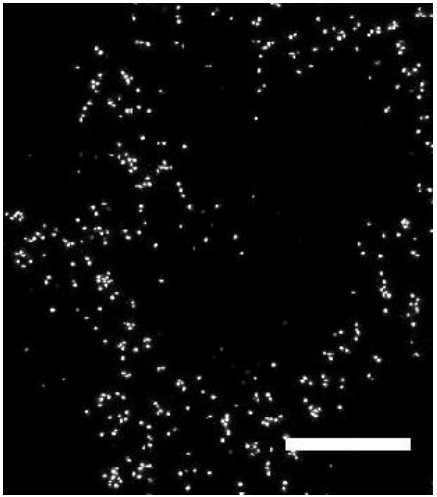






Toulouse, June 2012

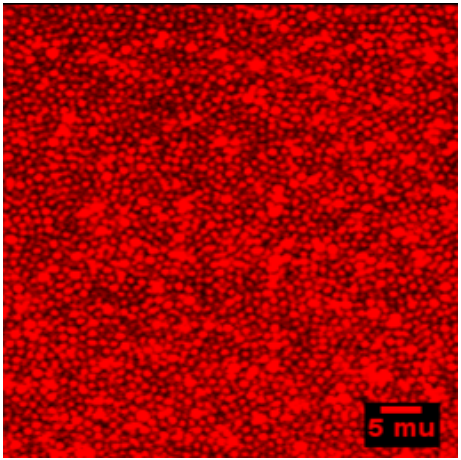
Soft Matter Lab, Memorial University



Low-density: Cluster phases in dipolar colloids

- Hugh Newman, M.Sc. (2008 - 2011)
- Amit Agarwal, post-doctoral researcher (2008 - 2009, now at DRDO, India)
- Ning Li, M.Sc. (2006 - 2008, now at Brandeis)
- **Simulation Collaborations:** Marek Bromberek (2009 -), Prof. I. Saika-Voivod, Ahmad Almudallal (Ph.D.), joint postdoctoral: Manuel Valera (now at SRU, PA).

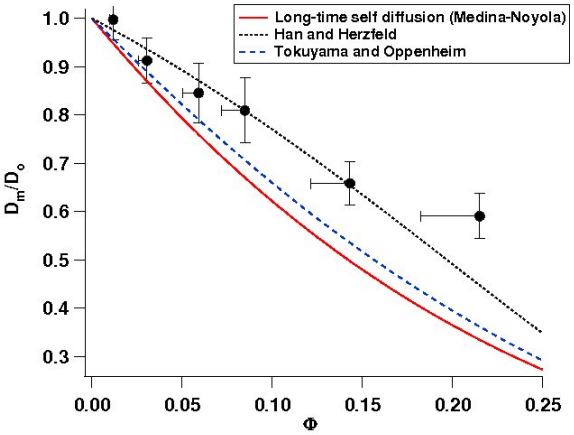
Soft Matter Lab, Memorial University



Ultrahigh-density: phases in ultrasoft+dipolar colloids

- Collaboration with Priti Mohanty and Peter Schurtenberger at Lund University.

Soft Matter Lab, Memorial University



Intermediate density: cluster phase in protein solutions

- Suliman Barhoum, Ph.D. (2008 -)
  Detection of Aggregate Structures in Protein and Micellar Solutions Using NMR Diffusometry

- **Funding:** NSERC, CFI, ACENet, MUCEP

What is Liquid?

- Fluid-solid transition in computer simulation of hard spheres: Alder & Wainwright, 1962.

What is "liquid"? Understanding the states of matter

J. A. Barker and D. Henderson

IBM Research Laboratory, Monterey and Cottle Roads, San Jose, California. 95193

Liquids exist in a relatively small part of the enormous range of temperatures and pressures existing in the universe. Nevertheless, they are of vital importance for physics and chemistry, for technology, and for life itself. A century of effort since the pioneering work of van der Waals has led to a fairly complete basic understanding of the static and dynamic physicochemical properties of liquids. Advances in statistical mechanics (the fundamental formulations of Gibbs and Boltzmann, integral equations and perturbation theories, computer simulations), in knowledge of intermolecular forces, and in experimental techniques, have all contributed to this. Thirty years ago the very existence of liquids seemed a little mysterious; today one can make fairly precise predictions of the solid–liquid–gas phase diagram and of the microscopic and macroscopic static and dynamic properties of liquids. This paper is a survey, with particular emphasis on equilibrium properties, of the theory which underlies that basic understanding, which is now at least comparable with our understanding of the physics of solids.

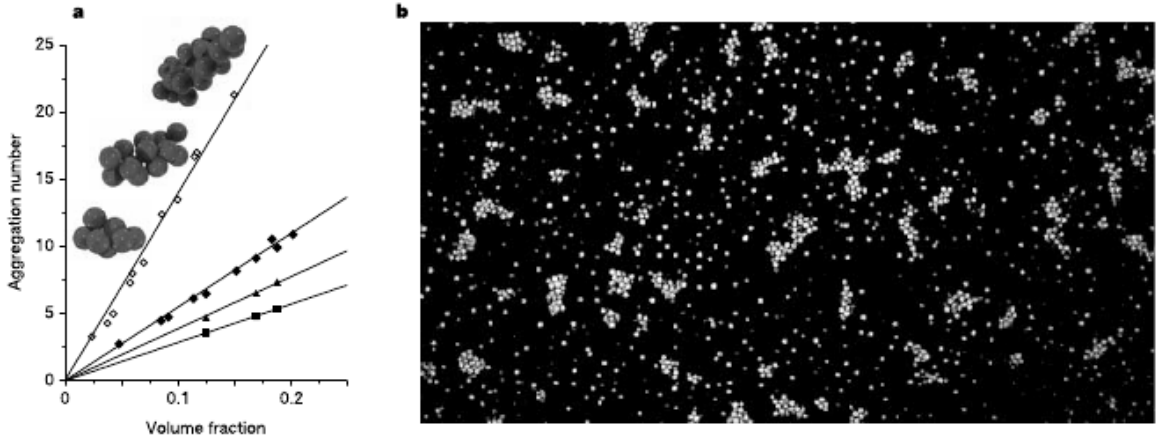
Reviews of Modern Physics, Vol. 48, No. 4, October 1976

- Existence of liquid state requires attractive interactions. In fact, a sensitive balance between attractions and excluded volume repulsions.

Cluster Phases

Generalization of the liquid state

- Competition of short-range attractions and long-range repulsions can give rise to clusters in proteins and colloids (Stradner et al., Nature 2004).



Protein Clusters

Colloidal Clusters

Clustering in Complex Fluids

Why would clusters have finite size in equilibrium?

- Micelles: Clustering arises from anisotropic interactions imposed by the hydrophobic-hydrophilic interface.
- Competition of interactions can lead to a free energy minimum at a finite, mesoscopic cluster size (Groenewold & Kegel, J. Phys. Chem. B,, 2001).

THE JOURNAL OF PHYSICAL CHEMISTRY B

SPECIAL ISSUE PREFACE

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Clustering in Complex Fluids

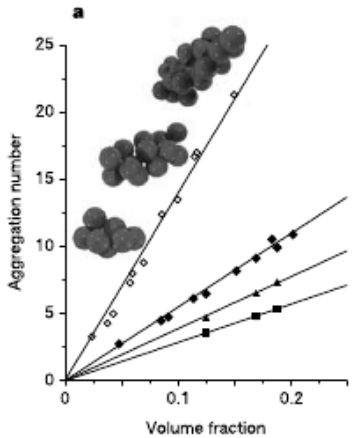
The tendency of molecules to associate with other molecules of the same species and to shun dissimilar molecules by bulk separation is well established. There is another kind of association, however, that is less understood in science: how do molecules or particles spontaneously form clusters that contain many particles or molecules and yet have a finite size? In the

where the interaction is purely repulsive, the precise shape of interparticle potential curve has critical, nonintuitive consequences. A hard-core repulsion with a softer repulsive shoulder (HCSS), for instance, forms a canonical sequence of phases with increasing particle density or pressure: a superlattice of spherical clusters, a 2D array of columnar clusters, multilamellar stacks,

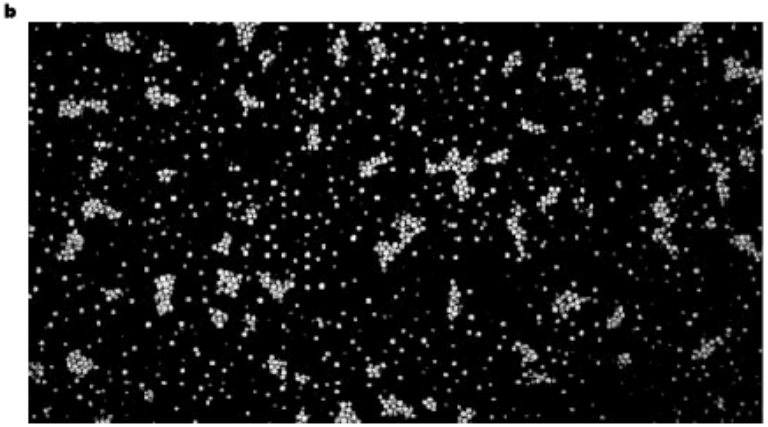
ACS Publications   dx.doi.org/10.1021/jp202724b | J. Phys. Chem. B 2011, 115, 7173–7174

Clusters in Protein Solutions

- How does one detect nanoscale clusters that are in constant motion?



Protein Clusters



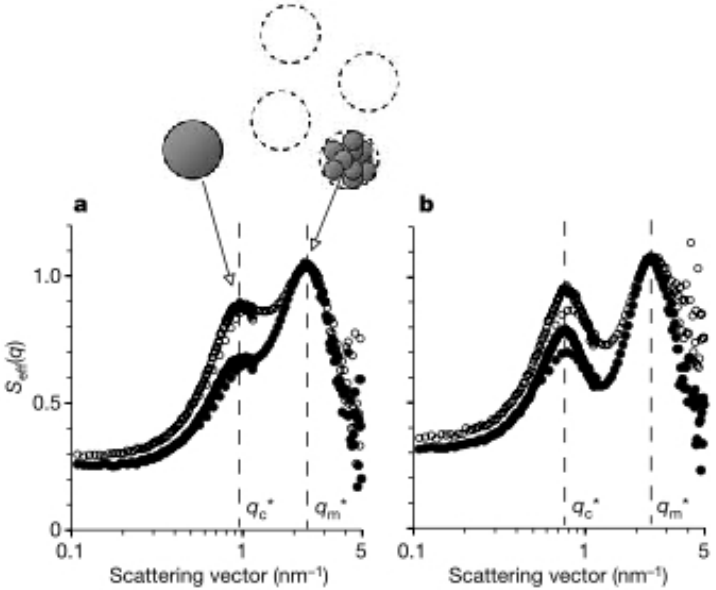
Colloidal Clusters

Do Proteins Form "Equilibrium" Clusters?

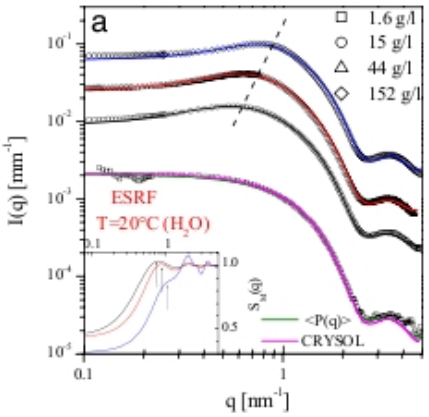
An "Interference Peak" in SANS

- The "monomer" peak is at $q_{\rm m} \approx 2 - 3$ nm^{-1}
- There is an "interference peak": $q_{\rm c} \approx 1$ nm^{-1}

Stradner et al, Nature 432, 492 (2004).



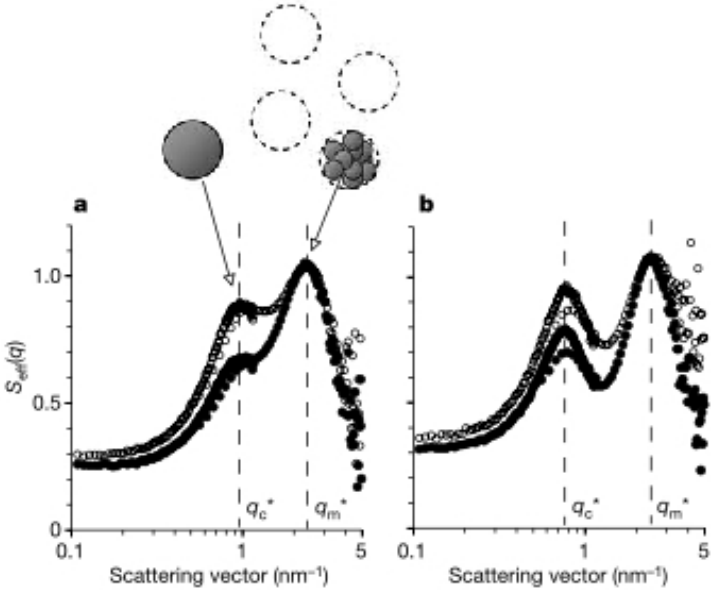
Shukla et al, PNAS 105, 5075 (2008).



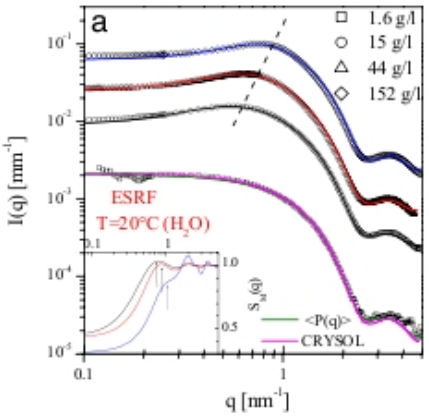
Do Proteins Form "Equilibrium" Clusters?

- Stradner et al: **YES!** q_c represents equilibrium protein clusters
- Shukla et al: **NO!** Peak position moves with concentration !
- We decided to test with a different technique: NMR.

Stradner et al, Nature 432, 492 (2004).



Shukla et al, PNAS 105, 5075 (2008).



Clusters in Protein Solutions

Neutron Spin Echo: Collective Diffusion at Short Times

- Commentary: "Different views from small angles"
- "Dynamic clusters at short times" (via D_c at $q \to 0$)

"macroscopic properties at the long time limit still determined by monomeric proteins"

PNAS

SEE COMMENTARY

Absence of equilibrium cluster phase in concentrated lysozyme solutions

Anuj Shukla*, Efstratios Mylonas†, Emanuela Di Cola*, Stephanie Finet*, Peter Timmins‡§, Theyencheri Narayanan*¶, and Dmitri I. Svergun‡§‖

*European Synchrotron Radiation Facility, 6 rue Jules Horowitz, F-38043 Grenoble Cedex 9, France; †European Molecular Biology Laboratory, Hamburg Outstation, c/o DESY, Notkestrasse 85, D-22603 Hamburg, Germany; ‡Institut Laue-Langevin, 6 rue Jules Horowitz, F-38042 Grenoble Cedex 9, France; and §Institute of Crystallography, Russian Academy of Sciences, Leninsky pr. 59, Moscow 117333, Russia

Edited by Alan R. Fersht, University of Cambridge, Cambridge, United Kingdom, and approved January 22, 2008 (received for review December 18, 2007)

PNAS

COMMENTARY

The different views from small angles

Jill Trewhella*

School of Molecular and Microbial Biosciences, University of Sydney, NSW 2006, Australia

The small-angle scattering of x-rays or neutrons from proteins in solution can provide important information about the structure of the protein and the nature of interactions or distance correlations among the protein molecules (1, 2). The tion-independent but does change with temperature and ionic strength. It is the lack of concentration dependence in the positions of both of these peaks that is the basis for their proposal of equilibrium cluster formation. In their article, Stradner *et al.* draw analogies with obser- extracted structure factor term by taking into account the asymmetric shape of lysozyme, and the higher q (concentration-independent) peak they obtain is attributed to the orientational coupling between the form and structure factors (11).

THE JOURNAL OF PHYSICAL CHEMISTRY Letters

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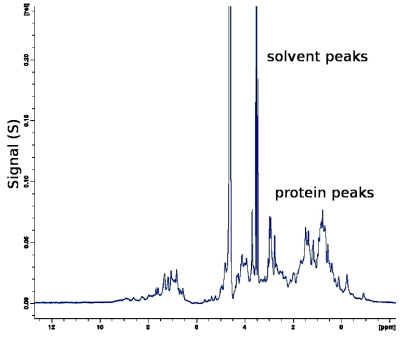
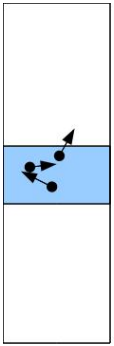
Formation of the Dynamic Clusters in Concentrated Lysozyme Protein Solutions

Lionel Porcar,† Peter Falus,† Wei-Ren Chen,‖ Antonio Faraone,§,∥ Emiliano Fratini,⊥ Kunlun Hong,# Piero Baglioni,⊥ and Yun Liu*,§,▽

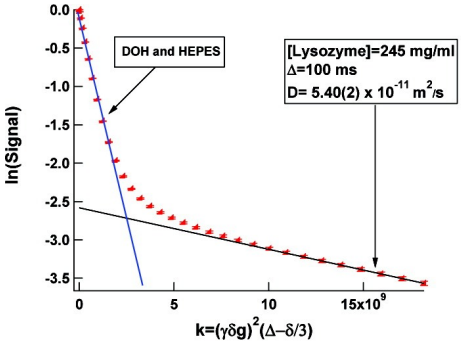
Pulsed Gradient NMR is a unique probe

- In a uniform magnetic field: Larmor frequency of a proton is not position dependent.
- In a field gradient: Larmor frequency is position-encoded. Coherence of signal is lost due to "dephasing"





"width of slice in resonance" is inversely proportional to gradient strength



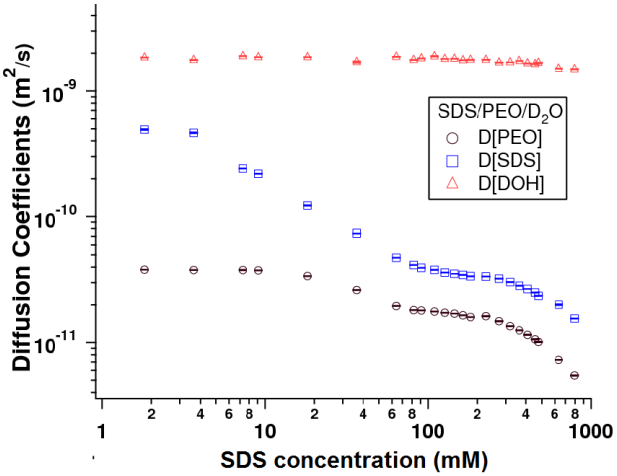
- Stimulated Echo: "a pulse sequence" that refocuses signal loss due to static fields
- Diffusion $\rightarrow$ irrecoverable signal loss $\rightarrow$ attenuation of echo.
- $S(g) = S(0)\exp(-kD)$, where $k \approx (\gamma g \delta)^2 \Delta$, Δ is the diffusion time.

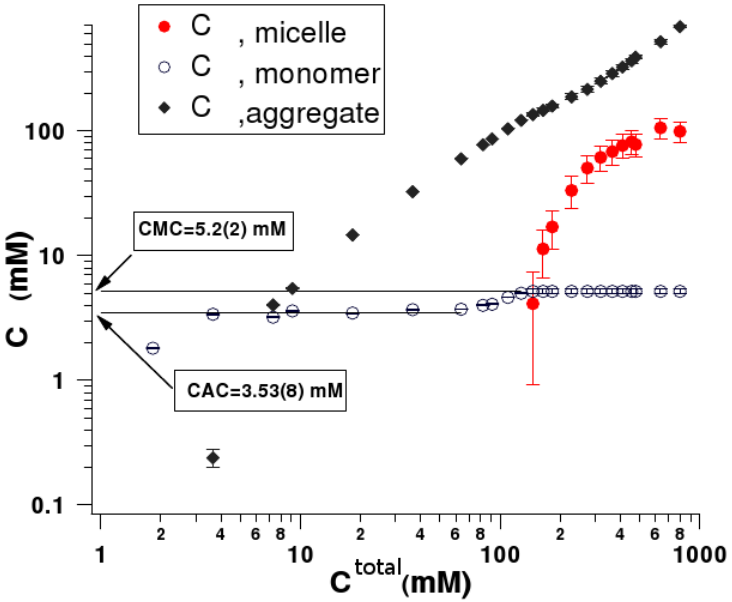
Polymer-surfactant clusters

- A two-site exchange model is known to work well in NMR of surfactant systems (Soderman & Stilbs, Prog. NMR Spec., 1994).

$$D_{observed} = \frac{bD_{mon} + (1-b)D_{agg}}{\text{Normalization}} \qquad (1)$$

- Polymer PEO (polyethyleneoxide), surfactant SDS (sodium dodecyl sulphate). Barhoum & Yethiraj, J. Chem. Phys. 132, 024909 (2010).





Effects of NMR Relaxation

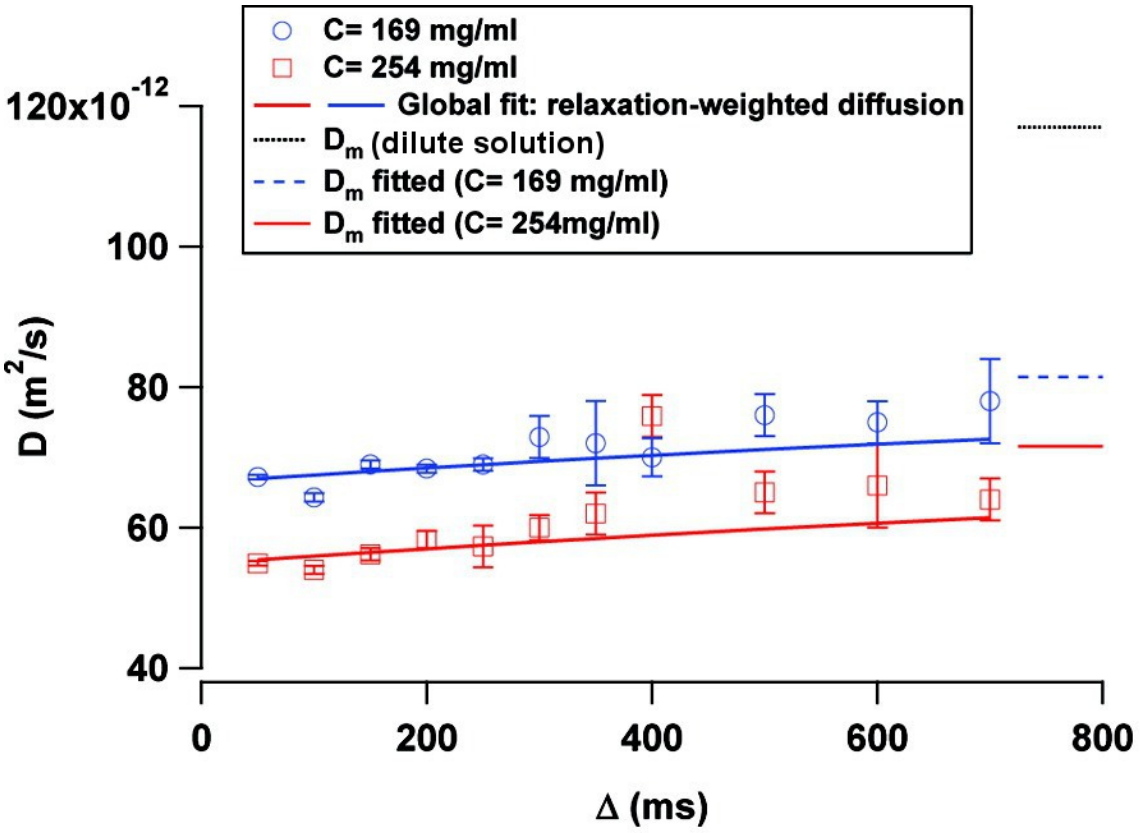
- Unique to NMR: ps - ns molecular correlation times give rise to ms - second NMR relaxation times.
- The relevant relaxation time in the stimulated echo is the longitudinal relaxation time T_1.

Relaxation-weighted Diffusion

- For single-species diffusion in the long-time limit: D cannot be a function of Δ.
- For two species the observed diffusion-coefficient is a relaxation-weighted average of D for each species ("m" for monomer, "a" for aggregate):

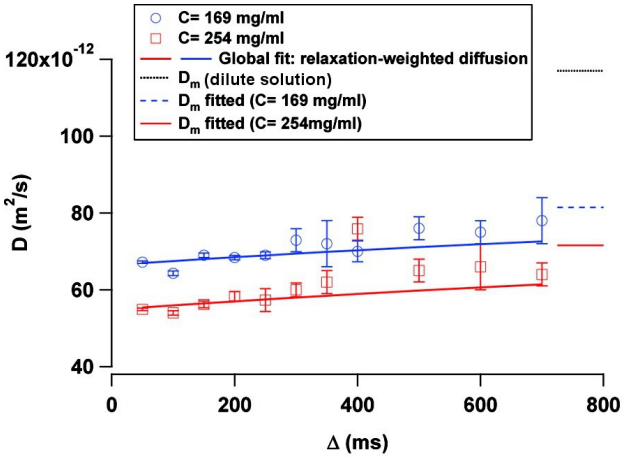
$$D_{observed} = \frac{[bD_m \exp(-\Delta/T_{1,m}) + (1-b)D_a \exp(-\Delta/T_{1,a})]}{\text{Normalization}} \quad (2)$$

Protein Solutions



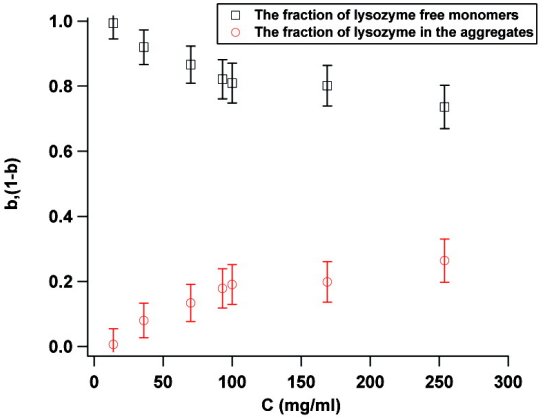
Protein Solutions

- We measure diffusion coefficient D in the long-time limit: $(\Delta >> \tau_{\text{Brownian}})$
- $D_{observed}$ vs protein volume fraction.
- $D_{observed}$ **increases with Δ: this is consistent with relaxation weighting.**

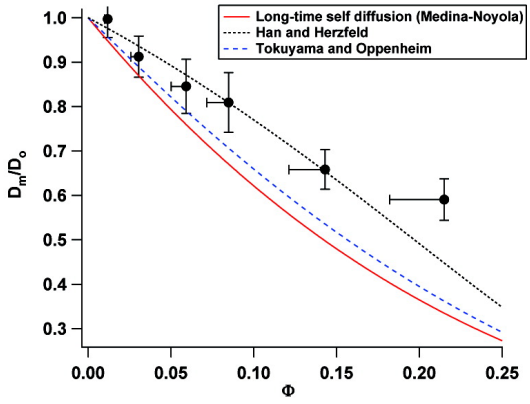


Equilibrium Clusters Exist

- We can fit different concentrations to obtain the monomer fraction b and aggregate fraction $1 - b$.
- Monomer diffusion D_m is consistent with simulations for crowded diffusion of model proteins (Han & Herzfeld, Biophys. J., 1993).



(a)

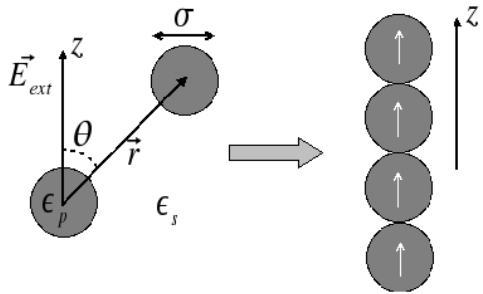


(b)

- **Main point:** short-range attractions and long-range repulsions *can* result in energetically favourable finite-size clusters.

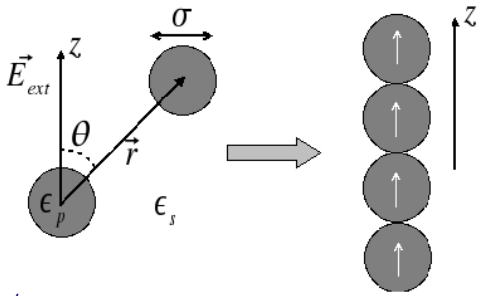
Barhoum, Yethiraj, J. Phys. Chem. B 2010.

Colloids with Dipolar Interactions



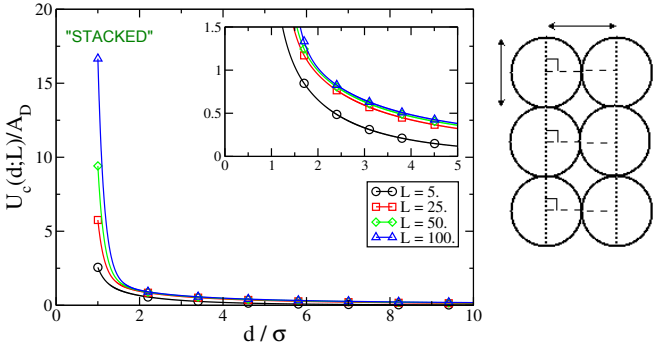
Colloids with Dipolar Interactions

Point Dipolar Approximation

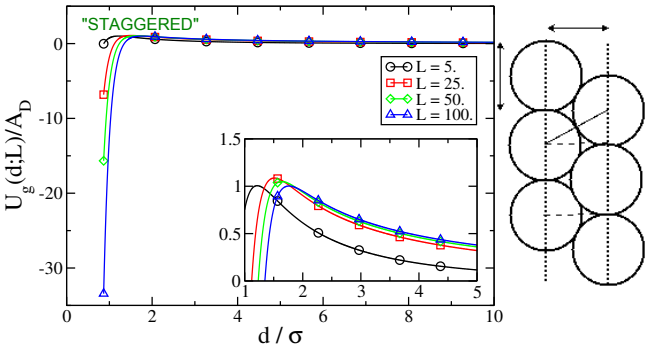


- Has inbuilt into it both repulsive and attractive interactions.
- External electric field $\vec{E}_{ext}$ induces dipoles.
- Dipoles interact:
  $U_{dip}(r)/k_BT \sim -[\sigma^6 E_{ext}^2/r^3]\,(3\cos^2\theta - 1)/2$
- Dipolar spheres self-organize into chains.
- Chains interact.

Stacked chains: repulsive.



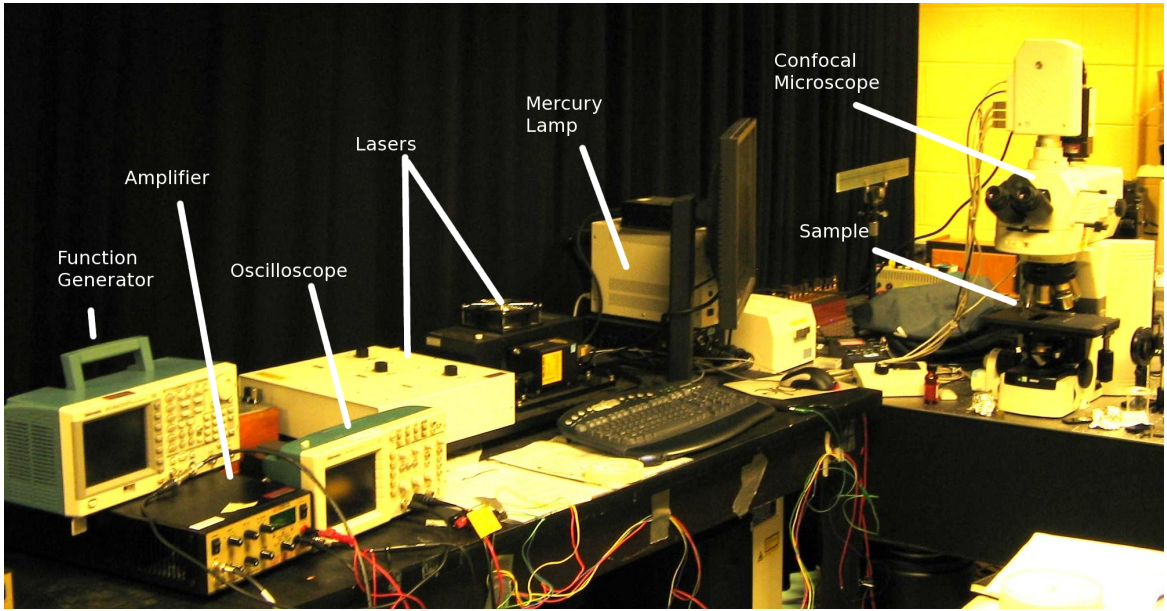
Staggered chains: attractive



Colloids in Electric Fields

Experimental

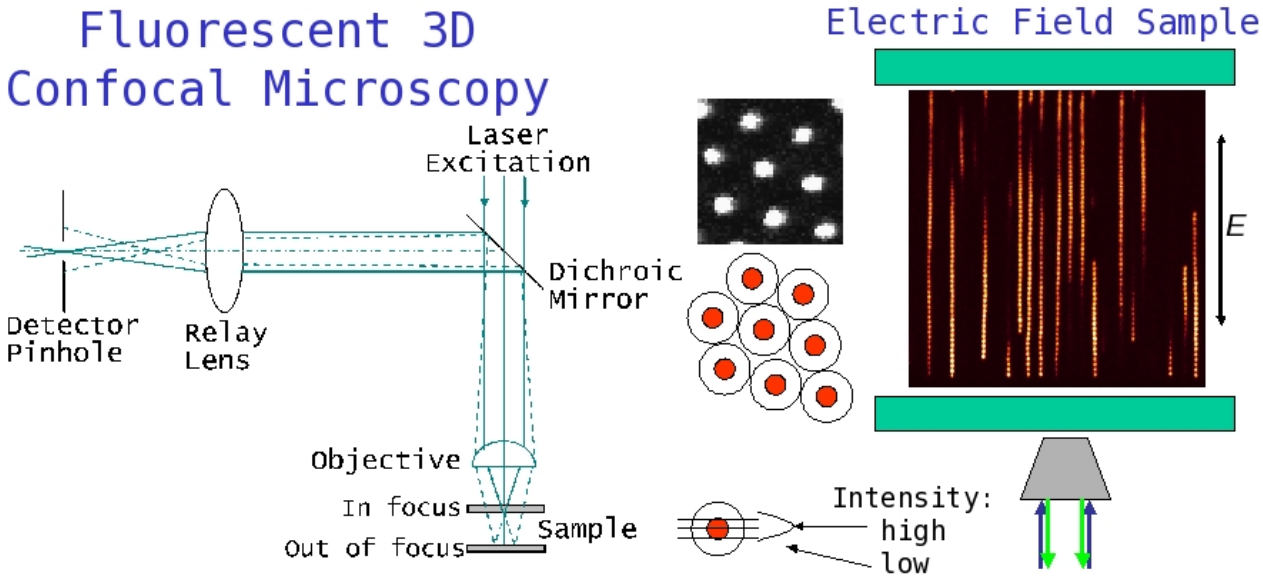
- Laser-scanning confocal microscopy.
- Brownian microspheres:
  silica $\sigma = 0.8\mu$m or PNIPAM $\sigma = 1.45\mu$m at 20C
- AC electric fields: **f $>$ 100 kHz, oscillating too fast for double layer)**



Colloids in Electric Fields

Experimental

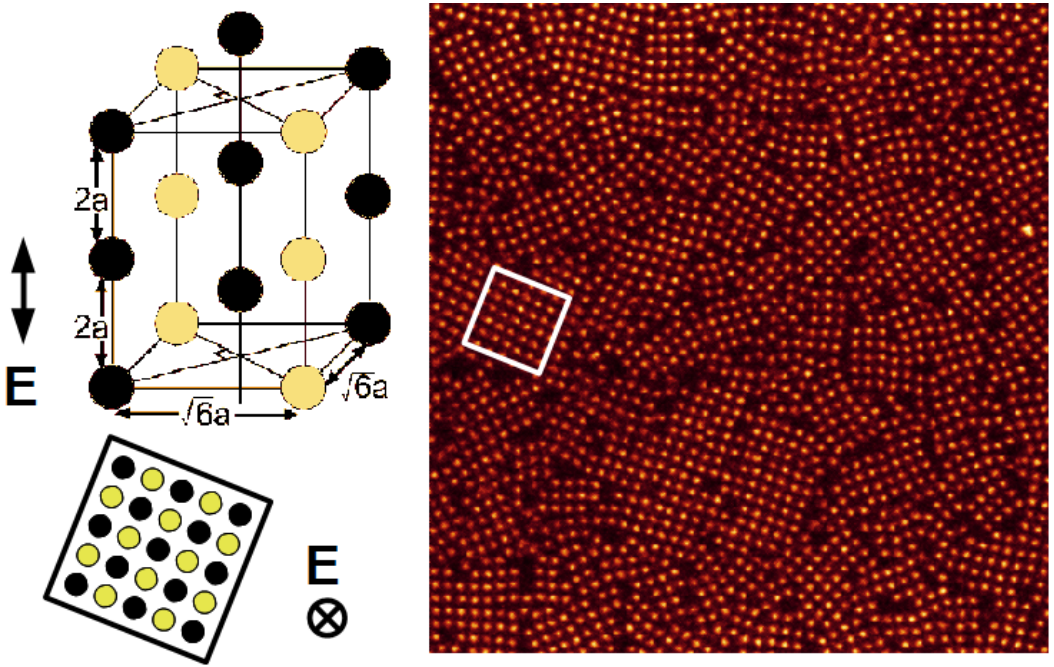
- Laser-scanning confocal microscopy
- Brownian ($\sigma = 0.8\mu$m) microspheres:
  fluorescent-core–non-fluorescent-shell silica colloids in water-DMSO
- AC electric fields: **f > 100 kHz, oscillating too fast for double layer)**



Colloids in Electric Fields are Dipolar

Dipolar colloids form body centred tetragonal (BCT) crystals.

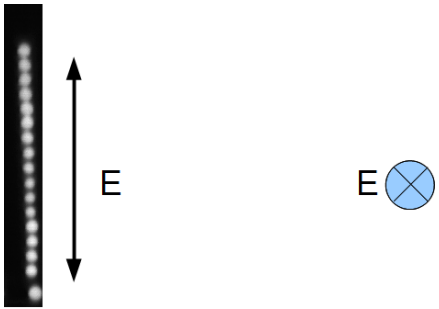
- BCT is the theoretically minimum energy structure:
  R. Tao et al, Phys. Rev. Lett., 1994.
- **Experiment: J.E. Martin et al, Phys. Rev. E, 1998;**
  U. Dassanayake et al, J. Chem. Phys., 2000.

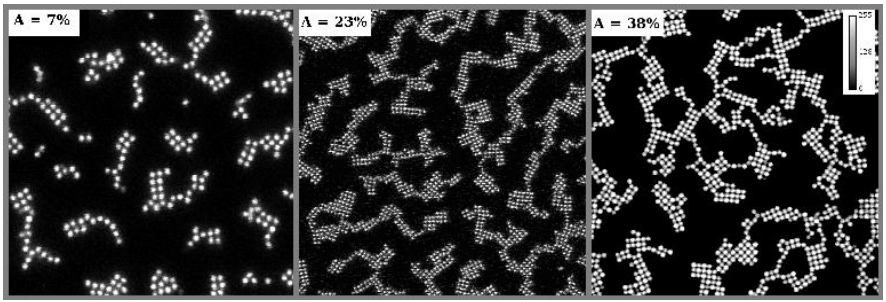


Microstructure at Lower Packing

Experiment (Yethiraj & van Blaaderen, Nature 2003, Int. J. Mod. Phys. 2002)

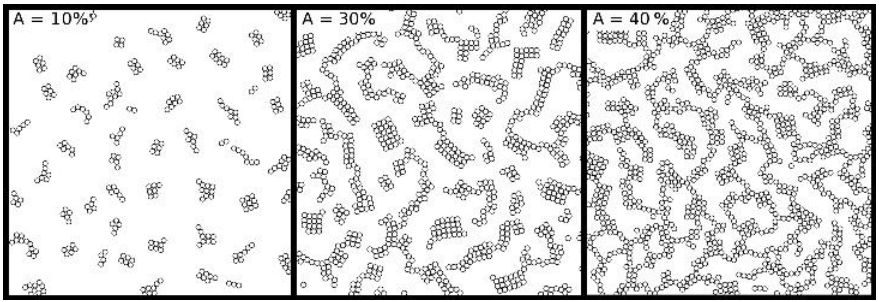
- **High Densities:** Percolating particulate regions, non-percolating particle-poor regions.
- **Intermediate densities:** Particulate clusters, percolating particle-poor regions.





2D Monte Carlo simulation (Almudallal & Saika-Voivod, Phys. Rev. E, 2011).

- Represent chains as particles with "stacked" or "staggered" effective interactions
- For $\phi > 5\%$, experiment and simulation agree.



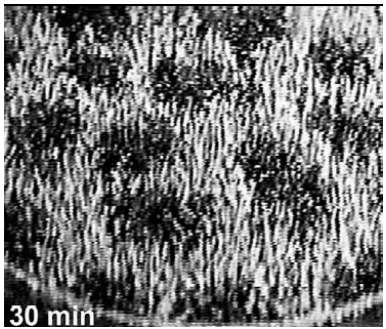
- 3D: phase diagram at moderate to high densities Hynninen et al, PRE, 2005.

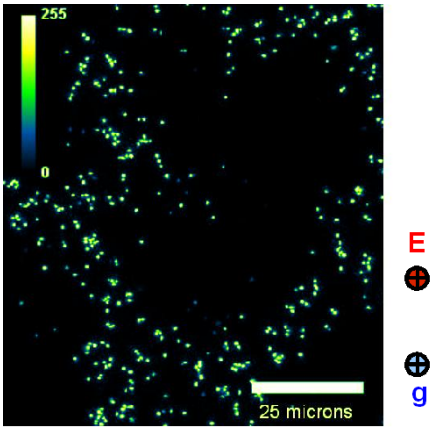
Coarsening of structures with time

Very Low Packing: The "Void Phase"

Unusual cellular structures at low densities ($\Phi < 4\%$)

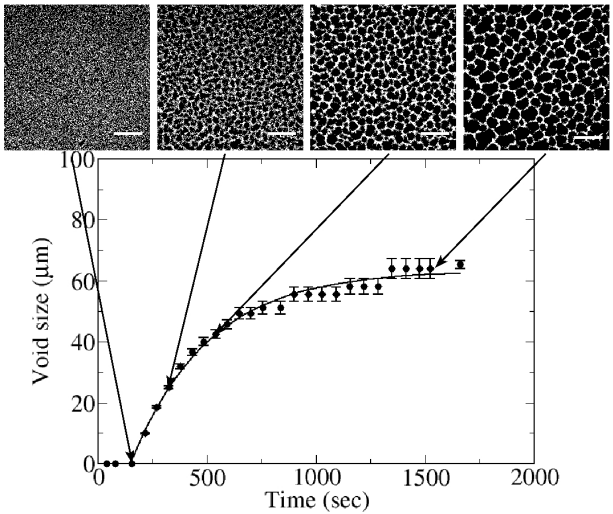
- **Granular dipolar:** A. Kumar, B. Khusid, A. Acrivos, Phys. Rev. Lett., 2005.
- **Colloidal dipolar:**
  A. Agarwal, A. Yethiraj, Phys. Rev. Lett., 2009.



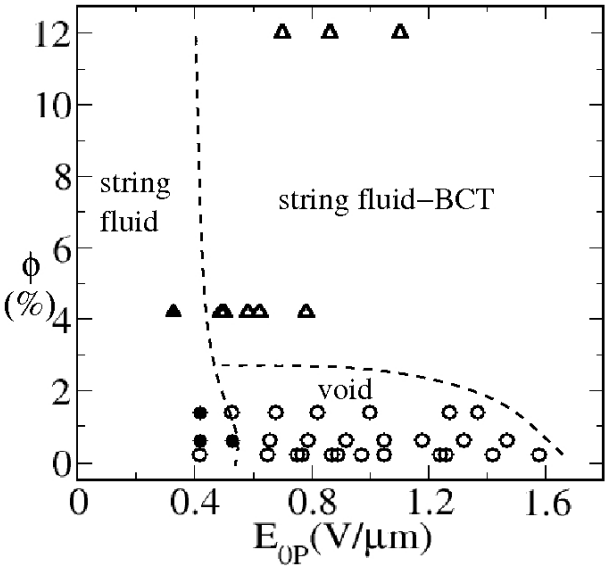


A Low-Density Network-forming Phase

Time Evolution of Voids



Phase Diagram



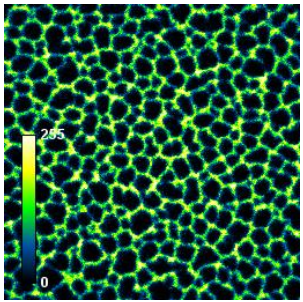
Mechanism:

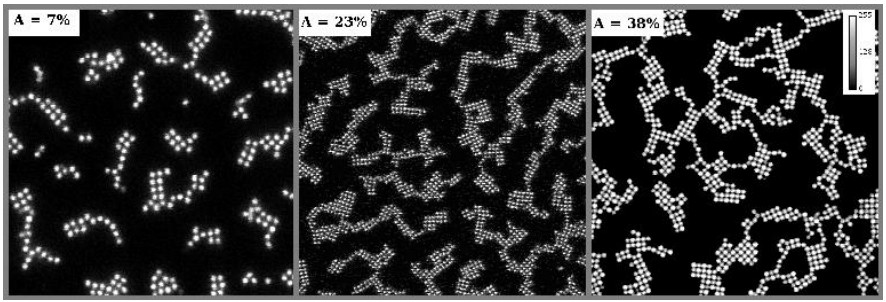
- Is likely an equilibrium structure: $t_{\text{obs}} = 5000 * \tau_{\text{Brownian}}$
- Void phase (percolating non-crystalline particle networks) only exists at low densities.
- The lengthscale increases with sample thickness.

“Re-entrant” Percolation of Clusters

Experiment

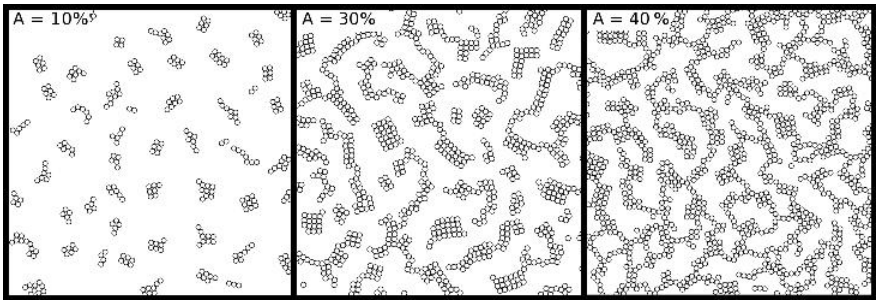
- **High Densities:** Percolating particulate regions, non-percolating particle-poor regions.
- **Intermediate densities:** Particulate clusters, percolating particle-poor regions.





- **At very low densities:** “re-entrant” percolation of particulate regions, surrounding voids (particle-poor regions): **not seen in 2D simulation.**

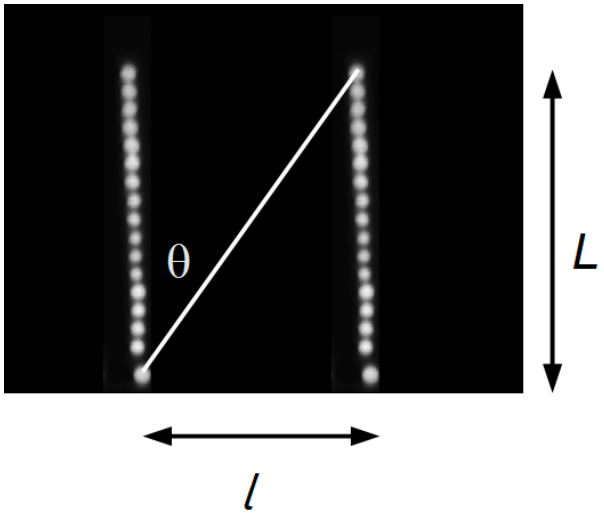
?



Mechanism for the void phase

Competing Interaction Forces

- A sensitive balance between intermediate-range attractive forces and shorter and longer range repulsions.
- Chain-chain undulations can produce fluctuation-induced attractions **(Halsey & Toor, PRL 1990)**.



- Beyond a lengthscale $\ell > L\tan(54°)$, repulsions dominate again.

Conclusion

Clusters in Dipolar Colloids

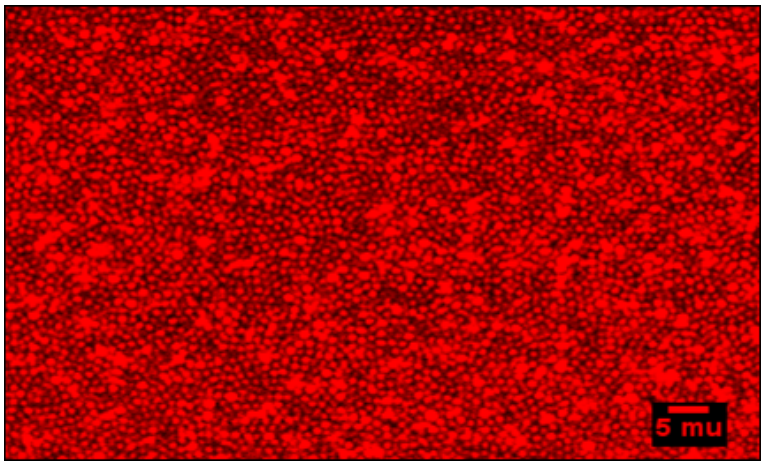
- Along the field direction, there are well-formed chains (a 1D crystal, albeit subject to strong fluctuations).
- **At large packings:** single-crystal or poly-crystalline BCT.
- **At lower packings:** crystalline cluster islands that do not merge to form one big blob.
- **At very low packing:** an unusual percolating cluster ("void") phase
- Void phase characterized by disordered microstructure in the plane perpendicular to the field.

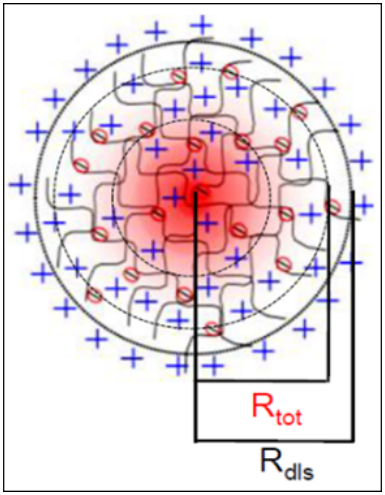
As-yet unanswered question

What gives rise to the percolating networks at ultra-low densities?

Ultrasoft and Dipolar Colloids

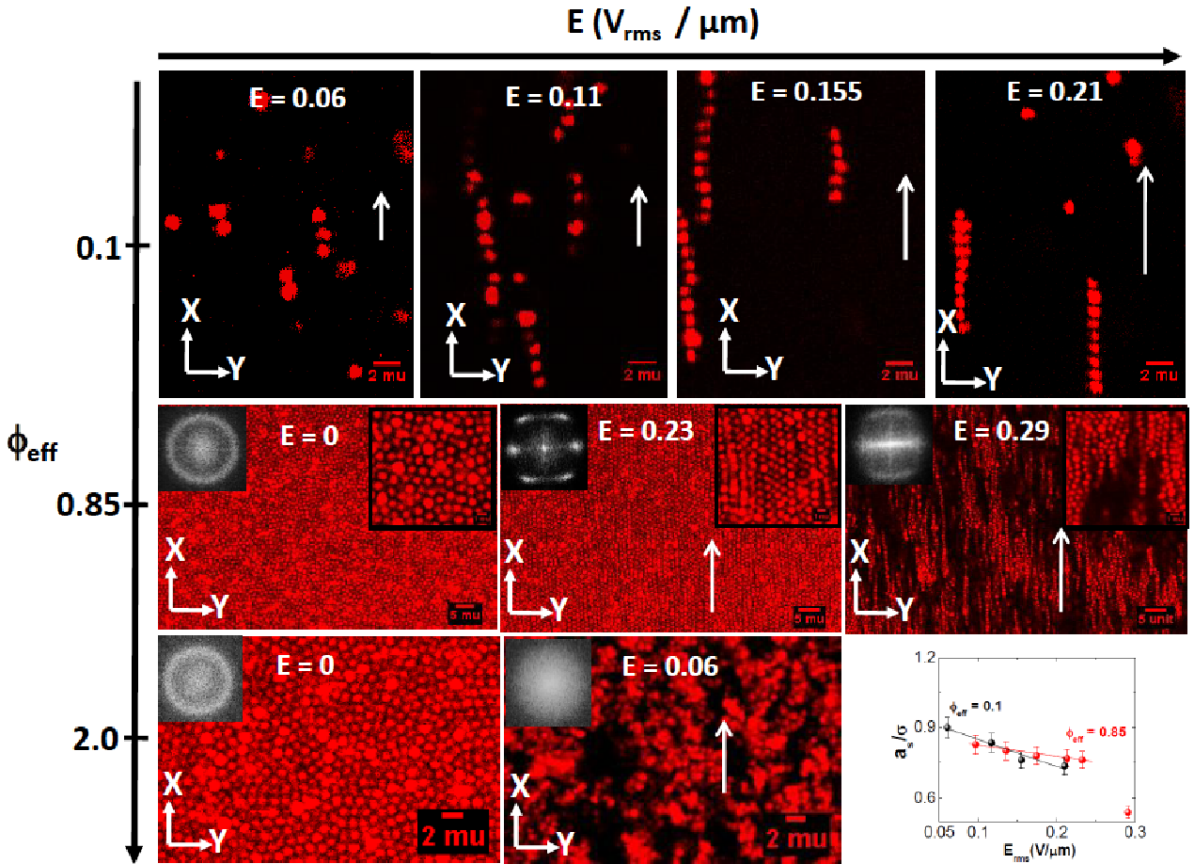
Amorphous State in Microgel colloids





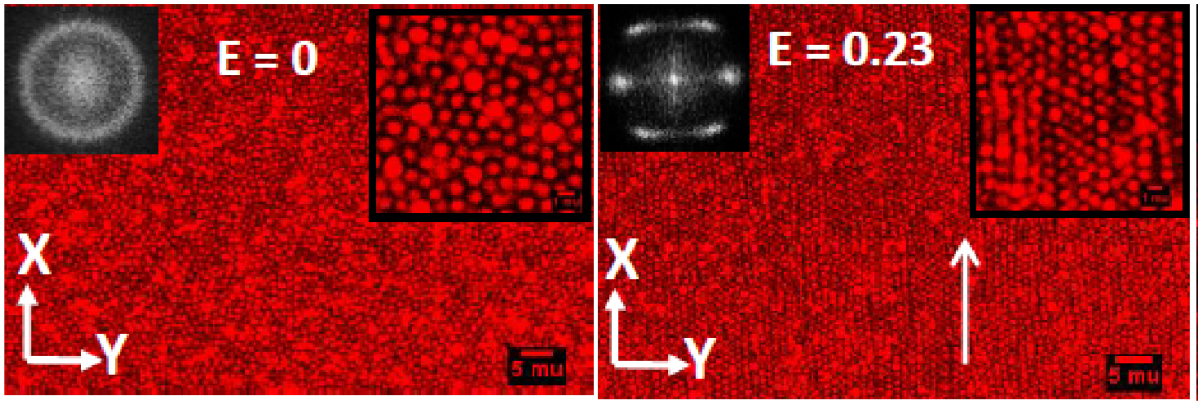
- Interactions Yukawa-like for $a_s > \sigma$, much softer for $a_s < \sigma$.
- How does the introducing anisotropy affect phase behaviour?
- Graded dielectric spheres: what is the nature of the electromagnetic interactions? Can we make better electrorheological fluids?

Field-packing fraction phase diagram



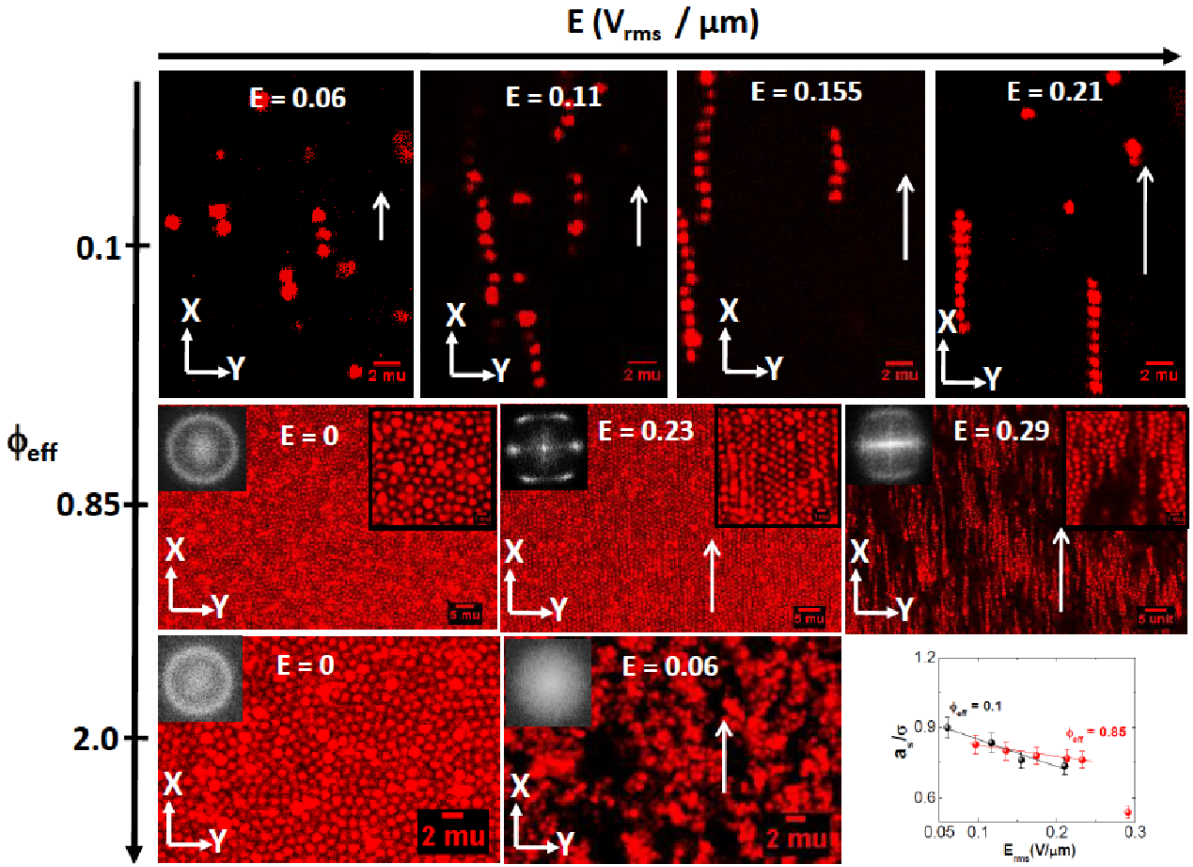
Field-driven transitions

Amorphous to crystalline: $\phi_{\text{eff}} = 0.85$



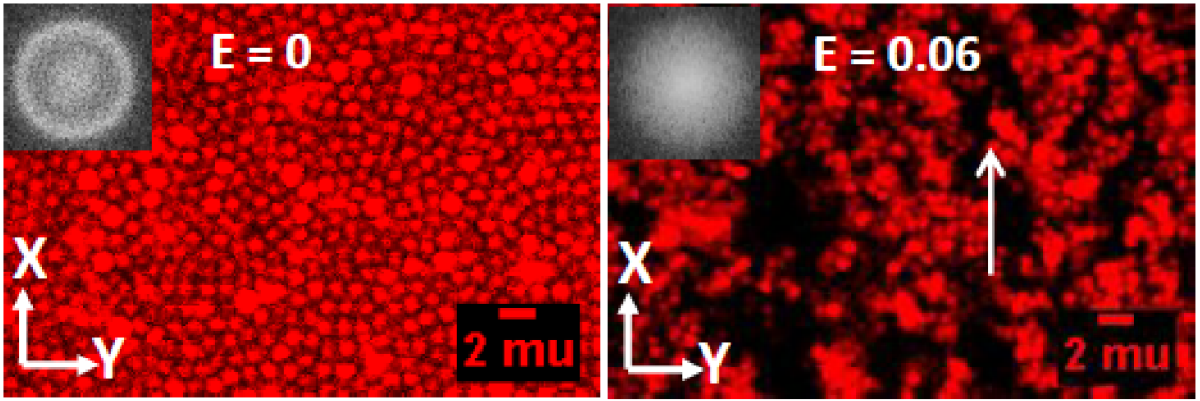
$\phi_{\text{eff}} = 0.85$, E $= 0.23$ V/μm.

Field-packing fraction phase diagram



Field-driven transitions

Amorphous to amorphous: $\phi_{\text{eff}} = 2.0$



- Field response at surprisingly low field strengths.
- Arrested phase separation at the highest packings: no sign of anisotropy!!
- Theoretical input welcome - probably should include the effects of mobile ions.

Conclusions

Dipolar colloids: percolating particle clusters at ultralow packing

- A 2D model captures physics at moderate and high densities.
- Intermediate-range attractions: dielectrophoresis ?
- Unanswered: where does the void lengthscale come from?

Agarwal & Yethiraj, Phys. Rev. Lett. (2009).

Ultrasoft, dipolar colloids: new phases at ultrahigh packing

- Structure formation at low fields: mobile ions must be important
- Amorphous to crystal phase transition
- Amorphous to amorphous transition.

Mohanty, Yethiraj & Schurtenberger, Phys. Rev. Lett. (2009).

Equilibrium Clusters in Proteins

- Clusters exist in equilibrium.
- Long-time dynamics is a weighted average of monomer and aggregate properties. Barhoum & Yethiraj, J. Phys. Chem. B (2010).

Thanks

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Funding and Contacts

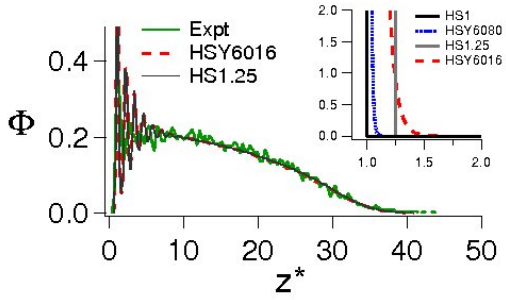
- NSERC, CFI, ACENet, MUCEP

- Email: ayethiraj@mun.ca; Web: softmatter.ca

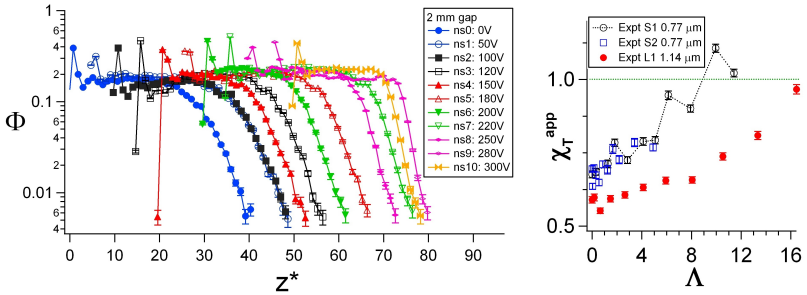
Colloids in Electric Fields ARE Dipolar

Can quantify this by measuring equations of state

In zero field:



As a function of field strength:

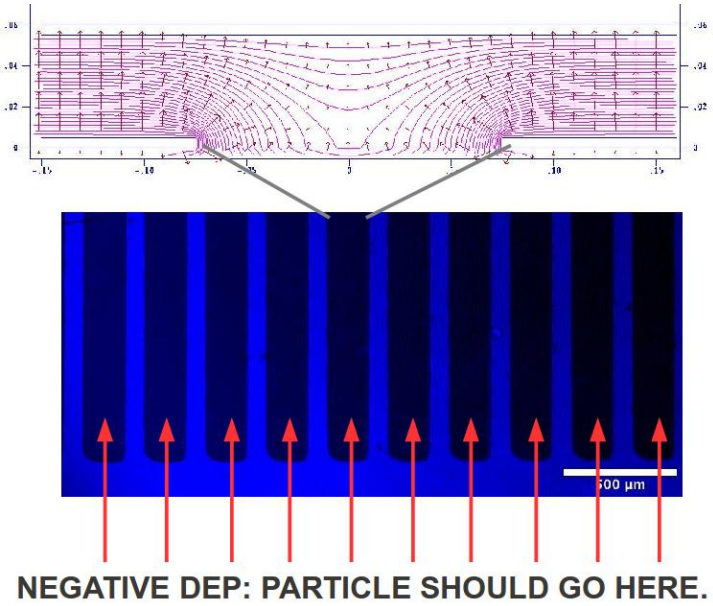


N. Li, H. Newman, M. Valera, I. Saika-Voivod, AY, Soft Matter, 2009.

Possible Origin of the Void Phase

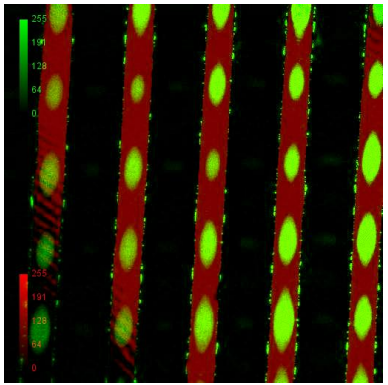
An intermediate-range attractive force ?

- Dielectrophoretic particle segregation with patterned electrodes.
- The stable configuration is the region between the electrodes.
- The centre of the electrode is locally stable close to the bottom.
- With unpatterned electrodes, the particle-chains *are* the non-uniformity! S



Patterning in 3D

- The location AND shape of clusters can be controlled.
- The size of the clusters can be controlled with frequency and (low!) field strength.



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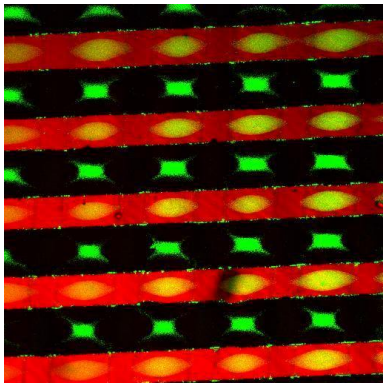

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