LA-SiGMA

Louisiana Alliance for Simulation-Guided Materials Applications

SD3: Biomolecular Materials

Hank Ashbaugh - Tulane University

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

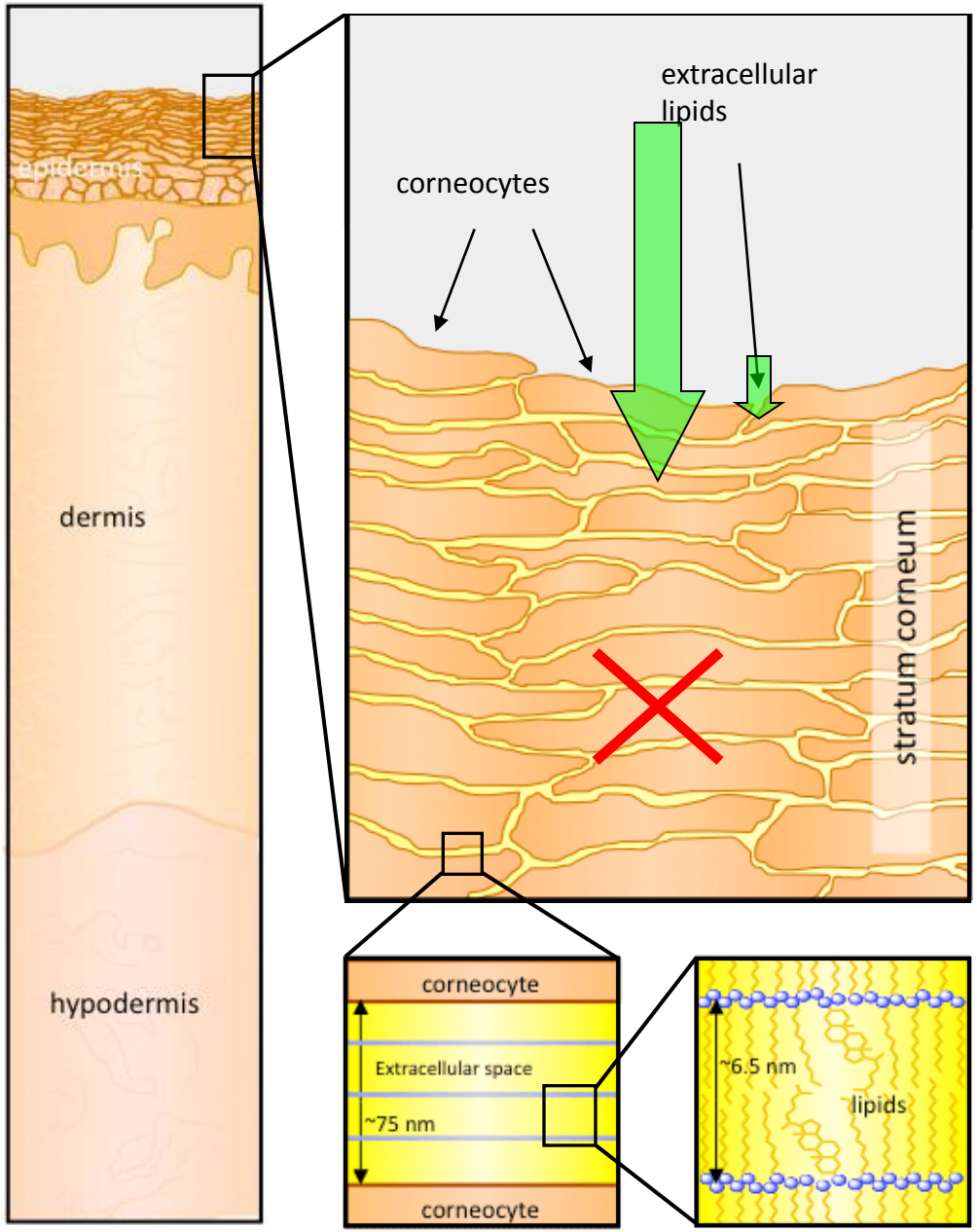
FOCUS 1

Unimolecular Delivery Vehicles

FOCUS 2

Self-Assembled Delivery Vehicles

The Problem: Skin Physiology

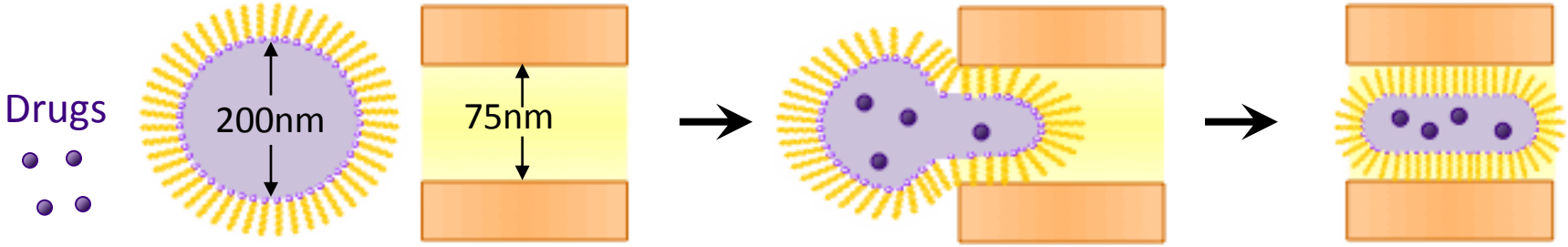


- The outermost layer of the skin, the stratum corneum, represents the most significant barrier to the transdermal delivery of therapeutics.
- The primary transport pathway through the stratum corneum involves diffusion through the lipids of the extracellular matrix.
- The extracellular lipids are organized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

The Problem: Delivery Vehicles

Self- Assembled Drug Delivery Vehicles (Focus 2)

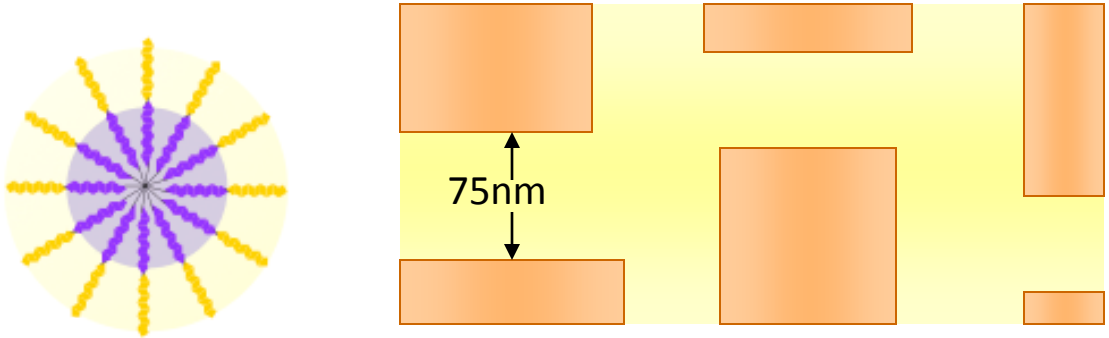
- Use self-assembled liposomes to transport polar drugs through lipid channels
- Amphiphiles selected to enable the liposomes to readily deform: transfersomes, ultradeformable liposomes, ethosomes.



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

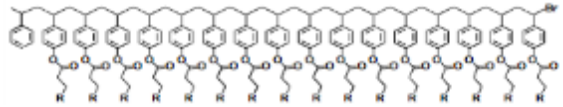
Explore Synthesis and Delivery with Both Classes of Vehicles to Optimize Design

SD3 Goals

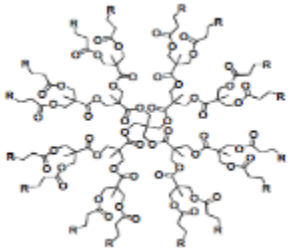
Goal: Develop novel biomolecular materials guided by computational/experimental collaboration for the encapsulation, delivery, and release of therapeutics to targeted tissues.

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

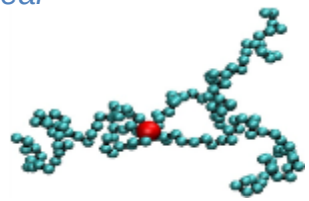
Polymeric Unimolecular Drug Delivery Vehicles



linear

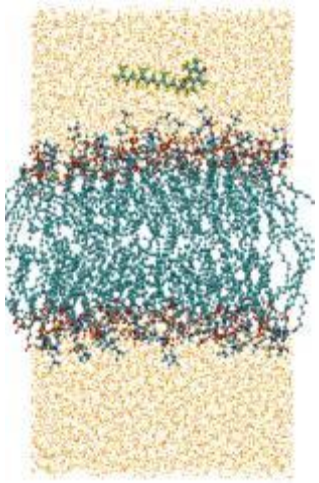


star/dendrimer

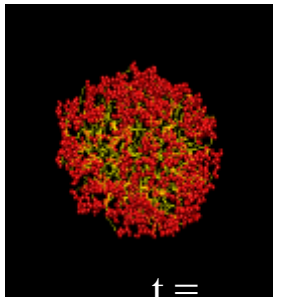


coarse-grained star

Self-Assembled Drug Delivery Vehicles

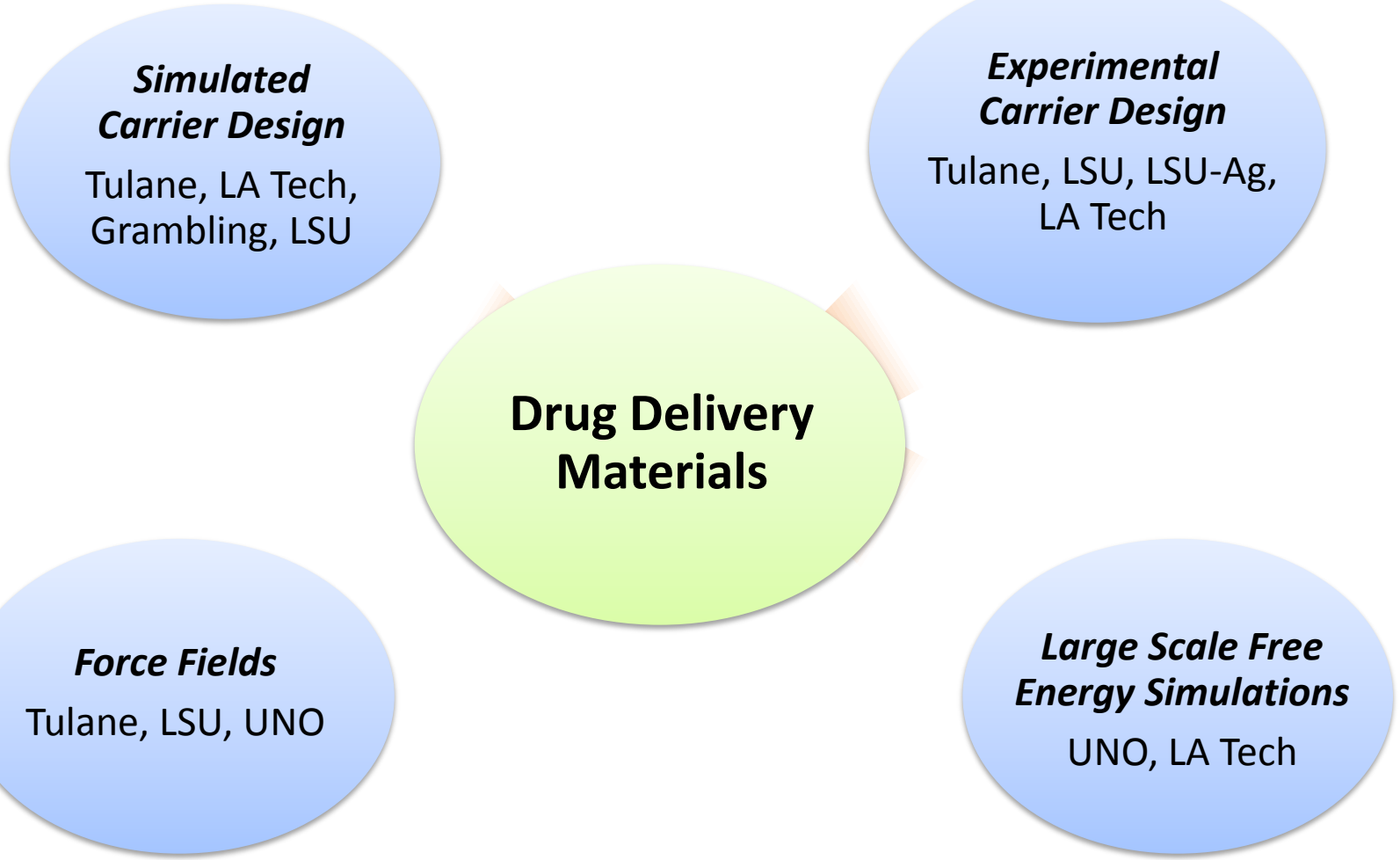


lipid bilayer



surfactant micelles

SD3 Research Themes

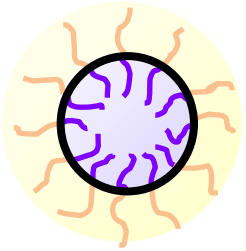


Focus 1

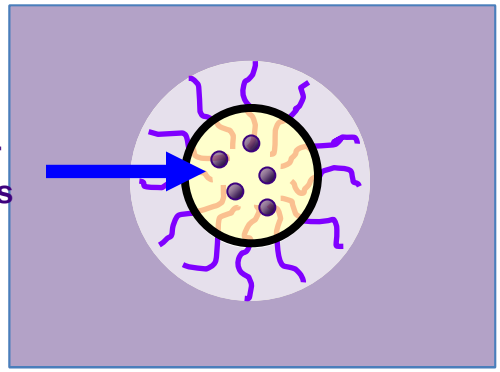
Synthesize modular core molecules and amphiphilic side chains

Grayson (TU)

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

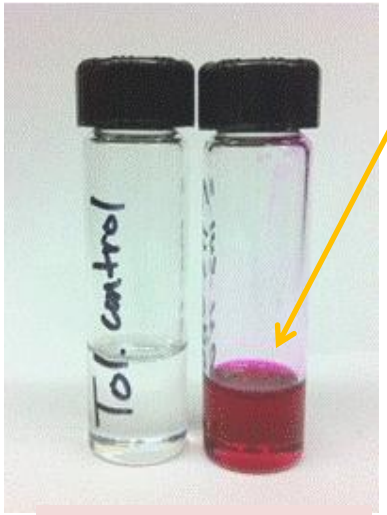


- **Styrenic backbone was cyclized using click coupling under high dilution**
- **Bifurcated amphiphiles were attached via click conjugation**



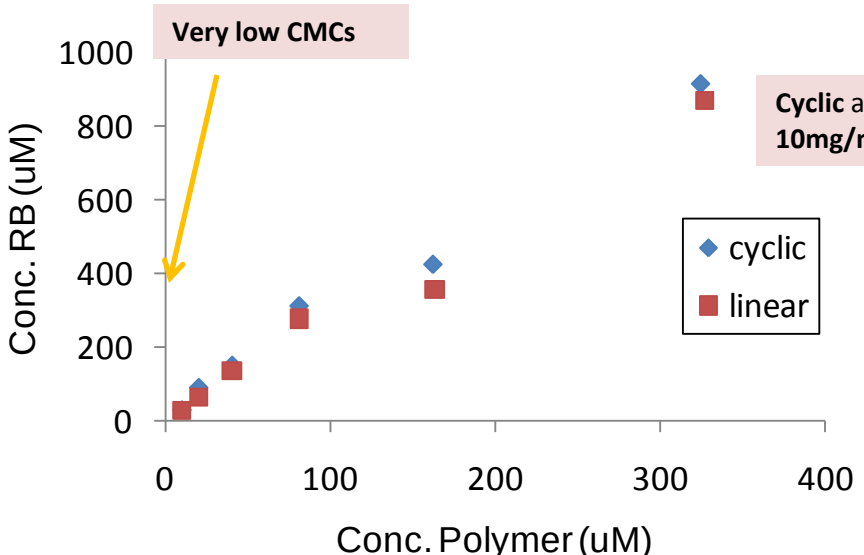
NonPolar → **Polar**

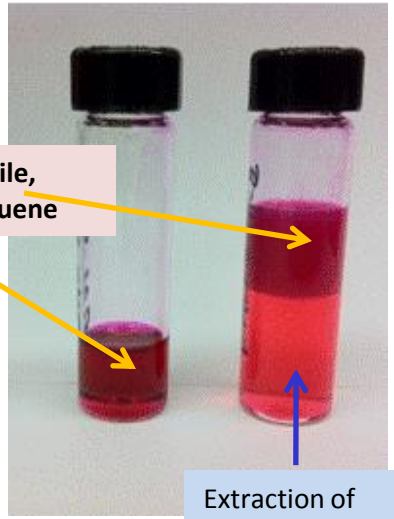
Willham, Kaitlin A.; Laurent ,B.A.; Grayson, S.M.. *Tetrahedron Lett.* **2008**, *49,* 2091-2094.
Laurent, Boyd A.; Grayson, Scott M. *Polym. Chem* **2012**



Cyclic amphiphile, 10mg/ml in toluene

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

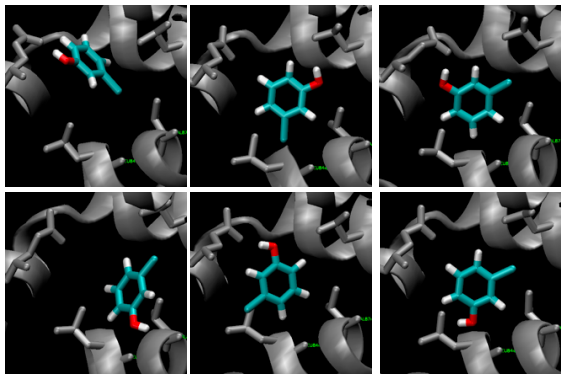


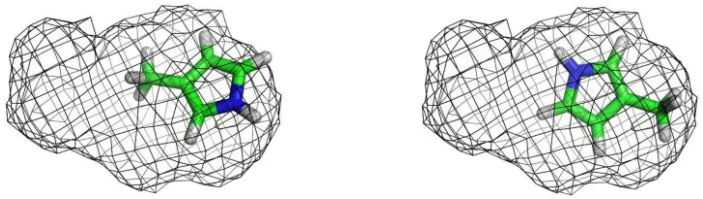


Focus 1

Evaluate Orientational Free Energy Contributions to Binding

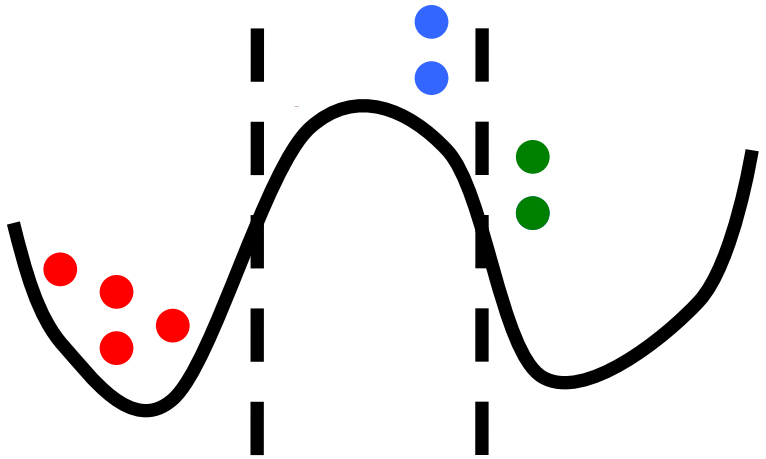
Mobley (UNO)

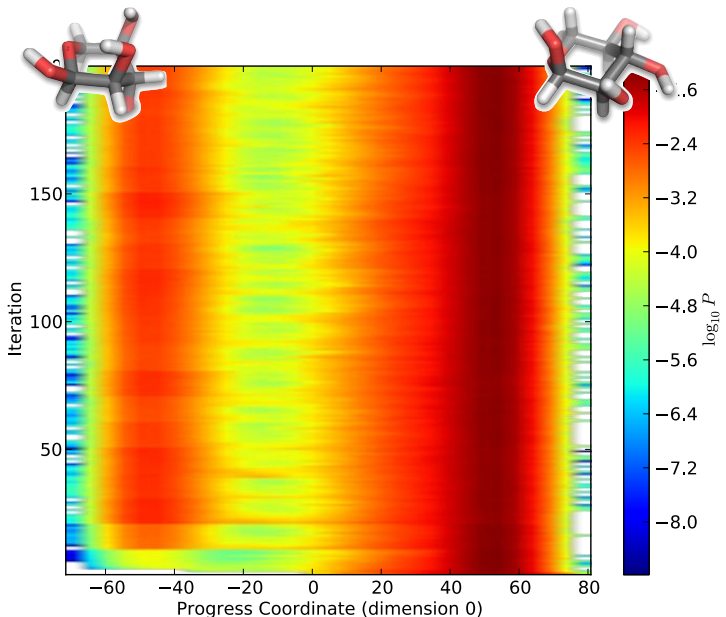




Multiple orientations must be sampled with poor transition probabilities

80mer

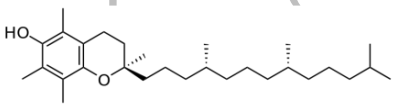




Use weighted ensemble techniques to correctly sample different binding orientations

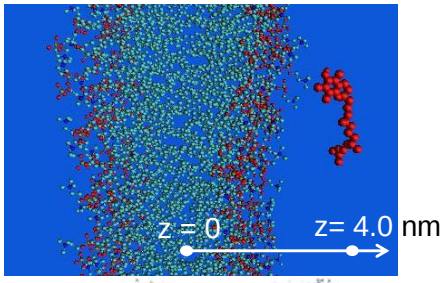
Interaction of α-tocopherol (vitamin E) with DMPC Lipid Bilayers

Moldovan (LSU)

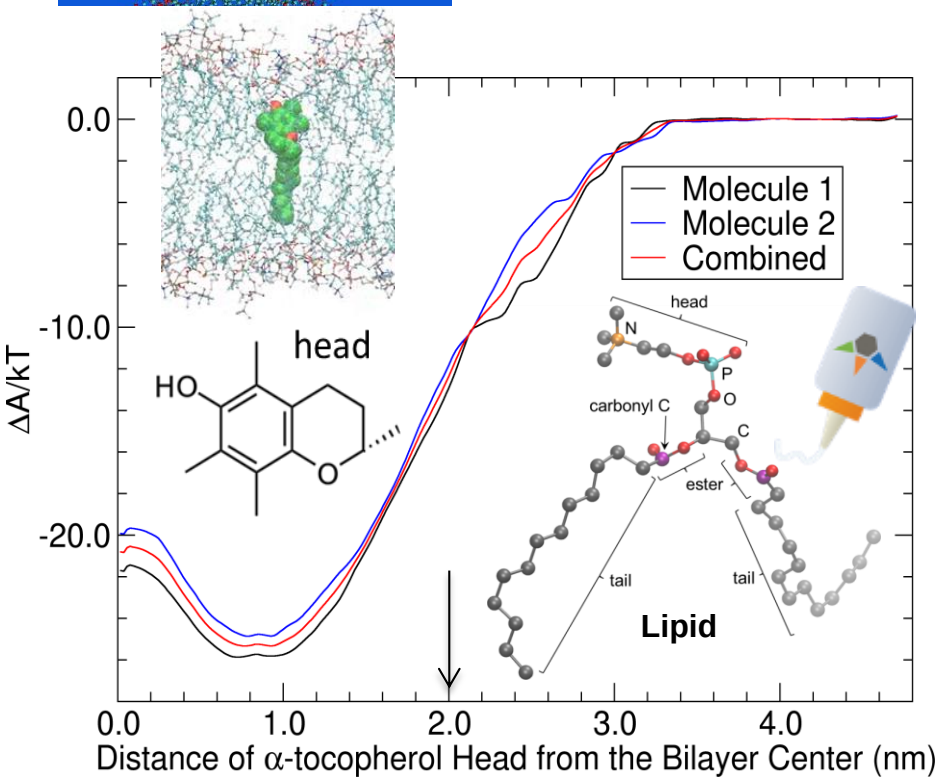


128 DMPC, 2 α-tocopherols (4.7 nm apart), 8890 water; 1 bar (semi-isotropic), 323K

47 window umbrella sampling; Run to PMF convergence (20 ns to 40 ns/window)



- α-tocopherol concentrates in narrow region, just below the membrane/water interface; even if low-abundant their concentration in this vital region can be high



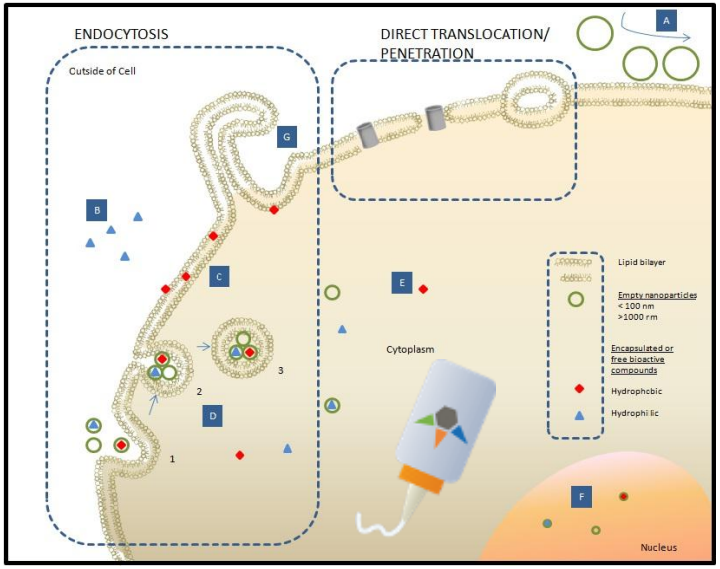
- α-tocopherol has very strong affinity for the lipid bilayers interior; spontaneously leaving a membrane is extremely rare

- α-tocopherols located in close proximity inside lipid bilayer aggregate spontaneously and hydrogen-bond with each other; unlikely that α-tocopherol is evenly distributed inside cell membranes

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

Sabliov, Moldovan (LSU)

Uptake Mechanisms

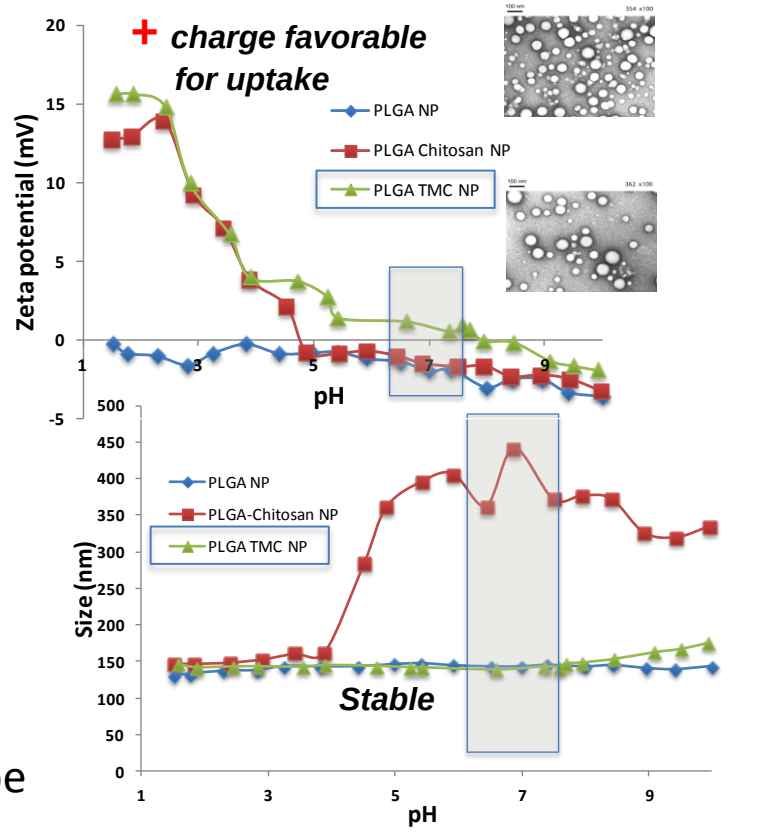


A Large particles may not easily transverse the membrane;

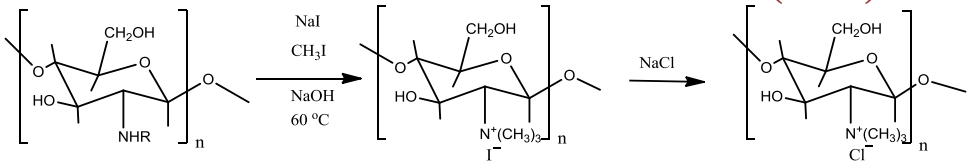
B Vesicle facilitated endocytosis pathway possible for smaller particle uptake;

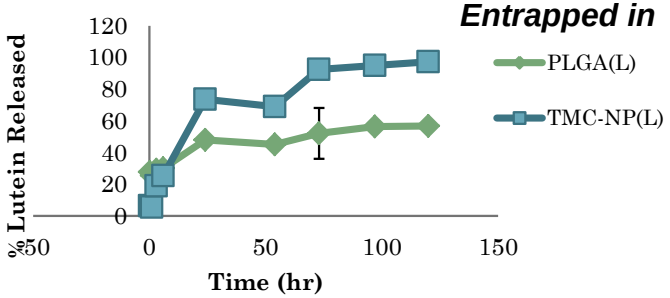
C Hydrophobic compounds remain in bilayer; particle potential carrier of hydrophobic compound into cytosol

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

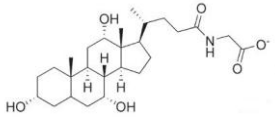


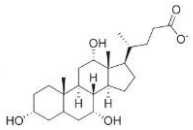


Intestinal Lutein (antioxidant) Release

MD simulation of bile salts aggregation into micelles

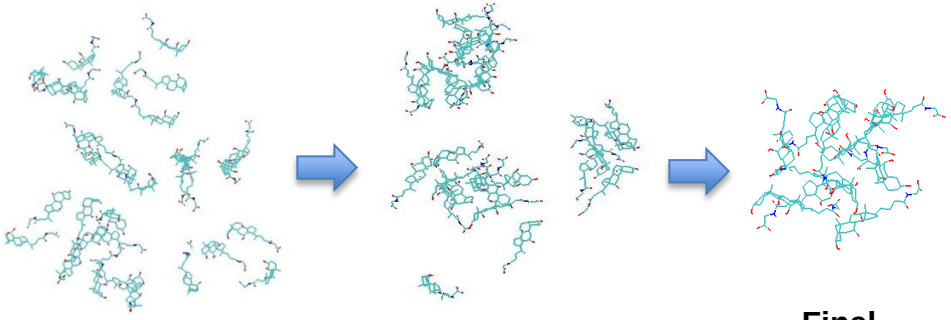
Moldovan (LSU), Sabliov (LSU)





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

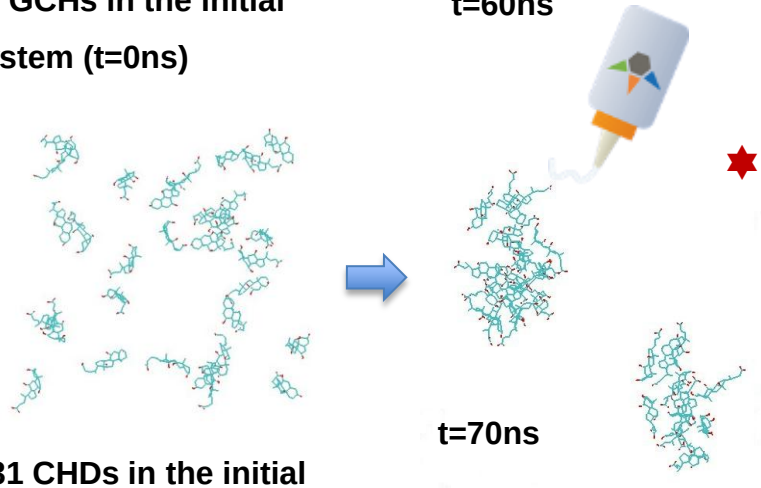


31 GCHs in the initial system (t=0ns)

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)

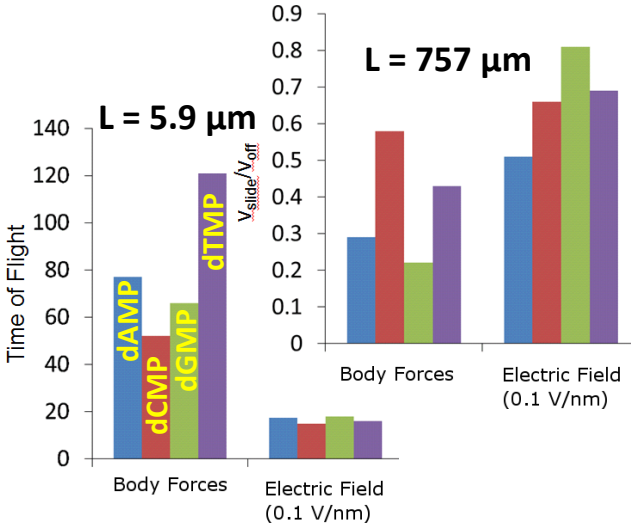
t=70ns

- 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

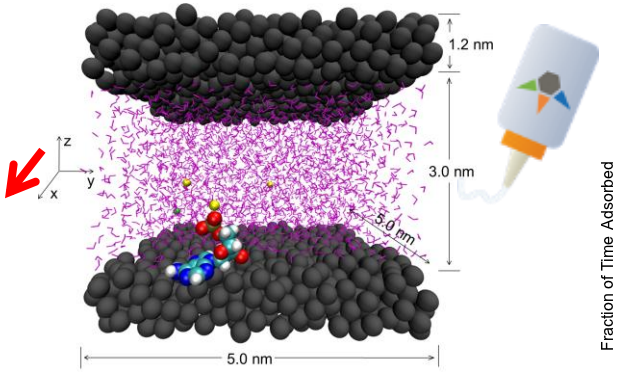
Moldovan, Nikitopoulos, Park (LSU), Soper (UNC)

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



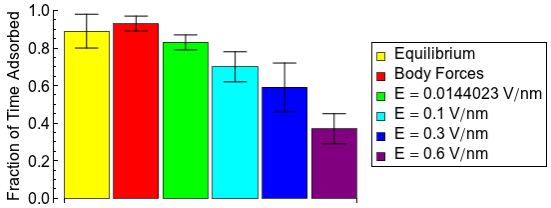
- Pressure Driven: dCMP & dTMP time-of-flight well separated
- Order of decreasing flight time (dTMP, dAMP, dGMP, dCMP) correlated with decreasing dNMP hydrophobicity order (dTMP, dAMP, dCMP, dGMP).

External forces
(body forces or electric field)



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

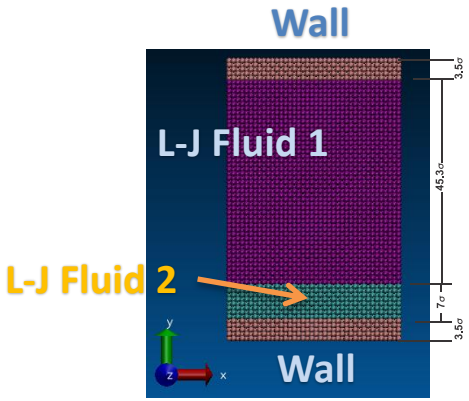
E-field effect (dTMP)



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

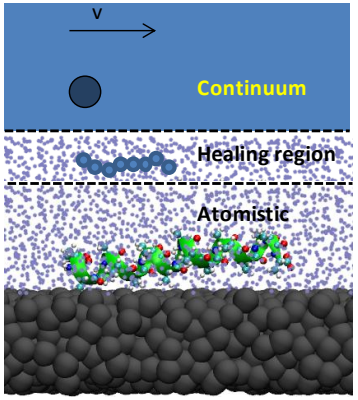
Hybrid MD/Continuum Techniques

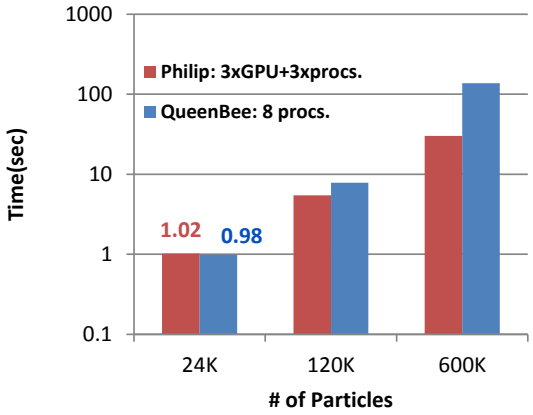
Moldovan, Nikitopoulos, Hall, Ramanujam (LSU)

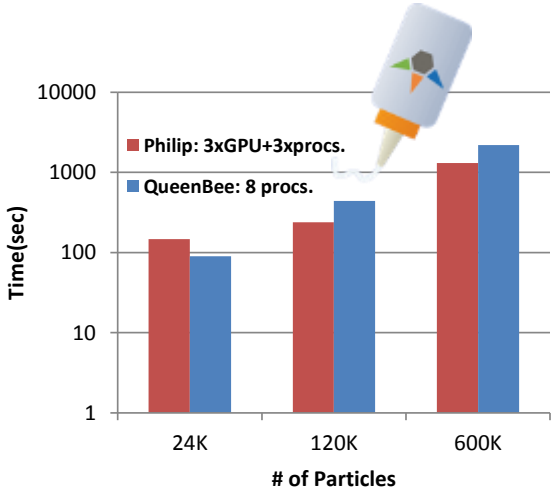


- Initiated extending hybrid code to multi-phase systems using the impulsively started Couette flow for Lennard-Jones Fluids as non-equilibrium test bed.

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



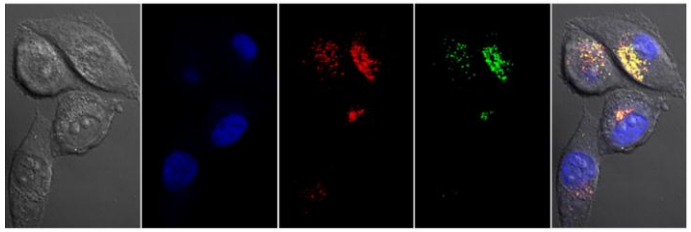




- Benchmarked hybrid MD/Continuum simulation on hybrid CPU/GPU platform.

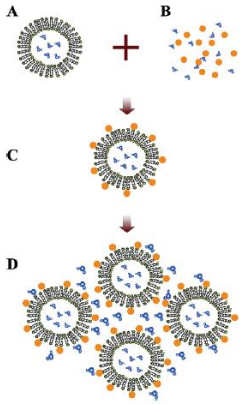
Liposome interactions - Experimental

Devireddy, Moldovan (LSU)

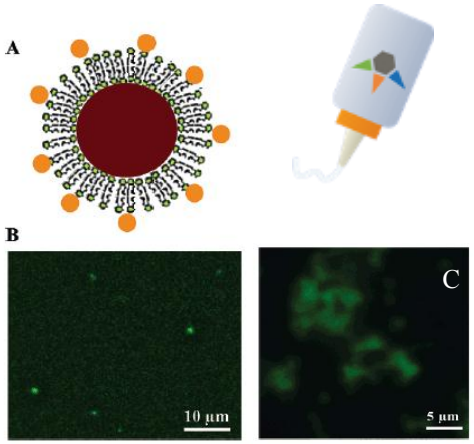


- Liposomes Interacting with HeLa Cells

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



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



- Assesing 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			*On Track*
Develop new atomic and coarse-grained force fields	X	X				*On Track*
Develop new hybrid MD/continuum, coarse-grained, and accelerated strategies to link length/time scales	X	X	X			*On Track*
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			*On Track*
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