Semester Projects

BIO-692, Spring 2023

DPD is good for measuring equilibrium properties of soft matter and following the self-assembly of soft materials or their response to (small) external perturbations.

In particular:

- measuring material properties whose typical scale is >> molecular size and therefore is averaged over many molecules
- response of a bulk material to an external perturbation
- comparing trends in properties or response as a molecular shape is varied systematically, e.g., increasing the tail length of a lipid on membrane properties, or an admixture of one species is added to a bulk species

Feasibility questions to ask

How many and which molecular properties can be realistically (i.e., in available time and with experimental relevance) modified? Select one or two for detailed study.

How big a system and how long a run are needed to get statistically-significant equilibrium results?

What are the sources of error and how can they be quantified?

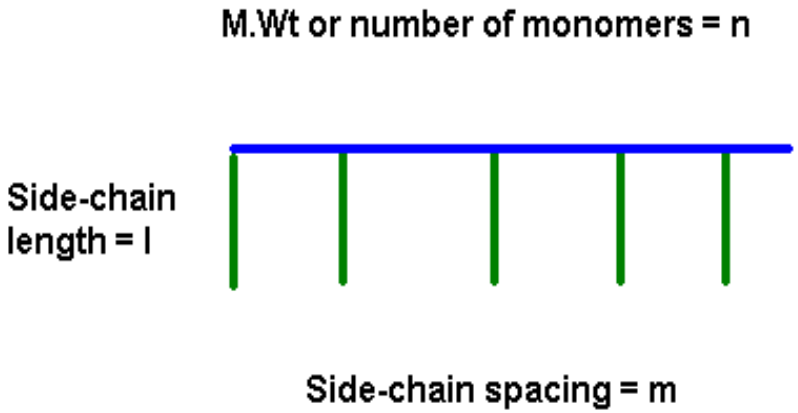
References

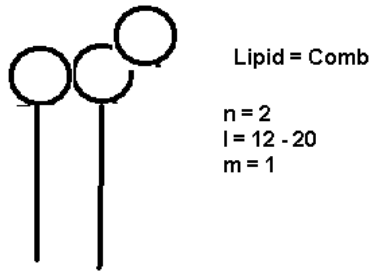
Groot and Warren, J. Chem. Phys. 107:4423 (1997)

Illya, Lipowsky, Shillcock, J. Chem. Phys. 122:244901 (2005)

Shillcock and Lipowsky, J. Chem. Phys. 117:5048 (2002)

Comb polymer aggregation





Lipids are a special case of a comb polymer

Comb polymers have a more complex architecture than lipids, and so have more properties that can be varied. This leads to a combinatorial explosion of parameters which makes a systematic study hard.

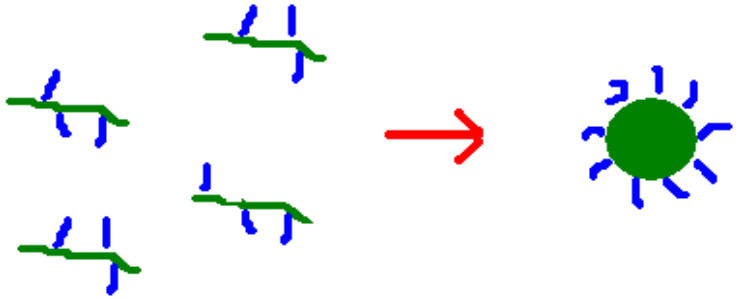
NB The same interaction parameters as for lipids are available for modification, see earlier tables for bead-bead forces, bond strength and bending stiffness. Obviously, there are more bead types though, which means more parameters.

How does molecular shape affect aggregate shape?

Expectations:

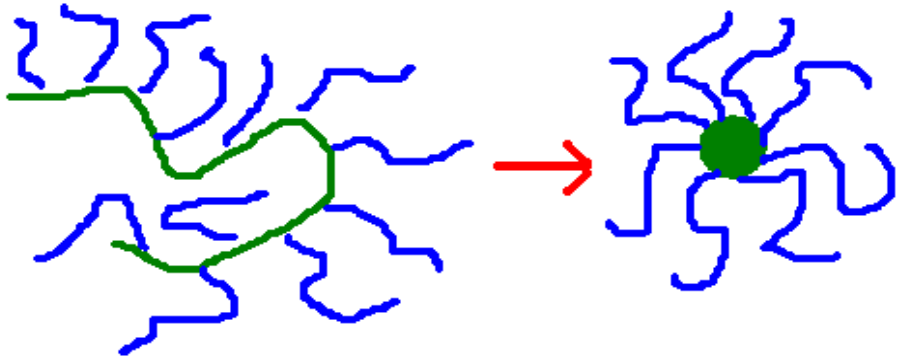
Low M.Wt ~ Short side-chains
~ long spacing

=> bare micelles
controlled by interfacial energy



High M.Wt ~ Long side-chains
~ short spacing

=>hairy micelles
controlled by side-chain entropy



What happens to combs between these two extremes? We have at least 6 parameters:

M. Wt ~ length of polymer

Side-chain length

Side-chain spacing

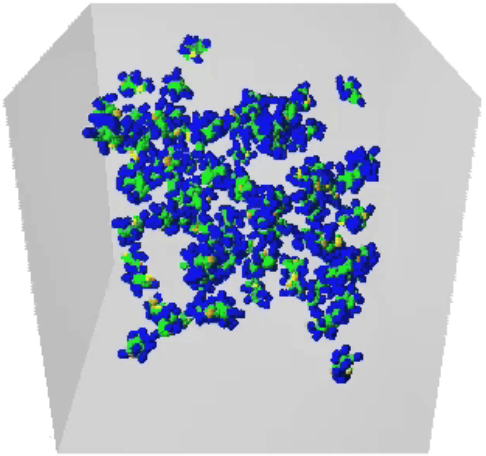
Backbone/side-chain chemistry (hydophobic/hydophilic) and stiffness

Concentration

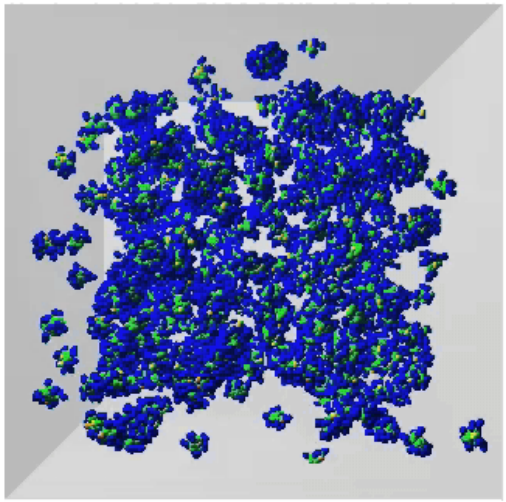
Let's fix the M. Wt and concentration and backbone chemistry:

Backbone is hydrophobic
Side-chains are hydrophilic
Concentration = 0.0004 in a box $(30\ nm)^3$ up to $(60\ nm)^3$
(about 2-10 mM)

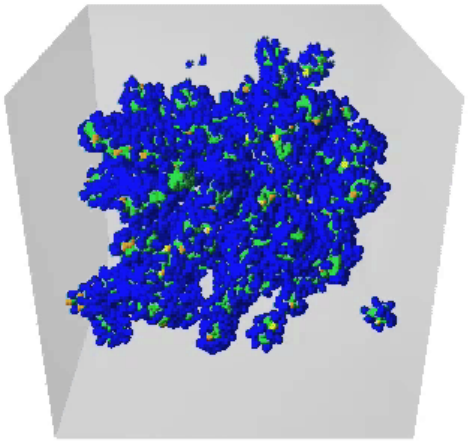
We might expect micelles here, with the backbone curled up into a sphere and the side-chains extending into the water phase like a diblock copolymer micelle.



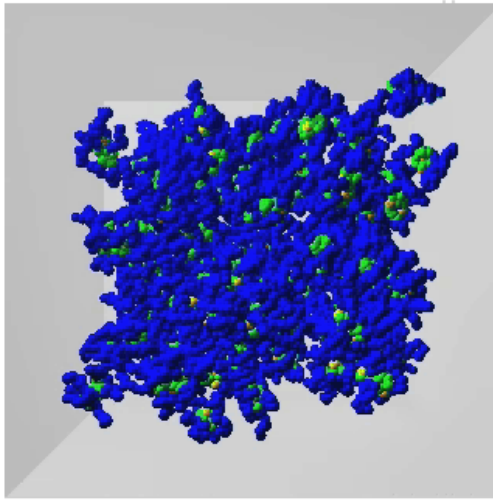
8 2 2 combs



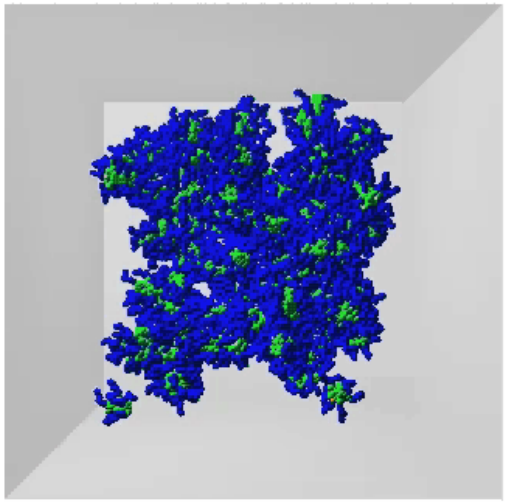
9 2 2 combs



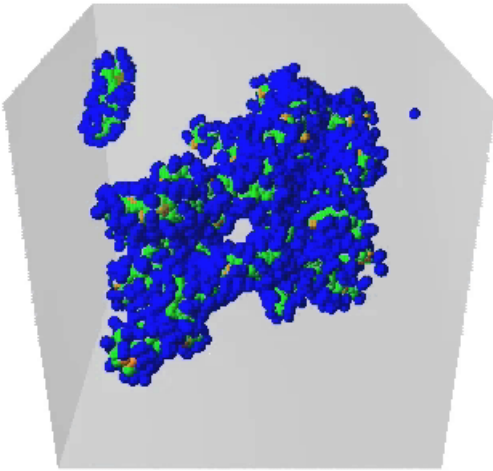
11 2 2 combs



8 6 2 combs



8 6 6 combs



11 2 2 combs - stiff backbone

Questions

What molecular properties can be easily and realistically modified?

What combinations of the molecular architecture parameters are most important for aggregate type?

How does the box size, i.e., boundary conditions, influence the aggregation?

How can one represent the results of many simulations most efficiently?

References

Supramolecular self-assembly of nonlinear amphiphilic and double hydrophilic block copolymers in aqueous solution.
Ge and Liu, *Macromol. Rapid Comms.* **2009**

DOI: 10.1002/marc.200900182

IDP droplet formation

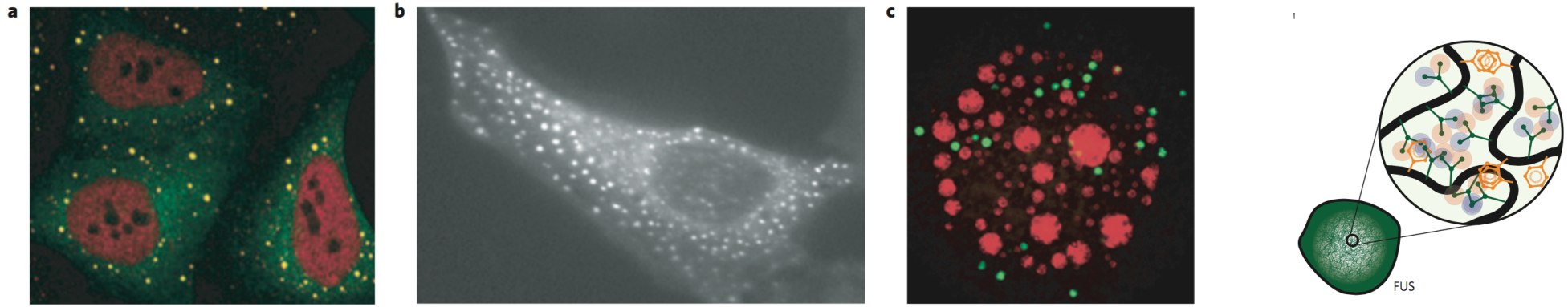


Figure 1 | Examples of membrane-less bodies in cells. a, P bodies (yellow) in tissue culture cells (adapted from ref. 63, NPG). **b**, Purinosomes (adapted from ref. 3, AAAS). **c**, Nucleoli (red) and histone locus bodies (green) in the nucleus of a large *X. laevis* oocyte (adapted from ref. 14, NPG).

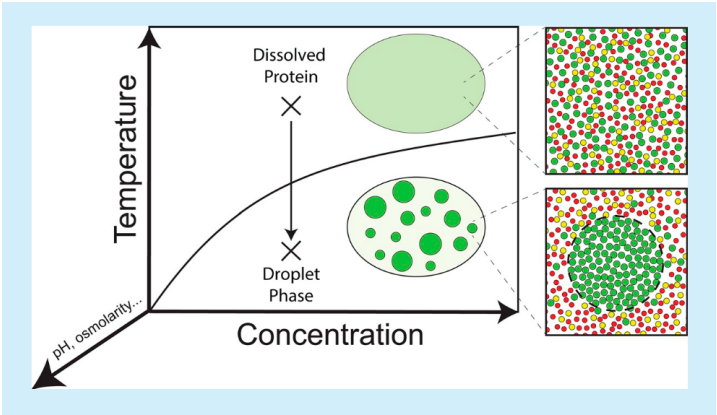
Brangwynne et al., Nature Phys. 11:899 (201

Very little is known about the necessary conditions for membraneless organelles; in vivo has large number of molecule types, in vitro can work with 2-5; but RNA and long proteins are hard to characterise.

Are time-scales for droplet formation within simulation reach?

How do we calibrate the interaction parameters?

What is a good theoretical model of droplet formation?



Brangwynne et al., J. Cell Biol. 203:875 (2013)

Questions

What types of molecule are required for droplet formation in vivo/in vitro?

What physico-chemical conditions are required?

What is the driving force for droplets?

What is a minimal model of droplets?

Can we simulate it? Length scale, time, composition, interactions

References

Brangwynne et al., J. Cell Biol. 203:875 (2013)

Brangwynne et al., Nature Phys. 11:899 (2015)

Harmon et al. Biophys. J. 112:565 (2017)

Jacobs and Frenkel Biophys. J. 112:683 (2017)

Membrane structure

Lipid Bilayer Geometric Properties

Key bilayer geometric properties are:

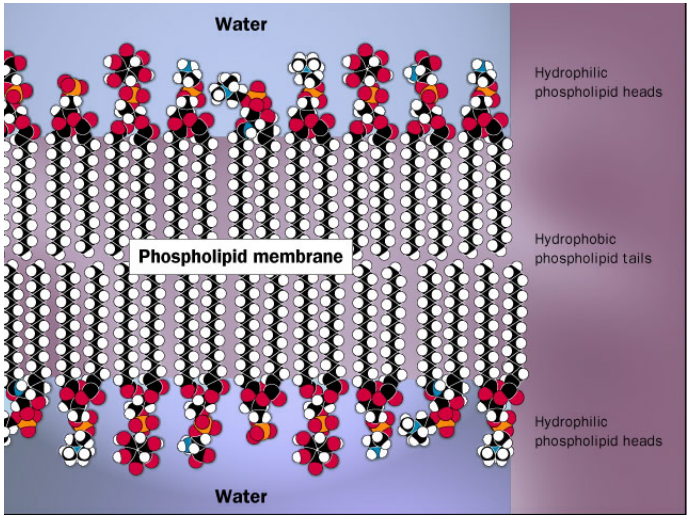
l_{me} , l_{ee} , Area per molecule

Natural bilayers have $l_{me}/l_{ee} \sim 2$,
i.e., two non-interdigitated monolayers.

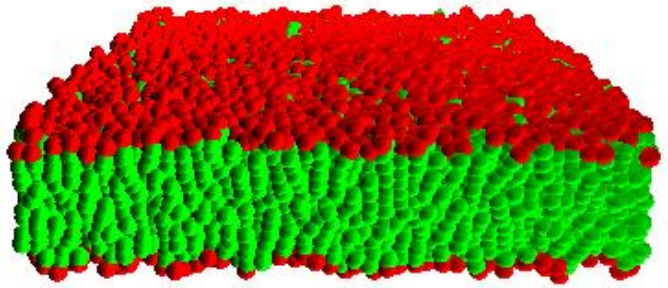
Hydrophobic region is ~ incompressible.

Simulated bilayer properties depend on:

- lipid headgroup size (H_2 = H H)
- lipid tail length (HT_4 = H T T T T) and number of tails (usually 1 - 4)
- hydrophobic effect a_{TW}
- tail length and stiffness



Source: chemistrypictures.org



Amphiphile Interaction Parameters

Amphiphile architecture: relative number of Head, H, and Tail, T, beads

Strong hydrophobic repulsion between W and T

Slight repulsion between H and T;

H and W represents hydrophilic headgroup

a_{ij}	H	T	W
H	25	50	35
T	50	25	75
W	35	75	25

Molecular architecture, chemistry (interaction parameters) and concentration determine which aggregates form in solution and their properties

DPD algorithm: Bonds

DPD Polymers are constructed by tying particles together with a quadratic potential (Hookean spring): the force law is

$$\mathbf{F}(\mathbf{r}_{ii+1}) = -k_2(|\,\mathbf{r}_{ii+1}\,| - r_{i0})\,\mathbf{r}_{ii+1}/|\,\mathbf{r}_{ii+1}\,|$$

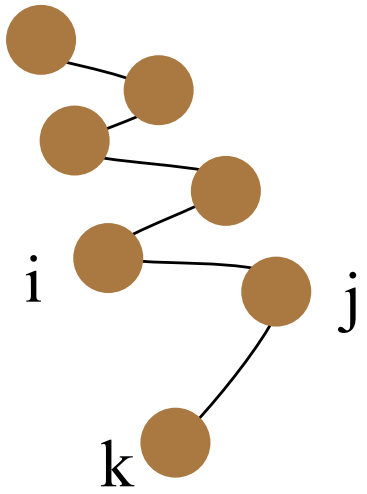
with i,i+1 representing adjacent particles in polymer. Note that k_2, r_0 may depend on the particle types.

Hydrocarbon chain stiffness may be included via a bending potential

$$V(ijk) = k_3(1 - \cos\phi_{ijk})$$

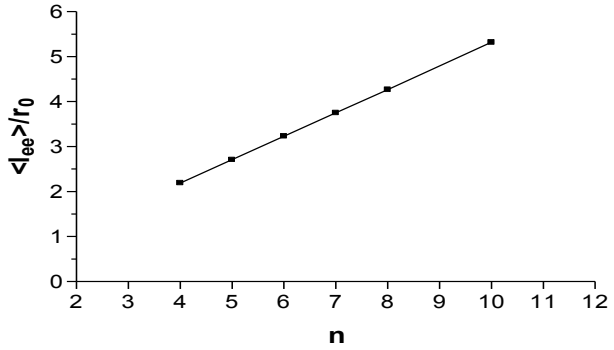
With ijk representing adjacent triples of beads.

Again, k_3 may depend on particle types.

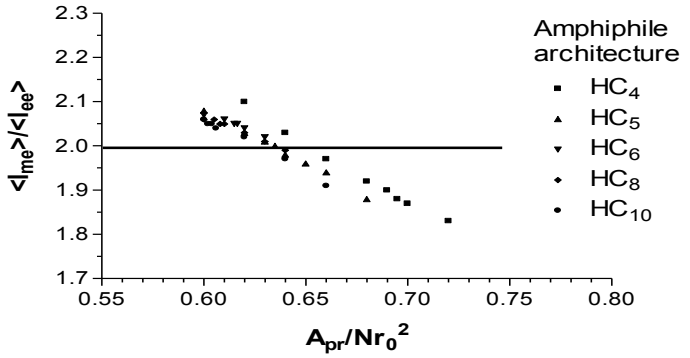


Lipid Bilayer Geometric Properties

l_{ee} is linear in tail length

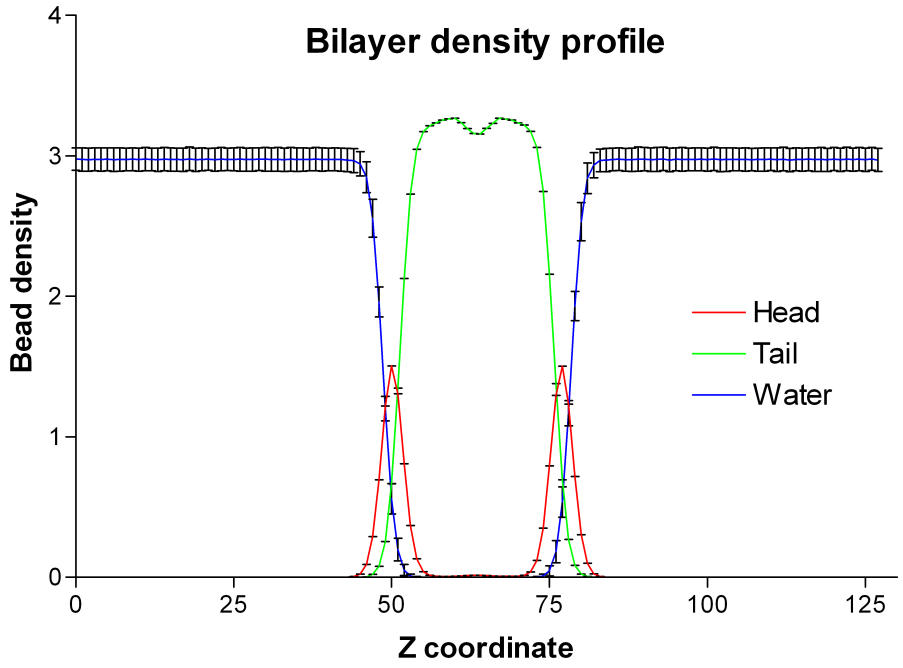


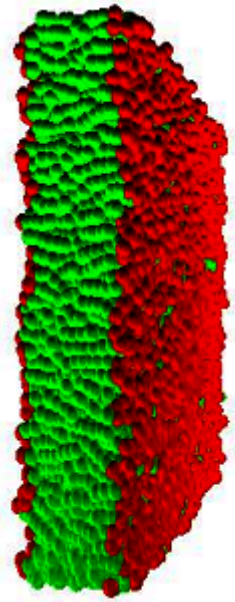
Membrane thickness is $l_{me} \sim 2.\ l_{ee}$ for small area expansions



Bead Density Profile Calculation

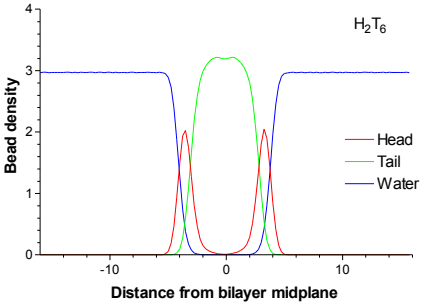
Divide the simulation box into slices of width $r_0/4$.
Count the beads of each type per slice; average over run

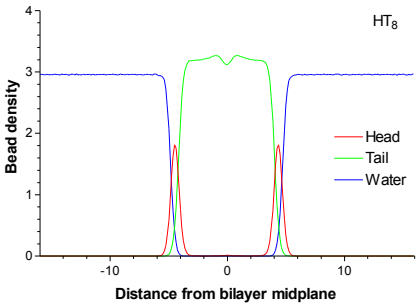


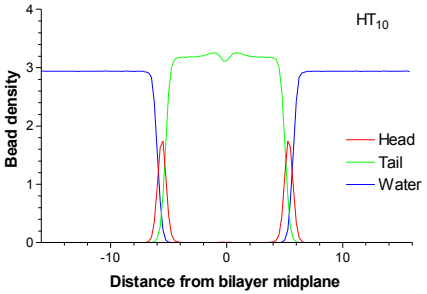


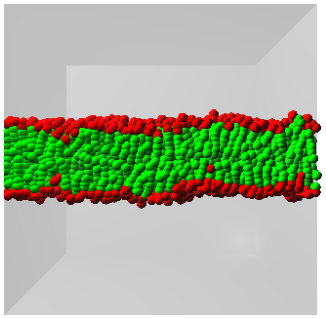
Bead Density Profiles for H_mT_n

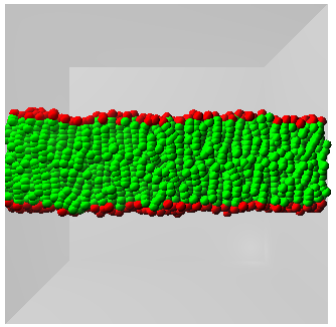
Hydrophobic region has uniform density

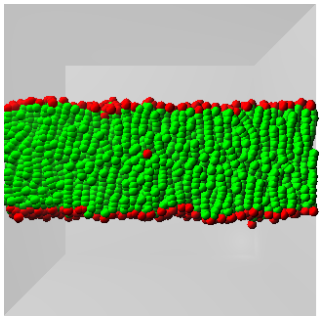




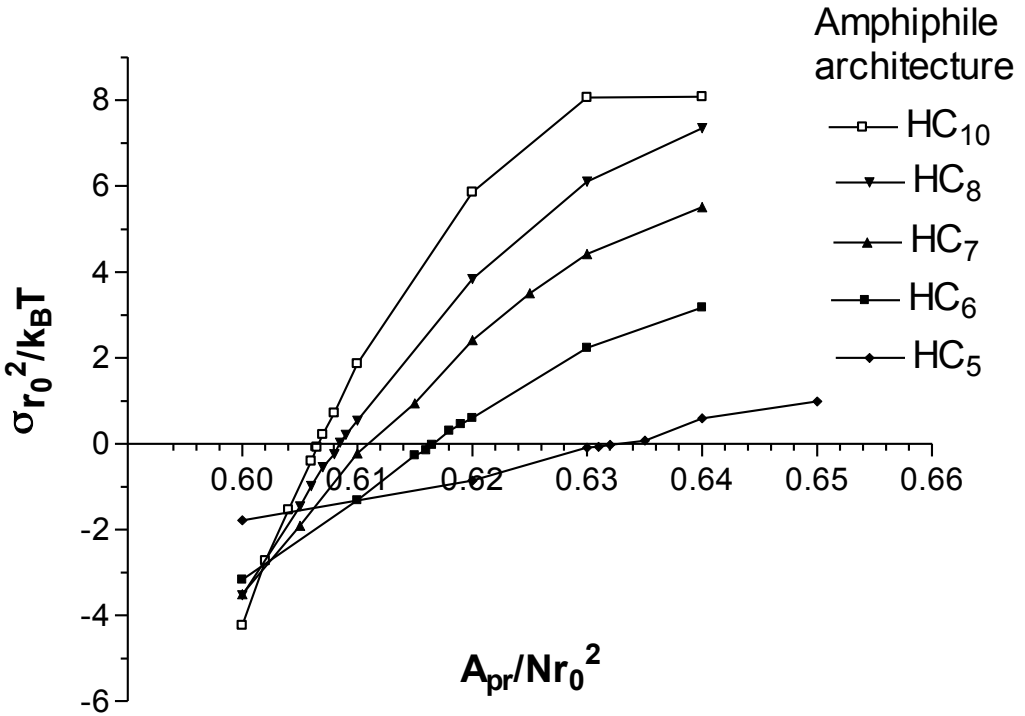






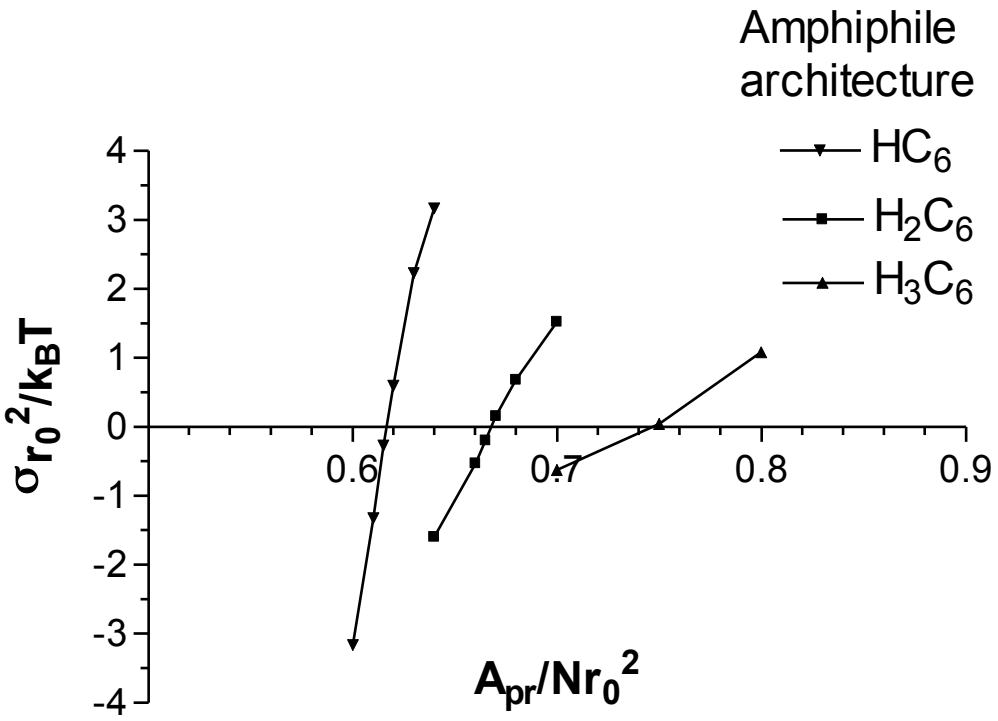


Bilayer Surface Tension



Integral of stress profile yields the surface tension

Headgroup Size



Amphiphile architecture modulates bilayer response to A/N

Simulating experiments like FRAP or FCS

Simulating a diffusion problem with DPD is good because it is easy to compare directly to experiments;

measuring a signal intensity is good because it is effectively a counting problem - what is the time series of the number of particles in a given region of space?

But diffusion problems can be very slow, especially if membranes or large aggregages are involved; hydrodynamic forces are long-range and can easily interfere with results for small system sizes.

Morphology phase diagram for self-assembled block copolymers (triblocks …

What morphologies do selected block copolymers adopt? Construct a phase diagram as the order, size and nature of the blocks is varied (lot of papers in the literature already on this).

Using more than one species gives more room for exotic structures but adds more parameters.

Material/mechanical properties of fluid protein droplets

Which material properties can be measured for a preassembled fluid droplet of sticky polymers?

- Internal diffusion of the constituent polymers
- Internal diffusion of small nanoparticles as function of radius
- Mechanical response to a compressive force applied to rigid slabs under constant force (or sinusoidal force)

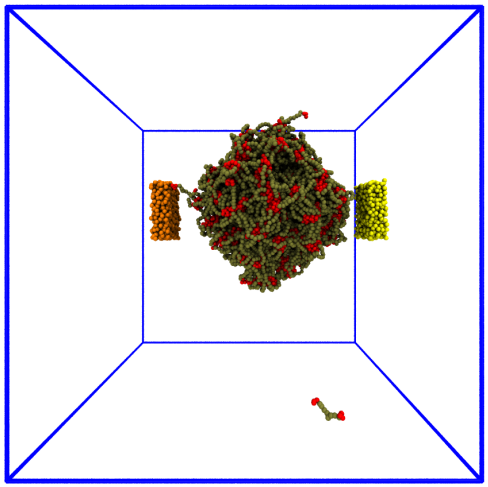
Drawbacks

System size must be large 48**3, so simulations are slow

Many parameters to scan

Inertia artifacts

How can observables be converted into experimental predictions?
i.e., need MLT conversion factors?



Condensing effect of droplet formation around DNA

Surface tension is a mesoscale property of fluids that is reproducible in DPD simulations (see Groot and Warren, J. Chem. Phys. 107:4423 (1997))

Experiments show that proteins condensing into a droplet on dsDNA can collapse it into a ball.

Parameters

- DNA length
- DNA Tension
- Protein concentration
- Protein self-adhesion energy
- Protein-DNA adhesion energy
- Temperature