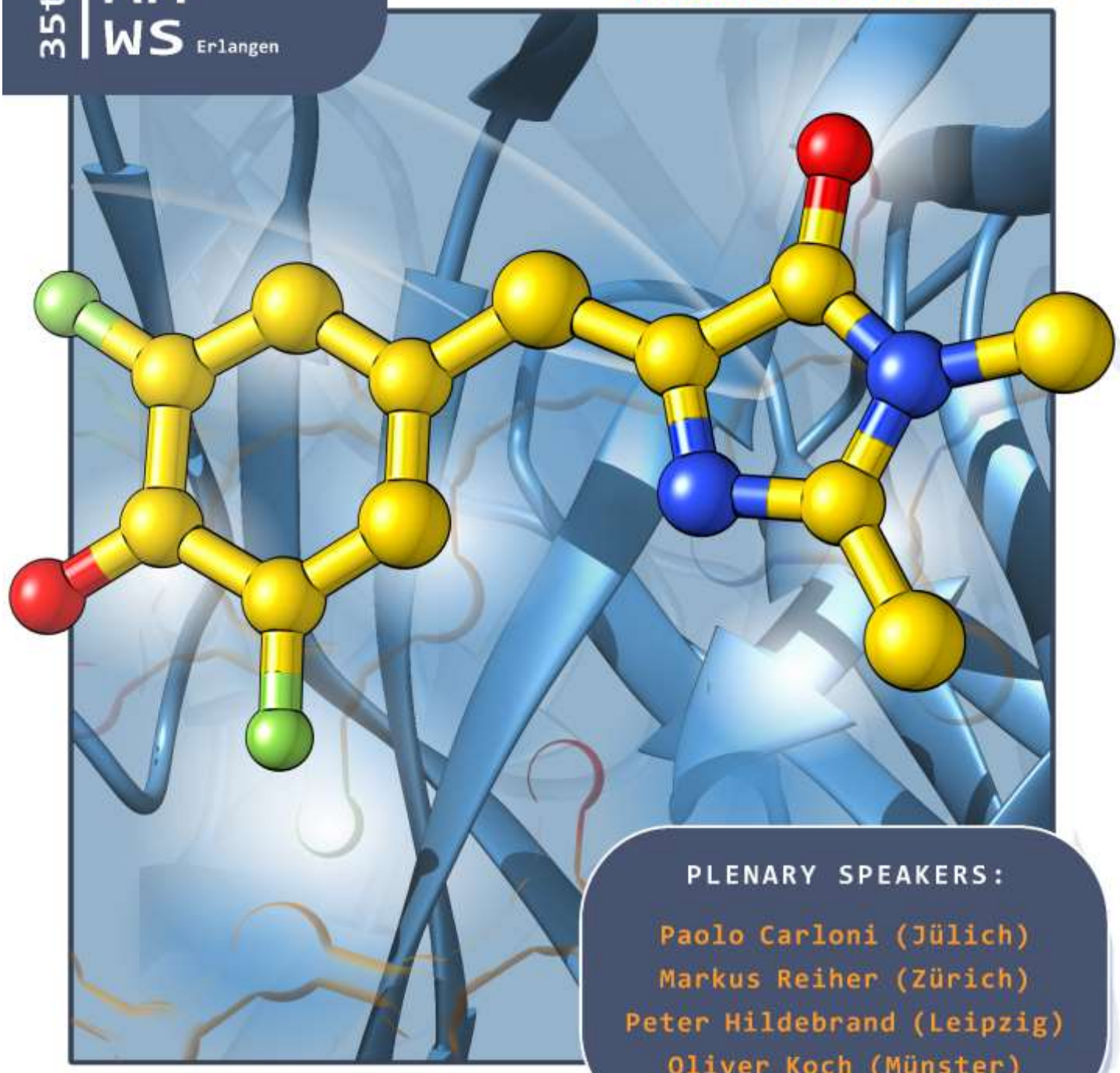
35th MMWS Erlangen

MMWS2023.MGMS-DS.DE



PLENARY SPEAKERS:

Paolo Carloni (Jülich)
Markus Reiher (Zürich)
Peter Hildebrand (Leipzig)
Oliver Koch (Münster)

13/03-15/03/2023

MOLECULAR MODELLING WORKSHOP ERLANGEN

molecular graphics modelling society

NHR FAU

C3 Computer Chemie Centrum

FAU Friedrich-Alexander-Universität Erlangen-Nürnberg

MOLECULAR MODELLING WORKSHOP 2023

Welcome to the 35th Molecular Modelling Workshop (MMWS)

This year's MMWS represents a welcome return to a "real" onsite conference after the pandemic. A lot has happened since the last event of this type: The old organic institute, which was the site of the MMWS for decades, has been superseded by the new Chemikum I, which is more impressive (and smells better) but outside the Erlangen city center.

Most significantly, Erlangen has become the home of NHR@FAU, a national Tier 2 supercomputer center that specializes in atomistic simulations. The concentration of expertise and hardware in one location represents a very important facility for molecular modeling in Germany.

We are therefore happy that this year's MMWS is supplemented by the inaugural symposium for NHR@FAU.

Scientifically, this MMWS2023 has no special focus, but rather seeks to represent as many different branches of molecular modeling as possible. This is also the reason that the individual sessions are not focused on subject areas. Just sit back enjoy lectures outside your specialization; we all learn from things we are not familiar with.

Scientific program

Prof. Dr. Tim Clark

Computer Chemie Centrum
CCC

Friedrich-Alexander-Universität
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91052 Erlangen, Germany

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PD Dr. Harald Lanig

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Hochleistungsrechnen Erlangen
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DEAR COLLEGUES,

the 35th Molecular Modeling Workshop 2023 (March 13th to 15th) in Erlangen provides researchers, postdoctoral scientists, and graduate students with the perfect opportunity to present their results to the molecular modeling community. Scientists at the beginning of their academic career are able to meet new colleagues in academia and industry, discuss their research topics and gain valuable feedback.

The aim of the Modeling Workshop is to also present research in progress. It is the perfect venue to introduce new methods in molecular modeling that can be applied to many disciplines. The workshop is suitable for everyone, those who want to gain experience in presentation skills and those who just want to network in a friendly relaxed environment.

The organisers welcome both poster or lecture contributions in English from all areas of molecular modeling including life sciences, physical sciences, material sciences and the nano sciences, including computational biology and chemistry, and cheminformatics.

Additionally, we offer online participation by transmitting all talks via ZOOM. Questions to the presenters will only be possible by the ZOOM chat function (no direct audio feedback). For this option, the conference fee reduces to 50%. Upon registration, you can select how to participate. If you decide to attend online, payment in advance via bank transfer is necessary. After receiving the money, we will send you a ZOOM link.

The deadline for registration and submission of abstracts for oral and poster presentation was February 26th, 2023.

Our plenary speakers this year are (in alphabetical order):

PROF. DR. PAOLO CARLONI
Forschungszentrum Jülich, Germany

PROF. DR. PETER HILDEBRAND
Universität Leipzig, Germany

PROF. DR. OLIVER KOCH
Westfälische Wilhelms-Universität Münster, Germany

PROF. DR. MARKUS REIHER
Eidgenössische Technische Hochschule Zürich, Germany

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.

Additionally, we are happy that, for the first time, the Wiley-VCH journal "Advanced Theory and Simulations" is providing several *book token awards* to outstanding workshop contributions.

MGMS-DS E.V. ANNUAL MEETING

The general meeting of the MGMS (German Section) will be held during the workshop. We cordially invite all conference delegates to participate in the annual meeting of the society!

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 mmws2020.mgms-ds.de

PRE-CONFERENCE WORKSHOP

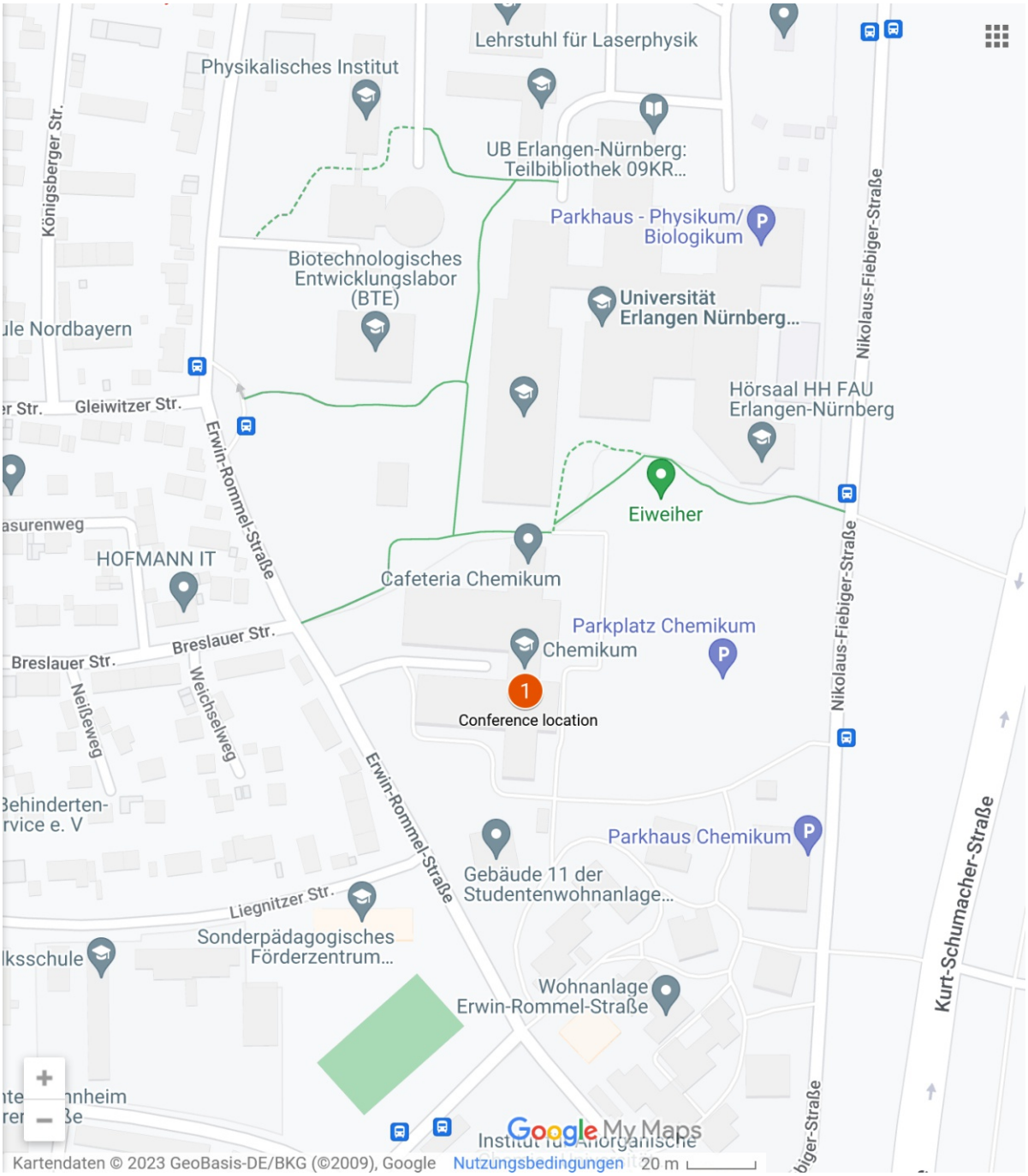
Due to the restart character of the event after the Corona pandemic and its new location, we had to skip the pre-conference workshop this year, unfortunately.

LOCATION

Conference location: All talks, coffee breaks, the poster sessions and the buffet dinner on Monday, March 13th 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 Gasthaus "Kitzmann Brauschänke" (https://braeuschaenke.de/), Südliche Stadtmauerstraße 25, 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 13th 2023

11:00-14:00	**Registration**
14:00-14:10	**Welcome remarks / Agenda review**
14:10-14:35	**L05: Conrad Hübler (Freiberg, Germany)** The Hungarian method revisited - Usage of combinatorial optimisation for structural comparison of conformers
14:35-15:00	**L02: Filipe Menezes (München, Germany)** From the catalytic mechanism of the glycyl radical enzyme pyruvate formate-lyase to the dynamics of its activation
15:00-15:50	**PLENARY LECTURE I: Paolo Carloni** MiMiC: A new, highly scalable QM/MM interface for biophysical applications
15:50-16:30	**Coffee Break**
16:30-16:55	**L03: Jacqueline C. Calderon (Erlangen, Germany)** The structural basis that drives ligand efficacy at the serotonin 5-HT1A receptor
16:55-17:20	**L04: Hebah Fatafta (Jülich, Germany)** Dissecting Membrane-Amyloid Peptide Interactions at the Atomic Level: Insights from Peptide Monomers and Oligomers
17:20-17:45	**L01: Simone Bonfrate (Marseille, France)** Simple and efficient electrostatic embedding QM/MM method for modelling condensed phases using periodic boundary conditions
18:00-19:00	**Annual Meeting of the MGMS-DS e.V.**
19:30	**Buffet – Dinner**

PROGRAM

Tuesday, March 14th 2023

09:00-09:25	**L06: Benedikt Frieg (Jülich, Germany)** Interdisciplinary insights into the influence of lipids on the formation of alpha-synuclein fibrils in Parkinson's disease
09:25-09:50	**L07: Rocco Gentile (Düsseldorf, Germany)** Molecular mechanisms underlying the activity regulation of the phospholipase PlaF from *P. aeruginosa* by free fatty acids
09:50-10:15	**L08: Anna Jäckering (Jülich, Germany)** Engineering PET-degrading enzymes - targeting the energy barrier for PET binding
10:15-10:55	**Conference Photo & Coffee Break**
10:55-11:20	**L09: Aswathy Muttathukattil (Erlangen, Germany)** Self-limiting Assembly in Systems of Bipods via Geometrical Frustration
11:20-12:10	**PLENARY LECTURE II: Markus Reiher** Prospects of Quantum Computing for Chemistry
12:10-13:30	**Lunch**
13:30-15:00	**POSTER SESSION**
15:00-15:25	**L10: Lisa Sophie Kersten (Düsseldorf, Germany)** Structural dynamics in plant receptor ETR1 after binding of ethylene and 1-methylcyclopropene
15:25-15:50	**L11: Fabian Sendzik (Dortmund, Germany)** Localization and decomposition of free energies in solution
15:50-16:10	**Coffee Break**
16:10-16:35	**L12: Marius F. W. Trollmann (Erlangen, Germany)** mRNA lipid nanoparticle phase transition
16:35-17:00	**L13: Joana Massa (Münster, Germany)** Metadynamics Simulations of FPR2: Using an Enhanced Sampling Method to Elucidate The Mode of Action of a Diverse Set of Ligands
17:00-17:25	**L14: Frank Beierlein (Erlangen, Germany)** DNA Repair Mechanisms: Molecular Simulations and Computational Alchemy
17:25-18:15	**PLENARY LECTURE III: Peter Hildebrand** Structural mechanism of Gs protein activation by the prototypical beta-2 adrenergic receptor
19:00	**Social Event: Kitzmann Brauschänke**

Wednesday, March 15th 2023

09:00-09:25	**L15: Gerhard Wellein (Erlangen, Germany)** The National High-Performance Computing Alliance: New infrastructure and opportunities for science and research at German universities
09:25-09:50	**L16: Alireza Ghasemi (Erlangen, Germany)** Machine Learning Interatomic Potentials: Reference Training Data on the Hands of Workflows
09:50-10:40	**PLENARY LECTURE IV: Oliver Koch** Neural Fingerprints: Structure- and activity-sensitive molecular representations based on neural networks for virtual screening approaches
10:40-11:10	**Coffee Break**
11:10-11:35	**L17: Anna Bochicchio (Schroedinger Germany)** Enabling Prediction of Protein-Protein Binding Affinities Using FEP+
11:35-12:00	**L18: Christian Ritterhof (Erlangen, Germany)** Accelerating plane wave based ab initio molecular dynamics by optimization of Fast-Fourier transforms for modern HPC architectures
12:00-12:25	**L19: Julian Konrad (Erlangen, Germany)** Multi-Scale Modelling of Epoxy Resin and Composites: from Curing to Fracture
12:00-12:25	**L20: Nicolas Tielker (Dortmund, Germany)** Recent advances in the Embedded Cluster Reference Interaction Site Model
15:30-15:50	**Poster & Lecture Awards, Closing**

Poster Session

POSTER SESSION

Tuesday, March 14th 2023 13:30-15:00

P01 **Jorge A. A. Balderas (Erlangen, Germany)**
Effect of N140D and T197A mutations on DNA repair enzyme Thymine DNA Glycosylase

P02 **Anton Arkhypov (Erlangen, Germany)**
Optimisation of electrophile reactivity

P03 **Frank Beierlein (Erlangen, Germany)**
DNA-Repair Mechanisms: Molecular Simulations and Computational Alchemy

P04 **Jacqueline Calderon (Erlangen, Germany)**
The structural basis that drives ligand efficacy at the serotonin 5-HAT_{1A} receptor

P05 **Marcus Conrad (Erlangen, Germany)**
Mechanics of Histamine: Computational analysis of protonation effects on H_1R binding

P06 **Maximilian Dejori (Erlangen, Germany)**
Quantum chemical analysis of structure and ion selectivity correlation of moieties derived from the [2.2.2] cryptand

P07 **Manuel Deubler (Erlangen, Germany)**
Structure-based design and optimization of ligands for novel antiviral strategies

P08 **Steffen Docter (Jülich, Germany)**
Amine Transaminase Engineering based on Constraint Network Analysis

P09 **Rustam Durdyyev (Erlangen, Germany)**
Modelling liquid flow through nanopores on the nanoscale

P10 **Lennart Eisel (Dortmund, Germany)**
Accurate prediction of acidity constants with an ONIOM embedded cluster RISM approach

P11 **Jules C. E. Ndongue (Erlangen, Germany)**
Towards automated exploration of enzymatic reactions

P12 **Federico Tomazic (Erlangen, Germany)**
Coarse-Grained Simulations of Ligand-Tethered Nano-Tripods

P13 **Lars Schumann (Dortmund, Germany)**
Identifying descriptors of the conductive state in small viral K^+ ion channels

P14 **Anselm H. C. Horn (Erlangen, Germany)**
Count on NHR@FAU for your Atomistic Simulations

Please kindly remove your posters on tuesday evening!

POSTER SESSION

Tuesday, March 14th 2023 13:30-15:00

P15 **Stephen Hummell (Boston, USA)**
digitalSELEX: In silico Platform for Designing Oligonucleotides

P16 **Eileen Socher (Erlangen, Germany)**
Molecular Case Study of a GALC Mutation Causing Infantile Krabbe Disease

P17 **Patrik Kibiesi (Dortmund, Germany)**
Recent advances in the Embedded Cluster Reference Interaction Site Model

P18 **Asad Kirsan (Erlangen, Germany)**
Metadynamics Simulations of Chemical Reactions in Solution

P19 **Joana Massa (Münster, Germany)**
KCa3.1 channel: Computational analysis of three known toxin inhibitors towards new extracellular inhibitors

P20 **Stefan Doste (Dortmund, Germany)**
Accurate NMR shift calculations for species in aqueous solution at ambient and high-pressure conditions

P21 **Debora Monego (Heidelberg, Germany)**
Size-dependent sedimentation of nanocrystals: the role of the ligand shell structure

P22 **Nathaniel Smith (Berlin, Germany)**
A combined deep learning and structure based cheminformatic approach to understand ligand blockage activity on the hERG channel

P23 **Christian Ritterhoff (Erlangen, Germany)**
Accelerating plane-wave-based ab initio molecular dynamics by optimization of Fast-Fourier transforms for modern HPC architectures

P24 **Simon Schäfer (Erlangen, Germany)**
Unlocking the Potential of Antibodies Against SARS-CoV-2: A Pipeline for Fast and Accurate Mapping of Interaction Sites with Free Energy Analysis

W01 **Felix Bänsch (Recklinghausen, Germany)**
A Calculation Pipeline for Differential Molecule Pair Interaction Energies

W02 **Felix Bänsch (Recklinghausen, Germany)**
MORTAR – A Rich Client Application for in silico Molecule Fragmentation; A Calculation Pipeline for Differential Molecule Pair Interaction Energies

All abstracts are available on the conference web site:
www.mmws2023.mgms-ds.de

Please kindly remove your posters at the end of the poster session!

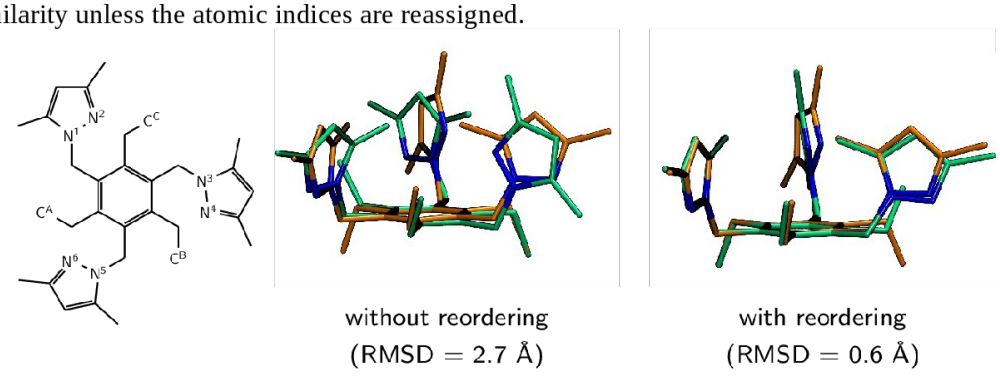
Abstracts

The Hungarian method revisited – Usage of combinatorial optimisation for structural comparison of conformers

Conrad Hübler

Institut für Physikalische Chemie, Technische Universität Freiberg, Leipziger Straße 29, 09599 Freiberg

Conformational search problems are mostly associated with finding the global minimum geometry of a structure of interest. The analyses of the potential surface using various molecular modelling methods reveal, that the most stable structures at a given lower level of theory (for example semiempirical methods) do not necessarily coincide with the most stable structures at a higher level of theory (for example density functional theory).[1] This may be overcome by re-evaluating and/or reoptimising all structures at a higher level of theory, resulting in an increase of the overall computational cost. Furthermore, molecules with some kind of symmetry may give rise to another challenge: Although the presence of symmetrically equivalent atoms can be helpful in quantum chemical calculations, "topological symmetry" in (sub)structures may prohibit the successful identification of identical or similar conformations in a set of conformational search results. As geometries are in general stored as a list of atoms with fixed order, the root mean square deviation (RMSD) between two structures may not represent the true similarity unless the atomic indices are reassigned.



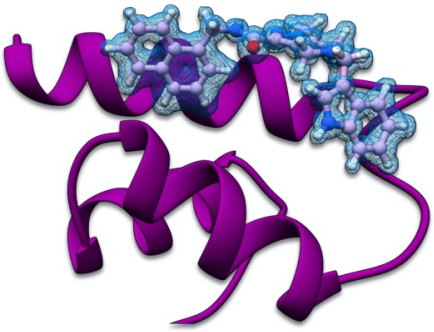
A general approach to the combinatorial optimisation problem was first proposed by Kuhn[2] and improved by Munkres.[3] The so-called Hungarian method was implemented for the use of structure comparison in a *python* tool available at https://github.com/charnley/rmsd.[4] However, there is a good chance that the plain Kuhn-Munkres approach does not result in the best reassignment of the atoms and hence the identification of duplicate or similar structures may fail. During the analysis of the supramolecular binding behavior of tripodalic receptors, both the reassignment problem of the atoms in case of two structures and a general conformational filtering with respect to the "topologically symmetric" structures were analysed in detail and a combined approach is now implemented in the program *curcuma*.[5] The conformational filter approach includes the Hungarian method with a well defined pre-aligning of the geometry for each pair of two structures and to pre-judge whether two structures are potentially similar and reassigning atomic indices may be fruitful. The pre-judging is based on the comparison of the total energies, rotational constants and Vietoris–Rips barcodes[6] which all are invariant with respect to the ordering of the atomic indices. However, they are in most cases not sufficient to correctly identify similar structures on their own.

[1] R. Sure, S. Grimme, *Chem. Commun.*, **2016**, *52*, 9893-9896. [2] H. W. Kuhn, *Nav. Res. Logist.*, **1955,** *2*, 83-97. [3] J. Munkres, *SIAM J. Appl. Math.*, **1957**, *5*, 32–38. [4] Calculate Root-mean-square deviation (RMSD) of Two Molecules Using Rotation, GitHub, http://github.com/charnley/rmsd, <1.5.1> [5] C. Hübler. (2020). conradhuebler/curcuma: Curcuma . Zenodo. https://doi.org/10.5281/zenodo.4302723. [6] U. Bauer, *J Appl. and Comput. Topology* **2021**, *5*, 391–423.

A Semi-Empirical Energy Decomposition Analysis for large (Bio)Molecular Systems

Filipe Menezes[a,*], Grzegorz M. Popowicz[a]

Helmholtz Zentrum Muenchen, Ingolstädter Landstraße 1, D-85764 Neuherberg



Quantum Chemical Energy Decomposition Analysis (EDA) is a valuable tool that permits understanding of the physical basis that leads to the formation of non-covalent interactions. Many algorithms have been proposed, which bring out several views over what is the physical basis that leads to binding. [1-10] Most of them are by construction compatible with Hartree-Fock or density functional methods, thus the system size that may be included in the calculations is quite limited. Treating systems of biological interest is unthinkable without severe truncation of the molecules. Nevertheless, EDA algorithms would be beneficial for the drug discovery communities in their efforts to develop better inhibitors: a more systematic view over the effects of certain structural modifications on the protein-ligand interactions.

Here we present a new Energy Decomposition Analysis fully compatible with semi-empirical quantum chemistry (NDDO and Tight Binding based). Due to the reduced computational cost of the underlying quantum mechanical methods, our new algorithm may be applied to large chemical systems, *e.g.*, of biological interest, using modest computational resources (a personal computer). We furthermore make our EDA algorithm atom specific. [10,11] Due to this construction, powerful interaction maps are constructed, which bring a deeper understanding of the role played by certain atoms/functional groups for the interactions with the biological target. The new semi-empirical EDA [12] will be available from our in-house semi-empirical package, ULYSSES. [13]

[1] K. Kitaura, K. Morokuma, *Int. J. Quantum Chem.*, **1976**, *10*, 325–340.
[2] P. Su, H. Li, *J. Chem. Phys.*, **2009**, *131*, 014102.
[3] B. Jeziorski, R. Moszynski, K. Szalewicz, *Chem. Rev.*, **1994**, *94*, 1887–1930.
[4] K. Szalewicz, *WIREs Comp. Mol. Sci.*, **2012**, 2, 254–272.
[5] A. J. van der Vaart, K. M. Merz, *J. Phys. Chem. A*, **1999**, *103*, 3321–3329.
[6] M. J. S. Phipps, T. Fox, C. S. Tautermann, C.-K. Skylaris, *Chem. Soc. Rev.*, **2015**, *44*, 3177–3211.
[7] P. Su, Z. Tang, W. Wu, *WIREs Comp. Mol. Sci.*, **2020**, *10*, e1460.
[8] P. R. Horn, Y. Mao, M. Head-Gordon, *J. Chem. Phys.*, **2016**, *144*, 114107.
[9] A. J. van der Vaart, K. M. Merz, *J. Phys. Chem. A*, **1999**, *103*, 3321–3329.
[10] K. Raha, et al., *J. Am. Chem. Soc.*, **2005**, *127*, 6583–6594.
[11] R. M. Parrish, C. D. Sherrill, *J. Chem. Phys.*, **2014**, *141*, 044115.
[12] F. Menezes, G. M. Popowicz, manuscript in preparation.
[13] F. Menezes, G. M. Popowicz, *J. Chem Inf. Model.*, **2022**, *62*, 3685.

MiMiC: A new, highly scalable QM/MM interface for biophysical applications

Paolo Carloni

Forschungszentrum Jülich, Wilhelm-Johnen-Str., 52428 Jülich, Germany

The structural basis that drives ligand efficacy at the serotonin 5-HT$_{1A}$ receptor

Jacqueline C. Calderón,[1] Passainte Ibrahim,[2] Dorothea Gobbo,[3,4] Francesco Luigi Gervasio,[3,4,5] and Timothy Clark[1]

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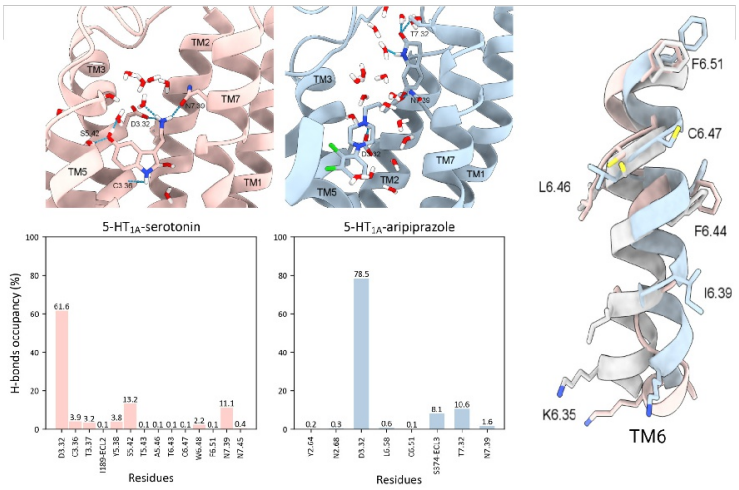
G-protein coupled receptors (GPCRs) are the largest superfamily of membrane proteins in the human genome; they modulate numerous physiological responses [1]. The 5-HT$_{1A}$ receptor, a Class A GPCR, is a member of the serotonergic receptor family, which is found in the central and peripheral nervous systems and activated by the neurotransmitter serotonin (5-hydroxytryptamine, 5-HT). Although the 5-HT$_{1A}$ receptor subtype is one of the most studied, since it is an important therapeutic target for several neuropsychiatric disorders, including anxiety, depression, and schizophrenia [2], the structural basis, which involves receptor dynamics, ligand efficacy and receptor activation, is largely unknown. Here, we use a metadynamics protocol based on the general activation index A^{100} [3] to study the activation of the 5-HT$_{1A}$ receptor. We show free-energy profiles for the serotonin receptor as binary (apo-receptor + G-protein-α-subunit and receptor + ligand) and ternary complexes with two prototypical orthosteric ligands; the full agonist serotonin and the partial agonist aripiprazole. The computed free-energy landscapes, specific interaction analysis and structural inspection suggest a combined mechanism that requires the action of both stabilizing intracellular and extracellular interactions in the receptor core for the full activation of the receptor. We have demonstrated the potential role of polar interaction networks in the receptor core as a regulator of the initial stages involved in receptor activation. In particular, our simulations have provided, on an atomistic level, direct evidence of the structural requirements that drive ligand efficacy at the 5-HT$_{1A}$ receptor. Thus, the results reported here constitute findings of remarkable value, not only for understanding the biophysical basis of signaling but also to provide the knowledge necessary to design more effective and less toxic drugs.



[1] T. K. Bjarnadóttir, et al., *Genomics* **2006**, *88*, 263-273.
[2] N. M. Barnes, et al., *Pharmacol. Rev.* **2021**, *73*, 310-520.
[3] P. Ibrahim, D. Wifling, T. Clark, *J. Chem. Inf. Comput.* **2019**, *59*, 3938-3945.

Dissecting Membrane-Amyloid Peptide Interactions at the Atomic Level: Insights from Peptide Monomers and Oligomers

Hebah Fatafta[1], Birgit Strodel[1, 2]
Computational Biochemistry Group
[1] *Institute of Biological Information Processing (IBI-7: Structural Biochemistry), Forschungszentrum Jülich, 52425 Jülich, Germany*
[2] *Institute of Theoretical and Computational Chemistry, Heinrich Heine University Düsseldorf, 40225 Düsseldorf, Germany*

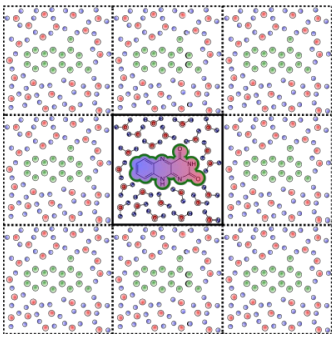
Growing evidence suggests that membrane surfaces may serve as templates for adsorption and aggregation of amyloid peptides, a process associated with cell dysfunction and death in devastating amyloid-associated diseases such as Alzheimer's disease and diabetes. However, the underlying molecular mechanism is not well understood. We performed microsecond molecular dynamics (MD) simulations to (i) investigate the interactions of amyloid beta-peptide (Aβ) and amylin (hIAPP) with lipid membranes, (ii) investigate the importance of histidine 18 of hIAPP by mutation to arginine, lysine, glutamate, (iii) model the influence of lipid composition on these interactions, including the composition of a neuronal membrane, and (iv) describe the effects of free lipids in the aqueous phase on peptide structure. For MD data analysis, we construct transition networks as they provide insight into conformational transitions and aggregation pathways. For Aβ, we reported a transition from disorder to order after binding to a small cluster of POPC lipids in solution, which is similar to the folding of Aβ triggered by its self-assembly. [1, 2] Gangliosides, on the other hand, as found in neuronal membranes, decrease order in Aβ due to competition for the formation of H-bonds with Aβ. [1] In the case of hIAPP, we found that membrane binding induced the formation of an amphipathic helix, which we hypothesized to be an intermediate step to hIAPP amyloid aggregation. [3] These studies provide valuable insight into the interactions between Aβ/hIAPP and various lipid bilayers, which is useful for understanding membrane-mediated cytotoxicity.

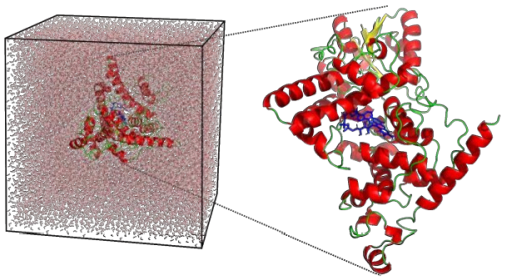
[1] Fatafta H, Khaled M, Sayyed-Ahmad A, Owen M., Strodel B., *PNAS*, **2021**, *118*, e2106210118.
[2] Fatafta H, Kav B., Bundschuh B., Loschwitz J., Strodel B., *Biophys Chem.*, **2022**, *280*, 106700.
[3] Khemtemourian L, Fatafta H, Davion B, Lecomte S, Castano S, Strodel B., *Front. Mol. Biosci*., **2022,** *9*, 849979.

Simple and efficient electrostatic embedding QM/MM method for modeling condensed phases using periodic boundary conditions

Simone Bonfrate, Nicolas Ferré, Miquel Huix-Rotllant

Aix-Marseille Univ, CNRS, ICR, Marseille, France





In this talk, I will present our recent development of a new, simple yet efficient electrostatic embedding Quantum Mechanical / Molecular Mechanics (QM/MM) model in Periodic Boundary Conditions (PBC).[1] Our method benefits from the *Nlog(N)* scaling of Smooth Particle Mesh Ewald (SPME),[2] for the treatment of long-range electrostatic interactions, and the advantages of Electrostatic Potential Fitted (ESPF) charge operators,[3] to approximately represent the QM density in replicas. This model allows the study of reactions and properties of condensed phase systems of arbitrary size.
To illustrate the efficiency of the method we have applied it to compute the lowest singlet excited state for a model of *Arabidopsis thaliana* cryptochrome 1 in water, which contains 93 000 atoms circa, using both Time-Dependent Density Functional Theory (TDDFT) and Restricted Open-Shell Kohn-Sham (ROKS), reproducing accurately the experimental absorption maximum.

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Interdisciplinary insights into the influence of lipids on the formation of α-synuclein fibrils in Parkinson's disease

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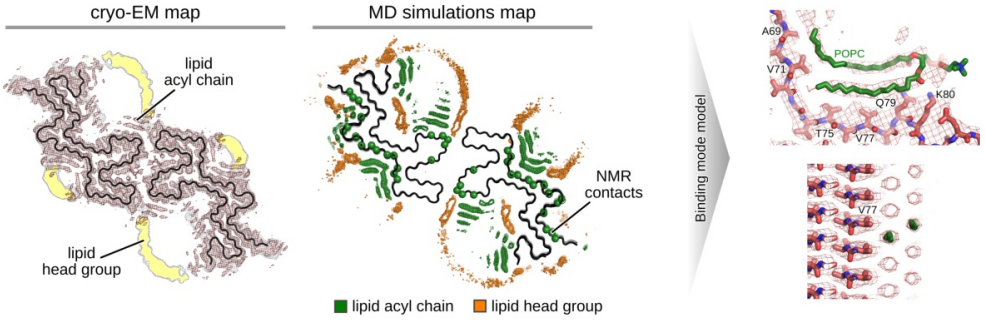

Parkinson's disease is the second most common neurodegenerative disease globally, and recent estimates suggest that more than ten million people worldwide suffer from it [1]. In this disease, α-synuclein proteins form thread-like structures called fibrils. When these fibrils clump together into Lewy bodies, the characteristic pathological hallmark of Parkinson's, they probably damage nerve cells [2]. Studies on the composition of Lewy bodies extracted postmortem from brain tissue of Parkinson's patients revealed that lipids and membranous organelles are also significant components [3]. However, although interactions between α-synuclein fibrils and lipids have been identified as relevant for Parkinson's pathogenesis, any molecular insights into their interactions have remained elusive.

Using cryo-electron microscopy, we visualized how lipid molecules bind to the fibril surface for the first time, thereby connecting the individual subunits [4]. Complemented by molecular dynamics simulations combined with solid-state nuclear magnetic resonance spectroscopy, we show how the lipid and protein elements interact within fibrils [4]. Together with our previous studies [5], these insights also indicate a mechanism for fibril-induced lipid extraction, which is likely to be involved in the development of Parkinson's. Specifically, one potential mechanism for cellular toxicity is the disruption of intracellular vesicles mediated by α-synuclein fibrils and oligomers, and therefore the modulation of these interactions may provide a promising strategy for future therapeutic interventions [6].

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Molecular mechanisms underlying the activity regulation of the phospholipase PlaF from P. aeruginosa by free fatty acids

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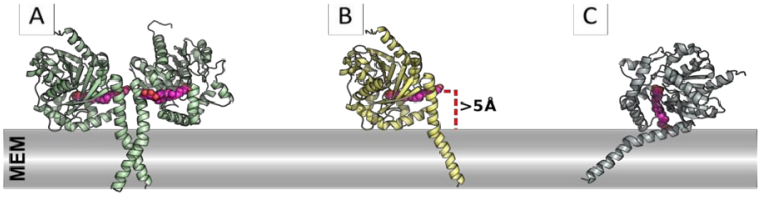
The Gram-negative Pseudomonas aeruginosa is an opportunistic pathogen that causes nosocomial infections by producing numerous virulence factors[1-3]. Among these factors, type A phospholipases (PLA) can contribute to host membrane damage and modulation of signaling networks in infected cells by modifying the membrane composition[2-3]. In this context, we focus on PlaF, a phospholipase A1 (PLA1).

This enzyme adopts a monomeric active and a dimeric inactive configuration[3]. A crystal structure of the dimeric PlaF (PDB_ID 6i8w) is available. Computational studies evaluated the dynamics and energetics of the dimerization process[3]. The results reveal that a single PlaF monomer can adopt a tilted configuration, which might facilitate phospholipid substrate access from the membrane. Furthermore, we elucidated the potential channeling mechanisms underlying substrate access and product egress in PlaF in accordance with the enzyme specificity and regioselectivity[4]. Additionally, we revealed that medium-sized free fatty acids (FFAs) can inhibit PlaF activity according to mixed inhibition kinetics[3]. However, the detailed molecular mechanism that governs the inhibition of PlaF by FFAs has remained elusive.

Here, we showed by molecular simulations that the presence of FFAs in the membrane affects the dynamics and the energetics of both PlaF dimer dissociation and monomer tilting. Moreover, free energy computations reveal an energetic stabilization of the dimeric inactive configuration, which was correlated to an increased FFA concentration in the membrane. Experimental studies also revealed that FFAs in the periplasmic space can inhibit PlaF activity. We propose a potential FFA-related mechanism of PlaF inhibition using free ligand diffusion simulations. Combined with experimental validations, the identification of FFA binding site(s) involved in the inhibition of PlaF can help design novel drugs against P. aeruginosa.



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Engineering PET-degrading enzymes – targeting the energy barrier for PET binding

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In view of the worsening climate crisis and increasing plastic waste pollution, scientific interest in the development of an environmentally friendly enzymatic degradation mechanism for plastics is growing. However, the bottleneck in the industrial application of enzymes for plastic waste recycling is their insufficient activity and partial lack of stability under industrial conditions. [1]

To this end, we investigated the binding behavior of highly active PET-degrading enzymes to polyethylene terephthalate (PET). Adsorption to the PET surface could be captured by classical molecular dynamics (MD) simulations. However, the entry of PET into the active site associated with the formation of productive binding poses was presumably hindered by an energy barrier limiting the activity of the enzyme. Using Hamiltonian Replica Exchange MD (HREMD) simulations, we were able to overcome this barrier and investigate entry pathways leading to productive conformations. In addition to hindering intramolecular PET interactions, we identified amino acids that potentially hinder entry into the binding site based on free energy surface profiles of amino acid-PET interaction. These residues serve as promising mutation sites to enhance PET degradation activity, which will be investigated *in vitro* in the future.

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Self-limiting Assembly in Systems of Bipods via Geometrical Frustration

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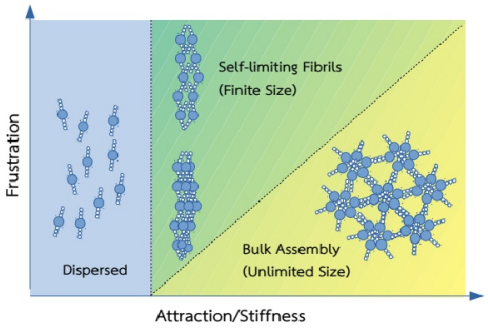
Self-limiting assembly arises when local interactions between building blocks are incompatible with forming uniform (bulk) materials, referred to as geometric frustration. Examples of assemblies with self-limiting includes protein filament bundles, twisted molecular crystals, chiral smectics and membranes [1,2]. It is challenging to use geometrical frustration as a design concept to create finite-size equilibrium assemblies in soft matter, despite major efforts to build a general theory on the subject.



In this study, we systematically control geometrical frustration in system of bipods to demonstrate self-limiting self-assembly. We deploy a minimal computational model consisting of a central sphere that connect to two attractive rigid rods diametrically via a flexible hinge. Regulating the flexibility (stiffness) of the hinge and rod attraction, formation of anisotropic fibrillar assemblies are observed. The lateral width of the fibrils can be controlled by the misfit introduced by the radius of the central sphere. Our model - the bipods - can be realized in experiments as nanoparticles with tethered polymer bundles, partially unfolded polymer globules and organic molecules.

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Prospects of Quantum Computing for Chemistry

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ETH Zurich

Many problems in molecular science and condensed-phase systems, which are both governed by the dynamics of electrons and atomic nuclei, demand an explicit quantum mechanical description. In such quantum problems, the representation of wave functions grows exponentially with system size, which poses a severe restriction on traditional approaches. However, such quantum problems should naturally benefit from digital quantum simulation on a number of logical qubits, as this would scale only linearly with system size. In recent years, we have considered quantum computing applications in molecular biology, catalysis, and physical chemistry in general, with a focus on how and where to establish a quantum advantage in these areas [1-5]. In my talk, I will elaborate on the potential benefits of quantum computing in these application areas, especially when compared to state-of-the-art traditional approaches.

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Structural dynamics in plant receptor ETR1 after binding of ethylene and 1-methylcyclopropene

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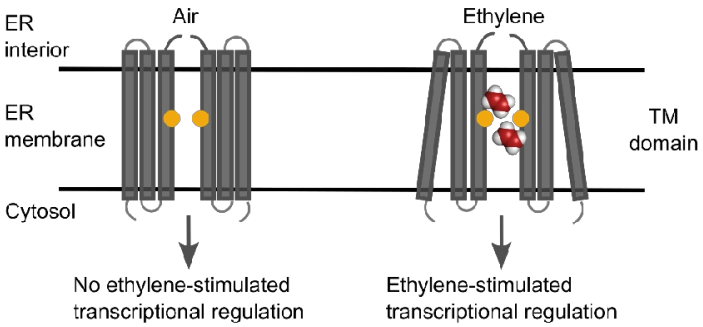
The small molecule ethylene is a gaseous plant hormone known to induce various developmental processes in plants such as seed germination, senescence, and fruit ripening after binding to the plant receptor ETR1 (ethylene response 1) in its transmembrane sensor domain (TMD).[1] The TMD obtains its high affinity and specificity for the chemically simple ethylene molecule through an essential copper cofactor, which also binds in the TMD. It is known that receptors bound to ethylene undergo conformational changes and therefore fail to activate downstream targets, which finally triggers the ethylene response of the plant and initiates the ripening of fruits. Additionally, many strained alkenes, such as 1-methylcyclopropene (1-MCP) are proven to be effective antagonists of ethylene responses that target ethylene receptors and therefore prevent fruit ripening. [2] However, it remains elusive, how ethylene binding deactivates ETR1, how the signal is transduced to downstream elements, and why 1-MCP functions as an ethylene antagonist.

Here, we show initial insights into how ethylene may deactivate ETR1 and how 1-MCP maintains ETR1 activity. Based on our predicted and experimentally validated model of the ETR1 TMD [3,4] and the characterized ethylene binding site [5], we generated an ETR1:Cu(I):ethylene TMD model [3] and developed parameters of ethylene or 1-MCP binding to Cu(I) employing a bonded model. Both the distances and force constants obtained indicate that 1-MCP interacts more strongly with copper than ethylene. The obtained trajectories of the ethylene-bound ETR1 TMD suggest directional movements of amino acids known to be associated with ethylene binding or signal transduction. These movements are less pronounced or absent in the unbound- or 1-MCP-bound states. Overall, these studies provide initial insights into how ethylene binding affects ETR1 structural dynamics, and how antagonists, such as 1-MCP, maintain ETR1 activity and will ideally provide an experimentally validated view of the structural dynamics of full-length ETR1 at the atomistic level. The latter is a prerequisite for understanding how ethylene binding is signaled to downstream elements.



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Localization and decomposition of free energies in solution

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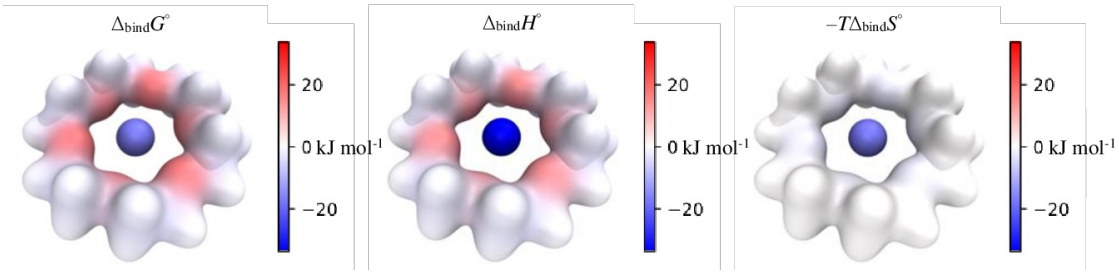
The Gibbs free energy is the relevant thermodynamic quantity to understand the direction and outcomes of chemical reactions or biophysical processes. It is directly associated with partition coefficients, solubilities, or binding constants for host-guest and protein-ligand complexes. Therefore, several experimental and computational methods are established to determine binding free energies. However, these methods only yield macroscopic quantities and offer no insight into individual contributions of the system's components. Interpreting these macroscopic quantities can be especially challenging, for instance, when the reaction Gibbs energy is relatively small due to underlying counteracting processes. [1]

In order to get a better insight into the reaction thermodynamics we here present approaches to decompose and localize free energy contributions using both classical force field (FF) and quantum mechanical (QM) methods. Both methods employ the decomposition of the reaction Gibbs free energy into energetic and entropic proportions, and furthermore split these into solvation and gas phase contributions.

In the QM approach, free energy decomposition is achieved by combining the embedded reference interaction site model (EC-RISM) for solvation thermodynamics with a normal mode analysis (NMA) calculation to obtain gas phase contributions. Moreover, to not only decompose but also localize the free energy contributions, we use the three-dimensional reference interaction site model (3D RISM) in the FF approach. Local solvation (free) energies and entropies can then be mapped onto individual molecular sites or groups. [2,3] Local energetic components are calculated using molecular dynamics simulations, while local vibrational entropy contributions can be obtained via NMA or density of states integration (DSI). [4,5]



With these novel approaches we can combine both the decomposition and localization aspects, as atom-wise contributions are not only calculated for the binding free energy but also for its thermodynamic components. These atom-local values can then be visualized and used to identify "hot spots" in terms of reaction sites or protein regions for, e.g., ligand binding. [4] Furthermore, major energetic and entropic contributions to the driving force can be identified. Exemplary applications include crown ether complexes and solvent-controlled supramolecular cage formation.

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mRNA lipid nanoparticle phase transition

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Crucial for mRNA-based vaccines are the composition, structure, and properties of lipid nanoparticles (LNPs) as their delivery vehicle. Using all-atom molecular dynamics simulations as a computational microscope, we provide an atomistic view of the structure of the Comirnaty vaccine LNP, its molecular organization, physicochemical properties, and insight in its pH-driven phase transition enabling mRNA release at atomistic resolution. At physiological pH, our simulations suggest an oil-like LNP core that is composed of the aminolipid ALC-0315 and cholesterol (ratio 72:28). It is surrounded by a lipid monolayer formed by distearoylphosphatidyl-choline (DSPC), ALC-0315, PEGylated lipids, and cholesterol at a ratio of 22:9:6:63. Protonated aminolipids enveloping mRNA formed inverted micellar structures that provide a shielding and likely protection from environmental factors. In contrast, at low pH, the Comirnaty lipid composition instead spontaneously formed lipid bilayers that display a high degree of elasticity. These pH-dependent lipid phases suggest that a change in pH of the environment upon LNP transfer to the endosome likely acts as trigger for cargo release from the LNP core by turning aminolipids inside out, thereby destabilizing both the LNP shell and the endosomal membrane.

Metadynamics Simulations of FPR2: Using an Enhanced Sampling Method to Elucidate The Mode of Action of a Diverse Set of Ligands

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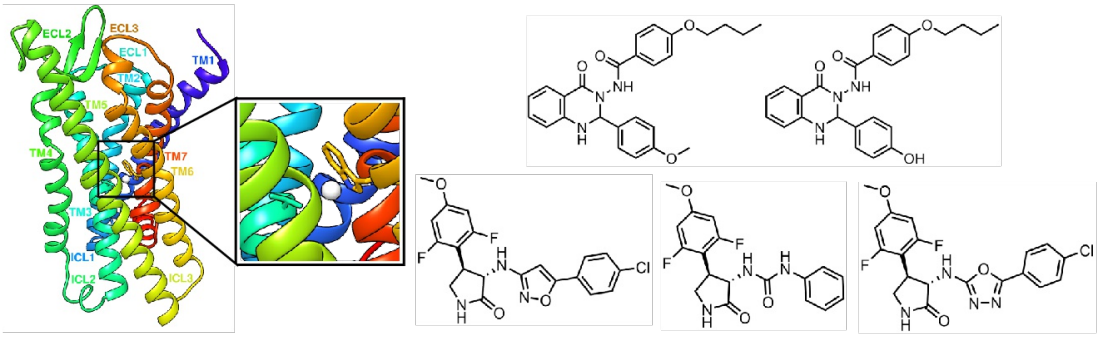

The Formyl Peptide Receptors (FPRs) belong to the class A of G-protein coupled receptors (GPCRs); the family has three members: FPR1, FPR2 and FPR3.
Seven transmembrane helices (TM) connected by three extracellular (ECL) and three intracellular loops (ICL) are characteristic for GPCRs, as illustrated in the left figure above. [1] FPRs play a key role in the host defense against microbes because they are located on immune cells like phagocytes that belong to the innate immune system. Thus, they are also involved in inflammatory diseases like Alzheimer's disease or cancer and are novel targets for the treatment of those diseases. [2] Several small molecules and peptides are known which either act as agonists, partial agonists or antagonists. [3,4] We selected some of the small molecules that represent these classes (see figure for examples) for further computational analyses including binding-mode identification, binding-pathway analysis and free energy of binding calculations using metadynamics simulations.
First, the molecules were docked into the orthosteric binding site of FPR2 of a cryo-EM structure in complex with a known peptide agonist (PDB ID 7wvw). The resulting FPR2 complex structures were used for µs-time scale metadynamics simulations conducted mainly on the Alex cluster of NHR@FAU in Erlangen using Gromacs and Plumed. The simulations were run following a protocol that was already described earlier by Saleh et al. [5]. The funnel is placed above the center between the Cα atoms of the residues Val113$^{3.40}$ and Trp254$^{6.48}$, as can be seen in the zoomed-in picture above. The residues are shown as sticks and the center is indicated by a white sphere.
With this approach, it was possible to simulate the binding/unbinding of the ligands and to determine the free energies of binding with sufficient accuracy. The global free energy minimum obtained corresponded well to the known binding poses and gave new insight into the binding mode of small-molecule ligands. This knowledge will be used to design novel ligands for FPR2. The results highlight the importance of a deep, hydrophobic pocket at the bottom of the orthosteric site and of three polar residues right above it. Furthermore, these data suggest comparable binding modes of small molecules and peptides, contrary to earlier results [6].

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DNA-Repair Mechanisms: Molecular Simulations and Computational Alchemy

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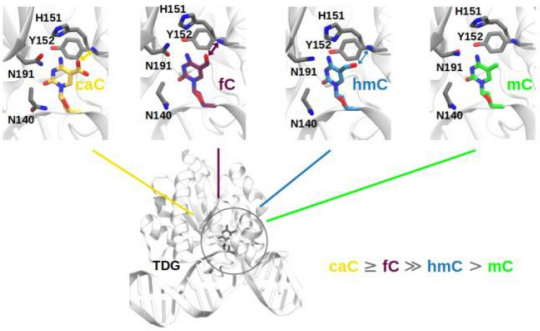

The DNA repair protein thymine DNA glycosylase (TDG) removes mispaired or damaged bases, such as oxidized methylcytosine, from DNA by cleavage of the glycosidic bond between the sugar and the target base flipped into the enzyme's active site. The enzyme is active against formyl-cytosine and carboxyl-cytosine, whereas the lower oxidized hydroxymethyl-cytosine and methyl-cytosine itself are not processed by the enzyme. To investigate the substrate specifity of TDG, we used extensive molecular dynamics simulations and thermodynamic integration of TDG complexed to DNA carrying one of four different (oxidized) methyl-cytosine bases methyl-cytosine (mC), hydroxymethyl-cytosine (hmC), formyl-cytosine (fC), or carboxyl-cytosine (caC), in extra- and intrahelical conformation, and in their amino- and imino-tautomeric forms. Our results indicate that discrimination of the oxidized methyl-cytosines does not take place in the initial complex formation before the base has been flipped out into the active site, and that imino-tautomers do not play a role in substrate recognition at this stage. For the extrahelical complexes, we observe a more favorable binding affinity of the higher oxidized forms, fC and caC, compared to the nonsubstrate bases hmC and mC. Despite rather comparable, reaction-competent conformations of the flipped bases in the active site of the enzyme, more and stronger interactions with active site residues account for the preferred binding of the higher oxidized bases. Overall, our computational results indicate that the enzyme discriminates the different oxidation forms of methyl-cytosine at the formation of the extrahelical complexes, and possibly also at a later chemical step.

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Mechanistic insights into G protein association with a G protein-coupled receptor

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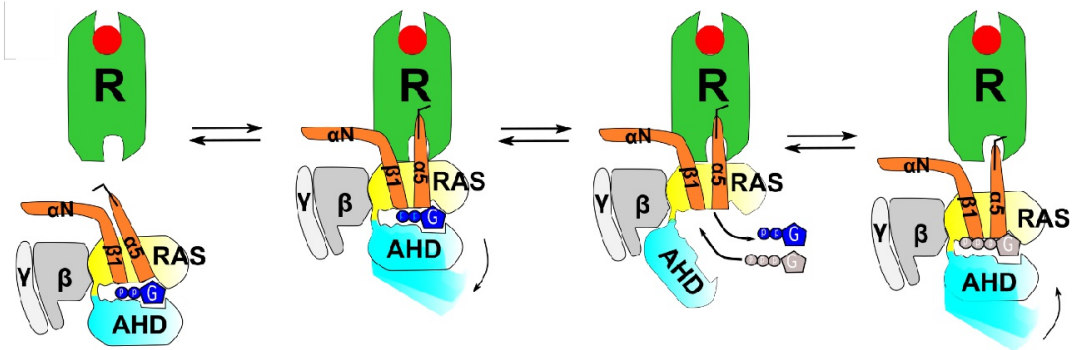

Heterotrimeric G proteins are activated by G protein-coupled receptors (GPCRs) mediating the exchange of guanine nucleotide in the Gα subunit. Using molecular dynamics (MD) simulations, we investigate atomistic details of the process of G protein association with a GPCR, describing the events that ultimately lead to ejection of GDP from its binding pocket in the Galpha subunit and formation of a nucleotide free R-G^{empty} complex. We simulated the first steps of this reaction sequence [1] for the β2AR-Gs signaling system, for which there is a wealth of biochemical, biophysical and structural data that can support further interpretation [2-4]. In classical all-atom μ-second (MD) simulations we observe association of membrane anchored Gs^{GDP} to the membrane embedded, agonist bound, β2-adrenoceptor (β2AR). We identify an extended binding interface of the receptor with the G protein compared to β2AR-Gs^{empty}, confirmed by site-directed mutagenesis and functional assays. Moreover, we observe major conformational changes at the nucleotide-binding pocket, significantly reducing the energy needed for GDP release. Our analysis sheds new light on the initial steps of receptor-mediated G protein activation and extends the limited view of nucleotide-free snapshots to include additional states and structural features responsible for signaling and G protein coupling specificity.

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The National High-Performance Computing Alliance: New infrastructure and opportunities for science and research at German universities

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In 2021 the NHR Alliance has been established which bundles the resources and competencies of high-performance computing at German universities. Infrastructures and services of the NHR centers are open to all researchers at German universities. The presentation introduces the NHR Alliance and focuses on offerings for the field of atomistic simulations.

https://www.nhr-verein.de/
https://hpc.fau.de/

Machine Learning Interatomic Potentials: Reference Training Data on the Hands of Workflows

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Machine learning interatomic potentials (MLIPs) have drawn great attention in recent years. A variety of satisfactory methods have been developed thus far. Nevertheless, a key success of every MLIP heavily relies on the quality of the training dataset whose generation typically requires considerable treatment by a qualified scientist. To generate diverse and comprehensive training reference data points, we employ workflows that execute in a cyclic process way the combination of crystal structure prediction (CSP) and training of MLIPs. The generated conformations in CSP runs are post-processed to exclude similar structures and append those which either fill the holes of the current feature space or expand it. All steps are performed automatically with minimal human intervention.

Neural Fingerprints: Structure- and activity-sensitive molecular representations based on neural networks for virtual screening approaches

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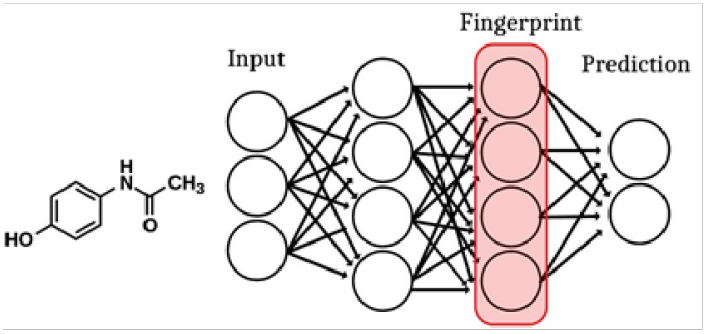
Similarity-based virtual screening remains an important technique in the early stages of the drug discovery process. Amongst other things, the success relies on the appropriate choice of the underlying molecular representation, the molecular fingerprint. Our work focuses on improving these molecular representations to encapsulate more domain-relevant information with the help of neural networks. This approach works by extracting activations of the last hidden layer of a trained neural network as a novel neural network fingerprint representation for similarity-based virtual screening.



We could show for kinase inhibitors [1] and natural products [2] that the neural fingerprints extracted from trained neural networks outperform other fingerprints in similarity search, by providing overall more active hits than any other. So, it is possible to generate domain-specific neural fingerprints as a structure- or activity-sensitive molecular representation through the usage of supervised training for neural networks. Interestingly, we found that GNNs, compared to simple MLPs, created worse neural fingerprints when trained on the same tasks. Additionally, we were able to extract a Natural Product Likeness Score[2], as an alternative measure of assessing how likely a molecule is a natural product.

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Enabling Prediction of Protein-Protein Binding Affinities Using FEP+

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Physics-based free energy perturbation (FEP) calculations provide accurate energetics while allowing conformational flexibility by using explicit solvent molecular dynamics (MD) simulations with a state-of-the-art force field. The accuracy and efficiency of these calculations can be improved through enhanced sampling protocols for mutating residue and nearby waters, effective handling of proline and charged amino acids, and automated parameterization of non-canonical amino acids. FEP+[1] and our new constant-pH molecular dynamics (CpHMD) implementation can account for protonation and tautomeric state changes, both upon binding/folding and at different pH values. Our approach was recently demonstrated in a real-world collaboration, where it was able to reduce cost and accelerate the development process significantly.

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Accelerating plane-wave-based ab initio molecular dynamics by optimization of Fast-Fourier transforms for modern HPC architectures

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The most important advantage of plane-wave basis sets is that wave functions can be transformed efficiently from reciprocal to real space and back by using the Fast-Fourier transform (FFT) algorithm. This allows to evaluate the kinetic and potential energy in reciprocal and real space, respectively, where both operators are diagonal. This reduces the computational cost for applying the Hamilton operator from N^2 to $NlogN$. However, the scalability of current FFT libraries is rather limited on today's HPC systems, which offer large numbers of compute nodes, each of them with many cores. Here we present our optimization of the FFTX library of the Quantum Espresso software package. Data distribution and communication patterns have been revised to make optimal use of combined MPI and OpenMP parallelization. Scalability is further increased by combining FFTs into batches and by introducing overlapping computation and communication. We implemented the revised FFTX library in our optimized version of the CPMD code [1], and we demonstrate the achieved acceleration by a series of benchmark simulations.

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Multi-Scale Modelling of Epoxy Resin and Composites: from Curing to Fracture

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Polymer modeling across time and length scales can bridge the gap from molecular considerations to the design of macroscopic components and requires understanding in a broad spectrum of physical and chemical phenomena. Quantum mechanical (QM) calculations provide the basis for the formation of atomistic polymer networks on the nano-scale with respect to thermodynamics. Monitoring dynamic processes along fracture by means of molecular dynamics (MM) enable development of coarse-grained models (CG).

We investigated the epoxy system of bisphenol-F-diglycidyl-ether (BFDGE) and 4,6-diethyl-2-methylbenzene-1,3-diamine (DETDA) regarding the crosslinking reaction, as well as bond dissociation, by development of a reactive Force Field, which facilitates our curing algorithm to reach the experimental crosslinking degree of 99% [1,2]. The resulting, reliable models fulfill bulk, especially the elastic properties, we derived from linear response theory [3]. Furthermore, we studied tensile deformation about inter-molecular reorganization processes along fracture processes and extrapolated occurring stresses to vanishing strain rates, which yielded in accordance with macroscopic specimens [2,3]. We also accomplished the transfer from molecular simulation to constitutive modeling by means of a multi-scale modeling capturing deformation and damage in epoxy resins [4]. Addressing the interplay of composite materials, we studied molecular structuring of epoxy at silica and cellulose interfaces [5] as well as corresponding forces along detaching processes [6]. In conclusion, there is a large body of atomistic-level insights available to provide the needed inputs for a coarse-grained setup. This setup will hence not rely on ad hoc assumptions, but directly feature the beforehand identified properties from QM and MM methods.

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Recent advances in the Embedded Cluster Reference Interaction Site Model

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The Embedded Cluster Reference Interaction Site Model (EC-RISM) is a well-established method to combine quantum-chemical calculations with the three-dimensional Reference Interaction Site Model (3D RISM). [1-3] This integral equation theory represents the solvent by the equilibrium distribution functions of its constituting atoms around the solute, from which thermodynamic properties such as the excess chemical potential and the partial molar volume are readily accessible. The quantum-chemical part of the EC-RISM method does not only provide the electrostatic part of solute-solvent interactions but also allows for the determination of observables from the solvent-polarized solute wave function, such as the electronic energy of the solvated molecule and spectroscopic information like infrared (IR) data, nuclear magnetic resonance (NMR) [4] and electron paramagnetic resonance (EPR) parameters. [5]

Quantitative results for the excess chemical potential have been obtained for water and organic solvents based on partial molar volume-based corrections, enabling the prediction of properties with high accuracy. In the SAMPL6 and SAMPL7 blind challenges, the acidity constants (pK_a) of diverse sets of compounds could be predicted with consistent RMSEs of 1.15 and 0.72 pK units, respectively. [6-8] Octanol-water partition coefficients (log P) of the challenge compounds on the other hand yielded a prediction range of 0.47-1.84, leaving room for improvement of organic phase models.

As a very recent development, the EC-RISM formalism was integrated directly into the SCF procedure of the popular quantum chemistry package ORCA. [9] In contrast to the established script-based approach, calculation of the electrostatic potential and of 3D RISM distribution functions are performed during the SCF iteration, saving considerable computational overhead. This approach also allows for the formulation of an analytic gradient enabling geometry optimizations on the EC-RISM free energy surface from which, for instance, pressure-dependent changes in molecular geometries and their influence on spectroscopic observables can be deduced. Early results indicate that the effect of small, pressure-induced changes in molecular structure on pressure-dependent NMR parameters can be significant.

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Effect of N140D and T197A mutations on DNA repair enzyme Thymine DNA Glycosylase

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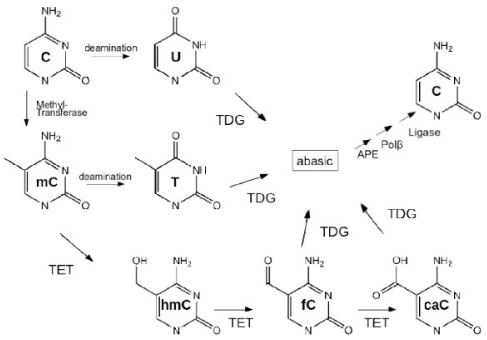
Thymine DNA Glycosylase (TDG) is an enzyme that participates in the DNA repair mechanism. Its primary role is to identify, and excise modified and mismatched bases, more specifically, Thymine, Uracyl or and oxidized form of Cytosine [1,2].



TDG's reaction mechanism involves the placement of a water molecule, that acts as a nucleophile, by two residues: N140 and T197 [3]. Mutating these residues inactivates or severely reduces enzyme activity. Interestingly, N140D mutated TDG is inactive against most substrates (except carboxyl cytosine), even though D140 could replace N140 in nucleophile placement [4].

Through atomistic MD simulations, we observed that a hydrogen bond network, involving N140 and T197, is crucial for the stability of the Protein-DNA complex formed during the excision mechanism. In the N140D mutation, the aspartate is unable to maintain most of the interactions of the network, and thus the complex becomes unstable, rendering TDG inactive. Protonation of D140 slightly alleviates this issue, acting as a surrogate of the amino group of N140, but the interactions formed are weaker than the wild-type enzyme. For T197A, some interactions of the network are kept, but the complex is not as stabilized as in wild-type, reducing TDG's activity drastically.

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Optimisation of electrophile reactivity

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Abstract

Electrophiles are widely used as drugs, thus optimising their reactivity can lead to a significant improvement of their selectivity. Existing ways of optimisation, like transition state search are quite expensive in terms of time, money and energy consumed. Finding a more efficient way to predict reactivity of electrophiles can allow to reduce the expenses for optimising the structure of an electrophile and achieve the desired reactivity.

DNA-Repair Mechanisms: Molecular Simulations and Computational Alchemy

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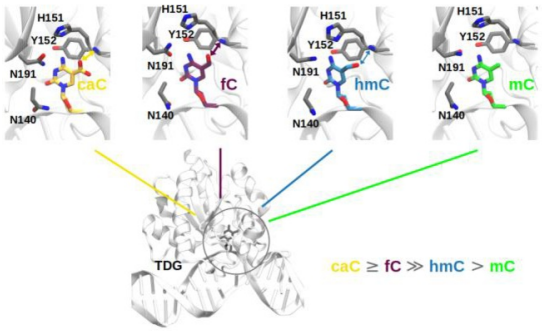

The DNA repair protein thymine DNA glycosylase (TDG) removes mispaired or damaged bases, such as oxidized methylcytosine, from DNA by cleavage of the glycosidic bond between the sugar and the target base flipped into the enzyme's active site. The enzyme is active against formyl-cytosine and carboxyl-cytosine, whereas the lower oxidized hydroxymethyl-cytosine and methyl-cytosine itself are not processed by the enzyme. To investigate the substrate specifity of TDG, we used extensive molecular dynamics simulations and thermodynamic integration of TDG complexed to DNA carrying one of four different (oxidized) methyl-cytosine bases methyl-cytosine (mC), hydroxymethyl-cytosine (hmC), formyl-cytosine (fC), or carboxyl-cytosine (caC), in extra- and intrahelical conformation, and in their amino- and imino-tautomeric forms. Our results indicate that discrimination of the oxidized methyl-cytosines does not take place in the initial complex formation before the base has been flipped out into the active site, and that imino-tautomers do not play a role in substrate recognition at this stage. For the extrahelical complexes, we observe a more favorable binding affinity of the higher oxidized forms, fC and caC, compared to the nonsubstrate bases hmC and mC. Despite rather comparable, reaction-competent conformations of the flipped bases in the active site of the enzyme, more and stronger interactions with active site residues account for the preferred binding of the higher oxidized bases. Overall, our computational results indicate that the enzyme discriminates the different oxidation forms of methyl-cytosine at the formation of the extrahelical complexes, and possibly also at a later chemical step.

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The structural basis that drives ligand efficacy at the serotonin 5-HT$_{1A}$ receptor

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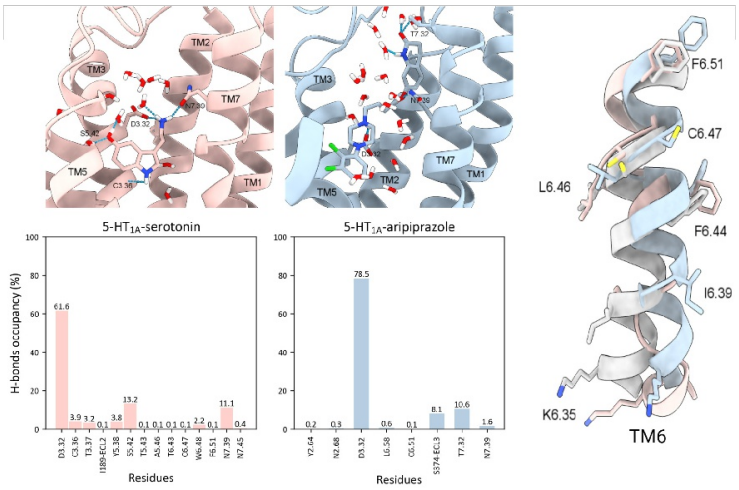
G-protein coupled receptors (GPCRs) are the largest superfamily of membrane proteins in the human genome; they modulate numerous physiological responses [1]. The 5-HT$_{1A}$ receptor, a Class A GPCR, is a member of the serotonergic receptor family, which is found in the central and peripheral nervous systems and activated by the neurotransmitter serotonin (5-hydroxytryptamine, 5-HT). Although the 5-HT$_{1A}$ receptor subtype is one of the most studied, since it is an important therapeutic target for several neuropsychiatric disorders, including anxiety, depression, and schizophrenia [2], the structural basis, which involves receptor dynamics, ligand efficacy and receptor activation, is largely unknown. Here, we use a metadynamics protocol based on the general activation index A^{100} [3] to study the activation of the 5-HT$_{1A}$ receptor. We show free-energy profiles for the serotonin receptor as binary (apo-receptor + G-protein-α-subunit and receptor + ligand) and ternary complexes with two prototypical orthosteric ligands; the full agonist serotonin and the partial agonist aripiprazole. The computed free-energy landscapes, specific interaction analysis and structural inspection suggest a combined mechanism that requires the action of both stabilizing intracellular and extracellular interactions in the receptor core for the full activation of the receptor. We have demonstrated the potential role of polar interaction networks in the receptor core as a regulator of the initial stages involved in receptor activation. In particular, our simulations have provided, on an atomistic level, direct evidence of the structural requirements that drive ligand efficacy at the 5-HT$_{1A}$ receptor. Thus, the results reported here constitute findings of remarkable value, not only for understanding the biophysical basis of signaling but also to provide the knowledge necessary to design more effective and less toxic drugs.



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Mechanics of Histamine: Computational analysis of protonation effects on H_1R binding.

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Based on a structure of the ternary histamine-H_1R-Gq complex, we investigated the role of different protonation states of histamine for binding the H_1-receptor. Molecular dynamics simulations revealed that the τ-tautomer of histamine formed stable interactions with the receptor. A π-tautomer, on the other hand, induces a rotation of the histamine ring by 180°. The simulations thus indicate that the τ-tautomer of histamine is the relevant protonation state that stabilizes the active ternary histamine-H_1R-G_q complex. In addition to the tautomers, the binding of a dicationic histamine was investigated, whose interaction with the H_1R was shown in a previous experimental study. The simulations demonstrated that the dication is less compatible with the ternary histamine-H_1R-G_q complex than the monocation and in one case even dissociates. The studies performed in this work thus provided contributions to the mechanistic understanding of histamine receptors, which may be used for future design approaches in drug development.

Quantum chemical analysis of structure and ion selectivity correlation of moieties derived from the [2.2.2] cryptand

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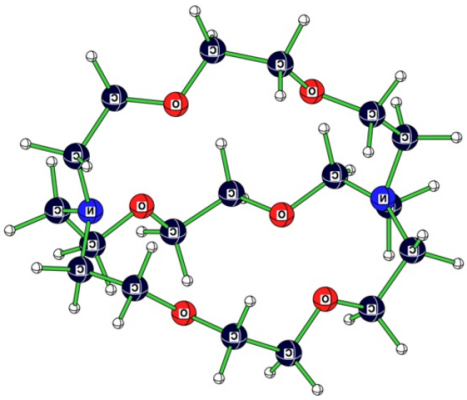

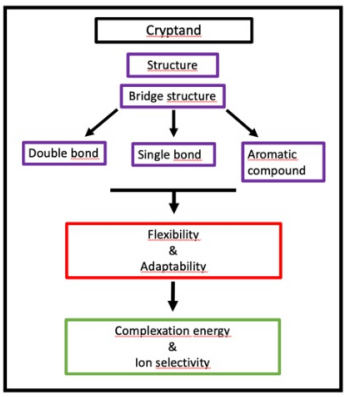

A great impact in the field of supramolecular chemistry was made by J.-M. Lehn and his coworkers in 1967 by the discovery of 4,7,13,16,21,24-(hexaoxa-1,10-diazabicyclo-[8.8.8] hexacosane, better known as [2.2.2].[1] Today, [2.2.2] is the most prominent Cryptand and commercially available as Kryptofix 222. The outstanding complexation properties of [2.2.2] for alkaline and earth metal ions were immediately recognized. This discovery earned Lehn together with Pedersen and Cram the Nobel Prize in 1987.

The field of supramolecular encapsulation chemistry has thus been given the task of studying the [2.2.2] cryptand and its related systems in order to gain a better understanding and, if necessary, to carry out optimizations.[2][3] But what factors influence complexation properties and can these factors be modified to achieve a desired complexation behavior?

Based on DFT (B3LYP/LANL2DZp) calculations we designed derivates of [2.2.2]. At first glance, the structures of derivates differ significantly in their flexibility. In order to understand the effect of the flexibility of the structure on the ion selectivity, different descriptors were applied.
Specifically, complexation energies, bond lengths, dihedral angles and cavity volumes were investigated and correlated to each other, leading to some novel and interesting insight into the influence of cryptand cage flexibility and cryptand cavity volume on the depth and width of the ligand complexation energy curve relative to ligand type, size and charge.

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Structure-based design and optimization of ligands for novel antiviral strategies

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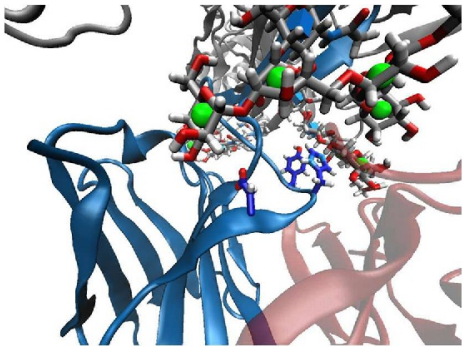
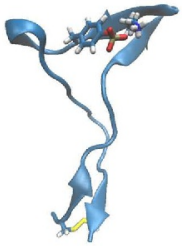
Broadly neutralizing antibodies that bind to viral fusion proteins represent a promising strategy for protection from viral infections. Such antibodies can be used for passive immunization and are currently tested in clinical trials, but they are expensive and difficult to produce. As an alternative, antibody-derived peptides may be used for this purpose. Suitable antibody sequences were identified using a newly developed computational pipeline that identifies interfaces in complexes of antibodies and viral fusion proteins. Application of this pipeline to 2050 interfaces of HIV-1 antibody-antigen complexes lead to several promising candidate peptides, which were investigated by molecular dynamics (MD) simulations.





The first peptides investigated by this MD-based optimization approach are from a sulfo-tyrosine containing broadly neutralizing antibody PG16. Optimization of the peptide length is based on the energetic analysis of the complex interface, which particularly focuses on the roles of glycans in the interaction. In addition, the effect of peptide cyclisation was assessed from microsecond MD-simulations of the free peptides. This approach resulted in a high-affinity peptide ligand that was experimentally demonstrated to exhibit a nanomolar affinity for the HIV-1 gp120 protein.

Amine Transaminase Engineering based on Constraint Network Analysis

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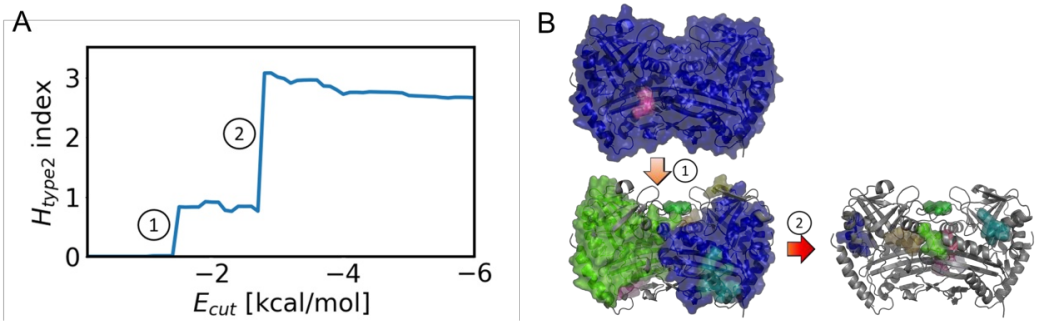
Amine transaminases (ATAs) are important enzymes for the production of chiral amines in the pharmaceutical and fine chemical industries. [1] However, the application of ATAs on novel substrates is often accompanied by several challenges. These include product and co-substrate inhibition effects as well as limited resistance to organic solvents needed for substrate solubilization. [2]

With our in-house software Constraint Network Analysis (CNA), we can study protein rigidity at the atomistic level and gain insights into structural changes during thermal unfolding. [3] This is achieved by monitoring changes in a cluster configuration entropy (H_{type2}) index while removing constraints between atoms according to a stepwise increasing cut-off energy (E_{cut}), to mimic the weakening of non-covalent interactions upon heating of the enzyme (Figure A). Based on this analysis, we aim to identify structural weak spots, i.e., residues that can be mutated to improve protein rigidity, in ATAs of fold type I and IV.

With the goal of stabilizing ATAs in reaction conditions with increased temperatures, organic solvents, and high co-substrate concentrations, we apply CNA on ATA structure ensembles generated via molecular dynamics simulations in both explicit water and mixed organic solvents. By applying this approach to ATA variants with known (de-)stabilizing mutations, we study changes in the unfolding behavior to ultimately propose novel stabilizing mutations.

Initial rigidity analysis of a dimeric fold type IV ATA representative (PBD-ID: 4CE5) shows a two-phase thermal unfolding process (Figure A), with the dimer interface destabilizing first, followed by decomposition of the rigid clusters in both monomer subunits (Figure B). This early insight can already be used to guide the engineering of this ATA to prioritize dimer interface stabilization, with the analysis of further ATA variants in progress.



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Modelling liquid flow through nanopores on the nanoscale

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Abstract

Liquid chromatography is one of the most important separation techniques and has proceeded mainly along empirical knowledge from the expansive collection of experimental data by using chromatographic methods, spectroscopic methods and technical innovations in column packing, particle technology and equipment design. However, a classic liquid chromatography column, is a cylinder densely packed with mesoporous silica particles whose surface has been mostly chemically modified. In this work, we investigated the physisorption of water to functionalized silica surfaces and hydrophilicity properties of surface by molecular dynamics simulations. We built on previously gathered knowledge on chromatography to establish a unified picture of stationary phase and solute mobility in liquid chromatography. In analogy to previous studies, we utilized a crystalline SBA-15 structure as starting point for our modeling approach. Furthermore, we investigate the effect of functionalization using different loadings with silanol group (Si-OH) and trimethylsilyl groups (O-SI-$(CH_3)_3$). With this strategy, we hope to understand the effect of functionalization of silica on the physisorption of water molecules at the nanometer scale.

Accurate prediction of acidity constants with an ONIOM embedded cluster RISM approach

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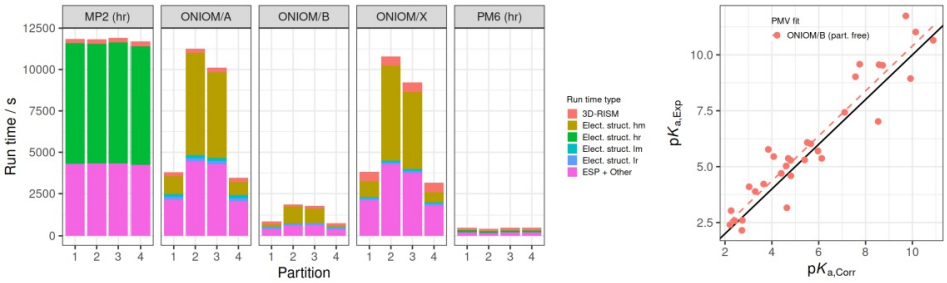
The accurate prediction of physicochemical properties such as acidity constants (pK_a) plays a decisive role for, e.g., modelling protein function or in the development of drug-like molecules. As cellular environments show a variety of different pH values, the pK_a of a titratable residue or drug therefore heavily influences the mode and strength with which a compound may bind to its target. Our previous strategy for predicting pK_a values for small molecules focused on modelling the compounds' thermodynamics in an aqueous environment by means of our "embedded cluster RISM" (EC-RISM) solvation model and first-principles quantum mechanical (QM) calculations. [1] However, the size of most biomolecular systems prevents the application of these QM methods, thus prohibiting the accurate and granular modelling of the solvent environment with EC-RISM. Since the first suggestion by Warshel and Levitt [2] multiscale methods have emerged as an effective tool to model large-scale chemical processes in various environments, thus offering a route to expand the range of system sizes that can be modelled via EC-RISM theory.



Here we present a novel multiscale solvation model which integrates a subtractive ONIOM(QM:SQM) [3] description of the solute into the EC-RISM formalism, combining established high-level QM methodology with EMPIRE [4] for the low-level semiempirical (SQM) component. We show how the set of equations used within this model can be derived, by similar approximations to the ones used for the ONIOM-PCM solvation model. [5] Extending previous schemes, [1] we develop an empirical correction to the solute's Gibbs energy, which is free of any ONIOM partitioning error. The resulting model is then validated for the SAMPL6 pK_a challenge dataset. [1,6] Our promising results show that the novel ONIOM-EC-RISM approach ranks equal in prediction quality with our previous full-QM EC-RISM methodology, while simultaneously drastically reducing the required computational cost. Thus, the model offers a step forward for modelling systems in solution up to biomolecular targets.

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Towards automated exploration of enzymatic reactions

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Mapping out a reaction mechanism involves optimizing the reactants and products, finding the transition state and following the reaction path connecting them. Enzymes, however, consist of several thousand atoms, and about one order of magnitude more electrons, a system size that is not easily tractable. Modelling enzymatic pathways is challenging because of the complexity of the system. 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" naïve. Instead many reaction pathways are conceivable, which might be different conceptually such as a dissociative vs. an associative pathway. One approach to overcome previous difficulties is to use transition network approach to sample conformational transitions in proteins, to explore enzymatic reaction pathways [1].

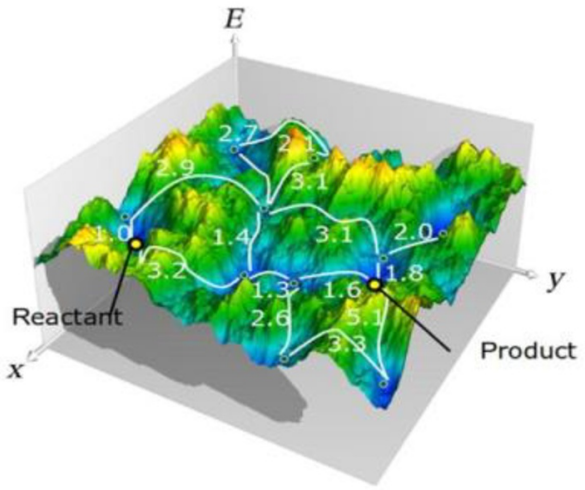

Figure: Schematic energy landscape with "valleys" (blue) and "mountains" (yellow/orange). Yellow points mark end states and green dots are intermediate states. White connections with transition barriers indicate a variety of possible pathways. Figure is taken from [1]

Carboxypeptidase A (CPA) an exopeptidase secreted by the pancreas which catalyzes the elimination of the C-terminal amino acid via hydrolysis, with a preference toward residues with hydrophobic side chains [2]. CPA occupies a special place in enzymology as the third enzyme whose three dimensional structure was determined with hight resolution by X-ray diffraction. Despite the abundance of structural information, however, there are still controversies concerning its catalytic mechanism.

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Coarse-Grained Simulations of Ligand-Tethered Nano-Tripods

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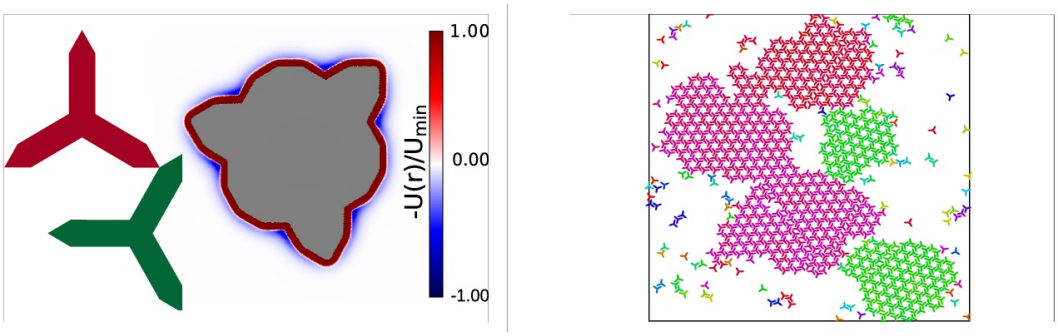
Ligands play important roles in nanocrystal assembly: they control the shape of nanocrystals, function as stabilizers, and determine the structure of the self-assembled superlattice. Two-dimensional nanocrystals, so-called nanoplates, are ideal model systems to study the effect of ligands as they can be synthetized with a range of aspect ratios and be functionalized highly controllably by ligands of different chemical species, molecular weight, and densities. Here, we present coarse-grained molecular dynamics simulation model to predict the self-assembled superlattices of nanoplates functionalized with ligands. We apply this framework to tripods, where we predict a number of distinct superlattices, among them chiral ones and with regular and controllable porosity. The coarse-grained simulation model describes the van der Waals interaction of the tripods that accounts for relative orientations via a generalized Derjaguin approximation by Monte Carlo integration over the nanocrystal surfaces. [1] The Monte Carlo results for the interaction potential are precalculated and tabulated for use in coarse-grained molecular dynamics simulations. We study the effect of tripod aspect ratio, ligand molecular weights and grafting densities, and thermodynamic conditions on the geometric structure of the self-assembled superlattices.



Our simulation results agree with experimental observations of rare earth oxide tripod particles and shade light on the complex superlattice formation pathways. Such pathways are not directly accessible by experiment. Our coarse-grained model and its predictions can be generalized to other convex and concave nanoplates and nanocrystals in three dimensions to evaluate the interplay of particle shape and patchy, directional ligand-induced interactions for the synthesis of functional nanostructures.

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Identifying descriptors of the conductive state in small viral K^+ ion channels

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Gating, the process of stochastic fluctuations between open and closed states of ion channels, is essential for regulating transmembrane ion fluxes in cells from all forms of live in the context of ion homeostasis and electrical signalling. The origin and intricacies of gating are not fully understood yet. The structure of a channel in its various gating states, which is controlled by its amino acid sequence, also directly influences ion selectivity. We here focus on a miniature model system for canonical tetrameric potassium channels, the virally coded Kcv_{PBCV-1}, comprised of only 94 amino acids per monomer. [1,2] In spite of its small size this channel protein still represents the highly conserved core pore module of all K^+ channels and shows all essential functional features like gating and selectivity.

To investigate the properties of ion channels in solution and embedded within a membrane environment molecular dynamics (MD) simulations are commonly utilized. Here, a homology model based on the NaK ion channel mutation NaK2K was used as initial structure. [3] By changing the K29 protonation state of Kcv_{PBCV-1} to a neutral form, we were able to observe multiple ion transitions in µs-timescale MD simulations. The resulting computed conductivity is compatible to experimental results including data from a mutant (K29A) that neutralized the cationic amino acid. From the trajectory data representative structures were computed by means of simulated annealing, [4,5] allowing direct comparison of the thermodynamic properties of structures at different K29 protonation states simulated at 0 and +425 mV respectively. For the first time, we could characterize the properties of solvent species within the confined geometry of a highly conductive Kcv_{PBCV-1} structure by means of the 3D Reference Interaction Site Model (3D RISM). [6]

Additionally, we could monitor and characterized the structural changes underlying a so-called "filter gating" in Kcv_{PBCV-1}. In this type of gating very negative voltages cause a fast inactivation of the channel. Here we find conformational changes of filter residues correlated with inactivation, consistent with literature. [7] The computed open channel time spans allow for the calculation of rate constants that can be directly compared to the corresponding values of channel fluctuations under similar conditions in experiments. The computational and experimental data are in good agreement, including the effect of modulating the KCl solvent concentration on the rate constant. Thus, we were able to successfully combine computational structure modelling and simulation with experimental functionality assessment in the same time window in a complementary manner.

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Count on NHR@FAU for your Atomistic Simulations

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The Erlangen National High-Performance Computing Center (NHR@FAU) at FAU Erlangen-Nürnberg [1] is one of the recently established national centers for HPC at German universities. Together with eight other institutions, they form the NHR-Alliance [2]. NHR@FAU operates large-scale HPC systems and provides HPC services, related user support, and HPC training to German universities.

NHR@FAU has a strong focus on atomistic simulations and 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 on chemical and biomolecular 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

digitalSELEX: *in silico* Platform for Designing Oligonucleotides

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Rapid identification of biological and chemical threats as well as rapid development of therapeutics is critical for the warfighter and maintaining combat readiness particularly in remote and austere locations. Antibodies have long been used for identifying pathogens on biosensor devices and as therapeutics to target both viral and bacterial pathogens. Aptamers are single-stranded oligonucleotides, RNA or DNA, and analogous to antibodies for their target recognition and range of applications. These oligonucleotides, however, are typically one-tenth the molecular weight of antibodies and can be chemically synthesized making them immune to batch variations like antibodies.

The gold standard method for identifying aptamers with both high affinity and specificity towards their target protein is achieved through a process known as a **S**ystematic **E**volution of **L**igands by **EX**ponential (SELEX) enrichment. There are multiple SELEX variations but typically consist of exposing an initial oligonucleotide library (~10^{15} molecules) to both target and non-target molecules over success rounds (10-15) prior to sequencing and then further *in vitro* validation.

While the SELEX method can produce high affinity aptamers (dissociation constants in the low nanomolar range), the repetitive nature and stringent counter-selection steps make the process both time consuming and expensive. The in vitro selection process limits applications aspects to only those replicated in the SELEX process (*e.g.,* temperature, pH, and ion concentration). There has been recent work to incorporate ML/AI algorithms into the SELEX process to improve the limited success rate. These combination works have been limited by the massive dataset required for aptamer development still requires *in vitro* selection, meaning environment dependence, and a lack of fidelity on actual nucleotide – amino acid interaction sites. To overcome the low success rate, improve cost, and reduce time, we have developed an *in silico* oligonucleotide design platform, digitalSELEX.

Our platform breaks down a target protein to identify and cluster accessible / biologically relevant atoms. Nucleotides are assigned to the corresponding amino acids and an initial sequence is optimized using a constrained genetic algorithm towards the desired application (*e.g.*, therapeutic or biosensor probe). The sequence then undergoes an *in silico* counter-selection step using molecular docking to optimize the nucleotide sequence with simultaneous random perturbations to ensure high affinity for the target and low affinity for non-target proteins. Once the oligonucleotide is designed, it is chemically synthesized, and the affinity and specificity are determined using flow cytometry. Our digitalSELEX platform reduces the aptamer identification process from several months to a few days while simultaneously reducing cost.

Molecular Case Study of a *GALC* Mutation Causing Infantile Krabbe Disease

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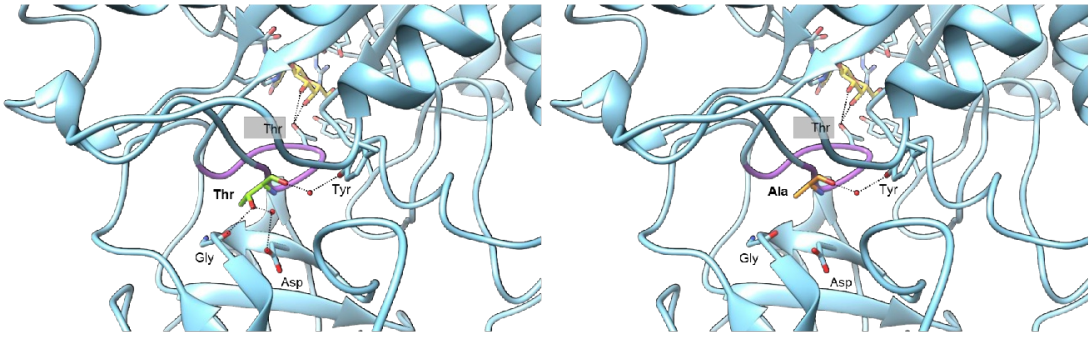
The Krabbe disease is a rare lysosomal disorder affecting the white matter of the central and peripheral nervous system. It is characterized by neurodegeneration and the severity depends on the age of onset. The most common form is the infantile Krabbe disease, which is usually diagnosed within the first year of life and has a high morbidity and mortality. The causes of this autosomal recessive disease are mutations in the *GALC* gene, which encodes the lysosomal enzyme galactocerebrosidase catalyzing the cleavage of galactose from galactocerebroside and galactosylsphingosine. This study presents a galactocerebrosidase variant found as homozygous mutation in the *GALC* gene of a little child with infantile Krabbe disease.



In order to investigate the effect of this mutation on the protein structure at the atomic level, at first, the homology model of the human galactocerebrosidase was build based on the crystal structure of its murine ortholog. In the second step, the structural stability of the mutated enzyme was analysed in several all-atom molecular dynamics (MD) simulations with protonation states corresponding to cytosolic pH (pH 7) and compared to the stability of the wild type enzyme under the same conditions. Furthermore, to account for the fact that the subcellular location of the galactocerebrosidase is the lysosome (pH 4.5-5.5), additional MD simulations were performed with protonation states corresponding to the acidic environment of the lysosome (pH 4.5). Differences in protein flexibility between the wild type and the mutated enzyme were only be observed at acidic pH and not at neutral pH. Similarly, effects of the mutation on the size of the binding pocket were observed at pH 4.5, although the mutation site itself is not part of the active site/binding site of the enzyme. Thus, these MD simulations provide insights into how this mutation affects the structure of the human galactocerebrosidase in the acidic environment of the lysosome.

Recent advances in the Embedded Cluster Reference Interaction Site Model

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The Embedded Cluster Reference Interaction Site Model (EC-RISM) is a well-established method to combine quantum-chemical calculations with the three-dimensional Reference Interaction Site Model (3D RISM). [1-3] This integral equation theory represents the solvent by the equilibrium distribution functions of its constituting atoms around the solute, from which thermodynamic properties such as the excess chemical potential and the partial molar volume are readily accessible. The quantum-chemical part of the EC-RISM method does not only provide the electrostatic part of solute-solvent interactions but also allows for the determination of observables from the solvent-polarized solute wave function, such as the electronic energy of the solvated molecule and spectroscopic information like infrared (IR) data, nuclear magnetic resonance (NMR) [4] and electron paramagnetic resonance (EPR) parameters. [5]

Quantitative results for the excess chemical potential have been obtained for water and organic solvents based on partial molar volume-based corrections, enabling the prediction of properties with high accuracy. In the SAMPL6 and SAMPL7 blind challenges, the acidity constants (pK_a) of diverse sets of compounds could be predicted with consistent RMSEs of 1.15 and 0.72 pK units, respectively. [6-8] Octanol-water partition coefficients (log P) of the challenge compounds on the other hand yielded a prediction range of 0.47-1.84, leaving room for improvement of organic phase models.

As a very recent development, the EC-RISM formalism was integrated directly into the SCF procedure of the popular quantum chemistry package ORCA. [9] In contrast to the established script-based approach, calculation of the electrostatic potential and of 3D RISM distribution functions are performed during the SCF iteration, saving considerable computational overhead. This approach also allows for the formulation of an analytic gradient enabling geometry optimizations on the EC-RISM free energy surface from which, for instance, pressure-dependent changes in molecular geometries and their influence on spectroscopic observables can be deduced. Early results indicate that the effect of small, pressure-induced changes in molecular structure on pressure-dependent NMR parameters can be significant.

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Metadynamics Simulations of Chemical Reactions in Solution

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The energy barrier is an important parameter in describing and understanding chemical reactions. However, its calculation - especially in the case of the free energy barrier - is a difficult task, since it cannot be easily obtained from molecular dynamics (MD) simulations.

Different methods have been proposed in order to reconstruct the free energy surface (FES) from MDs, such as Umbrella Sampling (US), Metadynamics (MTD) or the recently proposed Well-Sliced Metadynamics (WS-MTD) approach developed by Awasthi *et al.*[1], which is a combination of US and MTD.

In this work, four important chemical reactions have been investigated via standard MTD and WS-MTD in order to estimate the free energy barrier. The chosen reactions cover a range of different types and mechanisms, consisting of a Diels-Alder reaction, an aromatic decarboxylation, an aromatic Claisen rearrangement and the base-catalyzed hydrolysis of formamide. This selection thus includes a cycloaddition, an elimination, an intermolecular rearrangement as well as an OH^--addition.

Utilizing the CPMD code it was possible to obtain many ps long trajectories of the reactions in the gas phase as well as in an explicitly included solvent. From those trajectories, the FES were reconstructed using the WHAM code.

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KCa3.1 channel: Computational analysis of three known toxin inhibitors towards new extracellular inhibitors

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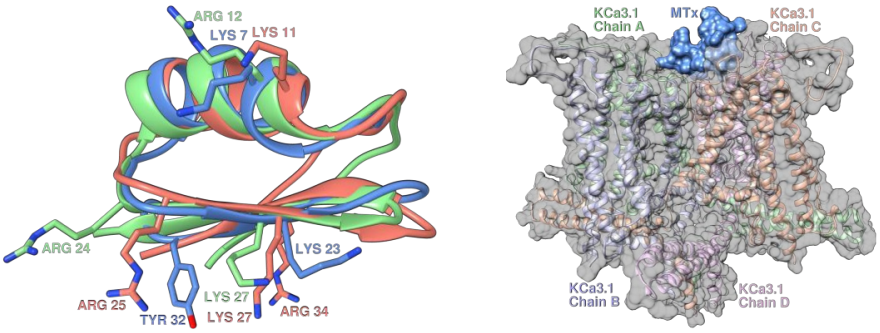

KCa3.1 is an ion channel that is important for immune regulation and the correct function of red blood cells and is associated with certain cancer types. [1]

Three toxins are known to bind to KCa3.1 from the extracellular site and they are called OSK1, Charbydotoxin (ChTx) and Maurotoxin (Mtx). [2] Based on the toxin structures and the available KCa3.1 channel (PDB ID 6cnm), a computational analysis was initiated to model the toxin binding. Initially, a sequence alignment of the three toxins was performed and revealed important conserved residues that are presumably important for binding. The structural alignment can be seen in the picture above and it is based on the available NMR structures of the toxins (PDB IDs 1sco, 2crd and 1txm). In this figure Mtx, ChTx and OSK1 are colored blue, orange and green, respectively. The important residues are shown as sticks.

Based on these results, a flexible peptide-protein docking experiment was performed for the toxins as a starting position for three Molecular Dynamics simulations. The resulting binding pose can be seen in the picture above. This led to a validated binding mode of the toxins that allowed to identify important residues for binding. In the future, a structure-based approach will be performed based on the important interactions identified to discover novel, small molecules by virtual-screening.

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Accurate NMR shift calculations for species in aqueous solution at ambient and high-pressure conditions

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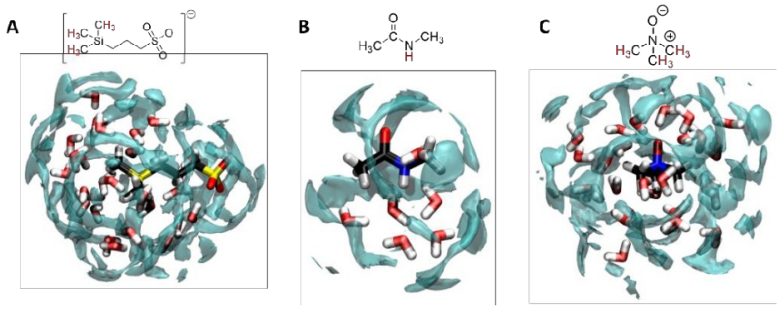
Nuclear magnetic resonance (NMR) spectroscopy is one of the main analytical techniques to investigate chemical systems, and a broad range of conditions including high pressure (*p*) can readily be investigated in NMR experiments. [1] In addition to experiments, computational methods have been employed to calculate NMR parameters and gain insight into experimentally inaccessible systems. An example for one of these systems is the effect of high-*p* conditions on small molecules and peptide conformations in water. [2] However, reaching quantitative agreement with experiments is still a challenging task even at ambient conditions due to the high structural sensitivity of NMR calculations, especially with respect to the accurate description of the solvent influence.

Here we show the first example of joining state-of-the-art computational methodologies, *ab initio* molecular dynamics simulations (AIMD) for generating microsolvated structural ensembles and "embedded cluster reference interaction site model" (EC-RISM [3]) calculations for predicting accurate NMR response parameters for species in aqueous solution, extending a previous approach for 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 demonstrate 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 general approach to hybrid solvent systems is transferable. However, one drawback in FFMD-generated ensembles can be traced back to the inaccurate description of hydrogen bonds which need further improvement.

For high-*p* NMR calculations we present the novel use of *p*-dependent geometry optimizations using EC-RISM. Despite small structural influence of pressure, the impact on *p*-dependent shifts matches the range of experimental changes, hence geometry change needs to be addressed.

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Size-dependent sedimentation of nanocrystals: the role of the ligand shell structure

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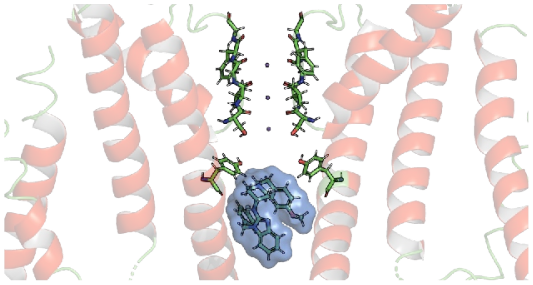
The chemical, electronic, optical, magnetic, and catalytic properties, as well as the self-assembly of hybrid inorganic-organic core-shell nanoparticles depend strongly on their size and composition. Hence, there is a pressing need for a reliable method that can provide full characterisation of these particles. Although transmission electron microscopy (TEM) provides high-resolution detail of a particle's size, shape, and structure, discerning the organic materials bound on the nanocrystal surface is still a challenge due to low atomic contrast. Yet, parameters related to the overall hybrid particle (inorganic core and organic shell) properties influence particles' solubility, electronic properties, assembly, and reactivity. In this context, analytical ultracentrifugation (AUC) appears as an alternative to characterise these particles in solution, being sensitive to changes in the density and size of both core and shell components of nanoparticles. We use molecular dynamics simulations (MD) to test the validity of the Stokes-Einstein-Sutherland (SES) equation for systems of CdSe quantum dots coated with alkanethiol ligands in chloroform and explain inconsistencies between the sedimentation trends observed in AUC experiments and the ones predicted for these particles in a Stokes flow. We find that varying the size of the particle changes the structure of the ligand shell and the way it interacts with the solvent and will dictate the diffusion and sedimentation behaviours of the nanocrystals.

A combined deep learning and structure based cheminformatic approach to understand ligand blockage activity on the hERG channel

Nathaniel Smith, David Bushiri Pwesombo, Han Sun

FMP-Berlin



The hERG (human *Ether-à-go-go*-Related Gene) encoded potassium channel Kv11.1 is highly expressed in heart tissue and is well-known for its contribution to the repolarisation of the cardiac action potential. Dysfunctional or drug inhibition of the hERG channel may cause prolongation of the QT interval (long QT syndrome), which leads to arrythmia, such as *torsades de pointes*. A number of common drugs have been shown to bind hERG channel, causing unwanted side effects. Therefore, tremendous effort has been put into assessing hERG-related cardiotoxicity in the preclinical stages of drug discovery.

The recent advancements in machine learning (ML) techniques have enabled the use of powerful cheminformatic approaches to predict the activities of small molecule ligands. However, generally a large amount of labeled dataset is required for training. The hERG channel is particularly appealing for ML-based approaches, as a high number of blockers have been previously identified from the screening of large collections of chemical libraries. Furthermore, the recent high-resolution cryo-EM structures of hERG channel [1,2] has enabled several structure-based studies on hERG inhibition.[3] In the current study, we aim to combine deep learning and structure-based cheminformatics approaches to understand ligand blockage activity on the hERG channel. We chose 298,016 molecules labeled for hERG inhibition from the hERGcentral database as the training dataset, where we calculated the molecular descriptors (PaDEL descriptors).[4] Different ML approaches, including deep neural networks (DNN) and graph neural networks (GNN), were trained on the aforementioned dataset to predict their activities. For training of GNN models, molecules were represented as graphs. We compared the accuracy obtained from different models. The positive outcomes of ML will be rationalised in the near future using molecular docking and molecular dynamics simulation. Furthermore, we envision extending this approach to identify small molecule modulators for other potassium channels where limited experimental data exist.

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Accelerating plane-wave-based ab initio molecular dynamics by optimization of Fast-Fourier transforms for modern HPC architectures

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The most important advantage of plane-wave basis sets is that wave functions can be transformed efficiently from reciprocal to real space and back by using the Fast-Fourier transform (FFT) algorithm. This allows to evaluate the kinetic and potential energy in reciprocal and real space, respectively, where both operators are diagonal. This reduces the computational cost for applying the Hamilton operator from N^2 to $NlogN$. However, the scalability of current FFT libraries is rather limited on today's HPC systems, which offer large numbers of compute nodes, each of them with many cores. Here we present our optimization of the FFTX library of the Quantum Espresso software package. Data distribution and communication patterns have been revised to make optimal use of combined MPI and OpenMP parallelization. Scalability is further increased by combining FFTs into batches and by introducing overlapping computation and communication. We implemented the revised FFTX library in our optimized version of the CPMD code [1], and we demonstrate the achieved acceleration by a series of benchmark simulations.

[1] T. Klöffel, G. Mathias, B. Meyer, *Comput. Phys. Commun.*, **2021**, 260, 107745

Unlocking the Potential of Antibodies Against SARS-COV-2: A Pipeline for Fast and Accurate Mapping of Interaction Sites with Free Energy Analysis

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In this study, we employed free energy interaction analysis to identify key interaction sites between SARS-COV-2 and antibody structures. Specifically, we generated a pipeline for efficient mapping of these interaction sites that can be used for multiple system pairs, or for a single pair using parallelized computing. Our pipeline significantly reduces the time and effort required for this analysis, making it a feasible approach for large-scale studies. Our results demonstrate that the interaction between SARS-COV-2 and antibody structures can be mapped with high accuracy using free energy interaction analysis [1].

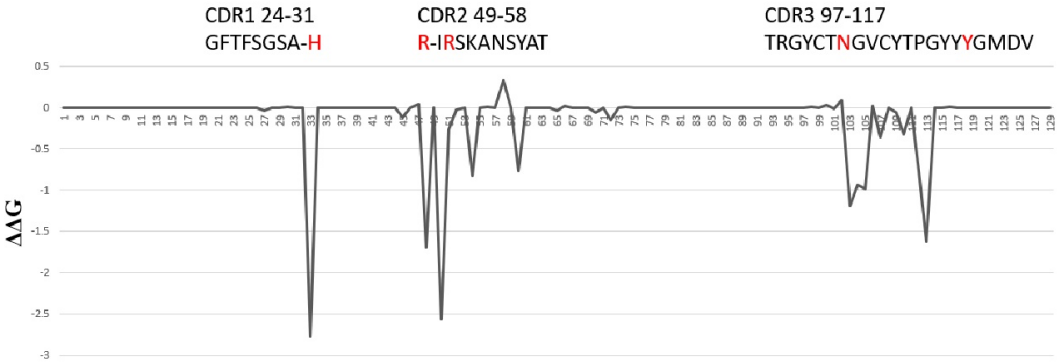

Fig. 1 Free energy mapping of an Anti-SARS-CoV-2 antibody binding interface. The most influential residues for each position are marked red and visualized on the antibody's paratope.

The technology can also be used to study protein-protein interactions in general. By mapping the key interaction sites between proteins, researchers can gain insights into the mechanism of interaction and the structural features of the protein complex. This information can help to identify potential drug targets and facilitate the design of peptide inhibitors that disrupt the protein-protein interaction [2]. For example, it could be used to study interactions between viral proteins and host proteins, as well as interactions between different signaling molecules.

Overall, the technology has the potential to significantly improve the understanding of protein-protein interactions and accelerate the development of effective therapies for a range of diseases.

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A Calculation Pipeline for Differential Molecule Pair Interaction Energies

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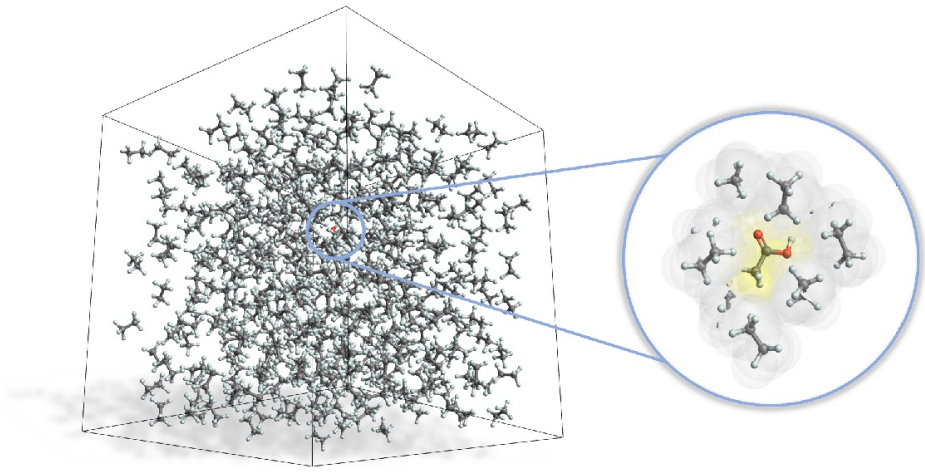
Dissipative Particle Dynamics (DPD) is a mesoscopic simulation technique for complex fluids and soft matter systems. Molecular Fragment DPD is a "bottom-up" variant, where particles are defined as small molecules with a molecular weight in the order of 100 Dalton. Larger molecules are composed of these "fragment molecule" particles, which are linked by harmonic springs to mimic covalent bonds and 3D spatial conformations. The conservative interaction between two DPD particles is characterized by an isotropic repulsion.



The open MIPET (Mesoscopic Interaction Parameter Estimation with Tinker) project aims at providing a force-field-based method for the consistent estimation of isotropic repulsions for pairs of small molecules which represent adequate DPD particles. A comprehensive set of these adequate particles is then utilized for biomolecular simulations containing peptides or proteins. Isotropic repulsions can be derived from Flory-Huggins interaction parameters which themselves are based on differential molecule pair interaction energies. The latter can be calculated from molecule pair coordination numbers and mutual molecule-molecule interactions [1]. These quantities are approximated by molecular mechanics simulations using the open TINKER package [2]. The full MIPET calculation pipeline is realized with the Wolfram Language [3] and uses the Mathematica system for execution and result evaluation.

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MORTAR – A Rich Client Application for *in silico* Molecule Fragmentation

Felix Bänsch [1,2], Jonas Schaub [1,2], Betül Sevindik [1], Samuel Behr [1], Julian Zander [1], Christoph Steinbeck [2], Achim Zielesny [1]

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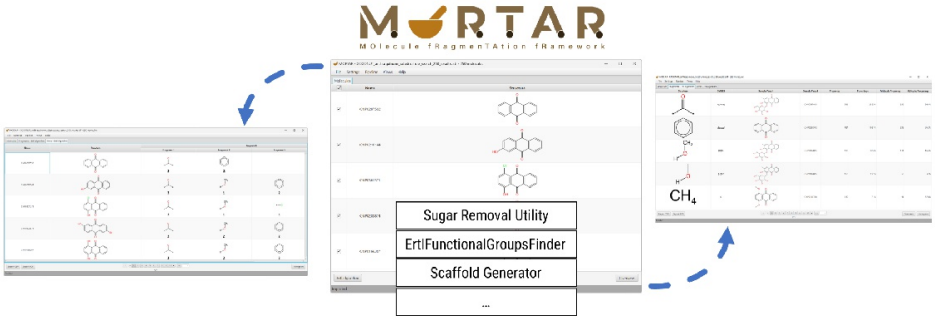
The process of developing and implementing computational algorithms to extract specific substructures from molecular graphs, known as *in silico* molecular fragmentation, is a repetitive task that involves multiple iterations of applying a set of rules to relevant structural data, followed by checking and adjusting the results. This requires a computational workflow that includes data import, fragmentation algorithm integration, and result visualization. When developing a new algorithm, this workflow is not readily available and must be built from scratch.



To address this problem, this work presents MORTAR (MOlecule fRagmenTAtion fRamework) [1], an open Java-based graphical user interface application that supports the development of new *in silico* molecule fragmentation algorithms as well as their availability after publication. The MORTAR application provides various visualization options for the fragmentation results of a group of molecules and basic analysis functions. Fragmentation algorithms can be integrated and developed within MORTAR using a special wrapper class. In addition, any combination of the available fragmentation methods can be used to run fragmentation pipelines. Currently, three fragmentation methods are integrated in MORTAR: ErtlFunctionalGroupsFinder [2], Sugar Removal Utility [3], and Scaffold Generator [4]. All cheminformatics functionality within MORTAR is implemented using the Chemistry Development Kit (CDK).

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