LA-SiGMA

Louisiana Alliance for Simulation-Guided Materials Applications

SD3 – Biomolecular Materials

Henry S. Ashbaugh

Tulane University

FOCUS 1

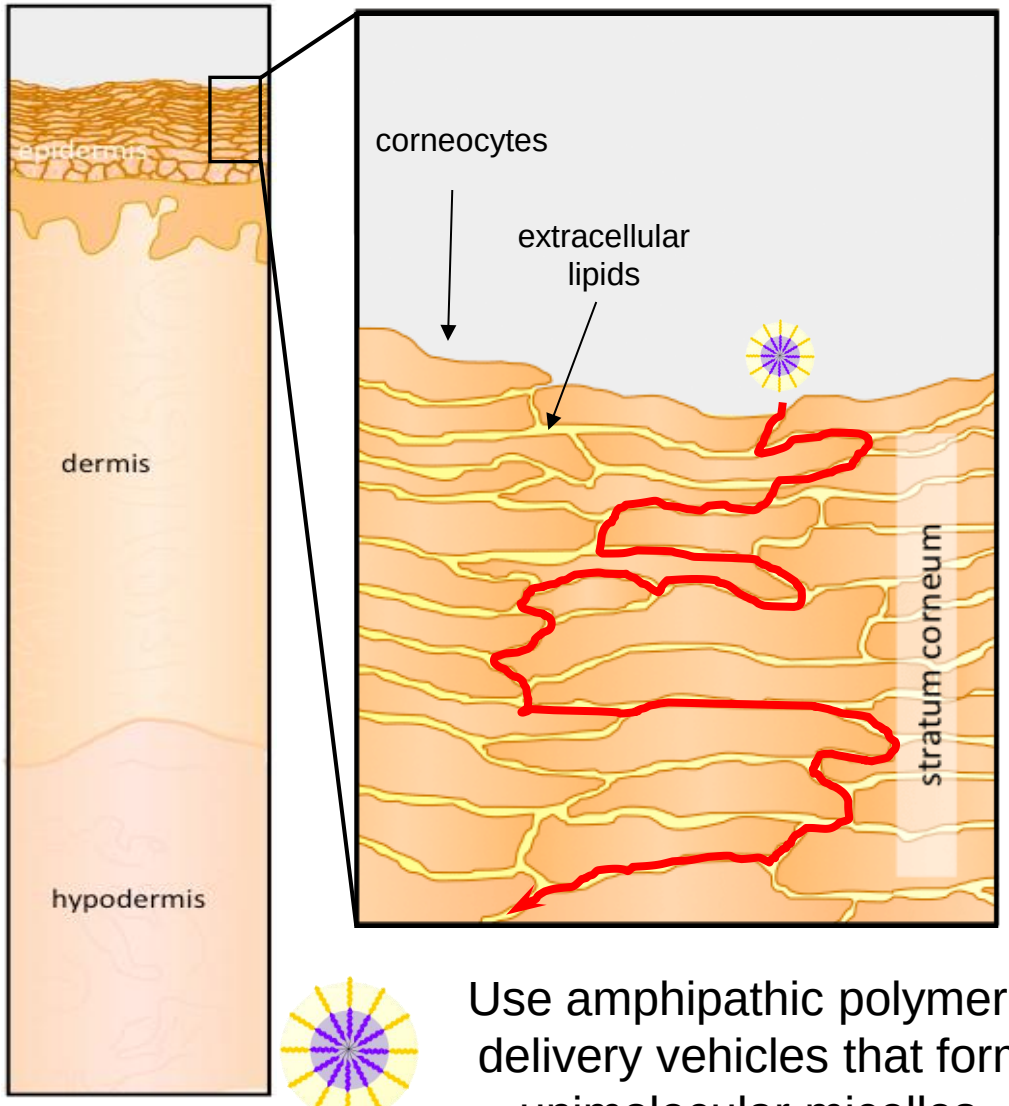
Unimolecular Drug Delivery Vehicles

FOCUS 2

Self-Assembled Drug Delivery Vehicles

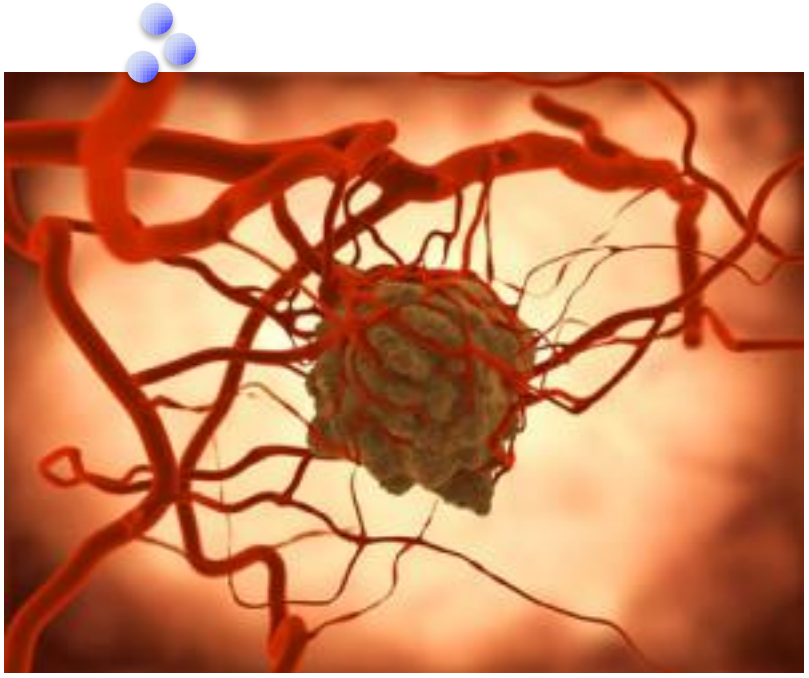
In Vivo Delivery Pathways

transdermal



Use amphipathic polymeric delivery vehicles that form unimolecular micelles.

vascular delivery to tumors



Nano-particles preferential delivered to tumors due to leaky vasculature

SD3 Research Themes

Simulated Carrier Design
Ashbaugh (Tulane), Moldovan (LSU), Derosa (LATech/Grambling), Jha (LSU), and Niktopoulos (LSU)

Experimental Carrier Design
Grayson (Tulane), Robinson(Tulane), Sabilov (LSU), Devireddy (LSU), and Lvov (LSU)

Drug Delivery Materials

Potential Development
Ashbaugh (Tulane), Reily (Xavier), Moldovan (LSU), and Rick (UNO), Brylinski (LSU)

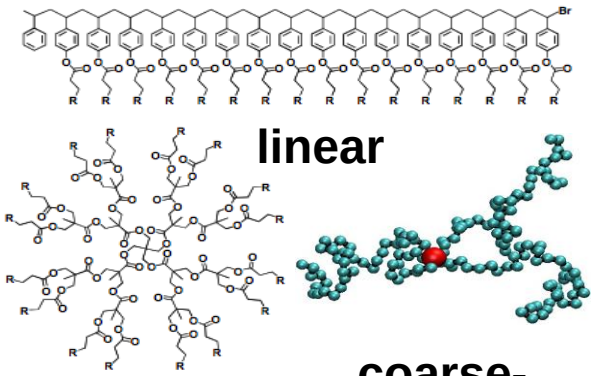
Free Energy/Docking Calculations
Reily (Xavier), Brylinski (LSU)

SD3 Goals

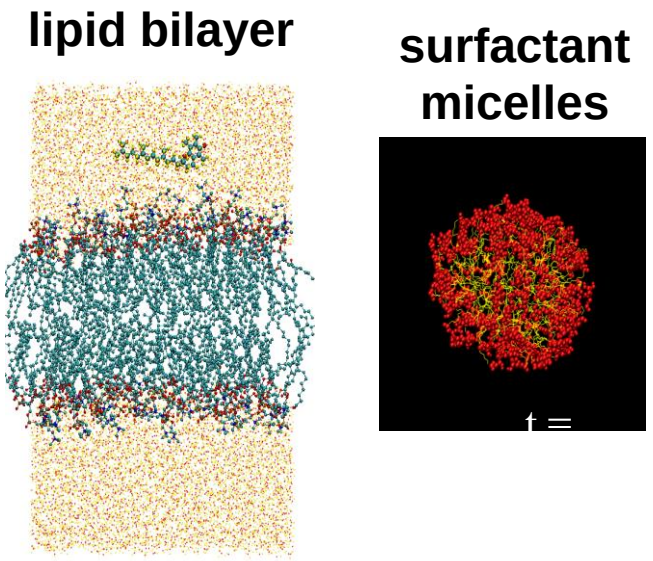
Goal: Develop novel biomolecular materials guided by computational/experimental collaboration for the encapsulation, delivery, and release of therapeutics to targeted tissues.

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

Focus 1: *Polymeric Unimolecular Drug Delivery Vehicles*



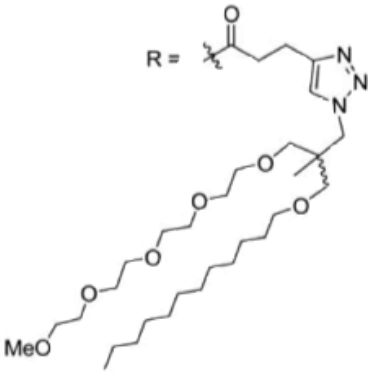
Focus 2: *Self-Assembled Drug Delivery Vehicles*

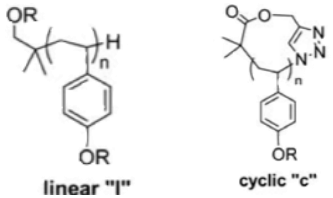


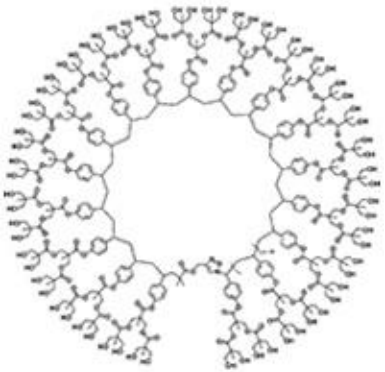
SD3 Milestones: Where we stand

Focus 1: Unimolecular Drug Delivery Vehicles

- *Synthesize modular set of amphipathic monomers/polymers (Grayson)*





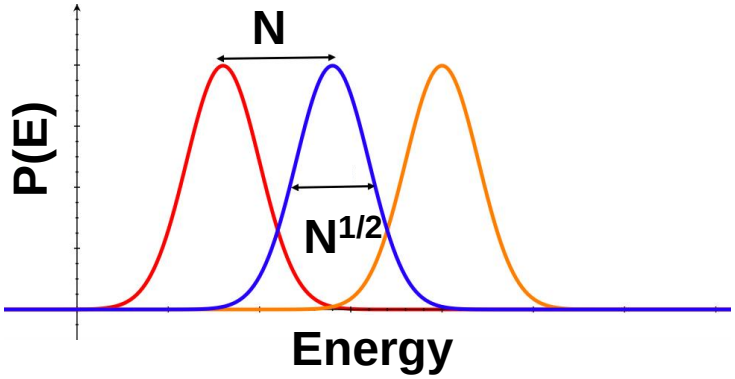


SD3 Milestones: Where we stand

Focus 1: Unimolecular Drug Delivery Vehicles

- ***Perform large scale MD simulations of polymeric micelles (Rick and Ashbaugh)***

Replica Exchange MD simulations required to sample polymer conformational degrees of freedom



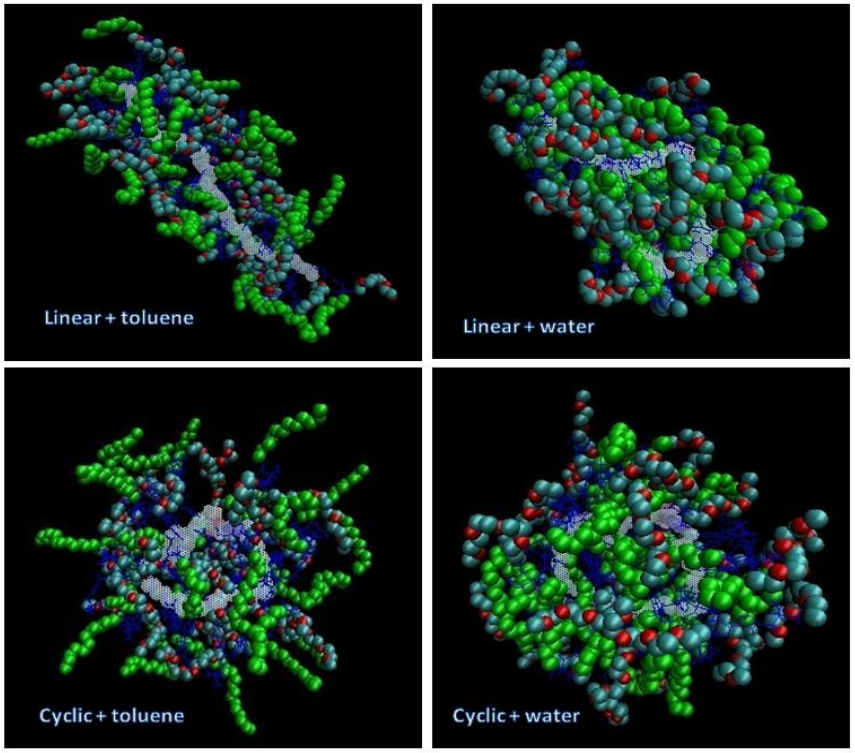
SD3 Milestones: Where we stand

Focus 1: Unimolecular Drug Delivery Vehicles

- *Perform large scale MD simulations of polymeric micelles (Rick and Ashbaugh)*

Polymer \ Solvent	Toluene	Water
Linear Polymer	26.5 Å	22.0 Å
Cyclic Polymer	18.9 Å	16.6 Å

REDS simulation snapshots

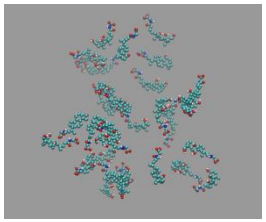


SD3 Milestones: Where we stand

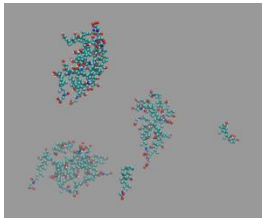
Focus 2: Self Assembled Drug Delivery Vehicles

Molecular dynamics simulation of bile salts
Moldovan (LSU)

Self-assembly of bile salts into micelles

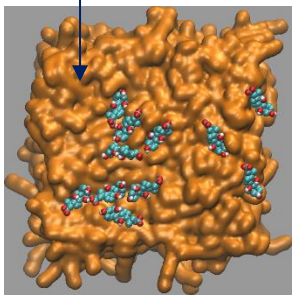


31 cholate or glycocholate ions in solution



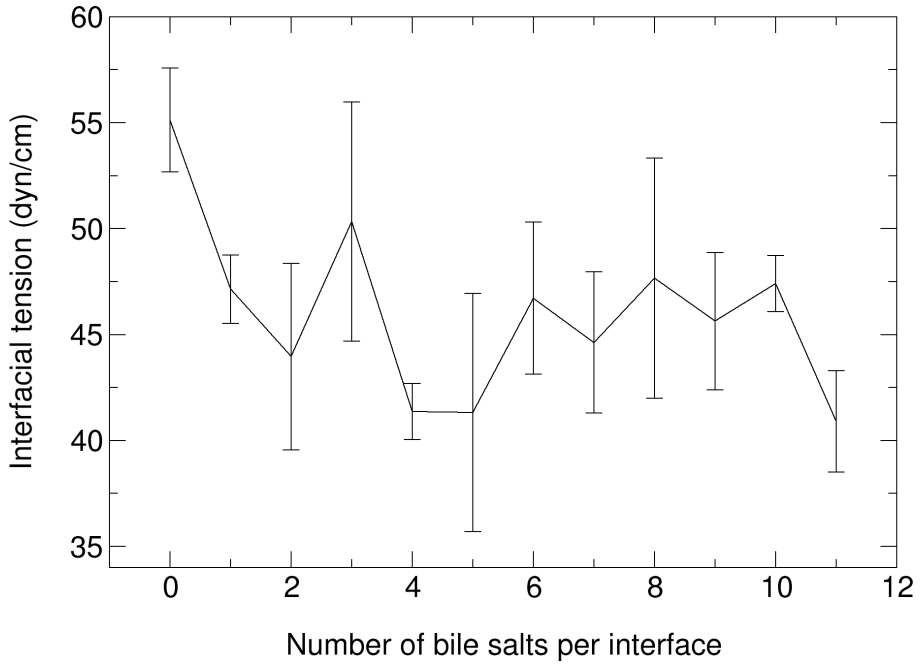
Micelles with 10-15 molecules per micelle

Vitamin E



11 cholate ions at the Vitamin E – aqueous interface

Interaction with a Vitamin E (α-tocopherol) phase



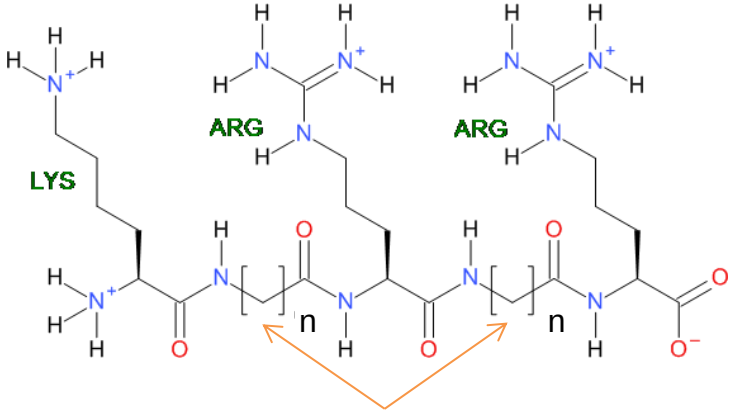
Assemblies containing bile salts or their derivatives have been used in drug delivery.

SD3 Milestones: Where we stand

Focus 2: Self Assembled Drug Delivery Vehicles

Molecular dynamics simulation of linear peptide analogs (LPAs)
Moldovan (LSU)

LPA structure



hydrocarbon segments (n = 4 to 13)

Interaction of single LPAs with 15% DPPS, 85% DPPC bilayers

n < 10: Charged groups are outside the bilayer, hydrocarbon segments are outside the lipid tail region

n >= 11: Charged groups are inside the bilayer, hydrocarbon segments are inside the hydrophobic lipid tail region.

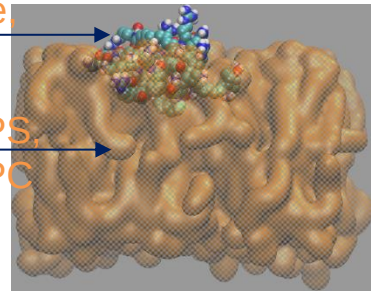
Experiments by Gupta et al.[1] showed that n = 7 LPAs do not affect bilayers substantially, but n = 11 LPAs do.

Micellization & interaction of a micelle with a bilayer

n = 4: no micellization
n = 11: 5-8 molecules/micelle

5 molecule, n = 11 micelle

15% DPPS, 85% DPPC bilayer



after 285 ns

Peptide analogs could be useful in drug delivery or as drugs themselves

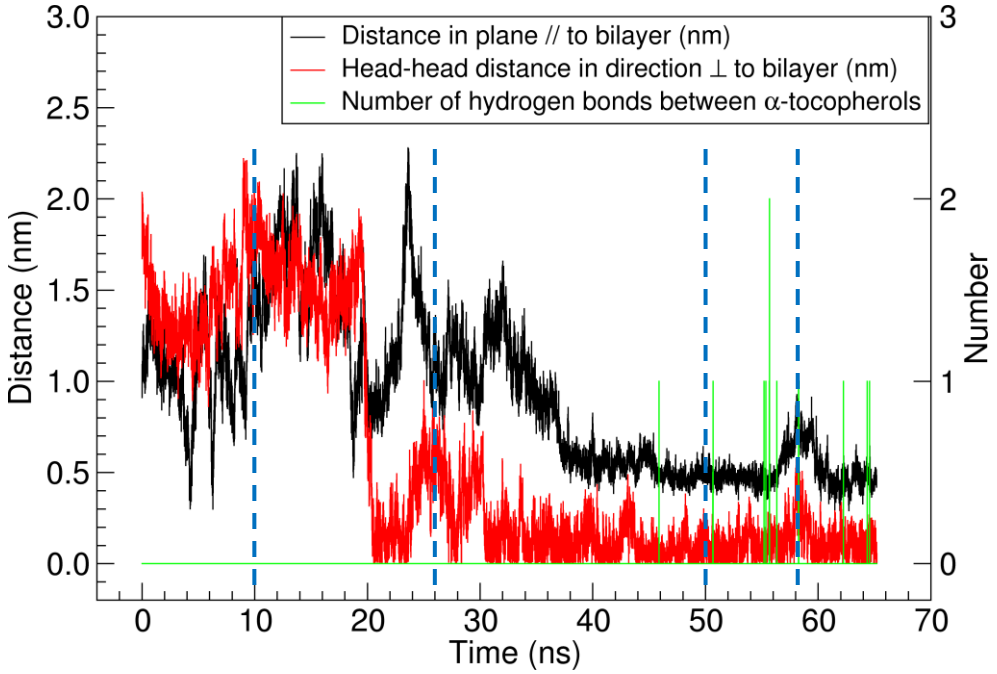
[1] A. Gupta *et al.*, *Eur. Biophys. J. Biophy.* ***40, 727 (2011).***

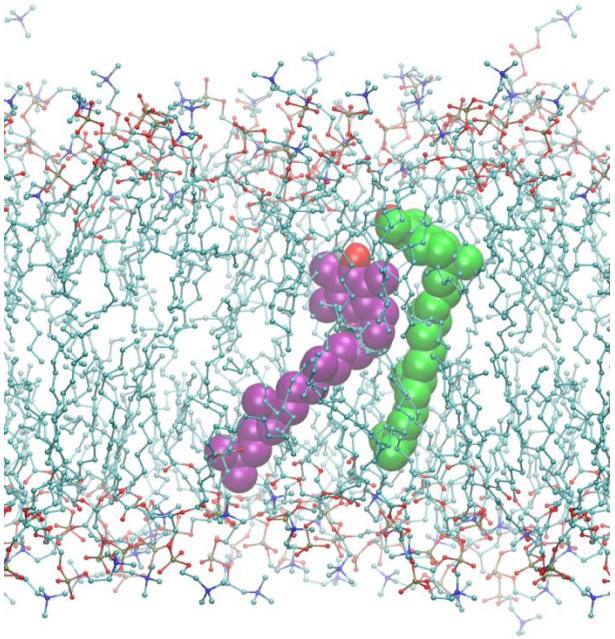
SD3 Milestones: Where we stand

Focus 2: Self Assembled Drug Delivery Vehicles

Molecular dynamics simulation of vitamin E in DMPC lipid bilayers
Moldovan (LSU)

Flip-flop and dimer aggregation





Free energy calculations show that flip-flop of 1 α-tocophoerol has a barrier of about 4 times the thermal energy, and dimer aggregation is favored by about 3.5 times the thermal energy.

Vitamin E acts as an antioxidant to protect unsaturated lipids in cell membranes.

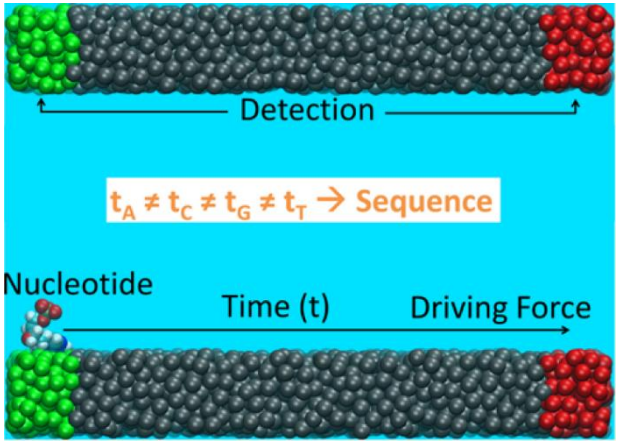
SD3 Milestones: Where we stand

Focus 2: Self Assembled Drug Delivery Vehicles

Molecular dynamics simulation of DNA nucleotides in nanoslits

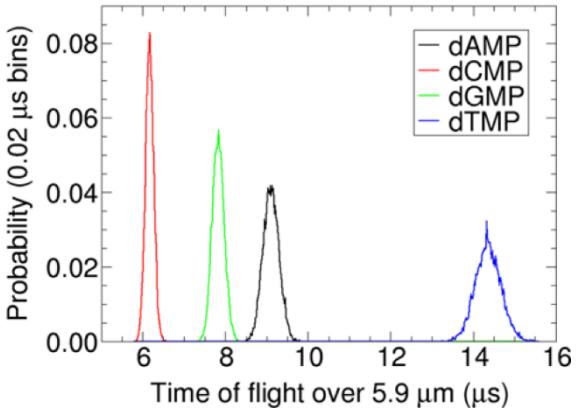
Moldovan (LSU), Nikitopoulos (LSU)

Time of flight based DNA sequencing



1 strand of double-stranded DNA might be cut up into individual nucleotides (dNMPs) and sent through nanochannels with sensors at multiple locations.

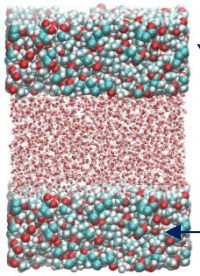
3 nm wide C nanoslit simulations



Extrapolation from simulations with dNMP velocities around 1 m/s → 5.9 µm channel length, 10 µs/dNMP

0.48 cm/s max velocity, nucleotide distribution across slit from equilibrium simulations, other assumptions → 250 µm channel, 390 ms/dNMP

More realistic conditions



Poly(methyl methacrylate PMMA walls

Equilibrium MD for average forces on dNMPs as a function of position

Single particle Brownian dynamics simulations with realistic driving forces and times

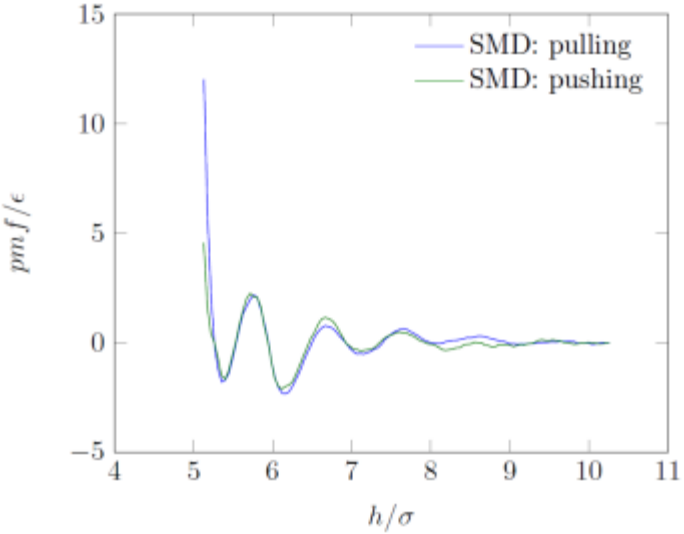
Time of flight based sequencing would only require the detection of the presence of a nucleotide and not its identity at each sensor.

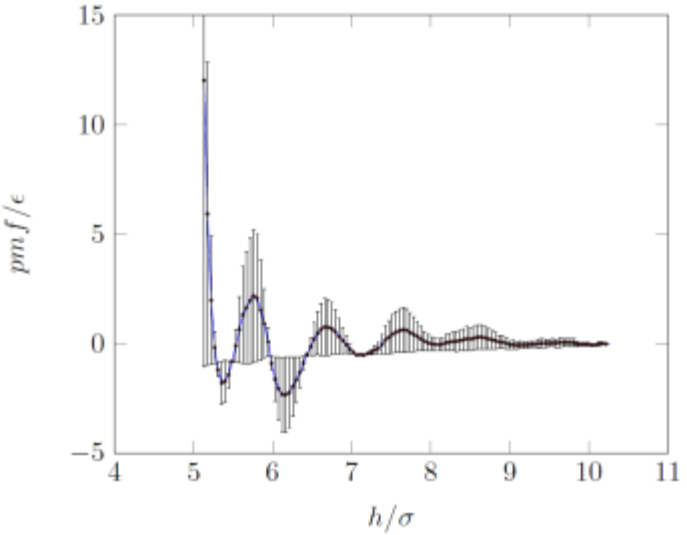
Focus 1 and 2

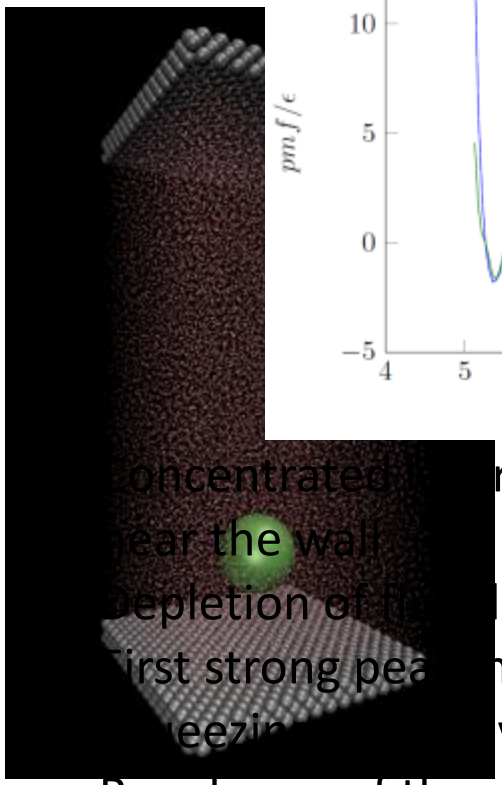
Molecular Simulations to obtain forces on a colloidal particle to be used in a developed hybrid MD/continuum

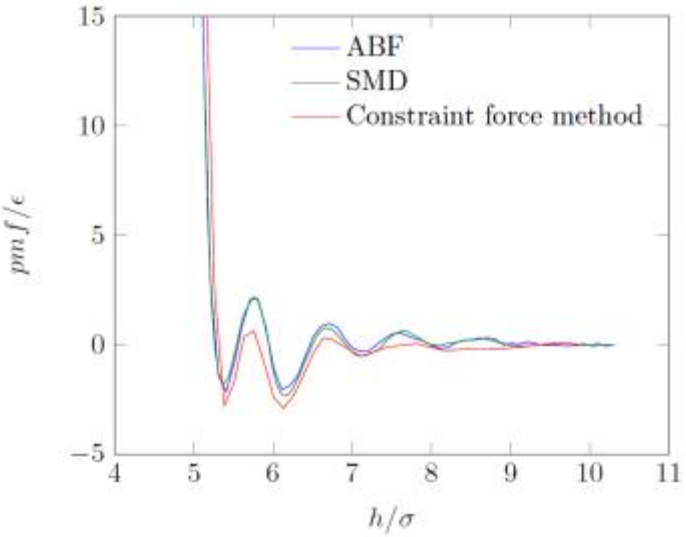
Moldovan (LSU), Nikitopoulos (LSU)

Potential of Mean Force (PMF) using SMD and ABF method









- Roughness of the wall can strongly affect the solvation force but not its presence

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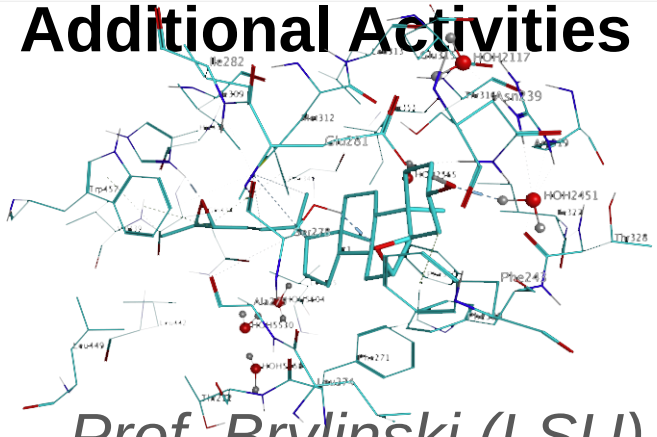
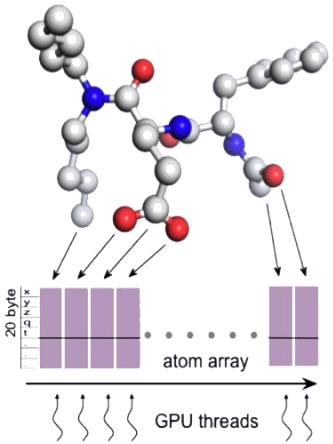
SD3 Milestones: Where we stand

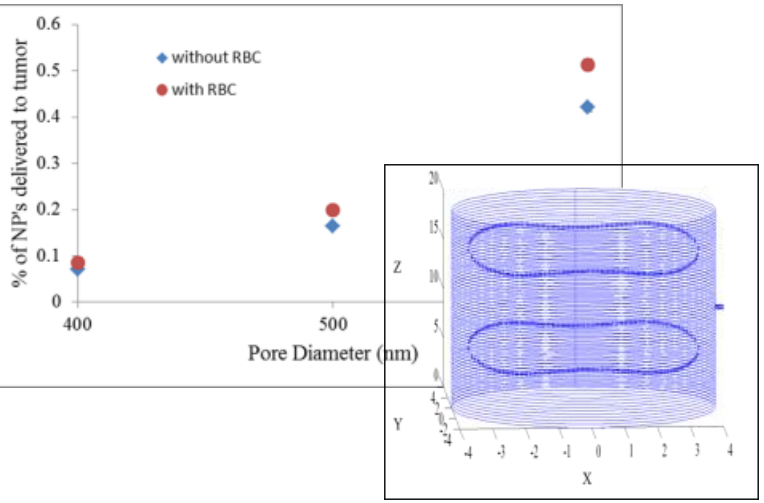
Additional Activities



Prof. Reily (Xavier) and students have studied docking of isoforms (α/β) of the liver X receptor to gauge fidelity of models at predicting selective binding.

Prof. Brylinski (LSU) and coworkers have developed ultra-fast Replica Exchange Monte Carlo ligand docking methods that take advantage of GPU computational efficiencies to screen drug candidates.





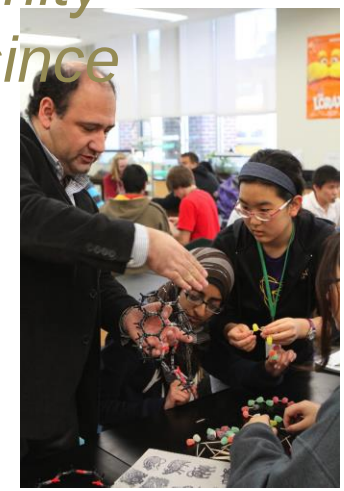
Prof. Derosa (LATech/Grambling) and students have worked on modeling nanoparticle uptake through leaky tumor capillaries and effect of red blood cells on delivery efficacy

SD3 Milestones

	Milestones	Y1	Y2	Y3	Y4	Y5	
Focus 1	Synthesize monomer library to explore polymer encapsulation based on architecture/chemistry	X	X	X	X	X	*On Track*
	Develop molecular potentials to model encapsulation in unimolecular micelles	X	X				*Done*
	Perform molecular simulations to model capture and release of drugs by unimolecular micelles	X	X	X	X	X	*On Track*
Focus 2	Synthesize, characterize, and assess new transmembrane drug delivery systems	X	X	X	X	X	*On Track*
	Experimentally utilize, validate, and improve the newly developed computational models for self-assembled drug carriers			X	X	X	*On Track*
	Use MD and CG methods to study the mechanisms of cellular absorption of drugs		X	X	X	X	*On Track*
	Develop new hybrid MD/continuum and coarse-grained accelerated simulation strategies to link length/time scales in biological systems	X	X	X	X	X	*On Track*

SD3 Outreach Activities

Profs. Ashbaugh and Grayson (Tulane) have taught "Chemistry and Engineering Science in the Community" at local high schools every Spring since 2007



Prof. Derosa (LATech/Grambling) has engaged high school classes across the state in Speaking of Science presentations

LSU SD3 researchers participated in nano-science demos at the LSU Super Science in Oct. 2012 with over 1600 people in attendance.