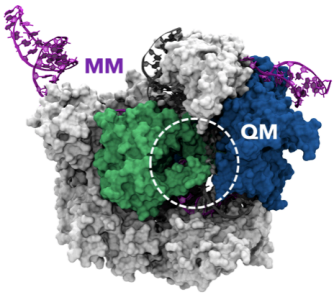
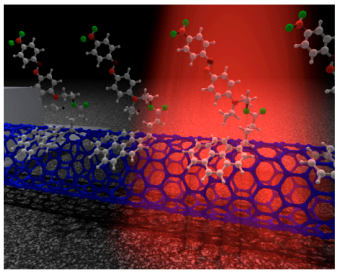
SOCAL THEOCHEM 5

Program



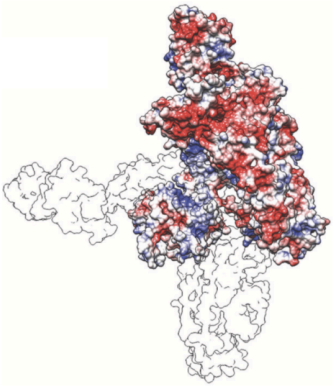
Palermo lab

Speakers



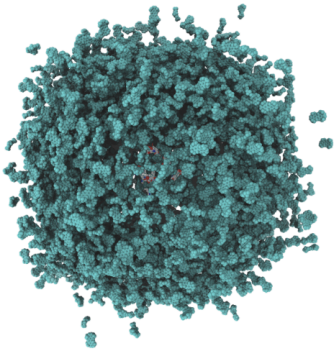
Wong lab

Location



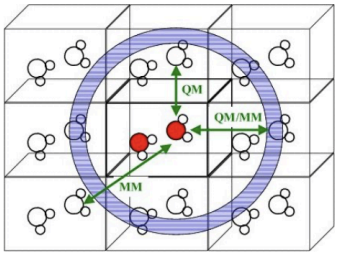
Morikis lab

Organizers



Chang lab

Registration



Beran lab

SoCal Theo Story

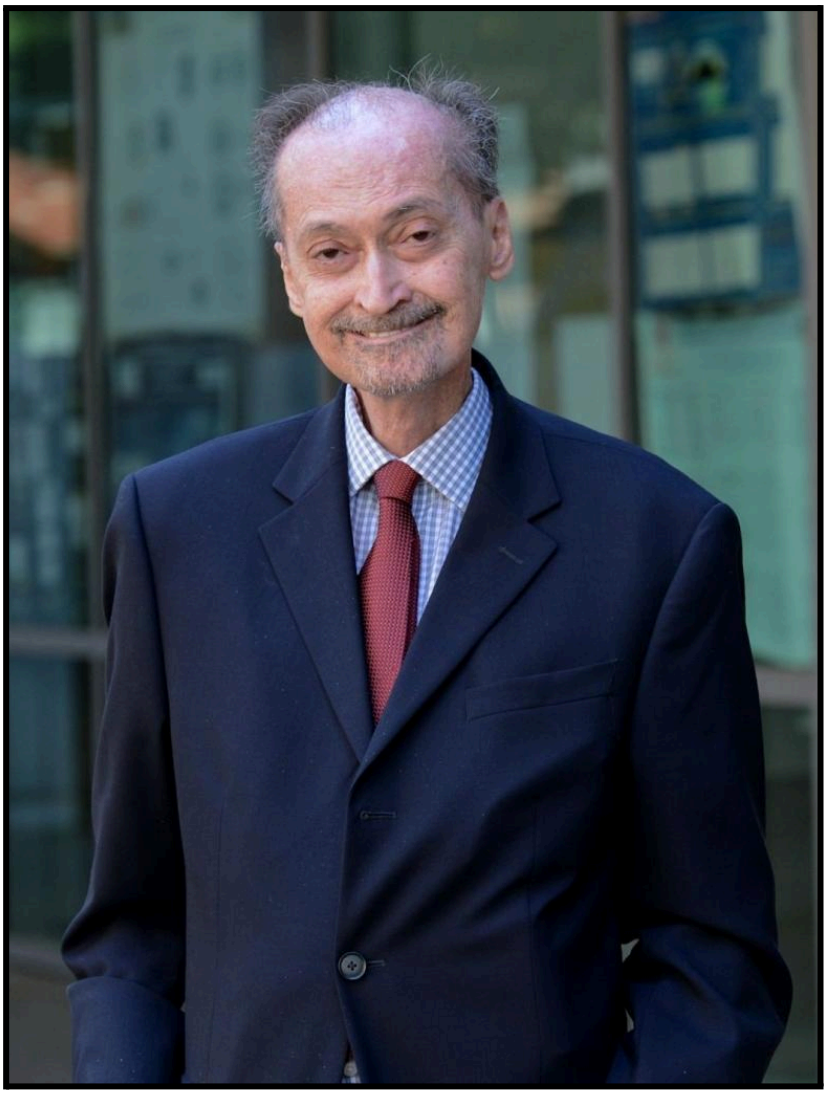
Scotty lab

October 15, 2022 – University of California Riverside

https://socaltheochem5.wordpress.com

A tribute to the work and accomplishments of Professor Dimitrios Morikis

Prof. Dimitrios Morikis



Professor Morikis earned a Ph.D. in Physics from Northeastern University and, following his postdoctoral work at Scripps Research Institute and UC San Diego, he began his professorial career at UC Riverside's Department of Chemical and Environmental Engineering. In 2006, he became a founding faculty member of the Department of Bioengineering and later became part of the faculty of the graduate program in Biomedical Sciences of the School of Medicine and of the Institute for Integrative Genome Biology.

He published more than 130 peer-reviewed research publications, importantly contributing to the understanding of the biophysics of the immune system, and was named a Fellow of the American Association for the Advancement of Science and a Fellow of the American Institute for Medical and Biological Engineering.

1 Description

About Dimitrios Morikis

Dimitrios Morikis, UC Riverside Professor of Bioengineering, passed away on May 27, 2019. Professor Morikis is well known for his work in immune-physics and immune-engineering, where he used physics and engineering approaches to understand molecular mechanisms of immunology, develop disease models, and design new drugs and molecular sensors for autoimmune and inflammatory diseases.

"Throughout the years, there was a natural evolution from biophysics to bioengineering via structural biology and computational chemistry, which is consistent with the evolution of my research interests and training," Professor Morikis said during an interview about how his research had shifted.

His research focus on immune system function came after a personal struggle with illness. "In 1994, I got sick with a life-threatening disease of the bone marrow. Thanks to modern medicine and after a strenuous process, I recovered and managed to get back to research," he explained during the interview. *"It was in 1995 when I decided to dedicate the rest of my research life in studying the molecular basis of immune system function and trying to develop means to fight immune-mediated diseases."*

Professor Morikis' most recent research was highly cross-disciplinary and focused on utilizing a blend of molecular-level and systems-level science and collaborations with researchers working on cell and tissue levels and in vivo studies. A prime focus of his work was the development of affordable potential pharmaceuticals for rare diseases. He led the immune-physics field as the Editor-in-Chief of BMC Biophysics.

This year's SoCal TheoChem is dedicated to Prof. Morikis as a tribute to his work and accomplishments. Professor Morikis was a founding faculty member of the Department of Bioengineering at the University of California, Riverside and his scientific energy was vital in shaping the program into what it is today. His research, however, extended well beyond our campus and has had an international impact. His passing on May 27, 2019 has left us with a tremendous void however, we are grateful for being among those whose lives he has touched. Professor Morikis was also a caring teacher and devoted mentor.

We hope this will inspire young scientists, students and postdocs in computational chemistry and biophysics.

2 About SoCal TheoChem

The Southern California Theoretical Chemistry symposium – SoCal TheoChem – is a yearly event bridging scientists in the field of theoretical chemistry in the vibrant research area of southern California.

Each year, scientists in the field of theoretical and computational chemistry meet in one of the University campuses of southern California to discuss the challenges and perspectives of the field.

Do not miss next year @UCLA!

2023 – University of California Los Angeles

Next year is gonna be @UCLA!

3 Program

Morning session

Check-in, Registration, Poster Setup, and Continental Breakfast

•	8:00 to 9:00

Welcome Remarks

•	9:00 to 9:20 *Opening Remarks* *A tribute to the work and accomplishments of Professor Dimitrios Morikis*

Keynote Speaker

•	9:20 to 10:00 – **Kieron Burke** *Modern Density Functional Theory*

Intermission

- 10:00 to 10:10

Pushing Frontiers of Biophysics

Chair: Giulia Palermo

•	10:10 to 10:40 – **Anastassia N. Alexandrova** *Enzymes as Molecular Capacitors*
•	10:40 to 11:00 – **Yi-Chun Lin*** *Molecular Permeability through Large-pore Channels*
•	11:00 to 11:30 – **Mohd Ahsan** *Principles of target DNA cleavage and role of Mg^{2+} in the catalysis of CRISPR-Cas9*
•	11:30 to 12:00 – **Gennady M. Verkhivker** *Conformational Landscaping and Mutational Cartography of the SARS-CoV-2 Spike Proteins: Probing Mechanisms of Antibody-Induced Neutralization and Allosteric Drug Discovery*
•	12:00 to 12:30 – **Jeremy Kua** *Thermodynamics of CHO Proto-Metabolites in Simple Autocatalytic Cycles*

Lunch and Posters

- 12:30 to 2:00

Afternoon session

Harnessing the Power of Quantum Mechanics

Co-chairs: Gregory Beran & Bryan Wong

•	2:00 to 2:30 – **Oleg V. Prezhdo** *Ab Initio Quantum Dynamics of Nanoscale Materials*
•	2:30 to 2:50 – **Claire Dickerson*** *Design Principles for Molecular Qubits*
•	2:50 to 3:10 – **Robin Grotjahn*** *Importance of Restoring Gauge Invariance in TDDFT Calculations with meta-GGA Functionals*
•	3:10 to 3:40 – **Benjamin J. Schwartz** *Can Ab Initio Simulations Explain the Structure and Properties of the Hydrated Electron?*
•	3:40 to 4:00 – **Kaushik D. Nanda*** *New Ab Initio Tools for Robust Modeling of Valence, X-ray, and Entangled Multiphoton Spectroscopic Processes*
•	4:00 to 4:20 – **Samuel Bekoe*** *Libkrylov, a Modular Open-Source Software Library for Extremely Large On-the-Fly Matrix Computations*

Intermission

- 4:20 to 4:30

Next-Generation Drug Discovery

Chair: Chia-en Chang

•	4:30 to 5:00 – **David Mobley** *Improving Binding Free Energy Calculations to Help Guide Pharmaceutical Discovery*
•	5:00 to 5:30 – **Talant Ruzmetov** *Bkit: Binding free energy and kinetics calculation toolkit for chemical and biomolecular systems*
•	5:30 to 6:00 – **Negin Forouzesh** *Improving the Accuracy of Implicit Solvents with Physics-Guided Neural Networks*

Concluding remarks and Reception

** Selected from contributed abstracts*

4 Abstracts

Modern Density Functional Theory

Kieron Burke

Departments of Chemistry and of Physics, UC Irvine

I will give an overview of modern density functional theory in chemistry and materials. This will include brief discussions of some areas I've worked in recently, including finding functionals with machine-learning, density-driven errors, semiclassical derivations, and warm dense matter. All recent work available from http:dft.uci.edu

Enzymes as Molecular Capacitors

Anastassia N. Alexandrova

Department of Chemistry and Biochemistry, UCLA
E-mail: ana@chem.ucla.edu

Proteins have been shown to produce intramolecular electric fields, preorganized to help enzymatic catalysis. Using IR probes placed in proteins, and measuring their Stark shift, it became possible to assess the local fields and correlate those with the reactivity. Note that electric fields are more global than a particular bond of the IR probe can witness, as well as highly heterogeneous throughout the active site, with likely implications for reactivity. We showed that the geometry of the overall active site electron density, ρ, is affected by protein electrostatics, and reports on the reactivity, serving as a sensitive and rigorous metric of electrostatic preorganization that is not limited to one bond. We have also developed methods to analyze the global E-fields directly in large volumes of the active site. Both 3-D ρ, and global E-fields can be correlated to enzyme activity, either in obvious ways, or via machine learning. While introducing these tools, I will show how E-field regulation appears to be omnipresent in large enzyme classes, including metalloenzymes, rather than limited to a few broadly studied proteins. In particular the functionality of Fe-heme proteins appears to be heavily regulated by E-fields, in addition to the known regulation provided by the axial ligand to the Fe.

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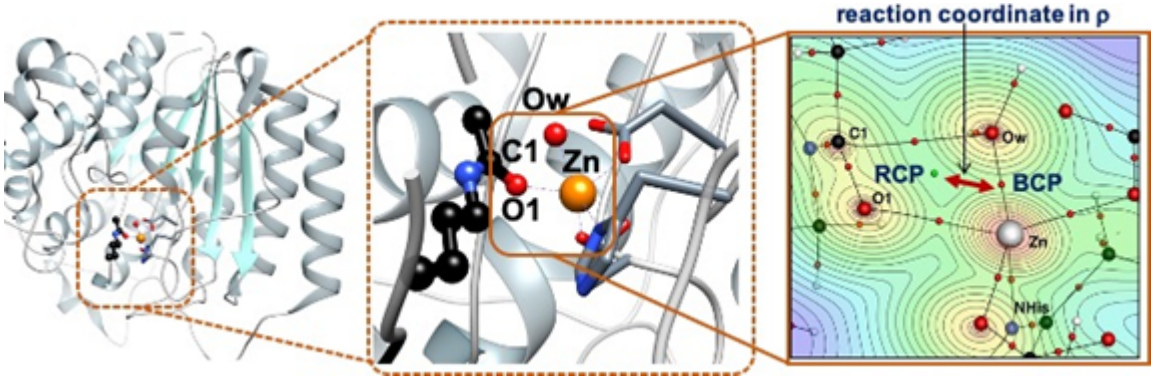
Hennefarth, M. R.; Alexandrova, A. N. Direct Look at the Electric Field in Ketosteroid Isomerase and its Variants. ***ACS Catal.*** **2020**, 10, 9915-9924.

Fuller, J.; Wilson, T. R.; Eberhart, M. E.; Alexandrova, A. N. Charge Density in Enzyme Active Site as a Descriptor of Electrostatic Preorganization. ***J. Chem. Inf. Model.*** **2019**,59, 2367-2373.

Morgenstern, A.; Jaszai, M.; Eberhart, M. E.; Alexandrova, A. N. Quantified Electrostatic Preorganization in Enzymes Using the Geometry of the Electron Charge Density. ***Chem. Sci.*** **2017**, *8*, 5010-5018.



Histone deacetylase, HDAC8, its active site with the bound substrate and the nucleophilic water activated by Zn, and ρ of the area, showing important CPs and the reaction coordinate in ρ.

Principles of Target DNA Cleavage and Role of Mg^{2+} in the Catalysis of CRISPR-Cas9

Mohd Ahsan, Łukasz Nierzwicki, Rohaine V. Hsu, Pablo R. Arantes, and Giulia Palermo

Department of Bioengineering, University of California Riverside, 900 University Avenue, Riverside, CA 52512, United States

At the core of the CRISPR-Cas9 genome-editing technology, the endonuclease Cas9 introduces site-specific breaks in DNA. However, precise mechanistic information to ameliorating Cas9 function is still missing. Here, multi-microsecond molecular dynamics, free-energy and multiscale simulations are combined with solution NMR and DNA cleavage experiments to resolve the catalytic mechanism of target DNA cleavage. We show that the conformation of an active HNH nuclease is tightly dependent on the catalytic Mg^{2+}, unveiling its cardinal structural role. This activated Mg^{2+}-bound HNH is consistently described through molecular simulations, solution NMR and DNA cleavage assays, revealing also that the protonation state of the catalytic H840 is strongly affected by active site mutations. Finally, *ab-initio* QM(DFT)/MM simulations and metadynamics establish the catalytic mechanism, showing that the catalysis is activated by H840 and completed by K866, rationalising DNA cleavage experiments. This information is critical to enhance the enzymatic function of CRISPR-Cas9 toward improved genome-editing.

References:

Ł. Nierzwicki, K. W. East, J. Binz, R. V. Hsu, M. Ahsan, P. R. Arantes, E. Skeens, M. Pacesa, M. Jinek, G. P. Lisi and G. Palermo. Principles of Target DNA Cleavage and Role of Mg2+ in the Catalysis of CRISPR-Cas9. ***Nature Catal.*** **2022**, *in press*. DOI: 10.1038/s41929-022-00848-6.

L. Casalino, Ł. Nierzwicki, M. Jinek, G. Palermo. Catalytic Mechanism of Non-Target DNA Cleavage Revealed by Ab-Initio Molecular Dynamics. ***ACS Catalysis*** **2020**, *22,* 13596–13605.

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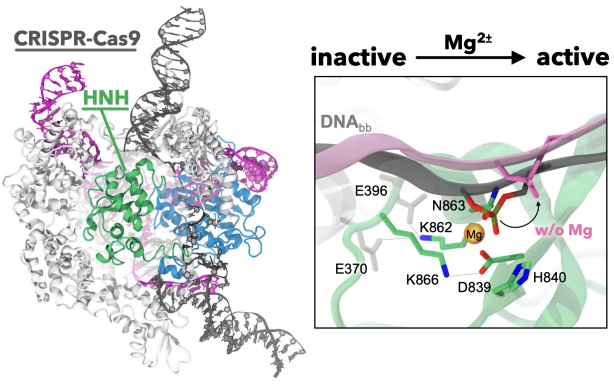

Conformational Landscaping and Mutational Cartography of the SARS-CoV-2 Spike Proteins: Probing Mechanisms of Antibody-Induced Neutralization and Allosteric Drug Discovery

Gennady M. Verkhivker

Department of Biomedical and Pharmaceutical Sciences, School of Pharmacy, Chapman University, Irvine CA ,USA

The coronavirus disease 2019 (COVID-19) pandemic associated with the severe acute respiratory syndrome (SARS) has been at the focal point of biomedical research. The structural and biochemical studies of the SARS-CoV-2 spike (S) glycoproteins and complexes with highly potent antibodies have revealed multiple conformation-dependent epitopes highlighting the link between conformational plasticity of spike proteins and capacity for eliciting specific binding and broad neutralization responses. We have developed an integrated computational strategy that includes bioinformatics sequence and coevolutionary analysis, atomistic biophysical simulations and perturbation-based network modeling of the SARS-CoV-2 spike complexes with antibodies targeting distinct epitopes to explore molecular mechanisms underlying binding-induced dynamics and allosteric signaling in the SARS-CoV-2 spike proteins. This computational approach was used to examine molecular mechanisms underlying functional effects of novel circulating mutational variants in the SARS-CoV-2 S protein. The results of our studies showed that circulating mutations and antibody-escaping mutations can target allosteric hotspots with sufficient dynamic plasticity and evolutionary adaptability to modulate binding with the host receptor, while reducing efficiency of antibody recognition and compromising the long-range allosteric communications in the SARS-CoV-2 spike proteins. These critical functional sites on the spike protein correspond to a group of versatile allosteric centers in which small perturbations can modulate collective motions, alter the global allosteric response and elicit binding resistance. We suggest that SARS-CoV-2 S protein may function as a functionally adaptable allosteric machine that exploits plasticity of allosteric regulatory centers to generate escape mutants that fine-tune response to antibody binding without compromising activity of the spike protein. I will discuss allosteric regulatory mechanisms of SARS-CoV-2 S proteins and approaches for therapeutic intervention of the SARS-CoV-2 spike binding with the host receptor by targeting hotspots of allosteric interactions and signal transmission in the SARS-CoV-2 proteins.

Thermodynamics of CHO Proto-Metabolites in Simple Autocatalytic Cycles

Jeremy Kua

University of San Diego

Using quantum chemistry, we explore the free energy landscape of chemical compounds containing carbon, hydrogen, and oxygen, that might be suitable to sustain a proto-metabolism before the advent of enzymes and more complex co-factors. We first analyze thermodynamic cycles of the core metabolites formed by CO2 fixation with H2 as reductant. Then using the simplest autocatalytic cycle as a framework, we explore the possibility of other cycles that may utilize chemical cousins of the core CHO metabolites. We find that paying attention to redox states illuminates which reactions are endergonic or exergonic. The role of acetate as the linchpin C2 species in an autocatalytic cycle and how it may be advantageous or disadvantageous compared to its chemical cousins (glycolaldehyde, glycolate, and glyoxalate) will be discussed.

Ab Initio Quantum Dynamics of Nanoscale Materials

Oleg V. Prezhdo

University of Southern California, Department of Chemistry, Los Angeles, CA 90089, USA
E-mail: prezhdo@usc.edu

Excited state dynamics play key roles in numerous molecular and nanoscale materials designed for photovoltaics and photo-catalysis. Controlling these far-from-equilibrium processes and steering them in desired directions require understanding of material's dynamical response on the nanometer scale and with fine time resolution. We couple real-time time-dependent density functional theory for the evolution of electrons with non-adiabatic molecular dynamics for atomic motions to model such non-equilibrium response in the time-domain and at the atomistic level. The talk will explain the simulation methodology [1,2] and will discuss several exciting applications among the broad variety of systems and processes studied in our group [3,4], including metal halide perovskites, transition metal dichalcogenides, semiconducting and metallic quantum dots, metallic and semiconducting films, polymers, molecular crystals, graphene, carbon nanotubes, etc. Photo-induced charge and energy transfer, plasmonic excitations, Auger-type processes, energy losses and charge recombination create many challenges due to qualitative differences between molecular and periodic, and organic and inorganic matter. Our simulations provide a unifying description of quantum dynamics on the nanoscale, characterize the timescales and branching ratios of competing processes, resolve debated issues, and generate theoretical guidelines for development of novel systems.

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3. W. Li, Y. She, A. S. Vasenko, O. V. Prezhdo, "Ab initio nonadiabatic molecular dynamics of charge carriers in metal halide perovskites", ***Nanoscale***, **13**, 10239-10265 (2021).
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Can Ab Initio Simulations Explain the Structure and Properties of the Hydrated Electron?

Benjamin J. Schwartz

Department of Chemistry and Biochemistry, UCLA

The hydrated electron is of interest to both theorists and experimentalists as a paradigm solution-phase quantum system. Although recent work has focused on ab initio molecular dynamics to study this system, even with relatively inexpensive quantum chemistry methods such as density functional theory (DFT), such calculations are still limited to at most a few tens of water molecules and only a few picoseconds duration. This leaves open the question as to whether the calculations are converged with respect to either system size or dynamical fluctuations. Moreover, there has been no ab initio work examining the temperature-dependent behavior of the hydrated electron, which has not been satisfactorily explained by simulation. In this work, we attempt to remedy this situation by running DFT- based ab initio simulations of the hydrated electron as a function of both box size and temperature. We show that the calculated properties of the hydrated electron are not converged even with simulation sizes up to 128 water molecules and durations of several tens of picoseconds. The simulations show significant changes in the water coordination and solvation structure with box size. Our temperature-dependent simulations predict a red-shift of the absorption spectrum (computed using TD-DFT with an optimally tuned range-separated hybrid functional) with increasing temperature, but the magnitude of the predicted red-shift is larger than that observed experimentally, and the absolute position of the calculated spectra are off by over half an eV. The spectral red-shift at high temperatures is accompanied by both a partial loss of structure of the electron's central cavity and an increased radius of gyration that pushes electron density onto and beyond the first solvation shell. Overall, although ab initio simulations can provide some insights into the temperature-dependent behavior of the hydrated electron, the simulation sizes and level of quantum chemistry theory that are currently accessible are inadequate for correctly describing the experimental properties of this fascinating object.

Improving Binding Free Energy Calculations to Help Guide Pharmaceutical Discovery

David Mobley

Department of Pharmaceutical Sciences, UCI

I will give an update on some recent work in my group to improve binding free energy calculations to help guide pharmaceutical drug discovery. In particular, I'll discuss our recent work on the Separated Topologies (SepTop) approach for relative binding free energy calculations, which allows binding free energies of ligands to be compared by replacing one ligand with another in the binding site, without requiring the ligands to share a common substructure. I'll discuss test applications of this approach doing scaffold hopping, and compare it to more traditional absolute and relative binding free energy calculations. I'll also give some very brief highlights from recent Open Force Field work which benefits binding calculations, as well.

Bkit: Binding Free Energy and Kinetics Calculation Toolkit for Chemical and Biomolecular Systems

Talant Ruzmetov[1], Ruben Montes[1], Jianan Sun[1], Si-Han Chen[2], Zhiye Tang[3], Chia-en A. Chang[1]

[1]Department of Chemistry, University of California at Riverside, Riverside, CA 92521, USA
[2]VantAI, USA
[3]Institute for Molecular Science, Myodaiji, Okazaki, Aichi 444-8585, Japan

Investigating drug binding kinetics, which involves understanding and approximating drug-target residence time, is important in estimating efficacy and selectivity of drug candidates. Consideration of partially bound intermediate states also provides a more accurate description and calculations for protein-ligand binding/unbinding free energy landscape, as well as understanding binding mechanisms. Here, we present a python library that calculates free energy and residence time based on Markovian transitions between states constructed by partitioning an unbinding path into multiple states, termed unbinding index. The unbinding pathways were generated by all atom explicit solvent molecular dynamics (MD) simulations with enhanced sampling technique, and the all-atom (3N-6) dimensions are reduced to 2 or 3 dimensions using principal component space. We use the binding/unbinding index in the reduced space that corresponds to a distinct protein-ligand conformation and the milestoning theory to construct the free energy profile along the path. Using cyclin-dependent kinase 8 with cyclin C (CDK8/CycC) and pyrazolourea ligands as our model system, we compare free energy calculations to experimental observations and design new ligands with preferred binding kinetics.

Improving the Accuracy of Implicit Solvents with Physics-Guided Neural Networks

Negin Forouzesh, Ph.D.

California State University, Los Angeles

Drug discovery is one of the most challenging tasks in biological sciences; it takes about 10-15 years and $2 billion on average to discover a new drug. The main goal of drug discovery is to identify drug-like compounds (ligands) capable of modulating specific biological targets (proteins). One key feature of protein-ligand interactions is the binding free energy change, ΔΔG, that occurs between the protein and the ligand upon the ligand's attachment. This physiochemical feature heavily dictates how strongly a protein and ligand interact and is particularly useful to understand for drug design. While wet-lab experiments accurately estimate ΔΔG, they are significantly slow, costly, and laborious. On the other hand, computational simulations enable significantly faster estimation of ΔΔG and shed light on the binding mechanism of various structures that could have been complicated to be examined otherwise. The implicit solvent framework, which treats solvent as a continuum with the dielectric and non-polar properties of water, offers a much more efficient estimation of ΔΔG compared to other computational methodologies, such as alchemical free energy methods. Despite noticeable progress in implicit solvent modeling, serious concerns about its accuracy stem from the underlying physical approximations.
This research will employ modern machine learning techniques to bridge the accuracy gap between a physics-based implicit solvent model and experimental references in ΔΔG calculations. In particular, experimental data is integrated into a generalized Born (GB) implicit solvent model so that with adherence to the physical model, new structural features could improve the accuracy. In addition to the model accuracy, it is essential to retain interpretability (that accounts for the model simplicity) and transferability (that assures consistent performance on different datasets). To this end, a novel multi-objective loss function is introduced that takes "accuracy", "interpretability", and "transferability" into consideration. Standard protein-ligand databases, benchmarks, and datasets are used for designing the proposed hybrid model, including host-guest systems, SAMPL challenge benchmarks, PDBbind, and BindingDB.

Posters*

Automated, Efficient and Rigorous Absolute Binding Free Energy Calculations

Steven Ayoub*, Michael Barton, Tyler Luchko****

*Department of Chemistry and Biochemistry, California State University Northridge
**Department of Physics and Astronomy, California State University Northridge

Accurate absolute binding free energy calculations using explicit solvent molecular simulations could enhance the success rate of structure-based drug design, however it is difficult to implement and time consuming. Therefore, we implement an approach that utilizes faster implicit solvents, such as generalized Born (GB), which greatly reduces computational cost. We adapted the double decoupling method (DDM), which uses conformational restraints and paired it with GB solvent to enhance convergence. The method is tested using the SAMPL4 challenge dataset and a range of restraint forces. The calculations in GB solvent (DDM/GB) achieved a slope 1.7 and R2 = 0.7. An MAE of 6.0 kcal/mol and an MSE of -5.9 kcal/mol. Our work attempts to reduce the computational expense of ABFE calculations by using implicit solvent models as well as automating and streamlining a python workflow package to perform all calculations of a novel thermodynamic cycle, post-processing, and data analysis.

** alphabetical order*

Structure and Dynamics of Off-Target Effects in CRISPR-Cas9

Pablo R. Arantes[1], Brandon P. Mitchell,[1] Aakash Saha,[1] Lukasz Nierzwicki,[1] Martin Pacesa,[2] Martin Jinek[2] and Giulia Palermo[1]

1. Department of Bioengineering and Chemistry, University California, Riverside, United States
2. Department of Biochemistry, University of Zurich (CH)

The occurrence of off-target mutations in CRISPR-Cas9 can limit the applicability of this technology in vivo. At the molecular level, off-target effects are the unselective cleavage of DNA sequences that do not fully match the guide RNA in Cas9. Using enhanced simulation methods, we probed the effect of DNA base pair mismatches in the dynamics of CRISPR-Cas9. We found that, depending on their position and nature, base pair mismatches can induce an opening of the RNA:DNA hybrid, which results in newly formed interactions with the catalytic HNH domain. These interactions can "lock" the HNH domain in an inactive state, exerting a conformational control. These findings were corroborated by several X-ray structures of Cas9 bound to off-target substrates. Based on this success, we used molecular simulations to predict the effect of mismatches at positions that were not captured in the crystallographic structures, providing a more complete overview of the structural and dynamic effects of DNA mismatches in Cas9. Together, these insights provide a structural rationale for the off-target activity of Cas9 and contribute to the rational design of guide RNAs and off-target prediction algorithms.

References:

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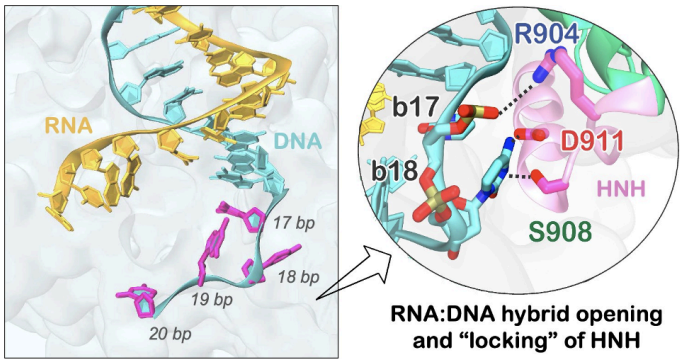

Equilibrium-nonequilibrium Ring-polymer Molecular Dynamics for Two-dimensional Vibrational Spectroscopy of Liquid Water

T. Begusic, X. Tao, G. A. Blake, T. F. Miller III

Division of Chemistry and Chemical Engineering, California Institute of Technology

Two-dimensional terahertz-Raman spectroscopic techniques [1-3] provide invaluable insight into molecular structure and dynamics of condensed-phase systems. However, corroborating experimental results with theory is difficult due to the high computational cost of incorporating quantum-mechanical effects in the simulations. Here, we present the equilibrium-nonequilibrium ring-polymer molecular dynamics (RPMD) [4], a practical computational method that can account for nuclear quantum effects on the two-time response function of nonlinear optical spectroscopy. Unlike a recently developed approach based on the double Kubo transformed (DKT) correlation function [5], our method is exact in the classical limit, where it reduces to the established equilibrium-nonequilibrium classical molecular dynamics method [6]. Using benchmark model calculations, we demonstrate the advantages of the equilibrium-nonequilibrium RPMD over classical and DKT-based approaches. Furthermore, we study the effect of temperature on the two-dimensional spectra of liquid water. We find that the spectral features associated with electrical anharmonic coupling between low-frequency intermolecular and high-frequency intramolecular modes are enhanced at higher temperature. This temperature dependence is associated directly with the tetrahedral order parameter, which measures the degree of structuring around a water molecule. Therefore, a clear structure-spectrum relationship is established, which could help guide future spectroscopic experiments towards understanding the structural and electrical properties of liquid water and water-based systems.

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Libkrylov, a Modular Open-Source Software Library for Extremely Large On-the-Fly Matrix Computations*

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Stable, efficient, and modular computational tools for solving large and dense eigenvalue and linear problems are critically important in all areas of quantum chemistry. Direct solution methods based on element-wise operations are virtually useless for the extremely large, dense or irregularly sparse coefficient matrices frequently encountered in electronic structure calculations; even explicit computation and storage of the coefficient matrices is often prohibitive. Many codes include custom matrix-free implementations of Krylov subspace algorithms for some types of large and dense linear problems. However, these implementations tend to be narrowly tailored to specific environments and deeply buried in — often proprietary — other code. I present libkrylov, an open-source library for solving matrix-free eigenvalue, linear and shifted-linear equations using Krylov subspace methods. The primary objectives of libkrylov are flexible application programming interface (API) design and modular structure, which enables integration with specialized matrix–vector evaluation “engines”. The flexible API of libkrylov features pluggable preconditioning, orthonormalization, and convergence control options. Diagonal (conjugate gradient, CG), Davidson, and Jacobi–Davidson preconditioners are available, along with orthonormal (conventional) and nonorthonormal schemes. The library is implemented in portable Fortran 2003 and takes advantage of the runtime polymorphism capabilities afforded by this standard. It can also be interfaced from C/C++ code bases through a simple function-based API.

** selected for short talk presentation*

Exploring Dimer Correction's Effect on Crystal Energies

Greg Beran and Cody Perry

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Crystal structure prediction has helped to assess relative energy differences in polymorphic crystals. While density functional theory (DFT) has lead to more efficient and accurate molecular crystal energies, errors in the intra- and intermolecular energies can lead to inaccuracies in predicted relative crystal energies. Monomer and dimer corrections to the baseline DFT model can help alleviate these errors, but performing the dimer corrections can be particularly computationally expensive. Given that the strength of the dimer interactions should decay with distance, and that even many lower-cost models are expected to describe longer-range interactions reasonably well, it becomes important to determine which dimers ought to have their intermolecular interaction description be refined with a higher-cost, higher-accuracy method.

For a challenging set of conformational polymorph crystals, dimer corrections were evaluated for dimer pairs with 4 A to 10 A inter-dimer distances using a variety of models ranging from simple density functionals all the way up to benchmarks at the coupled cluster singles, doubles, and perturbative triples level of theory. These corrections were applied to the crystal energies to determine where the most efficient dimer correction cutoff is. In all tested crystals, monomer corrections increased the accuracy of the relative crystal energies. In most systems, applying corrections for dimers up to 4 A apart increased the accuracy significantly, while performing corrections to dimers separated by 5-10 A impacted the relative energies only marginally. These results suggest that in cases where the DFT description of intermolecular interactions is potentially problematic, one should focus on refining the short-range "nearest-neighbor" dimer interactions within 4 A separation.

High-Temperature Decomposition of Diisopropyl Methylphosphonate on Alumina: Mechanistic Predictions from Ab Initio Molecular Dynamics

Sohag Biswas and Bryan M. Wong

University of California, Riverside

The enhanced degradation of organophosphorous-based chemical warfare agents (CWAs) on metal oxide surfaces holds immense promise for neutralization efforts; however, the underlying mechanisms in this process remain poorly understood. For the first time, we utilize large-scale quantum calculations to probe the high-temperature degradation of diisopropyl methylphosphonate (DIMP), a nerve agent simulant. Our Born–Oppenheimer molecular dynamics (BOMD) calculations show that the γ-Al2O3 surface shows immense promise for quickly adsorbing and destroying CWAs. We find that the alumina surface quickly adsorbs DIMP at all temperatures, and subsequent decomposition of DIMP proceeds via a propene elimination. Our BOMD calculations are complemented with metadynamics simulations to produce free energy paths, which show that the activation barrier decreases with temperature and that DIMP readily decomposes on γ-Al2O3. Our first-principle BOMD and metadynamics simulations provide crucial diagnostics for sarin decomposition models and mechanistic information for examining CWA decomposition reactions on other candidate metal oxide surfaces.

Understanding Charge Localization from Solvent Induced Symmetry Breaking through the Lens of Machine Learning

Will Borrelli, Ken Mei, Ben Schwartz

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For symmetric solutes in the condensed phase, the solvent imparts asymmetry in their local chemical environments. This solvent induced asymmetry is the deciding factor for the direction of charge transfer in condensed phase chemistry, notably in the photodissociation of homonuclear dimers. In this work, we use mixed quantum-classical molecular dynamics simulations to study the photodissociation of the sodium cation dimer in a weakly interacting solvent, liquid argon, to explore solvent motions that induce electron localization. We show that a contributing factor to the direction of charge transfer through symmetry breaking is spatial fluctuations in the solvent environment that lead to differing phases of photofragment-solvent collision times. Furthermore, using a machine learning model trained on a high dimensional description of the local solvent environment, we can sufficiently predict charge differences between each photofragment during photodissociation.

Machine-Learning Prediction of Condensed-Phase Electronic Spectroscopy with Atomistic Detail: Transfer Learning of Embedded Correlated Wavefunction Theory

Michael S. Chen[1], Yuezhi Mao[2], Prachi Gupta[3], Andrew Snider[3], Andres Montoya-Castillo[4], Tim J. Zuehlsdorff[5], Christine M. Isborn[3], Thomas E. Markland[1]

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Time-resolved, multidimensional optical spectroscopies provide a key tool to investigate the excited-state dynamics of chemical systems. Although theory has the potential to decode these spectra in terms of the underlying electronic and atomistic dynamics, the need for large numbers of excited-state electronic structure calculations severely limits first-principles predictions of multidimensional optical spectra for chromophores in the condensed phase via dynamical approaches. Recently we have circumvented this bottleneck by developing machine learning (ML) models fitted to predict excited-state energy gaps of chromophores in complex environments at the level of TDDFT. However, TDDFT severely underpredicts the width of the linear absorption spectrum for the GFP chromophore in water, making it necessary to apply higher-level, albeit considerably more computationally demanding, electronic structure methods to accurately simulate the electronic absorption spectra. Here we have developed a data-efficient ML model that leverages transfer learning to accurately predict electronic energy gaps at the level of EOM-CCSD embedded in DFT for the GFP chromophore in water. In applying our transfer-learning model to simulate linear and 2D electronic absorption spectra via a truncated cumulant approximation, we more accurately capture the width of the former and observe a dynamic Stokes shift that is more pronounced for the latter as compared to the corresponding TDDFT description. Underlying these differences is the stronger coupling of the chromophore's energy gap to the hydrogen-bonding environment predicted by the higher-level EOM-CCSD description.

Incorporating Nonlocal Exchange Effects to Assess Many-Body Quantum Properties in Nanowires

Yuan Chen and Bryan M. Wong

University of California, Riverside

Semiconductor nanowires remain an area of intense research interest due to their promise for next-generation electronics and potential architectures for quantum computing. Core-shell nanowires enable additional quantum effects and can confine two-dimensional electron gases around the semiconductor-semiconductor heterojunction interface, which can be further manipulated by external fields for various applications. The goal of this project is to incorporate nonlocal exchange effects, which would enable a more accurate calculation of many-body quantum properties.

The Effect of H, OH, Ketone, and Ether Surface Coverage on Structural and Electronic Properties of Diamond Surfaces

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Diamond has unique structural, thermal, and electronic properties that make it an interesting material for many device applications that operate in extreme conditions, such as radio-frequency field-effect transistors, power amplifiers, and communication satellites. To utilize the unique surface dependent electronic properties of the diamond surface, a comprehensive understanding of the surface adsorbate types and coverage is required. In this study, we performed Density Functional Theory (DFT) calculations of diamond (100) surfaces terminated with various percent coverages of H, OH, O in ketone configuration (Ketone), and O in ether configuration (Ether). At 25%, 50%, and 75% coverages, Ketone, where the O atom is double bonded with the surface C atom, was the most favorable. At 100% coverage, Ether, where the O atom is bridged between the two surface C atoms, was the most favorable. Analysis of the electronic properties reveals that at 100% coverage, Ketone has the smallest bandgap with a value of 0.87 eV, followed by Ether, then OH, and lastly H with the largest bandgap of 3.27 eV. Combinations of OH, Ketone, and Ether mixed with H produced a range of electronic properties that can provide flexibility in designing diamond-based devices. Overall, having various degrees of surface coverage of different functional groups terminated on the surface leads to the modification of electronic properties for engineering diamond surfaces.

Modeling Room Temperature Ionic Liquid and Calculating Translational Diffusion Coefficients Using AMOEBA GEM Polarizable Force Field

Dylan Daw

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Room-temperature ionic liquids (RTILs) are used in many applications, including batteries, fuel cells, and robots. Molecular dynamics simulations can be used to study RTILs quickly and efficiently; however, our models must first be shown to reproduce experimental results accurately. Therefore, we are testing our simulations protocol against translational diffusion measurements of a nitroxide probe molecule from electron paramagnetic resonance (EPR) experiments. We are using Tinker HP molecular dynamics software with in-house code to streamline the process of making and running a molecular dynamics simulation. We have two systems: one neat system consisting only of ions, with 216 pairs of 1-Ethyl-3-methylimidazolium cations and tetrafluoroborate anions, and another, larger system containing 720 pairs ions with four 14N-pDTEMPONE tracer probes at a dilution of 36mM. Both systems are being modeled at temperatures from 293K to 373K in 5K intervals. Diffusion coefficients of the smaller system have been calculated and are in good agreement with experiment.

Core-ionization of Liquid Water Provides Sensitive Probe of Local Structure

Sourav Dey and Anna I. Krylov

Department of Chemistry, University of Southern California

We present a new protocol for calculating the core-ionization spectra of liquid water. Since, the core level energies are characteristic to elements, the spectroscopic techniques based on the core electrons provide a powerful tool in probing the electronic structures of atoms and molecules. Moreover, the localized nature of core level electrons and subsequently its ionization/excitation makes X-ray based spectroscopies an excellent probe to study its bonding patterns and local environment. A core-valence separation- based technique implemented within the EOM-CC formalism had recently been developed to calculate the core-level states [1]. However, the existing protocols to construct valence ionization spectra does not accurately reproduce the experimental X- ray photoelectron spectra (XPS) in strongly hydrogen bonded environments like liquid water [2]. We simulate liquid water using molecular dynamics, both classical and ab initio. The ab initio molecular dynamics better reproduces the width of the spectra than TIP3P water. We find that the O 1s ionization energy converges very slowly with the size of the quantum system. The spectra calculated by considering all the water molecules up to the saturation of the first solvation shell in the quantum system gives a gap of 0.78 eV between the gas phase and condensed phase compared to 1.91 eV in the experiments [3].

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Design Principles for Molecular Qubits*

Claire Dickerson[1], Guozhu Zhu[2], Ashley Shin[1], Changling Zhao[2] , Ben Augenbraun[3], Wesley Campbell[2], John Doyle[3], Eric Hudson[2], Justin Caram[1], Anastassia Alexandrova[1]

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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.

** selected for short talk presentation*

Scalable Modeling of Transient Aggregation in gamma-D Crystallin via Network Hamiltonian Models

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Network Hamiltonian models (NHMs) are a method for topological coarse-graining of protein-protein interactions, in which each node corresponds to a protein, and edges are drawn between nodes representing proteins that are non-covalently bound. Here, this method is applied to aggregates of gammaD-crystallin, a structural protein of the eye lens implicated in cataract disease. The NHMs in this study are generated from atomistic simulations of equilibrium distributions of WT and the cataract-causing variant W42R, performed by Wong et al. (2019). Network models are shown to successfully reproduce the aggregate size and structure observed in the atomistic simulation, and provide information about the transient protein-protein interactions therein. The system size is scaled from the original 375 monomers to a system of 10000 monomers, revealing a lowering of the upper tail of the aggregate size distribution of the W42R variant. These results provide an example of the utility of NHMs for coarse-grained simulation of protein systems, as well as their ability to scale to large system sizes, reducing computational costs while retaining topological information about the system.

Modeling Variation in Structure and Dynamics of the SARS-CoV-2 Main Protease Across the Mutational Landscape

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The main protease of SARS-CoV-2 (Mpro) plays a critical role in viral replication; although it is relatively conserved, Mpro has nevertheless evolved over the course of the COVID-19 pandemic. Here, we examine phenotypic changes in clinically observed variants of Mpro, relative to the originally reported wild-type (WT) enzyme. Using atomistic molecular dynamics simulations, we examine effects of mutation on protein structure and dynamics. In addition to basic structural properties such as variation in surface area and torsion angles, we use protein structure networks (PSNs) and active site networks (ASNs) to evaluate functionally relevant features related to global cohesion and active site constraint. Substitution analysis shows a continuing trend toward more hydrophobic residues that is dependent on the location of the residue in primary, secondary, tertiary, and quaternary structure. Phylogenetic analysis provides additional evidence for the impact of selective pressure on mutation of Mpro. Overall, these analyses suggest evolutionary adaptation of Mpro toward more hydrophobicity and a less-constrained active site in response to the selective pressures of a novel host environment.

The Effects of GsMTx4 Toxin on Piezo Inhibition

Mekedlawit Efrem, Wenjuan Jiang, Yun Lyna Luo

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Touch, pain, hearing, and blood pressure regulation are driven by mechanoreceptors. Tension on these mechanoreceptors causes these proteins to act as a signaling intermediate, resulting in the opening of ion channels. Piezo 1 and 2 are mechanosensitive ion channels that open in response to membrane stretch, shear stress, and applied pressure. Despite the fact that Piezo 1 and 2 are present in most vertebrate tissues, there are no selective inhibitors that exist to date. The most common nonselective inhibitor to Piezo is GsMTx4 (Grammostola spatulata mechanotoxin 4). We hypothesize that toxin GsMTx4 inhibits Piezo through electrostatic interaction with Piezo with the extracellular region of the pore, blocking the entry and exit of cations. We tested this hypothesis using adaptive enhanced sampling MD simulations of the solved GsMTx4 structure and Piezo pore computational model obtained from our previous Anton2 simulations. Our Results indicate that GsMTx4 binds to Piezo1 through two binding sites. The primary site is at the interface of lipid bilayer and bottom of the Piezo1 cap. The secondary site is between two Piezo1 cap subunits. Pairwise contact frequency and interaction energy analysis suggest that the residue S2260, and residue E2257 from Piezo binds with residue F32 from the toxin. Further electrophysiology study of these mutants will reveal the fundamental inhibition mechanism of Piezo by a naturally occurring spider toxin GsMTx4.

Time-Reversal Symmetry in Electronic Structure

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Time-dependent electronic structure methods such as time-dependent Hartree-Fock, time-dependent density functional theory, and time-dependent correlated wavefunction theories are fundamental for the computation of molecular electronic response and excited state properties as well as time-dependent molecular dynamics beyond the weak-field limit. However, these approximate time-dependent electronic structure theories are marred by instabilities manifesting themselves, e.g., by complex excitation energies or disappearing solutions. We show that these instabilities can be related to (real) observables by extending the domain of physical states from a Hilbert space to a Krein space, which uses separate retarded and advanced components to describe time-dependent states. This state space affords an indefinite inner product whose isometries are SU(N,N) rotations. States with complex energies break time-reversal (T) symmetry, which is conserved in exact time-dependent quantum mechanics, but can break spontaneously in nonlinear approximate methods. We will show how T symmetry can be restored by imposing SU(N,N) symmetry. We propose that the resulting split-complex energies may be understood as physical deexcitation energies from an unstable reference. Numerical examples demonstrating how this approach extends the applicability of time-dependent electronic structure methods to cases previously considered intractable will be discussed.

Importance of Restoring Gauge Invariance in TDDFT Calculations with meta-GGA Functionals*

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While it is well-known that the gauge variance of the kinetic energy density τ gives rise to additional terms in the antisymmetric orbital rotation Hessian used in linear-response time-dependent density functional theory (TDDFT) for meta-generalized gradient approximations (mGGA), the effect this has on excitation energies is commonly considered negligible. Existing approaches to restore gauge-invariance (GINV) based on the paramagnetic current density have therefore not been extensively pursued.

Here, more pronounced but also highly variable effects of restoring GINV are reported for different mGGAs and different types of excitations. For a set of five Ni(II) complexes, average errors in excitation energies are reduced by 0.41 eV, 0.32 eV, and 0.10 eV for M06-2X, SCAN0, and TPSSh, respectively. It is shown that the functional dependence of the importance of imposing GINV can be linked to the derivative of the mGGA exchange energy integrand with respect to τ. A more comprehensive investigation of valence excitations in small main-group molecules reveals that n→π* excitations are significantly more affected by restoring GINV than most π→π* excitations with average changes of 0.17 eV vs 0.04 eV for M06-2X, which is rationalized by the more pronounced rotational motion of electron density from the occupied to the virtual molecular orbitals in n→π* excitations compared to most π→π* excitations.

These findings warrant a re-evaluation of previous gauge variant TDDFT results based on M06-2X and other mGGA-type functionals in benchmark and application studies.

Related publication:
R. Grotjahn, F. Furche, M. Kaupp. J. Chem. Phys. 2022, 157, 111102.

** selected for short talk presentation*

Insights into Regular and Resonant Auger Decay in Benzene Using Equation-of-motion Coupled-cluster Wave Functions

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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 this 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.

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Importance of Molecular Dynamics Equilibrium Protocol on Protein-lipid Interactions near Channel Pore

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Multiscale molecular dynamics (MD) simulations using Martini coarse-grained (CG) and all-atom (AA) forcer fields are commonly used in membrane protein studies. In particular, reverse-mapping an equilibrated CG model to an AA model offers an efficient way for preparing large membrane protein systems with complex protein shapes and lipid compositions. Here, we report that this hybrid CG-equilibrium-AA-production protocol may artificially increase lipid density and decrease hydration in ion channel pores walled with transmembrane gaps. To understand the origin of this conundrum, we conducted replicas of CG, AA, and reverse-mapped AA simulations of the pore domain of the mechanosensitive Piezo1 channel in a non-conducting conformation. Lipid/water density analysis and free energy calculations reveal that the lack of initial pore hydration allows adjacent lipids to enter the pore lumen through gaps between pore helices during CG simulation. Due to the mismatch between CG and AA lipid kinetics, these pore lipids remain trapped in the subsequent AA simulations, despite unfavorable binding free energy. We tested several CG equilibrium protocols and found that a protocol restraining the whole lipid produces pore hydration consistent with AA results, thus eliminating this artifact for further studies of lipid gating and protein-lipid interactions.
(https://www.biorxiv.org/content/10.1101/2021.11.28.470286v2)

Heterogeneous Electric Field Effects in Heme Enzyme Reactivity

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Electrostatic preorganization, the arrangement of charged groups in a protein to create an electric field that favors the transition state, is hypothesized to be a driving force in enzymatic catalysis. Heme-iron oxidoreductases provide an excellent system for studying electrostatic preorganization, due to their rigid active site structure and the importance of the Fe-O bond for reactivity. Heme oxidoreductases use molecular oxygen or hydrogen peroxide to form a highly reactive intermediate called Compound I, which contains an Fe(IV)=O center that is able to oxidize challenging substrates such as saturated hydrocarbons. We have studied the electric fields created by heme-iron proteins to elucidate the role of electrostatic preorganization in their function.

We have calculated the electric fields at the heme iron of ~200 heme-containing enzymes and found that the field tended to align along the Fe-O bond (Fz). The strength of the field correlates with function, with strongly activating Cys-ligated proteins having the highest Fz, less reactive Tyr-ligated proteins having a weaker Fz, and the least reactive His-ligated proteins having an Fz in the negative direction. These findings indicate a strong connection between electric field and function in heme-iron enzymes. Focusing on the heterogeneous field around the iron within cytochrome P450 enzymes, we next study field dynamics and differences in the fields between proteins belonging to the same class. Community algorithm groupings of the global electric field did not produce clear-cut communities within the P450 enzyme class. Furthermore, clustering a subset of enzymes over time during an MD trajectory erased all community distinctions between proteins, indicating that P450s share similar 3D electric fields. Field fluctuations are significant, however. Our next goals include elucidating the effects of field fluctuations on the heme-iron redox chemistry in P450 enzymes.

Phytochemicals as Inhibiting Agents for Chronic Myelogenous Leukemia: An In Silico Molecular Docking Analysis

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Chronic Myelogenous Leukemia (CML) is a myeloproliferative disorder characterized by the reciprocal translocation of Chromosomes 9 and 22. This translocation generates the BCR-ABL fusion protein, a constitutively active tyrosine kinase that drives CML pathogenesis via the activation of downstream effectors. Tyrosine kinase inhibitors (TKIs), the standard treatment against CML, have shown great therapeutic success; most CML patients treated with TKIs have a life expectancy similar to that of the general population. However, the T315I mutation confers nearly universal resistance to all TKIs, barring ponatinib, a third-generation pan-BCR-ABL/SRC kinase frequently associated with cardiovascular adverse events. Medicinal plants and their bioactive compounds have shown promise as chemopreventive agents in other cancers; phytochemicals are naturally occurring, widely available, and typically possess lower toxicity rates than their synthetic counterparts. As such, phytochemicals are promising synergistic complements and alternatives to chemically synthesized anticancer pharmaceuticals. The study investigated the potential of various bioactive phytochemicals as inhibitory agents against T315I mutant and wildtype BCR-ABL through a bioinformatics-based molecular docking analysis. A list of 73 phytochemical compounds with demonstrated anti-cancer properties was obtained from the scientific literature. The pharmacokinetics, druglikeness, and medicinal chemistry friendliness of the phytochemicals were evaluated; compounds that violated Lipinski's Rule of 5 were eliminated from the phytochemical library. The remaining compounds were docked against both the wildtype and T315I mutant BCR-ABL protein. Docking scores were compared against a set of six reference TKIs currently used to treat CML. The results of this study found that although none of the selected phytochemicals' binding affinity were higher than that of ponatinib and bafetinib in wildtype BCR-ABL, seven phytochemicals exhibited better binding affinity than the other four marketed pharmaceuticals. Kaempferol-7-O-Rhamnoside and L-Glutathione both had better binding affinities than all marketed control compounds in mutant T315I BCR-ABL. We propose these new inhibitors as strong candidates for further in vivo studies to serve as potential phytochemical-based antileukemic drugs.

MD-SAPT: Python Based Toolkit for Running Symmetry Adapted Perturbation Theory Calculations on Molecular Dynamics Trajectories

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Molecular dynamics (MD) simulations can identify important interactions in biomolecular systems and examine how these interactions change over the course of the simulation. Biomolecular interactions modeled with MD can be also analyzed in more detail using correlated electronic structure methods. To accomplish this, we developed MD-SAPT, an open-source Python package, to perform quantum calculations as a post-processing analysis of MD data to quantify and decompose non-covalent interaction energy. MD-SAPT has two modes of analysis: trajectory, which analyzes selected interaction pairs over the frames of an MD simulation, and docking, to examine the binding interactions between a protein and different ligands or compare different docking poses for one particular ligand to determine the relative magnitude of the interactions.

Molecular Permeability through Large-pore Channels*

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Various all-atom molecular dynamics (MD) simulation methods have been developed to compute free energies and crossing rates of ions and small molecules through ion channels. However, a systemic comparison across different methods is scarce. Using a carbon nanotube as a model of small conductance ion channel, we computed the single-channel permeability for potassium ion using umbrella sampling, Markovian milestoning, and steady-state flux under applied voltage. We show that all three methods captured consistent transport kinetic[1]. We then applied Markovian milestoning, and steady-state flux methods to study the permeation of a second messenger adenosine-3',5'-cyclophosphate (cAMP) through Connexin 26 (Cx26) hemichannel[1]. The connexin family is a diverse group of highly regulated non-β-barrel wide-pore channels permeable to biological signaling molecules. Despite their critical roles in mediating selective molecular signaling in health and disease, the molecular basis of permeation through these pores remains unclear. The potential of mean force (PMF) and the mean first passage times (MFPTs) of a single cAMP were computed from a total 16 μs multiple replicas Voronoi-tessellated Markovian milestoning simulations. Both voltage simulations and milestoning simulations revealed two cAMP binding sites and predicted cAMP permeability in similar range as experimental results. Binding constants and dissociation rates were computed from PMF and MFPTs. The protein dipole inside the pore produces an asymmetric PMF, reflected in unequal cAMP MFPTs in each direction once within the pore. PMFs under +/-200mV were derived from Markovian milestoning PMF. Overall, our study provides atomistic detailed mechanism of cAMP and demonstrated the feasibility of using non-equilibrium simulations and rare-even sampling method to study complex small molecule permeation for ion channel[2].

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** selected for short talk presentation*

Solvent Control of Chemical Identity Can Change Photodissociation into Photoisomerization

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In solution-phase chemistry, the solvent is often considered to be merely a medium that allows reacting solutes to encounter each other. In this work, however, we show that moderate locally specific solute–solvent interactions can affect not only the nature of the solute but also the types of reactive chemistry. We use quantum simulation methods to explore how solvent participation in solute chemical identity alters reactions involving the breaking of chemical bonds. In particular, we explore the photoexcitation dynamics of Na2+ dissolved in liquid tetrahydrofuran. In the gas phase, excitation of Na2+ directly leads to dissociation, but in solution, photoexcitation leads to an isomerization reaction involving rearrangement of the first-shell solvent molecules; this isomerization must go to completion before the solute can dissociate. Despite the complexity, the solution-phase reaction dynamics can be captured by a two-dimensional energy surface where one dimension involves only the isomerization of the first-shell solvent molecules.

Promoter-Poison Partnership Protects Platinum Performance in Coked Cluster Catalysts

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A perfect catalyst must exhibit “Goldilocks reactivity”; effective for the target process but not so unstable that side reactions occur, contaminating the product or deactivating the catalyst. Pt clusters are potent alkane dehydrogenation catalysts but suffer from deactivation by coke deposits formed by dehydrogenation of the alkene products. Surface-supported clusters isomerize rapidly during reactions, forming an ensemble of structures with diverse reactivities which can only be described with statistical mechanics. Realistic modelling for accurate predictions must account for this fluxional behavior. Using our ensemble modelling paradigm alongside experiment we developed nanoalloyed Pt4Ge/Al2O3 cluster catalysts which exhibit superior selectivity and activity for alkane dehydrogenation to alkenes. The principal catalytic species is Pt4GeC2, formed by total dehydrogenation of one ethane molecule, which exhibits self-limiting coking behavior. Electronic synergy between Ge and the incorporated coke turns a deactivation process into in-situ catalyst synthesis, where carbon is a co-dopant rather than a poison. The goal of catalyst design is often to avoid coking entirely, but our results show that a “symbiotic” approach can also work. We have completed the picture by assessing the dehydrogenation ability of Pt4 and Pt4C2 clusters and pinpointing the effect of Ge on cluster bonding. Finally, we use high-throughput global optimization to show that these bonding effects are applicable to a range of cluster sizes and compositions, opening the door to a new strategy for coke-resistant catalyst design.

Probabilistic Causal Network of GPCR-G protein interactions that Regulate G protein Coupling

Elizaveta Mukhaleva, Ning Ma, Grigoriy Gogoshin, Sergio Branciamore, Andrei Rodin, Nagarajan Vaidehi

Department of Computational & Quantitative Medicine, Beckman Research Institute of the City of Hope

The last decade has seen an explosion of high-resolution structures of G-protein coupled receptors (GPCRs) and their complexes with several G-proteins. Analysis of static structures and the sequence information on the residue contacts at the interface of GPCR-G protein show that GPCRs have not evolved consensus sequences for recognizing G proteins. More importantly, there is a paucity in information on the structural mechanisms by which GPCRs couple to G proteins whether it be selective or promiscuous coupling. This is because GPCR-G protein interface is dynamic and dynamic properties such as the chemical nature, spatiotemporal persistence and co-operativity of GPCR-G protein intermolecular contacts modulate the G protein coupling strength. Since GPCR-G-protein interactions are dynamic and transient, it is challenging to probe these structural determinants experimentally. In this work, we used a combination of Molecular Dynamics (MD) simulations and Bayesian Network (BN) models from Systems Biology field to decipher the GPCR-G protein residue pairs in the interface that play a critical role in coupling. By analyzing the spatial and temporal sampling of GPCR-Gα protein contacts from MD simulations of 6 GPCR-G protein complexes (consisting of 2Gs, 2Gi and 2Gq coupled complexes), we have derived causal BN models for each system. Using the node strength property of BN models we have identified the GPCR-Gα protein residue pairs that show high level of co-operativity and are causal to the G protein coupling. On the G protein side these co-operative causal residue pairs at the interface are located in the last 27 amino acids in the C-terminus of the G protein as well as in its core. We predict that these residues play a critical role in co-operativity of G protein coupling to the GPCR.

Monitoring Conical Intersection Passage in Molecule by X-ray Techniques

Yeonsig Nam, Daniel Keefer, and Shaul Mukamel

University of California, Irvine

We theoretically apply stimulated X-ray Raman (TRUECARS), time-resolved X-ray diffraction (TRXD), and transient X-ray absorption (TRXAS) techniques to probe conical intersection (CI) passage in 4-thiouracil. The S2 → S1 internal conversion is described by quantum nuclear wavepacket dynamics on a reduced reactive coordinate, where the potential energy surfaces are computed with high-level multireference method. The calculated excited state lifetime is in excellent agreement with experiments.

We critically discuss the capabilities and limitations of three techniques. We demonstrate that an off-resonant hybrid X-ray Raman probe (TRUECARS), giving a good combination of temporal and spectral resolution, offers background-free observation of temporal and energetic profiles of evolving vibronic coherence. Such information is only indirectly accessible in TRXAS when X-ray probe is resonantly tuned to core-to-valence transition energy and contribution of electronic population dominates the signal. A scattering measurement (TRXD) enable to image electron densities evolving during the CI passage. We find that three signals provide complementary information which is useful for studying photophysics in molecules.

New Ab Initio Tools for Robust Modeling of Valence, X-ray, and Entangled Multiphoton Spectroscopic Processes*

Kaushik D. Nanda and Anna I. Krylov

University of Southern California

Advances in radiation sources and instrumentation have given rise to a plethora of ever-growing spectroscopic techniques. Concomitant development of high-level ab initio methods that can reliably model and characterize light--matter interactions and complement experimental research, however, has lagged behind, which creates a bottleneck in fully exploiting the potential of these powerful spectroscopic techniques. We will present new developments in the equation-of-motion coupled-cluster framework that enable robust modeling of multiphoton spectroscopic processes in not only the valence regime but also in the X-ray and entangled-photon regimes.

** selected for short talk presentation*

The Impact of G-quadruplex Dynamics on Inter-tetrad Electronic Couplings: A Hybrid Computational Study

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The G-quadruplex is a fascinating nucleic acid motif with implications in biology, medicine and nanotechnologies. G-quadruplexes can form in the telomeres at the edges of chromosomes and in other guanine-rich regions of the genome. They can also be engineered for exploitation as biological materials for nanodevices. Their higher stiffness and higher charge transfer rates make them better candidates in nanodevices than duplex DNA. For the development of molecular nanowires, it is important to optimize electron transport along the wire axis. One powerful basis to do so is by manipulating the structure, based on known effects that structural changes have on electron transport. Here, we investigate such effects, by a combination of classical simulations of the structure and dynamics and quantum calculations of electronic couplings. We find that this structure-function relationship is complex. A single helix shape parameter alone does not embody such complexity, but rather a combination of distances and angles between stacked bases influences charge transfer efficiency. By analyzing linear combinations of shape descriptors for different topologies, we identify the structural features that most affect charge transfer efficiency. We discuss the transferability of the proposed model and the limiting effects of inherent flexibility.

The Effect of Interlayer Stacking Arrangements on the Electronic and Transport Properties of Donor-Acceptor COFs

Yuanhui Pan, Raja Ghosh, Ching-Hwa Ho, and Francesco Paesani

University of California, San Diego

Covalent organic frameworks (COFs), a class of crystalline porous organic polymers, have attracted significant attention over the last decade due to their chemical versatility, high surface area, and unique electronic properties. Here, we present a systematic theoretical analysis, based on first-principles calculations, of both structural and electronic properties of new multilayered COFs with periodic electron donor-acceptor units which form π-columnar arrays. Within each layer, the electron donors (metallophthalocyanines with copper centers) are located at the nodes of square lattices whose edge centers correspond to the electron acceptors (pyromellitic diimides). We consider different stacking geometries, including an eclipsed configuration, where the donors line up with donors and the acceptors line up with acceptors in the neighboring layers, and two staggered configurations, where for staggered I, the donors are on top of the acceptors from the neighboring layers, and for staggered II, the donors are on top of the central pores of the neighboring layers. Our results show that different stacking geometries lead to significantly different electronic and transport properties. Specifically, we find that the eclipsed one is metallic and displays high charge mobility along the stacking direction, while the staggered I displays highly localized charge states. Given these differences, we suggest that the eclipsed configuration may find applications in electronic devices, while the staggered I configuration may potentially be used as a catalyst. Overall, our analyses demonstrate that theoretical calculations provide molecular-level insights into composition-structure-property relationships of COFs which, complementing conductivity and spectroscopic measurements, can guide the design of new COFs tailored for specific applications.

Ab Initio Studies of Hydrated Electron:Cation Contact Pairs: Hydrated Electrons Simulated with DFT are too Kosmotropic

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The hydrated electron, an excess electron in liquid water, is a paradigm system that provides for a direct connection between experiment and quantum simulation. Although hydrated electrons often occur in the presence of electrolytes, there has been very little simulation work exploring how ions pair with excess electrons. In this work, we present the first ab initio simulations examining the interaction between a hydrated electron and a salt cation (Na+), with the goal of seeing whether DFT can properly account for electron:Na+ pairing and explain the experimentally-observed spectral blue shift. We find that the strength of ion pairing depends on where the simulated hydrated electron sits on the Hofmeister series. The Hofmeister series predicts that hydration structure-making (kosmostropic) cations tend to pair with kosmostropic anions, but not with hydration structure-breaking (chaotropic) anions. Based on its solvation entropy, we would expect the hydrated electron to be a strongly chaotropic anion that should have weak pairing with a kosmotropic cation like Na+. Weak pairing makes sense given that hydrated electrons in the presence of Na+ have their spectrum blue-shifted by only ~30 meV. With DFT-based ab initio dynamics, however, the spectrum of the hydrated electron is predicted to red-shift in the presence of Na+, a result in contrast with experiment. This is because the DFT-based hydrated electron is too kosmotropic, inducing such a significant reordering of the water in its first solvation shell that prioritizes water solvation over ion-pairing, causing the DFT-simulated spectrum to shift in the wrong direction. We also show that MQC simulations with a pseudopotential chosen to produce strongly chaotropic hydrated electrons shows weak ion pairing with Na+ and a predicted spectral blue-shift that is in excellent agreement with experiment. Thus, DFT is simply too low a level of theory to correctly capture the nature of this fascinating object.

Computationally Elucidating the Chemiexcitation of Dinoflagellate Luciferin

Gabriel Phun, Sergei Tretiak, Tammie Nelson, Filipp Furche

University of California, Irvine
Los Alamos National Lab

Bioluminescence is a biological process that converts chemical energy into light. Some enzymes and molecules that exhibit this phenomenon are functionally named luciferase and luciferin (LH2). A key step in the bioluminescent process is chemiexcitation, a nonadiabatic chemical reaction which results in an electronically excited species. While some mechanisms of bioluminescent systems such as firefly, bacterial, and coelenterate LH2 have been well studied, the mechanism of dinoflagellate LH2 is unknown. However, it is known that dinoflagellate LH2's mechanism is distinct from known bioluminescent mechanisms because no CO2 is formed in the process and the oxyLH2 form does not fluoresce. Two competing mechanisms, the chemiexcitation of LH2's E or Z gem-diolate form and dexter energy transfer (DET) from excited oxyLH2 to LH2, have been proposed in the literature. Here we propose a computational investigation into the chemiexcitation of dinoflagellate luciferin using nonadiabatic molecular dynamics (NAMD), explicit solvent molecules, state specific solvation, and machine learning (ML) (as time permits). We hypothesize that our study will predict chemiexcitation via NAMD quantum transitions from the ground to excited state, be able to distinguish between the two mechanisms, give mechanistic insight, and predict chemiexcitation quantum yields. This may foster the rational design of molecules for chemiexcitation.

Dynamics and Thermostability of the HNH Nuclease in Divergent Cas9 Species

Chinmai Pindi[1], Souvik Sinha[1], Helen B. Belato[2], Carmelissa Norbrun[2], Jinping Luo[3], Alexandra M. D'Ordine[2], Gerwald Jogl[2], George P. Lisi[2], Giulia Palermo[1]

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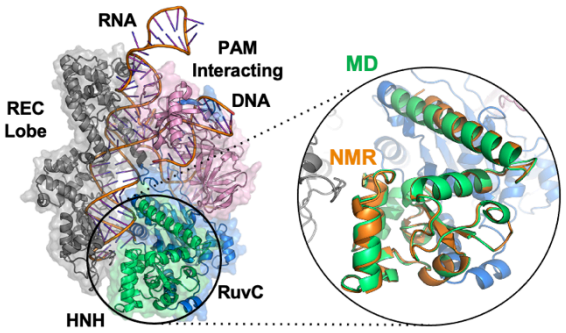

CRISPR-Cas9 is a powerful technology that has rapidly transformed genome editing. The Cas9 from *Streptococcus pyogenes* (*Sp*Cas9) is susceptible to degradation and unsuitable for applications requiring cleavage at elevated temperatures. A recently discovered Cas9 homolog from the thermophilic bacterium *Geobacillus strearothermophillus* (*Geo*Cas9) showed stability and enzymatic activity at a wider range of temperatures than that of SpCas9. The RNA-guided Cas9 protein uses its HNH endonuclease domain to cleave the DNA strand complementary to its endogenous guide RNA. In this study, we investigated the *Geo*HNH using extensive molecular dynamics (MD) simulations and solution NMR to assess its structure dynamics in comparison to the canonical mesophilic *Sp*HNH. We show that the mesophilic *Sp*HNH undergoes extensive μs-ms motion while its thermophilic counterpart, *Geo*HNH, was flexible on a faster timescale (ps-ns). While specific intradomain pathways were found to drive *Sp*HNH function, a non-specific and poorly formed signaling was found in *Geo*HNH. We also examined residue mutations in *Geo*HNH that have shown to increase the specificity in the SpCas9. The K597A mutation (corresponding to K855A in SpCas9) reduces the thermostability of *Geo*Cas9, disrupting a network of critical salt-bridge interactions. These findings show that K597A alters dynamics and structure of *Geo*Cas9, analogously to the specificity-enhancing K855A mutation in *Sp*Cas9, suggesting that lysine-to-alanine mutations might be critical for improving the specificity of *Geo*HNH and other Cas9 HNH domains. Our results provide the mechanistic differences between mesophilic and thermophilic Cas9 species which can aid in the development of alternate gene editing tools in mammalian cells.

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Membrane Enhances Vitamin D Production by Stabilization of Helical Previtamin D Conformers

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The phospholipid bilayer of epidermal skin cells has a crucial impact on natural vitamin D photosynthesis. On one hand it influences the conformationally controlled wavelength dependent photochemistry of vitamin D isomers, but it also has been found to enhance thermal [1,7]-hydrogen transfer in previtamin D (PreD), forming vitamin D. It is thought that these effects are mainly rooted in the conformational flexibility of PreD, the central compound in vitamin D photoequilibrium. To assess the influence of the phospholipid bilayer on natural vitamin D photosynthesis, we studied conformational equilibrium of PreD in dipalmitoylphosphatidylcholine (DPPC) phospholipid bilayers using classical molecular dynamics simulations. An accurate description of the torsional potential energy of previtamin D requires a balanced description of steric repulsion and π-orbital conjugation of its central hexatriene unit. To achieve this, we applied a correction map (CMAP) based on density functional theory to the CHARMM generalized force field (CGenFF). To sample the thermodynamic limit of the distribution of conformers, we applied the enhanced sampling methods replica exchange molecular dynamics (REMD) and the adaptive biasing force (ABF) sampling technique. Our simulations show that the DPPC bilayer leads to a stabilization of the helical g+Zg+ and g-Zg- conformers and a destabilization of t+Zt+ conformers. Since [1,7]-hydrogen transfer is only possible in helical conformers, this explains the enhanced vitamin D formation in the membrane. In agreement with a recent interpretation of spectroscopic results, we predict the g+Zg+ conformer to be preferred compared to the g-Zg- conformer. In addition, we show that photoinduced ring-opening of 7-dehydrocholesterol leads to a reduction of the order parameter of the membrane. The order parameter of the DPPC/previtamin D system, however, is still larger than for a pure DPPC membrane.

Deactivation Prevention of Subnano Cluster Catalysts: Role of Cluster Size and Dopant Concentration

Patricia Poths[1], Zixiang Hong[1], Edison Cummings[1], Elisa Jimenez-Izal[2,3], Borna Zandkarimi[1], Julen Munarriz[4], Anastassia N. Alexandrova[1,5]

[1]Department of Chemistry and Biochemistry, University of California, Los Angeles, Los Angeles, California 90095, [2]Polimero eta Material Aurreratuak: Fisika, Kimika eta Teknologia Saila, Kimika Fakultatea, Euskal Herriko Unibertsitatea (UPV/EHU) & Donostia International Physics Center (DIPC), M. de Lardizabal Pasealekua 3 Donostia, Euskadi (Spain), [3]IKERBASQUE, Basque Foundation for Science, Bilbao, Euskadi (Spain), [4]Departamento de Química Física y Analítica, Universidad de Oviedo, 33006 Oviedo, Spain, [5]California NanoSystem Institute University of California, Los Angeles, CA 90095

Subnano cluster catalysts are prime candidates for overcoming the typical limitations of bulk catalysts, by operating in a regime where “every atom counts”, allowing for unique size-dependent behavior. These clusters are highly fluxional, accessing a whole ensemble of isomers per cluster size, each of which can have unique reactivity. Often, the reactivity of a given cluster size is primarily driven by a higher-energy, metastable isomer. One dramatic drawback to these subnano clusters is that they are highly unstable, and can deactivate rapidly, rendering them useless as catalysts. Herein we explore multiple approaches towards the prevention of this deactivation. First, we demonstrate that the inherent fluxionality of TiO2- and Al2O3-supported Pt clusters accelerates their deactivation via sintering. However, we also identified “magic sinter-resistant” cluster sizes which are not consumed during the sintering process, indicating that careful size-selection should enable stabilization of cluster catalysts. Another typical approach to prevent cluster catalyst deactivation is to add a dopant to the cluster, such as Sn or Ge to Pt for ethane dehydrogenation. Both dopants have been proven experimentally to improve selectivity towards ethylene when dehydrogenating ethane; however this is only for specific compositions, such as Pt4Ge and Pt4Sn3. Here we demonstrate the role of dopant concentration and type on activity and selectivity for ethane dehydrogenation, using Pt4X0-4 clusters (X = Ge, Sn). Overall, we highlight the importance of operating within the fluxional paradigm for understanding and preventing deactivation processes in subnano cluster catalysts.

Discovering Low-Dimensional Manifolds within Potential Energy Surfaces

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The predictions of kinetics and mechanisms of complex chemical reactions are severely limited by the high dimensionality of potential energy surfaces (PESs). While most reactive processes are rationalized in terms of low-dimensional structures, such as internal reaction coordinates, these structures are obtained by means of energy minimizations and transition state (TS) searches on the full, high-dimensional PES. It is the strong and nonlinear coupling between reactive and nonreactive degrees of freedom (DOFs) that prevents dimensionality reduction by linear methods, for example, principal component analysis (PCA).

Here, I discuss methods for direct construction of low-dimensional manifolds within PESs, which locally approximate reactive DOFs, specifically bond breaks and bond formations. The manifolds of distance displacements (DD) is defined algorithmically using a random walk in R^3n-6 projected locally onto the set of interatomic distances. Since this construction does not rely on energy evaluations or TS searches, it can be carried out at minimal computational cost. Methods for construction of DD manifolds and dimension estimation are discussed.

DD manifolds have low local dimension d(loc), about an order of magnitude smaller than the PES dimension d(PES) or the number of interatomic distances d(int), despite covering the full space of atomic coordinates. Moreover, their dimension increases only slowly with the number of degrees of freedom. DD manifolds thus are convenient low-dimensional approximations to study chemical reaction dynamics using the methods of manifold learning.

Exploring β-cyclodextrin and Aspirin Dissociation Kinetics

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Physical forces govern bimolecular interactions, which occur in a rough energy landscape where both molecules frequently undergo conformational fluctuations during the binding and unbinding transition. Transient intermediate state interactions give rise to local barriers and are responsible for the aforementioned conformational changes. Here, we present a novel approach that offers computational tools to extract kinetic information from short molecular dynamics (MD) simulations. Our method uses all atom positions in the MD trajectory as collective variables and compresses it into three principal component modes. We divide the dissociation path into multiple regions, labeled as unbinding index, with disks in 3D principal component space and use milestoning theory to calculate transition kinetics and local free energy barriers. In this work, using β-cyclodextrin and the aspirin complex, we demonstrate free energy calculation, residence time estimation, and how our method can generalize to systems with multiple unbinding pathways.

Key Role of an Alpha-helical Lid in Driving the Target DNA Toward Catalysis in CRISPR-Cas12a

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CRISPR-Cas12a is an emerging gene editing system that came to the forefront with innovative applications such as rapid and ultrasensitive nucleic acid detection. At the core of this molecular complex, the RNA-guided Cas12a enzyme cleaves double stranded DNA using a single catalytic cleft in the RuvC domain. This opens an overarching question on how the spatially distant DNA target strand (TS) traverses toward the RuvC domain for its accommodation and subsequent cleavage in the catalytic core. Here, continuous tens of microsecond-long molecular dynamics and free-energy simulations reveal that an α-helical lid, located within the RuvC domain, plays a pivotal role in the traversal of the TS by anchoring the crRNA:TS hybrid and elegantly guiding the TS toward the RuvC core, as also corroborated by DNA cleavage experiments. In this mechanism, the Rec2 domain drives the DNA target strand toward the RuvC catalytic cleft, owing to concerted motions with the Nuc domain. While the REC2 domain pushes the TS inward into the core of the complex with its short alpha helices, the Nuc domain aids the bending and accommodation of the TS within the RuvC core by bending inward. The identified intermediates provide information on the critical residues involved in the biophysical process, holding promises for future engineering strategies aimed at improving the overall Cas12a activity.

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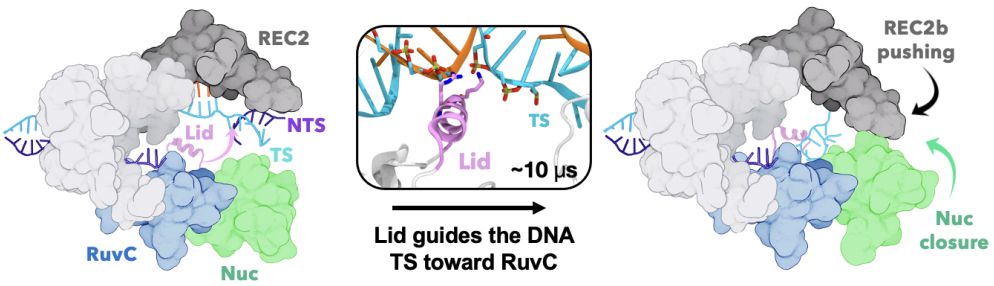

Implementing the Self Consistent Phonons Method in Turbomole

Colin Schiltz, Dmitrij Rappoport, Vladimir Mandelshtam

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The Self-Consistent Phonons (SCP) method allows for the inclusion of anharmonic effects implicitly in the harmonic approximation by minimizing the Gibbs-Bogolubov principle for the free energy of the system at a given temperature, which in turn gives the best temperature-dependent harmonic approximation for the given potential energy surface. This method provides the computational intermediate between the harmonic approximation and much more expensive methods such as basis set or path integral based methods that perturbation theory does not provide. Implementing the SCP method in the quantum chemistry program package Turbomole allows for straightforward usage of the SCP method with ab initio potentials. A "two grid" approach is introduced and improves convergence of the method, making SCP more general in application.

Defining the Allosteric Role of RNA in the CRISPR-associated Cas13a Protein

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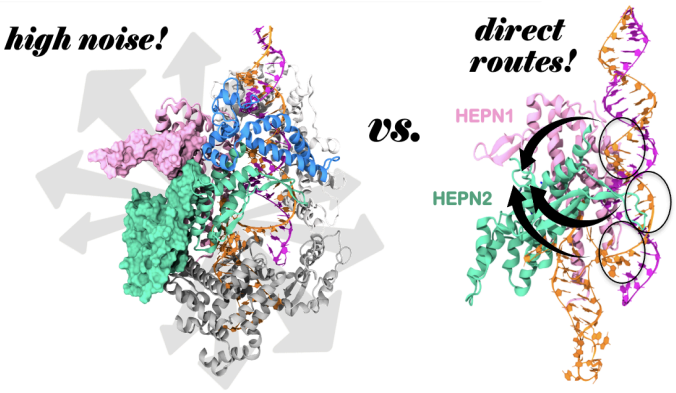
Cas13a is one of the latest additions in the CRISPR-Cas library that exclusively targets RNA, a remarkable property being leveraged for the development of tools for RNA detection, regulation, and imaging. Cas13a uses a CRISPR RNA (crRNA) sequence as a guide to target RNA sequences, which are cleaved through two Higher Eukaryotes and Prokaryotes Nucleotide (HEPN) catalytic domains. It has been demonstrated that the binding of a target RNA activates the spatially distant catalytic HEPN domains through allosteric regulation that has not been clarified. Here, extensive molecular simulations are combined with biochemical experiments to unravel the molecular basis of the RNA-mediated allosteric regulation in Cas13a. We reveal that the signal transduction pathway is activated by the target RNA and mediated by the interactions of the guide crRNA at the interface residues of HEPN domains. Perturbation in such interaction pattern, either in the presence of an extended crRNA-target RNA complementarity or in the complete absence of the target RNA, inactivate the catalytic cleft, proposing a molecular switch for Cas13a function. This characterization of the dynamic requirements underlying the RNA-mediated allosteric mechanism in Cas13a poses a fundamental understanding that can be instrumental in the development of advanced RNA-based editing and detection tools.



Analyzing the Effects of Graphene Hole Defect Size and Functional Groups on the Hydroxylation of Benzene

Oliver Solares, Sam Adler, Michael Groves

California State University, Fullerton

The current industrial method of synthesizing phenol, using metallic complexes as catalysts, is environmentally taxing. An alternative catalyst is graphene oxide, which is inexpensive and known to be an effective carbocatalyst. Understanding where a functional group on a model graphene system is most favorable, for the hydroxylation of benzene, is crucial in replicating the catalyst for the synthesis of phenol. This work intends to computationally determine the lowest energy position of three functional groups on graphene with varying hole defect size for the hydroxylation of benzene. Two, three, four, six, eight, and ten carbon atom sized hole defects were previously determined in-house and used for this work. Hydroxide, carboxylic acid, and sulfonic acid groups were placed on each of the physical hole defect systems. GPAW, a python-based density functional theory code, was used to calculate the most favorable local position of all atoms in the simulation. The energy of the graphene sheet and functional group were manually subtracted from the calculated energy of the system to yield the energy of formation for the novel C-O, C-C, or C-S bond. For the OH group simulations, the 6-carbon hole scenario was found to have the position of lowest energy of formation of -0.875eV for the O-C bond. The 6-carbon hole scenario also yielded the lowest energy of formation for the SO3H simulations at 1.014eV. For COOH, a 10-carbon hole scenario position was calculated to be the lowest energy at -0.025eV for the formation of the C-C bond. The calculated formation energies for the OH group for all hole defect sizes were noticeably lower than those of SO3H and COOH. 6 of the 18 cases had a functional group bond to graphene and form a bond with the carbon being sp3 hybridized while the remaining 12 resulted in a sp2 hybridized carbon.

Ritonavir-HIVp and xk263-HIVp Dissociation: Pathways, Energy and Comparison with Association

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Investigation of ligand-protein dissociation is crucial in understanding drug unbinding kinetics and deepening our understanding in molecular recognition. Ligand dissociation pathways may have different energy landscape and hence, affect ligand dissociation rate constant (koff). Interestingly, although experiments only provide one koff value, the ligand dissociation event can be an ensemble of multiple dissociation pathways. We therefore conducted unbiased all-atom molecular dynamics with reseeding approach to sample dissociation pathways of ritonavir-HIVp and xk263-HIVp comprehensively. Ritonavir and xk263 both favor unbinding between flap/loop region of HIVp even though these two ligands have distinct chemical structure. Ritonavir may unbind by diffusion on flap region while such pathway was not observed in xk263 dissociation due to significant hydrophobicity of xk263. Xk263 can unbind with minor HIVp flap motions while ritonavir always requires flap region to open. Van der Waals interaction energy is the dominate force during dissociation for both ligands. Ritonavir formed hydrogen bonds with multiple residues of HIVp. In contrast, H-Bonds between xk263 and HIVp were primarily restricted to Asp25, Asp124, Ile50 and Ile149. Root-mean-square deviation (RMSD) analysis on combined trajectories of ligand-protein binding/unbinding revealed that overlapping HIVp conformations, with open-flap and closed-flap, were observed in both ligand association and dissociation. Ritonavir exhibited significantly more overlapping conformations during binding/unbinding when compared to that of xk263. Our study provides insights of ligand-protein interaction and drug discovery in the aspect of unbinding kinetics.

Efficient Coarse-grained Simulations of Multiple Piezo Channels in Flat Membrane and Vesicles

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Piezo is a mechanosensitive cation channel serving a crucial role in sensing touch, tactile pain, breathing and blood pressure by converting applied force into electrical signals. Piezo comprises of 3 curved-blade like arms, 114 transmembrane helices, with an extracellular cap-like structure suspended over the central pore. Due to its shape and size, Piezo tends to depress its surrounding membrane forming a large dome shaped topology, creating various complications during standard MD techniques based on all-atom or Martini coarse-grained forcefields. Here, by employing a minimal coarse-grained model using LAMMPS program, we were able to overcome limitations of standard MD techniques and simulate lipid-protein and interprotein interactions and characterize possible packing of piezo channels at different functional states. Starting from a well-parameterized lipid bilayer and protein model, different numbers of piezo model were then inserted onto membranes of different bending rigidity. The flexibility of this CG model allowed us to investigate the propensity and topology of Piezo clustering under different channel densities, protein conformations, membrane bending rigidity, and membrane curvature. These results provide clearer insights into the clustering or non-clustering behavior of Piezo in different membrane bending rigidity and correlation between piezo neighbors based on their preferred orientations and conformations, hence bridging the gap between continuum elasticity theory and high-resolution imaging techniques.

Harnessing Natural Evolution and Computation Towards Systems Enzymology

Wenjun Xie, Arieh Warshel

University of Southern California

Rationally reprogramming enzyme catalysis requires systems-level knowledge of various enzyme mutations, which is extremely challenging. Learning from nature is inescapable to overcome this barrier. We recently distilled the evolutionary information from natural homologous sequences using a maximum-entropy model and established a connection between enzyme evolution and enzyme catalysis. The finding also provides a rational enzyme engineering approach, and about half of the predicted mutations improve enzyme catalytic power in experiment. Furthermore, we utilized natural evolution to systematically rationalize laboratory evolution of designer enzymes; we identified the sequence determinants for the selectivity of kinase covalent inhibitors and confirmed the insight using enzyme modeling. Overall, our studies show the availability of vast protein sequences from nature is promising to advance enzymology to a systems-level, an emerging field termed 'systems enzymology.'

Generalizable Machine-learned Functionals for Orbital-free Density Functional Theory

Ke Xu

Department of Physics, UC Irvine

Density Functional Theory (DFT) is one of the most popular quantum-based computational methods for physics and chemistry simulations. However, in most adaptations, it is prohibitively expensive for large-scale systems. Orbital-free Density Functional Theory (OF-DFT) is a considerably less expensive adaptation but current OF density functional approximations (DFAs) limit applicability due to low accuracy. Our goal in this project is to use Machine Learning (ML) to develop new, and presumably more generally accurate, functional approximations. We obtain training targets such as converged densities and energies from reference Kohn-Sham calculations. In each training step, we use a fully-differentiable optimizer to obtain converged OF-DFT densities, which allows us to calculate gradients from a loss which contains both energy density components, where the latter of which is rarely included in OF-DFT Machine Learning training. The aim is that the resulting DFAs from this training will generalize well to other systems outside of the training set. We report preliminary results, challenges, and future work.

Ultrafast Quantum Dynamics in Molecules Imaged by Novel Diffraction Methods

Haiwang Yong and Shaul Mukamel

University of California, Irvine

Ultrafast x-ray and electron diffraction techniques hold the promise for imaging quantum dynamics in molecules. Here we introduce three new experimental concepts that can reveal chemical dynamics unavailable otherwise. These include (a) a time-resolved twisted x-ray diffraction technique that can directly monitor the electronic coherences created as the molecule passes through a conical intersection [1], (b) a combined heterodyne x-ray and electron diffraction measurement that can directly image purely nuclear quantum dynamics [2] and (c) a self-heterodyne electron diffraction (SHED) technique that can directly image attosecond electron dynamics in real space [3].

References

[1] H. Yong, J. R. Rouxel, D. Keefer and S. Mukamel, Direct monitoring of conical intersection passage via electronic coherences in twisted x-ray diffraction, Phys. Rev. Lett. Accepted (2022).
[2] H. Yong, D. Keefer and S. Mukamel, Imaging purely-nuclear quantum dynamics in molecules by combined x-ray and electron diffraction, J. Am. Chem. Soc. 144, 7796-7804 (2022).
[3] H. Yong, S. Sun, B. Gu and S. Mukamel, Attosecond charge migration in molecules imaged by combined x-ray and electron diffraction, Under review in J. Am. Chem. Soc. (2022).

Characterizing the Dynamics of SH-dipeptide

Zixiao Zong and Carter T. Butts

University of California, Irvine

Serine-Histidine (SH-dipeptide) is a minimal peptide system with both hydrolase and peptide synthesis activity, and has been argued to be a potential candidate proto-enzyme in exobiological and/or origin-of-life settings. Here, we use a combination of machine learning and atomistic molecular dynamics to characterize the conformational landscape and dynamics of SH-dipeptide at ambient temperature, as a function of pH. We also compare the behavior of SH-dipeptide with Serine-Histidine-Aspartic Acid (SHD), a small peptide that emulates the most common serine hydrolase catalytic triad. We focus on identifying low-dimensional degrees of freedom that optimally impute the trajectory of the peptide as a whole, providing a framework that can be used for further studies of this system.

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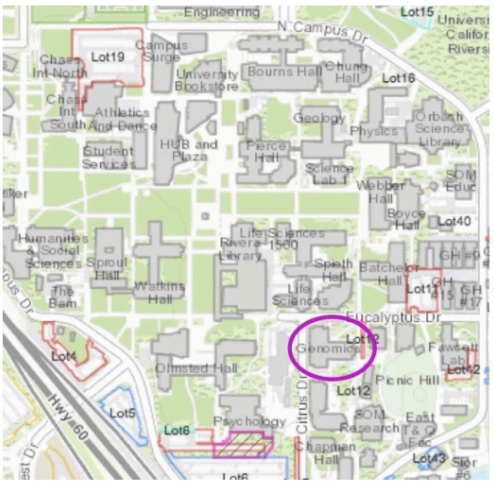
6 Location

Genomics Building

Eucalyptus Dr, Riverside, CA 92507

The SoCal TheoChem 5 will be held in the **Genomics Building** on Eucalyptus Dr, Riverside, CA 92507



To reach the Genomics Building follow the Interactive Campus Map or download a PDF of the Campus Map

The Genomics Building features a piece of Art by UCR Professor of Art Jim Isermann, you can't be wrong!

More information on our website:
https://socaltheochem5.wordpress.com/location/

7 Hotels

The UCR's friends and family have special rates at local hotels:

- Hyatt Place: $135.00 per night
- Mission Inn: $159.00 per night (weekdays) / $269.00 per night(weekends)
- Hampton Inn: $164.00 per night
- Courtyard Marriot: $189.00 per night

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