36th MMWS Erlangen

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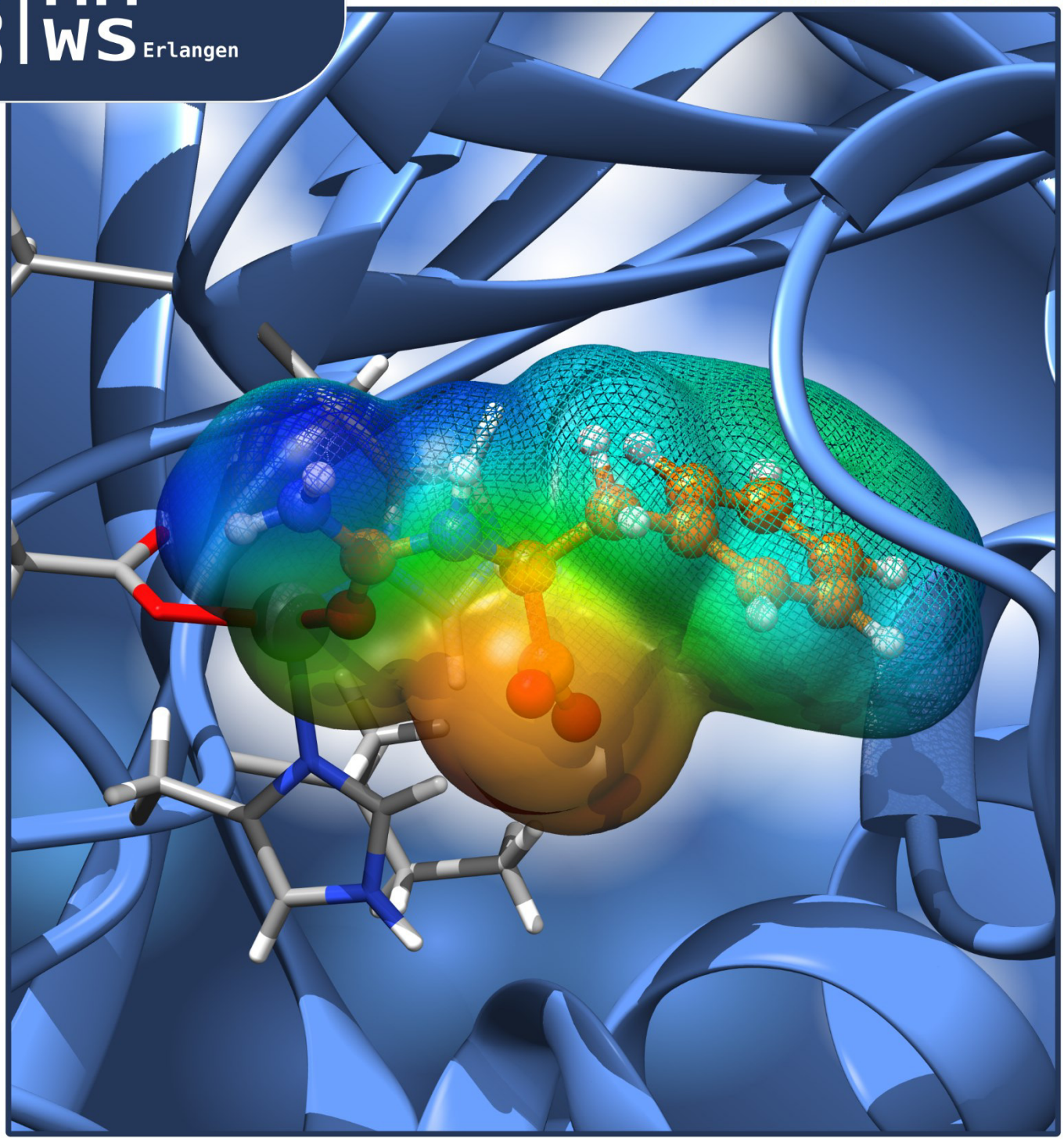


04/03-06/03/2024

MOLECULAR MODELLING WORKSHOP ERLANGEN

molecular graphics modelling society

NHR FAU

C3 Computer Chemie Centrum

FAU Friedrich-Alexander-Universität Erlangen-Nürnberg

MOLECULAR MODELLING WORKSHOP 2024

Welcome to the 36th Molecular Modelling Workshop (MMWS)

This year's workshop continues the successful and long-standing series of molecular modelling workshops held in Erlangen and organised by the *Molecular Graphics and Modelling Society - Deutschsprachige Sektion e.V.* (MGMS-DS). We are delighted to again cover a broad range of topics in the realm of molecular modelling – from modelling structures of complex biomolecules to AI-based approaches for molecular simulations. With the Chemikum I, located on the main campus of FAU, outside of the city centre, we are also happy to have a modern and representative venue that offers all facilities for our workshop – except perhaps for a nearby pub ;-) which is corrected by a social evening event on the second day of the workshop.

Erlangen is home to the national supercomputer centre NHR@FAU and we are grateful for continous support, in terms of Tier 2 computing faciliteis, but also in direct support of our modelling workshop. We are therefore happy to open the programme with an entire session with HPC-related presentations. Together with NHR@ZIB in Berlin and PC2 in Paderborn, NHR@FAU furthermore forms the Atomistic Simulation Center (ASC) and as such is hosting the German CECAM (Centre Européen de Calcul Atomique et Moléculaire) node on "Mathematics and Computation in Molecular Simulation". Promoting atomistic and molecular simulations is at the heart of the ASC and CECAM and as such our Molecular Modelling workshop is a very welcome event.

We are looking forward to three days of stimulating presentation on all subjects of molecular modelling, inspiring discussions, learning new things, and not the least: meeting old and making new friends.

Scientific program

Dr. Denis Schmidt

Medicinal Chemistry
Boehringer Ingelheim Pharma GmbH & Co. KG
Birkendofer Str. 65
88397 Biberach, Germany

denis.schmidt@boehringer-ingelheim.com

Technical coordination

Prof. Dr. Petra Imhof

Computer Chemie Centrum
Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU)
Nägelsbachstr. 25
91052 Erlangen, Germany
Tel: +49 (0)9131 85 20401
petra.imhof@fau.de

DEAR FRIENDS AND COLLEGUES,

the 36th Molecular Modeling Workshop 2024 (March 4th to 6th) in Erlangen offers an ideal platform for researchers, postdocs, and PhD students to showcase their findings to the molecular modelling community. This event enables young scientists to connect with peers from academia and industry, discuss their research, and receive valuable input from experienced researchers. Presentations of early-stage and ongoing research projects are highly encouraged.

The organizing comittee invites poster or lecture submissions in English, covering all fields of molecular modeling, such as physical sciences, material sciences, and life sciences including computational biology, chemistry, and cheminformatics. The workshop is designed for everyone, from those looking to improve their pesentation skills to those seeking networking opportunities in a casual, friendly atmosphere.

We are pleased to announce our plenary speakers (in alphabetical order) and are looking forward to seeing you for an inspirational Molecular Modelling Workshop in Erlangen!

DR. MATTHIAS DEGROOTE

Boehringer Ingelheim, Netherlands

PROF. DR. VAL GILLET

University Sheffield, UK

DR. ANDREAS W. GÖTZ

San Diego Supercomputer Center, USA

PROF. DR. SEREINA RINIKER

ETH Zürich, Switzerland

AWARDS

Traditionally, there will be two *Poster Awards* of 100 Euro each and three *Lecture Awards* for the best talks sponsored by the MGMS-DS:

1st Winner
Travel bursary to the Young Modellers Forum in the United Kingdom (travel expenses are reimbursed up to 500 Euro)

2nd Winner
up to 200 Euro travel expenses reimbursement

3rd Winner
up to 100 Euro travel expenses reimbursement

Only undergraduate and graduate research students qualify for the poster and lecture awards.

MGMS-DS E.V. ANNUAL MEETING

The general meeting of the MGMS, German Section (MGMS-DS e.V.) will be held during the workshop (in German language). We cordially invite all conference delegates to take the opportunity and join the society to participate in the annual meeting!

FEES

The conference fee amounts to 100 Euro (students: 50 Euro); online-only participation reduces the fee by 50%. This fee includes the annual membership fee for the MGMS-DS e.V.

WI-FI ACCESS

During the workshop, Wi-Fi access is possible via **eduroam** (SSID). Please have your Wi-Fi configured in advance or ask your local administrator for detailed information about your eduroam access. Links to general information about eduroam can be found on the workshop website mmws2024.mgms-ds.de

PRE- AND POST-CONFERENCE WORKSHOP

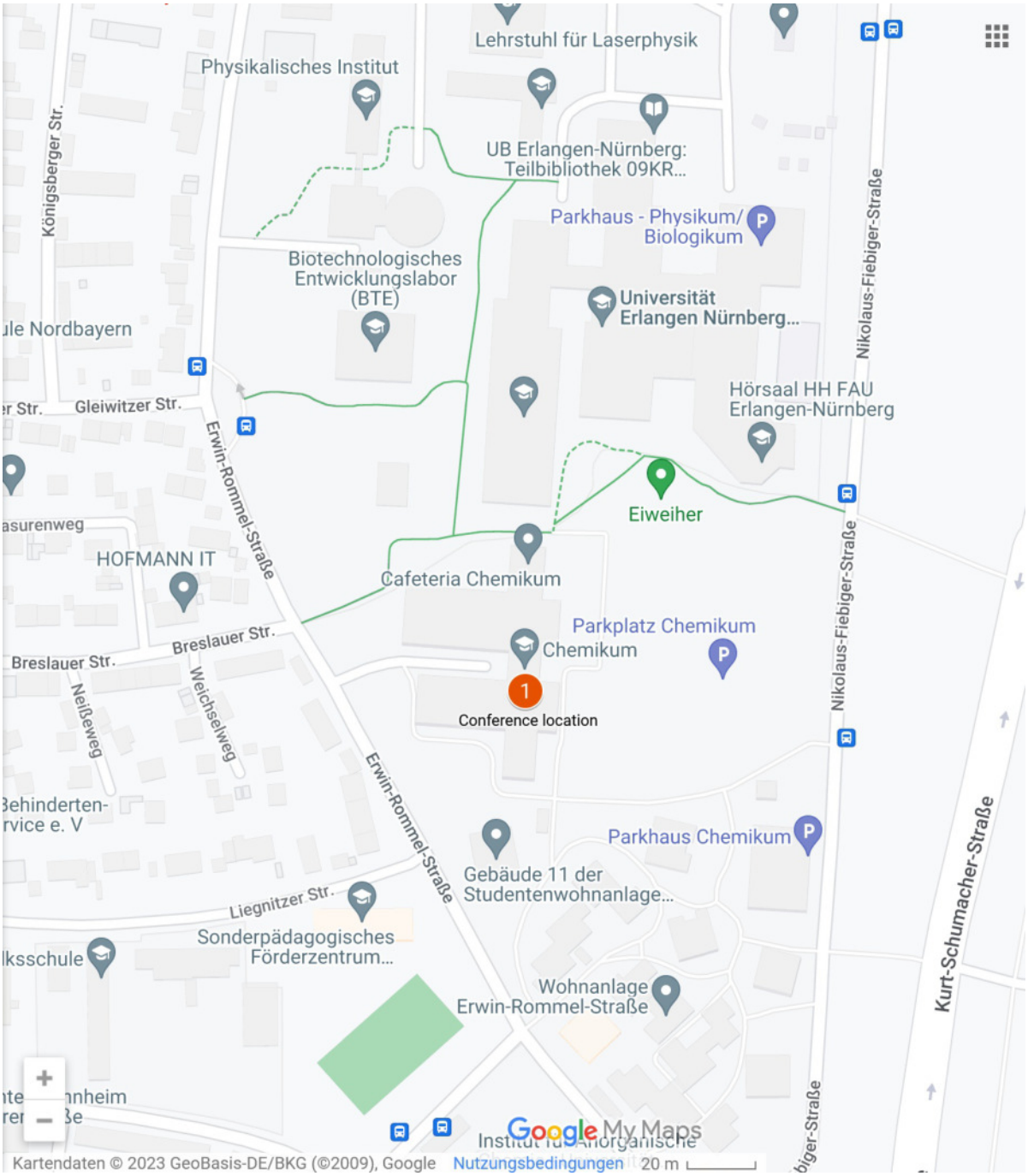
We are delighted to renew the pre-COVID tradition of workshops held before and after the conference. Addtionally, we are happy to provide you with an additional Satellite-Event – please inspect the lectures program for more details.

LOCATION

Conference location: All talks, coffee breaks, the poster sessions and the buffet dinner on Monday, March 4th will take place at the Chemikum I, Nikolaus-Fiebiger-Straße 10, 91058 Erlangen, located on the southern campus of the university. The registration desk is next to lecture hall C1.

The *Social Event "Visit at a typical Erlanger Gasthaus"* will take place at "Steinbach Bräu" (https://steinbach-braeu.de), Vierzigmannstraße 4, 91054 Erlangen, on Tuesday evening. Food and drinks will be available at your own expense.

Public transport is available (www.vgn.de) by bus line 287 or 293 from the city center / railway station to the southern campus ("Technische Fakultät").



Lectures Program

PROGRAM

Monday, March 4th 2024

11:00-14:00	**Registration**
10:00-12:00	**Pre-Conference Workshop** ProteinsPlus - Supporting Structure-Based Design on the Web (Center for Bioinformatics, Hamburg)
11:15-12:10	**Satellite-Event (Alexandre Tkatchenko, Luxemburg):** Towards Quantum Force Fields Using Quantum Charged Oscillators
14:00-14:10	**Welcome remarks / Agenda review**
14:10-14:35	**L01: Mohamadhosein Nosratjoo (Manchester, UK)** DL_FFLUX: A Machine-Learned Polarisable Force Field For Molecular Dynamics Simulations With Knowledgeable Atoms
14:35-15:00	**L02: Alexksandr Zlobin (Leipzig, Germany)** Charges and boundary terms: easy ways to spoil your QM/MM(MD) results
15:00-15:50	**PLENARY LECTURE I: Andreas W. Götz** GPU accelerated QM/MM molecular dynamics simulations of biomolecular systems
15:50-16:30	**Coffee Break**
16:30-16:55	**L03: Moritz Macht (Erlangen, Germany)** Molecular Modelling of Drug Formulation: From "tailor-made" Force Field to Stability Analysis of Carbamazepine Crystals
16:55-17:20	**L04: Rukmankesh Mehra (Bhilai, India)** Computing Viral Fitness: Towards a structure-based approach
17:20-17:45	**L05: Jonas Kaindl (Schroedinger GmbH, Germany)** Is The Functional Response of a Receptor Determined by the Thermodynamics of Ligand Binding?
18:00-19:00	**Annual Meeting of the MGMS-DS e.V.**
19:30	**Buffet – Dinner**

PROGRAM

Tuesday, March 5th 2024

09:00-09:25	**L06: Emília Valença de Aragão (Montpellier, France)** Modeling of liquid-liquid extraction of salts between an aqueous phase and a microemulsion
09:25-09:50	**L07: Lara Žiberna (Montpellier, France)** Understanding interface formation and extractant distribution at the liquid-liquid interface
09:50-10:15	**L08: Matthias Hennemann (CEPOS InSilico GmbH)** Large-scale CI: Band Gaps and Excited States in EMPIRE'24
10:15-10:55	**Conference Photo & Coffee Break**
10:55-11:20	**L09: Işılay Öztürk (Cagliari, Italy)** Systematic investigation of chelator-radiometals compounds by quantum chemical methods and molecular MD simulations
11:20-12:10	**PLENARY LECTURE II: Matthias DeGroote** A perspective on Drug-Design with quantum computers
12:10-13:30	**Lunch**
13:30-15:00	**POSTER SESSION**
15:00-15:25	**L10: Patrick Duchstein (Erlangen, Germany)** Calcium carbonate – an "unwanted material"
15:25-15:50	**L11: Erwann Guillam (Montpellier, France)** Molecular prediction of water transfer in water-octanol interfaces for liquid-liquid extraction
15:50-16:10	**Coffee Break**
16:10-16:35	**L12: Diego Liberati (Milano, Italy)** Integrating inferences simulation and deduction in molecular modeling
16:35-17:00	**L13: Christiane Ehrt (Hamburg, Germany)** Binding Site Prediction and Characterization with DoGSite3 – Method and Applications
17:00-17:25	**L14: Yılmaz Ozkılıç (Magdeburg, Germany)** Umbrella sampling identification of the elusive ´out´ conformational state of kynurenine 3-monooxygenase
17:25-18:15	**PLENARY LECTURE III: Sereina Riniker** Efficient free-energy calculations with a multi-state method
19:00	**Social Event: Steinbach-Bräu**

Wednesday, March 6th 2024

09:00-09:25	**L15: Albert Poater (Giroa, Spain)** DFT drives catalysis by predictions
09:25-09:50	**L16: Michael Strobli (Dortmund, Germany)** Tautomerization prediction as a testbed for theory-based experimental uncertainty analysis
09:50-10:40	**PLENARY LECTURE IV: Val Gillet** Reaction-based De Novo Design
10:40-11:10	**Coffee Break**
11:10-11:35	**L17: Malte Schokolowski (Hamburg Germany)** Multiple molecular superpositioning with a common core structure
11:35-12:00	**L18: Katarina Stanciakova (OpenEye Cadence)** Accurate Binding Pose Predicton with Induced-Fit Posing (IFP)
12:00-12:25	**L19: Milan Koèí (Prague, Czech Republic)** FireCore for modeling of self-assembling organic molecules on ionic substrates
12:25-12:50	**L20: Marina Günthert (Erlangen, Germany)** ML prediction of photoluminescence from high-thoughput density functional theory ground state properties on the example of $Cs_2Ag_xNa_{1-x}Bi_yIn_{1-y}Cl_6$
12:50-13:15	**Poster & Lecture Awards, Closing**
14:00-16:00	**Post-Conference Workshop:** Schrödinger Workshop: A beginners' guide to Structure Based Design

Poster Session

POSTER SESSION

Tuesday, March 5th 2023 13:30-15:00

P01 **Jorge A. A. Balderas (Erlangen, Germany)**
Insight into the active site conformation of DNA repair enzyme MBD4 from molecular simulations

P02 **Barışcan Arıcan (Erlangen, Germany)**
Modeling fracture formation and propagation in cured epoxy resins under mechanical stress

P03 **Emma Armstrong (Sheffield, UK)**
Water Ordering at Aqueous $CaCO_3$ Interfaces and the Interfacial Entropy of Formation

P04 **Frank Beierlein (Erlangen, Germany)**
In Silico Study of Binding of Camptothecin-Based Pro-Drugs to Human Carboxylesterase 2

P05 **Jan Borchert (Dortmund, Germany)**
Free energy surfaces of the ion conduction through the small viral potassium channel KcvPBCV-1

P06 **Jacqueline C. Calderón (Erlangen, Germany)**
Understanding α,γ-peptide efficacy and binding selectivity in the neuropeptide Y Y4-receptor

P07 **Arsha Cherian (Erlangen, Germany)**
Investigation of the impact of dissolved H_2 on the surface properties of ionic liquids

P08 **Christian Chodun (Dortmund, Germany)**
EC-RISM/MPNN-based hydration free energy models with application to tautomer equilibria

P09 **Christiane Ehrt (Hamburg, Germany)**
Binding Site Prediction and Characterization with DoGSite3: Method and Applications

P10 **Olena Denysenko (Erlangen, Germany)**
Identification and structural characterization of peptidic ligands for novel antiviral strategies against SARS-CoV-2

P11 **Rustam Durdyyev (Erlangen, Germany)**
Molecular simulation of separation of C_{60} and coronene in silica nanopores

P12 **Dilsah Nur Elmaci (Magdeburg, Germany)**
The Role of Disulfide Bonds in Structural Stability and Dynamics of Human TFF1

P13 **Alena Endres (Düsseldorf, Germany)**
Computational studies of substrate binding modes of PET44

Please kindly remove your posters on tuesday evening!

POSTER SESSION

Tuesday, March 5th 2023 13:30-15:00

P14 **Epee Ndongue Jules César (Erlangen, Germany)**
Towards a judicious choice of degrees of freedom to sample reaction paths of enzymatic reactions

P15 **Rupam Gayen (Erlangen, Germany)**
Molecular Modelling of a Mechanochemical reaction: The Case of 18-Crown-6 Ether and KCl

P16 **Tadeu Luiz Gomes Cabral (Magdeburg, Germany)**
Chiral Interactions at the Molecular Level: Insights from NMR and Computational Studies

P17 **Metehan Ilter (Magdeburg, Germany)**
Exploring the Multi-Stage Catalytic Cycle of Cezanne-1 through MD Simulations

P18 **Anna Kahler (Erlangen, Germany)**
Improving MD performance on HPC clusters through in-depth hardware knowledge and advanced program usage

P19 **Harald Lanig (Erlangen, Germany)**
Boost your Atomistic Simulations via NHR@FAU

P20 **Stefan Maste (Dortmund, Germany)**
The accuracy limit of aqueous chemical shift predictions

P21 **Carolin Müller (Erlangen, Germany)**
The alchemy of light: computational investigation of photoswitches and photomotors

P22 **Muhammad Mazhar Fareed (Verona, Italy)**
In silico investigation of nonsynonymous single nucleotide polymorphisms in BCL2 apoptosis regulator gene to design novel protein-based drugs against cancer

P23 **Eduard Neu (Erlangen, Germany)**
Elucidating Structural Determinants of Biased Signaling at the 5-HT1A G Protein-Coupled Receptor through Molecular Dynamics Simulation

P24 **Sampanna Pahi (Erlangen, Germany)**
Impact of Curing dynamics on the Microstructure and Properties of Epoxy Thermosets

P25 **Ana Beatriz Salazar-Arriaga (Mexico City, Mexico)**
Contaminant desorption from a dolomite plate with synthetic and bio surfactant molecules: A Molecular Dynamics study

Please kindly remove your posters on tuesday evening!

POSTER SESSION

Tuesday, March 5th 2023 13:30-15:00

P26 **Simon Schäfer (Erlangen, Germany)**
From Computational Analysis to Immune Evasion: Understanding the Interaction between SARS-COV-2 Spike Protein and Antibodies

P27 **Nicolas Tielker (Dortmund, Germany)**
Influence of conformational ensemble models on the prediction of toluene-water partition coefficients

P28 **Emília Valença de Aragão (Montpellier, France)**
Modeling of liquid-liquid extraction of salts between an aqueous phase and a microemulsion

P29 **Achim Zielesny (Recklinghausen, Germany)**
An automated Calculation Pipeline for Differential Pair Interaction Energies with Molecular Force Fields using the Tinker Molecular Modeling Package

All abstracts are available on the conference web site:
www.mmws2024.mgms-ds.de

Please kindly remove your posters on tuesday evening!

Abstracts

Towards Quantum Force Fields Using Quantum Charged Oscillators

Prof. Alexandre Tkatchenko

University of Luxemburg

Quantum Charged (or Drude) Oscillators (QDOs) [1,2] offer a fundamental framework for future fully quantum atomistic force fields. In this talk, I will first review the concepts and theory behind coupled QDOs and the many-body dispersion (MBD) method [2,3] in particular. Then, I will demonstrate how the QDO/MBD framework is applicable to describe interatomic induction, dispersion and exchange interactions [4,5]. Finally, recent extensions to describe interatomic vdW potentials at all distances and even covalently-bonded dimers will be shown [6,7,8]. These results, taken together, elucidate the high promise of the coupled QDO framework as a fully quantum atomistic force field that can be developed as a community effort.

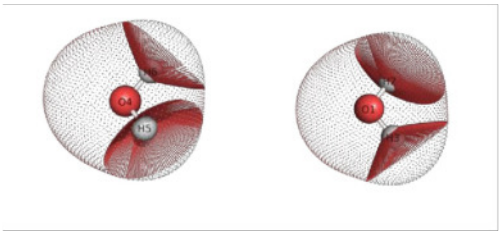
[1] Cipcigan et al., Electronic coarse graining: Predictive atomistic modeling of condensed matter, Rev. Mod. Phys. 91, 025003 (2019).
[2] Hermann et al., First-Principles Models for van der Waals Interactions in Molecules and Materials: Concepts, Theory, and Applications, Chem. Rev. 117, 4714 (2017).
[3] Tkatchenko et al., Accurate and Efficient Method for Many-Body van der Waals Interactions, Phys. Rev. Lett. 108, 236402 (2012).
[4] Karimpour et al., Molecular Interactions Induced by a Static Electric Field in Quantum Mechanics and Quantum Electrodynamics, J. Phys. Chem. Lett. 13, 2197 (2022).
[5] Fedorov et al., Quantum-Mechanical Relation between Atomic Dipole Polarizability and the van der Waals Radius, Phys. Rev. Lett. 121, 183401 (2018).
[6] Khabibrakhmanov et al., Universal Pairwise Interatomic van der Waals Potentials Based on Quantum Drude Oscillators, J. Chem. Theory Comput. 19, 7895 (2023).
[7] Sarkis et al., Modeling noncovalent interatomic interactions on a photonic quantum computer, Phys. Rev. Res. 5, 043072 (2023).
[8] Ditte et al., Quantum Drude Oscillators Coupled with Coulomb Potential as an Efficient Model for Bonded and Non-Covalent Interactions in Atomic Dimers, J. Chem. Phys., in print.

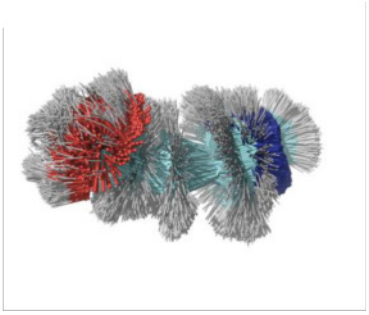
DL_FFLUX: A Machine-Learned Polarisable Force Field for Molecular Dynamics Simulations with Knowledgeable Atoms

Mohamadhosein Nosratjoo and Paul L.A. Popelier

Department of Chemistry, The University of Manchester, Oxford Road, Manchester M13 9PL, Great Britain

DL_FFLUX is a state-of-the-art force field that has been developed to make the idea of a universal force field a reality [1]. By its novel construct, DL_FFLUX "sees" the atoms and their electrons by utilising the quantum chemical topology (QCT) method. This results in quantum mechanically accurate **atomic** energies and multipole moments (MMs) in every step of an MD simulation. DL_FFLUX uses machine-learned models to predict these energies and flexible MMs [2]. A rather unique feature of this approach is that the machine learning does not carry out the atomic partitioning. Instead, QCT provides the atomic properties that are trained on, thereby guaranteeing their physical integrity. Our in-house FEREBUS [3] program is used to make models using the Gaussian Process Regression (GPR) method.





In this talk, the following questions will be answered:

1. Is it possible to have sub kcal/mol accuracy at speeds close to classical MD?
2. Can atoms be partitioned before machine learning?
3. Is it possible to have a non-bonded and non-parametrised force field?

References

[1] Symons, B.C., Bane, M.K. and Popelier, P.L.A, 2021. DL_FFLUX: a parallel, quantum chemical topology force field. *Journal of Chemical Theory and Computation*, *17*(11), pp.7043-7055.

[2] Symons, B.C. and Popelier, P.L.A., 2022. Flexible multipole moments in smooth particle mesh Ewald. *The Journal of chemical physics*, *156*(24).

[3] Burn, M. J.; Popelier, P. L. A., FEREBUS: a High-performance Modern Gaussian Process Regression Engine. Digital Discovery 2023, 2, 152-164.

Charges and boundary terms: easy ways to spoil your QM/MM(MD) results

Alexander Zlobin

Institute for Drug Discovery, Leipzig University, Leipzig, Germany

Hybrid quantum mechanical/molecular mechanical (QM/MM) simulations are a staple of modern computational biochemistry. A small portion of the molecular system is modeled with a more accurate QM approach, while everything else is kept under a much computationally cheaper MM description. To saturate open valencies on QM atoms when the subsystem is passed to the QM engine, capping hydrogen atoms are added. These atoms are called link atoms (LA) and are invisible to the MM engine. LA placed along a bond to a sizably charged MM atom will be heavily influenced by it. This results in artifacts called hyperpolarization, which bring a setup that does not bear much chemical sense. A number of elaborate schemes to correct the issue were proposed. However, they have got limited traction in popular QM/MM software.

In our recent work, we showed that neglecting the hyperpolarization correction while placing a LA on bond to the polar MM atom produced incorrect results [1]. In a case of subtilisin Carlsberg, we demonstrated that incorrect LA setup produces surprising outcomes that may be erroneously interpreted as groundbreaking results with regards to enzymatic mechanisms.

We then focused on how well different intra-backbone partitions reproduce backbone dynamics, a feature crucial to QM/MM MD. Here, a consideration of which MM terms are kept or deleted turned out to play the main role. Even with hyperpolarization correction schemes, only three intra-backbone boundaries produced correct results in dynamics when the classical scheme to omit angular and dihedral terms with only one MM atom was used. When these terms were retained (as in Amber suite), five out of six boundaries were mostly correct.

In our newest and yet unpublished work, we continue this study to investigate how well the sidechain dynamics is recapitulated in sidechain-only QM systems. Such a setup is very common in computational enzymology. We show that both classical and Amber schemes distort the rotation along $\chi 1$ and $\chi 2$ angles. We then propose an updated scheme that may be of interest to the broad biomolecular modeling community.

[1] A. Zlobin, J. Beliaeva, A. Golovin, *Journal of Chemical Information and Modeling*, **2023**, *63*, 546-560.

GPU accelerated QM/MM molecular dynamics simulations of biomolecular systems

Andreas W. Götz

San Diego Supercomputer Center, University of California San Diego, La Jolla, California, USA.

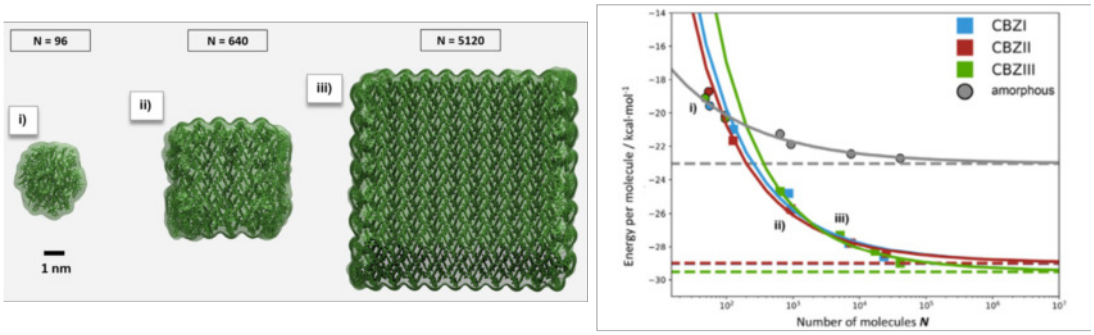
Mixed quantum mechanics / molecular mechanics (QM/MM) simulations couple the strength of quantum chemistry with the speed of molecular mechanics and thus enable simulations of local molecular properties and reaction mechanisms in complex environments such as enzymes and other condensed phase systems. However, QM/MM simulations are still orders of magnitude more computationally intensive than MM simulations, in particular if ab initio or density functional theory (DFT) Hamiltonians are employed. Efficient software implementations for modern computer architectures are thus essential to enable meaningful QM/MM molecular dynamics simulations. In this talk I will give an overview of QM/MM methods in the Amber software package for biomolecular simulations. I will focus on recent developments of QUICK and its integration with the molecular dynamics (MD) program sander, both of which are free and open-source programs distributed with AmberTools. QUICK is a quantum chemistry program for Hartree-Fock and DFT calculations with Gaussian basis functions that features an efficient implementation for massively parallel graphics processing unit (GPU) hardware. In QUICK the entire Fock matrix build and nuclear gradient calculation can be executed on single or multiple GPUs. This includes one-electron integrals (OEIs), two-electron repulsion integrals (ERIs), DFT exchange-correlation (XC) quadrature, and linear algebra operations. Both Nvidia and AMD hardware is supported. Efficient geometry optimizations are enabled via a recent integration of the open-source DL-FIND library, which includes both quasi-Newton based and more recently also machine learning-based optimizers. The interface of QUICK with sander enables high-performance ab initio QM/MM MD simulations including a range of free energy methods for the computation of reaction paths or binding free energies via alchemical transformations and bookending (end-point correction) methods. Importantly, the implementation in AmberTools 23 includes the ambient-potential composite Ewald method that incorporates long-range electrostatic interactions without truncation for condensed phase simulations under periodic boundary conditions. This integration makes it particularly easy to perform accurate QM/MM MD simulations without introducing numerical noise or neglecting potentially relevant electrostatic interactions between the QM and MM regions.

Molecular Modelling of Drug Formulation: From "tailor-made" Force Field to Stability Analysis of Carbamazepine Crystals

Moritz Macht

Friedrich-Alexander-University Erlangen-Nuernberg, Naegelsbachstr. 25, 91052 Erlangen, Germany

The polymorphism of drug crystals can be a challenging hurdle in drug formulation as in the case of Carbamazepine (CBZ) [1]. Decades of experimental studies were necessary to identify and rank the different polymorphs of CBZ, while also trying to enable a control on the formulation of CBZ. Meanwhile advancement in molecular simulation opens a window to techniques for prediction of polymorphs of newly developed drugs without the need of experimental data [2]. Therefore, molecular modelling provides exiting perspectives in the field of computer-aided drug formulation [3].



Starting with the generation of force field by minor tailor-made improvements to the widely established GAFF force field model, we outline a blueprint to adjust the general force field (FF) to a specialized use case. By analysis and optimization of single molecule interactions up to the bulk crystal systems, the intricacies of interactions in the model system and their respective interplay are elucidated.

With the help of molecular dynamics (MD) simulations, melting enthalpies are determined in comparison to experimental data. Despite inherent limitations of MD simulations in accuracy due to various factors, the gained insights of the MD simulations and the resulting elucidation of possible polymorphism control factors are presented.

In addition to the characterization of bulk systems, an outline of size dependent stability profiles is presented and shedding light onto the energy contributions of bulk, surface, and edge terms for the CBZ system with promoting different polymorphs under differing size confinements. Based on these findings a multi-step nucleation mechanism is proposed with varying aggregate behavior dependent on aggregate size [3,4].

[1] A. Grzesiak, M. Long, K. Kim, et al., *J. Pharm. Sci.*, **2003**, *92(11)*, 2260-2271.

[2] J. Anwar, D. Zahn, *Adv. Drug Deliv. Rev.*, **2017**, *117*, 47-70.

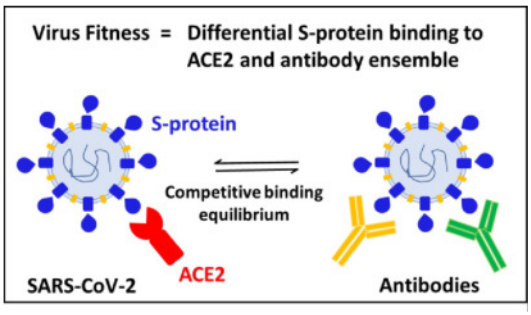
[3] A. Gadelmeier, M. Macht, D.Zahn, *J. Pharm. Sci.*, **2022**, *111(10)*, 2898-2906.

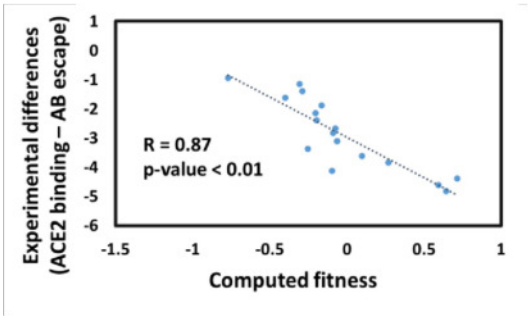
[4] D. Zahn, *ChemPhysChem*, **2015**, *16(10)*, 2069-2075.

Computing Viral Fitness: Towards a structure-based approach

Rukmankesh Mehra

Department of Chemistry, Indian Institute of Technology Bhilai, Bhilai, Durg 491001, Chhattisgarh, India. E-mail: rukmankesh@iitbhilai.ac.in.





Computing the impact of new emerging virus mutations is of major interest for understanding the evolutionary forces of the pathogen and for surveillance purposes. The SARS-CoV-2 spike-protein (S-protein) is central to the current vaccine development efforts. This protein binds to human ACE2 receptors as a critical step in host cell infection, but also to human antibodies that neutralizes the virus and prevents interaction with ACE2. We proposed that this host-virion interaction can be viewed as a competitive binding situation where the virion seeks to enter the human cell via ACE2 binding before the S-protein is bound to circulating antibodies [1-5]. If so, the thermochemical selectivity (differential binding affinity to ACE2 vs. the ensemble of circulating antibodies) defines the fraction of virions that infects cells before they are neutralized by antibodies. Combining the two binding events seems important as many individual mutations generically either strengthen or weaken binding to many proteins: Stronger binding to ACE2 is not a good fitness metric if the mutant at the same time leads to equally stronger binding to antibodies. Here, we defined a simple *fitness model* of SARS-CoV-2 based on the two binding properties of the S-protein to its human host cell-surface receptor ACE2 and a representative ensemble of diverse antibodies circulating in the human population [1,2]. We implemented the model using structure-based computation of all possible mutation effects averaged over 10 ACE2 complexes and 10 antibody complexes of the S-protein (~3,80,000 computed mutations) and study all possible mutations in the S-protein to provide a full heat map of estimated fitness effects. The use of many protein structures ensures much more robust estimates of the effects, and the selectivity model also takes advantage of systematic error cancellation by considering "differences between differences" in estimated binding affinities (changes in ACE2–AB selectivity), which is another novel advantage compared to computational or experimental fitness estimates based on just one of the binding events. The approach was validated by correlating our computed data with diverse experimental binding/escape data of ACE2 and antibodies [1-2]. Our computed fitness correlated well with the experimental fitness [1]. The method and our results should be of substantial interest, with a potential for use in surveillance as an early estimator of the potential concern of new arising mutations.

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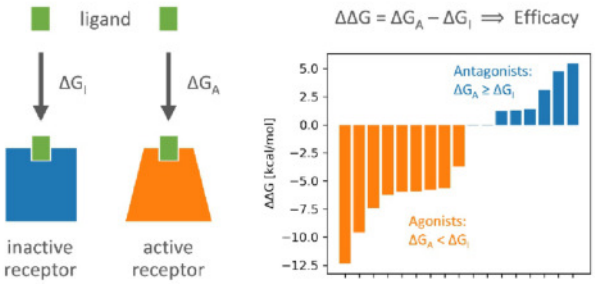
Is The Functional Response of a Receptor Determined by the Thermodynamics of Ligand Binding?

Martin Vögele[1], Bin W. Zhang[1], Jonas Kaindl[2], Lingle Wang[1]

[1] Schrödinger, Inc., 1540 Broadway 24th Floor, New York, NY 10036, United States
[2] Schrödinger GmbH, Glücksteinallee 25, 68163 Mannheim, Germany

While strong binding to its target protein is crucial for a molecule's drug efficacy, it is often insufficient alone. To produce a particular functional response, drugs need to either block the proteins' functions or modulate their activities by changing the conformational equilibrium. The binding free energy of a compound to its target is routinely calculated but the time scales for protein conformational changes are prohibitively long to be efficiently modeled via physics-based simulations. Thermodynamic principles suggest that binding free energies of the ligands with different receptor conformations may infer their efficacy. However, this hypothesis has not been thoroughly validated and its practical viability has remained under-explored. We introduce a robust protocol and an exhaustive study demonstrating that binding thermodynamics provides a strong predictor for the efficacy of a ligand. Using the Absolute-Binding Free Energy Perturbation (ABFEP) method, we assess ligands bound to both active and inactive forms of eight G protein–coupled receptors (GPCRs) and a nuclear receptor, then compare the resulting values for the binding free energy. Our findings suggest the occasional need for specialized restraints to model the respective conformational ensembles accurately, and we propose an efficient approach to set them up. Remarkably, our method categorizes ligands as agonists or antagonists with unparalleled accuracy across the various investigated receptors, all of which are important drug targets. By examining receptor ensembles and ligand poses, we identify necessary conditions and limitations for real-world application. Overall, our insights have significant implications for the drug discovery process as they allow detailed predictions of a ligand's effects on its target.



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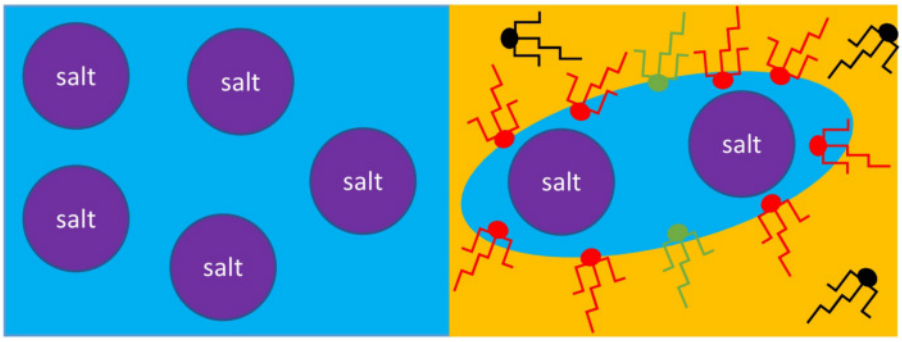
Modeling of liquid-liquid extraction of salts between an aqueous phase and a microemulsion

Emília Valença Ferreira de Aragão, Magali Duvail, Jean-François Dufrêche

Institut de Chimie Séparative de Marcoule, Univ. Montpellier, CEA, CNRS, ENSCM



Liquid-liquid extraction with aqueous-organic solvents is widely used for extraction and separation of lanthanides. In particular, it is used in nuclear fuel-cycle management, with processes such as PUREX (Plutonium Uranium Reduction Extraction) and DIAMEX (DIAMide Extraction). In those processes, an acidic aqueous phase containing lanthanide ions is put in contact with a solvent phase containing an extracting agent similar to a water-in-oil microemulsion. The extractant must be soluble in the microemulsion in both monomeric and aggregated forms, but insoluble in the water phase. Once the phases are in contact, the extractant molecules make complexes where the lanthanide ions are extracted together with water and acid.

A theoretical model [1] is employed to study the system at the equilibrium. The extractant is considered to be present in the microemulsion in three forms: as a monomer, in aggregation on a film complexing a salt and in aggregation on a film not complexing a salt. In the current work, the model was used to calculate the concentration of acid extracted into the organic phase given an initial concentration of acid in the aqueous phase and a given concentration of extractants in the solvent phase. Different parameters of the model, such as the dissociation constant of the acid, the number of extractants participating in the aggregate and the critical aggregate concentration were fitted in order to interpret the experimental extraction isotherms reported by Dourdain and colleagues [2].

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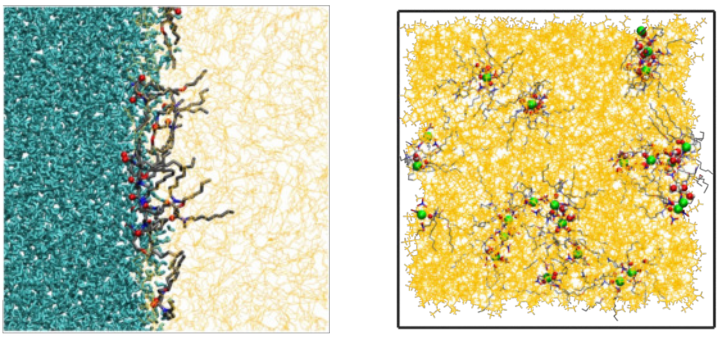
Understanding interface formation and extractant distribution at the liquid-liquid interface

L.Žiberna [1], P.Guilbaud [2], M.Duvail [1]

[1] ICSM, CEA, Univ Montpellier, CNRS, ENSCM, Site de Marcoule, BP 17171, F-30207 Bagnols-sur-Cèze, France

[2] CEA, DES, ISEC, DMRC, Univ Montpellier, BP 17171, F-30207 Bagnols-sur-Cèze, France



Lanthanide ions recycling has grown in importance in recent years as the demand for these elements has increased [1]. One of the approaches for recycling metals is liquid-liquid extraction, which selectively separates solutes based on the difference in their solubility between two immiscible liquids. In the nuclear industry, many processes based on liquid-liquid extraction are employed to recycle nuclear fuel, where lanthanide ions are separated from nuclear waste. DIAMEX (DIAMide Extraction) process is one such technique [2], where the reference molecule for separation of smaller lanthanides is N-N'-DiMethyl-N-N'dioctyl-2-hexylethoxymalonamide (DMDOHEMA) [2].

In our research, we use classical Molecular Dynamics (MD) to investigate the structural properties of the liquid-liquid interfaces between aqueous and organic phases with different amphiphilic extractant molecules. The main objective is to characterize and describe the species distribution at the interface and in bulk organic phase, comparing to the experimental results [3].

First, we investigated how the initial box configuration as well as the ratio between the two phases impacts the formation of the interface, the shape, and the structure of the interface in comparison with a theoretical thermodynamics model [4]. After validating the method for creating the interfaces by MD simulations, we studied the distribution of DMDOHEMA extractant molecules at the interface and in the bulk organic phase at various extractant concentrations. Additionally, our investigation extends to understanding the micelle formation with lanthanide cations (Eu^{3+}) and DMDOHEMA extractant within the bulk organic phase.

We extensively investigated the distribution and the structural properties of DMDOHEMA extractant at various concentrations, and we will apply the same approach to study TODGA extractant to compare the effect of structural differences on their behavior in the system. Furthermore, we will introduce Nd^{3+} cations into the system and explore the ion transfer from aqueous to organic phase, distribution of extractants, salts, and micelles formed in the system during extraction.

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Large-scale CI: Band Gaps and Excited States in EMPIRE'24

Matthias Hennemann

CEPOS InSilico GmbH, Schützenstraße 12, 96149 Breitengüßbach;
matthias.hennemann@ceposinsilico.com, www.ceposinsilico.com

The increasing role of quantum chemical calculations in drug and materials design has led to a demand for methods that can describe the electronic structures of large and complex systems. Semiempirical methods based on the neglect of diatomic differential overlap (NDDO) approximation (e.g., the MNDO, MNDO/d, AM1, AM1*, and PMx methods) are important representatives of such approaches. Many of these methods have been implemented in the massively parallel program EMPIRE, which makes the full quantum-mechanical treatment (electronic properties, geometry optimization, molecular dynamics) of systems containing 100,000 atoms or more on thousands of cores possible [1].

EMPIRE can, for example, be used in combination with a classical molecular dynamics (MD) code to perform electronic structure calculations on snapshots from an MD run on a periodic system. In addition, EMPIRE can perform MD calculations using semiempirical methods entirely, which enables the study of bond formation and dissociation processes [3].

Periodic boundary conditions (PBC) enable the treatment of condensed-phase systems, such as proteins in a periodic water box or solids. This allows molecular materials to be studied in their native environment. For semiempirical methods, the most practical way of implementing PBC is the cyclic-cluster approach in which the system is approximated by a supercell and by imposing Born-von Karman boundary conditions. Using a large unit cell allows the calculation to be performed entirely in real space. The main advantage of this technique is that program features like the calculation of local properties or excited states are directly transferable from nonperiodic calculations. EMPIRE is suitable for use on systems with unit cells up to 50,000 atoms (e.g., disordered and amorphous systems) [2].

Configuration interaction (CI) calculations can be used to study the properties of biradicals and excited states. In CI calculations, the MOs for the ground state are calculated and then used unchanged to construct a series of further electronic configurations (microstates) that are mixed to form new electronic states. CI calculations give not only the ground state, but also the excited states that result from mixing the microstates used. They can therefore be used for the calculation of band gaps, UV/vis spectra and second order hyperpolarizabilities etc. EMPIRE can perform CI calculations on systems containing 5,000 atoms or more.

Semiempirical UNO-CI in which unrestricted natural orbitals (UNOs) are used as the reference for CI calculations gives good results for the optical band gaps of organic semiconductors such as polyynes and polyacenes. The results of these semiempirical UNO-CI techniques are generally in better agreement with experiment than those obtained with the corresponding conventional semiempirical CI methods and often better than those obtained with far more computationally expensive methods such as time-dependent density-functional theory [4].

We now present EMPIRE'24 which uses a performance-optimized CI code, that enables the calculation of large systems at less computational cost.

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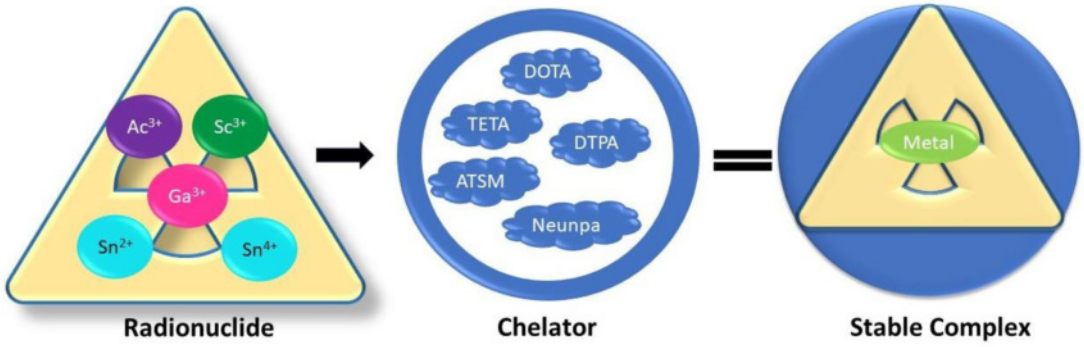
Systematic investigation of chelator-radiometals compounds by quantum chemical methods and molecular MD simulations

Işılay Öztürk*, Silvia Gervasoni, Camilla Guccione, Andrea Bosin, Paolo Ruggerone and Giuliano Malloci§
University of Cagliari, Department of Physics, Monserrato (Cagliari), I-09042, Italy
*iozturk@dsf.unica.it
§giuliano.malloci@dsf.unica.it

The development of stable radiometal complexes (i.e., a chelator moiety carrying a radionuclide) and the design of chelating systems are crucial aspects in the advancement of radiopharmaceuticals for diagnostic and therapeutic purposes in nuclear medicine (theranostics) [1,4]. Currently, there is no single chelator that is universally effective for all metals or radioconjugates. [2,3,4].



Different radioactive metals may have varying coordination numbers while interacting with the same chelator. The stability of chelators and metal complex structures is affected by the force constant and the coordination numbers [3]. We performed a systematic investigation on different chelator-radiometal compounds taken from the Cambridge Structure Database (CSD). We used quantum mechanics methods at the Density Functional Theory level and generated the General Amber Force Field parameters to perform microsecond-long molecular dynamics simulations in water solution. By considering different chelators (about 30) and radiometals (about 25), we could compare different physical-chemical properties of the chelator radiometal couples, such as selectivity, stability and coordination geometries.

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Perspective on drug design on quantum computers

Matthias DeGroote

Boehringer Ingelheim B.V., Basisweg 10, 1043 AP Amsterdam

The promised industrial applications of quantum computers often rest on their anticipated ability to perform accurate, efficient quantum chemical calculations. Computational drug discovery relies on accurate predictions of how candidate drugs interact with their targets in a cellular environment involving several thousands of atoms at finite temperatures. Although quantum computers are still far from being used as daily tools in the pharmaceutical industry, in this talk, I will explore the challenges and opportunities of applying quantum computers to drug design. Based on the findings from past and present projects by the Quantum Lab at Boehringer Ingelheim, I'll discuss the impact on industrial research and identify the substantial further developments needed to reach industrial relevance.

Calcium carbonate – an "unwanted material"

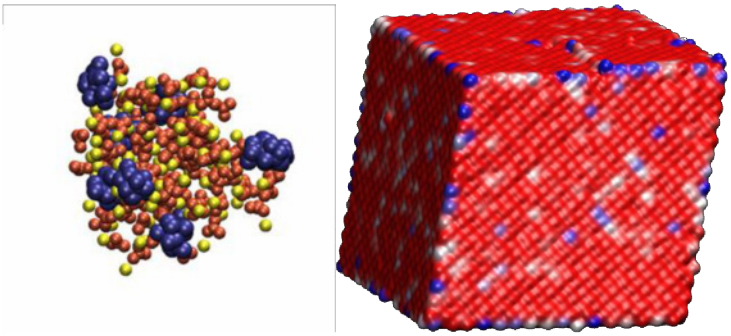
Patrick Duchstein[1], Stephan Wolf[2], Dirk Zahn[1]

[1]Computer Chemie Centrum, Friedrich-Alexander-Universität Erlangen-Nürnberg, 91052 Erlangen, Germany

[2]Department of Materials Science and Engineering, Friedrich-Alexander-Universität Erlangen-Nürnberg, 91058 Erlangen, Germany

Calcium carbonate, a ubiquitous material in nature, fulfills important structural functions for crustaceans, corals, mussels, and snails. In the household, however, it is largely undesirable. Kitchen cleaning agents, often working with alkaline pH values, unintentionally support calcite precipitation. Conversely, strongly acidic bathroom cleaners not only etch calcite, but also damage enameled surfaces. Despite its omnipresence and significance, our understanding of calcium carbonate structures in solution, calcite crystallization, and crystal dissolution remains rudimentary.

In this study, we present recent findings from investigating the interaction of precipitation-inhibiting additives with calcium carbonate in solution. Utilizing molecular dynamics simulations, we demonstrate how these small molecules dynamically interact with continuously evolving, entropically stabilized calcium carbonate networks in solution.[1] Furthermore, we construct a realistic model of a calcite nanoparticle, exhibiting a dislocation-induced continuous growth step. Our results illustrate how additives can effectively hinder further material deposition. Finally, we introduce a method for calculating instantaneous pK_a values specific to carbonate ions at the crystal surface and highlight the impact of acid-induced dissolution on the particle.[2]



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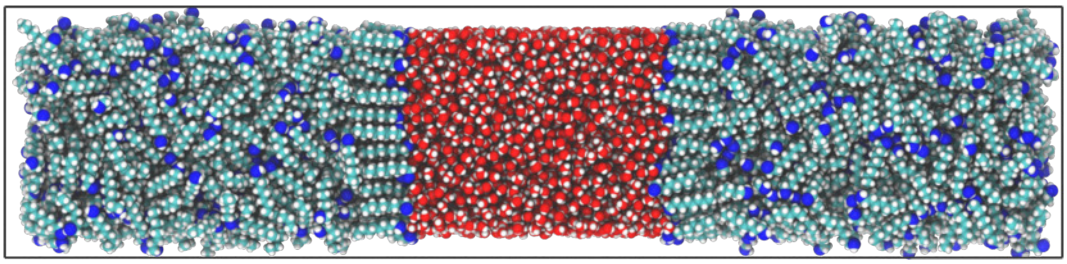
Molecular prediction of water transfer in water-octanol interfaces for liquid-liquid extraction

E. Guillam, M. Duvail and J.-F. Dufrêche

ICSM, CEA, Univ. Montpellier, CNRS, ENSCM, Marcoule, France.

erwann.guillam@cea.fr

Liquid-liquid extraction is a key extraction process used to selectively separate different solutes. One of the most important extraction systems is the water-octanol interface used in the industry to classify solutes based on their hydrophilicity [1]. The hydrophilicity of a solute, measured experimentally by its partition coefficient log(P), is linked to the Gibbs energy of transfer, which governs the solute transfer between the aqueous and the organic octanol phases [2].
This work deals with the prediction of the Gibbs energy of transfer of water molecules in water-octanol interfaces using Steered Molecular Dynamics (SMD), an out-of-equilibrium simulation technique for Molecular Dynamics. The SMD methodology uses a moving biasing harmonic potential to steer the water molecules from the aqueous phase to the organic phase, allowing for accurate sampling of the free energy landscape of the interface [3,4].
Calculating the molecular orientation revealed that the octanol molecules at the interface organize themselves in a rigid bilayer structure, as previously observed [5] (Fig. 1), preventing the water transfer toward octanol. SMD simulations were carried out to determine the Gibbs energy barrier of this interface, allowing a preliminary calculation of the water solubility in octanol.



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Integrating inferences simulation and deduction in molecular modeling

Diego Liberati

National Research Council of Italy

Standard molecular modeling is traditionally done via Schroedinger equations via the help of powerful tools helping to manage them atom by atom often needing High Performance Computing

When functional domains are known and for instance Plasmon measured in their specific effects, a simple Galerkin simulation touching all possible configurations for those domains even allows to forecast unknown mutants as in [1] for Sos1, then discovered.

Integrating eXplainable AI in the form of understandable rules Machine Learning [2], one can gain knowledge from data in the predicative logic form

if ... then ... else...,

immediately integrable to the theoretical priors, summing pros of both inference and deduction

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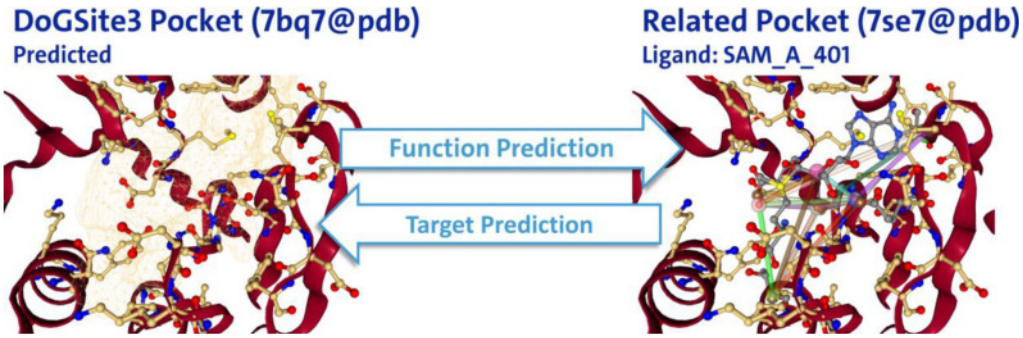
Binding Site Prediction and Characterization with DoGSite3 – Method and Applications

Christiane Ehrt, Joel Graef, Konrad Diedrich, Matthias Rarey

Universität Hamburg, ZBH - Center for Bioinformatics, Hamburg, Germany

The prediction and characterization of protein binding sites is a non-trivial endeavor. [1] However, it is a crucial methodology given the increasing numbers of predicted and experimentally determined protein structure models [2] and their impact on structure-based design applications such as function or off-target prediction. Given a structure of interest, the DoGSite algorithm predicts binding sites for yet uncharacterized proteins, enabling protein function prediction and binding site druggability estimation. [3,4]

Based on the first implementation of the grid-based DoGSite methodology, we developed DoGSite3. [5] The new implementation is characterized by more robust binding site boundaries, improved prediction accuracy, and a considerably lower run time. Its integration on the Proteins*Plus* web server (https://proteins.plus) enables easy access to predicted protein pockets and their descriptors, even for non-experienced users.



In this contribution, we will outline the basic methodology and optimization of the DoGSite3 algorithm, focusing on binding site characterization and prediction accuracy. Based on selected application examples, we will demonstrate the broad applicability of DoGSite3 in various structure-based design approaches, such as pocket annotation and function prediction by known protein-ligand complexes and the elucidation of potential off-targets for known drugs.

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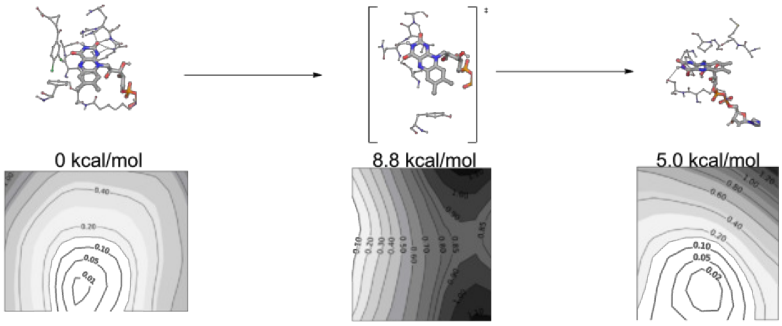
Umbrella sampling identification of the elusive ´*out*´ conformational state of kynurenine 3-monooxygenase

Yılmaz Özkılıç[a], Matthias Stein[a]

[a]*Molecular Simulations and Design Group, Max Planck Institute for Dynamics of Complex Technical Systems, Magdeburg, Germany*

Kynurenine 3-monooxygenase (KMO) is a member of the class A monooxygenase family which is characterized by the lack of a binding pocket for nicotinamide adenine dinucleotide phosphate (NADPH). It reduces the coenzyme flavin adenine dinucleotide (FAD) during the reductive half reaction. KMO hydroxylates L-kynurenine (L-Kyn) and releases the product 3-hydroxykynurenine (3-HK), which itself and its following compounds (3-hydroxyanthranilate (3-HanA) and quinolinate (Quin)) cause neurodegeneration [1]. L-Kyn is also a substrate to kynurenine aminotransferase (KAT) that converts it to the neuroprotective compound kynurenic acid (KynA) [2]. Decreasing the Quin/KynA ratio by inhibiting KMO is regarded as a possible way of treating neurodegeneration. Such inhibition would allow the treatment of central nervous system damages. Several successful inhibitors were developed over the years, but it was soon realized [3] that most of the inhibitors themselves cause the formation of neurodegenerative hydrogen peroxide (H_2O_2).



Molecular dynamics simulations of KMO and the inhibitor–KMO complexes were carried out using umbrella sampling to explore the free energy surface of the conversion from the ´*in*´ to the ´*out*´ conformational state change of the coenzyme FAD. In addition to the apo form of the enzyme, both a non-substrate effector inhibitor and a competitive inhibitor containing initial structures were utilized. A relative evaluation that allows the comparison of computationally obtained results with the experimental results is presented. This information is used to obtain the relative free energy change, e.g. the barrier associated with the conformational change and a model of the elusive ´*out*´ conformational state that was speculated but not observed experimentally. Ligand-residue interactions along the conformational change were determined to identify the influence of the effector.

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Efficient free-energy calculations with a multi-state method

Enveloping distribution sampling (EDS) allows the calculation of free-energy differences between multiple end states from a single simulation [1]. A reference-state Hamiltonian is simulated which envelopes the Hamiltonians of the end states. The challenge when using EDS is the determination of optimal parameters for the reference-state Hamiltonian. Previously, the choice of parameters for an EDS simulation with multiple end states was a non-trivial problem that limited the application of the methodology [2]. To overcome these limitations, we have generalized the replica-exchange EDS (RE-EDS) methodology to arbitrary systems [3,4]. By exchanging configurations between replicas with different parameters for the reference-state Hamiltonian, major parts of the problem to choose optimal parameters are circumvented. Algorithms to estimate the energy offsets and optimize the replica distribution have been developed and to automate the parameter optimization procedure. Our approach was tested successfully for inhibitors for a range of kinases [5,6]. RE-EDS is able to model up to 13 ligands simultaneously with high sampling efficiency, leading to a substantial decrease in computational cost when compared to pairwise methods.

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DFT drives catalysis by predictions

Albert Poater[a,*], Roger Monreal-Corona[a,*], Michele Tomasini[a,*], Anna Vidal-López[a,b,*], Artur Brotons-Rufes[a,*], Nicolas Joly[a,*], Sílvia Escayola[a,*]

a) Institut de Química Computacional i Catàlisi and Departament de Química, Universitat de Girona, C/ Maria Aurèlia Capmany 69, 17003, Girona, Catalonia, Spain; b) Department of Chemistry, Universitat Autònoma de Barcelona, Cerdanyola del Vallès, Catalonia, 08193, Spain;

**albert.poater@udg.edu*

Amidst the widespread enthusiasm for machine learning, one often-overlooked domain is predictive catalysis. In the realm of computational chemistry for sustainability, the research group advocates the maximum utilization of predictive catalysis, employing machine learning principles. Their endeavors extend beyond identifying reaction mechanisms; once the rate-determining step (rds) is established, the focus shifts to exploring alternative catalysts, aiming for more benign reaction conditions. The computational research spans various domains, encompassing processes such as olefin metathesis using Ru-based catalysts, gold chemistry for organometallic reactions, and green chemistry strategies for CO2 avoidance or reduction, including water oxidation catalysis and alcohol transformation to aldehydes with H2 generation as an energy source [1].

DFT calculations have unveiled the mechanisms underlying the formation of N-substituted hydrazones through the coupling of alcohols and hydrazine, achieved via sequential processes of acceptorless dehydrogenation and borrowing hydrogen [2,3]. This process, facilitated by a Mn-PNN pincer-based catalyst, aligns with green chemistry principles, releasing water and H2 as environmentally friendly byproducts. [3].

The research also delves into the reductive amination of aliphatic carbonyl compounds catalyzed by a Knölker-type iron catalyst. Utilizing DFT calculations and a detailed chemical structure analysis, the team investigates the reaction mechanism [4]. Armed with insights into the mechanism, various catalyst modifications are explored with the goal of steering catalytic reactions towards milder conditions (see Figure 1).

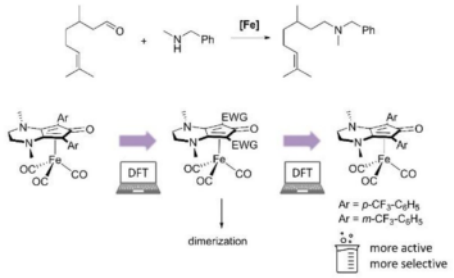

Figure 1. Two-step predictive catalysis approach for hydrogenation reactions with Knölker-type catalysts. A series of derivative Renaud catalysts with electron-withdrawing groups on the aryls of the cyclopentadienone improves the activity and selectivity.

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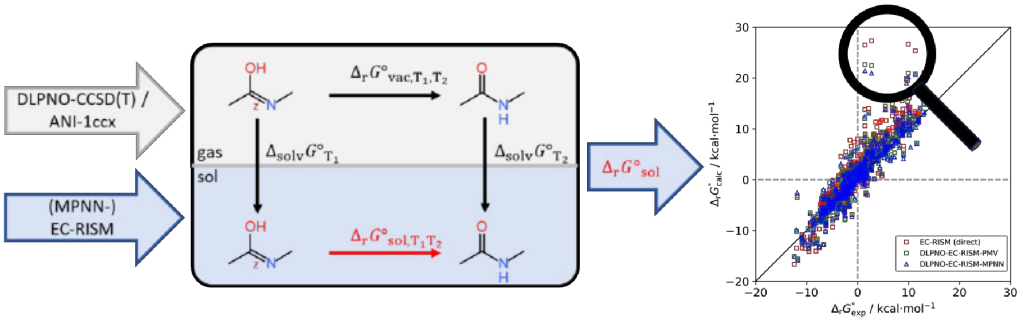
Tautomerization prediction as a testbed for theory-based experimental uncertainty analysis

Michael Strobl, Nicolas Tielker, Christian Chodun, Lukas Eberlein, Yannic Alber, Julia Jasper-Eberlein, Stefan M. Kast

Fakultät für Chemie und Chemische Biologie, Technische Universität Dortmund, 44227 Dortmund, Germany

Aqueous tautomer equilibria are highly relevant to a wide range of chemical and biological issues, e.g. DNA base-pairing or biological activity of drugs. [1,2] Despite the importance of these processes, experimental data is scarce and potentially unreliable due to the difficulties associated with the measurements. Complementary theoretical approaches aim at reliability and predictive power, but developing such models on the basis of unreliable datasets is difficult.

Here, different approaches to calculate free energies of tautomerization are applied to several tautomer equilibria datasets available, the SAMPL2 blind prediction challenge compounds, [3-5] the Tautomer Database [6] and the Tautobase. [1] The first ansatz is a direct approach derived solely from solution-phase properties provided by the Embedded Cluster Reference Interaction Site Model (EC-RISM). [7] In the second approach, an indirect thermodynamic route is chosen, which is complemented by gas phase free energies derived from either state-of-the-art DLPNO-CCSD(T) [8] calculations or quantum-based machine learning models like ANI-1ccx. [9] In this context, application of a machine learning-based optimization of EC-RISM is also investigated.



Subsequently, our best performing model combinations are compared with the literature, which allows us to construct a consensus dataset and perform a statistical analysis with particular emphasis on curating the reference datasets. Data points where the various theoretical approaches agree on a certain value range, but show a large deviation from the experimental reference, are then analyzed in more detail. Hence, we are able to identify suspicious database entries that may be based on problematic measurements or incorrect annotations. As a key result, an ordered set of tautomer pairs with increasing experimental uncertainty is produced, measured by increasing consensus prediction error. This curated dataset will more faithfully allow for training and evaluating novel computational methods.

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Reaction-based De Novo Design

Val Gillet

University of Sheffield

De novo design refers to the design of novel chemical entities from scratch to fit a set of constraints. In drug discovery these constraints are typically modelled properties such as bioactivity, measured as protein ligand binding or using a QSAR (Quantitative Structure Activity Relationship) model; drug-likeness measured, for example, using a model such as QED (Quantitative Estimate of Drug-likeness); selectivity to avoid off-target effects; and so on. De novo drug design techniques were first proposed more than 30 years ago, however, given the huge size of chemical space and the multiobjective nature of drug design, it remains a very challenging area of research. A key issue in de novo design, in addition to the design constraints mentioned above, is ensuring that the designed compounds are synthetically accessible. Early approaches were agnostic of synthesis and consequently their application was limited. More recently, synthetic accessibility has been addressed in two main ways. One is to embed synthesis directly within the de novo design algorithm itself, in what is known as reaction-based de novo design. The other approach is post-generation filtering of the generated molecules, using either simple models trained on molecular descriptors, or more sophisticated retrosynthetic methods. Post-generation filtering is the typical approach taken by modern deep learning methods. This talk will briefly review the evolution of de novo design methods and will then focus on our work on reaction-based de novo design, concluding with a case study as proof-of-concept.

Multiple molecular superpositioning with a common core structure

Malte Schokolowski, Christoph Noack, Niklas Paulicks, Marius Rüve, Mike Trzaska, Jule Würfel, Christian Meyenburg, Thorben Schulze, Matthias Rarey

Universität Hamburg, ZBH – Center for Bioinformatics, Hamburg, Germany

Molecular alignments play a pivotal role in drug design, especially when information about the structure of a target protein is lacking.

With a set of known binders, ligand-based approaches offer the chance to derive a pharmacophore model, facilitating the search for further potential ligands for the same binding site. Crucial for these ligand-based methods is that the ligands bind comparatively and have a similar binding geometry. Since compound series in drug discovery projects often share a common core structure, scaffold superposition can be utilized for an initial alignment of the molecules. While many alignment methods exist, approaches utilizing common core structures are still a niche. [1]

Based on these foundations, we developed an aligner for multiple small molecules called CoAler (https://github.com/ciw-project-2023/coaler) which utilizes the common core structure and superimposes dozens of small molecules in seconds to minutes on a standard desktop computer. CoAler is based on an algorithm called MolAlign, [2] which takes pre-generated conformers, performs pair-wise alignments for each conformer of each ligand and generates multiple ligand assemblies based on the pair-poses generated. Our implementation is developed in C++ using the open-source toolkit for cheminformatics RDKit [3] and is free to use for your own applications and workflows.

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Accurate Binding Pose Predicton with Induced-Fit Posing (IFP)

Katarina Stanciakova[1], Hyesu Jang[2]

[1]*OpenEye, Cadence Molecular Sciences, Ebertplatz 1, 50 668 Cologne, Germany*
[2]*OpenEye, Cadence Molecular Sciences, 9 Bisbee Court Suite D, Santa Fe, NM 87508, USA*

Abstract:
Accurate predicton of binding poses is a fundamental requirement in structure-based design. High accuracy can be easily achieved in lead optimization, where most molecules of interest share significant similarities in shape and chemical features with a known crystallographic ligand. However, in the hit-to-lead stage, multiple chemotypes are often pursued, many of which may not be similar in their 3D pose to known ligands, thus reducing the reliability and accuracy of pose prediction. We have recently introduced Induced-Fit Posing (IFP) to enhance pose prediction accuracy in hit-to-lead scenarios. IFP provides new pose prediction functionality combining docking with Short Trajectory Molecular Dynamics (STMD) to sample both ligand and protein binding site conformations. In this talk, we will present the basic protocol of this method as well as compare its accuracy with standard docking methods.

Keywords: Induced Fit Posing, Short Trajectory Molecular Dynamics, Binding pose

FireCore for modeling of self-assembling organic molecules on ionic substrates

Milan Koci, Prokop Hapala, Paolo Nicolini

Institute of Physics, Czech academy of Sciences, Prague, Czech Republic

The development of molecular nanotechnology hinges on our ability to predictably assemble molecular components in complex supramolecular structures. While atomic force microscopy (AFM) manipulation is an invaluable tool for prototyping molecular nanomachines, mass production requires deterministic self-assembly of simple building blocks. Atomistic simulations are crucial for developing reliable self-assemblers and nanomanipulation protocols, but they are hindered by the exponential increase in complexity of configuration space with the rising number of soft degrees of freedom, which complicates exhaustive exploration. To address this, we present a specialized classical force field (CFF) simulation package, FireCore (https://github.com/ProkopHapala/FireCore), tailored for flexible organic molecules interacting noncovalently with rigid substrates or AFM tips.

Unlike other CFF programs, FireCore is capable of leveraging massively parallel graphics processing units (GPUs) to accelerate simulations of small systems (<1000 atoms), by parallelization over many replicas of the same system. In addition, interaction of molecules with rigid substrates is accelerated by interpolation of grid projected non-covalent force-field (GridFF). Combination of all these techniques allows us to sample up to million molecular configurations per second on a single GPU accelerated workstation.
We will also introduce ongoing research focusing on rapid and efficient representation of molecular configurations, and evaluation of their similarity, which is a prerequisite for implementation of advanced global optimization and free energy sampling algorithms. This includes multi-level comparison, based on rotationally invariant descriptors such as principal axis, distribution of atomic species, as well as spatial hashing.

ML prediction of photoluminescence from high-throughput density functional theory ground state properties on the example of $Cs_2Ag_xNa_{1-x}Bi_yIn_{1-y}Cl_6$

Marina S. Günthert[1,3], Larry Lüer[1,2], Oleksandr Stroyuk[2], Oleksandra Raievska[2], Bernd Meyer[3], Christoph J. Brabec[1,2]

[1]Friedrich-Alexander-Universität Erlangen-Nürnberg, Materials for Electronics and Energy Technology (i-MEET), Martensstraße 7, 91058 Erlangen, Germany

[2]Forschungszentrum Jülich GmbH, Helmholtz-Institut Erlangen Nürnberg für Erneuerbare Energien (HI ERN), 91058 Erlangen, Germany

[3]Interdisciplinary Center for Molecular Materials (ICMM) and Computer Chemistry Center (CCC), Friedrich-Alexander-Universität Erlangen-Nürnberg, Nägelsbachstraße 25, Erlangen 91052, Germany

Lead-free halide double perovskites (LFHDP) have been an emerging material class for various applications in the field of optoelectronics over the last couple of years due to their environmental friendliness and exceptional stability.[1-2] The material class can be enlarged even further by substituting the Pb^{2+} ion not only with one M^{1+} and one M^{3+} ion but with two of each.[3-4] This adaption increases the number of possible materials immensely and gives rise to the demand for a different approach in material investigation: high-throughput (HTP) screening. HTP screening aims to analyze a vast material range in a reasonable time by applying automation techniques and the restriction to swift measurement methods. Overcoming this issue can be done by applying not only HTP experimental methods but also HTP computational methods. Density functional theory (DFT) is able to examine a perfectly controlled range of material compositions for complementary features. The combination of these strategies is a promising approach towards a HTP screening in novel materials discovery and is shown to be applicable on the example of $Cs_2Ag_xNa_{(1-x)}Bi_yIn_{(1-y)}Cl_6$. DFT has access to features like e. g. the lattice parameter, elastic properties and electronic properties whereas experimental methods investigate e. g. optical and vibrational material properties. Using the variety of ion combinations in this LFHDP structure with interchangeable ion ratios opens up a whole new field of materials which can be evaluated by the methods developed on the example of $Cs_2Ag_xNa_{(1-x)}Bi_yIn_{(1-y)}Cl_6$ and therefor to build up a database. Using machine learning algorithms on this database can lead to a deeper understanding of the coupling between the ion exchange and macroscopic material properties. This has be done by a minimum redundancy maximum relevance algorithm embedded in a Gaussian Process Regression to predict the photoluminescence characteristics of $Cs_2Ag_xNa_{(1-x)}Bi_yIn_{(1-y)}Cl_6$.[5]

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Insight into the active site conformation of DNA repair enzyme MBD4 from molecular simulations

Jorge Antonio Amador-Balderas[1], Frank Beierlein[1,2], Petra Imhof[1]

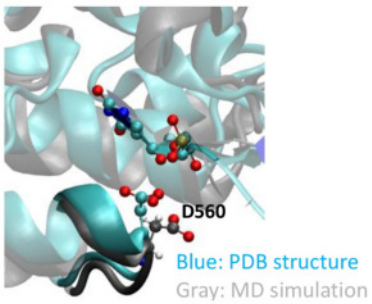
[1]*Department for Chemistry and Pharmacy Computer Chemistry Centre, Friedrich-Alexander University (FAU) Erlangen Nürnberg, Nägelsbachstraße 25, 91052 Erlangen, Germany*

[2]*Erlangen National High Performance Computing Center (NHR@FAU), Friedrich-Alexander University (FAU) Erlangen Nürnberg, Martensstraße 1, 91058 Erlangen, Germany*

Methyl-CpG Binding Domain 4 (MBD4) is an enzyme that belongs to a family of epigenetic regulator proteins (the MBD family), which all possess a domain that specifically binds to methyl-cytosine. However, only MBD4 has a C-terminus domain that has a glycosylase function, hence giving it the ability to participate in DNA repair [1].

It has been demonstrated that D560 is a key residue for MBD4's activity, and it has been suggested that it plays a role in nucleophile positioning. Interestingly, the D560N mutation is completely inactive, even though it could fulfill said role without any issue, indicating that D560 might have additional interactions that impact the activity of the glycosylase [2].

Through atomistic MD simulations, we observed that D560 deviates from the conformation that is shown in the crystal structure. This behavior was observed for different nucleotides, including Thymine, Uracyl (both are known susbtrates of MBD4) and Pseudo-Uridine (not a substrate, but was used to replicate the crystal structure) inside the active site. However, by changing the protonation state of D560, or by making the D560N mutation, said residue now displays the exact same conformation as in the crystal structure. This leads us to believe that the free protein displays more flexibility in the region where D560 is located than what is shown in the crystal structure. Our data suggest that D560 in the crystal is more likely neutral than in the originally proposed charged form.



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Modeling fracture formation and propagation in cured epoxy resins under mechanical stress

Barışcan Arıcan[1], Christian Wick[1], and Ana-Sunčana Smith[1,2]

[1]PULS Group, Institute for Theoretical Physics, IZNF, FAU Erlangen-Nürnberg, 91058 Erlangen — [2]Group of Computational Life Sciences, Division of Physical Chemistry, Ruder Bošković Institute, 10000 Zagreb, Croatia

Epoxy resins, integral in manufacturing, play a crucial role due to their versatility. Understanding fracture mechanisms in these materials is paramount for determining mechanical properties. This study focuses on developing a multiscale simulation framework, integrating molecular dynamics (MD) with quantum mechanics/molecular mechanics (QM/MM), to consecutively assess and break bonds, simulating fracture propagation. MD simulations of straining crosslinked epoxy resin extend until the potential occurrence of fracture-inducing bond breakage, determined by bond elongation and referred to as the classical threshold. Subsequently, QM/MM calculations are performed on a small subsystem excised from the main system, precisely identifying actual fracture events through spin contamination assessment. Reaction site topology is then updated with broken bond information to create or propagate the fracture. Classical criteria triggering QM/MM calculations are optimized, ensuring computational resources focus on relevant fracture events. This work provides valuable insights into epoxy resin fracture behavior, advancing our understanding of these materials at the molecular level.

Water Ordering at Aqueous $CaCO_3$ Interfaces and the Interfacial Entropy of Formation

E. Armstrong, S. Yeandel, C. Freeman and J. Harding

Department of Materials Science and Engineering, University of Sheffield, UK

Calcite and aragonite are two of the most common forms of crystalline calcium carbonate. Despite only a small difference in thermodynamic stability, calcite is observed precipitating far more often than aragonite [1]. Although some methods are known to induce aragonite production over calcite (inclusion of Mg2+ ions or high temperatures [2]), the control over polymorph selection in calcium carbonate is still of significant concern. In particular, the reasoning and understanding of the environmental influence on polymorph selection in these systems [3].

By calculating the interfacial free energies of a variety of calcium carbonate surfaces, we can determine the expected morphologies of the polymorphs as well as obtain a greater thermodynamic understanding of the formation of calcite and aragonite. In this work we have used a novel method [4], taking the Einstein crystal as the reference value in thermodynamic integration, to calculate the interfacial energies of calcite and aragonite surfaces with water. Previous methods have calculated interfacial energies and morphologies based on enthalpy alone, however the current technique also includes the entropic contribution.

Our results indicate that the {104} faces significantly dominate the hydrated calcite structure and have a much lower free energy than any other calcite face. For aragonite, there is far less difference in energy between the surfaces, supporting the variety of structures observed experimentally. The entropic contribution varied greatly for the aragonite surfaces, indicating its importance when calculating free energies and its potential part in the polymorph selection of calcium carbonate.

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In Silico Study of Binding of Camptothecin-Based Pro-Drugs to Human Carboxylesterase 2

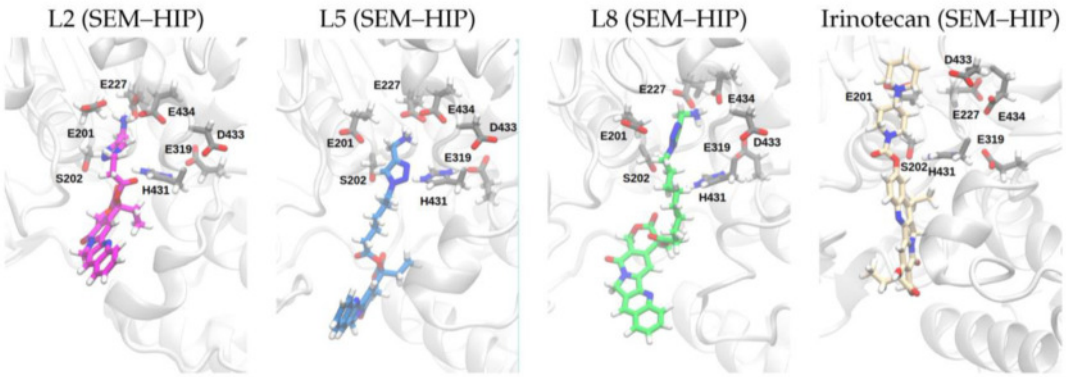
Frank Beierlein,[1,2] Anselm H. C. Horn,[2,3] Heinrich Sticht,[3] Andriy Mokhir,[4] Petra Imhof[1]

[1]*Department of Chemistry and Pharmacy, Computer Chemistry Center, Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU), Nägelsbachstraße 25, 91052 Erlangen, Germany*

[2]*Erlangen National High Performance Computing Center (NHR@FAU), Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU), Martensstraße 1, 91058 Erlangen, Germany*

[3]*Institute of Biochemistry, Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU), Fahrstraße 17, 91054 Erlangen, Germany*

[4]*Department of Chemistry and Pharmacy, Institute for Organic Chemistry, Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU), Nikolaus-Fiebiger-Straße 10, 91058 Erlangen, Germany*



Pro-drugs, which ideally release their active compound only at the site of action, i.e., in a cancer cell, are a promising approach towards an increased specificity and hence reduced side effects in chemotherapy. A popular form of pro-drugs is esters, which are activated upon their hydrolysis. Since carboxylesterases that catalyse such a hydrolysis reaction are also abundant in normal tissue, it is of great interest whether a putative pro-drug is a probable substrate of such an enzyme and hence bears the danger of being activated not just in the target environment, i.e., in cancer cells.

In this work, we study the binding mode of carboxylesters of the drug molecule camptothecin, which is an inhibitor of topoisomerase I, of varying size to human carboxylesterase 2 (HCE2) by molecular docking and molecular dynamics simulations. A comparison to irinotecan, known to be a substrate of HCE2, shows that all three pro-drugs analysed in this work can bind to the HCE2 protein, but not in a pose that is well suited for subsequent hydrolysis. Our data suggest, moreover, that for the irinotecan substrate, a reactant-competent pose is stabilised once the initial proton transfer from the putative nucleophile Ser202 to the His431 of the catalytic triad has already occurred. Our simulation work also shows that it is important to go beyond the static models obtained from molecular docking and include the flexibility of enzyme–ligand complexes in solvents and at a finite temperature. Under such conditions, the pro-drugs studied in this work are unlikely to be hydrolysed by the HCE2 enzyme, indicating a low risk of undesired drug release in normal tissue.

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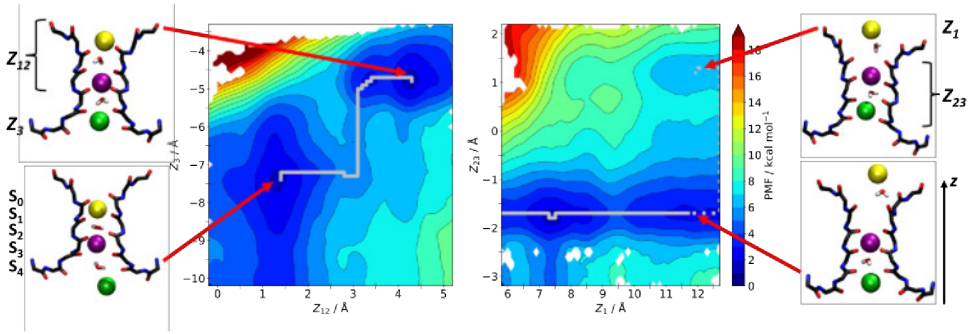
Free energy surfaces of the ion conduction through the small viral potassium channel Kcv_{PBCV-1}

Jan Borchert,[1] Lars Schumann,[1] Gerhard Thiel,[2] Stefan M. Kast[1]

[1]*Fakultät für Chemie und Chemische Biologie, Technische Universität Dortmund, 44227 Dortmund, Germany*

[2]*Fachbereich Biologie, Technische Universität Darmstadt, 64287 Darmstadt, Germany*

Potassium channels are transmembrane proteins that facilitate the selective transport of K^+ through the cell membrane. Therefore, they play a crucial role in numerous physiological processes and can be found in almost all organisms. Although a large number of studies of the conduction mechanisms through the selectivity filter have been carried out, it has not yet been possible to identify the dominating scheme, let alone the potential transferability of mechanistic features from one K^+ channel to another. Here we focus on the small tetrameric viral potassium channel Kcv_{PBCV-1} as a minimal model system. The tetrameric channel is composed of only 94 amino acids per monomer. [1,2] Despite its small size, the channel shares the same core pore module conserved in all K^+ channels.



Molecular dynamics (MD) simulations are a commonly used method for investigating ion channels in solution and embedded within a membrane environment. To facilitate sampling in high-barrier regions like the selectivity filter and hence enable the calculation of a free energy surface, enhanced sampling methods such as umbrella sampling (US) are applied. [3] Suitable structures for the US are obtained from an MD simulation at +425 mV, starting with a homology model based on the NaK2K ion channel. [4] Snapshots were chosen to ensure that the selectivity filter is occupied by three potassium ions with a water molecule between each ion. For the definition of collective coordinates governing transport, we refer to previous publications on KcsA. [5,6] Analogously, we split the conduction pathway into two 2D topographic maps where two ions are represented by their centre of gravity. Unbiasing of the data and calculation of the potential of mean force (PMF) were done by using the multistate Bennett acceptance ratio (MBAR). [7] The results obtained reveal the relevance of concerted ion motion along the transition pathway formed by selectivity filter binding sites, in agreement with findings obtained for KcsA. This therefore demonstrates that the specific transport mechanism investigated here is a common feature of K^+ channels with similar filter structure, despite otherwise strong structural differences.

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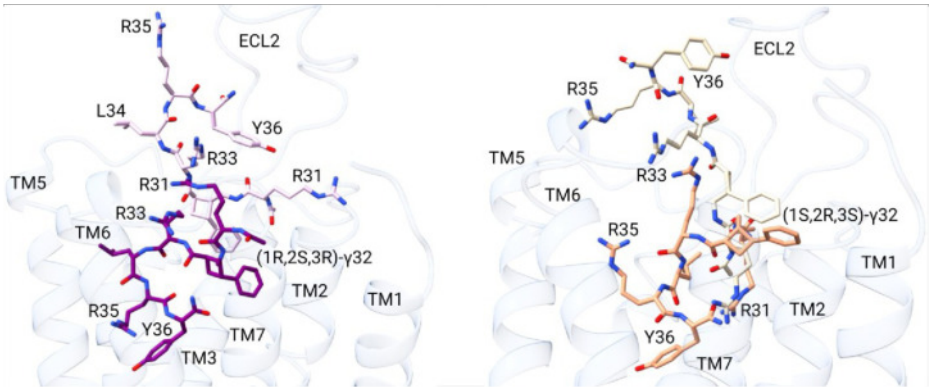
Understanding α,γ-peptide efficacy and binding selectivity in the neuropeptide Y Y_4-receptor

Jacqueline C. Calderón,[1] Eva Plut,[2] Max Keller,[3] Chiara Cabrele,[2] Oliver Reiser,[2] Francesco L. Gervasio[4], Timothy Clark[1]

[1]Computer-Chemistry-Center, Department of Chemistry and Pharmacy, Friedrich-Alexander-University Erlangen-Nürnberg, Nägelsbachstraße 25, 91052 Erlangen, Germany, [2]Institute of Organic Chemistry, Faculty of Chemistry and Pharmacy, University of Regensburg, 93040 Regensburg, Germany, [3]Institute of Pharmacy, Faculty of Chemistry and Pharmacy, University of Regensburg, D-93040 Regensburg, Germany, [4]Institute of Pharmaceutical Sciences of Western Switzerland, CH1206 Geneva, Switzerland.



The neuropeptide Y (NPY) receptor family comprises four physiologically relevant class A GPCRs, Y_1R, Y_2R, Y_4R, and Y_5R. The endogenous ligands of NPY receptors are the homologous 36-residue linear peptides NPY, peptide YY (PYY), and pancreatic polypeptide (PP). Because of its role in appetite suppression, the Y_4-receptor is an attractive therapeutic target against obesity. Unlike small molecules, peptides exhibit high conformational flexibility in their unbound states due to the large number of rotatable bonds along the backbone and in the side chains. In contrast, the receptor binding pocket imposes a stringent constraint on the conformation of these peptides. To date, few studies that allow us to gain insight into the molecular basis of ligand recognition on Y_4R-peptide systems have been reported. Computational methods are essential tools for investigating protein-ligand interactions and subsequent characterization of binding pockets. Providing details at an atomistic level of the main features related to the binding process will facilitate the rational development of Y_4R-selective ligands. We have studied two C-terminally amidated α,γ-hexapeptides (RSR/SRS) with sequence *Ac*-R31-γ-CBAA32-R33-L34-R35-Y36-NH_2, where γ-CBAA is the (1*R*,2*S*,3*R*)-configured 2-(aminomethyl)-3-phenylcyclobutanecarboxyl moiety (RSR) or its mirror image (SRS). Both peptides bind to Y_4R (K_i of RSR/SRS: 0.66/12 nM) and act as partial agonists (intrinsic activity of RSR/SRS: 50/39%). [1] To investigate the binding mode of the α,γ-hexapeptides, induced-fit docking, molecular dynamics and metadynamics simulations were performed. We found that the di-arginine motif R33-X-R35 of the peptide plays a prominent role in the interaction of the ligands with the Y_4R. A more stable network of H-bond and salt-bridge interactions between peptide RSR and Y_4R is suggested to be responsible for its observed higher binding affinity and potency, in comparison to peptide SRS. In addition, we applied a metadynamics-based protocol [2] to characterize the peptides' binding free-energy profiles. Comparison of the binding poses for global (orthosteric) and secondary (vestibule) minima indicates a significant role of the extracellular vestibule in driving the binding process. In the global minimum, peptide ligands show a binding pose in excellent agreement with that of the equilibrated starting structure. Most importantly, in agreement with previous studies, [3,4] the secondary minimum (vestibule binding pose) found for the α,γ-peptide SRS is proposed to play a role in its suggested antagonistic-like effect.

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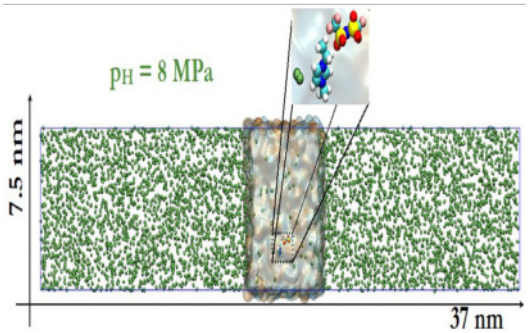
Investigation of the impact of dissolved H_2 on the surface properties of ionic liquids

Arsha Cherian, György Hantal, Christian Wick, and Ana-Suncana Smith

PULS Group, Institute for Theoretical Physics, IZNF,
FAU Erlangen- Nürnberg, 91058 Erlangen, Germany
Group for Computational Life Sciences,
Ruder Bošković Institute, Bijenička 54, HR-10000 Zagreb

SILP (Supported Ionic Liquid Phase) catalysis technology focuses on obtaining a heterogenised type of homogeneous catalytic systems where a thin film of ionic liquid (IL) containing a homogeneous catalyst is immobilised on the surface of a porous support material, which is commonly employed in hydrogen-involved catalysis systems. The dissolution of small, non-polar molecules of hydrogen in the ionic liquid film resulting in highly asymmetrical system in terms of molecular structures, is expected to have an influence in the thermophysical properties of IL which can subsequently affect the reaction kinetics and ultimately impact the overall reaction rate. In order to understand this influence of dissolved hydrogen on the surface properties of ILs, molecular dynamics (MD) simulations were conducted using GROMACS software in binary mixtures consisting of an ionic liquid (IL) with pressurized molecular hydrogen (H_2),between 298 and 393K over a broad pressure ranging from 1 to 30 MPa. We find that the addition of H_2 results in a decrease in the surface tension of both binary mixtures up to about 6 percent at higher pressures, which is more pronounced at lower temperatures. Furthermore, an enrichment of hydrogen is observed at the liquid-gas interface of these binary mixtures.



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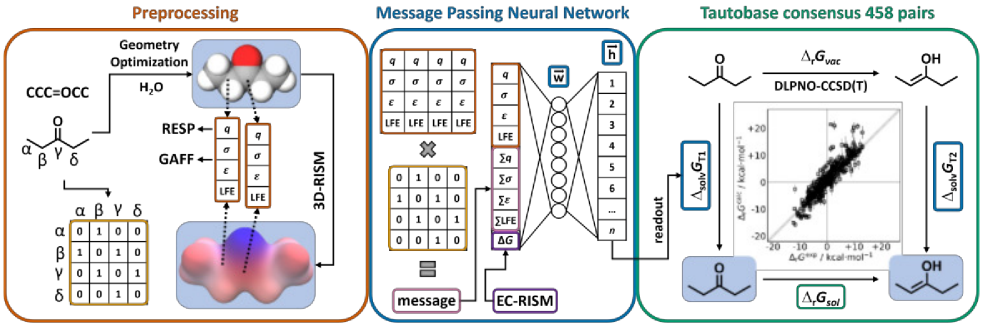
EC-RISM/MPNN-based hydration free energy models with application to tautomer equilibria

Christian Chodun, Yannic Alber, Michael Strobl, Nicolas Tielker, Lukas Eberlein, Florian Mrugalla, Julia Jasper, Jan Sleegers, Stefan M. Kast

Fakultät für Chemie und Chemische Biologie, Technische Universität Dortmund, 44227 Dortmund, Germany

The accurate prediction of hydration free energies (HFEs) is an important task in different areas, as the thermodynamic cost of solvation is one of the key factors in processes from protein-ligand binding to chemical reactions. Hence, much effort has been spent in predicting the HFE from electronic structure calculations and molecular dynamics simulations as well as, in recent years, machine learning (ML) methods, [1] for which large and reliable datasets are needed.



Training data dependence can be reduced using physics-informed ML, where measured or calculated properties representing the underlying physics of the molecules and their interactions are used as additional input features. [2] Here we present a physics-informed ML method that combines the Embedded Cluster Reference Interaction Site Model (EC-RISM) [3] with a Message Passing Neural Network (MPNN). [4] The solute is represented by a graph, where atoms are described by partial charges and Lennard-Jones parameters together with "local" atomic free energies (LFEs) [5,6] adding up to the total HFE. Augmenting with EC-RISM HFEs, we show state-of-the-art accuracy on independent HFE datasets, including SAMPL challenge data. [7,8]

This model is then used to predict the HFEs of tautomers which are combined with DLPNO-CCSD(T) [9] gas phase data to calculate aqueous tautomerization free energies. Applied to a literature consensus set of more than 450 pairs based on the Tautobase, [10] overall better agreement with experiment than other reported methods is obtained. By filtering according to an upper prediction error criterion, an ordered set with decreasing prediction accuracy is produced, allowing for the identification of suspicious database entries where measurement or annotation errors are likely.

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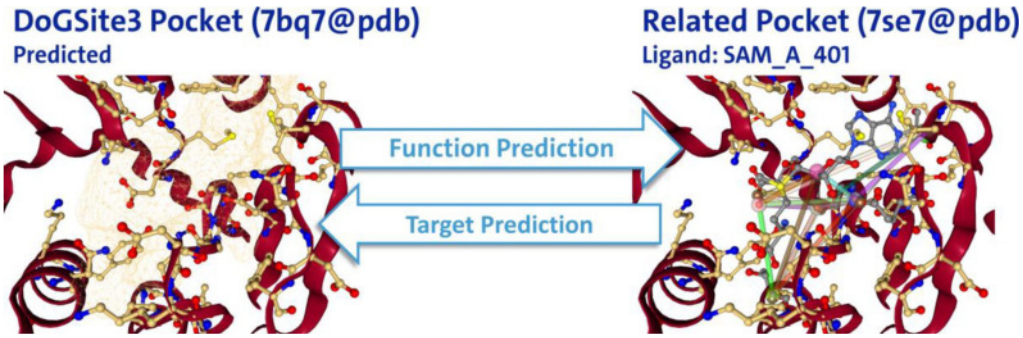
Binding Site Prediction and Characterization with DoGSite3 – Method and Applications

Christiane Ehrt, Joel Graef, Konrad Diedrich, Matthias Rarey

Universität Hamburg, ZBH - Center for Bioinformatics, Hamburg, Germany

The prediction and characterization of protein binding sites is a non-trivial endeavor. [1] However, it is a crucial methodology given the increasing numbers of predicted and experimentally determined protein structure models [2] and their impact on structure-based design applications such as function or off-target prediction. Given a structure of interest, the DoGSite algorithm predicts binding sites for yet uncharacterized proteins, enabling protein function prediction and binding site druggability estimation. [3,4]

Based on the first implementation of the grid-based DoGSite methodology, we developed DoGSite3. [5] The new implementation is characterized by more robust binding site boundaries, improved prediction accuracy, and a considerably lower run time. Its integration on the Proteins*Plus* web server (https://proteins.plus) enables easy access to predicted protein pockets and their descriptors, even for non-experienced users.



In this contribution, we will outline the basic methodology and optimization of the DoGSite3 algorithm, focusing on binding site characterization and prediction accuracy. Based on selected application examples, we will demonstrate the broad applicability of DoGSite3 in various structure-based design approaches, such as pocket annotation and function prediction by known protein-ligand complexes and the elucidation of potential off-targets for known drugs.

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Identification and structural characterization of peptidic ligands for novel antiviral strategies against SARS-CoV-2

Olena Denysenko[1], Anselm H.C. Horn[1,2], Nina Raasch[3], Lucas Weißenborn[3], Jutta Eichler[3], Heinrich Sticht[1,2]

[1]*Bioinformatics, Institute of Biochemistry, Friedrich-Alexander-Universität Erlangen-Nürnberg*
[2]*Erlangen National High Performance Computing Center (NHR@FAU), Friedrich-Alexander-Universität Erlangen-Nürnberg*
[3]*Department of Chemistry and Pharmacy, Friedrich-Alexander-Universität Erlangen-Nürnberg*

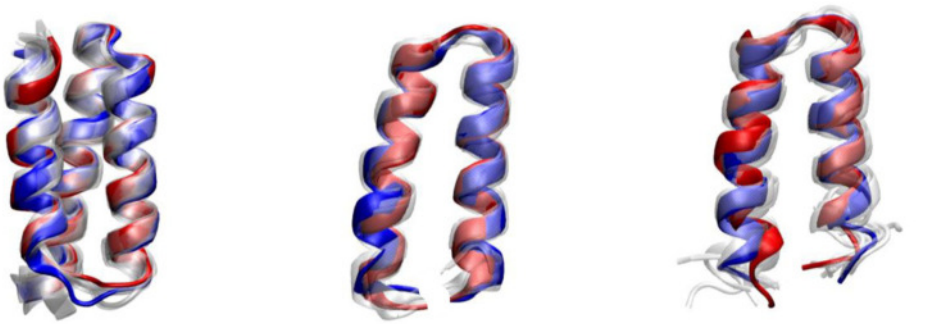
The COVID-19 pandemic, caused by the emergence of SARS-CoV-2, has not only engendered unprecedented global health challenges but has also underscored the urgent necessity for innovative antiviral therapeutic agents [1]. Antiviral peptides are fast-growing class of new drugs and are promising candidates for drug design.

Our study attempts to use the principles of structure-based computational drug design to engineer and refine antiviral peptides with a specific focus on targeting the Spike protein of SARS-CoV-2. The Spike protein plays a key role in viral entry and fusion and presents an enticing target for therapeutic intervention due to its pivotal role in facilitating viral infectivity [2].
To this end, we apply a multifaceted approach for peptide design that relies on the miniaturization of antibodies or other Spike-binding proteins (e.g. LCB1) [3].

By using computational techniques, particularly molecular dynamics (MD) simulations, we do not only characterize the bound state of these peptides, but also their conformational stability prior to binding.

The dynamics of peptides in their free states has a significant impact their subsequent interactions with target structures because the formation of stable binding-incompetent conformations may hamper the interaction with target proteins.

Preliminary findings from our MD investigations show a relationship between conformational stability of the free peptides and their ability to bind their target structures. This finding underscores that a comprehensive characterization of designed peptide ligands should also include an investigation of the unbound state.



LCB1 **S-S bond (LW25.13)** **Open form (LW25.1)**

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Molecular simulation of separation of C60 and coronene in silica nanopores

Rustam Durdyyev [1] , György Hantal[1], Ana-Sunčana Smith[1]
1. PULS Group, Friedrich-Alexander-Universität Erlangen-Nürnberg, Institute for Theoretical Physics, Interdisciplinary Center for Nanostructured Films (IZNF), Cauerstrasse 3, 91058 Erlangen, Germany

Abstract

Classical liquid chromatography is one of the most used techniques in the field of nanoparticle separation. This is achieved by driving the nanoparticle containing liquid through a column densely packed with meso and nonoporous particles. Separation efficiency can be improved through optimizing the interactions between the particles, the solvent and the pore surface using directed surface modifications or adjusting the solvent composition. Finding the best combination of solvents and functionalized surfaces is a complex optimization problem, which is often aided with molecular dynamics (MD) simulations. In this study, the diffusive transport of model nanoparticles, C60 fullerene and coronene was studied in nanoconfinement using molecular modelling. The MD simulations were carried out in a slit nanopore of fixed width made of crystalline, fully hydroxylated silica. As solvents, n-hexane and toluene mixtures of different compositions were used. Nanoparticle diffusivities computed both in the bulk and at the surface were used in our 2-state diffusion model to determine the solvent-dependent effective diffusivities of nanoparticles[1]. Our results help to rationalize the observed experimental retention time trends measured for C60 and coronene.

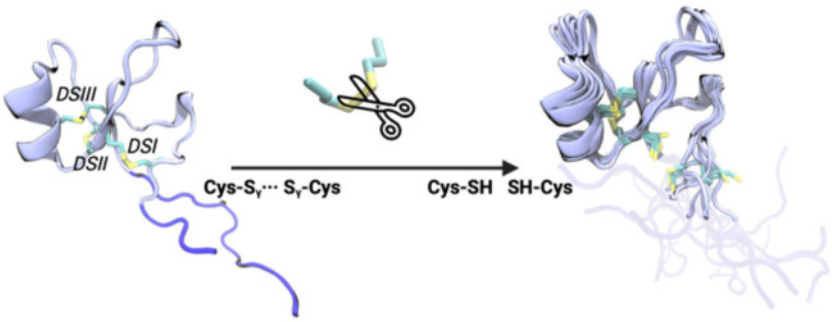
1.Andreas Baer, Paolo Malgaretti, Malte Kaspereit, Jens Harting, Ana-Sunčana Smith, Modelling diffusive transport of particles interacting with slit nanopore walls: The case of fullerenes in toluene filled alumina pores, vol 368, 2022, 0167-7322

The Role of Disulfide Bonds in Structural Stability and Dynamics of Human TFF1

Dilsah Nur Elmaci[a], Matthias Stein[a]

[a]*Max Planck Institute for Dynamics of Complex Technical Systems, Magdeburg, Germany.*

Mucosal epithelial cells secrete a variety of disulfide-rich small proteins, such as trefoil factors (TFFs), for the protection of the epithelial barrier and the maintenance of mucosal viscoelasticity. Human TFF1 is a small polypeptide consisting of sixty amino acids, primarily expressed in gastric surface mucous cells. TFF1 contains a highly conserved three-looped TFF domain stabilized by three intramolecular disulfide bonds between residues Cys7-Cys33, Cys17-Cys32, and Cys27-Cys44.[1] The distinctive spatial conformation of the TFF domain is associated with the adaptation of TFF proteins to a highly acidic environment and their resistance to thermal and proteolytic degradations.[2] However, the structural stability of TFF1 towards reduction and their relevance to its biological functions remained elusive. With this motivation, we performed microsecond-long atomistic molecular dynamics simulations to elucidate the role of the three disulfide bonds on the structural integrity and dynamics of the TFF domain. In human TFF1 these disulfide bonds were sequentially removed in all possible combinations (i.e. fully oxidized, mono-, di-, and fully reduced states). Our results show that, even though the removal of disulfide bonds induces some local alterations in the structure, the overall structural integrity and compactness of the domain remain almost unaffected. In particular, the inter-residue distance between Cys17 and Cys32 is preserved even when the disulfide bond is removed. This remarkable integrity of the TFF domain structure is attributed to the preservation of an extensive non-bonded interaction network within the domain. Despite the reduction of the disulfide bonds, the corresponding Cys residues are involved in additional interactions with nearby residues, further contributing to the domain stability.



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Computational studies of substrate binding modes of PET44

Alena Endres[1], Holger Gohlke[1,2]

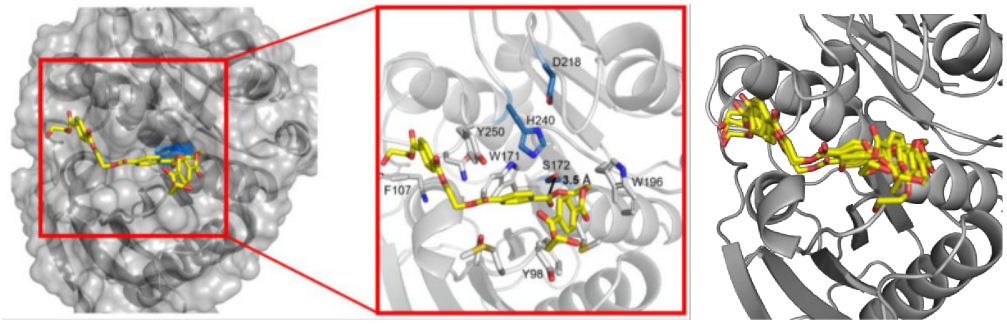
[1]*Institute for Pharmaceutical and Medicinal Chemistry, Heinrich-Heine-Universität Düsseldorf, 40225 Düsseldorf, Germany*

[2]*Institute of Bio- and Geosciences (IBG-4: Bioinformatics), Forschungszentrum Jülich, 52425 Jülich, Germany*

Each year around 400 million tons of plastic waste is produced, increasing yearly[1]. Degradation of these synthetic polymers can take up to 1000 years, and less than 10% of the plastic waste is recycled[2-3]. None of the current recycling methods is feasible for industrial applications[3], they are either leading to poor-quality plastic, air pollution, are energetically inefficient, or need to use harsh chemicals leading to toxic waste[2]. Polyethylene terephthalate (PET) is, with a production of around 33 million tons yearly, within the top five most produced synthetic polymers[1]. Because of its ester bonds, it can be biocatalytically degraded representing an environmentally friendly solution. However, currently known enzymes capable of cleaving PET (PETases) show low enzymatic activity, especially towards PET with high crystallinity as is the case in PET bottles, making those enzymes not available to use with postconsumer plastics[2-3]. Extending previous work on esterases[4] and petases[5], we here investigate the novel PETase PET44.

PET44 is a PETase identified, characterized, and crystallized by our collaborators. The PETase shows the typical fold of an α-/β-hydrolase with a catalytic groove containing the catalytic triad consisting of Ser-His-Asp. Computational studies were carried out investigating the possible binding modes of a PET-trimer, a PET-dimer and two dodecalactones via molecular docking consistent with the proposed catalytic mechanism as well as their robustness through molecular dynamics simulations as done in previous studies[5].

We show that all model substrates bind in the catalytic groove, mostly interacting with hydrophobic amino acids. The binding mode for the PET trimer, shown in the figure, places a central subunit located near the active site, leaving part of the last PET subunit to protrude outside the catalytic groove, near a tryptophane residue, which limits the accessible surface of the catalytic groove to one side. The central subunit close to the catalytic triad of the PET trimer shows low variability during the simulations indicating strong interactions, whereas the ends, especially the one protruding outside, show different confirmations due to the lack of interactions with the enzyme. This knowledge can help, combined with experimental validations, to redesign the catalytic groove of PETases to enhance their activity and therefore make them viable for industrial applications.



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Towards a judicious choice of degrees of freedom to sample reaction paths of enzymatic reactions

Epee Ndongue Jules César, Petra Imhof

[1]*Computer-Chemistry-Center, Department of Chemistry and Pharmacy, Friedrich-Alexander-Universität Erlangen-Nürnberg, Nägelsbachstr. 25, 91052 Erlangen, Germany*

Modeling enzymatic reaction pathways is a challenging and also computationally demanding task. The numerous degrees of freedom in an enzymatic system, out of which many can be relevant for the reaction and its energetic profile, at least indirectly, render the notion of "the reaction mechanism", read a single reaction pathway, naïve. One promising approach to tackle this issue is by using the transition network. Our system of interest, Carboxypeptidase A (CPA), which contains a divalent zinc ion in its active site, is an important exopeptidase secreted by the pancreas for digesting intake proteins in the metabolism cycle. It catalyzes the elimination of the C-terminal amino acid via hydrolysis, with a preference for residues with hydrophobic side chains.

Our goal: Develop a method to automatically sample the reaction pathways and find the most probable route by an automated choice of degrees of freedom for the sampling.

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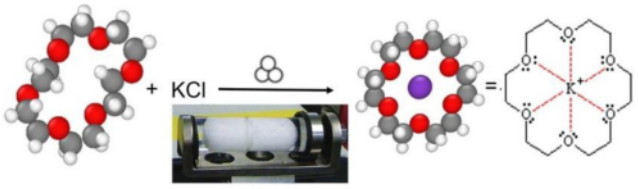
Molecular Modelling of a Mechanochemical reaction: The Case of 18-Crown-6 Ether and KCl

Rupam Gayen [a], Leonarda Vugrin,[b] Ivan Halasz,[b] Ana Sunčana Smith [a]

[a] PULS group, Department of physics, Friedrich Alexander Universität Erlangen-Nürnberg, 91058 Erlangen, Germany

[b] Division of Physical chemistry, Ruder Bošković Institute, Bijenička 54, HR-10000 Zagreb

Mechanochemistry is the area of chemistry that deals with transformations induced and/or aided by mechanical force [1]. The most common method employed in modern mechanochemistry is through ball milling (BM) but the inherent nature of it makes it difficult to experimentally investigate individual impacts due to moving parts and provide a molecular-level insight [2]. Therefore, molecular dynamics (MD) simulations come into play to provide a better picture.



Using Gromacs 2021.5 package, MD simulations were performed to understand milling mechanisms, analyse the deformations on crystal and evolution of a ball milling reaction. Two neutral, non-reactive and rigidly constrained balls were incorporated into our simulating model to induce mechanical force via inelastic collisions The solid-state mechanochemical complexation reaction between 18c6 and potassium chloride (KCl) was used as a model for our simulations. This integrated approach, wherein MD simulations helps in visualizing, validating experimental results and providing molecular level insight, contributes to a more holistic understanding of mechanochemical reactions.

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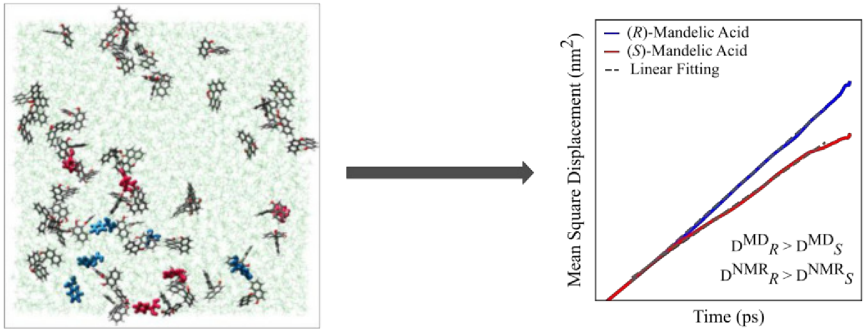
Chiral Interactions at the Molecular Level: Insights from NMR and Computational Studies

Tadeu Luiz Gomes Cabral[a,b], Claudio F Tormena[a], Matthias Stein[b]

[a]*Institute of Chemistry, Physical Organic Chemistry Lab, University of Campinas - UNICAMP, Campinas - São Paulo, Brazil*

[b]*Max Planck Institute for Dynamics of Complex Technical Systems, Molecular Simulation and Design Group, Magdeburg, Germany.*

The separation and identification of enantiomers is critical for the pharmaceutical, agricultural, and food industries. The matrix-assisted diffusion-ordered spectroscopy (DOSY) approach is emerging to evaluate chiral molecules employing a chiral matrix to separate enantiomeric mixtures via Nuclear Magnetic Resonance (NMR) spectroscopy. However, this method needs detailed insight into the chiral recognition modes and the complexation process at the molecular level.[1] Here, we integrate computational methods with experimental investigations to explain the differences in complexation between mandelic acid enantiomers and (*R*)-BINOL as a chiral matrix. ^{1}H and diffusion NMR measurements in $CDCl_3$ were carried out using the *Oneshot* pulse sequence.[2] at 25 °C on a 600 MHz spectrometer. DFT and molecular dynamics (MD) studies were performed to support experimental findings.[3] The experimental results reveal that the mandelic acid enantiomer exhibiting the highest shielding effect in the NMR spectrum shares the same chirality as the employed BINOL. On the other hand, it was observed that the enantiomer interacting more strongly (with a lower diffusion coefficient) has the opposite stereochemistry to the BINOL. DFT studies at the *M06-2x*/*cc-pVTZ* level confirm the preferred formation of enantioselective binding and emphasize the role of intermolecular hydrogen bonding to explain the observed shielding effect in the NMR spectrum. The MD simulations are able to give dynamic properties such as diffusion coefficients in good agreement with the experimental data. Additionally, the classical simulations offer valuable insights into the complexation process between (*R*)- and (*S*)-mandelic acid and BINOL over time, enhancing our understanding of experimental observations. This integrated approach illustrates the feasibility of enantiodiscrimination through NMR and underscores the indispensable role of theoretical studies in unveiling molecular recognition processes.



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Exploring the Multi-Stage Catalytic Cycle of Cezanne-1 through MD Simulations

Metehan Ilter[1], Eric Schulze-Niemand[1], Matthias Stein[1]

[1]Max Planck Institute for Dynamics of Complex Technical Systems, Molecular Simulations and Design Group, Magdeburg, Germany

Deubiquitylating enzymes (DUBs) catalyze the removal of ubiquitin (Ub) moieties attached to proteins by cleaving the iso-peptide bond between distal and proximal Ubs. Thus, DUBs play a pivotal role in the regulation of various cellular processes. The DUB Cezanne-1 selectively cleaves K11-linked polyUb chains. Although crystal structures of Cezanne-1 are available at different enzymatic stages, they do not reveal dynamic conformational changes. Crystal structures of diUb- and monoUb Cezanne-1 were resolved using activity-based probes that covalently attach to the catalytic cysteine residue, thus potentially altering the active site and substrate recognition [1].

Here, we employed full-atomistic molecular dynamics simulations to explore conformational changes during Cezanne-1 activation and its proteolytic activity by reconstituting the native substrate. [2] Our MD simulations reveal that the Ub-free Cezanne-1 shuttles between catalytically active and inactive states. Only the catalytically active, substrate-free Cezanne-1 allows the substrate access to the catalytic center. This, in turn, favors the catalytical activation of Cezanne-1 in a substrate-assisted activation process. Upon cleavage of the diUb's iso-peptide bond, the proximal Ub is prone to dissociate first from Cezanne-1, which leads to the catalytically inactive monoUb-bound state. This is followed by the release of the C-terminus of the distal Ub from the catalytic center and recovery of the Ub-free state.

To sum up, the activation and catalytic turnover of the DUB Cezanne-1 is a complex multi-stage cycle with various dynamic transitions that are unable to be deciphered based on static and non-native protein crystal structures.

[1] T. Mevissen, Y. Kulathu, M. et al., *Nature*, **2016**, 538(7625), 402–405
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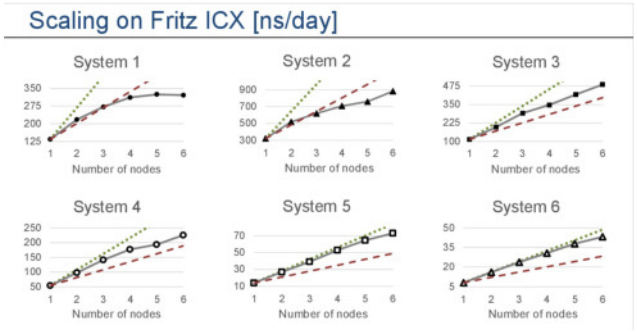
Improving MD performance on HPC clusters through in-depth hardware knowledge and advanced program usage

Anna Kahler, Thomas Zeiser, Gerhard Wellein
NHR@FAU, Friedrich-Alexander-Universität Erlangen-Nürnberg

Most modern MD simulation programs run out of the box on HPC clusters and yield reasonable performance results. To shed some light on the backgrounds of optimized performance, we present three case studies from user support.



First, an REMD simulation with GROMACS reached 124 ns/day for 26 replicas on 12 dual-socket Intel Ice Lake. We were able to port this simulation to eight NVIDIA A40 GPUs while retaining a performance of 120.6 ns/day, yielding a reduction in hardware costs by 2/3. Since the number of replicas is not a multiple of eight, porting required assignment of PP- and PME-tasks to the GPUs by hand.

The second case is about calling the GROMACS runtime correctly to obtain a performance gain, especially when dealing with a large simulation system of 2,600,000 atoms and a multiple GPU-setup. Starting from a performance of 11.8 ns/day on eight NVIDIA A40 GPUs, we nearly quadrupled performance to 20 ns/day on four A40 GPUs. Thus, about twice the performance on half of the resources by setting environment variables for improved GPU communication and adjusting runtime parameters.

Our third proof of in-depth hardware knowledge is represented by our third case where ORCA underperformed on our high throughput cluster: A single numerical calculation of molecular frequencies took 76.4 hours to finish. Multiple setups on various CPU architectures followed by detailed examinations sped up this simulation to 11 hours on the same node; the statically linked OpenBLAS library falsely detected the underlying hardware.

Boost your Atomistic Simulations via NHR@FAU

Harald Lanig, Anselm H. C. Horn

Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU)
Erlangen National High Performance Computing Center (NHR@FAU)
Martensstraße 1, 91058 Erlangen, Germany

The Erlangen National High-Performance Computing Center (NHR@FAU) at FAU Erlangen-Nürnberg [1] was recently established as a national center for HPC at German universities. Together with eight other institutions, it forms the NHR-Alliance [2]. NHR@FAU operates large-scale HPC systems and provides HPC services, related user support, and HPC training to German universities.

A strong focus of NHR@FAU lies on on atomistic simulations and it also provides tailored hardware solutions in this area. As a key component of the NHR program, it offers exceptional competence and conducts extensive research in the field of atomistic simulations of molecular structures, with broad applications in chemistry, life sciences, materials science, and physics. With the Atomic Structure Simulation Lab, NHR@FAU has established a Germany-wide unique interdisciplinary competence center, which helps users to select and use atomistic simulation methods in an HPC environment and actively accompanies and coordinates the development of high-performance simulation codes [3]. An interdisciplinary approach promises not only synergy effects, e.g., through the exchange and joint development of simulation and evaluation tools, but in particular a cross-fertilization of materials and life sciences, which often use the same or similar simulation techniques.

The HPC research activities at NHR@FAU focus on performance engineering and modelling, performance tools, and research software engineering. NHR@FAU investigates and further develops hardware-efficient building blocks, programming concepts, and numerical algorithms for scalable, efficient, and robust iterative sparse matrix applications and stencil-based solvers on large-scale HPC systems [4].

A further core project is the education and lifelong training of scientists and engineers. The close cooperation among theory, simulation, and experiment, which has a long tradition in Erlangen, ensures that the training is not aimed specifically at modelers but also made available to experimental colleagues. This is of particular importance in the light of increasing digitalization in science. The Atomic Structure Simulation Lab makes an essential contribution to the key technologies of scientific computing and scientific software development through the sustained concentration of methodological competence in both the application and development of computer codes and their hardware-related optimization.

[1] https://hpc.fau.de
[2] https://www.nhr-verein.de/en
[3] https://www.atomistic-simlab.hpc.fau.de
[4] https://www.perf-lab.hpc.fau.de

The accuracy limit of aqueous chemical shift predictions

Stefan Maste,[1] Tim Pongratz,[1] Bikramjit Sharma,[2] Ignacio J. Pickering,[3] Jinze Xue,[3] Adrian E. Roitberg,[3] Dominik Marx,[2] Stefan M. Kast [1]

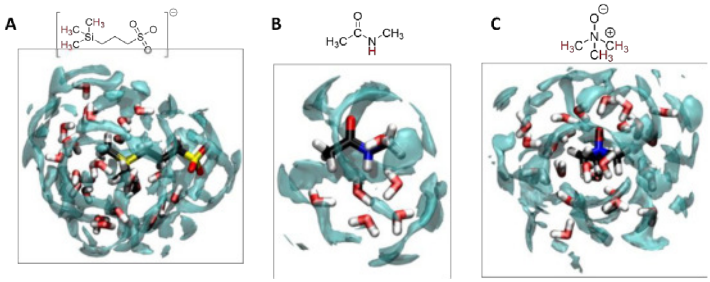
[1]*Fakultät für Chemie und Chemische Biologie, Technische Universität Dortmund, 44227 Dortmund, Germany*

[2]*Lehrstuhl für Theoretische Chemie, Ruhr-Universität Bochum, 44780 Bochum, Germany*

[3]*Department of Chemistry, University of Florida, Gainesville, FL 32611, USA*

Nuclear magnetic resonance (NMR) spectroscopy is one of the main analytical techniques to investigate chemical systems. [1] In addition to experiments, computational methods have been employed to calculate NMR parameters and gain insight into experimentally inaccessible systems. However, reaching quantitative agreement with experiments is still a challenging task due to the high structural sensitivity of NMR obsevables, especially with respect to the accurate description of the solvent influence.

Here we demonstrate that combining state-of-the-art computational methodologies, *ab initio* molecular dynamics simulations (AIMD) for generating locally solvated structural ensembles and Embedded Cluster Reference Interaction Site Model (EC-RISM) [2] calculations allows for predicting accurate NMR response parameters for species in aqueous solution [3], a protocol acievied by extending an earlier approach successfully applied to electron paramagnetic resonance (EPR) parameters. [4] Applied to the reference compound trimethylsilylpropanesulfonate (DSS) and target molecules *N*-methylacetamide (NMA) and trimethylamine *N*-oxide (TMAO), we show that a hybrid solvent system, consisting of a limited number of explicit water molecules in an EC-RISM background, achieves quantitative accuracy for chemical shifts and is considerably more efficient than previous approaches. [5]



Using the same hybrid solvent system in classical force field molecular dynamics simulations (FFMD) reveals that the approach is transferable. However, deficiencies in FFMD-generated ensembles can be traced back to the inaccurate description of hydrogen bonds as well as the distribution of intramolecular bond lengths.

As a third method to generate molecular ensembles, machine learning potentials such as ANI-2x [6] show an improvement in the intramolecular description of NMA compared to force fields. A modification of the training dataset yields an improved solvent distribution more closely resembling AIMD ensembles compared to FFMD.

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The alchemy of light: computational investigation of photoswitches and photomotors

M. Hartinger, T. E. Röhrkasten, C. Müller

FAU Erlangen-Nürnberg, Computer-Chemistry-Center, Nägelsbachstraße 25, 91052 Erlangen

Photochemistry holds great potential for sustainable chemistry. However, the lack of comprehensive design principles and detailed information on molecular excited-state structures hinders its full utilization. Quantum chemical simulations have emerged as indispensable tools for unraveling the intricate relationships between molecular structure and properties in photoexcited processes. Nevertheless, performing excited-state computations demands theoretical expertise and *a priori* knowledge of the photochemical properties of the system, such as spectroscopic data.

Addressing this challenge, our objective is to distill the rules and concepts governing photochemical reactions using quantum chemical data. To achieve this goal, we introduce the **S**urface **H**opping **N**ewly **I**nvented **T**raining **S**et for **E**xcited-state **L**earning (SHNITSEL) database [1], which contains computational data for various photoreactions. Specifically, we present excerpts from the database featuring sample molecules undergoing light-induced *cis/trans* isomerization (photoswitches) or directional rotation (photomotors).

[1] https://shnitsel.github.io

MGMS

In silico investigation of nonsynonymous single nucleotide polymorphisms in *BCL2* apoptosis regulator gene to design novel protein-based drugs against cancer

https://doi.org/10.1002/jcb.30330

Abstract:

BCL2 apoptosis regulator gene encodes Bcl-2 pro-survival protein, which plays an important role to evade apoptosis in various cancers. Moreover, single nucleotide polymorphisms (SNPs) in the *BCL2* gene can be nonsynonymous (nsSNPs), which might affect the protein stability and probably its function. Therefore, we implement cutting-edge computational techniques based on the Spherical Polar Fourier and Monte-Carlo algorithms to investigate the impact of these SNPs on the B cell lymphoma-2 (Bcl-2) stability and therapeutic potential of protein-based molecules to inhibit this protein. As a result, we identified two nsSNPs (Q118R and R129C) to be deleterious and highly conserved, having a negative effect on protein stability. Additionally, molecular docking and molecular dynamics simulations confirmed the decreased binding affinity of mutated Bcl-2 variants to bind three-helix bundle protein inhibitor as these mutations occurred in the protein−protein binding site. Overall, this computational approach investigating nsSNPs provides a useful basis for designing novel molecules to inhibit Bcl-2 pro-survival pathway in malignant cells.

KEYWORDS

Bcl-2 apoptosis regulator, cancer, molecular dynamics, nonsynonymous single nucleotide polymorphisms, posttranslational modifications, protein-based inhibitors.

Elucidating Structural Determinants of Biased Signaling at the 5-HT$_{1A}$ G Protein-Coupled Receptor through Molecular Dynamics Simulations

A. Ullrich[1,2], J. Schneider[1,2], J. M. Braz[3], **E. Neu[1,2]**, N. Staffen[1,2], M. Stanek[1,2], J. Bláhová[1,2], T. Hove[4], T. Albert[1,2], A. Allikalt[1,2], S. Löber[1,2], K. Bhardwaj[3], S. Rodriguez-Rosado[3], E. Fink[5], T. Rasmussen[4], H. Hübner[1,2], A. Inoue[6], B. K. Shoichet[5], A. J. Basbaum[3], B. Böttcher[4], D. Weikert[1,2], P. Gmeiner[1,2]

[1]Department of Chemistry and Pharmacy, Friedrich-Alexander-Universität Erlangen-Nürnberg, 91058 Erlangen, Germany [2]FAU NeW, 91058 Erlangen, Germany [3]Department of Anatomy, University of California, San Francisco, CA, USA [4]Rudolf-Virchow-Center, Julius-Maximilians-Universität, 97080 Würzburg, Germany [5]Department of Pharmaceutical Chemistry, University of California, San Francisco, CA, USA 6Graduate School of Pharmaceutical Sciences, Tohoku University, Sendai, 980-8578, Japan

G Protein-Coupled Receptors (GPCRs) represent a class of structurally conserved membrane proteins characterized by seven transmembrane helices, playing pivotal roles in diverse physiological functions. With over 800 coding genes attributed to this protein class, and nearly 30-40% of FDA-approved drugs targeting them, their significance in drug development is paramount. Notably, the myriad signaling pathways mediated by distinct G proteins and effector proteins like β-arrestin underscore the immense pharmacological potential of GPCRs.

In particular, the 5-HT$_{1A}$ receptor emerges as a compelling target for pain management. This study unveils the discovery of ST171, a novel compound exhibiting functional selectivity towards the G_i protein while displaying minimal recruitment of β-arrestin. Furthermore, whereas serotonin manifests a bell-shaped inhibition of cAMP formation—indicative of G_s protein recruitment at higher concentrations—ST171 demonstrates a sigmoidal inhibition curve, signifying exclusive G_i recruitment even at elevated concentrations. Molecular dynamics (MD) simulations elucidate that the interaction between the benzoxazinone moiety of ST171 and Tyr96$^{2.64}$ induces a notable impact on the TM2-TM3 distance, potentially accounting for ST171's preference for G_i over G_s. Additionally, the benzoxazinone moiety fosters hydrogen bond formation between Gln97$^{2.65}$ and Trp387$^{7.40}$, providing a mechanistic basis for ST171's selectivity towards G_i protein over β-arrestin.

Lastly, comparative simulations between the ternary and binary complex models reveal that the ST171-bound binary complex maintains its conformation consistently throughout the simulation, distinguishing it from other ligand-bound complexes. In summation, these findings hold promise for ushering in a new era of secure and efficacious analgesics.

Impact of Curing dynamics on the Microstructure and Properties of Epoxy Thermosets

Sampanna Pahi[1], Christian Wick[1], and Ana-Sunčana Smith[1,2]

[1]PULS Group, Institute for Theoretical Physics, IZNF, FAU Erlangen-Nürnberg, 91058 Erlangen, Germany — [2]Group of Computational Life Sciences, Ruder Bošković Institute, 10000 Zagreb, Croatia

Epoxy resins, essential in manufacturing, require an understanding of their curing kinetics for optimal properties. This study, using epoxy systems modeled with the recently developed Block Chemistry force-field[1], examines the impact of reaction kinetics on polymer chain formation. We employed a QM/MM methodology to optimize local reaction kinetics at the molecular level, enhancing curing precision. Quantum analyses and simulations showed that secondary reactions prompt early branching, while primary reactions lead to linear growth before crosslinking. Further, incorporating an isomeric mixture in the pre-polymer model resulted in denser packing, mirroring experimental densities. The study also includes loop size distribution analysis within the polymer matrix, crucial for assessing material rigidity and linking microstructural characteristics to macroscopic properties, enriching our understanding of the molecular structure-material behavior relationship in thermoset polymers.

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Contaminant desorption from a dolomite plate with synthetic and bio surfactant molecules: A Molecular Dynamics study

Ana Beatriz Salazar-Arriaga[1], Héctor Domínguez[1]

[1]Instituto de Investigaciones en Materiales IIM, UNAM, Ciudad Universitaria, 04510 México,Cd.Mx, betyann775@comunidad.unam.mx.

Using the molecular dynamics methodology, we study the desorption of contaminants on a dolomite plate, using surfactants. In this work two surfactants were used to compare their capacity to desorb hydrocarbons deposited on the solid surface, a synthetic surfactant, the sodium dodecyl sulfate (SDS) and the biosurfactant called surfactin. Additionally, a mixture of both surfactants was prepared at different proportions, to find an optimal concentration. The results show that the mixture presents the better desorption of the contaminants from the dolomite surface. Finally, we study the behavior of the systems in the presence of an electric field to see if it improves desorption.

From Computational Analysis to Immune Evasion: Understanding the Interaction between SARS-COV-2 Spike Protein and Antibodies

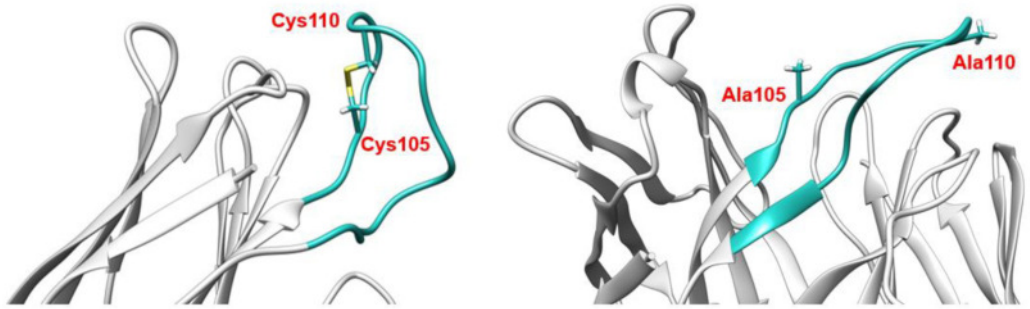
Simon Schäfer[a,b], Svenja Schorlemmer[b], Marcus Conrad[b], Lena Baus[a], Andrea Schneider[a] Anselm H.C. Horn [b], Thomas H. Winkler[a], Heinrich Sticht[b]

[a]Division of Genetics and [b]Division of Bioinformatics, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany

In this study, we employed free energy interaction analysis to identify key interaction sites between SARS-COV-2 spike protein and antibody structures. We generated a pipeline for mapping these interactions via in-silico alanine scans. Our results reveal the major interaction sites between the SARS-COV-2 spike protein and an early monoclonal neutralizing antibody. Noteworthy were the strong influence of the complementary determining loop structures CDR2 and CDR3 especially a tandem Arg motif in CDR2 and a disulfide inside the CDR3 that stabilises a kinked loop.

The neutralizing capabilities of this monoclonal antibody was strongly diminished against the beta virus variant. Structural analysis revealed that the E484K mutation of the beta variant causes electrostatic repulsion with the tandem Arg motif inside the CDR2. In an attempt to tackle the beta variant's escape mutations and to understand mechanisms of immune evasion, we utilized free energy interaction analysis to exchange all 20 amino acids and find potential antibody variants that restore binding capabilities. Potential AA exchanges produced only minor optimization potential. Experimental tests of these variants showed no restored neutralization against beta suggesting an evolutionary dead end for this type of antibody.

Variants without the intra CDR3 disulfide showed reduced binding against the WT variant and complete loss of binding against beta. MD simulation showed a more flexible CDR3 loop in the variant thus highlighting the role of cysteines for structural stabilization of CDRs.



MD simulation of free mab1-9 (left) and mab1-9 with intraloop Cys substituted by Ala (right) shows the CDR3 (cyan) and disulphide (yellow) to form a finger-like structure similar to the HIV PGT121 antibodies in the Ala mutant.

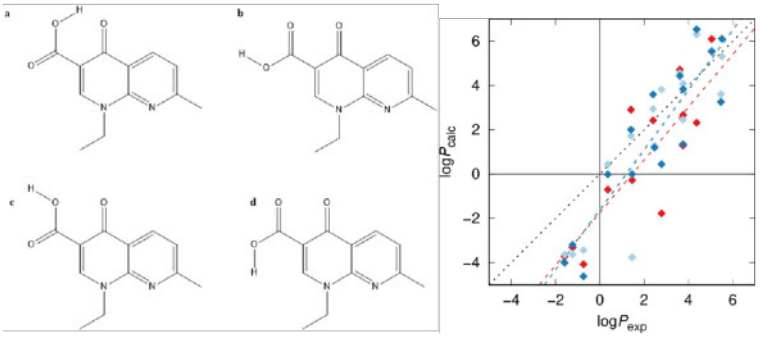
Influence of conformational ensemble models on the prediction of toluene-water partition coefficients

NicolasTielker[1], Michael Strobl[1], Christian Chodun[1], Stefan Güssregen[2], Christoph Riplinger[3], Anneke Dittmer[3], Bernardo de Souza[3], Stefan M. Kast[1]

[1]Fakultät für Chemie und Chemische Biologie, Technische Universität Dortmund, 44227 Dortmund, Germany, [2]Sanofi-Aventis Deutschland GmbH, R&D Integrated Drug Discovery, 65926 Frankfurt am Main, Germany, [3]FAccTs GmbH, 50677 Köln, Germany

In medicinal chemistry the octanol-water partition coefficient (log *P*) is frequently used as a physicochemical property to model the lipophilicity and oral bioavailability of druglike compounds. However, octanol is not an accurate representation of most biomembranes due to its ability to be both an acceptor and a donor in hydrogen bonds. The effect of this on the formation of intramolecular hydrogen bonds can be significant and will not be properly captured if the membrane is modeled as an octanol phase. [1] Furthermore, due to solvent interactions, the balance between intra- and intermolecular hydrogen bonds can drastically influence predicted partition coefficients. Hence, robust solvent-specific conformational search methods are needed.

To make progress in this direction, the SAMPL9 (Statistical Assessment of the Modeling of Proteins and Ligands) blind prediction challenge asked for toluene-water log *P* values of 16 common drugs, using an organic solvent that does not form hydrogen bonds with the solutes. This allows the investigation of radically different solvation properties in the aqueous and the organic phase. [2] To predict the toluene-water partition coefficients we employed the Embedded-Cluster Reference Interaction Site Model (EC-RISM) to represent both solvents in the calculations. [3,4] Reusing the well-established water model developed in earlier challenges and parametrizing a new, united atom toluene model made it possible to utilize the challenge as an external test set.



Finding the most energetically favorable conformation in different solvents is still an area of ongoing research. Investigation of three different conformational workflows revealed three salient points inviting further investigation. First, no single workflow was able to find the energetically most favorable conformation for all compounds. Second, even with some workflows yielding conformational energies >2.5 kcal mol^{-1} than the minimum found by other methods, often these errors were present in both solvents leading to error compensation. Finally, automated tautomer workflows can at times yield constitutional isomers that may be more energetically favorable but would not interconvert *in situ*. Surprisingly, these constitutional isomers still yield good partition coefficients, but other properties such as spectroscopic parameters would be critically affected, so care should be taken that such rearrangements are caught when large databases are investigated.

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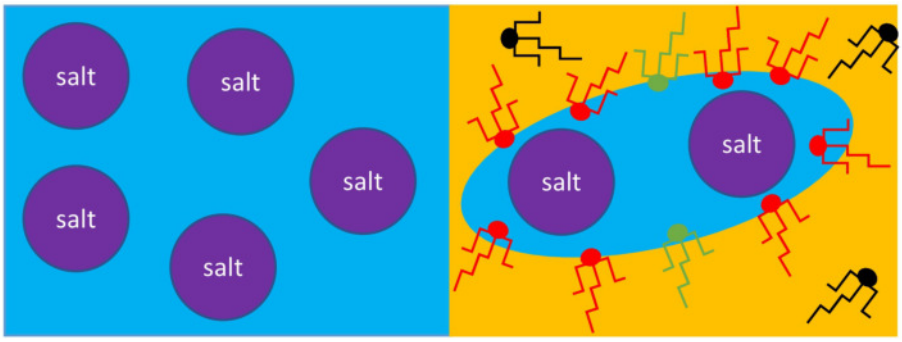
Modeling of liquid-liquid extraction of salts between an aqueous phase and a microemulsion

Emília Valença Ferreira de Aragão, Magali Duvail, Jean-François Dufrêche

Institut de Chimie Séparative de Marcoule, Univ. Montpellier, CEA, CNRS, ENSCM



Liquid-liquid extraction with aqueous-organic solvents is widely used for extraction and separation of lanthanides. In particular, it is used in nuclear fuel-cycle management, with processes such as PUREX (Plutonium Uranium Reduction Extraction) and DIAMEX (DIAMide Extraction). In those processes, an acidic aqueous phase containing lanthanide ions is put in contact with a solvent phase containing an extracting agent similar to a water-in-oil microemulsion. The extractant must be soluble in the microemulsion in both monomeric and aggregated forms, but insoluble in the water phase. Once the phases are in contact, the extractant molecules make complexes where the lanthanide ions are extracted together with water and acid.

A theoretical model [1] is employed to study the system at the equilibrium. The extractant is considered to be present in the microemulsion in three forms: as a monomer, in aggregation on a film complexing a salt and in aggregation on a film not complexing a salt. In the current work, the model was used to calculate the concentration of acid extracted into the organic phase given an initial concentration of acid in the aqueous phase and a given concentration of extractants in the solvent phase. Different parameters of the model, such as the dissociation constant of the acid, the number of extractants participating in the aggregate and the critical aggregate concentration were fitted in order to interpret the experimental extraction isotherms reported by Dourdain and colleagues [2].

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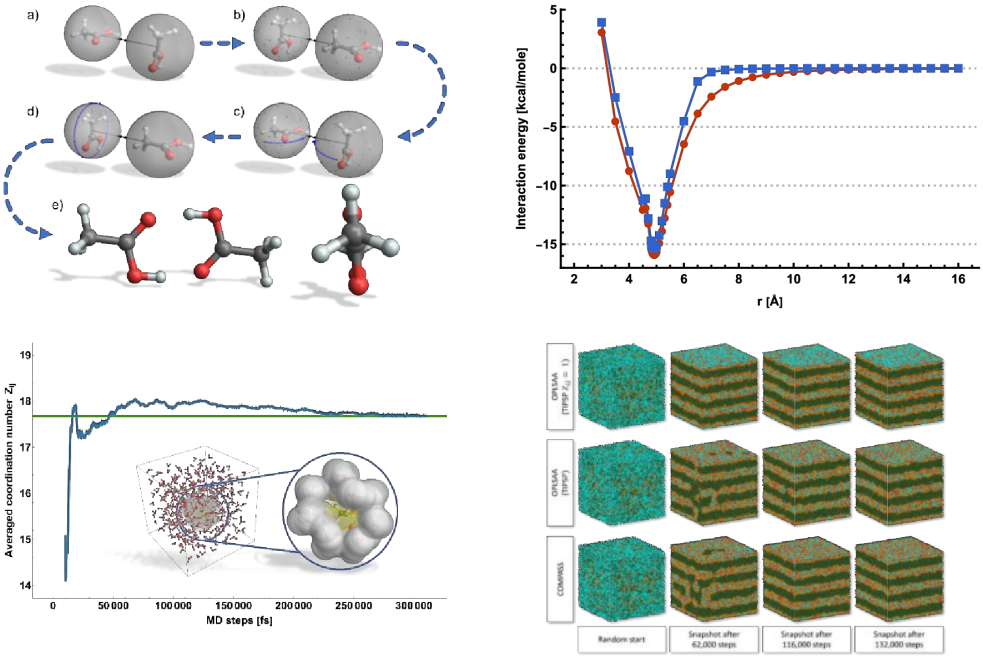
An automated Calculation Pipeline for Differential Pair Interaction Energies with Molecular Force Fields using the Tinker Molecular Modeling Package

Felix Bänsch [1,3], Mirco Daniel [1], Harald Lanig [2], Christoph Steinbeck [3], Achim Zielesny [1]

1 Institute for Bioinformatics and Cheminformatics, Westphalian University of Applied Sciences, Recklinghausen, Germany
2 Erlangen National High Performance Computing Center (NHR@FAU), Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU), Erlangen, Germany
3 Institute for Inorganic and Analytical Chemistry, Friedrich-Schiller University, Jena, Germany

An automated pipeline for comprehensive calculation of intermolecular interaction energies based on molecular force-fields using the Tinker molecular modelling package is presented. Starting with non-optimized chemically intuitive monomer structures, the pipeline allows the approximation of global minimum energy monomers and dimers, configuration sampling for various monomer-monomer distances, estimation of coordination numbers by molecular dynamics simulations, and the evaluation of differential pair interaction energies.



The latter are used to derive Flory-Huggins parameters and isotropic particle-particle repulsions for Dissipative Particle Dynamics (DPD). The computational results for force fields MM3, MMFF94, OPLSAA and AMOEBA09 are analyzed with Density Functional Theory (DFT) calculations and DPD simulations for a mixture of the non-ionic polyoxyethylene alkyl ether surfactant $C_{10}E_4$ with water to demonstrate the usefulness of the approach.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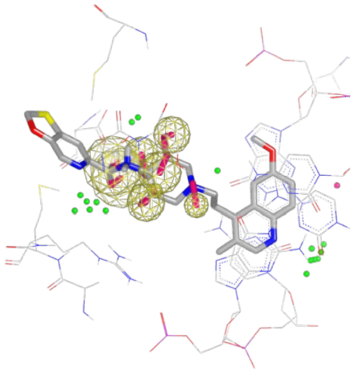

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Tel.:	+49 9131 - 85 26582
Fax:	+49 9131 - 85 26565
E-Mail:	info@mgms-ds.de
WWW:	www.mgms-ds.de
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