Large-Scale, Quantum-based Non-Adiabatic Molecular Dynamics Simulation of Materials in Extreme Conditions

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Extreme environments may involve conditions of high dynamic or static pressure (>30MPa), high strain, and high-strain rates (> 1km/s); low or high temperature (> 1200°C); highly corrosive or erosive conditions; high-radiation fluxes (> 100dpa); and high intensity electromagnetic fields (> 15T), alone or in combination. Developing materials that can operate reliably in such environments is critical to enabling technologies required for the next-generation of energy, spatial, transportation, medical, and military systems and devices, among many others. But major breakthroughs are required in theory, computation and experiments to elucidate the chemical, atomic and molecular, processes that occur within the bulk and at the surfaces of materials subjected to extreme operating conditions. Studying these states of matter through experimental observations has proven to be extremely challenging, if not impossible, primarily because they are hard to isolate and their time scales for changes are too rapid (<1 ps).

Consequently, synergistic approaches from theory and computation have taken center stage in enabling predictive calculations capable of steering experiments and material synthesis associated to extreme conditions. Yet, first-principles quantum mechanics simulation methods are inadequate for accurately describing the effects of thermal, mechanical, chemical or radiative excitations that may occur in materials operating under extreme conditions, or are impractical to use, except for very small systems (<100 atoms) over short timescales (10ps); including time-dependent Density Functional Theory or TDDFT. Furthermore, in the regime of a large number of electronic excitations, the electronic portion of the wavefunction contains contributions from many stationary states, and the Born-Oppenheimer approximation breaks down quickly. Therefore, a proper model capable of capturing and tracking the inherent processes would require describing non-adiabatic coupled electronic and nuclear motions for systems with 10's-100's eV excitations over long enough periods of time (>>ps).

With this in mind, we developed the electron Force Field method (Su et al, 2007) and demonstrated it is iso-efficiently scalable to millions of atoms (and electrons) over 10's of ns timescales (Jaramillo-Botero et al, 2011) on massively parallel processing architectures. In eFF, the electrons are defined explicitly as self- and pairwise-interacting particles via potentials derived from quantum mechanics and classical electrostatics, and their motions are propagated independently, making it possible to go beyond adiabatic dynamics. Unlike other fermionic molecular dynamics methods, our approach achieves a balanced description of both ground- state condensed systems and highly excited systems containing ionized electrons. eFF is uniquely suited to simulate the dynamics of materials in which many electronically excited states of matter can occur and coexist, and overcomes salient limitations of quantum mechanics methods.

We have successfully demonstrated its use in describing the thermodynamics of dense hydrogen over 0 to 100,000 K; the real-time dynamics of Auger fragmentation of diamond nanoparticles over fs ranges; electron stopping potentials in bulk materials; the dynamics of cascaded valence electron ionizations in shocked materials (e.g. polyethylene, silicon carbide and hydrocarbon molecules) during hypervelocity impact; and the electronic emissions during high strain rate brittle fracture of silicon; among others.

Yet, eFF is limited to low-Z elements of the periodic table (Z<6) and the simplicity of its Gaussian basis formulation has several limitations, including 1) the omission of the true electron exchange between same spin electrons, and 2) the lack of cusp conditions and nodal structures, which complicates scaling to higher Z's. This leads to incorrect descriptions for double and triple bonds, lone pairs, and aromatic pi electron systems. To address these problems rigorously, we have now developed the Gaussian Hartree Approximated (GHA) kernel within the eFF concept (Jaramillo-Botero, Xiao et al 2015). GHA incorporates formal energy penalties for singlet and triplet pairs and angular momentum projected effective core pseudo-potentials that account for cusp conditions and missing nodal structures.

I will present the underlying theory behind the new kernel and demonstrate its application on open challenges.

Rational Design of Multifunctional Antioxidants

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Abstract

Details on a strategy for computationally designing multifunctional antioxidants is presented. It comprises two stages. The first one involves non-electronic calculations, based on structure-activity relationships. In this stage several parameters are estimated to predict if the designed compounds fulfill the Lipinski's and Ghose's rules for orally active drugs, as well as the Veber criteria. In addition, the potential toxicity of the compounds is evaluated, as well as their synthetic accessibility. Details on the computational tools used for such estimations are provided. The second stage involves electronic calculations, within the frame of the density functional theory. In this stage, the radical-trapping (primary, or type I) and preventive (secondary, or type II) antioxidant capacity is predicted based on thermochemical and kinetic calculations, following the QM-ORSA (quantum mechanics based test for overall free radical scavenging activity) protocol.[1] Details on how to perform such calculations, including environmental effects such as the pH and the diffusion are provided. As an example of application, the rational design of some melatonin derivatives intended to be multifunctional antioxidants, and better to that purpose than the parent molecule, is presented.[2]

1. Annia Galano, Juan Raúl Alvarez-Idaboy "A Computational Methodology for Accurate Predictions of Rate Constants in Solution: Application to the Assessment of Primary Antioxidant Activity" *J. Comput. Chem*. **2013**, *34*, 2430–2445.

2. Annia Galano "Computational-Aided Design of Melatonin Analogues with Outstanding Multifunctional Antioxidant Capacity" *RSC Adv.* **2016**, *6*, 22951–22963.

Incomplete capsid formation: coarse-grained and elastic modeling

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We study the formation of stable incomplete capsids self-assembled from capsomers in solution by means of coarse-grained simulations and an elastic model. We show that during self-assembly, the favorable capsomer-capsomer binding energy competes with the unfavorable stresses generated by the rim of the caps and the elastic stretching due to the spontaneous curvature of the capsid. As a result of that competition, ribbon-shaped and incomplete capsids may emerge as stable structures on very specific conditions. We analyze the conditions required for this process to occur and the influence of the presence of an adsorbing surface in in vitro self-assembly.

A microcanonical-ensemble computer simulation method for discrete potential fluids

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Numerical simulations on statistical systems are usually performed in the canonical (NVT), Gibbs (NPT) or the Grand canonical (μVT) ensemble. On this talk an alternative Monte Carlo simulation method in the microcanonical (NVE) ensemble applied to Square-Well (SW) fluids is presented. The method can evaluate the inverse temperature as a function of the energy measuring the transition rates probabilities between macroscopic states. The main advantage of this method with respect to conventional methods (that control the temperature) is that in a single run one can cover a continuous range of temperatures. Applications of the method to obtain thermodynamic properties and the Helmhlotz free-energy high-temperature expansion coefficients are shown.

The Birth and Growth of Salt Crystals: Insights from Molecular Dynamics Simulations

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Molecular dynamics simulations are used to investigate the factors that influence the nucleation of salt crystals in supersaturated aqueous solution. Two salts, NaCl and LiF, will be considered. We describe a methodology for detecting solid-like clusters and following their evolution in time until they achieve nucleation or dissolve back into solution. Through an analysis of cluster lifetimes and multiple nucleation events, we demonstrate that for NaCl cluster size is not the only property that influences cluster stability and the probability of achieving nucleation. We define a parameter called the cluster crystallinity, which is a measure of the solid-like order of a particular cluster. We demonstrate that the cluster order has a strong influence on the lifetime and nucleation probability of clusters of equal size, with the lifetime and probability of nucleation increasing with increasing crystallinity. These observations remain true for clusters as small as six ions indicating that the structural factors are important even at the very earliest stages of crystal birth. For LiF, we show that ion solvation has a dominate influence on the rates of crystal nucleation and growth.

Programmable Matter

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An answer to these questions:

What is programmable matter?
What is the relation of auto-assemble with programmable matter?
What is the state of the art of programmable matter and auto-assemble?
What is the future of programmable matter and auto-assemble?

is attempted through examples of work done in our laboratory and also work performed by other authors.

Study of interactions between LPS-derivatives and the dimeric TLR4/MD-2 receptor complex by Molecular Dynamics simulations

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Abstract

Septic shock is a health problem of unknown and underestimated incidence in Mexico. Despite this, it is a prevalent health problem with severe social, occupational and economic implications. Fortunately, sepsis is a rare clinical complication for patients. But, once developed, it shows an extremely unfavorable prognostic aspect with mortal outcome of highest probability. The purpose of this research is to study the interactions of septic agent lipopolysaccharides (LPS) and derivatives with their biomolecular targets: the TLR4/MD-2 receptor complex by means of Molecular Dynamics (MD) simulations and other computational technics. Particularly, the phosphate group interactions of LPS and derivatives, and the binding site electrostatic properties are studied. Elucidating the action mechanism of this kind of ligands is fundamental to develop new drugs for sepsis treatment, because actually there in not a specific therapy. Previous to the MD analysis, a docking study has been carried out between lipid IVa (L4a), a LPS precursor which has dual species-dependent activity, and the TLR4/MD-2 complex receptor in a triangular place inside the complex called the "*Wedge*" for its three interaction interfaces. In the *Wedge* the amino acid residues interacting with phosphate groups of LPS or derivatives, have been mapped for three mammalian species (human, mouse, horse). Through MD, the positional preference of phosphate groups within the *Wedge* were tracked. The phosphate anions are known as the signaling functional groups. So their interaction with certain amino acids directly triggers the biological activity of LPS or its derivatives, which can lead to sepsis in an intercellular biochemical pathway. The results about the phosphate positional preferences obtained by MD were phosphate group interaction potential maps and the *Wedge* electrostatic properties analysis, they show that the species-specificity assumption for the phosphate groups is not correct. It showed a random-determined behavior, no related with the amino acid sequence species supported by a net charge analysis of the *Wedge*. The species-dependent effects of LPS-like molecules is due to other unknown factors not considered in this work, probably bulk steric effects. The acylation state of LPS-like ligands could be also an aspect to consider in the future. By the other hand, the MD simulation times were large in comparison with other studies, however it seems that larger periods of time are necessary. It is save to say that the dynamical behavior of the phosphates cannot reflect the reported activity for all species during 100 ns of simulation time, the phosphate anion did not show a realistic site preference under the influence of the other phosphate. It means that longer observation times are necessary or the MD technique could be combined with other methods to accelerate the dynamics of the system.

Determination of Free Energy Reaction Pathways Using Imidazolium Ionic Liquids as Catalysts by Molecular Simulations.

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Abstract

Ionic Liquids (ILs) are composed of opposite charge ions, but unlike common salt such as *sodium chloride*, ILs are in a liquid state at temperatures below 100 °C, even below 25 °C. [1] Applications of ILs include their use as *catalysts* in chemical reactions such as alkylation, [2] Diels-Alder, [3] KEMP elimination, [4] nucleophilic substitution (S_N2), [5] among others. [6] The understanding of molecular and atomic interactions between the reactants, transitions states and products allows the *design of* ILs as catalysts, in order to improve reaction yields and selectivities for specific chemical reactions. Molecular simulation provides an alternative for the elucidation of free energy reaction pathways in conjunction with simulation techniques such as the *Nudged Elastic Band* [7] (NEB), *umbrella sampling* [8] (US), and *Weighted Histogram Analysis Method* [9] in order to evaluate the performance of ILs as catalysts

The Free Energy reaction pathways for a couple of chemical reactions in the presence of ILs as catalysts, such as the KEMP elimination reaction [4] shown Figure 1, and an S_N2 Fluorination reaction, [5] were calculated in this work.

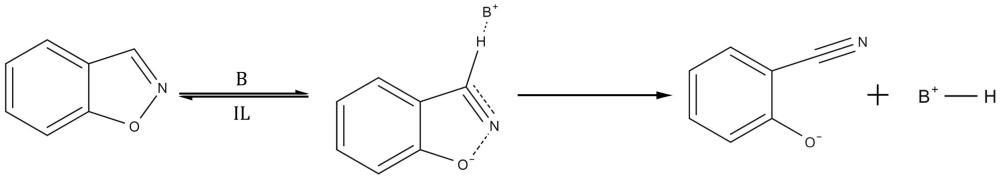

Figure 1. KEMP elimination reaction. *Benzisoxazole* reacts with an *amine* (B) to generate a transition state characterized by its semi-opened-ring and an *amine-hydrogen* interaction. [4]

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Surfactant molecules to promote removal of cadmium ions from solid surfaces: A complementary experimental-simulational study

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Abstract

Due to its high toxicity heavy metals are a global problematic of high concern. Sodium dodecyl sulfate (SDS) was used to interact with cadmium ions to demonstrate the efficiency of surfactant molecules to promote desorption from solid surfaces. Scanning electron and atomic force microscopy were employed to study desorption of cadmium ions from highly oriented pyrolytic graphite (HOPG), as a model to understand the removal of metallic ions from carbon substrates. Contact angle measurements were carried out to investigate the wettability behavior of the surfactant on the contaminated surface. The desorption mechanism from a microscopic level was studied by using molecular dynamic simulations. Density profiles, pair correlation functions and diffusion coefficients were analyzed to determine the cadmiumsurface interaction in the presence of surfactant molecules to improve ion detachment. Simulations showed that surfactant molecules moved in between the adsorbed cadmium ions and the graphite surface pushing up the metallic groups to improve metal desorption. The experimental and simulational results agree with atomic absorption spectroscopy results.

Keywords

Cadmium desorption by surfactants, Microscopic techniques, Contact angle, Molecular dynamics simulations

Interfacial Properties of Simple Fluids

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Nowadays, molecular simulation is a fundamental tool to calculate the thermodynamics properties (coexistence curve, surface tension, critical points, among others) of model systems. Calculating the thermodynamic properties of molecular systems from model potentials is one of the main aims of statistical mechanics. For that reason, model potentials (square well, Yukawa, Mie, Sutherland, and triangle well potentials) have been widely used to represent real systems. This has been done through different simulation techniques as well as theoretical approaches. Since early works, pairwise additive potentials have been helpful to understand the experimental behavior and to reproduce thermodynamic properties of real systems. Therefore, in this talk we will give a small review of the thermodynamics properties of model systems that have been made recently by our group.

New platform for the design and manufacture of patient-centric pharmaceuticals

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It has long been known that giving the same medication to multiple individuals does not have the same effect on each one. For the last six decades, pharmacotherapy has been based on subjecting every individual patient to the same dosing regimen, while the different degree of therapy success among them has been regarded as an expected “fact of life.” However, biomedical advances in the last twenty years have made revealed the underlying reasons for, and made it possible to objectively assess, the variability in therapy response among individuals. These developments have triggered the era of Patient-Centric and Personalized Medicine, which poses a game-changing challenge to pharmaceutical manufacturing. Simply put, existing pharmaceutical manufacturing methods were not conceived, nor are suitable for tailor-made therapy, that is, pharmaceuticals customized to the needs of specific group of patients or individuals.

We present a new platform for the design and manufacture of oral dosage forms (*pills*), developed to satisfy the patient-tailored (or subpopulation-tailored) requirements of personalized medicine. The approach is a paradigm shift, whereby pills are conceived as Integrated Systems, rather than as traditional compacts of powder blends. The new dosage forms (“3D Pills”) are assembled in modular form from prefabricated components, where each component performs a specific pharmaceutical function. The 3D Pills are assembled as 3D stacks of the prefabricated components in a fashion analogous to the manufacture of 3D Integrated Circuits. Each prefabricated component is a polymer composite wafer, whose particular function in the assembly is determined by the type of material embedded with the polymer (active pharmaceutical ingredient, solubilizer, disintegrant, absorption enhancer, pH modifier, ID/anti-counterfeiting element, etc.). The Integrated Systems approach to manufacturing makes it comparatively (to traditional manufacturing) a simple task to add or refine performance attributes of the pill, and/or quality related attributes to the dosage form by incorporation of additional/different functional composite wafers. The 3D Pill concept is patient-centered, such that precise dose adjustment, as well as drug release characteristics, can be achieved within the same platform, in order to meet the therapy requirements of the individual patient. The Integrated Systems approach to pharmaceutical manufacturing is suitable for just-in-time (JIT) manufacturing for individual patients, and scalable to (larger) patient sub-populations of indeterminate size.

Coarse-grained force field from multi saccharides to model polysaccharides

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- Florian Müller-Plathe (Technical University of Darmstadt)

Abstract

Natural polysaccharides are composed of basic pieces similar to a LEGO set with only a few different pieces; therefore, mainly all biological polysaccharides can be obtained with different combinations of these building blocks. Polysaccharides are compounds made up of many units of monosaccharides, dealing with a few and up to thousands of them. Glycosidic bonds that can be broken by hydrolysis link these units. These natural polymers derived from aldose or ketose via a condensation reaction.

To provide a structural base for the different biological roles that carbohydrates play, it is indispensable to be able to determine precisely the dynamic, thermodynamic and spatial properties of saccharides. This task is generally conducted using various different experimental techniques, such as X-ray, crystallography, and spectroscopy, to mention a few. This is complemented with studies made with Molecular Simulation and Computational Chemistry Modelling.

There are a few force fields that had been developed, specifically for carbohydrates that take into account atomistic interactions. However, for very large molecules, such as the case of polymers, these force fields are inefficient and require long simulation times to manage such interactions. Here is where “coarse grain” models come into play, by maintaining the essence of the most relevant interactions, the model is simplified by making a “map”, with the consequent reduction in calculation time.

Our goal is to obtain a new (more compact) force field through atomistic molecular dynamics simulations, using the CHARMM36 force field for mono, di, and oligosaccharides, together with the iterative Boltzmann inversion (IBI) method, to be able to describe with precision the behaviour of all the biological polysaccharides.

Boltzmann inversion (BI) in mostly used for bonded interaction, such as bonds, angles and torsion, it is structure-based, and for that, it only requires positions of atoms. The IBI is a natural extension of the BI method. Since the objective of the coarse-grained model is to reproduce the distribution functions of the reference system as accurately as possible, one can also iteratively refine the coarse-grained potentials using a numerical method. IBI can be used to refine both bonded and non-bonded interactions.

The first step is to obtain the atomistic simulation results. For that, we had been running simulations of several monosaccharides (pentoses and hexoses, presenting both, α and β configuration) at room pressure and temperature, using several molar concentrations. The chosen monosaccharides include several features of the configurations, such as rings of five or six atoms (furanoses and pyranoses). The nine disaccharides include the different kinds of glycoside linkage, and finally, a few oligosaccharides were also included in this set. The molecular dynamics simulations were running using the GROMACS package. From that we are analysis the obtained results using some GROMACS tools and getting radial distribution functions in order to do the mapping to obtain the coarse-grained model.

We have chosen two different ways to construct the coarse-grained model, using two and four beads, grouping the atoms of the sugar rings indifferent configurations. We are using the VOTCA project software to apply the IBI and IB techniques.