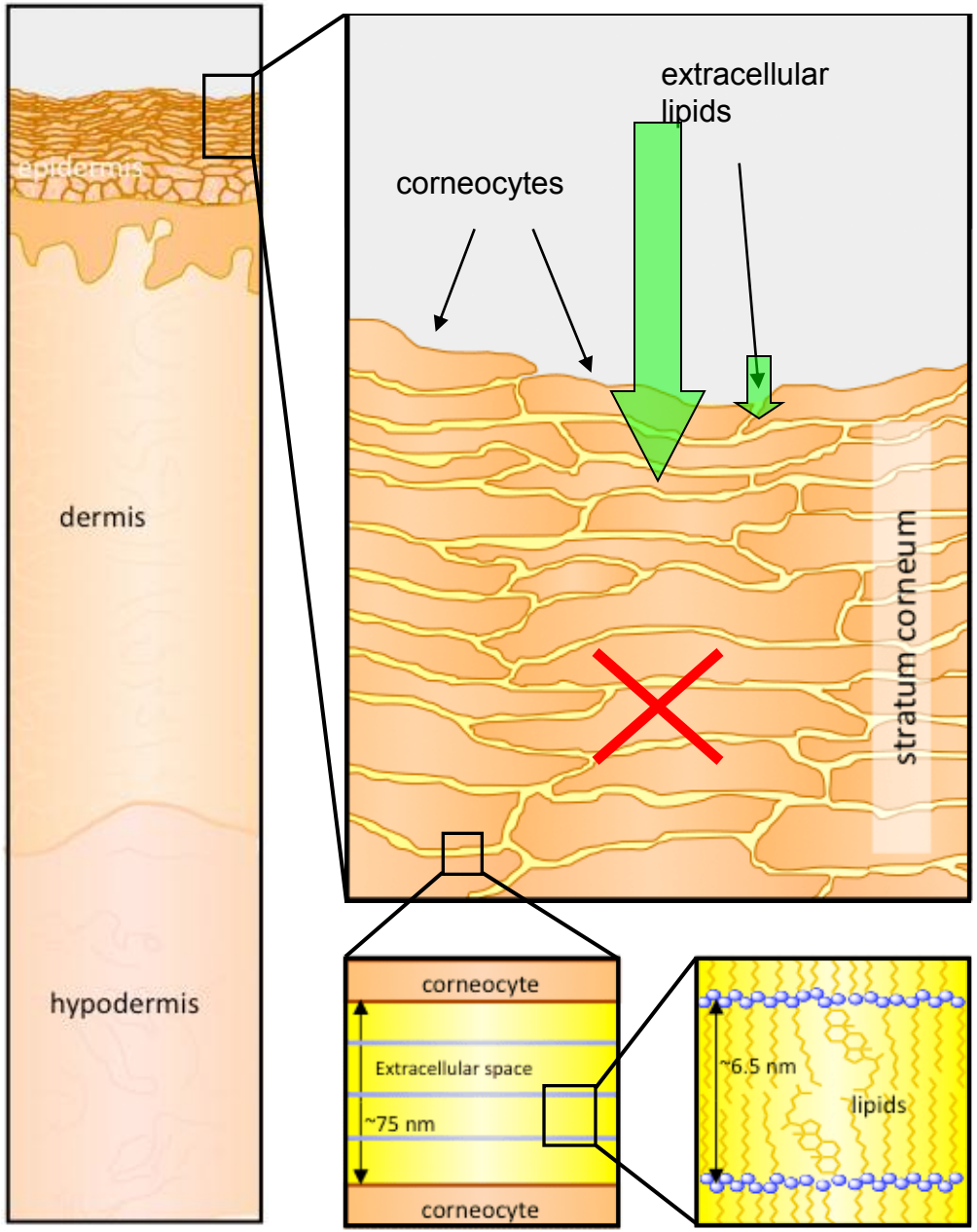
Louisiana Alliance for Simulation-Guided Materials Applications

SD3 – Biomolecular Materials

Hank Ashbaugh: Tulane University
Dorel Moldovan: Louisiana State University

The Problem: Skin Physiology



1) The outermost layer of the skin, the stratum corneum, represents the most significant barrier to the transdermal delivery of therapeutics.

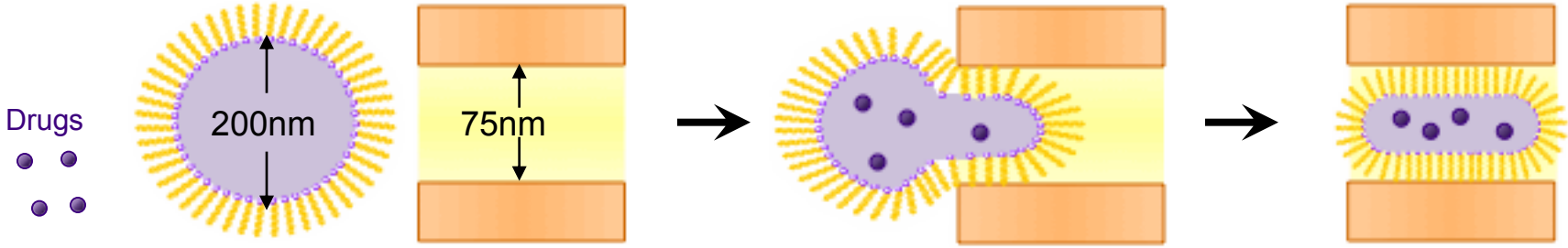
2) The primary transport pathway through the stratum corneum involves diffusion through the lipids of the extracellular matrix

3) The extracellular lipids are organized as multilamellar sheets inhibiting the transdermal diffusion of polar compounds

The Problem: Drug Delivery Vehicles

Self- Assembled Drug Delivery Vehicles (Focus 2)

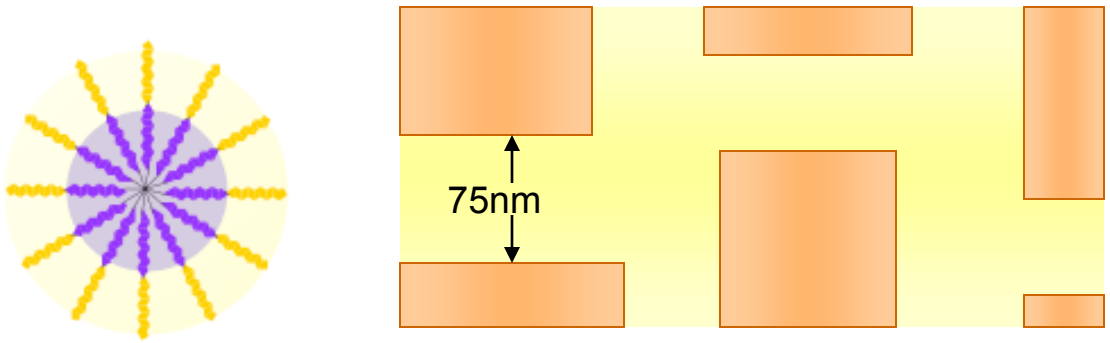
- Use self-assembled liposomes to transport polar drugs through lipid channels
- Amphiphiles selected to enable the liposomes to readily deform: transfersomes, ultradeformable liposomes, ethosomes.



Pros:
- Tunable assembled structures
- Inexpensive

Cons:
- Assembly size dictated by thermodynamics
- Assemblies disaggregate below CMC

Unimolecular Drug Delivery Vehicles (Focus 1)



Pros:
- Robust covalent assembly
- Vehicle size tunable from 5 nm to 50 nm

Cons:
- Expensive

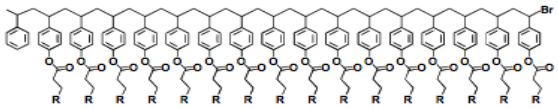
Explore Synthesis and Delivery with Both Classes of Vehicles to Optimize Design

SD3 Goals

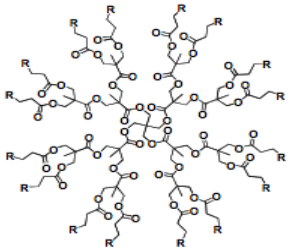
Goal: Develop novel biomolecular materials guided by computational/experimental collaboration for the encapsulation, delivery, and release of therapeutics to targeted tissues.

Simulation challenges: Carrier sizes (1 to 100nm), time scales for assembly/delivery (nanoseconds to miliseconds), accurate free energy evaluation, efficient use of computational resources

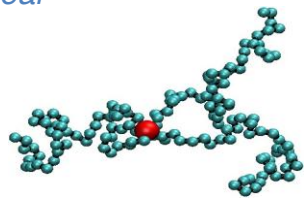
Polymeric Unimolecular Drug Delivery Vehicles



linear

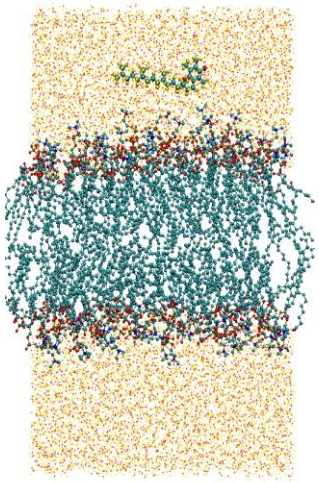


star/dendrimer

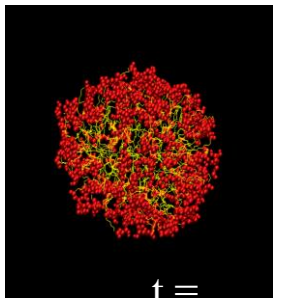


coarse-grained star

Self-Assembled Drug Delivery Vehicles

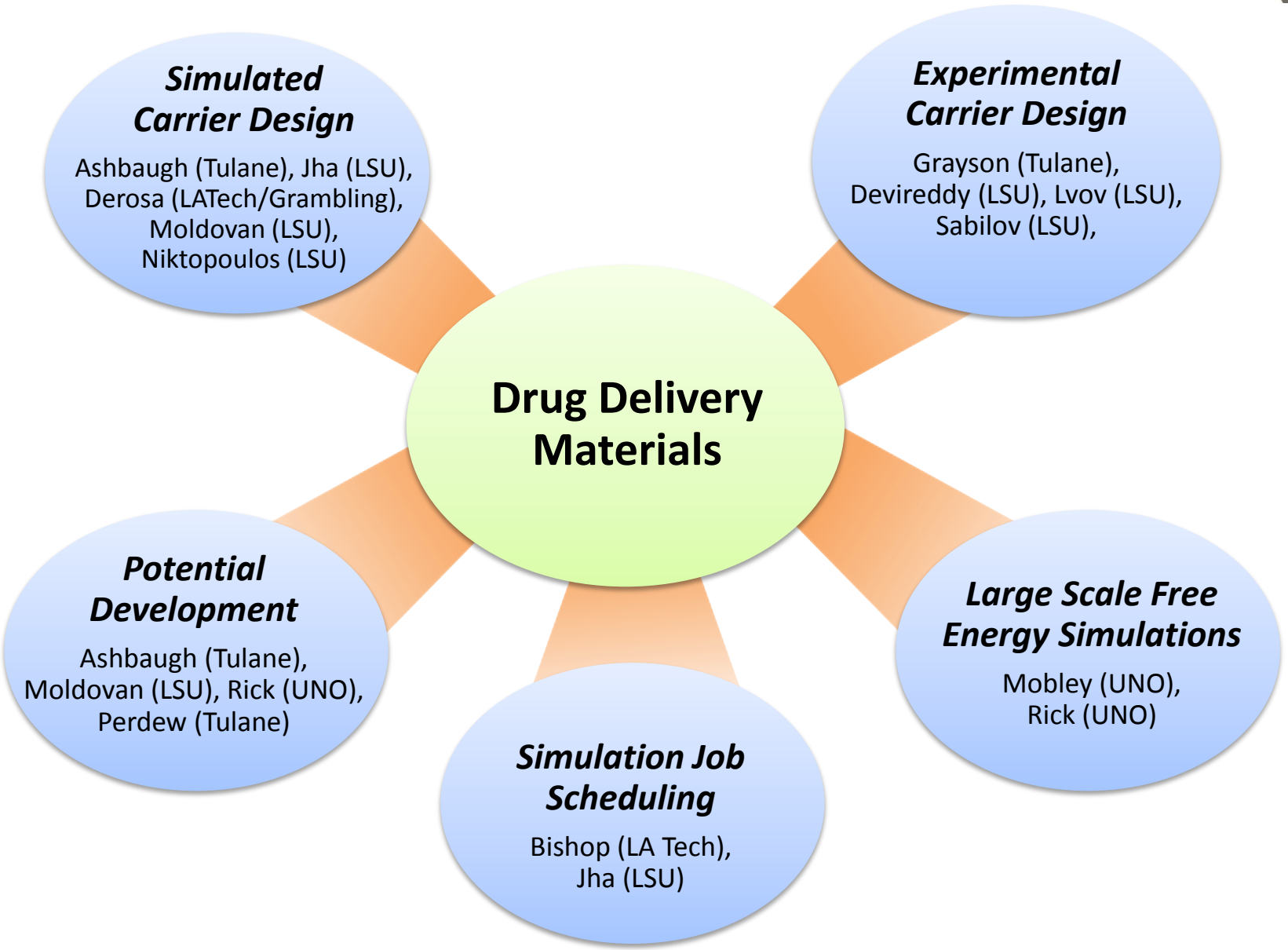


lipid bilayer



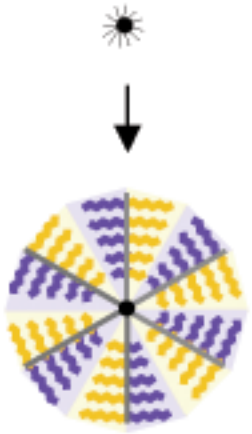
Surfactant micelles

SD3 Research Themes

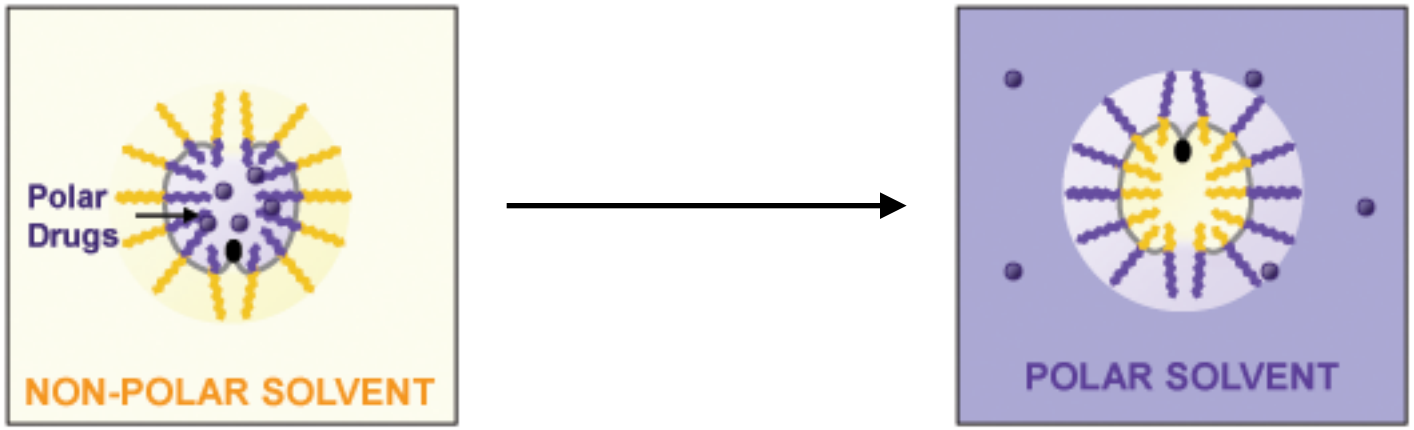


Janus Amphiphilic Homopolymers

Grayson (Tulane)



- Synthesis of dendritic tertiary bromide initiators
- Preparation of an amphiphilic monomer
- Atom Transfer Radical Polymerization (ATRP) of the amphiphilic monomer
- Characterization of conformation with change in polarity
- Characterization of encapsulation and release properties

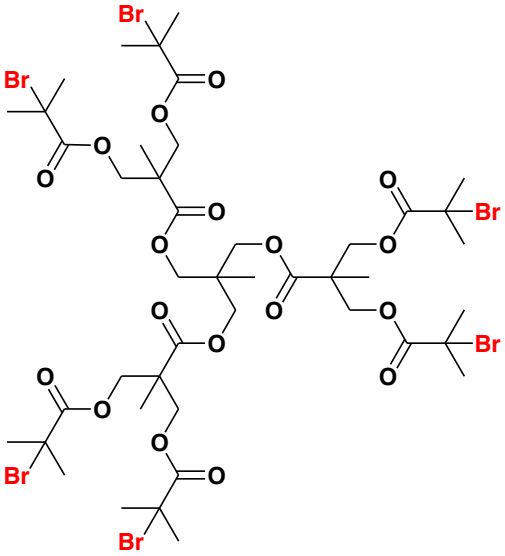


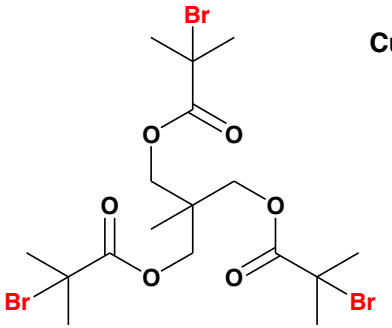
Encapsulation of polar drugs in non-polar environments

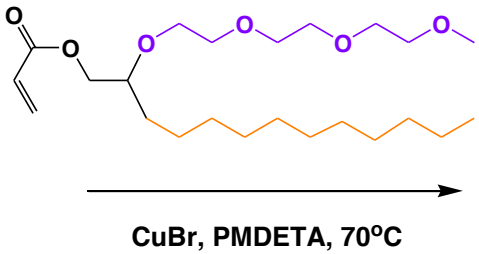
Inversion of structure & release of payload in polar environments

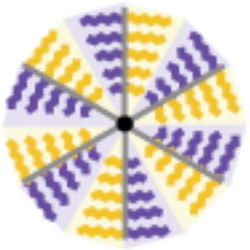
Janus Polymer ATRP Synthesis

Grayson (Tulane)

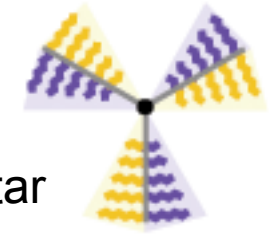








6-arm
Janus star

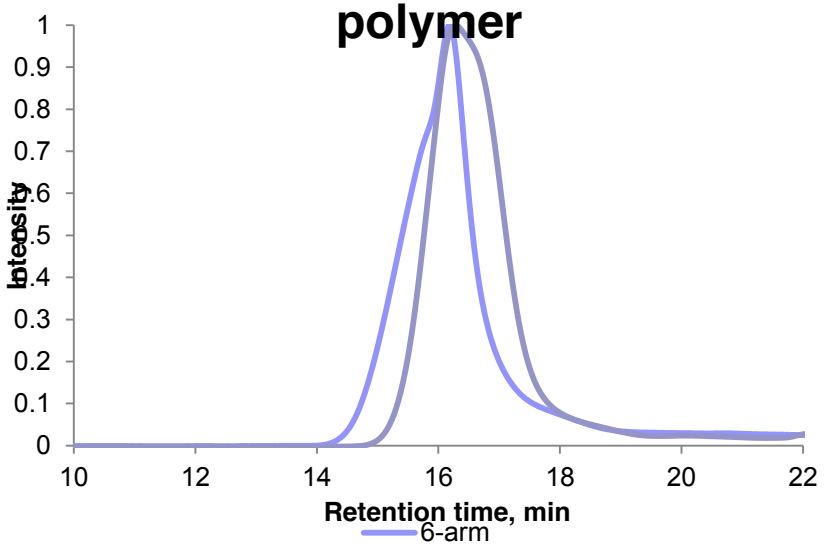


3-arm
Janus star

6-arm Core or 3-arm Core

	M.W.	PDI
3-arms	26.0k	1.41
6-arms	45.7k	1.72

GPC for 3-arms and 6-arms polymer

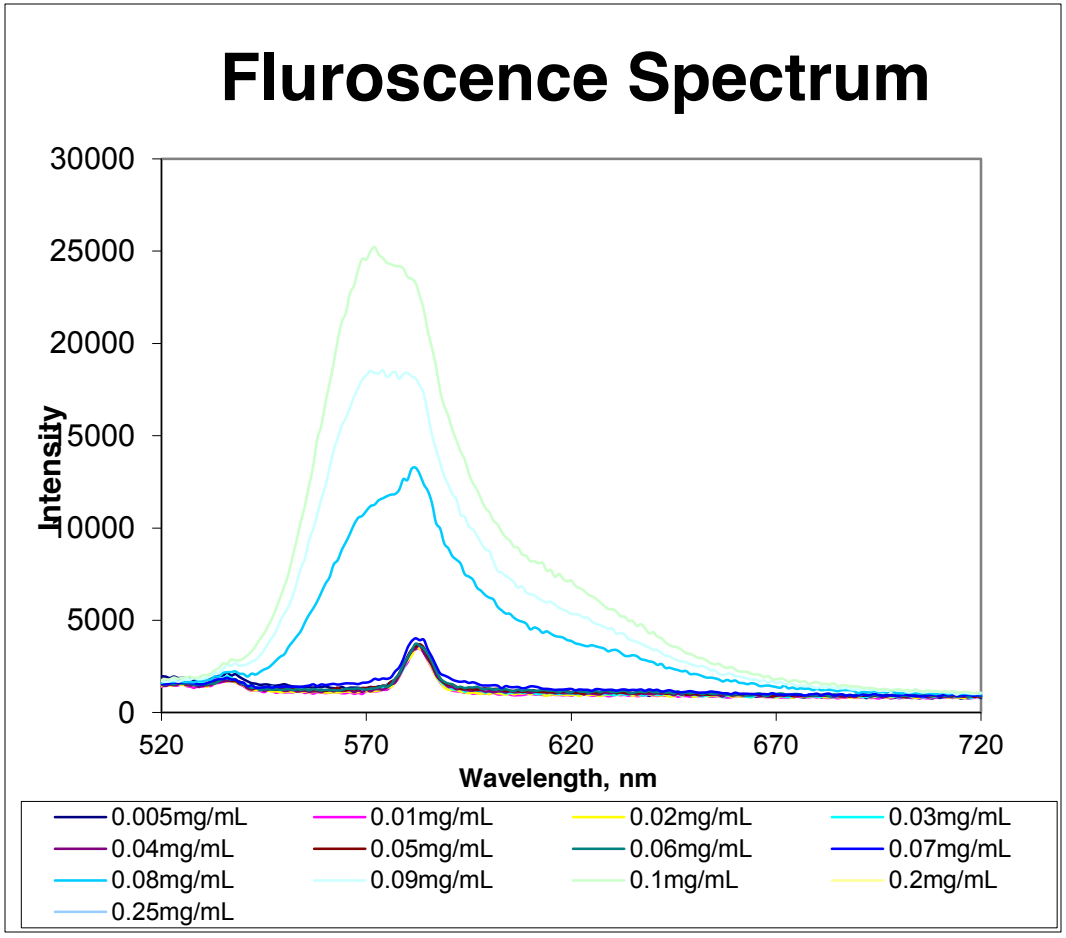


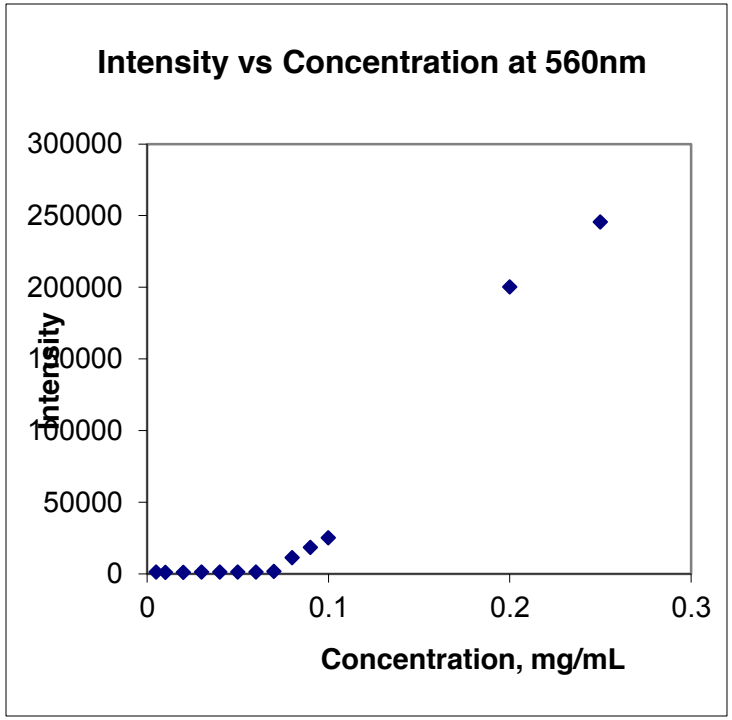
Y. Wang, S. Grayson

Janus Polymer Dye Encapsulation

Grayson (Tulane)

Encapsulation of Rose Bengal (UV active) within Janus Stars in Hexane





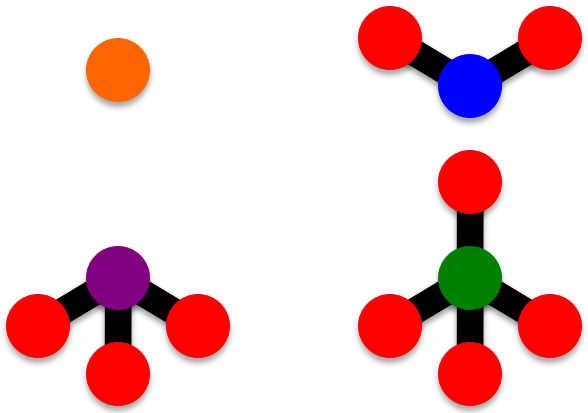
Critical micelle concentration: 0.07mg/mL

Y. Wang, S. Grayson

Solubility of Oils in Water

Ashbaugh (Tulane)

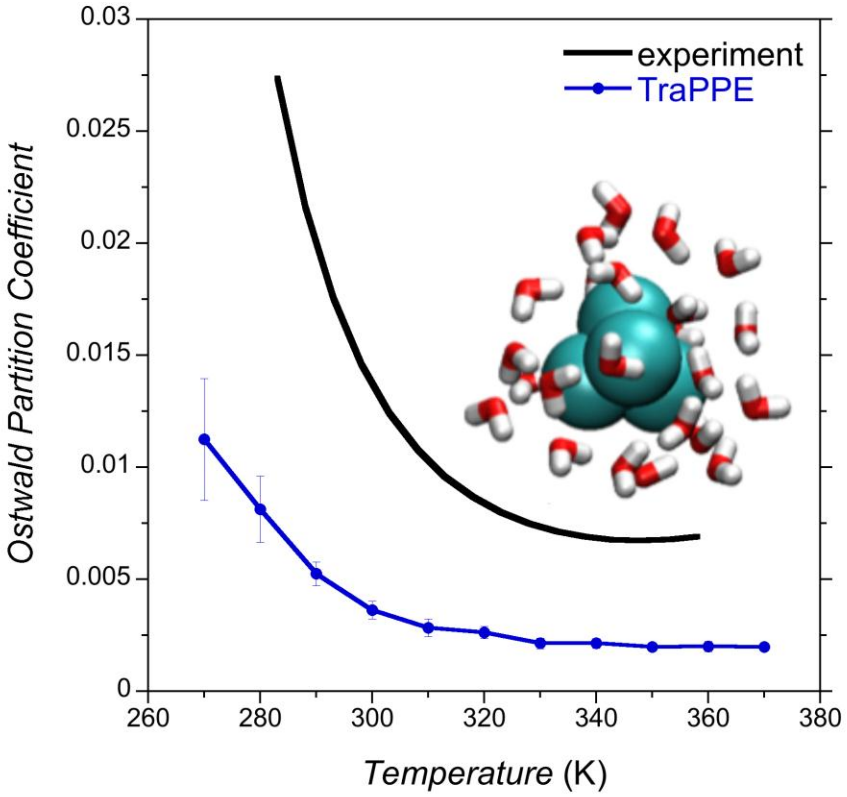
Linear and Branched Alkanes



Alkane Groups

- = CH_4
- = CH_3
- = CH_2
- = CH
- = C

Neopentane Solubility in Water



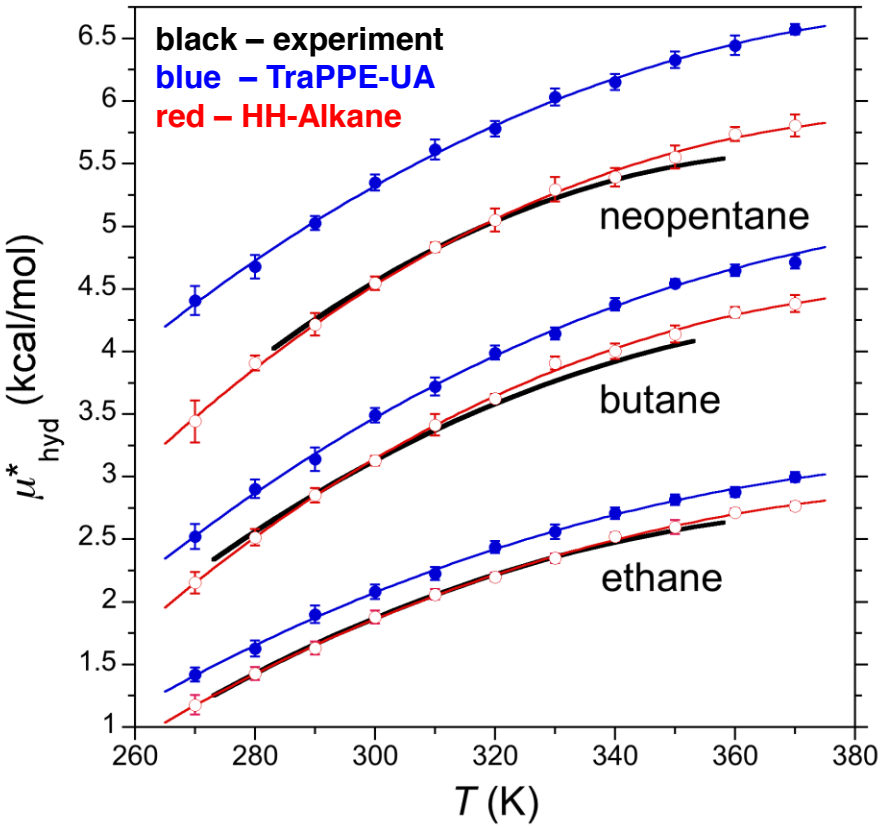
Water Model: TIP4P/2005
Alkane Model: TraPPE-UA

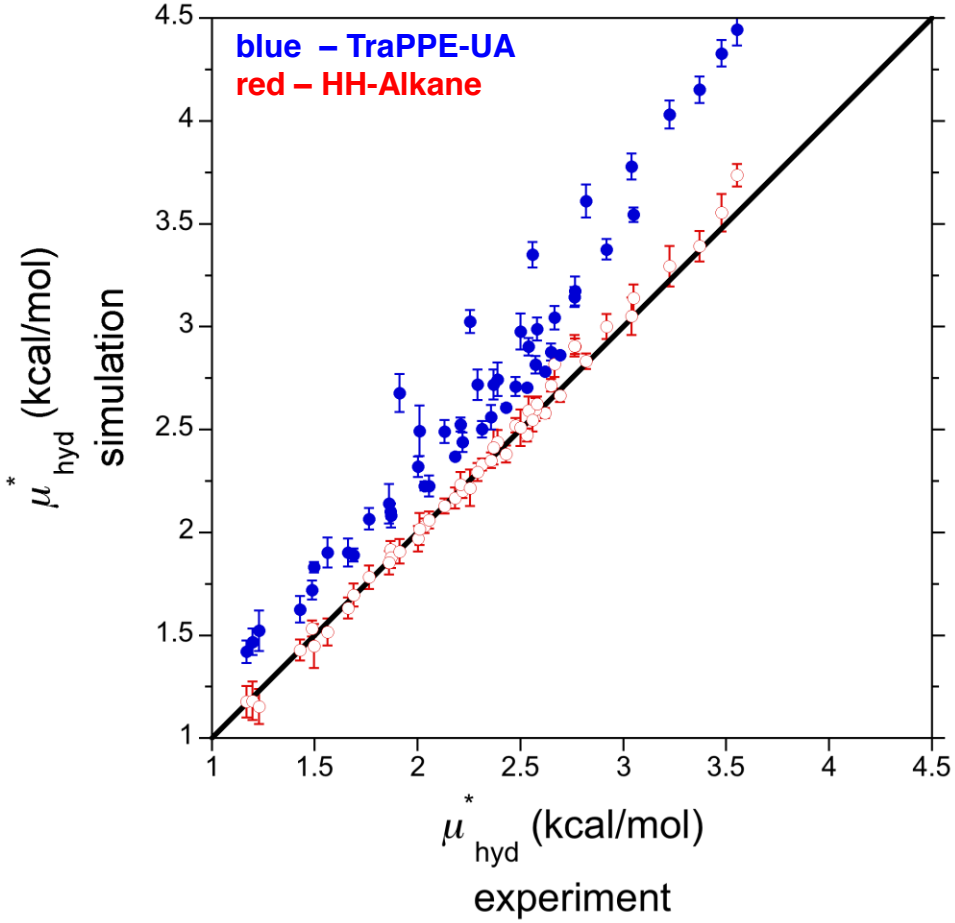
Optimize cross Interactions to reproduce solubility as a function of temperature

L. Liu, H. Ashbaugh

Solubility of Oils in Water

Ashbaugh (Tulane)





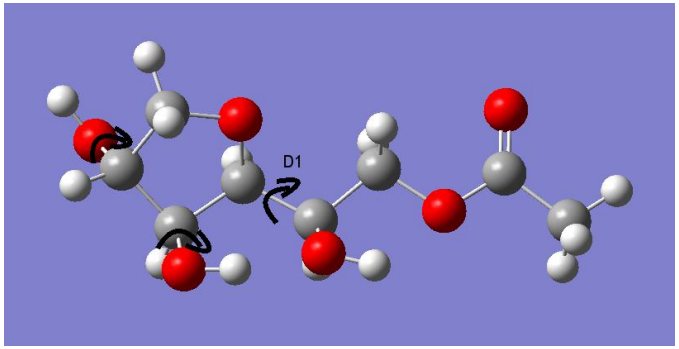
HH-Alkane model captures temperature dependence of hydrophobic hydration and is applicable to linear and branched alkanes

L. Liu, H. Ashbaugh

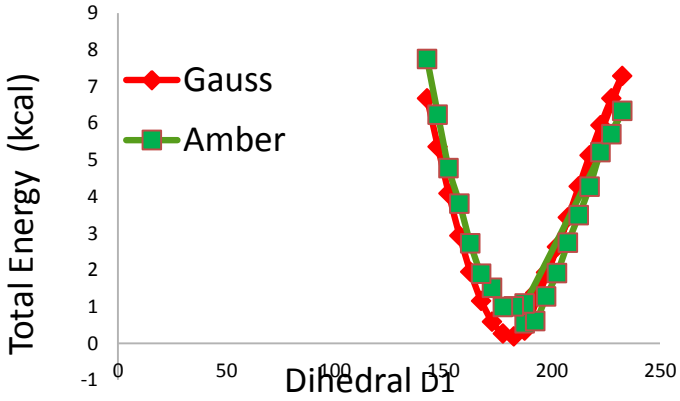
Development of Span 80 Force-Field

Thakur (LSU), Ashbaugh (Tulane), Moldovan (LSU)

- Develop new force field for Span80
  - Start with:
    - Initial geometry from Gaussview or Chemdraw.
    - AMBER-03 or GROMOS-53A6
  - Ab-initio calculations
    - Ab-initio calculations with G09, HF/6-311g(d)
    - QM to obtain minimum energy structure
    - QM-Mulliken, RESP or BCC charges
    - Relaxed scan of the three dihedral angles to obtain a set of conformers
  - MD calculations:
    - Optimize the FF parameters by fitting the MD energies to the corresponding QM profiles



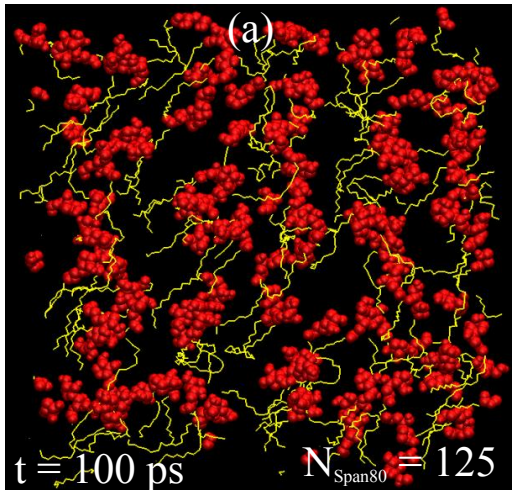
$$E_{\text{pair}} = \sum_{\text{bonds}} k_r(r - r_{\text{eq}})^2 + \sum_{\text{angles}} k_\theta(\theta - \theta_{\text{eq}})^2 + \sum_{\text{dihedrals}} \frac{v_n}{2} \times [1 + \cos(n\phi - \gamma)] + \sum_{i<j} \left[\frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^{6}} + \frac{q_i q_j}{\varepsilon R_{ij}}\right] \quad (1)$$

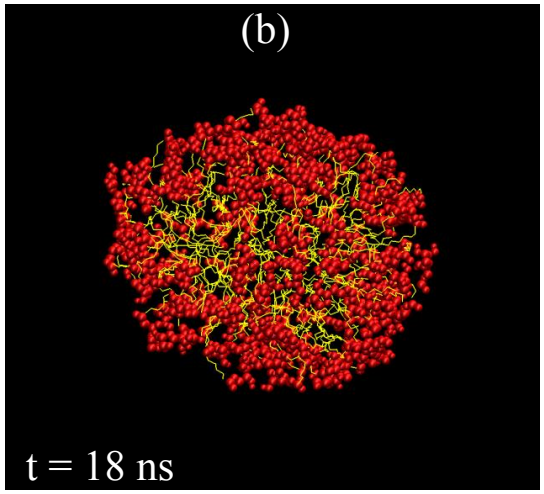


MD Simulation of Span 80 Assembly

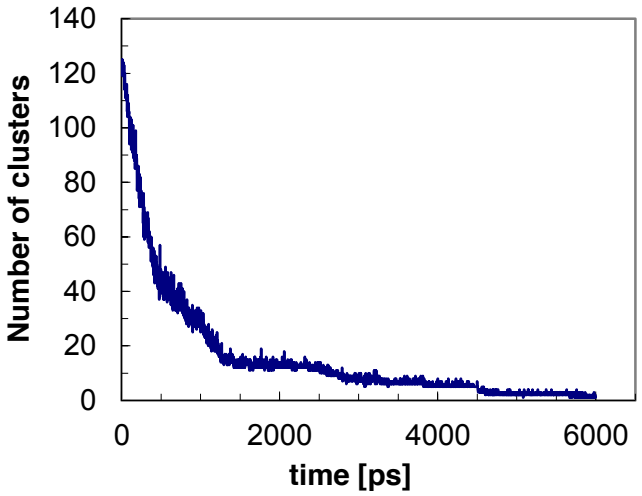
Moldovan (LSU), Sabliov (LSU-Ag)

Self-assembly of Span 80 into a single micelle





Kinetics of Span80 aggregation



MD simulations performed with GROMACS 4.0 on LONI supercomputers.

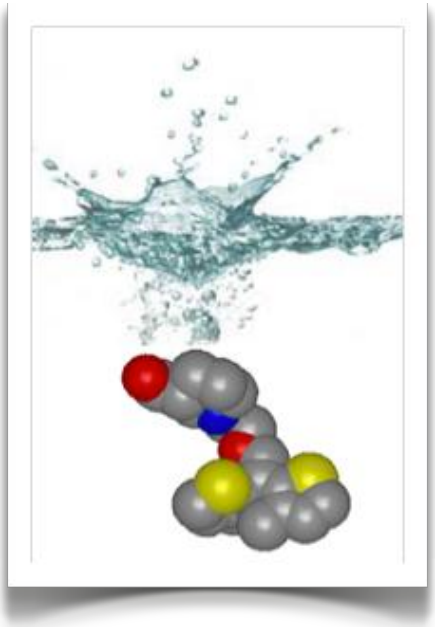
Force field parameters for Span 80 were generated using Gaussian, Amber and PRODRG2.5 server.

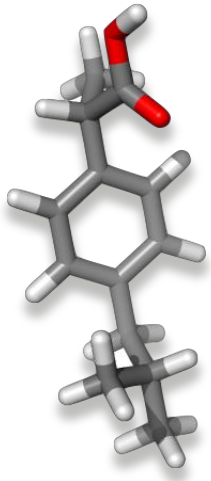
MD simulations show that at concentrations of 0.25 M Span 80 self-assemble spontaneously into micelles. The self-assembly process occurs in three stages: (i) aggregation in small clusters (~100ps); (ii) ripening stage, larger clusters grow at the expense of small ones; (iii) diffusion and coalescence of larger clusters.

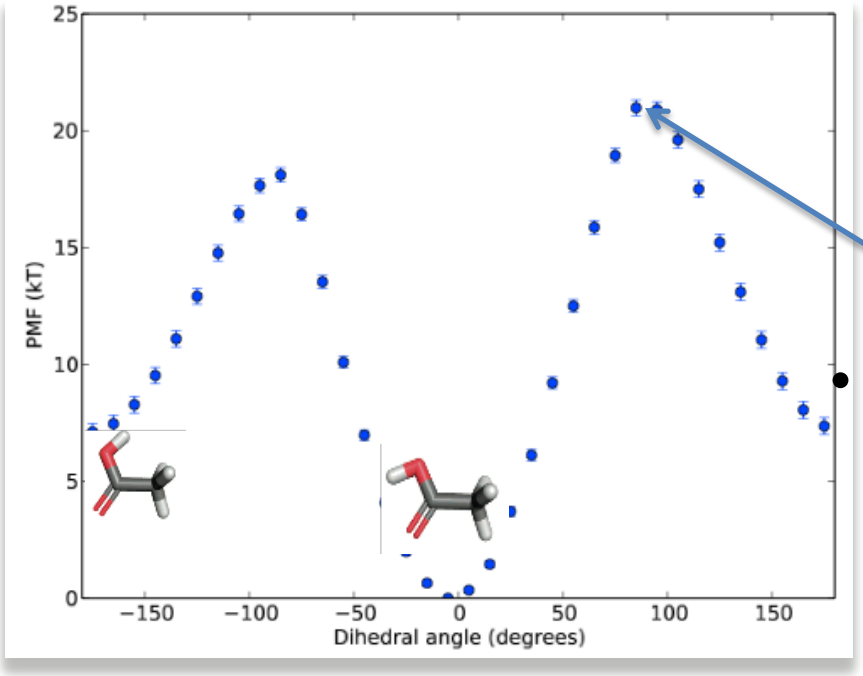
Time evolution of the number of Span 80 clusters supports the three stage self assembly mechanism.

Free Energies from Expanded Ensemble Simulations *Mobley (UNO), Maginn (Notre Dame)*

- Free energies of transfer play key roles in many processes including solubility, binding, aggregation
- Kinetic barriers challenge sampling, leading to errors



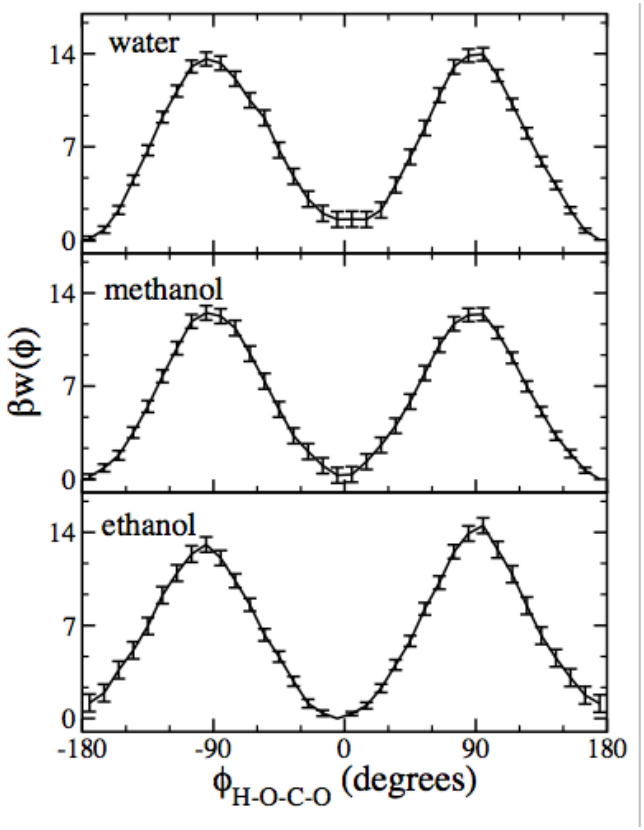




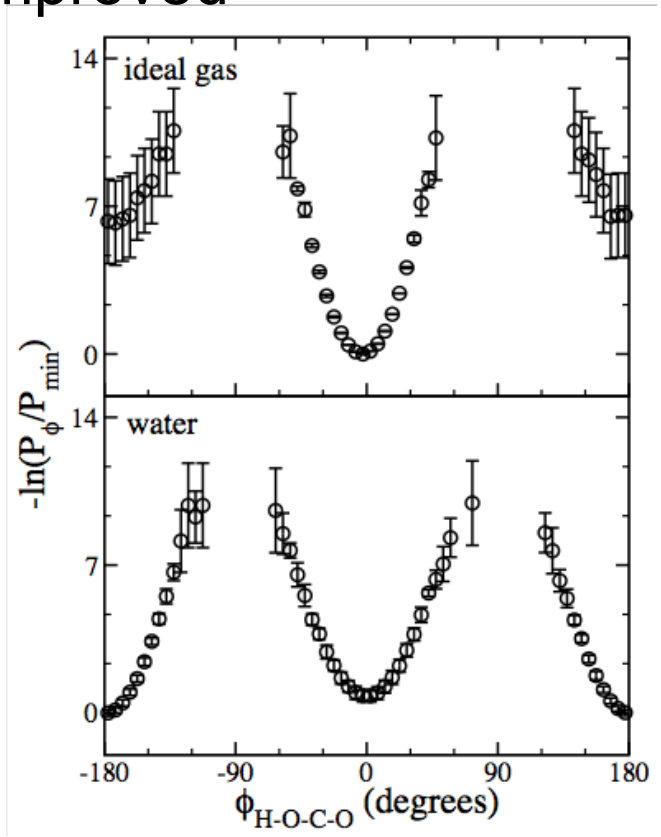
- 20 kT barrier; preferred conformation depends on environment

Free Energies from Expanded Ensemble Simulations *Mobley (UNO), Maginn (Notre Dame)*

Energy landscapes in different solvents difficult to sample

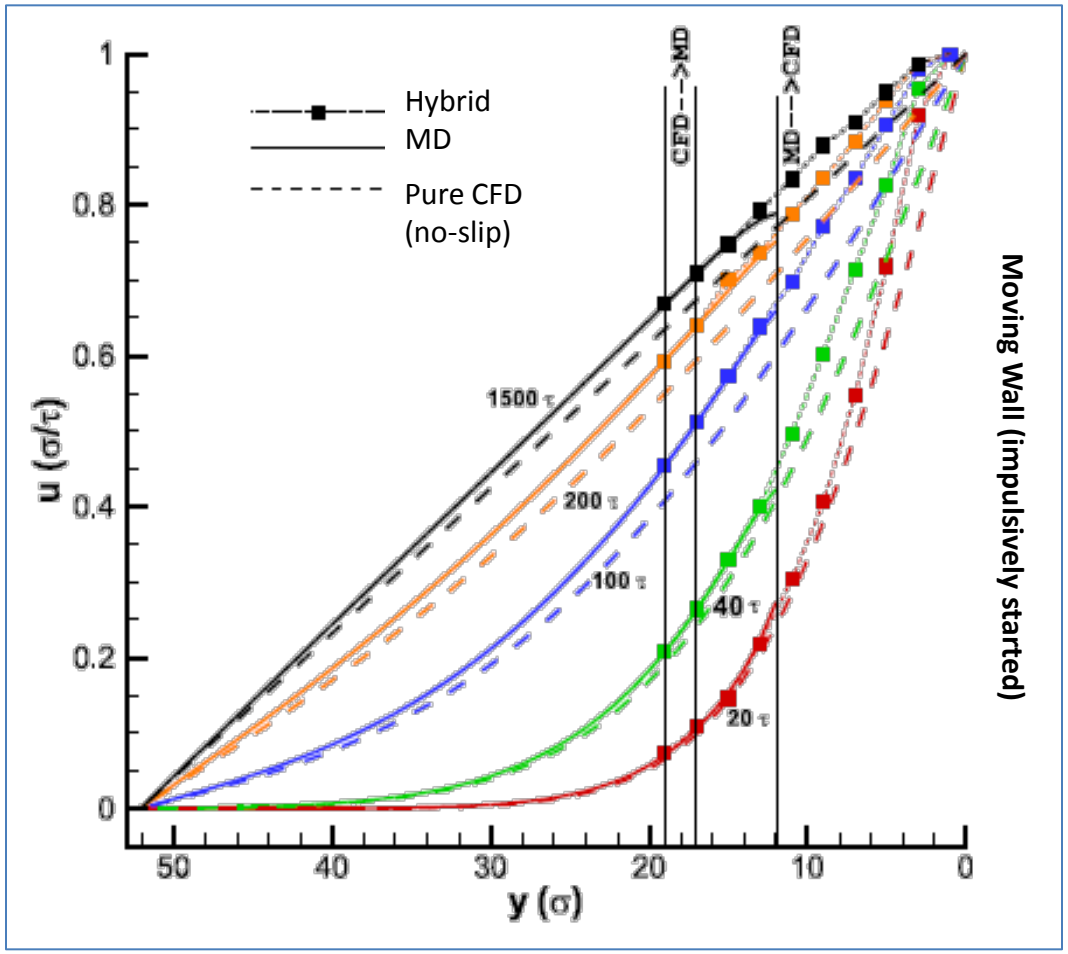


Actual sampling using expanded ensemble is vastly improved



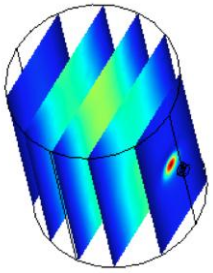
Hybrid MD/Continuum Simulations

Moldovan (LSU), Nikitopoulos (LSU)

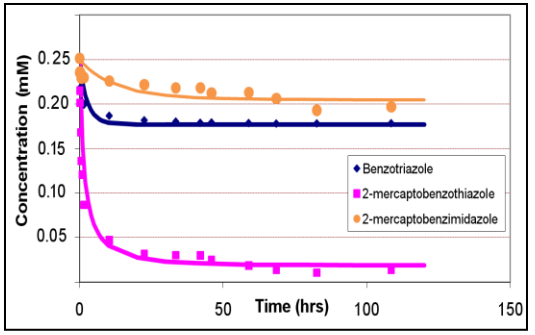


- Developed a general hybrid MD/continuum code for simulating non-equilibrium flows using LAMMPS (MD) and ANSYS/Fluent (continuum)
- Extensively tested code for impulsively started Couette flow for Lennard-Jones Fluid
- Established collaboration with Dr. Steve Plimpton (Sandia) to distribute through LAMMPS

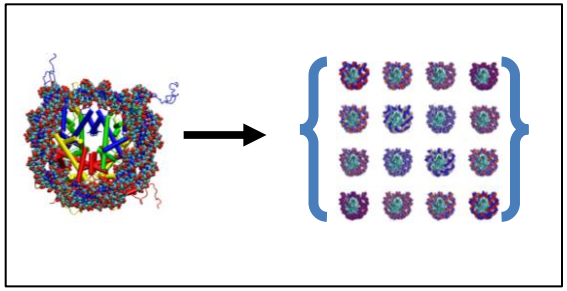
Additional Projects



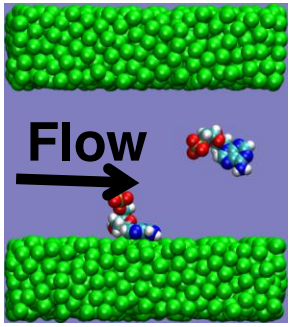
- Nanoparticle diffusion into tumors (Derosa)



- Diffusion in nanotubes, storage and release (Lvov, Derosa)



- Chromatin simulation and job scheduling (Bishop, Jha)



- DNA transport in nanochannels (Nikitopoulos, Moldovan)
- Nanoparticle/cell interactions (Sabilov, Devireddy, Moldovan, and Grayson)
- Assessment of nanoparticles on vesicle transport (Devireddy, Nikitopoulos, Sabilov, Moldovan)

SD3 Milestones

Milestones	Y1	Y2	Y3	Y4	Y5	
1. Synthesize modular library of core molecules and amphiphilic side chains to explore encapsulation based on architecture and chemistry	X	X	X			*On Track!*
2. Develop new inter-atomic interaction potentials and new coarse-grained force fields	X	X				*On Track!*
3. Develop new hybrid MD/continuum, coarse-grained, and accelerated strategies to link length/time scales	X	X	X			*On Track!*
4. Use mulitscale methods to explore role of architecture and solvent to optimize supramolecular vehicles			X	X	X	
5. Synthesize, characterize, and assess new self-assembled transmembrane drug delivery systems	X	X	X			*On Track!*
6. Validate computational models for drug carriers, self-assembling, and translocation through bio-membranes			X	X	X	
7. Use MD and CG methods to study the mechanisms of cellular absorption of drugs				X	X	

Questions?