



SD3: Biomolecular Materials

Hank Ashbaugh - Tulane University

Dimitris Nikitopoulos – LSU

Multi-scale simulation and synthesis of self-assembled and supramolecular drug delivery vehicles.

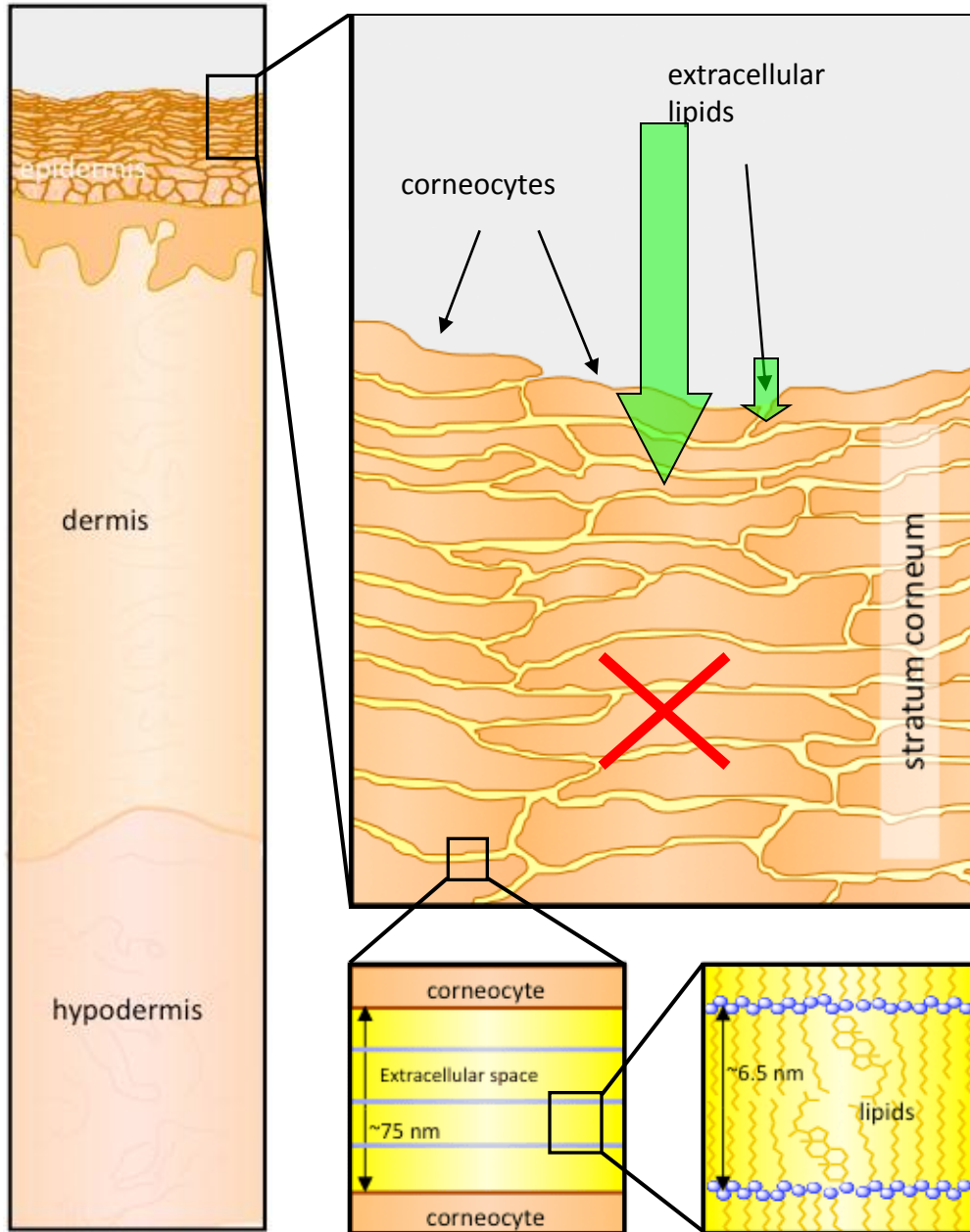
FOCUS 1

Unimolecular Delivery
Vehicles

FOCUS 2

Self-Assembled Delivery
Vehicles

The Problem: Skin Physiology



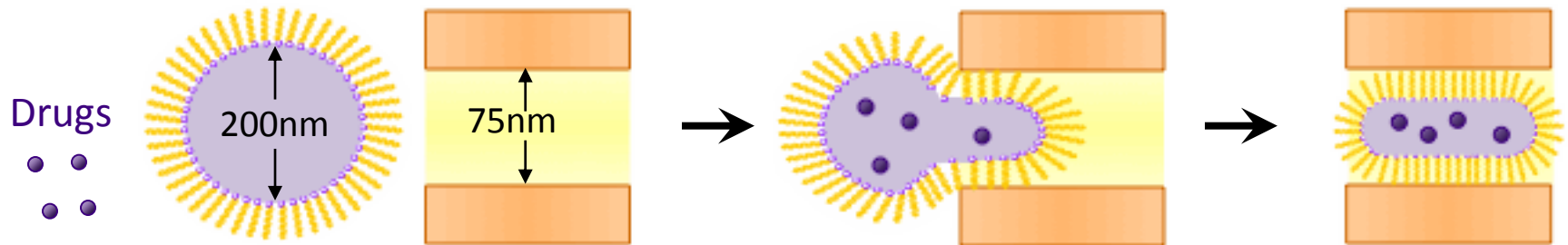
- The outermost layer of the skin, the stratum corneum, represents the most significant barrier to the transdermal delivery of therapeutics.
- The primary transport pathway through the stratum corneum involves diffusion through the lipids of the extracellular matrix.
- The extracellular lipids are organized as multilamellar sheets inhibiting the transdermal diffusion of polar compounds.

The Problem: Delivery Vehicles



Self-Assembled Drug Delivery Vehicles (Focus 2)

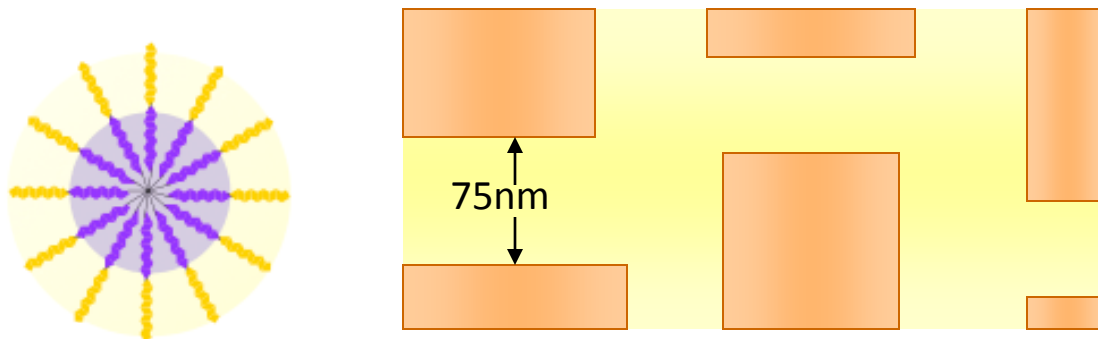
- Use self-assembled liposomes to transport polar drugs through lipid channels
- Amphiphiles selected to enable the liposomes to readily deform: transfersomes, ultradeformable liposomes, ethosomes.



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: - Complex synthesis
- Expensive

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

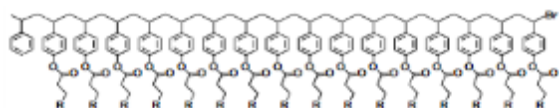
SD3 Goals



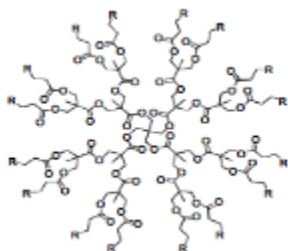
Goal: Develop novel biomolecular materials guided by computational/experimental collaboration for the encapsulation, delivery, and release of therapeutics to targeted tissues.

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

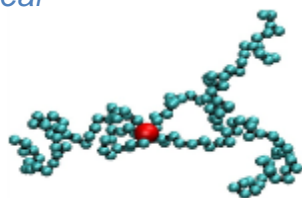
Polymeric Unimolecular Drug Delivery Vehicles



linear

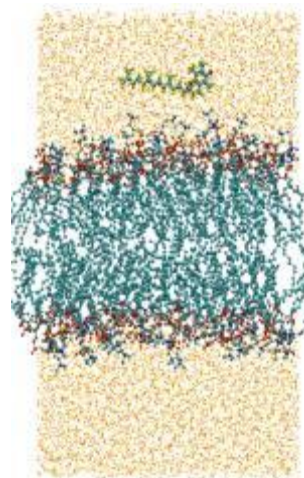


star/dendrimer

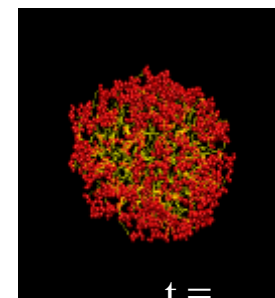


coarse-grained star

Self-Assembled Drug Delivery Vehicles



lipid bilayer



surfactant micelles

SD3 Research Themes



Simulated Carrier Design

Tulane, LA Tech,
Grambling, LSU

Experimental Carrier Design

Tulane, LSU, LSU-Ag,
LA Tech

Drug Delivery Materials

Force Fields

Tulane, LSU, UNO

Large Scale Free Energy Simulations

UNO, LA Tech

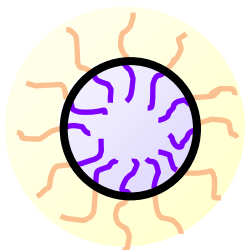
Focus 1

Synthesize modular core molecules and amphiphilic side chains

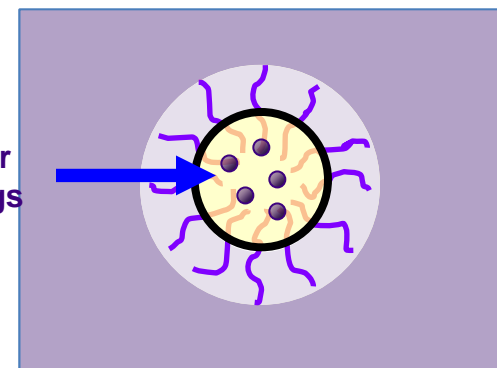
Grayson (TU)



Macrocyclic amphiphilic homopolymers are unique in that they are tethered at the interface between the polar and non-polar faces



- Styrenic backbone was cyclized using click coupling under high dilution
- Bifurcated amphiphiles were attached via click conjugation

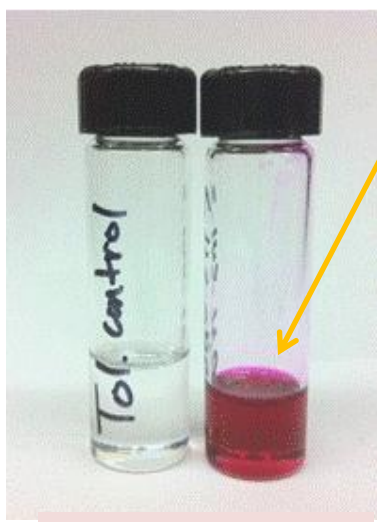


NonPolar → Polar

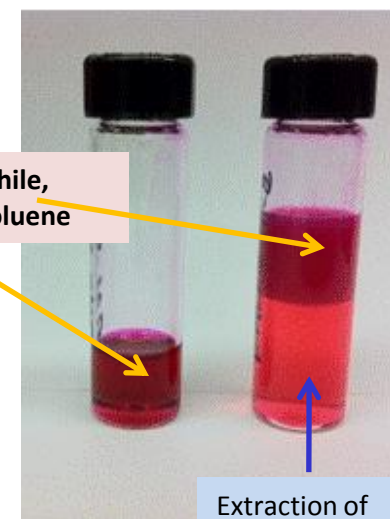
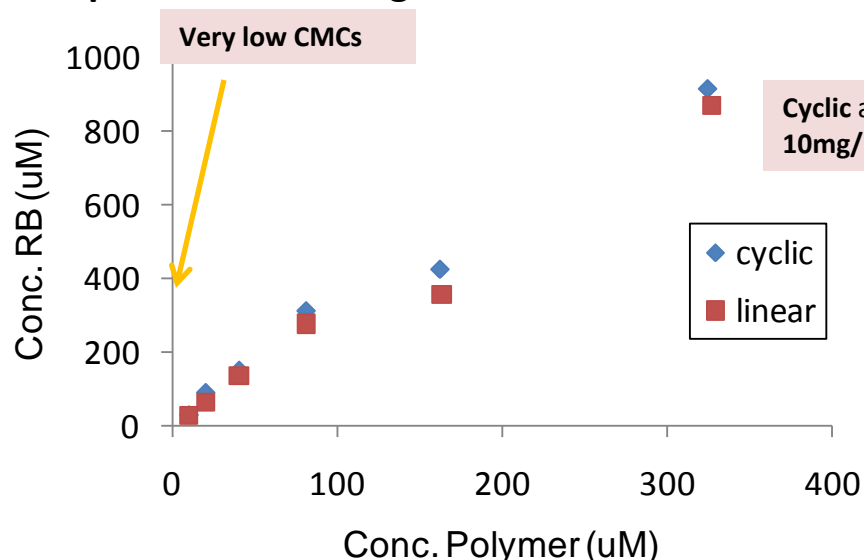
Willham, Kaitlin A.; Laurent, B.A.; Grayson, S.M.. *Tetrahedron Lett.* **2008**, *49*, 2091-2094.

Laurent, Boyd A.; Grayson, Scott M. *Polym. Chem* **2012**

Both linear and cyclic amphiphilic homopolymers encapsulate Rose Bengal in toluene solution



Cyclic amphiphile, 10mg/ml in toluene



Extraction of RB into water

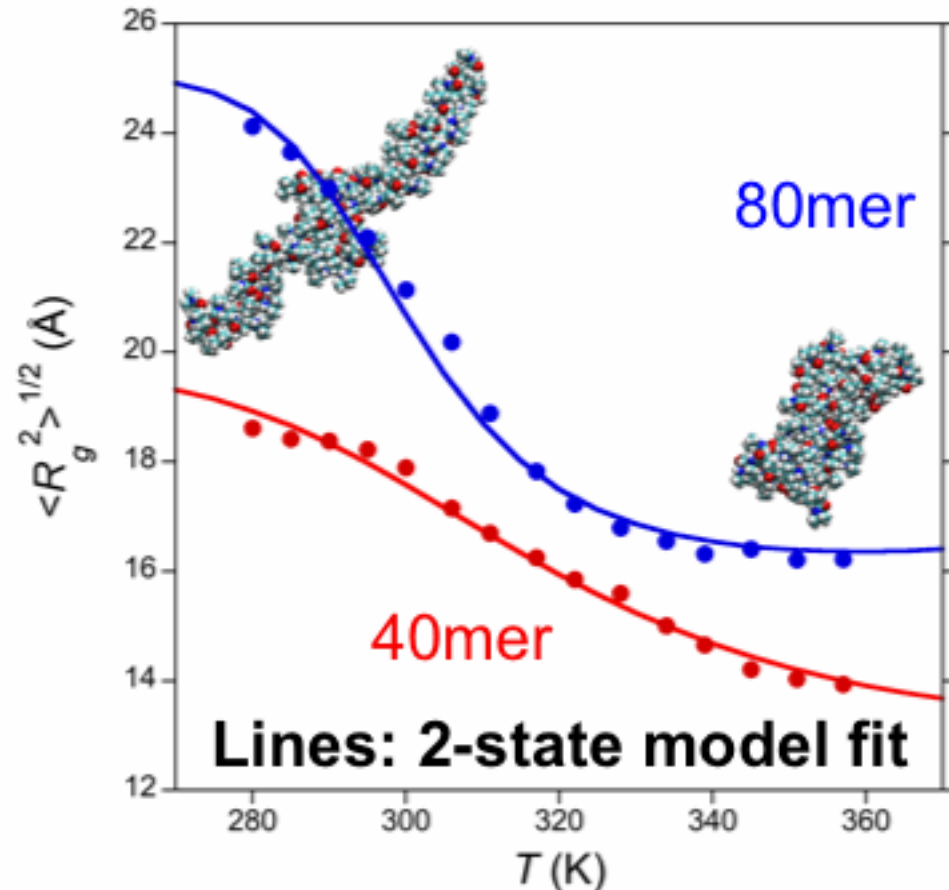
Focus 1

Delivery vehicle conformations in solution

Ashbaugh (TU), Grayson (TU), and Rick (UNO)

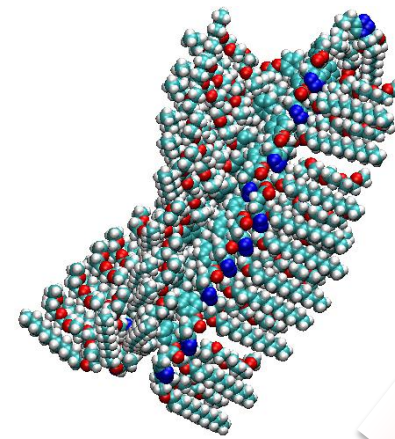


Temperature induced hydrophobic collapse of PNIPAM



Collapse can trigger release

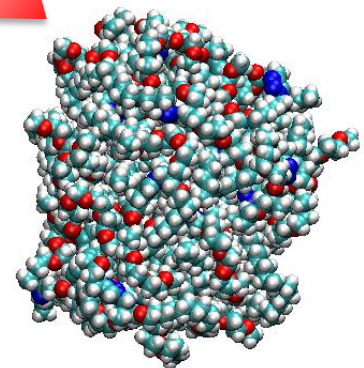
Amphiphilic polymer assembly



Initial linear polymer conformation



Collapsed unimolecular polymeric micelle in aqueous solution



Focus 1

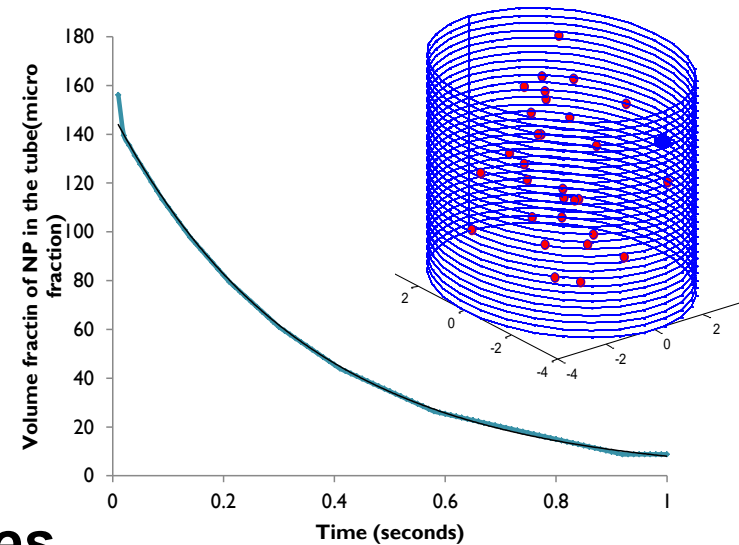
Delivery vehicle diffusion in heterogeneous media

Derosa (LaTech and Grambling) and Lvov (LaTech)



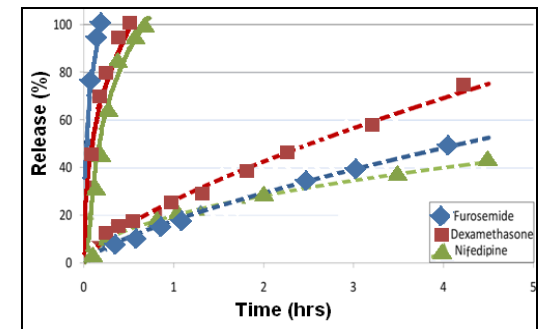
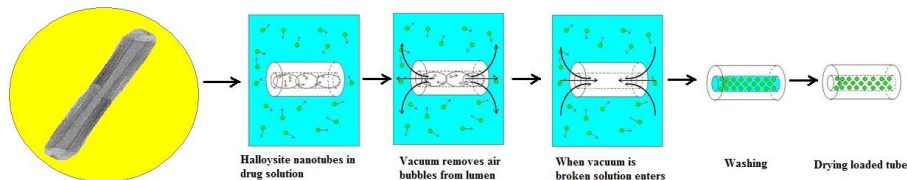
Nanoparticle diffusion in tumor blood vessels

- ❑ Fluid dynamics and Monte Carlo are combined to study the diffusion of nanoparticles in cancer tumor's blood vessel.
- ❑ Simulations predict diffusion efficiency as a function of blood and interstitial pressure, particle concentration in blood, particle size and pore size.
- ❑ Excellent agreement with experiment



Diffusion through tubular nanostructures

- ❑ Monte Carlo is used to simulate particles motion in a cylindrical geometry.
- ❑ Experiments are conducted and results used to parameterized the simulation, time scale has been incorporated based on experimental results
- ❑ Simulation will be used to guide the experiment into a more efficient release of particles from clay nanotubes

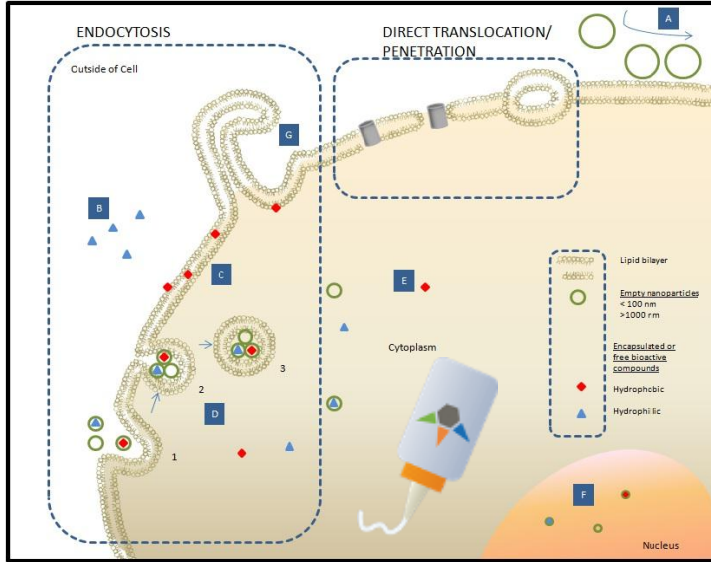


Cellular uptake and trafficking of poly(lactic-co-glycolic acid) nanoparticles: implications for antioxidant delivery

Sabliov, Moldovan (LSU)



Uptake Mechanisms



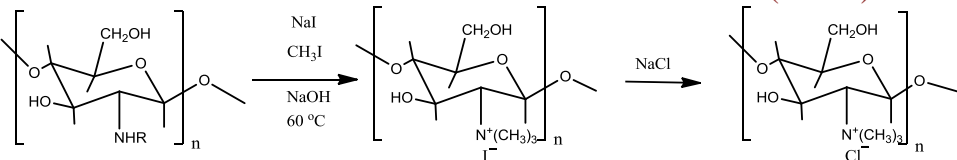
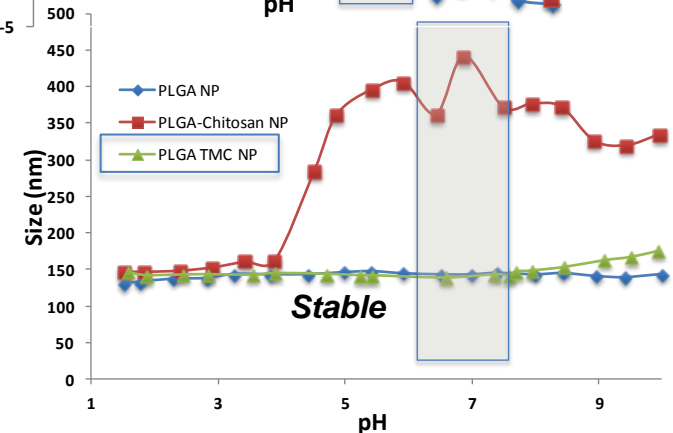
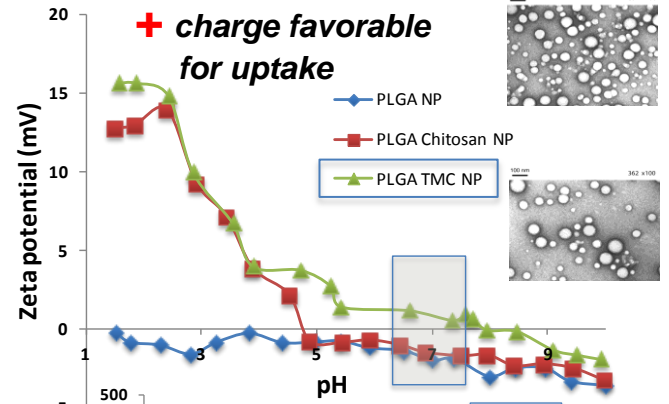
A Large particles may not easily transverse the membrane;

B Vesicle facilitated endocytosis pathway possible for smaller particle uptake;

C Hydrophobic compounds remain in bilayer; particle potential carrier of hydrophobic compound into cytosol

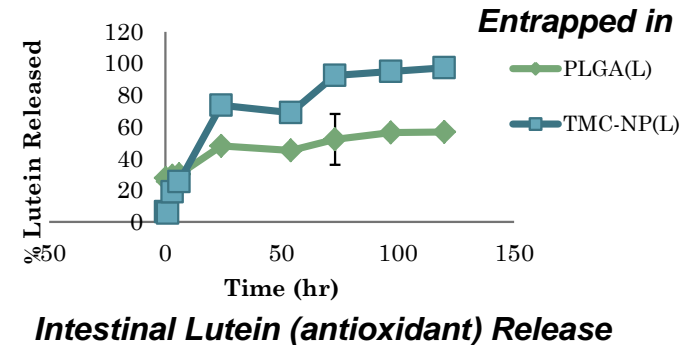
D; E Pinocytosis

★ Hypothesis: when entrapped in poly(lactic-co-glycolic acid) PLGA nanoparticles, vitamin E will be delivered to the cytosol, and be more active in protecting the cell from oxidation



Chitosan

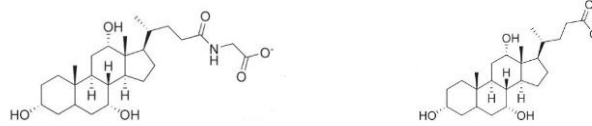
N-trimethyl chitosan



Intestinal Lutein (antioxidant) Release

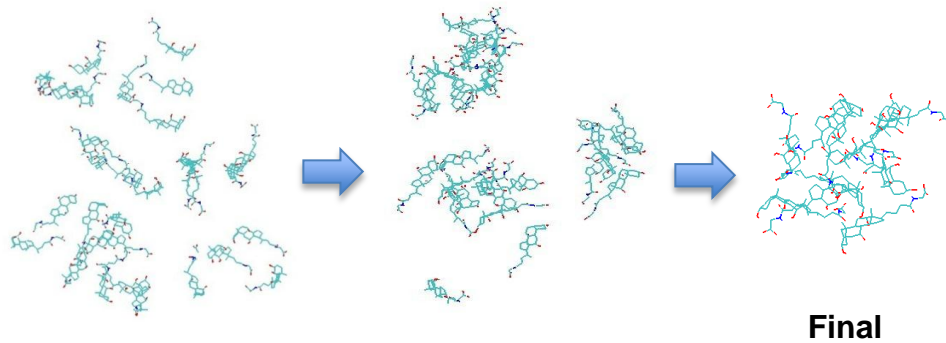
MD simulation of bile salts aggregation into micelles

Moldovan (LSU), Sabliov (LSU)



Self-assembly of glycocholates (GCH) and cholates (CHD) into a micelles

16,000 water molecules; 31 neutralizing Na⁺ ions, 0.15M background NaCl; 300K; 1 bar



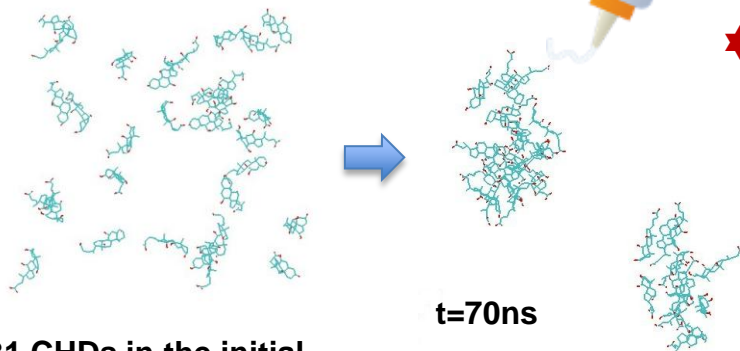
31 GCHs in the initial system (t=0ns)

t=60ns

Final

★ Understand bile-salts micelle formation and subsequent encapsulation of fatty acids

★ Towards developing and improving hydrophobic drug carriers with enhanced oral bioavailability.



31 CHDs in the initial system (t=0ns)

t=70ns

★ Investigate aggregation process, obtain micelle size distribution & shape/structure in larger systems (186 GCHs or CHDs).

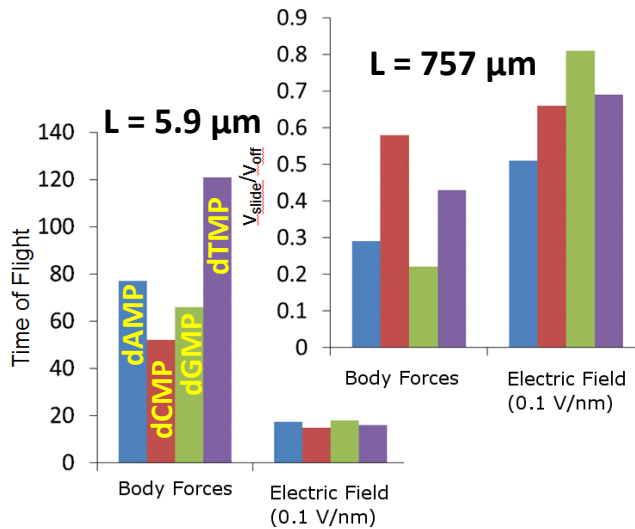
★ Insert oleic acid molecules into GCH system with preformed micelles to investigate oleic encapsulation.

Bio-material transport and interactions

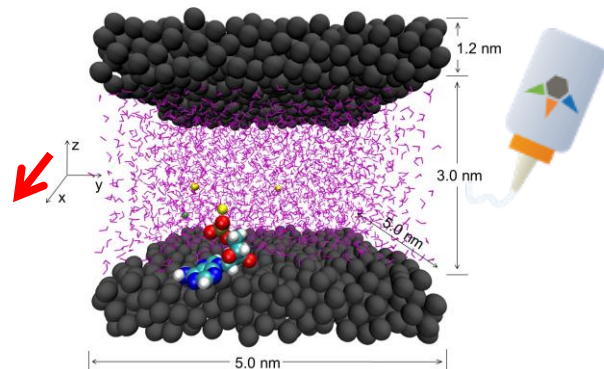
Moldovan, Nikitopoulos, Park (LSU), Soper (UNC)



CHARMM27 force-field for dNMP, TIP3P water, L-J carbon-like wall, neutralizing Na, Cl ions; 1 bar, 323K



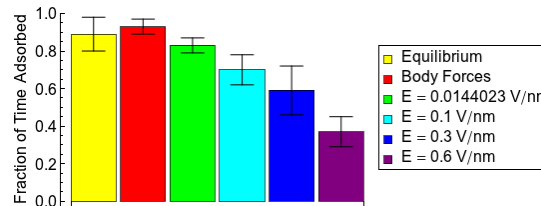
External forces
(body forces or electric field)



- ★ Pressure Driven: dCMP & dTMP time-of-flight well separated
- ★ Order of decreasing flight time (dTMP, dAMP, dGMP, dCMP) correlated with decreasing dNMP hydrophobicity order (dTMP, dAMP, dCMP, dGMP).

- ★ Higher dNMP velocities (overall and sliding) leads to little separation time-of-flight under the electric fields used.

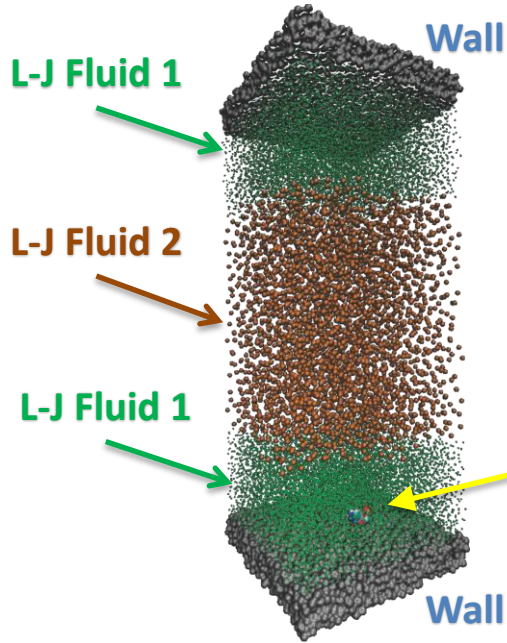
E-field effect (dTMP)



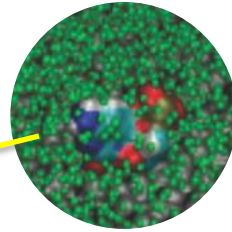
- ★ Fraction of time dTMP stays adsorbed on wall decreases with increasing E-field (velocity)

Hybrid MD/Continuum Techniques

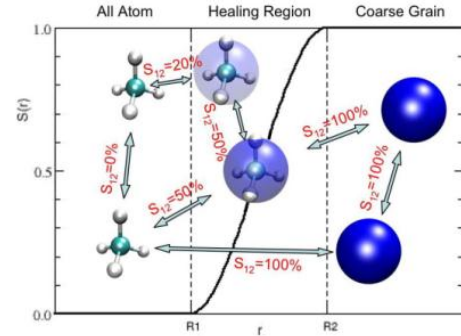
Moldovan, Nikitopoulos, Hall, Ramanujam (LSU)



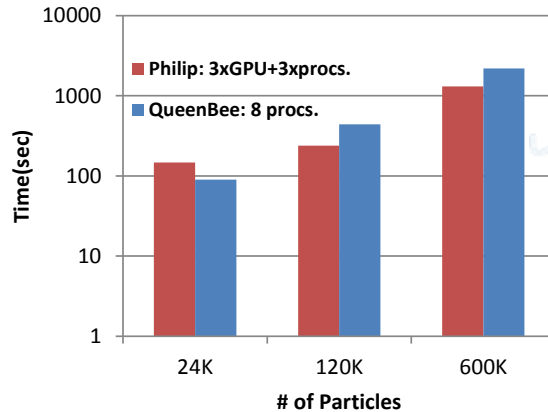
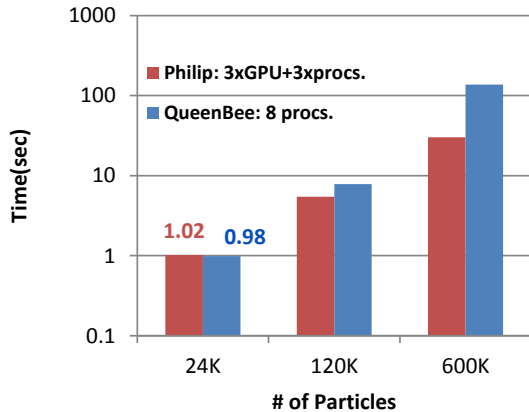
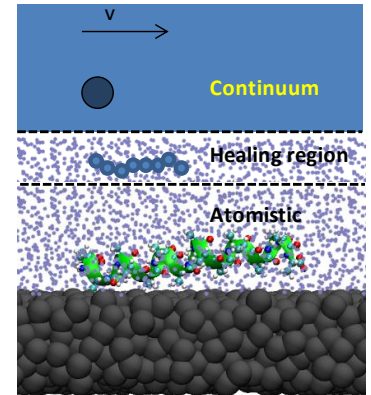
★ Initiated extending hybrid code to multi-phase systems using the impulsively started Couette flow for Lennard-Jones Fluids as non-equilibrium test bed.



Biomolecule(s)



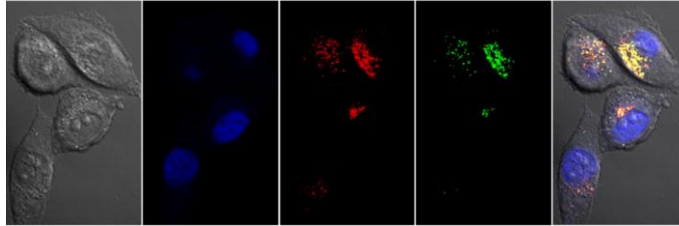
★ Initiated bio-molecule/particle transition development from Continuum to full MD in a Hybrid Simulation of transport.



★ Benchmarked hybrid MD/Continuum simulation on hybrid CPU/GPU platform.

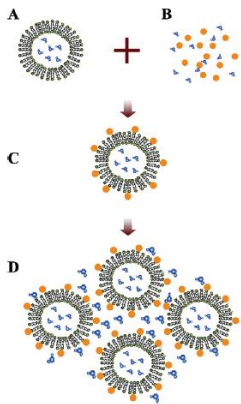
Liposome interactions - Experimental

Devireddy, Moldovan (LSU)



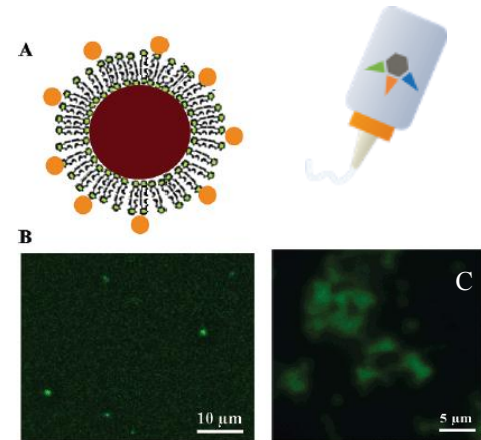
★ Liposomes Interacting with HeLa Cells

From left: Phase-contrast image; Nucleus stained with DAPI, 4',6-diamidino-2-phenylindole (marked in blue); Rhodamine labeled liposomes (marked in red); Lyso Tracker Green (marked in green) ; Composite image



★ Schematic illustration of the experimental strategy used to produce nanoparticle (20 nm \emptyset) - stabilized DLPC liposomes (200 nm \emptyset).

★ Assessing the permeability of DLPC liposomes by leakage of a fluorescent molecule (rhodamine B) with (Fig. B) and without (Fig. C) nanoparticles. Note that NPs stabilize the liposomes.



SD3 Milestones



Milestones	Y1	Y2	Y3	Y4	Y5	
Synthesize modular library of core monomers to explore novel encapsulation/delivery chemistries	X	X	X			<i>On Track</i>
Develop new atomic and coarse-grained force fields	X	X				<i>On Track</i>
Develop new hybrid MD/continuum, coarse-grained, and accelerated strategies to link length/time scales	X	X	X			<i>On Track</i>
Use multi-scale simulation methods to optimize supramolecular delivery vehicles			X	X	X	
Synthesize, characterize, and assess new self-assembled transmembrane drug delivery vehicles	X	X	X			<i>On Track</i>
Validate computational models for self-assembled drug carriers for bio-membrane translocation			X	X	X	
Use MD and CG methods to study the mechanisms of cellular absorption of drugs				X	X	

Anne Robinson (*Tulane*) has joined SD3 team

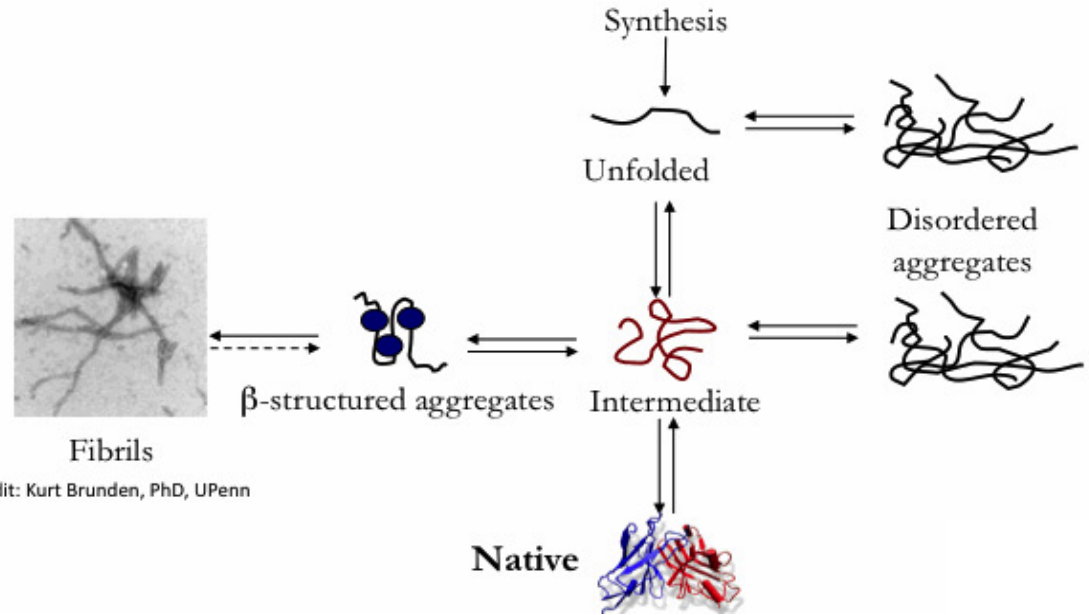
New Direction

Tau protein and fibril formation

Robinson and Ashbaugh (Tulane)



Protein misfolding leads to fibril formation



- What are the characteristics of the sequence that lead to fibril formation?
- Are there small molecules that could inhibit fibril formation?

Tau misfolding associated w/neurodegenerative disease



- Can we model fibril formation?
- Can we understand this behavior in vivo?