SoCal TheoChem

October 14, 2023
UCLA

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SoCalTheoChem - 6

Technical Program

8:30 am Arrival. Registration.

<u>Morning</u>

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Presiding: Harry Morgan
</div>

9:00 – 9:10 am   Anastassia and Ben - Introductory remarks

9:10 – 9:40 am   Francesco Paesani (UCSD)
　　　　　　　　　"Advancing Molecular Simulations with Data-Driven Many-Body Potentials"

9:40 – 10:10 am   Giulia Palermo (UC Riverside)
　　　　　　　　　"Dynamics and mechanisms of CRISPR-Cas9 through the lens of computational methods"

10:10 – 10:40 am   Shaul Mukamel (UC Irvine)
　　　　　"Ultrafast Elementary Molecular Events and Conical Intersections Monitored by X-ray Pulses, Quantum Light, and Optical Cavities"

10:40 – 11:00 am   *Coffee Break*

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Presiding: Nadine Bradbury
</div>

11:00 – 11:30 am   Maosheng Miao (California State University Northridge)
　　　　　　　　　"Quasi-atom Chemistry"

11:30– 12:00 pm   Joel Yuen-Zhou (UCSD)
　　　　　　　　　"Efficient quantum dynamics simulations of molecular polaritons"

12:00 – 1:00 pm   *Lunch*

12:30 – 2:30 pm   **Poster Session**

<u>Afternoon</u>

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Presiding: Huiling Shao
</div>

2:30 – 3:00 pm   Kendall Houk (UCLA)
　　　　　　　　　"Computational Exploration of Pericyclic Reactions"

3:00 – 3:30 pm   Zhen-Gang Wang (Caltech)
　　　　　　　　　"Origin of the Entropic Driving Force in Polyelectrolyte Complex Coacervation"

3:30 – 3:50 pm   *Coffee Break*

<div align="right">

Presiding: Will Laderer
</div>

3:50 – 4:20 pm   Jaime Marian (UCLA)
　　　　　　　　　"Synchronous parallel kinetic Monte Carlo for continuum diffusion-reaction systems"

4:20 – 4:35 pm   William R. Borrelli (UCLA)
　　　　　　　　　"Solvation Entropy Calculations for Different Models of the Hydrated Electron"

4:35 – 4:50 pm   Shobhit S. Chaturvedi (UCLA)
　　　　　　　　　"Directed Evolution Optimizes Electric Field in Protoglobin for Non-Native Catalysis"

4:50 – 5:05 pm   Pawel Wojcik (USC)
　　　　　　　　　"Chemical complexity as a resource in laser cooled polyatomic molecules"

Meeting Adjourn

Talks:

Advancing Molecular Simulations with Data-Driven Many-Body Potentials

Francesco Paesani
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Molecular simulations are instrumental in gaining detailed insights into the properties of complex systems, from biomolecules to materials. At the heart of these simulations is the potential energy function (PEF), which maps out the multi-dimensional energy landscape of the system in question. The accuracy of the PEF is crucial, as it dictates the realism and, consequently, the predictive power of any simulation. In principle, correlated wave function (WF) methods, such as coupled cluster with single, double, and perturbative triple excitations, i.e., CCSD(T), can provide an accurate description of molecular interactions from isolated molecules to condensed-phase systems. However, their computational cost limits their applications to systems with only a few tens of atoms. Conversely, conventional force fields (FFs) grounded in empirical parameterizations exhibit limited accuracy and lack predictive power, approximating molecular interactions with simplistic models based on harmonic potentials and classical Coulomb interactions. In this presentation, I will describe our data-driven many-body energy (MB-nrg) formalism,[1-6] which, exploiting the locality of quantum mechanics, bridges the gap between WF methods and FFs, paving the way for realistic computer simulations from the gas to the condensed phase.[7-11] MB-nrg seamlessly integrates data-driven machine-learned representations of individual many-body interactions with physics-based many-body models, all derived from CCSD(T) data. I will illustrate the accuracy, transferability, and predictive power of our MB-nrg potentials for various aqueous systems across different thermodynamic states and in different environments.[12-26]

Dynamics and mechanisms of CRISPR-Cas9 through the lens of computational methods

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The clustered regularly interspaced short palindromic repeat (CRISPR) genome-editing revolution established the beginning of a new era in life sciences. I will review the role of state-of-the-art computations in the CRISPR-Cas9 revolution, from the early refinement of cryo-EM data to enhanced simulations of large-scale conformational transitions. Molecular simulations reported a mechanism for RNA binding and the formation of a catalytically competent Cas9 enzyme, in agreement with subsequent structural studies. Inspired by single-molecule experiments, molecular dynamics offered a rationale for the onset of off-target effects, while graph theory unveiled the allosteric regulation. Finally, the use of a mixed quantum-classical approach established the catalytic mechanism of DNA cleavage. Overall, molecular simulations have been instrumental in understanding the dynamics and mechanism of CRISPR-Cas9, contributing to understanding function, catalysis, allostery, and specificity.

Ultrafast Elementary Molecular Events and Conical Intersections Monitored by X-ray Pulses, Quantum Light, and Optical Cavities

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Novel X-ray pulse sources from free-electron lasers and high-harmonic generation setups enable the monitoring of molecular events on unprecedented temporal, spatial and energetic scales. The attosecond duration of X-ray pulses, their large bandwidth over a large tunable energy range, and the atomic selectivity of core X-ray excitations offer a uniquely high spatial and temporal selectivity for non-linear spectroscopies. In this talk, we survey recent theoretical developments that design, simulate, and predict X ray spectroscopic signals revealing detailed information about the ultrafast passage through conical intersections. We show how the Orbital Angular Momentum of twisted X-ray light can be leveraged to detect coherences and time evolving chirality emerging at conical intersections due to the bifurcation of molecular wavepackets. Employing quantum light in nonlinear molecular spectroscopy has brought many novel opportunities to enhance the resolution and the selectivity of transition pathways. We will show how photoelectron signals generated by time-energy entangled photon pairs can monitor ultrafast excited state dynamics of molecules with high joint spectral and temporal resolutions, not subjected to the Fourier uncertainty limitation of classical light. This technique scales linearly with the pump intensity, allowing the study of fragile biological samples with low photon fluxes. Optical cavities provide another means for controlling the photochemistry and photophysics of molecules by making use of strong light–matter coupling without employing strong external laser pulses. We present a quantum dynamical study of charge migration in molecules by coupling to an optical cavity, which can activate and enhance targeted charge migration modes that are originally inactivated or suppressed in the bare molecule.

Quasi-atom Chemistry

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Even though quantum mechanics methods such as DFT can reproduce and predict most of the structures and properties of solid-state compounds, they do not provide a complete framework of concepts that can understand the mechanism of all phenomena. For example, why do the structures of elemental metals show an intricate pattern across the periodic table, and why do they undergo complex transitions on compression?[1] Also, why do the structures of many ionic compounds deviate from standard theory, e.g., KCl is stable in rocksalt instead of CsCl structure as predicted by Pauling's rule?[2] The systematic deviations from current bond theory and structural rules indicate that *some key features and concepts of solid-state have been missing*. This problem hinders the design of novel materials and the development of efficient machine learning models, as they strongly rely on the completeness of concept-based atom and bond descriptors, such as radii, ionization energies, or electron affiliations. Our recent work suggests that the presence of quasi-atoms is a very general phenomenon that happens in many metals under both zero and finite pressures.[3,4] In this framework, many *metals, especially the alkali and alkaline earth metals and early transition metals, should be viewed as chemical compounds consisting of both metal atoms and quasi-atoms.* This is not a simple shift of perspective because it leads to the explanations of many puzzles, such as the structure preference of elemental metals at ambient conditions and under high pressure,[3] the formation of high-pressure electrides,[4,5] and superconducting superhydrides,[6] intermetallic compounds, and two-dimensional and quasi-one-dimensional materials.

Efficient quantum dynamics simulations of molecular polaritons

Joel Yuen-Zhou
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The solution to the many-body quantum dynamics problem involving $N \gg 1$ molecules coupled to an optical cavity is discussed. A brute force simulation demands an exponential scaling $O(e^N)$ on

the computational resources needed to account for the electronic, nuclear, and photonic degrees of freedom. Permutational symmetries reduce the algorithmic scaling to polynomial $O(N^m)$ where m is the size of the vibrational basis. However, deploying a new trick that we have developed (which we term Collective dynamics Using Truncated-Equations, CUT-E), we dramatically reduce the problem to N-independent scaling. Molecular disorder does not modify this scaling. Examples are provided to demonstrate the practicality of these simulations and the physical intuition they provide.

Computational Exploration of Pericyclic Reactions
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Recent studies in our lab have focused on cycloaddition transition states for reactions of triene and tetraene cycloaddends. These higher order cycloadditions often involve ambimodal transition states that lead to two or more products. My group has explored many of these with DFT and molecular dynamics, and in part one of my talk, I will describe these results in detail. In part two, I will describe the exploration of a variety of pericyclic reactions, especially electrocyclizations. Woodward and Hoffmann outlined a strict set of rules about electrocyclizations: reactions involving 4n electrons are conrotatory, and 4n+2 are disrotatory. We have discovered that polar substituents can make these rules inoperative such that normal steric and torsional effects control stereoselectivity.[4] Predictions are made of reactions of this type. In part three, the role of pericyclic reactions in Nature is discussed. With Yi Tang, we have identified a class of enzymes known as "pericyclases."[5,6] Our recent computational studies on these enzyme-catalyzed pericyclic reactions will be described.

Origin of the Entropic Driving Force in Polyelectrolyte Complex Coacervation
Zhen-Gang Wang
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Mixing two solutions of oppositely charged polyelectrolytes under appropriate conditions results in a liquid–liquid phase separation into a polymer-rich coacervate phase and a coexisting polymer-poor supernatant phase. This polyelectrolyte complex coacervation (PCC) has received considerable attention in recent years due to its relevance to membraneless organelles in biology, and applications in biomedical and biomimetic systems. The complexation of oppositely charged polymers has been widely believed to be driven by the entropy gain due to counterion release. In this talk, we show that a large portion of the entropy change is due to solvent (water) reorganization, which we can extract by exploiting the temperature dependence of the dielectric constant. For weakly-to-moderately charged systems under common conditions (monovalent ions, room temperature in aqueous solvent), the solvent reorganization entropy, rather than the counterion release entropy, is the primary entropy contribution. We use this framework to examine the two elementary stages in the symmetric PCC—the complexation between a polycation and polyanion, and the subsequent condensation of the polycation–polyanion pairs by computing the potential of mean-force (PMF) using molecular dynamics simulation. From the calculated PMF, we find that the supernatant phase consists predominantly of polyion pairs with vanishingly small concentration of bare polyelectrolytes, and we provide an estimate of the spinodal of the supernatant phase. Finally, we show that prior to contact, two neutral polyion pairs weakly attract each other by mutually induced polarization, providing the initial driving force for the fusion of the pairs.

Synchronous parallel kinetic Monte Carlo for continuum diffusion-reaction systems
Jaime Marian
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The kinetic Monte Carlo (kMC) method is one of the most popular models to simulate species dynamics in chemo-physical systems, with applications in materials science, population dynamics, finance, weather predictions, etc. KMC provides stochastic realizations of the chemical master equation by sampling the physical coefficient matrix with exact probabilities and evolving a system in time through the probabilistic selection and execution of 'events'. However, the kMC method is notoriously difficult to parallelize, which has prevented the computational physics community from taking advantage of scalability in exascale computing platforms and architectures based on graphic processing units. Here we present a suite of parallel algorithms for kMC simulations formulated on the basis of perfect time synchronicity. Synchronicity is achieved by recourse to so-called 'null' events, which provide the mathematical flexibility to avoid causality errors in subdomain evolution. These algorithms are intended as a generalizations of the standard *n*-fold kMC method, and are easily implemented in parallel architectures. These methods are controlled approximations, in the sense that the errors incurred by ignoring boundary conflicts can be quantified intrinsically, during the course of a simulation, and decreased arbitrarily (controlled) by modifying a few problem-dependent simulation parameters. We apply the model to the simulation of general reaction-diffusion systems and scale-dependent critical exponents in billion-atom 3D Ising systems.

Solvation Entropy Calculations for Different Models of the Hydrated Electron

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The solvation entropy of small ions in solution is directly connected to their solvation structure and chemical behavior. Indeed, the sign of the solvation entropy provides a great deal of information about how ions structure the surrounding waters: ions with negative solvation entropies, known as kosmotropes, have highly-oriented, tight first solvation shells, while more hydrophobic ions with positive solvation entropies, known as chaotropes, tend to have water make hydrogen bonds around the ion. Bartels and Han [*J. Phys. Chem.* **1991**, 95, 5367] have shown that the hydrated electron has a large positive solvation entropy, making it a champion chaotrope for small ions in aqueous solution; this finding thus provides strong indirect information about the electron's solvation structure. Despite this experimental observation, there has been no effort to examine the solvation entropies of different simulation models of the hydrated electron. Such a comparison is especially important given that most simulations yield a hydrated electron with a strongly structured first solvation shell reminiscent of kosmotropic ions, suggesting that such simulations are producing an incorrect hydration structure. In this work, we use free-energy perturbation to calculate the solvation entropy of the hydrated electron for a series of common simulation models. We show that only a model with a 'soft' cavity can correctly predict the sign and magnitude of the hydrated electron's experimental solvation entropy; traditional cavity models predict solvation entropies that are off from experiment by over a factor of two, and other models yield an incorrect sign for the solvation entropy. We also examine other measures of the hydrated electron's solvation structure and kosmotropic/chaotropic character, such as ion pairing and water orientational relaxation dynamics, to provide the most detailed comparison of experiment to simulation.

Directed Evolution Optimizes Electric Field in Protoglobin for Non-Native Catalysis

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Protoglobin, a member of the globin family featuring heme, has emerged as a promising candidate for engineering catalysis in non-native reactions. Recent efforts in directed evolution have successfully modified Protoglobin to catalyze carbene transfer reactions using diazirines as carbene precursors. This study investigates whether directed evolution optimizes the electric field within Protoglobin to facilitate carbene transfer reaction. Utilizing dynamic trajectories from five replica molecular dynamics simulations of the wild-type (WT) Protoglobin and four directed evolution variants (LVRQ, LVRQL, GLVRSQL, and GLAVRSQLL), we conducted an extensive analysis of the 3D heterogeneous electric field. By combining this electric field analysis with quantum mechanics/molecular mechanics (QM/MM) reaction mechanism calculations, our study elucidates the impact of directed evolution on Protoglobin. Specifically, we reveal that, in tandem with stabilizing the substrate within the active site, directed evolution modifies the enzyme's electric field to promote the desired carbene transfer reaction. These findings underscore the pivotal role of electric field optimization in the enzyme scaffolds for engineering non-native reactions in enzymes.

Chemical complexity as a resource in laser cooled polyatomic molecules

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Laser cooling of molecules is a field that is largely established thanks to the concept of an optical cycling center (OCC); a functional group that allows scattering of photons off a molecule without heating up the molecule's internal degrees of freedom. The presence of an OCC in a molecule is also advantageous for applications of laser-cooled molecules, out of which the most popular are: tests of fundamental physics, construction of quantum information processing devices, or experiments on quantum state controlled chemistry.[1-5]

Since the first demonstration of the molecular laser cooling in 2010, there has been a constant progress in the field, with laser cooling of three- and six-atomic molecule achieved in 2017 and 2020, respectively.[6,7,8] The concept of a molecule functionalized with an OCC is actively explored theoretically and realized experimentally leading to many valuable lessons in design and use of such molecules.[9-15]

As the advances in the field allow for laser cooling of ever larger molecules, a new opportunity arises, a chance for leveraging the chemical complexity of the laser cooled molecules to a resource. I will present a theoretical exploration of this avenue with a focus on the molecular ability to exhibit isomerism. The idea will be presented with a use of a model photo-switch molecule: azobenzene functionalized with the CaO- as an OCC.

Posters:

1. Chemical templates that assemble the metal superhydrides

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The recent discoveries of metal superhydrides provide a new route to room-temperature superconductors.[1-4] However, their structure trends and the chemical driving force needed to dissociate H_2 and form H covalent network cannot be explained by direct metal-hydrogen bonds. Here, we show that the understanding of superhydrides formation needs a perspective beyond the traditional chemical bonds. By analyzing high-throughput calculation results of metals across the periodic table and in various lattices, we show that, after removing H, the remaining metal lattices exhibit large electron occupations of the nonatomic interstitial orbitals, which matches excellently to H lattices and their wavefunctions like a template.[5] Furthermore, H lattices consist of 3D aromatic building units that are greatly stabilized by chemical templates of metals near the $s-d$ border. This

theory can naturally explain the stability and structure trends of superhydrides and greatly enhance the efficiency of predicting new materials, such as two-metal superhydrides.

2. Abnormal behavior of Cs polyoxides and core reaction under high pressure

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High pressure has the potential to significantly facilitate the transformation of materials. As pressure increases, it can alter both the strength of chemical bonds and the oxidation states of atoms within a compound.[1] This modulation of pressure has been responsible for several discoveries of unconventional structures recently. A natural question then emerges: how are a material's properties affected when both its chemical bonds and atomic orbitals change under increasing pressure? To address this, both density functional theory alongside a crystal structure search method were used to analyze the behavior of Cs polyoxides under varying pressure levels. The results reveal a shift in the chemistry of the system via the activation of Cs 5sp core electrons.[2] Contrary to many other polyoxide systems where increased pressure can stabilize them,[3,4] the O–O bonds within Cs polyoxides are observed to break apart. This results in molecules and layered structures bonded through Cs–O covalent interactions. The observation of the CsO peroxide system was the most striking example. While this compound remains stable under standard atmospheric conditions, it undergoes a transition at a pressure of 221 GPa to form the aforementioned covalent interactions. This pressure-induced change is within the range of current high-pressure experimental techniques, allowing the potential for real-world experimental testing

3. Accelerating Crystal Structure Prediction via a Hybrid Many Body Interaction Methodology

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Predicting crystal polymorphism, that is the ability for molecular crystals to achieve different packing motifs, requires accurate treatment of a wide array of intra- and intermolecular interactions[1]. While high cost methods, such as CCSD(T) can accurately capture these forces, the computational cost of using such methodology remains prohibitive[2]. Fragment methods, such as the hybrid many body interaction (HMBI) method, which allow for low cost refinement of QM and MM structures[1], is of particular interest for accelerating the process of crystal structure prediction (CSP). By leveraging these refinements, as well as utilizing further refinements with density correction (dc) of the electron density[3], a fast, computationally inexpensive screening method can be constructed. Presented is this dc-HMBI methodology which quickly, approximately 50 times faster than a high cost DFT method, such as B86bPBE-XDM, ranks candidate MM structures generated at the start of a CSP search, and aims to screen this down from $\sim 10^3$ structures to $\sim 10^2$ structures, allowing for an acceleration of the overall CSP process.

4. Structural and electronic properties of borophene and BC3 over H-diamond (100)

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Diamond, an ultra-wide bandgap semiconductor, is being developed for robust transistors. Its interactions with 2D materials, like borophene and BC3, are of interest due to their unique properties [2-3]. Borophene, featuring a hexagonal boron lattice, was synthesized in 2015, and BC3, a stable

monolayer of boron and carbon, exhibits exceptional crystalline qualities [2,3]. However, the dynamics of their interactions with diamond(100) to form 2D heterostructures is still unknown. This research aims to understand the structural and electronic characteristics of hydrogen-terminated diamond(100) when combined with borophene and BC3.

In this study, we utilized the Density Functional Theory (DFT) method, implemented using the GPAW software package and the Atomic Simulation Environment (ASE). To calculate electronic properties, we employed the PBE exchange-correlation functional with the Tkatchenko-Scheffler van der Waals correction [4,5]. Calculations employed a finite difference (FD) approach with a 0.1791 Å grid spacing and a 5x10x1 k-point mesh. The analysis primarily examined 2D layers on hydrogen-terminated diamond (100) surfaces, investigating and superimposing both borophene and BC3 onto the H-diamond(100) surface.

A lattice mismatch exists between the 2D materials and H-diamond(100). Strain was introduced to H-diamond(100) in the x- and y-directions, yielding two scenarios: unstrained H-diamond(100) and strained H-diamond(100). For the borophene overlayer case, H-diamond(100) underwent 1.075% x-direction and 16.826% y-direction strain. For the BC3 overlayer case, a 5% x-direction strain on H-diamond(100) to address lattice mismatch. Analyzing lattice mismatch prompted independent scans to find optimal positions and identifying the lowest energy configuration. Once scans were completed, local minima were relaxed fully. Band structure analysis revealed properties of borophene and BC3, with h-BN comparisons for validation.

In the case of Borophene, strained H-diamond(100) showed a 2.223 Å van der Waals gap without an apparent band gap. Unstrained H-diamond(100) exhibited a 2.371 Å van der Waals gap for Borophene, again without an apparent band gap. Like graphene, borophene exhibits semi-metallic traits and strain-induced rippling on H-diamond (100) surface. For BC3, unstrained H-diamond(100) displayed a 2.549 Å van der Waals gap and a 0.018 eV bandgap. With a 5% strain in the H-diamond(100) configuration, the van der Waals gap widened to 2.586 Å, accompanied by an absence of a bandgap. Prior BC3 research revealed a present band gap of ~0.7eV, which vanishes on diamond. Notably, BC3 cases consistently show a small bandgap resembling h-BN behavior, implying tunable, semiconducting properties.

5. Design Principles for Molecular Qubits

Claire Dickerson, Barry Li, Guozhu Zhu, Ashley Shin, Changling Zhao, Eric Hudson, Wesley Campbell, Justin Caram, Anastassia Alexandrova
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Electronic excitations, induced by lasers, that decay directly to the initial electronic ground state are called optical cycling transitions. These transitions are used in quantum information and precision measurement for state initialization and readout. In this poster, we develop various design rules from chemical principles for ultranarrow molecular electronic transitions of large molecules, from organic to lanthanide inorganic complexes. We use various theoretical techniques, from DFT to ab initio multireference methods, to correctly predict these transitions to match experiment.

6. Organic radicals as optically-addressable molecular qubits

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Spin polarisation by optical pumping allows for qubit state preparation and is important to quantum computation. Current state-of-the-art implementations use solid-state spin defects, in particular nitrogen-vacancy (NV) centres[1]. In recent years, there has been growing interest in bottom-up molecular design of such qubit platforms, which offers higher tunability and better scalability, but thus far only organometallic molecular complexes have successfully produced optical-spin interfaces as robust as NV centres[2]. In this work, we propose a new theoretical design for a fully organic molecule capable of both qubit initialisation and readout via visible light. The open-shell nature of NV centres is recreated with organic biradicals and optical addressability can be achieved via photoluminescence. Our system provides a metal-free alternative to existing molecular colour centres and is experimentally feasible in light of recent reports of luminescent organic diradicals being synthesized[3].

7. Electronic structure of lanthanide molecular complexes with applications as single-molecule magnets and molecular spin qubits: A DFT study

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Strong spin-orbit coupling and large magnetic moments in f-block elements make them promising candidates for room-temperature quantum technological applications. F-block molecular complexes hold promise for advancing next-generation hard disk drives and serving as molecular spin qubits in quantum computation technologies. Through the chemical reduction of M^{3+} (where M represents rare-earth and actinide elements) in particular ligand environments involving cyclopentadienyl ligands, stable divalent complexes have been isolated. These contain the first examples of the formal +2 oxidation states for the rare-earth metals Y, Pr, Gd, Tb, Ho, Er, and Lu and for the actinides U and Th. Density functional theory (DFT) calculations and experimental characterizations have previously revealed that the novel divalent lanthanide complexes of $[(C_5H_4SiMe_3)_3Ln]^-$ adopt unconventional $4f^n5d^1$ electronic configurations[1] rather than the expected $4f^n$. The involvement of 5d orbitals in Ln^{2+} complexes could enhance their optical and magnetic properties.

In pursuit of novel divalent lanthanide molecular compounds, we employed DFT calculations with scalar-relativistic pseudopotentials to predict the electronic structures, structural parameters, and optical and magnetic properties of monometallic rare-earth neutral metallocenes. Hyperfine coupling constants (HFC) and g-tensors of lanthanocene complexes were also computed using all-electron calculations and the scalar relativistic exact two-component (X2C-SR) and spin-orbit two-component (X2C-SO) DFT approaches. As the ligand environment significantly influences the relative energies of the 5d/4f orbitals in lanthanide complexes, DFT-based assessment of Ln^{2+} electronic configurations become essential to elucidate their bonding and determine magnetic properties[3]. Simulated electronic and EPR spectra further validate these electronic configuration assignments. Notably, Lu and Ho molecular complexes display the most pronounced isotropic HFC among the lanthanocene complexes, suggesting large clock transitions akin to those in tris(aryloxide) $Lu(OAr^*)_3$ ($OAr^* = 2,6\ Ad_2\text{-}4\text{-}^tBu\text{-}C_6H_2O$, where Ad = adamantyl compound)[2].

8. Computationally Exploring the Photochemistry of a Model Brown Carbon Chromophore

Hayden Harkins[1], Celine Diep[1], Ruby Neisser[2], John Davis[2], Megan Alfieri[2], Daniel Tabor[3], Nathanael Kidwell[2], Andrew Petit[1]
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This research is working towards a better understanding of the photochemistry of brown carbon chromophores (BrCCs), and how they impact our climate. BrCCs are carbon-based, conjugated, molecules that exist in aerosol particles. They absorb ultraviolet and visible light, which impacts the radiative balance of our atmosphere. The absorption of the light can also lead to photochemistry which impacts the chemical composition and aging of aerosol particles.

In this study we focus on the model BrCC 2-phenylpyrrole (2PhyPyr). We first use high-level theory to map out the excited state potential energy surface(s) along the torsional coordinate. This allowed for the computational modeling of the electronic absorption spectrum of 2PhyPyr. The experimental spectrum abruptly terminates. We speculate that this reflects photolysis of the N-H bond. We are currently using CASSCF and NEVPT2 to map out the pathways for N-H photolysis. In the future, we aim to understand how micro-solvation affects this photochemistry.

9. First-principles prediction of wavelength-dependent product quantum yields of a second-generation molecular nanomotor

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Synthetic light-driven motors have promising potential for biomedical applications due to their temporal and spatial control. Applications include light-induced drug delivery[1] and the permeabilization of biological membranes.[2] Nanomotors are comprised of a polycyclic rotator and stator connected by a carbon-carbon double bond that isomerizes upon light irradiation, producing a rotary motion.[3]
To optimize functionality of nanomotors, it is necessary to gain a detailed understanding of the mechanism of action on an atomic level. To this end, we study the dynamics of the photoinduced Z-E isomerization of a light-driven, second-generation molecular nanomotor.[3] We use non-adiabatic molecular dynamics based on time-dependent density functional theory (TDDFT)[4] to predict the wavelength-dependent product quantum yields of Z-E isomerization. Using replica exchange molecular dynamics (REMD)[5] we obtain four different ground state conformers, labeled as aMsE, sMsE, aPuE and sPuE. From the ground state ensemble of structures, 375 were chosen for excited state non-adiabatic dynamics. The wavelength dependent product quantum yield was obtained by dividing the absorption spectrum averaged over the initial structures of the successful trajectories by the average absorption spectrum of the initial structures of all trajectories.[6,7]
Spectra were computed using TDDFT as well as second-order approximate coupled cluster theory (CC2).

10. Exploring the Mechanism of the Electronic Quenching of NO ($A^2\Sigma^+$) with

CH$_4$ and CO$_2$

Aerial Bridgers and Andrew S. Petit (Research Advisor)
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As a reactive atmospheric pollutant, NO has the potential to interact with other molecules in unique ways. The method of experimental detection, laser-induced fluorescence (LIF), measures NO along its $A^2\Sigma^+\leftarrow X^2\Pi$ transition band. Electronic quenching of NO ($A^2\Sigma^+$) through interaction with other molecules provides alternate photochemical pathways that fluorescence must compete with. Based on previous experimental studies, the electronic quenching cross section of the NO ($A^2\Sigma^+$)+CH$_4$ system is <0.001 Å^2 at 296 K and the NO ($A^2\Sigma^+$)+CO$_2$ system is 68.3 Å^2 at 294 K. This indicates that at a fairly significant level, electronic quenching is occurring for the CO$_2$ system, but is occurring at an almost negligible rate for the CH$_4$ system. Though extensive studies have been conducted for the ground state complex of the CH$_4$ system, which is seen to be C$_s$ symmetry due to the Jahn-Teller effect, only few experimental studies have been done on the excited state complex, leaving the geometry relatively unknown. For the CO$_2$ system, Burgos Paci et al.'s experimental study displayed results that confirmed the system's capability of electronic quenching due to the emission of vibrationally hot NO (X ^{2}P) in a range of vibrational states and the emission of CO$_2$ in its asymmetric stretching mode. However, no theoretical nor experimental studies have been conducted on the specific photochemical pathways that this quenching is occurring on.

In order to explore potential pathways for electronic quenching of both the NO ($A^2\Sigma^+$)+CH$_4$ and NO ($A^2\Sigma^+$)+CO$_2$ system, the long-range interactions and conical intersections are explored through the mapping of potential energy surfaces (PESs). The PESs are calculated at the EOM-EA-CCSD/d-aug-cc-pVTZ//EOM-EA-CCSD/aug-cc-pVDZ level of theory. This method is utilized in order to treat the valence, Rydberg electronic states, and open-shell character of NO in a balanced manner. While exploration of the NO ($A^2\Sigma^+$)+CH$_4$ system displayed that there is no obvious pathway to electronic quenching, as expected due to the very small quenching cross-section, it did yield favored C$_{3v}$ geometric confirmations for the excited state complex. For the NO ($A^2\Sigma^+$)+CO$_2$ system, long range interactions between N of NO and O of CO$_2$ are shown to be attractive, and further exploration demonstrates that this attraction increases as the distance between the molecules decreases. As the distance decreases, electronic density shifts from NO to CO$_2$, which is known as the harpoon mechanism. CO$_2$ is shown to transition from its typical linear confirmation into a bent confirmation as a result. The pathway from this linear to bent confirmation are demonstrated, along with an energetically downhill pathway to a conical intersection. Furthermore, reactive electronic quenching is explored. This work can potentially inform future velocity-map imaging experiments on the NO ($A^2\Sigma^+$)+CO$_2$ system.

11. Quantum theory of surface lattice resonances

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The in-plane interference of plasmonic nanoparticles arranged in one- or two-dimensional lattices can give rise to high-Q diffractive modes known as surface lattice resonances (SLRs)[1]. While these resonances and their wider applications have been extensively studied within classical electrodynamical treatments, a theory capable of treating the linear or nonlinear propagation of quantum light through these structures, e.g., in the presence of additional molecular emitters coupled to the lattice, is largely missing. To this end, we consider an array of metal nanoparticles coupled to the background electromagnetic field and derive the quantum input-output relations in frequency domain in the dipole approximation [2]. As a first application, we illustrate the applicability of our

formalism to molecular optomechanics and show how the high-Q factors provided by SLRs can be harnessed to achieve vibrational strong coupling (VSC) with a collective molecular vibrational mode coupled to the array. Finally, as a second application, we consider a scenario where the metallic nanoparticles are exchanged with three-level molecular quantum emitters and show the nonlinearity of the emitters can be used to switch the SLR condition between different electronic states.

12. A tale of C–H vibrational frequency shifts

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The vibrational frequency of a C–H (or its deuterated form C–D) single bond can be used as a reporter of local chemical environments. However, the physical origins leading to the red or blue shifts in the C–H stretch frequencies still remain elusive and are sometimes misinterpreted in literature. Here I will demonstrate how quantum chemistry calculations can be employed to unravel the distinct origins of C–H frequency shifts in different chemical compounds via 3 examples. I will start with an investigation of the C–H frequency shifts in the gas-phase H-bonded complexes formed between the fluoroform (CF_3H) molecule and a series of Lewis bases, for which the competition between Pauli repulsion and charge transfer effects determines whether the C–H frequency is blue- or red-shifted in a given complex.[1] I will then discuss the vibrational solvatochromism of two compounds: (i) *N*-cyclohexylformamide (with the aldehyde H deuterated) and (ii) 1-hexyne, whose C–D/C–H frequencies blue- and red-shift, respectively, as the solvent polarity increases. Using electronic structure calculations combined with molecular dynamics sampling, we demonstrated that the C–D blue shift in compound (i) can be explained under the framework of vibrational Stark effect and turns out to be a secondary effect of the substantial solvent electric field stabilizing the adjacent C=O bond.[2] In contrast, the substantial red shifts in 1-hexyne's C–H frequency in oxygen-containing solvents (e.g., DMSO) cannot be fully attributed to vibrational Stark effect, and we identified that charge transfer from those solvents (serving as Lewis bases) to alkyne's C–H bond plays a major role in inducing the large red shifts.[3] These examples show that the shifts in C–H stretch frequencies may arise from various physical origins and thus case-by-case investigation would be needed. The computational tools that we developed to investigate the vibrational frequency shifts in the gas or condensed phase will also be discussed. [4,5]

13. The Auger spectrum of benzene: Insights into the molecular-orbital framework

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X-ray based spectroscopies are used to probe the electronic structure of atoms and molecules. X-ray absorption creates electron vacancies in the core shell, leaving the molecule in a highly excited state. Such molecules with core vacancies predominantly decay via Auger process when comprised of light atoms. Auger decay is an autoionization process in which a valence electron fills the core hole and liberates sufficient energy to eject another electron to the ionization continuum. The theoretical modeling of Auger decay is challenging owing to the metastable nature of core-ionized (regular decay) or core-excited (resonant decay) states and the continuum nature of the ejected electron. One of the recent theoretical approaches for computing Auger decay rates is based on Feshbach-Fano resonance theory combined with the equation-of-motion coupled-cluster (EOM-CC) framework [1, 2]. In our study, we use this approach to compute the Auger spectrum of the benzene molecule. The theoretical modeling of the Auger spectrum of benzene is difficult owing to its high symmetry and multiple core orbitals. Our theoretical spectrum can reproduce the main features of the experimental spectrum and

shows the configuration mixing of decay channels. Our calculations also provide insights into the contribution of individual core-orbitals and decay channels to the Auger spectrum.

In the Feshbach-Fano approach, all the information about Auger decay from bound domain can be obtained from two-body Dyson functions. The two-body Dyson amplitudes connect the initial core-ionized or core-excited state with the final doubly or singly ionized valence states. Hence, an orbital picture analogous to the already existing Dyson orbitals (relevant for photoionization), or natural transition orbitals (relevant for absorption) is extremely beneficial for better understanding [3]. Therefore, we developed an algorithm to obtain the most compact form of two-boy Dyson amplitudes using singular value decomposition. We obtain the core holes, and valence holes after factorization using SVD. Thereby, we obtain an orbital picture of Auger decay derived from two-body Dyson amplitudes.

14. X-ray and Optical circular dichroism as local and global ultrafast chiral probes of [12] helicene racemization

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Chirality is a fundamental molecular property that plays a crucial role in biophysics and drug design. Optical Circular Dichroism (OCD) is a well-established chiral spectroscopic probe in the UV-visible regime. Chirality is most commonly associated with a localized chiral center. However, some compounds such as helicenes are chiral due to their screw-like global structure. In these highly conjugated systems, some electric and magnetic allowed transitions are distributed across the entire molecule and OCD thus probes the global molecular chirality. Recent advances of X-ray sources, in particular the control of their polarization and spatial profiles, are enabling X-ray Circular Dichroism (XCD), which in contrast to OCD, can exploit the localized and element-specific nature of X-ray electronic transitions. XCD therefore is more sensitive to local structures and the chirality probed with it can be referred to as local. During the racemization of helicene, between opposite helical structures, the screw handedness can flip locally, making the molecule globally achiral while retaining a local handedness. Here, we use the racemization mechanism of [12]helicene as a model to assess the capabilities of OCD and XCD as time-dependent probes for global and local chiralities, respectively. Our simulations demonstrate that XCD provides an excellent spectroscopic probe for the time-dependent local chirality of molecules.

15. Probing Vibronic Coherences and Aromaticity in Photoexcited Cyclooctatetraene with X-ray Spectroscopy

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Conical intersection (CI) dynamics and changes in aromaticity play a pivotal role in the exploration and control of photo-reactions in aromatic ring molecules. Real-time monitoring of their relaxation pathways remains a formidable experimental challenge. In this study, we simulate the photoinduced

non-adiabatic dynamics from S_3 to S_1 of cyclooctatetraene (COT), which involves multiple CIs, using ab initio multiple cloning dynamics within a multiconfigurational Ehrenfest framework. The calculated relaxation times show excellent agreement with experimental results[1].

We directly investigate the CI passages in COT using off-resonant X-ray Raman spectroscopy (TRUECARS) and time-resolved X-ray diffraction (TRXD). These techniques sensitively monitor the emergence of vibronic coherence and geometric conformation changes during the ultrafast dynamics. Firstly, we distinguish between two CIs using TRUECARS signals, which appear at different Raman shifts. Secondly, TRXD, where X-ray photons scatter off electron densities, allows us to resolve ultrafast changes in the aromaticity of COT. It can further distinguish between planar and non-planar geometries explored during the dynamics, e.g. two different tetraradical-type CIs. The knowledge gained from these measurements provides unique insights into fundamental chemical properties that dynamically change during non-adiabatic passages.

16. Predicting the photomechanical response of organic molecular crystals using first principles methods

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Photomechanical molecular crystals utilize photochemical reactions to convert light into mechanical work. There is a body of research into the creation and abilities of these crystals, but little research has been able to predict the effects of photochrome structure and crystal structure to the photomechanical response. Molecular modification is the method typically used to alter the photomechanical response; however, this process requires much trial and error. Predicting the photomechanical response *a priori* is of great interest, and computational methodologies can bridge this gap. Recently, a topochemical replacement methodology has been created that can predict *in silico* the photomechanical response of crystals. Utilizing periodic density functional theory (DFT), the product crystal can be predicted using the monomer crystal structure by replacing the reactant monomers with the reacted dimer pair topochemically. This method correctly predicted the experimentally known solid-state reacted dimer (SSRD) of 9-methyl anthracene (9MA) from first principles and helped to solve the SSRD crystal structure for 9-tertbutyl anthracene ester (9TBAE)[1]. Additionally, the maximum work densities can be predicted using the change in the unit cells, along with the predicted stress calculated from DFT.

The impact of polymorphism on photomechanical is still not yet known. Diarylethene (DAE) is a popular ring-opening/ring-closing photochrome that can undergo a reverse reaction utilizing a different wavelength of light. The photomechanical products of two DAE species were predicted utilizing the topochemical approach[2]. An order of magnitude variance (17-200 MJ/m^3) in maximum work densities is predicted, with the largest densities occurring in crystals that have large anisotropic expansions. Crystals that have smaller or more isotropic deformations yield lower maximum work densities. This work has revealed the key role polymorphism plays in photomechanical response, signifying the importance of crystal engineering.

While DAE helped to reveal the role polymorphism plays, the role of molecular modifications has yet to be explored. To determine the effects of halogenation on photochromes, the photomechanical responses of ten 9-anthracene (9AC) crystals with varying levels of halogenation were predicted[3]. Unlike DAE, the crystal packing motifs of these ten crystals are similar, allowing for comparison of the molecular modifications. The maximum work densities range from 15-70 MJ/m^3, again with the anisotropic deformations generating the largest work densities. The variance in photomechanical response from molecular modifications is smaller than the variance found in changing the packing

motif. Molecular engineering can be a useful tool to increase the maximum work density of a crystal but should be a secondary tool along with crystal engineering.

17. Change in Anti-Aromaticity Determines Photobasicity

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Photobases are molecules that become more basic in the excited state compared to the ground state. 5-aminoquinoline is one such example in which its K_b is 1.99 x 10^{-9} and its K_b^* is 15.9, indicating 11 orders of magnitude increase upon electronic excitation.[1] Both experimental and computational studies have quantified how excitation affects the thermodynamic driving force for excited state protonation. Previous work has hypothesized that the mechanism for photobasisity involves the transfer of charge onto a ring nitrogen atom.[2] However, the magnitude of this charge transfer is small. Recently, Judy Wu and co-workers explored aromatic photoacids and found that when excited, they become strongly anti-aromatic.[3] Excited-state deprotonation then relieves this anti-aromaticity, making the molecule more stable. This work employed the Nucleus Independent Chemical Shift (NICS) method. Here, we use NICS to explore the role of anti-aromaticity in photobases. We demonstrate that photobasicity strength is related to the relief of anti-aromaticity in the excited state. Overall, our work shines a new light on the underlying physical cause of photobasicity and has the potential to lead to the development of novel light-driven reactions and photocatalysts that employ photobases.

18. Intramolecular Hydrogen Bonding Enables a Zwitterionic Mechanism for Macrocyclic Peptide Formation: Computational Mechanistic Studies of CyClick Chemistry

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Macrocyclic peptides have become increasingly important in the pharmaceutical industry. We present a detailed computational investigation of the reaction mechanism of the recently developed "CyClick" chemistry to selectively form imidazolidinone cyclic peptides from linear peptide aldehydes, without using catalysts or directing groups (Angew. Chem. Int. Ed. 2019, 58, 19073--19080). We conducted computational mechanistic to investigate the effects of intramolecular hydrogen bonds (IMHBs) in promoting a kinetically facile zwitterionic mechanism in "CyClick" of pentapeptide aldehyde AFGPA. Our DFT calculations highlighted the importance of IMHB in pre-organization of the resting state, stabilization of the zwitterion intermediate, and the control of the product stereoselectivity. Furthermore, we have also identified that the low ring strain energy promotes the "CyClick" of hexapeptide aldehyde AAGPFA to form a thermodynamically more stable 15+5 imidazolidinone cyclic peptide product. In contrast, large ring strain energy suppresses "CyClick" reactivity of tetra peptide aldehyde AFPA from forming the 9+5 imidazolidinone cyclic peptide product.[1]

19. Analyzing the Effects of Hole Defect Size on pKa of Functional Groups Bonded to Graphene

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Carbo-catalysts have been effectively used in many reactions such as ring opening[1], oxidation[2], and rehydration[3] reactions. A common theme of these reactions is that they are driven by the acidity of the carbo-catalyst. A popular carbo-catalyst is graphene oxide (GO), which is known for having very reactive edge sites. GO also has naturally occurring defects and these

hole defects have the same reactive functionality as edge sites. Adding hole defects to GO can increase the reactivity of the carbo-catalyst, but currently there are no studies on the effects of hole defect size and shape on the reactivity of graphene oxide. This work intends to computationally determine the pKa of OH, COOH, and SO_3H on hole defect sizes ranging from 1 to 6 carbon atoms removed in pristine graphene. The position of these functional groups on the graphene hole defects were systematically determined by comparing DFT energies of the functional groups bonded to different sites on the defected system. GPAW, a python-based density functional theory code, was used to calculate the lowest energy position of functional groups on the defects as well as the Gibbs free energy associated with the proton transfer of the functional groups. The trend of ΔG relative to hole defect size will be presented as well as the comparison of ΔG and OH, COOH, and SO_3H functional groups.

20. Reaction Dynamics for Rearrangements of Cyclobutylidene

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Cyclobutylidene (**2**) is the presumed carbene intermediate in the thermal decomposition at 180°C in diethylcarbitol of the sodium salt of cyclobutanone tosylhydrazone via diazocyclobutane (**1**).[1] The reaction forms three products, methylenecyclopropane (**3**) (79%), cyclobutene (**4**) (18%), and 1,3-butadiene (**6**) (2%). Prior theoretical studies have identified three transition states, **TS1**, **TS2**, and **TS3** leading from cyclobutylidene (**2**) toward the reaction products.[1] **TS3** leads to bicyclobutane, which, together with cyclobutene, could be a precursor to 1,3-butadiene. These transition-state energies calculated at the B3LYP-GD3(BJ)/6-31G(d) level of theory agree well with those calculated by Schaefer et. al. at the CCSDT(Q) level of theory, supporting our use of this lower level of theory for trajectory calculations below. Although the relative energies of **TS1** and **TS2** predict a ratio of products **3** and **4** close to experiment based upon simple transition-state theory, our trajectory calculations show that these chemical reactions are more complicated, with dynamical factors playing a significant role in the formation of products. Using DFT-Born-Oppenheimer Molecular Dynamics (BOMD and ADMP) methods at the B3LYP-GD3(BJ)/6-31G(d) level of theory from the different transition states **TSNN**, **TS1**, **TS2**, or **TS3** lead to trajectories that give quite different product ratios from each of the transition states.

From **TSNN**, trajectories initially give **1** and **2**, followed by **3** (major) and **4** (minor), again consistent with experiment, and trace amounts of **5** and ethylene plus ethenylidene, typically within 1000 femtoseconds and as quickly as 10 femtoseconds. Trajectories from **TS1** give mainly **3** (major) and **4** (minor) in a somewhat shorter time frame. Trajectories from **TS2** give both **3** (major) and, as expected, **4** (major), while trajectories from **TS3** give mainly **5** (major), **3** (minor), and traces of **6** and ethylene plus ethenylidene. Thus, there is a large amount of branching and crossover to different products from each transition state in these reactions without formation of discrete long-lived intermediates. The energy surface for these very exothermic reactions, downhill by as much as 140 kcal/mol from **TSNN**, is quite complex with several additional transition states linking different products **3**, **4**, **5**, **6**, and ethylene and ethenylidene. The dynamical behavior and branching is not simply that from simple bifurcations at ridge-valley inflection points, but is the result of trajectories travelling over the energy surface with large amounts of excess vibrational energy along the way.

21. Network Hamiltonian Models for Rationalizing Phases of Diverse Amyloid Fibril Topologies

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Network Hamiltonian Models (NHMs) have proven to be a useful tool for studying protein aggregation[1]. NHMs are a scalable and computationally efficient solution for coarse-grained modeling of large systems of protein-protein interactions, and provide insight into the geometric constraints that determine the topology of protein aggregates. Here, we explore the topological phases produced by ranges of coefficients on a minimal set of four network terms - *edges* (t_e), *1-null-shared-partner* (t_{nsp1}), *2-null-shared-partner* (t_{nsp2}), and *2-star* (t_{2s}) - which have been chosen due to their ability to recapitulate amyloid fibril structures found in the PDB[2]. We rationalize phase boundaries between fibril-producing and non-fibrillar phases by comparing the relative effects of coefficient values on each network term, and elucidate the relationships between the topological forces that drive fibril formation. These results provide additional insight into the energetic differences between fibril topologies, and the sensitivity of the patterns of interaction between individual proteins that result in a variety of fibrillar and non-fibrillar aggregates.

22. Enhancing HMC Simulations: A Comparative Analysis of GB and 3D-RISM Models in Protein Structure Research

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The three-dimensional reference interaction site model (3D-RISM) of molecular solvation is an implicit solvent model that can calculate solvation density distributions and thermodynamics in close agreement with explicit solvent models. However, the computational expense of 3D-RISM is too large to use with molecular dynamics (MD) simulations, where solvation forces must be updated every timestep. To address this, we have implemented the hybrid Monte Carlo (HMC) method, which generates trial moves using MD with a fast generalized Born (GB) implicit solvent model, and then accepted or rejected the trial configuration using 3D-RISM. We have implemented HMC in a Python script, which utilizes the Amber molecular modeling suite to carry out MD simulations and energy evaluations. To gauge the impact of different GB implementations, we executed HMC simulations with varying trajectory lengths, using GB for MD and GB or 3D-RISM for energy evaluation with three different GB models (GB[HCT], GB[OBC], and GBn). HMC simulations using GB for the energy evaluations saw acceptance rates of 0.95 to 0.96, while HMC using 3D-RISM had acceptance rates of 0.19-0.56. Directly comparing the GB models for MD with 3D-RISM, at the same step size, the GBn model achieved the highest acceptance rate, while GB[HCT] had the lowest.

23. Tafamidis Drug Interaction with Transthyretin Protein Surrounding Environment in Individuals
with Transthyretin Amyloid Cardiomyopathy Using Hydrogen Bond Calculations and Energies from Computational Simulations

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Transthyretin Amyloidosis (ATTR) is a rare and progressive disease caused by the protein cascade and degradation of transthyretin (TTR), a protein used in the transportation of thyroxine and vitamin A. Dissociation of protein is characterized by the scission of the tetramer into dimers due to the kinetic instability of the faulty protein followed by rapid dissociation into monomers. Tafamidis (2-(3,5-dichlorophenyl)-1,3-benzoxaole-6-carboxylic acid) is currently the only drug approved by the FDA in the United States for the treatment of ATTR-CM through tetramer stabilization. Stabilization of TTR with Tafamidis occurs between the interaction between Tafamidis functional groups and the surrounding water environment through hydrogen bonds in seven possible binding sites within the TTR binding pockets. Modeled water and tafamidis structures, excluding pi-hydrogen bond

structures, are created with the Gauss 5.0 software, using optimization and frequency job type, DFT method (default spin, B3LYP), and basis set of 6-31G. Results show that the carboxyl functional group seems to forge the strongest and most stable hydrogen bond, having an electronic binding energy more than double that of regular a water dimer.

24. Protein Design with λ Dynamics

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High throughput methods for characterizing large protein sequence spaces are useful for driving protein design and understanding protein biophysics. Protein design is useful in many applications, including medicine, biocatalysis, and biotechnology. Gaps persist between experimental design methods that require some initial level of function, physical computational methods like Rosetta that suffer from low accuracy, and data driven computational methods that provide less physical insight. Molecular dynamics based alchemical free energy methods have been widely successful in computer-aided drug design for their rigorous physical basis and high accuracy, but are too computationally expensive for widespread use in protein design. λ dynamics is a highly scalable alchemical free energy method that is uniquely well-suited for computational protein design due to its ability to characterize mutations at many sites simultaneously. Initial retrospective studies of T4 lysozyme showed λ dynamics could evaluate stability changes of point mutations with high accuracy, and showed little loss of accuracy when evaluating several simultaneous mutations. Subsequent prospective studies of ribonuclease H demonstrated that λ dynamics can design within a space of 15 simultaneous mutations and predict stability changes within this sequence space with an unprecedented accuracy of 1.2 kcal/mol root mean square error. Because the mutations considered in ribonuclease H were all naturally occurring, they allow quantification of evolutionary selection pressure for stability and suggest it is quite high. Ongoing applications of λ dynamics include antibody repurposing within medicine, aldehyde synthesis within biocatalysis, and conducting peptide nanowire design within biotechnology.

25. A λ Dynamics-Based Approach to High-Throughput Design of Therapeutic Antibodies

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Recent progress in protein engineering has led to the development of novel types of antibodies with improved therapeutic properties, including augmented binding, specificity, and stability. Among these, neutralizing antibodies like monoclonal antibodies and nanobodies are actively researched for their potential as immunotherapeutic agents in combating cancer and emerging infectious diseases such as COVID-19. The target-to-hit stage is a well-established procedure in antibody drug discovery toward lead candidate optimization [1]. Still, exploring the vast libraries of possible mutations and their impact on binding affinity and stability renders the experimental phase a lengthy and expensive venture. In this direction, developing more accurate computational antibody design methods can mitigate the need for extensive experimental screening, thereby shortening the prolonged period of antibody drug development through winnowing down among the more promising candidate hits. Various methods have been developed for accurate prediction of changes in binding affinity in response to chemical modifications. Relative free energy perturbation (FEP) and thermodynamic integration are among these approaches [2,3]. However, the significant computational cost associated with these methods limits their application to small-molecule lead optimization, like protein-ligand [4].

Lambda dynamics, an approach introduced nearly three decades ago, is a valuable technique for assessing relative free energies in molecular simulations [5]. It efficiently samples perturbations, making it suitable for complex molecular systems. Lambda dynamics is similar to FEP in terms of partitioning the potential energy of the system as a linear function of λ, as a coupling parameter. However, treating the coupling parameter lambda as a dynamic variable interacting with the system's dynamics allows for the transformation between thermodynamic end states within a single simulation instead of multiple simulations in FEP. Recent developments have extended lambda dynamics to multisite lambda dynamics (MSλD), allowing the modeling of substituents in different parts of molecules. An efficient implementation of MSλD called BLaDE was introduced in 2021, which can perform alchemical free energy simulations on GPUs and significantly outperforms existing methods [6].

Despite all these endeavors in recent years toward faster and more accurate implementation of computational protein design, there is a lack of a benchmarking study to determine the efficiency of MSλD approach on predicting binding affinity in antibody-antigen as large-scale molecules drug design. Thus, this study aims to evaluate the impact of mutations on the antibody-antigens in the Antibody-Bind (AB-Bind) database by comparing the computational results from BLaDE implementation of MSλD with the existing experimentally determined changes in binding free energies (ΔΔG) across complexes in the AB-Bind database [7]. Overall, benchmarking the outcomes and refining the λ dynamics approach for better accuracy will lay the groundwork for future high-throughput antibody investigations by focusing on more promising mutations to realize the rapid development of immunotherapeutics and reducing tedious and costly functional assays.

26. Activation mechanism of the sweet taste heterodimer receptor

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Sweet taste is mediated by the heterodimer TAS1R2/TAS1R3, a class C G protein-coupled receptor (GPCR). GPCRS are transmembrane proteins and the target of one third of all drugs[1], and while the activation mechanism for class A receptors is well studied, the activation mechanism for class C is less understood[2]. In this work, we aim to further understand the activation mechanism of the sweet taste heterodimer.
TAS1 receptors are composed of a transmembrane domain (TMD), a Venus fly-trap domain (VFD) where ligands bind to, and a cysteine-rich domain (CRD) that connects them. Inside of the cell, a G-protein couples to the receptor and transduces the signal downstream. Past work[3] has determined the activation mechanism of the heteroceptor to include a sweet ligand binding to the VFD2 and stabilizing the closed conformation. Then, the CRD3 transduces the activation signal to form a TM6/TM6 interface of between the two receptors. Previous studies have not included the G protein in the simulations.
For the first time, we have performed metadynamics simulations of the full TAS1R2/TAS1R3 coupled to the G protein gustducin, bound to a series of ligands of varying sweetness. We observe that upon activation of the GPCR, the G-protein is able to induce GDP release; and are able to describe a sequence of signal transduction from the VFD2 to the activation of the Gα protein.

27. Interactive Molecular Docking Improved with Artificial Neural Networks and Human Spatial Perception

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This study explores the usefulness of the human 3D perception in navigating standard molecular dynamics (MD) simulations in order to improve their accuracy and performance. The primary objective of this research is to establish an artificial intelligent pipeline capable of predicting the optimal external force constant necessary for guiding the ligand to its docking site. The pipeline is trained using data acquired from several interactive docking-undocking MD simulations conducted on a Protein-Ligand pair within a virtual reality (VR) environment. This process is facilitated by an open-source framework called NARUPA which serves as a platform for obtaining spatial insights derived from human cognition. The specific Protein-Ligand pair under investigation involves HIV1 Protease and Amprenavir which binds to the active docking site characterized by two beta-hairpin flaps transitioning through various conformational states before ligand binding. The predicted force constant is applied to steer the ligand toward the binding pocket during AMBER's Adaptive Steered Molecular Dynamics (ASMD) simulations. This approach effectively eliminates the time that MD simulations typically require for comprehensive space sampling. Preliminary findings indicate that the interactive MD in VR (iMD-VR) environment yielded the fastest ligand docking process, followed by ASMD, while Particle Mesh Ewald Molecular Dynamics (PMEMD) simulations proved to be the most time-consuming. These results underscore the significance of human intuition, perception, and spatial understanding in expediting the molecular docking process.

28. Novel Biomolecular Fingerprint using Rule-based Graph Convolutional Network

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The use of fast *in silico* prediction methods for protein-ligand binding free energies holds significant promise for the initial phases of drug development. Numerous traditional physics-based models (e.g., implicit solvent models), however, tend to either neglect or heavily approximate entropic contributions to binding due to their computational complexity. Consequently, such methods often yield imprecise assessments of binding strength. Machine learning (ML) models provide accurate predictions and can often outperform physics-based models. They, however, are often prone to overfitting, and the interpretation of their results can be difficult. Physics-guided ML models combine the consistency of physics-based models with the accuracy of modern data-driven algorithms. This work integrates physics-based model conformational entropies into a graph convolutional network. We introduce a new neural network architecture (a rule-based graph convolutional network) that generates molecular fingerprints according to predefined rules specifically optimized for binding free energy calculations. Our results on 81 small host-guest systems demonstrate significant improvements in convergence and preventing overfitting. We additionally demonstrate the transferability of our proposed hybrid model by training it on the aforementioned host-guest systems and then testing it on six unrelated protein-ligand systems. Our new model shows little difference in training set accuracy compared to a previous model, but an order of magnitude improvement in test set accuracy. Finally, we show how the results of our hybrid model can be interpreted in a straightforward fashion.

29. Data-Driven Many-Body Framework for Organic and Biological Molecules

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Data-driven many-body energy (MB-nrg) potential energy functions (PEFs) provide predictive molecular models for large systems with quantum mechanical accuracy, positioning them as a powerful tool in investigating structural, thermodynamic, dynamical, and spectroscopical properties of generic molecular systems from the gas to the condensed phase. Two different molecular systems are studied in this project.

First, we are developing the first MB-nrg PEF for a ring-molecule, phloroglucinol (1,3,5-trihydroxy benzene) dihydrate, a highly effective organic ice nucleator[2]. A thorough understanding of phloroglucinol's ice-binding mechanism would allow us to harness its natural properties to promote ice crystallization through applications like weather engineering, and more efficient thermal storage techniques[2]. We show that our MB-nrg PEF describes the energetics of an isolated phloroglucinol molecule with high accuracy. We also present preliminary results for the interaction of phloroglucinol with water that represent the first step toward developing a comprehensive description of ice-binding molecules' interaction with water, their ice-binding sites, and the kinetics of ice nucleation and antifreeze behavior.

Second, we present our initial foray into data-driven many-body representations of amino acids. Recent advancement in high-resolution infrared spectroscopy has enabled the characterization of the hydration structure of protonated amino acids with a great level of detail[1]. Our goal is to provide a molecular-level interpretation of the spectral signatures observed experimentally. To this end, we are developing an MB-nrg PEF to model the hydration structure of protonated glycine, adding one water molecule at a time. By performing molecular dynamics simulation with our MB-nrg PEF we aim to provide fundamental insights into the hydration shells and hydration properties of protonated glycine that will enable direct comparisons with the experimental measurements. We envision future studies where our MB-nrg PEFs will allow for a microscopic characterization of proteins in solution.

30. Exploring Methods for Developing a Machine Learned Interatomic Potential for Ultra-High Temperature Ceramics

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Hafnium carbide (HfC) is well known for its high melting temperature, even among the group IV transition metal ceramics.[1] Due to this, HfC is considered an ultra-high temperature ceramic (UHTC) with many theorized applications such as ceramic coatings for aerospace vehicles, plasma facing components in fusion reactors, and absorber coatings for solar cells.[2,3] While HfC is theorized to have a melting point well above 3000°C, the material is also known to oxidize at temperatures as low as 500°C.[4] The conditions that HfC would experience in the aerospace would expose it to high temperature atmospheric oxygen and degrade the material by ablation to HfO_2.[5] In post mortem analyses of HfC exposed to similar conditions, the top layers of material are revealed to consist of HfO_2, while the middle layers are composed of an amalgam of Hafnium Oxycarbide (HfO_xC_y), and the bottom layers remain as pristine HfC.[6] It is known that HfO_2 is the main ablation product of HfC, but the interlayer between the HfO_2 and HfC remains of interest as it is seemingly capable of preventing oxygen from diffusing further into the ceramic composite. Experimental studies of HfOC can be quite expensive as well as dangerous. With this in mind, materials simulation is a potential alternative to bypass these restrictions. In this work we construct a database of diverse compositions of HfO_2, HfC and HfOC simulated using DFT and AIMD for use in developing a machine learned interatomic potential for the ceramic composite.

31. Machine Learning-Based Interatomic Potentials for Dynamic Simulations of Molecular CO_2

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Molecular dynamics simulations are fundamental for investigating molecular and material properties in fields like chemistry, materials science, and biology. Accurate predictions of energy and forces are crucial for complex systems, machine learning interatomic potentials offer efficient alternatives to computationally first principles methods. In this study, we generated a machine learning potential energy surface from CCSD(T) energy calculations and use it to compute atomic forces for CO_2 dimers. We then utilized the NequIP open-source machine learning tool to construct an equivariant interatomic potential, trained to the energy and force data of the carbon dioxide configurations. Subsequently, we conducted dynamic simulations with the use of the OpenMM machine learning algorithm. This study demonstrates the application of machine learning-based interatomic potentials to predict the weak intermolecular interactions within molecular carbon dioxide, contributing to an improved understanding of its properties, and facilitating advancements in various chemical and industrial processes.

32. Quantum Chemistry – Machine Learning Approach for Predicting Properties of Lewis acid – Lewis base Adducts

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Synthetic design that allows predictive control of electronic and thermodynamic properties of Lewis Acid – Lewis base (LA-LB) adducts remains elusive. This challenge must be addressed through complementary methods combining experimental with computational calculations. The computational approach is particularly important to predict properties that are challenging to obtain experimentally such as the charge transfer from LB to LA, and the LB binding atom for molecules with multiple LB binding atoms. Firstly, we show that density functional theory (DFT) calculation is a useful tool to provide insights into the bonding, electron population distribution and optical transitions of adducts between conjugated molecules and Lewis acids (CM-LA).[1] These adducts are potential candidates for applications in organic electronics and bioelectronics.[2,3] We also recognize a challenge of ab initio calculations is that that they can be computationally expensive and less straight-forward, especially for adducts of large conjugated molecules and Lewis acids. To address this challenge, we demonstrate that machine learning (ML) can accurately predict DFT-calculated properties including charge transfer, LB binding atom, and other electronic and thermodynamic properties of the adducts. Inputs for these prediction are molecular descriptors and fingerprints readily obtained from RDKit or RDKit-based packages.[4] Seven ML models, built from a dataset of over 1000 adducts, show exceptional performance in predicting charge transfer and other properties with the Pearson correlation coefficient up to 0.99.[5] For several ML models, the influence of each molecular descriptor on predicted properties can also be quantitatively evaluated. This contributes to the optimization of a priori design of Lewis adducts for future applications, especially in organic electronics.

33. Predicting Electronic Density of States Using a Euclidian Neural Network

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When attempting to screen and discover new materials, the prediction and analysis of chemical properties is typical; however, previously calculated data in present-day materials databases is limited.[4] This therefore presents an opportunity to explore efficient property prediction models. One such property is the electronic density of states (eDOS) which provides key insight into a material's electrical conductivity and optical absorption properties.[2] In this study, we predict the eDOS of inorganic crystals using a Euclidian neural network (e3nn), which efficiently accounts for symmetry information.[1,3] Structural and DOS data were gathered from the Materials Project for 1488 inorganic crystalline solids.[3] Each material's eDOS was evenly spaced (49, 100, 501 points) and smoothed using a Savitzky–Golay filter. The crystallographic structural data was processed into periodic graphs. To test data efficiency, we varied the number of data points for each material trained. To test model performance, we varied the number of layers and maximum allowed spherical harmonics. Results showed relatively good prediction of the eDOS for a given material. Future work includes additional hyperparameter tuning and predicting the eDOS and phonon density of states for molecular crystals.

34. Physics-guided Deep Generative Model for New Ligand Discovery

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Structure-based drug discovery aims to identify small molecules that can attach to a specific target protein and change its functionality. Recently, deep learning has shown great promise in generating drug-like molecules with specific biochemical features and conditioned with structural features. However, they usually fail to incorporate an essential factor: the underlying physics which guides molecular formation and binding in real-world scenarios. In this work, we describe a physics- guided deep generative model for new ligand discovery, conditioned not only on the binding site but also on physics-based features that describe the binding mechanism between a receptor and a ligand. The proposed hybrid model has been tested on large protein-ligand complexes and small host-guest systems. Using the top-N methodology, on average more than 75% of the generated structures by our hybrid model were stronger binders than the original reference ligand. 100% of them had higher ΔG_{bind} (affinity) values than the ones generated by the previous state-of-the-art method by an average margin of 1.88 kcal/mol. The visualization of the top-5 ligands generated by the proposed physics-guided model and the reference deep learning model demonstrate more feasible conformations and orientations by the former. The future directions include training and testing the hybrid model on larger datasets, adding more relevant physics-based features, and interpreting the deep learning outcomes from biophysical perspectives.

35. ParametrizANI: Fast, Accurate and Free Parametrization for Small Molecules

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In molecular studies, the accurate parametrization of small molecules stands as an essential yet growing demand. Addressing this, we introduce ParametrizANI, a tool crafted explicitly for establishing detailed protocols for dihedral parametrization using GAFF1 and OpenFF2 force fields.

The robust PyTorch-based program, TorchANI, forms the backbone of ParametrizANI, functioning as a benchmark to uphold precision in parametrization tasks. TorchANI3 plays a pivotal role in facilitating the training and inference of ANI (ANAKIN-ME) deep learning models which are fundamental in predicting potential energy surfaces and a spectrum of other molecular system attributes.

Our venture into developing ParametrizANI is not merely the creation of a tool but a stride toward fostering an environment where research is not restrained by limited resources. We embody an ethos of democratizing research, thereby equipping research groups of various scales to undertake dihedral parametrization with DFT-level precision.

The tool promises to unlock new horizons in molecular dynamics and related fields, serving as a stepping stone in advancing the scientific community's abilities in small molecule parametrization. For an in-depth exploration of its functionalities, we invite you to visit ParametrizANI on GitHub (https://github.com/pablo-arantes/ParametrizANI).

Our ambition extends beyond presenting a tool; it represents a pathway to a future replete with elevated understanding and skills in the parametrization of small molecules, aspiring to augment the capabilities of the scientific community as a whole.

36. Implementation of the Self-Consistent Phonons Method with Ab Initio Potentials (AI-SCP)

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The self-consistent phonons (SCP) method treats a quantum many-body system at thermal equilibrium while naturally incorporating anharmonic effects. SCP generates an effective temperature-dependent harmonic Hamiltonian, which is then used to estimate various dynamic and static properties of the system. While SCP has been shown to be a practical method (with calculations such as finding the anharmonic shift in the spectrum and structural properties of the system), it has yet to be proven practical with *ab initio* (AI) methods. The largest numerical hurdle comes from the evaluations of the Gaussian averages of the AI potential energy and its derivatives. By combining SCP with the quasi-Monte Carlo method, the Gaussian averages can be computed efficiently enough to combine SCP with AI potentials (AI-SCP). The use of quasi-Monte Carlo leads to a fast convergence (1/N instead of regular Monte Carlo's $1/\sqrt{N}$ convergence with N representing the number of Monte Carlo grid points) of the calculation with regards to the number of AI energy evaluations. Furthermore, if a numerically cheap approximation of the AI potential energy is available, then the two potentials can be combined in a 'two-grid' fashion to further increase efficiency. We chose water hexamer and naphthalene for our testing, and we show that the 'two-grid' approach has an order of magnitude increase in efficiency for both systems compared to a 'single-grid' calculation. With water hexamer presenting a challenge due to the large difference in the low (intermolecular) and high (intramolecular) frequency modes present in the system and naphthalene being comparatively a much simpler system, our results show that AI-SCP is a practical and general method especially when combined with a 'two-grid' approach. We have made the corresponding source codes available.

37. Predicting Accurate Singlet-Triplet Energy Gaps of Aryl Carbenes with Local Hybrid Functionals

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Carbenes are challenging for electronic structure methods due to the energetic proximity of their singlet and triplet spin states. Among standard density functional approximations (DFAs), only double hybrid functionals achieve chemical accuracy; additionally, the DFAs yielding accurate structures

typically do not perform well for spin-state energies. Here we investigate the performance of the class of local hybrid (LH) functionals to evaluate the adiabatic singlet-triplet (ST) splittings of carbenes against highly accurate wave-function based coupled cluster results for 18 aryl carbenes[1]. LHs use local mixing functions to allow for additional flexibility in the mixing of exact exchange and semilocal exchange[2]. The availability of efficient seminumerical implementations[3,4] of LHs allows the prediction of ST gaps with a computational effort and scaling with system size comparable to that of global hybrid DFAs. LH20t achieves chemical accuracy with a mean absolute error less than 1 kcal/mol. Results for other LHs range from 1.05 kcal/mol (LH12ct-SsirPW92) to 4.50 kcal/mol (LH14t-calPBE), depending on the details of the functional, in particular the local mixing function used. The new findings for carbenes are in agreement with earlier work for triplet excitations in the framework of time-dependent density functional theory, where LH20t[5] and the LH12ct functionals were also found to perform extraordinarily well[6,7]. The performance of other popular DFAs is also explored for comparison. This work suggests the value of local hybrids as a possible method for evaluating ST gaps of related carbenoids, thus potentially providing valuable insight for various biotechnological and medicinal applications.

38. Large Scale Optimally Tuned Hybrid-DFT with Deterministic/Fragmented-Stochastic Exchange

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We present an efficient approach to evaluate long-range separated hybrid exchange[1,2] for very large molecular systems with hundreds to thousands of correlated occupied states within the Generalized Kohn-Sham (GKS) DFT framework. The method begins with the KS orbitals and eigenenergies of an efficient plane-wave local- (or semi-local) DFT calculation. These states act as the initial basis to a GKS Hamiltonian that incorporates long-range exchange. A fractured plane-wave resolution of the identity is applied to the exchange part of the Coulomb interaction in the reciprocal space (or k-space), where long-wavelength (low-k) terms are evaluated deterministically while the remaining high-k terms (often millions) are solved in a sparse ("fragmented") stochastic basis.[3,4] Sparse compression, previously applied in the stochastic GW (sGW) method[5], enables random samplings of large data sets (e.g., a lengthy k-space grid) with high fidelity, and further the computational cost does not increase with system size. Similarly, here we apply stochastic samplings on the exchange interaction of the high-k contributions via "fragments" of fixed length.

To further reduce the computational cost, a projection of the Hamiltonian onto the top-valence and bottom-conduction (i.e., near Fermi level) states is performed, which suitably converges the HOMO and LUMO energies, and yields fundamental bandgaps comparable to established range-separated hybrid DFT (RSH-DFT) techniques. The exchange contribution of the occupied states that are not included in the top-valence set are accounted for through a perturbative scissor shift[6]. By truncating to this reduced active space and using a fragmented-stochastic auxiliary basis set, we develop a method that incorporates exact exchange but with much lower cost than the initial estimate local-DFT calculation. Although this method is formally cubic in scaling, it is in practice much gentler since only very few valence and conduction states need to be explicitly included in the evaluation of the exchange. The stochastic part handles the high-k components that carry numerically small contributions to the total exchange, therefore, the associated stochastic error is very small (<0.01 eV).

Next, we are going to extend this method beyond the scope of ground-state calculation to access the excited states with the GW-BSE (Bethe–Salpeter equation) technique. As has been established[5], and recently benchmarked[8], an RSH-DFT starting point better improves the BSE optical spectra when compared to experimental results over self-consistent iterations in the GW step. The present method,

in conjunction with stochastic *GW*-BSE, provides promise for reliable, accurate *ab-initio* excitonic information of very large molecular systems, such as chlorophyll complexes, and super-molecular structures, such as self-aggregating cyanine dyes.[10]

39. Massively Parallelized Real-Time Propagation via Plane-wave based Time-Dependent Density Functional Theory

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 Real-time time-dependent density functional theory (RT-TDDFT) is a promising approach for simulating quantum dynamics properties. However, RT-TDDFT calculations require substantial computational resources for large-scale systems, and novel numerical methods are needed to overcome these bottlenecks, such as enhancing the time propagator for the time-dependent Kohn-Sham equations.

In this research, we present an efficient, massively parallelized RT-TDDFT implementation in the C++ based QBOX package[1-4]. As benchmark applications, we evaluated the current density and optical absorption spectra of hexagonal boron nitride (h-BN) and a photo-driven reaction of the ozone-oxygen cycle. In addition, we also simulated second- and high-harmonic generation of monolayer and multilayer h-BN structures as a prototypical large-scale system to demonstrate the capabilities of our implementation. Using ultrasoft laser pulses and Ehrenfest dynamics calculations, we show that our RT-TDDFT calculation results are consistent with previously reported but are significantly faster due to enhanced algorithmic modifications that result in less MPI communication across CPU's.

40. Time-Dependent Density Functional Theory with Orthogonal Projector Augmented Wave Method

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The PAW method linearly maps smooth pseudo wavefunctions to highly oscillatory all-electron wavefunctions. Compared to norm-conserving pseudopotentials (NCPP), PAW has the advantage of requiring lower kinetic energy cutoffs and allowing larger grid spacing at the cost of having to solve for non-orthogonal wavefunctions. We have developed Orthogonal PAW (OPAW) to allow the use of PAW in methods that require orthogonal wavefunctions such as in sGW. In OPAW, the pseudo wavefunctions are transformed through the efficient application of powers of the PAW overlap operator resulting in an orthogonal eigenproblem without significantly increasing computation costs. Previously we developed OPAW with density functional theory (DFT)1. To make OPAW viable for methods that require time-dependent wavefunctions, we have developed time-dependent DFT with OPAW (OPAW-TDDFT). Using fourth-order Runge Kutta for the time-propagation, we compare calculations of absorption spectra for various hydrocarbons and chlorophyll to show a significant improvement in being able to use larger grid spacing as well as longer time steps when using OPAW-TDDFT over NCPP-TDDFT. The next stage of our project is to implement time-dependent Hartree OPAW (TDH-OPAW) into our stochastic GW (sGW) method. The GW approximation method is used to describe the quasiparticle behavior of highly correlated systems, however, it is computationally costly due to its fourth-order scaling with a system's size. We have previously developed Stochastic GW (sGW) which uses stochastic sampling to evaluate quantities including the

Green's function, G, and the screened Coulomb potential, W, enabling linear-scaling[2,3]. The initial versions of sGW utilized CPU parallelization and in this poster we also introduce a version of sGW utilizing CPU+GPU parallelization to improve computational speed. These two major developments of OPAW-TDDFT and GPU implementation will make sGW calculations of larger systems that include thousands of atoms feasible.

41. Overcoming the Charge-Transfer and Triplet Problem of TDDFT with a Two-Parameter Range-Separated Local Hybrid Functional

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The accurate theoretical description of both charge-transfer (CT) and triplet states is essential for progress in several highly active research areas, such as thermally activated delayed fluorescence, phosphorescent emitters, and singlet fission. Linear-response time-dependent density functional theory (TDDFT) is often the method of choice for treating excited states in large systems, but most exchange-correlation (XC) functionals notoriously underestimate CT[1,2] and/or triplet excitation energies.[3,4] Range-separated hybrid (RSH) functionals are a well-known remedy for the CT problem,[2,5] but they also underestimate triplet excitation energies.[6,7] To correct the triplet excitations, the Tamm-Dancoff Approximation (TDA) is often used because it systematically blue-shifts the excitation energies.[3,4] However, the lack of gauge invariance[8] and the dependence on error compensation make the TDA less desirable. Previous work on local hybrid (LH) functionals,[9,10] which use a real-space dependent local mixing function (LMF) to govern the mixing of semilocal and exact exchange energy densities, consistently shows that LHs based on a common t-LMF overcome the triplet problem of TDDFT.[7,11-13] For a set of 105 triplet excitation energies, the one-parameter LH12ct-SsirPW92 functional achieves an MAE of 0.14 eV without using the TDA.[7] Combining the concepts of RSHs and LHs leads to range-separated local hybrid (RSLH) functionals.[14,15] The recent 8-parameter ωLH22t functional was optimized for ground state thermochemistry and gives excellent CT energies, but the advantages for triplet excitations were much less pronounced (MAE: 0.24 eV).[15]

Here, the new RSLH functional ωLH23ct-sir is presented.[16] Its two parameters, the LMF prefactor and the range separation parameter, have been optimized for a training set of only 8 excitation energies. It is shown to provide excellent accuracy for both CT and triplet excitations across various test sets.[16] In particular, the triplet excitation energies are significantly improved over its thermochemically optimized predecessor (MAE: 0.17 eV).[16] As expected, ωLH23ct-sir loses some ground in terms of ground state energies and properties, but still performs reasonably well.[16] Using the efficient seminumerical implementation of Ref. 15, the computational cost scales similarly to other (rung 4) hybrids with a moderately larger prefactor of 2–3. ωLH23ct-sir may thus become a useful tool for studying photochemical problems involving excited states of different character and spin multiplicity.

42. Velocity-gauge real-time time-dependent density functional tight-binding for large-scale condensed matter systems

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We present a new velocity-gauge real-time, time-dependent density functional tight-binding (VG-rtTDDFTB) implementation in the open-source DFTB+ software package (https://dftbplus.org) for probing electronic excitations in large, condensed matter systems. Our VG-rtTDDFTB approach

enables real-time electron dynamics simulations of large, periodic, condensed matter systems containing thousands of atoms with a favorable computational scaling as a function of system size. We provide computational details and benchmark calculations to demonstrate its accuracy and computational parallelizability on a variety of large material systems. As a representative example, we calculate laser-induced electron dynamics in a 512-atom amorphous silicon supercell to highlight the large periodic systems that can be examined with our implementation. Taken together, our VG-rtTDDFTB approach enables new electron dynamics simulations of complex systems that require large periodic supercells, such as crystal defects, complex surfaces, nanowires, and amorphous materials.

43. Understanding the Mechanism Behind H_2 formation from Solvated Dielectron in Liquid Water

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Excess electrons drive chemistry by serving as intermediates in reactions important to fields of study ranging from radiation chemistry to biological processes. In particular, solvated dielectrons, in liquid water, participate in the generation of H_2.[1] Our investigations aim to elucidate the mechanism by which solvent-solute (H_2O-dielectron) interactions progress the making of H_2. We conducted dynamics studies on singlet (e_2^{2-}) and triplet ($e^- $--- e^-), sequentially injected in bulk water, using ab initio molecular dynamics (AIMD) adopted from the hybrid DFT functional, PBE0. Our results indicate a short-lived H^- intermediate followed almost immediately by the formation of H_2 for e_2^{2-}. In contrast, when e^---- e^- is flipped to singlet e_2^-, we observe H^- intermediates that are long-lived. A time distribution for the formation of H^-, among trajectories, indicates the importance of the environment around e_2^{2-}. We further investigate and compare hydrogen bonding for bulk water and the individual water molecules that form the e_2^{2-} cavity. We detect stabilization of water molecules involved in the reaction through hydrogen bonding.

44. Using Machine Learning to Understand the Causes of Quantum Decoherence in Solution-Phase Bond Breaking Reactions

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Decoherence is a fundamental phenomenon that occurs when an entangled quantum state interacts with its environment, leading to collapse of the wavefunction. The fact that decoherence occurs so easily provides one of the most fundamental limits on quantum computing. Despite this, there has been relatively little study of the precise chemical motions from the environment that cause decoherence. Here, we use quantum molecular dynamics simulations to explore a solution-phase molecular system, Na^+_2 in liquid Ar, in which solvent fluctuations induce decoherence and thus determine the products following the breaking of a one-electron chemical bond. In particular, we use machine learning to explore the solvent motions that determine decoherence by characterizing the solute-solvent environment as a high dimensional feature space that can predict localization of the bonding electron. The feature importance analysis shows that first reaching a requisite photofragment separation and then experiencing out-of-phase solvent collisions on the fragments are the non-equilibrium events underlying decoherence. Our work highlights both the utility of machine learning for interpreting complex solution-phase chemical processes as well as identifying the molecular underpinnings of quantum decoherence.

45. Multi-scale Molecular Dynamics Simulations of Active Supramolecular Materials

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Inspired by the adaptability observed in biological materials, self-assembly processes have attracted significant interest for their potentials to yield novel materials with unique properties. However, experimental methods have often fallen short in capturing the molecular details of the assembly process. In this study, we employ a multi-scale molecular dynamics simulation approach, complemented by NMR quantification, to investigate the mechanism of self-assembly in a redox-fueled bio-inspired system, which includes an aryl-containing cysteine-based thiol and its disulfide dimer. Contrary to conventional assumptions, we have uncovered a significant role played by the monomer precursor in the assembly process, with its presence varying with concentration and the extent of conversion of the monomer to the dimer. Experimental confirmation through NMR quantification underscores the concentration-dependent incorporation of monomers into the fibrous structures. Furthermore, our simulations also shed light on the diverse intermolecular interactions, including T-shaped and parallel π stacking, as well as hydrogen bonds, in stabilizing the aggregates. Notably, an open conformation of the dimer emerges as the preferred configuration within these aggregates. These findings contribute to the growing field of bio-inspired materials science by providing valuable mechanistic insights to guide the design and development of self-assembly materials with bio-mimetic functionalities.

46. Mean activity coefficient for ionic solutions: analyzing Amber MD current ionic models with Reference Interaction Site Model

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The ionic atmosphere surrounding nucleic acids is crucial to its structure and function; for example, stabilizing its structures[1-2] and modulating the binding of charged drugs.[3] The 3D reference interaction site model (3D-RISM) of molecular solvation is well suited to model ionic atmosphere over a wide range of concentrations for mixtures of ionic species. However, the quality of the 3D-RISM calculation depends strongly on the models of water and ions and, to date, these have not been optimized within the 3D-RISM framework. To address this, we optimized the parameters for monovalent ion using both the traditional 12-6 Lennard-Jones (LJ) model and the recently developed 12-6-4 LJ model for hydration free energy (HFE), ion-oxygen distances (IOD) and mean activity coefficients up to 1 molal. These were compared against the existing Joung-Cheatham[4] and Li-Merz[5] sets of ionic parameters for the TIP3P and SPC/E water models.

We observed that good agreement for the mean activity coefficient with experimental data depends on the water and potential models considered as well as the closure relation used. The root mean squared error (RMSE), taking all ions into account, for HFE and IOD computed with the Li-Merz LJ 12-6 parameters, SPC/E water model and PSE-3 closure relation were, respectively, 3.99 kcal/mol and 0.27 Å. Using the Li-Merz LJ 12-6-4 potential, we obtained HFE and IOD of 4.23 kcal/mol and 0.17 Å. By optimizing LJ 12-6 parameters for KCl salt, we observed a major improvement for HFE, as the relative errors for K^+ and Cl^- ions changed, respectively, from -1.41% and -5.86% to -1.97E-05% and -1.14E-05%. For the mean activity coefficient, we observed a change in the RMSE from 0.026 (the best combination was the Joung-Cheatham ionic parameters and SPC/E water model) to 0.014. Overall, we

found we were able to improve the HFE, IOD and mean activity coefficients by optimizing the LJ 12-6 model and do not need the LJ 12-6-4 model for monovalent ions.

47. Automates, efficient and rigorous absolute binding free energy calculations

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Identifying small drug-like molecules for therapeutic targets of interest is an ongoing effort in drug discovery. Accurate absolute binding free energy calculations (ABFEs) *in silico,* can reduce the time and cost of exploring a diverse set of potential drug candidates that may have been overlooked experimentally. These calculations usually employ explicit solvent models, however, they can be computationally demanding and are often difficult to implement and carry out. To circumvent these drawbacks, we introduced the software ISDDM.py, a Python automated workflow that implements an approach that uses faster implicit solvents, such as generalized Born (GB), which greatly reduces computational costs. We adapted the double decoupling method (DDM), which uses conformational restraints, and paired it with GB solvent to enhance convergence. The software is tested on 83 unique host-guest complex systems and reports encouraging results in estimating binding free energies. Our work here attempts to reduce the computational expense of absolute binding free energies by using implicit solvent models and the ISDDM.py package to handle all the input files, monitor the simulations, and perform post-analysis.

48. Dynamic properties of hydrated alkali metal ions predicted by many-body potential energy functions

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Alkali ions in solution have a significant effect on the surrounding water molecules, such as affecting strength of water-water interactions in the different solvation shells by altering the strength of the hydrogen bond network. In this study, the hydration structure and dynamics of alkali metal ions are investigated using many-body energy (MB-nrg) potential energy functions (PEFs). MB-nrg PEFs have previously been shown to accurately reproduce the EXAFS spectra of sodium and potassium ions in solution and shown to predict the correct hydration structure of these ions.[1] The present work aims to understand the water dynamics around alkali metal ions by studying the infrared spectrum, orientational dynamics, and residence time of water in the different hydration shells.

49. Developing a Data-Driven Many-Body Model for Triplet Oxygen Hydration with Chemical Accuracy

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Oxygen is essential for life on Earth, and its importance cannot be overstated. From respiration to cellular metabolism, to detoxification and therapeutics, hydrated and dissolved oxygen is recognized as an important system across many scientific disciplines. It plays a central role in several physical and chemical processes that span from complex living systems to industrial- and socioeconomic systems. For example, the dynamics of dissolved oxygen in marine ecosystems enable wildlife to live under specific thermodynamic conditions, and any difference to the concentration of dissolved oxygen can have significant detrimental effects. These dynamics depend on thermodynamic quantities like temperature, which is changing at an accelerating pace due to climate change[1].

Due to the central role that oxygen plays in a myriad of natural and industrial processes, developing a physics-based model that accurately describes oxygen–water interactions, from the gas to the condensed phase, will deepen our understanding of important aerobic phenomena and assist in tackling related challenges such as O_2 transport through biological media. To this end, the many-body energy (MB-nrg) formalism has been developed over the last decade as a data-driven many-body framework that combines the ansatz of the many-body expansion with high-level electronic structure theory for robust simulations of molecular simulations. Due to the functional form of MB-nrg PEFs, which is systematically improvable, they have been demonstrated to be transferable across phases, maintaining chemical accuracy from the dimer to the condensed phase. Importantly, it enables the descriptions of molecular systems at arbitrary *ab initio* accuracy with the computational cost of a polarizable force field. MB-nrg has been used to model molecular mixtures in water, like CO_2/H2O and CH_4/H_2O, accurately reproducing reference CCSD(T) energies and structural and chemical properties of the mixtures[2,3]. Now, we use the MB-nrg framework to gain molecular insights into the hydration of $^3O_2$.

Within the MB-nrg formalism, we derived many-body PEFs for $3 O_2$ (V_{1B}) and $3 O_2$-H_2O (V_{2B}) from domain-based local pair natural orbital unrestricted coupled-cluster theory, DLPNO-UCCSD(T), in combination with the F12 method to approximately extrapolate to the complete basis set. As DLPNO-UCCSD(T)-F12 is more efficient than the canonical treatment, it facilitates training the MB-nrg PEF on more extensive training sets without significant overhead. [4] Many-body energy decomposition analyses of $3 O_2 (H_2O)_N$ clusters suggest that low-order many-body interactions (e.g. 2-body and 3 body) are sufficient to describe the interaction energy of hydrated water clusters, and that 2-body interactions may play a deterministic role in characterizing the local hydration structure of dissolved oxygen.

In this context, by performing molecular dynamics simulation with our MB-nrg PEF we aim to provide fundamental insights into the structure and thermodynamic properties of triplet oxygen in aqueous solution. We will use molecular dynamics to show that DLPNO-UCCSD(T) and MB-nrg accurately describe dissolved oxygen in terms of both structural and thermodynamic properties. Importantly, this work represents the first MB-nrg model for open-shell molecules, extending the applicability of data-driven many-body simulations of open-shell molecules in realistic environments.