LA-SiGMA

Louisiana Alliance for Simulation-Guided Materials Applications

SD3 – Biomolecular Materials

Prof. Hank Ashbaugh Tulane University

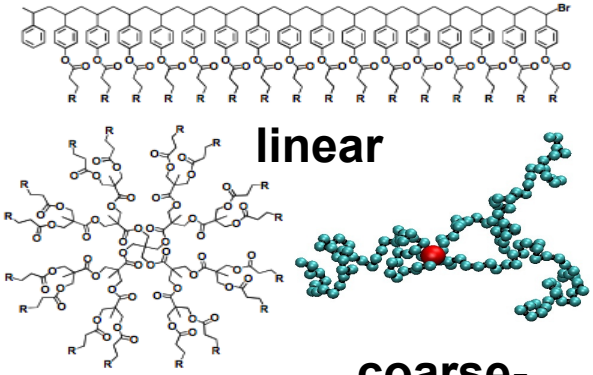
Prof. David Mobley University of New Orleans

SD3 Goals

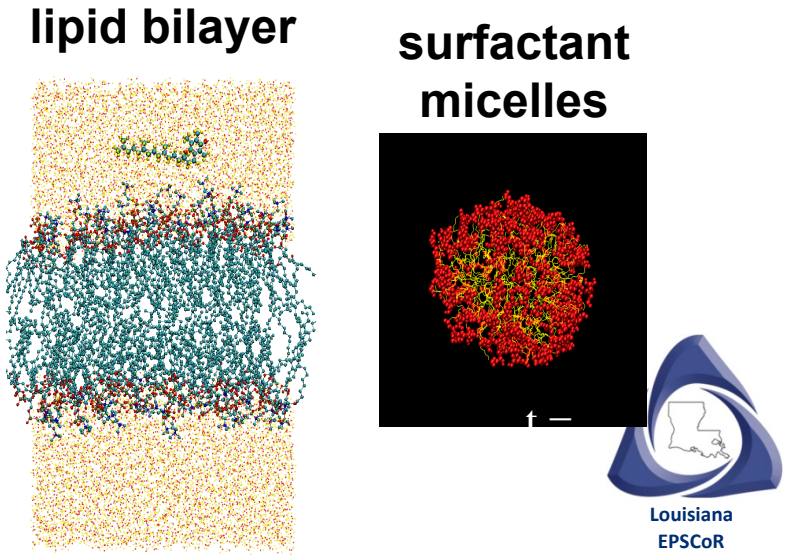
Goal: Develop novel biomolecular materials guided by computational/experimental collaboration for the encapsulation, delivery, and release of therapeutics to targeted tissues.

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



Self-Assembled Drug Delivery Vehicles



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SD3 Participants

Institutions Involved

Tulane University, Louisiana State University, Louisiana State University Agriculture Center, University of New Orleans, Louisiana Tech University, Grambling State University

Researcher Advisors Involved

Hank Ashbaugh (TU), Scott Grayson (TU), Tom Bishop (TU), John Perdew (TU), Dorel Moldovan (LSU), Dimitris Nikitopoulos (LSU), Ram Devireddy (LSU), Cristina Sabilov (LSU-Ag), David Mobley (UNO), Steve Rick (UNO), Pedro Derosa (LATech, GSU), Yuri Lvov (LATech)

Departments/Disciplines Involved

Chemical and Biomolecular Engineering (TU), Chemistry (TU, UNO, LATech), Mechanical Engineering (LSU), Biological and Agricultural Engineering (LSU-Ag), Physics (TU, LATech, GSU), Center for Computational Science (TU), Institute forMicromanufacturing (LATech)

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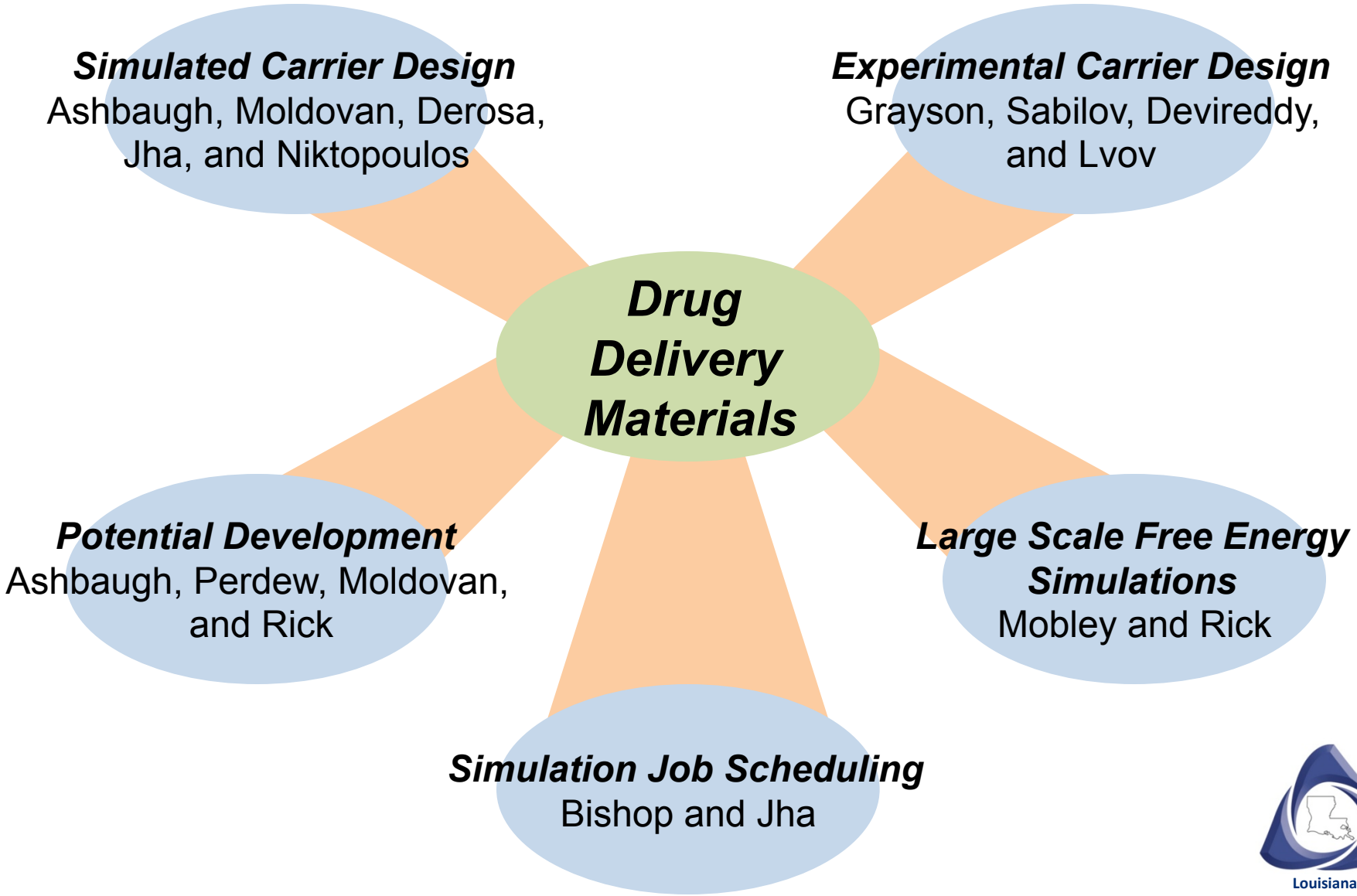
SD3 Research Themes



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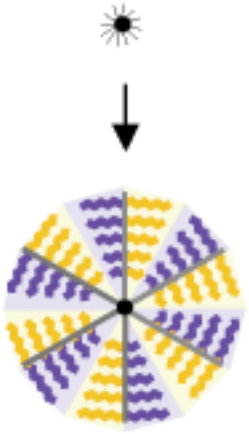
Janus Amphiphilic Homopolymers

- Synthesis of dendritic tertiary bromide initiators

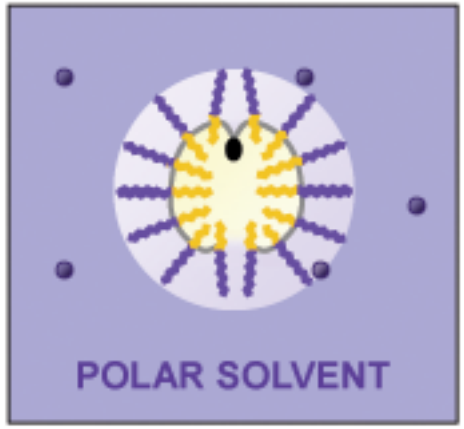


- Preparation of an amphiphilic monomer

- 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

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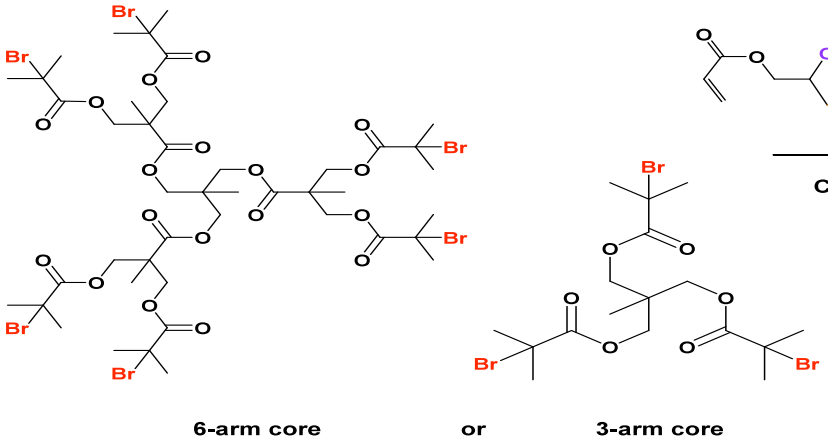
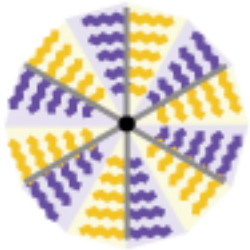
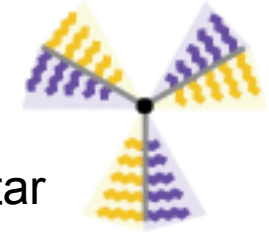
Janus Polymer ATRP Synthesis





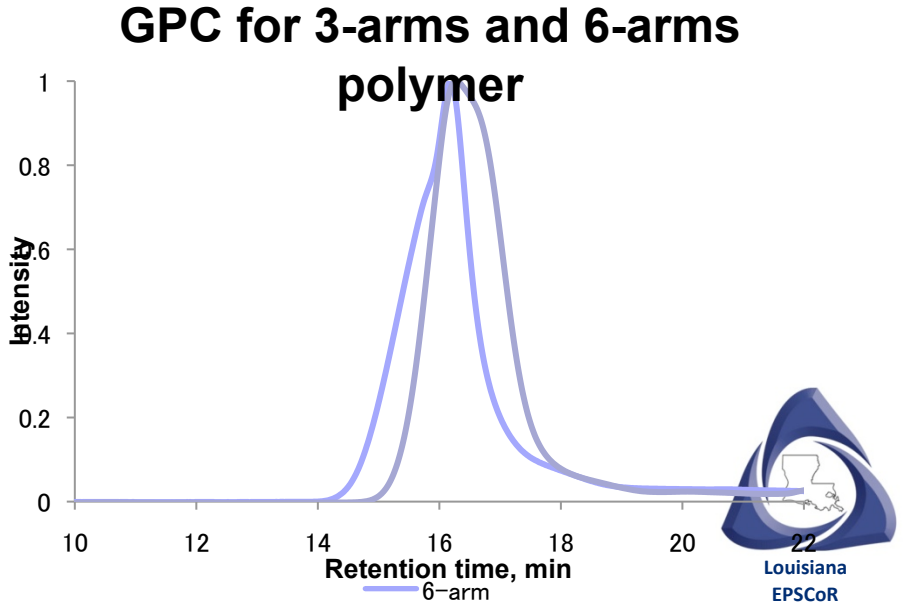
6-arm
Janus star



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



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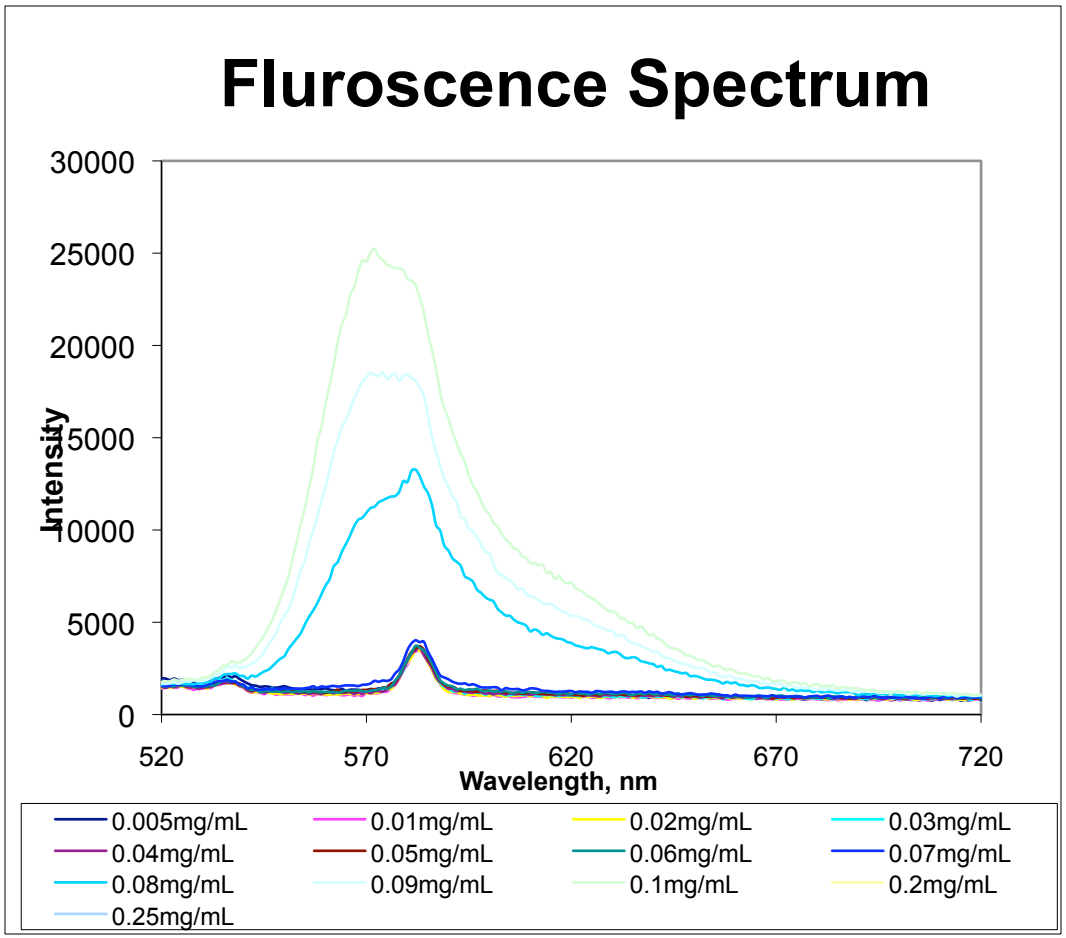
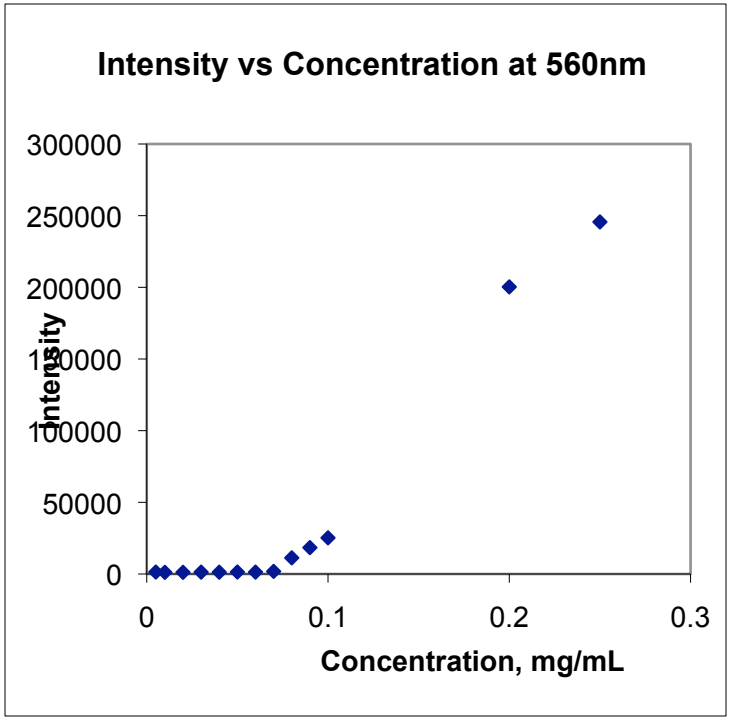
Janus Polymer Dye Encapsulation

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





Critical micelle concentration: 0.07mg/mL

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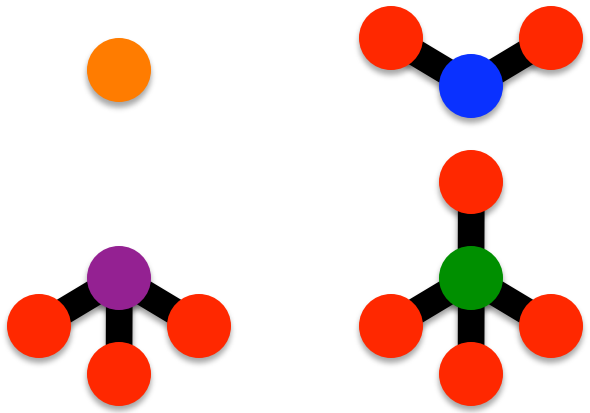
Hydrophobic Solubility

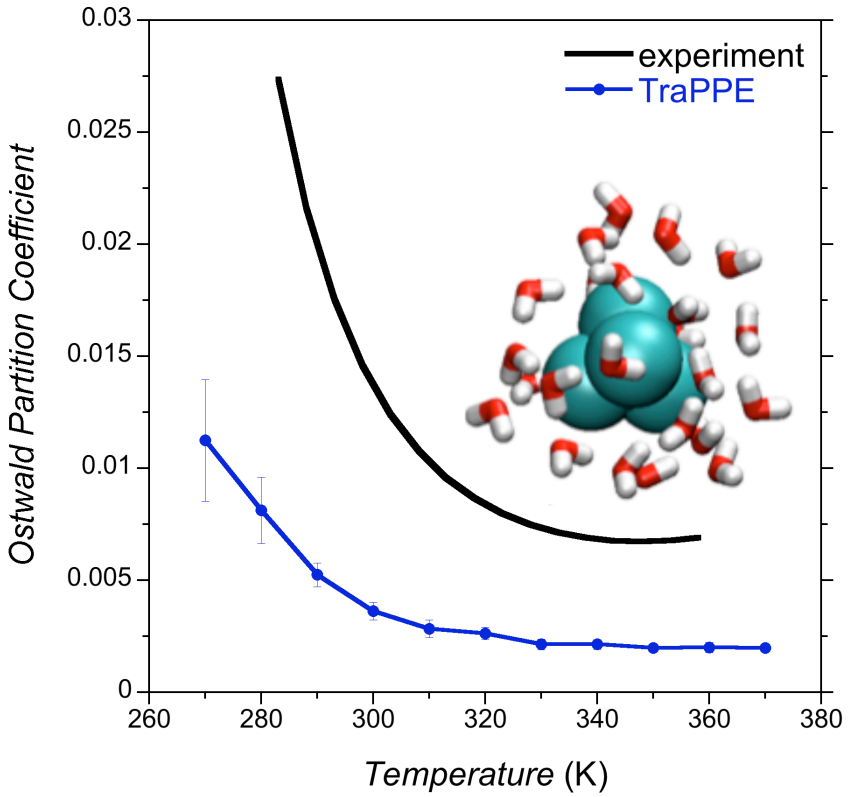
Linear and Branched Alkanes



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

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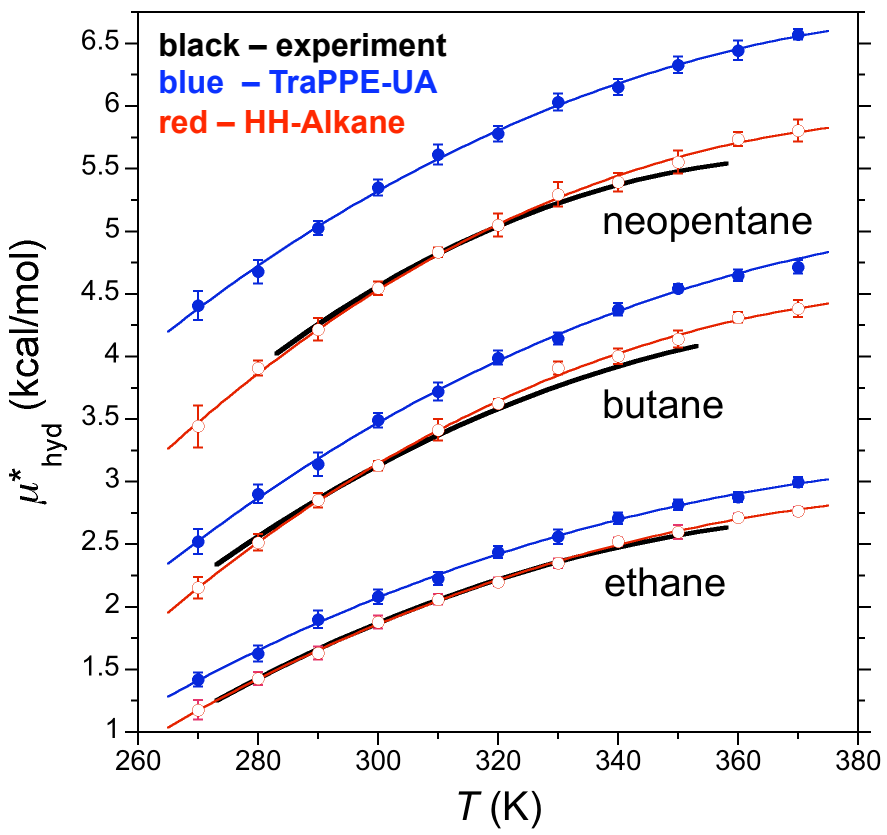
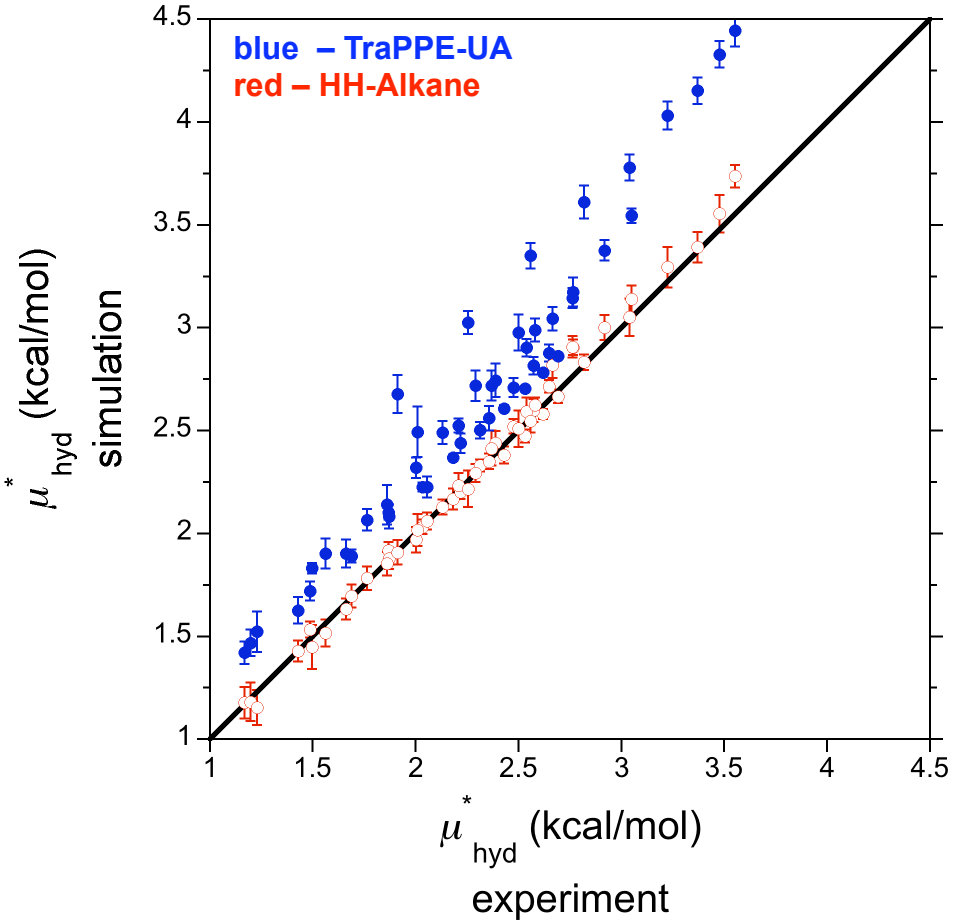
Hydrophobic Solubility





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

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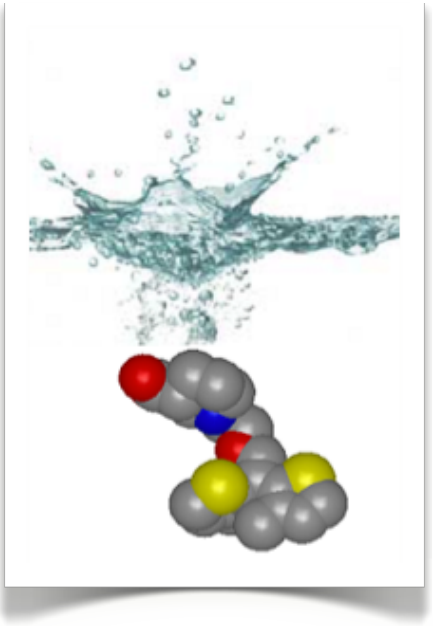
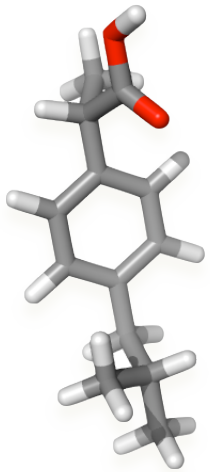
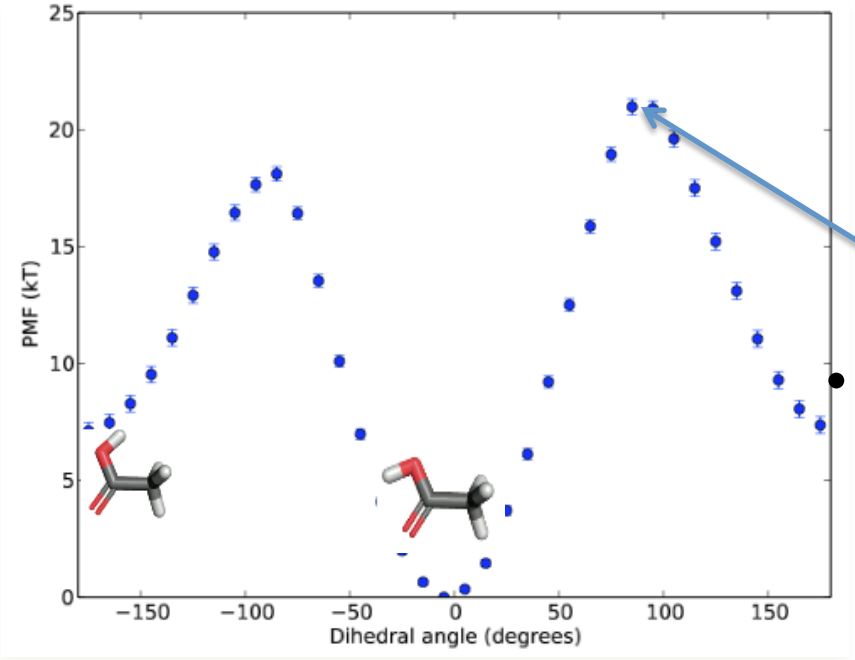
Enhanced Sampling of Molecules

- 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

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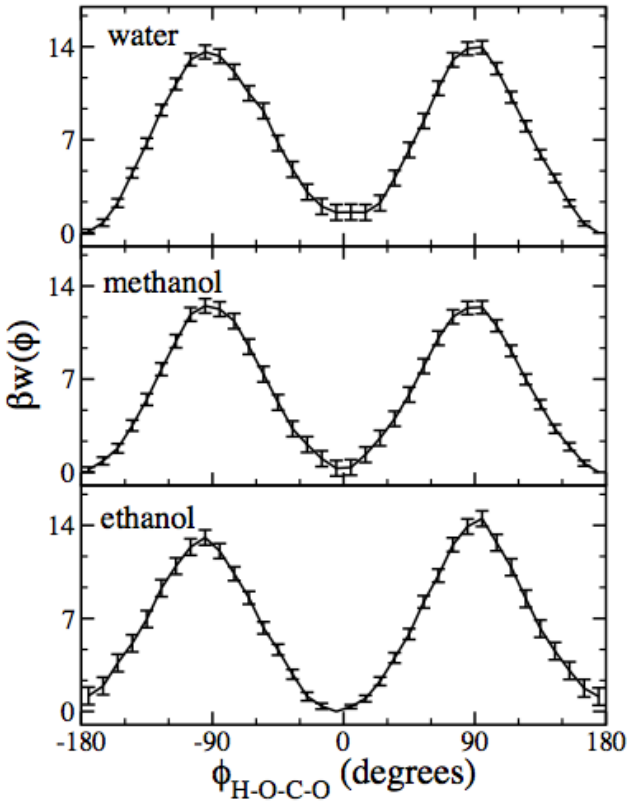
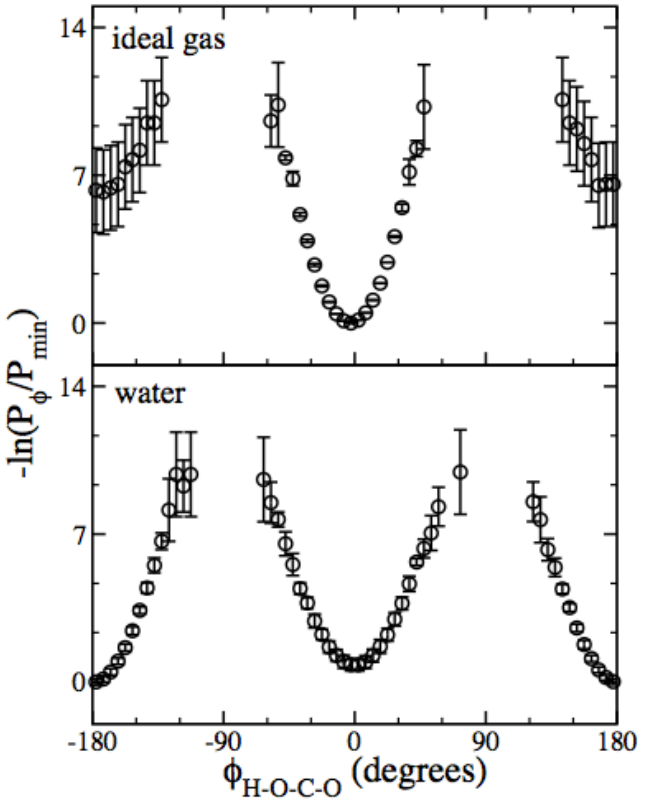
Enhanced Sampling of Molecules

Energy landscapes in different solvents difficult to sample



Actual sampling using expanded ensemble is vastly improved



A. Paluch, D. Mobley, E. Maginn

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MD Studies of Span80 Assembly

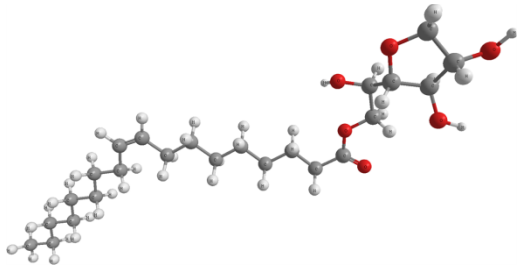
Objectives

- Develop, self-assembly based, improved delivery vehicles of poorly water-soluble drugs.
- Study the mechanism of self-assembly of Span80 into micelles.
- Develop reliable new force fields for novel molecules such as Span80 and vitamin E.

Simulation Methodology

- MD simulations using GROMACS 4.5 on CCT and LONI supercomputers.
- Initial force field parameters obtained from PRODRG2.5 web server.

Span80 molecule



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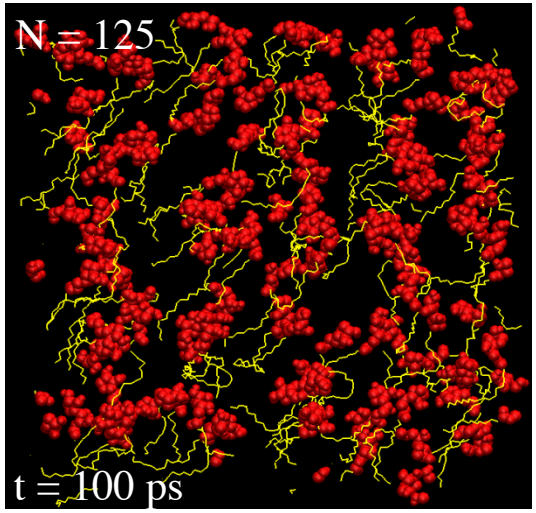
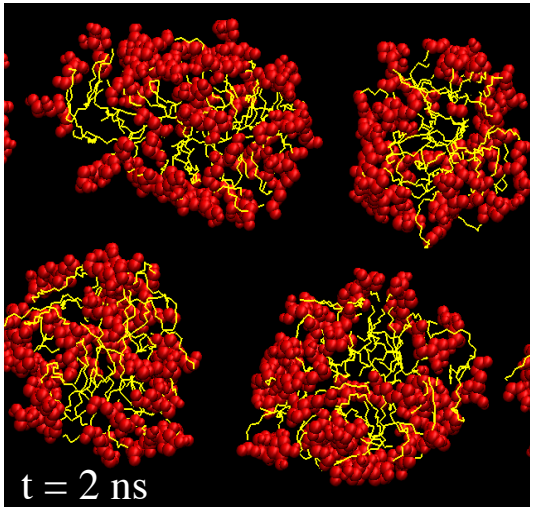
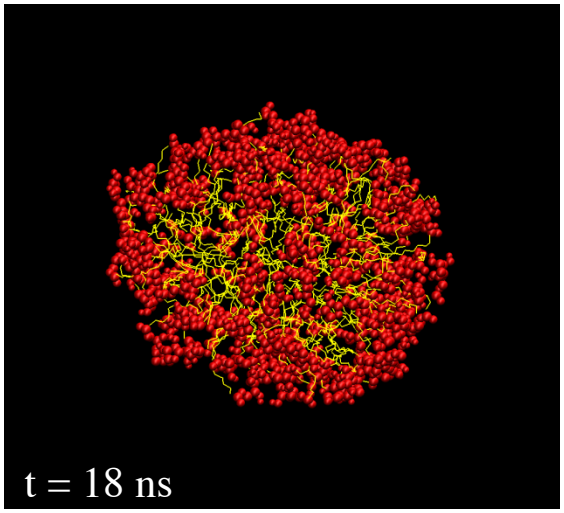
MD Studies of Span80 Assembly







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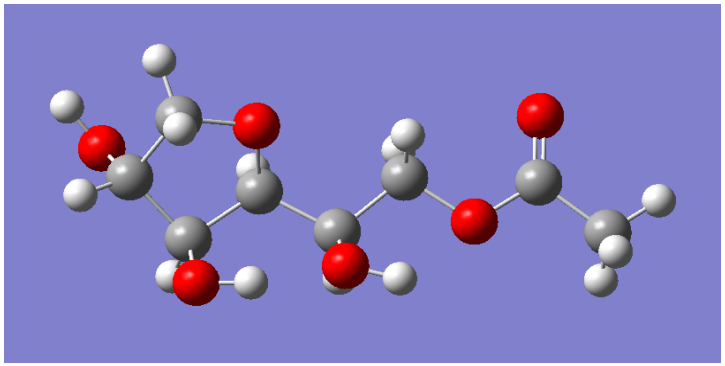
MD Studies of Span80 Assembly

- Develop new force field for Span80
  - Start with:
    - Initial geometry from Gaussview or Chemdraw.
    - AMBER-03 or GROMOS-53A6
  - Ab-initio calculations
    - QM to obtain global energy minimum struct.
    - QM-Mulliken or RESP charges
    - Relaxed scan of the three dihedral angles to obta a set of conformers
  - MD calculations:
    - Optimize the FF parameters by fitting the MD energies to the corresponding QM profiles



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

Here, r_{eq} and θ_{eq} are equilibration structural parameters; K_r, K_θ, V_n are force constants; n is multiplicity and γ is the phase angle for the torsional angle parameters. The A, B, and q parameters characterize the nonbonded potentials.

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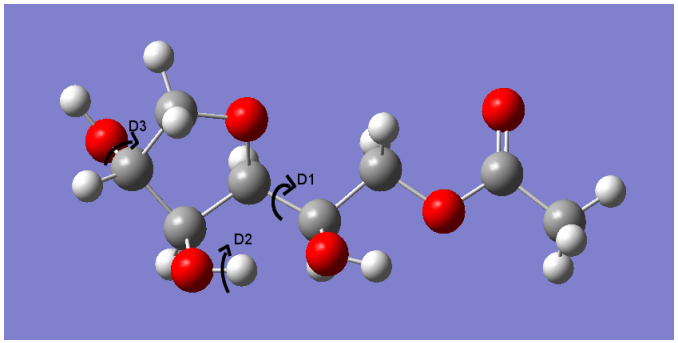
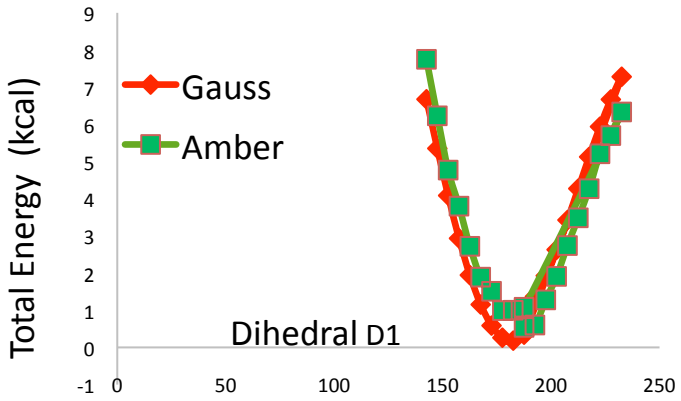
MD Studies of Span80 Assembly

- Develop new force field for Span80 (cont...)
  - Technical details:
    - Ab-initio calculations with G09, HF/6-311g(d)
    - QM-Mulliken or RESP charges
    - Relaxed multi-torsion scans
    - MD calculations with AMBER-03 or GROMOS-53A6
    - Test the new parameter set against various physical properties.





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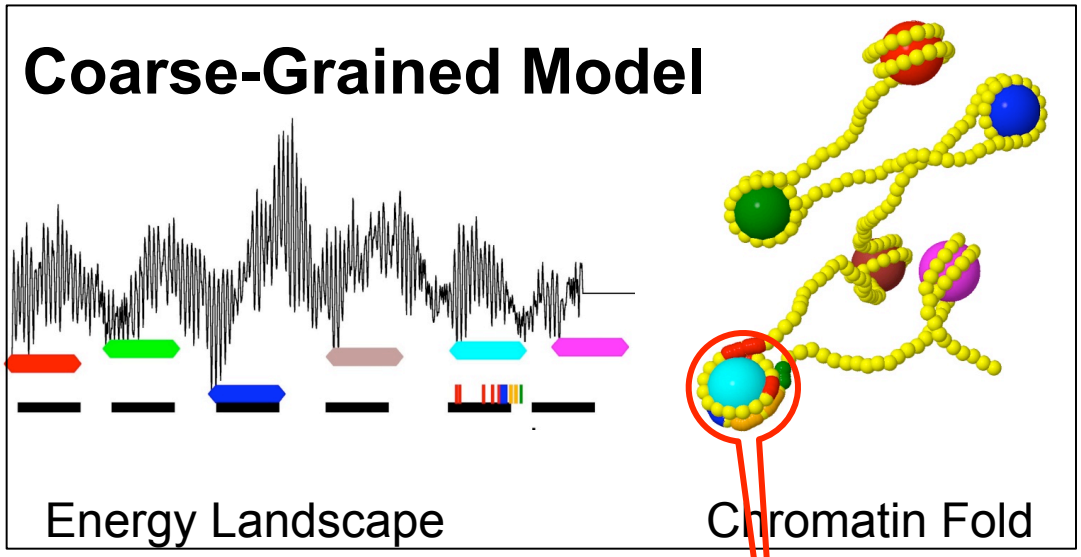
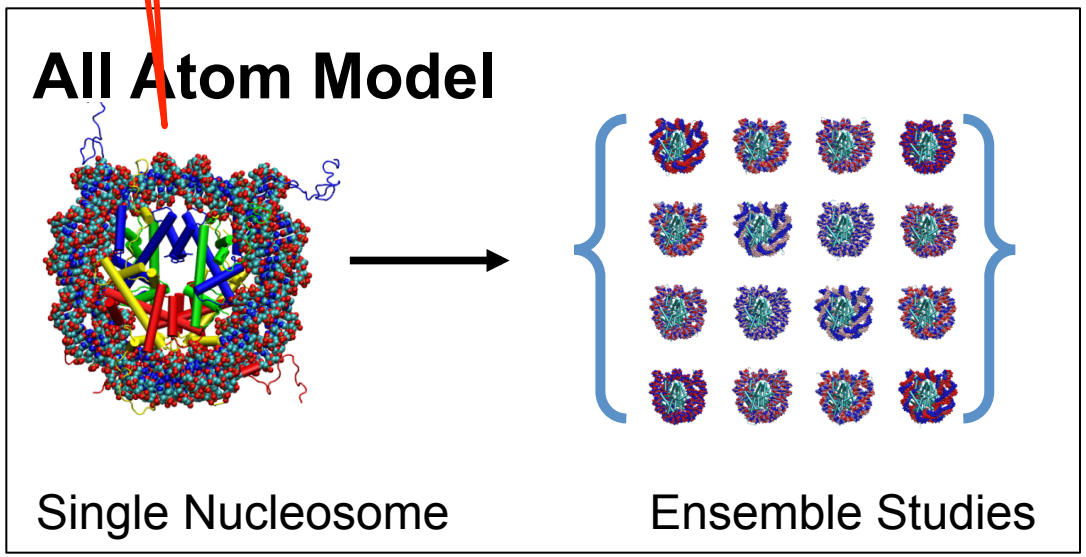
Chromatin Modeling on Multiscales





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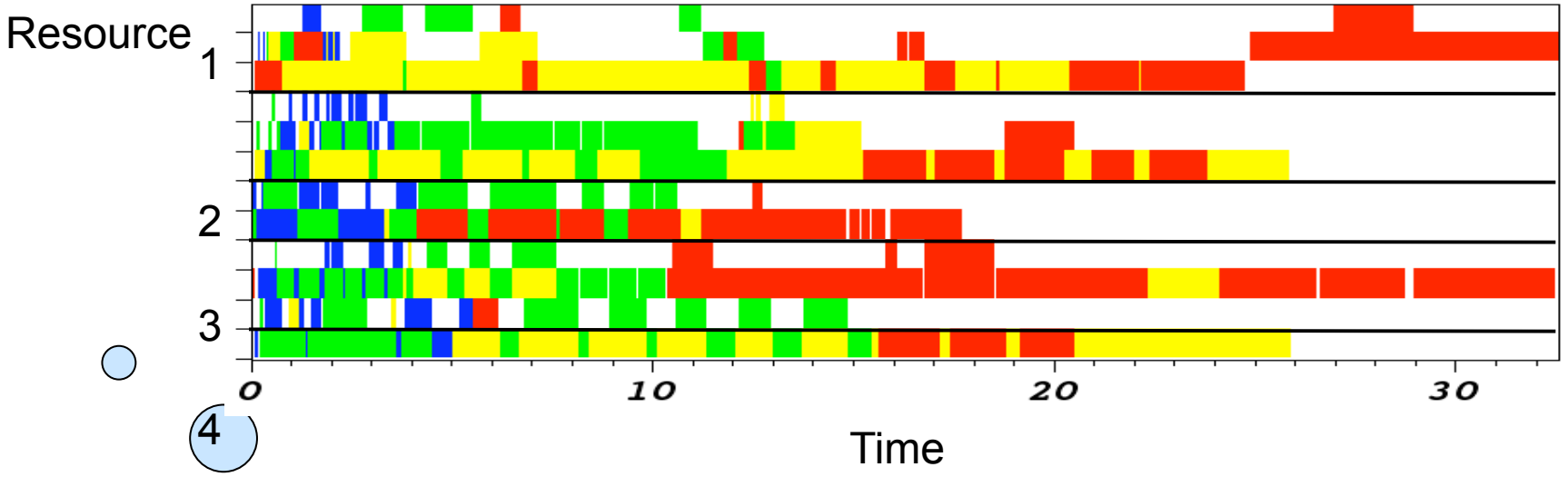
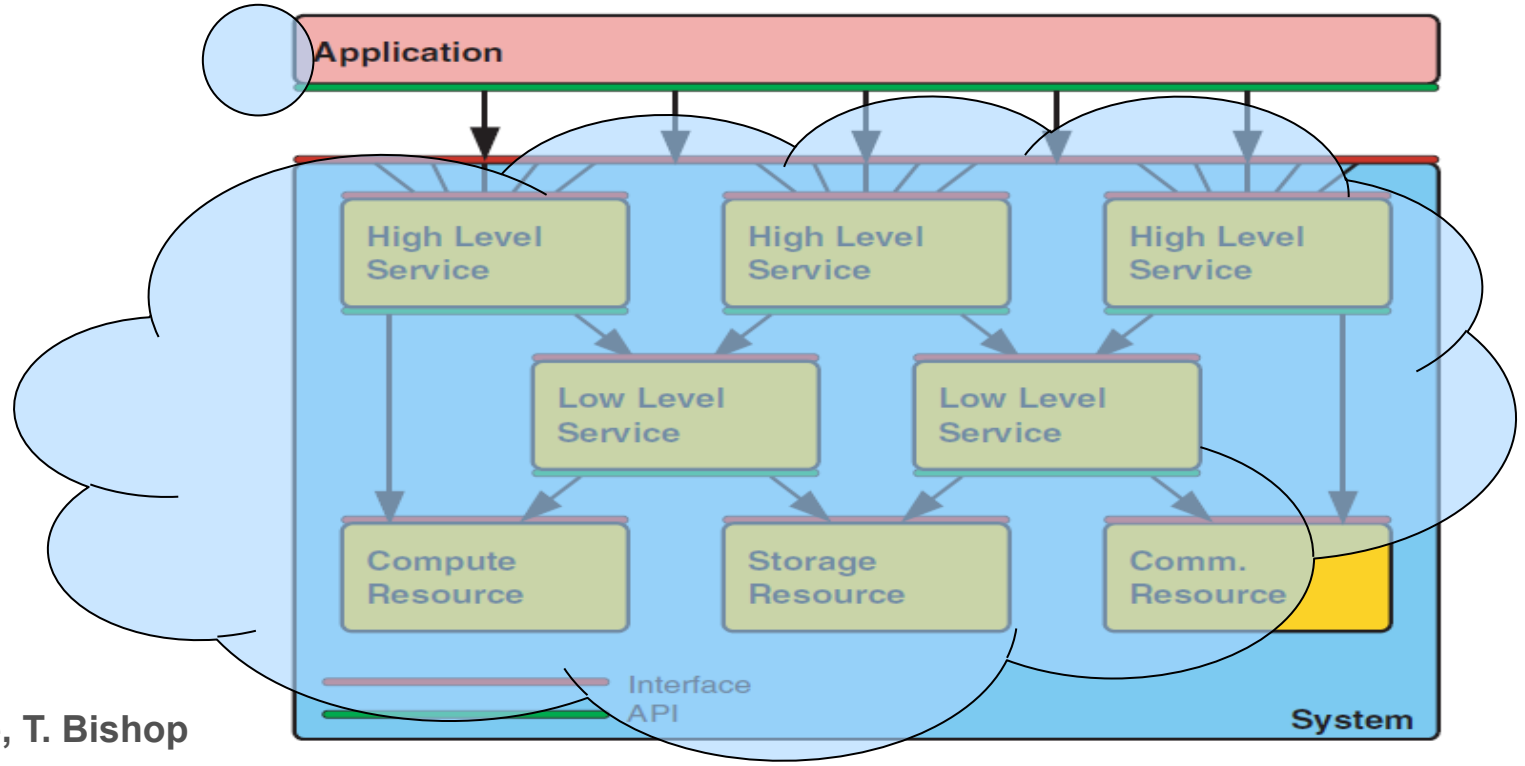
MD Simulations: ManyBigJobs





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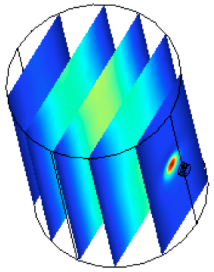
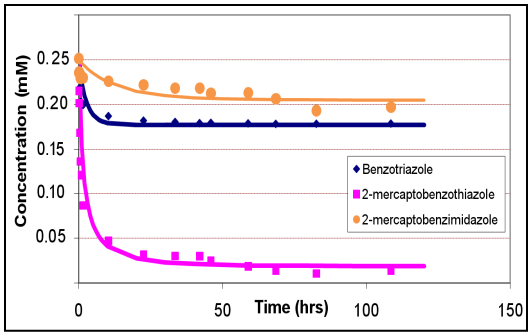
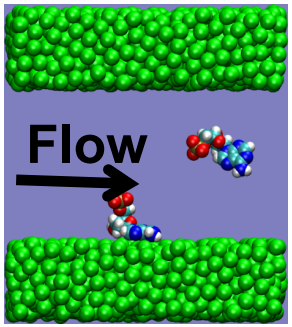
Additional Projects



- Nanoparticle diffusion into tumors (Derosa)



- Diffusion in nanotubes, storage and release (Lvov, Derosa)
- Hybrid MD/Continuum simulation methods (Jha, Moldovan, Nikitopoulos)



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

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Questions?