49th International Congress of Theoretical Chemists of Latin Expression
5 - 10 July 2026 | Universidade de Coimbra, Portugal

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QUITEL 2026
Theoretical Chemistry, MD & AI
Coimbra, Portugal

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QUITEL 2026
Theoretical Chemistry, MD & AI
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QUITEL 2026
Theoretical Chemistry, MD & AI
Coimbra, Portugal

SCIENTIFIC PROGRAMME

Sunday, 5 July

Sunday - July 5th				
Time	Type	Speaker	Affiliation (Country)	Talk Title
OPENING DAY				
14:00–16:30	Registration			Conference Registration Desk Open
16:30–16:45	Welcome Session			Opening Address & Welcome Ceremony (Auditorium)
OPENING KEYNOTES (Auditorium)				
16:45–17:30	Keynote — Special Presentation	Alejandro Toro-Labbé	Pontificia Universidad Católica de Chile, Chile	Perspectiva de los 100 años de la Mecánica Cuántica y de los 50 años de QUITEL
17:30-18:15	Keynote — Special Presentation	António Varandas	Universidade de Coimbra; Universidade de Vitória, Brazil; Qufu Normal University, China	Challenging the Curse of Size in Molecular Ab Initio Theory: Tiling for Shape, Extrapolation for Accuracy
SPECIAL CECAM SESSION (Auditorium)				
18:15-18:25	Opening	Andrea Cavalli	EPFL, Lausanne, Switzerland	CECAM - Centre Européen de Calcul Atomique et Moléculaire: Promoting fundamental research in atomistic and molecular simulation and modeling
18:25-18:35	Oral Communication	Lucia Palacios	Instituto de investigaciones en Fisico-Quimica Cordoba (INFIQC) - CONICET, Argentina	Accelerated exploration of the conformations of Transportan 10 and its interaction with cell membranes
18:35-18:45	Oral Communication	Lilyan Cunha Alves Pontes	Federal University of Paraíba (UFPB), Brazil	A Bond Overlap Perspective on Jahn–Teller Distortions in Transition Metal Complexes
18:45–20:30	Social Event			Welcome Cocktail Reception

QUITEL 2026

Theoretical Chemistry, MD & AI

Coimbra, Portugal

Monday, 6 July

Monday - July 6th				
Time	Type	Speaker	Affiliation (Country)	Talk Title
MORNING — KEYNOTES & INVITED TALKS (Auditorium)				
08:30–09:15	Keynote	Stefano Forli	Scripps Research Institute, La Jolla, USA	Toward Proteome-Wide Covalent Virtual Screening with Reactive Docking
09:15–09:50	Invited Plenary	Carmen Domene	University of Bath, United Kingdom	From Heat to Cold: Computational Studies of TRPV and TRPM8 Ion Channels
09:50–10:25	Invited Plenary	Célia Fonseca Guerra	Vrije Universiteit Amsterdam, Netherlands	Hydrogen bonds explained by Kohn-Sham Molecular Orbital Theory
10:25–11:00	Coffee Break			
MORNING — ORAL COMMUNICATIONS (11:00–12:20)				
SESSION A — 11:00–12:20 (Auditorium)				
11:00–11:20	Session A	Gino DiLabio	University of British Columbia, Canada	Faster and More Accurate DFT Modeling: Atom Center Potential-corrected M06-2X
11:20–11:40	Session A	Carlos Cardenas	Universidad de Chile, Chile	Conceptual DFT Reactivity Descriptors for Solids: From descriptors to Predict Interaction Energies
11:40–12:00	Session A	Daniel Conde-Torres	Universidade de Santiago de Compostela, Spain	A Physics-Based Generative Hamiltonian for Interface-Driven Peptide Design on Quantum Computers
12:00–12:20	Session A	Francesco Mazza	Scuola Normale Superiore, Italy	A Polarizable Multireference QM/MM Framework Based on Fluctuating Charges (FQ) and Fluctuating Dipoles (FQFμ): From Analytical Gradients to Anisotropic Interactions
SESSION B — 11:00–12:20 (Room B)				
11:00–11:20	Session B	Carles Curutchet	Fisicoquímica & Institut de Química Teòrica i Computacional, Spain	Characterization of protein conformational ensembles and protein-ligand binding from atomistic simulations of energy transfer
11:20–11:40	Session B	Fortuna Ponte	University of Calabria, Italy	Excited-State Driven Photoactivation in Pt(IV), Pt(IV)–Fe(II), and Ru(II) Complexes for Cancer Therapy: Insights from Computational Investigations
11:40–12:00	Session B	Liliana Mammino	University of Venda, South Africa	In Silico Investigation of the Antimalarial and Anticancer Activities of Selected Dimeric Acylphloroglucinols
12:00–12:20	Session B	Daniel J. V. A. Dos Santos	Universidade Lusófona, Portugal	On the Search for BmrA Pharmacological Inhibitors
12:20–14:00	Lunch			
AFTERNOON — KEYNOTES & INVITED TALKS (Auditorium)				
14:00–14:45	Keynote	Adrian Roitberg	University of Florida, Gainesville, USA	Machine-Learned potentials. Some history, some wishes, some regrets...
14:45–15:20	Invited Plenary	Tiziana Marino	University of Calabria, Italy	Advancements in PROMOCS on computational approaches to explore many aspects of enzymatic reactivity
15:20–15:55	Invited Plenary	G. Andrés Cisneros	University of Texas at Dallas, USA	Computational Discovery and Characterization of Disease Variants in their Biological Context
15:55–16:30	Coffee Break			
AFTERNOON — ORAL COMMUNICATIONS (16:30–17:30)				
SESSION A — 16:30–17:30 (Auditorium)				
16:30–16:50	Session A	Marzio Rosi	University of Perugia, Italy	A computational study of the reactions of N(2D) with monocyclic and polycyclic aromatic hydrocarbons and their role in the atmospheric chemistry of Titan
16:50–17:10	Session A	Barbara Herrera	Pontificia Universidad de Chile, Chile	DFT Analysis into the Reaction Mechanisms in Carbene and Metal Carbene reactions
17:10–17:30	Session A	Mateus Bergami	University of Mons, Belgium	Explicit Environmental Effects in Bulk Heterojunctions Using a QM/MM Framework
SESSION B — 16:30–17:30 (Room B)				
16:30–16:50	Session B	Matteo Rinaldi	Scuola Normale Superiore (SNS) Pisa, Italy	A polarizable embedding approach combining Density Matrix Renormalization Group and Fluctuating Charges for modeling electronic excitation energies in solution
16:50–17:10	Session B	Marcia Yineth Castillo Tarazona	Universidad de Los Andes, Colombia	An Integrative In Silico Framework for Machine Learning–Guided Structure-Based Virtual Screening to Identify Small Molecules Targeting Mutant p53 (R273H and R248H) at the DNA-Binding Interface
17:10–17:30	Session B	Filipe Carvalho	University of Coimbra, Portugal	Bigger Isn't Always Better: Comparing System Size, Hydration, and Software for Lipid Membrane Analysis
17:30–19:30	Poster Session			Poster Session 1 - Odd Numbers (Main Hallway)

QUITEL 2026
Theoretical Chemistry, MD & AI
Coimbra, Portugal

TUESDAY, 7 July

Tuesday - July 7th				
Time	Type	Speaker	Affiliation (Country)	Talk Title
MORNING — KEYNOTES & INVITED TALKS (Auditorium)				
08:30–09:15	Keynote	Andrea Cavalli	EPFL, Lausanne, Switzerland	Dynamical Docking and Binding Free Energy via Enhanced Sampling Methods
09:15–09:50	Invited Plenary	Sérgio M. Marques	Loschmidt Laboratories, Brno, Czech Republic	Fast Computational Analysis of Protein Tunnels and Ligand Transport in Dynamic Structures
09:50–10:25	Invited Plenary	Gian Pietro Miscione	Universidad de los Andes, Bogotá, Colombia	Integrated Computational and Experimental Discovery of Selective Inhibitors for Drosophila melanogaster Acetylcholinesterase
10:25–11:00	Coffee Break			
MORNING — ORAL COMMUNICATIONS (11:00–12:20)				
SESSION A — 11:00–12:20 (Auditorium)				
11:00–11:20	Session A	Angie Carolay Forero Girón	Pontificia Universidad Católica de Chile, Chile	Radicals in a Cage: Controlling Reactivity and Selectivity with Cucurbiturils
11:20–11:40	Session A	Vinícius Manzoni	Instituto de Física, Brazil	Theoretical insights into the pi → pi* transition and the large Stokes shift of a curcumin-based chromophore
11:40–12:00	Session A	Cauê P. Souza	University of Texas at Dallas / University of Kent, UK	Multiscale Simulation of Photo-Assisted Chemical Vapour Deposition
12:00–12:20	Session A	Lisset Noriega	Cinvestav-Mérida, Mexico	The Unexpected Stability of Geminal Diols in the CnH2n+2O2 (n=1-10) Family
SESSION B — 11:00–12:20				
11:00–11:20	Session B	Pablo Jaque	University of Chile, Chile	Uni and Bimodal BEP Relationships in Multi- and One- Bond Chemical Reactions: A Path-Dependent Analysis
11:20–11:40	Session B	Rodrigo Barriga	Research Institute for Medicines (iMed.ULisboa), Portugal	A Virtual Screening Campaign Targeting TIGIT: Identification of Small-Molecule Inhibitors
11:40–12:00	Session B	Federica Borzelli	Sapienza University of Rome, Italy	Computational modeling of 3-methylindole fluorescence: toward prediction of tryptophan emission and fluorescence decay
12:00–12:20	Session B	Alexandre Pérochon	Université de Poitiers, France	Conceptual DFT For And From The Excited States
12:20–14:00	Lunch			
AFTERNOON — KEYNOTES & INVITED TALKS (Auditorium)				
14:00–14:45	Keynote	Manuel Yáñez	Universidad Autónoma de Madrid, Spain	A scientific adventure that began at the III QUITEL: Is it possible to change the intrinsic reactivity of a system?
14:45–15:20	Invited Plenary	Annia Galano	Universidad Autónoma Metropolitana, Iztapalapa, Mexico	CADMA-Chem: A Computer-Assisted Protocol to Design Drugs for Multifactorial Diseases
15:20–15:55	Invited Plenary	Ilaria Ciofini	Chimie ParisTech, Paris, France	Modelling photophysical properties of molecular systems : from solution to crystals
15:55–16:30	Coffee Break			
SPECIAL SESSION (Auditorium)				
16:30–18:30	Special Session	Round Table		Special Session HPC (High Performance Computing)
20:00–22:30	Social Event			Visit to UC (University of Coimbra)

QUITEL 2026

Theoretical Chemistry, MD & AI

Coimbra, Portugal

Wednesday, 8 July

Wednesday - July 8th				
Time	Type	Speaker	Affiliation (Country)	Talk Title
MORNING — KEYNOTES & INVITED TALKS (Auditorium)				
08:30–09:15	Keynote	Alexandre Bonvin	Utrecht University, Netherlands	Solving 3D puzzles of biomolecular interactions by physics- and AI-based integrative modelling
09:15–09:50	Invited Plenary	Vlad Cojocaru	Babeș-Bolyai University, Cluj-Napoca, Romania	Pioneer transcription factors unravel nucleosomes under the computational nanoscope
09:50–10:25	Invited Plenary	Vicent Moliner	Universitat Jaume I, Castelló, Spain	Computational studies of enzyme catalysis: from inhibition to design
10:25–11:00	Coffee Break			
MORNING — ORAL COMMUNICATIONS (11:00–12:20)				
SESSION A — 11:00–12:20 (Auditorium)				
11:00–11:20	Session A	José R. B. Gomes	CICECO-Aveiro Institute of Materials, Portugal	Too Reactive, Too Passive, Just Right: Oxygen as a Control Parameter in Mo_2C Catalysis
11:20–11:40	Session A	Pietro Dal Cin	Scuola Normale Superiore, Italy	Hybrid QM/MM Approach For Computing Time-Resolved Photoelectron Spectra in Solution
11:40–12:00	Session A	Alfredo Palace	LAQV-REQUIMTE, Universidade de Évora, Portugal	T-290676 and T-2635 HIV Fusion Inhibitors Interact Strongly with Model Membranes: A Molecular Dynamics Study that Reveals
12:00–12:20	Session A	Nathalia Aceval	Facultad de Química, UdelaR, Montevideo, Uruguay	Computational and Experimental Insights into Pancreatic Lipase Inhibition by Bioactive Compounds from Stevia Rebaudiana Bertoni
SESSION B — 11:00–12:20 (Room B)				
11:00–11:20	Session B	Rodrigo Moreira	Universidad de la República, Uruguay	Comparative study of conformational dynamics of the Trypanosoma cruzi and human phosphatases: effects of pH and sensitivity to competitive metal inhibitors
11:20–11:40	Session B	Diana Vitorino	Biosystems and Integrative Sciences Institute, Universidade de Lisboa, Portugal	Protonation Dynamics at the DJ-1 Dimer Interface
11:40–12:00	Session B	Amanda Ribeiro Guimaraes	Instituto de Ciências Exatas, Brazil; United Kingdom	Targeting Glycosomal Protein Import in Trypanosoma: Molecular Dynamics Study of Pex5 Mimetic Inhibitors
12:00–12:20	Session B	Veronica Dominguez Benitez	Autonomous University of Puebla, Mexico	Intrinsic stability of sugar-phosphate backbone conformations explains structural diversity in minimal DNA fragments
12:20–14:00	Lunch			
AFTERNOON — KEYNOTES & INVITED TALKS (Auditorium)				
14:00–14:45	Keynote	Giuseppe Barca	Monash University, Melbourne, Australia	High-Performance Quantum Chemistry for AI-Driven Molecular Engineering Automata
14:45–15:20	Invited Plenary	Bernardo de Souza	FAccTs GmbH, Germany	Introducing SURFF: A New Simple, Universal and Robust Force Field with near Semi-Empirical accuracy for Large-Scale Molecular Modeling in ORCA
15:20–15:55	Invited Plenary	Benoît Champagne	University of Namur, Belgium	Computing the Nonlinear Optical Responses of Molecular Crystals: Multi-Scale versus Periodic Boundary Conditions Methods
15:55–16:30	Coffee Break			
AFTERNOON — ORAL COMMUNICATIONS (16:30–17:30)				
SESSION A — 16:30–17:30 (Auditorium)				
16:30–16:50	Session A	Alejandro Barranco Sainz	Instituto Politécnico Nacional, ESIME-Culhuacán, Mexico	DFT Study of Acetone Adsorption on Pristine and B-Doped Germanium Monolayers for Breath-Based Diabetes Sensing
16:50–17:10	Session A	Dafne Dayan Barranco Rivera	Instituto Politécnico Nacional, ESIME-Culhuacán, Mexico	Effects of dimensionality constraints on Na Diffusion in Ge and Si Nanostructures
17:10–17:30	Session A	Daniel A. Santos Oliveira	University of São Paulo, Brazil	How Fluorine Substituents Strengthen Aryl C–H Bonds
SESSION B — 16:30–17:30 (Room B)				
16:30–16:50	Session B	Efracio Mamani Flores	UNJBG, Peru	Theoretical modeling of the structural, electronic and transport properties of ZrNbCO2 Janus MXene for high-performance lithium storage
16:50–17:10	Session B	Giovanni Nottoli	Scuola Normale Superiore, Italy	Photoionization in aqueous solution using the polarizable QM/FQ embedding approach: a Tiresia-ADF multiscale framework
17:10–17:30	Session B	Komlanvi Sèvi Kaka	University of Namur, Belgium	Quantum chemistry investigation of the third-order nonlinear optical responses: From benchmark CCSD(T) to hybrid TDDFT//CCSD(T) approaches
17:30–19:30	Poster Session			Poster Session 2 - Even Numbers (Main Hallway)
20:00–22:00	Social Event			Official Conference Social Dinner (Quinta das Lágrimas)

QUITEL 2026
Theoretical Chemistry, MD & AI
Coimbra, Portugal

Thursday, 9 July

Thursday - July 9th				
Time	Type	Speaker	Affiliation (Country)	Talk Title
MORNING — KEYNOTES & INVITED TALKS (Auditorium)				
08:30–09:15	Keynote	Alicia Higueruelo	Isomorphic Labs, London, United Kingdom	An AI-first Approach to Rational Drug Design at Isomorphic Labs
09:15–09:50	Invited Plenary	Ramon Alain Miranda-Quintana	University of Florida, Gainesville, USA	Adventures in Vast Chemical Spaces
09:50–10:25	Invited Plenary	Margot Paulino	Faculty of Engineering, Universidad de Montevideo, Uruguay	Computational Synergies: Integrating Generative AI, Biomolecular Simulations, and Quantum Chemistry to Accelerate Drug Discovery
10:25–11:00	Coffee Break			
MORNING — ORAL COMMUNICATIONS (11:00–12:20)				
SESSION A — 11:00–12:20 (Auditorium)				
11:00–11:20	Session A	Ana Guimaraes	Institute of Chemical Research of Catalonia (ICIQ-CERCA), Spain	Metal Free, Light-Promoted Difunctionalization of Unactivated Alkenes: A DFT Study
11:20–11:40	Session A	Francisco Duarte	Biosystems & Integrative Sciences Institute, Ciências ULisboa, Portugal	A Statistical Analysis of Chalcogen Anisotropy in Differing Chemical Environments
11:40–12:00	Session A	Joana Sousa	University of Coimbra, Portugal	A computational study on the adsorption of antibiotics by chitosan functionalized with aromatic-aldehyde substituents
12:00–12:20	Session A	Joana Santos	University of Coimbra, Portugal	Bio-Inspired Amino Acid-Functionalized Chitosan for the Efficient Capture of Pesticides
SESSION B — 11:00–12:20 (Room B)				
11:00–11:20	Session B	Angel Rodriguez Leon	Northwestern University, USA	Assessing foundation variable-charge MLIPs for MoS2–ionic liquid interfaces: From benchmarks to fine-tuning
11:20–11:40	Session B	Gabriel Rodrigues	University of Southern Denmark, Denmark	Variational MC-PDFT including Range-Separation: Strong Correlation? Not so Strong Anymore
11:40–12:00	Session B	Volodymyr Koverga	REQUIMTE-LAQV, Faculty of Sciences, University of Porto, Portugal	Understanding Non-covalent Interactions in Ionic Liquid–Molecular Solvent Mixtures: A Combined Computational Approach
12:00–12:20	Session B	Felipe Fantuzzi	University of Kent, United Kingdom	Computational Astrochemistry of Molecules and Ices: From Interstellar Carriers to Radiation-Driven Chemistry
12:20–14:00	Lunch			
AFTERNOON — KEYNOTES & INVITED TALKS (Auditorium)				
14:00–14:45	Keynote	Marc Baaden	CNRS / IBPC, Paris, France	Electrons Crossing Membranes: a Finely Tuned Dance of Self-balancing Charges
14:45–15:20	Invited Plenary	Gabriel Merino	Cinvestav, Mérida, Mexico	Planar Hypercoordinate Atoms
14:20–15:55	Invited Plenary	Miguel San Miguel	Universidade Estadual de Campinas (UNICAMP), Brazil	Metal Oxide Semiconductors for Efficient ROS Generation: An Atomistic Perspective
15:55–16:30	Coffee Break			
AFTERNOON — SPECIAL SESSION - SOFTWARE				
16:30–17:30 (Auditorium)				
16:30–16:50	Special Session	Gabi Dias	Institute of Chemical Research of Catalonia (ICIQ), Tarragona, Spain	ioChem-BD: a Platform of Computational Chemistry and Materials Science Data Management
16:50–17:10	Special Session	Bernardo de Souza	FAccTs GmbH, Germany	The ORCA software: a broad overview and the next generation quantum chemistry
17:10–17:30	Special Session	Sergio Marques	Loschmidt Laboratories, Brno, Czech Republic	Caver Web 2.0: Interactive Web-Based Analysis of Protein Tunnels and Ligand Transport

QUITEL 2026
Theoretical Chemistry, MD & AI
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Friday, 10 July

Friday - July 10th				
Time	Type	Speaker	Affiliation (Country)	Talk Title
MORNING — KEYNOTES & INVITED TALKS (Auditorium)				
08:30–09:15	Keynote	Jean-Philip Piquemal	Sorbonne Université, Paris, France	A Quantum Foundation Model for Accurate Atomistic Simulations in Drug Design.
09:15–09:50	Invited Plenary	João B. L. Martins	University of Brasília, Brazil	Quantum Chemical Investigation of Brazilian Cerrado Natural Dyes as Sensitizers for Dye-Sensitized Solar Cells
09:50–10:25	Invited Plenary	Arménio Barbosa	Universidade Nova de Lisboa, Portugal	Computational Strategies for Affinity Ligand Discovery in Biotechnological Applications
10:25–11:00	Coffee Break			
MORNING — ORAL COMMUNICATIONS (11:00–11:40) (Auditorium)				
11:00–11:20	Session A	María Patricia Sánchez Gutiérrez	Autonomous University of Puebla (BUAP), Mexico	Influence of Methyl Group Position on the Stability of Stacked Methylxanthine Dimers
11:20–11:40	Session A	Carmela Felippa Ambort	National University of Córdoba, Argentina	Computational search for myelin-associated glycoprotein (MAG) binders that could modulate the neuroprotective properties of oligodendrocytes in neurodegenerative contexts
CLOSING SESSION (Auditorium)				
11:45-12:30	Closing Ceremony			Prizes Announcement & Conference Closing

KEYNOTE SPEAKERS

Monday, 6 July

(08:30-09:15)

IK - (26041) - TOWARD PROTEOME-WIDE COVALENT VIRTUAL SCREENING WITH REACTIVE DOCKING

Stefano Forli (United States of America)[1]
1 - Scripps Research Institute, USA

Abstract

Covalent inhibitors are central to modern drug discovery, but predicting where and how a reactive ligand will modify a target remains a major bottleneck. Reactive Docking, an MM-based extension of AutoDock, addresses two coupled questions — which residue reacts? and which ligand reacts? — with no prior knowledge of the site and no QM. The method has been generalized to virtually any nucleophilic residue (Cys, Tyr, Lys, His, Ser, …) and most warhead chemistries, validated on >400 complexes, >70 warheads, and >5,000 residues. Porting to AutoDock-GPU reduced per-ligand cost from ~45 min to ~2.5 s (>1000×), enabling proteome-scale screening.

Lightweight, interpretable ML models for intrinsic warhead and residue reactivity further sharpen predictions. Prospective applications demonstrate routine, proteome-wide covalent virtual screening within reach.

(14:00-14:45)

IK - (26030) - MACHINE-LEARNED POTENTIALS. SOME HISTORY, SOME WISHES, SOME REGRETS...

Adrian Roitberg (United States of America)[1]
1 - Department of Chemistry, University of Florida

Abstract

When one wants to work in a field where it is important to sample molecular conformations according to a distribution (e.g. Boltzmann), the standard view has been that one can either sample properly (i.e keep many structures, for which you need cheap computational methods) OR have accurate weights (i.e. Good energy calculations, which are expensive), but never both.

This general idea goes back to Dirac, who in 1929 wrote that we (theoretical physicists) need to design methods that are computationally tractable, but as accurate as possible.

In the early 2000's, a idea came to life asking: "Can a machine learning method learn quantum chemistry?" More precisely, can it learn and predict energies and forces for molecular systems with the same accuracy as actual QM calculations ? Surprisingly, the answer was YES, for a given molecular system. This enables the breaking of the problem described above. One could calculate energies very accurately, but at a very low cost, which enabled sampling !

In 2016 my group asked the follow up question: Can an ML method learn to predict energies and forces for ANY substance, given enough data? The answer was again, yes! We showed that one can create a Neural Network that can learn from a large dataset of diverse structures, and predict E and F with high accuracy for compounds outside the training dataset.

I will present some of the history of the field, show some our more recent results , and discuss some ideas as to where we might be going.

Tuesday, 7 July

(08:30-09:15)

IK - (26027) - DYNAMICAL DOCKING AND BINDING FREE ENERGY VIA ENHANCED SAMPLING METHODS

Andrea Cavalli (Switzerland)[1]
1 - CECAM-EPFL, Lausanne, Switzerland

Abstract

At the frontier of modern drug discovery, computational approaches have become crucial for identifying novel therapeutics. The critical challenge remains how to accurately simulate structural and energetic features of drug-target complexes without prohibitive computational costs. Understanding drug-target binding, along with the thermodynamics and kinetics associated with this interaction, is fundamental to optimizing lead candidates into preclinical compounds. To address these challenges, researchers are combining molecular dynamics (MD) with artificial intelligence to accelerate conformational space exploration and enable precise calculations of free energy differences and residence time.

This presentation overviews how MD techniques, augmented by machine learning, are transforming computational drug discovery, i.e., from static to dynamical docking. In this talk, we will report on their strengths and limitations, particularly in terms of free energy and kinetics estimations across large compound libraries. Retrospective validations vs. prospective predictions will also be reported and commented. Through recent case studies, we will analyze how these methods perform when applied to increasingly complex biological systems. The integration of MD, enhanced sampling, and machine learning may revolutionize the computational discovery of targeted therapeutics for precision medicine, potentially addressing significant unmet medical needs.

References

1. Ghidini A, Serra E & Cavalli A. On Free Energy Calculations in Drug Discovery. Acc. Chem. Res. 2025, 58,3137-3145.
2. Decherchi S & Cavalli A. Thermodynamics and Kinetics of Drug-Target Binding by Molecular Simulation.Chem. Rev. 2020, 120, 12788-12833.
3. Bernetti M, Masetti M, Rocchia W & Cavalli A. Kinetics of Drug Binding and Residence Time. Annu. Rev. Phys. Chem. 2019, 70, 143-171.
4. De Vivo M, Masetti M, Bottegoni G & Cavalli A. Role of Molecular Dynamics and Related Methods inDrug Discovery. J. Med. Chem. 2016, 59, 4035-61

Wednesday, 8 July

(08:30-09:15)

IK - (25882) - SOLVING 3D PUZZLES OF BIOMOLECULAR INTERACTIONS BY PHYSICS- AND AI-BASED INTEGRATIVE MODELLING

Alexandre Bonvin (Netherlands)[1]
1 - Utrecht University, Faculty of Science - Chemistry

Abstract

Understanding the structure, interactions, and dynamics of biomolecular macromolecules is key to unraveling cellular processes and advancing drug discovery. Accurate modelling of these complexes benefits greatly from incorporating diverse sources of experimental or predictive information. To this end, we have developed HADDOCK (https://www.bonvinlab.org/software), a versatile integrative modelling platform available as a web service (https://wenmr.science.uu.nl). HADDOCK can seamlessly combine data from biochemical, biophysical, and bioinformatics approaches to improve both sampling and scoring of biomolecular assemblies.

Over more than two decades of continuous development, we have also witnessed the transformative rise of AI in structure prediction. While AI has made remarkable progress, physics-based modelling remains essential, with many challenges still requiring their complementary strengths. In this talk, I will present recent advances in HADDOCK and showcase its applications, including examples where AI-generated predictions are combined with physics-based integrative modelling. In particular, I will highlight studies on antibody and nanobody–antigen complexes, demonstrating the synergy between AI and physics-based approaches.

(14:00-14:45)

IK - (25964) - HIGH-PERFORMANCE QUANTUM CHEMISTRY FOR AI-DRIVEN MOLECULAR ENGINEERING AUTOMATA

Giuseppe M. J. Barca (Australia)[1]
1 - Monash University, Australian National University, QDX Technologies

Abstract

Quantum chemistry is increasingly becoming a foundational computational layer for molecular engineering, providing the physical accuracy needed to guide molecular design, assess AI-generated hypotheses, and optimise candidate molecules. In this talk, I will discuss how GPU-native electronic-structure algorithms, large-scale molecular modelling and dynamics, precision-aware numerical methods, and high-throughput simulation workflows are extending the scale, speed, and practical reach of quantum chemical simulation. I will then describe how these capabilities can be integrated with AI models and agentic orchestration frameworks to support increasingly autonomous molecular engineering pipelines, in which simulation, prediction, design, and optimisation operate in closed-loop workflows for generating, evaluating, and refining molecular candidates.

Thursday, 9 July

(08:30-09:15)

IK - (25976) - AN AI-FIRST APPROACH TO RATIONAL DRUG DESIGN AT ISOMORPHIC LABS

Alicia Higueruelo (United Kingdom)[1]
1 - Isomorphic Labs

Abstract

Predicting biomolecular interactions is fundamental to rational drug design, yet achieving experimental accuracy and generalisability across novel chemical space remains a critical bottleneck. While deep learning approaches such as AlphaFold 3 have advanced structure prediction, benchmarks reveal that limitations persist in generalising to unexplored regions of molecular space. Here, we introduce the Isomorphic Labs Drug Design Engine (IsoDDE), a unified computational system designed to address this limitation. We demonstrate that IsoDDE more than doubles the accuracy of AlphaFold 3 on a challenging protein-ligand generalisation benchmark, successfully modelling complex out-of-distribution events such as induced fits, and accurately identifying novel binding pockets. Furthermore, we illustrate IsoDDE's utility as a scalable foundation for AI-driven drug design through its successful application in hitID campaigns.

Keywords: Drug Design AI

(14:00-14:45)

IK - (25866) - ELECTRONS CROSSING MEMBRANES: A FINELY TUNED DANCE OF SELF-BALANCING CHARGES

Etcheverry Baptiste (France)[1]; Baaden Marc (France)[2]; De La Lande Aurélien (France)[1]; Cailliez Fabien (France)[1]

1 - Université Paris Saclay, CNRS (UMR 8000), Institut de Chimie Physique, Orsay, France.; 2 - Université Paris Cité, CNRS, Laboratoire de Biochimie Théorique, F-75005 Paris, France

Abstract

Reactive oxygen species produced by NADPH oxidases (NOX) depend on electron transfer (ET) across cellular membranes via flavin and heme cofactors. We investigated the thermodynamics of inter-heme ET in the transmembrane domain of two NOX5 isoforms using extensive molecular dynamics simulations. Our comparative analysis of human and cyanobacterial NOX5 revealed that while membrane composition and protein sequence significantly alter individual component contributions to ET thermodynamics, remarkable compensatory effects maintain a consistently favorable overall free energy for electron transfer. Using linear response formalism, we decomposed free energy variations across system components and demonstrated how environmental factors adjust to preserve ET viability. This study provides the first evidence of membrane charge density effects on inter-heme ET, offering crucial insights into the self-regulating mechanisms governing electron transport in complex membrane systems.

Keywords: electron transfer, molecular dynamics, membrane transport, NADPH oxidases

Friday, 10 July

(08:30-09:15)

IK - (25979) - A QUANTUM FOUNDATION MODEL FOR ACCURATE ATOMISTIC SIMULATIONS IN DRUG DESIGN.

Jean-Philip Piquemal (France)[1]
1 - Sorbonne Université

Abstract

While artificial intelligence has revolutionized the prediction of static protein structures, characterizing their dynamics and interactions with drug candidates remains a computational bottleneck. Here, we introduce FeNNix-Bio1 [1], a foundation machine learning model designed to power accurate, reactive atomistic simulations of biological systems at an unprecedented speed and scalability. Trained exclusively on synthetic quantum chemistry data, FeNNix-Bio1 accurately captures complex condensed-phase phenomena such as ion solvation and subtle liquid water properties for which it outperforms state-of-the-art specialized force fields. In this presentation, I will illustrate its versatility across a full spectrum of drug design applications, including the calculation of hydration free energies (HFEs), the reversible folding of small proteins, the simulation of protein-ligand absolute binding free energies and chemical reactions. Notably, FeNNix-Bio1 sets a new standard for the precise prediction of HFEs for the more than 600 molecules of the Freesolv dataset, providing sub-kcal/mol accuracy. By enabling scalable, quantum-accurate molecular dynamics without the need for manual parametrization, FeNNix-Bio1 bridges the gap between static structure prediction and dynamic biological reality.

[1] A Foundation Model for Accurate Atomistic Simulations in Drug Design.T. Plé, O. Adjoua, A. Benali, E. Posenitskiy, C. Villot, L. Lagardère, J.-P.Piquemal, **2025**, submitted, DOI: 10.26434/chemrxiv-2025-f1hgn-v4

Keywords: Machine learning, Molecular dynamics, quantum chemistry, drug design, foundation model

HONOUR KEYNOTE

Sunday, 5 July

(16:45-17:30)

IK - (26029) - PERSPECTIVA DE LOS 100 AÑOS DE LA MECÁNICA CUÁNTICA Y DE LOS 50 AÑOS DE QUITEL

Alejandro Toro-Labbé (Chile)[1]

1 - Facultad de Química y de Farmacia, Pontificia Universidad Católica de Chile

Abstract

La mecánica cuántica ha impulsado avances decisivos en química, proporcionando marcos conceptuales rigurosos para explicar el comportamiento de la materia. En esta conferencia se analiza el surgimiento y la evolución de la mecánica cuántica desde una perspectiva química [1]. El desarrollo de la química cuántica se explica por la aplicación de principios cuánticos al estudio de sistemas moleculares, lo que ha permitido caracterizar estructuras electrónicas, propiedades moleculares y mecanismos de reactividad. Asimismo, se ofrece una síntesis histórica de los 50 años de QUITEL y de sus contribuciones a la química cuántica, destacando avances científicos fundamentales y la labor de personas que han impulsado vigorosamente el desarrollo de la disciplina en países de expresión latina.

[1] A. Toro-Labbé: A Chemical Perspective of the 100 Years of Quantum Mechanics, Pure Appl. Chem. 2025; 97(11): 1605–1619.

(17:30-18:15)

IK - (26028) - CHALLENGING THE CURSE OF SIZE IN MOLECULAR AB INITIO THEORY: TILING FOR SHAPE, EXTRAPOLATION FOR ACCURACY

A.J.C. Varandas (Portugal)[1,2,3]

1 - Department of Physics, Qufu Normal University, China; 2 - Department of Physics, Universidade Federal do Espírito Santo, 29075-910 Vitória, Brazil; 3 - Coimbra Chemistry Centre, University of Coimbra, 3004-535 Coimbra, Portugal

Abstract

No problem has an exact solution in Physics and Chemistry. Although the Born-Oppenheimer approximation is one century old [1] and the involved issues are highly error-resilient, today's computing is mostly designed to deliver accurate solutions at very high cost. Yet, a study in astrochemistry points up: CO2 emissions amount per astronomer to something equivalent to 5 times the global average [2]. Thence, is 100% accuracy required while experiments are themselves error affected? Are brute-force calculations for molecules and molecular materials fully reliable? Alternatively stated: is the curse of size not calling for a distinct strategy? A challenging attitude is suggested. When shape is at stake, tiling, thus focusing on the tiles that the molecule/material embeds [3,4]. Indeed, the results even leave one speculating whether the tiles can be "visible" in the parent [4]. If accuracy is at stake, extrapolation to the complete basis set (CBS) limit via an asymptotic theory is suggested, covering energies, tensorial properties, optimized geometries, and vibrational frequencies [5-8]. Notably, extrapolation with sub-minimal basis sets may even help harnessing the FCI capabilities of quantum computing [9]. Moreover, extrapolation via asymptotic theories is suggested for quantum reaction dynamics [6], since accuracy is affordable only for few-atom systems. To sum up, attitudinal-green computing is advocated to replace ongoing attitudinal-red one.

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Tuesday, 7 July

(14:00-14:45)

IK - (25958) - A SCIENTIFIC ADVENTURE THAT BEGAN AT THE III QUITEL: IS IT POSSIBLE TO CHANGE THE INTRINSIC REACTIVITY OF A SYSTEM?

Manuel Yáñez (Spain)[1]

1 - Departamento de Química, Facultad de Ciencias, and Institute for Advanced Research in Chemical Sciences (IAdChem), Universidad Autónoma de Madrid, 28049 Madrid, Spain

Abstract

At my first international conference, the III QUITEL (Granada, Spain), I presented my first work in theoretical chemistry, focused on the study of chemical reactivity, at that time using semiempirical methods. Over time, my interest in this topic came to focus on what is known as intrinsic reactivity, and in this field I directed part of my efforts toward answering the question that appears in the title of my talk. An electron-deficient system is expected to behave as an efficient electron acceptor. This trend is observed in triel and in alkaline-earth derivatives. However, diborane(4) represents a notable exception. Despite its electron deficiency, its bonding characteristics make it a proton acceptor rather than an electron acceptor. This highly unconventional behavior is further enhanced upon complexation with nitrogen bases. As shown in Figure 1, coordination of B_2H_4 with ammonia or guanidine significantly increases its electrostatic potential (MEP), making it much more attractive. At the same time, the molecular orbital localized between the two boron atoms and the associated monosynaptic basin linked to the non-nuclear attractor between them are preserved, increasing the electron density in that region. As a result, these complexes act as highly efficient proton sponges [1]. Their basicity—expressed in terms of equilibrium constants—is up to six orders of magnitude greater than that of 1,8-bis(dimethylamino)naphthalene, the prototype “proton sponge.” The effect is even more pronounced when both boron atoms interact with two independent nitrogen bases, leading to new complexes that behave as extraordinarily strong proton sponges, with basicities exceeding that of the classical proton sponge by more than ten orders of magnitude.

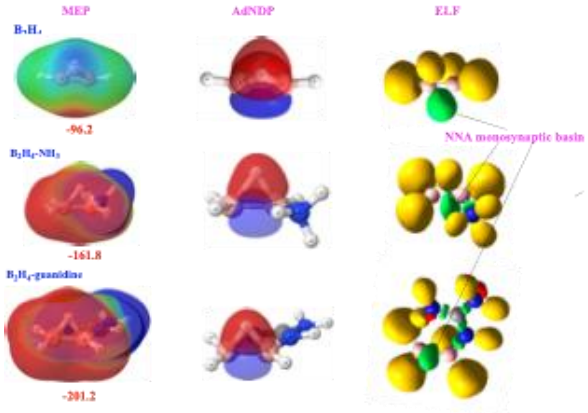

Figure 1. Electrostatic potential maps (MEP, kJ·mol^{-1}), molecular orbitals obtained using the AdNDP method, and electron localization function (ELF) maps for diborane(4) and its complexes with ammonia and guanidine.

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A significant portion of the results presented here was obtained in collaboration with several researchers, including Ibon Alkorta, M. Merced Montero-Campillo, José Elguero, and Otilia Mó, among many others whose names are too numerous to list here.

Keywords: Intrinsic reactivity; electron-deficent systems; proton sponges; G4 calculations

PLENARY SPEAKERS

Monday, 6 July

(09:15-09:50)

IP – (26132) FROM HEAT TO COLD: COMPUTATIONAL STUDIES OF TRPV1 AND TRPM8 CHANNELS

Carmen Domene (United Kingdom)[1]
1 - Department of Chemistry, University of Bath, (United Kingdom)

Abstract

Temperature sensation is essential for survival and is mediated by a subset of transient receptor potential (TRP) ion channels that respond to thermal stimuli. Among these, TRPV1 and TRPM8 channels play central roles in sensing heat and cold, respectively. Despite extensive experimental characterization, the molecular mechanisms by which temperature modulates their structure and function remain incompletely understood.

In this talk, I will present computational studies of TRPV1 and TRPM8 channels that combine molecular dynamics simulations with Site Identification by Ligand Competitive Saturation (SILCS). This integrated approach characterizes lipid–protein interactions and potential ligand-binding hotspots that influence gating transitions. Enhanced sampling techniques are used to access transient states associated with channel activation and ion permeation, while SILCS mapping systematically identifies functionally relevant interaction sites.

Together, these results provide molecular-level insight into the physical principles underlying thermosensation and complement experimental studies by revealing transient states and interactions that are difficult to access directly.

(09:50-10:25)

IP - (25986) - HYDROGEN BONDS EXPLAINED BY KOHN-SHAM MOLECULAR ORBITAL THEORY

Célia Fonseca Guerra (Netherlands)[1]
1 - Vrije Universiteit Amsterdam

Abstract

Hydrogen bonds are ubiquitous in biological and supramolecular chemistry. Nevertheless, they are still largely depicted in an oversimplified manner—convenient for use but often inadequate in explaining or even qualitatively reproducing experimental observations. In my lecture, I present a state-of-the-art physical model, founded on quantitative molecular orbital theory, which offers a quantum-mechanically sound yet intuitive approach to the fascinating complexity of the hydrogen bond. The latter can be deconstructed into comprehensible contributions, such as electrostatic interactions, covalent bonding, and Pauli repulsion between occupied orbitals. Complex and seemingly exotic phenomena are demystified and explained in a unified way: definition of hydrogen bonding, [1,2] role of aromaticity in hydrogen bonds,[3-6] variations in hydrogen bond lengths and energies due to steric repulsion,[7]legitimacy of the secondary electrostatic interaction model[8] and hydrogen bond donor capability of carboxamides, thioamides and selenoamides.[9-11]

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Nederlandse Organisatie voor Wetenschappelijk (NWO).

Keywords: hydrogen bond, Molecular Orbital Theory, Energy Decomposition Analysis

(14:45-15:20)

IP - (25873) - ADVANCEMENTS IN PROMOCS ON COMPUTATIONAL APPROACHES TO EXPLORE MANY ASPECTS OF ENZYMATIC REACTIVITY

Tiziana Marino (Italy)[1]
1 - Dipartimento di Chimica e Tecnologie Chimiche Università della Calabria, I-87036 Rende (CS), Italy

Abstract

Enzymes are extraordinarily potent catalysts of chemical processes. They accomplish remarkable accelerations in rate and do so with remarkable specificity. Determining the fundamental reason for the high efficiency of enzymes is a highly intriguing and challenging topic and of high practical importance. One of the main objectives of the research of protein function is to gain a better understanding of the mechanisms by which they accomplish these catalytic capabilities. Investigation of biomolecular processes is challenging because of the intrinsic multiscale hierarchical organization in system size and time in which chemical and chemical-physical phenomena occur. The increasing accuracy of computational approaches and of computer architectures allows one to properly describe reaction paths involved in both activation/inhibition of enzymes.

Since there is no set scale in the setting of a biological reaction or cascade—a situation in which a group of proteins, cofactors, and tiny molecules work together to produce function—systems biology is a perfect example of a multi-scale field. In our lab different computational methodologies are used for investigating the performance of some important biological systems. In particular, quantum mechanical (QM) methods based on density functional theory, molecular docking, molecular mechanics, and molecular dynamics (MD) are applied.

Some biological systems will be examined with the aim to provide atomistic insights on important and complex processes.

Financial support from Dipartimento di Chimica e Tecnologie Chimiche, Università della Calabria, is acknowledged. Parts of the computations were performed adopting resources of the Leonardo cluster (project ID: HP10CEZM7C) from ISCRA, and of supercomputer from DIBAF Department, University of Tuscia (courtesy of Professor Nico Sanna).

The computing re- sources and the related technical support used for this work have been provided by CRESCO/ENEAGRID High-Performance Computing infrastructure and its staff. CRESCO/ENEAGRID High Performance Computing infrastructure is funded by ENEA, the Italian National Agency for New Technologies, Energy and Sustainable Economic Development and by Italian and European research programs, see http://www.cresco.enea.it/english for information.

Keywords: PES, dynamic behaviour, rate determining step, structural elements, catalytic behaviour, allostery

(15:20-15:55)

IP - (26031) - COMPUTATIONAL DISCOVERY AND CHARACTERIZATION OF DISEASE VARIANTS IN THEIR BIOLOGICAL CONTEXT

G. Andrés Cisneros (United States of America)[1,2]

1 - Department of Physics, University of Texas at Dallas, Richardson, TX, 75803; 2 - Department of Chemistry & Biochemistry, University of Texas at Dallas, Richardson, TX, 75803

Abstract

Molecular simulations with classical potentials or hybrid classical/quantum approaches have been very successful for the study of a large variety of complex systems. Advances in computational performance have enabled the development of approaches that provide increased accuracy by introducing novel methodologies and representations. In this talk we will present a new approach for disease biomarker discovery and characterization, and discuss the application of classical and hybrid quantum mechanics/molecular mechanics (QM/MM) simulations for biomarker characterization including its application for selected cancer examples.

Tuesday, 7 July

(09:15-09:50)

IP - (25913) - FAST COMPUTATIONAL ANALYSIS OF PROTEIN TUNNELS AND LIGAND TRANSPORT IN DYNAMIC STRUCTURES

Sérgio M. Marques (Czech Republic)[1]; Ondrej Vavra (Czech Republic)[1]; Sime on Borko (Czech Republic)[1]; Petra Nemcova (Czech Republic)[2]; Jiri Filipovic (Czech Republic)[2]; Vojtech Vonasek (Czech Republic)[3]; Jiri Damborsky (Czech Republic)[1]; David Bednar (Czech Republic)[1]

1 - Loschmidt Laboratories, Department of Experimental Biology and RECETOX, Faculty of Science, Masaryk University, Brno, Czech Republic International Clinical Research Center, St. Anne's University Hospital Brno, Brno, Czech Republic; 2 – Institute of Computer Science, Masaryk University, Brno, Czech Republic; 3 – Faculty of Electrical Engineering, Czech Technical University Prague, Prague, Czech Republic

Abstract

Proteins serve as essential catalysts in an expanding array of biotechnological applications, from green chemistry to biopharmaceuticals. However, their industrial utility is frequently constrained by suboptimal stability or catalytic efficiency. While traditional rational design focuses on active site residues, many enzymes possess buried catalytic centers where performance is governed by the transport of molecules through the protein scaffold. In these systems, molecular tunnels act as critical communication pathways between the active site and the bulk solvent.

This presentation details an integrated computational workflow utilizing the Caver software suite to analyze these pathways within dynamic structural ensembles. Caver 3.0 facilitates the high-throughput identification and characterization of tunnels within large molecular dynamics (MD) trajectories [1]. By accounting for protein flexibility, it identifies transiently open pathways and provides rigorous statistical analysis of tunnel geometry and bottleneck dynamics. CaverDock bridges the gap between geometry and kinetics [2]. This tool uses a specialized docking algorithm to rapidly simulate ligand movement through identified tunnels. It generates comprehensive transport energy profiles and identifies physical and energetic bottlenecks, enabling rapid screening of substrates or inhibitors without the high computational cost of steered molecular dynamics or equivalent. Caver Web 2.0 [3] provides a unified, automated platform that integrates these algorithms, simplifying the setup and execution of complex transport analyses and enabling researchers to move seamlessly from structural data to the identification of mutagenesis hotspots or potent inhibitors.

Here, we demonstrate how combining these tools enables the study and redesign of protein tunnels to enhance substrate specificity and catalytic throughput. We further

highlight recent advancements in the pipelines, including improved algorithms in CaverDock for incorporating protein flexibility within cost-effective frameworks [4]. Collectively, these tools provide a fast yet robust approach for investigating biological mechanisms and for the rational engineering of protein transport pathways.

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Acknowledgements: This project was supported by the European Union's Horizon Europe Framework Programme under the grant agreement No. 101136607 (CLARA).

Keywords: Enzyme tunnels, Caver, Ligand Transport, CaverDock, Docking, Protein Flexibility

(09:50-10:25)

IP - (26040) - INTEGRATED COMPUTATIONAL AND EXPERIMENTAL DISCOVERY OF SELECTIVE INHIBITORS FOR DROSOPHILA MELANOGASTER ACETYLCHOLINESTERASE

Gian Pietro Miscione (Colombia)[1]; Daniel Ruyardi Restrepo Barbosa (Colombia)[1]

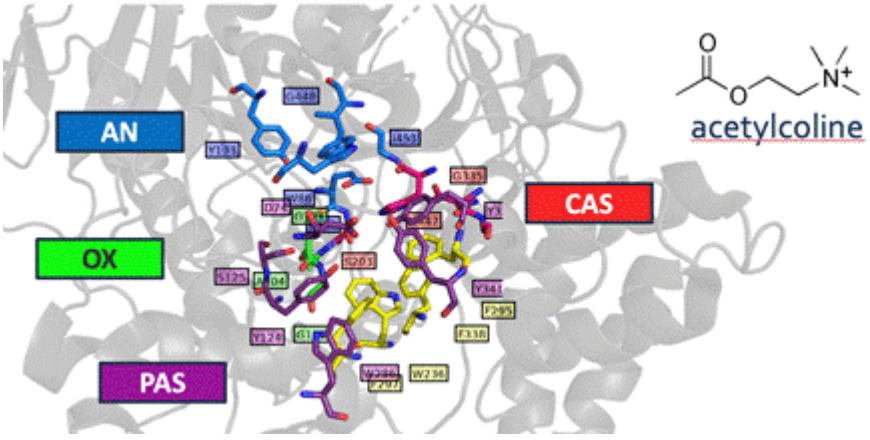
1 - COBO Computational Bio-Organic Chemistry Bogotá, Chemistry Department, Universidad de los Andes, Cra 1 No 18A-12, 111711 Bogotá, Colombia

Abstract

Approximately 20% of agricultural crops in Colombia are lost to biotic factors like insect pests. Traditional organophosphate pesticides like chlorpyrifos control insects by inhibiting acetylcholinesterase (AChE), an enzyme responsible for degrading the neurotransmitter acetylcholine. However, because humans share this vital enzyme, these pesticides present severe toxicity risks and have been widely banned.

This works aimed to identify selective inhibitors of *Drosophila melanogaster* (fruit fly), prioritizing compounds with higher affinity for this enzymatic variant over human AChE as a strategy to develop safer alternatives to conventional insecticides.

A virtual screening of volatile organic compounds with chemical properties similar to AChE inhibitor tacrine led to the selection of four promising candidates (AD9, AD10, AD14, and AD19). These compounds were analyzed using advanced computational techniques, including molecular docking, molecular dynamics, and free energy perturbation (FEP) calculations to evaluate their interactions with AChE from fruit flies, humans, and electric eels. The results highlighted AD10 (propyl 3,4,5-trihydroxybenzene-1-carboxylate) as the most selective compound, exhibiting significantly higher affinity for fruit fly AChE compared to the human and electric eel enzymes.



To optimize this lead, rational modifications were introduced to exploit unoccupied subpockets in the fruit fly binding site, generating three derivatives: AD10-Met, AD10-OH, and AD10-Ph. FEP calculations showed that two derivatives enhanced binding affinity, yielding significantly negative $DG_{binding}$. These results demonstrate that this computational strategy is a powerful tool for elucidating molecular interaction mechanisms, and for rationally designing potent, eco-friendly, and species-selective insecticides.

Keywords: Acetylcholinesterase, Drosophila melanogaster, Free Energy Perturbation, Molecular dynamics, Enzymes

(14:45-15:20)

IP - (25937) - CADMA-CHEM: A COMPUTER-ASSISTED PROTOCOL TO DESIGN DRUGS FOR MULTIFACTORIAL DISEASES

Annia Galano (Mexico)[1]
1 - Universidad Autónoma Metropolitana, Unidad Iztapalapa

Abstract

The protocol Computer-Assisted Design of Multifunctional Antioxidants based on Chemical properties (CADMA-Chem) is presented. It is currently the only protocol that simultaneously involves the analyses of drug-like behavior, toxicity, manufacturability, versatile antioxidant protection, receptor–ligand binding affinities and interaction similarity indexes. It provides a starting point that helps accelerating the discovery of oral drugs for multifactorial human health disorders. The dM38 melatonin derivative is used as a study case to illustrate the protocol in detail. It is proposed as a promising candidate for the treatment of Parkinson's and Alzheimer's diseases. It has the desired properties of oral-drugs, is better than Trolox for scavenging free radicals, chelates redox metals, prevents the •OH production via Fenton-like reactions, repairs oxidative damage in biomolecules, and acts as a polygenic neuroprotector by inhibiting catechol-O-methyl transferase (COMT), acetylcholinesterase (AChE) and monoamine oxidase B (MAOB).

Keywords: drug design, drug-like behavior, toxicity, manufacturability, versatile antioxidant protection, receptor–ligand interactions

(15:20-15:55)

IP - (25865) - MODELLING PHOTOPHYSICAL PROPERTIES OF MOLECULAR SYSTEMS: FROM SOLUTION TO CRYSTALS

Ilaria Ciofini (France)[1]
1 - Chimie ParisTech, PSL University, CNRS, Institute of Chemistry for Life and Health Sciences

Abstract

This contribution will focus on the methods allowing to model the photophysical behavior of molecular systems in condensed phases and their modulation due to aggregation. From a methodological point of view, it will be shown how electrostatic embedding schemes can be applied to accurately model localized excited states in solids by taking into account the electrostatic environment of the crystal, without treating the entire system quantum mechanically. In order to fully recover long-range effects generated by the crystalline environment, we have proposed and applied in the last years the so called "SC-Ewald" approach [1,2] starting from the original work of Derenzo et collaborators [3].

In this contribution it will be shown how such an approach can be used to model the photophysical properties of different systems [4,5] as well as various complex processes (aggregation induced emission,[6] or mechanochromism [7] in molecular crystals). Finally, a Gaussian charge-based (GC) electrostatic embedding scheme will be discussed, as a robust alternative to PC models for excited-state calculations in solids. [8]

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Keywords: photophysical properties, DFT TD-DFT, electrostatic embedding

Wednesday, 8 July

(09:15-09:50)

IP - (26130) - PIONEER TRANSCRIPTION FACTORS UNRAVEL NUCLEOSOMES UNDER THE COMPUTATIONAL NANOSCOPE

Vlad Cojocaru (Romenia)[1]
Computational Structural Biochemistry Group, STAR-UBB Institute, Babeş-Bolyai University, Cluj-Napoca, Romania

Abstract

Transcription factors such as Oct4 and Sox2 are essential proteins that bind DNA regulatory elements to establish gene regulation programs for defining cellular identity. They recognize genomic DNA while wrapped in nuclear chromatin. Chromatin is a highly dynamic structure formed from arrays of fundamental units that adopt different sizes and shapes. The fundamental unit is the nucleosome and wraps 147 base pairs of DNA around a histone core formed by 4 heterodimers of histone proteins. DNA recognition by transcription factors is highly dependent on the local chromatin structure. In nucleosome depleted regions, Oct4 and Sox2 recognize DNA mostly together via a cooperative heterodimerization mechanism involving DNA-mediated allosteric mechanisms. When nucleosomes are present, Oct4 and Sox2 recognize their binding sites on wrapped DNA and induce local opening of nucleosomes and chromatin. Because of this ability, they were are known as pioneer transcription factors. We are now starting to understand the mechanisms by which pioneer transcription factors unravel genomic DNA wrapped in nucleosomes. I will present how we are discovering key details of these mechanisms, including allosteric effects on nucleosome conformation with the computational nanoscope using molecular modeling and molecular dynamics simulations. Our findings highlight the power of the computational nanoscope in predicting functional dynamic effects in protein-DNA interactions.

(09:50-10:25)

IP - (26039) - COMPUTATIONAL STUDIES OF ENZYME CATALYSIS: FROM INHIBITION TO DESIGN

K. Świderek (Spain)[1]; V. De Sousa-Batista (Spain)[1]; A. Fernández-De-La-Pradilla (Spain)[1]; K. Arafet (Spain)[1]; V. Moliner (Spain)[1]

1 - BioComp Group, Institute of Advanced Materials (INAM), Universitat Jaume I, 12071 Castelló, Spain

Abstract

Computational chemistry techniques that combine quantum chemistry and classical molecular mechanics (QM/MM) have been extensively applied to the study of enzyme catalysis. The integration of these approaches with experimental methods has enabled a detailed understanding of the reaction mechanisms of these complex yet highly efficient biocatalysts at the molecular level. This synergy has opened new avenues for the rational design of enzyme inhibitors with potential therapeutic applications, as well as for the engineering of novel enzymes for industrial purposes, such as the depolymerization of plastics.

In this contribution, we will present recent computational studies carried out in our laboratory in close collaboration with experimental groups. These studies are focused on the design of cysteine protease inhibitors based on a detailed characterization of the full inhibition mechanism,[1,2] as well as on the development of a new computational strategy for enzyme design. This strategy is based on combining the most favorable electrostatic features of different enzymes that exhibit catalytic activity toward a common reaction.[3-5] Our efforts in enzyme engineering have been directed toward the depolymerization of PET and PUR.[6-9]

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(14:45-15:20)

IP - (25953) - INTRODUCING SURFF: A NEW SIMPLE, UNIVERSAL AND ROBUST FORCE FIELD WITH NEAR SEMI-EMPIRICAL ACCURACY FOR LARGE-SCALE MOLECULAR MODELING IN ORCA

Markus Bursch (Germany)[1]; Hagen Neugebauer (Germany)[1]; Christoph Plett (Germany)[1]; Christoph Riplinger (Germany)[1]; Bernardo De Souza (Germany)[1]
1 - FACCTs GmbH

Abstract

Here we introduce SURFF (Simple, Universal and Robust Force Field), a physics-based force field designed for fast and stable molecular modeling across a wide range of chemical systems. SURFF is built around a compact functional form with a small number of global parameters and does not require atom-specific parametrization. Its main design goals were robustness, transferability, and linear-scaling performance across the entire periodic table, which was achieved and will be demonstrated in this presentation.

The energy expression includes electrostatics, polarization, dispersion, and Pauli repulsion. Directional effects arising from lone pairs, π systems, and σ-holes are treated explicitly through angular modulation of both attractive and repulsive terms. This allows SURFF to describe hydrogen-bond directionality, anisotropic short-range repulsion, and geometrical distortions without introducing element- or environment-dependent parameters.

SURFF has been evaluated on large benchmark sets covering conformational energies, torsional profiles, and noncovalent interactions. On these targets, the accuracy is significantly higher than established force fields and, in many cases, approaches that of modern semiempirical methods like GFN2-xTB[1], while remaining much cheaper computationally. The physically motivated construction leads to stable behavior outside the benchmark domain, which is essential for structure exploration.

The method is implemented as a plugin to the ORCA[2] program package and scales linearly with system size. Due to its low computational and memory overhead, SURFF can be applied to systems ranging from small molecules to very large molecular assemblies, including systems with several hundred thousand atoms. Within ORCA, SURFF can be used for structure generation, conformational sampling, QM/MM and docking-type applications, and serves as an efficient pre-screening step prior to higher-level electronic structure calculations.

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Keywords: SURFF, universal force-field, conformational search, QM/MM, Molecular dynamics

(15:20-15:55)

IP - (25960) - COMPUTING THE NONLINEAR OPTICAL RESPONSES OF MOLECULAR CRYSTALS: MULTI-SCALE VERSUS PERIODIC BOUNDARY CONDITIONS METHODS

Benoît Champagne (Belgium)[1]
1 - University of Namur

Abstract

The presentation compares the use of two, completely different, approaches to determine the second-order nonlinear optical (NLO) properties of molecular crystals, emphasizing on the strategies to account for solid state effects.

On the one hand, the crystal second-order NLO responses are obtained in one step, adopting crystal orbital periodic boundary conditions (PBC) calculations [1]. On the one hand, the simulations are carried out in two steps combining i) first principles evaluations of the molecular properties (the polarizabilities and first hyperpolarizabilities) using a surrounding of point charges to describe the crystal polarization field with ii) electrostatic interaction schemes to account for electric field screening – also called local field – effects in order to determine the crystal responses from the molecular ones [2]. Several aspects of these simulations (e.g. DFT with different exchange-correlation functionals *versus* wavefunction calculations) are discussed at the light of comparisons with experiment [1-2].

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Keywords: Solid State Chemistry, Nonlinear Optical Responses

Thursday, 9 Luly

(09:15-09:50)

IP – (26141) - ADVENTURES IN VAST CHEMICAL SPACES

Ramon Miranda-Quintana[1]

1 - Department of Chemistry and Quantum Theory Project, University of Florida

Abstract

Chemical similarity underpins all unsupervised learning techniques in cheminformatics and AI for drug discovery. Here, efficiently identifying and organizing similar compounds within ever-growing chemical libraries remains a central challenge, as naïve approaches scale quadratically with database size and rapidly exceed available computational resources. We have tackled this problem with hyper-efficient (linear scaling) algorithms that quantify the diversity of arbitrary chemical libraries, leading to novel sampling, exploration, and visualization techniques. In particular, we developed BitBIRCH, a novel clustering algorithm specifically tailored for chemical applications, capable of partitioning ultra-large molecular datasets into similarity-based clusters with unprecedented efficiency. BitBIRCH scales linearly with the number of molecules, enabling the processing of billions of compounds in only a few hours using modest hardware (greatly reducing the computational burden to process full DELs, at a fraction of the time). Beyond clustering, we exploit this partitioning as the foundation to find activity cliffs, visualize large libraries, and speedup the search and sampling in these spaces. More recently, we have been leveraging BitBIRCH to dissect combinatorial (synthon-based) libraries spanning trillions of compounds. Our results demonstrate how similarity-driven clustering and indexing can transform virtual screening workflows, making them scalable, hardware-light, and accessible to a broader range of researchers.

(09:50-10:25)

IP - (25983) - COMPUTATIONAL SYNERGIES: INTEGRATING GENERATIVE AI, BIOMOLECULAR SIMULATIONS, AND QUANTUM CHEMISTRY TO ACCELERATE DRUG DISCOVERY

Margot Paulino Zunini (Uruguay)[1]
1 - Facultad de Ingenieria, Universidad de Montevideo. Facultad de Química, Universidad de la República

Abstract

Through the use of artificial intelligence tools, a complete pipeline was established. Starting from a set of pharmacological targets, the process generates compounds with high affinity, selecting the most promising candidates. Following laboratory synthesis and screening, the resulting candidates were further evaluated, including assessment of their chemical properties.

As a proof of concept, an application was developed for the design of highly effective and selective compounds against a specific class of parasites, structured across four phases. In the first stage, the capacity to predict protein–ligand interactions was established. In subsequent stages, novel structures were generated whilst preserving key interaction patterns. A generative network was then developed and integrated to produce new designs satisfying specific binding constraints. Finally, the designed compounds were subjected to a refinement procedure incorporating pharmacological filters, originality criteria, and structural requirements.

The process generated thousands of novel candidate compounds which, upon further filtering, yielded a focused set of leads with favorable properties — including high affinity for the target, low affinity for human counterparts, and compliance with standard drug-likeness criteria.

As an outcome of the entire process, a set of novel molecules were obtained that fulfil the fundamental requirements demanded of bioactive compounds: high originality, synthetic feasibility, safety profile, and drug-likeness.

With regard to the selected targets, their functional classifications were assessed and found to consist predominantly of enzymes relevant to parasite survival — targets that are both extensively validated and of critical importance in the development of antiparasitic agents.

Finally, the most potent molecules will be further evaluated for a potential dual mechanism of action that may substantially impact the long-sought understanding of how this class of compounds works.

Keywords: AI, Biomolecular simulations, Quantum Chemistry, Drug Discovery

(14:45-15:20)

IP - (26033) - PLANAR HYPERCOORDINATE ATOMS

Gabriel Merino (Mexico)[1]

1 - Departamento de Física Aplicada, Centro de Investigación y de Estudios Avanzados Unidad Mérida, Km. 6 Antigua carretera a Progreso Apdo. Postal 73, Cordemex, 97310, Mérida, Yuc., México

Abstract

The structural diversity of molecules that contain carbon is remarkable. By combining with only a handful of other elements, carbon forms chains, rings, and polyhedra that make up much of the material world we perceive. This versatility is traditionally rationalized by two simple construction rules. First, carbon forms at most four bonds (tetracoordination). Second, tetracoordinate carbon adopts a tetrahedral geometry. The consistency of these rules, and the apparent lack of exceptions, played a central role in the development and consolidation of chemistry throughout the twentieth century.

However, the current literature contains well-characterized systems with pentacoordinate, hexacoordinate, and even heptacoordinate carbon atoms. Moreover, there are systems in which carbon remains tetracoordinate but adopts a planar geometry. This talk aims to show that carbon extends beyond the tetrahedral paradigm. This perspective is accompanied by the development of new models to describe bonding in these “nonclassical” systems, as well as new heuristics to explore chemical space, ultimately reshaping our understanding of carbon chemistry. These conceptual frameworks have also been extended to other main-group elements, including halogens.

(14:20-15:55)

IP - (25850) - METAL OXIDE SEMICONDUCTORS FOR EFFICIENT ROS GENERATION: AN ATOMISTIC PERSPECTIVE

Miguel San-Miguel (Brazil)[1]
1 - Universidade Estadual de Campinas (Unicamp)

Abstract

Reactive oxygen species (ROS) are key intermediates in photocatalytic processes, owing to their strong oxidative character and central role in applications such as water purification and pollutant degradation. Beyond environmental remediation, ROS are also associated with oxidative damage in biological systems, enabling applications in antimicrobial and antiviral technologies.

In this contribution, we report recent advances from our group toward a fundamental understanding of ROS generation on silver-based metal oxide surfaces. We first address the structural stability and surface properties of these materials using atomistic *ab initio* thermodynamics. Building on this framework, we employ density functional theory (DFT) and *ab initio* molecular dynamics (AIMD) simulations to investigate the activation pathways of oxygen and water at the atomic scale. Our results provide detailed insights into the mechanisms of ROS formation and identify key factors controlling their generation, offering guidelines for the rational design of efficient ROS-active materials.

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Keywords: Ag-based Semiconductor Materials, Reactive Oxygen Species (ROS), DFT and Ab Initio Molecular Dynamics Simulations, Ab Initio Thermodynamics, Surface Reactivity

Friday, 10 July

(09:15-09:50)

IP - (25863) - QUANTUM CHEMICAL INVESTIGATION OF BRAZILIAN CERRADO NATURAL DYES AS SENSITIZERS FOR DYE-SENSITIZED SOLAR CELLS

Gustavo Gomes De Souza (Brazil)[1]; José Roberto Dos Santos Politi (Brazil)[1]; João B. L. Martins (Brazil)[1]

1 - University of Brasília

Abstract

The present study investigates the electronic, structural, and optical properties of natural dyes extracted from the Brazilian Cerrado (a savannah biome), aiming at their application as sensitizers in dye-sensitized solar cells (DSSCs). Initially, a database containing 12 promising dyes was constructed. These dyes were selected based on criteria of regional abundance, photochemical stability, and absorption in the visible region. The selected dyes were classified into different chemical classes: carotenoids (β-carotene, bixin, and lutein), flavonoids (quercetin and rutin), betalains (betanin), and polyphenolics (cyanidin, chalcone, alizarin, gallic acid, and procyanidin). The structures and electronic properties of the dyes were obtained through geometric optimization at the ωB97XD/def2-TZVP level of theory, combined with the implicit solvation model SMD (in water). The minimum-energy nature of each structure was confirmed by the absence of imaginary frequencies in the harmonic vibrational analysis calculations. The results regarding the electronic properties reveal significant differences among the dye classes. Carotenoids exhibited the smallest HOMO-LUMO gaps (5.61–5.75 eV), resulting from their extended π-conjugation, which favors electronic excitation, higher polarizability, and greater potential for intermolecular charge transfer. In contrast, the polyphenolics showed higher HOMO-LUMO gaps (7.49–9.15 eV), conferring greater electronic stability and lower photochemical reactivity. The dipole moments varied significantly, with minimum values for β-carotene (0.1755 D) and maximum values for rutin (14.9332 D). This reflects the influence of hydroxyl groups and glycosidic residues on molecular polarity, directly affecting affinity with aqueous solvents and interfaces in DSSCs. TD-DFT calculations, performed at the same level of theory as the geometry optimization, demonstrated that carotenoids are the most promising for photovoltaic applications. They exhibit intense absorptions in the visible region (λ_{max} between 487 and 497 nm), high oscillator strengths (up to 4.1198 for β-carotene), and light-harvesting efficiency (LHE) superior to 99.8%, with transitions predominantly of the π→π* type. In contrast, flavonoids, betalains, and other polyphenolics concentrated their absorptions mainly in the ultraviolet region (λ_{max} between 194 and 413 nm), presenting lower oscillator strengths (0.6385–1.135) and reduced LHE (77–93%), which limits their optical performance when used individually. These results, obtained from the isolated dyes, highlight the high potential of carotenoids as efficient and sustainable sensitizers for

DSSCs. The study fills theoretical gaps in the rational exploration of Brazilian biodiversity and provides subsidies for bioinspired molecular design in D-π-A type architectures. The next stage of the research, consists of modeling the adsorption of these dyes onto the TiO_2 surface in the anatase phase, using the ONIOM hybrid approach. This analysis will allow the evaluation of spectral shifts, orbital energy alignment, and electron injection efficiency at the dye–TiO_2 interface, thereby establishing a solid theoretical foundation for the development of low-cost and highly sustainable DSSCs.

CAPES, CNPq, FAPDF, UnB

Keywords: DSSC, TD-DFT, NATURAL DYES

(09:50-10:25)

OC - (26110) - COMPUTATIONAL STRATEGIES FOR AFFINITY LIGAND DISCOVERY IN BIOTECHNOLOGICAL APPLICATIONS

Arménio Barbosa (Portugal)[1]; Jéssica Rodrigues (Portugal)[1]; João Pires (Portugal)[1]; Carlos F. Costa (Portugal)[1]; A. Margarida Dias (Portugal)[1]; Cecília Roque (Portugal)[1]

1 – UCIBIO, i4HB – Chemistry Department, NOVA School of Science and Technology, NOVA University Lisbon, Almada

Abstract

In the past decades, molecular modeling and simulation of biomolecules became standard techniques in several research and development areas, mainly in pharmaceutical, chemistry, biochemistry and materials science. Simulations of biomolecules and small molecules have become more accessible, user-friendly, and easily realized with non-experts. The flexibility of these techniques allows them to be applied to other areas like biomaterials and niche biotechnological areas such as protein affinity purification and biosensing.

A multidisciplinary approach in the discovery of new affinity ligands will be presented, with *in silico* approaches giving insights on putative molecular interactions of affinity ligands to their targets and the influence of binding and elution buffers. Successful integration of molecular modeling in this field has been evaluated in the development of synthetic ligands for purification of: antibodies[1], chicken IgY, and antigen-binding fragments; Human Serum Albumin (HSA) [2]; and SARS-CoV 2 Virus Like Particles (VLPs) [3]; and a small protein scaffold, WW, also revealed affinity for HSA [4].

The integration of molecular modeling and simulation protocols in multidisciplinary projects has been proven to be key in innovation, and with the current fast advances it has become essential to provide structural insights that are fundamentally difficult to obtain experimentally.

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49th International Congress of Theoretical Chemists of Latin Expression
5 - 10 July 2026 | Universidade de Coimbra, Portugal

ORAL COMMUNICATIONS

ORAL COMMUNICATIONS

Sunday, 5 July

(18:25-18:35) – Auditorium

OC - (26042) - ACCELERATED EXPLORATION OF THE CONFORMATIONS OF TRANSPORTAN 10 AND ITS INTERACTION WITH CELL MEMBRANES

Lucia Palacios (Argentina)[1]; S. A. Paz (Argentina)[1]
1 - Instituto de investigaciones en Fisico-Quimica Cordoba (INFIQC) - CONICET, Argentina

Abstract

The development of efficient drug delivery systems remains a significant challenge, particularly for targeting complex biological barriers. In this context, cell-penetrating peptides (CPPs) constitute a promising strategy due to their ability to translocate across cell membranes and carry diverse therapeutic cargo. With the ultimate aim of enabling the rational design and control of these vectors, significant efforts have been directed toward understanding the mechanisms by which known CPPs selectively permeate specific membranes. Characterizing the structural conformations that these peptides adopt upon interacting with different lipid environments is therefore essential to elucidate their translocation mechanisms and improve their design.

To overcome the timescale limitations of conventional sampling, we employed temperature-accelerated molecular dynamics (TAMD), a relatively novel technique that remains underutilized in peptide–membrane studies, although it is particularly well suited for accelerating the exploration of a large number of collective variables. By defining backbone dihedral angles as collective variables, TAMD enables a simultaneous and accelerated exploration of a high-dimensional conformational space, going beyond the capabilities of standard enhanced sampling approaches. The resulting high-dimensional datasets require complementary analysis tools, motivating the use of multivariate statistical methods and unsupervised learning techniques to extract relevant structural information from the accelerated trajectories.

Through this combined approach, we identify key structural differences between membrane-bound and membrane-free states, as well as the specific contacts established with each membrane type. These results reveal how the lipid environment shapes the conformational behavior of TP10 and highlight the potential of TAMD-based strategies, coupled with data-driven analysis, to uncover mechanistic insights that are difficult to access with conventional methodologies.

(18:35-18:45) – Auditorium

OC - (26043) - A BOND OVERLAP PERSPECTIVE ON JAHN–TELLER DISTORTIONS IN TRANSITION METAL COMPLEXES

L. C. A. Pontes (Brazil)[1]; C. V. Santos (Brazil)[1]; B. M. T. C. Peluzo (Brazil)[1]; E. Kraka (Brazil)[1]; R. T. Moura Jr (Brazil)[1]

1 - Federal University of Paraíba (UFPB), Brazil

Abstract

The Jahn–Teller (JT) effect introduces significant changes in electronic structure and bonding patterns. Systems affected by these distortions require appropriate theoretical models for their study. The bond overlap (OP) model and its topological extension (TOP) have been successfully applied to elucidate chemical bonding, as previously demonstrated in studies of triphenol systems and 4f orbital excitation processes in lanthanides. In this work, we apply the OP/TOP method to analyze bonding in two sets of complexes with experimental evidence of the JT effect. The complexes studied include $[Cr(OH_2)_6]^{3+}$, $[Cr(OH_2)_6]^{2+}$, $[Fe(CN)_6]^{4-}$, and $[Fe(CN)_6]^{3-}$. We also evaluate recent developments in the Chemical Bond Overlap Software (ChemBOS), designed for OP/TOP bonding analysis, with particular emphasis on its ability to process MCSCF wavefunctions. Wavefunctions of the complexes were calculated using Density Functional Theory (DFT) and Complete Active Space Self-Consistent Field (CASSCF) methods with the ORCA package. Chemical bonding was assessed using OP/TOP methodologies in ChemBOS and QTAIM. The results show that OP/TOP descriptors consistently capture bonding changes associated with JT distortions, including pronounced elongations in the Cr(II) complex and slight contractions of Fe(III) bonds. Overall, this approach provides a reliable description of bonding variations induced by the JT effect.

Monday, 6 July

(Session A | 11:00-11:20) - Auditorium

OC - (25940) - FASTER AND MORE ACCURATE DFT MODELING: ATOM CENTER POTENTIAL-CORRECTED M06-2X

Zhehan Jia (Canada)[1]; Mahsa Nazemi Ashani (Canada)[1]; Alberto Otero De La Roza (Spain)[1]; Gino Dilabio (Canada)[1]

1 - The University of British Columbia

Abstract

Despite ongoing improvements in density functional theory (DFT), common exchange-correlation functionals often fail to reach "chemical accuracy" (<1 kcal/mol) in the prediction of molecular thermochemical properties. This limitation is exacerbated in molecular systems of realistic size, where the use of small-to-medium basis sets introduces significant basis-set incompleteness error (BSIE).

In this work, we present a robust method to mitigate both functional and basis-set errors through the application of atom-centered potentials (ACPs). ACPs are one-electron potentials with the same functional form of effective core potentials and are trained to correct a low-level DFT method toward high-level reference data (e.g., CCSD(T)/CBS). We specifically developed ACPs for a wide range of atoms (H, B, C, N, O, F, Si, P, S, and Cl) optimized for use with M06-2X/6-31+G(d,p).

The resulting M06-2X /6-31+G(d,p)-ACP method was validated against diverse datasets, demonstrating performance that rivals or exceeds significantly more expensive methods. For example:

·Bond Dissociation Energies (BDEs): On the BSE49 set of ~4500 bond energies, ACPs achieve chemical accuracy and show an improvement over M06-2X/def2-TZVP by a factor of 2.5.

·Kinetics and Barrier Heights: In the challenging CYCLO70 set of pericyclic reactions, the ACP approach gives an MAE of 1.2 kcal/mol, outperforming M06-2X/aug-cc-pVTZ by over 2 kcal/mol. On the W1-SN2-BH dataset of more than 1800 S_N2 reactions, ACPs approach the accuracy of ωB97M-2/def2-QZVPPD functional but at a computational cost two orders of magnitude lower.

·General Thermochemistry: On the GSCDB137 database of >8000 thermochemical properties, ACPs reduce overall MAEs for thermochemistry and barrier height subsets by ~25% compared to the uncorrected method.

·Noncovalent Interactions: For large molecular systems (ExL8 dataset containing up to 1000 atoms), the ACP approach achieved mean percent absolute errors below 10%, out-performing M06-2X with larger triple-zeta basis sets.

By correcting for BSIE and functional deficiencies simultaneously, the M06-2X/6-31+G(d,p)-ACP method provides a route to high-accuracy thermochemical modeling

without increasing computational costs over the uncorrected method. The approach is particularly suited for large-scale mechanistic studies where high-level wavefunction methods are computationally prohibitive. The potentials are easily implemented in standard quantum chemistry software, such as Gaussian-16, via a simple modification of input files, and therefore are able to provide a seamless upgrade for existing computational chemistry workflows.

Keywords: Atom centered potentials, Density Functional Theory, Accurate thermochemistry

(Session A | 11:20-11:40) - Auditorium

OC - (25924) - CONCEPTUAL DFT REACTIVITY DESCRIPTORS FOR SOLIDS: FROM DESCRIPTORS TO PREDICT INTERACTION ENERGIES

Carlos Cardenas (Chile)[1]; Tatiana Gomez (Chile)[2]

1 - Universidad de Chile; 2 - Theoretical and Computational Chemistry Center, Institute of Applied Sciences, Faculty of Engineering, Universidad Autonoma de Chile, Del Valle Sur 534, Huechuraba, Santiago, Chile

Abstract

Conceptual Density Functional Theory (cDFT) provides a rigorous framework to rationalize chemical reactivity through density-based response functions. Its extension to solids, however, is hindered by formal and computational challenges associated with periodic boundary conditions and charged systems. Here, we further develop cDFT descriptors for extended systems, focusing on the Fukui function and its associated electrostatic potential.

We analyze different strategies to compute these quantities in solids, highlighting the impact of compensating background charges and electronic relaxation. By introducing practical correction schemes, we obtain physically meaningful Fukui functions and Fukui potentials for metallic and semiconducting surfaces. These descriptors consistently identify reactive regions and capture trends in surface reactivity.

Crucially, we show that these quantities can be embedded within a cDFT perturbation theory framework to predict interaction energies between atomic species and surfaces. The resulting model separates electrostatic and charge-transfer contributions, enabling the estimation of adsorption trends without explicit total-energy calculations. Applications to prototypical surfaces reproduce the ordering of interaction energies for reducing and oxidizing species, demonstrating predictive capability.

These results establish cDFT as a predictive framework for surface chemistry, bridging chemical bonding concepts and materials modeling.

We acknowledge ANID for the grant Proyecto Exploración 132500444 and CEDENNA CIA250002. Powered@NLHPC: This research was partially supported by the supercomputing infrastructure of the NLHPC (CCSS210001).

Keywords: Conceptual DFT

(Session A | 11:40-12:00) - Auditorium

OC - (25849) - A PHYSICS-BASED GENERATIVE HAMILTONIAN FOR INTERFACE-DRIVEN PEPTIDE DESIGN ON QUANTUM COMPUTERS

Daniel Conde-Torres (Spain)[1]; Rebeca Gagarcía-Fandiño (Spain)[1]; Ángel Piñeiro (Spain)[1]
1 - Universidade de Santiago de Compostela

Abstract

Antimicrobial peptides (AMPs) operate at heterogeneous membrane interfaces, where folding and sequence design are intrinsically coupled and computationally intractable (NP-hard) [1]. Capturing their environment-dependent conformational transitions—particularly the disorder-to-α-helix shift upon membrane binding—remains a major challenge for classical approaches [2,3].

Here, we introduce a unified, physics-based generative Hamiltonian framework that simultaneously addresses AMP folding and inverse design under heterogeneous conditions. The model integrates residue-specific helix propensities, pairwise interactions, electrostatics, and environment-dependent solvation terms into a single, physically interpretable energy landscape, extending previous interface-aware quantum-inspired folding approaches [2].

We develop two complementary algorithms. First, we extend quantum-compatible folding methods to predict peptide conformations at hydrophilic–hydrophobic interfaces without additional qubit overhead relative to homogeneous systems, preserving resource efficiency in line with current quantum algorithms [2,3]. This approach is validated on model 10-residue peptides with distinct physicochemical profiles. Second, we tackle the inverse problem by designing sequences from predefined α-helical scaffolds using multi-environment optimization objectives that encode stability, robustness, and membrane selectivity, building on recent advances in AMP specificity and membrane targeting [3].

Both problems are formulated as Quadratic Unconstrained Binary Optimization models [4], enabling direct compatibility with quantum and quantum-inspired hardware. The framework reproduces expected limiting behaviors across polar and apolar media, captures the preferential stabilization of amphipathic helices at anionic interfaces, and generates libraries of membrane-selective AMP-like candidates with consistent cross-environment performance.

Overall, this work establishes a scalable and physically grounded route toward environment-conditioned peptide design, demonstrating how quantum-enabled methodologies can address key bottlenecks in biomolecular simulation and accelerate the discovery of next-generation peptide therapeutics.

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Keywords: Quadratic Unconstrained Binary Optimization, Antimicrobial peptides, Molecular Dynamics, Quantum Computing, Peptide folding, Membrane interface

(Session A | 12:00-12:20) - Auditorium

OC - (25885) - A POLARIZABLE MULTIREFERENCE QM/MM FRAMEWORK BASED ON FLUCTUATING CHARGES (FQ) AND FLUCTUATING DIPOLES (FQFM): FROM ANALYTICAL GRADIENTS TO ANISOTROPIC INTERACTIONS

Francesco Mazza (Italy)[1]; Chiara Cappelli (Italy)[1]
1 - Scuola Normale Superiore, Piazza dei Cavalieri 7, I-56126 Pisa, Italy

Asbtract

Accurate modeling of molecules in complex environments, such as aqueous solution, represents a longstanding challenge in computational chemistry, as standard approaches like TD-DFT or continuum solvation models often fail [1,2] when dealing with inherently multiconfigurational systems or processes in protic and polar solvents, such as conjugated organic molecules and photochemical reactions in aqueous solution. To address these limitations, we have developed a multiscale QM/MM framework [3] coupling the Multiconfigurational Self-Consistent Field (MCSCF) method [4] with two fully polarizable force fields: the Fluctuating Charges (FQ) [5] and the Fluctuating Charges and Fluctuating Dipoles (FQFμ) [6] models. In both cases, the environment responds dynamically to the solute electron density, explicitly accounting for mutual polarization effects.

The MCSCF/FQ approach has been recently extended to the calculation of analytical nuclear gradients [7], enabling the computation of geometrical and spectroscopic properties. As an illustrative application, vibronic spectra of benzene and phenol in aqueous solution have been computed at the CASSCF/FQ level of theory, achieving a remarkable reproduction of the main experimental features.

Building on this foundation, the framework has been further extended to the MCSCF/FQFμ model [8], where the environment is described by both fluctuating charges and fluctuating dipoles. The inclusion of polarizable dipoles increases the computational cost but enables a more accurate description of directional solute-solvent interactions, most notably hydrogen bonding, whose anisotropic nature requires higher-order multipole terms for an accurate representation. The resulting framework aims to further improve the simulation of a broad range of spectroscopic properties, including chiroptical spectra, for multiconfigurational systems in realistic environments.

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Keywords: multiscale model, multireference, polarizable embedding, QM/MM, molecular spectroscopy, aqueous solution

(Session B | 11:00-11:20) – Room B

OC - (25853) - CHARACTERIZATION OF PROTEIN CONFORMATIONAL ENSEMBLES AND PROTEIN-LIGAND BINDING FROM ATOMISTIC SIMULATIONS OF ENERGY TRANSFER

Carles Curutchet (Spain)[1]

1 - Departament de Farmàcia i Tecnologia Farmacèutica, i Fisicoquímica & Institut de Química Teòrica i Computacional, Facultat de Farmàcia i Ciències de l'Alimentació, Universitat de Barcelona, Spain

Abstract

Modelling the interplay between structure and energy transfer in biosystems is a considerable challenge due to the multiple space and time scales involved.[1] Depending on the specific case under study, different computational protocols can be adopted combining classical simulations with multiscale quantum/classical methods. Here we will overview the application of multiscale protocols to the simulation of Förster resonance energy transfer (FRET) experiments applied to determine conformational ensembles of the partially disordered protein calmodulin, or to identify protein-ligand binding sites in human serum albumin (HSA).

First, we investigate how structure determines the FRET properties of the partially disordered protein calmodulin, with a particular focus on the impact of Förster approximations regarding dielectric screening effects.[2] We combine MD simulations in the μs timescale with a an efficient methodology beyond Förster dipole approximation based on electrostatic potential-fitted transition charges coupled to an atomistic polarizable environment,[3] showing that environment screening effects significantly bias the characterization of the balance between compact and extended conformations in disordered ensembles. Then, we apply this protocol to study the binding of a library of fluorescent small molecules to HSA, and show that atomistic FRET simulations are able to accurately reproduce the binding sites of known binders like naproxen, carprofen, and indomethacin, and reveal novel binding scenarios for other molecules.[4]

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We thank financial support from the State Research Agency/Spanish Ministry of Science, Innovation and Universities (AEI/10.13039/501100011033; grants PID2023-151584NB-I00 and CEX2021-001202-M) and the Catalan Agència de Gestió d'Ajuts Universitaris i de Recerca from Generalitat de Catalunya (GENCAT; 2021SGR00671).

Keywords: energy transfer, calmodulin, human serum albumin, molecular dynamics, protein-ligand binding

(Session B | 11:20-11:40) – Room B

OC - (25943) - EXCITED-STATE DRIVEN PHOTOACTIVATION IN PT(IV), PT(IV)–FE(II), AND RU(II) COMPLEXES FOR CANCER THERAPY: INSIGHTS FROM COMPUTATIONAL INVESTIGATIONS

Fortuna Ponte (Italy)[1]
1 - university of calabria

Abstract

Photoactivated therapies represent a promising strategy for the selective treatment of cancer, allowing precise spatiotemporal control of cytotoxic activity and minimizing side effects on healthy tissues. In this context, excited states accessible to metal complexes play a crucial role, as their nature and interplay determine the photophysical and photochemical processes underlying both Photodynamic Therapy (PDT) and Photoactivated Chemotherapy (PACT). In particular, photoactive metal complexes offer high structural versatility and unique photophysical properties, including the ability to efficiently access triplet states via intersystem crossing, thereby opening reactive pathways capable of generating cytotoxic species such as singlet oxygen or radical intermediates, under both normoxic and hypoxic conditions.

In this work, the study will focus on photoactive metal complexes, with particular attention to Pt(IV) complexes, Pt(IV)–Fe(II) conjugates, and Ru(II) systems. Pt(IV) complexes can act as photoactivatable prodrugs, while Pt(IV)–Fe(II) conjugates may enhance light absorption and promote charge-transfer processes leading to the formation of reactive oxygen species (ROS) species. Ru(II) complexes, on the other hand, are well known for their highly tunable excited-state properties, making them suitable candidates for PACT and combined PDT/PACT applications. Special emphasis will be placed on the investigation of their excited-state properties and on elucidating the mechanisms of photoactivation.

Computational approaches will be employed to achieve these goals, in particular Density Functional Theory (DFT) and Time-Dependent DFT (TD-DFT), which will be used to characterize the excited-state energy landscape. Key processes such as charge transfer, intersystem crossing, and light-induced ligand dissociation will be analyzed in detail. These studies will provide insight into how structural and electronic factors influence photoreactive pathways, including the generation of reactive species and the photorelease of ligands responsible for cytotoxic activity.

Keywords: Photoactivated Chemotherapy (PACT), Photodynamic Therapy (PDT), Excited states, Cancer Therapy

(Session B | 11:40-12:00) – Room B

P43 - IN SILICO INVESTIGATION OF THE ANTIMALARIAL AND ANTICANCER ACTIVITIES OF SELECTED DIMERIC ACYLPHLOROGLUCINOLS

Liliana Mammino (South Africa)[1]; Neani Tshilande (South Africa)[1]
1 - University of Venda

Abstract

Acylphloroglucinols (ACPLs) are derivatives of phloroglucinol (1,3,5-trihydroxybenzene) characterized by the presence of at least one acyl group, R-C=O; various substituents may be present in the positions meta to the acyl group. They are largely present in natural sources and exhibit various biological activities [1]. Dimeric acylphloroglucinols (D-ACPLs) are ACPLs whose molecules consist of two acylphloroglucinol moieties linked by a methylene bridge. They are mostly present in *Hypericum* species.

The current work focuses on D-ACPLs for which antimalarial and/or anticancer activities have been reported – with the two activities often being present for the same compound. The viability of the two potentialities was investigated using molecular docking against the active sites of selected cancer-related and malaria-related proteins (BRAF V600E, CDK-2, EGFR, PI3K, JAK3, Topo I, HER2, and HSP90 for cancer, and Falcipain-2 (FP-2), Plasmepsin II (PM II), PfLDH, PfDHODH, PfMDH and PfPMT for malaria). The study utilized the Schrödinger suite. Two sets of docking studies were performed: in vacuo and with the presence of a certain number of explicit water molecules. This enabled evaluations of ligand–protein binding modes, including the types of interactions involved, the role of water molecules in complex stabilization, and the permanence of key interactions in the two contexts. The results show that D-ACPLs can form stable complexes with the active sites of several proteins. Hydrogen bonds are the strongest interactions, with one or more phenol OHs of the ligand acting as donors and often also the sp^2 O of the acyl group acting as acceptor; weaker interactions, such as hydrophobic interactions, may also be present. Water molecules often enhance binding stability by bridging the H-bonds' donor and acceptor. Most of the investigated D-ACPLs show favorable binding affinities across several anticancer and antimalarial targets – a multi-target potential enabling the expectation of greater overall action efficacy.

Additionally, ADMET (administration, distribution, metabolism, excretion, toxicity) profiling was performed to evaluate drug-likeness and the physicochemical properties generally related to drug viability and safety.

The obtained results enable a comparison of potential activities, thus identifying the D-ACPLs which might be the most promising candidates for further investigation in view of their possible development into antimalarial and anticancer drugs. The fact that many D-ACPLs exhibit both activities is particularly interesting because the development costs of one drug would lead to two pharmacological applications.

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The authors express their gratitude to the Center for High performance Computing (CHPC) in Cape Town (South Africa) for providing the computational facilities.

Keywords: ADMET, anticancers, antimalarials, dimeric-acylphloroglucinols, hydrogen bonding, molecular docking

(Session B | 12:00-12:20) – Room B

OC - (25936) - ON THE SEARCH FOR BMRA PHARMACOLOGICAL INHIBITORS

Festus O. Ogungbemiro (Portugal)[1]; Daniel J. V. A. Dos Santos (Portugal)[1]

1 - CBIOS— Center for Research in Biosciences and Health Technologies, Universidade Lusófona, Lisboa, Portugal

Abstract

Multidrug resistance (MDR) remains a critical barrier in the treatment of infectious diseases and cancer, largely driven by the overexpression of ATP-binding cassette (ABC) transporters such as BmrA in bacteria and key human homologs including P-gp, BCRP, and MRP1. These transporters actively efflux a broad range of therapeutic agents, lowering intracellular drug concentrations and compromising treatment efficacy. In this work, BmrA is employed as a model system to advance the development of innovative pharmacological modulators targeting MDR.

We focus on a recently identified allosteric binding site by our laboratory, located at the intracellular interface between the nucleotide-binding domains (NBDs) and transmembrane domains (TMDs). In contrast to the canonical polyspecific drug-binding pocket buried within the lipid bilayer, this site is structurally conserved yet sequence-divergent, offering a unique opportunity for selective targeting. Notably, we have shown by analogous studies in P-gp that ligand binding at this site disrupts the conformational coupling required for ATP hydrolysis and substrate translocation, resulting in a non-competitive inhibition of efflux activity.

To characterize this site in BmrA, we performed extensive molecular dynamics simulations at physiological conditions on the apo transporter as well as substrate-bound systems (single- and dual-substrate conditions), reaching the microsecond timescale. These simulations reveal distinct conformational ensembles and highlight the dynamic coupling between the NBDs and TMDs mediated by the allosteric region. Principal component analysis (PCA) and clustering approaches were used to identify dominant motions and extract representative structures, including extreme conformations along the first eigenvector that capture functionally relevant transitions.

Our analysis uncovers a well-defined, enzyme-like pocket with persistent interaction hotspots and reduced conformational heterogeneity compared to the canonical drug-binding cavity. Importantly, sequence divergence within this structurally conserved motif supports the feasibility of designing BmrA-specific inhibitors with reduced off-target effects.

Representative structures corresponding to global minima and highly populated clusters from both apo and holo states are being used as templates for structure-based virtual screening campaigns targeting this allosteric pocket. These efforts are complemented by the evaluation of conformational selection versus induced-fit mechanisms in ligand recognition.

Overall, this study provides a dynamical and structural framework for targeting a novel allosteric site in BmrA, establishing a proof-of-concept for the rational design of non-competitive MDR modulators. The insights gained are expected to be transferable to clinically relevant ABC transporters, paving the way for next-generation strategies to overcome drug resistance.

We acknowledge the *Fundação para a Ciência e Tecnologia* (FCT) for funding under contract UID/04567/2025. ILIND is also acknowledged for funding through projects FAZER+/ILIND/CBIOS/1/2025 and COFAC/ILIND/CBIOS/2/2023.

Keywords: Drug Resistance, Multidrug resistance reversal, ABC transporters, Molecular Dynamics, Computational Medicinal Chemistry

(Session A | 16:30-16:50) - Auditorium

OC - (25961) - A COMPUTATIONAL STUDY OF THE REACTIONS OF N(2D) WITH MONOCYCLIC AND POLYCYCLIC AROMATIC HYDROCARBONS AND THEIR ROLE IN THE ATMOSPHERIC CHEMISTRY OF TITAN

Marzio Rosi (Italy)[1]; Luca Mancini (Italy)[2]; Dimitrios Skouteris (Italy)[3]; Piergiorgio Casavecchia (Italy)[2]; Gianmarco Vanuzzo (Italy)[2]; Nadia Balucani (Italy)[2]

1 - Department of Civil and Environmental Engineering, University of Perugia; 2 - Department of Chemistry, Biology and Biotechnologies, University of Perugia; 3 - Master.Tec s.r.l.

Abstract

Atomic nitrogen in its ^{4}S ground state exhibits very low reactivity with closed shell molecules, while in its first electronically excited ^{2}D state shows a significant reactivity with hydrocarbons. Gas-phase reactions of N(^{2}D) with simple hydrocarbons lead to the formation of (prebiotic) N-containing organic molecules (nitriles, imines and radicals). These reactions are active in the upper atmosphere of Saturn's moon Titan and might have played an important role in nitrogen fixation in the primitive upper terrestrial atmosphere. The products of these reactions are the precursors of larger N-containing molecules, which form the dense haze aerosols that cover Titan. If anything similar to Titan's haze has ever existed on our planet, it is reasonable to imagine that, once deposited on the surface of the oceans, further chemical evolution might have transformed these molecules into amino acids and nucleobases.

In this contribution, we report on a theoretical characterization of the reaction involving N(^{2}D) and monocyclic aromatic hydrocarbons, like benzene, toluene and pyridine, as well as simple polycyclic aromatic hydrocarbons (PAHs) like naphthalene and phenanthrene. Our study shows that the reaction mechanism established for N(^{2}D) and monocyclic aromatic compounds also applies to small polycyclic aromatic hydrocarbons. Our results indicate that π bond conjugation in fused rings does not interfere with the reaction mechanisms, even though several strained rings are formed along the minimum energy path. In all cases investigated, the main reaction channels occur via ring-contraction mechanisms that involve the elimination of HCN and the formation of cyclopentadienyl, substituted cyclopentadienyl, indenyl, and fluorenyl radicals. At first sight, these reactions contrast the growth of larger aromatic structures, since there is a loss of aromaticity in the ring attacked by N(^{2}D). However, the products formed in ring-contraction mechanisms are resonance-stabilized radicals known to contribute to PAHs formation in various media.

N(^{2}D) is produced in Titan's upper atmosphere, where benzene peaks and aerosol formation starts. Therefore, these reactions, along with others leading to the formation of the first ring, can contribute to the formation of PAHs. Minor channels lead to the formation of 7 membered cyclic compounds incorporating N, the evolution of which remains to be determined. Another general conclusion is that aromatic rings are less

resistant to chemical attack by energetic reactants, such as electronically excited species, than previously believed.

MR acknowledges financial support under the National Recovery and Resilience Plan (NRRP), Mission 4, Component 2, Investment 1.1, Call for tender No. 104 published on 2.2.2022 by the Italian Ministry of University and Research (MUR), funded by the European Union – NextGenerationEU– Project Title 2022JC2Y93 Chemical Origins: linking the fossil composition of the Solar System with the chemistry of protoplanetary disks – CUP J53D23001600006 - Grant Assignment Decree No. 962 adopted on 30.06.2023 by the Italian Ministry of Ministry of University and Research (MUR).

Keywords: Ab initio calculations, Potential energy surface, Density Functional Calculations, Titan, Polycyclic aromatic hydrocarbons

(Session A | 16:50-17:10) - Auditorium

OC - (25788) - DFT ANALYSIS INTO THE REACTION MECHANISMS IN CARBENE AND METAL CARBENE REACTIONS.

Barbara Herrera (Chile)[1]

1 - QTC, Escuela de Quimica, Facultad de Quimica y de Farmacia, Pontificia Universidad de Chile

Abstract

In this work, we discuss aspects of the reaction mechanisms in 1,3 dipolar cycloadditions mediated by a carbene catalyst, and C-H activations using metal carbenes. Both reactions are key reactions in the synthetic organic chemistry toolbox towards sustainable green processes.

We have made DFT/B3LYP/6-311+G** calculations on the classic 1,3 dipolar cycloaddition of 2-butine and fulminic acid catalyzed by 1,3-di-terc-butyl-imidazole [1]. We have obtained the reaction mechanism involving three different processes, being the most favored one that involves two TS and two intermediaries. The analysis of the mechanism was made using Conceptual Density Functional Theory (CDFT) [2], Reaction Force [3], NBO and NPA [4] analysis, understanding the difference between the non-catalyzed reaction channel and the one that follows with the action of the catalyst.

For the metal-carbene C-H activations involving Cu and Ni carbenoids or metal carbenes [5], we used DFT/M06-2X/cc-pVDZ methodology and LANL2DZ basis set in the metallic systems. The CDFT [2] analysis along with NBO and NPA[4] allowed us to stablish the mechanism of C-H activations, selecting the most favorable reactions, and the relation of the local electrophilicity represented by the condensed Dual Descriptor in the carbenoid carbon (Δf(Cα)) [6] and the height of the barriers.

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Keywords: Carbene, Carbenoids, Catalysis, Cycloadditions, C-H Activations

(Session A | 17:10-17:30) - Auditorium

OC - (25946) - EXPLICIT ENVIRONMENTAL EFFECTS IN BULK HETEROJUNCTIONS USING A QM/MM FRAMEWORK

Mateus Bergami (Sweden)[3]; Leandro Franco (Belgium)[1]; Danillo Valverde (Belgium)[2]; Moyses Araujo (Sweden)[3,4]

1 - Laboratory for Chemistry of Novel Materials, University of Mons, Belgium; 2 - Namur Institute of Structured Matter, University of Namur, Belgium; 3 - Department of Engineering and Physics, Karlstad University, Sweden; 4 - Materials Theory Division, Department of Physics and Astronomy, Uppsala University, Sweden

Abstract

Solution-processed organic semiconductors play a central role in the performance of organic photovoltaic devices, yet their complex and disordered nature presents significant challenges for theoretical modeling. Accurate treatment of environmental effects remains a central challenge in the quantum chemical description of such materials. In this work, we present a QM/MM framework to investigate bulk heterojunctions (BHJ) thin films, extending our previously developed protocol, applied to systems such as PF5-Y5 and Y6 films, to donor-acceptor blends based on PM6 combined with Y6 and L8-BO. The approach follows a sequential QM/MM strategy in which atomistic configurations are first generated through classical molecular dynamics simulations using an evaporation protocol to model the transition from solution to thin-film conditions, followed by electronic structure calculations on representative snapshots with a quantum mechanical region embedded in a molecular mechanics environment. Within this framework, environmental effects are incorporated either through continuum models or via a polarizable electrostatic embedding scheme that provides an explicit atomistic description of the surrounding medium without requiring prior knowledge of macroscopic dielectric constants, which is particularly advantageous in the context of rapidly emerging materials where such parameters are often unavailable. We apply this approach to investigate electronic properties, including UV-Vis absorption spectra and low-lying excited states, showing how local electrostatic environments influence electronic structure and excited-state character. Importantly, the explicit embedding treatment reveals variations in excited-state behavior driven by the anisotropic nature of the thin film environment, highlighting the role of directional electrostatic interactions in these disordered systems. These results highlight the ability of multiscale QM/MM approaches to connect realistic thin-film structures with excited-state properties, providing new understanding into the electronic properties of next-generation organic photovoltaic materials.

We acknowledge the Carl Trygger Foundation (Grant No. CTS 23:2987) for the financial support. The computations were enabled by resources provided by the National Academic Infrastructure for Supercomputing in Sweden (NAISS) and the Swedish National Infrastructure for Computing (SNIC) at the National Supercomputer Centre (NSC) at

Linköping University, partially funded by the Swedish Research Council through Grant Agreement Nos. 2022-06725 and 2018-05973.

Keywords: Bulk Heterojunctions, QM/MM Methods, Polarizable Embedding, Excited-State Properties

(Session B | 16:30-16:50) – Room B

OC - (25862) - A POLARIZABLE EMBEDDING APPROACH COMBINING DENSITY MATRIX RENORMALIZATION GROUP AND FLUCTUATING CHARGES FOR MODELING ELECTRONIC EXCITATION ENERGIES IN SOLUTION

Matteo Rinaldi (Italy)[1]; Sepali Chiara (Italy)[1]; Alicia Marie Kirk (Italy)[1]; Claudio Amovilli (Italy)[2]; Chiara Cappelli (Italy)[1]

1 - Scuola Normale Superiore (SNS) Pisa; 2 - Dipartimento di Chimica e Chimica Industriale, Università di Pisa

Abstract

The investigation of electronic transitions in solution is a useful tool to gather information on systems involved in relevant biological or chemical processes. However, solvated systems are composed of a very large number of atoms; therefore, from a computational point of view, a reasonable way to address this is to resort to multiscale modeling.[1,2] Among these methods, hybrid Quantum Mechanics /Molecular Mechanics (QM/MM) methods have proven to be particularly successful[3,4] since they are capable of describing specific solute-solvent interactions, such as hydrogen bonding patterns, which can play a role in shaping spectroscopic signals.[5]

Many interesting solvated systems contain a solute with a complex electronic structure that needs to be described by an accurate multiconfigurational QM approach, such as conjugated systems, chromophores in photosensitive proteins or transition metal enzymes. To this purpose, we present a QM/MM strategy based on the coupling of the Density Matrix Renormalization Group (DMRG)[6,7] method to the Fluctuating Charges (FQ) force field (DMRG/FQ).[9] This is based on the framework of our recent CASSCF/FQ[8] method and permits treating large solute molecules using active spaces of more than 20 electrons in 20 orbitals.

The resulting DMRG/FQ method is then applied to the calculation of electronic excitation energies and solvatochromic shifts of a set of molecules in solution, benchmarked against experimental data, which paves the way for future applications on biological systems.

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Keywords: DMRG, Embedding, multiscale modeling, solvation, electronic excitations, solute-solvent, mutual polarization

(Session B | 16:50-17:10) – Room B

OC - (25879) - AN INTEGRATIVE IN SILICO FRAMEWORK FOR MACHINE LEARNING–GUIDED STRUCTURE-BASED VIRTUAL SCREENING TO IDENTIFY SMALL MOLECULES TARGETING MUTANT P53 (R273H AND R248H) AT THE DNA-BINDING INTERFACE

Marcia Yineth Castillo Tarazona (Colombia)[1]; Gian Pietro Miscione (Colombia)[1]
1 - Universidad de los Andes

Abstract

Mutations in the tumor suppressor protein p53, particularly R273H and R248H, are strongly associated with resistance to standard colorectal cancer therapies such as oxaliplatin, irinotecan, and 5-fluorouracil.[1] These mutations impair DNA binding and disrupt apoptosis, promoting uncontrolled cell proliferation.[2] Although several small molecules have shown cytotoxic effects in vitro, none have advanced to approved therapies,[3] highlighting the need for improved discovery strategies.

Here, we present a machine learning (ML)–guided, structure-based virtual screening framework integrating molecular docking and ML to prioritize small molecules targeting the mutant p53 DNA-binding interface. Docking defines the structural interaction space, while ML is used as an early-stage filter to reduce chemical space prior to structure-based evaluation. The framework is further compatible with molecular dynamics simulations and binding free energy calculations for downstream validation.

A curated dataset of 1,569 compounds with reported cytotoxicity was used to develop predictive models. Decoy enrichment (1:50 ratio) was evaluated but did not improve performance;[4] therefore, the original dataset was retained. Six ML models were benchmarked: Random Forest, Support Vector Machine, XGBoost, Deep Neural Networks, Artificial Neural Networks, and Graph Neural Networks. Models used protein–ligand extended connectivity (PLEC) descriptors derived from validated docking poses and graph-based molecular representations (ConvMol).

PLEC-SVM and ConvMol-GNN achieved the best performance, with PR-AUC values of 0.794 and 0.685, respectively, and strong early enrichment (NEF1%) of 0.8 ± 0.07 and 1.0 ± 0.0, outperforming conventional scoring functions such as Glide, Smina, CNN-Score, and SCORCH. Chemical diversity analysis using Morgan fingerprints, Tanimoto similarity, and hierarchical clustering (threshold = 0.7) confirmed model robustness against chemotype redundancy.

Using PLEC-SVM, 28 compounds were prioritized with predicted activity probabilities above 0.68. The corresponding mutant p53–ligand docking complexes were already defined during PLEC construction, ensuring consistency between structural representations and ML features.

Docking complexes were further evaluated using HADDOCK2.4[5] to model the p53–ligand–DNA assembly at the mutation interface. A DNA structure derived from the wild-type p53–DNA complex (PDB ID: 4MZR)[6] was used, allowing DNA flexibility while keeping protein

and ligands rigid. This enabled assessment of ligand-mediated stabilization of mutant p53–DNA interactions. Comparative docking between wild-type and mutant systems identified two promising candidates with improved predicted binding affinity.
Overall, this study demonstrates that integrating machine learning into structure-based virtual screening provides an efficient prioritization strategy for targeting mutant p53 (R273H and R248H). The proposed framework offers a scalable pipeline for candidate selection and will be extended with molecular dynamics and binding free energy calculations for further refinement.

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Universidad de los Andes,Faculty of Science, Prj.Code INV-2026-230-3653.

Keywords: Machine learning, structure-based virtual screening, molecular docking, p53 mutation, protein–DNA interaction, drug repositioning

(Session B | 17:10-17:30) – Room B

OC - (25860) - BIGGER ISN'T ALWAYS BETTER: COMPARING SYSTEM SIZE, HYDRATION, AND SOFTWARE FOR LIPID MEMBRANE ANALYSIS

Filipe Carvalho (Portugal)[1]; Pedro Maximiano (Portugal)[2]; Pedro Simões (Portugal)[1]; Mohtadin Hashemi (United States of America)[2]

1 - University of Coimbra, CERES, Department of Chemical Engineering, Rua Sílvio de Lima, Coimbra, 3030-790, Portugal; 2 - Department of Physics, Auburn University, Leach Science Center 3126, Auburn, AL, 36849-5319, USA

Abstract

While Molecular Dynamic (MD) simulations are a powerful tool for studying cellular membrane systems, the results can be sensitive to the bilayer model, analysis workflow, and software. Rather than making these choices blindly, we devised a systematic benchmarking study to inform this decision and probe how system size and hydration influence the properties routinely reported. To this end, we ran 500 ns all-atom simulations of POPC bilayers containing 128, 256, 512, and 1024 lipids at 40, 80, and 160 waters per lipid, and computed the area per lipid (APL), bilayer thickness, deuterium order parameter, headgroup orientation, and lateral diffusion coefficient using CPPTRAJ, GROMACS, MDAnalysis, and LiPyphilic. The average values of APL, thickness, order parameter, and headgroup orientation were largely independent of system size and hydration within the ranges explored, with larger systems mainly reducing the statistical variance between replicates. The hydration independence suggests that POPC is fully hydrated at 40 waters per lipid, above which additional water no longer perturbs the structural observables. In contrast, lateral diffusion was sensitive to both parameters, with a non-monotonic dependence on system size. The 128-lipid system failed uniquely at higher hydrations (80W and 160W), exhibiting artificially inflated diffusion coefficients and large inter-replicate variance despite remaining geometrically stable. We attribute this to collective translational motions that cannot be averaged out in a bilayer patch containing only 64 lipids per leaflet, with thicker water layers further reducing hydrodynamic damping between periodic images. These observations establish 256 lipids as the practical minimum for reliable dynamic-property analysis, while structural averages can be recovered from smaller systems. Across software packages, the four tools agreed closely for APL and thickness, while a known limitation of the GROMACS gmx order tool produced artifacts at unsaturated carbons, and performance benchmarks identified CPPTRAJ as the fastest serial tool across all properties examined. Building on the software side of these results, CPPTRAJ and the property-calculation methodology validated in the benchmarking study were adopted for subsequent work on protein–membrane systems, where the same pipeline was used to quantify how α-synuclein and Aβ42 adsorption affects the APL, thickness, lateral diffusion, headgroup tilt, and local curvature. In this contribution, I present the core findings of the benchmarking study and illustrate how its software-

related conclusions inform a validated, reproducible methodology for protein–membrane MD analysis.This work was completed in part with resources provided by the Auburn University Easley Cluster and University of Coimbra CERES research center, which is supported by FCT, within the projects DOI: 10.54499/UID/00102/2025 (Base and Programmatic funding) and DOI: 10.54499/UID/PRR/00102/2025.

Keywords: Membrane properties, Molecular Dynamics simulations, Software benchmark, Lipid bilayer, Lipid hydration

Tuesday, 7 July

(Session A | 11:00-11:20) - Auditorium

OC - (25877) - RADICALS IN A CAGE: CONTROLLING REACTIVITY AND SELECTIVITY WITH CUCURBITURILS

Angie Carolay Forero Girón (Chile)[1]; Margarita E. Aliaga (Chile)[1]; Alejandro Toro-Labbé (Chile)[1]; Camilo Lopéz Alarcón (Chile)[1]
1 - Pontificia Universidad Catolica de Chile

Abstract

Recent studies have highlighted the potential of supramolecular approaches to regulate radical stability, reactivity, and overall behavior. In 2023, it was reported that the formation of an azocompound@CB[n] host–guest complex enabled control over the photochemical generation of peroxyl radicals under 365 nm irradiation [1,2]. In that work, combined experimental and theoretical analyses confirmed the inclusion of the well-known radical precursor 2,2′-azobis(2-methylpropionamidine) dihydrochloride (AAPH) within cucurbit[7]uril (CB[7]). The resulting AAPH@CB[7] complex enhanced the yield of AAPH-derived radicals (R•) compared with free AAPH, while also increasing the oxidation efficiency toward several targets, including pyrogallol red, tryptophan, and tryptophan-containing peptides.

Motivated by these findings, we theoretically investigated the formation of CB[7] inclusion complexes with other commonly used azo compounds as radical precursors, as well as their influence on radical generation. Our results indicate that both the charge distribution and the position of functional groups along the azo compound backbone are key factors governing encapsulation within the CB[7] cavity. Noncovalent interactions, particularly hydrogen bonding and van der Waals forces, play a central role in stabilizing the azocompound@CB[7] complexes and in determining the subsequent fate of the photogenerated radicals. Depending on the initial host–guest arrangement, the radicals may remain inside or outside the CB[7] cavity, thereby modulating their reactivity toward surrounding species [3].

In addition, we theoretically explored the inclusion of tryptophan within CB[8] and the photolysis of this complex at 254 nm, which led to the formation of five distinct stereoisomers of ditryptophan inside the host cavity. Our findings revealed that the supramolecular orientation of tryptophan within cucurbituril selectively favors one stereoisomeric pair, demonstrating the ability of confinement effects to direct photochemical selectivity.

[1] RSC Adv. 14 (2024) 35980-35991. Doi: 10.1039/D4RA07150F
[2] J. Mol. Liq. 389 (2023) 122840. Doi: 10.1016/j.molliq.2023.122840
[3] J. Mol. Model. 30 (2024) 337. Doi: 10.1007/s00894-024-06132-7

This work was supported by FONDECYT grants No. 1220459 (to CLA), No. 1210751 (to MEA), No 1241224 (ATL) and Postdoctoral Fellowship No. 3240525 (to AFG).

(Session A | 11:20-11:40) - Auditorium

OC - (25746) - THEORETICAL INSIGHTS INTO THE PI → PI* TRANSITION AND THE LARGE STOKES SHIFT OF A CURCUMIN-BASED CHROMOPHORE

Catharina B. De Araújo (Brazil)[1]; Lennon Rodrigues Oliveira (Brazil)[1]; Danillo Valverde (Belgium)[2]; Rodrigo Gester (Brazil)[3]; Kaline Coutinho (Brazil)[4]; Sylvio Canuto (Brazil)[4]; Vinícius Manzoni (Brazil)[1]

1 - Instituto de Física, Universidade Federal de Alagoas, 57072-970 Maceió, AL, Brazil; 2 - Laboratory for Computational Modeling of Functional Materials, University of Namur, Rue de Bruxelles 61, 5000 Namur, Belgium; 3 - Faculdade de Física, Universidade Federal do Sul e Sudeste do Pará, 68507-590 Marabá, PA, Brazil; 4 - Instituto de Física, Universidade de São Paulo, Rua do Matão 1371, 05588-090 São Paulo-SP, Brazil

Abstract

We investigate the photophysical properties and excited-state behavior of a curcumin-based chromophore (CCM) in aprotic solvents using a combination of TD-DFT and multiconfigurational approaches. Particular attention is given to the nature of the π → π* transition and the origin of the large Stokes shift observed experimentally. Our results reveal that the $S_0 \rightarrow S_1$ transition exhibits a mixed locally excited (LE) and intramolecular charge transfer (CT) character, with the CT contribution playing a dominant role in the electronic reorganization upon excitation. Charge transfer occurs from the N,N-dimethylaniline donor groups to the central acceptor core, as supported by natural transition orbitals and population analysis. Multiconfigurational calculations corroborate this picture and indicate that fluorescence arises from a relaxed bright ππ* state with mixed LE–CT character. The lowest excited state corresponds to a dark nπ* state with negligible oscillator strength, lying slightly below the emissive state. This energetic ordering is key to understanding the emission mechanism.The large Stokes shift is found to correlate linearly with solvent polarity, consistent with significant dipole moment changes upon excitation. Overall, our results provide a consistent physical picture of the excited-state landscape and highlight the role of charge transfer in governing the optical response of curcumin-based systems, with implications for the design of functional fluorophores.

This work was supported by the National Institute of Science and Technology for Complex Fluids (INCT-FCx), the São Paulo Research Foundation (FAPESP, grant no. 2014/50983-3), and
the Alagoas Research Foundation (FAPEAL). We thank the computer support from LaMCAD/UFG. We also acknowledge the continuous support from CNPq and CAPES.

Keywords: Curcumin, Intramolecular charge transfer, DFT, Stokes shift

(Session A | 11:40-12:00) - Auditorium

OC - (25945) - MULTISCALE SIMULATION OF PHOTO-ASSISTED CHEMICAL VAPOUR DEPOSITION

Cauê P. Souza (United Kingdom)[3]; Alexey V. Verkhovtsev (Germany)[2]; Amy V. Walker (United States of America)[1]; Nigel J. Mason (United Kingdom)[4]; Andrey V. Solov'Yov (Germany)[2]; Lisa Mcelwee-White (United States of America)[5]; Matija Zlatar (Serbia)[6]; Felipe Fantuzzi (United Kingdom)[3]

1 - Department of Materials Science and Engineering, University of Texas at Dallas, 800 W. Campbell Rd, Richardson, Texas 75080, USA; 2 - MBN Research Center, Altenhöferallee 3, Frankfurt am Main 60438, Germany; 3 - School of Natural Sciences, University of Kent, Park Wood Rd, Canterbury CT2 7NH, UK; 4 - School of Engineering, Mathematics and Physics, University of Kent, Park Wood Rd, Canterbury CT2 7NH, UK; 5 - Department of Chemistry, University of Florida, Gainesville, Florida 32611, USA; 6 - Institute of Chemistry, Technology and Metallurgy, University of Belgrade, Njegoševa 12, Belgrade 11000, Serbia

Abstract

Traditional chemical vapour deposition (CVD) is a key nanofabrication method, particularly for area-selective deposition (ASD). However, its need for high temperatures (>200°C) risks damaging sensitive substrates like organic thin films (OTFs) in photodevices, driving demand for low-temperature alternatives. Photo-assisted CVD (PACVD) [1,2] enables metal deposition via light-activated precursors near room temperature. Ruthenium-containing precursors show particular promise [3,4]. To better understand and optimize PACVD, computational models are essential. This work presents a multiscale computational approach to simulate PACVD experiments via three modular blocks: (1) accurate modelling of self-assembled monolayers (SAMs) of alkanethiols on Au as model OTFs; (2) investigation of photochemical behaviour of key precursors under irradiation; and (3) full PACVD process simulation.

As an excellent OTF model, alkanethiol SAMs on Au were chosen as PACVD substrates. Their structural features (adsorption patterns, chain conformations, superlattice arrangement) are computationally challenging. In a recent study [5], we systematically evaluated bonded interactions, atomic charges, and Lennard–Jones parameters affecting pristine and functionalized alkanethiol SAMs on Au(100) and Au(111). Our parameter set replicates key experimental trends, including the $(\sqrt{3} \times \sqrt{3})\,\mathrm{R30°}$ hexagonal head-group arrangement and the $c(4 \times 2)$ superlattice on Au(111). This validated framework enables detailed studies of surface nature, orientation, and chain length effects.

The photodissociation mechanisms of ruthenium π-diene carbonyl complexes—promising PACVD precursors—remain unclear. Using static quantum-chemical calculations (DFT/TDDFT) [6], we mapped the excited-state dissociation landscape of (η^4-diene)$Ru(CO)_3$ precursors (diene = BuD, MBuD, CHD, COT, CBuD). Ground-state DFT optimizations and Ru–ligand scans, combined with TDDFT excitations and adiabatic singlet

potential energy surfaces, identified CO- and diene-loss pathways. Results reveal favourable stepwise routes to unsaturated fragments, providing a basis for non-adiabatic dynamics, irradiation-driven molecular dynamics, time-resolved spectroscopy, and multiscale PACVD simulations.

These studies form the basis for further investigation of irradiation-driven chemistry in SAMs using the reactive CHARMM force field [7] and irradiation-driven molecular dynamics method [8] implemented in MBN Explorer [9]. Together, these tools will enable multiscale modelling of PACVD on alkanethiol SAM substrates, as demonstrated experimentally [1,2]. We conclude by highlighting future research perspectives along this direction.

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Keywords: TDDFT, excited states, alkanethiol SAMs, PACVD, molecular dynamics, multiscale simulation

(Session A | 12:00-12:20) - Auditorium

OC - (25731) - THE UNEXPECTED STABILITY OF GEMINAL DIOLS IN THE CNH2N+2O2 (N=1-10) FAMILY

Lisset Noriega (Mexico)[1]; Aura Gomez-Heredia (Mexico)[1]; Filiberto Ortíz-Chi (Mexico)[2]; Gabriel Merino (Mexico)[1]

1 - Cinvestav-Mérida; 2 - Secihiti-Cinvestav-Mérida

Abstract

Geminal diols ($R_2C(OH)_2$), characterized by two hydroxyl groups bonded to the same carbon atom, are known for their pronounced instability at room temperature due to rapid dehydration. This has limited their experimental characterization, as they tend to decompose into simpler species and are not commercially available in pure form. Among the two possible CH_4O_2 isomers, methanediol is the most stable, while the peroxide form is over 60 kcal/mol less stable. This trend persists in larger systems such as $C_2H_6O_2$ and $C_3H_8O_2$, where geminal diols also emerge as the most stable isomers.

In this study, we explored the isomeric landscape of $C_nH_{2n+2}O_2$ (n = 1–10) to evaluate whether geminal diols consistently represent the most stable structures of their potential energy surfaces. We employed SmilX to generate all possible structural isomers, followed by pre-optimization using the ANI neural network model. The most stable isomers of each system were further refined at the M06-2X-D3/aug-cc-pVTZ level with Grimme's D3 dispersion corrections.

Our results reveal that geminal diols consistently represent the most stable isomers across all systems. Additionally, we investigated the thermal decomposition pathways of the most stable geminal diols for n = 1–5. The activation barriers range from 45.4 kcal/mol (methanediol) to 41.1 kcal/mol (2,2-pentanediol), suggesting a gradual decrease in barrier height with increasing carbon chain length. We also examined the catalytic effects of various species, diminishing the energy barrier up to 15 kcal/mol. Since thermodynamic arguments alone cannot explain the rapid decomposition of geminal diols, reaction rate constants were computed using Canonical Variational Transition State Theory (CVT) with Small-Curvature Tunneling (SCT) corrections. Compared to vicinal diols such as ethylene glycol, geminal diols exhibit rate constants up to 20 orders of magnitude larger. At temperatures ≤100 K, tunneling increases reaction rates by more than 38 orders of magnitude, explaining their reactivity despite large classical activation barriers. These results demonstrate that the stability of geminal diols cannot be understood solely from thermodynamic arguments, highlighting the critical role of quantum mechanical tunneling in governing their low-temperature chemistry.

The authors thankfully acknowledge computer resources, technical advice and support provided by Laboratorio Nacional de Supercómputo del Sureste de México (LNS), a member of the CONAHCYT national laboratories, with project No. 202601018N. A.G.-H.

and L.N. acknowledge Secihti for financial support through PhD and postdoctoral fellowships, respectively.

Keywords: Isomer stability, Geminal diol, Potential Energy Surfaces, Unimolecular decomposition

(Session B | 11:00-11:20) – Room B

CO - (25975) - UNI AND BIMODAL BEP RELATIONSHIPS IN MULTI- AND ONE-BOND CHEMICAL REACTIONS: A PATH-DEPENDENT ANALYSIS

Sebastián Richter (Chile)[1]; César Barrales-Martínez (Chile)[2]; Pablo Jaque (Chile)[1]
1 - Department of Organic and Physical Chemistry, University of Chile; 2 - Department of Chemistry, University of Bio-Bio

Abstract

Bell–Evans–Polanyi (BEP) relationships constitute one of the fundamental connections between thermodynamics and kinetics in chemical reactivity, relating activation barriers to reaction energies within homologous reaction series. However, significant deviations from linear BEP behavior frequently arise in multi-bond and one-bond chemical reactions, where the degree of synchronicity between elementary events becomes a determining factor. In this work, we develop a unified mechanistic framework to rationalize both uni- and bimodal BEP relationships through use of reaction-path-dependent descriptors of (a)synchronicity.

Two representative classes of reactions were investigated using density functional theory calculations and reaction force constant analysis: 1,3-dipolar cycloadditions and C(sp^3)–H oxidations by dioxiranes proceeding through hydrogen atom transfer (HAT)-type mechanisms, as multi- and one-bond chemical reactions, respectively. In addition, the combination of thermodynamic descriptor of asynchroncity η and κ(ξ) reveals that increasing thermodynamic imbalance leads to broader transition regions and greater kinetic decoupling, reorganizing scattered BEP data into mechanistically consistent trends with lower intrinsic barriers for asynchronous pathways in double proton transfer reactions. In C(sp^3)–H oxidations, bimodal BEP relationships emerge only when reactions are grouped according to mechanistically consistent pathways. Reaction force constant analysis uncovers hidden sequential character and changes in the rate-determining step, explaining differences in slopes and intercepts between saturated and unsaturated substrates.

Overall, the results demonstrate that BEP validity, deviations, and bimodal behavior are strongly governed by the degree of (a)synchronicity and by the evolution of elementary events along the reaction coordinate. The complementary use of η and κ(ξ) provides a transferable strategy for interpreting mechanistic complexity in multi- and one-bond chemical reactions and for connecting thermodynamic bias with kinetic decoupling effects.

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DOI:10.1039/d6cp00743k.

Acknowledgments: The authors thank to the Fondecyt-Anid grant Nº 1231241. SR thanks to ANID-Chile for a PhD fellowship Nº 21211222. CB-M thanks to the Fondecyt-Anid grant Nº 11240351.

Keywords: Reaction Force Constant, Hydrogen-Atom-Transfer, Double Proton Transfer, 1,3-dipolar cycloaddition, Thermodynamic Descriptors, BEP Principle

(Session B | 11:20-11:40) – Room B

OC - (25848) - A VIRTUAL SCREENING CAMPAIGN TARGETING TIGIT: IDENTIFICATION OF SMALL-MOLECULE INHIBITORS

Rodrigo Barriga (Portugal)[1]; Rita C. Acúrcio (Portugal)[1]; Helena F. Florindo (Portugal)[1]; Rita C. Guedes (Portugal)[1]

1 - Research Institute for Medicines (iMed.Ulisboa), Faculty of Pharmacy, University of Lisbon, Lisbon, Portugal

Abstract

T cell immunoreceptor with Ig and ITIM domains (TIGIT) is an immune checkpoint receptor whose overexpression in cancer patients suppresses T- and Natural Killer (NK) cell–mediated antitumor responses and correlates with poor prognosis. No TIGIT-targeting drugs are approved, and several Phase III antibodies were recently discontinued due to limited efficacy. Only a single small-molecule inhibitor (AUR-106) is in Phase I trials, and no crystal structures of TIGIT bound to small molecules exist [1].

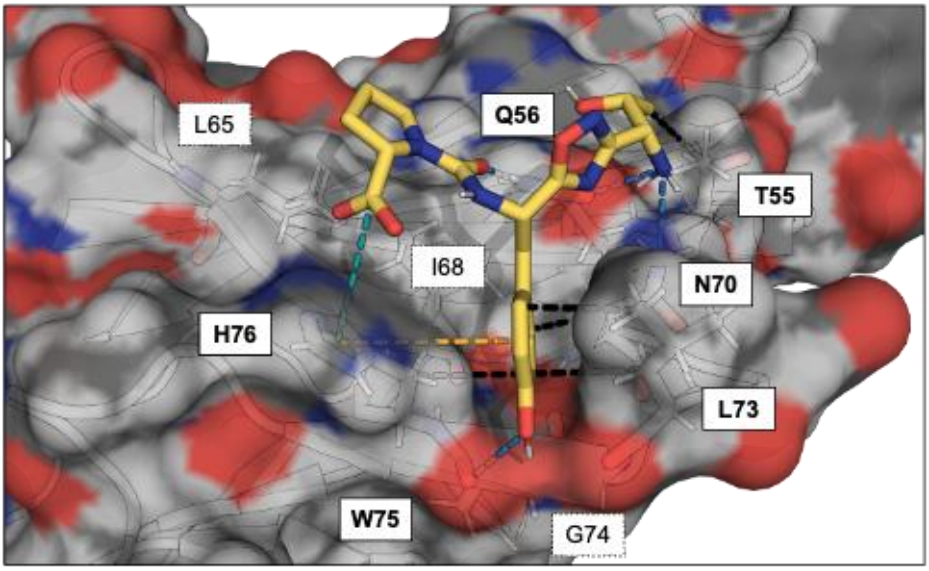
To identify novel inhibitors, we performed a structure-based virtual screening campaign. All Protein Data Bank (PDB) TIGIT structures were analyzed, and interactions with antibodies and biological receptors were mapped using Protein–Ligand Interaction Profiler (PLIP), highlighting key residues Q56, N58, L65, I68, N70, L73, and H76. Blind docking of a reference compound from the AUR-106 patent (WO2019175799A2) [2] using SMINA and GNINA revealed a binding pocket at the receptor–binding partner interface. The compound's interactions resembled those observed with antibodies and biological receptors, and it consistently adopted similar poses across different conformers using PDB entry 3UDW, providing confidence in the selected pocket (further confirmed with SiteFinder from Molecular Operating Environment (MOE)) and protein structure.

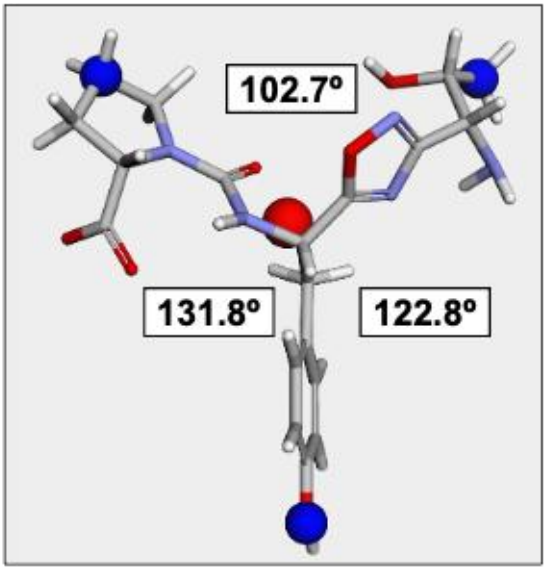
Visual inspection indicated that the pocket can accommodate T/Y-shaped molecules. Commercial databases such as Enamine and ChemBridge were screened and filtered sequentially based on docking score, predicted interactions matching the reference compound, visual inspection, ability to adopt T/Y-shaped conformations - assessed using a custom Python script - and purchasability. Screening of over one million compounds resulted in 37 purchasable candidates. A central hydrophobic aromatic scaffold emerged as a key pharmacophoric feature, enabling stabilizing cation–π and hydrophobic interactions, with H76 acting as a primary anchoring residue.

Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) predictions revealed potential toxicity concerns for some of the identified compounds, highlighting the need for further optimization. Ongoing molecular dynamics (MD) simulations using GROMACS with the GROMOS54A7 force field aim to evaluate the stability of the protein–ligand complexes prior to experimental validation.

Overall, the identified hits represent promising starting points for the development of small-molecule TIGIT inhibitors and may provide viable alternatives to recently unsuccessful antibody-based therapeutic strategies.

Residues	Interactions
T55	HYD
Q56	HB (2)
N70	HYD, HB
L73	HYD (2)
W75	HB
H76	HYD, SB, cation-π





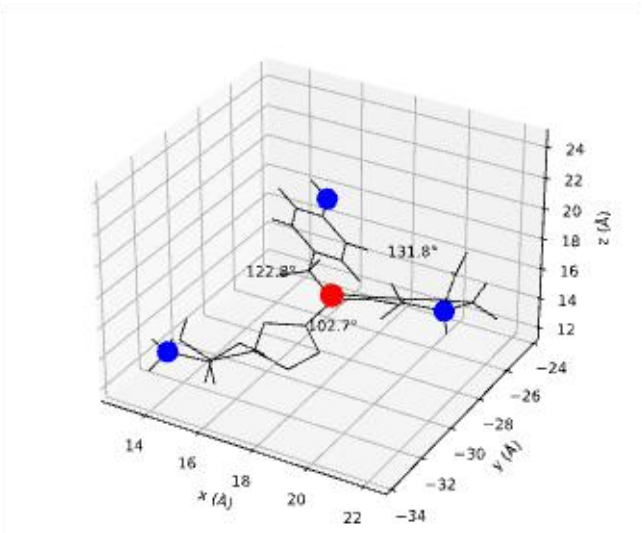


Figure 1 - Representative binding pose of the reference compound.

Acknowledgements:
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Keywords: Immune Checkpoint Inhibitors, Molecular Docking, Small-molecule Inhibitors, Structure-based Drug Design, TIGIT, Virtual Screening

(Session B | 11:40-12:00) – Room B

OC - (25897) - COMPUTATIONAL MODELING OF 3-METHYLINDOLE FLUORESCENCE: TOWARD PREDICTION OF TRYPTOPHAN EMISSION AND FLUORESCENCE DECAY

Federica Borzelli (Italy)[1]; Marco D'abramo (Italy)[1]; Andrea Amadei (Italy)[2]
1 - Department of Chemistry, Sapienza University of Rome, Rome, Italy; 2 - Department of Chemical Science and Technologies, University of Rome Tor Vergata, Rome, Italy

Abstract

Tryptophan fluorescence is widely used as an intrinsic probe of protein structure and dynamics. However, the quantitative interpretation of its emission spectrum and fluorescence decay remains challenging, as the relative stability, relaxation pathways, and radiative properties of the chromophore are strongly affected by the surrounding environment.

In this study, we modeled both the fluorescence emission spectrum and the excited-state relaxation kinetics of 3-methylindole (3MI) in water by means of the Molecular Dynamics–Perturbed Matrix Method (MD-PMM) [1]. This strategy has previously proven effective for modeling such properties of similar systems [2]. Although indole is commonly used as the minimal quantum-center model for tryptophan photophysics, 3MI provides a closer analogue of the tryptophan chromophore, due to the methyl substituent at the 3-position. Establishing the photophysical behavior of 3MI in water is therefore a preliminary step toward its use as a quantum center for predicting tryptophan emission spectra and fluorescence decay in protein environments.

From high-level quantum-mechanical calculations, two bright states, denoted by analogy with tryptophan as La and Lb, together with the dark πσ* state, were identified as the relevant excited states of 3MI. After performing MD simulations in water in the corresponding state-specific ensembles, we employed the MD-PMM framework to reconstruct the emission spectrum and derive a kinetic scheme for the excited-state relaxation of 3MI in water. The resulting spectrum, relaxation constants, fluorescence lifetime, and quantum yield show good agreement with available experimental data [3]. These results support the use of 3MI as a promising quantum center for future, more accurate predictions of tryptophan fluorescence spectra and decay kinetics in protein environments.

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We acknowledge ISCRA for awarding this project access to the LEONARDO supercomputer, owned by the EuroHPC Joint Undertaking, hosted by CINECA (Italy).

Keywords: 3-methylindole, Fluorescence modeling, Excited-state kinetics, Molecular Dynamics

(Session B | 12:00-12:20) – Room B

OC - (25891) - CONCEPTUAL DFT FOR AND FROM THE EXCITED STATES

Alexandre Pérochon (France)[1]; Frédéric Guégan (France)[1]
1 - IC2MP, UMR-7285 CNRS, Université de Poitiers, Poitiers

Abstract

Conceptual DFT (CDFT) is broadly interpreted as a branch of DFT linking quantum calculations and chemical properties. It is based on the Hohenberg and Kohn theorems, implying that CDFT reactivity descriptors can only be used to describe the ground state. Since chemistry is not just about the ground state — photochemistry, for example, deals with excited states — an excited states extension would be of a great interest.

Descriptors of CDFT are expressed as response functions to perturbations either in the external potential or the number of electrons. Following the idea of a perturbation of the external potential, in 2020 Guégan et al. used the Rayleigh-Schrödinger perturbation theory (RSPT) coupled with TDDFT to formulate a set of polarization descriptors [1,2].

The interest in this approach is that RSPT is formulated in any state, hence the polarization descriptions can be quite straightforwardly extended to excited states.
In this presentation, I will illustrate how such an extension can be provided, and show the potential of the development on some prototypical molecular systems. I will also show how an alternative development, relying on the relation between the polarization descriptors and the linear response function of CDFT, [3] can help in addressing the issues RSPT sometimes present (deviation from weak perturbation regime).

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Keywords: Conceptual DFT, excited states, TDDFT, polarization descriptors, reactivity

Wednesday, 8 July

(Session A | 11:00-11:20) - Auditorium

OC - (25874) - TOO REACTIVE, TOO PASSIVE, JUST RIGHT: OXYGEN AS A CONTROL PARAMETER IN MO_2C CATALYSIS

José D. Gouveia (Portugal)[2]; José R. B. Gomes (Portugal)[1]

1 - CICECO-Aveiro Institute of Materials, Department of Chemistry, University of Aveiro, Aveiro, Portugal; 2 - CICECO-Aveiro Institute of Materials, Department of Physics, University of Aveiro, Aveiro, Portugal

Abstract

The catalytic performance of MXenes is governed not only by their transition-metal carbide cores but, critically, by the chemistry of their surface terminations. Here, we demonstrate how surface oxygen coverage functions as a tunable control parameter that drives Mo_2C MXenes across regimes of excessive reactivity, optimal catalytic turnover, and complete passivation.

Using density functional theory, reaction energy profiling, and transition-state calculations, we investigate the forward and reverse water–gas shift (WGS) reactions on Mo_2C surfaces with systematically varied terminations. Pristine Mo_2C binds key intermediates too strongly, resulting in overly exothermic adsorption and large barriers for product desorption. In contrast, fully oxygen-terminated Mo_2CO_2 is effectively inert: the oxygen overlayer blocks active Mo sites, weakens adsorbate interactions, and introduces prohibitive dissociation barriers. Between these extremes lies the catalytically relevant regime. Partial oxygen coverage restores activity by exposing a controlled fraction of Mo sites and tuning adsorption energies toward the Sabatier optimum.

This mechanistic framework resolves the long-standing discrepancy between theoretical predictions of inactivity for fully O-terminated Mo_2C and the experimentally observed WGS activity of real Mo_2CT_x catalysts, which inherently feature mixed terminations and vacancy defects. More broadly, it establishes a transferable design principle: surface oxygen coverage is not merely a structural detail, but a key, tunable parameter governing catalytic behavior.

By elucidating how surface terminations reshape reaction energetics, this work provides actionable guidelines for engineering MXene catalysts with tailored reactivity. These findings underscore the role of computational chemistry in uncovering termination-dependent mechanisms and advancing the rational design of high-performance carbide-based catalysts.

This work was developed within the scope of projects CICECO–Aveiro Institute of Materials, UID/50011 and LA/P/0006/2020 (DOI 10.54499/LA/P/0006/2020), financed by national funds through the FCT/MCTES (PIDDAC) and MINIONS, 2024.16387.PEX (DOI

10.54499/2024.16387.PEX). JDG thanks the Portuguese Foundation for Science and Technology (FCT) through the grant with Ref. 2023.06511.CEECIND, in the scope of the Individual Call to Scientific Employment Stimulus – 6th Edition.

Keywords: MXene, Density functional theory, Heterogeneous Catalysis, Water gas shift reaction

(Session A | 11:20-11:40) - Auditorium

OC - (25922) - HYBRID QM/MM APPROACH FOR COMPUTING TIME-RESOLVED PHOTOELECTRON SPECTRA IN SOLUTION

Pietro Dal Cin (Italy)[1]; Chiara Cappelli (Italy)[1]; Meseret Bezabih (United States of America)[2]; Massimo Olivucci (Italy)[2,3]

1 - Scuola Normale Superiore; 2 - Bowling Green State University; 3 - Università degli studi di Siena

Abstract

Accurately modeling molecular systems in realistic environments is essential for understanding light-driven processes of interest in natural and photo-pharmacological studies. Computational methods must account for both electron correlation effects and an atomistic description of the environment when simulating spectral properties [1]. Multiscale QM/MM modeling [2,3] addresses this issue by treating the solute with an accurate QM method while representing solvent molecules as classical multipoles, preserving atomistic detail at reduced computational cost.

In this work, the photodynamics of a biomimetic molecule [4] are studied using a hybrid scheme for the calculation of time-resolved photoelectron spectra. Non-adiabatic dynamics simulations are performed using electrostatic embedding methods [5], while the corresponding TRPES is calculated at spaced intervals through a more accurate polarizable QM/MM approach [6] that combines CASSCF/CASPT2 with the fluctuating charges (FQ) model [7]. For this purpose, detachment energies and Dyson norms are calculated across the trajectories ensemble and convoluted in time to recover the final time-resolved spectrum [8].

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Keywords: TRPES, Polarizable embedding, Multiscale QM/MM methods, Non-adiabatic dynamics, Acqueous solution, Fluctuating Charges

(Session A | 11:40-12:00) - Auditorium

OC - T-290676 AND T-2635 HIV FUSION INHIBITORS INTERACT STRONGLY WITH MODEL MEMBRANES: A MOLECULAR DYNAMICS STUDY THAT REVEALS PEPTIDE BEHAVIOR, STRUCTURE, AND DYNAMICS

António Do Canto (Portugal)[1,2]; Catarina Grazina (Portugal)[2]; Alfredo Carvalho (Portugal)[1,2,3]

1 - LAQV-REQUIMTE, Universidade de Évora; 2 - Departamento de Química e Bioquímica, Escola de Ciências e Tecnologia, Universidade de Évora; 3 - MARE, Universidade de Évora

Abstract

T-290676 and T-2635 are part of a more recent generation of HIV fusion inhibitor peptides (FIs), specifically developed to retain and increase their effectiveness against HIV strains that have acquired resistance to earlier peptide treatments. Prior studies have demonstrated that peptides like these are capable of associating with model membranes in both the liquid-disordered (L_d) and liquid-ordered (L_o) phases. This interaction with membranes appears to be a critical aspect of their mechanism of action and has been positively correlated to their antiviral potency. To further investigate these interactions, molecular dynamics (MD) simulations were employed to address peptide function using two types of model membranes: one composed exclusively of 1-palmitoyl-2-oleoyl-phosphatidylcholine (POPC), a model of a fluid membrane, and another consisting of a 1:1 mixture of POPC and cholesterol (Chol), a model of a more ordered and rigid membrane. The simulation results showed that both T-290676 and T-2635 have a strong affinity for both types of membranes, with significantly greater capability of interaction than earlier fusion inhibitors, such as T-20 and T-1249. This stronger membrane association further emphasizes peptide-membrane interaction as a key part in their enhanced inhibitory effectiveness. Additionally, our findings suggest that structural features, such as peptide helicity and the ability to form hydrogen bonds with cholesterol, also play a significant role in inhibiting the fusion process.

Alfredo Carvalho would like to acknowledge the support of Fundação para a Ciência e a Tecnologia (FCT) through the multi-year funding program UID/04292/2025 (DOI: https://doi.org/10.54499/UID/04292/2025).

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The authors would like also to acknowledge with gratitude the support of the HPC Chair of Universidade de Évora (https://catedrahpc.uevora.pt/) for both computational time and disk space for data storage.

Keywords: AIDS, HIV fusion inhibition, lipid-peptide interaction, biomembrane simulations, POPC, Cholesterol

(Session A | 12:00-12:20) - Auditorium

OC - (25737) - COMPUTATIONAL AND EXPERIMENTAL INSIGHTS INTO PANCREATIC LIPASE INHIBITION BY BIOACTIVE COMPOUNDS FROM STEVIA REBAUDIANA BERTONI

Nathalia Aceval (Uruguay)[1,2]; Jorge Cantero (Uruguay)[1,3]; Silvio Claudio Da Costa Silva (Brazil)[4]; Jeffrey Pearson (United Kingdom)[5]; Margot Paulino (Uruguay)[1]

1 - Área Bioinformática, DETEMA, Facultad de Química, UdelaR, Montevideo, Uruguay.; 2 - Dirección de Investigación, Facultad de Ingeniería Agronómica, Universidad Nacional del Este, Minga Guazú, Paraguay.; 3 - Centro de Investigaciones Médicas, Facultad de Ciencias de la Salud, Universidad Nacional del Este, Minga Guazú, Paraguay.; 4 - Departamento de Bioquímica, Centro de Ciências Biológicas, Universidade Estadual de Maringá, Maringá, Brasil.; 5 - Pearson Lab, Biosciences Institute, Medical School, Newcastle University, Newcastle Upon Tyne, UK

Abstract

Obesity is a major global health challenge associated with high dietary fat intake and efficient intestinal lipid absorption mediated by pancreatic lipase. Inhibition of this enzyme represents an important strategy for obesity management. Although the synthetic inhibitor Orlistat® is effective, its use is often limited by adverse side effects, highlighting the need for natural alternatives. In this study, we investigated the inhibitory potential of crude and purified extracts of *Stevia rebaudiana* Bertoniagainst porcine pancreatic lipase (PPL) using combined experimental and computational approaches. *In vitro* assays revealed a strong dose-dependent inhibitory activity for crude extracts, reaching 95.15 ± 10.18% inhibition at 5 mg/mL, with an IC_{50} of 2.84 ± 0.02 mg/mL. In contrast, purified fractions showed no significant inhibition, suggesting synergistic effects among multiple phytochemicals present in the crude extract.To explore the molecular basis of this activity, molecular docking simulations were performed using the crystallographic structure of PPL (PDB ID: 1ETH). Twelve compounds identified in *Stevia* extracts were evaluated, including steviol glycosides and phenolic constituents. The results revealed high binding affinities for Rebaudioside A (–9.01 kcal/mol) and Stevioside (–8.91 kcal/mol), comparable to Orlistat (–8.30 kcal/mol). These ligands interacted with key catalytic residues including Ser153, Asp206, Phe216, and His264.Molecular dynamics simulations (100 ns) were performed using NAMD with the CHARMM36 force field under periodic boundary conditions. Interaction energy analyses showed that Rebaudioside A exhibited the strongest interaction energy (–244.62 ± 17.97 kcal/mol), followed by Stevioside (–186.69 ± 13.35 kcal/mol), both surpassing Orlistat. Electrostatic interactions were dominant in the stabilization of the enzyme–ligand complexes.These results highlight *Stevia rebaudiana* Bertoni as a promising natural source of pancreatic lipase inhibitors and demonstrate the usefulness of multiscale computational approaches to explore the molecular mechanisms underlying bioactive natural products.

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Comisión Sectorial de Investigación Científica (CSIC).
Universidade Estadual de Maringá (UEM).
Newcastle University.
Aelious Biotech.

Keywords: Pancreatic lipase inhibition, Molecular dynamics, steviol glycosides, Molecular docking

(Session B | 11:00-11:20) – Room B

OC - (25729) - COMPARATIVE STUDY OF CONFORMATIONAL DYNAMICS OF THE TRYPANOSOMA CRUZI AND HUMAN PHOSPHATASES: EFFECTS OF PH AND SENSITIVITY TO COMPETITIVE METAL INHIBITORS

Rodrigo Moreira (Uruguay)[1,2,3]; Gonzalo Scalese (Uruguay)[1,4]; Dinorah Gambino (Uruguay)[1]; E. Laura Coitiño (Uruguay)[5,6]

1 - Área Química Inorgánica, DEC, Facultad de Química, Universidad de la República, Uruguay; 2 - Programa de Posgrado de Facultad de Química, Universidad de la República, Uruguay; 3 - PEDECIBA – Programa de Desarrollo de las Ciencias Básicas, Uruguay; 4 - Laboratory Redox Biology of Trypanosomes, Institut Pasteur de Montevideo, Uruguay; 5 - Laboratorio de Química Teórica y Computacional (LQTC), Instituto de Química Biológica, Facultad de Ciencias; 6 - Centro de Investigaciones Biomédicas (CEINBIO), Universidad de la República, Uruguay

Abstract

Protein tyrosine phosphatases (**PTP**s) are key regulators of cellular signaling and relevant therapeutic targets.[1] While human **PTP** 1B (**PTP1B**) has been extensively characterized, the homologous enzyme from *Trypanosoma cruzi* (***Tc*PTP1**), the etiological agent of Chagas disease, remains comparatively unexplored. Despite the proposed relevance of **PTP**s as drug targets in trypanosomatid parasites, their structural and dynamics features are still insufficiently understood.[2,3]

We investigated the conformational dynamics of **PTP1B** and ***Tc*PTP1** through conventional and accelerated molecular dynamics simulations at two *in vitro* relevant pH values (5.5 and 7.5) assessing how protonation-state changes modulate protein flexibility, active-site accessibility, and the equilibrium between typical open (inactive) and closed (active) conformations. Special attention was given to the behavior of functionally important regions, including the WPD loop and surrounding structural elements involved in catalysis and substrate recognition.[4]

Conformational landscapes were analyzed using principal component analysis (PCA) and hierarchical clustering (HC). PCA allowed to identify dominant collective motions associated with loop rearrangements and domain breathing, while HC analysis enabled the extraction of representative conformational states under each pH condition. **PTP1B** displays motions consistent with previous experimental and computational reports[5] whereas ***Tc*PTP1** exhibits distinct, strongly pH-dependent shifts between open and closed states, suggesting differential sensitivity to environmental conditions.

To assess the factors governing the interaction of metal-based competitive inhibitors—including vanadate, tungstate, and molybdate, well-known phosphate mimetics for **PTP**s—DFT calculations were performed on a reduced active-site model at the B3LYP-D3/6-31G(d,p) level of theory for C/H/S/O/N atoms and LANL2DZ ECPs for the transition metals and phosphorous, applying a continuum PCM-IEF solvation model. Our results highlight

how metal identity, coordination environment, and protonation-state modulate binding strength and geometry, providing a molecular rationale for explaining differences in inhibitor affinity.

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Programa de Desarrollo de las Ciencias Básicas (PEDECIBA)-Uruguay.
Comisión académica de Posgrados (CAP-UdelaR)

Keywords: Tyrosine phosphatases, Trypanosoma cruzi, metal inhibitors, vanadate

(Session B – 11:20-11:40) – Room B

OC - (25925) - PROTONATION DYNAMICS AT THE DJ-1 DIMER INTERFACE

Diana Vitorino (Portugal)[1]; Miguel Machuqueiro (Portugal)[1]

1 - BioISI: Biosystems and Integrative Sciences Institute, Faculdade de Ciências, Universidade de Lisboa

Abstract

DJ-1, also known as Parkinson's Disease (PD) Protein 7 (PARK7), is a multifunctional protein that acts as an oxidative stress sensor, protecting dopaminergic neurons from aggregation and neurodegeneration associated with PD. Under physiological conditions, DJ-1 naturally exists as a homodimer, with monomeric DJ-1 being prone to degradation and unable to exert protective functions. Therefore, DJ-1's ability to maintain its dimeric state is central not only to its structural integrity but also to its biochemical activity. Mutations in DJ-1, such as L166P, can compromise dimerization [1]. During dimerization, a characteristic type of hydrogen bond between two acidic residues, Glu15 and Asp24, is established in the dimer interface. This interaction has been proposed to regulate the stability of the dimer interface, as it requires the protonation of at least one acid to suppress electrostatic repulsion [2].

In this study, we employ Constant-pH Molecular Dynamics (CpHMD) simulations using the GROMOS 54A7 force field to gain insights into how protonation dictates the formation of stabilizing H-bonds between the acidic residues. CpHMD is a state-of-the-art technique that allows simultaneous sampling of the conformational and protonation states of titrable amino acid residues at a fixed pH over the simulation time. Wild-type and L166P monomeric and dimeric DJ-1 systems were built, equilibrated, and simulated at five pH values (4.2, 5.2, 6.2, 7.2, and 8.2) with five replicas each to obtain titration curves. This range encompasses physiological pH, where DJ-1 is predominantly distributed, as well as more acidic conditions that represent stress or pathological pH levels.

Both monomeric and dimeric forms of DJ-1 (wild-type and mutant) remained structurally stable throughout the simulations, with no signs of dimer dissociation. However, the protonation behavior of Asp24 and Glu15 differed significantly between the two states, as dimerization induced larger pKa shifts, consistent with desolvation at the dimer interface. The dimeric form showed that at least one carboxylic acid remains protonated, allowing the stabilizing DJ-1 hydrogen bond to form. Herewith, an asymmetry in pKa values was observed between the two pairs of the aforementioned carboxylic acids. Furthermore, the two monomers show some degree of asymmetry relative to one another. As a symmetrical homodimer, the two DJ-1 monomers are expected to exhibit the same protonation behavior. With this, we are extending the current simulation time in the hope of attaining convergence. These findings show that protonation strongly modulates dimerization, as the DJ-1 dimer can accommodate this stabilizing interaction.

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Keywords: CpHMD simulations, Dimerization, DJ-1 protein, Protein Stability, Protonation States

(Session B | 11:40-12:00) – Room B

OC - (25898) - TARGETING GLYCOSOMAL PROTEIN IMPORT IN TRYPANOSOMA: MOLECULAR DYNAMICS STUDY OF PEX5 MIMETIC INHIBITORS

Amanda Ribeiro Guimaraes (United Kingdom)[3]; Esther R. S. Paz (Brazil)[1]; Allison Serrano-Trejos (Colombia)[2]; Chonny Herrera-Acevedo (Colombia)[2]; Iván Rivilla (Spain)[5]; Óscar R. Ballesteros (Spain)[4]; Guilherme A. M. Jardim (Brazil)[1]; Eufrânio N. Da Silva Júnior (Brazil)[1]; Felipe Fantuzzi (United Kingdom)[3]

1 - Instituto de Ciências Exatas, Departamento de Química, Universidade Federal de Minas Gerais, Belo Horizonte, MG, 31270–901 Brazil; 2 - Department of Chemical Engineering, Universidad ECCI, Carrera 19 # 49–20, 111311 Bogotá D.C., Colombia; 3 - School of Natural Sciences, University of Kent; 4 - Donostia International Physics Center (DIPC), Donostia/San Sebastian 20018, Spain.; 5 - Department of Organic Chemistry I, Center of Innovation in Advanced Chemistry (ORFEO−CINQA), Faculty of Chemistry, University of the Basque Country (UPV/ EHU), Donostia International Physics Center (DIPC), IKERBASQUE, Basque Foundation for Science, Spain

Abstract

Human trypanosomiases remain a major public health challenge in endemic regions (*Lancet.* 2003;362:1469–1480) and are caused by protozoan parasites of the genus *Trypanosoma*, including *T. cruzi*, the causative agent of Chagas disease (*BMJ.* 2003;326:1444.), and *T. brucei*, responsible for human African trypanosomiasis (*Nat Rev Microbiol.* 2004;2:186.). In these parasites, glycolysis occurs within glycosomes, specialized peroxisome-like organelles that are essential for parasite survival and metabolism. Glycosomal biogenesis and maintenance depend on the import of cytosolic enzymes through a highly regulated machinery mediated by peroxins (Pex proteins) (*Mol Biochem Parasitol.* 2019;229:62–74). Protein import into glycosomes is initiated by recognition of peroxisomal targeting signals (PTS), most commonly PTS1, by the soluble receptor Pex5. The C-terminal tetratricopeptide repeat (TPR) domain of Pex5 is responsible for cargo recognition, while its intrinsically disordered N-terminal region mediates docking and translocation at the glycosomal membrane (*Nat Struct Biol.* 2000;7:1091–1095). After cargo recognition, the Pex5–cargo complex interacts with membrane-associated proteins, primarily Pex14 and Pex13, to enable translocation into the organelle lumen. Among these components, Pex14 plays a central role in docking the complex at the membrane and is therefore considered a promising therapeutic target. (*J Biol Chem.* 2001;276:34524–34529). Current chemotherapy for Chagas disease relies mainly on benznidazole and nifurtimox, drugs that present important limitations, including reduced efficacy during the chronic phase and frequent adverse effects. These shortcomings highlight the urgent need for novel therapeutic strategies with improved efficacy and safety profiles. Because glycosomal protein import is essential for parasite viability, disruption of the Pex5–Pex14 protein–protein interaction has emerged as an

attractive approach for antiparasitic drug development (*Am J Trop Med Hyg.* 2017;97:1289–1303). A detailed molecular understanding of both the Pex5–Pex14 interaction and the binding of small-molecule inhibitors to Pex14 is critical for rational drug design. Structural and energetic characterization of these systems can reveal the determinants of binding affinity and specificity, thereby supporting the optimization of novel inhibitory compounds. In this work, computational approaches were employed to investigate the Pex5–Pex14 interaction and Pex14–inhibitor complexes. Quantum Mechanics Calculations, Molecular Docking and Molecular Dynamics simulations were used to characterize binding modes, interaction networks, and complex stability. The results provide insights into the molecular basis of glycosomal protein import and contribute to the development of new inhibitors targeting *Trypanosoma* species.

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Keywords: Pex5–Pex14 interaction, Pex14–inhibitor complexes, Molecular Dynamics, drug design, Trypanosomiases

(Session B | 12:00-12:20) – Room B

OC - (25948) - INTRINSIC STABILITY OF SUGAR-PHOSPHATE BACKBONE CONFORMATIONS EXPLAINS STRUCTURAL DIVERSITY IN MINIMAL DNA FRAGMENTS

Veronica Dominguez Benitez (Mexico)[1]; Alexandra Deriabina (Mexico)[1]; Selene Lozano Huitzil (Mexico)[1]; Eduardo Gonzalez Jimenez (Mexico)[1]; Rosendo L. Lozada Morales (Mexico)[1]; Valeri Poltev (Mexico)[1]

1 - Faculty of Physical and Mathematical Sciences, Autonomous University of Puebla, Puebla, México

Abstract

DNA's structural diversity extends beyond canonical A- and B-form duplexes and encompasses a wide range of experimentally observed conformations. Understanding why this diversity arises is a central problem in DNA structural analysis. In this work, we examine how the intrinsic stability of the sugar-phosphate backbone (SPB) affects conformational behavior in minimal DNA fragments.

We perform DFT (PBE, M05-2X) and MP2 optimization calculations on minimal SPB fragments from selected nucleotide conformational classes (NtCs). This extends our earlier work from the 2021 Computation article "*Understanding the Origin of Structural Diversity of DNA Double Helix*". Our results show that NtCs can be systematically divided into two groups: (i) classes with SPB torsions being close to the local energy minima of a separate SPB fragment, and (ii) classes that do not exhibit such correspondence.

This distinction has direct structural consequences. Fragments associated with SPB minima tend to preserve their conformational features upon optimization, whereas those lacking intrinsic backbone stability undergo significant structural rearrangements. These findings provide a physical basis for understanding the conformational variability observed in DNA structures and show that the intrinsic stability and energy of the sugar-phosphate backbone play a central role in controlling conformational diversity at the fragment level.

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Keywords: DNA conformational diversity, Sugar-phosphate backbone minimal fragments, Nucleotide conformational classes (NtC), Minimal DNA fragments, Structural stability

(Session A | 16:30-16:50) - Auditorium

OC - (25727) - DFT STUDY OF ACETONE ADSORPTION ON PRISTINE AND B-DOPED GERMANIUM MONOLAYERS FOR BREATH-BASED DIABETES SENSING

Alejandro Barranco Sainz (Mexico)[1]; Francisco De Santiago (Mexico)[2]; Álvaro Miranda (Mexico)[1]; Miguel Cruz-Irisson (Mexico)[1]

1 - Instituto Politécnico Nacional, ESIME-Culhuacán; 2 - Instituto de Física, Universidad Nacional Autónoma de México

Abstract

Acetone (C_3H_6O) is a waste product generated when the body uses fats as an energy source instead of glucose, a condition that occurs when insulin production is insufficient. Therefore, it constitutes a relevant biomarker for the non-invasive diagnosis of diabetes through breath analysis. Nanostructured materials are particularly attractive for biosensing applications due to their high surface-to-volume ratio, enhanced chemical reactivity, and remarkable sensitivity, which promote adsorption processes and electronic transduction mechanisms [1,2]. The effects of adsorbed acetone on the properties of nanostructures, such as monolayers, have not been sufficiently studied.

In this work, the adsorption of acetone on a germanium monolayer (GeML) was investigated using density functional theory (DFT) in both pristine and boron-doped configurations (GeML+B), with the aim of evaluating the effect of doping on the adsorbate–surface interaction and the electronic response of the system.

The results indicate that boron doping slightly increases the adsorption energy, from 0.57 eV to 0.60 eV, suggesting a stronger interaction in the doped system. A charge transfer on the order of ~0.18 |e| is observed, along with a significant increase in the work function from 4.40 eV to 4.63 eV, evidencing a noticeable modification of the surface electronic properties induced by the dopant. The recovery times remain in the millisecond range, although they are longer in the doped monolayer, consistent with the greater stability of the adsorbed state.

Overall, these results demonstrate that boron doping effectively modulates the interaction and electronic response of germanium monolayers toward acetone, highlighting their potential as active materials for breath-based biomarker sensing applications.

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Keywords: Germanium monolayers, Acetone, DFT, Sensors

(Session A | 16:50-17:10) - Auditorium

OC - (25728) - EFFECTS OF DIMENSIONALITY CONSTRAINTS ON NA DIFFUSION IN GE AND SI NANOSTRUCTURES

Dafne Dayan Barranco Rivera (Mexico)[1]; Fernando Salazar (Mexico)[1]; Alejandro Trejo (Mexico)[1]

1 - Instituto Politécnico Nacional, ESIME-Culhuacán

Abstract

Given the challenges faced by current batteries, the search for new materials that improve their lifetime and efficiency has become a priority. To this end, nanomaterials and semiconductors have shown great promise for the development of new anodic materials. Nevertheless, the ionic mobility in these structures remains rather unexplored. In this study, we present a density functional theory (DFT) analysis of the diffusion of a sodium (Na) atom in germanium (Ge) and silicon (Si) structures, considering bulk, monolayer, and nanowire configurations. For this purpose, the LST and QST algorithms implemented in the Dmol^3 code, part of the Materials Studio software, were used. The model considers the initial and final positions of the Na atom in each reaction scenario. In the case of the bulk material, the selected positions for Na are two equivalent T_d sites, which represent the centers of the tetrahedra formed by four atoms in the diamond-type structure. In the nanowire, two trajectories are studied: the first consists of diffusion from a T_d site on the surface toward the interior of the structure, and the second between two nearby T_d sites within the nanowire itself. Similarly, in the Ge and Si monolayers, the reactant and product sites correspond to two equivalent hexagonal positions on the surface, where the Na atom is located 1.5 Å above the monolayer. The results indicate that the diffusion pathway of the Na atom is symmetric in the bulk structure for both Ge and Si, with the Ge pathway being energetically more favorable. In monolayers, the potential barrier is lower in Ge than in Si. On the other hand, the diffusion pathway is asymmetric in both nanowires; however, it is observed that Na requires less energy to enter the Ge nanowire and subsequently to move within it between two T_d sites. These findings highlight the influence of dimensionality and atomic interactions on Na atom diffusion, particularly on the potential energy barriers imposed by structural and dimensionality constraints. This study provides valuable insight into the mechanisms of Na diffusion in Ge- and Si-based materials and their impact on the charge–discharge cycles of battery electrodes.

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Keywords: DFT, Nanowires, Sodium, Semiconductors

(Session A | 17:10-17:30) - Auditorium

OC - (25923) - HOW FLUORINE SUBSTITUENTS STRENGTHEN ARYL C–H BONDS

Daniel A. Santos Oliveira (Brazil)[1,2]; Daniela Rodrigues Silva (Brazil)[2]; Ataualpa Braga (Brazil)[1]; Célia Fonseca Guerra (Netherlands)[2]; Robin N. Perutz (United Kingdom)[3]; Odile Eisenstein (France)[4,5]; F. Matthias Bickelhaupt (Netherlands)[2,6,7]

1 - University of São Paulo; 2 - Vrije Universiteit Amsterdam; 3 - University of York; 4 - University Montpellier; 5 - University of Oslo; 6 - Radboud University; 7 - University of Johannesburg

Abstract

Fluorine substitution is known to significantly modify the physical and chemical properties of aromatic systems, including an intriguing strengthening of aryl C–H bonds. Despite extensive experimental and computational studies, the fundamental origin of this effect remains insufficiently understood. In this work, [1] we provide a quantitative molecular-level explanation for the strengthening of C–H bonds in (poly)fluorinated benzenes (C_6R_5H, R = H, F) using Kohn–Sham molecular orbital (KS-MO) theory in combination with the activation strain model (ASM) and energy decomposition analysis (EDA).

Our results confirm that C–H bond strengthening upon fluorination is systematic and largely additive, with a pronounced regioselectivity following the order ortho >> para > meta. The strengthening is primarily driven by a reduction in Pauli repulsion between the singly occupied hydrogen 1s orbital and the closed-shell orbitals of the aryl radical fragment. This reduction originates from the strong inductive effect of fluorine, which polarizes the electron density of the aryl σ-system away from the C–H bonding region, thereby decreasing same-spin orbital overlap.

To assess the generality of the proposed mechanism, we extend our analysis to monosubstituted benzenes bearing other substituents (R = Cl, Br, I, Li). Although all halogens lead to stronger C–H bonds compared to benzene, the trends in bond strength follow the electronegativity of the substituent, decreasing as the electron-withdrawing character diminishes along the halogen series. Phenyllithium represents the opposite extreme, where the substituent is less electronegative than hydrogen and exhibits an electron-donating character, resulting in significantly weaker C–H bonds due to increased Pauli repulsion.

These findings provide a consistent and physically grounded explanation for C–H bond strengthening in fluorinated aromatics and highlight the key role of Pauli repulsion as a governing factor in chemical bonding trends.

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Keywords: Chemical bonding, Bond energy, DFT, Inductive effects, Steric effects

(Session B | 16:30-16:50) – Room B

OC - (25939) - THEORETICAL MODELING OF THE STRUCTURAL, ELECTRONIC AND TRANSPORT PROPERTIES OF $ZRNBCO_2$ JANUS MXENE FOR HIGH-PERFORMANCE LITHIUM STORAGE

Efracio Mamani Flores (Peru)[1]
1 - UNJBG

Abstract

The escalating global demand for efficient energy storage devices has intensified the search for novel two-dimensional (2D) materials capable of surpassing the limits of conventional graphite anodes. Among these, Janus MXenes have emerged as a promising class of materials due to their broken mirror symmetry, which induces unique electronic and electrochemical properties. In this study, we utilize first-principles density functional theory (DFT) calculations to systematically investigate the structural, electronic, and transport properties of the bimetallic $ZrNbCO_2$ Janus MXene.

The stability of the $ZrNbCO_2$ monolayer was rigorously validated. Dynamical stability was confirmed by the absence of imaginary frequencies in the phonon dispersion spectra, while mechanical integrity was verified through the satisfaction of the Born-Huang criteria. Furthermore, *ab initio* molecular dynamics (AIMD) simulations demonstrated that the structure remains thermally stable at room temperature, ensuring its viability for practical operating conditions.

Our investigation of Lithium (Li) adsorption behavior on both terminations (ZrO and NbO sides) revealed significant adsorption energies of -3.22 eV and -3.30 eV, respectively. Notably, the material exhibits exceptional transport properties, with remarkably low diffusion energy barriers of 89 meV on the ZrO surface and 202 meV on the NbO surface. These correlate to high diffusion coefficients (1.33×10^{-7} cm^2/s and 5.71×10^{-9} cm^2/s), which are critical for high-rate performance. The structure supports a maximum stoichiometry of $Li_6ZrNbCO_2$, yielding a high theoretical storage capacity of 596.07 mAh/g. With an average open-circuit voltage (OCV) of 1.05 V, $ZrNbCO_2$ Janus MXene demonstrates superior potential as a next-generation anode material for high-performance Lithium-ion batteries (LIBs).

We sincerely thank the Jorge Basadre Grohmann National University (Peru) for its continued support of the research project “Theoretical modeling of the structural, electronic, and ionic transport properties of LiNbO3 electrolytes used in solid-state batteries”, approved by Rectoral Resolution No. 15056-2025-UNJBG.

Keywords: Janus MXenes, Density Functional Theory (DFT), Lithium-ion batteries, Diffusion kinetics, Energy storage.

(Session B| 16:50-17:10) – Room B

OC - (25921) - PHOTOIONIZATION IN AQUEOUS SOLUTION USING THE POLARIZABLE QM/FQ EMBEDDING APPROACH: A TIRESIA-ADF MULTISCALE FRAMEWORK

Giovanni Nottoli (Italy)[1]; Piero Decleva (Italy)[2]; Chiara Cappelli (Italy)[1]
1 - Scuola Normale Superiore; 2 - Università degli studi di Trieste

Abstract

The calculation of molecular photoionization observables in the gas phase has reached a high level of accuracy in recent years, thanks to the development of several well-established theoretical approaches [1]. Among these, continuum density functional theory (DFT) methods based on multicentric B-spline basis functions within the static-exchange (SE) approximation have proven particularly effective for providing quantitative results across multiple ionization channels [2]. At the core of this approach is the Tiresia code, which solves the one-particle Schrödinger equation for positive energies by representing the wavefunction through a hybrid basis: a long-range One Center Expansion (OCE) to describe the asymptotic region and a set of short-range LCAO-like atomic spheres to handle the Coulomb singularities at the nuclei [1, 2]. The use of B-splines, which are polynomial pieces defined over a grid of knots, allows the basis to approach numerical completeness within a finite spherical box of radius Rmax, accurately capturing the highly oscillatory nature of the electronic continuum states [1, 2].

On the other hand, the theoretical study of the same properties in solution has received significantly less attention, despite the increasing availability of experimental data from liquid-jet photoelectron spectroscopy (LJ-PES) [3, 4]. The complexity of the solvent environment, characterized by directional interactions such as hydrogen bonding and local correlations, makes traditional implicit models often inadequate for capturing the local response of the medium. Here we introduce a QM/MM multiscale strategy that combines a B-Spline SE-DFT description of the solute with a fully polarizable embedding based on the fluctuating charges (FQ) model [5, 6]. This coupling enables a correct description of mutual solute–solvent polarization: the solute's electronic density polarizes the classical environment, while the self-consistently induced solvent charges act as an explicit polarization term in the solute's Hamiltonian [5, 7].

To bridge the gap between microscopic snapshots and macroscopic observables, we employ statistical sampling by extracting hundreds of solute–solvent configurations from Molecular Dynamics trajectories. Photoionization observables, including total and channel-resolved cross sections (σ) and angular distribution parameters (β), are computed for each configuration and subsequently averaged to account for statistical fluctuations [7]. The method is first validated on the water dimer and then applied to alanine in aqueous solution [3].

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Keywords: QM/MM Multiscale Method, Fluctuating Charges, Continuum Basis Set, Static-Exchange DFT, Aqueous Solution, PES and Photoelectron Circular Dichroism

(Session B | 17:10-17:30) – Room B

OC - (25736) - QUANTUM CHEMISTRY INVESTIGATION OF THE THIRD-ORDER NONLINEAR OPTICAL RESPONSES: FROM BENCHMARK CCSD(T) TO HYBRID TDDFT//CCSD(T) APPROACHES

Komlanvi Sèvi Kaka (Belgium)[1]; Frédéric Castet (France)[2]
1 - University of Namur; 2 - University of Bordeaux

Abstract

At the molecular scale, the second hyperpolarizability (γ) characterizes third-order nonlinear optical phenomena such as the static Kerr effect (dc-Kerr), the (static) electric field-induced second harmonic generation (EFISHG), the third harmonic generation (THG), and the third harmonic scattering (THS). Recent experimental THS measurements[1] have renewed the interest for calculating and interpreting γ but also for applications in photonic and sensing. However, accurate predictions remain challenging due to the importance of electron correlation, frequency dispersion, and solvent effects. Here, highly correlated γ of solvated push-pull molecules are investigated using a multi-step computational protocol, demonstrating its ability to predict and interpret γ responses.

(i) First, the prototypical push-pull *p*-nitroaniline molecule is used to assess the performance of density functional theory (DFT) and wavefunction (WF) methods against CCSD(T) reference calculations. Among WF methods, MP2 offers the best accuracy/cost ratio for computing the static γ (γ(0)). In contrast, the calculation of γ with cost-effective DFT XCFs remains a point of focus, since most global and range-separated hybrid XCFs underestimate γ(0) by at least 15%, even after tuning the range-separation parameter. The double-hybrid B2-PLYP functional provides accurate γ estimates thanks to its inclusion of second-order perturbation theory (PT2) correlation and large amount of Hartree-Fock exchange but it is less cost-effective.[2]

(ii) Building on this benchmarking, a hybrid computational approach was developed to compute frequency-dependent correlated *γ* values of solvated donor–acceptor benzene derivatives, taking advantage of the validation of the multiplicative scheme separating electron correlation and frequency-dispersion effects. γ(0) values were computed at the CCSD(T) level using an implicit SMD solvation model, while frequency-dependent dc-Kerr and EFISHG responses were obtained at the SMD/CAM-B3LYP level to extract Bishop's A coefficients[3] and predict the THG responses. Additional SMD/CPKS calculations provided γ(0) and γ(THG)/γ(0) dispersion factors, which were combined through a multiplicative scheme to yield frequency-dependent CCSD(T) THG values. The hybrid protocol reproduces the experimental trends for these donor–acceptor benzene derivatives with excellent linear correlation, although absolute γ values remain systematically overestimated. Finally, the γ amplitudes were rationalized in terms of Hammett parameters, which quantify substituent effects, and bond order alternation in the phenyl ring, related to its quinoid character.[4]

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The calculations were performed on the computers of the « Consortium des équipements de Calcul Intensif (CÉCI) » (http://www.ceci-hpc.be), including those of the « UNamur Technological Platform of High-Performance Computing (PTCI) » (http://www.ptci.unamur.be) and those of the Tier-1 supercomputer of the Fédération Wallonie-Bruxelles, for which we gratefully acknowledge the financial support from the FNRS-FRFC, the Walloon Region, and the University of Namur (Conventions No. U.G006.15, U.G018.19, U.G011.22, RW1610468, RW/GEQ2016, RW 1117545, and RW2110213).

Keywords: Nonlinear optical properties, Donor–acceptor benzene derivatives, Frequency-dispersion effects, Solvent effects, Electron correlation effects

Thursday, 9 July

(Session A | 11:00-11:20) - Auditorium

OC - (25870) - METAL FREE, LIGHT-PROMOTED DIFUNCTIONALIZATION OF UNACTIVATED ALKENES: A DFT STUDY

Ana Guimaraes (Spain)[2]; Rakesh Maiti (Germany)[3]; Aritra Nath (Germany)[3]; Sergey Bagnich (Germany)[3]; Anna Köhler (Germany)[3]; Shoubhik Das (Germany)[3]; Feliu Maseras (Germany)[1]

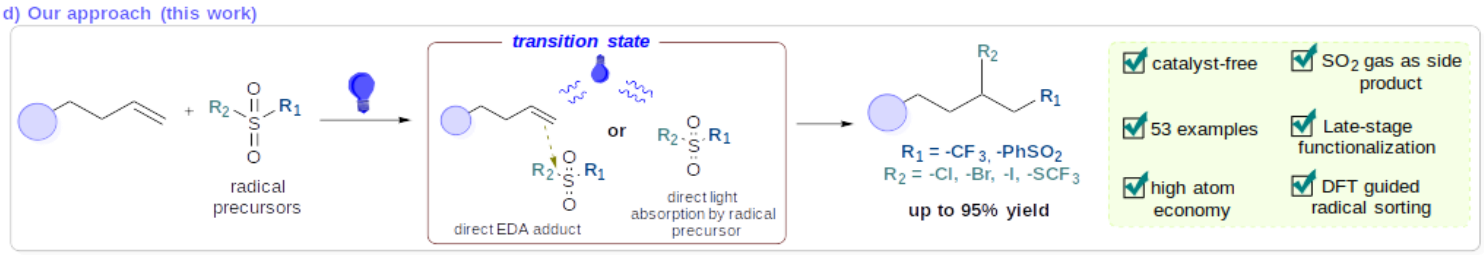
1 - Institute of Chemical Research of Catalonia (ICIQ-CERCA), Tarragona, Spain; 2 - Universitat Rovira i Virgili, Departament de Química Física i Inorgànica, Tarragona, Spain; 3 - Universität Bayreuth, Departament of Organic Chemistry, Bayeruth, Germany

Abstract

The difunctionalization of alkenes offers a direct and efficient strategy for building structurally complex molecules bearing diverse and versatile functional groups. Although a wide range of difunctionalization methods have been reported, the majority of them depend on transition-metal catalysis, including classical approaches such as the Erchinger process.

To overcome these limitations, we propose a metal-free, light-driven strategy guided by DFT calculations. This approach enables the generation of two reactive radical intermediates that engage in predictable transformations with unactivated alkenes. The computed mechanism reveals the formation of transient open-shell species that drive a selective difunctionalization process.

Our strategy takes advantage of the unique reactivity of sulfonyl compounds, which can either undergo direct photoexcitation or form electron donor–acceptor (EDA) complexes. The resulting radical intermediates react with unactivated alkenes, enabling polarity-matched, selective functionalization without the need for preactivation steps.



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Keywords: DFT, photochemistry, difunctionalization, unactivated alkenes

(Session A | 11:20-11:40) - Auditorium

OC - (25899) - A STATISTICAL ANALYSIS OF CHALCOGEN ANISOTROPY IN DIFFERING CHEMICAL ENVIRONMENTS.

Francisco Duarte (Portugal)[1]; Paulo Costa (Portugal)[1]
1 - BioISI - Biosystems & Integrative Sciences Institute, Ciências ULisboa

Abstract

The term σ-hole refers to a localized region of positive electrostatic potential along the extension of a covalent bond, and these regions can engage in directional noncovalent interactions with nucleophilic sites in so-called σ-hole interactions, of which the halogen bond (R–X···B interaction) is the most extensively studied [1]. The magnitude of these σ-holes, associated with the maxima of the electrostatic potential on a molecular surface, is strongly correlated with the interaction energy; thus, the analysis of the electrostatic potential can provide valuable insights into the relationship between electrostatic anisotropy and the chemical environment. In the context of halogen bonding, a comprehensive statistical analysis of σ-holes in more than 2500 halo-containing molecules was previously performed, providing a structural rationale for the preferences observed in these interactions [2]. These σ-hole interactions are not restricted to halogen atoms, and chalcogen bonds (ChBs) [3], a subclass of σ-hole interactions involving Group 16 elements, have attracted increasing attention in several fields of chemistry and biology, owing to their applications in molecular recognition, drug design, and catalysis. Among chalcogens, sulfur is particularly interesting, being far more prevalent than the heavier chalcogens in biomolecules and drugs. Given the wide variety of coordination patterns, the systematic characterization of the electrostatic anisotropy associated with sulfur atoms is not straightforward, although it could be essential for understanding the potential formation of ChBs and for improving classical force-field methods. In this communication, a systematic statistical analysis of the electrostatic potential of approximately 2000 sulfur-containing compounds is presented. The analysis, based on QM-generated ESPs and extrema analysis using the Multiwfn tool, provides insights into chalcogen bonding and helps rationalize observed binding patterns. Additionally, QM calculations were performed on complexes formed between ChB-donor molecules and simple Lewis bases to verify the presence of σ-hole interactions across different sulfur atom families. This characterization may help to improve electrostatic descriptors used in the identification and prediction of noncovalent interactions and assist in the development of improved force-field models capable of capturing σ-hole interactions.

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Keywords: σ-hole interactions, chalcogen bonds, electrostatic potential (ESP), noncovalent interactions, uantum mechanical (QM) calculations

(Session A | 11:40-12:00) - Auditorium

OC - (25955) - A COMPUTATIONAL STUDY ON THE ADSORPTION OF ANTIBIOTICS BY CHITOSAN FUNCTIONALIZED WITH AROMATIC-ALDEHYDE SUBSTITUENTS

Joana Sousa (Portugal)[1]; Artur Valente (Portugal)[1]; Paulo Abreu (Portugal)[1]; Jorge Marques (Portugal)[1]

1 - CQC-IMS, Department of Chemistry, University of Coimbra

Abstract

Antibiotics play a crucial role in the treatment of bacterial infections, but their overuse has caused widespread in the environment and contamination of water bodies. This contamination is closely related to the rise of antibiotic-resistant bacteria, one of the most global public-health challenges[1]. Among different water treatment strategies, adsorption stands out due to its simplicity, efficiency, and low cost, motivating the development of new adsorbent materials[2]. Chitosan is a naturally derived polysaccharide that is abundant, non-toxic and biodegradable. Although free hydroxyl and amino groups provides the conditions for chitosan to be a good adsorbent, its efficiency for antibiotic removal remains limited[1]. In this work, molecular dynamics (MD) simulations and electronic-structure calculations were used to unveil the possible adsorption mechanism of tetracycline (TC), ciprofloxacin (CPX), levofloxacin (LVX) and cephalexin (CLX) on chitosan (CTS) and on chitosan functionalized with aromatic aldehydes (RCA, RCN, RCS, corresponding to CTS functionalized with 9-anthracenecarboxaldehyde, naphthaldehyde and salicylaldehyde, derivatives, respectively). All MD simulations employed the AMBER force field (GAFF2 parameters)[3] and TIP4P-2005 water model[4]. Optimization of the structure geometries were performed at DFT level using the B3LYP functional[5] with the 6-311G++(d,p) basis set, including Grimme´s DFT-D3 dispersion correction with Becke-Johnson damping[6]. The adsorption of antibiotics in different protonation states was also evaluated. Results indicate that increasing the number of aromatic rings in the adsorbent enhances antibiotic adsorption. The protonation state plays a key role for TC and CLX, while CPX and LVX exhibit more stable adsorption with lower pH sensibility and stronger interactions, particularly with RCA and RCN. The interaction mechanism is mainly governed by weak intermolecular forces, including van der Waals, π-π interactions, and occasional hydrogen bonding.

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Keywords: Chitosan, Antibiotics, Molecular dynamics simulations, Electronic-structure calculations

(Session A | 12:00-12:20) – Auditorium

OC - (25954) - BIO-INSPIRED AMINO ACID-FUNCTIONALIZED CHITOSAN FOR THE EFFICIENT CAPTURE OF PESTICIDES

Joana Santos (Portugal)[1]; Paulo Abreu (Portugal)[1]; Jorge Marques (Portugal)[1]
1 - CQC-IMS, Department of Chemistry, University of Coimbra

Abstract

The extensive use of pesticides has raised concerns regarding soil and water contamination, motivating the development of efficient and sustainable materials for the removal of pesticides from water [1]. Chitosan is a promising bio-based adsorbent due to its biodegradability and chemical versatility; however, its affinity toward small organic pollutants remains limited. Herein, we present a computational strategy to guide the design of amino acid-functionalized chitosan materials with enhanced adsorption toward neonicotinoid insecticides and triazine herbicides [2]. A multi-stage computational protocol, inspired by pesticide–protein binding, was employed to identify key amino acids for functionalization, combining molecular docking, molecular dynamics (MD) simulations, and electronic-structure calculations. The selected amino acids were then incorporated into chitosan-based models, and their adsorption efficiency was evaluated through long, multiple-replica MD simulations in aqueous solution using the GAFF2 force field. Representative neonicotinoid (imidacloprid, acetamiprid, thiacloprid, clothianidin, and *S*- and *R*-dinotefuran enantiomers) and triazine (atrazine, simazine, propazine, terbuthylazine, and cyanazine) compounds were considered. To characterize adsorption enhancement

and intermolecular interactions, several properties were calculated, including radial distribution functions, contact-time analysis, and interaction energies. The results reveal that functionalization with aromatic residues, particularly tryptophan and tyrosine, significantly enhances adsorption by stabilizing pesticide–chitosan complexes. This work establishes a transferable protocol for the rational design of bio-inspired adsorbent materials for pesticide removal from water.

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UID/PRR2/00313/2025 through the Projects UID/PRR/00313/2025 (https://doi.org/10.54499/UID/PRR2/00313/2025), UID/00313/2025 (https://doi.org/10.54499/UID/00313/2025) and LA/P/0056/2020. FCT is also acknowledged for a PhD grant to J.R.C. Santos (2022.12451.BD) and for the provision of computational time in the supercomputer resources Deucalion (reference: 2024.10822.CPCA.A1) and INCD Cirrus HPC cluster (Reference: 2023.10584.CPCA.A2). This publication is also based upon work of COST Action CA21101 "Confined molecular systems: from a new generation of materials to the stars" (COSY) supported by COST (European Cooperation in Science and Technology).

Keywords: Molecular Dynamics, Pesticides, Chitosan, Adsorption

(Session B | 11:00-11:20) – Room B

OC - (25854) - ASSESSING FOUNDATION VARIABLE-CHARGE MLIPS FOR MOS2–IONIC LIQUID INTERFACES: FROM BENCHMARKS TO FINE-TUNING

Angel Rodriguez Leon (United States of America)[1]
1 - Northwestern University

Abstract

Two-dimensional materials interfaced with ionic liquids can be designed to emulate biological neurons, where ionic and electronic transport are intrinsically coupled, making them promising candidates for energy-efficient, brain-inspired computational architectures. Machine learning interatomic potentials (MLIPs) with variable charge capabilities provide an effective approach for modeling these systems, allowing computation of transport properties from charge fluctuation responses and capturing both charge redistribution and interfacial electrochemical processes.
Here, we assess foundation MLIPs for MoS2–ionic liquid systems, including both standard models that predict energies and forces and a charge-aware variant. The standard MLIPs are shown to reproduce qualitative interfacial energetics. The variable-charged MLIP model captures sulfur vacancy-induced charge redistribution in MoS2 but exhibits unphysical charge transfer at interfaces and underestimates interlayer binding energies compared to other MLIPs and density functional theory. These limitations reflect the distinct physics and chemistry of 2D material interfaces, differing from the systems used in model training.

To enable fine-tuning of the variable-charge potential, a training dataset is built using a reduction and classification protocol applied to MD simulations generated with robust foundation MLIPs, covering adsorption at MoS2 surfaces, confinement, defects, and phase transitions. This approach reduces thousands of frames to a few hundred representative structures while preserving chemical diversity.
This study highlights the need for interface-specific fine-tuning before MLIPs with variable charges can be reliably applied to 2D materials with ionic liquids. It provides a diagnostic benchmark and a compact, chemically diverse dataset for future large-scale simulations of mixed ionic and electronic transport in these systems.

Keywords: Machine learning interatomic potentials, semiconducting nanochannels, fine-tuning, ionic-electronic coupling

(Session B | 11:20-11:40) – Room B

OC - (25942) - VARIATIONAL MC-PDFT INCLUDING RANGE-SEPARATION: STRONG CORRELATION? NOT SO STRONG ANYMORE

Gabriel Rodrigues (Denmark)[1]; Erik Hedegård (Denmark)[1]
1 - University of Southern Denmark

Abstract

Strongly correlated systems remain a challenge in modern computational chemistry, as DFT often fails to describe them quantitatively, and more adequate methods are too expensive for most practical purposes. However, the proper treatment of strong correlation is extremely important because it frequently appears in ordinary cases such as metallic complexes and excited states. It is therefore critical to develop accurate, but less costly methods. For this, multiconfigurational pair-density functional theory (MC-PDFT) has shown significant potential due to its proper treatment of static correlation while efficiently incorporating dynamic correlation through the pair-density potential. However, most existing implementations compute the PDFT energy in a post-SCF manner, thus ignoring the orbital relaxation effects induced by the pair-density exchange-correlation functional.

In this work, we present recent investigations [1,2] of the performance of our new variational implementation [3] of MC-PDFT developed in the MultiPsi software [4]. It includes translated functionals of GGA and hybrid-GGA form, as well as a new scheme for range separation (MC-sr-PDFT) [5], both for state-specific (SS) and state-averaged (SA) wavefunctions.

We showcase results of variational SA-MC-(sr-)PDFT for excited states of small open-shell molecules and organic chromophores, and, using the state-specific formalism, the singlet–triplet gaps of large conjugated hydrocarbons with potential for quantum applications. Our results already show that when range separation is included, MC-sr-PDFT is comparable to NEVPT4, being (for small radicals) remarkably superior to regular DFT or EOM-CCSD, with mean absolute errors against MRCISD+Q as low as 0.06 eV.

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[3] Scott, M.; Rodrigues, G. L. S.; Li, X.; Delcey, M. G. *J. Chem. Theory Comput.* **2024**, 20 (6), 2423–2432. DOI: 10.1021/acs.jctc.3c01240.
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[5] Jørgensen, F. K.; Kjellgren, E. R.; Jensen, H. J. A.; Hedegård, E. D. *J. Chem. Phys.* **2025**, 162 (3), 034104. DOI: 10.1063/5.0234346.

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and Independent Research Fund Denmark (grant no. 2064-00002B) for support. GLSR is cofunded by the European Union and SDU Climate Cluster, at the University of Southern Denmark under grant agreement No. 101177011. Views and opinions expressed are however those of the author only and do not necessarily reflect those of the European Union or the European Research Executive Agency. Neither the European Union nor the granting authority can be held responsible for them. Computer resources where obtained through Danish e-infrastructure corroboration (DeiC).

Keywords: Multiconfigurational method, MC-PDFT, range-separated functionals, pair-density, variational MC-PDFT, electronic structure methods

(Session B | 11:40-12:00) – Room B

OC - (26131) - UNDERSTANDING NON-COVALENT INTERACTIONS IN IONIC LIQUID-MOLECULAR SOLVENT MIXTURES: A COMBINED COMPUTATIONAL APPROACH

Volodymyr Koverga (Portugal)[1]; Iuliia V. Voroshylova (Portugal)[1]; Abdenacer Idrissi (France)[2]; Toshiyuki Takamuku (Japan)[3]; Oleg N. Kalugin (Ukraine)[4]; M. Natália D. S. Cordeiro (Portugal)[1]

1 - LAQV@REQUIMTE, Faculty of Sciences, University of Porto, Department of Chemistry and Biochemistry, Rua do Campo Alegre, 4169-007 Porto, Portugal; 2 - CNRS, UMR 8516-LASIRe, Laboratoire Avancé de Spectroscopie pour les Interactions, la réactivité et l'Environement, Universiy of Lille, Lille F-59000, France; 3 - Department of Chemistry and Applied Chemistry, Faculty of Science and Engineering, Saga University, Honjo-machi, Saga 840-8502, Japan; 4 - Education and Research Institute of Chemistry, V.N. Karazin Kharkiv National University, Kharkiv 61022, Ukraine

Abstract

Non-covalent interactions play a central role in determining the microscopic organization and macroscopic physicochemical properties of binary mixtures of ionic liquids (ILs) with molecular solvents. In this regard, we propose the concept of a combined computational approach that integrates the complementary advantages of classical molecular dynamics simulations and quantum-chemical calculations.

Using the statistical distribution of geometric descriptors of hydrogen bonding[1] in a minimal set of representative configurations – cation, anion, and solvent – this approach makes it possible to analyze the electron density between the nearest interacting components as a function of IL composition in the mixture.[2] The approach was validated for 1-butyl-3-methylimidazolium-based IL mixtures by comparison with experimental ^{1}H NMR chemical shift variations. This comparison provides a direct test of whether the geometric descriptors extracted from molecular dynamics trajectories capture the local environments that are most relevant for the experimentally observed NMR response.

Beyond the calculation of chemical shifts, complementary electronic structure analyses were used to clarify the physical origin of the NMR trends. Non-covalent interaction, NCI, analysis was employed to quantify attractive and repulsive regions between neighboring species, natural bond orbital, NBO, analysis provided an estimate of charge transfer contributions to hydrogen bonding, and quantum theory of atoms in molecules analysis, QTAIM, was used to characterize the redistribution of electron density at the bond critical point level.

The results show that the evolution of ^{1}H NMR chemical shifts can be rationalized in terms of changes in the nearest neighboring environment of the imidazolium cation and the balance between cation···anion and cation···solvent interactions. Thus, the proposed framework provides a molecular-level bridge between classical trajectory analysis, quantum-chemical electronic structure descriptors and experimental NMR observables.

[1] Koverga *et al*. *J. Phys. Chem. B*, 2019, 123, 28, 6065-6075
[2] Voroshylova *et al*. Theoretical and Computational Approaches to Predicting Ionic Liquid Properties, *Elsevier*, 2020, 105-146

(Session B | 12:00-12:20) – Room B

OC - (25949) - COMPUTATIONAL ASTROCHEMISTRY OF MOLECULES AND ICES: FROM INTERSTELLAR CARRIERS TO RADIATION-DRIVEN CHEMISTRY

Felipe Fantuzzi (United Kingdom)[1]
1 - University of Kent

Abstract

Astrochemical environments contain a rich diversity of molecules, radicals, ions, and icy materials that are continuously exposed to energetic radiation, low temperatures, and non-equilibrium chemical conditions. Understanding how these species form, survive, fragment, and contribute to molecular complexity requires a close connection between quantum chemical modelling, spectroscopy, laboratory, and astronomical observations. This contribution discusses recent computational studies carried out by us on the structure, stability, spectroscopy, and radiation-driven chemistry of molecules and ices relevant to the interstellar medium and Solar System environments. The first part focuses on gas-phase molecular carriers and reactive intermediates. We examine magnesium-bearing carbon chains, for which our calculations reveal a clear alternation between linear global minima for even-numbered MgC*n*H species and cyclic structures for odd-numbered analogues (*J. Comp. Chem.* **2025**, *46*, e70031). The enhanced stability of the corresponding anions is also considered in the context of future astronomical detection. We then discuss boronyl-bearing carbon chains as possible gas-phase carriers of interstellar boron (*ACS Earth Space Chem.* **2025**, *9*, 2045). Although these species present favourable calculated properties, including high dipole moments and thermodynamic stability, their detection may be limited by competitive decomposition pathways and the low cosmic abundance of boron. The second part addresses radiation-driven processes and spectral modelling. Born–Oppenheimer molecular dynamics simulations show how energetic processing of saturated organic molecules can favour fragmentation pathways leading to unsaturated, π-rich products, helping to rationalise the coexistence of saturated complex organics and unsaturated nitriles in molecular clouds such as G+0.693-0.027 (*Chem. Sci.* **2025**, *16*, 3051). In parallel, ongoing work on the computational simulation of vacuum-ultraviolet absorption spectra of astrochemical ices is presented, using molecular cluster models to reproduce and assign experimental spectra of cryogenic H2O, CO, and O2 ices. These studies illustrate how computational chemistry can support the identification of new molecular targets, interpret laboratory spectra, and clarify the chemical transformations that shape molecular complexity in space.

The author is grateful to all collaborators and co-authors involved in the studies presented here. Financial support from the Royal Society (ICAO\R1\241112), COST Action MultIChem (CA20129), and COST Action PLANETS (CA22133) is gratefully acknowledged.

Keywords: astrochemistry, interstellar medium, astrophysical ices, quantum chemistry

(Special Session | 16:30-16:50) - Auditorium

OC - (26051) - IOCHEM-BD: A PLATFORM OF COMPUTATIONAL CHEMISTRY AND MATERIALS SCIENCE DATA MANAGEMENT

Gabi Dias (Spain)[1]
1 - Institute of Chemical Research of Catalonia (ICIQ), Tarragona, Spain

Abstract

Computational chemists routinely generate large volumes of heterogeneous output files from multiple software packages, often stored in ad hoc folder structures with limited metadata and poor standardization. This makes it difficult to track calculations, reproduce results, or reuse data across projects and collaborators, creating a major bottleneck as datasets grow in size and complexity. Open Data practices guided by the FAIR principles (Findable, Accessible, Interoperable, and Reusable) are essential to address these challenges. ioChem-BD is a digital platform developed to support theoretical and computational chemistry by enabling researchers to organize, curate, and publish their data in a structured and searchable manner. The platform supports outputs from quantum chemistry and molecular dynamics codes, facilitates metadata enrichment, automated generation of supporting information, and interactive visualization with tools such as JSmol. It also enables controlled publication, including embargo options and DOI assignment. Advanced features (including a REST API, command-line client, and Python libraries) allow seamless integration with custom workflows and automated pipelines, supporting large-scale data analysis. By leveraging ioChem-BD, researchers can transform raw simulation outputs into well-curated, reusable knowledge, ensuring reproducibility, FAIR compliance, and fostering collaboration while maximizing the impact of their computational research.

[1] M. Álvarez-Moreno, C. de Graaf, N. López, F. Maseras, J. M. Poblet, C. Bo, J. Chem. Inf. Model., 2015, 55, 95–103.
[2] C. Bo, F. Maseras, N. López, Nat. Catal., 2018, 1, 809–810.

(Special Session | 16:50-17:10) - Auditorium

OC – (26134) - THE ORCA SOFTWARE: A BROAD OVERVIEW AND THE NEXT GENERATION QUANTUM CHEMISTRY

Bernardo de Souza[1]
1 - *FACCTs GmbH, Germany*

Abstract

ORCA is a fast, robust, and scalable quantum chemistry software package designed for a broad range of applications in computational chemistry. With more than 25 years of continuous development, it has grown into one of the world's most widely used electronic structure programs, with over 100,000 registered users.

ORCA is developed through a close collaboration between the Max Planck Institute for Coal Research (MPI KOFO) in Mülheim an der Ruhr, under the direction of its original author, Prof. Frank Neese, and FACCTs GmbH. Its development is driven by a multidisciplinary team of PhD students, postdoctoral researchers, group leaders, and software developers, with many of the recent advances and popular new features originating from the FACCTs development team.

This talk will present a brief overview of ORCA's history, development philosophy, and software infrastructure, followed by highlights of recent methodological and algorithmic advances. We will also provide a preview of several new capabilities that will be included in the upcoming release, bringing the audience up to date with the latest developments from both FACCTs and the Max Planck Institute.

[1] Neese, F., *Wiley Interdisciplinary Reviews: Computational Molecular Science*, 2025, 15, e70019.

(Special Session | 17:10-17:30) - Auditorium

OC - (26108) - CAVER WEB 2.0: INTERACTIVE WEB-BASED ANALYSIS OF PROTEIN TUNNELS AND LIGAND TRANSPORT

Sérgio M. Marques (Czech Republic)[1,2]; Simeon Borko (Czech Republic)[1,2]; Ondrej Vavra (Czech Republic)[1,2]; Jiri Damborsky (Czech Republic)[1,2]; David Bednar (Czech Republic)[1,2]
1 - Loschmidt Laboratories, Department of Experimental Biology and RECETOX, Faculty of Science, Masaryk University, Brno, Czech Republic; 2- International Clinical Research Center, St. Anne's University Hospital Brno, Brno, Czech Republic

Abstract

Cavities, tunnels, and channels are common structural features that dictate protein function. It is estimated that more than 64% of known enzymes contain one or more functional tunnels [1,2], which enable and regulate the transport of substrates and products into and out of buried active sites, directly impacting substrate specificity, stability, and catalytic activity. While experimentally tracking ligand passage through these dense structural networks remains challenging, computational methods provide vital, atomic-level insights into potential transport pathways.

Traditionally, mapping these ligand trajectories requires resource-intensive molecular dynamics (MD) simulations or complex enhanced sampling workflows that demand extensive computational expertise. To bridge this gap, Caver Web 2.0 [3] (https://loschmidt.chemi.muni.cz/caverweb/) was developed as an intuitive, all-in-one web platform that makes advanced tunnel and transport analysis universally accessible. Powered by Caver 3.0 [4] and the CaverDock 1.2 [5], the platform computes protein cavities and tunnels, and models ligand transport using an optimized iterative docking algorithm based on AutoDock Vina, guided through geometry-based pathways.

Caver Web 2.0 [3] has integrated powerful new functionalities, including: (1) the automated generation of protein structural ensembles via MD simulations, (2) the analysis of dynamic tunnels across these ensembles, (3) the prediction of ensemble-based ligand trajectories using CaverDock, and (4) customizable ligand libraries for virtual screening. Additionally, the platform newly supports high-throughput virtual screening utilizing FDA/EMA-approved drug libraries and user-defined datasets.

This demonstration will showcase the enhanced capabilities of Caver Web 2.0. We will walk through the automated pipeline from basic structural input to the generation of detailed energy profiles and interactive visual trajectories. By removing the steep technical barriers of command-line setups and tedious data formatting, Caver Web 2.0 empowers biochemists and protein engineers to rapidly screen, visualize, and analyze ligand transport dynamics directly within their web browser.

Acknowledgements: This project was supported by the European Union's Horizon Europe Framework Programme under the grant agreement No. 101136607 (CLARA).

References

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[5] Vavra, O. et al. *Bioinformatics.* **2019**, *35*, 4986.

Friday, 10 July

(Session A | 11:00-11:20) - Auditorium

OC - (25947) - INFLUENCE OF METHYL GROUP POSITION ON THE STABILITY OF STACKED METHYLXANTHINE DIMERS

Rosendo Leovigildo Lozada Morales (Mexico)[2]; Alexandra Deriabina (Mexico)[1]; Eduardo González Jiménez (Mexico)[1]; María Patricia Sánchez Gutiérrez (Mexico)[1]

1 - Faculty of Physical and Mathematical Sciences, Autonomous University of Puebla (BUAP); 2 - Faculty of Physical and Mathematical Sciences, Autonomous University of Puebla (BUAP)

Abstract

Stacking interactions play a fundamental role in various biological processes, including the structural organization of the DNA double helix and protein folding. These interactions are predominantly observed in aromatic molecules, such as methylxanthines. Caffeine, theophylline, theobromine, and paraxanthine are xanthine derivatives that differ in the number and position of methyl groups (CH3) in their structure, making them ideal model systems for investigating the effects of methylation on intermolecular stacking. Previous studies have shown that methylation enhances both self-association and hetero-association in biologically relevant aromatic molecules such as purines and pyrimidines.

Methylxanthines tend to form stacked complexes in crystalline environments. Experimental and computational studies on caffeine have identified five arrangements of stacked dimers, among which the parallel face-to-back p2 configuration is the most frequently observed. The predominance of this configuration enables a controlled analysis of the influence of the presence and position of methyl functional groups on the geometry and the interaction energy of the stacked dimer.

In this work, we perform a detailed analysis of the non-covalent interactions present in the p2 stacked dimer of xanthine and its methylated derivatives using the Density Functional Theory (DFT) with PBE0-DH/6-311++G**. The analysis was aided by the Quantum Theory of Atoms in Molecules (QTAIM), Non-Covalent Interactions (NCI), and Natural Bond Orbital (NBO) analysis with the aim of identifying and quantifying the energetic contributions that stabilize these important supramolecular structures.

NBO analysis further shows that methylation introduces specific intermolecular charge-transfer channels whose importance depends strongly on the local stacking environment QTAIM analysis reveals two main classes of bond critical points: those associated with C–H···O(N) contacts and those corresponding to dispersive interactions between heavy atoms (C···C, C···N, C···O, and N···O), which define five- and six-membered topological rings. The energy associated with C–H···O(N) interactions substantially contribute to the interaction energy of stacked methylxanthines dimers, accounting for up to thirty percent of the interaction energy in the case of caffeine.

These results demonstrate that methylation modulates the stability of stacked methylxanthine dimers not by substantially altering their overall geometry, but by introducing additional weak interactions that act cooperatively. So, the findings provide new insight into the molecular factors governing π-stacking in biologically relevant heteroaromatic systems.

The authors thankfully acknowledge computer resources, technical advice and support provided by Laboratorio Nacional de Supercómputo del Sureste de México (LNS), a member of the CONACYT national laboratories, with project No 202503056C.
This research was funded by CONAHCYT (CF-2023-G-1051) and VIEP-BUAP (100261355-VIEP2024).

Keywords: caffeine, methylxanthines; stacking interactions; QTAIM; NCI; C–H···O(N) interactions.

(Session A | 11:20-11:40) - Auditorium

OC - (26044) - COMPUTATIONAL SEARCH FOR MYELIN-ASSOCIATED GLYCOPROTEIN (MAG) BINDERS THAT COULD MODULATE THE NEUROPROTECTIVE PROPERTIES OF OLIGODENDROCYTES IN NEURODEGENERATIVE CONTEXTS

C. Felippa Ambort (Argentina)[1]; A. L. Degano (Argentina)[1]; R. Quiroga (Argentina)[1]
1 - Department of Theoretical and Computational Chemistry (INFIQ - CONICET), School of Chemical Sciences, National University of Córdoba, Argentina

Abstract

Myelin-Associated Glycoprotein (MAG/ Siglec 4) is a cell-surface protein belonging to the family of immunoglobulin-type lectins that bind to sialic acid (Siglecs). MAG is expressed in myelinating oligodendrocytes of the central nervous system and is located in the periaxonal space. Particularly, it has high binding specificity for the motif Neu5Acα2-3Galβ1-3GalNAc present in GT1a and GD1b gangliosides. From a structural level, this binding is mediated by a highly conserved Arg118 residue in its V domain, that forms a salt bridge with the carboxyl group of sialic acid. After its activation, MAG plays an important role in triggering glutamate reuptake following injury, thereby generating a neuroprotective, antioxidant effect on oligodendrocytes and neighboring neurons. This response is particularly relevant in neurodegenerative diseases like stroke and multiple sclerosis, where oxidative stress and glutamate overload are prevalent.

In this context, the aim of this study is to identify potential molecular activators or inhibitors of MAG with high affinity and selectivity, using molecular docking and virtual screening of structurally diverse compound libraries (ej. ZINC20). To this end, the 2VINARDO scoring function is employed; this function is based on AutoDock Vina and has been developed by Dr. Rodrigo Quiroga and Dr. Marcos A. Villareal. 2VINARDO improves the description of ligand-protein non-covalent interactions by expanding atom types (C, O, N and S) and increasing the number of evaluated parameters. Despite these advantages, validation of the scoring function is required when performing molecular docking with large, complex and flexible molecules such as gangliosides, in order to assess its ability to accurately describe the protein–ligand complexes under study.

As part of the 2VINARDO validation process, a re-docking protocol was carried out using seven crystallographic structures of proteins from the Siglec family with their co-crystallized ligands, including MAG. The objective was to evaluate the ability of the scoring function to reproduce the interaction energies and the experimental positions of the protein-ligand complexes. In all cases, the function was successful in predicting ligand poses with RMSD values below 2Å. Key interactions were conserved, particularly hydrogen bonds involving the Arg118 residue. Subsequently, the effect of the side-chain flexibility within the binding site was evaluated to achieve a more accurate representation of sialic acid recognition in ligands. In addition, this analysis is being extended to compounds with

experimentally determined binding affinities (Kd) for MAG, for which no complex structure is available; the aim of this last step is to assess the predictive performance of 2VINARDO in terms of binding energy.

Overall, the validation process establishes a solid basis for large-scale virtual screening of molecular libraries, aiming to find bioactive compounds that are selective for MAG with minimal cross-reactivity towards other Siglecs. Ultimately, this study may contribute to the development of novel therapeutic agents capable of inducing MAG-mediated neuroprotection in neurodegenerative diseases and excitotoxicity conditions.

OC - (25893) - MOLECULAR DYNAMICS OF NEURONAL MEMBRANES AND ION CHANNELS UNDER ULTRASOUND AND LASER STIMULATION: IMPLICATIONS FOR ALZHEIMER'S DISEASE

Phuong Nguyen (France)[1]
1 - Laboratoire de Biochimie Théorique, UMR8266 CNRS et Université Paris Cité

Abstract

Altered membrane mechanics and ion channel dysfunction are key features of Alzheimer's disease (AD) pathology. In this talk, we will present molecular dynamics simulations that reveal how differences in membrane elasticity between healthy and AD neurons affect amyloid-beta (Aβ) interactions and the structural stability of ion channels. The first part will focus on equilibrium membrane properties, showing how reduced elasticity in AD membranes enhances Aβ binding and destabilizes channel conformation [1,2]. In the second part, we will discuss how laser and ultrasound stimulation modulate membrane structure and ion transport. Specifically, laser can dissociate ion channels [3], while ultrasound induces pore formation and regulates ion current [4], offering a potential route for drug delivery and neuromodulation in AD treatment. These findings provide molecular-level insights into the altered biophysical properties of AD neuronal membranes and the therapeutic potential of non-invasive physical stimuli.

1) Structure and Elasticity of Healthy and Alzheimer's Disease Cell Membranes Revealed by Molecular Dynamics Simulations. Mai, T. L. and Nguyen, H. T. and Derreumaux, P. and **Nguyen, Phuong H**. PROTEINS 2023 (10.1002/prot.26508)

2) Elastic Constants of Normal and Cancer Cell Membranes Revealed by Molecular Dynamics Simulations. Viet, Man and Linh, Nguyen and Li, Mai Suan and Derreumaux, Philippe and Wang, Junmei and **Nguyen, Phuong H.** PHYSICAL CHEMISTRY CHEMICAL PHYSICS 24, 6225 (2022)

3) Nonequilibrium Molecular Dynamics Simulations of Infrared laser-induced dissociation of a tetrameric Abeta42 beta-barrel in a neuronal membrane model. Viet, Man and Wang, Junmei and Derreumaux, Philippe and **Nguyen, Phuong H.** CHEMISTRY AND PHYSICS OF LIPIDS 234, 105030 (2021)

4) Interaction mechanism between the focused ultrasound and lipid membrane at the molecular level. Viet, Man and Li, Mai Suan and Junmei, Wang and Derreumaux, Philippe and **Nguyen, Phuong H**. JOURNAL OF CHEMICAL PHYSICS 150, 215101 (2019).

Keywords: Alzheimer's disease, membrane, ion channel

POSTERS

49th International Congress of Theoretical Chemists of Latin Expression
5 - 10 July 2026 | Universidade de Coimbra, Portugal

POSTERS

Monday, 6 July

P01 - NITROGEN-TO-AMMONIA CONVERSION ON SULPHUR-TERMINATED MOLYBDENUM CARBIDE MXENES

Daniela Abreu (Portugal)[1]; José Richard Gomes (Portugal)[1]; José Daniel Gouveia (Portugal)[1]
1 - Universidade de Aveiro, CICECO

Abstract

Ammonia (NH_3) is an essential feedstock for fertilizers and industry, and a promising hydrogen carrier. However, its large-scale production through the Haber-Bosch process remains energy-intensive, requiring harsh conditions to cleave the N≡N bond. This process contributes significantly to global energy consumption and greenhouse gas emissions, urging scientists to find more effective and greener catalysts to N_2 reduction to NH_3.

MXenes have emerged as versatile materials for many important applications, including catalysis, either as the active component, due to its high conductivity and high specific surface area, or as a support for single-atom catalysts (SACs), enhancing their properties. Other applications include energy storage, electromagnetic shielding, sensing, water purification, and electronics [1].

In this communication, we present the results of a computational study, based on density-functional theory, using the PBE-D3 approach, on sulphur-terminated molybdenum carbide (Mo_2CS_2), both in its pristine form and with metallic atoms as SACs for N_2 reduction to NH_3. In particular, we analyse the thermodynamics and kinetics of nitrogen adsorption, activation and hydrogenation, assessing the potential of this MXene as a sustainable catalyst for ammonia production.

This work was developed within the scope of the project CICECO – Aveiro Institute of Materials, UID/50011 and LA/P/0006/2020 (DOI 10.54499/LA/P/0006/2020), financed by national funds through the FCT/MCTES (PIDDAC).

Keywords: MXenes, Ammonia, Catalyst, Nanozyme, DFT

PO3 - COMPUTATIONAL AND EXPERIMENTAL INSIGHTS INTO PANCREATIC LIPASE INHIBITION BY BIOACTIVE COMPOUNDS FROM STEVIA REBAUDIANA BERTONI

Nathalia Aceval (Uruguay)[1,2]; Jorge Cantero (Uruguay)[1,3]; Silvio Claudio Da Costa Silva (Brazil)[4]; Jeffrey Pearson (United Kingdom)[5]; Margot Paulino (Uruguay)[1]

1 - Área Bioinformática, DETEMA, Facultad de Química, UdelaR, Montevideo, Uruguay.; 2 - Dirección de Investigación, Facultad de Ingeniería Agronómica, Universidad Nacional del Este, Minga Guazú, Paraguay.; 3 - Centro de Investigaciones Médicas, Facultad de Ciencias de la Salud, Universidad Nacional del Este, Minga Guazú, Paraguay.; 4 - Departamento de Bioquímica, Centro de Ciências Biológicas, Universidade Estadual de Maringá, Maringá, Brasil.; 5 - Pearson Lab, Biosciences Institute, Medical School, Newcastle University, Newcastle Upon Tyne, UK

Abstract

Obesity is a major global health challenge associated with high dietary fat intake and efficient intestinal lipid absorption mediated by pancreatic lipase. Inhibition of this enzyme represents an important strategy for obesity management. Although the synthetic inhibitor Orlistat® is effective, its use is often limited by adverse side effects, highlighting the need for natural alternatives. In this study, we investigated the inhibitory potential of crude and purified extracts of *Stevia rebaudiana* Bertoniagainst porcine pancreatic lipase (PPL) using combined experimental and computational approaches. *In vitro* assays revealed a strong dose-dependent inhibitory activity for crude extracts, reaching 95.15 ± 10.18% inhibition at 5 mg/mL, with an IC_{50} of 2.84 ± 0.02 mg/mL. In contrast, purified fractions showed no significant inhibition, suggesting synergistic effects among multiple phytochemicals present in the crude extract.To explore the molecular basis of this activity, molecular docking simulations were performed using the crystallographic structure of PPL (PDB ID: 1ETH). Twelve compounds identified in *Stevia* extracts were evaluated, including steviol glycosides and phenolic constituents. The results revealed high binding affinities for Rebaudioside A (–9.01 kcal/mol) and Stevioside (–8.91 kcal/mol), comparable to Orlistat (–8.30 kcal/mol). These ligands interacted with key catalytic residues including Ser153, Asp206, Phe216, and His264.Molecular dynamics simulations (100 ns) were performed using NAMD with the CHARMM36 force field under periodic boundary conditions. Interaction energy analyses showed that Rebaudioside A exhibited the strongest interaction energy (–244.62 ± 17.97 kcal/mol), followed by Stevioside (–186.69 ± 13.35 kcal/mol), both surpassing Orlistat. Electrostatic interactions were dominant in the stabilization of the enzyme–ligand complexes.These results highlight *Stevia rebaudiana* Bertoni as a promising natural source of pancreatic lipase inhibitors and demonstrate the usefulness of multiscale computational approaches to explore the molecular mechanisms underlying bioactive natural products.

Agencia Nacional de Investigación e Innovación (ANII). PD_NAC_2022_1_173008.

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Universidade Estadual de Maringá (UEM).
Newcastle University.
Aelious Biotech.

Keywords: Pancreatic lipase inhibition, Molecular dynamics, steviol glycosides, Molecular docking

P05 - MECHANISTIC INSIGHTS INTO LOOP DYNAMICS AND LIGAND BINDING OF GH6 CELLOBIOHYDROLASES

Shabir Ahmad (Brazil)[1]; Munir .S Skaf (Brazil)[1]
1 - Institute of Chemistry and Center for Computing in Engineering & Sciences, University of Campinas – UNICAMP. Campinas, SP 13084-862, Brazil.

Abstract

The catalytic mechanism of inverting glycoside hydrolases (GHs), especially those from family 6 (GH6), is still not completely understood. These enzymes are essential components of cellulase systems responsible for breaking down cellulose, one of the main structural materials found in plant biomass. As cellobiohydrolases (CBHs), GH6 enzymes cleave 1,4-β-d-glycosidic bonds from the ends of cellulose chains, releasing cellobiose and glucose during the degradation process. Among the different CBH families, GH6 enzymes such as Cel6A from Humicola insolens are particularly interesting because the roles of several catalytic residues are still unclear. The enzyme contains a tunnel-shaped active site surrounded by flexible loops that continuously open and close, controlling substrate entry, binding, and movement during catalysis. Understanding how these loop motions influence enzyme activity is important for explaining the efficiency of GH6 cellulases. To explore these structural changes, molecular dynamics (MD) simulations were performed on the wild-type Cel6A enzyme and two mutants, D405N and D416A. The simulations revealed that the wild-type enzyme retains a high degree of loop flexibility, allowing the catalytic tunnel to switch between open and closed states that are necessary for effective substrate processing. In contrast, both mutants showed noticeably reduced loop movement, indicating that Asp405 and Asp416 are important for maintaining the dynamic behavior of the active site.We gratefully acknowledge the Coaraci Supercomputer for the computational resources provided through FAPESP grant #2019/17874-0, and the Center for Computing in Engineering and Sciences (CCES) at University of Campinas through FAPESP grant #2013/08293-7. We also acknowledge financial support from São Paulo Research Foundation under project grant #2022/07372-0.

Keywords: Cellobiohydrolase (CBH), Cel6A, Loop dynamics

P07- PYCBS: A PYTHON PACKAGE FOR COMPLETE BASIS SET EXTRAPOLATION

Fabio Delgado Alpízar (Cuba)[1]; Alberto Guerra Barroso (Chile)[2]; Luis Montero Cabrera (Cuba)[1]; Pedro Caridade (Portugal)[3]; Antonio Varandas (Portugal)[3]

1 - Laboratorio de Química Computacional y Teórica, Facultad de Química, Universidad de La Habana; 2 - Programa de Doctorado en Fisicoquímica Molecular, Facultad de Ciencias Exactas, Universidad Andrés Bello; 3 - Department of Chemistry, and Chemistry Centre, University of Coimbra

Abstract

The slow convergence of molecular energies and properties with respect to basis set size remains a major limitation of high-accuracy electronic structure methods. Extrapolation to the complete basis set (CBS) limit with an asymptotic theory provides a systematic route toward the exact solution of the elec-tronic Schrödinger equation while reducing the basis set superposition error, yet its routine application is hindered by the diversity of availables chemes and the lack of unified, extensible tools. We present Py-CBS, an open source Python framework designed for flexible and reproducible CBS extrapolations. The program implements a wide range of established extrapolation schemes and extends CBS methodologies beyond total energies to tensorial properties and vibrational frequencies. In addition, PyCBS introduces an approach that enables geometry optimization directly at the CBS level. Representative applicationsillustrate the capabilities of the code, and best-practice recommendations are provided for robust and efficient CBS extrapolations.

Keywords: Complete basis set, electronic structure calculations, ab initio calculations, molecular properties

P09 - VIRTUAL SCREENING OF A PETASIS-UGI LIBRARY FOR SYNTHETIC AFFINITY LIGAND DISCOVERY

Jéssica Rodrigues (Portugal)[2]; João Pires (Portugal)[1]; Cecília Roque (Portugal)[1]; Arménio Barbosa (Portugal)[1]

1 - UCIBIO, i4HB – Chemistry Department, NOVA School of Science and Technology, NOVA University Lisbon, Almada, Portugal; 2 - ITQB, Avenida da República (EAN), Instituto de Tecnologia Química e Biológica António Xavier da Universidade Nova de Lisboa, 2780-157, Oeiras, Portugal

Abstract

Atomic-scale in silico approaches play a pivotal role in the design and discovery of affinity ligands, providing molecular-level insights into ligand–target interactions and the influence of binding and elution conditions. Molecular modeling has been successfully applied to the development of synthetic ligands for the purification of antibodies and antigen-binding fragments (1), Human Serum Albumin (HSA) (2), and viral spike proteins (3). Building on these advances, a High-Throughput Virtual Screening (HTVS) pipeline was developed to accelerate the discovery of novel synthetic affinity ligands for biopharmaceutical purification.

We built a large virtual library of candidate molecules by combining chemical building blocks through a well-established synthetic reaction scheme. After an initial filtering step, we screened this library computationally using docking software to predict how well each molecule would bind to its target. The most promising candidates were then subjected to more rigorous simulations to refine binding predictions and estimate binding strength. Our library contained over 15 million unique compounds. From this pool, computational screening identified five candidate ligands with strong predicted affinity for trastuzumab, a widely used therapeutic antibody, which are now being tested experimentally. This work demonstrates that large-scale virtual screening using this chemical framework is a practical and cost-effective strategy for discovering new purification ligands across a wide range of biological targets.

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Keywords: Docking, Molecular Dynamics, Affinity Ligand

P11 - REDUCED-SCALING SIMULATIONS OF HIGHER-ORDER RESONANCE RAMAN TRANSITIONS

Andrea Bianchi (Italy)[1]; Julien Bloino (Italy)[1]
1 - Scuola Normale Superiore

Abstract

Resonance Raman (RR) and its chiral expansion (RROA) provide detailed insight into electronically excited states, but the accurate prediction of their spectra remains a challenge. Sum-over-states formulations face the curse of infinite summation boundaries, while the growing complexity of cross-correlation functions complicates the derivation of analytic forms within the alternative path-integral formalism beyond fundamental transitions from the ground state.

We present a new automated path-integral framework for RR and RROA that treats arbitrary vibrational transitions, including overtones, combination bands, and hot bands, while incorporating Herzberg-Teller effects and Duschinsky rotation. The method rewrites the relevant quantities in terms of low-rank intermediates, generates the resulting expressions symbolically, identifies equivalent contractions by canonicalization, and evaluates them through optimized contraction paths with intermediate reuse. This eliminates transition-specific manual derivations and avoids the explicit construction of high-rank correlation tensors. Relative to existing explicit-tensor formulations, the resulting contractions display improved asymptotic scaling for several higher-order transition classes. Benchmark calculations against time-independent reference results show near-exact agreement across multiple transition families. We further use the framework to analyze finite-temperature effects through hot-band contributions and to demonstrate transferability to chiral spectroscopy in a two-state RROA application. Overall, the method makes higher-order RR and RROA simulations far more practical and provides a unified route to systematic studies of resonant vibrational spectroscopy.

Keywords: Resonance Raman, spectroscopy, Raman

P13 - BREAKDOWN OF LINEAR RESPONSE IN INTERACTING POLYMERIC FLUIDS: INSIGHTS FROM RECOIL DYNAMICS

José Rafael Bordin (Brazil)[1,2]; Matthias Fuchs (Germany)[2]
1 - Universidade Federal de Pelotas; 2 - Universität Konstanz

Abstract

Understanding how intermolecular interactions govern the dynamical response of complex fluids is a central problem in theoretical chemistry. In this work, we investigate the breakdown of linear response in interacting polymeric fluids using Langevin dynamics simulations. By tuning the strength of monomer–monomer interactions, we generate fluid states ranging from purely repulsive dispersions to transiently bonded networks. The system response to a localized perturbation is probed through the recoil dynamics of a tagged particle, which provides direct access to the underlying relaxation mechanisms. We show that weakly interacting systems display a near-linear response, while increasing attraction leads to pronounced deviations associated with transient binding and collective rearrangements. The response exhibits a non-monotonic dependence on interaction strength, reflecting a competition between structural arrest and stress storage. These results establish a direct link between effective interactions, microstructure, and emergent dynamical response, providing a microscopic framework to understand memory effects in polymeric and associating fluids.

Keywords: Memory effects, Linear response theory, Soft matter chemistry, Non-Markovian dynamics, Molecular simulations

P15 - MAPPING LIGAND FUNCTION ACROSS GPCR-A17 RECEPTORS WITH ENSEMBLE MACHINE LEARNING

Ana Beatriz Caniceiro (Portugal)[1,2,3,4]; Ana Miguel Amorim (Portugal)[1,2,3,4]; Nícia Rosário-Ferreira (Portugal)[1,2,3,4]; Irina S. Moreira (Portugal)[2,3,4]

1 - PURR.AI, IPN Incubadora, Rua Pedro Nunes, Ed C, 3030-199 Coimbra, Portugal.; 2 - CNC-UC - Center for Neuroscience and Cell Biology, University of Coimbra, Rua Larga, Ed FMUC, Piso 1, 3004-504 Coimbra, Portugal.; 3 - CiBB - Centre for Innovative Biomedicine and Biotechnology, University of Coimbra, Rua Larga, Ed FMUC, Piso 1, 3004-504 Coimbra, Portugal.; 4 - Department of Life Sciences, University of Coimbra, Cal.ada Martim de Freitas, 3000-456 Coimbra, Portugal.

Abstract

G Protein-Coupled Receptors (GPCRs) are the most drugged protein family in human therapeutics. Within the GPCR-A17 subfamily, which includes dopamine, serotonin, adrenergic, and trace amine-associated receptors, precise classification of ligand function is critical for drug development. Existing machine learning (ML) models are limited to binary classification (agonist vs. antagonist) and do not account for modulators, a pharmacologically relevant class that acts through allosteric mechanisms.

GPCR-A17 MAAP (Modulator, Agonist, and Antagonist Predictor) combines XGBoost, Random Forest, and LightGBM in a blending ensemble trained on 6,919 receptor-ligand pairs from ChEMBL, the Guide to Pharmacology, and the Therapeutic Target Database. Each interaction is represented by 625 Mold2 molecular descriptors and 1,024 ProtTrans protein embeddings, capturing both ligand chemistry and receptor features. A Ki-filtered model was built on a curated subset of 4,274 interactions with experimentally validated binding affinity data. On unseen ligands, GPCR-A17 MAAP achieved an F1 score of 0.7151 and AUC of 0.8591. The Ki-filtered model pushed these numbers to 0.8267 and 0.9032, with the modulator F1 score jumping from 0.50 to 0.76. The performance gain was not driven by Ki as a feature but by data quality; that is, interactions with measured Ki values reflected more rigorous experimental conditions, producing a cleaner training signal. Protein embeddings consistently ranked among the most important features, confirming that ligand function is receptor-dependent and cannot be predicted from chemistry alone.

GPCR-A17 MAAP is the first model to classify GPCR-A17 ligands across three functional categories. It works from sequence data, making it applicable even when structural data is unavailable. Tested on compounds never seen during training, it provides predictions that match known pharmacology. This is a useful tool for prioritising candidates early in drug discovery, before expensive experiments begin [1].

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Keywords: Drug Discovery, Machine Learning, Binding affinity, GPCR subfamily A17

P17 - T-290676 AND T-2635 HIV FUSION INHIBITORS INTERACT STRONGLY WITH MODEL MEMBRANES: A MOLECULAR DYNAMICS STUDY THAT REVEALS PEPTIDE BEHAVIOR, STRUCTURE, AND DYNAMICS

António Do Canto (Portugal)[1,2]; Catarina Grazina (Portugal)[2]; Alfredo Carvalho (Portugal)[1,2,3]

1 - LAQV-REQUIMTE, Universidade de Évora; 2 - Departamento de Química e Bioquímica, Escola de Ciências e Tecnologia, Universidade de Évora; 3 - MARE, Universidade de Évora

Abstract

T-290676 and T-2635 are part of a more recent generation of HIV fusion inhibitor peptides (FIs), specifically developed to retain and increase their effectiveness against HIV strains that have acquired resistance to earlier peptide treatments. Prior studies have demonstrated that peptides like these are capable of associating with model membranes in both the liquid-disordered (L_d) and liquid-ordered (L_o) phases. This interaction with membranes appears to be a critical aspect of their mechanism of action and has been positively correlated to their antiviral potency. To further investigate these interactions, molecular dynamics (MD) simulations were employed to address peptide function using two types of model membranes: one composed exclusively of 1-palmitoyl-2-oleoyl-phosphatidylcholine (POPC), a model of a fluid membrane, and another consisting of a 1:1 mixture of POPC and cholesterol (Chol), a model of a more ordered and rigid membrane. The simulation results showed that both T-290676 and T-2635 have a strong affinity for both types of membranes, with significantly greater capability of interaction than earlier fusion inhibitors, such as T-20 and T-1249. This stronger membrane association further emphasizes peptide-membrane interaction as a key part in their enhanced inhibitory effectiveness. Additionally, our findings suggest that structural features, such as peptide helicity and the ability to form hydrogen bonds with cholesterol, also play a significant role in inhibiting the fusion process.

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Keywords: AIDS, HIV fusion inhibition, lipid-peptide interaction, biomembrane simulations, POPC, Cholesterol

P19 - DFT INVESTIGATION OF DIELS–ALDER REACTIONS BETWEEN DISUBSTITUTED FURANS AND ETHYLENE: UNCATALYZED VERSUS LEWIS ACID-CATALYZED PATHWAYS

Mohamed Chellegui (Belgium)[1]

1 - Theoretical Chemistry Laboratory, Namur Institute of Structured Matter, University of Namur, 5000 Namur, Belgium

Abstract

La réaction de Diels-Alder [4+2] (DA) est une transformation clé en chimie organique et un outil puissant pour la valorisation des furanes issus de la biomasse en composés chimiques à haute valeur ajoutée. Cependant, des études expérimentales ont montré que la réactivité des dièmes dérivés du furane vis-à-vis de l'éthylène est très sensible à la nature des substituants, conduisant souvent à des rendements faibles, voire négligeables [1]. Les groupements fortement électroattracteurs, tels que les acides carboxyliques, désactivent significativement le cycle furane, tandis que des stratégies de protection fonctionnelle ont permis d'améliorer la formation du produit [1]. Ces observations soulignent la nécessité d'une compréhension mécanistique plus approfondie des relations structure-réactivité dans ces systèmes.

Dans ce contexte, la théorie de la fonctionnelle de la densité (DFT) au niveau M06-2X/6-311+G(d,p) est utilisée pour étudier les mécanismes des réactions de Diels-Alder (DA) non catalysées et catalysées par $AlCl_3$ entre les dérivés du furane **1a** – **h** et l'éthylène **2** (Schéma **1**) [2], comme présenté dans cette affiche. Les calculs DFT indiquent que toutes les réactions DA non catalysées présentent une barrière d'activation élevée et un caractère faiblement polaire, voire apolaire. En revanche, la coordination de $AlCl_3$ avec l'éthylène (mécanisme NED) ou avec le diène (mécanisme IED) entraîne une diminution significative de l'énergie libre d'activation de Gibbs et renforce la polarité du processus. D'un point de vue mécanistique, l'analyse par la théorie de l'évolution des liaisons (BET) [3] montre que les réactions non catalysées impliquant des dièmes symétriquement substitués en positions 1 et 4 se déroulent selon un mécanisme synchrone en une seule étape, tandis que les systèmes asymétriquement substitués suivent une voie réactionnelle légèrement asynchrone en une seule étape. Pour les réactions catalysées par $AlCl_3$, les mécanismes NED et IED se déroulent tous deux via un mécanisme en une seule étape fortement asynchrone, caractérisé par une formation asynchrone des deux nouvelles liaisons C–C.

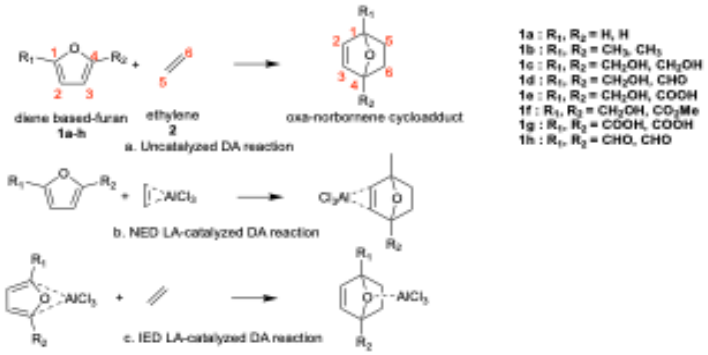

Schéma 1. Réactions DA non catalysées et catalysées par $AlCl_3$ entre les diènes à base de furane **1a** - **h** et l'éthylène **2** .

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Keywords: Biomass, furan derivatives, ethylene, Diels-Alder reaction, DFT calculations

PO23 - MACHINE LEARNING FORCE FIELDS FOR ZNCL2-BASED DEEP EUTECTIC ELECTROLYTES: DEVELOPMENT AND PRELIMINARY VALIDATION

Eudes Eterno Fileti (Brazil)[1]
1 - Universidade Federal de São Paulo

Abstract

Zinc-based electrolytes, particularly those derived from $ZnCl_2$ in water, urea, and deep eutectic solvents (DES), have emerged as promising candidates for next-generation aqueous zinc-ion batteries. Their electrochemical performance is strongly governed by the local coordination environment of Zn^{2+}, which varies dramatically with composition; from octahedral $[Zn(H_2O)_6]^{2+}$ in dilute aqueous solutions to tetrahedral Zn-Cl/urea coordination in anhydrous DES formulations. Capturing this structural complexity across relevant compositions and temperatures demands simulation approaches that combine quantum-mechanical accuracy with the timescales accessible to classical molecular dynamics. Machine learning force fields offer precisely this balance.

In this work, we report the development and preliminary validation of a MACE-based machine learning interatomic potential (MLIP) for a $ZnCl_2$/urea/H_2O electrolyte at a 1:2:3:1 molar ratio. The reference dataset was generated from ten independent ab initio molecular dynamics trajectories CP2K, employing PBE-D3 with a DZVP-MOLOPT-SR-GTH basis and GTH-PBE-q12 pseudopotential for Zn, ~10,000 configurations sampled at 300, 400, and 500 K. Single-point energy and force recalculations at a higher level of theory (PBE-D3, 650 Ry cutoff) were performed to build a balanced training set of ~2,800 frames. The MACE-MP-0 small foundation model was fine-tuned using aMACEing, yielding RMSEs of 1.8 meV/atom (energies) and 25.3 meV/Å (forces) on a held-out validation set; well within accuracy thresholds for production-quality MLIPs. Parity plots confirm negligible systematic bias across the full validation set.

The validated MACE potential was deployed in LAMMPS for machine learning molecular dynamics simulations using a 2×2×2 supercell (~4,000 atoms, 35.7 Å box). Preliminary results at 300 K show a well-equilibrated liquid phase. Future simulations spanning 300-400 K are planned to characterize structural (radial distribution functions, Zn^{2+} coordination numbers) and dynamical (diffusion coefficients, ionic conductivity via Einstein–Helfand formalism) properties as a function of temperature. These calculations will provide fundamental insight into the ionic transport mechanisms governing the electrochemical behavior of this class of electrolytes.

This work was developed within the scope of the project CICECO-Aveiro Institute of Materials, UID/50011/2025 (DOI 10.54499/UID/50011/2025) & LA/P/0006/2020 (DOI 10.54499/LA/P/0006/2020), financed by national funds through the FCT/MCTES (PIDDAC). E.E.F thanks Brazilian agencies FAPESP and CNPq for support. JAPC and EEF acknowledge FCT for the financial support through Grant Agreement nº FCT/Mobility/1335482321/2024-25. This work was partially supported by the Laboratório

Nacional de Computação Científica (LNCC, Brazil), providing HPC resources of the Santos Dumont supercomputer.

Keywords: machine learning force fields, ab initio molecular dynamics, deep eutectic solvents, $ZnCl_2$ electrolytes

P25 - LIGAND-DRIVEN GEOMETRIC DESCRIPTORS FOR THE ACTIVATION AND SELECTIVITY OF [RU(TPY)(L-PY)(ACCN)] CO2 REDUCTION PRE-CATALYSTS

Maurício Portiolli Franco (Brazil)[1]; Giovana Vitiello Teixeira (Brazil)[1]; André Luiz Barboza Formiga (Brazil)[1]
1 - University of Campinas

Abstract

The electrocatalytic reduction of CO2 to CO in anhydrous media hinges on the successful formation of a hexacoordinated metallocarboxylate intermediate via a M-CO2 bond. Using the well-studied [Ru(tpy)(bpy)S]2+ complex as a model (where tpy is terpyridine, bpy is bipyridine, and S is a coordinated solvent molecule), this study computationally investigates a series of ruthenium pre-catalysts. By substituting one pyridine of the bidentate ligand for various 5-membered rings - including 1,2,3-triazole (123-trz), oxazole (oz), pyrrole (pyrr), pyrazole (prz), or an N-heterocyclic carbene (NHC) - the influence of ligand architecture on reduction potentials and activation barriers was explored using DFT (TPSSh/def2-svp) with implicit solvation of acetonitrile.

Electronic Structure and Reduction Potentials

The reaction pathway generally involves two successive reductions followed by the dissociation of the solvent to generate a pentacoordinated species, which then facilitates CO2 association. The localization of these electronic transitions is highly ligand-dependent. For complexes featuring pyrr, prz, and NHC, both reductions are localized on the tpy ligand, resulting in a more negative potential for the second reduction compared to the bpy, 123-trz, and oz analogs. In the latter group, the second reduction occurs on the bidentate ligand, generating an open-shell species [Ru(tpy•)(py-L•)AcCN]. These systems, which distribute electrons across both ligands, exhibit reduction potentials at least 0.15 V more positive than those that sequester both electrons on the terpyridine.

However, experimental discrepancies for NHC suggest that dissociation may occur as early as the first reduction. To optimize these potentials, extending the pi-system (e.g., adding a benzo group to the ligand backbone) can stabilize the non-ligand pi* molecular orbital energy, bringing it closer to the tpy levels and lowering the second reduction potential.

Kinetics and Selectivity

The activation of the pre-catalyst [Ru(tpy)(py-L)(AcCN)] is characterized by a slow dissociation step followed by a fast CO2 association. Dissociation barriers range from 20.9 kcal/mol (oz) to 15.4 kcal/mol (pyrr), while association barriers vary from 8.7 kcal/mol (NHC) to 4.0 kcal/mol (prz). Interestingly, a ligand with a higher dissociation barrier may still yield a higher Turnover Frequency (TOF) if the activation/deactivation equilibrium is not the rate-limiting step of the full catalytic cycle.The distribution of cis and trans isomers during CO2 association is governed by geometric distortion and ligand-specific electronic effects. Strongly donating ligands, such as NHC and pyrrole, favor trans addition, whereas weaker donors result in higher barriers and reduced selectivity. The cis:trans ratio follows

an exponential dependence on the pentacoordinate distortion parameter consistent with Eyring kinetics. Ultimately, the N-Ru-L angle serves as a simple, intuitive descriptor for predicting isomer preference and relative selectivity in these ruthenium-based systems.

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Keywords: CO2 reduction, electrocatalysis, reaction mechanism, ligand design, electronic effects, pentacoordinated complex

P27 - REACTIVITY OF AU2PT2 CLUSTERS SUPPORTED ON TIC (001): INSIGHTS INTO AMMONIA–BORANE ACTIVATION AND HYDROGEN RELEASE

Tatiana Gómez (Chile)[1]; Andrea Echeverri (Chile)[3]; Alejandro Montoy (Australia)[2]; Carlos Cárdenas (Chile)[3]

1 - Universidad Autónoma de Chile; 2 - The University of Sydney; 3 - Universidad de Chile

Abstract

Ammonia borane (NH_3BH_3, AB) is a promising chemical hydrogen carrier due to its high hydrogen content; however, achieving efficient low-temperature hydrogen release remains challenging. In this work, we perform a density functional theory (DFT) study of AB adsorption and dehydrogenation on the TiC(001) surface and on Au_2Pt_2 clusters supported on TiC(001), elucidating the roles of both the carbide support and the bimetallic cluster in controlling hydrogen-release mechanisms.

The clean TiC(001) surface actively participates in AB activation, promoting sequential B–H and N–H bond cleavage with moderate activation barriers (0.62 and 0.31 eV). In contrast, the presence of supported Au_2Pt_2 clusters dramatically enhances catalytic performance, rendering the first hydrogen-release step from the $–BH_3$ fragment essentially barrierless. This behavior is confirmed by CI-NEB calculations and finite-temperature molecular dynamics simulations, which reveal fast hydrogen dissociation occurring within a few picoseconds even at room temperature.

Subsequent hydrogen spillover from Pt sites to surface carbon atoms and further hydrogen dissociation steps proceed through exceptionally low activation barriers (< 0.30 eV). Compared with a wide range of reported catalytic systems, Au_2Pt_2/TiC(001) exhibits one of the lowest energy requirements for initiating AB dehydrogenation. These results highlight the strong synergistic effect between bimetallic Au–Pt clusters and polar carbide support, providing valuable design principles for efficient heterogeneous catalysts for hydrogen release from chemical hydrogen carriers.

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P31 - TOWARDS MODELLING AN ASYMMETRIC VIRAL TRIMER: SEQUENCE-GUIDED ANALYSIS OF MONKEYPOX A29L

Dmitrij Gritsok (Portugal)[1]; Sérgio Sousa (Portugal)[2]; Martin Hedström (Portugal)[3]; Maria Montenegro (Portugal)[1]; Célia Amorim (Portugal)[1]

1 - LAQV@REQUIMTE, Department of Chemical Sciences, Faculty of Pharmacy, University of Porto, Porto, Portugal; 2 - LAQV@REQUIMTE, BioSIM – Department of Medicine, Faculty of Medicine, University of Porto, Porto, Portugal; 3 - Division of Biotechnology and Applied Microbiology, Department of Process and Life Science Engineering, Lund University, Lund, Sweden

Abstract

The monkeypox virus A29L (OPG154) envelope protein (110 aa) is a key viral entry machinery component, proposed to form a trimeric complex. Structural data from the homologous Vaccinia virus A27L protein is limited to a truncated construct (residues 21-84). With reliable template data confined mainly to the central coiled-coil, the full-length architecture and quaternary assembly mode of A29L remain unresolved.

To address this, we constructed a sequence-informed framework to verify the structural modelling of A29L. A curated dataset of 56 orthologs across the *Chordopoxvirinae* subfamily was analysed using IQ-TREE 3, revealing a strongly genus-resolved topology with marked lineage-specific divergence. *Orthopoxvirus* sequences form a highly compact clade, whereas *Capripoxvirus*, *Cervidpoxvirus*, and *Yatapoxvirus* exhibit extended branch lengths indicative of substantial sequence remodelling. Notably, standard A29L orthologs are absent in several genera (e.g., *Avipoxvirus*, *Molluscipoxvirus*), which instead encode longer A26L-like paralogs, highlighting significant evolutionary plasticity within the OPG153/OPG154 interaction network.

Multiple sequence alignment and entropy profiling reveal a non-uniform conservation landscape. Strong conservation is restricted to the C-terminal region (residues 80-105), a few residues at the N-term, strict positional fixation of proline residues and leucine zipper heptad repeats, supporting a structurally constrained oligomerization interface. The canonical double-cysteine motif (C71-C72) is highly conserved (75%; 91%) across the majority of the subfamily, serving a dual role in inter-chain stabilization and A26L-interaction. In stark contrast, divergent lineages demonstrate complete loss of this double-cysteine staple (*Capripoxvirus*, *Cervidpoxvirus*) and replacement of the orthopoxvirus-specific heparin-binding motif (KKPE/KNPE) with an alternative EEPN signature, suggesting functional diversification in host-receptor engagement.

These sequence-derived constraints are subsequently employed to evaluate A29L assembly predictions. Standard structure prediction pipelines, including AlphaFold3, RoseTTAFold3, OpenFold3, exhibited a bias toward symmetric (C3) assemblies and failed to capture alternative conformations. In contrast, alternative approaches, such as Chai-1 and Boltz-2, when guided by geometric constraints, enabled exploration of asymmetric

arrangements. The resulting models showed high confidence scores (iPTM > 0.8 and pTM > 0.8 for Boltz-2). Structures were energy-minimized using YASARA and validated with MolProbity, yielding excellent stereochemical quality (clashscore 0.0, MolProbity score ~0.5, and >99% residues in favored Ramachandran regions).

This structurally constrained model of A29L assembly provides a foundation for future studies of viral entry and antibody recognition, offering a more realistic quaternary framework that supersedes monomer-based approximations commonly used in epitope mapping and docking studies.

This work received financial support from the PT national funds (FCT/MECI, Fundação para a Ciência e Tecnologia and Ministério da Educação, Ciência e Inovação) through the project UID/50006/2025 DOI 10.54499/UID/50006/2025 – Laboratório Associado para a Química Verde – Tecnologias e Processos Limpos. Dmitrij Gritsok is grateful to FCT (Fundação para a Ciência e Tecnologia) for his PhD research grant with ref. PRT/BD/154971/2023 established within EUGLOH–U.Porto protocol.

P33 - THEORETICAL STUDY OF THE MECHANISM OF ADENINE FORMATION UNDER INTERSTELLAR MEDIUM CONDITIONS

Manuel Retamal Rojas (Chile)[1]; Soledad Gutiérrez-Oliva (Chile)[1]

1 - Laboratorio de Química Teórica Computacional (QTC), Facultad de Química y de Farmacia, Pontificia Universidad Católica de Chile, Santiago, Avenida Vicuña Mackenna 4860, Santiago, Chile

Abstract

Astrochemistry is a branch of astronomy that focuses on investigating the evolution of atoms and molecules in the universe. One of its primary objectives is to enhance our understanding of prebiotic chemistry, which involves the chemical processes that may have occurred prior to the emergence of life on Earth [1].

Accordingly, this research proposes a new mechanism for the formation of adenine ($C_5H_5N_5$) in the interstellar medium (ISM), based on the investigation of a previously reported mechanism in which formamide (H_2NCHO) and vinyl cyanide (C_2H_3CN) are used as reactants to form 1H-pyrimidin-2-one, a direct precursor of pyrimidines [2]. In contrast, instead of using formamide in the aforementioned reaction, this study employs formamidine (CH_4N_2) and vinyl cyanide (C_2H_3CN) to promote the formation of adenine ($C_5H_5N_5$) in the gas phase.

Therefore, electronic structure calculations were carried out, and both global properties—such as energy, reaction force, and electron flux, among others—and local properties along the reaction coordinate will be analyzed using theoretical chemistry methods and computational tools. Based on Density Functional Theory (DFT), calculations in this study will be performed using the M06 functional and the 6-311++G(d,p) basis set [3,2]

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P35 - MOLECULAR DYNAMICS INSIGHTS INTO THE INTERACTION OF OMCS FILAMENTS IN THE REALISTIC BACTERIAL MEMBRANE ENVIRONMENT

Duangnapa Kiriwan (Portugal)[1]; Sergio F. Sousa (Portugal)[1,2]

1 - LAQV/REQUIMTE, BioSIM, Department of Biomedicine, Faculty of Medicine, University of Porto, Porto, Portugal; 2 - CERES, BIA Lab, Department of Chemical Engineering, FCTUC, University of Coimbra, Coimbra, Portugal

Abstract

Geobacter sulfurreducens is a well-known electricigens that generates electricity through extracellular electron transfer (EET). The multi-heme c-type cytochrome OmcS is a key component in the formation of conductive protein nanowires. Despite its importance, the long-term structural dynamics and the physical interaction between OmcS and the bacterial outer membrane remain unclear. In this study, we used all-atom molecular dynamics (MD) simulation to investigate the conformation landscape of *Omcs* within a realistic asymmetric bilayer that mimicked the *G.sulfurreducens* outer membrane. We propose a realistic model of the membrane-bound Omcs network required for extracellular electron transport.

The membrane system was constructed using the CHARMM-GUI Membrane Builder, featuring an asymmetric bilayer mimicking Gram-negative bacteria: lipopolysaccharide (LPS) in the upper leaflet and a lipid mixture (80% POPE and 20% POPG) in the lower leaflet. All-atom MD simulations were initiated from the cryo-EM structure (PDB ID: 6EF8) of the OmcS dimer. The simulation was performed using Amber20 for 1 µs, with temperature maintained at 30 °C.

The structural stability of the multi-heme Omcs was evaluated throughout long-simulations. The inter heme Fe-Fe distance across the production trajectories confirms that the conductive protein maintain high structural integrity when embedded in the asymmetric bilayer. Our results show that the heme-heme stable arrangement exhibits small fluctuations (average standard deviation < 0.6 Å) over the last 600 nanoseconds. These findings show that the physical interaction between OmcS filaments and the lipopolysaccharide (LPS)-rich interface does not affect the geometry required for long-range electron transmission. This study proposes a realistic model for understanding how *G. sulfurreducens* promotes extracellular electron transport across complicated biological surfaces.

This work was carried out within the support of the CERES Centre and supported by national funds from FCT through the projects https://doi.org/10.54499/UID/00102/ 2025 and https://doi.org/10.54499/UID/PRR/00102/2025. This work received financial support from the PT national funds (FCT/MECI, Fundação para a Ciência e Tecnologia and Ministério da Educação, Ciência e Inovação) through the project UID/50006/2025 DOI 10.54499/UID/50006/2025 -Laboratório Associado para a Química Verde - Tecnologias e Processos Limpos and 2024.00762.BD.

Keywords: Extracellular electron transfer (EET), OmcS Nanowires, molecular dynamics (MD) simulation

P37 - PORE-SIZE CONTROL OF ION PACKING AND CHARGING DYNAMICS IN IONIC-LIQUID SUPERCAPACITORS

Volodymyr Koverga (Portugal)[1]; Maria Natalia Dias Soeiro Cordeiro (Portugal)[1]; Vladislav B. Ivanistsev (Latvia)[2]; Iuliia Voroshylova (Portugal)[1]

1 - REQUIMTE-LAQV, Department of Chemistry and Biochemistry, Faculty of Sciences, University of Porto; 2 - Department of Chemistry, University of Latvia

Abstract

Electric double-layer capacitors (EDLCs) are promising energy-storage devices for applications requiring fast charge and discharge. Their energy and power performance are strongly governed by pore size, electrolyte properties and electrode-electrolyte interactions.[1] Here, we use atomistic molecular dynamics simulations to investigate how the size of slit pores controls ion packing, charge separation and ion dynamics in model supercapacitor electrodes.

The main objects of the study were carbon slit-pore electrodes with well-defined pore widths between 0.75 and 1.5 nm, simulated under constant-potential conditions.[2] The pores were filled with the ionic liquid 1-ethyl-3-methylimidazolium hexafluorophosphate. This model system allowed us to isolate the effect of pore width on the confined electrolyte structure and charging response. For each pore size, we analyzed ion density profiles, in-pore layering, charge distribution, ion mobility inside the pore and capacitance-potential behavior. Special attention was given to pore widths comparable to the characteristic size of the electrolyte ions, where confinement and interionic correlations are expected to be strongest.

The simulations show that pore size is not only a geometrical parameter but a factor that changes the charging mechanism. In narrow pores, ion packing is restricted by the pore walls and the applied potential induces ordered layers of counterions and co-ions. Such confinement can enhance charge storage by promoting dense ion arrangements near the charged carbon surface. At the same time, too strong confinement can slow down ion exchange between the pore and the external electrolyte region. Wider pores provide more space for ion rearrangement and easier transport, but the stored charge can be packed less efficiently. Therefore, the optimal pore size is a compromise between high capacitance and sufficient ion mobility.[3]

Our results support the idea that rational supercapacitor design should not optimize electrode and electrolyte properties separately. Instead, pore width must be selected together with ion size and electrolyte composition. Therefore, the pore-size/electrolyte-size relationship should be treated as a central design descriptor for EDLCs.

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Keywords: EDLC, ionic liquids, molecular dynamics, slit-pore

P43 - IN SILICO INVESTIGATION OF THE ANTIMALARIAL AND ANTICANCER ACTIVITIES OF SELECTED DIMERIC ACYLPHLOROGLUCINOLS

Liliana Mammino (South Africa)[1]; Neani Tshilande (South Africa)[1]
1 - University of Venda

Abstract

Acylphloroglucinols (ACPLs) are derivatives of phloroglucinol (1,3,5-trihydroxybenzene) characterized by the presence of at least one acyl group, R-C=O; various substituents may be present in the positions meta to the acyl group. They are largely present in natural sources and exhibit various biological activities [1]. Dimeric acylphloroglucinols (D-ACPLs) are ACPLs whose molecules consist of two acylphloroglucinol moieties linked by a methylene bridge. They are mostly present in *Hypericum* species.

The current work focuses on D-ACPLs for which antimalarial and/or anticancer activities have been reported – with the two activities often being present for the same compound. The viability of the two potentialities was investigated using molecular docking against the active sites of selected cancer-related and malaria-related proteins (BRAF V600E, CDK-2, EGFR, PI3K, JAK3, Topo I, HER2, and HSP90 for cancer, and Falcipain-2 (FP-2), Plasmepsin II (PM II), PfLDH, PfDHODH, PfMDH and PfPMT for malaria). The study utilized the Schrödinger suite. Two sets of docking studies were performed: in vacuo and with the presence of a certain number of explicit water molecules. This enabled evaluations of ligand–protein binding modes, including the types of interactions involved, the role of water molecules in complex stabilization, and the permanence of key interactions in the two contexts. The results show that D-ACPLs can form stable complexes with the active sites of several proteins. Hydrogen bonds are the strongest interactions, with one or more phenol OHs of the ligand acting as donors and often also the sp^2 O of the acyl group acting as acceptor; weaker interactions, such as hydrophobic interactions, may also be present. Water molecules often enhance binding stability by bridging the H-bonds' donor and acceptor. Most of the investigated D-ACPLs show favorable binding affinities across several anticancer and antimalarial targets – a multi-target potential enabling the expectation of greater overall action efficacy.

Additionally, ADMET (administration, distribution, metabolism, excretion, toxicity) profiling was performed to evaluate drug-likeness and the physicochemical properties generally related to drug viability and safety.

The obtained results enable a comparison of potential activities, thus identifying the D-ACPLs which might be the most promising candidates for further investigation in view of their possible development into antimalarial and anticancer drugs. The fact that many D-ACPLs exhibit both activities is particularly interesting because the development costs of one drug would lead to two pharmacological applications.

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The authors express their gratitude to the Center for High performance Computing (CHPC) in Cape Town (South Africa) for providing the computational facilities.

Keywords: ADMET, anticancers, antimalarials, dimeric-acylphloroglucinols, hydrogen bonding, molecular docking

P45 - RATIONAL DESIGN OF DEFECTIVE SULFUR-TERMINATED TA_2C MXENE FOR AMMONIA PRODUCTION: A FIRST-PRINCIPLES STUDY

Nicolas Ferreira Martins (Brazil)[1,2]; Daniela Alves Abreu (Portugal)[2]; José Daniel Gouveia (Portugal)[2]; José Richard Baptista Gomes (Portugal)[2]; Julio Ricardo Sambrano (Brazil)[1]

1 - Modeling and Molecular Simulation Group, São Paulo State University (UNESP), School of Sciences, Bauru, 17033-360, SP, Brazil; 2 - CICECO – Aveiro Institute of Materials, Department of Chemistry, University of Aveiro, Campus Universitário de Santiago, 3810-193 Aveiro, Portugal

Abstract

Ammonia (NH3) is a chemical product that is continuously produced due to its importance as both a fertilizer and an energy carrier in industry. In the first stage of the Nitrogen Reduction Reaction (NRR), extreme conditions, such as high pressure, are required to break the strong triple bond of N_2. To address this challenge and enable a more favorable pathway for NH3 formation, new catalysts have been designed to activate nitrogen from a computational perspective [1]. Among two-dimensional (2D) materials, MXenes stand out as promising candidates due to their rich transition metal composition and synthetic versatility, particularly arising from the variety of possible surface terminations [2]. However, most homogeneously terminated MXenes are known to be inert or weakly reactive toward molecules such as N2 [3], requiring alternative design strategies to tune their catalytic properties. In this context, this work investigates the nitrogen fixation mechanism on the synthesized S-terminated Ta2C (Ta2CS2) MXene [4] by introducing sulfur vacancies into its structure. The results were obtained using Density Functional Theory (DFT) simulations, and key parameters such as adsorption energies, maximum energy barriers, and charge transfer were also evaluated.

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Keywords: Mxene, ammonia, electrocatalysis, DFT, Tantalum

P47 - THEORETICAL STUDY OF THE INTERACTIONS OF GRAPHENE OXIDE AND SANDSTONE SURFACES

Anderson Arboleda-Lamus (United Kingdom)[1]; Christian Forero (Colombia)[2]; Nicolas Santos (Colombia)[3]; Enrique Mejia-Ospino (Colombia)[3]

1 - Department of Physics, King's College London, London WC2R 2LS, UK; 2 - Laboratorio de Espectroscopia Atómica y Molecular (LEAM), Universidad Industrial de Santander, 680002 Bucaramanga, Colombia; 3 - Grupo de Investigación en Tomografía Computarizada para Caracterización de Yacimientos (GIT), Universidad Industrial de Santander, 680002 Bucaramanga, Colombia

Abstract

Molecular dynamics simulations were performed to investigate the transfer and detachment energies of graphene oxide (GO) and pristine graphene sheets at both liquid–liquid and solid–liquid interfaces. The umbrella sampling technique was employed to compute potential of mean force (PMF) profiles, enabling a quantitative assessment of how several factors influence these processes: (i) the degree of oxidation of GO sheets, (ii) the surface chemistry of sandstone, and (iii) the nature of reservoir fluids. Water and toluene were selected as representative models of the aqueous phase and crude oil, respectively. The sandstone surface was modeled using the (001) crystallographic plane of α-quartz at two saturation states: Q3 and Q4. The Q3 surface, enriched in silanol groups, exhibited hydrophilic behavior, whereas the Q4 surface, composed primarily of siloxane groups, displayed hydrophobic character. The results indicate that GO sheets exhibit significant interfacial activity that increases with the degree of oxidation. Higher oxidation enhances solubility in the aqueous phase while reducing affinity for the crude oil model. In contrast, pristine graphene is interfacially inactive and preferentially partitions into the toluene phase. Sheet detachment from the rock surface was found to depend strongly on surface chemistry, oxidation level, and reservoir fluid characteristics. The most energetically favorable detachment occurs at the Q3–aqueous interface, with free energies below 12.8 kcal/mol, followed by the Q4–crude oil interface, with values below 53.8 kcal/mol. The highest detachment energies were observed at the Q3–crude oil and Q4–aqueous interfaces, reaching values up to 90.7 kcal/mol. Notably, inverse trends in sheet behavior across these interfaces highlight the complex interplay between surface chemistry, fluid environment, and oxidation degree in governing interfacial stability.Vicerectoría de Investigaciones, Universidad Industrial de Santander, Programa de Movilidad

Keywords: Graphene Oxide, Sandstone, Molecular Dynamics

P49 - MULTI-TARGET IN SILICO SCREENING OF BIOACTIVE PEPTIDES AGAINST HYPERTENSION, ALZHEIMER AND DIABETES FROM EU-AUTHORISED EDIBLE INSECTS

Tatiana Melo (Portugal)[1,2,3]; Sérgio F. Sousa (Portugal)[3,4]; Isabel Mafra (Portugal)[1]; Tânia G. Tavares (Portugal)[2]; Carla S. S. Teixeira (Portugal)[1]

1 - REQUIMTE/LAQV, Faculty of Pharmacy, University of Porto, Porto, Portugal; 2 - LEPABE, ALiCE, Faculty of Engineering, University of Porto, Porto, Portugal; 3 - REQUIMTE/LAQV, BioSIM - Department of Biomedicine, Faculty of Medicine, Universidade do Porto, Porto, Portugal; 4 - CERES, BIA Lab, Department of Chemical Engineering, Faculty of Sciences and Technology, Universidade de Coimbra, Coimbra, Portugal

Abstract

The integration of edible insects into the European food market, supported by the recent authorizations of *Tenebrio molitor*, *Acheta domesticus*, *Locusta migratoria* and *Alphitobius diaperinus* as novel foods, marks a significant step towards sustainable nutrition. Beyond their protein content, these species represent a potential source of bioactive peptides; therefore, it is also essential to explore their secondary biological benefits. This study aims to perform a comprehensive and comparative *in silico* screening of peptides derived from these four species, focusing on their ability to provide multi-target inhibitors for enzymes associated with cardiac and pulmonary fibrosis, hypertension, Alzheimer's disease and diabetes.

The methodology followed an *in silico* workflow where protein sequences from the selected insect species were retrieved from Swiss-Prot (UniProtKB) and a simulation of the gastrointestinal digestion was employed using the BIOPEP-UWM server. The resulting peptide libraries were screened via molecular docking (GOLD software, PLP score function) against five therapeutic targets: the C-domain (cACE, PDB 6F9T) and N-domain (nACE, PDB: 6EN5) of the somatic Angiotensin-I converting enzyme (sACE); human acetylcholinesterase (hAChE, PDB: 4EY7) and human butyrylcholinesterase (hBChE, PDB: 5NN0); and dipeptidyl peptidase 4 (DPP4, PDB: 4A5S). ADMET profiling via pepADMET was performed to predict favourable intestinal absorption, blood-brain barrier permeability and toxicity for all the resulting fragments. Computational screening enabled the identification of high-potential candidates with distinct inhibitory profiles across the targeted enzymes. The analysis prioritised sequences exhibiting inhibitory activity against cholinesterases and DPP4 as well as sACE domain selectivity, while filtering for favourable bioavailability and safety profiles.

This work advances the characterization of bioactive peptides in EU-authorised insect species. By identifying novel sequences with potential effects on fibrosis, hypertension, diabetes and neurodegeneration, this study supports the development of functional foods that promote health within sustainable food systems, in alignment with the objectives of European Green Deal.

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Keywords: Edible Insects, Bioactive Peptides, Molecular Docking, Hypertension, Alzheimer, Diabetes

P51 - DETERMINATION OF THE MINIMUM FREE ENERGY PATH (MFEP) OF THE INTRAMEMBRANE HYDROLYSIS MECHANISM CATALYZED BY Γ-SECRETASE USING THE ADAPTIVE STRING METHOD (ASM)

Cristian Hernando Rivera Moyano (Colombia)[1]; Carlos Ramos Guzman (Colombia)[2]; Gian Pietro Misciones (Colombia)[1]
1 - Universidad de los Andes; 2 - Bristol University

Abstract

This research focuses on the hydrolysis mechanism carried out by γ-secretase, a transmembrane protease responsible for processing the β-amyloid peptide (Aβ), whose abnormal accumulation is strongly associated with Alzheimer's disease. γ-secretase cleaves the Leu49–Val50 peptide bond of the C99 substrate derived from the amyloid precursor protein (APP) through a catalytic dyad (Asp257–Asp385), likely activated by a water molecule confined within a polar cavity in the membrane. Understanding the atomic-level details of this process, including water activation, protonation equilibria, formation of the tetrahedral intermediate (gem-diol), amide bond cleavage, and catalyst regeneration, is essential for the rational design of selective modulators that reduce toxic Aβ production without affecting pathways such as Notch signaling.

Previous studies have provided key insights. Bhattarai et al. (2020) reported spontaneous activation of γ-secretase using Gaussian accelerated molecular dynamics, revealing a hydrogen-bond network involving the catalytic aspartates, APP, and water. Wu et al. (2024) investigated the conformational dynamics of the complex and described the minimum energy path for the first step, corresponding to gem-diol formation, considered rate-determining. However, the minimum free energy path (MFEP) connecting reactants and products remains unresolved. In addition, previous studies were limited to only two collective variables, restricting analysis to early stages and preventing exploration of amide bond cleavage and catalyst regeneration.

To overcome these limitations, this project employs the adaptive string method with multiple collective variables. This approach enables a complete description of the catalytic mechanism, capturing all relevant steps and allowing accurate tracking of structural and electronic evolution. It also facilitates identification of previously unobserved intermediates and transition states.

This methodology will provide the MFEP, quantify free energy barriers, and clarify the acid–base mechanism, as well as the role of the Asp–Asp dyad and lipid environment in stabilizing transition states. The results will support the rational design of selective γ-secretase modulators with potential therapeutic applications in Alzheimer's disease.

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Keywords: γ-secretase, Adaptive string method, Minimum free energy path, Alzheimer's disease

P53 - ADSORPTION FREE ENERGIES OF ASPHALTENE-LIKE POLYAROMATICS ON SILICA: HETEROATOM EFFECTS AND PH-DRIVEN SURFACE CHARGING

Leonardo Muñoz-Rugeles (Colombia)[1]; Jorge M. Del C (Mexico)[2]
1 - Universidad Industrial de Santander; 2 - Universidad Nacional Autónoma de México

Abstract

Asphaltene deposition on mineral surfaces is a major flow-assurance challenge that lowers oil recovery and complicates drilling and production operations. Because deposition is governed by molecular-scale interfacial interactions, quantitative adsorption thermodynamics are needed to guide the formulation of drilling/production fluids and mitigation strategies. Here we use atomistic molecular dynamics to quantify how heteroatom chemistry and pH-controlled silica surface protonation modulate adsorption of asphaltene-like polyaromatics.

We computed PMF profiles (ΔA) for four polyaromatic model compounds containing N, O, or S heteroatoms on hydroxylated silica surfaces (silanol density 4.5 groups nm^{-2}) and on a fully dehydroxylated surface. The polyaromatic models containing N, O, and S were 3*H*-benzo[*e*]indole, naphtho[2,1-*b*]furan, and naphtho[2,1-*b*]thiophene, respectively, while 3*H*-cyclopenta[*a*]naphthalene was used as the heteroatom-free reference compound (CH_2). pH effects were represented by deprotonating 0%, 10%, and 20% of silanol groups (corresponding to pH 3, 6, and 9, respectively) and adding Na^+ counterions to maintain electroneutrality.

All simulations were performed using GROMACS, with the INTERFACE force field for the silica surface, CGenFF for the polyaromatic solutes, and TIP3P for water. After energy minimization and NVT/NPT equilibration, adsorption free-energy profiles were obtained via umbrella sampling along the surface–solute separation coordinate (1.6–0.3 nm; 14 windows; force constant k = 1000 kJ mol^{-1} nm^{-2}; 50 ns per window) and analyzed using both WHAM and MBAR.

At pH 3, adsorption strengths depend only weakly on heteroatom identity, with ΔA values being very similar. Representative ΔA values at pH 3 are −3.29 ± 0.07 kJ/mol for N, −3.37 ± 0.07 kJ/mol for O, −3.92 ± 0.13 kJ/mol for S, and −3.76 ± 0.26 kJ/mol for CH_2. In contrast, increasing pH disfavors the adsorption process, consistent with enhanced electrostatic repulsion from negatively charged siloxide sites, leading to significant changes in the shape of the PMF profiles. The ΔA minima for the N compound at pH 3, 6, and 9 are −3.29 ± 0.07, -2.74 ± 0.15, and −1.19 ± 0.28 kJ/mol, respectively. Overall, these results indicate that pH-driven surface charging can outweigh heteroatom effects and should be explicitly considered when designing operating conditions and formulations to control asphaltene deposition on silica-rich substrates. The findings reported here contribute to the rational design of improved enhanced oil recovery technologies.

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Keywords: Molecular dynamics, Potential of mean force, Umbrella sampling, Asphaltenes, Silica surfaces, Enhanced oil recovery

P55 - HIERARCHICAL INTEGRATION OF MACHINE LEARNING SCORING, ADMET PROFILING, AND MM/GBSA FREE ENERGY CALCULATIONS FOR ULTRA-LARGE VIRTUAL SCREENING: A CASE STUDY ON A. BAUMANNII GYRB INHIBITORS

Didier Nivón-Ramírez (Mexico)[1]; Uriel Martínez-López (Mexico)[1]; Ana E. Hernandez (Mexico)[1]; Rodolfo Gómez-Balderas (Mexico)[1]

1 - Laboratorio de Fisicoquímica Analítica, Unidad de Investigación Multidisciplinaria, Facultad de Estudios Superiores Cuautitlán, Universidad Nacional Autónoma de México, Cuautitlán Izcalli, Estado de México 54714, México.

Abstract

Acinetobacter baumannii represents a critical-priority pathogen according to the World Health Organization, primarily due to the widespread emergence of carbapenem-resistant strains. The development of alternative therapeutic strategies is urgent. DNA gyrase, particularly its GyrB subunit ATPase domain, constitutes a promising yet underexplored target for antibiotic development, especially given the resistance mutations affecting traditional quinolone binding sites in the GyrA subunit. To identify novel ATPase inhibitors of A. baumannii DNA gyrase through a comprehensive computational workflow integrating physicochemical filtering, molecular docking, and molecular dynamics simulations. A hierarchical virtual screening protocol was applied to approximately 95 million compounds from the Enamine REAL database. The workflow included: (1) Lipinski's Rule of Five filtering, (2) Hergenrother's eNTRY rules for Gram-negative permeability, (3) PAINS removal, (4) ADMET profiling using ADMET-AI, and (5) consensus molecular docking with GNINA utilizing CNN-based scoring functions. Top-ranked candidates underwent 400 ns all-atom molecular dynamics simulations using GROMACS, followed by MM-GBSA binding free energy calculations and per-residue energy decomposition analysis. The filtering cascade reduced the initial library to 11,464 drug-like compounds with favorable pharmacokinetic profiles. Consensus docking (ΔGbinding ≤ -8.0 kcal/mol and CNN_pose ≥ 0.8) identified 230 candidates. Five commercially available compounds were selected for molecular dynamics studies. These candidates demonstrated superior aqueous solubility (logS: -1.21 to -2.37) compared to novobiocin (-5.18) and reduced plasma protein binding (20.71-39.97%) versus novobiocin (77.78%). MM-GBSA calculations revealed binding free energies ranging from -27.91 to -39.97 kcal/mol, with compound Es25804170 showing the most favorable energy (-39.97 kcal/mol). Per-residue decomposition identified GLU64 and ASP87 as dominant energetic contributors through salt-bridge interactions with the primary amine moiety. RMSD analysis confirmed structural stability throughout simulations, with values plateauing at 1.8-4.5 Å. This integrated computational approach successfully identified five promising lead candidates with enhanced pharmacokinetic properties and strong predicted binding affinity to the ATPase site of A. baumannii DNA gyrase. The identified compounds represent viable candidates for experimental validation through antibacterial susceptibility assays, potentially contributing to the development of

novel therapeutics against multidrug-resistant Gram-negative pathogens.This work was supported by UNAM-PAPIIT IN222224, FES-Cuautitlán Research Chairs Program grant CI2463, computational resources provided by LANCAD-UNAM-DGTIC-058 and the National Supercomputing Center (CNS-IPICYT) through grant TKII-E-0924-I-300924-46/PR-45. D.N-R. thanks SECIHTI for the PhD scholarship (CVU 926574).

Keywords: DNA Gyrase, Molecular Docking, Molecular Dynamics, Acinetobacter baumannii, Virtual Screening

P59 - USING QSAR MODELS TO REFINE THE ANTIMICROBIAL PEPTIDE LFCIN17-30 AGAINST MYCOBACTERIUM ABSCESSUS

Gabriel S. Oliveira (Portugal)[3,4]; Sérgio F. Sousa (Portugal)[1,2]; Maria Salomé Gomes (Portugal)[3,4]; Tânia Silva (Portugal)[3,4]

1 - CERES, BIA Lab, Departamento de Engenharia Química, Faculdade de Ciências e Tecnologia da Universidade de Coimbra /; 2 - LAQV/REQUIMTE - BioSIM, Departamento de Biomedicina, Faculdade de Medicina da Universidade do Porto.; 3 - ICBAS - Instituto de Ciências Biomédicas Abel Salazar da Universidade do Porto; 4 - i3S - Instituto de Investigação e Inovação em Saúde da Universidade do Porto

Abstract

Known for their high antibiotic resistance, mycobacterial infections require therapies based on multi-drug regimens, leading to poor patient compliance, low cure rates, and recurrence. Mycobacteria that do not cause tuberculosis or leprosy are identified as non-tuberculous mycobacteria, with infections caused by *Mycobacterium abscessus* being the most difficult to treat, often compared to multidrug-resistant tuberculosis [1]. Thus, there is an urgent need for new and effective drugs. Considering this, our work aimed to optimise a peptide known to be active against non-tuberculous mycobacteria – LFcin17-30 [2].

This work aimed to optimize a highly active peptide against *M. avium* [2] – the bovine lactoferricin peptide LFcin17-30. We used a positional scanning library containing 222 peptides that differ in only one amino acid from LFcin17-30. Other modifications were included, such as scrambled, reversed and split sequences. The peptides were tested against both *M. abscessus* and *M. avium* growing in planktonic cultures and inside macrophages, since these are intracellular bacteria, at different concentrations. Quantitative structure-activity relationship models were independently derived by relating the peptides' activities with their molecular descriptors. Afterwards, a virtual set of 100,000 peptides, created with specific constraints based on the initial library, was passed through each model to predict activity. 50 peptides (25 active and 25 inactive) were selected from the virtual library to evaluate the models' performance. The true/false positive/negative rates will be used to validate their accuracy.

Screening of the initial library revealed the peptide regions where specific modifications could improve the activity of the parental peptide. The results showed that the alterations that yielded higher activities were different for each experimental setting. These findings were then supported by the generated QSAR models, which, despite having overlaps in general descriptors, still showed distinct specific ones with varying weighting factors across the different settings.

With this work, we aimed to identify new antimicrobial peptides active against *M. abscessus*, based on the initial peptide LFcin17-30 which was used to generate the positional scanning libraries that were used as input data for the QSAR models.

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This work is supported by the ICBAS BiotechHealth PhD Program and financed by national funds through FCT – Fundação para a Ciência e a Tecnologia, I.P, within the project PTDC/BIA-MIC/3458/2020, and PhD fellowship 2021.07335.BD to the author.

Keywords: nontuberculous mycobacteria, QSAR, positional scanning library, antimicrobial peptides

P61 - TOWARDS A FULL-POTENTIAL ALGEBRAIC KKR FORMALISM FOR MODELING REACTIVITY IN LAYERED DOUBLE HYDROXIDES

Isaac Samael Beltran Orta (Mexico)[1]; Roberto Flores Moreno (Mexico)[2]; Bernardo Antonio Zuñiga Gutierrez (Mexico)[1]

1 - University of Guadalajara (UDG) - CUCEI; 2 - University of Guadalajara (UDG) - CUCEI,

Abstract

The rigorous computational modeling of Layered Double Hydroxides (LDHs) and brucite-like structures faces a convergence of theoretical obstacles: the compositional disorder inherent to isomorphic doping, the strong spatial anisotropy of the interlayer hydrogen-bond network, and the need to map catalytic active sites analytically. Conventional Density Functional Theory (DFT) approaches relying on massive supercells become computationally prohibitive when exploring continuous compositional phase spaces. To overcome these limitations, we report the development of a computational module based on Algebraic Multiple Scattering Theory (AMST) within the auxiliary DFT framework of Nagual/deMon2k. Unlike traditional Korringa-Kohn-Rostoker (KKR) methods restricted by muffin-tin approximations and numerically unstable radial integrators, AMST expresses the periodic Green's function entirely within a finite Gaussian orbital (LCGTO) basis. This allows for an exact full-potential treatment of the highly anisotropic interlaminar regions. We present the current implementation status of the core scattering operators and the iterative resolution of the structural Dyson equation via preconditioned GMRES. We demonstrate the baseline stability of the method through early validation tests. Furthermore, we outline the roadmap for coupling this stable algebraic architecture with the Coherent Potential Approximation (CPA), which will ultimately allow the direct analytical extraction of local reactivity descriptors (such as Fukui functions) from the energy-integrated Green's function to accurately predict catalytic behavior in doped LDH materials.I would like to express my sincere gratitude to my advisors, Dr. Roberto Flores Moreno and Dr. Bernardo Antonio Zúñiga Gutiérrez, for their invaluable academic guidance and continuous support. Additionally, I extend my gratitude to the University of Guadalajara and the University Center of Exact Sciences and Engineering (CUCEI) for their institutional backing and the facilities provided. Finally, I deeply acknowledge and appreciate the financial support granted through the SECIHTI scholarship for master's students, which has been fundamental to the development of this research.

Keywords: Layered Double Hydroxides (LDHs), Algebraic Multiple Scattering Theory (AMST), Density Functional Theory (DFT), Coherent Potential Approximation (CPA), Catalytic Reactivity

P63 - PHOTOISOMERIZATION MECHANISM AND THERMAL STABILITY OF HETEROARYL AZO MOLECULAR SWITCH

Didier Nivón-Ramírez (Mexico)[1]; León Daniel Ponce-Perez (Mexico)[1]; Emir Alejandro Galván-García (Mexico)[1]; Rodolfo Gómez-Balderas (Mexico)[1]

1 - Laboratorio de Físicoquimica Analítica, Unidad de Investigación Multidisciplinaria, Facultad de Estudios Superiores Cuautitlán, Universidad Nacional Autónoma de México, Cuautitlán Izcalli, Estado de México, Mexico

Abstract

Azobenzene-based molecular switches isomerize reversibly between E and Z forms upon light irradiation, enabling applications in photopharmacology, data storage, and smart materials. While the effect of simple heterocyclic substitution on photoisomerization has been explored, the introduction of an oxathiazole ring—incorporating three distinct heteroatoms (O, S, N) and an sp^3-hybridized carbon—remains poor explored. This unusual atomic disposition breaks the planarity of the azo dye and enables intramolecular contacts that can dramatically alter excited-state dynamics and thermal stability. Here, we present a comprehensive computational study of 5-(phenyldiazenyl)-1,4,2-oxathiazole (Ot) using time-dependent density functional theory (TDDFT) at the B3LYP/cc-pVDZ level. E and Z ground-state geometries were optimized, potential energy surfaces along rotation (C–N=N–C torsion) and inversion (N=N–C angle) were constructed, and the S_1/S_0 conical intersection was located. The rotation pathway is barrierless in S_1, with a $CI(S_1/S_0)$ at ~90° torsion acting as an efficient funnel for ultrafast E ↔ Z photoisomerization. The computed UV-Vis spectrum reveals a hypsochromic shift of the π←n band relative to azobenzene. Topological analysis of the electron density uncovers a noncovalent C–H···π interaction between the heterocycle and the phenyl ring in the Z isomer, which stabilizes this form and raises the thermal back-isomerization barrier. In contrast, natural transition orbital (NTO) analysis shows that the π←π transition in Ot possesses significant intramolecular charge-transfer character. Eyring transition state theory predicts a thermal half-life of ~1.6 years for Z-Ot at 298 K— longer than typical heteroaryl azo switches lacking such stabilization. These findings establish the oxathiazole core as a great motif for achieving exceptional bistability (this means for E and Z), providing a clear design guideline for photochromic systems requiring long-term Z isomer persistence.This work was supported by the Secretaría de Ciencia, Humanidades, Tecnología e Innovación (SECIHTI, CVU 1218329), the UNAM-PAPIIT program (grant IN224526), the FES-Cuautitlán Research Chairs (CI2463), DGTIC-UNAM (LANCAD-UNAM-DGTIC-058), and the National Supercomputing Center of IPICyT (grant TKII-E-0924-I-300924-46/PR-45).

Keywords: photoisomerization, molecular switches, heteroaryl azo, conical intersection, half-life, noncovalent interaction

P67 - MOLECULAR MODELING OF FLAVONOID INTERACTIONS WITH PHOSPHOLIPASE-MEDIATED INFLAMMATORY PATHWAYS INVOLVED IN HEPATIC INJURY

Airam Roggero (Portugal)[1]; Fabio Martins (Portugal)[1]; Marcos Toyama (Brazil)[3]; Adeilso Bispo (Brazil)[3]; Caroline Ramos (Brazil)[3]; Willian Bezerra (Brazil)[3]; Pedro Loyola (Brazil)[3]; Paloma Borges (Brazil)[3]; Sergio Sousa (Portugal)[1,2]

1 - LAQV/REQUIMTE – BioSIM, Department of Biomedicine, Faculty of Medicine, University of Porto.; 2 - CERES, BIA Lab, Department of Chemical Engineering, FCTUC, University of Coimbra; 3 - BIOMOLPEP, Department of Biology, Institute of Biosciences UNESP/CLP, Brazil

Abstract

Phospholipase-driven lipid remodeling plays a fundamental role in inflammatory processes associated with hepatic damage. Enzymes such as secretory phospholipase A2(sPLA2) and cytosolic phospholipase A2(cPLA2) catalyze the hydrolysis of membrane phospholipids, releasing arachidonic acid and initiating the biosynthesis of pro-inflammatory mediators. Understanding how small molecules interact with these enzymes is essential for the development of novel modulators of inflammatory lipid metabolism. In this work, we employed a computational chemistry approach to investigate the interaction of the flavonoids morin and kaempferol with key enzymes involved in phospholipid remodeling and inflammatory signaling. Molecular docking and Moleuclar Dynamic Simulations (MD) with binding free-energy calculations were performed to evaluate ligand binding to sPLA2, cPLA2, cyclooxygenase-2 (COX-2), LPCAT3, ACSM, and PRDX6. The results revealed stable binding modes within catalytic regions and hydrophobic channels associated with phospholipid recognition, suggesting that these natural compounds may interfere with arachidonic acid release and downstream inflammatory pathways. To complement the computational analysis, enzymatic assays and spectroscopic techniques were used to investigate ligand–protein interactions and potential structural effects on the enzymes. In addition, biochemical markers associated with hepatic injury were evaluated in a murine model of inflammation induced by secretory PLA2. The combined computational and experimental results provide molecular-level insights into how flavonoids may modulate phospholipase-related inflammatory pathways. These findings highlight the potential of natural compounds as modulators of lipid-mediated inflammation and demonstrate the value of theoretical and computational chemistry approaches in understanding biomolecular recognition processes relevant to inflammatory diseases.

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the PT national funds (FCT/MECI, Fundação para a Ciência e Tecnologia and Ministério da Educação, Ciência e Inovação) through the project UID/50006/2025 DOI 10.54499/UID/50006/2025 -Laboratório Associado para a Química Verde - Tecnologias e Processos Limpos.

Keywords: Molecular docking, Flavonoids, Phospholipase A2, Computational chemistry, Inflammatory lipid metabolism, Drug–enzyme interactions

P69 - HYDROGEN PEROXIDE CONCENTRATIONS AND DISTRIBUTION IN EXTRACELLULAR MEDIA OF HUMAN TISSUES - A MODELLING ANALYSIS

Arthur Itacarambi (Portugal)[2]; Marcos Gouveia (Portugal)[2]; Rui Travasso (Portugal)[2]; Armindo Salvador (Portugal)[1]

1 - CNC – Centre for Neuroscience and Cell Biology, University of Coimbra; 2 - CFisUC, Department of Physics, University of Coimbra

Abstract

Hydrogen peroxide (H2O2) release to the extracellular space (ECS) by NADPH oxidases (NOX) and dual oxidases (DUOX) regulates important physiological and pathological processes, including wound healing, immune signaling, and redox-dependent cell communication. However, the concentrations and spatial distribution of H2O2 in the ECS of non-vascular tissues remain poorly characterized, hampering our understanding of the underlying signaling mechanisms and the design of physiologically realistic experimental protocols.

We developed a series of reaction-diffusion mathematical models to investigate the steady-state concentrations and spatial distribution of H2O2 in the ECS of non-vascular human tissues, systematically examining the contributions of five key determinants: (i) H2O2 release rates by cells, (ii) spatial localization of release sites, (iii) plasma membrane permeability, (iv) the ratio of ECS volume to membrane surface area, and (v) the extent to which intracellular antioxidant clearance outcompetes H2O2 efflux. Models range from simple analytical solutions for idealized planar and spherical geometries to numerical reaction-diffusion simulations that incorporate detailed cytosolic H2O2 metabolism, including the peroxiredoxin/thioredoxin/thioredoxin reductase and glutathione peroxidase/glutathione systems.

Our results show that the localization of NOX2 in discrete nanoscale clusters at the neutrophil plasma membrane — as occurs at nascent phagocytic cups — generates steep (100 nm scale) local H2O2 gradients in the ECS. The local concentration in the ECS of a 30-nm wide cell-cell junction near a maximally activated typical 30-nm radius cluster barely attains 0.5 uM, which causes just a minimal local oxidation of the cytosolic redox pools. This maximal concentration is little influenced by the permeability constant of the membranes facing the ECS, and increases sublinearly with cluster area, not exceeding 1.6 uM even for a large, 60-nm radius, cluster. These results pose strong lower bounds on the required sensitivity of intracellular H2O2-signal-transduction mechanisms operating under physiological (non-stress) conditions.

On the other hand, the combined action of the 800-1000 clusters present on an active neutrophil generates H2O2 at a rate that can overwhelm the cytosolic reductive capacity

of adhering cells. Under these conditions H2O2 clearance from the ECS is no longer permeation-limited and concentrations may approach 100 uM, but with a spatial range limited to the immediately adjacent cells.

These results establish quantitative upper bounds for extracellular H2O2 concentrations in human tissues, clarify the length scales over which H2O2-mediated paracrine signaling can operate, and provide a mechanistic framework for interpreting experimental observations of redox-dependent cell communication.Work co-funded by the EU Recovery and Resilience Facility and Portuguese national funds via FCT – Fundação para a Ciência e a Tecnologia, under projects, LA/P/0058/2020 [DOI: 10.54499/LA/P/0058/2020], UID/PRR/4539/2025 [DOI: 10.54499/UID/PRR/04539/2025], UID/04539/2025, UID/PRR/00313/2025 (https://doi.org/10.54499/UID/PRR/00313/2025), UID/00313/2025 (https://doi.org/10.54499/UID/00313/2025) and special complementary funds provided by FCT (project LA/P/0056/2020) and by COMPETE 2030, Portugal 2030 and the European Union with reference COMPETE2030-FEDER-00929300.

Keywords: Reaction-diffusion model, Mathematical model, Hydrogen peroxide, Redox signaling, Extracellular space, NADPH oxidase

P73 - COMPUTATIONAL STUDY OF HYDROGEN PEROXIDE INTERACTION WITH MYOGLOBIN AND HORSERADISH PEROXIDASE: A COMPARATIVE STUDY

Eugenia Rodríguez Scaglia (Argentina)[2]; Bianca Korcsog (Argentina)[2]; Candela Celene Galarza Pirola (Argentina)[2]; Jonathan Alexis Córdova (Ecuador)[1,2]; Darío Estrin (Argentina)[1,2]; Luciana Capece (Argentina)[1,2]

1 - CONICET - Universidad de Buenos Aires, Instituto de Química-Física de los Materiales, Medio Ambiente y Energía (INQUIMAE), Buenos Aires, Argentina; 2 - Departamento de Química Inorgánica, Analítica y Química Física, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Buenos Aires, Argentina

Abstract

Peroxidases are widely spread hemeproteins that catalyze the oxidation of diverse substrates, initiated by the coordination of hydrogen peroxide (H2O2) to the iron in the heme group. In that context, the goal of this study is to investigate the reactivity of H2O2 with hemeproteins, focusing on the first step of the reaction, which corresponds to the formation of the H2O2 complex which leads to compound 0 (Cpd0).
To achieve this, we selected as representative examples the protein horseradish peroxidase (HRP)[1][2,3] and ferric myoglobin (Mb), a model hemeprotein, previously studied in our group for a list of small ligands. Interestingly, HRP displays a 10^7 M-1s-1 catalytic constant for the formation of Cpd0, while in Mb this constant is estimated in 10^2 M-1s-1. The molecular basis for this difference is still unknown, but the differential configuration of the distal cavity might play a crucial role. While Mb displays a histidine residue close to the distal coordination site, in HRP the closest residue to the distal ligand corresponds to an arginine(R38), with a histidine(H42) also present in the distal cavity but further from the binding site. Indeed, the reaction constant for Cpd0 formation is reduced to 10^4 M-1s-1 and to 10^2 M-1s-1 in the R38L and H42L mutations, respectively.[5] It is discussed whether there is a water molecule bound to the iron in HRP, so we studied the residence time of water molecules close to a binding distance to figure this out. We also studied the migration of H2O2 from the solvent to the active site and the first step of the mechanism, consisting of the binding of H2O2 to the iron to form Cpd0. We considered the selected HRP mutants: R38L and H42L, to further analyze how the proteic environment affects H2O2 binding.

This study was carried out through a combination of computational methods such as: classic molecular dynamics simulations (MD), multiple steered molecular dynamics (MSMD) and hybrid quantum mechanics/molecular mechanics (QM/MM) calculations. Comparing the results in both proteins, we analyzed the role of HRP's active site configuration as the facilitator of H2O2 binding. We emphasize the differences in reactivity that occur because of the active site architecture that is unique to each system. The results show that H2O2 -as in Mb- can easily access the active site through two

independent channels, which are influenced by the distal residues' conformation. Additionally, we observed that the water molecule present in the distal site is only weakly bound to the iron, probably facilitating the formation of Cpd0 with respect to Mb. Overall, the results from this work allow to shed light on the molecular aspects that allow the highly efficient H2O2 binding in HRP.

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Keywords: Hemeproteins, Computational simulations, Molecular Dynamics, Hydrogen peroxide, QM/MM, Free energy

PO79 - COMPUTATIONAL EXPLORATION OF SPIDER SILK SPIDROINS AS A SOURCE OF BIOACTIVE PEPTIDE MOTIFS

Marco Antonio Benamú (Uruguay)[2]; Isabel Volz (Uruguay)[1]
1 - Laboratorio de Investigaciones Biológicas Aplicadas, Sede Rivera, Cenur Noreste, Universidad de la República.; 2 - Laboratorio Ecotoxicología de Artrópodos Terrestres, Sede Rivera, Cenur Noreste, Universidad de la República.

Abstract

For many years, spider silk has attracted scientific interest mainly because of its remarkable mechanical properties, especially its strength and elasticity. However, recent studies suggest that spider silk may have functions beyond its structural role. In particular, growing evidence indicates that spider silk can interact with microbial communities and may contribute to protective biological processes. In this study, we explored spider silk proteins using a computational peptide-mining approach to investigate whether spidroin sequences may contain hidden peptide motifs with potential antimicrobial and antiviral activity. The protein sequences used in this study were retrieved from UniProt and included aciniform, major ampullate, minor ampullate, and tubuliform spidroins from several spider species. Some of these proteins belonged to *Latrodectus geometricus*, a species previously reported in Uruguay. To explore their potential bioactive regions, was developed a computational pipeline that fragmented each protein into overlapping peptides of 20 amino acids using a sliding-window strategy. This approach generated 3,855 peptide fragments. These peptides were then screened based on physicochemical features frequently associated with antimicrobial peptides, such as positive charge, moderate hydrophobicity, and lower glycine content. Filtering identified 415 AMP-like candidate peptides. Candidate origin tracking revealed a marked enrichment of peptide candidates derived from aciniform spidroins, particularly AcSp1 proteins from *Latrodectus geometricus*. Selected candidates were further evaluated using multiple independent prediction platforms, including DBAASP, CAMP, ToxinPred, and HeliQuest, to assess predicted antimicrobial activity, antiviral potential, toxicity, hemolytic properties, and structural characteristics. A short peptide motif, **VFRAIYKRGTRK**, appeared several times among the best-ranked candidates. Different prediction platforms produced similar results for this peptide. Possible antiviral activity was predicted mainly against Zika virus, Dengue virus, and SARS-CoV-2. Toxicity and hemolysis analyses also suggested a low probability of harmful effects under the tested in silico conditions. Overall, these in silico findings point to spider silk proteins, especially aciniform spidroins, as a possible source of unexplored bioactive peptide motifs.

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Keywords: in silico analysis, spider silk, peptide-mining, bioactive peptides

Wednesday, 8 July

P02 - COMPUTATIONAL STUDY OF CARBON DIOXIDE CAPTURE BY GRAPHENE OXIDE

Paulo E. Abreu (Portugal)[1]; Joana R. C. Santos (Portugal)[1]; Jorge M. C. Marques (Portugal)[1]
1 - CQC-IMS, Department of Chemistry, University of Coimbra

Abstract

Carbon dioxide has a lot of industrial applications (used as a solvent when present as a supercritical fluid) but is one of the greenhouse gases that are present in the atmosphere, with its concentration having increased steadily since the beginning of the industrial revolution reaching a record new level in April 2026 (431ppm)[1]. There have been some studies both experimental and/or computational studying the interaction of graphene oxide (GO) with CO_2 with some promising results when using graphene oxide foams [2]. We propose to study this interaction by doing Molecular Dynamics (MD) with several models of GO containing varying amounts of epoxy or hydroxyl groups. We modeled CO_2 using the rigid Elementary Physical Model 2 (EPM2)[3] and for the various graphene oxides we used the MakeGraphitics [4] library to generate the topology in the OPLS forcefield and it was converted to GROMACS[5] format using a program developed by one of us.

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Keywords: Molecular Dynamics, Graphene Oxide, Carbon Capture and Storage

P04 - MIRA - MODELLING INSIGHTS OF REGULATORY AGING

Sofia P. Agostinho (Portugal)[1,2,3,4]; Nícia Rosário-Ferreira (Portugal)[1,5]; Irina S. Moreira (Portugal)[1,5,6,7,8]

1 - PURR.AI, Rua Pedro Nunes, IPN Incubadora, Ed C, 3030-199 Coimbra, Portugal.; 2 - Department of Bioengineering, Instituto Superior Técnico, University of Lisbon, Lisbon, Portugal.; 3 - Instituto de Telecomunicações (IT), Lisbon, Portugal; 4 - iBB – Institute for Bioengineering and Biosciences, Instituto Superior Técnico, Universidade de Lisboa, Lisbon, Portugal; 5 - CoLAB4Ageing - Sítio Paço das Escolas, Reitoria da Universidade de Coimbra, Coimbra, Portugal.; 6 - CNC-UC - Center for Neuroscience and Cell Biology, University of Coimbra, Coimbra, Portugal.; 7 - CiBB - Centre for Innovative Biomedicine and Biotechnology, University of Coimbra, Coimbra, Portugal.; 8 - Department of Life Sciences, University of Coimbra, Calçada Martim de Freitas, Coimbra, Portugal.

Abstract

Age-related neurological diseases are characterised by the progressive structural and functional degeneration of the nervous system. With a rapidly aging population, the global burden of these conditions is increasing, coupled with a lack of effective treatments. This underscores the critical unmet need for more efficient models to study aging processes, disease mechanisms, and identify potential therapeutic targets.

MIRA is designed as a robust digital assistant that supports information discovery, hypothesis generation, and strategic research planning in the context of age-related neurological disorders by leveraging methodologies that have been successfully applied in space systems engineering. Central to MIRA's approach is the integration of diverse, openly available multi-omics datasets, which, when combined with biological language models, enables the construction of a comprehensive and dynamic knowledge base focused on neurological aging.

As a central knowledge hub, MIRA facilitates multi-omics data integration and accelerates discovery, ultimately deepening our understanding of the complex biological processes that distinguish healthy aging from disease and contributing to Modelling Insights of Regulatory Aging.

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Keywords: Aging, Digital Assistant, Multi-Omics, Biological Language Models

P06 - A STRATEGY TO COUNTER ANTIBIOTIC RESISTANCE

Beatriz C. Almeida (Portugal)[1,2]; Pedro Ferreira (Portugal)[3]; Ricardo Monteiro (Portugal)[1,2]; Pedro A. Fernandes (Portugal)[3]; Didier Cabanes (Portugal)[1,2]

1 - i3S – Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Porto, Portugal; 2 - IBMC – Instituto de Biologia Molecular e Celular, Universidade do Porto, Porto, Portugal; 3 - LAQV, REQUIMTE, Departamento de Química e Bioquímica, Faculdade de Ciências, Universidade do Porto, Rua do Campo Alegre, s/n, Porto 4169-007, Portugal

Abstract

Antibiotic efficiency is declining rapidly as bacterial resistance spreads worldwide, and very few drugs have reached the market. Traditionally, antimicrobial strategies have focused on disrupting bacterial growth and viability. Although highly effective, these approaches exert strong selective pressure on microbial populations, promoting the emergence of resistant strains. Rather than focusing on therapeutics that affect bacterial viability, an alternative approach is to target virulence and resistance mechanisms that are important during infection but not essential for bacterial growth. To succeed with these novel anti-virulence strategies, it is essential to identify and characterize conserved virulence factors to enable the rational design of targeted therapeutics.

Previously, we identified the wall teichoic acid (WTA) glycosyltransferase RmlT as a determinant of virulence and antimicrobial resistance in *Listeria monocytogenes*, a major Gram-positive foodborne pathogen. More recently, we structurally characterized RmlT, revealing the catalytic architecture responsible for donor and acceptor substrate recognition. As RmlT is not essential for bacterial growth, it represents a promising target for next-generation anti-virulence and antibiotic-adjuvant strategies. The overall objective of our work is to establish WTA glycosylation as a tractable therapeutic target in Gram-positive bacteria, while contributing to the development of innovative approaches to combat antibiotic-resistant infections.

Here, we combined structural and computational biology approaches to investigate the catalytic mechanism of RmlT. From QM/MM calculations, we obtained insights about the mechanism of action of the RmlT:dTDP-Rha:PolyRobP complex. These findings advance our understanding of RmlT catalysis and support future structure-based drug design efforts.

In summary, this work targets an underexplored therapeutic pathway and provides proof of concept for anti-infective strategies targeting virulence rather than viability against antibiotic-resistant Gram-positive pathogens.

Keywords: Antibiotic resistance, QM/MM, RmlT, Listeria monocytogenes

P08 - SEQUENCE-BASED ARTIFICIAL INTELLIGENCE AND LEAKAGE-CONTROLLED BENCHMARKING FOR VIRAL PROTEIN–LIGAND INTERACTION PREDICTION

Amb Amorim (Portugal)[1,2,3,4,5]; C Marques-Pereira (Portugal)[1,2,3]; T. Almeida (Portugal)[6]; N. Rosário-Ferreira (Portugal)[4,5]; H. S. Pinto (Portugal)[6,7]; C. Vaz (Portugal)[6,8]; A. Francisco (Portugal)[6,7]; I. S. Moreira (Portugal)[1,3,5]

1 - CNC - Center for Neuroscience and Cell Biology, Center for Innovative Biomedicine and Biotechnology, University of Coimbra, Coimbra 3004–504, Portugal.; 2 - PhD in Biosciences, Department of Life Sciences, University of Coimbra, Calçada Martim de Freitas, 3000-456 Coimbra, Portugal.; 3 - Department of Life Sciences, University of Coimbra, Calçada Martim de Freitas, 3000-456 Coimbra, Portugal.; 4 - PURR.AI, Rua Pedro Nunes, IPN Incubadora, Ed C, 3030-199 Coimbra, Portugal.; 5 - CoLAB4Ageing - Sítio Paço das Escolas, Reitoria da Universidade de Coimbra, 3000-530 Coimbra, Portugal.; 6 - INESC-ID Lisboa, Lisbon, Portugal.; 7 - Instituto Superior Técnico, University of Lisbon, Lisbon, Portugal.; 8 - Instituto Superior de Engenharia de Lisboa, Instituto Politécnico de Lisboa, Portugal.

Abstract

Viruses remain a major global health challenge, whereas antiviral drug discovery is often limited by the lack of viral protein structural data. Most computational methods for identifying ligand-binding regions rely on high-quality three-dimensional models, thereby limiting their use for emerging or poorly characterised viruses. Sequence-driven artificial intelligence offers a scalable alternative for predicting interaction sites without structural information.

We developed a virus-specific deep learning framework to identify ligand-interacting residues directly from amino acid sequences and ligand descriptors. To support this work, we assembled a curated benchmark dataset derived from the Protein Data Bank containing more than 10,000 viral protein chains and approximately 13,000 filtered interaction complexes. To obtain biologically realistic performance estimates, we implemented leakage-controlled evaluation strategies based on protein sequence clustering and ligand scaffold partitioning.

Protein features were generated using transformer-based language models, including ESM2 and ProtTrans, and ligands were represented through physicochemical molecular descriptors. These features were integrated into machine learning and deep learning architectures for residue-level interaction prediction. Across multiple validation settings, multilayer perceptron models consistently outperformed gradient boosting approaches, particularly when combined with ESM2 embeddings. The models generalised effectively to unseen ligand scaffolds, whereas performance decreased more substantially for distant viral proteins, highlighting the importance of protein sequence context for interaction prediction.

This work introduces a large-scale leakage-controlled resource and a scalable sequence-driven artificial intelligence framework for viral protein–ligand interaction prediction, supporting antiviral drug discovery in settings where structural data are limited or unavailable [1].

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Keywords: viral drug discovery, viral drug–target interactions, deep learning, supervised learning, viral ligand binding site, neural networks

P10 - IMPACT OF SOLVENT EFFECTS AND CONFORMATIONAL SAMPLING ON THE NMR LONGE-RANGE JFH SPIN-SPIN COUPLING CONSTANTS

Patrick R. Batista (Brazil)[1]; Laiza B. Loureiro (Brazil)[1]; Cassia Chiari (Brazil)[1]; Cláudio F. Tormena (Brazil)[1]

1 - Institute of Chemistry, University of Campinas

Abstract

Understanding solvent effects and conformational flexibility is essential for accurately describing NMR spin-spin coupling constants (SSCC) in organic molecules. Fluorine imparts distinctive physicochemical, electronic, biological, and reactivity properties to molecules, often makingfluorinated compounds markedly different from their non-fluorinated counterparts. As a result, organofluorine compounds have become important building blocks and precursors in organic chemistry, with particularly significant applications in the pharmaceutical industry. In particular, long-range heteronuclear SSCC such as J_{FH} are highly sensitive to subtle variations in molecular geometry and electronic structure, which may arise from intramolecular conformational changes as well as from specific and nonspecific solute-solvent interactions. We investigated the transmission pathway of long-range J_{FH} in three fluorine-containing molecules: 2-fluorobenzamide (FB), *N,N*-dimethyl-2-fluorobenzamide (DMFB), and 2-fluoroacetophenone (FA). To this end, we employed *ab initio* molecular dynamics (AIMD) and metadynamics simulations with explicit solvation in DMSO. The *J*-couplings between the fluorine and hydrogen atoms from the -NH_2 and -CH_3 groups attached to the carbonyl moiety were calculated by DFT as ensemble-averaged values over AIMD-sampled configurations, including both solute and solvent molecules. The measured J_{FH} values were -2.2 Hz for FB, 0.2 and 1.2 Hz for DMFB, and 4.2 Hz for FA. Good agreement between experimental and theoretical data was obtained for FB and FA, with calculated J_{FH} of -2.3 and 4.2 Hz, respectively. This represents a significant improvement over DFT calculations based on static optimized geometries, which yielded calculated values of -7.1 and 4.5 Hz. These results highlight the fundamental role of solvent in governing the conformational sampling of these molecules and, consequently, in accurately describing their SSCC theoretically. For the DMFB, however, only one of the calculated J_{FH} values showed good agreement with the experiment, indicating that the conformational space was not adequately sampled by AIMD. To address this issue, metadynamics (MD) simulations were performed using the dihedral angle associated with rotation about the C-C bond in the [Ph]-C-C-[C=O] moiety. The NMR calculations based on configurations sampled from the MD trajectory yielded coupling values of 0.1 and 1.1 Hz in excellent agreement with experimental data. These results also represent a clear improvement over conventional DFT calculations, which yield values of 0.4 and 2.8 Hz. We also investigated the J_{FH} transmission pathways using the Natural Localized Molecular Orbital decomposition analysis. The results revealed that the J_{FH} in these fluorinated systems arise from specific orbital interactions involving fluorine lone pairs and σ-bond

orbitals. In FB, the coupling is predominantly hydrogen-bond-assisted ($^{1h}J_{FH}$), whereas in FA and DMFB it is transmitted through a mixed-orbital pathway involving methyl C-H bonds engaged in a non-conventional C-H···F hydrogen bond ($^{1h}J_{FH}$), together with contributions from C-C and C-N bonds ($^{6}J_{FH}$), leading to a different sign and magnitude of the SSCC.

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Keywords: Spin-spin coupling, NMR, Fluorine, Molecular dynamics, Metadynamics, Solvent effect

P12 - AI-ASSISTED AND PHYSICS-REFINED MODELING OF HUMAN VOLTAGE-GATED SODIUM CHANNELS FOR SELECTIVE TARGET DISCOVERY

João Pedro Boazinha (Portugal)[1]; João Pedro Carneiro (Portugal)[2]; Nuno M.F.S.A. Cerqueira (Portugal)[1]; Sérgio F. Sousa (Portugal)[1,3]

1 - LAQV/REQUIMTE – BioSIM – Department of Biomedicine, Faculty of Medicine, University of Porto, Porto, Portugal; 2 - Universidade Católica Portuguesa, CBQF - Centro de Biotecnologia e Química Fina – Laboratório Associado, Escola Superior de Biotecnologia, Porto, Portugal; 3 - CERES, BIA Lab, Department of Chemical Engineering, FCTUC, University of Coimbra, Rua Sílvio Lima, Coimbra, Portugal

Abstract

Voltage-gated sodium channels (NaVs) are membrane proteins that alternate between closed and open conformations in response to changes in membrane voltage. This transition permits Na^+ entry into excitable cells such as neurons and muscle fibers. It is fundamental for the initiation and propagation of action potentials, which support neuronal firing, muscle contraction, and electrical signaling throughout the body[1, 2].

In humans, NaV isoforms show distinct tissue distributions and biophysical characteristics that underlie their specialized functions. NaV1.1, NaV1.2, NaV1.3, and NaV1.6 are key contributors to central nervous system excitability, NaV1.4 is responsible for skeletal muscle contraction, NaV1.5 triggers cardiac action potentials, and NaV1.7, NaV1.8, and NaV1.9 are involved in peripheral pain transmission. Because of this diversity, achieving isoform selectivity remains both a major challenge and a major opportunity in drug discovery[1, 2].

A complete atomic-resolution picture of human NaV channels is still lacking, since available X-ray and cryo-EM structures are limited, missing for many isoforms, or structurally incomplete.

Here, we present a hybrid modelling approach that combines artificial intelligence with physics-based refinement to build realistic models of NaV channels in a human-like cytoplasmic environment. The workflow included: (1) generating the five best full-length structures with AlphaFold3 in association with auxiliary subunits; (2) comparing these models with those produced by AlphaFold2, Chai-1, Boltz-2, and partial experimental structures from the Protein Data Bank using RMSD values; (3) manually adjusting loops in PyMol to correct topological issues; (4) constructing a heterogeneous biomembrane with Packmol-Memgen using lipid compositions representative of human cells; and (5) refining the final systems through molecular dynamics simulations with Lipid21, and ff14SB force fields.

Overall, these results highlight structural differences among NaV isoforms that may be useful for designing compounds that selectively target specific channels while minimizing off-target effects.

This work was carried out within the support of the CERES Centre and supported by national funds from FCT through the projects https://doi.org/10.54499/UID/00102/ 2025 and https://doi.org/10.54499/UID/PRR/00102/2025. This work received financial support from the PT national funds (FCT/MECI, Fundação para a Ciência e Tecnologia and Ministério da Educação, Ciência e Inovação) through the project UID/50006/2025 DOI 10.54499/UID/50006/2025 -Laboratório Associado para a Química Verde - Tecnologias e Processos Limpos and FCT (2023.04909.BDANA)

Keywords: AI-Tools, Voltage-Gated Sodium Channel, NaV, AlphaFold

P14 - ELUCIDATING CHIRAL COMPLEXATION IN DIFFUSION-NMR WITH MULTISCALE SIMULATIONS AND MACHINE LEARNING

Tadeu Luiz Gomes Cabral (Brazil)[1,2]; Matthias Stein (Brazil)[2]; Claudio Francisco Tormena (Brazil)[1]

1 - UNICAMP; 2 - Max Planck Institute for Dynamics of Complex Technical Systems

Abstract

Enantiomers play a crucial role in pharmaceuticals, agrochemicals, and food systems due to their distinct physicochemical and biological properties; however, assigning absolute configuration remains a persistent challenge for both experimental and theoretical methods.[1] Matrix-assisted diffusion-ordered spectroscopy (DOSY), using chiral resolving agents, has emerged as a promising approach for enantiomer differentiation, although its effectiveness is often limited by subtle resolution and an incomplete molecular-level understanding.[2] In this study, we employ a chiral macrocycle (Chirabite-AR, MAC) as a resolving matrix to enhance enantiodifferentiation and enable the assignment of the absolute configuration of mandelic acid (MA) enantiomers via diffusion-NMR. ^{1}H-DOSY and selective ^{1}H-ROESY experiments were performed in $CDCl_3$ at 500 and 600 MHz. The results reveal the stereopreference of the macrocycle for (*S*)-MA, evidenced by a lower diffusion coefficient and greater shielding relative to (*R*)-MA. Computational investigations, including classical molecular dynamics, metadynamics, and density functional theory, show that this enantioselectivity arises when the macrocycle adopts a *closed* conformation rather than the expected *open* structure. Temperature-dependent NMR experiments further support a dynamic equilibrium between *open* and *closed* MAC forms, consistent with simulations. To enhance conformational sampling and capture the complex free-energy landscape, machine learning interatomic potentials were employed, enabling efficient exploration of host–guest configurations and providing deeper insight into the stability and dynamics of the complexes. Overall, the combined results demonstrate that only the *closed* MAC–MA complex accounts for both diffusion and chemical shift behavior, identifying it as the key structure responsible for enantiodifferentiation. This study highlights the critical role of conformational flexibility in chiral recognition and underscores the value of combining diffusion-NMR with advanced simulation techniques, including machine learning, to elucidate enantioselective mechanisms in solution.

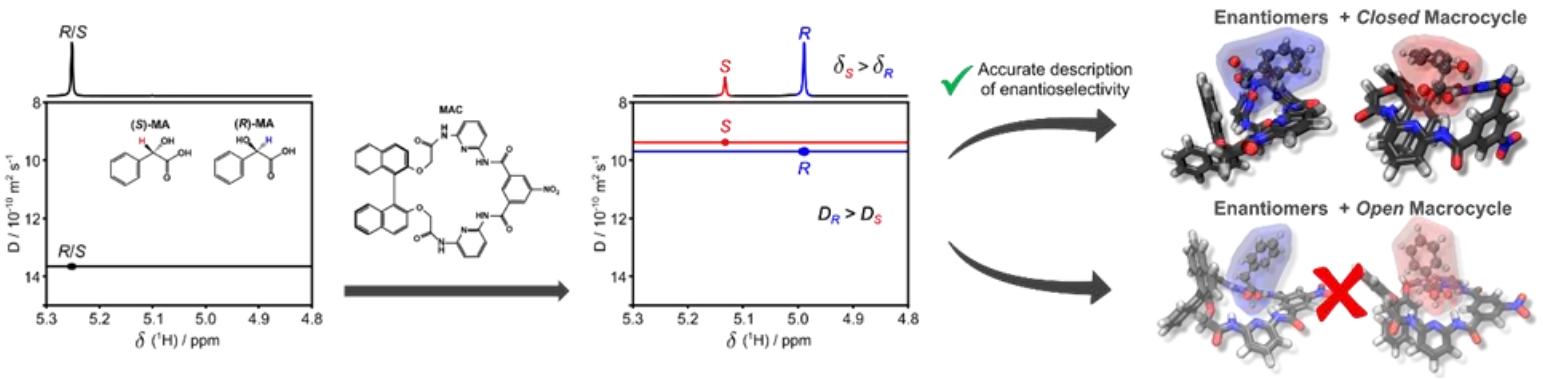

Figure: ^{1}H-DOSY of an enantiomeric mixture of mandelic acid (MA, left) and same mixture in the presence of the chiral macrocycle (MAC, middle). Low-energy structures of the complexes formed between MA enantiomers with two distinct MAC conformations (right).

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FAPESP (#2021/05081-5, 2023/07116-6, 2020/10246-0, and 2022/11152-5) and MPG

Keywords: Enantiodifferentiation, DFT, MD, MTD, MLIP, diffusion-NMR

P16 - DYNAMIC PHARMACOPHORE MODELING FOR DRUG DISCOVERY IN TREATMENT OF ALZHEIMER'S DISEASE.

Jesús Antonio González Caraballo (Colombia)[1]; Gian Pietro Miscione (Colombia)[2]; Dorian Armando Acevedo Castro (Colombia)[3]
1 - Student; 2 - Tutor; 3 - co-tutor

Abstract

Alzheimer's disease is characterized by chronic neuroinflammation and progressive neurodegeneration, where the endocannabinoid system plays a key regulatory role [1–3]. Monoacylglycerol lipase (MAGL) is a promising therapeutic target, as it hydrolyzes 2-arachidonoylglycerol (2-AG) into arachidonic acid, a precursor of pro-inflammatory prostaglandins. Thus, MAGL inhibition preserves neuroprotective 2-AG levels while reducing inflammatory mediators.

An integrated computational platform combining machine learning, structural modeling, and molecular dynamics was developed to identify potential MAGL inhibitors, incorporating dynamic pharmacophore modeling concepts [4]. Initially, 4,842 compounds were retrieved from BindingDB, and 2,132 with IC50 < 100 nM were selected. These were clustered using LigPrep (Schrödinger Maestro) with radial fingerprints, Tanimoto similarity, Ward linkage, and Kelley penalty, yielding 131 clusters.

Cluster selection was based on IC50 < 44.37 nM, structural diversity ≥ 0.373, and cluster size > 16, resulting in 18 clusters. One medoid per cluster was selected, and redundancy was reduced using an average Tanimoto similarity threshold of 0.2424. A complementary Farthest-First Traversal approach ensured structural diversity [5], leading to 12 representative clusters.

Multiple machine learning models were trained (Logistic Regression, SVC, Decision Trees, Random Forest, and MLP), applying appropriate data splitting strategies [6]. Random Forest showed the best performance (ROC-AUC = 0.9987) and was used as the primary filter.

Fifteen MAGL crystal structures were analyzed to identify key residues (5 Å cutoff), defining the extended binding pocket. The 7L4W structure was selected as the optimal receptor (pocket volume: 647.927 Å³), considering limitations of Induced Fit Docking (IFD). IFD with the 12 medoids and a positive control (4F) revealed key hydrogen bond interactions with ALA51, SER122, and MET123, while the control reproduced interactions with ARG57 and HIS121.

The best poses underwent 50 ns molecular dynamics simulations with pocket restraints, showing stable behavior. Five conformations per trajectory were extracted and used for ensemble rigid docking (XP). Finally, the YN1 scoring function was applied to prioritize compounds for ligand-based pharmacophore modeling.

The proposed workflow includes: (1) machine learning filtering, (2) ligand-based pharmacophore modeling, (3) induced fit docking, and (4) molecular dynamics

simulations. This approach improves screening reliability, captures protein flexibility, and accelerates the identification of candidates targeting neuroinflammation in Alzheimer's disease.

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Keywords: virtual screening, MAGL, Machine Learning, ligand based pharmacophore, Endocannabinoid System

P18 - ATMOSPHERIC OXIDATION OF CLOMAZONE INITIATED BY HO● RADICALS: MECHANISTIC, KINETIC, AND ECOTOXICITY STUDIES

Madhumita Chakraborty (France)[1]; Sonia Taamalli (France)[1]; Céline Toubin (France)[2]; Duy Quang Dao (Vietnam)[3]; Michal Pitoňák (Slovakia)[4]; Florent Louis (France)[1]

1 - Univ. Lille, CNRS, UMR 8522, PhysicoChimie des Processus de Combustion et de l'Atmosphère – PC2A, Lille, France; 2 - Univ. Lille, CNRS, UMR 8523, Physique des Lasers Atomes et Molécules – PhLAM, Lille, France; 3 - Institute of Research and Development, Duy Tan University, Da Nang, 55000, Vietnam; 4 - Department of Physical and Theoretical Chemistry, Faculty of Natural Sciences, Comenius University, Bratislava, Slovakia

Abstract

The extensive use of herbicides in modern agriculture raises concerns about their environmental persistence and their potential transformation into secondary pollutants. Clomazone, a widely applied pre-emergence herbicide, is frequently detected in environmental compartments due to its mobility and partial resistance to degradation. In aquatic and atmospheric systems, hydroxyl radicals (HO●) act as highly reactive oxidants, initiating degradation that can produce transformation products with altered stability and toxicity. A detailed molecular-level investigation of HO●-initiated degradation is therefore essential for accurate environmental risk assessment.

In this study, clomazone reactions with HO● were explored using density functional theory (DFT) at the M06-2X//6-311++G(d,p) level of theory in both the gaseous and aqueous phases. Aqueous-phase effects were included with the SMD implicit solvation model. Kinetic parameters were calculated for both phases. Branching ratio analysis identified dominant degradation channels, and the major secondary intermediates were subjected to successive oxidative transformations to simulate multigenerational environmental degradation, yielding thermodynamically stable end products.

Ecotoxicity of stable products was predicted using ECOSAR for acute and chronic toxicity toward fish, daphnia, and green algae, and T.E.S.T for mutagenicity, developmental toxicity, neurotoxicity, and bioaccumulation. In vitro studies suggest clomazone can inhibit acetylcholinesterase (AChE), indicating potential neurotoxic effects. To evaluate this, molecular docking and molecular dynamics simulations were performed to assess binding affinities, stability, and interaction patterns with AChE. Noncovalent interactions, including hydrogen bonding, electrostatic, and van der Waals forces, were analyzed to elucidate potential mechanism of enzyme inhibition.

This talk will present and discuss the results obtained for the clomazone herbicide.

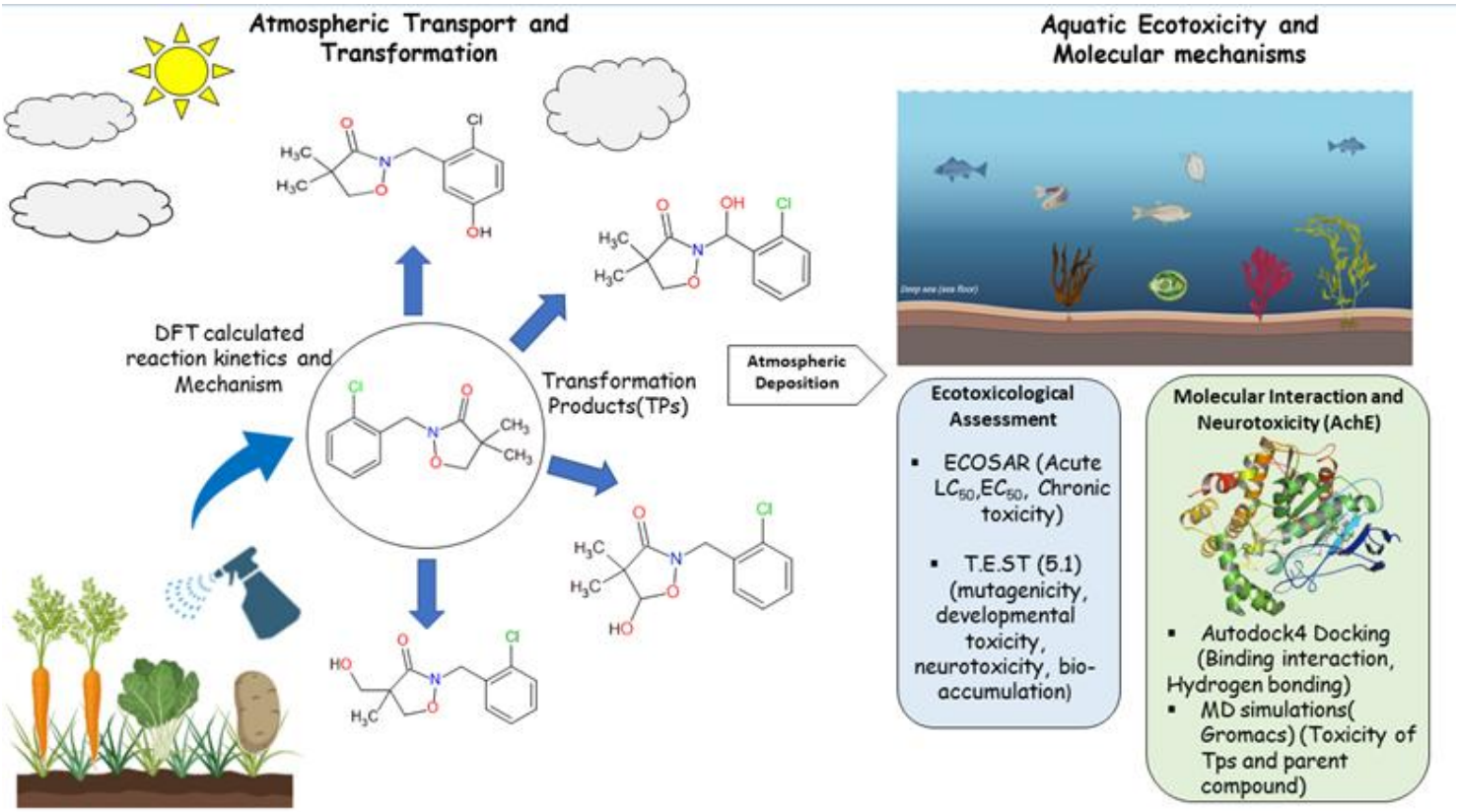

Figure 1: Atmospheric transformation, environmental fate, and ecotoxicological assessment of clomazone and its secondary pollutants

Computational resources: University of Lille and the HPC facility clara@uniba.sk at Comenius University in Bratislava.

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Keywords: clomazone; environment; contaminants; reaction mechanisms; kinetics; ecotoxicity; molecular simulations

P20 - INFLUENCE OF PROTEIN CONFORMATIONAL DYNAMICS ON CATALYTIC REACTIVITY IN PETASE

Clauber Henrique Souza Da Costa (Brazil)[1]; Sergio Martí (Spain)[2]; Vicent Moliner (Spain)[2]; Munir Skaf (Brazil)[1]

1 - Institute of Chemistry and Center for Computing in Engineering & Sciences, University of Campinas – UNICAMP. Campinas, SP 13084-862, Brazil.; 2 - Institute of Advanced Materials (INAM), Universitat Jaume I, 12071 Castelló, Spain.

Abstract

Plastics have become indispensable to modern society, yet their accumulating environmental burden constitutes one of the most pressing global crises of our time. Among the biological solutions emerging to address this challenge, PETase, an enzyme produced by the bacterium Ideonella sakaiensis, has garnered considerable attention for its capacity to degrade poly(ethylene terephthalate) (PET), one of the most widely manufactured synthetic polymers [1]. Conformational changes in PETase and its variants reveal that structural rearrangements in the enzyme may affect its catalytic efficiency, highlighting those small changes in key regions can lead to gains or losses in activity. This emphasizes the relevance of considering the entire set of accessible conformations to thoroughly understand the mechanisms of PET degradation. This work presents the first integrated analysis of PETase conformational changes and their direct impact on the catalytic mechanism. We investigate how structural modifications of the enzyme can influence the reaction mechanism in PET degradation, using molecular dynamics simulations with classical and and hybrid QM/MM potentials [2-4]. Our findings show that the substrate-free enzyme adopts multiple minimum energy states, capable of pre-organizing the active site to accomodate the substrate. Upon substrate binding, additional structural changes occur, such as active site reorganization, which are fundamental for the activation of the catalytic site and substrate stabilization. Characterizing the states appearing along the chemical steps through the generation of the Free Energy Landscape (FEL). The mechanism reaction enzyme, using PMFs withi in corretions M06-2X/6-31+G(d,p):AM1/MM simulations, revealed that the catalytic reaction can follow different conformational pathways, one of them (MC1) clearly being the most efficient in terms of energy barriers and intermediates stability for the PETase. The conformational states of the Michaelis complex directly influence the PET degradation mechanism. These structural modifications affect the stability of tetrahedral intermediates and transition states, ultimately regulating the progression of the reaction. The integrated approach adopted in this study provides valuable insights into the relationship between conformational dynamics and enzyme activity, paving the way for the optimization of biocatalysts. Furthermore, it illustrates how enzyme conformational changes can directly impact each step of the reaction process.

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Clauber H. S. da Costa: Fapesp (2022/04703-5; 2023/13707-7); Cepid-CCES (2013/08293-7); Coaraci Supercomputer Fapesp 2019/17874-0.

Research developed with access the computing resources of COARACI Supercomputer provided by Center for Computing in Engineering & Sciences (CCES - UNICAMP).

Keywords: PETase, Reaction Mechanism, Conformational Dynamics, QM/MM simulations

P22 - THEORETICAL INVESTIGATION OF TUNABLE AND REVERSIBLE REDOX-RESPONSIVE FLUORESCENT METALLOCENE-BASED PROBES

Niccolo' Dipace (France)[1]; Ilaria Ciofini (France)[1]
1 - Chimie ParisTech - PSL

Abstract

The development of biocompatible redox-reversible fluorescent probes has significant potential for the real-time detection of reactive oxygen and nitrogen species (ROS/RNS) in biological systems. This work focuses on the design of novel tunable metallocene-based probes capable of targeting specific cellular membranes and subcellular organelles. The photophysical behavior of such systems is depending on the efficiency of Photoinduced Electron Transfer (PeT), a well-known de-excitation mechanism. Designed as potent analytical sensors, the target systems typically follow a fluorophore–spacer–receptor architecture, where the PeT process facilitates the detection of redox changes.

To design and characterize new dyads, a rigorously benchmarked computational workflow combining Density Functional Theory (DFT) and Time-Dependent DFT (TD-DFT) for ground- and excited-state analysis is presented, including classical Molecular Dynamics (MD) to provide high-resolution structural and dynamical insights.

Metallocene–rhodamine dyads were initially investigated using Density Functional Theory (DFT) to evaluate their ground state electrochemical properties. Subsequent TD-DFT calculations were employed to characterize their absorption spectra and charge-transfer dynamics, revealing distinct electronic behaviors among the studied structures. Extensive conformational analyses was also performed.

Subsequently, a modified dyads featuring a hydrophobic aliphatic chain designed to enhance interaction with membrane lipid components was investigated via classical Molecular Dynamics (MD) simulations. Customized force-field parameters were also developed. The MD simulations captured a solvent-induced folding of the lipidic chain toward the dye’s aromatic core.

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Keywords: DFT, TD-DFT, MD, Fluorescent probes, Metallocene–rhodamine dyads

P24 - TUNING THE ELECTRONIC AND ANCHORING PROPERTIES OF BENZODITHIAZOLE-BASED HOLE TRANSPORT MATERIALS FOR PEROVSKITES: A DFT APPROACH

Mariana Margarido Do Amaral Fonseca (Brazil)[1]; João Paulo Cachaneski Lopes (Brazil)[2]; Augusto Batagin Neto (Brazil)[2]

1 - São Paulo State University (UNESP) -ICE/Itapeva, Brasil; 2 - São Paulo State University (UNESP) - ICE-DCT, Brasil

Abstract

The transition towards sustainable energy sources strongly drives the study of perovskite solar cells (PSCs). These devices offer high conversion efficiency, however, stability issues and inefficient charge transport at the interfaces still represent significant challenges to their large-scale production. In this work, we seek to explore chemical modifications of the terminal groups of benzodithiazole (BDT)-based hole transport materials (HTM), aiming to improve their interface with perovskite active layers. Density functional theory (DFT)-based calculations were conducted to assess the anchoring capacity of each modified structure as well their effect into the electronic structure. The results demonstrate that the inclusion of specific side groups alters the local reactivity of the molecules, particularly highlighting the potential of catecholate, 2,6-bis(iminomethyl)phenol and 2,6-bis(thiomethyl)pyridine groups as efficient anchoring centers. The electronic properties of the compounds can be modulated by the number of modified ligands. In summary, our study demonstrates the plausibility of obtaining efficient BDT-based hole transport materials with improved anchoring properties for application in perovskite solar cells.The authors thank FAPESP (Proc. 2025/22838-3, 2025/09784-1) for the financial support.

Keywords: Perovskite Solar Cells, Benzodithiazole, Density Functional Theory (DFT)

P26 - HOW CONFORMER GENERATION SHAPES COSMO-RS SOLUBILITY PREDICTIONS

André Gomes (Portugal)[1,2]; José Granjo (Portugal)[2]; Paulo Costa (Portugal)[1]
1 - BioISI - Biosystems & Integrative Sciences Institute, Ciências ULisboa; 2 - Hovione R&D, Hovione FarmaCiência S.A.

Abstract

The pharmaceutical industry is placing growing emphasis on improving efficiency, reducing costs, and accelerating drug development timelines. A key challenge in these steps is the accurate prediction of physicochemical properties such as solubility, which strongly impact compound development and bioavailability. Quantum mechanics (QM)-based methods provide detailed molecular insights and can reduce the dependence on experimental screening, but their adoption remains limited due to a traditional high computational cost. Also, the generation of appropriate molecular conformers plays a critical role in the accuracy of QM-based predictions since inadequate or poorly representative conformational sampling can introduce significant errors in calculated properties such as solubility. Consequently, robust and relevant conformer generation is essential for achieving consistent and accurate predictive performance.

In this communication, we will provide the results of a systematic evaluation of the influence of different conformer generation strategies on COSMO-RS-based predictions of solubility, while also evaluating the trade-off between computational efficiency and predictive accuracy, with a focus on enabling scalable and automated workflows [1]. The study was performed using a dataset comprising 185 commercially available molecules with experimental solubility values across a wide range of organic solvents. Using SMILES representations as the initial input, fully automated workflows, using four distinct conformer generation strategies that differ in a priori complexity and time efficiency, were implemented and tested, ranging from simple RDKit-based approaches to more elaborate semiempirical and density functional theory (DFT)-based approaches. The resulting conformations underwent DFT calculations to obtain the σ-profiles, which were subsequently used for COSMO-RS solubility predictions with openCOSMO-RS. Despite the methodological differences and varying computational costs, all workflows achieve comparable performance across the dataset, with the low-solubility regime remaining a key issue in solubility modeling. To assess sampling and solvent effects, we performed an exploratory analysis of conformer ensemble strategies and solvent-aware conformer selection for representative systems. Incorporating solvent effects during conformer selection enhances predictive accuracy for systems governed by intramolecular interactions, such as hydrogen bonding.

Overall, these findings provide practical guidance for the selection of conformer generation strategies in QM-based high-throughput COSMO-RS workflows, also highlighting solvent-aware conformer selection as a computationally efficient route to improve the robustness of solubility predictions. By integrating these methodologies, we

developed a streamlined computational pipeline that reduces manual intervention and improves compatibility between QM modeling and industrial drug discovery applications.

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Keywords: Solubility, Quantum Mechanical Calculations, COSMO-RS, Process Automatization, Pharmaceutical Industry

P28 - MOLECULAR INTERACTIONS GOVERNING CHLORPROPAMIDE INCLUSION WITHIN ALFA- AN BETA-CYCLODEXTRIN

Rodolfo Gómez-Balderas (Mexico)[1]; Emir A. Galván-García (Mexico)[1]; Luis I. Reyes-García (Mexico)[1]; Rosario Moya-Hernández (Mexico)[1]; Norma Rodríguez-Laguna (Mexico)[1]; Estrella Ramos (Mexico)[2]

1 - Laboratorio de Fisicoquímica Analítica, Unidad de Investigación Multidisciplinaria, FES Cuautitlán, Universidad Nacional Autónoma de México. Cuautitlán Izcalli, 54714, Edo. México, México.; 2 - Instituto de Investigaciones en Materiales, Universidad Nacional Autónoma de México, CU, Coyoacán, 04510 Ciudad de México, México.

Abstract

Chlorpropamide (CPM, IUPAC name 1-(4-chlorophenyl)sulfonyl-3-propylurea) is a sulfonylurea antidiabetic drug with poor water solubility. On the other hand, cyclodextrins (CDs) are cyclic oligosaccharides composed of α(1→4)-linked glucose units [1]. The naturally occurring CDs consist of six, seven, or eight glucopyranose units and are designated as α-cyclodextrin (α-CD), β-cyclodextrin (βCD), and γ-cyclodextrin (γ-CD), respectively. CPM solubility can be enhanced by complexation with either α-CD or β-CD. Given that the pKa of CPM lies between 4.6 and 4.9 [2-4], at physiological pH approximately 99% of the drug exists in its anionic form, making its study particularly relevant. Using DFT calculations at the M06-2X/6-311G(d,p)+SMD level, we investigated the inclusion complexes of neutral and anionic CPM with α-CD and β-CD in aqueous solution.

A conformational analysis of free CPM in water revealed an ensemble of low-energy conformers within 0.5 kcal mol^{-1}, coexisting prior to inclusion. Upon complexation, α-CD and β-CD stabilize different binding modes: in α-CD, the propyl chain is inside the cavity, whereas in β-CD, the aromatic ring and the sulfonylurea fragment lie within the cavity, these results agree with inclusion of tolbutamide reported by Ueda [5]. Evaluation of the stability also shows that inclusion through the secondary rim of the cyclodextrin is favored.

The inclusion complexes exhibit a network of spatially distributed weak interactions, characterized by the Independent Gradient Model (IGM) and the Quantum Theory of Atoms in Molecules (QTAIM). Notably, topological analysis of the electron density ρ(r) reveals a stark contrast between the two ionization states: for neutral CPM, stabilization arises from diffuse interaction networks rather than from strong, directional hydrogen bonds. In contrast, for the physiologically relevant anionic form CPM^-, the urea fragment acts as a common molecular anchor, establishing a directional network of hydrogen bonds that reinforces complex stability irrespective of the cyclodextrin type or binding mode.

Our results support a conformational selection mechanism, where the pre-existing ensemble of free CPM conformers in solution governs the inclusion process. These

findings provide atomistic insight into cyclodextrin–drug recognition, useful for the rational design of drug delivery systems.

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Keywords: Chlorpropamide, Cyclodextrins, Weak Interactions

P30 - THEORETICAL INVESTIGATION OF SENSING EFFICIENCY ON ZNO, WO3 AND ZNO/WO3 NANOHETEROJUNCTION: CO AND NH3 OXIDATION MECHANISMS

Lourdes Gracia (Spain)[1,2]; Felipe Lipsky (Spain)[1,4]; Rafael Ciola (Spain)[1]; Juan Andrés (Spain)[1]; Elson Longo (Spain)[3]; Isabelle Leão (Spain)[1,3]

1 - Departament of Physical and Analytical Chemistry, Universitat Jaume I, Castelló de la Plana, Spain.; 2 - Department of Physical Chemistry, University of Valencia, Burjassot, Spain; 3 - Center for Development of Functional Materials, UFSCAR, São Carlos, Brazil; 4 - Physical Chemistry Department. Institute of Chemistry, Unicamp, Brazil

Abstract

The increasing demand for real-time monitoring of environmental conditions and toxic gases has highlighted the importance of developing advanced sensor materials. Among these, semiconducting metal oxides such as ZnO or WO_3 have emerged as promising candidates due to their high sensitivity in detecting reducing gases, particularly volatile organic compounds (VOCs) in breath, low cost, and compatibility with electronic devices. Several studies demonstrated the high sensitivity and, more recently, the operability of these sensors at room temperature [1-2]. The construction of heterojunction interfaces, enables the effective establishment of an electric field at the interface, which facilitates the enhancement of charge separation, modulation of energy band structure and charge conduction at heterojunction interfaces, thus further enhancing the formation of reactive oxygen species (ROSs), thereby maintaining their strong redox capabilities [3-5]. Nevertheless, although ZnO, WO_3, and their heterostructures have made some progress in the field of gas-sensitive sensing, there are still challenges in realizing practical applications for gas detection, especially in terms of lowering the operating temperature and improving the selectivity. In this sense, Density Functional Theory (DFT) has become a crucial tool for investigating gas adsorption at the atomic level, enabling researchers to optimize material characteristics for improved sensor performance [6]. The sensing mechanism in metal oxides relies on changes in its electrical conductivity when exposed to target gas molecules: (i) in ambient air, oxygen is adsorbed on selective sites of the metal oxide surface and captures electrons from the conduction band to form ROSs (superoxide and peroxide ions); (ii) this leaves behind positively charged donors and creates of an electron-depleted region on the metal oxide surface; (iii) reducing gas molecules like CO or NH_3 react with the ROSs; (iv) this releases the trapped electrons back to the metal oxide conduction band, thereby decreasing the resistance.

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Red Española de Supercomputación (RES) projects QHS-2025-3-0042 and QHS-2025-3-0011.

Keywords: DFT, nanoheterojunction, sensor, ZnO/WO3

P32 - POLARIZABLE FORCE FIELDS IN BIOMOLECULAR ELECTROSTATICS: A REGULARIZED FEM-BEM APPROACH FOR THE POISSON-BOLTZMANN EQUATION.

Felipe Vicencio Hidalgo (Chile)[1]; Chistopher D. Cooper (Chile)[1]
1 - Universidad Técnica Federico Santa María

Abstract

Continuum models are widely used in the study of biomolecular electrostatics, for example, to model the dissolution process of a biomolecule in an aqueous medium. In this framework, the solute is represented as a low-dielectric cavity containing a charge distribution parameterized by force fields, immersed in an infinite high-dielectric continuum solvent, with the electrostatic potential governed by the Poisson-Boltzmann equation. Standard force fields use a collection of point charges to describe the charge distribution inside the biomolecules; however, polarizable force fields offer a more realistic description by incorporating high-order multipole moments and polarizability. In this work, we present a regularized Finite element method (FEM) and Boundary Element method (BEM) formulation of the Poisson-Boltzmann equation compatible with polarizable force fields within an implicit-solvent model, with particular focus on overcoming the numerical challenges introduced by higher-order multipolar sources. The electrostatic problem is solved by a coupled FEM-BEM scheme, where the solute domain is modeled by FEM while the solvent is modeled by BEM. This coupling provides flexibility for more elaborate models that consider space-varying dielectric functions and naturally accommodates the nonlinear PBE in highly charged systems. Although polarizable force fields have been coupled to the linearized Poisson-Boltzmann equation, the nonlinear form is required for highly charged systems such as RNA and DNA. The point-multipole singularities inherent to polarizable force fields introduce numerical instabilities in the FEM discretization, which affect the accuracy of derived quantities such as the electric field used in polarization calculations or the solvation energy. To overcome this, a regularized formulation of the coupled system is used, decomposing the potential into a singular and regular components. Validation against analytical solutions for the linear case demonstrates improved numerical stability and convergence of the regularized formulation compared to the standard approach, laying the groundwork for the full nonlinear extension.

Keywords: Biomolecular electrostatics, Poisson-Boltzmann equation, Polarizable force fields, Implicit-solvent model, Finite element method, Boundary elements method

P34 - MOLECULAR DYNAMICS OF A NOVEL POLYETHYLENE TEREPHTHALATE (PET) ACTIVE ENZYME MAY HAVE STRUCTURALLY DIVERGENT BEHAVIOR FROM KNOWN PETASES

Luiz Patrick Cordeiro Josino (Brazil)[1]; Clauber Henrique Souza Da Costa (Brazil)[1]; Iara Ciancaglini (Brazil)[1]; Fabio M. Squina (Brazil)[2]; Munir S. Skaf (Brazil)[1]
1 - University of Campinas; 2 - University of Sorocaba

Abstract

Plastic-active enzymes are being widely studied for chemical recycling of long-time waste accumulation of plastics, such as poly(ethylene terephthalate) (PET). PETase from Ideonella sakaiensis (IsPETase) has been a target of protein engineering since its discovery, breaking PET into its monomers. Derived from another ongoing study in our group, I1_Pazy (I1) was identified through sequence-based screening, with putative similarities in lipolytic genes in metagenomes, as a novel thermophilic PET hydrolase (Ciancaglini, I. et al., 2025). I1 shows optimal activity at 50 °C and pH 8.0, an energy barrier similar to IsPETase (WT - wild type), around 18 kcal/mol, with a Tm of 68 °C, with high-crystallinity PET. Thus, I1 can be used to design thermostable and more efficient PET hydrolases. Here, classical molecular dynamics (MD) was applied to study these systems. Crucially, we identified a previously unreported catalytic-like triad that dynamically replaces the canonical arrangement. While the classical triad dissociates under unconstrained conditions, this alternative grouping forms stable hydrogen bonds throughout the MD trajectory. RMSD analysis of I1, LCC and WT showed good alignment. As IsPETase, I1 also have two disulfide bridges at C50:C14 and C241:C244, but in different positions from WT. Similarly, in the oxyanion hole position, which are Y87' and M161' in WT, are Thr and Gln residues in I1, respectively T62 and Q131. The catalytic triad of apo system breaks its interactions without constraint, but with 50 kcal·mol^{-1}·Å^{-2}, the catalytic triad S130, H204, and D175 in 200 ns of simulation were quite stable with the applied force. Unconstrained, the approach of H129 to the catalytic serine and the repulsion of H204 is observed, in a competitive mechanism. Furthermore, the loop containing D175 was very flexible, breaking the hydrogen bond (HB) of the guanidine group that stabilizes the catalytic histidine. E152 gets close to H129 during the MD and forms a HB. At several points, simultaneous formation of the interaction between S130, H129, and E152 was noticed, and with His204 and Asp175 being very distant from both the catalytic serine and each other. We theorize that a possible triad (that might be catalytic) was forming between these three residues. With the PCA, it was possible to see that the AF3 structure fluctuates considerably more in the conformational space along the MD than the EXP structure of I1. This was confirmed by the PCA-based Free Energy Landscape (FEL), which shows convergence to at least 3 minimum energy structures with AF3, and only one with the crystal. Despite this, the predominant minimum in the AF3 MD is present in the same region of the conformational energy space as the EXP minimum structure, showing that

both converge to the same global minimum. Those structures presented an open conformation, in relation to the catalytic site cavity, with the residues of the catalytic triad. Molecular docking with the PET trimer and the MD of the complex revealed that even with constraints on the oxyanion hole (as in literature), PET dissociates from the site and I1 assumes the open conformation again. This shows us that other restrictions are necessary in those simulations. Further, we will investigate how the catalytic site actually behaves and test other synthetic polymers as a substrate for I1.

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Keywords: PET hydrolase, Molecular Dynamics, Enzyme Engineering, Plastic degradation, Catalytic triad

P36 - STRUCTURAL AND FUNCTIONAL CHARACTERIZATION OF AN AGO2 VARIANT IDENTIFIED IN CANCER CELL LINES

Minna Korkalainen (Finland)[1]; Antti Salo (Finland)[1]; Vijay Saxena (Finland)[1]; Piia Bartos (Finland)[1]

1 - University of Eastern Finland

Abstract

Argonaute 2 (Ago2) is a key component of the RNA-induced silencing complex (RISC), regulating gene expression through binding of short guide RNAs and cleavage of target mRNA. The protein consists of 859 amino acids and contains four conserved domains (PAZ, PIWI, MID, and N-terminal) as well as L1/L2 linker regions, forming a crescent-shaped structure that accommodates guide RNA binding. Catalytic activity is mediated by a conserved metal-coordinating tetrad (DEDH) located within the PIWI domain.

We have expressed Ago2 in-house using Ago2-coding mRNA derived from a cancer cell line. In addition to the full-length (wild-type) protein, we identified a variant lacking a substantial portion of the PIWI domain that does not appear to be reported in existing literature. This variant has since been detected in additional cell lines and appears to be more prevalent in cancer-derived samples compared to healthy tissue sources.

The structural and functional properties of this Ago2 variant remain unclear. Given the extent of the PIWI-domain deletion, significant structural and functional alterations are expected. As the variant originates from cancer-associated samples, its potential biological relevance is of particular interest. To investigate this, we combine experimental data with structural modeling and molecular dynamics simulations.

A preliminary structural model of the variant was constructed using AlphaFold3 [1], homology modeling, and structural information from the wild-type Ago2 protein. Model stability was assessed using short molecular dynamics simulations, followed by extended simulations of stable conformations. The goal was to evaluate how structural rearrangements influence RNA binding and whether loss of catalytic residues affects the ability to support mRNA cleavage. Comparative simulations of wild-type and variant proteins were performed to identify structural and dynamic differences.

Molecular dynamics simulations were carried out using the AMBER ff19SB force field for proteins and the OL3 force field for RNA [2]. Systems were solvated in explicit water using the OPC model and neutralized at physiological ionic strength (0.15 M). All simulations were energy-minimized, equilibrated, and heated to 310 K. To enhance conformational sampling and reduce bias toward local minima, multiple independent 500 ns simulations were performed, complemented by adaptive sampling strategies in which under-sampled conformational states were used to initiate subsequent simulations [3].

Preliminary results suggest that, despite the truncation of the PIWI domain, residual structural elements may undergo rearrangements around the catalytic magnesium ion that could partially preserve features associated with catalytic activity. These findings

provide a basis for further investigation into the functional implications of Ago2 isoforms and their potential relevance in disease contexts such as cancer.

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Keywords: Argonaute 2 (Ago2), AMBER, PIWI domain, Protein-RNA interactions, Cancer biology

P38 - PREDICTING APTAMER-PROTEIN ASSOCIATION BY COMBINING AI-BASED METHODS AND PHYSICS-BASED APPROACHES

Félix Dias (Portugal)[2]; Sérgio Sousa (Portugal)[3]; Elisa Leitner (Austria)[1]
1 - Elisa Leitner; 2 - Félix Dias; 3 - Sérgio F. Sousa

Abstract

Aptamers are synthetic, singlestranded DNA or RNA oligonucleotides capable of folding into complex secondary and tertiary structures.^1 These three-dimensional shapes allow them to bind to a wide spectrumnof targets, including proteins and small molecules, with high affinity and specificity.

Aptamers have multiple uses, including disease diagnostics, bioassays and tissue staining. They are also a compelling alternative to monoclonal antibodies, with multiple advantages to the later, like high thermal stability, higher modifiability, lower manufacturing costs, shorter generation time and no batch-to-batch variability.

A comprehensive structural understanding of aptamer-target interactions remains a challenge, as traditional discovery via SELEX yields only sequence data and lacks 3D structural insights.

Consequently, computational approaches are emerging as essential alternatives to streamline Discovery and characterize binding mechanisms.^2

Here, we explore and evaluate multiple hybrid modeling workflows that combine artificial intelligence with physics-based methods to predict aptamer-protein complexes directly from FASTA sequences. To identify the most robust predictive pipeline, our ongoing comparative testing includes: (1) generating initial complex structures using various AI co-folding platforms^3 ; (2) comparing these AI-generated models against traditional data-driven docking approaches, such as HADDOCK; and (3)

validating the structural stability and interaction dynamics of the predicted complexes through molecular Dynamics (MD) simulations using standard biomolecular force fields.

Overall, this comparative work aims to determine the optimal combination of deep-learning structural generation and classical physical simulations. Ultimately, we seek to establish a reliable, high-throughput computational framework for aptamer discovery and optimization.

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P40 - MIXED METAL OXIDES IN GAS PHASE: THE STUDY OF THE FEALO3+ AND AL2O3+ CLUSTERS

Tatiana C. Penna (Germany)[2,3]; Vicente Zamudio-Bayer (Germany)[4]; J. Tobias Lau (Germany)[4]; Knut R. Asmis (Germany)[2,3]; Joachim Sauer (Germany)[1]; Michael Roemelt (Germany)[1]; Lucas W. De Lima (Germany)[1]

1 - Humboldt-Universitaet zu Berlin; 2 - Wilhelm-Ostwald Institut für Physikalische und Theoretische Chemie, Universität Leipzig; 3 - Fritz-Haber-Institut der Max-Planck-Gesellschaft; 4 - Abteilung fuer Hochempfindliche Roentgenspektroskopie, Helmholtz-Zentrum Berlin fuer Materialien und Energie

Abstract

Elucidating the atomistic structure of active sites in heterogeneous catalysis remains a fundamental challenge, owing to their intrinsic complexity and dynamic nature under operating conditions. The study of those systems involves techniques such as matrix isolation and gas-phase clusters, which enable detailed structural and electronic characterisation at the molecular level. In the realm of gas-phase clusters experiments, the investigation of mixed metal oxide catalysts uses state-of-the-art action spectroscopy approaches, where mass-selected ions (emulating the catalyst's active site) are characterised by techniques such as infrared photodissociation spectroscopy (IRPD) and X-ray absorption spectroscopy (XAS) [1]. Aluminium oxide (alumina) is a prototypical oxide material widely employed in heterogeneous catalysis, both as an active phase and as a support, due to its chemical and physical properties. The incorporation of transition metals into the alumina framework has emerged as an effective strategy to tailor catalytic performance, for instance, in isobutane synthesis [2]. In this regard, the study of the active site of iron-doped alumina is pivotal to understanding its catalytic activity. Herein, FeAlO3+ and AlO3+ clusters were investigated as model systems for iron-doped alumina active sites by combining IRPD and XAS with electronic structure calculations. Structural assignment is achieved through comparison of experimental spectra with simulated harmonic infrared and X-ray absorption spectra at the oxygen K-edge. The results indicate that the measured cluster adopts a "key-like" structural motif exhibiting a C2v symmetry.

Further insight into the electronic structure is obtained from X-ray absorption spectroscopy at both the oxygen K-edge and iron L-edge. The combined analysis reveals that $FeAlO_3^+$ is best described as an oxyl species with a general septet spin state, in which the iron centre is in the +3 oxidation state.

These findings afford a detailed atomistic picture of a prototypical iron-doped alumina motif, highlighting the power of combining action spectroscopy with simulations to resolve structure–property relationships in complex oxide systems. This work provides fundamental insights into the nature of the active sites in mixed metal oxides and establishes a framework for the rational design of improved catalytic materials.

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Keywords: Theoretical spectroscopy, Infrared spectroscopy, X-ray absorption spectroscopy, Mass spectrometry, Gas phase cluster chemistry

P42 - IN SILICO ENGINEERING OF PEPTIDE LIGANDS FOR CONTROLLED ENZYME IMMOBILISATION ON G-C_3N_4

António Carvalheira (Portugal)[1]; Benedita Machado (Portugal)[1]; Mariana Figueiredo (Portugal)[1]; Tânia Tavares (Portugal)[2]; Carla Teixeira (Portugal)[3]; Sérgio Sousa (Portugal)[4,5]
1 - Faculty of Engineering, University of Porto, Porto, Portugal; 2 - LEPABE, ALiCE, Faculty of Engineering, University of Porto, Porto, Portugal; 3 - REQUIMTE-LAQV, Faculty of Pharmacy, University of Porto, Portugal; 4 - REQUIMTE-LAQV, BioSIM, Faculty of Medicine, University of Porto, Portugal; 5 - CERES, BIA Lab, Department of Chemical Engineering, FCTUC, University of Coimbra, Portugal

Abstract

Enzyme immobilisation is a widely used strategy to improve enzyme stability, reusability, and operational performance in biocatalytic processes. However, conventional immobilisation methods often results in partial loss of enzymatic activity due to the random orientation of enzymes on the support surface. Graphitic carbon nitride (g-C_3N_4) has emerged as a promising support material due to its high surface area, chemical stability, and tunable surface functionality. The introduction of molecular ligands onto the g-C_3N_4 surface may improve enzyme orientation and catalytic accessibility by promoting specific interactions between the enzyme and the immobilisation matrix.

In this study, a computational approach was developed to rationally engineer selective immobilisation supports for proteolytic enzymes. The approach is being developed using two distinct enzymatic targets as test cases: Cardosin A, a plant-derived aspartic protease from *Cynara cardunculus* L., and Alcalase, a commercial microbial serine protease. The approach starts with the creation of 3D models of the enzymes, using X-ray crystallography data complemented when necessary, with AI-based protein structure prediction methods. Cavity-based approaches such as Fpocket are then employed to identify putative binding cavities on the distal side of the enzymes, opposite to the active site, not to interfere with their normal proteolytic activity. A library of approximately 9000 known peptides was then screened against each enzyme through structure-based virtual screening (GOLD software, PLP scoring function). Top-scoring peptides were structurally characterised. The results provide a set of candidate peptide ligands with predicted favourable binding modes for each enzyme, supporting the development of rational immobilisation strategies for these proteases on g-C_3N_4 surfaces by peptide-based functionalization of these surfaces.

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Keywords: Enzyme immobilisation, Graphitic carbon nitride, Molecular docking, Cardosin A, Alcalase, Ligand selection

P44 - INVESTIGATING THE ROLE OF VACANCY ENGINEERING IN ENHANCING POLYSULFIDE ANCHORING AND CONVERSION ON DOUBLE MO2TI2C3O2 MXENE

Fredy Mamami Gonzalo (Brazil)[1]; Nicolas Ferreira Martins (Brazil)[1]; Lucas Ferreira Neto (Brazil)[1]; José Artigas Dos Santos Laranjeira (Brazil)[1]; Victor José Ramirez Rivera (Brazil)[1]; Julio Ricardo Sambrano (Brazil)[1]

1 - Modeling and Molecular Simulation Group, São Paulo State University (UNESP), School of Sciences, Bauru, 17033-360, SP, Brazil

Abstract

Lithium-sulfur batteries (LSBs) have emerged as promising energy-storage technology due to the low cost of sulfur and their high theoretical energy density [1]. However, efficient anchoring materials capable of capturing lithium polysulfides (LiPSs) and catalyzing their conversion are essential to accelerate charge-discharge kinetics and suppress the shuttle effect [2]. MXene-like materials are attractive candidates for LSBs owing to their high electrical conductivity and abundant catalytic sites. Double-ordered MXenes such as $Mo_2Ti_2C_3$ have been synthesized through different routes as promising new structures within this class of materials [3]. However, there are no reported studies regarding their potential application in lithium–sulfur batteries (LSBs). Here, we investigate, through first-principles calculations, the O-terminated $Mo_2Ti_2C_3$ MXene, since oxygen is the predominant surface termination after synthesis. Additionally, to better understand the feasibility of this MXene in practical applications, we introduced lattice defects, namely single vacancies (V_{Mo}, V_{Ti}, V_C, and V_O). Our results confirm the efficient anchoring ability of the pristine MXene, with adsorption energies ranging from −1.39 to −3.39 eV, which are superior to those of commonly used electrolytes such as DME and DOL (−0.72 to −0.89 eV). On the other hand, defective $Mo_2Ti_2C_3O_2$ MXenes significantly strengthens the interaction with lithium polysulfides, particularly in the presence of V_{Mo} and V_O vacancies, where adsorption energies reach −6.06 and −7.25 eV for the Li_2S cluster, respectively. Gibbs free energy profiles indicate that, despite the stronger binding, defective MXenes do not hinder reaction kinetics. On the contrary, the rate-determining steps (RDS) are lower for defective structures than for the pristine MXene, highlighting the beneficial role of single vacancies in enhancing polysulfide conversion on $Mo_2Ti_2C_3O_2$ MXenes.

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Keywords: MXene, defects, lithium-sulfur, DFT, polysulfide

P46 - IN SILICO DISCOVERY AND OPTIMIZATION OF SELECTIVE LIGANDS FOR TARGETED PROTEIN DEGRADATION IN MACHADO-JOSEPH DISEASE

Fábio G. Martins (Portugal)[1,2]; Filipe Rocha (Portugal)[3]; Fernanda Borges (Portugal)[4,5]; Patrícia Maciel (Portugal)[6,7]; Sérgio F. Sousa (Portugal)[2,8]

1 - Rise-Health, School of Medicine and Biomedical Sciences (ICBAS), University of Porto, Porto, Portugal; 2 - LAQV/REQUIMTE, BioSIM, Department of Biomedicine, Faculty of Medicine, University of Porto, Alameda Professor Hernâni Monteiro, Porto, Portugal; 3 - . LAQV/REQUIMTE, BioSIM, Department of Biomedicine, Faculty of Medicine, University of Porto, Alameda Professor Hernâni Monteiro, Porto, Portugal; 4 - Rise-Health, Department of Chemistry and Biochemistry, Faculty of Sciences, University of Porto, Campo Alegre, 4169-007 Porto, Portugal; 5 - Rise-Health, Department of Biomedicine, Faculty of Medicine, University of Porto, Porto, Portugal; 6 - Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Braga, Portugal; 7 - ICVS/3B's - PT Government Associate Laboratory, Guimaraes, Braga, Portugal; 8 - . CERES, BIA Lab, Department of Chemical Engineering, FCTUC, University of Coimbra, Rua Sílvio Lima, Pólo II – Pinhal de Marrocos, 3030-790 Coimbra, Portugal

Abstract

Machado-Joseph Disease (MJD) is a fatal neurodegenerative disorder caused by the expansion of a polyglutamine (polyQ) tract in the Ataxin-3 protein, leading to toxic intracellular aggregation. Current therapeutic strategies are limited, requiring novel approaches for the elimination of toxic protein species[1,2].

In this work, full atomistic models of wild-type and mutant Ataxin-3 were constructed by integrating experimental structural data with AlphaFold-generated models. These were validated via 1 µs molecular dynamics (MD) simulations performed with Amber 18[3]. Clustering analysis followed to identify dominant conformations. Pocket-hunting algorithms, such as DeepSite[4], Fpocket[5] or CASTp[6], were employed to locate mutant-selective cavities. A virtual screening protocol was executed, using GOLD[7], on a library of around 90,000 compounds. This was followed by pharmacophore-base refinement, to optimize pocket complementarity and PROTAC linker compatibility.

A selective pocket was identified at the Josephin Domain/polyQ interface. Notably, MD simulations revealed a top-performing ligand migrating to a previously undiscovered, highly stable cavity involving residues Gln154 and Gln324. This cavity offers an ideal orientation for the attachment of a PROTAC linker.

Overall, this study establishes a robust computational framework for the identification of mutant-selective binding sites in Ataxin-3. The discovery of a stable, selective cavity and compatible scaffolds lays the foundation of the development of the first PROTAC-based therapy for MJD. Future work will leverage advanced AI-generated protein models to further validate and optimize these discoveries.

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Keywords: MD simulations, Machado-Joseph Disease, AI-generated Models

P48 - CYANOBACTERIAL PEPTIDES AS DUAL ACHE/BCHE INHIBITORS FOR ALZHEIMER'S DISEASE: AN IN SILICO SCREENING APPROACH

Rita Biltes (Portugal)[1,2]; Tatiana Melo (Portugal)[1,3,4]; Tânia Tavares (Portugal)[3]; Isabel Cunha (Portugal)[2]; Sérgio F. Sousa (Portugal)[4,5]; Carla S. S. Teixeira (Portugal)[1]; Isabel Mafra (Portugal)[1]

1 - REQUIMTE/LAQV, Faculty of Pharmacy, University of Porto, Portugal; 2 - CIIMAR/CIMAR, University of Porto, Portugal; 3 - LEPABE, ALiCE, Faculty of Engineering, University of Porto, Porto, Portugal; 4 - REQUIMTE/LAQV, BioSIM, Faculty of Medicine, University of Porto, Portugal; 5 - CERES, BIA Lab, Department of Chemical Engineering, FCTUC, University of Coimbra, Portugal

Abstract

Cyanobacteria are ubiquitous photosynthetic microorganisms found in diverse environments with high protein content (50–70%), being related as sustainable sources of bioactive compounds. Among these, bioactive peptides have attracted increasing attention for their therapeutic potential. Acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) are key enzymes involved in cholinergic signalling and their dysregulation is associated with Alzheimer's disease (AD). While AChE plays a central role in acetylcholine hydrolysis, elevated BChE levels have been linked to amyloid-β plaque formation. As both enzymes contribute independently to AD progression, dual inhibition represents a promising therapeutic strategy. In this study, an *in silico* protocol was developed to identify cyanobacteria-derived peptides with dual AChE/BChE inhibitory potential. A total of 450 proteins from 17 cyanobacterial species and strains were subjected to simulated gastrointestinal digestion to generate peptide libraries. These peptides were screened using molecular docking (GOLD software, PLP scoring function) against human AChE (PDB ID: 4EY7) and human BChE (PDB ID: 5NN0). Top-scoring peptides (normalised score > 2.5; score difference −3 to +3 to ensure dual inhibitory activity) were further evaluated for toxicity, intestinal permeability, and blood–brain barrier (BBB) penetration using pepADMET. A subset of 149 peptides was prioritised, of which 69 showed moderate to good Caco-2 permeability (−5.99 to −4.381 log cm/s), supporting their potential for intestinal absorption. Regarding BBB permeability, only four peptides were predicted not to cross the barrier, while the remaining candidates showed moderate to high permeability. Based on permeability, toxicity, and occurrence in commonly consumed cyanobacteria, six peptides (EQPDL, QPAAW, QDVVK, IQW, IATQH, and GAEEF) were selected for molecular dynamics simulations. Peptides demonstrating strong binding affinity will be synthesised and subjected to *in vitro* validation to confirm their inhibitory activity. Overall, this study highlights cyanobacteria as a sustainable and promising source of dual cholinesterase inhibitory peptides with favourable predicted pharmacokinetic properties.

This work was funded by national funds (FCT/MECI) through projects INSPIRE (2024.14868.PEX), REQUIMTE (UID/50006/2025), LEPABE (UID/00511/2025), and ALiCE (LA/P/0045/2020). R. Biltes acknowledges the support of a PhD grant (2025.02540.BD).

Keywords: Edible cyanobacteria, Bioactive Peptides, Molecular Docking, Alzheimer's disease

P52 - MECHANISTIC AND KINETIC MAPPING OF HYDROXY-2-PYRIDONES AS REPAIR AGENTS FOR TYROSYL AND TRYPTOPHANYL RADICALS

Leonardo Muñoz-Rugeles (Colombia)[1]; Juan Raúl Alvarez-Idaboy (Mexico)[2]
1 - Universidad Industrial de Santander; 2 - Universidad Nacional Autónoma de México

Abstract

Oxidative damage to proteins often proceeds through tyrosyl and tryptophanyl radical intermediates, which can trigger irreversible cross-linking and loss of function. Here we computationally assess four mono-hydroxylated 2-pyridones (OH at C3, C4, C5, or C6) as "repair" agents for Tyr(−H)•, Trp(−H)•, and Trp•+ in aqueous solution, and we map how OH position and acid–base speciation control mechanism and rate.

All electronic-structure calculations were performed with DFT at the M05-2X/6-31+G(d,p) level, including thermal corrections at 298.15 K. Solvent effects of water were modeled with the SMD continuum approach. Minima and transition states were characterized by frequency analysis (NIMAG = 0/1) and intrinsic reaction coordinate checks when needed. Thermochemical screening was used to identify the most favorable repair channels, focusing on formal hydrogen transfer (FHT) and single-electron transfer (SET). For exergonic pathways, overall rate constants were obtained with the QM-ORSA protocol, explicitly correcting for physiological pH 7.4 through computed pK_a values and mole fractions of neutral/anionic species; SET barriers were analyzed within Marcus theory, including solvent reorganization contributions.

The results predict that three pyridones can repair Tyr(−H)•, and two are fast enough to compete with dityrosine formation (~10^8 M^{-1} s^{-1}): the C3 and C5 isomers reach k_{total} = 2.24×10^8 and 1.17×10^8 M^{-1} s^{-1}, respectively. Tyr repair proceeds through proton-coupled electron transfer (PCET), and a sequential proton-gain/PCET (SPG-PCET) route is identified for the C6 isomer, whose activity at pH 7.4 is limited by speciation (k_{total} = 9.19×10^5 M^{-1} s^{-1}). For tryptophan, all four pyridones reduce Trp•+ predominantly via a proton–electron sequential transfer (PEST) manifold; the C6 anion dominates the kinetics (k_{total} = 6.96×10^7 M^{-1} s^{-1}), whereas the remaining isomers are ~10^5 M^{-1} s^{-1}, suggesting limited suppression of Trp–Trp cross-linking in small peptides. Overall, hydroxy-2-pyridones emerge as promising scaffolds for designing radical-repair antioxidants, and the mechanistic/kinetic framework provides quantitative criteria to guide further optimization.

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JRA-I acknowledges the support of DGTIC at Universidad Nacional Autónoma de México through the Grant No. LANCAD UNAM-DGTIC-192 project.

Keywords: Hydroxy-2-pyridones, Radical repair, Proton-coupled electron transfer (PCET), Density functional theory (DFT), QM-ORSA kinetics, Tyrosyl and tryptophanyl radicals

P56 - STRUCTURE-BASED IDENTIFICATION OF SMALL-MOLECULE NORA INHIBITORS THAT RECAPITULATE FAB-BINDING MOTIFS

Festus Ogungbemiro (Portugal)[1]; Vera Isca (Portugal)[1]; Patricia Rijo (Portugal)[1,2,3]; Daniel Dos Santos (Portugal)[1,2]

1 - CBIOS, Center for Research in Biosciences and Health Technologies, Universidade Lusófona, Lisboa, Portugal; 2 - Research Institute for Medicines (iMed.ULisboa), Faculty of Farmacy, Universidade de Lisboa, Lisboa, Portugal; 3 - Center of Structural Chemistry, Institute of Molecular Sciences, University of Lisbon, Lisbon, Portugal

Abstract

The NorA efflux pump of *Staphylococcus aureus* plays a central role in resistance to hydrophilic fluoroquinolones, making it an attractive target for efflux pump inhibitor (EPI) discovery. Recent cryo-EM structures of NorA complexed with Fab25 (PDB: 7LO7) and Fab36 (PDB: 7LO8) revealed conformationally distinct inhibitory states, with Fab36 exhibiting deeper binding and ~9-fold stronger affinity [1]. Leveraging these structural insights, this study employed a dual-strategy computational workflow to identify small molecules capable of replicating Fab-mediated inhibition. NorA–Fab25 and NorA–Fab36 complexes were prepared and superimposed to define a consensus inhibitory hotspot across TM4, TM5, TM7, TM8 and TM10. Both Fab-defined and full-pore docking grids were generated, enabling orthosteric and channel-blocking exploration. A curated set of 114 reference NorA inhibitors was docked using QVina to validate grid performance, followed by complex-based pharmacophore modeling derived directly from Fab36 interactions. Three pharmacophore hypotheses were constructed and screened against 2.54 million ChEMBL compounds [2], yielding filtered hit candidates predicted to reproduce key Fab contacts with Asn137, Phe140, Glu222, Phe303 and Asp307.

Top-ranked hits will be subjected to experimental validation using *S. aureus* 1199 (wild-type; basal NorA expression) and 1199B (quinolones resistante; NorA-overexpressing) strains. Planned assays include MIC determination, EtBr accumulation and efflux inhibition, SYTOX-Green membrane-permeability profiling, cytotoxicity and selectivity index evaluation, time-kill kinetics, synergy determination via checkerboard FIC, qRT-PCR/Western blot analysis of NorA expression, and resistance-induction studies. This integrated computational-experimental approach aims to identify potent, selective, novel, and non-cytotoxic NorA-Fab-mimetic inhibitors capable of restoring quinolone susceptibility and overcoming efflux-mediated resistance in *S. aureus*.

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Keywords: NorA Efflux Pump, Fab-Mimetic Inhibitors, Quinolone Resistance, Pharmacophore Modeling, Molecular Dynamics Simulation, Structure-Based Drug Design

PO58 - INTERCHANGEABLE META- AND PARA-SELECTIVITY IN PD-CATALYZED C–H FUNCTIONALIZATION REACTIONS USING NONCOVALENT INTERACTIONS

Daniel A. Santos Oliveira (Brazil)[1,2]; Ataualpa Braga (Brazil)[1]; Diego C. Araujo (Brazil)[1]
1 - University of São Paulo; 2 - Vrije Universiteit Amsterdam

Abstract

The use of molecular templates capable of exploiting noncovalent interactions to achieve *meta*- or *para*-selectivity in aryl C–H functionalization reactions has received significant attention in recent years. [1] In this work, [2] we provide a detailed computational study, based on Density Functional Theory, on the use of urea-based molecular templates in palladium-catalyzed aryl C–H functionalization to afford *meta*- or *para*-olefinated products Our initial tests focused on the molecular template developed experimentally by Li and coworkers [3] to achieve *meta*-olefinated carbonyl-containing products. The directing template has been shown to be essential in lowering activation barriers as well as in controlling selectivity, enabling a clear distinction between *ortho*- and *meta*-C–H activation barriers. Our studies on the origin of regioselectivity suggest that hydrogen bonds between the urea protons and the carbonyl moiety of the substrates favor *ortho*-selectivity over *meta* and *para*. In contrast, *meta*-selectivity is governed by secondary interactions between the urea substituent and the catalyst, which are enhanced by the phenyl substituent.

After understanding the origins of selectivity, we focused on template modifications to achieve para-selectivity by weakening both the secondary interactions, which can be accomplished by introducing a bulky substituent on the urea moiety, and the hydrogen bonds at the *ortho* position, which can be achieved by increasing the length of the template.

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Keywords: C–H olefination, Noncovalent interactions, Palladium, Catalysis, DFT

P60 - T-RAMD STUDY OF PET FRAGMENT RELEASE BY PETASE FROM IDEONELLA SAKAIENSIS: IMPLICATIONS FOR ENZYME ENGINEERING

Maycon Oliveira (Brazil)[1]; Jerônimo Lameira (Brazil)[1]; F. Javier Luque (Spain)[2]
1 - Universidade Federal do Pará; 2 - University of Barcelona

Abstract

Plastics currently are one of the major fractions of solid waste released by human activity into the environment, leading to increasing environmental deterioration. A major critical issue is the presence of microplastics, which have been detected in animals and humans. Therefore, there is a growing need for biodegradable strategies to minimize the impact of these materials. To this end, we evaluated the kinetic parameters associated with the release of a PET fragment from the PETase enzyme, aiming to provide mechanistic insights for the design of engineered enzymes with enhanced catalytic activity. The τ-RAMD (τ-Random Acceleration Molecular Dynamics) method was employed to investigate the dissociation process, analyzing release pathways, residence time (τ), and dissociation rate constant (k_{off}), which is estimated to be 6.2×10^7 s^{-1}. This indicates a fast product release, consistent with efficient catalytic turnover. Despite variability among trajectories, a consistent dissociation behavior was observed, involving multiple unbinding pathways. During dissociation, the catalytic site becomes progressively exposed, and key residues such as Ser160 and His237 are highlighted as they become accessible for binding of a new substrate molecule, enabling the polymer degradation cycle. This approach allows evaluation of how structural modifications affect the balance between substrate affinity and product release, contributing to the design of more efficient PET-degrading enzymes.

The authors thanks the Fundação Amazônica de Amparo a Estudos e Pesquisas (FAPESPA), the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) for additional financial support and the PDSE project. The authors also acknowledge the Centro de Servicios Científicos y Universitarios de Cataluña (CSUC, Barcelona) for providing access to high-performance computing facilities, and the Coari Supercomputing Center (COARACI), Universidade Estadual de Campinas (UNICAMP), for computational resources and technical support.

Keywords: Biodegradation; Residence time; Dissociation rate constant

P62 - ASYMMETRIC DOUBLE-WELL POTENTIALS ALLOWING CONFLUENT HEUN WAVE FUNCTIONS

Jose Peña (Mexico)[1]; Javier Morales-Tellez (Mexico)[2]; Jesús García-Martínez (Mexico)[3]; Jesús García-Ravelo (Mexico)[2]; Jesús Morales-Rivas (Mexico)[1]

1 - Universidad Autónoma Metropolitana Azc; 2 - Instituto Politécnico Nacional, ESFM, Secc. Graduados; 3 - TecNM-Tecnológico de Estudios Superiores de Ixtapaluca, División de Ingeniería Biomédica

Abstract

In this work, by an appropriate generating function, the confluent Heun differential equation is transformed into a Schrödinger-like differential equation, thus identifying a multi-parameter exponential-type potential [1]. Particularly, families of hyperbolic potentials are also obtained. Indeed, we found that a suitable selection of the parameters involved gives rise to solvable one-dimensional double-well asymmetric potentials which, together with the tunneling effect, play a relevant role in the study of different quantum chemical systems [2]. Unlike symmetric double well potentials, this type of asymmetric wells are useful in quantum chemistry for modeling systems where particles can move between two sites with different potential energies. Such asymmetry along with information entropy (Shannon-Fisher) to measure uncertainties, can be used to explain the localization-delocalization effect of particles in this type of wells [3]. The method can be extended to obtain triple-well potentials that could be useful as interaction models in quantum chemistry and Brownian diffusion processes where the diffusion motion is better described in triple-well potential than in potentials with simple or double wells [4].

Keywords: Asymmetric double-well, Heun functions, Schrödinger-like equation

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Keywords: Asymmetric double-well, Confluent Heun functions, Schrödinger-like equation

P64 - MOLECULAR INSIGHTS INTO MICROHYDRATED DNA BASES: FROM COOPERATIVE STABILIZATION TO KINETIC REGULATION OF TAUTOMERISM

Murillo Halo Queiroz (Brazil)[1]; Tiago Vinicius Alves (Brazil)[1]; Roberto Rivelino (Brazil)[1]
1 - Universidade Federal da Bahia

Abstract

In DNA, hydrogen bonds determine base pairing, maintain tautomeric equilibria, and also mediate interactions with surrounding water and ions, governing its physicochemical properties and its biological function. In this work, we employ hybrid (B3LYP-D3(BJ)) and meta-hybrid (M06-2X) density functional approximations, combined with the Quantum Theory of Atoms in Molecules (QTAIM) and Time-Dependent DFT (TD-DFT) to investigate microhydrated clusters of Thymine [1] and 2,4-Dithiothymine (n = 1 to 3 water molecules). [2] Hydrogen bond interaction energies were estimated using a density based approach developed in our group.[3] A saturation threshold for cooperative hydrogen bonding was observed at four water molecules hydration, where the electronic density (ρH-bond) at critical points becomes stabilized.[1] Regarding tautomerization, we found that while a two-water "proton-wire" lowers the enol-to-keto barrier to 4.3 kcal/mol, a third water molecule acts as a kinetic regulator, increasing the barrier to 5.5 kcal/mol. [2] This structural modification, where the ring compromises its aromatic character in favor of intermolecular stabilization, indicates that certain hydration patterns may prolong the lifetime of rare tautomers. In 2,4-dithiothymine,[4] we demonstrate that sulfur substitution shifts the absorption to the UVA window (~360 nm) and creates a triplet trap stabilized by Baird-aromaticity. This stabilization persists under microhydration.

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Keywords: Microhydration, DNA tautomerism, QTAIM, Kinetic regulation

P66 - SHANNON AND RÉNYI ENTROPIES OF MOLECULAR DENSITIES UNDER ATOMIC PARTITIONING: INSIGHTS INTO EXTENSITY AND AN INCOMPLETE DESCRIPTION OF ELECTRON CORRELATION

Diogo J. L. Rodrigues (Portugal)[1]; Angél Martín Pendás (Spain)[1]; Evelio Francisco (Spain)[1]
1 - Department of Physical and Analytical Chemistry, Faculty of Chemistry, University of Oviedo, Av. Julian Claveria 8, 33006 Oviedo, Spain

Abstract

In this work we demonstrate, using the particular case of entropic descriptors based on classical information theory, that static correlation in molecules is not accurately contained within electron-density based objects. Traditional descriptors relying solely on the electron-density thus fall fundamentally short in multi-reference scenarios. Our findings suggest that higher-dimensional Hilbert-space objects should be used to build accurate descriptors of electron correlation.

We investigate the reliability of information-theoretic measures based on the electron-density and shape-function, specifically Shannon and Rényi entropies, as descriptors of electronic correlation. By establishing a rigorous decomposition of these entropic measures into additive and nonadditive contributions, supported on a Mulliken-like atomic partition of molecules, we systematically analyze the asymptotic behavior of the entropies at the infinite-internuclear-distance limit to assess the problem of static correlation and extensivity. Our algebraic and numerical analysis reveals several flaws in the use of these density-based descriptors. We demonstrate that for minimal-basis and different theoretical levels, the Shannon and R\'enyi entropies fail to encode the amount of static correlation conveyed by the underlying wavefunction. Conversely, shape-function Shannon entropies and Rényi entropies (for $\alpha \neq 1$) violate extensivity.

In larger basis sets, uncorrelated Hartree-Fock densities consistently overestimate entropy compared to sufficiently correlated (e.g., full-valence-CAS) densities. Moreover, the entropies for insufficiently correlated methods violate extensivity. These findings indicate that electron-density-based measures are insufficient for capturing static correlation, suggesting that robust entropic descriptors should be constructed from higher-dimensional Hilbert-space objects.

(This work as been accepted for publication in: International Journal of Quantum Chemistry)

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Keywords: Shannon Entropy, Rényi Entropy, Static Correlation, Extensivity, Shape Function, Information Theory

P68 - A COMPUTATIONAL INVESTIGATION OF GAS-PHASE AND MODEL ICE-SURFACE REACTIONS OF S(1D) WITH WATER AND METHANOL AND IMPLICATIONS FOR COSMOCHEMISTRY/ASTROCHEMISTRY

Marzio Rosi (Italy)[1]; Andrea Giustini (Italy)[1]; Gabriella Di Genova (Italy)[2]; Dimitrios Skouteris (Italy)[3]; Cecilia Ceccarelli (France)[4]; Albert Rimola (Spain)[5]; Nadia Balucani (Italy)[6]
1 - Department of Civil and Environmental Engineering, University of Perugia; 2 - Department of Chemistry Biology and Biotechnologies, University of Perugia; 3 - Master-Tec s.r.l.; 4 - Université Grenoble Alpes, CNRS, IPAG; 5 - Departament de Quimica, Universitat Autonoma de Barcelona, Catalunia; 6 - nadia.balucani@unipg.it

Abstract

The chemistry leading to interstellar sulphur-bearing organic molecules is still in need to be fully characterized. Sulphur is present in space with an abundance of 16 ppm and it is an interesting element for prebiotic chemistry since it is present in amino acids and several other biomolecules. Simple S-containing species, such as OCS, CS, CH_3SH, H_2CS, as well as C_2S and C_3S, have been detected in a variety of objects. More complex sulphur species have been detected in the coma of the comet 67P/Churyumov-Grasimenko, such as CH_4OS, C_2H_6OS, C_3H_6OS and CH_4S_2.

In this contribution, we present a theoretical investigation of two reactions involving atomic sulphur in its first electronically excited state, ^1D, with two molecules, water and methanol, which are abundant in interstellar/cometary ice. S(^1D) can be produced on the ice surface by UV-induced photodissociation of precursor molecules, such as OCS, that is, one of the few molecules for which a secure identification in interstellar ice has been provided. The ^1D state is metastable with a long radiative lifetime and is very reactive, differently from the case of the ground ^3P state of atomic sulphur.

The role of electronically excited metastable atoms in the ice chemistry has been recently considered in the research groups of Oberg and Herbst for the similar case of atomic oxygen. According to those studies, the formation of O(^1D) opens up new reaction pathways which are not amenable in the case of the O(^3P) reactions. According to our results, the SO(a $^1\Delta_g$) + H_2 channel is the only open channel for the S(^1D) + H_2O reaction, while many channels are open for the S(^1D) + CH_3OH reaction. For the latter case, statistical estimates of the product branching fractions indicate that the main channels are those leading to CH_2OH + SH, H_2CO + H_2S, H_2CS + H_2O, and CH_3 + HSO. The mechanism of the related O(^1D) + CH_3SH reaction has also been unveiled.

To gain some insight into the possible effects of additional water molecules, as in ice or liquid water matrices, we have also analyzed how the two reactions behave when four, and then eighteen, additional water molecules are added. The conclusion is that the initial intermediates formed by the insertion or addition mechanism − namely HOSH (hydrogenthioperoxide) and H_2OS for S(^1D) + H_2O and CH_2OHSH (mercaptomethanol), CH_4OS and CH_3OSH (methyl thioperoxide) for S(^1D) + CH_3OH, as well as CH_3SOH (methyl

sulfenic acid) for $O(^1D) + CH_3SH$ − will probably be stabilized by the interaction with the additional water molecules.

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Keywords: Astrochemistry, Ab initio methods, Density Functional Theory, Sulphur, Interstellar Medium

P74 - CONSTANT-PH MOLECULAR DYNAMICS: ACCURACY AND REPRODUCIBILITY

João G. N. Sequeira (Portugal)[1]; Ana T. Figueiredo (Portugal)[1]; Nuno F. B. Oliveira (Portugal)[1]; Miguel Machuqueiro (Portugal)[1]
1 - University of Lisbon - BioISI

Abstract

Constant-pH molecular dynamics (CpHMD) enables the explicit coupling between protonation-state sampling and molecular dynamics simulations, providing a powerful framework to investigate pH-dependent biomolecular processes. Despite its relevance, broader adoption of CpHMD remains limited by methodological challenges that affect both simulation accuracy and computational accessibility.

In the stochastic titration CpHMD method, Poisson–Boltzmann calculations are used to evaluate protonation-state transitions, making the method particularly sensitive to the Lennard–Jones (LJ) radii employed in the electrostatic model. Since the radii currently used were originally derived for older force fields, they may not optimally represent modern biomolecular parameter sets. We are therefore systematically evaluating alternative LJ radii for the supported force fields.

To further improve reproducibility and portability, we have also developed a containerized CpHMD workflow integrating established tools such as GROMACS and DelPhi within an Apptainer environment, enabling consistent execution across heterogeneous HPC infrastructures, including ARM-based systems.

Together, these efforts aim to improve the accuracy, robustness, and accessibility of CpHMD simulations, strengthening the methodological foundation for pH-dependent molecular modeling in the broader theoretical chemistry community.

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Keywords: Constant-pH Molecular Dynamics, High-Performance Computing (HPC), Poisson–Boltzmann

P76 - ELUCIDATING THE DFG-FLIP CONFORMATIONAL LANDSCAPE OF GSK-3B TO VALIDATE GENERATIVE AI-DESIGNED INHIBITORS VIA MOLECULAR DYNAMICS SIMULATIONS

Daniel S. De Sousa (Brazil)[1]; Albérico B. F. Da Silva (Brazil)[1]
1 - University of São Paulo - USP

Abstract

Glycogen synthase kinase 3 beta (GSK-3β) remains a critical yet challenging therapeutic target for neurodegenerative disorders, cancer, and diabetes due to the difficulty in achieving kinase selectivity. We successfully deployed generative artificial intelligence (GenAI) and quantum mechanics-based deep learning (QSAR/DFT) models to design novel GSK-3β inhibitor candidates. To overcome off-target liabilities associated with the highly conserved ATP-binding site, targeting the inactive "DFG-out" conformation (Type II inhibition) offers a viable strategy. In this continuation study, we aimed to dynamically validate our GenAI-designed compounds by mapping the conformational landscape of the GSK-3β DFG motif (Asp200-Phe201-Gly202) and evaluating ligand stability within the DFG-out state. We conducted extensive Molecular Dynamics (MD) and enhanced sampling simulations (Well-Tempered Metadynamics) to capture the thermodynamically challenging DFG-flip. Structural transitions were tracked over 500 ns by monitoring key geometric parameters, including the Activation Loop and P-Loop RMSD, the αC-β3 distance, F201 χ_1 and χ_2 dihedral distributions, and the critical regulatory salt bridges (K85-E97 and K85-D200). The Free Energy Surface (FES), mapped along the Asp200 ψ and Phe201 ϕ dihedral angles, demonstrated convergence and revealed distinct thermodynamic minima, successfully capturing the stable DFG-out conformation. The isolated DFG states (in/out) was subsequently utilized to test both known literature inhibitors and the novel GenAI-derived candidates. Trajectory analysis confirmed that the designed molecular entities maintain favorable interaction profiles, structural stability, and binding modes comparable to reference compounds. These findings structurally validate our deep learning-driven drug design pipeline and provide a dynamic rationale for the prioritization of these novel GSK-3β candidates for further preclinical evaluation.

Suggested Reading / References:

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Keywords: GSK-3B, GenAI, Metadynamics, Inhibitors, Neurodegenerative disorders, Cancer

P80 - A BOND OVERLAP PERSPECTIVE ON JAHN–TELLER DISTORTIONS IN TRANSITION METAL COMPLEXES

L. C. A. Pontes (Brazil)[1]; C. V. Santos (Brazil)[1]; B. M. T. C. Peluzo (Brazil)[1]; E. Kraka (Brazil)[1]; R. T. Moura Jr (Brazil)[1]

1 - Federal University of Paraíba (UFPB), Brazil

Abstract

The Jahn–Teller (JT) effect introduces significant changes in electronic structure and bonding patterns. Systems affected by these distortions require appropriate theoretical models for their study. The bond overlap (OP) model and its topological extension (TOP) have been successfully applied to elucidate chemical bonding, as previously demonstrated in studies of triphenol systems and 4f orbital excitation processes in lanthanides. In this work, we apply the OP/TOP method to analyze bonding in two sets of complexes with experimental evidence of the JT effect. The complexes studied include $[Cr(OH_2)_6]^{3+}$, $[Cr(OH_2)_6]^{2+}$, $[Fe(CN)_6]^{4-}$, and $[Fe(CN)_6]^{3-}$. We also evaluate recent developments in the Chemical Bond Overlap Software (ChemBOS), designed for OP/TOP bonding analysis, with particular emphasis on its ability to process MCSCF wavefunctions. Wavefunctions of the complexes were calculated using Density Functional Theory (DFT) and Complete Active Space Self-Consistent Field (CASSCF) methods with the ORCA package. Chemical bonding was assessed using OP/TOP methodologies in ChemBOS and QTAIM. The results show that OP/TOP descriptors consistently capture bonding changes associated with JT distortions, including pronounced elongations in the Cr(II) complex and slight contractions of Fe(III) bonds. Overall, this approach provides a reliable description of bonding variations induced by the JT effect.

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