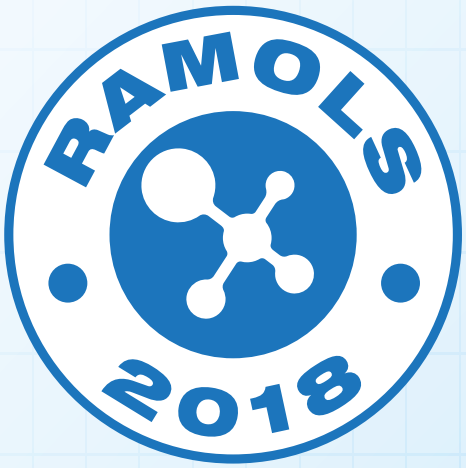

A DISCUSSION MEETING ON "RECENT ADVANCES IN MOLECULAR SIMULATIONS"

8th February – 11th February, 2018

Organized by:

Thematic Unit of Excellence in Computational Materials Science

Venue:

Auditorium, Solid State & Structural Chemistry Unit
Indian Institute of Science Bangalore-560012

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Indian Institute of Science

Bangalore-560012

8th February, 2018 Thursday

REGISTRATION: 8:30 – 9:15 AM

Timings	Speakers name	Title
9:15 AM – 9:30 AM	**Welcome and Introduction**	
9:30 AM - 10:15 AM	**Marcel Sluiter** Delft University of Technology, The Netherlands	Cluster Expansions for Realistic Precipitation Kinetics: Guinier-Preston Zone Formation in an Al 2a/o Cu Alloy
10:15 AM - 10:45 AM	**Govardhan P. Reddy** Indian Institute of Science, Bangalore	Toroidal Condensates by Semiflexible Polymer Chains
TEA 10.45 AM - 11.15 AM		
11:15 AM - 11:45 AM	**Nisanth N. Nair** Department of Chemistry, Indian Institute of Technology, Kanpur	Temperature Accelerated Sliced Sampling: An Efficient Approach for Exploring Complex High Dimensional Free Energy Landscape
11:45 AM - 12:15 PM	**Abhijit Chatterjee** Indian Institute of Technology Bombay, Mumbai.	A Nano-Thermodynamic Model for Capturing Size-Dependent Phase Behavior of Multi-Metal Alloy Nanoparticles
12:15 PM - 12:45 PM	**Manish Jain** Indian Institute of Science, Bangalore	Temperature Dependent Layer Breathing Modes in Two Dimensional Materials
LUNCH 12:45 PM – 2:00 PM		
2:00 PM - 2:45 PM	**Shiang-Tai Lin** National Taiwan University, Taiwan	The Two-Phase Thermodynamic Approach for Absolute Entropy and Free Energy from Molecular Dynamics Simulations
2:45 PM - 3:15 PM	**Sudeep Punnathanam** Indian Institute of Science, Bangalore	Calculation of Excess Free Energy of Molecular Solids Comprised of Flexible Molecules Using Einstein Molecule Method
TEA/POSTER 3:15 PM – 4:45 PM		
4:45 PM – 5:05 PM	**Subbarao Kanchi** Indian Institute of Science, Bangalore	pH Controlled Gating of Toxic Protein Pores by Dendrimers
5:05 PM – 5:25 PM	**Anustup Chakraborty** Tata Institute of Fundamental Research, Mumbai	Unfolding of Proteins in Solutions Under Constant Electric Fields: Computational Studies on Ubiquitin
DINNER – 7:00 PM		

9th February, 2018 Friday

Timings	Speakers name	Title
9:30 AM - 10:15 AM	**Kurt Kremer** Max Planck Institute for Polymer Research, Germany	Open Systems Simulations of Macromolecular Solutes through Adaptive Resolutions Simulations (AdResS)
10:15 AM - 10:45 AM	**Pradip Kr. Ghorai** Department of Chemical Sciences, Indian Institute of Science Education and Research (IISER) Kolkata, Mohanpur	Structure and Dynamics of Ionic Liquids in Presence of Other Solvent and in Confinement
TEA 10.45 AM - 11.15 AM		
11:15 AM - 11:45 AM	**S. Ramasesha** Indian Institute of Science, Bangalore	Quantum Phase Transitions in Skewed Two Legged Ladders
11:45 AM – 12:15 PM	**Padma Kumar Padmanabhan** IIT Guwahati, Guwahati	Ab Initio Molecular Dynamics Studies of Inorganic -Selenium and -Arsenic Species in Aqueous Media
12:15 PM - 12:45 PM	**N. Arul Murugan** KTH Royal Institute of Technology, Stockholm, Sweden	Developing Multiscale Approaches for doing Predictive Medicinal Chemistry
LUNCH 12:45 PM – 2:00 PM		
2:00 PM - 2:30 PM	**Satyavani Vemparala** The Institute of Mathematical Sciences, Chennai	Membrane Active Biomimetic Polymers: Aspects of Acquired Functional Structures, Detection of Membrane Defects and Sequestration of Charged Lipids
2:30 PM - 3:00 PM	**Meher Prakash** Jawaharlal Nehru Centre for Advanced Scientific Research, Bangalore	Mechanism of Insertion, Self-Assembly of Small Double-Mimic Molecules for Selective Disruption of Membranes in a Proposed Antibiotic Action
3:00 PM – 3:30 PM	**Anand Srivastava** Indian Institute of Science, Bangalore.	Mechanistic Insights into Pleckstrin-Homology Domain (PHD) Activity in Dynamin Mediated Fission"
TEA/POSTER 3:30PM – 4:45 PM		
4:45 PM – 5:45 PM	**DISCUSSION**	
DINNER – 7:00 PM		

10th February, 2018 Saturday

Timings	Speakers name	Title
9:30 AM - 10:15 AM	**Biman Bagchi** Solid State & Structural Chemistry Unit, Indian Institute of Science, Bangalore.	Mode Coupling Theory Approach to Ionic Conductivity, Rotational Diffusion, and Electrochemical Transport
10:15 AM - 10:45 AM	**Jayanth K. Singh** Indian Institute of Technology Kanpur, Kanpur.	Phonon Thermal Transport in β-Cu2Se Using an ab initio Derived Force Field
TEA 10.45 AM - 11.15 AM		
11:15 AM - 11:45 AM	**Chandan Dasgupta** Indian Institute of Science, Bangalore.	Glass Transition in Supercooled Liquids with Medium Range Crystalline Order
11:45 AM - 12:15 PM	**K. G. Ayappa** Indian Institute of Science, Bangalore.	Determine the Presence of Glassy States in Confined Fluids
LUNCH 12:15 PM – 2:00 PM		
2:00 PM - 2:30 PM	**Sanjoy Bandopadhyay** Indian Institute of Technology, Kharagpur	Conformational Features of Amyloid Beta Peptides and their Aggregates in Aqueous Environment
2:30 PM - 3:00 PM	**Suman Chakrabarty** NISER Bhubaneswar, Odisha	Molecular Thermodynamics of Bio-molecular Signaling and Recognition
3:00 PM – 3:30 PM	**Debashree Ghosh** Indian Association for the Cultivation of Science, Kolkata	Photo-Processes in Biological Systems – Need for Hybrid QM/MM with Polarization
TEA 3:30 PM – 4:00 PM		
4:00 PM - 4:45 PM	**Balasubramanian Sundaram** Jawaharlal Nehru Centre for Advanced Scientific Research, Bengaluru	Modelling Supramolecular Polymers
4:45 PM - 5:15 PM	**Manju Sharma** University of Hyderabad, Hyderabad.	Paracetamol Pre-nucleation in Biocompatible Polymers – Interplay of Topology and Interactions
5:15 PM – 5:35 PM	**Madhurima Jana** National Institute of Technology Rourkela, Odisha	Effects of Ethanol on an Enzymatic Protein Chymotrypsin Inhibitor 2
5:35 PM – 5:55 PM	**Pradeep Pant** Indian Institute of Technology Delhi, New Delhi	Design and characterization of symmetric nucleic acids via molecular dynamics simulations.
5:55 PM – 6:15 PM	**Anvy Moly Tom** The Institute of Mathematical Sciences, Chennai	Aggregation of flexible polyelectrolytes: Phase diagram and dynamics
FREE		

11th February, 2018 Sunday

Timings	Speakers name	Title
9:30 AM - 10:00 AM	**Aparna Chakrabarti** Raja Ramanna Centre for Advanced Technology (RRCAT), Indore	Chemistry and Physics of Two-Dimensional Monolayers: Aluminene and Other Systems
10:00 AM - 10:30 AM	**A. V. Anil Kumar** NISER, Jatni	Molecular Dynamics Simulations of Colloids in Confinement
TEA 10:30 AM – 11:00 AM		
11:00 AM – 11:30 AM	**Ravi Venkatramani** Tata Institute of Fundamental Research, Mumbai.	Optical Charge Transfer Transitions in Proteins Arising from Charged Amino Acids: New Label Free Spectroscopic Markers to Probe Protein Structure and Dynamics
11:30 AM - 12:00 PM	**Prabal Maiti** Indian Institute of Science, Bangalore	Charge transport in molecular systems
LUNCH		

Cluster Expansions for Realistic Precipitation Kinetics: Guinier-Preston Zone Formation in an Al 2a/o Cu Alloy

Xi Zhang and Marcel H. F. Sluiter

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Abstract

A method for performing kinetic lattice gas Monte Carlo simulations for the early stages of clustering and precipitation in substitutional alloys is presented and applied.

Cluster expansions are used both for the thermodynamic states and for configuration dependent diffusion activation barriers in order to simulate realistically both thermodynamic driving forces and kinetic pathways.

The method is applied to an aluminium 2 atomic percent copper alloy.

The cluster expansion is shown to be capable of describing the morphology of Guinier-Preston (GP) zones of type I and II although a large set of effective cluster interactions is required.

The configuration dependence, and thereby the local composition dependence, of diffusivities is investigated in detail. It is found that in Al-Cu diffusion activation energies vary by a factor of five depending on the local distribution of Al and Cu atoms. The kinetics and evolution of clustering and precipitation is shown to differ significantly when modeled using constant or local configuration dependent activation barriers for diffusion.

Although both constant and local configuration dependent activation diffusion barriers yield the experimentally observed succession of GP-I and GP-II zones in Al-Cu alloys, the details of the early stages of precipitation differ significantly.

Toroidal Condensates by Semiflexible Polymer Chains

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Abstract

Deciphering the principles of DNA condensation is important to understand problems such as genome packing and DNA compaction for delivery in gene therapy. DNA molecules condense into toroids and spindles upon the addition of multivalent ions. Nucleation of a loop in the semiflexible DNA chain is critical for both the toroid and spindle formation. To understand the structural differences in the nucleated loop, which cause bifurcation in the condensation pathways leading to toroid or spindle formation, we performed molecular dynamics simulations using a coarse-grained bead-spring polymer model. We find that the formation of a toroid or a spindle is correlated with the orientation of the chain segments close to the loop closure in the nucleated loop. Simulations show that toroids grow in size, when spindles in solution interact with a pre-existing toroid and merge into it by spooling around the circumference of the toroid forming multimolecular toroidal condensates. The merging of spindles with toroids is facile, indicating that this should be the dominant pathway through which the toroids grow in size. The Steinhardt bond order parameter analysis of the toroid cross-section shows that the chains pack in a hexagonal fashion. In agreement with the experiments there are regions in the toroid with good hexagonal packing and also with considerable disorder. The disorder in packing is due to the defects, which are propagated during the growth of toroids. In addition to the well-known crossover defect, we have identified three other forms of defects.

Temperature Accelerated Sliced Sampling: An Efficient Approach for Exploring Complex High Dimensional Free Energy Landscapes

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Abstract

Biased sampling of collective coordinates is a widely used strategy to accelerate rare events and compute free energy changes in molecular dynamics simulations. Computational efficiency of such methods decreases with increasing number of collective coordinates and is often limited to 2 or 3 coordinates. This severely limits the predictive power of the enhanced sampling approaches. Here we propose a new method called Temperature Accelerated Sliced Sampling (TASS) which integrates temperature acceleration with umbrella sampling and/or metadynamics sampling in a manner that a large number of orthogonal collective coordinates could be sampled simultaneously. TASS also allows one to add or remove collective coordinates perpendicular to the umbrella sampling coordinates as required. The approach allows one to perform a controlled exploration of a complex free energy landscape that is broad and unbound, like in the case of A+B type reactions, drug binding etc. After demonstrating the accuracy of our method, I will demonstrate its applications in sampling complex chemical reactions using first principles and QM/MM based molecular dynamics.

A Nano-Thermodynamic Model for Capturing Size-Dependent Phase Behavior of Multi-Metal Alloy Nanoparticles

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Abstract

Multi-metal alloy nanoparticles (NPs) offer new avenues for exploration and design of nanoscale-properties, e.g., catalytic, electronic and optical, by virtue of their tunable composition. A method that can provide accurate prediction of size-, shape- and composition-dependent elemental distribution associated with nanomaterials and enable such exploration is crucially missing. A nano-thermodynamic model based on distribution coefficients is introduced in this talk to fill this gap. Distribution coefficients are employed to predict surface segregation in NPs as a function of the NP size and composition. Key concepts of this new theory are demonstrated with Au-Pt-Pd, Ag-Au-Pd and Ni-Pt-Pd, which are found to exhibit complex size-dependent segregation behavior with 2-6 nm NPs and relatively weaker size-dependence beyond 6 nm.

Temperature Dependent Layer Breathing Modes in Two Dimensional Materials

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Abstract

Relative out of plane displacements of the constituent layers of two-dimensional materials gives rise to unique low-frequency breathing modes. By computing the height-height correlation functions in momentum space, we show that the layer breathing modes (LBMs) can be mapped consistently to vibrations of a simple linear chain model. Our calculated thickness dependence of LBM frequencies for few-layer (FL) graphene and molybdenum disulphide (MoS_2) are in excellent agreement with available experiments. Our results show a redshift of LBM frequency with increase in temperature, which is a direct consequence of anharmonicities present in the interlayer interaction. We also predict the thickness and temperature dependence of LBM frequencies for FL hexagonal boron nitride (hBN). Our study provides a simple and efficient way to probe the interlayer interaction for layered materials and their heterostructures, with the inclusion of anharmonic effects.

The Two-Phase Thermodynamic Approach for Absolute Entropy and Free Energy from Molecular Dynamics Simulations

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Abstract

The entropy and free energy analysis are important for understanding the driving force of spontaneous processes. However, there is no instrument for direct measurement of these two properties. In this presentation, we introduce a novel approach for determination of such properties from molecular dynamic simulations. The method calculates the entropy and free energy based on the vibrational density of state (DOS), which is decomposed into a gas-like and a solid-like component. Proper statistical mechanical weighting functions are applied to each DOS components, respectively, yielding highly accurate results for the system in gas, liquid, and even solid states. Unlike conventional methods based on thermodynamic integration or particle insertion, which can be very computational demanding, this new method, referred to as the two-phase thermodynamic (2PT) model, can provide accurate thermodynamic properties (with corrections for quantum effects) from a single molecular dynamic trajectory of about 20 ps, which is orders of magnitude more efficient than any conventional methods. The highly efficient nature of 2PT opens up new opportunities to directly obtain energy and absolute values of entropy for problems that were very difficult to access before. In this talk, we will introduce the fundamental basis of the 2PT theory and illustrate some recent developments both in theory and in applications.

Calculation of Excess Free Energy of Molecular Solids Comprised of Flexible Molecules Using Einstein Molecule Method

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Abstract

Knowledge of free energies of crystalline solid phases is pivotal in determination of phase equilibria, however, their computations using molecular simulations is quite challenging. In this talk, I demonstrate how the Einstein molecule method can be used to compute the excess free energies of crystalline molecular solids comprising of molecules described by flexible models. This work can be viewed as an extension of the method described in J. Chem. Phys. v139, a034104, 2013. In this article, we present our calculations of the free energies of ice-Ih described by q-TIP4P/F model and Orcinol Form I described by the OPLA-AA forcefield. The free energies computed for ice-Ih are in agreement with previous reported results and those of Orcinol are shown to be thermodynamically consistent. We demonstrate that the efficiency of our calculations compares favorably with existing methods. The method described here can be easily implemented in popular publicly available molecular dynamics packages without any modification to their existing source codes.

pH Controlled Gating of Toxic Protein Pores by Dendrimers

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Abstract

Designing effective nanoscale blockers for membrane inserted pores formed by pore forming toxins, which are expressed by several virulent bacterial strains, on a target cell membrane is a challenging and active area of research. Here we demonstrate that PAMAM dendrimers can act as effective pH-controlled gating devices once the pore has been formed. We have used fully atomistic molecular dynamics (MD) simulations to characterize the cytolysin A (ClyA) protein pores modified with fifth generation (G5) PAMAM dendrimers. Our results show that the PAMAM dendrimer, in either its protonated (P) or nonprotonated (NP) states can spontaneously enter the protein lumen. Protonated dendrimers interact strongly with the negatively charged protein pore lumen. As a consequence, P dendrimers assume a more expanded configuration efficiently blocking the pore when compared with the more compact configuration adopted by the neutral NP dendrimers creating a greater void space for the passage of water and ions. To quantify the effective blockage of the protein pore, we have calculated the pore conductance as well as the residence times by applying a weak force on the ions/water. Ionic currents are reduced by 91% for the P dendrimers and 31% for the NP dendrimers. The preferential binding of Cl^- counter ions to the P dendrimer creates a zone of high Cl^- concentration in the vicinity of the internalized dendrimer and a high concentration of K^+ ions in the transmembrane region of the pore lumen. In addition to steric effects, this induced charge segregation for the P dendrimer effectively blocks ionic transport through the pore. Our investigation shows that the bio-compatible PAMAM dendrimers can potentially be used to develop therapeutic protocols based on the pH sensitive gating of pores formed by pore forming toxins to mitigate bacterial infections.

Unfolding of Proteins in Solutions Under Constant Electric Fields: Computational Studies on Ubiquitin

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Abstract

There are many instances in biology (cell membranes) as well as in nano-technology (Surface Plasmon based imaging and bio-sensing) where biomolecules are exposed to strong electric fields. Depending on the spatio-temporal profile, intensity and exposure time, external electric fields can deform protein structure. Molecular Dynamics (MD) simulation is one way to look at the protein dynamics in presence of electric field. Using Ubiquitin as model system and MD simulation as a computational tool, in this project our aim is to develop a general framework to describe electric-field induced protein unfolding in terms of structural properties of protein like dipole moment, charge distribution. Our initial studies on Ubiquitin in constant electric field of different strengths suggest connection between unfolding event and time evolution of protein dipole. Based on simulation results we compare pathways of mechanical and electric field induced unfolding events for Ubiquitin. Furthermore, using simulation results as a guideline, we want to build a predictive model that might provide insights on the response of protein structure to external electric field.

Open Systems Simulations of Macromolecular Solutes through Adaptive Resolutions Simulations (AdResS)

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Abstract

The relation between atomistic structure, architecture, molecular weight and material properties is of basic concern of modern soft matter science. A typical additional focus is the relation between structure and function in nanoscopic molecular assemblies. Here computer simulations on different levels of resolution play an increasingly important role. This is achieved by two different approaches, namely by sequential multiscale descriptions or adaptive schemes, which allow for a free exchange of particles (atoms, molecules) between the different levels of resolution. The latter is the topic of the present lecture. The extension to open systems MD (grand canonical MD) as well as recent Hamiltonian based molecular dynamics and Monte Carlo adaptive resolution methods will be discussed.

Typical applications are solvation of polymers in mixed good solvents, called co(non)solvency, hydration layers of large solutes, the combination of all atom and elastic network description of proteins and protein ligand binding or the classical with path integral quantum description combination for liquids.

Part of this work has been supported by the ERC Advanced Grant MOLPROCOMP

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Structure and Dynamics of Ionic Liquids in Presence of Other Solvent and in Confinement

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Abstract

Composition dependent structural and dynamical properties of different room temperature ionic liquids (RTILs) have been investigated in presence of water and alcohols by using all-atom molecular dynamics simulation and density functional theory (DFT). Structure and dynamics of IL strongly depend on the concentration of other solvent. Voronoi polyhedral analysis of IL exhibits strong dependent of local environment on water and alcohol concentration. Void and neck distributions in voronoi tessellation are approximately Gaussian for pure IL but upon subsequent addition of other solvent, the distributions deviate from it's Gassian behaviour with an assymetric broadening having long tail of exponential decay at large void radius at large water concentration. The increase in void space and neck size at high water concentration facilitates movement of each ion, thus decreases dynamical heterogeneity (DH) and their reorientation time and increases self-diffusion coefficient significantly.

Quantum Phase Transitions in Skewed Two Legged Ladders

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Abstract

Quantum Phase Transitions (QPT) in spin chains has been well studied. However, spin or Fermion ladders have not attracted the same attention. Our earlier studies on fused azulenes [1], which can be viewed as a two-legged ladder with skewed rungs, showed surprising ground states as the system size increased. In order to understand this phenomenon in detail, we studied general two legged ladders with skewed rungs in spin systems. The quantum phases of these systems are obtained using exact diagonalization of systems with up to 26 spins and by density-matrix renormalization-group calculations to 500 spins. The ladders have isotropic anti ferromagnetic (AF) exchange $J_2 > 0$ between first neighbors in the legs, variable isotropic AF exchange J_1 between some first neighbors in different legs, and an unpaired spin per odd-membered ring when $J_1 >> J_2$. Ladders with skewed rungs and variable J_1 have frustrated AF interactions leading to multiple quantum phases: AF at small J_1, either ferromagnetic or AF at large J_1, as well as bond-order-wave phases or reentrant AF (singlet) phases at intermediate J_1 [2].

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Ab Initio Molecular Dynamics Studies of Inorganic -Selenium and -Arsenic Species in Aqueous Media

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Abstract

Water contamination is one of the major threats to humanity especially in developing countries. The causes of surface/ground-water contamination is attributed to various anthropogenic activities such as, agricultural run-off waters, drainage from industries, nuclear waste disposal, etc., or to natural geochemical processes such as, volcanic activity and dissolution from mineral deposits. Thus, depending on the geography, the sources as well as severity of the contaminant species varies. Understanding the microscopic nature of interaction between the contaminant species and water is very useful in developing strategies for water remediation processes. The presentation will cover the nature of hydration, hydrogen bonding and spectroscopic signatures of two major water borne contaminants, namely selenium (Se) and arsenic (As), as evidenced from our recent ab-initio molecular dynamics simulations.

Developing Multiscale Approaches for Doing Predictive Medicinal Chemistry

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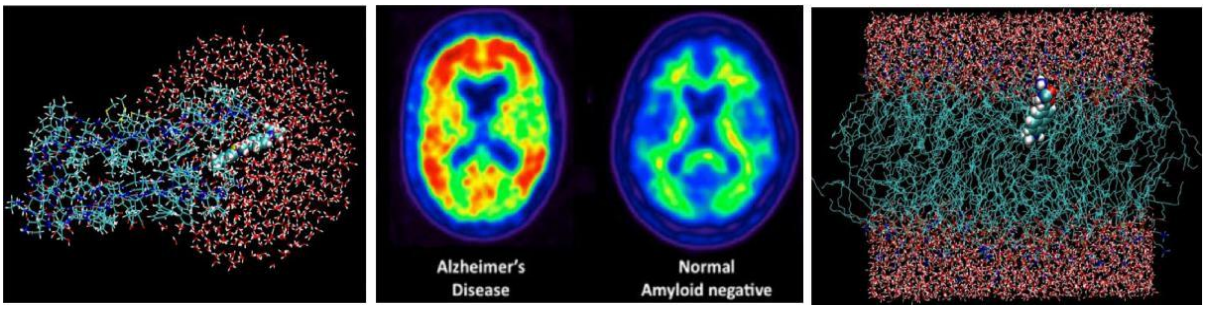
Abstract



We have entered into an era of "rising superbugs and falling wonderdrugs" where human healthcare is being challenged by growing drug resistant microorganisms. As the number of drugs and imaging agents approved keeps decreasing in recent years, it is urgent to develop novel imaging agents for early diagnosis of various diseases and effective drugs for the treatment[1-2]. The binding affinity and binding specificity and target specific spectroscopic properties of the lead compounds are the few quantities which we need to optimize for their use as drugs and diagnostic agents. Instead of trial and error based experimental screening which is also expensive and time taking for finding lead compounds, we will have to use rational computational approaches to make steady progress in the healthcare sector. At the positive side, we are provided with huge chemical space (small molecule database), and protein database and genomics (targets database) and exascale computing. But we have not made much progress due to the limited accuracy of the computational methods for calculating the binding affinity, spectroscopic and other properties relevant for drug/diagnostic agents optimization. In this presentation, I will discuss about developing hybrid QM/MM and fragmentation scheme based multiscale approaches suitable for calculating the binding free energies reliably and modeling optical properties of molecules in presence of target biomacromolecules. Case studies involving binding affinity calculation for PET tracers and "optical tracking" of biomolecules like amyloid fibril, membrane, enzymes and DNA will be presented in some detail[3-8].

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Membrane Active Biomimetic Polymers: Aspects of Acquired Functional Structures, Detection of Membrane Defects and Sequestration of Charged Lipids

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Abstract

All antimicrobial agents are inherently membrane-active and the complex interactions involved can lead to considerable conformational changes in the agents, while also inducing structural rearrangements of membrane lipids. Such structural modifications can trigger series of events enabling the agent to affect the structural integrity of the microbial membrane or translocate to the interior of the microbial cell. Therapeutic use of such agents requires a detailed understanding of the interaction of such antimicrobial agents with bacterial membranes. In spite of considerable effort put in to probe the relationship between secondary structure and mode of antimicrobial action over the past two decades through experiments and simulations, a detailed understanding of the same is yet to be achieved. Furthermore, recent experimental and simulation results suggest that built-in well-defined secondary conformations such as α-helix or β-sheet may not be the essential feature of potent antimicrobial agents, but rather the ability of these agents to acquire amphiphilic conformations, involving the spatial separation of charged and hydrophobic moieties, near the bacterial membrane. It is also of interest to probe how these agents detect and differentiate between mammalian and bacterial membranes. In this talk, I will present our ongoing simulation work in this area and address certain crucial aspects of biomimetic polymers in their action as antimicrobial agents including their ability to acquire functionally relevant structures near membranes with no built-in secondary structure, their ability to detect head-group packing defects in membranes and their unique ability to sequester charged lipids and induce phase separation, eventually leading to possible lysis of cells.

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Mechanism of Insertion, Self-Assembly of Small Double-Mimic Molecules for Selective Disruption of Membranes in a Proposed Antibiotic Action

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Abstract

Emerging antibiotic resistance threatens to take us to the pre-penicillin days. One way of countering this problem is to design drugs that selectively disrupt bacterial membranes, so development of resistance by mutations is not easy. A new class of small cationic molecules which mimic naturally occurring antimicrobial peptides (AMPs) in function and the alkyl chain of membranes in structure have been developed. These double-mimic molecules have the potential to serve as an alternative to the conventional drugs, especially to the antimicrobial peptides, because of the ease of their synthesis. However, the mechanism of action of these molecules is not known, although experiments suggest that the integrity of the bacterial membranes is compromised. While molecular dynamics simulations seem like a possible way to elucidate these mechanisms, sampling biologically interesting phenomena in simulations is a challenge and even AMP-membrane interactions, about which decades old mechanistic hypotheses exist, have not been investigated to atomic level details to date. In this work, we use advanced all-atom molecular dynamics simulations to investigate the interaction between two double mimic molecules, with prototypical bacterial and red blood cell membranes. The simulations demonstrate the interactions of the cationic groups of drug candidates with the head group of the lipid molecules, thinning the membrane, suggesting the possibility of disruption. Interestingly these molecules act by self-assembly. The all atom molecular dynamics highlight how the subtle differences in the charge separations and the length of the alkyl chains lead to a differential activity on anionic bilayers.

Mechanistic Insights into Pleckstrin-Homology Domain (PHD) Activity in Dynamin Mediated Fission

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Abstract

Dynamin, a large multi-domain GTPase, catalyzes membrane fission in a highly regulated manner by oligomerizing into helical collar around the neck of endocytic vesicles. The collar (and the underlying membrane neck) constricts in the presence of GTP and leads to leakage-free fission of the vesicle upon GTP hydrolysis.[1] Classical dynamin associates with the plasma membrane-localized phosphatidylinostol-4,5-biphosphate (PIP2) through the centrally located pleckstrin-homology domain (PHD). However, PHD is known to be a dispensable domain as fission can take place in its absence, as is the case with extant bacterial and mitochondrial dynamins.[2] Nevertheless, the functional role of PHD seems to go beyond that of an adaptor domain as the rate of fission slows down manifold in absence of PHD.[3] Also, the importance of PHD cannot be undermined as mutations in the domain can lead to diseases such as Charcot-Marie-Tooth (CMT) and centronuclear myopathy (CMT).[4,5] In this work, we have combined together advance sampling methods (metadynamics), molecular dynamics based all-atom and coarse-grained simulations, and fission-assay based experiments to explore the molecular basis of the PHD interactions with membranes. We report the molecular-level insights into the possible role of PHDs as catalysts in dynamin-induced membrane fission during synaptic vesicles recycling. Using metadynamics-based free energy calculations, we also extract the docking geometry of PHD with the inositol lipid, identify the participating residues in the membrane association and we suggest mutations in PHD that seem to affect the rate of membrane fission. We validate these predictions through experiments using fission assays.[6] We also find that PHDs make the membrane more pliable for fission as revealed from the undulation spectra calculations. Also, curvature analyses on PHDs bound membranes show a complex local curvature landscape, which can be used to explain the intricate role that PHDs play as fission-favoring motif in the dynamin machinery.

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Mode Coupling Theory Approach to Ionic Conductivity, Rotational Diffusion, and Electrochemical Transport

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Abstract

In certain sense, the dielectric friction based approach to ionic conductivity contained ingredients of mode coupling theory because Onsager's reaction field concept embodies the inherent role of density fluctuations on dielectric friction and ion diffusion. We carry out mode coupling theory analysis, aided by computer simulations, to describe ion-solvent interactions on both translational and rotational diffusions. We use MCT to derive the classical laws of electrochemistry (Debye-Huckel-Onsager, Debye-Falkenhagen and Onsager-Fuoss). Our new expressions provide better agreement, and at the same time serve to modernize classical electrochemistry.

Phonon Thermal Transport in β-Cu_2Se Using an Ab Initio Derived Force Field

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Abstract

An interaction potential model has been developed [1], for the first time, for β-Cu_2Se using *ab initio* derived data. The structure and elastic constants of β-Cu_2Se using the derived force field are within a few percent of density functional theory (DFT) derived structure and elastic constants and reported experimental structure. The derived force field also shows remarkable ability to reproduce the temperature dependent behaviour of the specific heat and thermal expansion coefficient. The thermal structure evolution of the β-Cu_2Se is studied by performing the molecular dynamics (MD) simulations using the derived force field. The simulation results demonstrate that the Cu ions move around the equilibrium lattice position within the temperature range of 500–800 K. However, at a temperature > 800 K, the Cu ions start diffusing within the material, while the Se ions remain in their lattice position. Further we used the DFT and MD simulations to study the thermal transport properties associated with the thermal structure evolution of β-Cu_2Se. Thermal conductivity of β-Cu_2Se is calculated over a temperature range of 400–1000 K using reverse non-equilibrium molecular dynamics simulations [2]. The thermal conductivity calculated using MD simulations decreases monotonically with increasing temperature, which is in line with the reported experimental data. The average phonon mean free path evaluated using the kinetic theory, found to be within the range of 1.0–1.5 Å, decreases with increasing temperature. Furthermore, we have investigated the temperature-dependent heat transport phenomena using phonon density of states, calculated using MD simulations. The phonon modes are found to shift towards low-frequency numbers with increasing temperature, indicating lower heat carrying capacity of the material and in agreement with the computed thermal conductivity.

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Glass Transition in Supercooled Liquids with Medium Range Crystalline Order

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Abstract

Growth of medium range crystalline order (MRCO) has been observed in various model systems to be associated with glassy behaviour. Such observations raise the question about the eventual state reached by a glass former, if allowed to relax for sufficiently long times. Is a slowly growing crystalline order responsible for slow dynamics? Are the molecular mechanisms for glass transition in liquids with and without MRCO the same? If yes, glass formers with MRCO provide a paradigm for understanding glassy behaviour generically. If not, systems with MRCO form a new class of glass forming materials whose molecular mechanism for slow dynamics may be easier to understand in terms of growing crystalline order, and should be approached in that manner, even while they will not provide generic insights. We have performed extensive molecular dynamics simulations of a number of glass forming liquids in two dimensions and shown that the static and dynamic properties of glasses with MRCO are different from other glass forming liquids with no predominant local order. We also resolve an important issue regarding the so-called point-to-set method for determining static length scales, and demonstrate it to be a robust, order agnostic, method for determining static correlation lengths in glass formers.

This work was carried out in collaboration with I. Tah, S. Karmakar, S. Sengupta and S. Sastry.

Determine the Presence of Glassy States in Confined Fluids

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Abstract

We study the state of fluids confined between two surfaces separated by a few molecular diameters of the confined fluid, with the primary focus of ascertaining if the fluid possesses glass-like characteristics. Using a molecular model for octa methyl cyclo tetra siloxane (OMCTS) which has been widely used in surface force experiments, we carry out molecular dynamics simulations for temperatures ranging from 5 to 35 K above the melting point for the OMCTS model used in this study. OMCTS is found to orient with a wide distribution of orientations with respect to the mica surface and the self-intermediate scattering function is found to decay with increasing relaxation times as the surface separation is decreased. The two-step relaxation in the scattering function, a signature of glassy dynamics, distinctly evolves as the temperature is lowered. However, even at 5 K above the melting point, we do not observe any signatures of freezing. Free energy computations reveal that significant sub-cooling is required to observe a freezing transition.

Conformational Features of Amyloid Beta Peptides and their Aggregates in Aqueous Environment

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Abstract

Alzheimer's disease (AD) is a debilitating neurodegenerative disease that has become a major threat to public health[1]. It is widely accepted that extracellular deposition of amyloid beta (Aβ) peptides into toxic soluble oligomers and insoluble fibrils in the brain is primarily responsible for AD[2]. However, a number of recent studies suggest the soluble oligomers to be more neurotoxic than the insoluble fibrils[3]. Hence, of late, attention has been shifted toward characterization of the Aβ peptide monomers and small oligomers formed by them, rather than focusing on the insoluble fibrils to understand the aggregation mechanism.

We have carried out molecular dynamics (MD) simulations to explore the conformational features and hydration characteristics of an ensemble of full-length $A\beta_{42}$ peptide. The calculations revealed fluctuating conformations of the peptide monomers with the formation and breaking of different secondary structural elements. In particular, we notice that the Aβ monomers exhibit propensity to either retain or transform into a helical form toward the N-terminal end and a β-strand-like form near the C-terminal end[4]. Importantly, we identified relatively weakly bound water molecules around the hydrophobic hp1 and hp2 segments of the peptide, which are likely to be displaced easily during the hydrophobic collapse that leads to Aβ aggregation at higher peptide concentrations. Recently, we have also studied the size-dependent (pentamer (O_5) to tetradecamer(O_{14})) structural characteristics and thermodynamic stabilities of $A\beta_{17-42}$ protofilaments.[5] Analysis of the free energy profiles of the aggregates showed that the higher order protofilaments (beyond O_{10}) undergo conformational transitions between two minimum free energy states separated by small barriers, while the smaller ones (O_5 and O_8) remain in single deep minima surrounded by high barriers. It is demonstrated that O_{10} is the crossover point for which the distortion of the protofilament is maximum, beyond which the peptides tend to rearrange themselves in an intermediate state and eventually transform into more stable conformations. Our calculations further revealed simultaneous existence of both highly ordered two-coordinated and randomly oriented three-coordinated water molecules within the spatially heterogeneous confined topology of the protofilament cores[6]. On the basis of our findings, we proposed that simultaneous presence of both types of core water molecules plays equally important roles in controlling the growth and stability of the Aβ aggregates. We have also made attempts to probe the early stages of Aβ aggregation process starting from monomers with varying secondary structural contents[7]. The analysis showed that helix-helix linkage plays an important role in bringing the unstructured segments of the Aβ peptides closer for self-assembly. Importantly, it is demonstrated that the contribution originating from the nonpolar interactions between the peptides and the corresponding nonpolar solvation more than compensate the weakening effect of unfavorable inter-peptide electrostatic interactions, thereby stabilizing the nucleated oligomer.

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Molecular Thermodynamics of Bio-Molecular Signaling and Recognition

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Abstract

Cell signaling involves a fascinatingly complex network of interacting protein molecules, where information might flow through protein-protein interactions or remote signaling within a single protein (allostery). Errors (mutations) in these signaling networks often leads to fatal diseases like cancer, immune disorder etc. Thus it is extremely crucial and challenging to develop an understanding of the molecular mechanism of these signaling processes towards development of potential inhibitors. We have used molecular dynamics simulations in conjunction with energy decomposition analysis to gain valuable molecular insights regarding the thermodynamic basis of such biomolecular signal transduction and recognition.

In this talk, I shall discuss two representative success stories: (i) Nucleotide dependent (GTP/GDP) conformational selection in Rho GTPases and how the water mediated hydrophobic interactions might play a crucial role in effector recognition. (ii) Electrostatic basis of dynamical allostery and signaling pathways in a PDZ domain protein. Allostery without structural changes has often been attributed to dynamics and/or entropic effects. Here we demonstrate that a "population shift" of highly coordinated hydrogen bonds and salt bridges might lead to the allosteric modulation. Thus, dynamical effects are consequences of modification in the underlying energy landscape.

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3. Photo-Processes in Biological Systems – Need for Hybrid QM/MM with Polarization

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Abstract

Photo-processes in biology are fundamental to life itself, e.g., photosynthesis and light harvesting. However, accurate description of such processes is challenging, especially considering the need to depict the complex environment with sufficient accuracy. It requires a large number of degrees of freedom to be described and therefore, become impossible for any ab initio or purely quantum mechanical method. Hybrid quantum mechanical molecular mechanical (QM/MM) methods, that combine the accuracy of quantum mechanical methods and the speed and versatility of molecular mechanical methods, are used for these systems. Effective fragment potential (EFP)[1] is a sophisticated, polarizable and non-empirical molecular mechanical method that is capable of treating the long-range electrostatics and short range non-covalent interactions with sufficient accuracy. On the other hand, these systems are multi-reference in nature, and therefore, multi-reference electronic structure methods, such as spin flip MP2[2] and equation-of-motion coupled cluster or MP2 (EOM-CC or EOM-MP2) need to be used. We have developed hybrid methods based on EFP and EOM-MP2.[3] In this talk, I will present some applications of the hybrid techniques to understand the excited state processes, especially in biological systems.[4]

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Modelling Supramolecular Polymers

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Abstract

Molecules interacting via weak, noncovalent, reversible interactions can aggregate in solution along one or more dimensions to form supramolecular polymers. The mechanism of their self-assembly proceeds via either of two mechanisms: cooperative or isodesmic which can be differentiated through the association constant (K) between the molecules. In the former, K depends on the length of the oligomer while it is independent of the oligomer size for an isodesmic growth. Recent advances in this field have enabled big applications in optoelectronics, solar cells, light harvesting etc. Supramolecular polymerization also aids in our understanding of assemblies in biology.

Atomistic and coarse grained molecular dynamics simulations on chemically specific models enable us to understand the microscopic processes, thermodynamics, structure and dynamics in supramolecular polymerization. Illustrative examples from well-studied systems, Benzene-1,3,5-tricarboxamide (BTA) and perylene bisimides (PBI) will be presented. It is shown that the presence of motifs in the molecule which leads to a long-range interaction along the stacking direction leads to a cooperative growth of the polymer. Furthermore, the application of an external electric field on the liquid crystalline phase of a C3 symmetric supramolecular system exhibits not only a reversal of polarization, but also that of the handedness of the stack.

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Paracetamol Pre-Nucleation in Biocompatible Polymers – Interplay of Topology and Interactions

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Abstract

Heterogeneous nucleation of molecular systems in solution is a grand challenge. The current understanding of heterogeneous nucleation is limited only to simple, model systems like Lennard- Jones particles due to lack of apriori knowledge of reaction coordinates and simulation techniques to explore heterogeneous nucleation of complex molecules in solution. We proposed that direct molecular dynamics simulations techniques could be employed to study the factors that effect aggregation (pre-nucleation) in complex systems and could be correlated with factors that control nucleation. In this direction, we elucidated the role of topology and interactions in the formation of pre-nucleation aggregates of paracetamol in porous, polyethyelene glycol diacrylate (PEGDA) polymers and thin films of cellulose derivatives using direct molecular dynamics simulations techniques [1,2]. The simulation results for probabilities of formation of paracetamol aggregates are consistent with experimentally observed rates of paracetamol nucleation in different polymers. The study of pre-nucleation stages using direct molecular dynamics simulation techniques could provide a faster route to generate libraries of polymers that could be employed to enhance heterogeneous nucleation of paracetamol.

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Effects of Ethanol on an Enzymatic Protein Chymotrypsin Inhibitor 2

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Abstract

Proteins are involved in a wide spectrum of biological activities within organisms. The folded native structure of a protein is highly sensitive towards the nature of solvent under specific environmental conditions. With the change of solvent's physicochemical properties protein's native structure can be disrupted.[1,2] Several proteins interact with membrane surface and the binary mixture of water-alcohol can be a good model system that represents hydrophobic-hydrophilic character of membrane surface.[3] Among various monohydric alcohols, ethanol is widely used as a cosolvent in biology due to its unusual behavior at several concentrations. In this discussion, I shall be concentrating on exploring the behavior of a small enzymatic protein, Chymotrypsin Inhibitor 2 in water-ethanol binary mixtures at several ethanol concentrations and temperatures.[4] Special attentions will be paid to identify the origin of the protein's conformational disorder in water-ethanol mixed solutions.[5,6]

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Design and Characterization of Symmetric Nucleic Acids via Molecular Dynamics Simulations

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Abstract

Molecular dynamics simulations have evolved as a powerful tool to further our understanding of the interactions and processes at the molecular level which otherwise still evades us. Essentially, the rapid advancements in the areas of force field development and computational protocols have incorporated more dynamism in the field of molecular simulations.

To keep myself in alignment with the furtherance of MD, I would like to attend the discussion meeting on "Recent Advances in Molecular Simulations". I am looking forward to attend the lectures of invited speakers about the advances in molecular simulations, force field development and this great learning opportunity would be helpful for me in order to generate numerical solutions to the biomolecular problems.

I would also like to present a poster entitled "Symmetric nucleic acids[1]", wherein we reported design and characterization of some novel symmetric nucleic acids via MD simulations. Besides stimulating academic curiosity, we believe that these symmetric nucleic acids could be of potential synthetic and therapeutic value on par with the peptide nucleic acids which are quite popular.

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Aggregation of Flexible Polyelectrolytes: Phase Diagram and Dynamics

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Abstract

Similarly charged polymers in solution, known as polyelectrolytes, are known to form aggregated structures in the presence of oppositely charged counterions. Understanding the dependence of the equilibrium phases and the dynamics of the process of aggregation on parameters such as backbone flexibility and charge density of such polymers is crucial for insights into various biological processes which involve biological polyelectrolytes such as protein, DNA, etc. Here, we use large-scale coarse-grained molecular dynamics simulations to obtain the phase diagram of the aggregated structures of flexible charged polymers and characterize the morphology of the aggregates as well as the aggregation dynamics, in the presence of trivalent counterions. Three different phases are observed depending on the charge density: no aggregation, a finite bundle phase where multiple small aggregates coexist with a large aggregate and a fully phase separated phase. We show that the flexibility of the polymer backbone causes strong entanglement between charged polymers leading to additional time scales in the aggregation process. Such slowing down of the aggregation dynamics results in the exponent, characterizing the power law decay of the number of aggregates with time, to be dependent on the charge density of the polymers. These results are contrary to those obtained for rigid polyelectrolytes, emphasizing the role of backbone flexibility.

Chemistry and Physics of Two-Dimensional Monolayers: Aluminene and Other Systems

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Abstract

Research in the field of low-dimensional materials is interesting because of various fascinating properties associated with these materials. Two dimensional single atom monolayer structures are made up of purely one kind of atom and these materials exhibit many novel properties which differ much from their bulk counterparts, as has been seen in case of graphene. We have predicted one such material, based on aluminium atom, namely, aluminene. The properties of this material have been compared with those of graphene. Another novel set of structures based on group IV-VI atoms which is expected to behave like phospherene has been predicted by us recently. In this presentation, we discuss the chemistry and physics of these systems as to why these may be interesting from fundamental and application points of view.

Molecular Dynamics Simulations of Colloids in Confinement

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Abstract

Confined fluids can exhibit substantially different properties from their bulk counter-parts. Recently it has been shown that for a fluid in a slit geometry, the dynamics of the confined and unconfined degrees of freedom decouple under strong confinement. We have carried out molecular dynamics simulations of colloids confined by parallel walls. As the confinement becomes stronger, a diverging time scale emerges which marks the 3D to 2D crossover. The scaling behavior and density dependence of this time scale will be discussed.

Optical Charge Transfer Transitions in Proteins Arising from Charged Amino Acids: New Label Free Spectroscopic Markers to Probe Protein Structure and Dynamics

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Abstract

The absorption of light by proteins induces charge transfer (CT) transitions in the UV-visible wavelength range of the electromagnetic spectrum. Well known examples of chromophores which exhibit CT transitions include metal-ligand complexes and the protein backbone. In this talk I will introduce recently discovered optical CT transitions in proteins arising from amino acids with charged side-chains (Lys, Glu, Arg, Asp, and doubly protonated His) and post translationally phophorylated amino acids (Ser, Thr and Tyr). Results from time dependent density functional theory calculations coupled with classical molecular dynamics simulations show that all charged amino acids present a directed electronic donor-bridge-acceptor paradigm with facile photoinduced charge separations. The new CT transitions are highly sensitive to the interactions among charged sidechains imposed by protein tertiary fold and to the dynamics and solvation of the chromophore. In fact, the environment of the charged chromophores can modulate the spectral range of these transitions to produce protein UV-Visible absorption between 200-800 nm. These results open up a new optical window to study prominent proteins of biomedical relevance which are rich in charged amino acids.

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Charge Transport in Molecular Systems

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Abstract

Understanding charge transport in various molecular systems is of fundamental interest in rapidly growing field of molecular electronics. The mechanism of the charge transport in molecular systems is very much system specific. Depending on the size, shape and the arrangement of different moieties in the molecule the mechanism varies from diffusive to completely ballistic in nature. In this talk, I will describe the transport of charge in a variety of molecular systems like discotic liquid crystals, dsDNA and Dendrimer melt. We show that thermally activated hopping mechanism as described in the framework of Marcus-Hush formalism is adequate to describe the charge transport in these systems. We employ multiscale modelling technique combining molecular dynamics simulation, quantum mechanical calculation and kinetic Monte Carlo simulation to get the charge carrier mobility in these systems.

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