A coarse grained lipid model for studying inhomogeneous membrane interfaces

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Abstract

The proposed research focuses on the refinement, validation and application of a novel mesoscale model for biological membranes. Individual lipids are treated as short polymers formed from a chain of beads with unique interaction potentials. The model distinguishes itself from most other lipid models in the literature by capturing the hydrophobic effect implicitly via effective lipid-lipid interactions; there is no need for explicit simulation of solvent. Preliminary studies show that this model behaves in accord with many of the expected properties of lipid bilayers including: fluid behavior of the lipids, realistic magnitudes of elastic moduli (bending and compression), self assembly of the bilayer structure and faithful reproduction of the inhomogeneous distribution of stresses across the bilayer. Although a handful of other solvent-free lipid models are discussed in the literature, none of them capture all of these important physical properties of experimental bilayer systems.

Three specific sub-projects are proposed for the one-year funding cycle of this award. The original lipid model will be refined to reproduce a range of bending moduli consistent with experimental bilayer systems. A theoretical framework and analysis protocol will be developed to better assess the performance of this (and other) coarse-grained model as compared to fully-atomic simulations. Potentials of mean force will be calculated numerically for various geometries of membrane inclusions to better understand experiments and to create a bridge between experimental results and theoretical work.

Max Watson, the student who will be funded, is both very strong scientifically and has an unusually outgoing and friendly personality. He will certainly make the most out of his time at LANL and will have no difficulty whatsoever quickly fitting into a new environment and working with others. The interactions he will have at LANL will broaden his exposure to biophysics and theoretical/computational biology beyond what is possible at UCSB. It is hoped that this seed funding will lay the groundwork for a future proposal to the NIH. While the model is appropriate as-is to address generic questions of physical and biophysical interest, the refinements and detailed analysis proposed herein should demonstrate the viability of this approach for questions of biological interest.

1 Technical description

The details of our lipid model may be found in the original literature [1, 2, 3] and Fig. 1 provides an illustration of the model as implemented within simulations. We stress that the key advantage to our approach over competing membrane models in the literature is our handling of the aqueous solvent implicitly through effective lipid-lipid interactions. Our coarse-grained solvent-free level of description results in substantial computational savings relative to more detailed models that include explicit solvent. We have recently implemented the model within the LAMMPS (Large-scale Atomic/Molecular Massively Parallel Simulator) software package and are confident that the parallel computation capabilities of LAMMPS combined with the simplicity of our model will allow us to carry out the simulations proposed below. Simulations will be carried out on the 256 processor "Dell Cluster" housed in the California Nanosystems Institute at UCSB, the 164 core cluster, "cocktail," of Gnanakaran's group and the "FOD" computing cluster of T-division of LANL.

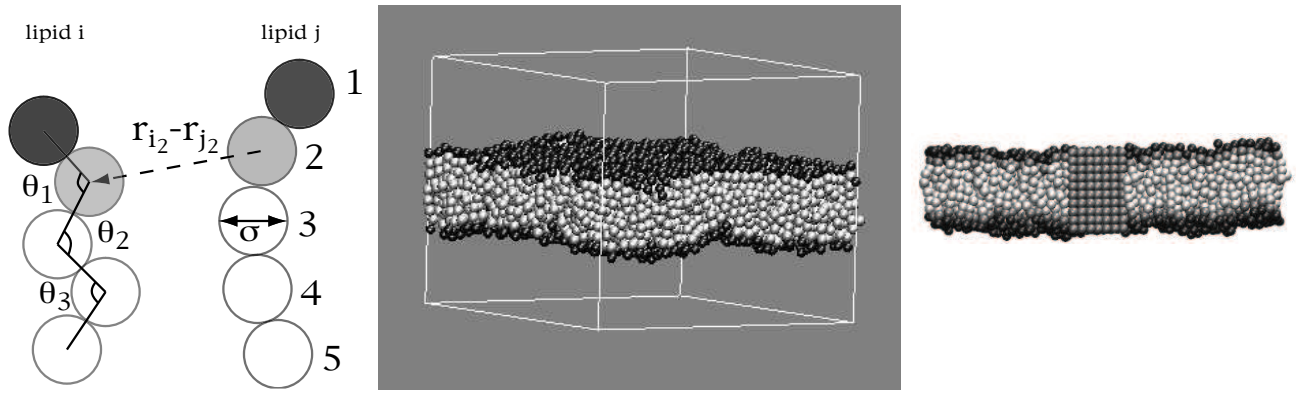

Figure 1: LEFT: Individual lipids are represented as a chain of beads that interact via potentials specified in the provided references. "Head" beads are shown in dark gray, "central" beads in light gray and "tail" beads in white. Hydrophobic interactions are captured via a long-ranged potential acting between all pairs of central beads; this interaction promotes stability of the bilayer structure while maintaining membrane fluidity and is the key ingredient in the model. CENTER: Snapshot of a stable fluid membrane composed of 1352 such lipids. The outlines specify the size of the cubic simulation box (periodic boundary conditions) of edge length $\sim 25\sigma$ (slight variations in box shape occur over the course of our constant tension simulations). For clarity, only the head beads are dark in this picture, central and tail beads are rendered identically light. RIGHT: Snapshot of a lipid bilayer with a coarse-grained integral membrane protein inclusion.

We propose three closely related extensions to this modeling with the dual aims of extending the practical capabilities of simulations to realistically treat biological systems and understanding the nature of interactions between multiple inclusions within the bilayer (proteins and/or nanoparticles). **Goal 1, reduction of bending rigidity of the bilayer:** The elastic properties of the current model do fall within the range of values observed for single-component phospholipid bilayers, however the bending rigidity of our bilayers are on the high side of reported values (around $40k_BT$). The first goal of the project will be to adjust the parameters of the model to allow for a

range of bending rigidities down to approximately $10k_BT$, while preserving other elastic properties and the bilayer stress profile. It is certainly possible to reduce the bilayer rigidity by tuning model parameters - one similar model in the literature has done so [4]. The challenge, however, is to reduce the bending rigidity while preserving the characteristic inhomogeneous distribution of stresses across the bilayer, which is essential to a proper modeling of membrane biophysics at the mesoscale; this is unprecedented among aggressively coarse-grained bilayer models in the literature. We will systematically explore the parameter space of the model to find systems of low bending rigidity that simultaneously preserve bilayer stresses. Although computationally intensive, this portion of the project is completely straightforward and will be carried out in parallel with the other goals outlined below.

Goal 2, development of tools to rigorously assess the validity of coarse-grained lipid models: One of the major challenges for coarse-grained modeling efforts lies in finding appropriate metrics to critically assess model performance. In the arena of coarse-grained lipid models we have made some progress in this area, by developing software to analyze bilayer elastic properties as well as the stress profile [2, 5]. The level of theory behind this analysis is an elastic treatment of the shape of the two monolayer leaflets comprising the bilayer. In recent work, we have found this level of theory to be inconsistent with direct simulations that measure the potential of mean force (PMF) between two integral membrane proteins [6]. A likely contributor to this theoretical failure may be the implicit assumption of our theory that the lipids are always oriented perpendicular to the tangent plane of their home monolayers. We will extend our theoretical analysis to account for deviations and fluctuations in lipid tilt. This will enable a more robust means to compare coarse-grained results with fully atomic simulations and may lead to a more satisfactory explanation for the interactions observed between two membrane inclusions.

Goal 3, calculation of membrane-mediated interactions between multiple membrane inclusions: Computational limitations currently preclude the direct calculation of PMFs between membrane inclusions using detailed (fully atomic) simulations. Although an abundance of theoretical work has been performed related to predicting interactions between membrane inclusions, refined experimental work is only just now beginning to appear [7, 8]. A major complication involved in theoretical interpretation of experiment is the fact that theoretical work traditionally focuses on two-body interactions, whereas experiments typically involve closely packed assemblies of many particles. There is no reason to expect pairwise additivity of the forces involved and it is critical to perform simulations to both test the performance of analytical theories (as currently formulated) and to determine the extent of non-pairwise additivity in the forces. We will directly calculate PMFs (via umbrella sampling and the weighted histogram analysis method "WHAM") for dimer, trimer and hexamer assemblies of protein inclusions using coarse-grained models to represent the inorganic nanoparticles from ref. [8] and proteorhodopsin proteins from ref. [7]. (see Fig. 1) This will provide a bridge between experiment and theory (see goal 2) to help us begin to understand the complex behavior of inhomogeneous lipid-bilayer membrane systems.

It is anticipated that goals 1 and 2 presented above will be carried out primarily at UCSB, assisted by the expertise of the Brown group. The PMF calculations will be carried out primarily at LANL, assisted by the expertise of the Gnanakaran group.

2 Estimated costs

The proposed work will be carried out by Max Watson, a graduate student in Frank Brown's group at UCSB. Max will spend the first nine months of the award period (October 2009 - June 2010) at UCSB and the final three months (July 2010 - September 2010) at LANL working with S. "Gnana" Gnanakaran. We request funding for Max's tuition, fees and stipend/benefits for the UCSB academic year, for Max's travel to/from Los Alamos, for Max's housing expenses in Los Alamos and his three month salary at Los Alamos as detailed below.

The research described in this proposal is not funded by any other extramural source, however we emphasize that the work is complementary to other projects that are ongoing in the groups of Brown and Gnanakaran. In particular, Brown maintains a group of two graduate students and two postdocs - all of whom are conducting research related to membrane biophysics. Gnanakaran maintains a group of two postdocs and two summer students at LANL with expertise in the simulation algorithms related to molecular and coarse-grained dynamics. The proposed work will therefore be heavily supported in indirect fashion by the cohort of researchers Max will be surrounded by as well as the existing resources of the two labs.

anticipated costs

- 9 months UCSB tuition/fees/benefits/stipend (GSR 5): $30,874
- 3 months LANL salary/housing/travel: $25,000
- total: $ 55,874

References

[1] G. Brannigan, P. F. Philips, and F. L.H. Brown. Flexible lipid bilayers in implicit solvent. *Phys. Rev. E*, 72:011915, 2005.

[2] G. Brannigan and F. L.H. Brown. A consistent model for thermal fluctuations and protein induced deformations in lipid bilayers. *Biophys. J.*, 90:1501–1520, 2006.

[3] G. Brannigan and F. L. H. Brown. A model for lipid bilayers in implicit solvent. In G. Voth, editor, *Coarse-Graining of Condensed Phase and Biomolecular Systems*, pages 41–58. Taylor and Francis, New York, 2008.

[4] Ira R. Cooke, Kurt Kremer, and Markus Deserno. Tunable generic model for fluid bilayer membranes. *Phys. Rev. E*, 72:011506, 2005.

[5] G. Brannigan and F. L. H. Brown. Contributions of gaussian curvature and non-constant lipid volume to protein deformation of lipid bilayers. *Biophys. J.*, 92:864–876, 2007.

[6] B. West, F. L. H. Brown, and F. Schmid. Membrane-protein interactions in a generic coarse-grained model for lipid bilayers, 2009.

[7] H. J. Liang, G. Whited, C. Nguyen, and G. D. Stucky. The directed cooperative assembly of proteorhodopsin into 2d and 3d polarized arrays. *Proc. Nat. Acad. Sci. USA*, 104:8212–8217, 2007.

[8] D. Constantin, B. Pansu, M. Imperor, P. Davidson, and F. Ribot. Repulsion between inorganic particles inserted within surfactant bilayers. *Phys. Rev. Lett.*, 101:098101, 2008.

Biographical Sketch for Frank L. H. Brown

Professional Preparation

University of California, Berkeley	Chemistry	B.S.	1994
	Applied Mathematics	B.A.	1994
Massachusetts Institute of Technology	Physical Chemistry	Ph.D.	1998
University of California, San Diego	Biophysical Chemistry	postdoc	1998-2001

Appointments

Professor, Dept. of Chem. & Biochem. and of Physics, UCSB	2009
Associate Professor, Dept. of Chem. & Biochem. and of Physics, UCSB	2007-2008
Assistant Professor, Dept. of Chem. & Biochem., UCSB	2001-2007
Yen Fellow, Institute for Biophysical Dynamics, University of Chicago	2001

Publications related to the proposed research

- *Hybrid Elastic and Discrete-Particle Approach to Biomembrane Dynamics with Application to the Mobility of Curved Integral Membrane Proteins*, A. Naji, P. Atzberger and F. L. H. Brown, Physical Review Letters, **102**, 138102 (2009).
- *Elastic Modeling of Biomembranes and Lipid Bilayers*, F. L. H. Brown, Annual Reviews of Physical Chemistry, **59**, 685-712 (2008).
- *Contributions of Gaussian curvature and non-constant lipid volume to protein deformation of lipid bilayers*, G. Brannigan and F. L. H. Brown, Biophysical Journal, **92**, 864-876 (2007).
- *A Consistent model for thermal fluctuations and protein induced deformations in lipid bilayers*, G. Brannigan and F. L. H. Brown, Biophysical Journal, **90**, 1501-1520 (2006).
- *Flexible lipid bilayers in implicit solvent,* G. Brannigan, P. F. Philips and F. L. H. Brown, Physical Review E, **72**, 011915 (2005).

Other Significant Publications

- *Membrane-Protein Interactions in a Generic Coarse-Grained Model for Lipid Bilayers*, B. West, F. L. H. Brown and F. Schmid, Biophysical Journal, **96**, 101-115 (2009).
- *Cytoskeleton mediated effective elastic properties of model red blood cell membranes*, R. Zhang and F. L. H. Brown, Journal of Chemical Physics, **129**, 065101 (2008).
- *Analysis of Shape, Fluctuations and Dynamics in Intermembrane Junctions*, L. Lin, J. Groves and F. L. H. Brown, Biophysical Journal, **91**, 3600-3606 (2006).
- *Nonequilibrium membrane fluctuations driven by active proteins*, L. C.-L. Lin, N. Gov and F. L. H. Brown, Journal of Chemical Physics, **124**, 074903 (2006).
- *Generating Function Methods in Single-Molecule Spectroscopy,* F. L. H. Brown, Accounts of Chemical Research, **39**, 363-373 (2006).

Synergistic Activities

- Development of a graduate level statistical mechanics (SM) curriculum for the chemistry department at UCSB. Prior to my arrival at UCSB, the department offered a single class in SM that was only offered occasionally (less than once every other year). I have expanded this single course to a regularly offered three quarter sequence consisting of one quarter of equilibrium SM, one quarter of non-equilibrium SM and one quarter of computational methods. These courses attract students from varied departments including Chemistry, Physics, Chemical Engineering, Mechanical Engineering and Geosciences.
- Development of an undergraduate physical chemistry sequence for biochemistry majors. I am currently developing this yearlong sequence to be taken by biochemists in lieu of the traditional sequence taken by chemistry majors at UCSB. This is the first significant change to the biochemistry major at UCSB to be undertaken since the major was initiated ten years ago.
- PI on an NSF-MRI acquisition grant for and director of UCSB's Beowulf class supercomputer facility. This shared computer resource is available for both research and advanced graduate level coursework across all scientific/engineering departments at UCSB.
- Participation in the Jackson State University/University of California partnership project, the UCSB Physics Circus and the UCSB Chemistry Outreach programs at UCSB. These programs are designed to promote interest in college and graduate school among underrepresented minority students at Jackson State University and among K-12 students living in or near Santa Barbara.
- Co-Organizer of the international workshop "Theory, Modeling and Evaluation of Single-Molecule Measurements" (Leiden Univeristy, the Netherlands, April 2007) and co-editor of the companion book "Theory and Evaluation of Single-Molecule Signals" which is in the final stages of production by World Scientific publishing.

Collaborators & Other Affiliations

Collaborators (July 2004-present)

Paul Atzberger (UCSB); Tobias Baumgart (U. Penn.); Jianshu Cao (MIT);
Jay Groves (UC Berkeley); Nir Gov (Weizmann Institute); Mahn Wan Kim (KAIST, Korea); Everett Lipman (UCSB); Philip Pincus (UCSB); Joan-Emma Shea (UCSB)

Co-Editors (July 2006-present)

Eli Barkai (Bar-Ilan University); Michel Orrit (Leiden University); Haw Yang (UC Berkeley)

Graduate and Postdoctoral Advisors

Robert Silbey (MIT, graduate advisor); J. Andrew McCammon (UCSD, postdoctoral advisor);
Kent R. Wilson (deceased, postdoctoral advisor)

Thesis Advisor (5 total) and Postgraduate-Scholar Sponsor (6 total)

Golan Bel (LANL); Grace Brannigan (U. Penn); Brian Camley (UCSB); Yong Seok Jho (UCSB); Lawrence Lin (US State Department); Ali Naji (UCSB); Evgeni Penev (UCSB);
Joel Varley (UCSB); Max Watson (UCSB); Rui Zhang (Georgia Tech.); Yujun Zheng (Shandong U., China)

Gnana S. Gnanakaran **Theoretical Biology and Biophysics Group (T-6), LANL**

RESEARCH INTERESTS

Research interest lies at the interface of biology and the physical sciences. The general thrust of my research program is aimed at developing and applying computational methodologies to understand structural characteristics and thermodynamics of peptides, proteins and carbohydrates in aqueous solution.

EDUCATION

PhD Physical Chemistry University of Pennsylvania, Philadelphia, PA 19104 1990 - 1998
Thesis Title: Role of solvent on chemical reaction dynamics of small molecules

BS Chemistry Virginia Commonwealth University, Richmond, VA 1986 - 1989

PROFESSIONAL EXPERIENCE

Technical Staff Member: Theoretical Biology and Biophysics Group, Theory Div. 2005 - present
Topic: Application of computational structural biology methods for health and energy securities

Postdoctoral Research Associate: Theoretical Biology and Biophysics Group 2001 - 2004
Topic: Conformational dynamics, stability and folding studies of short peptides

Postdoctoral Fellow: Dept. of Chemistry University of Pennsylvania, Philadelphia, PA 1999 - 2001
Topic: Structure determination from vibrational mode couplings deduced from 2D-IR

Research Assistant: Dept. of Biochemistry, Medical College of Virginia, Richmond, V 1989 - 1990
Topic: Determination of ancestor gene sequence of wheat germ agglutinin

CURRENT RESEARCH PROJECTS

One-step Biomass Conversion (LDRD/DOE) - Looking to Nature for solutions to energy security, specifically bioethanol industry. Focuses on revolutionizing cost and efficiency of biomass conversion to sugar.

Host and Viral Genetics – HIV (NIH/NIAID) - Characterize acute infection and vaccine for HIV, Structural characterization of variable regions of HIV envelope proteins

Global Aids Vaccine Enterprise (GATES) - Comprehensive Antibody Vaccine, Immune Monitoring Consort. Analysis and interpretation of complex patterns of immunological reactivity and sequence variation

Receptor Aggregation and its Effects (NIH) - Quantitative understanding of the receptor aggregation in membrane for detailed mathematical models of the early events of cell signaling

Understanding Drug Resistance and Co-infectivity in HIV and TB Infections (LDRD/DOE) - Develop clinical approaches to diagnose the stage of infection. Structural basis of drug resistance

RECENT PUBLICATIONS (2009 - 2007)

B. Korber and **S. Gnanakaran**. The implications of patterns in HIV Diversity for neutralizing antibody induction and susceptibility. Curr Opin in HIV and AIDS. in press (2009).

Tongye Shen and **S. Gnanakaran**. The stability of cellulose: A statistical perspective from a coarse grained model of hydrogen bond network. Biophys. J., 96, 3032-3040 (2009) –highlighted in cover]

Rebecca M., Tongye Shen, **S. Gnanakaran** and Cynthia A. Derdeyn. Appreciating HIV-1 Diversity: Subtypic Differences in Env. AIDS Res. and Hum. Retroviruses 25, 237-248 (2009).

Smita S. Kulkarni, Alan Lapedes, Haili Tang, **S. Gnanakaran**, Marcus G. Daniels, Ming Zhang, Tanmoy Bhattacharya, Ming Li, Victoria R. Polonis, Francine E. McCutchan, Lynn Morris, Dennis Ellenberger, Salvatore T. Butera, Robert C. Bollinger, Bette T. Korber, Ramesh S. Paranjape, and David C. Montefiori. Highly complex neutralization determinants on a monophyletic lineage of newly transmitted subtype C HIV-1 Env clones from India. Virology 385, 505-20 (2009)

D. Paschek, M. Puhse, A. Perez-Goicochea, **S. Gnanakaran**, A.E. Garcia, S. Decatur, A. Geiger and R. Winter. 2008. The solvent dependent shift of the amide-I band of a fully solvated peptide in Methanol/ Water mixture as a local probe for the solvent composition in the peptide/solvent interface. Chemphyschem. 9, 2742-50 (2008).

M.Vuyisich, **S. Gnanakaran**, JA. Lovchik, Rick Lyons, G. Gupta. A dual-purpose protein ligand for effective therapy and sensitive diagnosis of anthrax. Protein J. 27, 292-302 (2008)

S. Gnanakaran, B. Scott, T.M McCleskey and A. E. Garcia. Perturbation of Local Solvent Structure bSmall Dication: Structural, Spectroscopic and Reactive Properties of Beryllium Ion in Water, *J. Phys. Chem. B*, 112, 2958-2963 (2008).

Erzsebet Ravasz, **S. Gnanakaran** and Zoltan Toroczkai, Network Structure of Protein Folding Pathways, *submitted* available at arXiv:0705.0912v1 [q-bio.BM]. (2008).

Brian L. Scott, T. Mark McCleskey, A. Chaudhary, E. Hong-Geller, and **S. Gnanakaran**, Bioinorganic chemistry and associated immunology of Chronic Beryllium Disease, *Chem. Comm.*, 25, 2837-2847 (2008).
S. Gnanakaran, Dorothy Lang, Marcus Daniels, Tanmoy Bhattacharya, Cynthia A. Derdeyn, and Bette Korber. Clade Specific Differences in HIV-1: Diversity and Correlations in C3-V4 Regions of gp120. *J. Virol.* 81:4886-4891 (2007).
M. Kunkel, M. Vuyisich, S. Gnanakaran, G.E. Bruening, A.M. Dandekar, E. Civerolo, J.J. Marchalonis and G. Gupta. Rapid clearance of bacteria and their toxins: Development of therapeutic proteins. *Crit. Rev. Immuno.*, 27, 233-245 (2007).
Rong, R., **S. Gnanakaran**, J.M. Decker, F. Bibollet-Ruche, J. Taylor, J.N. Sfakianos, J.L. Mokili, M. Muldoon, J. Mulenga, S. Allen, B.H. Hahn, G.M. Shaw, J.L. Blackwell, B.T. Korber, E. Hunter, and C.A. Derdeyn. Unique Mutational patterns in the envelope 2 amphipathic helix and acquisition of length in gp120 hypervariable domains are associated with resistance to autologous neutralization of subtype C HIV type 1. *J. Virol.* 81:5658-5668 (2007).
M. Vuyisich, **S. Gnanakaran**, J.A. Lovchik, CR. Lyons, K.L. DeBord, and G. Gupta. Novel therapy for anthrax. *J. Biomol. Struct. Dyn.* 24:727-728 (2007).

MENTORING

Summer Student (2008 -present) –Andrea Asztalos (Notre Dame) networks & agent based model
Postdoc (2007-present) – Dr. Tongye Shen working on the multiscale modeling of cellulose
PhD Thesis Committee (2009 -) – Megan Murphy, Immun. & Mol. Pathogenesis, Emory Univ.

ONGOING INITIATIVES

-Organizer of the conference, *Energy for the 20th Century*, to be held from May 18 thru 22, 2009
-Organizer of the conference, *Proteins under Pressure*, held from Jan.20 thru 25, 2008.

PUBLIC LECTURES

Proteins behaving badly: Link between misfolding & Alzheimer's disease. LosAlamos, 8/08, Santa Fe 2/09

PATENTS

Part of the PCT Patent (S-112,799) filed by Duke Univ Acute Transmitted HIV Envelope Signatures

RECENT TALKS / PRESENTATIONS (2009 -2008)

-Transmission signatures of Clade B Virus.
Talk. AIDS Vaccine Meeting, Cape Town, South Africa. Oct. 2008
-Structural Alterations of a Vaccine Target: Clade specific differences and immune escape of gp120
AIDS Vaccine Meeting, Cape Town, South Africa. Oct. 2008
-Finding a Needle in a Hay Stack: Transmission signatures of Clade B Virus.
Talk. CHAVI Annual Meeting. Sept. 2008
-Proteins behaving badly: Link between misfolding and Alzheimer's disease.
Lecture. Q-Bio Summer School. July 2008
-Proteins folding topology from conformation networks.
Annual Symposium of the protein Society. San Diego, CA July 2008
-Conformational Dynamics of Medically Relevant Peptides and Proteins.
Invited Talk. TASME 2008. Toronto,Canada. July 2008
-Conformational Variability and Folding of Peptides and Carbohydrates.
BBCS Capability review. Los Alamos, NM May 2008.
-Modeling the properties of cellulose microfibrils.
Talk, American Chemical Sociiety National Meeting, New Orleans, LA. April 2008
-Structural Aspects of Positive Selection Driven by Immune Response.
Talk. HIV Dynamics and Evolution. Santa Fe, NM, April 2008
-What studies need to be acquired/analyzed to define neutralization signatures in HIV-1 Env?
Talk. CHAVI discovery Team Meeting, Durham, NC. January 2008.
-Interfacing Spectral Measurements with Theoretical Simulations:Pressure & Thermal Denaturation
Talk, Proteins under Pressure, Santa Fe, NM, January 2008