Development and application of advanced potentials and QM/MM methods

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Computational simulations to investigate condensed and biological systems have become commonplace. In most cases, the potentials involved make substantial approximations, especially for the non–bonded interactions. We have contributed to the development of the multipolar/polarizable AMOEBA force field and developed a novel force field, called the Gaussian Electrostatic Model (GEM), that employs explicit molecular charge densities. We will present results for the development and application of AMOEBA for water and imidazolium-based ionic liquids using a parametrization paradigm based on Quantum Mechanics, as well as results for an initial water model termed GEM*. We have also developed a new QM/MM package called LICHEM that enables the use of these advanced potentials providing for a significantly more accurate description of the classical environment. This package also includes a new method based on the minimum image convention and a novel smoothing function (QM/MM–LREC) that provides a straightforward way to include long–range electrostatic effects in QM/MM. We will present the latest capabilities of LICHEM including implementation of chain–of–replica methods for path simulations, and the extension of QM/MM–LREC for multipolar/polarizable QM/MM simulations.

Molecular Simulations on Biological Systems

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Biological systems are sets of molecules from living organisms whose astounding properties have been developed by eons of evolution. These characteristics include not only high affinity for their natural ligands but also strong selectivity; also, regulation of their functions, efficient catalysis and addressing their proper folding to the functional conformation. Molecular simulations on these systems have attempted during more than three decades, with the aim to identify the molecular basis of their biological function and also to predict the effect of mutations or modifications in their structure or the changes required to appropriate tuning of their function. Three main difficulties have arisen from them: their huge number of atoms, the delicate balance between attractive and repulsive interactions among their parts, and the solvent and entropic effects. In the recent years the technological improvement has produced both unbelievable computing power, and also trillions of bites of biological data. In this talk a comparison between those progresses will be compared and discussed. Also, other computational challenges from the biological ambit will be discussed in terms of their molecular representation and simulation focusing on whole genome analysis, omics sciences, drug design, stability prediction, and medical purposes.

“Free energy of the Square-Well fluid by Singular Value Decomposition”

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The thermodynamics of Square-Well fluids of variable range has been a subject of interest for decades. The free-energy of these systems is nowadays known from molecular simulations by various authors, following the high-temperature perturbation theory of Barker and Henderson. Nevertheless, appropriate analytic expressions to the terms in the perturbation expansion, which are functions of density and temperature, have not been found previously. Here, we propose a procedure, based on the technique of Singular Value Decomposition, that renders separate components depending on density and temperature, and which admits a simple rendering in terms of orthonormal polynomials. The whole interval of SW ranges is covered, from those very short to the van der Waals limit. The method should be useful in other 2-variable problems of statistical thermodynamics.

Applications of Coarse-Grained Molecular Modeling

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In many materials and biomolecular systems, the problems of interest span time and/or length scales that make traditional all-atom approaches challenging. Coarse-grained (CG) models, where each site represents a collection of atomic or molecular units, have emerged as a valuable alternative to accelerate progress on these challenging problems. In this presentation, I will discuss examples from our group where we have applied CG modeling and advanced sampling techniques to address problems in lipid membranes and DNA. In the case lipid membranes, we show how the cooperative dynamics of lipid molecules naturally give rise to transient clusters of highly mobile and immobile regions of the membrane. We discuss the potential role of such dynamic heterogeneity for biological processes and the potential formation of lipid raft structures. In the case of DNA, we examine the ability of a three-site-per-nucleotide model to mimic the experimentally measured properties of four-way junction DNA, which plays a central role in genetic recombination and DNA repair. If time allows, we will also discuss a more extreme coarse-grained model for DNA that can be used to predict the phase diagram of nanoparticle lattices, where the lattice structure is dictated by DNA linkages between nanoparticles.

"Phase behavior of Langmuir monolayers with ionic molecular heads"

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ABSTRACT

We have carried out Monte Carlo simulations of a Langmuir monolayer coarse-grained molecular model. Taking into account that the hydrophilic groups can be ionized by modulating acid-base interactions, we have studied the phase behavior of a molecular model that incorporates the short-range steric and long-range ionic interactions. The simulations were carried out in the temperature range where there is a competition of these interactions. Different order parameters were calculated and analyzed for several values of the reduced surface pressure and temperature. For most of the surface pressures two directions of molecular tilt were found: (i) towards the nearest neighbor (NN) at low temperatures and (ii) towards next-nearest neighbors (NNN) at higher temperatures. We also found the coexistence of the NN and NNN at intermediate temperatures and high surface pressure values. A low-temperature reentrant disorder-order-disorder transition in the positions of the molecular heads and in the tails collective tilt was found for all the surface pressure values. It was also encountered that the molecular tails arranged forming “rotating patterns” at intermediate temperatures and at intermediate surface pressures. We estimated the monolayer’s surface pressure versus temperature and the temperature versus area per molecule phase diagrams. It was found that the Liquid Expanded (LE) ↔ Liquid Condensed (LC) phase transition shifts to smaller temperatures when the molecular heads carry an ion, in qualitative agreement with experimental observations of fatty acid monolayers with ionic head groups. Two surface pressure versus area per molecule isotherms were also calculated. One at low temperatures near the LC-NN ↔ LC-NNN transitions and the other at higher temperatures close to the LE ↔ LC transitions. From these isotherms the monolayer’s area compression modulus was obtained and its variation ranges in the LE and LC phases were found to be consistent with the experimental values.

Reactive Monte Carlo Method to study sorption of gases in solid surfaces.

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The reactive Monte Carlo (RxMC) method has been proposed to describe the sorption of gases in solid materials. Due to the possibility to work chemical reactions in this method, not only it is possible to study physisorption but also chemisorption of fluids in solid substrates. In particular we investigate gas sorption in three different solid structures, FCC, simple cubic and disordered arrays. In each case two different models were used to simulate the particles of the solid; the first model considered rigid particles whereas in the second one the particles were allowed to vibrate around their equilibrium positions. It was observed that sorption always enhanced with the last model and it was used to explain the unusual behavior of actual experiments of CO2 in lithium ceramics.

Molecular Simulation: a tool in Computational Biology applications.

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Biomolecules perform important functions in living organisms such as energy storage, building cell structures, or metabolizing nutrients. In order to function, biomolecules display a conformational dynamics often at different time scales, and yet modulated by the cellular environment. Hence, Molecular Simulation methods emerge as a strategy to decipher the structure fluctuations potentially linked to the biological function. In this work we present selected results from molecular dynamics trajectories of proteins and peptides in a membrane environment. Thus stressing the potential applications of these techniques in advancing our understanding of the cellular processes.

From Monte Carlo methods to drug discovery

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Molecular mechanics (MM) simulations have become crucial to understand biophysical and biochemical processes. In these simulations, an accurate generation of the ensemble is essential to ensure valid estimations of the system properties. Traditionally, Molecular dynamics (MD) have become the main algorithm to explore the conformational space in molecular systems. In contrast, as MD is expensive computationally speaking, different Monte Carlo (MC) approaches have been developed to speed up the conformational sampling producing equivalent ensembles. This talk will be focused on the description of two MC algorithms (PELE[1,2] and MCPRO[3]) which have been successfully applied to study the protein-ligand binding process.

PELE is a heuristic algorithm that combines a MC stochastic approach with structural prediction techniques for fast mapping of molecular biophysics. It is capable of accurately reproducing long time scale processes in only a few hours of CPU. It has been used to study ligand migration, protein/NA conformational sampling and ligand binding process. Recently, PELE has been successfully applied to estimates absolute binding free energies through Markov State Models.[4] On the other hand, MCPRO performs statistical mechanics simulations in NPT and NVT ensembles performing small and localized MC perturbations. MCPRO is mostly applied for estimation of relative and absolute binding free energies using free energy perturbation theory.

The talk will cover different examples were both algorithms have been successfully applied showing the main capabilities.

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Phase Behavior of Lollipop-Shaped Hard Particles in Two Dimensions

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Moderate differences in the molecular details may produce noticeable changes in the symmetry of the resulting phase behavior. Characteristics such chirality, polarity, anisotropy keeping bounded the molecular volume seem to generate phases having different n-fold symmetries. In this work, a comparison of two quite similar hard two-dimensional toy models is presented. Both models are geometrically polar and have almost the same anisotropy but one of the does not have chiral characteristic. The lack of molecular chirality of the model presented here has lollipop shape, seems to provide more routes of molecular self-assembly, resulting in tetratic and triatic phase behavior. The model used to compare with, has chiral structure reported in [Armas-Perez et al., Phys. Rev. E 83, 051709 (2011)], only develops nematic and smectic features. Using an isobaric and isochoric Monte Carlo simulations we support the conclusions. To characterize the phases founded, n-fold order parameters such as the nematic, tetratic as well as their correlations.

Molecular modeling of carbon dioxide hydrates: comparison of different approaches

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Remarkable research efforts have been performed concerning the analysis of hydrates and organic clathrates using different theoretical approaches such as molecular equations of state, molecular simulations including both Molecular Dynamics and Monte Carlo techniques, and different ab initio Quantum Mechanics approaches[1-3]. In this work, CO_2 type I hydrates have been studied using Molecular Dynamics, electronic Density Functional Theory (DFT) and the Quantum Theory of Atoms in Molecules (QTAIM). First, the CO_2 hydrate three phase equilibrium line has been estimated using different existing rigid non polarizable molecular models and the direct coexistence Molecular Dynamics technique. Then, the energetic interactions between guest and host molecules have been evaluated from a different perspective, using DFT, allowing to evaluate the limitations of the hypothesis usually admitted within the thermodynamic modeling of gas hydrates. Several mechanisms for transport of guest molecules inside hydrates have been proposed so far in literature, and previous results have pointed out the apparent imposibility of some guests passing directly through faces connecting adjacent cages without destroying the water structure. Both types of cells included in the structure of type I hydrate were modeled as isolated double semi-flexible atomic systems. Interaction potentials of guest molecules with the enclathrating cell, when moving between neighbour cells were calculated using B3LYP/6-311+g(d,p) DFT approximation. The obtained results show that direct transitions are feasible through hexagonal and pentagonal faces without compromising the overall structure integrity in opposition to other results previously reported in literature. This stability has been explored using the QTAIM theory and reveals that even in the case that some bond may break during the transition, all of them are recovered because the face distorsion is absorbed locally by the hydrogen bond network. This technique allows also to determine the guest preferential orientations inside the hydrate cell, and in this case the usually neglected interaction among guests plays a key role to reproduce in detail available experimental results. The validity of the theory level selected has been stated, and the high anisotropy of the guest-cell interaction potential for the molecules analysed is shown, which may be considered in the formulation of hydrate thermodynamic models as equations of state, and also for the description of transport properties.

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