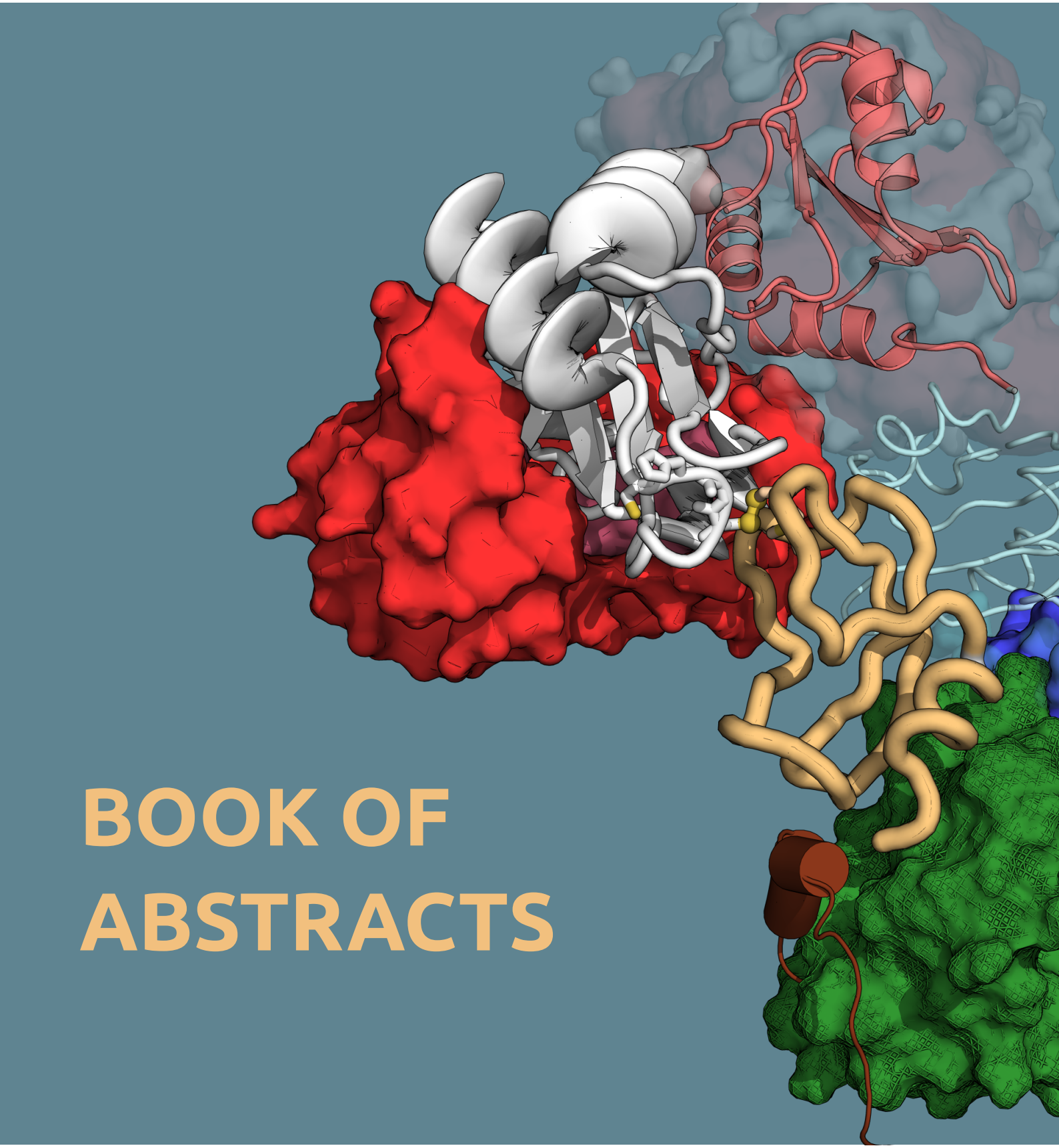
THEOBIO2026
FUNCHAL, MADEIRA

10TH THEORETICAL BIOPHYSICS
INTERNATIONAL SYMPOSIUM

18-22 OCTOBER



BOOK OF ABSTRACTS

LAQV requimte
LABORATÓRIO ASSOCIADO PARA A QUÍMICA VERDE

U.PORTO

Madeira. Belongs to all

Chemistry Europe
European Chemical Societies Publishing

Sociedade Portuguesa de Química



THEOBIO2026

FUNCHAL, MADEIRA

BOOK OF ABSTRACTS

10TH THEORETICAL BIOPHYSICS INTERNATIONAL SYMPOSIUM

FUNCHAL · MADEIRA · PORTUGAL

18-22 OCTOBER 2026

Organized by LAQV,REQUIMTE · University of Porto

LAQV requimte
LABORATÓRIO ASSOCIADO PARA A QUÍMICA VERDE

U.PORTO

Madeira. Belongs to all

Chemistry Europe
European Chemical Societies Publishing

Sociedade Portuguesa de Química

Welcome message

Dear Colleague,

The organizing committee of the 10th Theoretical Biophysics International Symposium welcomes you to Madeira, Portugal. We wish all participants an enjoyable and fruitful meeting.

The scientific programme of this symposium was chosen to stimulate a valuable discussion that could be able to involve all the different fields here represented. We hope that the warm climate of Madeira could further potentiate this free exchange of opinions.

We further hope that it will promote scientific debate that extends far beyond the five days scheduled for this meeting.

Thank you for being with us in Madeira.



Sincerely,
Maria João Ramos
On behalf of the organizing committee.



All rights reserved: ® Carlos Gouveia
Image used with permission

Scientific Committee

Carlo Adamo, Institute of Chemistry for Life and Health Sciences, France

Francesca Mocci, Università degli Studi di Cagliari, Italy

Leif Eriksson, Göteborgs Universitet, Sweden

Maria João Ramos, Universidade do Porto, Portugal

Nino Russo, Università della Calabria, Italy

Xabier Lopez, Euskal Herriko Unibertsitatea, Spain

Organizing Committee

Alexandre Pinto

Ana Rita Calixto

António Ribeiro

Joana Silva

João Coimbra

João Sousa

Juliana Amorim

Luís Teixeira

Maria João Ramos

Pedro Fernandes

Pedro Ferreira

Pedro Paiva

Rodolfo Caeiro

Rui Neves



All rights reserved: ® Nuno Dias
Image used with permission

Preface

The 10th edition of the Theoretical Biophysics Symposium (TheoBio 2026) will be held from 18th-22nd October 2026, at the Hotel Meliá Madeira Mare in Funchal (Madeira Island, Portugal).

TheoBio is a long-standing symposium that brings together leading researchers covering a broad spectrum of topics in theoretical biophysics and theoretical & computational biochemistry/biology.

Building on the successful tradition of TheoBio symposiums held in Donostia, Örebro, Cetraro, Roscoff, Funchal and Cagliari, the TheoBio 2026 edition will host 36 talks from leading researchers working on the modelling of complex biomolecular processes, from protein dynamics and engineering to enzyme reactivity and drug design/kinetics. You can also expect selected invited talks by leading experimentalists, in an effort to tighten the bond between theory and experiment. Over 60 poster communications will also be presented at TheoBio 2026, and the top three poster communications will receive prizes sponsored by Chemistry Europe.

Please visit our website at https://theobio2026.com for further information.



All rights reserved: ® Francisco Correia
Image used with permission

Table of Contents

Welcome message i

Scientific Committee iii

Organizing Committee iii

Preface iv

Event Info 2

General Information *3*

Map *3*

Programme at a Glance *4*

Detailed Programme *5*

Social Programme *7*

Invited Lectures 8

Poster Session 1 – Porto 46

Poster Session 2 – Madeira 78

List of Participants 110

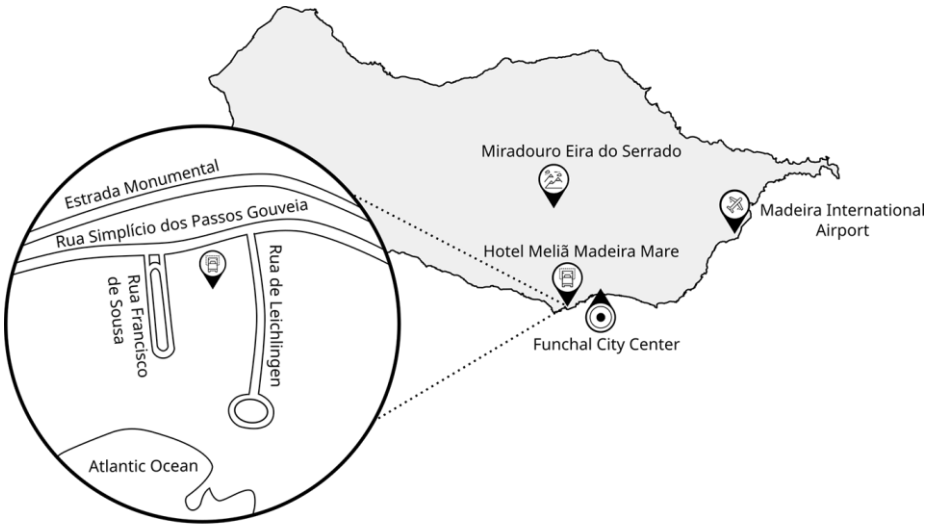
Sponsors 114

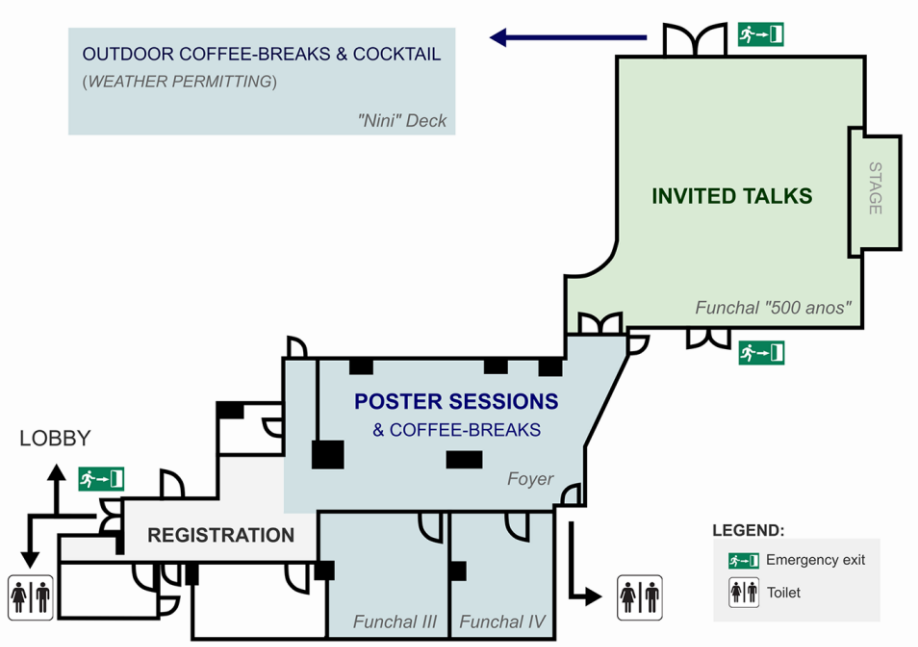
Event Info

General Information

Venue	Hotel Meliá Madeira Mare, Funchal, Madeira, Portugal
Dates	Sunday 18 – Thursday 22 October 2026
Registration desk	Sun 18 Oct (from 14:00); daily from 08:30 to 09:00
Hotel Contact Details	+351 291724140 or melia.madeira@meliaportugal.com
Emergency	112 (European emergency number)
Organisation Contact	info@theobio2026.com

Map





Programme at a Glance

	October 18	October 19	October 20	October 21	October 22
08:30		**registration**			
09:00		Michele Parrinello	Stefan Grimme	Modesto Orozco	Sílvia Osuna
09:30		Christophe Chipot	Ilaria Ciofini	Alessandra Magistrato	Maria Fátima Lucas
10:00		Umberto Raucci	Tanja van Mourik	Stacey Wetmore	Xiang Sheng
10:30		**coffee break**			
11:00		Paolo Carloni	Iñaki Tuñón	William Jorgensen	Adrian Mulholland
11:30		Tiziana Marino	Rong-Zhen Liao	Carme Rovira	Ulf Ryde
12:00		Miguel Machuqueiro	Mario Prejanò	Marco De Vivo	Xabier Lopez
12:30		Ana Cunha	Angela Parise	Marta Alberto	Carlo Adamo
13:00		**lunch break**			**closing session**
13:30					
14:00					
14:30		Peter Westh	Feliu Maseras	David Peralta *Chemistry Europe*	
15:00		Vicent Moliner	Jaroslav Burda		
15:30	**registration**	Nathalie Reuter	Francesca Mocci	*poster prize award*	
16:00		Michele Cascella	Jens Preben Morth	*bus departure*	
16:30		**poster session 1**	**poster session 2**	*Visit to Miradouro da Eira do Serrado*	
17:00	**opening and reception**				
17:30					
18:00		*Ocean-side walk to Praia Formosa*	*Guided walk - Funchal historic centre*	*Gala Dinner at Eira do Serrado*	
18:30					

Detailed Programme

Sunday, 18 October

Time	Speaker	Title	Ref.
14:00 – 17:00	Registration		
17:00 – 18:30	*Opening session & Welcome Reception*		

Monday, 19 October

Time	Speaker	Title	Ref.
08:30	Registration		
Session 1 · 09:00–10:30			
09:00	Michele Parrinello	A Principled Approach to Enhanced Sampling	IL01
09:30	Christophe Chipot	Learning Rare Events: Do We Still Need Enhanced Sampling?	IL02
10:00	Umberto Raucci	Unraveling Enzymatic Reactivity with Probability-Based Simulations	IL03
10:30	Coffee break		
Session 2 · 11:00–13:00			
11:00	Paolo Carloni	*Multiscale simulations of neuroreceptors*	IL04
11:30	Tiziana Marino	Deciphering Allosteric Regulations Using Molecular Dynamics Simulations: the case of ADLH2	IL05
12:00	Miguel Machuqueiro	Computational Methods to Model pH Effects in Biomolecules	IL06
12:30	Ana Cunha	Targeted cancer therapies via membrane-active peptidic Anchors	IL07
13:00	Lunch break		
Session 3 · 14:30–16:30			
14:30	Peter Westh	Kinetics of heterogeneous enzyme reactions	IL08
15:00	Vicent Moliner	Computation-Guided Design of Novel Enzymes for the Recycling and Upcycling of Synthetic Polymers	IL09
15:30	Nathalie Reuter	Allosteric control of lipid transfer proteins by membrane lipids	IL10
16:00	Michele Cascella	Antimicrobial peptide activity by induced lipid dynamics – new insights on functional mechanisms by combined experimental and computational investigation	IL11
16:30 – 18:00	Poster Session 1 – Porto · coffee break		
18:00	*Ocean-side walk to Praia Formosa*		

Tuesday, 20 October

Time	Speaker	Title	Ref.
08:30	Registration		
Session 4 · 09:00–10:30			
09:00	Stefan Grimme	Making Quantum Chemistry Fast Enough: Dispersion and Tight-Binding for Large Systems	IL12
09:30	Ilaria Ciofini	Adaptable Range Separated Hybrids for the description photophysical properties	IL13
10:00	Tanja van Mourik	Halogen bonding to aromatic systems	IL14
10:30	Coffee break		
Session 5 · 11:00–13:00			
11:00	Iñaki Tuñón	Phosphoanhydride Hydrolysis from Solution to Biomolecular Motors: Insights from Machine Learning Potentials and QM/MM Simulations	IL15

Time	Speaker	Title	Ref.
11:30	Rong-Zhen Liao	QM and QM/MM Exploration of C–H Activation in Radical Enzymes	IL16
12:00	Mario Prejanò	Enantioselectivity in Enzymes: Challenges for Modelers	IL17
12:30	Angela Parise	Beyond the Static Structure: Decoding the Regulatory Logic of Rho GTPases via QM/MM and MD simulations	IL18
13:00	Lunch break		
Session 6 · 14:30–16:30			
14:30	Feliu Maseras	Computing the barrier for single electron transfer in enzymatic catalysis and beyond	IL19
15:00	Jaroslav Burda	Thioredoxin Reductase: PAET from NADP to diCys redox center and blocking of the Cys-Sec second redox site	IL20
15:30	Francesca Mocci	Get into the (Minor) Groove: How Polyamines Dance, Hug, and Bond with DNA	IL21
16:00	Jens Preben Morth	EnZight: A web server for structure-guided identification of additive substitutional hotspots in enzymes	IL22
16:30 – 18:00	Poster Session 2 – Madeira · coffee break		
18:00	*Guided Walk - Funchal historic centre*		

Wednesday, 21 October

Time	Speaker	Title	Ref.
08:30	Registration		
Session 7 · 09:00–10:30			
09:00	Modesto Orozco	Exploring the mutiple faces of nucleic acids	IL23
09:30	Alessandra Magistrato	Molecular Mechanism of Natural and Artificial Ribozymes	IL24
10:00	Stacey Wetmore	Reading Between the Bases: Understanding Nucleic Acid Modifications Through Multiscale Modeling	IL25
10:30	Coffee break		
Session 8 · 11:00–13:00			
11:00	William Jorgensen	Evolution of Computer-Aided Drug Discovery	IL26
11:30	Carme Rovira	Unexpected Catalytic Strategies in Carbohydrate-Active Enzymes	IL27
12:00	Marco De Vivo	Decoding Biochemical Complexity with Simulations and AI-Enhanced Sampling	IL28
12:30	Marta Alberto	Light-Driven Mechanisms in Anticancer Phototherapy: Mode Switches, Coligand Effects and Membrane interactions	IL29
13:00	Lunch break		
14:30 – 15:30	David Peralta	AI Tools in Publishing and Research: Best Practices and Examples	Sponsor Talk
15:30 – 16:00	Poster prizes		
16:30 – 18:00	*Visit to Miradouro da Eira do Serrado*		
from 18:00	*Gala Dinner*		

Thursday, 22 October

Time	Speaker	Title	Ref.
08:30	Registration		
Session 9 · 09:00–10:30			
09:00	Sílvia Osuna	Allosteric network reprogramming for rational enzyme design	IL30
09:30	Maria Fátima Lucas	How Much Physics Do We Really Need to Design an Industrial Enzyme?	IL31

Time	Speaker	Title	Ref.
10:00	Xiang Sheng	Mechanism-Guided Reprogramming of Enzyme Functions	IL32
10:30	Coffee break		
Session 10 · 11:00–13:00			
11:00	Adrian Mulholland	Multiscale simulation for protein design and enzyme evolution: from drug resistance to biocatalysis	IL33
11:30	Ulf Ryde	Development and testing of QM/MM calculations	IL34
12:00	Xabier Lopez	Environment-dependent sticker strength in biomolecular condensates from simulations and quantum chemistry	IL35
12:30	Carlo Adamo	Noncovalent weak interactions with DFT: from molecules to biogenic crystals	IL36
13:00 – 13:30	**Closing session**		

Social Programme

Mon 19 Oct: Ocean-side walk to Praia Formosa

A relaxed walk along Madeira's beautiful Atlantic coastline to Praia Formosa, offering spectacular ocean views and a chance to unwind after the scientific sessions. An opportunity to enjoy the island's coastal scenery while continuing conversations with the TheoBio participants in an informal setting.

Tue 20 Oct: Walk at Funchal centro histórico

Discover the history and character of Funchal on a guided walk through its historic centre. Along the way, we will explore some of the city's most emblematic streets, squares and landmarks, while learning about the people, traditions and events that have shaped Madeira's capital over the centuries. A relaxed opportunity to experience Funchal beyond the conference venue in the company of the TheoBio participants.

Wed 21 Oct: Visit to Miradouro da Eira do Serrado, followed by the Gala Dinner

A private coach will take us through Madeira's spectacular mountain scenery to the Miradouro da Eira do Serrado, with breathtaking views over the dramatic peaks and Curral das Freiras valley below. This visit will take place on the way to the Gala Dinner and is therefore reserved for participants who have registered to attend it. The TheoBio2026 Gala Dinner will offer fine food and drink, lively conversation, and celebration. The bus trips should take around 45 minutes.

Invited Lectures

A Principled Approach to Enhanced Sampling

Florian M. Dietrich, Michele Parrinello*

Fondazione Istituto Italiano di Tecnologia

* Presenting author

Molecular Dynamics simulations are a valuable tool for investigating a wide variety of phenomena at the atomistic scale. However, it is this very high resolution that limits the time scales accessible to such simulations. Typically, this difficulty is alleviated by deploying methods that require knowledge of the system's metastable states and an approximation of the reaction coordinate, referred to as a collective variable.

Here, we propose a new enhanced sampling method which requires neither. We build our approach on the observation that in rarely occurring events like phase transition or protein folding processes, there is a trade-off between enthalpy and entropy. It is rare fluctuations in these quantities which eventually result in a transition.

Thus, we describe the state of the system via the distributions of single particle energies or of appropriately defined per-atom entropies. We then devise an algorithm that favours sampling the distribution tails, thus facilitating high-energy barrier crossing and the discovery of new states, with null or minimal prior knowledge of the system. We demonstrate the generality of our approach by successfully simulating protein folding, ligand binding to receptors, and crystallising an undercooled metal melt starting just from the unfolded state, the apo state, and the liquid state respectively.

Learning Rare Events: Do We Still Need Enhanced Sampling?

Chris Chipot*

CNRS
University of Illinois at Urbana-Champaign and University of Chicago
* Presenting author

Rare molecular transitions underlie essential biological processes but are notoriously difficult to capture atomistically. I will present a unified, committor-based machine-learning framework that addresses both the mechanisms and kinetics of rare biomolecular events without relying on hand-crafted reaction coordinates. First, I will introduce Gen-COMPAS, a generative committor-guided path-sampling method combining denoising diffusion models with committor-based filtering to reconstruct transition pathways, transition-state ensembles, and free-energy landscapes from endpoint structures with remarkably little aggregate sampling. I will then present a variational multistate committor network that extends the committor concept to networks of metastable states. Trained on finite-lag trajectory data, it learns state-resolved commitment probabilities and identifies transition regions, dominant pathways, effective kinetic networks, transition rates, and mean first-passage times, while providing diagnostics for incomplete state decompositions. Applications to mini-protein folding, peptide isomerization, ion-channel gating, and molecular-motor rotation demonstrate that these generative and variational approaches can recover both mechanistic detail and long-timescale kinetic organization. Together, they point toward a new paradigm in biophysical modeling: using AI to learn the geometry of rare transitions and the kinetic architecture of metastable-state networks directly from molecular data.

References

[1] A. Megías, S. Contreras Arredondo, C. G. Chen, C. Tang, B. Roux, and C. Chipot, 'Iterative variational learning of committor-consistent transition pathways using artificial neural networks', Nat. Comput. Sci., vol. 5, pp. 592–602, 2025.
[2] C. G. Chen, C. Tang, A. Megías, R. A. Talmazan, S. C. Arredondo, B. Roux, and C. Chipot, 'Following the committor flow: A data-driven discovery of transition pathways', J. Chem. Theory Comput., vol. 22, pp. 1258–1265, 2026.
[3] S. C. Contreras Arredondo, C. Tang, R. A. Talmazan, A. Megías, C. G. Chen, and C. Chipot, 'Learning the committor without collective variables', Nat. Comput. Sci., vol. 6, pp. 350–357, 2026.
[4] C. Tang, M. P. Pandey, C. G. Chen, A. Megías, F. Dehez, and C. Chipot, 'Breaking Timescales with Generative Sampling of Conformational Transitions', Nature, 2026, in press. doi: 10.48550/arXiv.2510.24979.

Funding and acknowledgments: C.C. acknowledges the European Research Council (project 101097272 "MilliInMicro"), the Université de Lorraine through its Lorraine Université d'Excellence initiative, the Région Grand-Est (project "Respire"), and the Métropole du Grand Nancy (project "ARC"). M.P.P. acknowledges the funding from the Agence Nationale de la Recherche (ANR, Pestipenta ANR-21-CE11-0016). The authors are indebted to Professors Benoît Roux (University of Chicago), John Baenziger (University of Ottawa), and Daniel Zuckerman (Oregon Health & Science University), as well as Drs. Radu Talmazan and Sergio Contreras Arredondo (Université de Lorraine) for fruitful discussions. D.E. Shaw Research (DESRES) is also gratefully acknowledged for provision of reference molecular dynamics trajectories.

Unraveling Enzymatic Reactivity with Probability-Based Simulations

Umberto Raucci*, Sudip Das, Alessandro Berselli, Rui Neves, Maria J. Ramos, Michele Parrinello
Italian Institute of Technology
* Presenting author

In complex biomolecular environments, catalytic events arise from ensembles of fluctuating structures, and often enzymatic efficiency depends on how probability and reactive flux are distributed across competing pathways. Here, we present a probability distribution-based view of enzymatic reactivity, in which catalytic activity is understood not from a single transition state structure or minimum free energy pathway, but from the ensemble of reactive configurations.

A machine learning-based committor framework provides a practical route to this description [1,2]. By sampling transition state ensembles and weighting configurations according to their contribution to reaction dynamics, the method helps identifying the molecular degrees of freedom that control catalytic activity [3].

This perspective is illustrated through two enzymatic systems. In human pancreatic α-amylase, the hydrolysis of maltopentaose is shaped by competing pathways that differ in subtle hydrogen-bond and water arrangements within the catalytic pocket [3-5]. These fluctuations modulate the probability of productive transition state configurations and therefore influence the reaction rate.

In plastic-degrading enzymes, this committor-derived information was used to propose new mutations to reshape the distribution of reactive flux, favor more productive catalytic pathways, and improve enzymatic activity [6].

Together, these examples show how probability-based simulations can transform mechanistic insight into enzyme design principles. By revealing which configurations dominate the reaction flux and how mutations redistribute their statistical weight, the committor framework provides a transferable strategy for engineering novel enzymes.

References

[1]. Kang P., Trizio E., Parrinello M., Nat. Comput. Science, 4, 451, 2024
[2]. Trizio E., Kang P., Parrinello M., Nat. Comput. Science, 5, 582, 2025
[3]. Das S., Raucci U., Trizio E., Kang P., Neves R., Ramos M., Parrinello M., ACS Catal., 15, 9785, 2025
[4]. Das S., Raucci U., Neves R., Ramos M., Parrinello M., ACS Catal., 13, 8092, 2023
[5]. Das S., Raucci U., Neves R., Ramos M., Parrinello M., PNAS., 121, e2416621121, 2024
[6]. Berselli A., Trizio E., Raucci U., Ramos M., Menziani C., Muniz Miranda F., Parrinello M., Chem, 12, 103201, 2026

Multiscale simulations of neuroreceptors

Paolo Carloni*

Jülich Research Centre

* Presenting author

In this talk, we will focus on simulations (from quantum to coarse grain) of key steps of the accumulation and release of one of the most important neurotransmitters, in the human brain, the glutamate. We will conclude the talk with a perspective of connecting our molecular simulations with simulations at the neuronal level.

Deciphering Allosteric Regulations Using Molecular Dynamics Simulations: the case of ALHD2

Tiziana Marino*

Dipartimento di Chimica e Tecnologie Chimiche

* Presenting author

Allosteric regulation controls many biological processes by propagating conformational changes from allosteric sites to orthosteric (functional) ones. [1] Elucidating the communication pathways between these sites is essential to understand biochemistry and engineer proteins with novel functions via mutagenesis. Additionally, these pathways serve as ideal targets for small-molecule inhibitors or activators requiring high spatial and temporal selectivity. To map these pathways, network theory-based methods can analyze pairwise correlations from molecular dynamics (MD) simulations, utilizing molecular descriptors as indicators of allosteric information flow.

The present study [2] investigates how the European variant of mitochondrial aldehyde dehydrogenase (ALDH2) interacts with quercetin (QUE) and its metabolite miquelianin (MIQ), evaluated in both their neutral and negatively charged forms, which differently contribute to the onset of red wine-induced headaches (RWH) experimentally observed [3].

To better understand the mechanisms behind RWH, the binding interactions of ALDH2 with QUE and MIQ were deeply analyzed. Both flavonoids were analyzed to clarify their distinct roles in enzyme inhibition.

Furthermore, network theory [4] was used to provide a powerful framework aimed to decipher the communication channels between the allosteric site and the orthogonal one, utilizing molecular descriptors to analyze pairwise correlations extracted from the previous MD simulations.

References

[1] S. J. Wodak et al., "Allostery in its many disguises: From theory to applications," Structure vol. 27, pp 566–578, 2019. https://doi.org/10.1016/j.str.2019.01.003

[2] A. Dodaro, G. Ciardullo, I. Rivalta, L. Wu, M. Prejanò, Y. Li , T. Marino "Flavonoids binding ALDH2 enzyme: inhibition mechanism and allostery unveiled by molecular dynamics study" J. Chem Inf Mod. submitted

[3] A. Devi, M. Levin, A.L. Waterhouse, "Inhibition of ALDH2 by Quercetin Glucuronide Suggests a New Hypothesis to Explain Red Wine Headaches". Sci. Rep., vol. 13, n. 1, 19503, 2023. https://doi.org/10.1038/s41598-023-46203-y.

[4] F. Maschietto, B. Allen, G.W. Kyro, V.S. Batista "MDiGest: A Python package for describing allostery from molecular dynamics simulations" J Chem Phys 158, 215103, 2023. doi: 10.1063/5.0140453.

[5] F. Iannone et al., "CRESCO ENEA HPC clusters: a working example of a multifabric GPFS Spectrum Scale layout," 2019 International Conference on HPCS, Dublin, Ireland, 2019, pp. 1051-1052.

Funding and acknowledgments: "The computing resources and the related technical support used for this work have been provided by CRESCO/ENEAGRID High Performance Computing infrastructure and its staff [5]. 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 programmes, seehttp://www.cresco.enea.it/english for information".

Computational Methods to Model pH Effects in Biomolecules

Miguel Machuqueiro*

BioISI: Biosystems and Integrative Sciences Institute, Departamento de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, 1749-016 Lisboa, Portugal

* Presenting author

Constant pH molecular dynamics (CpHMD) simulations are a powerful computational tool that couples the conformational space of biomolecules and pH by allowing the protonation states of ionizable sites to change dynamically in response to the environment [1]. This represents a substantial improvement over traditional MD simulations that use fixed protonation states, as it provides a more realistic representation of pH effects on molecular shape, function, and binding. This representation is more difficult to capture accurately in inhomogeneous media using state-of-the-art computational methodologies [2,3]. Recent developments have focused on enhancing the accuracy and efficiency of these methods, enabling their application to larger and more complex systems, such as protein-drug complexes and membrane proteins. We will introduce our latest methodological developments, such as combining CpHMD with enhanced sampling techniques [3,4] to study the impact of pH on various biomolecules. Several challenges will also be covered, including its high computational cost, the need for more accurate force fields, and the need for sufficient conformational sampling.

References

[1] Gomes, A. M. M., Costa, P. J., Machuqueiro, M. (2023) BBA Advances, 4, 100099.
[2] Teixeira, V. H., Vila-Viçosa, D., Reis, P. B. P. S., Machuqueiro, M. (2016) J. Chem. Theory Comput., 12, 930-934.
[3] Oliveira, N. F. B., Reis, P. B. P. S., Machuqueiro, M. (2026) J. Phys. Chem. B, 130, 4270-4282
[4] Oliveira, N. F. B., Machuqueiro, M. (2022) J. Chem. Inf. Model., 62, 2550.

Funding and acknowledgments: We acknowledge financial support from FCT through project 2024.17739.PEX (https://doi.org/10.54499/2024.17739.PEX) and UID/04046/2025 (https://doi.org/10.54499/UID/04046/2025).

Targeted cancer therapies via membrane-active peptidic Anchors

Ana V. Cunha*

Oak Ridge National Laboratory

* Presenting author

Phosphatidylserine (PS), normally restricted to the inner leaflet of the plasma membrane, is aberrantly exposed on the surface of many cancer cells, providing a compelling membrane target for selective therapeutic intervention [1-3]. PS exposure has been exploited by several classes of anticancer agents, including cationic and amphiphilic peptides that preferentially interact with negatively charged tumor membranes [4-5]. Here, we present the design and characterization of synthetic peptidic anchors that selectively recognize PS-enriched membranes and modulate their structural integrity. These peptides combine cationic and amphiphilic features to preferentially associate with negatively charged outer leaflets of tumor cells, consistent with previous observations that membrane PS enhances the binding and activity of anticancer peptides [4-5]. Upon binding, the anchors insert into the membrane interface and induce localized disorder, leading to bilayer thinning and disruption of lipid packing. Biophysical and cellular analyses reveal that this interaction results in increased membrane permeability and destabilization without requiring complete membrane lysis. Importantly, selective targeting of PS enables preferential activity toward cancer cells while minimizing effects on non-malignant membranes. This work establishes PS-directed membrane remodeling as a strategy for cancer therapy and introduces membrane-thinning peptidic anchors as a new class of agents for tumor-selective membrane disruption.

References

[1] B. Sharma and S. S. Kanwar, "Phosphatidylserine: A cancer cell targeting biomarker," Semin. Cancer Biol., vol. 52, pp. 17–25, 2018, doi: 10.1016/j.semcancer.2017.08.012.

[2] "Phosphatidylserine externalization as immune checkpoint in cancer," 2024.

[3] "Dys-regulated phosphatidylserine externalization as a cell intrinsic immune escape mechanism in cancer," 2025.

[4] C. Wang et al., "Melanoma cell surface-expressed phosphatidylserine as a therapeutic target for cationic anticancer peptide, temporin-1CEa," J. Drug Target., 2016.

[5] S. Riedl et al., "Human lactoferricin derived di-peptides deploying loop structures induce apoptosis specifically in cancer cells through targeting membranous phosphatidylserine," Biochim. Biophys. Acta Biomembr., vol. 1848, pp. 2918–2931, 2015, doi: 10.1016/j.bbamem.2015.07.018.

Funding and acknowledgments: This manuscript has been authored by UT-Battelle, LLC, under contract DE-AC05-00OR22725 with the US Department of Energy (DOE). The United States Government retains and the publisher, by accepting the article for publication, acknowledges that the United States Government retains a non-exclusive, paid up, irrevocable, world-wide license to publish or reproduce the published form of this manuscript, or allow others to do so, for United States Government purposes. The Department of Energy will provide public access to these results of federally sponsored research in accordance with the DOE Public Access Plan (http://energy.gov/downloads/doe-public-access-plan). This research used resources of the Oak Ridge Leadership Computing Facility at the Oak Ridge National Laboratory, which is supported by the Advanced Scientific Computing Research programs in the Office of Science of the U.S. Department of Energy under Contract No. DE-AC05-00OR22725.

Kinetics of heterogeneous enzyme reactions

Peter Westh[1]*, Jeppe Kari[2]

[1] *Technical University of Denmark, Department of Biotechnology and Biomedicine, DK-2800 Lyngby, Denmark*
[2] *Roskilde University, Department of Science and Environment, DK-4000 Roskilde, Denmark*

* Presenting author

Our understanding of enzyme catalysis rests on structure-function relationships, and the key tool for linking data across these two domains is the kinetic description of the reaction. Enzyme kinetics, grounded in mass-action approaches and often simplified by steady-state assumptions, has been tremendously successful in this regard. However, the available kinetic machinery almost exclusively describes homogeneous reactions in the aqueous bulk. Yet heterogeneous enzyme reactions at interfaces are common in vivo and dominant within industrial enzyme applications.

In this presentation, we discuss the eccentricities of heterogeneous enzyme reactions and whether these unusual characteristics require adapting kinetic models before they can be fairly applied to reactions at interfaces. The discussion will use examples of insoluble substrates, such as cellulose and plastic waste, and touch on enzyme reactions at the gas-liquid interface. We will propose a simple steady-state model for insoluble substrates and discuss how well-known tools from textbooks on non-biochemical heterogeneous catalysis may be applied to enzyme reactions. Finally, we will try to point out fruitful areas in the field for future computational work.

Funding and acknowledgments: We are grateful for the funding provided by the Novo Nordisk Foundation and Innovation Fund Denmark.

Computation-Guided Design of Novel Enzymes for the Recycling and Upcycling of Synthetic Polymers

K. Świderek, V. de Sousa-Batista, K. Arafet, S. Martí, V. Moliner*

Universitat Jaume I

* Presenting author

Over the past decades, the interest in designing new enzymes to solve practical challenges in all branches of science and technology has increased notably, most importantly due to large strides made in directed evolution approaches in contrast to more traditional rational design approaches. We will present in this communication a new computational strategy to design novel biocatalysts based on the sum of the best electrostatic properties of different enzymes that show certain catalytic activity on a common reaction.[1-4] The computational protocol has been applied on the re-design of the protein scaffolds from existing promiscuous enzymes. The free energy landscape obtained with QM/MM multiscale methods for proposed new variants predicts measured increased catalytic activity over the original wild-type enzyme. Our computational predictions have been experimentally confirmed by comparing the kinetic data measured with the wild-type and the mutated enzymes. Regardless of the intrinsic limitations, the simplicity of the presented approach offers a new route based on computational technique to (re)design new enzymes.

Recent results obtained in our laboratory oriented towards the design of new enzymes, and in particular for the depolymerization of synthetic polymers such as PET and PU, will be summa-rized in this communication.[5-8]

References

[1] M.A. Galmés, E. García-Junceda, K. Świderek, V. Moliner ACS Catal. 2020, 10, 1938-1946.
[2] D. De Raffele, S. Martí, V. Moliner ACS Catal. 2020, 10, 7871.
[3] M. A. Galmés, A. R. Nödling, L. Luk, K. Świderek, V. Moliner ACS Catal. 2021, 11, 8635.
[4] M. A. Galmés, A. R. Nödling, H. Kaining, L. Luk, K. Świderek, V. Moliner Chem. Sci. 2022, 13, 4779.
[5] K. Świderek, S. Velasco-Lozano, M.A. Galmés, I. Olazabal, H. Sardon, F. López-Gallego, V. Moliner. Nat. Commun. 2023, 14:3556
[6] K. Świderek, S. Martí, K. Arafet, V. Moliner. Faraday Discuss. 2024, 252, 323.
[7] K. Świderek, K. Arafet, V. de Sousa Batista, D. Grajales-Hernánde

Funding and acknowledgments: "Spanish Ministerio de Ciencia, Innovación y Universidades / Agencia Estatal de Investigación" and by European Regional Development Fund (refs. PID2024-160737OB-I00 and CNS2024-154238), the Generalitat Valenciana (PROMETEO with ref. CIPROM/2026/17), as well as the local computational resources funded by the Generalitat Valenciana - European Regional Development Fund (REF: IDIFEDER/2021/02).

Allosteric control of lipid transfer proteins by membrane lipids

Mahmoud Moqadam, Camille Cuveillier, Reza Talandasthi, Parveen Gartan, Anne-Claude Gavin, Nathalie Reuter*

University of Bergen, Department of Chemistry
University of Bergen, Computational Biology Unit
* Presenting author

Lipid transfer proteins (LTPs) transfer lipids between intracellular membranes through non-vesicular mechanisms and regulate lipid homeostasis. Despite a wealth of structural data, little is known about the mechanisms by which LTPs desorb lipids from well-organized membranes. We investigated 3 LTPs from the family of StAR-related lipid transfer domains (STARD): STARD2 (phosphatidylcholine transfer domain), STARD4 (sterol transfer domain), and STARD11 (ceramide transfer domain in CERT multidomain protein). We used a combination of multiscale molecular simulations and free energy calculations to investigate the mechanisms for extraction (or release) of their cargo lipids from (or into) their donor (or acceptor) membranes. We used multicomponent lipid bilayers modeling the plasma membrane and relevant organelle membranes. The simulations revealed similarities in binding orientation of the three proteins to lipid bilayers, but also striking differences in their sensitivity to lipid composition. We propose detailed models for the mechanism of lipid uptake/release in START domains, and highlight mechanistic differences between structurally similar proteins [1-4]. Our models are supported by experimental data.

References

[1] Talandashti, J Mol Biol, 2024
[2] Talandasthi, J Phys Chem Lett, 2024
[3] Moqadam, J Phys Chem B, 2024,
[4] Titeca, Nature, 2026

Antimicrobial peptide activity by induced lipid dynamics – new insights on functional mechanisms by combined experimental and computational investigation

Vladimir R. Koynarev, Manuela L. Nader, Henrique M. Cezar, R. Lund, Michele Cascella*

Hylleraas Centre, University of Oslo

* Presenting author

Antimicrobial peptides (AMPs) are highly potent and broad-spectrum antibiotics, found as components of the innate immune system in almost all forms of life. Despite being commonly accepted that the mechanism of action of AMPs is associated with the permeabilisation of the cell membrane, the structural and dynamical means by which this occurs are still heavily debated. By combining experimental time-resolved small angle X-ray and neutron scattering [1] with multi-scale simulations and integrative modelling [2], we have been able to dissect how single AMPs are able to catalyse scrambling of lipids in the cell membranes, leading to the opening of transient water channels [3]. These are sufficient to induce rapid ion transport discharge, yielding salt equilibration in a few tens of milliseconds. Diffusional models are in quantitative agreement with the transient formation of such channels, while contradict the traditional picture of structurally stable self-assembled transmembrane AMP pores [4]. Our study opens the way to a deep rethinking of AMP activity, necessarily including dynamic effects into the big picture [5].

References

[1] J. E. Nielsen, V. A. Bjørnestad, V. Pipich, H. Jenssen and R. Lund. J. Colloid Interface Sci. 582, 793-802, 2021.
[2] H. M. Cezar, V. A. Bjørnestad, S. Prévost, R. Lund and M. Cascella. Small Struct. 6, 2400553, 2025.
[3] M. Carrer, J. E. Nielsen, H. M. Cezar, R. Lund, M. Cascella and T. A. Soares. J. Phys. Chem. Lett. 14, 7014-7019, 2023.
[4] V. R. Koynarev, M. L. Nader, K. K. A. Borgos, H. M. Cezar, T. Narayanan, L. Porcar, M. Cascella and R. Lund. Proc. Natl. Acad. Sci. USA 122, e2517944122, 2025.
[5] B. Mehrafrooz. Proc. Natl. Acad. Sci. USA 122, e2529116122, 2025.

Funding and acknowledgments: Research Council of Norway (RCN): grant Nos. 315666, 262695.

Making Quantum Chemistry Fast Enough: Dispersion and Tight-Binding for Large Systems

Stefan Grimme*

Mulliken Center for Theoretical Chemistry, University of Bonn

* Presenting author

We present two complementary advances in semiempirical electronic structure and dispersion methodology: the third-generation tight-binding model g-xTB and the next-generation D5 dispersion correction.

The g-xTB method incorporates non-local Fock exchange and novel many-center Hamiltonian terms including atomic correction potentials. Another central ingredient is the adaptive q-vSZP minimal basis set, which achieves typical double-zeta quality through environmentally driven orbital "breathing" described via on-the-fly EEQ charges and coordination numbers. g-xTB targets true general-purpose applicability across all elements Z=1–103, including explicit f-electron treatment for lanthanides/actinides, and approaches the accuracy of the ωB97M-V/aTZ reference at only about 1.5 times the cost of GFN2-xTB. The talk covers the underlying tight-binding theory, implementation of the analytic gradient, and benchmarks across thermochemistry, conformational and non-covalent interaction test sets.

DFT-D5 addresses key shortcomings of DFT-D4. Environment-dependent dispersion coefficients are obtained via physically motivated double-linear interpolation over charge and coordination number, replacing the empirical scaling function of D4. The reference molecule library is expanded to AX_Y^q systems including non-equilibrium geometries, eliminating spurious potential-energy surface artifacts from missing interpolation nodes. C6, C8, and C9 coefficients are computed exactly via the Casimir–Polder relation, and polarizabilities are evaluated at the r2SCAN30(X2C)/x2c-da(T/Q)Z* TDDFT level. The resulting dispersion coefficients show excellent agreement with experimental DOSD reference data.

Adaptable Range Separated Hybrids for the description of photophysical properties

Tianhong Yan, Carlo Adamo, Ilaria Ciofini*

ICLeHS, CNRS, ChimiParistech-PSL

* Presenting author

With the aim of accurately describe absorption and emission properties of molecular systems in solution and complex enviroments, in this contribution we will present a procedure to tune Range Separated Hybrids enabling a balanced description of both Local (LE) and Charge Transfer (CT) excited states. This novel approach is based on the use of the computed effective electron-hole distance to tune the range-separation parameter [1].

Our aim is to propose a way to derive Density Functional Approximations that keep the optimal accuracy of global hybrid for local excited states and cure their misleading behavior leading to underestimate the energy of CT states of inter- and intra-molecular character. To this end, while keeping a strict respect of the exact asymptotic behavior obtained by imposing full HF exchange at long range, we propose to tune the range-split parameter depending on the hole-electron separation computed for the CT states of interest evaluated using density based descriptors [2-3]. This procedure enables to define a system dependent range separation parameter optimal for the treatment of both CT states and LE excited states. Its performance for the description of emission properties will also be presented [4].

References

[1] T. Yan, A. Bonardi, C. Adamo, I. Ciofini J. Chem. Theory Comput. 2025, 21, 4, 1892–1904
[2] T. Le Bahers, C. Adamo, I. Ciofini J Chem Theory Comput 7 (2011) 2498–2506.
[3] F. Maschietto, M. Campetella, J. Sanz-García, C. Adamo, I. Ciofini J Chem Phys. 154 (2021) 204102.
[4] T. Yan, C. Adamo, I. Ciofini J Comput Chem (2025) 46, e70275

Funding and acknowledgments: I.C. gratefully acknowledges fundings from the French National Agency (ANR) under the project TheoBioDy (ANR-21-CE29-0028). T.Y. acknowledges financial support from the China Scholarship Council (grant no. 202308440240). This work was also supported by the European Union (ERC, project MaMa, n. 101097351).

Halogen bonding to aromatic systems

Tanja van Mourik*

University of St Andrews, St Andrews (UK)

* Presenting author

Interactions involving aromatic systems are fundamental to biology, underpinning molecular recognition, structural stability, and many essential biological processes. Understanding these interactions at the molecular level is key to the rational design of new therapeutics. While hydrogen bonding to aromatic π-systems has been studied extensively, the corresponding role of halogen bonding remains comparatively unexplored.

In this presentation, I will examine how small molecules interact with aromatic systems ranging from benzene to the curved π-surfaces of coronene and corannulene. Using density functional theory, we map the complete potential energy landscapes of these complexes, revealing not only their preferred binding modes but also the pathways connecting them. Our results uncover surprisingly intricate energy landscapes, with numerous shallow minima separated by low barriers, highlighting the dynamic nature of halogen–π interactions. These findings provide new insight into a largely overlooked class of non-covalent interactions and lay the groundwork for exploiting halogen bonding in molecular design.

Funding and acknowledgments: We gratefully acknowledge computational support via the EaStCHEM Research Computing Facility.

Phosphoanhydride Hydrolysis from Solution to Biomolecular Motors: Insights from Machine Learning Potentials and QM/MM Simulations

Adrián García-Martínez, Javier J. Ruiz-López, Kirill Zinovjev, Damien Laage, Iñaki Tuñón*

Departamento de Química Física, Universidad de Valencia (Spain)
Department of Chemistry, École Normale Supérieure (France)
* Presenting author

Phosphoanhydride hydrolysis is one of the most fundamental chemical reactions in biology. By coupling ATP or GTP cleavage to structural changes, enzymes convert chemical free energy into regulation, signalling and mechanical work. However, the atomistic mechanisms of phosphate hydrolysis, and the way in which the released free energy is channelled into protein motion, remain difficult to establish experimentally and computationally.

In this contribution, we will discuss how multiscale simulations can connect phosphate chemistry in aqueous solution with the behaviour of ATP- and GTP-hydrolysing enzymes. First, we will present simulations of pyrophosphate hydrolysis in water using density-functional-theory-quality machine-learning potentials combined with transition path sampling and free-energy methods. These calculations allow all solvent molecules to participate reactively and reveal how protonation and Mg^{2+} coordination modulate the diversity of the transition-state ensemble. This provides a molecular reference for understanding ATP and GTP hydrolysis in proteins.

We will then show how hybrid QM/MM simulations describe the enzymatic reaction in two representative systems. In RhoA activated by p50RhoGAP, GTP hydrolysis proceeds through a metaphosphate-like intermediate and involves a non-trivial proton-transfer mechanism assisted by the amide–imide tautomerism of the catalytic glutamine. In Zika NS3 helicase, ATP hydrolysis is coupled to the conformational landscape of motif V, a conserved loop connecting the ATPase and RNA-binding sites. Product formation and phosphate release reshape this landscape, allowing Gly415 to act as a γ-phosphate sensor and supporting a ratchet-like mechanism for this biomolecular motor.

Together, we will discuss how machine-learning potentials and QM/MM free-energy simulations can provide a unified view of phosphate hydrolysis, from solution chemistry to enzymatic catalysis and chemically driven protein motion.

References

[1] García-Martínez, A.; de la Puente, M.; Cunin, M.; Zinovjev, K.; Ruiz-Pernía, J. J.; Laage, D.; Tuñón, I. Protonation and Magnesium Ions Shape the Transition State Diversity of Phosphoanhydride Hydrolysis in Water. Nat. Commun. 2026. https://doi.org/10.1038/s41467-026-73697-7.

[2] Pardos, J.; García-Martínez, A.; Ruiz-Pernía, J. J.; Tuñón, I. Mechanistic Insights into GTP Hydrolysis by the RhoA Protein: Catalytic Impact of Glutamine Tautomerism. ACS Catal. 2025, 15, 4415–4428. https://doi.org/10.1021/acscatal.5c00719.

[3] García-Martínez, A.; Zinovjev, K.; Ruiz-Pernía, J. J.; Tuñón, I. Conformational Changes and ATP Hydrolysis in Zika Helicase: The Molecular Basis of a Biomolecular Motor Unveiled by Multiscale Simulations. J. Am. Chem. Soc. 2023, 145, 24809–24819. https://doi.org/10.1021/jacs.3c09015

Funding and acknowledgments: The authors acknowledge financial support from AEI and ERDF "A way of making Europe" through grant PID2024-157213NB-I00, and from Generalitat Valenciana through grant PROMETEO CIPROM/2021/079. Computational resources were provided by the Barcelona Supercomputing Center, including access to MareNostrum and by Universitat de València (Tirant). K.Z. acknowledges support from EUR2025-165005. We also thank our collaborators and technical staff for their assistance with simulations and data analysis.

QM and QM/MM Exploration of C–H Activation in Radical Enzymes

Rong-zhen Liao*

Huazhong University of Science and Technology

* Presenting author

Radical enzymes catalyze many key biochemical reactions by generating and utilizing highly reactive radical species. Investigation and elucidation of the catalytic mechanisms of radical enzymes could provide important theoretical support for experimental chemists to develop novel organic synthetic strategies and achieve precise control over reaction selectivity. Given the high reactivity and extremely short lifetimes of radical species in radical enzyme-catalyzed reactions, it is difficult to directly capture and characterize radical intermediates experimentally. Quantum chemical cluster calculations, molecular dynamics simulations, and hybrid quantum mechanics/molecular mechanics (QM/MM) calculations were employed to investigate the catalytic mechanisms and selectivity origins of several SAM radical enzymes and glycyl radical enzymes, including Mmp10, TokK, IseG, CutC, HypD, and HplG. These results may provide a foundation for the experimental engineering and design of radical enzymes to regulate the selectivity of enzymatic reactions.

References

[1] Wen-Hao Deng, You Lu, Rong-Zhen Liao J. Chem. Inf. Model. 2021, 61, 5871.
[2] Wen-Hao Deng, Rong-Zhen Liao Chem. Commun. 2022, 58, 7144.
[3] Wen-Hao Deng, Rong-Zhen Liao Chem. Eur. J. 2023, 29, e202202995.
[4] Wen-Hao Deng, Rong-Zhen Liao J. Chem. Inf. Model. 2024, 64, 4168.
[5] Wen-Hao Deng, You Lu, Rong-Zhen Liao J. Catal. 2024, 439, 115736.
[6] Yi-Qian Yang, Wen-Hao Deng, Rong-Zhen Liao J. Phys. Chem. B 2025, 129, 5438.

Funding and acknowledgments: This work was supported by the National Natural Science Foundation of China (22273028 and 22571107)

Enantioselectivity in Enzymes: Challenges for Modelers

Mario Prejanò*
Università della Calabria
* Presenting author

Enzymes are exceptional catalytic machines that make chemical reactions with incomparable time with respect to reactions in solutions. Whether it is about studying life-linked processes, designing an effective drug, or optimizing their use at industrial level, a good computational model can contribute to a deep understanding of the enzymes activity. Nowadays, with modern molecular modeling tools it is indeed possible to investigate the whole catalytic cycle of an enzyme, from the binding of the substrate to the release of the product, providing helpful atomistic details that can promote fast advances in a number of research fields. This aspect becomes for relevant when dealing with enantioselectivity, for which orientation of the substrate or of the catalytic agent can favor an enantiomenr over the other one.

At this purpose, discussion will be centered on results from selected recent investigations on enantioselectivity in enzymatic environment, [1,2] focusing on the computational approach (based on ffMD simulation and full QM calculations) that was selected to answer specific questions.

Advantages and disadvantages of each strategy will be further discussed, highlighting current challenges that a modeler has to deal with.

References

[1] M. Prejanò, X. Sheng, F. Himo, ChemistryOpen 11 (2022), e202100250.
[2] J. Gooderham et al., Catal. Sci. Technol. 15 (2025), 3113.

Beyond the Static Structure: Decoding the Regulatory Logic of Rho GTPases via QM/MM and MD simulations

Angela Parise*, Sofia Cresca, Sara Alunno Rufini, Riccardo Rozza, Karolina Mitusinska, Jana Aupic, Alessandra Magistrato

CNR-IOM at SISSA

* Presenting author

Small Rho GTPases function as molecular switches in eukaryotic cells, cycling between active (GTP-bound) and inactive (GDP-bound) states to orchestrate key signaling pathways. This cycle is finely tuned by GTPase-activating proteins (GAPs), which trigger GTP hydrolysis, and guanine nucleotide exchange factors (GEFs), which facilitate GDP/GTP exchange [1]. Despite their central role in cancer and infectious diseases, a full atomic-leve understanding of their activation and deactivation remains a challenge due to the complex chemical and conformational transitions involved.

In this contribution, a comprehensive multiscale simulation study is presented to decode the regulatory mechanisms underlying Rho GTPases at the atomic scale. By integrating classical and hybrid QM/MM Molecular Dynamics (MD) with enhanced sampling techniques, the gap between static structures and biological function is bridged. Specifically, the investigation focuses on: (i) the GTP hydrolysis mechanism of RhoA, promoted by GTPase-activating proteins [2]; (ii) GDP/GTP exchange mechanisms of Rho GTPases, in both wild-type and cancer-associated isoforms [3,4]; and (iii) their involvement in pathological conditions, including cancer progression and other pathological contexts. [5]

References

1. A. Parise, S. Cresca, A. Magistrato Expert Opin Drug Discov, 2024, 1-21.
2. A. Parise, R. Rozza, K. Mitusinska, J. Aupic, A. Magistrato, Glutamine Tautomerization Drives RhoGAP-Aided GTP Hydrolysis in Small Rho GTPases, JACS, 2026, 148 (27): 28776–28787.
3. A. Parise, A. Magistrato Protein Science, 2024, 33 (4), e4939.
4. S. Cresca, A. Parise, A. Magistrato, JCIM, 2024, 64 (24), 9474-9486.
5. A. Parise, I. Manini, E. Pobega, S. Couvaucezach, L. Secco, F. Simonelli, S. Mastantuono, C. di Loreto, A. Pizzignach, M. Skrap, M. Vindigni, R. Sgarra, G. Manfioletti, D. Cesselli, A. Magistrato Eur. J. Med. Chem. 2025, 117704.

Funding and acknowledgments: Italian Association for Cancer Research (AIRC) and "PRP@CERIC – Pathogen Readiness Platform for CERIC-ERIC Upgrade" funded by the European Union through the National Recovery and Resilience Plan (NRRP).

Computing the barrier for single electron transfer in enzymatic catalysis and beyond

Feliu Maseras*

Institute of Chemical Research of Catalonia (ICIQ)

* Presenting author

Single-electron transfer (SET) and energy transfer (EnT) events play a central role in modern biochemistry and synthetic chemistry and are key for the potential role of electro- and photocatalysis. These steps appear also in enzymatic processes, including oxido- reduction processes in cytochromes. While the application of computational chemistry methods to elucidate conventional reaction mechanisms that involve bond breaking/formation processes is well established nowadays, the analysis of SET and EnT mechanisms still represents a challenge for computational chemistry. Consequently, their possible contribution to reaction mechanisms is often overlooked or limited to analysis of their thermodynamics.

The problem with SET or EnT is that the barriers are not controlled by a transition state, but by an outer sphere process. The barriers for these processes are typically computed via Marcus theory,[1] which is in principle clear, but has given rise to a variety of interpretations in the chemical bibliography. We have also applied it in some cases.[2,3] In particular, there is a key reorganization parameter, lambda, that can be computed in different ways that are not always clearly specified in publications. We will try to introduce some clarity on the topic and propose a systematic procedure.

References

[1] R. A. Marcus, 'Electron Transfer Reactions in Chemistry: Theory and Experiment (Nobel Lecture)', Angew. Chem. Int. Edit. Engl., vol. 32, no. 8, pp. 1111-1121, Aug. 1993, doi: 10.1002/anie.199311113.

[2] A. de Aguirre, I. Funes-Ardoiz and and F. Maseras, 'Four Oxidation States in a Single Photoredox Nickel-Based Catalytic Cycle: A Computational Study', Angew. Chem. Int. Edit., vol 58, no. 12, Jan. 2019, pp. 3898-3902, doi: 10.1002/anie.201814233.

[3] A. Solé-Daura and F. Maseras, 'Straightforward Computational Determination of Energy-Transfer Kinetics through the Application of the Marcus Theory', Chem. Sci., vol. 15, no. 34, pp. 13650-13658, Sep. 2024, doi: 10.1039/d4sc03352c.

Thioredoxin Reductase: PAET from NADP to diCys redox center and blocking of the Cys-Sec second redox site

Juraj Pavolko, Milan Riha, Jaroslav V. Burda*

Charles University

* Presenting author

Thioredoxin reductase (TrxR) belongs to the family of reduction enzymes responsible for elimination of ROS in cells. In natural state TrxR is arranged in hexamer associate where three pairs of monomeric units represent working unit. Electron flux starts from reduced form of NADP coenzyme transferring electron pair via FAD coenzyme to first diCys redox center. While these three parts are in close vicinity and proton assisted electron transfer (PAET) can be expected as a reduction mechanism, final reduction pathway to the second redox Cys-Sec center occurs through helix channel ca 10 Å long. Moreover, this second redox unit is localized in the C-terminus of second monomer unit. From literature, it is known (or better generally accepted) that this Cys-Sec is the place where enzymatic activity can be successfully blocked. Gold(I) metallodrugs were reported as effective complexes capable for such a blocking coordination.

Get into the (Minor) Groove: How Polyamines Dance, Hug, and Bond with DNA

Sergiy Perepelytsya[1,2], Tudor Vasiliu[3], Aatto Laaksonen[3,4,5,6], Leon De Villiers Engelbrecht[6,7], Francesca Mocci[7,*]

[1] *Bogolyubov Institute for Theoretical Physics of the National Academy of Sciences of Ukraine, 03143 Kyiv, Ukraine*
[2] *Kyiv Academic University, Kyiv, Ukraine*
[3] *Centre of Advanced Research in Bionanoconjugates and Biopolymers, "Petru Poni" Institute of Macromolecular Chemistry of the Romanian Academy, 700487 Iași, Romania*
[4] *Department of Chemistry, Division of Physical Chemistry, Arrhenius Laboratory, Stockholm University, 106 91 Stockholm, Sweden*
[5] *State Key Laboratory of Materials-Oriented and Chemical Engineering, Nanjing Tech University, 210009 Nanjing, P. R. China*
[6] *Department of Engineering Sciences and Mathematics, Division of Energy Science, Luleå University of Technology, 97187 Luleå, Sweden*
[7] *Department of Chemical and Geological Sciences, University of Cagliari, 09042 Monserrato, Italy*
* Presenting author

Polyamines are ubiquitous biological counterions that play a central role in DNA organization, stabilization, and condensation. Despite decades of experimental and theoretical investigation, the molecular mechanisms underlying polyamine binding, conformational adaptation, and DNA-mediated self-organization remain only partially understood. Here, we present atomistic molecular dynamics studies aimed at elucidating the interplay between DNA sequence, confinement, and polyamine flexibility, focusing on spermidine^{3+}, one of the most abundant natural polyamines in living cells.

Microsecond-scale simulations reveal that spermidine explores a diverse conformational landscape shaped by DNA and the local electrostatic environment [1]. Multiple binding modes emerge within the minor groove, major groove, and phosphate regions of the double helix, displaying clear sequence-dependent preferences. AT-rich sequences favor stable localization within the minor groove, whereas distinct interaction patterns are observed in GC-rich regions. The intrinsic flexibility of spermidine enables transient and persistent bridges between DNA phosphates, promoting DNA-DNA attraction and higher-order organization [2].

We further investigate how confinement between neighboring DNA helices modulates polyamine structure and dynamics. Simulations of parallel DNA fragments at controlled separations show that restricted environments reshape the conformational ensemble of spermidine and enhance cross-linking configurations capable of mediating interhelical interactions [3]. These results provide a molecular-level picture of how polyamines facilitate DNA compaction under crowded biological conditions.

Overall, our findings reveal how sequence, confinement, and polyamine flexibility cooperate in DNA organization. More broadly, they advance our understanding of multivalent organic counterions in genome organization and provide perspectives for the design of DNA-based nanomaterials [4].

References

[1] S. Perepelytsya, T. Vasiliu, A. Laaksonen, L. Engelbrecht, and F. Mocci, "Conformational flexibility of spermidine3+ interacting with DNA double helix," J. Mol. Liq., vol. 389, p. 122828, 2023, doi: 10.1016/j.molliq.2023.122828.
[2] F. Mocci, A. Laaksonen, L. Engelbrecht, T. Vasiliu, and S. Perepelytsya, "DNA-polyamine interactions: Insight from molecular dynamics simulations on the sequence-specific binding of spermidine3+," Soft Matter Syst. Biomed. Appl., pp. 163-192, 2022, doi: 10.1007/978-3-030-80924-9_6.
[3] T. Vasiliu, F. Mocci, A. Laaksonen, L. Engelbrecht, and S. Perepelytsya, "Caging polycations: Effect of increasing confinement on the modes of interaction of spermidine3+ with DNA double helices," Front. Chem., vol. 10, p. 836994, 2022, doi: 10.3389/fchem.2022.836994.
[4] S. Perepelytsya, D. Piatnytskyi, T. Bubon, N. Cibotariu, A. Laaksonen, and F. Mocci, "Ions as architects of DNA nanostructures" Small Struct., vol. 7, e202500786, 2026, doi: 10.1002/sstr.202500786.

Funding and acknowledgments: Funding This work received support from the European Union's Horizon Europe Research and Innovation Programme under grant agreement No. 101086667 (BioMat4CAST). S.P. acknowledges support from the National Academy of Sciences of Ukraine (project No. 0123U102290); A.L. from the Swedish Research Council (VR); L.D.V.E. from the Kempe Foundation; and F.M. and L.D.V.E. from Progetto Fondazione di Sardegna (CUP F72F20000230007) and Regione Autonoma della Sardegna (RASSR81788-2017). Acknowledgements The authors acknowledge COST Action CA21101, "Confined Molecular Systems: From a New Generation of Materials to the Stars" (COSY), supported by COST. Computational resources and technical support were provided by PDC through the National Academic Infrastructure for Supercomputing in Sweden (NAISS) and by the Swedish National Infrastructure for Computing (SNIC).

EnZight: A web server for structure-guided identification of additive substitutional hotspots in enzymes

Rune Rahbek Østergaard[1,2], Mikkel Lyskjær Jensen[1,2], Suzana Siebenhaar[1,2], Deniz Bicer[1,3], Peter Wad Sackett[4], Alexander Andersen[2], Matteo Tiberti[5], Elena Papaleo[4,5], Serina Robinson[6,7], Søren Skou Thirup[1,3], Peter Westh[1,2], Laura Rotilio[1,2], Jens Preben Morth[1,2]*

[1] *EnZync Center for Enzymatic Deconstruction of Thermoset Plastics*
[2] *Department of Biotechnology and Biomedicine, Technical University of Denmark, Søltofts Plads, DK-2800, Kongens Lyngby, Denmark*
[3] *Interdisciplinary Nanoscience Center (iNANO), Aarhus University, Gustav Wieds Vej 14, DK-8000, Aarhus, Denmark*
[4] *Department of Health Technology, Technical University of Denmark, Ørsteds Plads, DK-2800, Kongens Lyngby, Denmark*
[5] *Cancer Structural Biology, Danish Cancer Institute, Strandboulevarden 49, DK-2100 Copenhagen, Denmark*
[6] *Eawag, Swiss Federal Institute of Aquatic Science and Technology, CH-8600 Dübendorf, Switzerland*
[7] *Institute for Biogeochemistry and Pollutant Dynamics, ETH Zürich, Universitätsstrasse 16, CH-8092 Zürich, Switzerland*

* Presenting author

Homologous protein structures encode rich information about tolerated sequence variation, yet turning this information into actionable enzyme design strategies remains difficult. We introduce EnZight, a user-friendly web server that combines homologous structural alignment with intuitive visualization to pinpoint substitution hotspots within protein cores. By aligning homologous structures, EnZight identifies positions where the local structural environment is conserved even as the residue itself varies across homologs—a signature that helps predict substitutions likely to preserve fold integrity while tuning function and thermostability. The platform also generates interactive structural outputs, allowing users to visually inspect and prioritize candidate substitutions.

To validate EnZight, we applied it to a polyurethane-degrading amidase as a proof-of-concept case study. From 47 designed variants, 98% expressed successfully, reflecting the high foldability of the predicted substitutions. Multiple substitutions improved catalytic turnover and thermostability simultaneously, and beneficial mutations combined additively—allowing incremental, stepwise gains through combination. The top-performing triple mutant achieved a six-fold increase in catalytic turnover alongside a 2 °C rise in apparent melting temperature. EnZight also enhanced activity toward flutamide, a pharmaceutical micropollutant, underscoring its versatility for optimizing enzymes across diverse substrates.

Funding and acknowledgments: EnZync is supported by Challenge grant NNF22OC0072891 from the Novo Nordisk Foundation. We are grateful to the rest of the EnZync consortium members for constructive and helpful feedback. The X-ray diffraction data were collected at the Biomax beamline operated by MAXIV storage ring (MAXIV, Lund, Sweden), proposal number 20250330 (EnZync: Structural Characterization of Thermoset Plastic Degrading Enzymes). We thank Catalyze4X for assistance with crystallization and shipping and data collection, grant NNF24OC0088714.

Exploring the multiple faces of nucleic acids

Modesto Orozco*

IRB Barcelona and University of Barcelona

* Presenting author

Nucleic acids are fascinating multiscale system expanding over a size scale from Angstrom to meter and involved on processes taking place in a time scale from femtosecond to hours. This multiscale nature makes necessary the development of multiphysic approaches that should cover from atomistic detail of nucleic acids reactivity to the representation of entire chromatin fibers. I will summarized in my talk recent advances of our team in this long-term purpose.

Molecular Mechanism of Natural and Artificial Ribozymes

Alessandra Magistrato*

National Research Council-Institute of Material Foundry (CNR-IOM) at Scuola Internazionale Superiore di Studi Avanzati (SISSA), Trieste (Italy)

* Presenting author

Complex protein/RNA macromolecular engines, catalyze formation of mature messenger and ribosomal and transfer RNAs from their precursors, giving rise to functional RNAs. In this talk I will illustrate how atomic-level simulations at classical and QM/MM level have contributed to elucidate: the chemical details of premature-messenger and premature-ribosomal RNA splicing performed by the spliceosome and RNAse MRP [1-3], as well as) the mechanism of natural and synthetic RNA modifying enzymes and ribozymes such as METTL6 [4] and MTR1 [5].

References

[1] Borišek, J.; Aupič, J.; Magistrato, A. All-Atom Simulations Decrypt the Molecular Terms of RNA Catalysis in the Exon-Ligation Step of the Spliceosome. ACS Catal. 2020, 10, 5328

[2] Aupič, J.; Borišek, J., Fica, S.M.; Galej, W.P.; Magistrato A. Monovalent metal ion binding promotes the first transesterification reaction in the spliceosome Nature Communications 2023 14 (1), 8482

[3] Borišek, J.; Aupič, J.; Magistrato A Third Metal Ion Dictates the Catalytic Activity of the Two-Metal-Ion Pre-Ribosomal RNA-Processing Machinery Angewandte Chemie International Edition 2024 63 (44), e202405819

[4] Aupič, J.; Hollmer, I.; Tengo, L.; Sehr P.; Kowalinski, E.; Magistrato A. Recognition and catalytic mechanism of tRNA m3C methyltransferase METTL6 BioRXiv 2025 https://doi.org/10.1101/2025.06.25.660299

[5] Aupič, J.; Chen, H.; Scheitl, C. P.M.; Höbartner, C.; Magistrato A. Nat Comm 2026

Reading Between the Bases: Understanding Nucleic Acid Modifications Through Multiscale Modeling

Stacey D. Wetmore*

Department of Chemistry and Biochemistry, University of Lethbridge, 4401 University Drive West, Lethbridge, AB, Canada

* Presenting author

Nucleic acids are the most basic molecules of life, being tasked with storing and transmitting genetic information in all living organisms. To enhance nucleic acid programmability and stability, and aid the formation of functional 3D shapes, the nucleotide building blocks of DNA and RNA are commonly modified in nature. Indeed, DNA nucleobases are methylated to control gene expression, while the identification of hundreds of distinct modifications in RNA has led to the emerging field of epitranscriptomics. Furthermore, the ease of synthesis of nucleic acids functionalized at any nucleobase, sugar, or phosphate site, as well as the ability of modifications to impact pairing, chemical stability, conformation, and interactions with proteins, has led to the development of a wealth of unique modifications with far-reaching applications. For example, modified nucleic acids have been designed for medicinal uses such as drugs, vaccines, bioprobes, antimicrobials and tissue engineering, as well as for nanomaterials to build nanowires, nanomachines and nanorobots. Unfortunately, the lack of known structure–function relationships for a range of modified nucleic acids raises questions such as how nature deals with aberrant modifications, why nature introduces modifications, and how modifications can be used to their full potential in valued applications. The overarching objective of the research performed in the Wetmore lab is to use computer modeling to gain a fundamental understanding of the chemistry of modified nucleic acids, with the aim of filling knowledge gaps by gaining a greater understanding of the role of nucleic acid modifications in nature and improving the design of original modified nucleotides for novel applications. In this talk, I will discuss some of our recent work that investigates the diverse chemistry of modified nucleic acids.

Evolution of Computer-Aided Drug Discovery

William L. Jorgensen*

Yale University

* Presenting author

Over the last thirty years, computer modeling has evolved into an essential, widespread activity in drug discovery. The contributions of our group have been in multiple areas including virtual screening, prediction of ADME properties, and FEP-guided lead optimization. The advances were all accompanied by development of new software including the BOMB program for de novo design, QikProp for AI-based estimation of pharmacological properties and metabolites, and MCPRO for Monte Carlo simulations of protein-ligand complexes. To pursue prospective studies, our efforts were expanded to include synthesis, biological assaying, and crystallography. Emphasis has been placed on optimization of the hits from virtual screening to yield potent, drug-like inhibitors. MC/FEP simulations are used to identify the most promising choices for substituents on rings, heterocycles, and linking groups. The illustrated applications center on inhibitor design for HIV-1 reverse transcriptase and SARS-CoV-2 main protease. Micromolar leads have been rapidly advanced to low nanomolar inhibitors. Key computational issues are also addressed.

References

(1) Computer-Aided Discovery of Anti-HIV Agents. Jorgensen, W. L. Bioorg. Med. Chem. 2016, 24, 4768-4788.

(2) Potent non-covalent inhibitors of the main protease of SARS-CoV-2 from molecular sculpting of the drug parampanel guided by free-energy perturbation calculations. Zhang, C.-H.; Stone, E. A.; Deshmukh, M.; Ippolito, J. A.; Ghahremanpour, M. M.; Tirado-Rives, J.; Spasov, K. A.; Zhang, S.; Takeo, Y.; Kudalkar, S. N.; Liang, Z.; Isaacs, F.; Lindenbach, B.; Miller, S. J.; Anderson, K. S.; Jorgensen, W. L. ACS Central Sci. 2021, 7, 467-475.

(3) Computation of Absolute Binding Free Energies for Non-covalent Inhibitors with SARS-CoV-2 Main Protease. Ghahremanpour, M.; Saar, A.; Tirado-Rives, J.; Jorgensen, W. L. J. Chem. Info. Model. 2023, 63, 5309-5218.

Funding and acknowledgments: Gratitude is expressed to the US National Institutes of Health for support.

Unexpected Catalytic Strategies in Carbohydrate-Active Enzymes

Carme Rovira*

Universitat de Barcelona

* Presenting author

Glycosidases (GHs) and glycosyltransferases (GTs) are the key enzymes responsible for the degradation and biosynthesis of carbohydrates in nature. Understanding their catalytic mechanisms is therefore a central goal in glycoscience, with important implications for the rational design of enzyme inhibitors, probes, and synthetic tools. By combining state-of-the-art ab initio quantum mechanics/molecular mechanics (QM/MM) simulations with structural and biochemical data, our work has uncovered unexpected catalytic strategies in several GHs and GTs. For GHs, these studies have challenged established views of substrate preactivation, revealing that some exo-acting enzymes can catalyze glycosidic bond cleavage without imposing the substrate distortion commonly observed in endo-GHs [1]. We have also identified alternative catalytic mechanisms that depart from the from the classical Koshland picture [2]. For GTs, we have uncovered both classical and previously unrecognized catalytic strategies, including O- and N-glycosylation reactions [3], thereby providing a mechanistic basis for the design of inhibitors, covalent probes, and bioorthogonal chemical tools [4]. Together, these findings illustrate how molecular simulations can reveal unexpected enzymatic chemistry and connect atomic-level understanding with molecular design.

References

[1] M. A. B. Morais, A. Nin-Hill, and C. Rovira, 'Glycosidase mechanisms: Sugar conformations and reactivity in endo- and exo-acting enzymes', Curr. Opin. Chem. Biol., vol. 74, 102282, 2023, doi: 10.1016/j.cbpa.2023.102282.

[2] L. F. Sobala et al., 'An Epoxide Intermediate in Glycosidase Catalysis', ACS Cent. Sci., vol. 6, no. 5, pp. 760–770, , doi: 10.1021/acscentsci.0c00111.

[3] B. Piniello et al., 'Mechanism of Bacterial Arginine N-Glycosylation: A Chemically Challenging Post-Translational Modification', ACS Catal., vol. 16, no. 3, pp. 2550–2562, Feb. 2026, doi: 10.1021/acscatal.5c07775.

[4] M. B. L. Vriends et al., 'Oseltamivir Aziridines Are Potent Influenza Neuraminidase Inhibitors and Imaging Agents', Proc. Natl. Acad. Sci. U.S.A., vol. 123, no. 13, Art. no. e2504045123, Mar. 2026, doi: 10.1073/pnas.2504045123.

Funding and acknowledgments: This work was supported by the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme (ERC-2020-SyG-951231, CARBOCENTRE) and by the Spanish Ministry of Science, Innovation and Universities/AEI through grant PID2023-147939NB-I00.

Decoding Biochemical Complexity with Simulations and AI-Enhanced Sampling

Marco De Vivo*

Italian Institute of Technology

* Presenting author

I will present our efforts to use molecular simulations and AI-guided enhanced sampling to understand complex chemical processes that often involve functional conformational changes, which are difficult to capture and interpret unambiguously experimentally. Examples will include group II introns, self-splicing ribozymes that are evolutionarily and chemically related to the eukaryotic spliceosome. I will illustrate how we use simulations to delve into the mechanism by which the RNA core of splicing machineries, including the megadalton human spliceosome, operates at the atomic scale. In this regard, I will also discuss our current efforts to guide the design of RNA-targeted small molecules using free-energy perturbation calculations. I will also present our computational investigations of the mechanistic steps in nucleic acid polymerization catalyzed by DNA polymerases, which pose increasingly complex mechanistic questions and for which identifying the appropriate collective variable is inherently challenging. This exemplifies well the benefit of deep-learning-guided enhanced sampling of the configurational space. Overall, these examples demonstrate how atomistic molecular simulations can nowadays enable the prospective exploration of ultra-large, realistic multicomponent protein/nucleic acid systems.

Light-Driven Mechanisms in Anticancer Phototherapy: Mode Switches, Coligand Effects and Membrane interactions

Marta Erminia Alberto*

University of Calabria, CTC Department, Rende (CS), Italy
University of Milan Bicocca, DISAT Department, Milan, Italy

* Presenting author

This contribution presents recent applications of multiscale approaches (DFT/(QR)TDDFT, QM/MM, MD) to elucidate the distinctive photophysical features of metallic complexes with notable hypoxia activity, focusing on mode switches and coligand effects. In addition to the well-known Type I/Type II quenching mechanisms and triplet-state relaxation pathways, our studies investigate the interactions of light-activated molecules with DNA in the context of PDT/PCT agents, as well as with cell membranes [1–2]. This includes exploring the mechanisms of insertion into the bilayer core and disruption of membrane structure, highlighting their key roles in determining biological activity.

References

[1] A. G. Ritacca, A. M. A. Abdelgawwad, A. Talgatov, C. G. Cameron, S. A. McFarland*, A. Francés-Monerris*, M. E. Alberto*, Inorg. Chem., 2026, doi: 10.1021/acs.inorgchem.6c01825.

[2] M. A. Abdelgawwad, D. Roca-Sanjuán, M. E. Alberto*, A. Francés-Monerris*, J. Chem. Inf. Model., vol. 66, no. 12, pp. 7154–7167, Jun. 2026, doi: 10.1021/acs.jcim.6c00922.

Funding and acknowledgments: PRIN D.D.104/2022 PNRRM4.C2.1.1. ProjectCode: 2022AN47CA CUP:H53D23003820001, funded by the European Union Next Generation EU–Project Title"LA-G4-DACA"–Grant Assignment DD862,16/06/2023.

AI Tools in Publishing and Research: Best Practices and Examples

David Peralta*

ChemMedChem / Wiley-VCH, Wiley-VCH Publishing Development, Physical Sciences, Chemistry Department

* Presenting author

This workshop gives a rudimentary introduction to generative AI tools and their ethical and practical considerations and implications in the world of publishing. We will also discuss the accepted policies for AI and its role in the future of publishing. The talk ends with some examples of AI tools that might be useful for writing and research organization.

References

[1] Wiley. Guide for Using AI Tools in Your Research. Accessed October 2026, Available at https://www.wiley.com/publishing/article/ai-guidelines#author.

Allosteric network reprogramming for rational enzyme design

Cristina Duran, Guillem Casadevall, Sílvia Osuna*

Institut de Química Computacional i Catàlisi and Departament de Química, Universitat de Girona, Girona, Spain
ICREA, Barcelona, Spain

* Presenting author

Enzymes exist as an ensemble of conformational states, whose populations can be altered through substrate binding, allosteric interactions, post-translational modifications, and even by introducing mutations into their sequence. In many enzymatic systems, full catalytic potential is only retained when in the presence of binding partners, either from additional proteins to generate heterocomplexes or from the formation of homo-oligomers.[1] Despite progresses and recent advances in generative models for protein design,[2] designing efficient enzymes and predicting oligomeric assemblies presenting a tight communication for enhancing a specific catalytic function remains challenging. Such tightly intertwined enzymatic assemblies modulate the conformational heterogeneity of the systems and allow the adoption of the multiple catalytically relevant conformational states needed for catalysis.[3]

In this talk, we will explore our developed computational pipelines that integrate AlphaFold2 with quantum mechanics and molecular dynamics simulations to guide enzyme design and foster protein assembly, thereby enabling the cooperative interactions and conformational transitions crucial for enhanced catalytic performance. [3-5] We will also discuss how our approach, which combines coevolutionary analysis and correlation-mediated allosteric networks, can be used to redesign enzymes and modify protein–protein interfaces for improved catalytic activity.[3, 5] Over the years, our work with diverse enzyme systems has generated strong evidence that rational design strategies can effectively yield active enzyme variants.[5,6] Moreover, we demonstrate that the current challenge of predicting distal active sites to enhance functionality in computational enzyme design can ultimately be met. [3]

References

[1] Goodsell, DS; Olson, AJ. Annu Rev Biophys 2000, 29, 105-153
[2] Casadevall, G.; Duran, C.; Osuna, S., JACS Au 2023, 3, 1554.
[3] Osuna, S., WIREs Comput Mol Sci. 2020, e1502.
[4] Casadevall, G.; Duran, C.; Estévez-Gay, M.; Osuna, S., Prot. Sci. 2022, 31, e4426.
[5] Duran, C.; Kinateder, T.; Hiefinger, C.; Sterner, R.; Osuna, S., ACS Catal., 2024, 14, 16986–16995
[6] Duran, C.; Hiefinger, C.; Kinateder, T.; Poveda, A.; Uhl, P.; Jiménez-Barbero, J.; Sterner, R.; Osuna, S., submitted for publication.

How Much Physics Do We Really Need to Design an Industrial Enzyme?

Maria Fátima Lucas*

Zymvol Biomodeling SL. C/ Pau Claris, 94, 3B - 08010 Barcelona, Spain

* Presenting author

Computational enzyme design sits at an unusual intersection between molecular accuracy and industrial decision-making. While rigorous descriptions of enzymatic catalysis require consideration of conformational sampling, reaction energetics and dynamics, industrial enzyme development imposes an additional constraint: predictions must be sufficiently fast and scalable to outperform experimental search.

Drawing on more than 150 industrial projects, I will discuss how physics-based approaches can guide enzyme discovery and engineering using comparatively small experimental libraries, including the identification of productive substrate poses, access and egress pathways, and functionally important distal residues. Examples will include computationally guided peroxygenase engineering, discovery of industrial ketoreductases, prediction of distal mutations and their impact on activity, stability and immobilization, and machine-learning-guided engineering.

I will conclude by discussing the emerging opportunity to combine molecular simulations, experimentally validated structure–function data and AI models capable of learning richer representations of physical systems, as well as the remaining challenge of connecting molecular design to economically viable industrial scale-up.

References

Molina-Espeja et al. (2016), Synthesis of 1-Naphthol by a Natural Peroxygenase Engineered by Directed Evolution, ChemBioChem, DOI: https://doi.org/10.1002/cbic.201500493

Sosa et. al., (2024), In silico enzyme screening identifies an SDR ketoreductase from Thermus caliditerrae as an attractive biocatalyst and promising candidate for protein engineering, Frontiers in Chemical Biology, DOI: https://doi.org/10.3389/fchbi.2024.1425501

Casilli et al. (2024), Computation-guided engineering of distal mutations in an artificial enzyme, Faraday Discussions 252, 262–278,DOI: https://doi.org/10.1039/d4fd00069b

De Simone et al. (2024), Distal mutations enhance efficiency of free and immobilized NOV1 dioxygenase for vanillin synthesis, Journal of Biotechnology 391, 92–98, DOI DOI: 10.1016/j.jbiotec.2024.06.012

Hassankalhori et al., (2026), Engineering acid-sensing ion channel 1a with disrupted desensitization: a computer-guided approach, in review.

Mechanism-Guided Reprogramming of Enzyme Functions

Xiang Sheng*

Tianjin Institute of Industrial Biotechnology, Chinese Academy of Sciences, Tianjin 300308; China National Technology Innovation Center for Synthetic Biology, Tianjin 300308, China

* Presenting author

Understanding the catalytic mechanisms of enzymes is essential for designing new functions and creating novel biocatalysts. Multiscale computational modeling allows us to examine structural and energetic changes along reaction pathways at atomic resolution, thereby clarifying how activity and selectivity are controlled. Such insights yield mechanistic details that are often inaccessible by experiment and provide a rational basis for enzyme engineering. In this talk, I will present our recent work on mechanism-guided design of new enzymatic functions. A few examples will be highlighted, including the computational design of an (R)-selective norcoclaurine synthase with stereoselectivity not observed in nature, and the redesign of a nitrilase to switch its activity from hydrolysis to hydration. These studies not only advance the fundamental understanding of enzyme catalysis but also deliver novel enzymes with new selectivities or new reaction types, offering practical routes to more efficient biocatalysts for synthetic applications.

Multiscale simulation for protein design and enzyme evolution: from drug resistance to biocatalysis

Adrian Mulholland*
University of Bristol
* Presenting author

Combined quantum mechanics/molecular mechanics (QM/MM) methods have proved widely useful in modelling of reactions in proteins (identifying mechanisms and catalytic interactions) in protein-ligand binding and enzyme inhibition, in spectroscopy and other electronic structure calculations on biomolecules. Recent examples of QM/MM modelling of enzyme-catalysed reactions include the mechanism of choline cleavage in the glycyl radical enzyme choline trimethylamine-lyase (CutC) [1] and identifying the interactions that distinguish between substrates (oxytocin) and inhibitors (angiotensin IV) of insulin-regulated aminopeptidase (IRAP) [2]. QM/MM simulations have revealed mechanisms of bacterial enzymes that break down beta-lactams, causing antibiotic resistance [3]. QM/MM simulations also reveal determinants of their catalytic activity. They show that the active site electric field is a crucial factor in catalysis, e.g. in determining the ability of class A beta-lactamases to hydrolyse carbapenems [4]. Electric fields are optimized in natural enzymes for specific catalytic activities and provide a guide for enzyme design [5]. Electric field calculations and molecular dynamics simulations can be included in enzyme design to accelerate enzyme engineering and design [6]. Correlated ab initio methods, which can give chemically accurate productions of reaction barriers, can be applied, e.g. ab initio QM embedded in DFT, all within a MM environment in multiscale calculations, to overcome limitations of DFT [7]. QM/MM simulations can generate data to train efficient machine learning models of reactivity, which can provide accurate, efficient models for reaction simulations. QM/MM calculations can also investigate and predict electronic properties of proteins such as spectra [8] and can be included in practical protein design and engineering workflows to optimize such properties e.g. in the design and development of proteins as photovoltaics and for biomolecular electronics [9].

References

[1] Hanževački M. et al. J. Phys. Chem. B 129 9322 (2025)
[2] Hanževački M. et al. J. Chem. Inf. Model. 65 6261 (2025)
[3] Beer M. et al. ACS Infectious Diseases 8 1521 (2022)
[4] Jabeen H. et al. ACS Catalysis 14 7166 (2024)
[5] Suardíaz R. et al. Angew. Chem. Int. Ed. 64 e202515743 (2025)
[6] Merlicek L.P. et al. Angew. Chem. Int. Ed. 64 e202507031 (2025)
[7] Ranaghan K.E. et al. J. Chem. Inf. Model. 59 2063 (2019)
[8] Pfalzgraf HE et al. Chemical Science 16 16266-16283 (2025)
[9] Hutchins GH et al. Proceedings of the National Academy of Sciences USA 120 e2306046120 (2023)

Funding and acknowledgments: This work is part of a project that has received funding from the European Research Council under the European Horizon 2020 research and innovation program (PREDACTED Advanced Grant Agreement no. 101021207) to A.J.M.

Development and testing of QM/MM calculations

Diletta Boldrini, Ellen Nilsson, Xiaoli Sun, Ulf Ryde*

Lund University

* Presenting author

Combined quantum mechanical and molecular mechanical (QM/MM) calculations is a popular approach to study chemical reactions in enzymes and solvent.1 It employs quantum mechanical (QM) calculations for a small portion of the system, whereas the remainders are treated by molecular mechanics (MM) calculations. Thereby, the method may combine the accuracy of the QM calculations with the speed of the MM calculations. There exist many variants of QM/MM, e.g. additive or subtractive schemes, mechanical, electrostatic or polarised embedding, and different treatments of cut bonds and charge redistribution schemes.1, 2 Recently, we have done development and testing of QM/MM methods:

• Inspired by a study Krylov and coworkers on SARS-CoV-2 main protease3 we have investigated the reproducibility of QM/MM for this enzyme,4 as well as sulfite reductase. We compare three QM/MM software (ComQum, ORCA and AMBER), investigating the convergence using the big-QM approach5 and examining how the results depend on different setups of the protein.

• We compare the accuracy of different QM/MM charge redistribution schemes for the treatment of H-link atoms.

• We have investigated how charges are best obtained for metal sites both in molecular dynamics and QM/MM calculations.

I will discuss some of these results in my lecture.

References

(1) Senn, H. M.; Thiel, W. QM/MM methods for biomolecular systems. Angew. Chem. Int. Ed. 2009, 48 (7), 1198-1229. DOI: 10.1002/anie.200802019.

(2) Cao, L.; Ryde, U. On the difference between additive and subtractive QM/MM calculations. Front. Chem. 2018, 6, 89-89. DOI: 10.3389/fchem.2018.00089.

(3) Giudetti, G.; Polyakov, I.; Grigorenko, B. L.; Faraji, S.; Nemukhin, A. V.; Krylov, A. I. How Reproducible Are QM/MM Simulations? J Chem Theory Comput 2022, 18 (8), 5056-5067. DOI: 10.1021/acs.jctc.2c00286

(4) Sun, X.; Ryde, U. Reproducibility of QM/MM Calculations for the SARS-CoV-2 Main Protease. J Chem Theory Comput 2025, 21, 7711-7723. DOI: 10.1021/acs.jctc.5c00841

(5) Hu, L.; Eliasson, J.; Heimdal, J.; Ryde, U. Do quantum mechanichanical energies calculated for small models of protein-active sites converge. J. Phys. Chem. A 2009, 113 (43), 11793-11800. DOI: 10.1021/jp9029024.

Funding and acknowledgments: This investigation has been supported by grants from the Swedish research council (project 2022-04978). The computations were enabled by resources provided by LUNARC, the Centre for Scientific and Technical Computing at Lund University, and by the National Academic Infrastructure for Supercomputing in Sweden (NAISS) at NSC at Linköping University (Tetralith) and PDC at KTH Royal Institute of Technology (Dardel), partially funded by the Swedish Research Council through grant agreements no. 2022-06725 and 2018-05973.

Environment-dependent sticker strength in biomolecular condensates from simulations and quantum chemistry

David de Sancho, Lydia Armentia, Xabier Lopez*

Euskal Herriko Unibertsitatea and Donostia International Physics Center

* Presenting author

Biomolecular condensates are held together by "sticker" residues in disordered protein regions, mainly tyrosine (Tyr), phenylalanine (Phe), arginine (Arg) and lysine (Lys). Experiments show that Tyr and Arg are stronger stickers than Phe and Lys. For the aromatics, though, this goes against hydrophobicity scales and contact statistics from folded proteins, which favour Phe. We address this by combining atomistic MD of minimal peptide condensates, non-equilibrium alchemical free energy calculations and Density Functional Theory. Transfer free energies show that Tyr is favoured over Phe inside the condensate. This comes from stronger interactions and from Tyr hydrogen bonding with water in the hydrated dense phase. QM calculations reveal a crossover: as the dielectric constant of the medium decreases, as in a protein core, the hierarchy reverses and Phe becomes the stronger sticker. In contrast, Arg > Lys holds in every environment. This is driven mainly by the large dehydration penalty of Lys rather than by cation–π interactions. These results show how the chemical environment tunes protein–protein interactions and give a physical basis for the molecular grammar of phase separation.

References

[1] D. De Sancho and X. Lopez, 'Crossover in aromatic amino acid interaction strength between tyrosine and phenylalanine in biomolecular condensates', eLife, vol. 14, Art. no. RP104950, Dec. 2025, doi: 10.7554/eLife.104950.

[2] L. Armentia, X. López, and D. De Sancho, 'Molecular determinants of arginine versus lysine cation–π interactions in biomolecular condensates', Commun. Chem., vol. 9, Art. no. 279, 2026, doi: 10.1038/s42004-026-02075-7.

Funding and acknowledgments: The work has been financed by the Basque Government through Projects IT1584-22 and IT2067-26, and grant PID2024-158678NB-I00 funded by MICIU/AEI/10.13039/501100011033 and"ERDF A way of making Europe". Lydia Armentia acknowledges support from the Jesús de Gangoiti Foundation. The authors also thank the IZO-SGI SGIker (UPV/EHU/ERDF,EU) DIPC for technical and human support and for the allocation of computational resources. The authors thankfully acknowledge RES resources provided by the Barcelona Supercomputing Centre in MareNostrum5 (BCV-2025-2-0002).

Noncovalent weak interactions with DFT: from molecules to biogenic crystals

Carlo Adamo*

Chimie ParisTech

* Presenting author

Weak non-covalent interactions are ubiquitous in chemistry, yet they remain a challenging problem for most density functional approximations. The inclusion of empirical dispersion corrections has proven to be an effective strategy for overcoming many of these limitations. However, these approaches may exhibit shortcomings when applied to nonstandard systems, such as molecules far from equilibrium or large molecular clusters. In this presentation, we will discuss these issues through a series of examples, ranging from isolated molecular systems to biologically relevant molecular crystals [1,2]. We will also present alternative approaches, developed within the framework of density functional theory, that provide a more physically grounded description of these challenging interactions [3,4].

References

[1] Briccolani-Bandini, L.; Gnnanapareddy, B.; Labat, F.; Brémond, E.; Sancho-García, J. C.; Otero-de-la-Roza, A.; Scalmani, G.; Frisch, M. J.; Cardini, G.; DiLabio, G. A.; Adamo, C. J. Phys. Chem. Lett. 2026, 17 (3), 703–711

[2] Senou, P.; Adamo, C.; Labat, F. J. Phys. Chem. C 2025, 129, 8404–8416

[3] J. S. García, É. Brémond, M. Campetella, I. Ciofini, C. Adamo, J. Chem. Theory Comput., 2019, 15, 2944.

[4] E. Brémond, H. Li, J. C. Sancho-García, C. Adamo J. Phys. Chem. A, 2022, 126, 2590–2599.

Funding and acknowledgments: Funded by the European Union (ERC, project MaMa, n. 101097351). Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union or the European Research Council Executive Agency. Neither the European Union nor the granting authority can be held responsible for them.

Poster Session 1 – *Porto*

Machine-Learning Framework for Excitation Energies of Chromophores in Polarizable Environments

Chris John*, Edoardo Cignoni, Lorenzo Cupellini, Benedetta Mennucci

Department of Chemistry and Industrial Chemistry

* Presenting author

Multiscale methods integrating quantum chemical descriptions with molecular mechanics (MM) represent the standard modeling strategy employed to investigate properties and processes of molecules embedded in complex biological matrices.[1-3] Statistically meaningful calculations however must require performing quantum mechanics/MM (QM/MM) calculations over a sufficiently large ensemble of configurations, a task that remains computationally demanding. This challenge becomes particularly critical when investigating multichromophoric assemblies, such as light-harvesting complexes, employed by photosynthetic organisms to capture and funnel solar energy to the reaction centers. The protein matrix and surrounding solvent provide the specific electrostatic and polarization environment that tunes the excitation energies of the individual chromophores, thereby determining the efficiency of light harvesting. The large number of polarizable QM/MM calculations needed can represent a significant computational bottleneck. Machine-learning (ML) techniques offer a way out of this computational challenge.

Herein, we present an ML framework capable of predicting the different environmental contributions to excitation energies of chromophores in a polarizable embedding.[4] Our ML models are built in a hierarchical structure to capture both the effect of ground-state polarization and the response of the polarizable environment to the electronic transition. With the use of the right descriptors, the models trained on electrostatic-embedding QM/MM calculations are able to successfully predict the effects of a polarizable environment on excitation energies. The ML models are applied to three prototypical photosynthetic chromophores (chlorophyll a, chlorophyll b, and lutein) and are used to reproduce the excitonic structure of a multichromophoric system unseen in the training set to a level of accuracy offered by a polarizable QM/MM calculation, while taking a fraction of the time.

References

1. Senn, H. M.; Thiel, W. QM/MM Methods for Biomolecular Systems. Angew. Chem., Int. Ed. 2009, 48, 1198–1229.
2. Boulanger, E.; Harvey, J. N. QM/MM Methods for Free Energies and Photochemistry. Curr. Opin. Struct. Biol. 2018, 49, 72–76.
3. Mennucci, B.; Corni, S. Multiscale Modelling of Photoinduced Processes in Composite Systems. Nat. Rev. Chem. 2019, 3, 315.
4. John, C.; Cignoni, E.; Cupellini, L.; Mennucci, B. Machine-Learning Framework for Excitation Energies of Chromophores in Polarizable Environments. J. Chem. Inf. Model. 2026, 66, 2030–2040.

Funding and acknowledgments: C.J. acknowledges the Italian Ministry of University and Research for the funding provided by the European Union-NextGenerationEU-PNRR, Mission 4 Component 2 Investment line 1.2. L.C. and B.M. acknowledge financial support from the Italian MUR through the PRIN 2022 grant 2022N8PBLM (PhotoControl). L.C. and B.M. also acknowledge financial support from ICSC-Centro Nazionale di Ricerca in high-performance computing, big data, and quantum computing, funded by the European Union-NextGeneration EU-PNRR, Mission 4 Component 2 Investment line 1.4.

The catalytic cycle of a fatty acid photodecarboxylase from a multiscale QM/MM approach

Giacomo Londi*, Benedetta Mennucci

University of Pisa, Department of Chemistry and Industrial Chemistry, Pisa, Italy

* Presenting author

Fatty acid photodecarboxylases from Chlorella variabilis (CvFAPs) are rare photoenzymes that catalyze light-driven, redox-neutral decarboxylation of fatty acids into C1-shortened hydrocarbons,[1,2] although several key steps of their catalytic mechanism remain unclear.

Here, we use a multiscale computational approach combining classical MD and QM/MM MD simulations to characterize the full catalytic cycle. We first investigate the protein-driven forward electron transfer (fET) from the fatty acid substrate to photoexcited flavin cofactor. Our results reveal that fET triggers active-site rearrangements, including reorganization of a nearby water molecule into a hydrogen bond with the flavin and migration of the substrate carboxylate away from the cofactor, collectively enabling a downhill electron transfer on the hundreds of picoseconds timescale. Subsequent QM/MM MD simulations show that the resulting fatty acid radical undergoes rapid decarboxylation within a few picoseconds, overcoming a small activation barrier (~2 kcal/mol).[3] We then examine the termination step, finding that the alkyl radical is mainly quenched via proton transfer from a conserved arginine (scenario B), while bicarbonate formation involving water is only rarely observed (scenario A), suggesting a minor role at room temperature.[4] Finally, excited-state QM/MM calculations indicate that different active-site configurations reproduce similar red shifts in flavin absorption, consistent with transient FADRS species.[2,5]

Overall, this work provides a coherent molecular picture of CvFAP catalysis, highlighting the interplay between active-site electrostatics and water dynamics.

References

[1] D. Sorigué et al., Science, 2017, 357, 903–907. https://www.science.org/doi/10.1126/science.aan6349
[2] D. Sorigué et al., Science, 2021, 372, eabd5687. https://www.science.org/doi/10.1126/science.abd5687
[3] G. Londi et al., JACS Au, 2025, 5, 1, 158–168. https://doi.org/10.1021/jacsau.4c00853
[4] A. Bonvalet et al., ACS Catal, 2026, 16, 6, 5744–5756. https://doi.org/10.1021/acscatal.5c08787
[5] D. Heyes et al., ACS Catal, 2020, 10, 12, 6691–6696. https://doi.org/10.1021/acscatal.0c01684

Funding and acknowledgments: This work has been supported by the Italian Ministry of University and Research for funding provided by the European Union-NextGenerationEU-PNRR, Missione 4, Componente 2, Linea di investimento 1.2 (CUP I53C24002050006) and by the Italian Ministry of University and Research (Fondo Italiano per la Scienza, FIS 2) under the grant FIS-2023-00430.

Probing the impact of histone PTMs on guanine ionization potential in the nucleosome: a multiscale MD/QM-MM study

Sébastien Menant*, Natacha Gillet

CNRS, ENS de Lyon, LCH, UMR 5182, 69342, Lyon cedex 07, France

* Presenting author

The Nucleosome Core Particle (NCP) is the primary unit of chromatin, in which 147 base pairs of DNA are wrapped around an octamer of four types of histone proteins (H2A, H2B, H3 and H4). The disordered N-terminal tails of histones are the target of Post-Translational Modifications (PTMs), which regulate the chromatin accessibility and are implicated in numerous diseases including cancer. [1] Among PTMs, lysine acetylations neutralise the positive charge of the modified residue, altering histone tail dynamics and modulating histone-DNA interactions. [2] Our previous FO-DFTB/MM studies on unmodified NCP have shown that guanine IPs are heterogeneously distributed, with hot spots of high IP correlated with the proximity of positively charged histone residues. [3] This can impact the formation of DNA-damages such as DNA-protein cross-link, after guanine oxidations. [4] Understanding how PTMs modulate guanine IPs within the NCP is therefore of great interest to connect epigenetic and oxidative damage. We performed microsecond all-atom molecular dynamics simulation of the NCP with and without H2B tail acetylation, using the OPC water model with the ff19SB and OL15 force fields, on both, the 1KX5 containing the alpha-palindromic sequence, and the Widom-601 sequence. Guanine Ionization Potentials (IPs) were computed using the FO-DFTB/MM framework. Preliminary results suggest that acetylation affects guanine IPs both at sites close to and far from the PTMs and the DNA sequence modulates the amplitude of this effect. This underlines that both chemical properties and conformational landscape of the tail can tune the DNA sensitivity with regards to oxidative damages.

References

[1] D. Corujo and M. Buschbeck, « Post-Translational Modifications of H2A Histone Variants and Their Role in Cancer », Cancers, vol. 10, no 3, p. 59, Feb. 2018, doi: 10.3390/cancers10030059.

[2] R. Patel, A. Onyema, P. K. Tang, and S. M. Loverde, « Conformational Dynamics of the Nucleosomal Histone H2B Tails Revealed by Molecular Dynamics Simulations », J. Chem. Inf. Model., vol. 64, no 12, p. 4709 4726, Jun. 2024, doi: 10.1021/acs.jcim.4c00059.

[3] M. Kermarrec, E. Dumont, and N. Gillet, « What tunes guanine ionization potential in a nucleosome? An all-in-one systematic QM/MM assessment », Biophysical Journal, vol. 123, no 18, p. 3100 3106, Sept. 2024, doi: 10.1016/j.bpj.2024.07.009.

[4] T. Wen, M. Kermarrec, E. Dumont, N. Gillet, and M. M. Greenberg, « DNA–Histone Cross-Link Formation via Hole Trapping in Nucleosome Core Particles », J. Am. Chem. Soc., vol. 145, no 43, p. 23702 23714, Nov. 2023, doi: 10.1021/jacs.3c08135.

Tuning protein function through allosteric communication networks

Lucas Lee, Olivia Enny, Patrick J. Loria, Victor S. Batista, Federica Maschietto*

Université Paris Cité, Institute de Biologie Physico-Chimique, CNRS, Paris, 75005

* Presenting author

Allosteric regulation provides a route to tune protein function through perturbations applied away from the active site. Harnessing this mechanism requires understanding how local perturbations redistribute communication across a protein and how these changes can be mapped quantitatively. We address these challenges by combining experiments with network analysis of molecular dynamics simulations.

Using imidazole glycerol phosphate synthase as a model system, we combine molecular dynamics, kinetics and NMR to investigate how interface mutations alter allosteric function. The mutations reshape interface dynamics and produce distinct changes in substrate affinity and catalytic activation, shifting the balance between K-type and V-type regulation. These results show that local perturbations reprogram enzyme function by redistributing allosteric communication.

They also expose a methodological limitation: protein communication is commonly represented using residue interaction networks, where conventional analyses identify a single optimal pathway mediating allosteric information transfer, although small variations in MD-derived correlations can cause abrupt, replica-dependent path switching. To address this, we reformulate protein communication as a weighted ensemble of optimal and near-optimal paths sampled by beam search. Path costs define a Gibbs distribution, and edge traffic is computed as the expected usage of each interaction across the ensemble.

Applied to KRAS, where extensive mutational and state-specific functional data are available, ensemble traffic converges with increasing beam width, is more reproducible than shortest-path and alternative network measures, and resolves state-dependent communication differences associated with mutational effects. This formalism provides a convergent, experimentally testable mapping of allosteric routes, enabling mechanistic interpretation and the identification of perturbations capable of tuning protein function.

References

Maschietto, F.; Enny, O.; Chaudhuri, A.; Batista, V. S.; Loria, J. P. Rewiring V-type and K-type enzyme allostery through subunit interface mutations. bioRxiv (2026). DOI: 10.64898/2026.05.29.728626.

Maschietto, F.; Allen, B.; Kyro, G. W.; Batista, V. S. MDiGest: A Python package for describing allostery from molecular dynamics simulations. J. Chem. Phys. 158, 215103 (2023). DOI: 10.1063/5.0147415.

Weng, C.; Faure, A. J.; Escobedo, A.; Lehner, B. The energetic and allosteric landscape for KRAS inhibition. Nature 626, 643–652 (2024). DOI: 10.1038/s41586-023-06954-0.

Funding and acknowledgments: We thank CNRS and the Fondation de la Maison de la Chimie for funding

Second-Shell Hydrogen Bond Engineering Tunes Catalytic Aspartate Polarization and Transition State Stabilization in IsMHETase

Kristine S. R. Clausen[1], Alexandre V. Pinto[2,*], Robin Dorau[3], Malene B. Keller[1], Kenneth Jensen[3], Kim Borch[3], Pedro A. Fernandes[2], Alexandre L. Magalhães[2], Maria J. Ramos[2], Peter Westh[1]

[1] *Department of Biotechnology and Biomedicine, Protein Chemistry and Enzyme Technology Section, Technical University of Denmark, 2800 Kgs. Lyngby, Denmark*

[2] *LAQV/Requimte, Departamento de Química e Bioquímica, Faculdade de Ciências da Universidade do Porto, Rua do Campo Alegre, s/n, 4169-007 Porto, Portugal*

[3] *Novonesis, Biologiens Vej 2, 2800 Kgs. Lyngby, Denmark*

* Presenting author

The catalytic aspartate of serine hydrolases drives transition state stabilization through charge relay within the conserved Asp-His-Ser triad. While the roles of the catalytic histidine and serine in nucleophilic attack are well established, the electrostatic environment surrounding the aspartate and its potential as an engineering target remains largely unexplored. Using IsMHETase from Ideonella sakaiensis as a model system, we show that a single substitution at a substrate-binding residue, F495H, considerably enhances polarization of the Asp492-His528 dyad at the tran-sition state of the rate-limiting deacylation step, yielding a 3.4-fold increase in kcat. His495 achieves this effect not by altering substrate binding affinity but through conformational dynamics that reshape the hydrogen bond network around the neighboring Asp492, lowering its predicted pKa, increasing dyad polarization at the transition state, and ultimately amplifying electrostatic stabi-lization of the developing oxyanion.[1] QM/MM umbrella sampling at the SCC-DFTB/Amber ff14SB level corroborates a reduced free energy barrier for deacylation in the F495H variant, and Mulliken charge analysis of transition state ensembles confirms both stronger dyad polarization and a higher negative charge on the tetrahedral oxyanion relative to wild type. Together, these findings identify the hydrogen bond network surrounding the catalytic aspartate as a sensitive electrostatic handle for modulating transition state stabilization in serine hydrolases, with direct implications for the rational engineering of plastic-degrading enzymes.

References

[1] K. S. R. Clausen et al., “Enhancing the catalytic performance of IsMHETase through electrostatic engineering of the active site,” Chem Circularity, p. 100117, Aug. 2026, doi: 10.1016/j.checir.2026.100117.

Funding and acknowledgments: K.S.R.C. and P.W. thank Jesper Brask (Novonesis) for preparing MHET for enzyme analysis. We are thankful for the financial support from the Innovation Fund Denmark (grant 0224-00033A) and the Novo Nordisk Foundation (grant NNF17SA0028392). A.V.P. gratefully acknowledges financial support from the Fundação para a Ciência e a Tecnologia (FCT) through a PhD fellowship (reference 2021.05918.BD), as well as funding from the EnZync (Center for Enzymatic Deconstruction of Thermoset Plastics) project (reference 0072891) awarded through a research fellowship. A.V.P., P.A.F., A.L.M., and M.J.R. acknowledge financial support from Portuguese national funds (FCT/MECI - Fundação para a Ciência e a Tecnologia and Ministério da Educação, Ciência e Inovação) through the project UID/50006/2025 - Laboratório Associado para a Química Verde - Tecnologias e Processos Limpos. A.V.P., P.A.F., A.L.M., and M.J.R. also acknowledge the European High-Performance Computing Joint Undertaking (EuroHPC JU) for granting access to Deucalion, the petascale EuroHPC supercomputer located in Guimarães, Portugal, under proposal 2025.00056.CPCA.A3.

Mechanistic Insights into PET Hydrolysis by a Novel PETase from QM/MM Simulations

Clauber Henrique Souza da Costa[1]*, Luiz Patrick Cordeiro Josino[1], Fabio M. Squina[2], Munir Skaf[1]

[1] *Institute of Chemistry and Center for Computing in Engineering & Sciences (CCES), University of Campinas (UNICAMP), Campinas, São Paulo, Brazil*

[2] *Laboratory of Molecular Sciences, University of Sorocaba (UNISO), Sorocaba, SP, Brazil*

* Presenting author

Plastic accumulation has become a major environmental challenge, driving the search for efficient biocatalysts for poly(ethylene terephthalate) (PET) degradation. In an ongoing study, I1_Pazy (I1) was identified by sequence-based metagenomic screening as a novel thermophilic PET hydrolase with similarity to lipolytic enzymes. I1 exhibits optimal activity at 50 °C and pH 8.0, a melting temperature (Tm) of 68 °C, activity toward highly crystalline PET, and a calculated catalytic free-energy barrier (~18 kcal mol^{-1}) comparable to wild-type IsPETase. Here, we investigated the catalytic mechanism of I1 and evaluated a Proposed Catalytic Triad (PCT) relative to the Canonical Catalytic Triad (CCT). Two mechanistic pathways were characterized using classical molecular dynamics (MD) and hybrid quantum mechanics/molecular mechanics (QM/MM) simulations. Free energy surfaces (FESs), obtained from potentials of mean force (PMFs), enabled a detailed description of the reaction mechanism. Both pathways follow a four-step mechanism comprising acylation and deacylation, with formation of the first tetrahedral intermediate (TI1) during the initial step, consistent with previously reported PETase mechanisms. However, significant differences were observed. For the CCT pathway, the rate-limiting step is the second acylation step, whereas for the PCT pathway the highest free-energy barrier occurs during the fourth step, corresponding to deacylation. These findings support the existence of a potential alternative catalytic triad and expand the current understanding of PET hydrolysis. They also provide a foundation for rational enzyme engineering, site-directed mutagenesis, and computational protein design toward more efficient PET-degrading biocatalysts.

References

Yoshida, S. et al. A bacterium that degrades and assimilates poly(ethylene terephthalate). Science (1979) 351, 1196–1199 (2016).

Austin, H. P. et al. Characterization and engineering of a plastic-degrading aromatic polyesterase. Proc Natl Acad Sci U S A 115, E4350–E4357 (2018);

Boneta, S., Arafet, K. & Moliner, V. QM/MM Study of the Enzymatic Biodegradation Mechanism of Polyethylene Terephthalate. J Chem Inf Model 61, 3041–3051 (2021);

dos Santos, A. M., da Costa, C. H. S., Silva, P. H. A., Skaf, M. S. & Lameira, J. Exploring the Reaction Mechanism of Polyethylene Terephthalate Biodegradation through QM/MM Approach. J Phys Chem B 128, 7486–7499 (2024);

Martí, S., Moliner, V. & Tuñón, I. Improving the QM/MM Description of Chemical Processes: A Dual Level Strategy To Explore the Potential Energy Surface in Very Large Systems. [J. Chem. Theory Comput. 1, 1008–1016 (2005)]. J Chem Theory Comput 2, 216 (2006);

Funding and acknowledgments: Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP, Grants 2013/08293-7, 2022/04695-2, 2022/04703-5, 2025/13827-8 and 2025/15191-3), Coaraci Supercomputer for computer time (Fapesp grant: 2019/17874-0) and the Center for Computing in Engineering and Sciences at Unicamp (Fapesp grant: 2013/08293-7).

Unexpected advantages of physics-aware ML/MM potentials

Kirill Zinovjev*
Universidad de Valencia
* Presenting author

QM/MM molecular dynamics simulations are the state-of-the-art approach for computational studies of reactivity in condensed phase, including enzyme catalysis: they can handle systems consisting of hundreds of thousands of atoms, while allowing the breaking and formation of chemical bonds in a small region described by a QM method. Nevertheless, even cheap QM methods (such as DFT) often struggle to provide sufficient sampling of the environment, forcing the use of unreliable but fast semiempirical methods.

A way to overcome this speed-accuracy trade-off is to replace QM methods with machine-learning potentials (MLPs). The promise of MLPs is to provide an accuracy close to QM while being orders of magnitude faster. However, in contrast to QM methods, which can naturally include the MM environment, ML potentials can generally only predict gas-phase energies. This limitation gave rise to specialized ML/MM potentials that are trained to reproduce QM/MM energies by explicitly providing the MM environment to the ML model.

A different approach is taken by the Electrostatic ML Embedding (EMLE) scheme [1]. Instead of training the model on reference QM/MM energies, EMLE relies on physical models of electron density and polarizability to predict the response of the ML region to external fields. I show that, in addition to producing highly transferable models due to training exclusively on gas-phase data, the EMLE scheme leads to several unexpected applications beyond simply mimicking QM/MM. For instance, EMLE provides predictions of Raman spectra, avoids the charge spill-out issue present in QM/MM [2], and enables the development of enhanced sampling methods impossible with standard QM/MM or naïve ML/MM potentials. These results show how understanding of molecular systems can inspire ML architectures that go beyond brute-force energy fitting and pave the way for the development of physically-motivated ML models that are efficient, accurate, and transferable.

References

[1] K. Zinovjev, "Electrostatic embedding of machine learning potentials," J. Chem. Theory Comput., vol. 19, no. 6, pp. 1888–1897, Mar. 2023, doi: 10.1021/acs.jctc.2c00914.
[2] V. Gradisteanu et al., "Simulating enzyme catalysis with electrostatically embedded machine learning potentials," Chem. Sci., vol. 17, no. 17, pp. 8542–8556, May 2026, doi: 10.1039/D6SC01156J.

Funding and acknowledgments: Grant RYC2024-051397-I, funded by MICIU/AEI/10.13039/501100011033 and by the ESF+. Grant EUR2025-165005, funded by MICIU/AEI/10.13039/501100011033. The author acknowledges the Tirant and Artemisa supercomputers of the University of Valencia and MareNostrum5 of Barcelona Supercomputing Center (projects QH-2024-1-0005 and QH-2024-2-0009) for computational resources.

Multiscale Simulations Reveal How DNA Topology Reorganizes GCN4 Recognition

Gioacchino Schifino[1,*], Rosanna Mattossovich[2], Rosa Merlo[2], Mikael Widersten[1], Antonino Caliò[3], Annalisa Pastore[4], Antonietta Parracino[1], Anna Valenti[2]

[1] *Department of Chemistry - BMC, Uppsala University, Uppsala, Sweden*
[2] *Institute of Biosciences and BioResources, National Research Council of Italy, Naples, Italy*
[3] *Univ. Grenoble Alpes, CNRS, LiPhy, Saint-Martin-d'Hères, France*
[4] *Institute of Brain Sciences, Hammersmith Hospital, London, UK; The Wohl Institute, King's College London, London, UK; Elettra Sincrotrone Trieste, Trieste, Italy*

* Presenting author

DNA supercoiling links local protein–DNA recognition to the global mechanics of topologically constrained genomes. Here, we use multi-replica coarse-grained simulations to characterize a covalently closed plasmid containing a specific GCN4 recognition site across four topological states and multiple protein-loading conditions. The simulations combine oxDNA2 with a DNA-network model including an explicit electrostatic term developed for this work, enabling analysis of writhe, global shape, nonlocal DNA contacts, target-site geometry, and collective protein organization [1].

Supercoiling does not induce a simple monotonic compaction response. Instead, its sign and magnitude generate distinct conformational landscapes and reshape the three-dimensional environment of the GCN4 site. Positive supercoiling promotes contacts between contour-distant DNA regions, increases DNA-rich environments near the target, and favours GCN4 arrangements compatible with interactions across separated DNA segments. Protein loading further stabilizes selected topology-dependent contacts and shifts the preferred writhe while preserving substantial conformational heterogeneity.

These findings support a capture–recapture mechanism in which topology regulates target localization by organizing potential DNA landing surfaces rather than simply altering plasmid size [2]. Unlike reduced minicircle models focused on local effects [1], this full-plasmid approach reveals long-range DNA-contact and protein-organization patterns inaccessible to smaller systems. It also complements atomistic and SAXS-guided descriptions of the local GCN4–DNA ensemble [3], identifying supercoiling as a multiscale regulator of transcription-factor recognition.

References

[1] R. Mattossovich et al., "DNA Supercoiling Modulates bZIP Transcription Factor-DNA Interaction," bioRxiv, 2026, doi:10.64898/2026.05.06.722604.
[2] B. van den Broek et al., "How DNA Coiling Enhances Target Localization by Proteins," Proceedings of the National Academy of Sciences of the USA, 105, 15738-15742, 2008.
[3] A. Caliò et al., "DNA Binding Drives Phase Separation of the Gcn4 bZIP Domain and Reveals Its Conformational Ensemble in the Diluted and Condensate Phases," bioRxiv, 2026, doi:10.64898/2026.02.10.704833.

Funding and acknowledgments: This work was supported by the European Union through the iSenseDNA project (grant agreement No. 101046920). Computational resources were provided by NAISS, funded by the Swedish Research Council.

Binding Mechanism, Design and Synthesis of Fibroblast Activation Protein Inhibitors

Joep W. Wals[1]*, Rui P. P. Neves[2], Pedro A. Fernandes[2], Hans De Winter[1]

[1] *Laboratory of Medicinal Chemistry, Department of Pharmaceutical Sciences, University of Antwerp, Universiteitsplein 1, 2610 Wilrijk, Belgium*

[2] *LAQV@REQUIMTE, Departamento de Química e Bioquímica, Faculdade de Ciências, Universidade do Porto, Rua do Campo Alegre s/n, 4169-007 Porto, Portugal*

* Presenting author

Fibroblast activation protein (FAP) is an enzyme highly expressed in cancer-associated fibroblasts. Over the past years, several FAP inhibitors (FAPIs) have been developed for tumor imaging. These approaches typically involve covalently linking a metal-loaded chelator to a small molecule ligand that targets FAP. Prolonged tumor retention of FAPIs is desirable to support theranostic applications, which integrate both diagnostic and therapeutic functions. Therefore, we sought to elucidate the binding mechanism of our in-house–designed FAPI lead compound, UAMC-1110. Initial molecular dynamics simulations yielded a noncovalent binding pose of the ligand. Subsequently, QM/MM calculations were performed to investigate the covalent binding mechanism of UAMC-1110. Our results corroborate that the compound forms a covalent complex with the receptor through a reaction pathway that begins with proton transfer from S624 to H734, followed by a concerted, asynchronous nucleophilic attack of S624 on the nitrile warhead. The resulting imidate anion is stabilized via two possible routes: (1) protonation mediated by H734 through two water molecules, and (2) direct protonation by Y541 followed by reprotonation. Covalent MD simulations reveal that H734 interacts more frequently with the imidate anion than Y541, identifying a previously unrecognized and kinetically favored protonation pathway via H734, further supported by water-density and Gibbs energy calculations. Simulations of the final product state additionally indicate that neither residue remains in proximity to the covalent adduct, making reversibility of the reaction complex unlikely and instead suggesting hydrolysis as the most plausible mechanism for complex dissociation. Based on these computational findings, we designed and synthesized novel inhibitors incorporating an alternative warhead to improve tumor retention for theranostic applications.

References

Wals JW, Neves RPP, Fernandes PA, De Winter H (2026) Binding mechanism of UAMC-1110 to fibroblast activation protein. Journal of Chemical Information and Modeling 66(12):7179–7189.

Funding and acknowledgments: J.W.W. received a travel grant from the Fonds Wetenschappelijk Onderzoek Grant V427319N. The computational resources for this project were provided by the VSC (Flemish Supercomputer Center; gpr_compute_2023_037) and the EuroCC Belgium (LUMI-BE; project_465000650). R.P.P.N. thanks FCT for funding through the Individual Call to Scientific Employment Stimulus (ref. 2021.00391.CEECIND/CP1662/CT0003 DOI: https//doi.org/10.54499/2021.00391.CEECIND/CP1662/CT0003). 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.

Automating the Exploration of Enzyme Mechanistic Space

Matilde M. M. Sousa [1], Rui P. P. Neves [2], Maria J. Ramos [2], Pedro. A. Fernandes [2], António J. M. Ribeiro [1]*
1. LAQV, REQUIMTE - Faculty of Pharmacy of University of Porto, Portugal.
2. LAQV, REQUIMTE - Faculty of Sciences of University of Porto, Portugal.
* Presenting author

Do enzymes always follow the same linear sequence of catalytic steps, or are mechanisms better described as a network of possible chemical pathways? Most descriptions of enzyme mechanisms are a single sequence of intermediates and chemical transformations, even though an active site may in principle support several routes between reactants and products. Alternative mechanisms are not systematically investigated because evaluating individual mechanism proposals with QM/MM calculations is still technically demanding, requiring substantial manual effort and months of work for experienced researchers.

We have been developing computational tools designed to overcome these limitations and make the exploration of enzyme mechanisms more systematic. EzMechanism automatically generates mechanistic proposals using the three-dimensional structure of the active site and catalytic rules derived from previously characterized enzymes from the M-CSA (Mechanism and Catalytic Site Atlas). Applying this approach to a diverse set of enzymes shows that alternative pathways can be hypothesized, involving changes in the order of catalytic events, the participation of different residues, or substantially different chemical transformations.

Generating plausible pathways, however, is only the first step. Establishing whether these alternatives are actually accessible requires estimating their energetics. We are therefore currently extending this previous work with new tools that couple automated mechanism generation with QM/MM calculations, reducing the amount of manual work required to test individual mechanistic hypotheses. Our longer-term goal is to move from studying linear mechanisms towards a more systematic characterization of the chemical space that enzyme active sites can explore.

References

1. Ribeiro, A. J. M.; Riziotis, I. G.; Tyzack, J. D.; Borkakoti, N.; Thornton, J. M. EzMechanism: An Automated Tool to Propose Catalytic Mechanisms of Enzyme Reactions. Nat Methods 2023, 20 (10), 1516–1522. https://doi.org/10.1038/s41592-023-02006-7
2. Ribeiro, A. J. M.; Holliday, G. L.; Furnham, N.; Tyzack, J. D.; Ferris, K.; Thornton, J. M. Mechanism and Catalytic Site Atlas (M-CSA): A Database of Enzyme Reaction Mechanisms and Active Sites. Nucleic Acids Res 2018, 46 (D1), D618–D623. https://doi.org/10.1093/nar/gkx1012
3. Ribeiro, A. J. M.; Fernandes, P. A.; Ramos, M. J. Off the Beaten (Catalytic) Path: Charting the Mechanistic Space of Enzyme Reactions. J. Chem. Phys. 2025, 163 (13), 134102. https://doi.org/10.1063/5.0288283

Funding and acknowledgments: This work received financial support from 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. AJMR also acknowledges project 2022.03058.CEECIND/CP1724/CT0005 (DOI: 10.54499/2022.03058.CEECIND/CP1724/CT0005), and RPPN acknowledges project 2021.00391.CEECIND/CP1662/CT0003 (DOI: 10.54499/2021.00391.CEECIND/CP1662/CT0003).

Toward a Balanced Description of DNA Structure: OL24, A/B Equilibria, and the Role of Solvent

Marie Zgarbová*, Petr Jurečka

Department of Physics, University of Ostrava, Czech Republic
Department of Physical Chemistry, Palacky University Olomouc, Czech Republic

* Presenting author

Accurate representation of DNA conformational equilibria remains a central challenge in molecular simulations, particularly for transitions coupled to sugar puckering and backbone flexibility. The balance between A- and B-DNA forms plays a key role in protein–DNA recognition and in the structural properties of DNA/RNA hybrid duplexes, yet it is highly sensitive to force field parameterization. Here, we assess the performance of a recently introduced DNA force field (OL24 [1]) in describing A/B conformational equilibria and sugar puckering across a range of systems, including canonical DNA duplexes, DNA/RNA hybrids, and selected protein–DNA complexes. The results are compared with established force fields to identify systematic trends and remaining limitations. We show that OL24 improves the description of the A/B equilibrium by increasing the population of A-like conformations and providing a more balanced representation of sugar pucker states, while preserving the structural stability of canonical B-DNA. We further examine the role of explicit solvent models in modulating these equilibria and related structural features, highlighting the impact of solvent representation on DNA conformational behavior.

References

[1] M. Zgarbova, J. Sponer, and P. Jurecka, 'Refinement of the Sugar Puckering Torsion Potential in the AMBER DNA Force Field', J. Chem. Theory Comput., vol. 21, no. 2, pp. 833-846, Jan. 2025, doi: 10.1021/acs.jctc.4c01100

Funding and acknowledgments: This contribution has been produced with the financial support of the European Union under the LERCO project number CZ.10.03.01/00/22_003/0000003 via the Operational Programme Just Transition.

A First Principle-Based Design of a Supramolecular Cage for Efficient Methane Capture and Selective Oxidation

Dinesh Singh*, Shakir Ali Siddiqui, Sason Shaik, Kshatresh Dutta Dubey

Ph.D. scholar at Shiv Nadar Institution of Eminence, Delhi, India

* Presenting author

The selective conversion of methane to methanol presents a considerable challenge in catalysis, due to the strong C-H bond of methane and its low polarizability, which means that oxidising methane in a catalytic system is inherently difficult. Supramolecular cages can provide a useful approach to solving this problem by using host-guest chemistry to confine the methane in a designed microenvironment and exerting control on the methane oxidation reaction surface in the host cage. In this study, we designed a series of porphyrin-based supramolecular cages, with substituents placed to generate localised electric fields. These electric fields modified the electronic environment in which the confinement and oxidation occur, resulting in tuned activation of methane and selective oxidation towards methanol. We showed that by varying the substituent pattern, the efficacy or catalytic efficiency was modified with the cages optimised in conversion and selectivity compared to normal homogeneous catalysts. Computational estimates showed that the local electric field decreases the activation barrier and stabilises the intermediate and product of the intended reaction. Our work paves the way for the rational design of supramolecular catalysts with tailored electronic properties, offering a sustainable and efficient alternative for methane valorisation.

References

[1] Siddiqui, S. A.; Stuyver, T.; Shaik, S.; Dubey, K. D. Designed Local Electric Fields— Promising Tools for Enzyme Engineering, Jacs Au, vol. 3, no. 12, pp. 3259-3269, Dec. 2023, doi: 10.1021/jacsau.3c00536

[2] Shaik, S.; Danovich, D.; Kalita, S.; Dubey, K. D. Oriented electric fields— Universal catalysts. Acc. Chem. Res.,vol. 58, no. 19, pp. 3071-3080, Sep. 2025, doi: 10.1021/acs.accounts.5c00508

[3] Hong, S.; Rohman, M. R.; Jia, J.; Kim, Y.; Moon, D.; Kim, Y.; Ko, Y. H.; Lee, E.; Kim, K. Porphyrin boxes: rationally designed porous organic cages, Angew. Chem. Int. Ed., vol. 54, no. 45, pp. 13241-13244, Aug. 2015, doi: 10.1002/anie.201505531

Funding and acknowledgments: I would like to acknowledge my supervisor, Dr. Kshatresh Dutta Dubey, for his support and guidance, and Shiv Nadar Foundation for funding.

Computational insights into the catalytic mechanism of the Urethanase UMG-SP1

Javier Sanabria-Montalbán, Kirill Zinovjev, Iñaki Tuñón, Juan Aragó*

Instituto de Ciencia Molecular (ICMol) / Universitat de València

* Presenting author

Polyurethane (PU) is a widely used plastic, but it is difficult to degrade naturally. For this reason, enzymatic biodegradation has emerged as an attractive and green biotechnology to depolymerize several hydrolysable plastics. Recently, a family of urethanases able to break down low molecular weight dicarbamates and even PUs have been discovered.[1] Although the catalytic mechanism of these enzymes has been investigated in the last years,[2,3,4] many aspects remain to be unveiled. To understand the molecular origin of the PU-degrading enzyme's catalytic activity, a computational study of the UMG-SP1 enzyme has been carried out by employing classical and hybrid QM/MM molecular dynamics simulations. After testing several mechanisms, our work shows that the UMG-SP1 urethanase displays a strong preference for the cleavage of the C-N bond in the acylation step over the C-O (as reported in previous studies [4]) with the TDA-DEG dicarbamate ligand. In the proposed mechanism, the energy barrier for the acylation and deacylation steps are predicted to be quite similar (19.5 and 18.5 kcal·mol−1, respectively) and the values are consistent with the experimentally determined barrier (17.8 kcal·mol−1).

References

[1] Y. Branson et al., "Urethanases for the Enzymatic Hydrolysis of Low Molecular Weight Carbamates and the Recycling of Polyurethanes," Angew. Chemie Int. Ed., vol. 62, no. 9, p. e202216220, Feb. 2023, doi: 10.1002/anie.202216220.

[2] P. Paiva et al., "Unveiling the enzymatic pathway of UMG-SP2 urethanase: insights into polyurethane degradation at the atomic level," Chem. Sci., vol. 16, no. 5, pp. 2437–2452, 2025, doi: 10.1039/D4SC06688J.

[3] K. Świderek, K. Arafet, V. de Sousa Batista, D. Grajales-Hernández, F. López-Gallego, and V. Moliner, "Insights into the Catalytic Activity of a Metagenome-Derived Urethanase," J. Am. Chem. Soc., vol. 147, p. 42511, Nov. 2025, doi: 10.1021/jacs.5c13147.

[4] M. Zheng et al., "Computational Redesign of a Urethanase for Efficient Polyurethane Depolymerization," ACS Catal., vol. 16, no. 7, pp. 6577–6588, Apr. 2026, doi: 10.1021/acscatal.5c08984.

Funding and acknowledgments: Financial support by the PID2024-162840NB-I00 project funded by MICIU/AEI/10.13039/501100011033 and by ERDF/EU "ERDF A way of making Europe" is gratefully acknowledged.

Temperature-Dependent Conformational Equilibrium of RNA 2'-OH Groups in Molecular Dynamics

Jan Salomon*, Petr Jurečka

Palacky University Olomouc

* Presenting author

The orientation of the 2'-OH group plays an important role in the conformational equilibria of RNA, particularly in non-canonical motifs. Stabilizing signature interactions are often associated with a hydroxyl group being oriented toward the nucleobase. In stem regions, however, the equilibrium is more nuanced. NMR studies have arrived at conflicting conclusions [1], some supporting a base-oriented conformation [2], while others favor a torsion directed toward the backbone [3]. A recent joint X-ray and neutron diffraction study resolved the ambiguity of the 2'-OH orientation in the Sarcin-Ricin Loop by direct observation of hydrogen positions at low temperature.[4] We use low-temperature molecular dynamic simulations to reproduce these conformational equilibria and study their dependence on temperature. Our goal is to reconcile contradictory experimental findings and evaluate the ability of current OL3 AMBER force field to accurately describe the conformational preferences of the 2'-OH group in RNA.

References

[1] J. Fohrer, M. Hennig, and T. Carlomagno. "Influence of the 2'-Hydroxyl Group Conformation on the Stability of A-form Helices in RNA". In: Journal of Molecular Biology 356.2 (2006), pp. 280–287. doi: https://doi.org/10.1016/j.jmb.2005.11.043.

[2] J. Ying and A. Bax. "2'-Hydroxyl Proton Positions in Helical RNA from Simultaneously Measured Heteronuclear Scalar Couplings and NOEs". In: Journal of the American Chemical Society 128.26 (2006), pp. 8372–8373. doi: 10.1021/ja0606226.

[3] S. Nozinovic et al. "Determination of the Conformation of the 2'OH Group in RNA by NMR Spectroscopy and DFT Calculations". In: Angewandte Chemie International Edition 50.23 (2011), pp. 5397–5400. doi: https://doi.org/10.1002/anie.201007844.

[4] Joel M Harp et al. "Cryo neutron crystallography demonstrates influence of RNA 2'-OH orientation on conformation, sugar pucker and water structure". In: Nucleic Acids Research 50.13 (July 2022), pp. 7721–7738. doi: 10.1093/nar/gkac577.

Funding and acknowledgments: This work is supported by the IGA_PrF_2025_003 grant of the Internal Grant Agency of Palacký University Olomouc.

Distinct Effects of Osmolytes on Spondweni Virus Maturation

Camila Assis Tavares*, Wilson Alberto Tárraga, Leandro Martínez

Institute of Chemistry, Universidade Estadual de Campinas (UNICAMP), Campinas, SP, Brazil
Center for Computational Engineering & Science, Universidade Estadual de Campinas (UNICAMP), Campinas, SP, Brazil
* Presenting author

Spondweni virus (SPOV) is an emerging mosquito-borne flavivirus whose geographical distribution and potential public health impact may expand as climate change alters vector habitats [1]. Like other flaviviruses, SPOV undergoes a maturation process involving proteolytic cleavage of the pr protein and large-scale reorganization of the viral envelope [2]. Understanding how the solvent environment influences this transition is essential for elucidating the physicochemical factors governing viral stability and infectivity. To investigate the physicochemical determinants of SPOV maturation, the immature-to-mature transition was treated as a conversion between two native states. Osmolyte effects were quantified through transfer free energy calculations based on Tanford, Auton & Bolen and Creamer models, using PDBTools.jl [3], and the total cleavage-associated m-value was decomposed into contributions from the common structural region and the cleaved pr protein. This framework enabled analysis of immature and mature particle stability, as well as backbone, side-chain, E-protein, and M-protein contributions under different osmolyte conditions. Protective osmolytes, including trehalose, TMAO, sucrose, sarcosine, generally promoted favorable interactions with the viral envelope, whereas urea displayed the strongest destabilizing effect. The magnitude of these effects varied between immature and mature structures, indicating that osmolyte sensitivity depends on structural organization. Osmolyte interactions were found to be heterogeneously distributed among viral components. Structural mapping revealed distinct patterns of stabilization and destabilization across the immature and mature envelopes under different solvent conditions. These findings provide a thermodynamic framework for understanding how osmolytes modulate SPOV maturation and establish a basis for residue-level analyses linking solvent effects to viral subunit function.

References

[1] NELSON, Amy N.; PLOSS, Alexander. Emerging mosquito-borne flaviviruses. MBio, v. 15, n. 12, p. e02946-24, 2024.
[2] MUKHOPADHYAY, Suchetana; KUHN, Richard J.; ROSSMANN, Michael G. A structural perspective of the flavivirus life cycle. Nature Reviews Microbiology, v. 3, n. 1, p. 13-22, 2005.
[3] MARTÍNEZ, Leandro; LIMA, Ana BB. PDBTools. jl: A Lightweight and High-Performance Julia Package for Molecular Structure File Handling and Analysis. Journal of Chemical Information and Modeling, v. 66, n. 11, p. 6204-6210, 2026.

Funding and acknowledgments: The authors acknowledge the financial support of FAPESP (2013/08293-7, 2018/24293-0, and 2023/14353-4). Research was developed with the assistance of computing resources of COARACI (2019/17874-0), provided by the Center for Computational Engineering & Science (CCES-Unicamp).

Molecular Dynamics of Substrate Positioning in the Flavivirus NS5 Methyltransferase

Ana Rita Calixto*

LAQV/REQUIMTE, Departamento de Química e Bioquímica, Faculdade de Ciências Universidade do Porto, Rua do Campo Alegre, s/n, 4169-007 Porto, Portugal

* Presenting author

Flaviviruses are responsible for important human diseases such as dengue, Zika, yellow fever and Japanese encephalitis. Their highly conserved NS5 protein plays essential roles in viral RNA replication and maturation, making it a relevant target for antiviral development. The N-terminal methyltransferase domain of NS5 (MTase) modifies the viral RNA 5’ cap through sequential N7- and 2'-O-methylation, a process required for RNA stability, efficient translation and evasion of host immune recognition. However, how the RNA 5’ cap is positioned for these consecutive reactions remains poorly understood. This is particularly relevant because the experimentally observed cap-binding site is distinct from the proposed N7-methylation site, suggesting that substrate repositioning may be required before catalysis can occur (1, 2).

In this work, we combined Boltz-2 structure prediction with molecular dynamics simulations to explore the positioning and dynamics of RNA cap analogues within the flavivirus MTase active site. For a cap analogue representing the initial methylation step, we observed spontaneous repositioning from the crystallographic cap-binding pocket towards the region of the N7-methylation site during a 1 μs simulation. The conformations sampled along this transition were consistent with the Boltz-2 predicted complex, suggesting that cap repositioning may contribute to the catalytic process.

We also analysed an N7-methylated cap analogue to extend the study to the second methylation step. Overall, the simulations point to substrate mobility as an important feature of flavivirus RNA cap methylation and provide a useful starting point for future QM/MM studies of the catalytic mechanism.

References

[1] L. W. Ng, Y. K. Cheng, W. S. Aik and W. Han, 'Reposition pathways of GTP in NS5 methyltransferase revealed by enhanced molecular dynamics simulations'. Phys Chem Chem Phys, vol. 27, pp. 12738-12751, Jun. 2025, doi:10.1039/d5cp00438a

[2] H. P. Dong et al., 'West nile virus methyltransferase catalyzes two methylations of the viral RNA cap through a substrate-repositioning mechanism'. J Virol, vol 82, pp. 4295-4307, Feb. 2008, doi:10.1128/JVI.02202-07

Funding and acknowledgments: 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 - Laboratório Associado para a Química Verde - Tecnologias e Processos Limpos. This work was produced with the support of EuroHPC JU, funded by FCT I.P. Advanced Computing Project 2024.07911.CPCA.A2, platform Deucalion. ARC thanks FCT for funding through the Individual Call to Scientific Employment Stimulus (2021.00645.CEECIND/CP1662/CT0001).

Modeling of Ligands in Sodium and Potassium Channels - New Insights

W.Nowak*, B.Niklas, K.Walczewska-Szewc, J.Rydzewski

Institute of Physics, N. Copernicus University, Toruń, Poland

* Presenting author

Life is based, i.a., on ion channels. I order to understand better mechanism of action of insecticides and repelents we have constructed a model of Na_V channel of mosquito and made extensive studies of diffusion paths of selected Ligands in this system. We indicated critical role of so-called fenestrations in this system and studied mechanism of inactivation (1-3).

Another project aimed in exploring possibility of optical control of Kir6.2 human potassium channel present in inslet cells in pancreas. Mutations in this channel lead to diabetes. Recently possibility of control of K+ flow via photoactivated sulfonylureas has been demonstrated. We modeled dynamics of this channel in the presence of ground state and excited state ligand, pointing out structural and dynamical changes induced by light absorption (4).

References

(1) B.Niklas et al., Int.J. Mol. Sci. 24(2023)10334
(2) B.Niklas et al., Int. J. Biol. Macromol. (2025) 149078
(3) B.Niklas et al., BMC Biology 24 (2026) 141
(4) K.Walczewska-Szewc, W.Nowak, J.Phys. Chem. B 125 (2021) 13111.

Funding and acknowledgments: Polish NCN support for BN and JR is acknowledged. WN and co-co-autorski thank UMK IDUB for support. Parts of computations were performed at ICM (Warsaw), TASK(Gdańsk) and LUMI (Finland).

New developments in AMBER Force Field family for More Reliable DNA and Protein–DNA Simulations

Petr Jurečka*, Marie Zgarbová

University of Ostrava, Ostrava, Czech Republic and Palacky University, Olomouc, Czech Republic

* Presenting author

Over the years, the OL family of force fields has improved the description of both canonical and noncanonical DNA and RNA molecules. Here, we review the parameterization methodology and recent developments, focusing on the OL21 and OL24 versions, which improve the description of noncanonical α/γ conformations and the A/B-DNA equilibrium. Existing AMBER force field variants underpopulate the north (C3'-endo) sugar pucker, compromising simulations of protein–DNA systems that require B-to-A transitions. The OL24 refinement of deoxyribose puckering brings the A/B equilibrium into better agreement with experimental data while also improving the description of canonical B-DNA, DNA–RNA hybrids, and protein-induced conformational adaptation. Combined with the earlier α/γ correction introduced in OL21, OL24 provides a coherent framework for general DNA and protein–DNA simulations. We also assess the compatibility of the OL force fields with Electronic Continuum Correction (ECC) charge scaling and evaluate the usefulness of Lorentz–Berthelot combining rules.

Machine Learning-guided Screening of Peptide Databases towards clinically relevant GPCRs

João Sousa[1]*, Bruna Areias[1], Joana Ribeiro[1], Maria Inês Quintelas[1], António José Ribeiro[2], Pedro Alexandrino Fernandes[1]

[1] *LAQV, REQUIMTE, Departamento de Química e Bioquímica, Faculdade de Ciências, Universidade do Porto, Rua do Campo Alegre s/n, 4169-007, Porto, Portugal*

[2] *LAQV, REQUIMTE, Laboratório de Química Orgânica e Farmacêutica, Departamento de Ciências Químicas, Faculdade de Farmácia, Universidade do Porto, 4050-313 Porto, Portugal*

* Presenting author

G-protein coupled receptors (GPCRs) represent the largest family of human drug targets and play a key role in cancer, metabolic disorders, and autoimmune diseases. Peptide-derived drugs are particularly attractive candidates due to their high selectivity and potency, enabled by extensive interactions with their targets.[1] However, predicting peptide binding modes remains a major challenge in drug discovery, as classical molecular docking algorithms struggle to handle the conformational freedom of flexible peptides. Machine learning (ML)-based structure prediction methods offer a promising alternative by modeling peptide-receptor complexes with higher accuracy and sampling efficiency.[2] In this work, we developed a virtual screening (VS) pipeline to identify bioactive peptides from large natural databases, including UniProt, ConoServer, and DINeR. We first benchmarked several scoring approaches using Receiver Operating Characteristic (ROC) analysis against a pool of known peptide binders and respective decoys. ColabFold-based structure prediction combined with the Local Interaction Scoring (LIS) metric achieved the best discrimination performance, with an AUC of 0.89, outperforming HADDOCK, prodigy and GOLD's CHEMPLP. We then applied this pipeline to predict the binding of over 20,000 peptides against 12 GPCR targets from the angiotensin, neurotensin, opioid, and vasopressin/oxytocin subfamilies. Several peptides were identified with predicted binding scores exceeding those of the known endogenous ligands. Notably, for a subset of Kunitz-type peptides, our pipeline's rankings were consistent with experimental binding assay data, validating our approach. Experimental validation of top-ranked candidates is currently underway. This work demonstrates the utility of ML-based structural prediction in peptide-focused virtual screening and highlights the potential of natural peptide diversity as a source of novel GPCR-targeting drug candidates.

References

[1] E. Muratspahić, M. Freissmuth, and C. W. Gruber, 'Nature-derived peptides: A growing niche for GPCR ligand discovery', Trends Pharmacol. Sci., vol. 40, no. 5, pp. 309–326, May 2019, doi: 10.1016/j.tips.2019.03.004.

[2] L. Dijkhof, T. Rönkkö, H. von Vegesack, J. Lenzing, and A. Hauser, 'Deep learning in GPCR drug discovery: benchmarking the path to accurate peptide binding', Brief. Bioinform., vol. 26, no. 2, pp. 1–10, 2025, doi: 10.1093/bib/bbaf186.

Funding and acknowledgments: 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 BiodivNBS/0009/2023 DOI: https://doi.org/10.54499/BiodivNBS/0009/2023. FCT is acknowledged for funding through the Scientific Employment Stimulus – Individual Call: JPMS ref. 2024.07973.CEECIND and. AJR ref. 2022.03058.CEECIND/CP1724/CT0005. JR acknowledges FCT funding through her PhD Studentship 2025.02402.BD, doi: 10.54499/2025.02402.BD. JPMS and PAF also acknowledge FCT for granting access to the Deucalion HPC facility through the Advanced Computing Project Call, under projects 2025.11147.CPCA.A3 and 2025.00045.CPCA.A2.

Machine learning potentials for accurate and efficient multiscale enzymatic Diels – Alder reaction modelling

Magdalena Maria Kazmierczak[1*], Elliot Chan[2], Chris Willis[2], Marc van der Kamp[1]

[1] *School of Biochemistry, University of Bristol, Bristol, BS8 1TD, United Kingdom*
[2] *School of Chemistry, University of Bristol, Bristol, BS8 1TS, United Kingdom*
* Presenting author

To perform efficient computational screening of reactions catalysed by enzymes, an efficient multiscale potential needs to be selected. Usually, this involves a trade-off between accuracy and efficiency: either substantial sampling with semi-empirical methods or limited sampling with more accurate DFT are applied in QM/MM. Here, we propose the use of machine learning potentials [1] applied together with electrostatic machine learning embedding (EMLE) [2] as an alternative to the traditional QM/MM calculations. This ML(EMLE)/MM approach has already been proven to reduce the computational cost to below the level of semi-empirical QM/MM, and reproduce DFT-level QM/MM free energy profiles [2].

We currently focus our research on two Diels-Alderases. AbyU has been proven to be highly stable and mutable [3,4], and can act on multiple substrates. Initial benchmarking using ML(EMLE)/MM indicated nanoseconds of simulations per day could be performed with the accuracy in energy and structures at the DFT-level. The EMLE approach is required to accurately capture the influence of the enzyme electric field on the reaction. Recently discovered Diels-Alderase – Cyc15b – demonstrates high activity and opposite stereoselectivity to AbyU, making it perfect candidate for the rational design of wide range of products.

Present research is focused on applying ML(EMLE)/MM to non-natural Diels-Alder reactions catalysed by AbyU and Cyc15b with substrates previously synthesised and tested by our experimental partners. The ultimate goal is to test this workflow with wide range of enzyme variants and demonstrate the potential of ML(EMLE)/MM approach for efficient screening of enzyme variants.

References

[1] Young T. A. et al. Reaction dynamics of Diels–Alder reactions from machine learned potentials, Phys. Chem. Chem. Phys. 24 20820 — 20827 (2022)
[2] Zinovjev K. et al. emle-engine: A Flexible Electrostatic Machine Learning Embedding Package for Multiscale Molecular Dynamics Simulations, J. Chem. Theory Comput. 20 11 4514 — 4522 (2024)
[3] Byrne M. J. et al. The Catalytic Mechanism of a Natural Diels-Alderase Revealed in Molecular Detail., J Am Chem Soc 138 6095 — 6098 (2016)
[4] Maschio L. et al. Delineation of the Complete Reaction Cycle of a Natural Diels-Alderase., Chem. Sci. (2025)

Funding and acknowledgments: SWBio BBSRC for funding the project

Preferential binding at the Carbohydrate-Binding Module and exclusion at the Catalytic Domain underlying Cel7A inhibition by monosaccharides

Ander Francisco Pereira*, Leandro Martínez, Munir S. Skaf

UNICAMP

* Presenting author

The enzymatic depolymerization of lignocellulosic biomass is crucial for the sustainable production of biofuels and biochemicals. The cellobiohydrolase Cel7A is a critical enzyme in this process, hydrolyzing cellulose to generate cellobiose. Both the product (cellobiose) and monosaccharides from side reactions (glucose, mannose, and xylose) are known inhibitors of Cel7A, with effects on the Carbohydrate-Binding Module (CBM) and the Catalytic Domain (CD). Previous work suggests that, while glucose directly affects the catalytic rate (kcat), mannose and xylose primarily decrease the association rate (kon) and processivity of the enzyme. In this study, we employ all-atom molecular dynamics simulations with solvation analyses using minimum-distance distribution functions and the Kirkwood-Buff solution theory to provide a microscopic rationale for these observations. Our results reveal a noticeable contrast in the solvation preferences of the two domains: while sugars are preferentially excluded from the CD, the CBM exhibits preferential sugar binding, with high sugar density at the planar binding face (notably around Y5, Y31, Y32), and around I11, S15, and V27. Xylose, the most potent experimental inhibitor, displays the highest density near the CBM tyrosine residues, which could effectively interfere with the enzyme's anchoring of cellulose. Furthermore, we observe localized sugar accumulation at the CD tunnel entrance and within the tunnel-binding loops (B2, B3, and A3), providing a physical mechanism to obstruct the processive cycle. By reconciling solvation preferences with specific-site interactions, these results contribute to understanding how glucose and hemicellulose-derived sugars (mannose and xylose) inhibit Cel7A, offering insights for the design of more robust enzymatic cocktails.

References

ZHAI, R., Jinguang H., and Saddler, J. N. Bioresource technology, v.258, p. 79-87, 2018. Available at: https://doi.org/10.1016/j.biortech.2017.12.006

JIANG, X., Heng, T. L., Mu, Y., Zhai, R., & Jin, M. Bioresource Technology, v. 437, n. 133060, 2025. Available at: https://doi.org/10.1016/j.biortech.2025.133060

MARTÍNEZ, L. & Shimizu, S. Journal of Chemical Theory and Computation. v. 13, n. 12, p. 6358-6372, 2017. Available at: https://doi.org/10.1021/acs.jctc.7b00599

Funding and acknowledgments: The authors acknowledge the financial support of FAPESP (2018/24293-0, 2013/08293-7, 2018/14274-9, 2019/17874-0, and 2025/03933-5), CAPES 206-04/092018, and CNPq (301909/2022-9). Research developed with the help of CENAPAD-SP (National Center for High-Performance Processing in São Paulo), project UNICAMP / FINEP - MCTI, and the Coaraci Supercomputer at UNICAMP.

Molecular Basis of Osmolyte-Modulated SARS-CoV-2 NSP9 Dimer Dissociation from Free Energy and Preferential Solvation Analyses

Jéssica de Oliveira Araújo*, Leandro Martínez

Universidade Estadual de Campinas - UNICAMP

* Presenting author

The dimerization of the non-structural protein 9 (NSP9) of SARS-CoV-2 is essential for its biological function and provides an appropriate model to investigate how osmolytes interfere with protein-protein interactions. In this work, we combine molecular dynamics simulations, free energy calculations, and solvation analyses to investigate the effects of trimethylamine N-oxide (TMAO) and urea on the dissociation mechanism. Dissociation was characterized using steered molecular dynamics, followed by umbrella sampling simulations in pure water and aqueous solutions containing TMAO or urea in a concentration range of 0.5-3.0 M, simulations were performed using Gromacs[1]. The molecular basis of the stability changes induced by osmolytes was investigated by determining m-values along the dissociation trajectory, using two complementary approaches: the Tanford transfer model, based on the free transfer energies of osmolytes, and the Kirkwood-Buff integrals (KBI), which quantify the variations in preferential solvation between the dimeric and dissociated states[2], [3]. The potential of mean force (PMF) profiles revealed opposite, concentration-dependent effects for the two osmolytes. The increase in TMAO concentration progressively enhanced the stability of the dimer, raising the free energy dissociation barrier to over 21 kcal mol^{-1} at 3.0 M, while urea destabilized the dimer, reducing the barrier to approximately 16 kcal mol^{-1}. Both the Tanford approach and the KBI produced consistent trends for the m-value: positive values for TMAO indicate the preferential stabilization of the dimeric state, while negative values for urea reflect the stabilization of the dissociated states through favorable solvation[4]. These results establish a consistent molecular and thermodynamic framework that associates preferential solvation with changes in the free energy landscape of NSP9 dimer dissociation, providing mechanistic insights into how osmolytes regulate protein-protein stability.

References

[1] J. A. Lemkul and D. R. Bevan, “Assessing the stability of Alzheimer’s amyloid protofibrils using molecular dynamics,” J Phys Chem B, vol. 114, no. 4, pp. 1652–1660, Feb. 2010.

[2] L. Martínez, “ComplexMixtures.jl: Investigating the structure of solutions of complex-shaped molecules from a solvent-shell perspective,” J. Mol. Liq., vol. 347, no. 117945, p. 117945, Feb. 2022.

[3] L. Martínez and A. B. B. Lima, “PDBTools.jl: A Lightweight and High-Performance Julia Package for Molecular Structure File Handling and Analysis,” J Chem Inf Model, vol. 66, no. 11, pp. 6204–6210, Jun. 2026.

[4] M. Auton and D. W. Bolen, “Application of the transfer model to understand how naturally occurring osmolytes affect protein stability,” Methods Enzymol, vol. 428, pp. 397–418, 2007.

Funding and acknowledgments: The authors acknowledge the financial support of FAPESP (2023/13899-3, 2013/08293-7, 2019/17874-0). Research developed with access the computing resources of COARACI Supercomputer provided by Center for Computing in Engineering & Sciences (CCES - UNICAMP).

Active learning of coarse-grained interactions from atomistic models of peptides

Manuela L. Nader*, Henrique M. Cezar, Sigbjørn L. Bore, Michele Cascella

Hylleraas Centre, University of Oslo

* Presenting author

Molecular dynamics simulations are a powerful tool for probing diverse biological phenomena, providing insights at resolutions that are often inaccessible to experimental techniques. Atomistic simulations, in particular, can faithfully capture the behavior of biomolecules with great detail. Yet, even with substantial advances in computational power, the range of systems and processes that can be studied remains limited by accessible size and timescales. Coarse graining (CG) offers a promising strategy to overcome these constraints by reducing the level of chemical detail. This is commonly realized through bottom-up approaches, which involve defining a mapping from high-resolution models to CG representations and constructing effective potentials that approximate the many-body potential of mean force (PMF) of the mapped ensemble (1). However, traditional CG methods frequently face challenges related to transferability and representability, stemming from their dependence on pairwise potentials and the intrinsic loss of information associated with reducing degrees of freedom (2,3). Recent progress in deep neural networks has enabled the development of machine learning potentials, which provide a computationally efficient and highly accurate alternative (4). In contrast to pairwise potentials, these models can capture complex many-body atomic interactions (5). The present work introduces a new framework for training machine learning potentials for coarse-grained interactions. To this end, we employ a recently proposed active learning strategy in combination with adversarial attacks to learn the thermodynamics of different peptides (6).

References

1. K. M. Kidder, R. J. Szukalo, and W. G. Noid, Eur. Phys. J. B, vol. 94, no. 7, Art. no. 153, Jul. 2021, doi: 10.1140/epjb/s10051-021-00153-4.
2. P. Ge, L. Zhang, and H. Lei, J. Chem. Phys., vol. 158, no. 6, Art. no. 064104, Feb. 2023, doi: 10.1063/5.0131567.
3. S. Y. Joshi and S. A. Deshmukh, Mol. Simul., vol. 47, nos. 10–11, pp. 786–803, Jul. 2021, doi: 10.1080/08927022.2020.1828583.
4. S. Doerr, M. Majewski, A. Pérez, A. Krämer, C. Clementi, F. Noé, T. Giorgino, and G. De Fabritiis, J. Chem. Theory Comput., vol. 17, no. 4, pp. 2355–2363, Apr. 2021, doi: 10.1021/acs.jctc.0c01343.
5. J. Wang, S. Olsson, C. Wehmeyer, A. Pérez, N. E. Charron, G. de Fabritiis, F. Noé, and C. Clementi, ACS Cent. Sci., vol. 5, no. 5, pp. 755–767, May 2019, doi: 10.1021/acscentsci.8b00913.
6. H. M. Cezar, T. Bodenstein, H. A. Sveinsson, M. Ledum, S. Reine, and S. L. Bore, npj Comput. Mater., vol. 11, no. 1, Art. no. 200, Jul. 2025, doi: 10.1038/s41524-025-01703-5.

Atomistic Modelling of a Realistic FapC Functional Amyloid Fibril

Pedro Ferreira[1*], Samuel Peña-Díaz[2], Daniel E. Otzen[2], Maria Joao Ramos[1]

[1] *LAQV@REQUIMTE, Departamento de Química e Bioquímica, Faculdade de Ciências, Universidade do Porto, Rua do Campo Alegre s/n, 4169-007, Porto, Portugal*

[2] *Interdisciplinary Nanoscience Center (iNANO), Aarhus University, Gustav Wieds Vej 14, DK, Aarhus C, 8000 Denmark*

* Presenting author

Functional bacterial amyloids (FuBAs) are highly ordered protein assemblies that contribute to the structural stability of bacterial biofilms and have recently attracted interest as robust biomaterials with potential catalytic properties. FapC, the major amyloid-forming protein of the Pseudomonas Fap system, forms fibrils characterized by a structured amyloid core surrounded by more flexible regions. However, experimentally determined structures necessarily represent only short fibrillar segments and do not fully capture the extended architecture required for realistic molecular simulations.

Here, we develop an atomistic model of an extended FapC fibril suitable for large-scale molecular dynamics simulations. The experimentally resolved fibrillar architecture is preserved as the structural framework, while unresolved regions are reconstructed using complementary experimental structures and structure-prediction approaches. The resulting monomers are assembled according to the experimentally determined helical symmetry to generate an extended fibril containing 60 FapC units, corresponding to approximately one complete helical turn. Periodic boundary conditions along the fibril axis are then used to represent an effectively continuous amyloid fibre while minimizing artificial end effects.

The resulting model provides a physically realistic framework for investigating the structural dynamics and molecular recognition properties of FapC at scales beyond those directly accessible experimentally. Molecular dynamics simulations are used to assess fibril stability and preservation of the experimentally observed architecture. Preliminary simulations with small-molecule substrates further illustrate how this framework can be used to explore substrate adsorption and identify local catalytic environments that may contribute to the reported catalytic activity of functional amyloids.

References

[1] D. Otzen and R. Riek, "Functional Amyloids," Cold Spring Harb. Perspect. Biol., vol. 11, no. 12, Art. no. a033860, Dec. 2019, doi: 10.1101/cshperspect.a033860.

[2] S. Peña-Díaz, W. P. Olsen, H. Wang, and D. E. Otzen, "Functional Amyloids: The Biomaterials of Tomorrow?," Adv. Mater., vol. 36, Art. no. 2312823, 2024, doi: 10.1002/adma.202312823.

[3] S. Peña-Díaz, Y. Jiang, Z. Zhang, A. Daugberg, P. Ferreira, M. López Hernández, C. Mittal, M. J. Ramos, J. S. Pedersen, M. K. D. Dueholm, C. Qin, H. Wang, and D. E. Otzen, "The Importance of Being Imperfect: Structure and Function of Bacterial Amyloid," Adv. Sci., vol. 13, no. 4, Art. no. e17090, Jan. 2026, doi: 10.1002/advs.202517090.

Funding and acknowledgments: P.F. and M.J.R. acknowledge financial support from Portuguese national funds through FCT/MECI (Fundação para a Ciência e a Tecnologia and Ministério da Educação, Ciência e Inovação) under project UID/50006/2025 – Laboratório Associado para a Química Verde – Tecnologias e Processos Limpos. P.F. and M.J.R. also acknowledge FCT for granting access to the Deucalion HPC facility through the Advanced Computing Project Call, under project 2025.13567.CPCA. P.F. is funded by FCT (DOI: 10.54499/CEECINST/00136/2021/CP2820/CT0002). D.E.O. is supported by the Independent Research Fund Denmark (grant no. 3103-00285B), the Novo Nordisk Foundation (grant nos. NNF22OC007891 and NNF24OC0090669), and the Lundbeck Foundation (grant nos. R276-2018-671 and R453-2024-359).

Beyond Geometric Cutoffs: Agnostic Free-Energy-Based Approaches for Characterizing Noncovalent Interactions in Molecular Dynamics Simulations

Paulo J. Costa*

BioISI - Biosystems & Integrative Sciences Institute, Ciências ULisboa

* Presenting author

In recent years, our group has focused on understanding σ-hole interactions, particularly halogen bonds (XBs) [1], in biological systems using MD simulations. Besides protein-ligand recognition [2] and drug-membrane interactions [3], we also assessed the quality of force-field parametrizations [4] and contributed to the broader understanding of σ-hole interactions in medicinal chemistry [5]. These studies, while consistently showing the relevance of XBs and of the ubiquitous hydrogen bond (HB) in biomolecular recognition, also exposed a fundamental methodological limitation: their identification in MD trajectories remains largely dependent on geometric cutoffs based on distance and angle. Such an approach often fails to classify weak, transient, or borderline interactions, complicating comparisons across different molecular systems. To overcome this limitation, we tested agnostic free-energy-based approaches that use a statistically grounded characterization of the interactions. Rather than imposing predefined cutoffs, the interactions are assigned directly from the underlying probability distributions, as the basins emerge naturally from the sampled configurational space. The first approach extends free-energy basin analyses previously used to classify protein conformational states to the characterization of noncovalent interactions using three-dimensional free-energy surfaces built from distance, angle, and free energy. To improve computational efficiency while preserving the physical basis of the method, we also tested a method that exploits the distribution of interaction potential energies to identify interacting states from two-dimensional free-energy landscapes. Together, these approaches establish an agnostic framework for characterizing directional noncovalent interactions in MD simulations, providing a physically motivated alternative to conventional geometry-based analyses.

References

[1] P. J. Costa, “The halogen bond: Nature and applications,” Phys. Sci. Rev., vol. 2, no. 11, Oct. 2017, doi: 10.1515/psr-2017-0136.

[2] R. Nunes, D. Vila-Viçosa, M. Machuqueiro, P. J. Costa, “Biomolecular Simulations of Halogen Bonds with a GROMOS Force Field,” J. Chem. Theory Comput., vol. 14, no. 10, pp. 5383–5392, Sep. 2018, doi: 10.1021/acs.jctc.8b00278

[3] R. S. Nunes, D. Vila-Viçosa, P. J. Costa, “Halogen Bonding: An Underestimated Player in Membrane–Ligand Interactions,” J. Am. Chem. Soc., vol. 143, no. 11, pp. 4253–4267, Mar. 2021, doi: 10.1021/jacs.0c12470.

[4] A. Fortuna, P. J. Costa, “Assessment of Halogen Off-Center Point-Charge Models Using Explicit Solvent Simulations,” J. Chem. Inf. Model., vol. 63, no. 23, pp. 7464–7475, Nov. 2023, doi: 10.1021/acs.jcim.3c01561.

[5] A. Fortuna, A. M. M. Gomes, P. J. Costa, “Impact of Halogen Anisotropy on the Membrane Permeability of Halogenated Drugs,” May 2026, doi: 10.26434/chemrxiv.15004082/v1.

Funding and acknowledgments: This work was funded by Fundação para a Ciência e a Tecnologia (FCT) and co-financed by the European Union, under exploratory project 2024.16247.PEX (DOI: 10.54499/2024.16247.PEX). FCT is also acknowledged for project UID/04046/2025 (DOI: 10.54499/UID/04046/2025) awarded to Biosystems and Integrative Sciences Institute (BioISI), and for the Advanced Computing project 2023.10475.CPCA (DOI: 10.54499/2023.10475.CPCA.A2), awarded to PJC. PJC also acknowledges FCT and the Portuguese Recovery and Resilience Plan (PRR) for his contract under the FCT-Tenure program (2023.15441.TENURE.008/CP00003/CT00005).

Does Size Matter? Choosing the QM Region in QM/MM

Daniel Marke[1,*], Ulf Ryde[2], Erik D. Hedegård[3], Erna K. Wieduwilt[1]

[1] *Physical Chemistry, Faculty of Chemistry, Centre for Water and Environmental Research (ZWU) and Center of Medical Biotechnology (ZMB), University of Duisburg-Essen, Universitätsstraße 5, Essen 45141, Germany*
[2] *Division of Computational Chemistry, Lund University, Chemical Centre, P.O. Box 124, SE-221 00 Lund, Sweden*
[3] *Department of Physics, Chemistry, and Pharmacy, University of Southern Denmark, Campusvej 55, Odense DK-5230, Denmark*
* Presenting author

Hybrid quantum mechanics/molecular mechanics (QM/MM) methods have become indispensable for investigating enzymatic reaction mechanisms [1]. However, a major challenge remains the definition of the QM region [2]. Although numerous methods and guidelines for QM-region construction have been proposed, no universally applicable protocol exists for selecting which atoms or residues should be treated quantum mechanically [2], [3], [4]. Consequently, QM-region construction remains highly user dependent, with potentially significant implications for the accuracy and reproducibility of calculated reaction energetics [2].

This ongoing work uses the lytic polysaccharide monooxygenase (LPMO) LsAA9A as a representative case study to investigate how QM-region selection influences calculated reaction energetics. Previous QM/MM studies of LsAA9A have shown that describing the hydrogen atom abstraction from the substate requires careful consideration of structural conformations [5]. Building on these findings, we examine the impact of QM-region selection on the energetics of the hydrogen atom abstraction reaction. By systematically varying the size of the QM region surrounding the copper active site, we aim to evaluate the sensitivity of the calculated energetics to QM-region definition and provide insight into strategies for QM-region construction.

References

[1] U. Ryde, "QM/MM Calculations on Proteins," Methods in Enzymology, vol. 577, pp. 119–158, 2016, doi: 10.1016/bs.mie.2016.05.014.
[2] H. J. Kulik, J. Zhang, J. P. Klinman, and T. J. Martínez, "How large should the QM region be in QM/MM calculations?," J. Phys. Chem. B, vol. 120, no. 44, pp. 11381–11394, 2016, doi: 10.1021/acs.jpcb.6b07814.
[3] M. Karelina and H. J. Kulik, "Systematic QM region determination in QM/MM simulation," J. Chem. Theory Comput., vol. 13, no. 2, pp. 563–576, 2017, doi: 10.1021/acs.jctc.6b01049.
[4] C. Brunken and M. Reiher, "Automated construction of quantum-classical hybrid models," J. Chem. Theory Comput., vol. 17, no. 6, pp. 3797–3813, 2021, doi: 10.1021/acs.jctc.1c00178.
[5] M. M. Hagemann, U. Ryde, and E. D. Hedegård, "How structural dynamics influence the substrate oxidation energetics in lytic polysaccharide monooxygenases," Inorg. Chem. Front., vol. 12, no. 24, pp. 8352–8362, Dec. 2025, doi: 10.1039/D5QI01590A.

Funding and acknowledgments: The authors gratefully acknowledge the computing time granted by the Center for Computational Sciences and Simulation (CCSS) of the Universität of Duisburg-Essen and provided on the supercomputer amplitUDE (DFG project 459398823; grant ID INST 20876/423-1 FUGG) at the Zentrum für Informations- und Mediendienste (ZIM). The authors also thank the Ministry of Culture and Science of the Federal State of North Rhine-Westphalia (NRW Return Grant) for support.

photo-CIDNP effect of 5-Deazariboflavin and desmethyl derivates

Jannis Tesche*, Sabrina Panther, Stefan Weber

Albert-Ludwig University Freiburg

* Presenting author

5-Deazariboflavin (5-dRF) constitutes the catalytic core of the natural cofactors F420 and F0, which mediate low-potential hydride transfer and participate in light-induced biological reactions across various microorganisms [1]. In this work 5-dRF and it's desmethyl derivates were investigated using density functional theory (DFT) calculations which were correlated with photo-CIDNP NMR measurements to model the electronic structure of transient radical intermediates and evaluate their isotropic hyperfine coupling constants (HFCCs) [2]. Photochemically induced dynamic nuclear polarization (photo-CIDNP) NMR spectroscopy directly yields key insights into the radical-pair mechanism, transient spin states, and experimental HFCCs of short-lived radical species by generating hyperpolarized NMR signals through spin-correlated radical pairs [3,4]. In combination with tryptophan as a photo-excited electron donor, photo-CIDNP measurements on 5-dRF and three desmethyl derivatives confirmed a radical-pair mechanism for all derivatives and demonstrated that the experimental nuclear polarization directly correlates with the calculated electron spin density distributions. Complementary UV/Vis and fluorescence spectroscopy measurements were conducted to evaluate the fundamental photophysical properties, electronic absorption, and fluorescence quantum yields of the 5-dRF derivatives.

References

[1] Ney, B.; et al. The Redox Cofactor F420 Protects Mycobacteria from Diverse Antimicrobial Compounds and Mediates a Reductive Detoxification System. Appl. Environ. Microbiol. 2016, 82 (23), 6810–6818.

[2] Pompe, N. NMR and photo-CIDNP studies on blue-light photoreceptor proteins and model systems, Ph.D. Dissertation, 2020.

[3] Kuhn, L. T., Ed. Hyperpolarization Methods in NMR Spectroscopy; Topics in Current Chemistry; Springer: Berlin, Heidelberg, 2013; Vol. 338.

[4] Okuno, Y.; Cavagnero, S. Photochemically Induced Dynamic Nuclear Polarization: Basic Principles and Applications. In eMagRes; Harris, R. K., Wasylishen, R. L., Eds.; John Wiley & Sons, Ltd: Chichester, UK, 2007; pp 283–314.

Multiscale Design of Peptide-Based Non-Viral Gene Delivery Vectors: Combining Experimental Development with In Silico Modeling

Dragos Peptanariu*, Razvan Puf, Mariana Pinteala

Center of Advanced Research in Bionanoconjugates and Biopolymers, "Petru Poni" Institute of Macromolecular Chemistry of Romanian Academy, 41A Grigore Ghica Voda Alley, Iasi 700487, Romania

* Presenting author

Non-viral gene delivery systems offer a safer alternative to viral vectors due to their low immunogenicity, high loading capacity, and structural versatility. However, achieving efficient nucleic acid delivery while maintaining low toxicity remains a significant challenge. We present a rational design strategy for the development of multifunctional non-viral vectors, progressing from synthetic polymeric architectures toward biodegradable peptide-based delivery systems.

Our previous work established a series of core-based vectors employing fullerene, cyclic siloxane, cyclodextrin, and polyrotaxane scaffolds functionalized with branched poly(ethyleneimine) and polyethylene glycol. These architectures demonstrated efficient DNA condensation and transfection, highlighting the importance of molecular architecture in determining biological performance. These findings provided the design principles for a new generation of peptide-based vectors.

The newly developed peptide-based multi-arm vectors retain the favorable structural characteristics of earlier systems while introducing biodegradable and biocompatible building blocks suitable for future in vivo applications. Their modular design enables straightforward optimization of physicochemical properties and biological activity.

To complement the experimental approach, constant-pH molecular dynamics (CpHMD) simulations are employed to investigate pH-dependent conformational changes in the secondary structure of the peptide. Based on these results, the vectors will subsequently be assembled under the most appropriate pH conditions, followed by the investigation of their interactions with nucleic acids and the resulting polyplex stability.

The integration of experimental characterization with in silico modeling establishes a multiscale framework for the development of next-generation non-viral gene delivery systems.

Funding and acknowledgments: This work is supported by European Union's Horizon Europe research and innovation programme under grant agreement No 101086667, project BioMat4CAST (BioMat4CAST - "Petru Poni" Institute of Macromolecular Chemistry Multi-Scale In Silico Laboratory for Complex and Smart Biomaterials.

Molecular Dynamics-Guided Engineering of a Thermostable Amidase for Polyurethane Hydrolysis: Mechanistic Insights from Simulation and Experiment

Pedro Paiva[1,2*], Rosie Graham[2,3], Daniel E. Otzen[2,3], Pedro Alexandrino Fernandes[1,2], Maria João Ramos[1,2]

[1] *LAQV@REQUIMTE, Departamento de Química e Bioquímica, Faculdade de Ciências, Universidade do Porto, Rua do Campo Alegre s/n, 4169-007, Porto, Portugal*

[2] *EnZync Center for Enzymatic Deconstruction of Thermoset Plastics*

[3] *Department of Molecular Biology and Genetics, Aarhus University, Gustav Wieds Vej 14, DK-8000, Aarhus, Denmark*

* Presenting author

Polyurethane (PUR) thermosets are among the most chemically recalcitrant classes of synthetic polymers, and their enzymatic deconstruction remains a largely unsolved challenge.[1,2] We present a structure- and dynamics-driven engineering campaign targeting a recently identified thermostable amidase-signature enzyme with intrinsic PUR-hydrolytic activity.[3] Using molecular dynamics (MD) simulations of PUR oligomers bound to the enzyme's crystal structure, we mapped persistent substrate-contact regions across the active site and identified candidate residues for targeted mutagenesis. This computational contact analysis guided the design of 29 single and double mutants, several of which were experimentally validated, showing up to 5-fold improvements in PUR-substrate hydrolysis whilst retaining or enhancing thermostability. The top-performing variant achieved a 20-fold gain in catalytic efficiency on a polyether-PUR analogue, and MD simulations of this variant reveal tighter substrate burial and enhanced π–π stacking interactions, consistent with the observed kinetic improvements. The kcat-dominant nature of the improvement, with K M largely unchanged, points toward preferential transition-state stabilisation rather than ground-state affinity enhancement, as supported by the distributional analysis of catalytic distances observed in the MD simulations. Engineered variants were shown to catalyse hydrolysis of untreated commercial thermoset PUR foam, confirmed by monomer release and surface erosion. This work establishes MD-guided contact mapping as a broadly applicable feed-forward strategy for enzyme engineering, and positions the amidase-signature fold as a tractable scaffold for plastic biocatalysis.

References

[1] de Souza, F.M., Sulaiman, M.R., and Gupta, R.K. (2021). Materials and Chemistry of Polyurethanes. In Materials and Chemistry of Flame-Retardant Polyurethanes Volume 1: A Fundamental Approach, (American Chemical Society), pp. 1–36. DOI:10.1021/bk-2021-1399.ch001

[2] Tournier, V., Duquesne, S., Guillamot, F., Cramail, H., Taton, D., Marty, A., and Andre, I. (2023). Enzymes' Power for Plastics Degradation. Chem Rev. DOI: 10.1021/acs.chemrev.2c00644.

[3] Bendtsen, M.K., Møllebjerg, A., Peña-Díaz, S., Graham, R., Petersen, N.C., Isaksen, B.N., Carstensen, M., Johansen, M.B., Sommerfeldt, A., Petersen, A.R., et al. (2026). Environmental identification of novel enzymes for polyurethane and polyamide degradation. Angewandte Chemie International Edition, e6159643, DOI: 10.1002/anie.6159643

Funding and acknowledgments: This work is supported by the Novo Nordisk Foundation through the Challenge Grant NNF22OC0072891 to the Center EnZync. We are grateful to Troels Skydstrup's research group for sharing polymer samples, Bjarke Donslund for constructive discussions and the rest of the EnZync consortium for many constructive discussions. We also gratefully acknowledge Pia Bomholt Jensen (Center for Electromicrobiology, Aarhus University) for her support with image data collection and the Biophysics & Biochemistry Core Facility at Aarhus University for equipment access. PP, PAF, and MJR acknowledge the 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 - Laboratório Associado para a Química Verde Tecnologias e Processos Limpos. PP, PAF, and MJR would further like to thank the European High-Performance Computing Joint Undertaking (EuroHPC JU) that granted access to Deucalion, the petascale EuroHPC supercomputer located in Guimarães, Portugal, under proposal 2025.00056.CPCA.A3.

Ensemble Reweighting Elucidates the Molecular Determinants of Complex Environments: How TFE Stabilizes the α-Helix Through Local Interactions

Lucas Verona de Araujo*, Leandro Martínez

Instituto de Química, Universidade Estadual de Campinas
Center for Computing in Engineering & Science, Universidade Estadual de Campinas - UNICAMP, Campinas, SP, Brazil
* Presenting author

Rationalizing molecular determinants of collective behavior from simulations is challenging, as thermodynamic information must be extracted from a fine balance of multiple chemical interactions. Qualitative structural analysis can provide correlations between specific interactions and thermodynamic changes, but quantitative links between interactions and macroscopic observables can improve the molecular description of the system [1]. Here, we developed an ensemble reweighting procedure that computes derivatives of thermodynamic properties with respect to perturbations in solute–solvent interactions, quantifying the response of the chemical equilibrium. We used our approach to study the folding of $(AAQAA)_3$ in aqueous solutions of TFE (0, 20, 40, 50, 60, 80 and 100% v/v). Perturbative potentials were modeled from the potential of mean force of peptide–water and peptide–TFE minimum-distance distribution functions [2] and applied to reweight the original ensemble. Enhancing TFE interactions with alanine side chains promotes folding at low concentration of TFE (20%) but progressively destabilizes the helix as the TFE fraction increases, which reflects saturation of the peptide's hydrophobic surface, beyond which partial unfolding exposes methyl groups to accommodate excess TFE contacts. Additionally, favoring TFE interactions with glutamine side chains stabilizes the helix across all concentrations, indicating that hydrophobic solvation by TFE is the primary folding driver, assisted by TFE clustering around polar side chains [3]. The framework yields a quantitative microscopic picture of the folding, inaccessible through structural analysis alone, addressing TFE's stabilizing role as its capacity to dehydrate the peptide surface. The approach is applicable to study other molecular events governed by competing interactions, including protein–ligand binding and stability modulation by mutations, with potential applications to improve drug, solvent, and protein design.

References

[1] S. Mehdi, Z. Smith, L. Herron, Z. Zou, and P. Tiwary, "Enhanced Sampling with Machine Learning," Annu. Rev. Phys. Chem., vol. 75, no. 1, pp. 347–370, Jun. 2024, doi: 10.1146/annurev-physchem-083122-125941.

[2] L. Martínez and S. Shimizu, "Molecular Interpretation of Preferential Interactions in Protein Solvation: A Solvent-Shell Perspective by Means of Minimum-Distance Distribution Functions," J. Chem. Theory Comput., vol. 13, no. 12, pp. 6358–6372, Dec. 2017, doi: 10.1021/acs.jctc.7b00599.

[3] W. Barber-Armstrong, M. Sridharan, and S. M. Decatur, "Stabilization of Helical Conformation in Model Peptides by 2,2,2-Trifluoroethanol: An FTIR Study," in Peptides: The Wave of the Future, M. Lebl and R. A. Houghten, Eds., Dordrecht: Springer Netherlands, 2001, pp. 367–368. doi: 10.1007/978-94-010-0464

Funding and acknowledgments: The authors acknowledge the financial support of FAPESP 2019/17874-0 (Coaraci Supercomputer), 2013/08293-7 (Center for Computing in Engineering and Sciences at Unicamp) and 2024/21000-3.

∂-HyMD: A Massively Parallel Differentiable Molecular Dynamics Framework for Automatic Force-Field Optimization

Matteo Orlandi*, Vinicius Firmino dos Santos, Henrique Musseli Cezar, Piero Procacci, Marco Pagliai, Thereza A. Soares, Michele Cascella

Dipartimento di Chimica "Ugo Schiff", Università degli Studi di Firenze, Via della Lastruccia 3, 50019 Sesto Fiorentino, Italy
Dipartimento di Neuroscienze, Psicologia, Area del Farmaco e Salute del Bambino, Università degli Studi di Firenze, Via Ugo Schiff 6, 50019 Sesto Fiorentino, Italy
Institute of Physics, University of São Paulo, São Paulo 05508-090, Brazil
Hylleraas Centre for Quantum Molecular Sciences and Department of Chemistry, University of Oslo, PO Box 1033 Blindern, 0315 Oslo, Norway

* Presenting author

Driven by advanced high-performance computing architectures and GPU acceleration, classical molecular dynamics simulations are steadily breaking their boundaries in both time and size domains. However, their predictive fidelity remains anchored to the accuracy of the underlying empirical force fields. While differentiable Molecular Dynamics (∂-MD) offers a powerful top-down approach for gradient-based force field parameter optimization, existing frameworks are frequently limited by single-scale architectures or by the lack of full integration for commonly used functional forms in condensed matter simulations. In this work, we present ∂-HyMD, a massively parallel, multi-scale, differentiable MD engine coded for high-throughput force field reparameterization. Built natively on the JAX and MPI4JAX frameworks, ∂-HyMD achieves hardware acceleration on modern GPU clusters and expands the parameterization paradigm by concurrently handling both all-atom and coarse-grained molecular representations. ∂-HyMD introduces a fully differentiable Smooth Particle Mesh Ewald implementation, ensuring physical rigor for long-range interactions without losing analytic gradient connectivity. Leveraging JAX's native vectorization mechanics together with just-in-time XLA compilation, ∂-HyMD enables the simultaneous, batch-mode optimization of entire chemical libraries of compounds directly against target properties derived from experimental measurements as well as ab initio calculations. This combination of multi-scale versatility, long-range accuracy and multi-node scalability establishes ∂-HyMD as a comprehensive tool for autonomous and ready-to-use force field development. The code was tested on two coarse-grained systems (a polymer and a membrane) modeled with the Martini FF, and one atomistic metalloprotein simulated with AMBER14SB.

Funding and acknowledgments: Authors thank the support of the Research Council of Norway through the Centre of Excellence Hylleraas Centre for Quantum Molecular Sciences (grant number 262695), Sigma2 – the National infrastructure for high-performance computing and data storage in Norway (grant numbers NN4654K and NS4654K) and the São Paulo State Research Foundation (FAPESP) Gran tNumbers 2022/07231-7 and 2025/26640-3. Part of the computing resources and the related technical support used for this work have been provided by the CINECA High Performance Computing center (HP10BB7GUS, HP10CPGB3B). TAS acknowledges the National Council for Scientific and Technological Development (CNPq)for productivity fellowship. V.S. acknowledges CAPES for financial support through a six-month doctoral research stay at the University of Oslo (UiO), Norway.

Poster Session 2 – *Madeira*

From single antennas to supercomplexes: first-principles modeling of light-harvesting in plant photosystems

Elena Betti*, Lorenzo Cupellini, Benedetta Mennucci

University of Pisa

* Presenting author

Photosynthetic organisms rely on large biomolecular machines, called photosystems (PS), to convert solar energy into chemical energy [1]. In plants, PSI and II are formed upon aggregation of an antenna system, which harvests light, and a core complex, which hosts the catalytic reaction centers. Excitation energy transfer (EET) to the reaction centers occurs with very high efficiency [2]. Time-resolved spectroscopies and cryo-EM techniques revealed a variety of optical features and supramolecular arrangements across different supercomplexes, despite the close similarity between the antenna constituents. The variety, size, and complexity of these systems prevent an immediate understanding of strategies for efficient light harvesting just from structural and spectroscopic information. Computational, structure-based models have the potential of bridging the atomistic detail and the bulk behavior. In this contribution, we show a novel strategy, combining structural refinement and QM/MM excitonic calculations, which can fully characterize the energy landscape and predict photophysical properties of large photosystems from first principles. All excited-state quantities are computed on the actual photosystem's structure, overcoming a common limitation of previous models and directly accounting for the effect of supercomplex formation on the properties of the pigments. The temporal and spatial dimensions of the excitation dynamics can then be extensively explored through analysis of trapping times and population fluxes across different excitation conditions. We applied our model to plant PSII [3] and PSI [4], gaining new insights on light-harvesting in the two systems and characterizing diverse strategies implemented to achieve efficient light conversion.

References

[1] T. Mirkovic, E. E. Ostroumov, J. M. Anna, R. van Grondelle, Govindjee, and G. D. Scholes, "Light absorption and energy transfer in the antenna complexes of photosynthetic organisms", Chem. Rev., vol. 117, no. 2, pp. 249–293, Jan. 2017, doi: 10.1021/acs.chemrev.6b00002.

[2] R. Croce and H. van Amerongen, "Light harvesting in oxygenic photosynthesis: Structural biology meets spectroscopy", Science, vol. 369, no. 6506, Aug. 2020, doi: 10.1126/science.aay2058.

[3] E. Betti, L. Cupellini, and B. Mennucci, "Quantum chemical modeling of energy flow and photoprotection in photosystem II", Cell Rep. Phys. Sci., vol. 7, no. 2, Art. no. 103099, Feb. 2026, doi: 10.1016/j.xcrp.2026.103099.

[4] E. Betti, L. Cupellini, "Energy transfer pathways in plant Photosystem I from first-principles modeling", ChemRxiv, Apr. 2026, doi: 10.26434/chemrxiv.15001874/v1.

In silico Identification of Polyurethane degrading Enzymes via the use of PyJess

Rodolfo Caeiro[1,2*], Pedro Paiva[1,2], António J. M. Ribeiro[3], Maria J. Ramos[1,2]

[1] *LAQV, REQUIMTE, Departamento de Química e Bioquímica, Faculdade de Ciências, Universidade do Porto, Rua do Campo Alegre s/n, 4169-007 Porto, Portugal*

[2] *EnZync Center for Enzymatic Deconstruction of Thermoset Plastics*

[3] *LAQV, REQUIMTE, Laboratório de Química Orgânica e Farmacêutica, Departamento de Ciências Químicas, Faculdade de Farmácia, Universidade do Porto, Rua de Jorge Viterbo Ferreira no. 228, Porto, Portugal, 4050-313*

* Presenting author

There are currently over one hundred million proteins described in the UniProt Database [1]. Of these, only a fraction has been identified to have the capacity to degrade plastic polymers. A pre-screening methodology to identify polyurethane degrading enzymes via the use of the PyJess program [2] is presented here. PyJess viability was initially assessed by applying it to a set of homologous proteins. Afterwards, PyJess was applied to a set of over 500 thousand proteins [3]. Resulting proteins were selected according to whether they had been identified to possess enzymatic activity and the solvent exposure of the active site residues was used to rank the list of candidates. For structures generated using AlphaFold [4] the pLLDT was used to futher narrow down the list of candidates. Using this methodology the initial list was reduced to a list of 20 enzymes that are likely to possess polyurethane degrading activity. Although this methodology was developed for polyurethane degrading enzymes, it is expected to also be applicable to any type of plastic degrading enzyme.

References

[1] A. Bairoch et al., “The Universal Protein Resource (UniProt),” Nucleic Acids Research, vol. 33, pp. D154–D159, 2005.

[2] A. Bairoch and B. Boeckmann, “The SWISS-PROT protein sequence data bank,” Nucleic Acids Research, vol. 19, suppl., pp. 2247–2249, 1991.

[3] R. E. Hackett, I. G. Riziotis, M. Larralde, A. J. M. Ribeiro, G. Zeller, and J. M. Thornton, “Investigating enzyme function by geometric matching of catalytic motifs,” bioRxiv, 2026, preprint.

[4] J. Jumper et al., “Highly accurate protein structure prediction with AlphaFold,” Nature, vol. 596, pp. 583–589, 2021.

Funding and acknowledgments: The authors would like to thank the EnZync consortium, and the financial support received by the Novo Nordisk Fonden, under project NNF22OC0072891 (Challenge Programme 2022 – Recycling or a Sustainable Society).

Assigning the Low-Energy Excitons in Far-Red Photosystem II through Atomistic Modeling

Samuele Giannini*, Luca Ancillotti, Lorenzo Cupellini

University of Pisa

* Presenting author

Far-red light photoacclimation extends the spectral range of oxygenic photosynthesis through the incorporation of chlorophylls (Chls) d and f into natural Photosystems, but the energetic organization of these pigments remains poorly understood [1]. Here, we combine electronic-structure calculations with atomistic QM/MM and polarizable QM/MM approaches [2] to determine the site energies, electronic couplings, and excitonic structure of the far-red PSII from Synechococcus sp. PCC 7335 [3]. In particular, we use benchmark calculations against spin-component-scaled CC2 to assess the accuracy of long-range corrected density functionals for describing the relative energetics of Chls a, d, and f. Our calculations reveal that the energetic tuning of the far-red pigments is governed primarily by protein electrostatics, whereas structural distortions and environmental polarization make comparatively minor contributions. We found significant excitonic interactions within the subset of CP47 chlorophylls, while the reaction-center Chl d remains largely localized [4]. The resulting excitonic Hamiltonian quantitatively reproduces both the far-red absorption spectrum and the sequence of exciton energies extracted from two-dimensional electronic spectroscopy, enabling a first-principles assignment of the low-energy excitons to specific Chl f and Chl d pigments. These results provide an atomistic picture of the far-red excitonic landscape and establish a quantitative basis for future simulations of excitation-energy transfer and charge separation in far-red photosystems.

References

[1] Elias, E.; Oliver, T. J.; Croce, R. Annual Review of Physical Chemistry 2024, 75, 231–256.
[2] Cupellini, L.; Bondanza, M.; Nottoli, M.; Mennucci, B. Biochim. Biophys. Acta - Bioenerg. 2020, 1861, 148049.
[3] Gisriel, C. et. al Journal of Biological Chemistry 2022, 298, 101424
[4] Giannini, S., Ancillotti L., Cupellini L., (submitted 2026)

Beyond Descriptors: Graph Neural Networks for Large-Scale Docking Score Prediction

Marián Gall[1,3*], Lukas Bucinsky[1], Ján Matúška[1], Michal Pitoňák[2,3], Marek Štekláč[1,3]

[1] *Faculty of Chemical and Food Technology, Slovak University of Technology in Bratislava, Slovak Republic*
[2] *Faculty of Natural Sciences, Comenius University in Bratislava, Slovak Republic*
[3] *Centre of Operations of the Slovak Academy of Sciences, Bratislava, Slovak Republic*

* Presenting author

Fast and reliable docking-score prediction is a key prerequisite for prioritizing candidate molecules in large-scale virtual screening. Here, we develop and benchmark machine-learning models for predicting docking scores of inhibitors targeting the SARS-CoV-2 main protease (Mpro). Reference scores were obtained with AutoDock Vina 1.2.2 using the standard AutoDock scoring function.

Building on our previous work on optimized SOAP-based predictors, we compare two descriptor-based models, employing molecular and atomic Smooth Overlap of Atomic Positions (SOAP) representations [1], with three geometry-aware graph neural networks (GNNs): ViSNet [2], DimeNet++ [3], and PaiNN [4]. Unlike fixed descriptors, these GNNs learn from atomic identities and three-dimensional molecular structures directly; their directional or equivariant message-passing schemes can encode molecular geometry explicitly.

All models were trained on the in vivo dataset (approximately 60,000 compounds) and evaluated on an independent in vitro only dataset (approximately 170,000 compounds), providing a demanding test of transferability. A dedicated hyperparameter-optimization procedure was carried out for each architecture to identify suitable model capacity, message-passing depth, learning schedule, and regularization settings before the final comparison.

The optimized GNN and SOAP models are compared in terms of docking-score prediction accuracy, generalization to the independent dataset, and computational requirements. This systematic benchmark clarifies whether modern equivariant GNNs offer a practical advantage over established atomic and molecular SOAP representations for high-throughput, docking-guided drug discovery.

References

[1] A. P. Bartók, R. Kondor, and G. Csányi, 'On representing chemical environments,' Phys. Rev. B, vol. 87, no. 18, Art. no. 184115, May 2013, doi: 10.1103/PhysRevB.87.184115.
[2] Y. Wang et al., 'Enhancing geometric representations for molecules with equivariant vector-scalar interactive message passing,' Nat. Commun., vol. 15, Art. no. 313, Jan. 2024, doi: 10.1038/s41467-023-43720-2.
[3] J. Gasteiger, S. Giri, J. T. Margraf, and S. Günnemann, 'Fast and uncertainty-aware directional message passing for non-equilibrium molecules,' arXiv:2011.14115, Nov. 2020, doi: 10.48550/arXiv.2011.14115.
[4] K. T. Schütt, O. T. Unke, and M. Gastegger, 'Equivariant message passing for the prediction of tensorial properties and molecular spectra,' in Proc. 38th Int. Conf. Mach. Learn. (ICML), PMLR, vol. 139, Jul. 2021, pp. 9377-9388.

Funding and acknowledgments: We are grateful for financial support to VEGA grant nos. 1/0175/23, 1/0324/24, and 1/0254/24 and APVV grant nos. APVV-20-0127, APVV-24-0207, and VV-MVP-24-0039. The National Competence Centre for HPC at SAS (Project Code 311070AKF2) funded by ERD Fund, EU Structural Funds Informatization of Society, Operational Program Integrated Infrastructure is acknowledged for computational resources made available.

Molecular Aspects of Asphaltene Solvation: Kirkwood-Buff Analysis of Archipelago and Continental Structures in Toluene and n-Heptane

Lucas Avila Pinheiro*, Leandro Martínez

Unicamp

* Presenting author

Asphaltenes are the heaviest and most polar fraction of crude oil, defined operationally by solubility, soluble in toluene, insoluble in n-heptane. Their precipitation causes severe losses in oil production and refining, yet the molecular origin of this solubility contrast remains unclear, largely because most simulations rely on idealized model structures rather than experimentally derived ones.

We investigate the solvation of nine asphaltenes taken from a curated experimental dataset [1], four archipelago and five continental, in toluene and in n-heptane. Parameters follow OPLS-AA, with atomic charges obtained through a GFN2-xTB / B3LYP-def2-SVP / M06-2X-def2-TZVP protocol using CM5 charges [4] scaled by 1.2 for condensed-phase consistency. Molecular dynamics simulations were run with NAMD at five temperatures (298-423 K), with three independent replicas per system.

Solvation was analyzed through minimum-distance distribution functions (MDDFs) and the corresponding Kirkwood-Buff (KB) integrals [2,3], which are suitable for solutes of irregular shape and allow decomposition of the distributions into contributions of individual atomic groups, separating the roles of the aromatic core, the aliphatic periphery, and the heteroatoms (S, N, O).

The KB integrals separate the two architectures without overlap at every temperature studied, at 298 K, continental structures (c54, c65) converge to -144 and -164 cm³/mol, whereas archipelago structures (a2, a7) reach -262 and -304 cm³/mol; the gap persists across 288-308 K range and is roughly an order of magnitude larger than the variation of each structure with temperature. Whether this reflects molecular topology or size is under investigation, as the two are correlated in the present set; ongoing work normalizes the KB integrals by molecular size and enlarges the set to decouple the effects, extends the campaign to n-heptane, and adds a Van't Hoff analysis of the solvation thermodynamics.

References

[1] M. Franke, S. Arsala, F. Tahiry, S.-O. Gingras, and A. K. Sharma, 'Curated dataset of asphaltene structures', Data Brief, vol. 52, p. 109907, Feb. 2024, doi: 10.1016/j.dib.2023.109907.

[2] B. Schuler, G. Meyer, D. Peña, O. C. Mullins, and L. Gross, 'Unraveling the molecular structures of asphaltenes by atomic force microscopy', J. Am. Chem. Soc., vol. 137, no. 31, pp. 9870–9876, Aug. 2015, doi: 10.1021/jacs.5b04056.

[3] L. Martínez, 'ComplexMixtures.jl: Investigating the structure of solutions of complex-shaped molecules from a solvent-shell perspective', J. Mol. Liq., vol. 347, p. 117945, Feb. 2022, doi: 10.1016/j.molliq.2021.117945.

[4] L. Martínez and S. Shimizu, 'Molecular interpretation of preferential interactions in protein solvation', J. Chem. Theory Comput., vol. 13, no. 12, pp. 6358–6372, Dec. 2017, doi: 10.1021/acs.jctc.7b00599.

Funding and acknowledgments: This work was supported by the São Paulo Research Foundation (FAPESP), grant 2025/14969-0. The author thanks Prof. Leandro Martínez for supervision and the Institute of Chemistry, University of Campinas (UNICAMP). We thank the Coaraci Supercomputer for computer time (FAPESP grant 2019/17874-0) and the Center for Computing in Engineering and Sciences at Unicamp (FAPESP grant 2013/08293-7).

Atomistic characterization of cell-penetrating peptide insertion into biologically relevant lipid membranes

Andrei Neamtu[1]*, Dragos Isac[2], Brindusa Alina Petre[3]

[1] *Centre of Advanced Research in Bionanoconjugates and Biopolymers, "Petru Poni" Institute of Macromolecular Chemistry, Iasi, Romania; Department of Physiology, "Grigore T. Popa" University of Medicine and Pharmacy, Iasi, Romania*
[2] *Centre of Advanced Research in Bionanoconjugates and Biopolymers, "Petru Poni" Institute of Macromolecular Chemistry, Iasi, Romania*
[3] *Faculty of Chemistry, "Al. I. Cuza" University of Iasi, Romania*
* Presenting author

Cell-penetrating peptides (CPPs) represent promising vectors for intracellular drug delivery[1]. However, the molecular mechanisms governing their interaction with biological membranes remain incompletely understood[2]. In this study, we employed conventional and umbrella sampling molecular dynamics simulations[3] to investigate the membrane insertion and translocation of a fluorescent labelled model peptide (CGNKRTR) in lipid bilayers of increasing complexity, including DOPC/Chol (80/20), DOPC/DOPS/Chol (50/30/20), POPC/Chol (80/20), and asymmetric plasma membrane-like systems. Conventional simulations (100 ns–1 μs) were combined with umbrella sampling calculations (51 windows × 100 ns) to characterize peptide conformational dynamics and the associated free-energy landscapes. Across all membrane compositions, the peptide exhibited a dynamic equilibrium between surface-adsorbed, collapsed, and transmembrane conformations. Transverse insertion emerged as the most stable state, whereas collapsed conformations within the bilayer core represented transient intermediates during membrane penetration. Potential of mean force calculations identified distinct free-energy minima corresponding to the transmembrane state, with partition barriers of approximately 18 kcal/mol in DOPC and 8 kcal/mol in POPC membranes, highlighting the influence of bilayer thickness and lipid composition on peptide stability. In negatively charged and cholesterol-containing membranes, surface-adsorbed states were preferentially stabilized, while asymmetric plasma membrane models revealed preferential peptide partitioning into sphingomyelin- and POPS-enriched domains. Based on these results, we propose a multistep membrane translocation mechanism involving surface adsorption, transient collapsed intermediates, transmembrane insertion, and desorption. These findings provide atomistic insight into CPP–membrane interactions and the role of membrane composition in peptide translocation.

References

[1] M. C. Morris, S. Deshayes, F. Heitz, and G. Divita, "Cell-penetrating peptides: from molecular mechanisms to therapeutics," Biology of the Cell, vol. 100, no. 4, pp. 201–217, Apr. 2008, doi: 10.1042/BC20070116.
[2] H. Derakhshankhah and S. Jafari, "Cell penetrating peptides: A concise review with emphasis on biomedical applications," Biomedicine & Pharmacotherapy, vol. 108, pp. 1090–1096, Dec. 2018, doi: 10.1016/j.biopha.2018.09.097.
[3] J. Ouyang, Y. Sheng, and W. Wang, "Recent Advances of Studies on Cell-Penetrating Peptides Based on Molecular Dynamics Simulations," Cells, vol. 11, no. 24, p. 4016, Dec. 2022, doi: 10.3390/cells11244016.

Funding and acknowledgments: This work is supported by European Union's Horizon Europe research and innovation programme under grant agreement No 101086667, project BioMat4CAST (BioMat4CAST - "Petru Poni" Institute of Macromolecular Chemistry Multi-Scale In Silico Laboratory for Complex and Smart Biomaterials).

Using machine-learning collective variables to characterize the sulphide oxidation reaction by bacterial sulphide:quinone reductases

Rui P. P. Neves [1*], Umberto Raucci [2], Michele Parrinello [2]

1 LAQV/REQUIMTE, Departamento de Química e Bioquímica, Faculdade de Ciências Universidade do Porto, Rua do Campo Alegre, s/n, 4169-007 Porto, Portugal

2 Italian Institute of Technology, Genova, GE 16163, Italy

* Presenting author

Machine-learning collective variables (ML CV) have proved powerful allies to tackle enzyme reaction mechanisms via enhanced sampling simulations.[1, 2] We report the application of ML CVs and enhanced sampling simulations to study the reaction mechanism of sulphide oxidation by bacterial sulphide:quinone reductases (SQR), a central enzyme for bacterial growth in sulphur-rich environments that uses the pollutant hydrogen sulphide gas as an electron donor to produce sulphur globules that can be retrieved as a feedstock.[3] Using data from umbrella sampling simulations at the PBE/MM level, we trained a feed-forward neural network outputting the committor function for the reaction under study, from defined sets of simple geometrical descriptors and using the Kolmogorov functional as a loss function. The trained ML-committor was used as CV to explore sulphide oxidation in SQR with on-the-fly probability enhanced sampling (OPES) simulations at the PBE/MM level. In particular, we used the OPES-VK scheme by Trizio et al., which combines the OPES and Kolmogorov bias (VK) to efficiently explore both the reaction space and the transition state region.[2, 4] Our results confirm that this strategy promotes transitions between reactants and products right after the first training round, although transition state sampling is still inefficient. It can also competently identify other stable basins for the reaction. Optimal characterization of the transition state ensemble requires training of new ML committor CVs through an active learning process, where the data from previous OPES-VK simulations is used to train the new ML-committor CVs for subsequent simulation rounds.[4] We discuss our preliminary results using ML CVs against those from umbrella sampling simulations, showing how ML CVs can be powerful objects to describe more generalized reaction coordinates to assist rational enzyme engineering campaigns targeting enzyme active sites.

References

[1] R. P. P. Neves et al., "Methods for the establishment of enzymatic mechanisms – from QM to ML," Chem Sci, vol. 17, no. 34, pp. 16108-16150, 2026, doi: 10.1039/d6sc02180h.

[2] S. Das et al., "A Machine Learning-Driven, Probability-Based Approach to Enzyme Catalysis," (in English), ACS Catal., vol. 15, no. 11, pp. 9785-9792, May 27 2025, doi: 10.1021/acscatal.5c02431.

[3] M. Marcia, U. Ermler, G. H. Peng, and H. Michel, "The structure of Aquifex aeolicus sulfide:quinone oxidoreductase, a basis to understand sulfide detoxification and respiration," (in English), Proc Natl Acad Sci USA, vol. 106, no. 24, pp. 9625-9630, Jun 16 2009, doi: 10.1073/pnas.0904165106.

[4] E. Trizio, P. Kang, and M. Parrinello, "Everything everywhere all at once: a probability-based enhanced sampling approach to rare events," Nat Comput Sci, vol. 5, no. 7, pp. 582-591, 2025/07/01 2025, doi: 10.1038/s43588-025-00799-5.

Funding and acknowledgments: 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 COST Action COZYME, CA21162, supported by COST (European Cooperation in Science and Technology). R.P.P.N. further thanks the Atomistic Simulations group at the Center for Human Technologies (IIT, Genoa) and FCT for funding through the Individual Call to Scientific Employment Stimulus (Ref. 2021.00391.CEECIND/CP1662/CT0003 DOI: https://doi.org/10.54499/2021.00391.CEECIND/CP1662/CT0003).

Towards Biomolecular Simulations of Chalcogen Bonds: Assessment of Extra-Point Models for Sulfur

Francisco P. E. Duarte*, Paulo J. Costa

BioISI - Biosystems and Integrative Sciences Institute, Departamento de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, Portugal

* Presenting author

The term σ-hole refers to a localized region of positive electrostatic potential along the extension of a covalent bond. These regions can engage in directional noncovalent interactions with nucleophilic sites, giving rise to the so-called σ-hole interactions, of which the halogen bond (R–X···B interaction) is the most extensively studied [1]. However, σ-hole interactions are not restricted to halogen atoms, and chalcogen bonds (ChBs) [2], a subclass 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 chalcogen atoms, sulfur is particularly relevant, as it is far more prevalent than the heavier chalcogens in biomolecules and drugs.

Standard force fields typically rely on atomic point charges, which fail to properly describe interactions arising from the electrostatic anisotropy of atoms such as sulfur. Following a statistical analysis of the electrostatic surface potential of sulfur-containing molecules, in this work, we assess several extra-points (EPs) that emulate sulfur anisotropy against experimental hydration free energies for a dataset of 44 sulfur-containing molecules. For such purposes, EP RESP charges were fitted at different positions, and three independent 10 ns MD simulations for each molecule and each EP model were run, followed by alchemical free-energy calculations using the MBAR method to determine hydration free energies.

Our results show that placing EPs at selected positions yields hydration free energies comparable to those obtained with the standard model without EPs, indicating that the explicit representation of the σ-hole does not compromise the prediction of other thermodynamic properties, while enabling the description of ChBs. These results provide a suitable starting point for the future study of ChBs in biological systems using MD simulations.

References

[1] P. J. Costa, "The halogen bond: Nature and applications," Physical Sciences Reviews, vol. 2, no. 11, Oct. 2017, doi: 10.1515/psr-2017-0136.

[2] M. H. Kolář, P. Carloni, and P. Hobza, "Statistical analysis of σ-holes: a novel complementary view on halogen bonding," Phys. Chem. Chem. Phys., vol. 16, no. 36, pp. 19111–19114, 2014, doi: 10.1039/c4cp02621g.

Funding and acknowledgments: This work was funded by Fundação para a Ciência e a Tecnologia (FCT) and co-financed by the European Union, under exploratory project 2024.16247.PEX (DOI: 10.54499/2024.16247.PEX). FCT is also acknowledged for project UID/04046/2025 (DOI: 10.54499/UID/04046/2025) awarded to Biosystems and Integrative Sciences Institute (BioISI), and for the Advanced Computing project 2023.10475.CPCA (DOI: 10.54499/2023.10475.CPCA.A2), awarded to PJC. PJC also acknowledges FCT and the Portuguese Recovery and Resilience Plan (PRR) for his contract under the FCT-Tenure program (2023.15441.TENURE.008/CP00003/CT00005).

Molecular insights of hydration level effect on softwood cell walls

Carlos G. T. Batista*, Munir S. Skaf

Institute of Chemistry, Center for Computing in Engineering & Sciences, State University of Campinas; Campinas, SP, 13084-862, Brazil

* Presenting author

Molecular architecture and the water role in modulating the structural properties of the plant cell wall are not fully understood. The mechanical stress applied to fresh wood can exceed the yield point without breaking it, while the wood fully recovers its shape after the stress ceases [1]. Remarkably, dried wood cannot overcome its elastic deformation limit, suffering brittle failure and breaking in experiments [2]. Thus, water may play a crucial role alongside lignocellulose polymers, modulating polymer interactions and supporting the cell wall architecture. In this work, we adapt an atomistic spruce lignocellulosic model to evaluate how hydration content influences polymeric interactions using molecular dynamics simulations [3]. The major modification on the original model involves the O-methylation of glucuronic acids in arabinoglucuronoxylan, which increases the structural hydrophobicity of the xylan side chains. Also, DMSO was used to prepare systems with different water content, preventing vacuum spots and facilitating hydrophobic interactions. Although it is not a natural component of plant cell walls, experimental evidence shows that DMSO favors lignin aggregation, and we expect it to enhance lignin-lignin and lignin-carbohydrate interactions [4]. DMSO is miscible with water in all proportions, acting as a cosolvent that allows testing hydrophobic effects at higher DMSO content without introducing phase transition artifacts in simulations. Therefore, we prepared systems with different water:DMSO proportions, ranging the from 0 to 1. All the systems have been equilibrated on NAMD3 software with CHARMM36 force field for 1 μs. Here, we aim to discuss the water diffusion in this different system, such as the conformational changes on hemicellulose chains and how they are related to cellulose and lignin-rich environments. Such as, we are working on the application of MDDF theory to elucidate water and hydrophobic effects on plant cell wall systems.

References

[1] J. Keckes et al., 'Cell-wall recovery after irreversible deformation of wood', Nat. Mater., vol. 2, no. 12, pp. 810–813, Dec. 2003, doi: 10.1038/nmat1019.

[2] G. Kifetew et al., 'The effect of drying on wood fracture surfaces from specimens loaded in wet condition', Wood Sci. Technol., vol. 32, no. 2, pp. 83–94, 1998, doi: 10.1007/BF00702589.

[3] L. N. Trentin et al., 'Unraveling the Mechanical Behavior of Softwood Secondary Cell Walls through Atomistic Simulations', Biomacromolecules, vol. 26, no. 6, pp. 3395–3409, Jun. 2025, doi: 10.1021/acs.biomac.4c01806.

[4] W. Zhao et al., 'From Lignin Subunits to Aggregates: Insights into Lignin Solubilization', Green Chem., vol. 19, no. 14, pp. 3272–3281, 2017. doi: 10.1039/c7gc00944e

Funding and acknowledgments: The work was supported by CAPES, CNPq (140772/2023-5), and FAPESP (grants 2025/11743-1 and 2013/08293-7). Besides, the authors acknowledge the computational resources provided by CENAPAD-SP (Centro Nacional de Processamento de Alto Desempenho em São Paulo) and COARACI Supercomputer at UNICAMP (FAPESP grant 2019/17874-0).

Multi-Scale Modeling of Metabolic Pathways

Miljan Dašić*, Ashwathi Poolamanna, Mehrnoosh Khodam Hazrati, Štěpán Timr

Heyrovský Institute of the Czech Academy of Sciences

* Presenting author

Spatial organization of enzymes, molecular interactions, and macromolecular crowding are increasingly recognized as key regulators of intracellular metabolic processes.

While each of these factors has been studied individually, their combined effect across multiple spatial and temporal scales remains insufficiently understood.

Here we present a multi-scale computational framework that connects molecular-level dynamics with pathway-level reaction kinetics. At the nanoscopic scale, coarse-grained molecular dynamics (MD) simulations performed with LAMMPS software package are used to characterize enzyme–substrate interactions and substrate diffusion in crowded environments containing either attractive or repulsive crowders.

The resulting diffusion coefficients and kinetic parameters are subsequently incorporated into stochastic particle-based reaction–diffusion (RD) simulations with Smoldyn software package, enabling quantitative investigation of multi-step metabolic pathways at cellular length and time scales. This integrated approach allows us to systematically assess how crowding, non-specific molecular interactions, and enzyme spatial organization jointly influence substrate transport, reaction dynamics, and overall metabolic pathway efficiency. Our results show that these factors can substantially modulate both molecular transport and pathway flux, emphasizing the importance of incorporating spatial heterogeneity and stochasticity into computational models of cellular metabolism.

Funding and acknowledgments: This work was supported by the Czech Science Foundation (Grant No. 23-06437S).

Comparative QM/MM Investigation of O_2 Binding in Arthropod Hemocyanins: Structural and Energetic Insights Across Species

Rachele Zunino[1*], Francesca Fasulo[1], Michele Pavone[2], Ana Belén Muñoz-García[1]

[1] *Department of Physics "Ettore Pancini", University of Naples Federico II, Complesso Universitario Monte Sant'Angelo Via Cintia 21, Naples 80126, Italy*

[2] *Department of Chemical Sciences, University of Naples Federico II, Complesso Universitario Monte Sant'Angelo Via Cintia 21, Naples 80126, Italy*

* Presenting author

Hemocyanin (Hc) is a copper-containing protein responsible for the reversible binding and transport of molecular oxygen in arthropods and mollusks. Beyond its respiratory function, Hc participates in diverse immune-related and redox processes, underscoring its multifunctional biological role.[1] Its active site, highly conserved across species despite substantial differences in sequence and structure, consists of a type-3 dicopper center in which each copper ion is coordinated by three histidine residues. Reversible O_2 binding occurs through coordination between the two copper ions and is accompanied by significant structural rearrangements that facilitate efficient O_2 uptake and release.[2] Despite extensive experimental characterization of Hc structure and its O_2-binding mechanism, computational investigations have largely focused on the Hc of Limulus polyphemus.[3,4] Consequently, the molecular factors governing O_2 affinity across arthropod species, particularly in relation to the transition from marine to terrestrial habitats, remain poorly understood.

In this work, we combine molecular dynamics simulations with QM/MM calculations to characterize the deoxy and oxy states of the binuclear copper site in Hcs from several representative arthropod species. Our results reveal marked differences in O_2-binding energetics among species, while oxygenation is consistently accompanied by a contraction of the Cu–Cu distance and the formation of a peroxide-like adduct. The analysis further suggests that second-sphere interactions, including hydrogen-bonding networks and local solvent organization around the active site, contribute to the modulation of O_2 affinity and the stabilization of the oxy state.

Overall, this study provides new atomistic insights into the structure–function relationships of arthropod Hcs and contributes to a better understanding of how variations in the active-site environment may influence the O_2-binding properties of these respiratory proteins.

References

[1] C. J. Coates and E. M. Costa-Paiva, "Multifunctional Roles of Hemocyanins," in Vertebrate and Invertebrate Respiratory Proteins, Lipoproteins and Other Body Fluid Proteins, U. Hoeger and J. R. Harris, Eds., ser. Subcellular Biochemistry, vol. 94. Cham, Switzerland: Springer, 2020, pp. 233–250.

[2] K. A. Magnus, B. Hazes, H. Ton-That, C. Bonaventura, J. Bonaventura, and W. G. J. Hol, "Crystallographic Analysis of Oxygenated and Deoxygenated States of Arthropod Hemocyanin Shows Unusual Differences," Proteins: Struct., Funct., Genet., vol. 19, no. 4, pp. 302–309, Aug. 1994.

[3] T. Saito and W. Thiel, "Quantum Mechanics/Molecular Mechanics Study of Oxygen Binding in Hemocyanin," J. Phys. Chem. B, vol. 118, no. 19, pp. 5034–5043, May 2014.

[4] F. Fasulo, A. Terán, M. Pavone, and A. B. Muñoz-García, "Revisiting Oxygen Transport Features of Hemocyanin with NEVPT2 Level QM/MM Calculations," J. Chem. Theory Comput., vol. 21, no. 4, pp. 2108–2117, Feb. 2025.

Funding and acknowledgments: The authors thank the Human Frontier Science Program for financial support (Grant RGY0056/2022). The HPC computer facilities at the UNINA Computational Center for Chemical Sciences are kindly acknowledged. The authors also thank Dr. Aaron Terán for useful discussions.

Solvation Effects Of Choline-derived Ionic Liquids On Plasmodium falciparum Proteins: A Molecular Dynamics Study

Pamella Cristiny Carneiro da Silva*, Leandro Martínez

Universidade Estadual de Campinas
Center for Computing in Engineering and Sciences
* Presenting author

The effects of ionic liquids (ILs) on proteins are well known and widely studied for various applications [1]. Compared to conventional solvents, ILs exhibit several advantageous properties as excellent solvation ability, and high thermal stability. Biocompatible ionic liquids (Bio-Ils) retain these properties while maintaining manageable toxicity levels, making them attractive for pharmaceutical applications [2]. In this work, Hamiltonian Replica Exchange Molecular Dynamics were employed to investigate the effect of concentration changes in choline-based ILs on the stability and structure of Plasmodium falciparum proteins. The proteins AMA1, MSP1, and MSP2 were studied in aqueous solutions of choline geranate (CAGE), choline lactate (CAL), and choline chloride (CACL) at concentrations of 0.125 M, 0.250 M, 0.5 M, 1.0 M, and 2.0 M. Solvation structures were characterized using Kirkwood–Buff (KB) solution theory [3] that revealed distinct behaviors among the Bio-ILs. CACL behaves similarly to a conventional salt, showing minimal variation in solvation effects of the concentration and acting as a preferentially excluded, protein-stabilizing cosolvent. In contrast, CAGE and CAL exhibit behavior typical of Bio-ILs: their affinities vary with concentration. Although they are not completely excluded from the protein surface, their compensated electrostatic interactions, modulated by the nature of both cations and anions, contribute to protein stabilization. Structural analyses based on RMSD and RMSF indicate that the cosolvents maintain protein structures in their functional conformations. In AMA1, key residues in disordered regions: K489, R503, K508, and R512 were stabilized. The spatial distributions of relevant functional groups of each cosolvent were further characterized using Minimum Distance Distribution Functions and KB. These approaches enabled a molecular-level understanding of protein–cosolvent interactions and their impact on protein stability.

References

[1] V. Piccoli and L. Martínez, "Cation Hydrophobicity Effects on Protein Solvation in Aqueous Ionic Liquids," J. Phys. Chem. B, vol. 129, no. 27, pp. 6765–6776, May 2025, doi: 10.1021/acs.jpcb.5c00779.

[2] Y.-L. Wang et al., "Microstructural and Dynamical Heterogeneities in Ionic Liquids," Chem. Rev., vol. 120, no. 13, pp. 5798–5877, 2020, doi: 10.1021/acs.chemrev.9b00693.

[3] I. L. Shulgin and E. Ruckenstein, "The Kirkwood–Buff theory of solutions and the local composition of liquid mixtures," J. Phys. Chem. B, vol. 110, no. 25, pp. 12707–12713, 2006, doi: 10.1021/jp060636y.

Funding and acknowledgments: The authors acknowledge the financial support of FAPESP (2018/24293-0, 2013/08293-7). Research developed with the help of CENAPAD-SP (National Center for High Performance Processing in São Paulo), project UNICAMP / FINEP - MCTI.

Zinc-Assisted SF3b Complex Covalent Inhibition by Spliceostatin A

Riccardo Rozza*, Angela Parise, Jana Aupič, Angelo Spinello, Vlad Pena, Alessandra Magistrato

CNR - Istituto Officina dei Materiali (IOM) c/o SISSA via Bonomea 265, 34136, Trieste, Italy
Department of Biological, Chemical and Pharmaceutical Sciences and Technologies, University of Palermo 90128 Palermo,Italy
Research Group Mechanisms and Regulation of RNA Splicing, The Institute of Cancer Research 237 Fulham Road, London, SW3 6JB
* Presenting author

Pre-mRNA splicing is catalyzed by the spliceosome (SPL), a dynamic ribonucleoprotein machinery that removes the non-coding region of the pre-mRNA, the introns, and joins the coding ones, the exons. SPL progresses through the E, A, B, Bact, B*, C, C*, P, and ILS complexes and assembles de novo at each cycle, involving more than 100 proteins and 5 small nuclear ribonucleoproteins, U1, U2, U4, U5, and U6 snRNPs. During the A-state formation, the SF3b complex stabilizes the U2–intron duplex and accommodates the bulged branch-point adenosine at the interface of its two components SF3B1–PHF5A, frequentely altered in cancers [1,2]. This pocket is targeted by spliceostatin A (SSA), an antitumor splicing modulator that covalently modifies Cys26 of the PHF5A $ZnCys_4$ zinc finger without ejecting Zn^{2+} [3,4]. Yet, the molecular determinants that activate this normally zinc-coordinated cysteine remain unclear.

Here, we combined extensive all-atom classical molecular dynamics (MD), QM/MM MD, and QM/MM thermodynamic integration (TI) to reconstruct the Cys26–SSA coupling mechanism and quantify its energetics. Classical MD identified two noncovalent SSA-binding poses, but only the thermodynamically favored one pre-organized the epoxide for attack. QM/MM MD and TI showed that distortion of the $ZnCys_4$ coordination sphere weakens the Zn–Cys26 bond, promotes water–cysteine exchange, and generates a reactive thiolate. Cys26 then opens the SSA epoxide, assisted by an Asp34–Lys29 proton relay. QM/MM TI revealed a low activation barrier and a strongly exergonic reaction. Finally, a bioinformatic survey of Protein Data Bank structures identified putative spliceosomal zinc-finger motifs flanked by nearby acidic–basic residue pairs, suggesting that SSA-inspired covalent inhibitors could be developed for additional zinc-finger-containing targets.

References

[1] S. Rinaldi et al., 'Frontiers and challenges of computing ncRNAs biogenesis, function and modulation', J. Chem. Theory Comput., vol. 20, no. 3, pp. 993–1018, Feb. 2024, doi: 10.1021/acs.jctc.3c01239.
[2] R. Rozza et al., 'Role of computational and structural biology in the development of small-molecule modulators of the spliceosome', Expert Opin. Drug Discov., vol. 17, no. 10, pp. 1095–1109, Oct. 2022, doi: 10.1080/17460441.2022.2114452.
[3] T. Teng et al., 'Splicing modulators act at the branch point adenosine binding pocket defined by the PHF5A–SF3b complex', Nat. Commun., vol. 8, Art. no. 15522, May 2017, doi: 10.1038/ncomms15522.
[4] C. Cretu et al., 'Structural basis of intron selection by U2 snRNP in the presence of covalent inhibitors', Nat. Commun., vol. 12, Art. no. 4491, Jul. 2021, doi: 10.1038/s41467-021-24741-1.

Funding and acknowledgments: AIRC IG 24514 and IsCc6_SF3bMod

Catalytic Pathway of UMG-SP3-mediated Urethane Bond Hydrolysis

Luís M. C. Teixeira*, Pedro Paiva, Laura Rotilio, Alexander Sandahl, Peter Westh, Jens P. Morth, Daniel E. Otzen, Pedro A. Fernandes, Maria J. Ramos

LAQV@REQUIMTE, Departamento de Química e Bioquímica, Faculdade de Ciências, Universidade do Porto, Rua do Campo Alegre s/n, Porto, Portugal
EnZync Center for Enzymatic Deconstruction of Thermoset Plastics
Department of Biotechnology and Biomedicine, Technical University of Denmark, Søltofts Plads, Kongens Lyngby, Denmark
Teknologisk Institut, Kongsvang Alle 29, Aarhus, Denmark
Interdisciplinary Nanoscience Center (iNANO). Aarhus University, Gustav Wieds Vej 14, DK-8000 Aarhus, Denmark
* Presenting author

Polyurethane (PU) is the sixth most used synthetic polymer, due to its versatility and lowcost manufacture.[1]. However, PU waste has been ineffectively managed, yielding environmental and public health concerns.[2] In an attempt to resolve this issue, academia and industry efforts have been made to discover enzymes that are able to depolymerize PU. One of the first discovered urethanases was UMG-SP3.[3] Paiva et. al. established the catalytic mechanism for the urethane bond hydrolysis catalyzed by UMGSP2 (UMG-SP3 homologue), confirming the potential of this type of enzymes for depolymerizing industrial-like PU monomers.[4] The mechanism was established using a static single-conformation quantum mechanics/molecular mechanism (QM/MM) scheme, meaning enzyme dynamics were not accounted for, which could impact catalysis. In addition, UMG-SP3 is a different enzyme, meaning the structural differences might influence the chosen mechanistic path. Therefore, we studied UMG-SP3 using a QM/MM molecular dynamics scheme. Accordingly, we observed that the mechanism occurred along two steps: an acylation step followed by a deacylation step. The first step was the rate-limiting one and culminated in the formation of the acyl-enzyme and release of alcohol. Subsequently, the second stage culminated in the regeneration of the enzyme and the release of a highly unstable carbamic product, which quickly decarboxylates in an enzyme-independent manner. In accordance with previous studies, UMG-SP3 exhibited preference to cleave the C-O side instead of the C-N side. This study confirms the current mechanistic proposal for this type of enzyme and opens the door for rational engineering of more efficient enzymes for PU depolymerization.

References

[1] Plastics Europe Plastics - The Facts 2023. An analysis of European latest plastics production, demand and waste data; Plastics Europe, 2024
[2] Kemona, A. and et. al. Polyurethane Recycling and Disposal: Methods and Prospects. Polymers 2020, 12, 1752, DOI: 10.3390/polym12081752
[3] Branson, Y. and et. al. Urethanases for the Enzymatic Hydrolysis of Low Molecular Weight Carbamates and the Recycling of Polyurethanes, Angew Chem. Int. Ed. Engl., 2023, 62 , e202216220
[4] Paiva, P. and et. al. Unveiling the Enzymatic Pathway of UMG-SP2 Urethanase: Insights into Polyurethane Degradation at the Atomic Level. Chem. Sci. 2025, 16, 2437– 2452, DOI: 10.1039/D4SC06688J

Funding and acknowledgments: The authors would like to thank the members of the En'Zync consortium for helpful discussions and feedback. We are grateful for the financial support received by the Novo Nordisk Fonden, under project NNF22OC0072891 (Challenge Programme 2022 - Recycling or a Sustainable Society). 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 -Laboratório Associado para a Química Verde - Tecnologias e Processos Limpos. LMCT, PP, PAF, and MJR would further like to thank the European High-Performance Computing Joint Undertaking (EuroHPC JU) that granted access to MeluXina, the petascale EuroHPC supercomputer located in Bissen, Luxembourg, under proposal EHPC-REG2023R03-163. LMCT would also like to thank FCT/MECI for funding his PhD project through the grant 2024.05090.BD (https://doi.org/10.54499/2024.05090.BD).

Computational Insights into the Enzymatic Biodegradation of Oligosaccharides from Pathogenic E. coli Biofilms by Glycoside Hydrolases

Neidy S.S. dos Santos*, Clauber H.S. da Costa, Carlos G.T. Batista, Munir S. Skaf

Institute of Chemistry and Center for Computing in Engineering & Sciences (CCES), University of Campinas (UNICAMP), 13084-862, Campinas, SP, Brazil

* Presenting author

Biofilm formation by Escherichia coli is a defense mechanism against antimicrobial agents, characterized by a complex extracellular polymeric substance (EPS) matrix composed of decorated cellulose [1]. Enzymatic degradation using carbohydrate-active enzymes (CAZymes), particularly cellulases, has proven to be a compelling strategy for EPS matrix disruption. Cocktails of recombinant cellulases from Thermothelomyces thermophilus combining exoglucanases (TthCel6A and TthCel7A) with the endoglucanase (TthCel7B) have shown experimental efficacy in degrading E. coli biofilms [2]. However, the molecular mechanisms governing how the zwitterionic nature of decorations affects enzyme-substrate recognition remain poorly understood. In this study, we investigate the molecular interactions between the glycoside hydrolases TthCel6A, TthCel7A, and TthCel7B and both native and decorated cellulose. Our approach integrates homology modeling, molecular docking, extensive molecular dynamics simulations, and quantum-classical QM/MM calculations. Our findings reveal a previously uncharacterized interaction where decorations act as electrostatic anchors within the catalytic tunnels of processive exoglucanases (TthCel6A and TthCel7A). This intensified electrostatic stabilization traps the polysaccharide chain, hindering sequential cleavage. In contrast, the non-processive endoglucanase (TthCel7B) retains greater conformational flexibility, allowing for EPS cleavage and subsequent dissociation to hydrolyze new chains. We observed that structural changes in the loops near the active site and specific interactions such as salt bridges and exclusive charge interactions work together to stabilize the complex. Our findings elucidate how chemical modifications in bacterial biofilms regulate cellulases activity and provide insights for the rational development of enzyme cocktails for biofilms.

References

[1] H.-C. Flemming and S. Wuertz, 'Bacteria and archaea on Earth and their abundance in biofilms', Nat. Rev. Microbiol., vol. 17, pp. 247–260, 2019, doi: 10.1038/s41579-019-0158-9.

[2] L. V. B. Samaniego, S. L. Scandelau, C. R. Silva, S. Pratavieira, V. O. A. Pellegrini, A. N. G. Dabul, L. A. Esmerino, M. de Oliveira Neto, R. T. Hernandes, F. Segato, M. Pileggi, and I. Polikarpov, 'Thermothelomyces thermophilus exo- and endo-glucanases as tools for pathogenic E. coli biofilm degradation', Sci. Rep., vol. 14, no. 22576, pp. 22576, 2024, doi: 10.1038/s41598-024-70144-9.

Funding and acknowledgments: UNICAMP, IQ, CAPES [88887.991092/2024-00; 88887.999131/2024-00], CNPQ [140772/2023-5], FAPESP, CEPID, COARACI Supercomputer [2013/08293-7; 2019/17874-0; 2022/04695-2; 2022/04703-5; 2024/19027-0, 2025/11743-1].

Metalloporphenes for the Oxygen Evolution Reaction: A DFT Study

Ondrej Tkáč*, Michal Malček

Institute of Physical Chemistry and Chemical Physics, Faculty of Chemical and Food Technology, Slovak University of Technology in Bratislava, Radlinského 9, 812 37 Bratislava, Slovakia

* Presenting author

Porphene is a two-dimensional (2D) analogue of graphene, consisting of fully fused porphyrin subunits. The incorporation of transition metal atoms into the porphene framework allows tuning of its electronic properties, making metalloporphenes promising materials for a wide range of applications, including electrocatalysis [1]. Zn-porphene, the first experimentally synthesized 2D metalloporphene, contains Zn atoms coordinated by four nitrogen atoms of the porphyrin core [2]. Electrocatalytic water splitting is considered one of the most promising green approaches for sustainable hydrogen production. It involves two coupled half-reactions, namely the hydrogen evolution reaction (HER) and the oxygen evolution reaction (OER) [3]. In this study, metalloporphenes containing different first-row transition metals were investigated as potential electrocatalysts for OER using density functional theory (DFT). The adsorption of the key OER intermediates (*OH, *O, and *OOH) as well as the reactants and products (H2O and O2) on the studied metalloporphenes was evaluated and further analysed using density of states and quantum theory of atoms in molecules analyses. To represent the porphene framework, DFT calculations of 2D metalloporphenes were performed employing periodic boundary conditions (PBC). For comparison purposes, the finite hydrogen-terminated metalloporphyrin subunits were also considered as computationally less demanding reference systems. This study aims to identify promising metalloporphenes as electrocatalysts for the oxygen evolution reaction.

References

[1] I. Pavlak, L. Matasović, E. A. Buchanan, J. Michl, and I. Rončević, "Electronic Structure of Metalloporphenes, Antiaromatic Analogues of Graphene," J. Am. Chem. Soc., vol. 146, no. 6, pp. 3992–4000, Feb. 2024, doi: 10.1021/jacs.3c12079.

[2] T. F. Magnera, P. I. Dron, J. P. Bozzone, M. Jovanovic, I. Rončević, W. Bu, E. M. Miller, C. T. Rogers, and J. Michl, "Porphene and Porphite as Porphyrin Analogs of Graphene and Graphite," Nat. Commun., vol. 14, p. 6308, Oct. 2023, doi: 10.1038/s41467-023-41461-w.

[3] B. Yao, Y. He, S. Wang, H. Sun, and X. Liu, "Recent Advances in Porphyrin-Based Systems for Electrochemical Oxygen Evolution Reaction," Int. J. Mol. Sci., vol. 23, no. 11, p. 6036, May 2022, doi: 10.3390/ijms23116036.

Funding and acknowledgments: We are grateful to the Slovak Grant Agencies APVV (contract No. APVV-24-0460) and VEGA (contract No. 1/0324/24) for financial support.

cations lead the dance: modelling cation adsorption on lipid membranes

Michele Turelli*, Ilaria Ciofini

Chimie ParisTech - PSL

* Presenting author

Lipid membranes allow the definition of distinct cellular environments, enabling the conditions for a variety of important processes. Their involvement goes beyond a simple structural role as their dynamical response influence essential events like membrane fusion[1]. Many variables participate in defining this response, among them the interaction with ions is known to modulate the mechanical properties of lipid layers [2].

Using molecular dynamics (MD), we investigate the adsorption of biologically relevant cations (Ca^{2+},Li^{+}, K^{+}, Mg^{2+}) on a model bilayer of 128 DOPC phospholipids under standard conditions. Our simulations track this adsorption from dissolved cations to the formation and reorganisation of complexes with waters and lipid headgroups up to simulated times of 0.3–0.5 µs.

Structural and dynamical analyses reveal distinct binding propensities and stoichiometries of stable complexes. For readily adsorbed cations, we assess their impact on lipid order, kinetics, membrane hydration, and we evaluate typical timescales of complex evolution, while also exploring how ion force field descriptions may affect these results. Density functional theory calculations on MD-extracted complexes are performed to refine the description of the interactions and provide estimates for binding enthalpies. The simulated data highlights the strong propensity of Li^{+} and Ca^{2+} to form stable complexes in contrast with K^{+} and Mg^{2+}, at least with the specific lipid species selected.

Despite the substantial gap in scales, these results are consistent with membrane fusion data reported for vesicles selectively exposed to these cations.

References

[1] A. Martín-Molina, C. Rodríguez-Beas and J. Faraudo, 'Effect of Calcium and Magnesium on Phosphatidylserine Membranes: Experiments and All-Atomic Simulations', Biophys. J., 102, 2095-2103, May 2012, doi: 10.1016/j.bpj.2012.03.009.

[2] L. Bunel, V. Adrien, J. Coleman, P. Heo and F. Pincet, 'Lithium fine tunes lipid membranes through phospholipid binding', Sci. Rep., 15, 13366, Apr 2025, doi: 10.1038/s41598-025-97828-0.

Mapping the Molecular Pathways Underlying Na+ and Ca2+ Selectivity in Human ASIC1a

Joana Ribeiro da Silva*, Pedro Ferreira, Maria João Ramos, Pedro Alexandrino Fernandes

LAQV-REQUIMTE, Dep. Química e Bioquímica, Faculdade de Ciências do Porto, Rua do Campo Alegre, S/N, 4169-007 Porto, Portugal

* Presenting author

Extracellular acidification sets the Acid-Sensing Ion Channel 1a (ASIC1a) in motion, but the story that follows is written by the ions that cross it. As a proton-gated cation channel, ASIC1a preferentially conducts Na+ while displaying limited Ca2+ permeability [1],[2]. Although comparatively low, Ca2+ permeability has been associated with synaptic signalling and acidosis-associated neuronal injury [3], making the molecular basis of ASIC1a ion selectivity particularly relevant. Despite extensive characterization [2], it remains unclear how ions access the conductive pathway and how the channel distinguishes between them.

To follow the ions along their permeation pathway, we performed 1 μs molecular dynamics (MD) simulations of human ASIC1a in a realistic asymmetric mammalian membrane [4], under baseline membrane electrostatics and a physiologically relevant transmembrane potential.

Spontaneous permeation events showed that ions access the pore through lateral fenestrations. However, we determined that fenestral access alone was insufficient for conduction, as productive permeation required a continuously hydrated pore.

We carried out umbrella sampling simulations, which revealed how these pathways discriminate between Na+ and Ca2+. The resulting potentials of mean force showed that Ca2+ presents a substantially higher barrier than Na+, with the Ca2+ principal barrier being located above the GAS belt, the narrowest region of the pore, while the Na+ barrier was centered within this constriction. We linked this energetic difference to the distinct ion-specific rearrangements through ion coordination analysis.Towards the GAS belt, Na+ displayed compensated hydration-shell reorganization and transient interactions with pore residues, while Ca2+ underwent a less favorable and more energetically costly coordination rearrangement.

Together, our findings help trace the molecular story of Na+ and Ca2+ through ASIC1a, from their entry to selective permeation.

References

[1] D. S. K. Samways, A. B. Harkins, and T. M. Egan, “Native and recombinant ASIC1a receptors conduct negligible Ca2+ entry,” Cell Calcium, vol. 45, no. 4, pp. 319–325, Apr. 2009, doi: 10.1016/j.ceca.2008.12.002.

[2] R. Waldmann, G. Champigny, F. Bassilana, C. Heurteaux, and M. Lazdunski, “A proton-gated cation channel involved in acid-sensing,” Nature, vol. 386, pp. 173–177, 1997, doi: 10.1038/386173a0.

[3] O. Yermolaieva, A. S. Leonard, M. K. Schnizler, F. M. Abboud, and M. J. Welsh, “Extracellular acidosis increases neuronal cell calcium by activating acid-sensing ion channel 1a,” Proc. Natl. Acad. Sci. U.S.A., vol. 101, no. 17, pp. 6752–6757, 2004, doi: 10.1073/pnas.0308636100.

[4] I. D. Pogozheva et al., “Comparative molecular dynamics simulation studies of realistic eukaryotic, prokaryotic, and archaeal membranes,” J. Chem. Inf. Model., vol. 62, no. 4, pp. 1036–1051, Feb. 2022, doi: 10.1021/acs.jcim.1c01514.

Funding and acknowledgments: This work was funded by Fundação para a Ciência e a Tecnologia (FCT), PhD Studentship 2025.02402.BD, “From Injury to Recovery: The Role of hASIC1a in Pain and Neurocardiac Protection”, doi: 10.54499/2025.02402.BD.

Machine learning-assisted multiscale modelling of photoenzyme reactivity

Miguel de la Puente*, Giacomo Londi, Silvia De Nardo, Patrizia Mazzeo, Lorenzo Cupellini, Benedetta Mennucci

Department of Chemistry and Industrial Chemistry, University of Pisa, 56124 Pisa, Italy

* Presenting author

Photoenzymes are rare in nature, yet highly efficient photocatalysts, capable of promoting non-spontaneous photochemical reactions. The rational design of synthetic photoenzymes is thus of great interest for applications ranging from biofuels to medicinal chemistry. In particular, fatty acid photodecarboxylases (FAPs) catalyze the decarboxylation of fatty acids under blue light irradiation through a catalytic cycle involving a radical intermediate formed after electron transfer (ET) from the substrate to a flavin cofactor [1].

Recent studies [2,3] have proposed mutations that successfully alter the natural reactivity of FAP enzymes, enabling the formation of cyclic alkane products from linear fatty acids, highlighting FAPs as an extremely promising platform for controlling radical reactivity.

Here, we employ a combination of machine learning-assisted multiscale methodologies to investigate the photocatalytic cycle of one of the most promising experimentally designed FAP mutants. First, by combining a foundational machine learning potential [4] with highly accurate QM/MM calculations in a polarizable embedding scheme [5], we found that mutations enlarging the active site hinder the ET process by increasing the propensity of the substrate to bind farther from the flavin cofactor.

Subsequently, we employed state-of-the-art ML/MM simulations within an electrostatic embedding scheme [6] to investigate the formation of a cyclic intermediate after ET. Formation of this intermediate requires the radical substrate generated after decarboxylation to diffuse away from its position pre-ET toward regions of the active site enlarged by the mutations. Our calculations reveal a cyclization timescale competitive with the formation of the linear product and provide important mechanistic insights across the multiple timescales of this complex photocatalytic cycle.

References

[1] G. Londi et al., "Protein-Driven Electron-Transfer Process in a Fatty Acid Photodecarboxylase," JACS Au, vol. 5, pp. 158–168, 2025.
[2] S. Ju et al., "Stereodivergent photobiocatalytic radical cyclization through the repurposing and directed evolution of fatty acid photodecarboxylases," Nature Chem., vol. 16, pp. 1339–1347, 2024.
[3] F. Weissensteiner et al., "Establishing the Fatty Acid Photodecarboxylase CvFAP as a Platform for Photobiocatalytic Radical Transformations," ACS Catal., vol. 16, pp. 7758–7770, 2026.
[4] D. P. Kovács et al., "MACE-OFF: Short-Range Transferable Machine Learning Force Fields for Organic Molecules," J. Am. Chem. Soc., vol. 147, no. 21, pp. 17598–17611, 2025.
[5] M. Nottoli et al., "QM/AMOEBA description of properties and dynamics of embedded molecules," WIREs Comp. Mol. Sci., vol. 13, no. 6, e1674, 2023.
[6] P. Mazzeo et al., Digit. Discov., vol. 3, pp. 2560-2571, 2024

Funding and acknowledgments: This work has been supported by the Italian Ministry of University and Research (Fondo Italiano per la Scienza, FIS 2) under the grant FIS-2023-00430.

OGG1 activities deeply investigated via molecular dynamics simulations: from novel ORCAs' behavior rationalization to atomistic details of conformational control

Alessia Dodaro*, Tiziana Marino, Mario Prejanò, Maurice Michel

Dipartimento di Chimica e Tecnologie Chimiche, Università della Calabria, ponte P.Bucci, Cubo 14C, Rende Italy

* Presenting author

8-Oxoguanine DNA glycosylase 1 (OGG1) is a key enzyme in the base excision repair (BER) pathway, playing a crucial role in maintaining genomic integrity. Given its emerging pharmacological relevance, our research focuses firstly on novel small-molecule organocatalytic switches (ORCAs) designed to enhance OGG1 activity, [1] whose mechanism of action was deeply investigated through advanced computational techniques, molecular dynamics simulations and umbrella sampling in a second stage [2]. The synergistic analysis, biochemical experiments and computational data, allow to install artificial bifunctionality of the enzyme and to explain at the atomistic level the AP lyase function of OGG1 by either β and β-δ elimination by the means of ORCAs. The computational contribution revealed in particular to be essential to capture the key effector of Asp268, whose plasticity controls the OGG1 catalysis on the apurinic/apyrimidinic sites. [2] Our findings pave the way for designing new ORCAs capable of controlling the base excision repair mechanism, with crucial implications for cancer therapy.

References

[1]M. Varga et al., 'Giving an Enzyme Scissors: Serotonin Derivatives as Potent Organocatalytic Switches for DNA Repair Enzyme OGG1', J. Med. Chem., vol. 68, no. 21, pp. 22455–22483, Nov. 2025, doi: 10.1021/acs.jmedchem.5c01454.

[2]A. Dodaro et al., "Conformational Control of OGG1 over Apurinic/Apyrimidinic Sites Enables an Efficient Apurinic/Apyrimidinic Lyase Function," ACS Catal., 2026, doi: 10.1021/acscatal.6c03575.

Acid Ceramidase: A Molecular Dynamics and Molecular Docking Study

Vanda Boršová[a,*], Adriána Dunárová[a], Lukáš Bučinský[a], Marek Štekláč[a,b], Pavol Štefík[a], Boris Lakatoš[a]

[a] *Slovak University of Technology, Radlinskeho 9, Bratislava, SK 812 37, Slovakia*
[b] *Slovak Academy of Sciences, Dúbravská cesta č. 9, SK 845 35 Bratislava, Slovakia*
* Presenting author

Acid ceramidase (AC) is a lysosomal enzyme that plays a key role in sphingolipid metabolism. It catalyzes the hydrolysis of ceramides into sphingosine and a fatty acid, thereby regulating the balance of bioactive lipids involved in cell proliferation, differentiation, and apoptosis. Dysfunction of acid ceramidase is associated with several inherited disorders and cancers, making it an important therapeutic target [1,2].

Ceramides are the natural substrates of acid ceramidase, and their intracellular levels are directly regulated by the enzyme's activity. In addition to naturally occurring ceramides, synthetic analogues have also become the subject of intensive research, as they can interact with the enzyme's active site and act as inhibitors. The nature of these interactions, including the possibility of covalent binding, can significantly influence their inhibitory potency [3,4].

The aim of this work is to investigate the interactions between acid ceramidase and selected natural and synthetic ligands using modern computational methods. Molecular docking will be employed to predict ligand binding modes, which will subsequently be validated by molecular dynamics simulations [5]. A detailed characterization of the interactions within the enzyme's active site and of the binding mechanism will be achieved using QM/MM calculations. Together, these computational approaches will contribute to a better understanding of the mechanism of acid ceramidase inhibition and provide a foundation for the rational design of novel inhibitors.

References

[1] N. Coant, W. Sakamoto, C. Mao, and Y. A. Hannun, "Ceramidases, roles in sphingolipid metabolism and in health and disease," Adv. Biol. Regul., vol. 63, pp. 122–131, Jan. 2017, doi: 10.1016/j.jbior.2016.10.002.
[2] F. Parveen, D. Bender, S.-H. Law, V. K. Mishra, C.-C. Chen, and L.-Y. Ke, "Role of Ceramidases in Sphingolipid Metabolism and Human Diseases," Cells, vol. 8, no. 12, Art. no. 1573, Dec. 2019, doi: 10.3390/cells8121573.
[3] A. Dementiev, et al., "Molecular Mechanism of Inhibition of Acid Ceramidase by Carmofur," J. Med. Chem., vol. 62, no. 2, pp. 987–992, Jan. 2019, doi: 10.1021/acs.jmedchem.8b01723.
[4] A. Gebai, A. Gorelik, Z. Li, K. Illes, and B. Nagar, "Structural basis for the activation of acid ceramidase," Nat. Commun., vol. 9, no. 1, Art. no. 1621, Apr. 2018, doi: 10.1038/s41467-018-03844-2.
[5] M. Abraham et al., "GROMACS 2026.0 Manual," Zenodo, 2026, doi: 10.5281/zenodo.18299930.

Funding and acknowledgments: This research was supported by the Slovak Grant Agency VEGA (contract no. 1/0175/23) and the Slovak Science and Technology Assistance Agency (contract nos. APVV-20-0213 and APVV-24-0207).

Activation of orange carotenoid protein requires a photoisomerization

Amanda Arcidiacono*, Mattia Bondanza, Lorenzo Cupellini, Benedetta Mennucci

University of Pisa

* Presenting author

The orange carotenoid protein (OCP) is a photoactive protein involved in the photoprotection of cyanobacterial antenna complexes [1]. Through two H-bonds in its C-terminal domain, OCP binds a keto-carotenoid (such as canthaxanthin) which is involved in the light-activation of OCP and finally acts as a quencher in the protoprotective mechanism. Absorption of blue light by the resting-state orange OCP (OCPo) causes the translocation of the carotenoid into the N-terminal domain and ultimately the separation of the two domains and forming the active red OCPr state [2]. However, the photochemical mechanism that drives H-bond dissociation and carotenoid translocation is still unknown.

In a previous work, we proposed a trans-to-cis photoisomerization of OCP-bound canthaxanthin as a possible activation mechanism [3]. The cis isomer, however, is not observed in the structure of OCPr bound to the antenna complexes, therefore the chromophore must undergo to another isomerization once the active state is reached.

Here, we characterized the photoproduct with QM/MM simulations and we show that only the cis photoproduct possesses the spectroscopic features observed in transient absorption spectroscopy [2]. Then, by performing enhanced sampling simulations with umbrella sampling-replica exchanged molecular dynamics (US-REMD), we demonstrate that the photoisomerization is a prerequisite for enabling carotenoid translocation. Finally, we explore the role of multiphoton absorption in facilitating the recovery of the all-trans canthaxanthin, by performing nonadiabatic QM/MM simulations of the final active state. [4]

References

[1] C. A. Kerfeld et al., 'Crystal Structure of a Cyanobacterial Water-Soluble Carotenoid Binding Protein', Structure, vol. 11, no. 1, pp. 55–65, Jan. 2003, doi: 10.1016/S0969-2126(02)00936-X.

[2] P. E. Konold et al., 'Photoactivation Mechanism, Timing of Protein Secondary Structure Dynamics and Carotenoid Translocation in the Orange Carotenoid Protein', J. Am. Chem. Soc., vol. 141, no. 1, pp. 520–530, Jan. 2019, doi: 10.1021/jacs.8b11373.

[3] A. Arcidiacono et al., 'How Orange Carotenoid Protein Controls the Excited State Dynamics of Canthaxanthin', Chem. Sci., vol. 14, no. 40, pp. 11158–11169, Oct. 2023, doi: 10.1039/D3SC02662K.

[4] A. Arcidiacono et al., 'Atomistic Simulations Reveal the Photoactivation Mechanism of a Carotenoid-Binding Photoreceptor', PNAS, vol. 123, no. 11, e2515214123, Mar. 2026, doi: 10.1073/pnas.2515214123.

Venom PLA2 Proteins: How They Disrupt Lipid Membranes

João T. S. Coimbra[1,*], Rui Rachão[1,2], Maria J. Ramos[1], Pedro A. Fernandes[1]

[1] *LAQV, REQUIMTE, Departamento de Química e Bioquímica, Faculdade de Ciências, Universidade do Porto, rua do Campo Alegre s/n, 4169-007 Porto, Portugal*

[2] *Graduate School of Integrated Science and Technology, Nagasaki University, Bunkyo-machi 1-14, Nagasaki, 852-8521, Japan*

* Presenting author

Phospholipases A2-like (PLA2-like) proteins are key yet incompletely understood toxins in viper venom [1]. They destabilise eukaryotic membranes, triggering uncontrolled calcium influx and cell death. We investigated calcium translocation through membranes containing the C-terminal segment of a toxic Bothrops asper Lys49 PLA2-like protein, a process linked to skeletal cell death [2]. The C-terminal segment is critical for toxicity, as 13-mer peptides from this region can replicate several effects of the full protein [3]. Using molecular dynamics simulations and umbrella sampling, we translocated calcium along the bilayer normal with and without the 13-mer peptide. Results showed that the peptide disrupts the membrane, drawing water molecules inside and thinning the bilayer. This lowers the free energy barrier for calcium translocation by ca. 24–51 kJ/mol, depending on bilayer composition. Higher peptide concentrations amplify local membrane perturbations, further reducing the barrier.

We have also assessed the stability of PLA2-like dimers and monomers in both solution and membrane environments, confirming the relevance of the two dimeric conformations previously identified by crystallography [4]. Currently, we are investigating the synergistic interplay between these structural PLA2-like toxins and catalytic PLA2 variants, exploring how their combined presence alters membrane integrity beyond individual effects. Integrating these enzymatic pathways with the ion-translocation mechanisms of myotoxic PLA2-like proteins will provide a unified understanding of venom-induced cytotoxicity across diverse protein classes.

References

[1] B. Lomonte, 'Lys49 myotoxins, secreted phospholipase A2-like proteins of viperid venoms: A comprehensive re-view', Toxicon, vol. 224, pp. 107024, Mar. 2023, doi: 10.1016/j.toxicon.2023.107024

[2] J. T. S. Coimbra, A. Gissler, E. Nitor, K. Rostamipour, A. V. Cunha, M. J. Ramos and P. A. Fernandes, 'Venomous Peptides: Molecular Origin of the Toxicity of Snake Venom PLA2-like Peptides', JACS Au, vol. 4, pp. 4295-4306, Nov. 2024, doi: 10.1021/jacsau.4c00646

[3] M. Cintra-Francischinelli, P. Pizzo, Y. Angulo, J. M. Gutiérrez, C. Montecucco and B. Lomonte, 'The C-terminal region of a Lys49 myotoxin mediates Ca2+ influx in C2C12 myotubes', Toxicon, vol. 55, pp. 590-596, Feb. 2010, doi: 10.1016/j.toxicon.2009.10.013

[4] R. Rachão, J. T. S. Coimbra, M. J. Ramos, J.-M. Gutiérrez, B. Lomonte and P. A. Fernandes, 'Molecular dynamics of Lys49 PLA2-like toxins: Insights into solution and membrane-bound conformations', Toxicon, vol. 267, pp. 108581, Nov. 2025, doi: 10.1016/j.toxicon.2025.108581

Funding and acknowledgments: 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. Additional funding was provided by FCT through project PTDC/QUI-OUT/1401/2020. Computational resources were provided by HPC-UÉ, funded by FCT I.P. Advanced Computing Projects 2021.09753.CPCA and 2023.10650.CPCA (Oblivion platform). JTSC acknowledges FCT funding through the Institutional Call to Scientific Employment Stimulus (2023.14741.TENURE.002/CP00058/CT00005).

Complexes of DNA three-way junctions

Nicolas Chéron*, Cécilia Hognon

CNRS / Laboratoire de Biochimie Théorique
Université Paris Cité

* Presenting author

DNA is a highly flexible biomolecule, which can adopt several types of structures besides the well-known double helix. When the sequence is made of direct repeats, DNA can locally form a three-way junction (TWJ) where three strands form a structure with a prismatic cavity. Such structures can be deleterious and ~40 so-called direct expansions diseases have been identified. However, targeting these structures can be beneficial, since when the cavity is filled with a proper ligand, the replication of the cell is hampered. Thus, stabilizing TWJ with good ligands can lead to cell deaths, and ligands for TWJ are putative anti-cancer drugs.

Several promizing ligands were identified by our experimentalist colleagues [1], but the optimization and rational design of new ligands is a long and tedious task, limitated by the complexity of the organic synthesis [2]. We have thus decided to rely on computational chemistry to (1) reproduce experimental data, and (2) propose new ligands. The main physico-chemical data to characterize the DNA/ligand interactions are folding temperatures, and we have thus designed a simulation protocole to compute folding temperature. After initial failure with brute force calculations, hamiltonian replica exchange simulations (with the REST2 framework) were successfull and a satisfactory correlation between computational data and experimental temperatures were obtained. Thus, we have developed a protocol that can be used prior to synthesis to screen ligands [3].

References

[1] K. Duskova, P. Lejault, E. Benchimol, R. Guillot, S. Britton, A. Granzhan, D. Monchaud, J. Am. Chem. Soc., Vol. 142, pp 424–435, 2020, doi: 10.1021/jacs.9b11150.
[2] J. Zell, K. Duskova, L. Chouh, M. Bossaert, N. Chéron, A. Granzhan, S. Britton, D. Monchaud, Nuc. Ac. Res., Vol. 19, pp 10275–10288, 2021, doi: 10.1093/nar/gkab796.
[3] A. Pipier, T. Chetot, A. Kalamatianou, N. Martin, S. Britton, N. Chéron, L. Trantírek, A. Granzhan, D. Monchaud, Angew. Chem. Int. Ed., Vol. 63, e202409780, 2024, doi: 10.1002/anie.202409780.

Funding and acknowledgments: CNRS Agence Nationale de la Recherche (ANR-22-CE44-0039-01) HPC ressources of CINES and IDRIS (2023–077156)

Non-canonical α/γ backbone conformations in DNA and protein-DNA complexes

Elizabeth Kolářová*, Petr Jurečka

Palacky University

* Presenting author

Protein–DNA interactions frequently induce local distortions of the DNA backbone, including bending, curvature, and transient noncanonical conformations that are essential for molecular recognition. These structural changes are often associated with stabilization of the A-like DNA state, characterized by a C3'-endo sugar pucker and specific backbone torsion angles. Accurately reproducing these conformations remains a challenge for molecular dynamics (MD) simulations and depends strongly on the choice of force field. While the AMBER DNA force fields bsc1, OL15, and OL21 reliably describe canonical B-DNA, they tend to underestimate the stability of A-like and protein induced conformational states.

The recently developed OL24 force field introduces refinements to the deoxyribose pucker and χ torsion, providing a more balanced A/B equilibrium and improved stabilization of biologically relevant noncanonical conformations. In this study, we compare the performance of bsc1, OL15, OL21, and OL24 using MD simulations of several endonuclease–DNA complexes. The force fields are evaluated based on their ability to preserve the A-like (AA) state, defined by the sugar pucker and χ torsion, in comparison with experimental structural data. Our results demonstrate that OL24 more effectively maintains protein-induced DNA conformations, yielding structural ensembles that better reflect experimentally observed DNA behavior.

References

[1] Zgarbova, M.; Sponer, J.; Jurecka, P, Refinement of the Sugar Puckering Torsion Potential in the AMBER DNA Force Field. J. Chem. Theory Comput. 2025, doi: 10.1021/acs.jctc.4c01100

[2] Zgarbova, M.; Sponer, J.; Otyepka, M.; Cheatham, T. E.; Galindo-Murillo, R.; Jurecka, P., Refinement of the Sugar-Phosphate Backbone Torsion Beta for the AMBER Force Fields Improves the Description of Z-DNA and B-DNA. J. Chem. Theory Comput. 2015, 11 (12), 5723-5736

Funding and acknowledgments: This work was supported by the IGA PřF UP project IGA_PrF_2026_002 and by the ELIXIR CZ Research Infrastructure.

Trajectory-Resolved Occlusion Index (TROI): A Monte Carlo Framework for Directional Steric Accessibility Around Reactive Centers

Maciej Spiegel*

Department of Organic Chemistry and Pharmaceutical Technology, Faculty of Pharmacy, Wroclaw Medical University, Wroclaw, Poland

* Presenting author

Steric hindrance governs reactivity and selectivity, yet it is usually captured by single, direction-averaged numbers that cannot show how accessibility changes with the direction of approach. We present the Trajectory-Resolved Occlusion Index (TROI), a Monte Carlo method that places a spherical probe at any distance and direction (θ, φ) around a reactive center and reports the percentage of its volume overlapping the van der Waals volumes (scaled Bondi radii) of surrounding atoms.

Directions are defined in a molecule-intrinsic frame built from user-selected reference atoms, so results are independent of input orientation. For transition-state geometries, TROI extracts the attack trajectory directly from the attacking atom and excludes the attacking fragment itself, so the nucleophile does not occlude its own path. The same framework yields distance profiles, 2D (d–θ) and sky (θ–φ) maps, and a 3D accessible-approach envelope in which a direction counts as open only if its Wilson confidence bound stays below a threshold across a confirmation window. Further modes cover probe-size selectivity profiles, trigonal-bipyramidal nucleophile/leaving-group checks, analog series, and conformational ensembles of MD snapshots.

TROI turns steric hindrance from a single number into a directional, statistically controlled map for mechanistic studies and catalyst design.

Funding and acknowledgments: The work presented here was carried out as part of a research project supported by Wroclaw Medical University under grant number SUBK.D090.26.003.

Modeling the Smallest Green Fluorophore: Explicit Solvation in HINA's Fluorescence Simulation

Carlo Albani*, Mario Barbatti, Lea M. Ibele

Aix-Marseille University

* Presenting author

3-Hydroxyisonicotinealdehyde (HINA) has recently attracted significant interest as a size-record-breaking, pH-dependent fluorophore[1][2]. While its cationic and neutral forms exhibit a low-yield blue emission, the anionic form features an intense green fluorescence in water. This anionic species shows a remarkable quantum yield of approximately 15% and an exceptionally large experimental Stokes shift. Such unique photophysical properties make HINA a promising candidate for biological sensing applications.

However, a clear theoretical explanation behind these properties is still lacking. In particular, the exact mechanism by which the solvent modulates the emission of both the neutral and anionic forms, as well as its contribution to the large Stokes shift of the anion, remains unresolved. In this work, steady state absorption and fluorescence spectra of HINA were calculated by treating the solvent both implicitly (CPCM) and explicitly. To model the condensed-phase electronic spectra, two standard approaches were evaluated, namely quantum harmonic Wigner Sampling (WS) and thermal molecular dynamics sampling. On one hand, WS accounts for Zero-Point Energy (ZPE) within a computationally efficient framework, but it intrinsically fails to describe structural anharmonicities in soft environments. On the other hand, thermal Quantum Mechanics/Molecular Mechanics schemes can natively capture large-scale anharmonic motions, though these dynamic simulations completely omit ZPE effects[3] .

This work highlights that modeling fluorescence in soft environments remains a highly non-trivial challenge. Our simulations reveal that HINA’s emission properties are governed by a tight, mutual coupling between the chromophore and the solvent. Therefore, the structural conformation of the solute and the dynamic rearrangement of the surrounding water molecules are strictly interdependent.

References

[1] - Kang, R.; Talamini, L.; D'Este, E.; Mar;ns Estevão, B.; De Cola, L.; Klopper, W.; Biedermann, F. Chem. Sci. 2021, 12 (4), 1392–1397. DOI: 10.1039/d0sc05557c

[2] - Liu, Q.; Tang, Z.; Zhou, P . J. Lumin. 2022, 247, 118878. DOI: 10.1016/j.jlumin.2022.11887

[3] - Zobel, J. P.; Heindl, M.; Nogueira, J. J.; Gonzalez, L. J. Chem. Theory Comput. 2018, 14 (7), 3661–3672. DOI: 10.1021/acs.jctc.8b00198

Funding and acknowledgments: Funding: Amidex Project Computational Resources: Mesocentre AMU

Investigating the Effects of Naturally-Occurring RNA Modifications on Protein Synthesis: A Molecular Dynamics Simulation Study

M. Clara Cunha*, Stacey D. Wetmore

Department of Chemistry and Biochemistry, University of Lethbridge, 4401 University Drive West, Lethbridge, Alberta, Canada T1K 3M4

* Presenting author

Protein synthesis relies on molecular interactions between the ribosome, transfer RNA (tRNA), and messenger RNA (mRNA). To ensure accurate translation of genetic information, cells employ a wide range of RNA chemical modifications. tRNA modifications are abundant and believed to be essential for maintaining RNA stability and translational fidelity, as well as limiting amino acid misincorporation.1 In contrast, enzymatically-introduced mRNA modifications may impact protein output by stabilizing transcripts or acting as a recognition piece for targeted degradation,2 adding another layer to translation regulation. Indeed, disruptions in tRNA and mRNA modification pathways have been linked to translational imbalance, neurological diseases3 and gastric cancers,4 among other ailments. However, the molecular mechanisms underlying the effects of tRNA or mRNA modifications on ribosomal translation remain poorly understood. Although experimental approaches have demonstrated the impact of select modifications on protein synthesis rates,3 capturing the dynamic interactions involved in codon recognition within the ribosome is difficult with experimental methods. To address this knowledge gap, the present work employs molecular dynamics (MD) simulations to investigate the effects of different tRNA and mRNA modifications at distinct positions during codon recognition within the ribosome. By developing an appropriate computational model and providing a dynamic, atomic-level perspective on codon–anticodon interactions, this work advances our understanding of how RNA modifications contribute to translational imbalance in disease.

References

1. T. Suzuki, 'The expanding world of tRNA modifications and their disease relevance', Nat. Rev. Mol. Cell Biol., pp. 375–392, Mar. 2021, doi: 10.1038/s41580-021-00342-0.
2. S. H. Boo and Y. K. Kim, 'The emerging role of RNA modifications in the regulation of mRNA stability', Exp. Mol. Med., pp 400–408, Mar. 2020, doi: 10.1038/s12276-020-0407-z.
3. T. Karlsborn, H. Tukenmez, C. Chen, et al, 'Familial dysautonomia (FD) patients have reduced levels of the modified wobble nucleoside mcm5s2u in tRNA', Biochem. Biophys. Res. Commun., vol. 454, pp. 441–445, Oct. 2014, doi: 10.1016/j.bbrc.2014.10.116
4. T. H. M. Chan, A. Qamra, K. T. Tan, et al, 'ADAR-Mediated RNA editing predicts progression and prognosis of gastric cancer', Gastroenterol., vol. 15, no. 4, pp. 637–650, Oct. 2016, doi: 10.1053/j.gastro.2016.06.043.

Funding and acknowledgments: We greatly appreciate the computational resources provided by the Digital Research Alliance of Canada (the Alliance). This work was funded by the Natural Sciences and Engineering Research Council (NSERC) of Canada [2025-04391], the Canada Research Chair Program [2021-00484], and the University of Lethbridge.

From catalysis to inhibition: mechanistic insights into major snake venom enzymes guide rational inhibitor design

Juliana Castro-Amorim*, Maria J. Ramos, Pedro A. Fernandes

LAQV, University of Porto

* Presenting author

Snakebite envenoming poses an urgent global health crisis, causing ~ 130k deaths and ~ 400k permanent disabilities every year. It predominantly affects remote and impoverished tropical and subtropical regions of Asia, Latin America and Africa [1]. Medically important vipers such as Daboia russelii, Bothrops asper, and Bitis arietans produce venoms rich in three highly toxic enzymes: metalloproteases, phospholipases A2, and serine proteases, together with lower-abundance hyaluronidases that act as venom "spreading factors". These toxins cause life-threatening coagulopathies, haemorrhage, tissue damage and necrosis [2]. Despite their critical role in envenoming, their catalytic mechanisms remained poorly understood until recently, limiting the rational design of small-molecule inhibitors.

To address this gap, we developed a collective study of these enzymes' catalytic mechanisms using hybrid quantum mechanics/molecular mechanics (QM/MM) approaches at the B3LYP and/or PBE/AMBER levels [. Our results reveal the step-by-step catalytic pathways, their respective rate-limiting steps and characterise the corresponding transition states. We further compared functional group arrangements in the computed rate-limiting transition states with those of experimentally characterised inhibitors, revealing strong structural agreement [3, 4, 5]. Together, these results provide mechanistic insight into major snake venom toxins and establish a bridge towards the rational design of novel transition-state analogue inhibitors, with potential applications ranging from snakebite therapeutics to other clinically relevant disorders.

References

[1] World Health Organization, Global Report on Neglected Tropical Diseases, 2025.

[2] T. Tasoulis and G. K. Isbister, "A current perspective on snake venom composition and constituent protein families," Arch. Toxicol., vol. 97, no. 1, pp. 133–153, 2023, doi: 10.1007/s00204-022-03420-0.

[3] J. Castro-Amorim et al., "Unraveling the reaction mechanism of Russell's viper venom factor X activator: A paradigm for the reactivity of zinc metalloproteinases?," J. Chem. Inf. Model., vol. 63, no. 13, pp. 4056–4069, 2023, doi: 10.1021/acs.jcim.2c01156.

[4] J. Castro-Amorim et al., "Beyond Fang's Fury: A computational study of the enzyme–membrane interaction and catalytic pathway of the snake venom phospholipase A2 toxin," Chem. Sci., vol. 16, no. 4, pp. 1974–1985, 2025, doi: 10.1039/d4sc06511e.

[5] J. Castro-Amorim et al., "Mechanism of hyaluronic acid hydrolysis catalyzed by snake venom hyaluronidase," J. Chem. Inf. Model., vol. 66, no. 7, pp. 4033–4048, 2026, doi: 10.1021/acs.jcim.5c025

Funding and acknowledgments: 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. Juliana Castro-Amorim thanks FCT for financing her PhD project through the grant 2024.05812.BD.

Influence of Copper Coordination on the Antioxidant and Biomolecular Properties of Flavonoids

M. Štekláč[1,2*], M. Malček[1,2], V. Boršová[1], R. Raptová, P. Gajdoš[3], S. Veveričová[3], M. Čertík[3], M. Valko[1], V. Brezová, M. Malček Šimunková[1]

[1] *Department of Physical Chemistry, Institute of Physical Chemistry and Chemical Physics, Faculty of Chemical and Food Technology, Slovak University of Technology, Bratislava, Slovakia*
[2] *Computing Center, Centre of Operations of the Slovak Academy of Sciences, Bratislava, Slovakia*
[3] *Institute of Biotechnology, Faculty of Chemical and Food Technology, Slovak University of Technology, Bratislava, Slovakia*
* Presenting author

Flavonoids readily coordinate transition metal ions, giving rise to complexes with physicochemical and biological properties that differ markedly from those of the parent compounds. To elucidate the impact of metal complexation, we investigated Cu(II) with baicalein, scutellarein, and acacetin and assessed the consequences for their antioxidant activity and interactions with biologically relevant macromolecules.

Complex formation was characterized using UV–Vis, fluorescence, and EPR spectroscopy together with density functional theory calculations. The interactions of the ligands and their Cu(II) complexes with calf thymus DNA and human serum albumin were further investigated by molecular docking and molecular dynamics simulations [1-3].

Copper coordination substantially modifies the electronic structure of the flavonoids, leading to altered radical-scavenging behaviour and reduced synergistic antioxidant effects with biological reductants. At the same time, Cu(II) complexation strengthens DNA binding and induces structural perturbations of the double helix. Interactions with human serum albumin reveal that metal coordination also affects protein recognition by altering binding-site preference, binding affinity, and ligand-induced conformational dynamics.

Together, these findings demonstrate that Cu(II) acts as an important modulator of flavonoid function, shifting the balance between antioxidant activity and biomolecular recognition. The combined experimental and computational approach provides molecular-level insight into the mechanisms governing metal–flavonoid interactions and contributes to the rational design of metal-based polyphenol systems with potential biomedical applications.

References

[1] Štekláč M, Malček M, Gajdoš P, et al; “Antioxidant effect, DNA-binding, and transport of the flavonoid acacetin influenced by the presence of redox-active Cu(II) ion: Spectroscopic and in silico study”, J Inorg Biochem, vol. 264, pp. 112802, 2025.
[2] Malček Šimunková M, Štekláč M, Raptová R, et al; “The effect of Cu(II) ion on antioxidant and DNA-binding mechanism of baicalein and scutellarein: Spectroscopic, theoretical, and molecular docking study”, Appl Organomet Chem, vol. 38, no. 4, pp. 7390, 2024.
[3] Boršová V, Malček Šimunková M, and Štekláč M (2026) “Exploring The Interaction of Flavonoids Baicalein and Scutellarein with Human Serum Albumin: Spectroscopic and Computational Study”, under review.

Funding and acknowledgments: We are grateful for financial support to VEGA grant nos. 1/0175/23, 1/0324/24, and 1/0524/24 and APVV grant nos. APVV-23-0006, APVV-24-0207, and VV-MVP-24-0039. The National Competence Centre for HPC at SAS (Project Code 311070AKF2) funded by ERD Fund, EU Structural Funds Informatization of Society, Operational Program Integrated Infrastructure is acknowledged for computational resources made available.

Collaborate to Decorrelate: Hamiltonian Replica Exchange Transition Interface Sampling (HRETIS)

An Ghysels[1]*

[1] *BioMMedA, Ghent University*

* Presenting author

Computational approaches for estimating thermodynamic properties such as free energies and binding affinities have seen significant progress. However, predicting kinetic properties for drug binding/unbinding rates and membrane permeation, remains a greater challenge as the underlying events are often rare and slow. These processes are largely inaccessible to conventional molecular dynamics (MD) simulations, which are limited by timescale and sampling efficiency.

This contribution shows how our new developments in path sampling methods can be used to create unbiased membrane permeation trajectories. ∞RETIS is the most advanced variant of the replica exchange transition interface sampling (RETIS) algorithm, featuring asynchronous swaps in the infinite swapping limit. This design enables efficient parallelization across CPUs and GPUs, dramatically accelerating convergence. ∞RETIS is applied to study the membrane permeation of 5-aminolevulinic acid (5-ALA), a hydrophilic drug used in photodynamic therapy and fluorescence-guided surgery. From unbiased trajectories, we compute key kinetic metrics including permeability, mean first passage times, and conditional committor, using a weighted histogram analysis method (WHAM) approach. Additionally, the unbiased trajectories elucidate the mechanistic details of 5-ALA permeation, highlighting how molecular orientation and hydration within the membrane influence successful translocation. The mechanism will be interpreted using the concept of a history-dependent free energy (conditional free energy). Finally, an outlook to combining the concept of Hamiltonian exchange with path sampling will be presented, which we found to enhance the sampling exploration in path space.

In conclusion, ∞RETIS can resolve the full kinetic pathway of a permeant crossing a phospholipid bilayer, demonstrating its capability to capture rare event dynamics in biologically and pharmaceutically relevant systems.

References

[1] S. Roet, D.T. Zhang, T.S. van Erp, Exchanging replicas with unequal cost, infinitely and permanently. The J. Phys. Chem. A 126, 8878–8886 (2022), doi: 10.1021/acs.jpca.2c06004.

[2] S. Safaei, L. Baldauf, T.S. van Erp, A. Ghysels, Exact kinetics of drug permeation using transition interface sampling. The J. Phys. Chem. B 129, 10019–10034 (2025), doi: 10.1021/acs.jpcb.5c05025.

[3] T.S. van Erp, D.T. Zhang, E. Wils, S. Safaei, A. Ghysels, Generalized path reweighting and history-dependent free energies. The J. Chem. Phys. 164, 214107 (2026), doi: 10.1063/5.0326023.

[4] S. Safaei, P. Rezaee, A. Ghysels, Collaborate to decorrelate in path space: Hamiltonian replica exchange transition interface sampling (HRETIS), submitted.

Funding and acknowledgments: The computational resources (Stevin Supercomputer Infrastructure) and services used in this work were provided by the VSC (Flemish Supercomputer Center), funded by Ghent University, FWO and the Flemish Government – department EWI. Acknowledgment of funding of the FWO (projects G002520N, G094023N, and K222825N), BOF of Ghent University, and the European Union (ERC Consolidator grant, 101086145 PASTIME).

List of Participants

Presenting Author	Affiliation	Country
Carlo Adamo	ChimieParisTech-PSL, CNRS	France
Carlo Albani	Aix-Marseille University	France
Marta Alberto	University of Calabria	Italy
Juliana Amorim	LAQV, University of Porto	Portugal
Juan Aragó	University of Valencia	Spain
Jéssica de Oliveira Araújo	State University of Campinas	Brazil
Lucas Verona de Araujo	State University of Campinas	Brazil
Amanda Arcidiacono	University of Pisa	Italy
Carlos Guilherme Tissi Batista	State University of Campinas	Brazil
Elena Betti	University of Pisa	Italy
Vanda Boršová	Slovak University of Technology in Bratislava	Slovakia
Jaroslav Burda	Charles University	Czech Republic
Rodolfo Caeiro	LAQV, University of Porto	Portugal
Ana Rita Calixto	LAQV, University of Porto	Portugal
Paolo Carloni	Jülich Research Centre	Germany
Michele Cascella	University of Oslo	Norway
Nicolas Chéron	Université Paris Cité, CNRS	France
Christophe Chipot	University of Lorraine, CNRS	France
Ilaria Ciofini	ChimieParisTech-PSL, CNRS	France
João Coimbra	LAQV, University of Porto	Portugal
Clauber Henrique Souza da Costa	State University of Campinas	Brazil
Paulo J. Costa	University of Lisbon	Portugal
Ana Cunha	Oak Ridge National Laboratory	United States
Clara Cunha	University of Lethbridge	Canada
Miljan Dašić	Heyrovský Institute of the Czech Academy of Sciences	Czech Republic
Alessia Dodaro	University of Calabria	Italy
Francisco P. E. Duarte	University of Lisbon	Portugal
Pedro Alexandrino Fernandes	LAQV, University of Porto	Portugal
Pedro Ferreira	LAQV, University of Porto	Portugal
Antonio Francés-Monerris	University of Valencia	Spain
Marián Gall	Slovak University of Technology in Bratislava	Slovakia
Samuele Giannini	University of Pisa	Italy
Stefan Grimme	University of Bonn	Germany
Cristian Iloaie	Humani Charleroi	Belgium
Chris John	University of Pisa	Italy
William Jorgensen	Yale University	United States
Petr Jurečka	University of Ostrava	Czech Republic
Magdalena Kazmierczak	University of Bristol	United Kingdom
Elizabeth Kolářová	Palacký University Olomouc	Czech Republic
Rong-Zhen Liao	Huazhong University of Science and Technology	China
Giacomo Londi	University of Pisa	Italy
Modesto Orozco López	IRB Barcelona	Spain
Xabier Lopez	University of the Basque Country	Spain
Maria Fátima Lucas	Zymvol Biomodeling	Spain
Miguel Machuqueiro	University of Lisbon	Portugal

Alessandra Magistrato	CNR-IOM at SISSA	Italy
Tiziana Marino	University of Calabria	Italy
Daniel Marke	University of Duisburg-Essen	Germany
Miguel de la Puente Martinez	University of Pisa	Italy
Federica Maschietto	Université Paris Cité, CNRS	France
Feliu Maseras	Institute of Chemical Research of Catalonia	Spain
Sébastien Menant	ENS de Lyon, CNRS	France
Francesca Mocci	University of Cagliari	Italy
Vicent Moliner	Jaume I University	Spain
Jens Preben Morth	Technical University of Denmark	Denmark
Tanja van Mourik	University of St Andrews	United Kingdom
Adrian Mulholland	University of Bristol	United Kingdom
Manuela Leal Nader	University of Oslo	Norway
Andrei Neamtu	Petru Poni Institute of Macromolecular Chemistry	Romania
Rui Neves	LAQV, University of Porto	Portugal
Wiesław Nowak	Nicolaus Copernicus University in Toruń	Poland
Matteo Orlandi	University of Florence	Italy
Sílvia Osuna	University of Girona	Spain
Pedro Paiva	LAQV, University of Porto	Portugal
Angela Parise	CNR-IOM at SISSA	Italy
Michele Parrinello	Italian Institute of Technology	Italy
Dragos Peptanariu	Petru Poni Institute of Macromolecular Chemistry	Romania
David Peralta	Chemistry Europe / Wiley-VCH	Germany
Ander Francisco Pereira	State University of Campinas	Brazil
Lucas Avila Pinheiro	State University of Campinas	Brazil
Alexandre Pinto	LAQV, University of Porto	Portugal
Mario Prejanò	University of Calabria	Italy
Maria João Ramos	LAQV, University of Porto	Portugal
Umberto Raucci	Italian Institute of Technology	Italy
Nathalie Reuter	University of Bergen	Norway
António Ribeiro	LAQV, University of Porto	Portugal
Carme Rovira	University of Barcelona	Spain
Riccardo Rozza	CNR-IOM at SISSA	Italy
Ulf Ryde	Lund University	Sweden
Jan Salomon	Palacký University Olomouc	Czech Republic
Neidy Samara Sousa dos Santos	State University of Campinas	Brazil
Gioacchino Schifino	Uppsala University	Sweden
Xiang Sheng	Tianjin Institute of Industrial Biotechnology, Chinese Academy of Sciences	China
Joana Silva	LAQV, University of Porto	Portugal
Pamella Cristiny Carneiro da Silva	State University of Campinas	Brazil
Dinesh Singh	Shiv Nadar Institution of Eminence	India
João Sousa	LAQV, University of Porto	Portugal
Maciej Spiegel	Wroclaw Medical University	Poland
Marek Štekláč	Slovak University of Technology in Bratislava	Slovakia
Camila Assis Tavares	State University of Campinas	Brazil
Luís Teixeira	LAQV, University of Porto	Portugal

Jannis Tesche	University of Freiburg	Germany
Ondrej Tkáč	Slovak University of Technology in Bratislava	Slovakia
Iñaki Tuñón	University of Valencia	Spain
Michele Turelli	ChimieParisTech-PSL, CNRS	France
Marco De Vivo	Italian Institute of Technology	Italy
Joep Wals	University of Antwerp	Belgium
Peter Westh	Technical University of Denmark	Denmark
Stacey Wetmore	University of Lethbridge	Canada
Marie Zgarbová	University of Ostrava	Czech Republic
Kirill Zinovjev	University of Valencia	Spain
Rachele Zunino	University of Naples Federico II	Italy

Sponsors

Institutional partners

LAQV requimte
LABORATÓRIO ASSOCIADO PARA A QUÍMICA VERDE

U.PORTO

Supporting partners

Madeira . Belongs to all

Sociedade Portuguesa de Química

Chemistry Europe
European Chemical Societies Publishing

Chemistry Europe

European Chemical Societies Publishing



Chemistry Europe

- **16** chemical societies
- From **15** European countries
- Which co-own **21** scholarly journals
- Over **22,9** million downloads in 2024
- Over **140,000** articles published since 1995
- With **150** Chemistry Europe Fellows and **8** Honorary Fellows recognized for excellence in chemistry

www.chemistry-europe.org

- Analysis & Sensing
- Analytical Science Advances
- Batteries & Supercaps
- ChemBioChem
- ChemCatChem
- ChemElectroChem
- ChemFoodChem
- ChemistryEurope
- Chemistry - A European Journal
- Chemistry - Methods
- ChemistryOpen
- ChemistrySelect
- ChemMedChem
- ChemPhotoChem
- ChemPhysChem
- ChemPlusChem
- ChemSusChem
- ChemSystemsChem
- Electrochemical Science Advances
- European Journal of Inorganic Chemistry
- European Journal of Organic Chemistry

Open Access

Chemistry Europe
European Chemical Societies Publishing

published in partnership with

WILEY VCH

Chemistry Europe Fact Sheet

16 chemical societies, **15** European countries.

Family of high-quality scholarly chemistry journals, covering a very broad range of disciplines.

Journals:
www.chemistry-europe.org

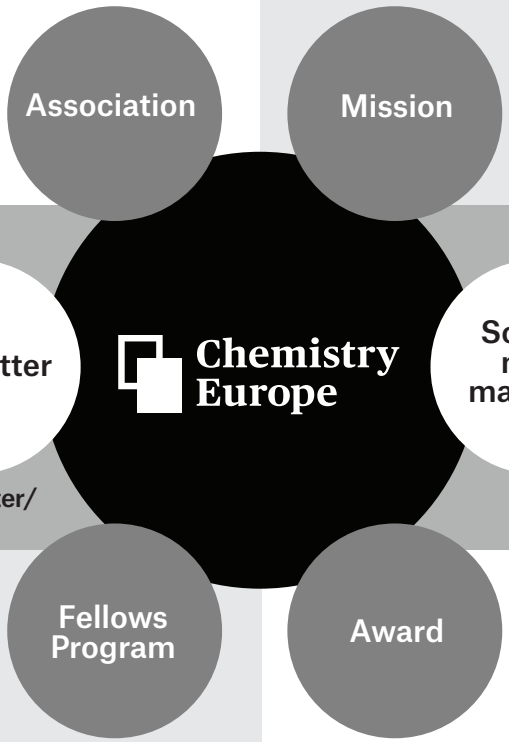
Societies:
www.chemistryviews.org/chemistry-europe-member-societies/

Evaluate, publish, disseminate, and amplify the scientific excellence of chemistry researchers from around the globe in high-quality publications.

Supports its members at every stage of their careers as they strive to solve the challenges that impact humankind.

Values integrity, openness, diversity, cooperation, and freedom of thought.

Hub: www.chemistry-europe.org



3 per year, free

www.chemistryviews.org/register/

ChemistryViews

What is happening in the global chemistry community

Strong focus on the people behind the science.

www.chemistryviews.org

Recognizes members for their outstanding achievements and contributions and their service to at least one member society.

www.chemistryviews.org/fellows/

Recognizes outstanding contributions to chemistry.

Includes prize money of EUR 10,000 and a certificate

Open to individuals worldwide, regardless of their affiliation with *Chemistry Europe* societies.
www.chemistryviews.org/chemistryeuropeaward/

@ChemEurope

Hub:
www.chemistry-europe.org

linkedin.com/company/chemeurope/



All rights reserved: ® Francisco Correia
Image used with permission