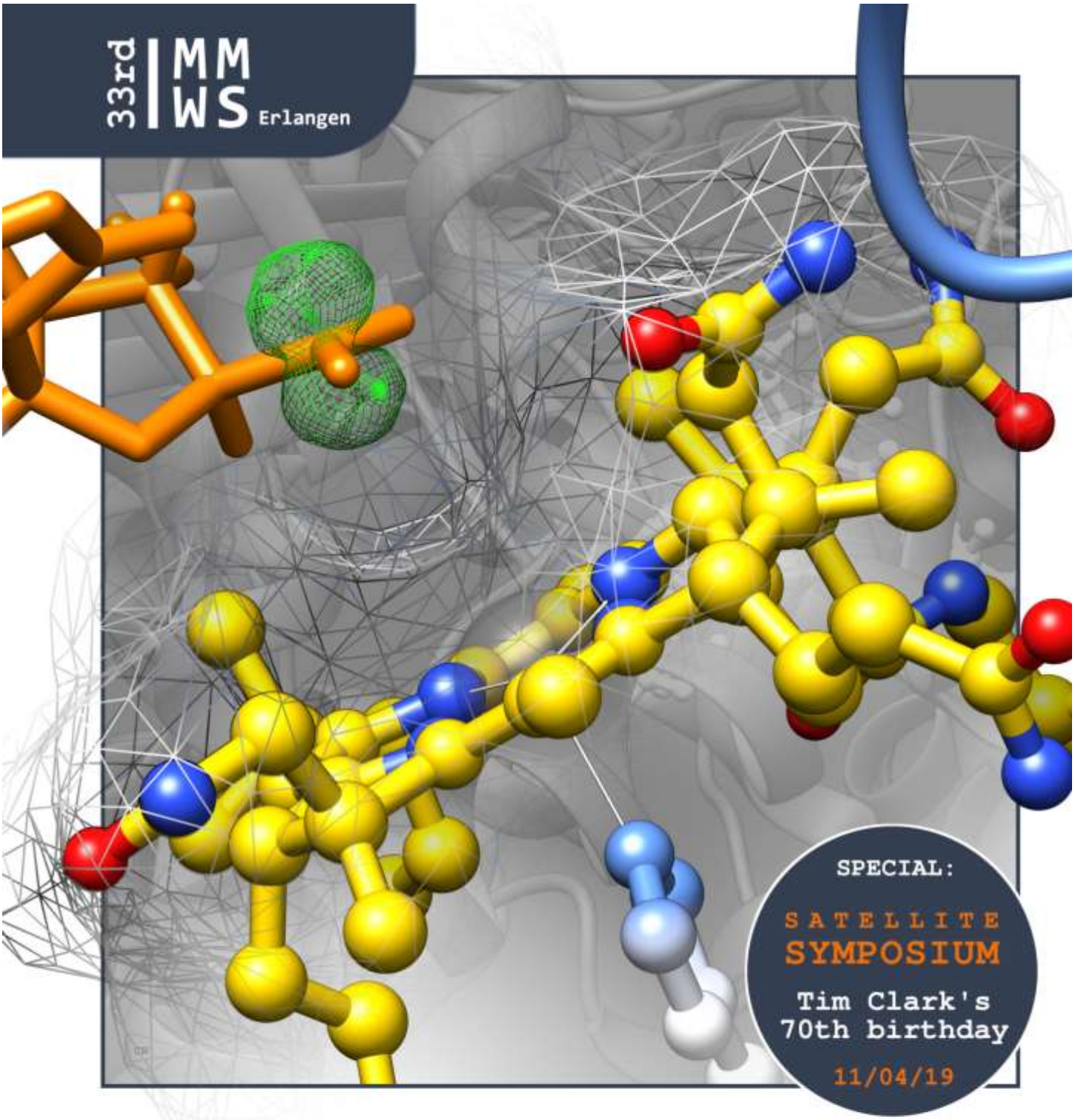
33rd MMWS Erlangen



SPECIAL:

SATELLITE SYMPOSIUM

Tim Clark's 70th birthday

11/04/19

MOLECULAR MODELLING WORKSHOP ERLANGEN

08/04–10/04/19 MMWS2019.MGMS-DS.DE

MOLECULAR MODELLING WORKSHOP 2019

Monday, April, 8th - Wednesday, April, 10th 2019

Welcome to the 33rd Molecular Modelling Workshop (MMWS).

This is the 17th Workshop to be held in Erlangen. The first 16 were known as the *Darmstadt Molecular Modelling Workshop* and, as the name suggests, took place in Darmstadt under the leadership of Jürgen Brickmann and his group. The eighth MMWS (1994) was the first to take place under the auspices of the Molecular Graphics and Modelling Society – Deutschsprachige Sektion (MGMS-DS e.V.), which has been responsible ever since. The MMWS has taken place in the Institute of Organic Chemistry in Erlangen since the 17th edition in 2003.

This years's MMWS represents the second part of the intermission in the conference venue's continuity: Since Organic, Medicinal and Pharmaceutical Chemistry in Erlangen moved into the new Chemikum, the venue of the workshop temporarily moved into the Institute of Biochemistry in 2018, which belongs to the Medical Faculty of the Friedrich-Alexander-Universität Erlangen-Nürnberg. The workshop's location, however, will move to the new Chemikum building in 2020. Again, the technical conference management of the Computer-Chemie-Centrum, CCC, is supported by the Bioinformatics group headed by Heinrich Sticht. This year's scientific MMWS program has been thoroughly compiled by Paul Czodrowski from the Technische Universität Dortmund.

The MMWS can look back on a long history of giving graduate students and postdocs the opportunity to present their work. It predates the annual Young Modellers' forum organized by the parent MGMS in London and the equivalent workshop run by the Association of Molecular Modellers in Australasia in association with the MGMS. We are proud that the MMWS has become a fixture in the molecular modelling scene in Europe and that it continues to provide students and young researchers with a stage to present their work.

This time, we have four plenary speakers for our MMWS. We are happy to welcome Matthias Bremer from Merck KGaA (Darmstadt, Germany), Ruth Brenk from the University of Bergen (Norway), Bernd Meyer from the Friedrich-Alexander-Universität Erlangen-Nürnberg (Germany), and Rochus Schmid from the Ruhr-Universität Bochum (Germany) as our plenary speakers this year for the focal topics of computational materials science, modelling in biochemistry, as well as molecular modelling of coordination polymers, respectively. By combining these four excellent plenary speakers, we intend to enable MMWS to keep pace with the rapidly changing face of modelling in Europe and the rest of the world and to provide inspiration for young modellers.

Now please enjoy the 33rd Molecular Modelling Workshop.

Scientific program

Prof. Dr. Paul Czodrowski

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DEAR COLLEGUES,

The 33rd Molecular Modelling Workshop (April, 8th – 10th 2019) in Erlangen provides research students and new postdoctoral scientists the perfect opportunity to present their research to the molecular modelling community. Scientists at the beginning of their academic careers are able to meet new colleagues in academia and industry.

Every year, the organisers welcome both poster and lecture contributions from all areas of molecular modelling including life sciences, physical sciences, material sciences, and the nano sciences.

The aim of the Modelling Workshop is to introduce research in progress. The workshop is the perfect venue to introduce new methods in molecular modelling 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.

Contributions are welcome
from all areas of molecular modelling -
from the life sciences, computational biology,
computational chemistry to materials sciences.

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

DR. MATTHIAS BREMER

Merck KGaA, Darmstadt, Germany

PROF. DR. RUTH BRENK

University of Bergen, Norway

PROF. DR. BERND MEYER

Friedrich-Alexander-Universität Erlangen-Nürnberg, Germany

PROF. DR. ROCHUS SCHMID

Ruhr-Universität Bochum, Germany

AWARDS

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

1st Winner

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

2nd Winner

up to 200 Euro travel expenses reimbursement

3rd Winner

up to 100 Euro travel expenses reimbursement

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

MGMS-DS E.V. ANNUAL MEETING

The general meeting of the MGMS (German Section) 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). 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 mmws2019.mgms-ds.de

SYMPOSIUM IN HONOR OF TIM CLARK'S 70TH BIRTHDAY

The MMWS2019 is succeeded by a symposium with keynote speakers who are active in areas of interest to Tim Clark. This symposium will take place on April 11th, 2019, in the **Chemikum** (Nikolaus-Fiebiger-Str. 10, 91058 Erlangen).

There is no additional conference fee for participants of the MMWS.

LOCATION

The Pre-conference Workshop about the Schrödinger Suite takes place at the Computer-Chemistry-Center (CCC), Nägelsbachstr. 25 (see conference web page for details).

Conference location: All talks, coffee breaks, the poster sessions and the buffet dinner on Monday, April 8th will take place at the Institute for Biochemistry, Fahrstr. 17, 91054 Erlangen (and *not* at the old location, i.e. Institute for Organic Chemistry, Henkestr. 42).

The *Social Event "Visit at a typical Erlanger Gasthaus – Biergarten"* will take place at Gasthaus "Steinbach Bräu", Vierzigmannstr. 4 (www.steinbach-braeu.de) on Tuesday evening. Food and drinks will be available at your own expense.

IMPORTANT NOTE:

The Social Event will *not* take place at Gasthaus "Steinbach Bräu".

Please learn the actual location from the organizers' announcements at the conference – thank you.

Dr. Matthias Bremer

Matthias Bremer studied chemistry at the University of Erlangen-Nuremberg and earned a PhD in 1989 with Paul von Ragué Schleyer. After postdoctoral research as a Feodor Lynen-Fellow at the University of California at Berkeley with Andrew Streitwieser, he joined the Liquid Crystals Division of Merck KGaA in Darmstadt in early 1991, where he is now a Scientific Director.

Together with two colleagues from Merck he received the 2003 German Future Prize of the Federal President for the development of liquid crystals for flat panel LCD-Television. He is a Fellow of the Royal Society of Chemistry, a board member of the German Liquid Crystal Society and has published more than 60 scientific papers and over 130 patents and patent applications.

Since 2009 he has been teaching at the Justus Liebig-University Gießen and currently is an Honorary Professor in the Department of Organic Chemistry.

Prof. Dr. Ruth Brenk

Ruth Brenk is a pharmacist by training. In 2003, she obtained her PhD from the University of Marburg (Germany). The research that led to her thesis was conducted under the guidance of Prof. Gerhard Klebe. Afterwards, she joined the group of Prof. Brian Shoichet at the University of California, San Francisco (UCSF) as a postdoc. This research stay was funded by the Ernst Schering Foundation.

In 2005, she became a Lecturer at the University of Dundee (UK). There, she headed the computational chemistry group of the Drug Discovery Unit (DDU) and was a member of the decision-making core group of the unit. In addition, she also started her own research group in the area of structure-based drug design. In 2012, she became Junior professor at the Institute of Pharmacy at the Johannes-Gutenberg University Mainz (Germany) and in 2015 she was appointed as full professor at the University of Bergen (Norway), where she is leading a research group in the area of structure-based drug design and molecular recognition. She is also heading the core facility for Biophysics, Structural Biology, and Screening (BiSS).

In 2013, she was awarded the Young Investigator Price of the German Pharmaceutical Society (DPhG).

Prof. Dr. Bernd Meyer

Bernd Meyer is professor for Computational Chemistry at the Interdisciplinary Center for Molecular Materials (ICMM) and the Computer-Chemistry-Center (CCC) at the Friedrich-Alexander-University Erlangen-Nürnberg (FAU).

He studied Physics and Mathematics at the University of Stuttgart and obtained his PhD in Physics at the Max-Planck-Institute for Metals Research in 1998. After a postdoc stay with David Vanderbilt at Rutgers University in New Jersey, USA, he went to the Ruhr-University Bochum where he did his Habilitation with Dominik Marx in 2006. He was visiting scientist at Iowa State University in Ames, the Indian Institut of Technology in Kanpur (IITK) and the University of St Andrews in the UK. His research focuses on the study of chemical processes at surfaces and interfaces using quantum-chemical methods and molecular dynamics.

Prof. Dr. Rochus Schmid

Rochus Schmid studied chemistry at the Technische Universität München (TUM) and received his PhD in the group of Wolfgang A. Herrmann in 1997. After a postdoctoral stay with Tom Ziegler at the University of Calgary (Canada) he returned to the TUM in 1999. In 2003 he joined the group Roland A. Fischer at the Ruhr-Universität Bochum, where he finished his Habilitation in 2009 on the topic “Atomistic Models in Materials Chemistry”.

In 2015 he was appointed Professor (apl) of Inorganic Chemistry. He is leading the research group “Computational Materials Chemistry” at the chair of Inorganic Chemistry II at the Ruhr-Univerität Bochum, and is focusing on multiscale simulations using ab initio parametrized force fields for porous coordination polymers and other hybrid materials.

Lectures Program

PROGRAM

Monday, April 8th 2019

11:00-13:00	**Pre-conference workshop**
11:00-14:00	**Registration**
14:00-14:10	**Welcome remarks / Agenda review**
14:10-14:40	**L01: Svenja J. Wörner (Mainz, Germany)** Clarifying the role of 3-body correlations for determining optimal coarse-grained pair potentials
14:40-15:10	**L02: Christian R. Wick (Erlangen, Germany)** From force fields to QM/MM and back: modelling chemical change in coenzyme B12 dependent enzymes
15:10-16:10	**PLENARY LECTURE I: Rochus Schmid** Force fields for porous coordination polymers – a tricky business
16:10-16:30	**Coffee Break**
16:30-17:00	**L03: Tatu Lindroos (Darmstadt, Germany)** Digital biology for better antibody-drug conjugates – modelling cell-level pharmacokinetics
17:00-17:30	**L04: Lukas Eberlein (Dortmund, Germany)** Tautomerism of nucleic acid building blocks at ambient and extreme conditions
17:30-18:00	**L05: Dan Cannon (Schrödinger)** Performing hit identification and lead optimization at very large scale
18:00-19:00	**Annual Meeting of the MGMS-DS e.V.**
19:30	**Buffet – Dinner**

Program

Tuesday, April 9th 2019

08:30-09:00	**L06: Christian A. Söldner (Erlangen, Germany)** Binding of histamine to the H1 receptor: a molecular dynamics study
09:00-09:30	**L07: Ya Chen (Hamburg, Germany)** NP-Scout: machine learning models for the identification and visualization of the natural product-likeness of small molecules
09:30-10:00	**L08: Andreas Klamt (COSMOlogic)** COSMOplex: A new paradigm for simulating self-organizing systems
10:00-10:30	**Conference Photo & Coffee Break**
10:30-11:00	**L09: Julia B. Jasper (Dortmund, Germany)** Thermodynamic signatures of protein hydration sites and their correlation with ligand features
11:00-12:00	**Plenary Lecture II: Ruth Brenk** Structure-based design of riboswitch ligands and selective NMT inhibitors
12:00-13:30	**Lunch**
13:30-14:15	**Poster announcements**
14:15-15:30	**Poster Session**
15:30-16:00	**L10: Tobias Klöffel (Erlangen, Germany)** Boosting the scalability of Car-Parrinello molecular dynamics for large-scale simulations of solid-liquid interfaces
16:00-16:30	**Coffee Break**
16:30-17:00	**L11: Christina de Bruyn Kops (Hamburg, Germany)** Metabolite structure prediction focused on the cytochrome P450 enzyme family
17:00-17:30	**L12: Krzysztof K. Bojarski (Gdańsk, Poland)** Computational insights into procathepsin maturation mediated by glycosaminoglycans
17:30-18:30	**Plenary Lecture III: Bernd Meyer** Chemistry at the solid-liquid interface
19:00	**Social Event: Bierkeller (Steinbach Bräu)**

PROGRAM

Wednesday, April 10th 2019

08:30-09:00	**L13: Benedikt Frieg (Düsseldorf, Germany)** Mechanism of fully-reversible, pH-sensitive inhibition of human glutamine synthetase by tyrosine nitration
09:00-09:30	**L14: Christina Nutschel (Jülich, Germany)** Large-scale analysis of protein thermostability and detergent tolerance
09:30-10:00	**L15: Max Niegl (MTU Aero Engines)** Aero engines, computational chemistry and REACH: how does that match together?
10:00-10:30	**Coffee Break**
10:30-11:00	**L16: Gunther Stahl (Openeye)** REAL-ly large-scale virtual screening – traversing enormous regions of chemical space with the GPU and CPU
11:00-11:30	**L17: Till El Harrar (Jülich, Germany)** Comprehensive description of interactions of ionic liquid ions with BsLipA
11:30-12:00	**L18: Adrià Gil (Lisbon, Portugal)** Unravelling the mechanisms of cytotoxicity for phenanthroline derivatives: interaction with DNA
12:00-13:30	**Lunch**
13:30-14:00	**L19: Sebastian Gsänger (Erlangen, Germany)** Vipster – a novel editor and visualization tool for periodic structures
14:00-14:30	**L20: Bernd Engels (Würzburg, Germany)** Simulation of photo-induced processes at organic-organic interfaces
14:30-15:30	**PLENARY LECTURE IV: Matthias Bremer** Quantum chemistry in the design of liquid crystals for display applications
15:30-16:00	**Poster & Lecture awards, Closing**

SYMPOSIUM IN HONOR OF TIM CLARK'S 70TH BIRTHDAY

Thursday, April 11th 2019

08:50-09:00	**Welcome**
09:00-09:45	**K1: Francesco Gervasio (London, UK)** Modelling ligand binding and allostery in kinases and GPCRs with enhanced-sampling algorithms
09:45-10:05	**L1: Christof Jäger (Nottingham, UK)** Reaction control in radical SAM enzymes: how nature plays with radical and redox reactivity
10:05-10:50	**K2: Stefan Kast (Dortmund, Germany)** From macroscopic to local molecular thermodynamics
10:50-11:20	**Coffee Break**
11:20-11:40	**L2: Hakan Kayı (Ankara, Turkey)** Design of the tellurium-containing semiconducting polymers
11:40-12:25	**K3: Peter Hildebrand (Leipzig, Germany)** Role of structural dynamics for GPCR signaling
12:25-13:30	**Lunch**
13:30-14:15	**K4: Holger Gohlke (Düsseldorf, Germany)** What to gain from protein statics
14:15-14:35	**L3: Johannes Margraf (München, Germany)** Correlation energy densities from coupled cluster theory
14:35-14:55	**L4: Pavlo Dral (Mülheim, Germany)** The ODMx methods: new consistent semiempirical methods
14:55-15:30	**Coffee Break**
15:30-16:15	**K5: Jon Essex (Southampton, UK)** The role of water in mediating biomolecular binding: from water locations to their impact on binding affinity
16:15-17:00	**Surprise, Surprise!**
17:00	**Closing remarks**

Poster Session

POSTER SESSION

Tuesday, April 9th 2019 14:15-15:30

P01 **Yannic Alber (Dortmund, Germany)**
Localization of protein-ligand binding thermodynamics

P02 **[retracted]**

P03 **Frank R. Beierlein (Erlangen, Germany)**
A multi-technique approach to DNA structure determination

P04 **Sebastian Bothe (Würzburg, Germany)**
Computational approaches to identify small-molecule inhibitors for the N-domain of p97

P05 **Dušan Ćoćić (Kragujevac, Serbia)**
Relative stability of homo- and hetero-bimetallic PD(II) and Pt(II) complexes compared to their mononuclear analogues

P06 **Marcus Conrad (Erlangen, Germany)**
Design and optimization of mimetic peptide probes

P07 **Lukas Eberlein (Dortmund, Germany)**
Tautomerism of nucleic acid building blocks at ambient and extreme conditions

P08 **Till El Harrar (Jülich, Germany)**
Comprehensive description of interactions of ionic liquid ions with *B*sLipA

P09 **David Gnandt (Freiburg, Germany)**
A dielectric theory view of biomolecular charge transfer

P10 **Sonja C. Herdlinger (Salzburg, Austria)**
Pharmacophore-based identification of chemical tool compunds inhibiting 17β-hydroxysteroid dehydrogenase 14 (17β-HSD14)

P11 **[retracted]**

P12 **Christophe Jardin (Nürnberg, Germany)**
Elucidating zinc binding to the voltage-gated proton channel hHv1 using computer simulations

P13 **Tatu Lindroos (Computational Chemistry & Biology)**
Digital biology for better antibody-drug conjugates – modelling cell-level pharmacokinetics

P14 **[retracted]**

POSTER SESSION

Tuesday, April 9th 2019 14:15-15:30

P15 **Tobias Müller (Erlangen, Germany)**
Adsorption of organic molecules with high dipole moment on the Au(111) surface

P16 **[retracted]**

P17 **Simon Schäfer (Erlangen, Germany)**
Computational analysis of human heavy chain CDR3 repertoires: the paradox of tyrosine rich antibodies in memory B cell repertoires

P18 **Lars Schumann (Dortmund, Germany)**
Analysis of gating behavior and microscopic water structure in small viral K^+-ion channels

P19 **Nursel A. Selçuki (Izmir, Turkey)**
Intermolecular interactions between dopamine and promazine using computational methods

P20 **Cenk Selçuki (Izmir, Turkey)**
Investigation of the tacrine-saccharin complex: a combined computational and experimental study

P21 **Florian Song (London, UK)**
A novel methodology for encoding hydrophobic interactions in atomistic graphs constructed from biomolecular structures

P22 **Anselm H. C. Horn (Erlangen, Germany)**
Role of N-terminal residues for structural stability of triangular Aβ40 fibrillar oligomers

P23 **Chetna Tyagi (Szeged, Hungary)**
Using accelerated molecular dynamics to retrieve conformational ensemble of alamethicin

P24 **Navista S. O. Ujiantari (Innsbruck, Austria)**
Comparison of the pharmacophore features of agonists and antagonists in β3-adrenergic receptors

P25 **David Wifling (Regensburg, Germany)**
Basal histamine H4 receptor activation: ligand mimicry by the diphenylalanine motif

P26 **Florian Wullschläger (Erlangen, Germany)**
Atomistic simulations of chemical graphene exfoliation and carbon nanotube synthesis and of extended defects in bilayer graphene

Please kindly remove your posters on tuesday evening!

All abstracts are available on the conference web site:
www.mmws2019.mgms-ds.de

Abstracts

Clarifying the role of 3-body correlations for determining optimal coarse-grained pair potentials

Svenja J. Wörner, Kurt Kremer, Tristan Bereau, Joseph F. Rudzinki

Max Planck Institute for Polymer Research, Mainz, Germany

While providing a large degree of accuracy, fully atomistic molecular dynamics simulations are computationally expensive. Coarse-grained models represent multiple atoms with one bead, reducing the number of particles in the system as well as the number of degrees of freedom. Consequently, larger systems and longer timescales become accessible.

Accurate bottom-up coarse-grained models ideally reproduce all relevant properties of the underlying atomistic system, such as structure, thermodynamics and dynamics. Structure-based coarse-graining methods often determine optimal pair potentials for reproducing a given set of radial distribution functions. These procedures treat many-body correlations that arise in the condensed phase in various ways. Direct Boltzmann inversion, for example, assumes there are no correlations present in the system, resulting in potentials that tend to overcompensate for the missing correlations. Force matching, on the other hand, uses 3-body correlations from an underlying atomistic model to determine the optimal potentials. This can also result in inadequate potentials, since the coarse-grained model is often incapable of precisely reproducing the atomistic correlations.

In this work, we apply the generalized-Yvon-Born-Green integral equation framework to explore the interplay between 2- and 3-body contributions to the pair mean force in coarse-grained models of liquids. As a model system, we consider a one-site per molecule representation for liquid water with isotropic pair interactions. Prominent tetrahedral packing generates 3-body correlations that cannot be reproduced by the coarse-grained model. Our analysis suggests two complementary approaches for directly modifying the atomistic 3-body correlations to more accurately reflect the correlations generated by the coarse-grained models.

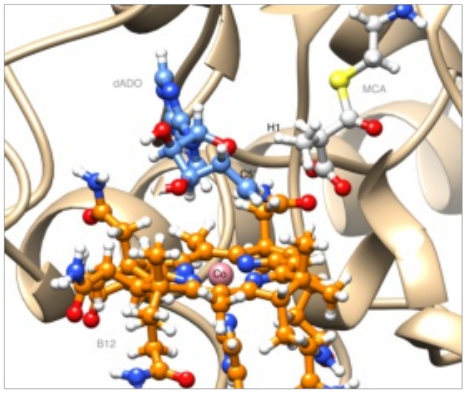
From Force Fields to QM/MM and back: Modelling chemical change in coenzyme B_{12} dependent enzymes

Christian R. Wick[1], Marko Hanževački[2], Ana-S. Smith[1,2] and David M. Smith[2]

[1]*Theoretische Physik I, FAU Erlangen-Nürnberg, Nägelsbachstr. 49b (EAM), Erlangen, Germany*

[2]*Division of Physical Chemistry, Ruđer Bošković Institute, Bijenička 54, Zagreb, Croatia*

Coenzyme B_{12} (5'-deoxyadenosylcob(III)alamin, dAdoCbl) is one of the most prominent organometallic cofactors due to the presence of a carbon-cobalt (Co-C) bond, which is the key to enzymatic reactions utilizing coenzyme B_{12} as a cofactor: The homolytic cleavage of the Co-C bond, which leads to the formation of a 5'-dAdo radical, is highly encouraged in the enzymatic environment compared to the nonenzymatic reaction. In a (subsequent or concerted) second step, the 5'-dAdo radical is involved in an H-atom transfer reaction, generating a substrate radical and 5'-dAdo. However, the accurate theoretical description of both elementary reactions is challenging. Model system design, the treatment of dispersion and solvent effects as well as basis set size can lead to large variance in the computed Bond Dissociation Enthalpy (BDE) for the homolytic cleavage of the Co-C bond.[1,2,3] Concomitantly, the accurate description of the H-atom transfer reaction is known to be very sensitive to the level of theory applied.[3–7] Nevertheless, there are model chemistries that enable an accurate and balanced description of both reactions, Co-C cleavage and H-atom transfer. We discuss the differences between typical model systems, the effects of dispersion and solution corrections and finally present a suitable ONIOM(QM/MM) setup that simultaneously reduces the computational costs and retains the accuracy of non-approximate calculations on the full coenzyme system, for both types of reactions.[3] This information can be used to produce even more cost-effective empirical Hamiltonians such as the Empirical Valence Bond (EVB) method, which reduces the computational cost to a MM type description of the system and a single diagonalization of a NxN (N = 2 or 3) matrix. This allows us to investigate the free energy profile related to the enzymatic transformations within the enzyme with MD simulations on larger time-scales, while retaining the QM/MM accuracy.



[1] Z. Qu, A. Hansen, S. Grimme, *J. Chem. Theory Comput.* **2015**, *11*, 1037-1045.
[2] K. P. Kepp, *J. Phys. Chem. A* **2014**, *118*, 7104-7117.
[3] C.R. Wick, D.M. Smith, *J. Phys. Chem. A* **2018**, *122*, 1747–1755.
[4] M. L. Coote, *J. Phys. Chem. A* **2014**, *108*, 3865-3872.
[5] B. Durbeej, G. M. Sandala, D. Bucher, D. M. Smith, L. Radom, *Chem. – Eur. J.* **2009**, *15*, 8578-8585.
[6] D. J. Henry, C. J. Parkinson, P. M. Mayer, L. Radom, *J. Phys. Chem. A* **2001**, *105*, 6750-6756.
[7] Kovačević, B.; Barić, D.; Babić, D.; Bilić, L.; Hanževački, M.; Sandala, G. M.; Radom, L.; Smith, D. M. *J. Am. Chem. Soc.* **2018**, *140*, 8487–8496.

Force fields for porous coordination polymers - a tricky business

Rochus Schmid, Computational Materials Chemistry group, Chair of Inorganic Chemistry 2, Ruhr-University Bochum, Bochum, Germany.

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Porous coordination polymers (also known as metal-organic frameworks) are a new and exciting class of porous materials because of their tunability and flexibility. For the theoretical modeling on the other hand, these advantages are a challenge. Because of the mere size of the systems and the need to sample configurational space, a treatment by *ab initio* MD methods is computationally demanding and impossible for routine calculations. Force field models need to be sufficiently accurate to get the proper balance between entropic and energetic contributions. For the organic linker part such parameterizations exist, but for the coordination environments a sufficiently accurate molecular mechanics parameterization is not straight forward. Over the years our group has developed MOF-FF for this purpose, which is a first-principles parameterized force field [1]. In the presentation I will discuss the peculiarities of the force field and the evolutionary strategy parameterization approach. Recently we have developed a hierarchical automated parameter assignment (HAPA) scheme, which retrieves parameters automatically from our MOF+ website (https://www.mofplus.org). I will show how this can be used to investigate the thermal opening of specific MOFs, which undergo a phase transformation from a closed to an open pore structure by increasing the temperature (Figure 1). In addition, also the current limits of such force field models will be discussed for selected application problems.

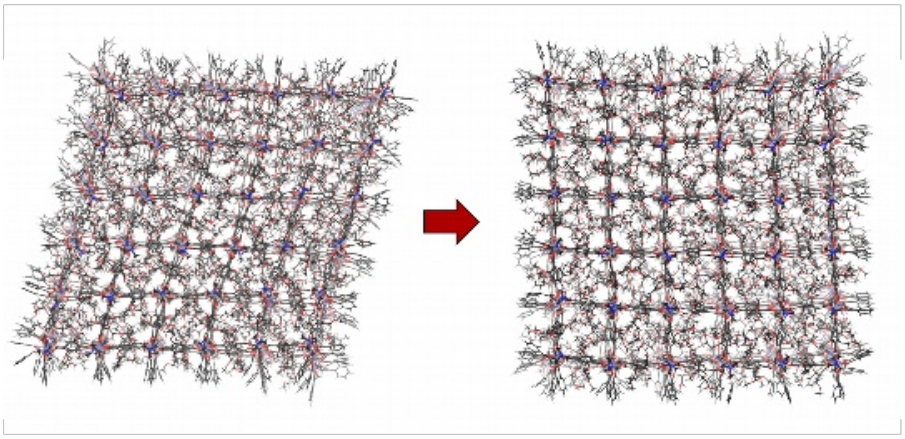


Figure 1: Opening of a 6x6x6 BME-fu-MOF nanoparticle ($Cu(BME\text{-}bdc)_2(dabco)$, BME-bdc: 2,5-bismethoxyethoxy-benzenedicarboxylate) by heating from 300K to 500K.

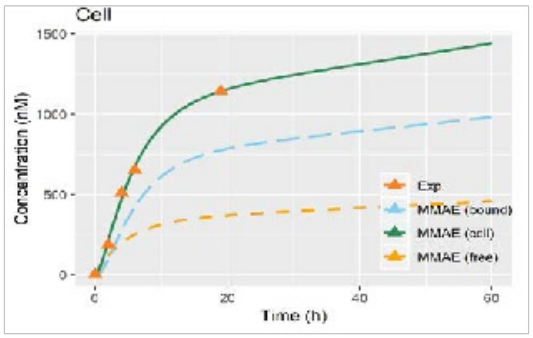
[1] a) M. Tafipolsky, R. Schmid, *J. Phys. Chem. B* **2009**, *113*, 1341-1352. b) S. Bureekaew, S. Amirjalayer, M. Tafipolsky, C. Spickermann, T. K. Roy, R. Schmid, *Phys. Stat. Sol. B* **2013**, *250*, 1128-1141. c) J. P. Dürholt, G. Fraux, F.-X. Coudert, R. Schmid *J. Chem. Theory Comput.* **2019**, *just accepted* **DOI:** *10.1021/acs.jctc.8b01041*.

Digital Biology for Better Antibody-Drug Conjugates – Modelling Cell-Level Pharmacokinetics

Tatu Lindroos[1], Stanley Sweeney-Lasch[2], Stefan Hecht[2], Michael Krug[1]

Computational Chemistry & Biology[1], ADC Design and Characterization [2]
Discovery Technologies, Merck KGaA, Frankfurter Str. 250, 64293 Darmstadt, Germany

Antibody drug conjugates (ADCs) are therapeutic molecules that are aimed to deliver highly potent cytotoxic agents specifically to tumor cells with the help of a tumor-targeting monoclonal antibody that is linked to the payload drug. In a cell-level view, the ADCs bind to antigens expressed on the surface of the tumor cell. The ADC-antigen complexes get internalized, the linkers are cleaved, and the drug released. However, the ADC can already deconjugate outside the cell, depending on the properties of the linker and the drug. Free payload drug can also influx and efflux into and out of the cell. All these processes can be described mathematically with rate constants and differential equations. Accurate quantitative characterization of cellular ADC disposition could help in understanding and improving design of ADCs.



We used a model by Singh and Shah [1], built for trastuzumab-valine-citrulline-monomethyl auristatin E (Trastuzumab-vc-MMAE), to explore how different ADC constructs might behave in a cell-level system. Taking internal experimental data from an uptake assay of MMAE and from measuring the internalization of trastuzumab-vc-MMAE, we could fit the model to the ADCs used at Merck. Extending the model to also handle cell killing lead us to link ADC properties, like drug-antibody ratio and permeability, to predicted IC50 values.

The model was implemented with R Shiny library which gave it an easy-to-access browser interface and deployed on Docker container platform which enabled experimental scientists to use the tool from anywhere in the intranet. The project source code was managed in company's internal GitLab to aid collaborative development, and a one-button build-and-deploy pipeline enabled rapid prototyping with fast feedback from the users.

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Tautomerism of nucleic acid building blocks at ambient and extreme conditions

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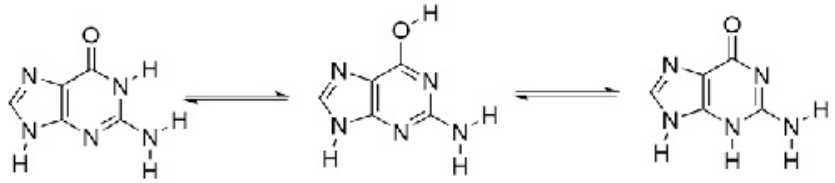
Extreme conditions such as high hydrostatic pressure or temperature as exhibited at deep sea hydrothermal vents, where water can exist either in liquid or in a supercritical form, influence structure and behavior of biologically active molecules. Knowledge of their environmentally modulated conformational, tautomeric and protonation state preferences is essential to understand their behavior in solution and mode of action in the organism. An accurate pH-, temperature- and pressure-dependent characterization of these properties in solution is of vital importance but poses a challenge to both experiment and theory even for well-studied compounds such as nucleic acid building blocks. Experimentally, rapid conformational changes and the fast proton transfer between multiple tautomeric forms make elucidating these equilibria cumbersome especially under extreme conditions, while the theoretical task is complicated due to the environmental effect on both electronic structure and solvent distributions.

We here predict tautomeric and conformational equilibria of natural and non-natural nucleobases in water under various environmental conditions by the methodology employed within the SAMPL blind prediction challenges for tautomers, distribution coefficients and acidity constants [1-3] of small molecules. Solvent effects on energetics and spectroscopic parameters in quantum-chemical calculations are considered using the "embedded cluster reference interaction site model" (EC-RISM) developed by us, which has been demonstrated to provide accurate estimates of thermodynamic quantities and spectroscopic features in solution even for high pressure solvents [4]. Refining the EC-RISM workflow with a coupled-cluster extrapolation, which allows treatment of electron correlation effects with high accuracy, is used to further improve the quality of tautomer predictions.



We obtain the contributions of all accessible states to the molecular ensemble as a function of pH, pressure and temperature as well as their respective relevance for understanding experimental NMR spectra. Preliminary results indicate remarkable tautomeric stability of natural nucleobases which could hint at tautomerism being an evolutionary relevant chemical optimization target.

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[3] N. Tielker, L. Eberlein, S. Güssregen, S. M. Kast, *J. Comput.-Aided Mol. Des.* **2018**, 32, 1151-1163.

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Performing Hit Identification and Lead Optimization at Very Large Scale

Dan Cannon

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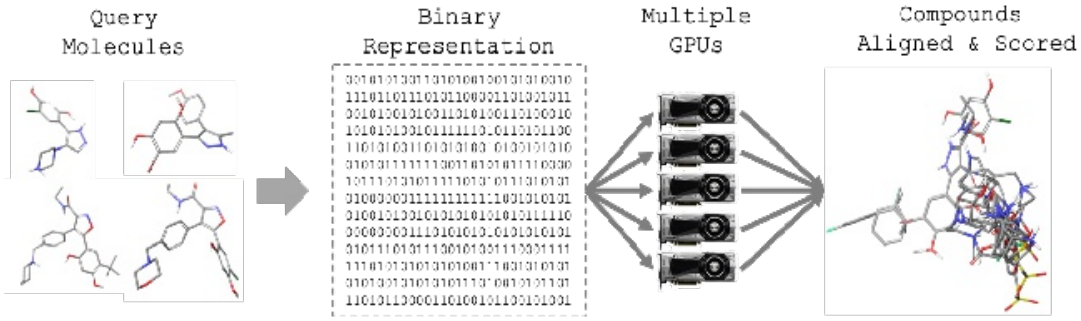

It has been estimated there are around 10^60 potential organic molecules with MW < 500, considering only basic structural rules, yet traditional virtual screening decks include up to tens of millions of compounds and design-make-test-analyze (DMTA) cycles in lead optimization generally evaluate tens to low thousands of compounds. Bridging these gaps are on-demand synthesizable screening libraries and synthetically tractable enumerated libraries on the order of millions to low billions of compounds. To virtually screen such massive libraries of compounds using 3D information within project timelines of drug discovery projects, GPU-based shape screening methods have demonstrated considerable utility. They often outperform pharmacophore methods while being easier to apply to more diverse collections of known hits. In this presentation we introduce a GPU enabled algorithm based on the previously described CPU implementation [1] and describe how it can impact lead discovery projects using your existing local or cloud GPU resources, even when screening >1 billion compounds.

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Binding of histamine to the H_1 receptor: a molecular dynamics study

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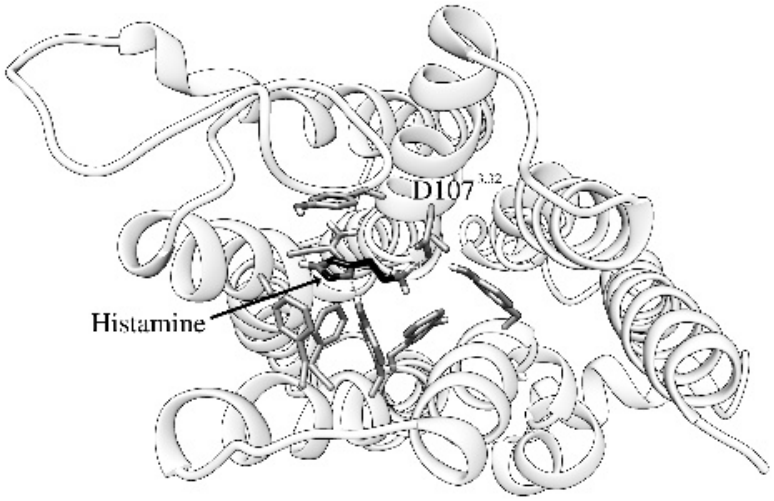
Binding of histamine to the G-protein coupled histamine H_1 receptor plays an important role in the context of allergic reactions [1]; however, no crystal structure of the resulting complex is available yet. To deduce the histamine binding site, we performed unbiased molecular dynamics (MD) simulations on a microsecond time scale, which allowed to monitor one binding event, in which particularly the residues of the extracellular loop 2 were involved in the initial recognition process.

The final histamine binding pose in the orthosteric pocket is characterised by interactions with $Asp107^{3.32}$, $Tyr108^{3.33}$, $Thr194^{5.43}$, $Asn198^{5.46}$, $Trp428^{6.48}$, $Tyr431^{6.51}$, $Phe432^{6.52}$, and $Phe435^{6.55}$, which is in agreement with existing mutational data [2–4]. The conformational stability of the obtained complex structure was subsequently confirmed in 2 μs equilibrium MD simulations, and a metadynamics simulation proved that the detected binding site represents an energy minimum.

A complementary investigation of a D107A mutant, which has experimentally been shown to abolish ligand binding [2], revealed that this exchange results in a significantly weaker interaction and enhanced ligand dynamics. This finding underlines the importance of the electrostatic interaction between the histamine ammonium group and the side chain of $Asp107^{3.32}$ for histamine binding.



Final binding mode of histamine to the H_1 receptor. Histamine and the most important interacting residues of the receptor are shown as sticks. For clarity, the histamine carbon atoms are coloured in black.

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The work presented in this talk has been published:
C.A. Söldner, A.H.C. Horn, H. Sticht, *J Mol Model*, **2018**, 24, 346

NP-Scout: Machine Learning Models for the Identification and Visualization of the Natural Product-Likeness of Small Molecules

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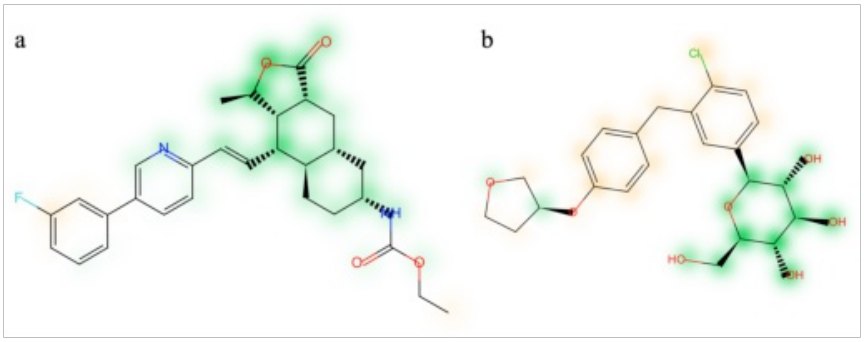
Natural products (NPs) remain the most productive source of inspiration in drug discovery [1]. NPs are highly diverse in chemical structure, exhibit a broad range of activities relevant to human health, and cover regions of the chemical space not or only rarely populated by synthetic molecules (SMs) [2, 3]. However, only an estimated 10% of all known NPs are readily obtainable for testing [4], and despite the rarity of materials, vendors most commonly offer mixed libraries of unlabeled (semi-) SMs and NPs.

We have devised a machine learning approach ("NP-Scout") [5] that not only allows the discrimination of NPs and SMs but also enables the quantification of NP-likeness and the visualization of regions in molecules that are NP-like. NP-Scout uses random forest classifiers trained on more than 265,000 NPs and SMs compiled from a total of 27 data sources. The suitability of two-dimensional molecular descriptors, MACCS keys and Morgan2 fingerprints was explored for model building. On independent test sets, NP-Scout models reached areas under the receiver operating characteristic curves (AUCs) of up to 0.997 and Matthews correlation coefficients (MCCs) of 0.954 and higher. The method was successfully tested also on data from the Dictionary of Natural Products, ChEMBL and further resources. Similarity maps generated from the models highlight atoms that contribute to the classification of small molecules as NPs or SMs. This allows, for example, also the identification of NP derivatives, as shown below by the example of the NP derivatives (a) vorapaxar and (b) empagliflozin (atoms highlighted in green are recognized as NP-like, atoms highlighted in orange as SM-like). The best-performing models are accessible via a free web service at http://npscout.zbh.uni-hamburg.de/npscout.



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COSMO*plex*: A new paradigm for simulating self-organizing systems

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3) *Universite of Compiegne, France*

The efficient combination of quantum chemical calculations with statistical thermodynamics COSMO-RS has become an important alternative to force-field based simulations for the accurate prediction of free energies of molecules in liquid systems [1]. While it originally was restricted to homogeneous liquids, it later has been extended to the prediction of the free energy of molecules in inhomogeneous systems as micelles, bio-membranes, or liquid interfaces, but these calculations were based on external input about the structure of the inhomogeneous system [2]. Recently an extension of COSMO-RS named COSMO*plex* has been developed, which allows for the self-consistent prediction of the structure and the free energies of molecules in self-organizing inhomogeneous systems. This extends the application range to many new areas, as the prediction of micellar structure and critical micelle concentrations, finite loading effects in micelles and bio-membranes, free energies and structure of liquid interfaces, micro-emulsions, and many more of similar problems, which often are of huge practical importance. COSMO*plex* [3] is approximately 10000 times faster than comparable molecular dynamics calculations and it is based on the same molecular interaction description as used in COSMO-RS. It does not require any re-parameterization, nor coarse graining. Thus it opens up completely new perspectives and possibilities for the simulation and screening of properties of inhomogeneous systems.

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Thermodynamic signatures of protein hydration sites and their correlation with ligand features

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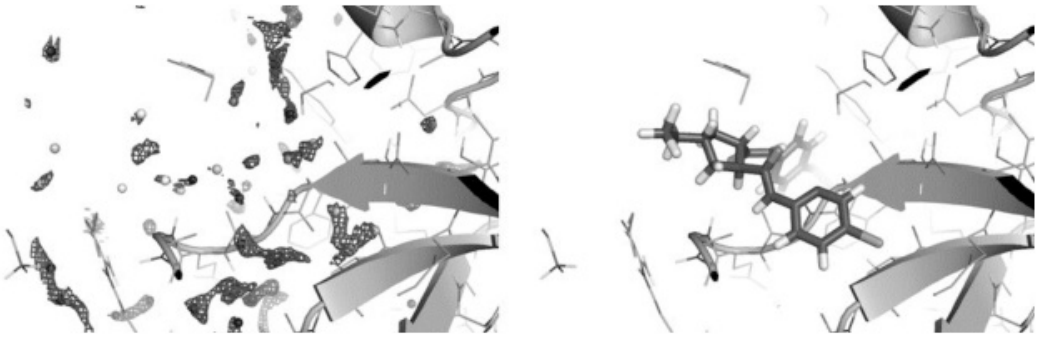
During the drug discovery process, initial hit compounds that were identified by high throughput screening are usually optimized via structure-based drug design (SBDD) [1]. In an iterative process, specific groups of the molecule are varied and the impact of these modifications on binding affinity is assessed. The introduction of new groups or modifications is typically directed by pharmacophores, compound comparison and chemical intuition which all reflect the complex interplay of protein-ligand interactions and their modulation by the solvent. To complement the SBDD toolbox with novel physics-based approaches, we here present results from our approach to predict local contributions of water molecules in binding sites to the solvation free energy [2], applied to a range of target proteins. We particularly focus on the question to what extent the thermodynamics of protein-ligand interaction is already imprinted on the hydration signatures within a binding site.

To this end, we employ the three-dimensional (3D) reference interaction site model (RISM) integral equation theory for predicting localized binding site water molecules in *apo* proteins along with their thermodynamic signatures that are relevant for rationalizing properties of the ligand groups which replace them [2]. For the proteins in the pdbBind core set [3] we analyze to what extent water molecules classified as "happy" and "unhappy" (depending on their favorable or unfavorable contribution to the hydration free energy) correlate with different types of ligand atoms displacing them in the *holo* complex. Thus, we elucidate the relevance and limitations of this methodology to aid the design or modification of a ligand to target a solvent-occupied binding site region.



Together with the 3D RISM-based binding free energy localization and local probe thermodynamics approaches recently developed in our group, this information yields an in-depth picture of the thermodynamic contributions of direct and solvent-mediated interactions in a protein ligand complex. Perspectives for using these data in the context of machine learning approaches to predict protein-ligand interactions and for design purposes are also discussed.

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Structure-based design of riboswitch ligands and selective NMT inhibitors

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Structure-based ligand design is an integral part of modern drug discovery. This approach makes use of the knowledge of the crystal structure of the target for the design of new ligands. In my group, we develop computational methods for structure-based design and apply such methods for the design of new ligands. In this seminar, I will report on different aspects of structure-based drug discovery. One the one hand side, I will present our ongoing efforts to design riboswitch ligands. Riboswitches are part of the 5' untranslated region of mRNA. With little precedence for drug design efforts for RNA, they can be considered to be challenging targets. One the other side, I will present an approach on how to dissect molecular driving forces to design selective inhibitors which is an import goal in many drug discovery projects.

Boosting the Scalability of Car-Parrinello Molecular Dynamics for Large-Scale Simulations of Solid-Liquid Interfaces

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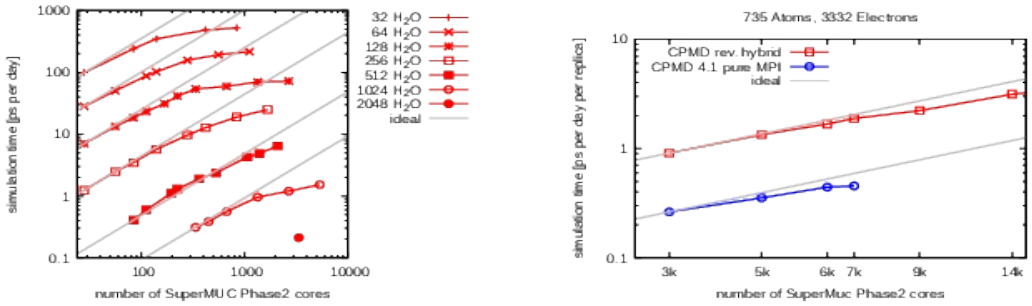
[2]Institute of Chemistry, Jan Kochanowski University, Kielce, Poland

[3]Leibniz Supercomputing Centre of the Bavarian Academy of Sciences and Humanities Garching



We present our recent optimizations of the ultra-soft pseudo-potential (USPP) code path of the ab inito Car-Parrinello molecular dynamics program CPMD (www.cpmd.org). All relevant USPP routines have been revised to fully support hybrid MPI+OpenMP parallelization. For two time-critical routines, namely the multiple distributed 3d FFTs of the electronic states and a key distributed matrix-matrix multiplication, we have implemented hybrid parallel algorithms with overlapping computation and communication. The achievements in performance and scalability are demonstrated on simulations of liquid water with 128 and up to 2048 molecules. Performance evaluation shows gains of up to one order of magnitude and around 50% peak performance on the node level. The improved CPMD code has been applied to sample the free energy landscape for a hydrolysis reaction in explicit liquid water on a ZnO surface as catalyst. The unit cell contained 735 atoms and 3332 electrons. A 50 ps trajectory required about 10 days on 18 SuperMUC2 compute nodes.

Metabolite Structure Prediction Focused on the Cytochrome P450 Enzyme Family

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Biotransformation of small organic molecules can result in metabolites with greatly modified biological and physicochemical properties compared to those of the parent compound, [1] hence, knowledge of the metabolic fate of xenobiotics in humans is vital for the development of safe and effective drugs. Regioselectivity prediction, the prediction of the locations in the molecule where metabolic reactions are initiated, is an aspect of metabolism prediction that is often an aim in and of itself but can also be applied as an initial step towards predicting the structures of the metabolites.

Here we examine the effect of an initial regioselectivity prediction step on the quantity and quality of metabolite structures that can be generated. We have developed a strategy for metabolite structure prediction that is based on FAME 2, [2] our recently-developed and highly effective machine learning method for human cytochrome P450 (CYP) regioselectivity prediction. As part of this strategy, we have assembled a thorough collection of known CYP-mediated reactions based on the scientific literature and chemical knowledge. By applying these reactions to the sites of metabolism predicted by FAME 2, we are able to correctly predict the majority of known metabolites while lowering false-positive prediction rates compared to the application of the reactions to all atom positions in the parent compounds.

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Computational insights into procathepsin maturation mediated by glycosaminoglycans

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Cathepsins, lysosomal proteases are present in many living organisms [1]. The majority of cathepsins are cysteine proteases with a few exceptions: cathepsin A and G are serine proteases and cathepsin D and E are aspartyl proteases [2]. Cathepsins function in extracellular matrix and play a crucial role in various biological processes including bone resorption, intracellular proteolysis, regulation of programmed cell death or degradation of antimicrobial peptides/proteins depending on the type of the cathepsin. Their malfunction in organism may lead to many serious diseases, such as pycnodysostosis, osteoporosis, rheumatoid arthritis, osteoarthitis, asthma, psoriasis, atherosclerosis, cancer, obesity autoimmune disorders and viral infection depending on the type of cathepsin. Therefore, it is important to understand the molecular basis of those processes.

It is known that cathepsin activity can be mediated by glycosaminoglycans (GAGs), a class of linear anionic and periodic polysaccharides [3]. Each GAG (excluding keratan sulfate) consists of a recurring disaccharide unit in which one aminosugar and one uronic acid are present. Like cathepsins, GAGs are also present in extracellular matrix, in which they are involved in diverse processes such as angiogenesis, anticoagulation, adhesion and signaling cascades [4]. The interactions between GAGs and their protein targets that are responsible for aforementioned processes and are electrostatic driven.

In addition to cathepsins, active enzymes, GAGs can also form complexes with procathepsins, inactive proenzymes [5]. In procathepsin, a propeptide part covers a cathepsin active site rendering its inactivity. In order to enable the process of maturation, an another procathepsin molecule, either of the same or other type has to be present in order to activate a procathepsin. In addition, it is known that GAGs can mediate this process. GAG binding on procathepsin surface can induce conformational change of a zymogen that leads to the exposure of active site. However, the detailed description of the maturation process mediated by GAGs at atomic level which could explain the obtained experimental data is still unavailable. Moreover, it is still unknown whether the maturation mechanism is conserved among different procathepsins.

In our approach we used several computational methodologies in order to get deeper understanding of procathepsin maturation process mediated by GAGs. Modeled GAG structures were docked to conformational ensemble of procathepsin models calculated with coarse-grained UNRES force field [6]. Afterwards, complex structures were simulated by the molecular dynamics approach. Post-processing free energy analysis of the produced molecular dynamics trajectories by various approaches such as Molecular Mechanics-Poisson Boltzmann with the entropy calculations by normal mode, quasi harmonic analysis or potential of mean force approach provided us valuable data on the stability of the complex. Moreover, with additional per-residue analysis of free energy we identified aminoacid residues that contribute mostly to the interactions between receptor and ligand and in turn – to overall stability of a complex.

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Chemistry at the solid-liquid interface

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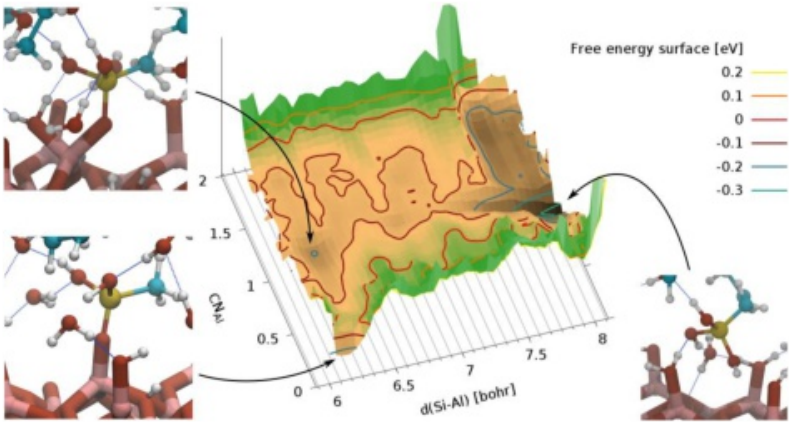

Chemical functionalization of surfaces, i.e. the covalent attachment of molecules, is usually done by wet-chemical processes. In our research we use *ab initio* molecular dynamics (AIMD) together with acceleration techniques such as metadynamics to obtain fundamental insights into the mechanisms of molecular adsorption, reaction and binding at such solid-liquid interfaces. This will be illustrated by two examples, the anchoring of a typical silanol linker unit to aluminum oxide via condensation reactions in the presence of liquid isopropanol and the oxidation chemistry of graphite by intercalation with liquid sulfuric acid.

In the first example we will focus on the identification of relevant transition state structures, the role of residual water at the surface and the impact of proton dynamics at the interface. For the intercalated graphite we will discuss the stability of oxygen species in the presence of sulfuric acid and we show that oxidation and ideal crystallinity reduce the molecular friction and thereby facilitate a fast and efficient intercalation [1]. The graphite intercalation compound furthermore serves as a well-defined model system of a confined liquid for which we studied the impact of confinement on the dynamics of the liquid, the stability of the hydrogen-bond network and the kinetics of proton diffusion. These time consuming AIMD simulations only became possible with our recent improvements in the Car-Parrinello Molecular Dynamics (CPMD) code [2].

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Mechanism of fully-reversible, pH-sensitive inhibition of human glutamine synthetase by tyrosine nitration.

Benedikt Frieg[1,2], Boris Görg[3], Natalia Qvartskhava[3], Mohanraj Gopalswamy[1], Thomas Jeitner[4], Nadine Homeyer[1], Dieter Häussinger[3*] and Holger Gohlke[1,2*]

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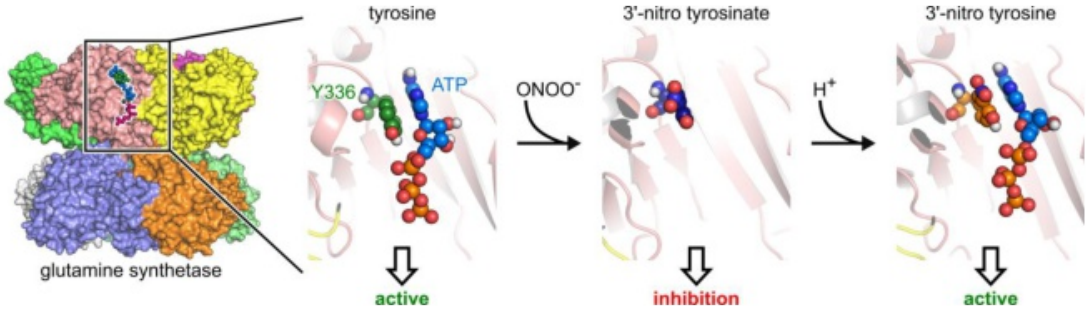

Glutamine synthetase (GS) catalyzes the ATP-dependent ligation of toxic ammonia and glutamate to glutamine, the most substantial free amino acid. This reaction – and therefore GS – are indispensable for the human nitrogen metabolism [1, 2] and changes in GS catalytic activity have been linked to a broad range of neurological diseases [3, 4]. In particular, GS catalytic activity is highly sensitivity to tyrosine nitration, a post-translation modification under "nitroxidative stress" conditions, which causes GS inhibition [5, 6]. As to human GS, nitration of tyrosine 336 (Y336) inhibits GS activity [5]. Although Y336 nitration modifies key properties of the amino acid, the molecular mechanism by which Y336 nitration inhibits GS, however, is not understood.

Here, we show by means of unbiased MD simulations, binding and configurational free energy computations that Y336 nitration hampers substrate (ATP) binding, but only in the deprotonated and negatively-charged state of residue 336. By contrast, for the protonated and neutral state, our computations indicate an increased binding affinity for ATP. pK_a computations of nitrated Y336 within GS predict a pK_a of ~4. Thus, at physiological pH nitrated Y336 exists almost exclusively in the deprotonated and negatively-charged state. *In vitro* experiments confirm these predictions, in that, the catalytic activity of nitrated GS is decreased at pH 7 and pH 6, but not at pH 4. These results indicate a novel, fully reversible, pH-sensitive mechanism for the regulation of GS activity.

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Large-scale analysis of protein thermostability and detergent tolerance

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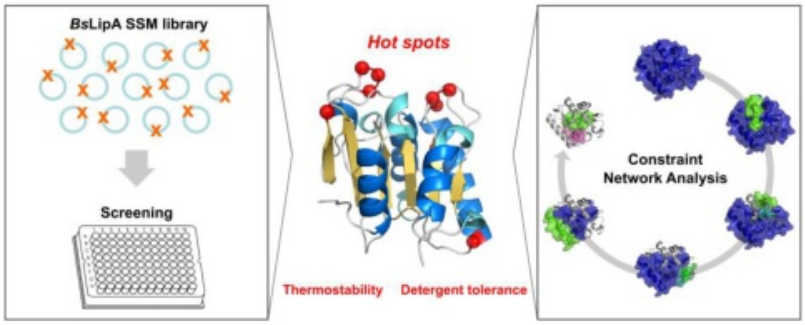
Understanding how structure and activity of proteins are related to their (thermo-)stability [1-2] or tolerance against solvents [3] and detergents [4] is of utmost importance in protein engineering. However, until now, the role and impact of the location and type of substitution on protein properties has been predominantly studied from analyses of only a few protein variants or large-scale studies over data sets of many proteins, only contributing a few variants each. Furthermore, most analyses considered only one protein property at a time. Here, for the first time, we exhaustively characterize changes in thermostability *and* detergent tolerance for a complete site-saturation mutagenesis (SSM) library containing 3439 single variants of the *Bacillus subtilis* lipase A (*Bs*LipA). To establish a set of generally applicable guidelines regarding improved protein thermostability *and* / *or* detergent tolerance, we identified *hot spot* residues, i.e. those with a high likelihood to yield stabilized variants, and probed if they can be predicted based on protein structural characteristics or via rigidity theory-based Constraint Network Analysis (CNA) [5]. The main outcome is that CNA can precisely predict *hot spots* for rational protein design aiming at improved protein thermostability *and* / *or* detergent tolerance.



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Aero Engines, Computational Chemistry and REACH

How does that match together?

Dr. Max Niegl,

MTU Aero Engines AG

A lot of chemical processes like e.g. functional chrome plating and anti-corrosion coatings are used to build and repair parts for aero engines.

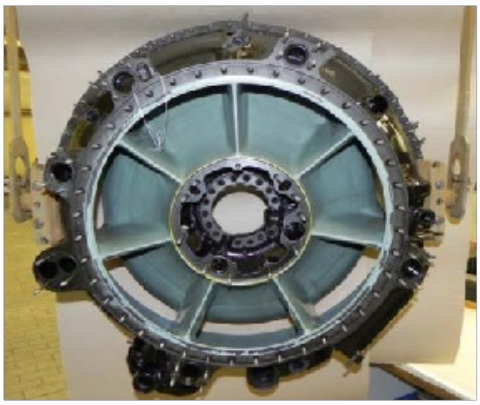
During the last 13 years European chemical legislation existing under the umbrella of REACH (Registration Evaluation Authorization of Chemicals) and its authority ECHA (European Chemical Agency) identifies chemical substances e.g. used for the production of aero engines as svhc (substances of very high concern) and restricts their further use.

Therefore it is necessary to find alternative substances and processes which are svhc free and fulfill the technical and safety requirements for aero engines parts.

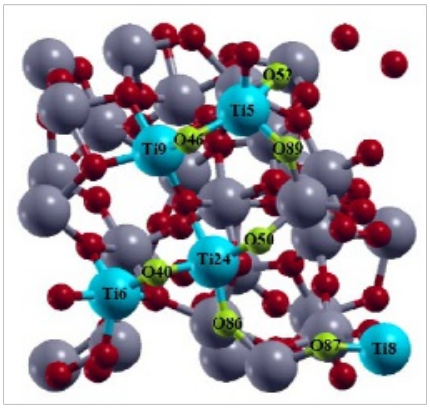
During this process of technological development the use of computational chemistry methods predicts us technical properties of alternative chemicals. We can understand the coating mechanism in detail and finally introduce svhc free coating systems in our production lines.

In the past years these methods helped use to develop chromium (VI) free anti corrosion coatings and chromium (VI) free passivation processes.

Aero engines: Overhauled and ready for assembly



Turbine intermediate casing with anti-corrosion coating



Adhesion simulation on TiO_2 surfaces

REAL-ly large-scale Virtual Screening -
Traversing Enormous Regions of Chemical Space with the GPU and CPU

Gunther Stahl

OpenEye Scientific Software Ltd. Zweigniederlassung Deutschland

The sheer size of the universe of molecules (variously estimated to be between 10^{40} and 10^{60} [1]) is daunting. The number of molecules in a particular library or collection has, until recently, dictated the methods that can be used to search it; only very rapid graph-based methods were fast enough to search hundreds of millions of molecules in a reasonable time and with reasonable computational resources [2]. However, the advent of the cloud as a routine compute resource enables new approaches to the rapid searching of previously intractably large chemical spaces, as it allows cost-effective access to both CPU and GPU-enabled search.

In this presentation we will demonstrate shape similarity searching with FastROCS [3], the GPU version of the widely used lead discovery tool ROCS [4]. We will briefly present how porting to the GPU enabled us to accelerate shape searching by over 3 orders of magnitude and yet maintain identical virtual screening performance. The unprecedented speed of the current version of FastROCS (> 20 million molecules/GPU/minute) enables searching of enormous libraries in a matter of minutes. We will illustrate this capability by searching parts of the Enamine REAL library [5].

Searching the full Enamine REAL database (1.4 Billion enumerated molecules) requires the great parallelizability of computation on the cloud. We will present results on searching the entirety of the REAL library using both FastROCS and OpenEye's high-throughput docking tool [6], FRED. To our knowledge these are the largest scale virtual screens so far conducted, being over an order of magnitude larger than the largest screens reported to date [7].

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Comprehensive description of interactions of ionic liquid ions with *Bs*LipA

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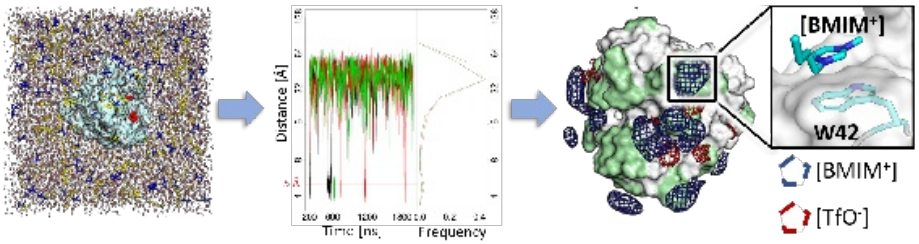

Ionic liquids (IL) and seawater are attractive (co-)solvents for biocatalysis due to their unique properties such as negligible vapor pressure respectively high abundance of seawater on earth [1,2] but, at the same time, influence activity and stability of enzymes in a complex manner [3]. However, this influence is not fully understood at the molecular level, and a general approach to guide protein engineering towards enzymes with improved IL and salt resistance has remained elusive. We aim at establishing a comprehensive description of the interactions of IL-/salt ions with the Lipase A from *Bacillus subtilis* (*Bs*LipA). Therefore, we employ molecular dynamics (MD) simulations to fundamentally understand the influences these solvents pose on proteins.
Our results reveal that MD simulations of *Bs*LipA in IL are feasible and successfully identify interaction sites of the IL ions with *Bs*LipA. We found multiple distinctive interaction sites of both the IL cation and the respective anion, which are in good accordance to recently published MD- and X-ray crystallography studies [4,5]. Interestingly, IL lead to only minor changes of the global protein structure but induce large changes in local intramolecular interactions of *Bs*LipA. This includes deep-reaching perturbations of the intramolecular H-bond network as well as changes in the ratio of active to inactive state conformations of the catalytic site, thus affecting both the catalytic site residues and the protein core. These results give new insights into the molecular effects of IL ions on *Bs*LipA activity in full atomic detail.
The knowledge derived from MD simulations will be applied to adapt a computationally highly efficient graph- and rigidity theory-based approach (Constraint Network Analysis) previously used successfully in the context of protein thermostability for the application with IL [6]. To experimentally validate and refine our model, a complete site-saturation mutagenesis library covering all possible single amino acid mutations of *Bs*LipA is available [7].

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Unravelling the Mechanisms of Cytotoxicity for Phenanthroline Derivatives: Interaction with DNA

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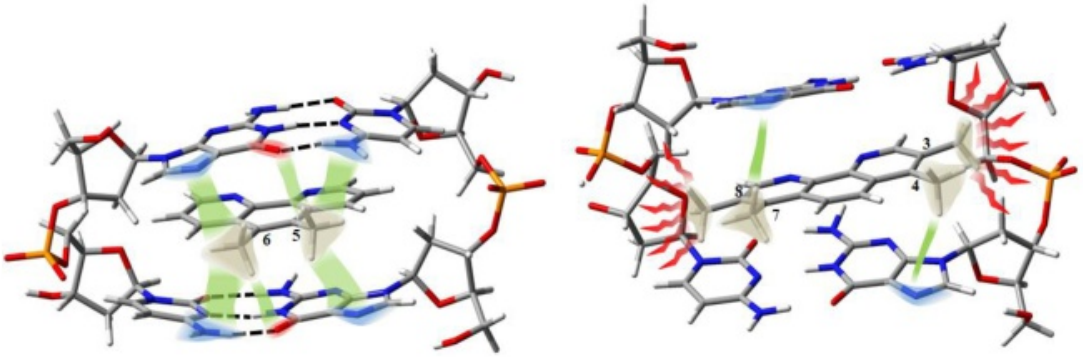

Flat ligands, alone or within metal complexes, are active against tumor cells and may be used in chemotherapy.[1] The activity of these drugs is related to their mode of interaction with DNA being the intercalation mode identified as the cytotoxic mode against tumor cells.[1,2] 1,10-phenanthroline (phen) was demonstrated to be effective towards several tumor cell lines,[3] and their derivatives also showed cytotoxicity. Moreover, it was observed that this cytotoxicity was deeply connected to the number and position of the functional groups incorporated in phen.[3] Different studies on the intercalation of small molecules in DNA have appeared in the bibliography during the last years [4,5] and some debate still remains about the intercalation/deintercalation process [4-7] and the mechanism that could explain the modulation of the cytotoxicity. In our work, we try to rationalize the role of weak interactions with the stability of the interaction and we extrapolate our results to the cytotoxic effects. The systems were mainly optimized by using semiempirical methods including dispersion effects. We also carried out DFT calculations including dispersion effects for the Energy Decomposition Analysis (EDA) and to perform the Quantum Theory of Atoms in Molecules (QTAIM) and the Non-Covalent Interaction (NCI) analyses to obtain topological pictures of the weak interactions that rules the intercalation process. Solvent effects were also taken into account by continuum approaches. Our results confirm the importance of weak interactions and we extrapolate the link with the cytotoxicity by means of a subtle balance between the stabilizing weak interactions and the destabilizing steric contribution. The role of desolvation energy is also crucial when looking at the stability of the studied systems.

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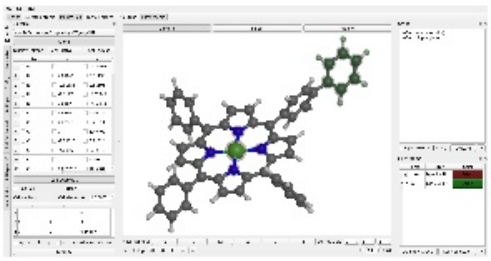
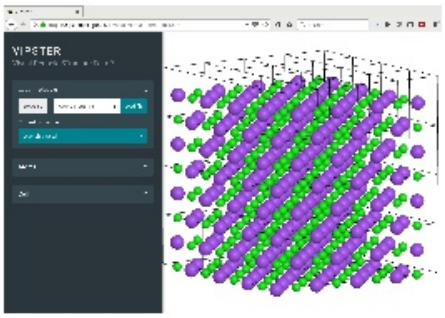
Vipster – A novel editor and visualization tool for periodic structures

Sebastian Gsänger, Jonathan Gruber, and Bernd Meyer

Interdisciplinary Center for Molecular Materials and Computer-Chemistry-Center, FAU Erlangen-Nürnberg





When preparing structures for atomistic simulations or analyzing their results, one often has to decide between editing and visualization software. This is even more prevalent when dealing with periodic calculations, for which support has often been added to established programs as an afterthought. Here we present our endeavor to fill this gap with a portable and self-contained package that handles periodicity as a primary property. Utilizing modern platform-independent technology, we provide a featureful desktop client for all major operating systems, as well as a lightweight browser-based client and a scripting-interface via python.

Website: *https://sgsaenger.github.io/vipster/*

SIMULATION OF PHOTO-INDUCED PROCESSES AT ORGANIC-ORGANIC INTERFACES

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In the present work we focus on investigations about photo-induced processes in thin organic films and at the organic-organic interfaces. Their accurate description and understanding are prerequisites for the design opto-electronic devices such as organic solar cells or light emitting diodes. In organic solar cells, separation of optically excited electron-hole pairs and long-range charge transport play an important role for the efficiency. Both are largely influenced by the film structure and the molecular orientation at interfaces between electron donor (D) and acceptor (A) molecules. In our presentation we briefly mention the dimer approach which successfully delivered atomistic pictures for photo-induced relaxation effects in aggregates and allowed a correct description of the energy disorder in the vicinity of amorphous interfaces.[1,2] Furthermore, we focus on our simulations about the individual steps of the light to energy conversion process in the vicinity of the interfaces of organic solar cells [3] and describe recent works about the interpretation of femtosecond (fs) time-resolved second harmonic generation (TR-SHG) in DIP-PDIR-CN_2 interfaces.[4]

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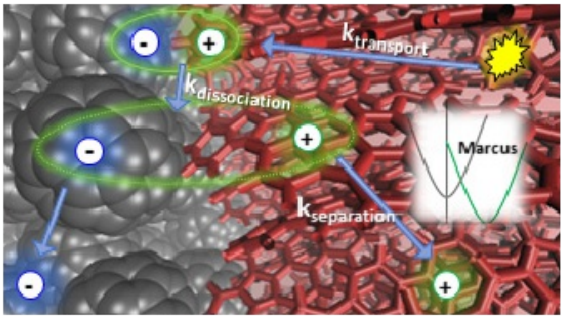

Figure 1: Various processes at organic-organic interfaces

Quantum Chemistry in the Design of Liquid Crystals for Display Applications

Matthias Bremer

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Since the late 1970s LCDs have grown from Band-Aid size in pocket calculators to ultra-high definition television displays with diagonals of more than one hundred inch. At the same time, the development of liquid crystalline materials for device applications has advanced from relatively simple polar materials (nitriles and esters) to liquid crystals with fluorinated structural elements and fluorinated polar functional groups. The design and optimization of such materials was supported to a large extent by computational quantum chemistry. Pertinent examples for this, such as negative birefringence in calamitic nematic materials, "functional" bridge elements, hypervalent sulfur fluorides, highly polar dielectrically negative indane-derivatives, and the relevance of fluorinated materials to the reliability of LCDs in general will be discussed.

Modelling ligand binding and allostery in kinases and GPCRs with enhanced-sampling algorithms

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Institute of Structural and Molecular Biology

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Allosteric regulation plays a fundamental role in biology. In signalling proteins such as protein kinases and G protein-coupled receptors (GPCRs), ligand binding to allosteric sites are able to up- or down-regulate the catalytic activity and activate downstream signalling cascades. Understanding the molecular mechanisms underlying the observed allosteric effects is of great importance for the rational design of novel biologically active allosteric regulators. One major challenge and opportunity in computational chemistry is the accurate description of the conformational landscape prior to and upon the binding of the allosteric regulator. To this aim we have developed, tested and successfully applied various enhanced sampling algorithms (based on Metadynamics and/or Hamiltonian replica exchange) together with atomistic simulations. Here we show how these methods were successfully used to compute complex conformational landscapes associated with kinase and GPCR activation and predict how they change in response to ligand binding and post-translational modifications.[1-8] We also show how atomistic simulations were used to reveal a previously unknown catalytic activity of glutamine synthetase.[9]

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Reaction control in radical SAM enzymes: How nature plays with radical and redox reactivity

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How enzymes have developed to catalyse and control specific reactions is one of the most complex questions necessary to understand in order to be able to rationally influence enzyme activity and selectivity for medicinal and biotechnological applications. Intriguingly interesting in this concept are enzymes that need to control highly reactive intermediates that tend to undergo rapid stabilising side reactions, like radicals.

Radical *S*-adenosylmethionine (SAM) dependent enzymes [1] share the communality to initiate radical intermediates vie hydrogen abstraction reactions controlled by SAM and the redox chemistry associated with central iron sulfur clusters. They are perfectly designed to control these highly reactive intermediates in order to facilitate and drive the desired reaction involved in number of biosynthetic pathways towards anti-viral, anti-cancer and antibiotic products. [2]

Complex radical ring rearrangements like in the example of 7-carboxy-7-deazaguanine (CDG) synthase (QueE) [3] are a particular speciality of rSAM enzymes and we recently demonstrated how these rearrangements need to be fine-tuned by controlling the thermodynamics of the central radical clock reaction. [4] Here, we show how the enzymes control the reactivity of the radical rearrangement and how efficient computational assessment of thermodynamic reaction profiles through calculating radical stabilization energies (RSEs) [5] of key intermediates from simulation ensembles can be used for screening for alternative substrates and designing radical enzymes with improved substrate range and turnover.

A second key influencing parameter for many examples in enzyme catalysis is the internal electrostatic field in the enzyme active site, often referred to as electrostatic preorganization. [6] Recently Shaik *et al.* [7] and others demonstrated how externally orientated electric fields can influence biocatalytic reaction rates by orders of magnitude. Hydrogen abstraction reactions and effects on the reactivity of metal clusters in enzymes, both important in radical SAM enzyme catalysis, are prone to be highly influenced by changes in the surrounding electrostatic field. Along similar lines to the example of QueE, we will discuss very recent investigations on the role of orientated electric fields at different stages of rSAM enzyme catalysis.

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From macroscopic to local molecular thermodynamics

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Molecular thermodynamics reflects the driving forces governing chemical processes, accounting for direct and solvent-mediated interactions and entropic contributions, where the latter originates from both structural flexibility and solvent degrees of freedom. By definition, thermodynamics is a macroscopic approach to molecular energetics as a large number of atomic degrees of freedom or energy states leads to a small number of thermodynamic quantities that can be measured experimentally; this is the domain of statistical thermodynamics. From a predictive perspective, two approaches are available to tackle the problem, molecular simulations (molecular dynamics or Monte-Carlo) and, with special emphasis on solvation features, liquid state theory. Both depend on knowledge of intra-solute and –solvent and solute-solvent interactions which can be determined from force fields or quantum-chemical calculations. In this context, the question arises whether these macroscopic thermodynamic features can be mapped to *local*, i.e. atom or group based components that would allow for an analysis of the impact of local changes on macroscopic data, a key feature of molecular design.

In this talk, the perspective of liquid state theory, more specifically the integral equation approach known as 3D RISM (reference interaction site model) theory is outlined for the prediction of thermodynamic quantities and their localization. Starting with the basic elements and practically useful approximations, it will be demonstrated that predictive models can be developed by combining 3D RISM with quantum chemistry in the form of the embedded cluster (EC-)RISM method [1-3]. Following-up on these benchmarks, physically sound localization methods are outlined and discussed. In particular, a local picture of hydration thermodynamics is developed which can be utilized for drug discovery [4], the energetic and entropic components of solvation thermodynamics are analyzed [5], and preliminary results are presented for the localization of binding free energies in host-guest complexes [6]. The talk concludes with a perspective on exploiting local thermodynamics in the context of machine learning for addressing the molecular design challenge.

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Design of the tellurium-containing semiconducting polymers

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A series of donor-acceptor-donor (D-A-D) type semiconducting polymers containing tellurium atom in their acceptor units were designed and their structural and electronic properties were investigated by using density functional theory (DFT). Energy levels for highest occupied molecular orbitals and lowest unoccupied molecular orbitals were calculated, and then the electronic band gap values, which directly affects the electronic properties of the semiconducting polymers, were obtained for all the systems being investigated. The results of our investigations implied that the use of tellurium atoms in the acceptor units significantly decreases the electronic band gap which results with providing superior conducting properties to these polymers. Due to their superior electronic properties, these polymers may find important applications, such as in photovoltaic and electrochromic devices. During the study, we performed all DFT calculations by using Becke three-parameter hybrid exchange-correlation functional combined with Lee-Yang-Parr correlation functional and the LANL2DZ basis set.

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Role of structural dynamics for GPCR signaling

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G Protein coupled receptors (GPCRs) are one of the most heavily investigated drug targets in the pharmaceutical industry covering different pathological areas including cancer, cardiovascular disorders, diabetes, central nervous system disorders, obesity, inflammation, and pain. A present key interest of the pharmaceutical industry is to design GPCR-targeted drugs with improved specificity and reduced side effects. This is challenging as one and the same receptor can activate different intracellular downstream signalling proteins such as heterotrimeric G proteins ($G\alpha\beta\gamma$, α-families Gi, Gs, Gq, G12/13) or arrestins (arrestin 1–4), resulting in different (either wanted or unwanted) cellular and physiological responses. Understanding the molecular mechanism of this coupling promiscuity is thus a major question in current receptor research.

I will summarize our attempts to elucidate coupling specificity in G protein coupled receptor signalling using molecular dynamics simulations referencing related experimental work. According to our knowledge based concept, structural flexibility plays a key role in specific recognition and binding of G proteins to active receptors. Our concept of receptor G protein coupling specificity may pave the way for novel concepts and approaches to develop drugs with limited side effects. Computer simulations are available through web-services developed in my laboratory using innovative approaches for interactive visualisation of even huge amounts of data.

What to gain from protein statics

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G-protein coupled receptors (GPCR) serve as relays for recognizing signals outside the cell, which are transmitted through the membrane to initiate cellular signaling cascades. Their diverse physiological responses in living cells established GPCRs as important drug targets. Binding of extracellular modulators either induce, inhibit, or alter the activation of GPCRs by stimulating different signaling pathways. However, despite increasing structural information of GPCRs, complemented by intensive computational studies, a detailed knowledge of the signaling mechanisms in GPCRs has remained elusive.

Recently, we introduced a rigorous approximation of vibrational entropy changes upon ligand binding based on analyzing constraint network representations (1) of biomolecular complexes.(2) We also formulated an ensemble- and rigidity theory-based free energy perturbation approach to analyze dynamic allostery.(3) In this work, we apply these methodologies, first, to analyze how different extracellular modulators affect signaling of the GPCRs β_2 adrenoreceptor (β2AR) and μ-opioid receptor (MOR). Based on altered stability characteristics of the GPCRs, our approaches allow discriminating between agonist, antagonist, and inverse agonist binding and reveal different pathways of connected residues in both β2AR and MOR depending on the type of extracellular modulator. Second, we investigate why the human histamine H_4 receptor (hH_4R) shows a high degree of constitutive activity in contrast to mouse H_4R (mH_4R). By sequence comparison, molecular dynamics simulations, and rigidity analyses, we identify, and experimentally validate, residues in the extracellular loop 2 region of hH_4R that apparently mimic agonist binding and, thus, lead to basal activity.

Overall, our results shed new light on signaling mechanisms in GPCRs at an atomistic level and demonstrate that the rigidity theory-based analysis of dynamic allostery provides a computationally cheap, yet information-rich, way to scrutinize the role of ligands and sequence variations for GPCR signaling.

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Correlation Energy Densities from Coupled Cluster Theory

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(Semi-)local density functional approximations (DFAs) are the workhorse electronic structure methods in condensed matter theory and surface science. Central to defining such DFAs is the exchange-correlation energy density e_{xc}, a spatial function that yields the exchange-correlation energy E_{xc} upon integration.

Unlike E_{xc}, e_{xc} is not uniquely defined. Indeed, there are infinitely many functions that integrate to the correct E_{xc} for a given electron density ρ. The challenge for constructing a useful DFA is to find a systematic connection between ρ and ε_{xc}. While several empirical and rigorous approaches to this problem are known, there has been little innovation with respect to the fundamental functional forms of DFAs in recent years.

Herein, we discuss a less explored route to constructing DFAs. Specifically, a recipe for deriving e_{xc} directly from many-body wavefunctions is presented. The corresponding energy densities are analyzed and (semi-)local approximations are presented. The extension to non-local DFAs will be discussed.

The ODM*x* Methods: New Consistent Semiempirical Methods

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Recently we have introduced two new NDDO-based semiempirical quantum-chemical (SQC) methods ODM2 and ODM3 (ODM*x*), which include orthogonalization and dispersion corrections along with penetration integrals and core–valence interactions as integral parts.[1] These corrections are important for improving the underlying NDDO model[2] and for obtaining more accurate SQC methods.[3-4] The ODM*x* methods build upon the NDDO-based SQC methods OM*x*[3] with D3-dispersion corrections including three-body terms for Axilrod–Teller–Muto dispersion interactions (D3T). In the new methods, the historical convention of assuming that the SCF atomization energy is equal to the atomization enthalpy at 298 K is abandoned. In addition, the ODM*x* methods are parametrized not only with regard to ground-state properties, but also vertical excitation energies, because of the frequent use of general-purpose SQC methods for excited-state calculations and dynamics simulations.

Mean Absolute Errors

		MNDO	OM2	OM2-D3T	ODM2
Heats of formation (CHNO set)	kcal/mol	6.36	3.05	5.10	2.64
Noncovalent interaction energies (S66x8 set)	kcal/mol	9.48	1.93	0.79	0.75
Vertical excitation energies (Thiel's set)	eV	1.11	0.46	0.46	0.35
Atomization energies w/o ZPVE at 0 K (TAE140 set)	kcal/mol	20.13	14.93	14.27	4.89
corrected		11.90	4.81	4.64	

The ODMx methods perform consistently better than other SQC methods for a broad range of properties ranging from ground-state to excited-state properties and noncovalent interactions. They manifest the successes in SQC method improvement since 1977, when the first successful general-purpose SQC method MNDO was introduced.

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The role of water in mediating biomolecular binding: from water locations to their impact on binding affinity

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Water plays an intimate role in protein-ligand binding, not only through solvation/desolvation effects, but more subtly through the formation of direct interactions between the protein and ligand in the binding site. The targeting of bound water molecules for displacement as part of ligand optimization is a long invoked paradigm based around the release of configurational entropy, but there are many examples where displacing water leads to a loss in ligand binding affinity. Quantitatively accurate approaches to address this problem are arguable inadequate – water displacement and ligand interactions are intimately related and difficult to disentangle both experimentally and, hitherto, computationally.

We have a long-standing interest in developing and using Grand Canonical Monte Carlo (GCMC) simulation approaches to explore water binding in protein-ligand systems. Through GCMC we are able to locate water molecules with good accuracy when compared against crystal structures. More significantly, the simulations clearly demonstrate the important role of water cooperativity; the mutual stabilization of water molecules means that individual water molecules cannot always be considered in isolation, but rather as part of a network.

GCMC allows water binding sites and network binding free energies to be simultaneously calculated. In addition, by combining GCMC with alchemical perturbations of the ligand, networks of bound water molecules are able to adapt and maintain equilibrium with bulk water as the perturbation proceeds. Furthermore, the ability to extract active-site hydration free energies allows the deconvolution of protein-ligand binding free energies into separate protein- and water-mediated components, thereby providing rich, additional detail to the structure-activity relationship (SAR).

In this presentation, our underlying methodology GCMC methodology will be described, together with examples of its application to water placement, binding free energy calculations, and protein-ligand affinity prediction.

Surprise, Surprise!

Localization of protein-ligand binding thermodynamics

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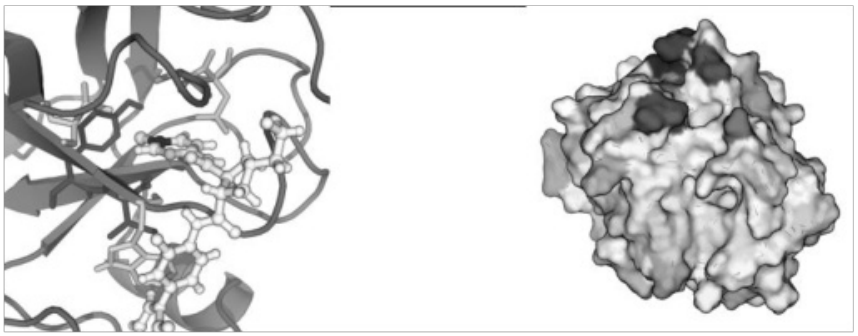
In the early stages of the drug discovery process, promising compounds, for example obtained by high throughput screening of large databases, are often optimized via structure-based drug design (SBDD) [1]. Here, specific groups of the compounds are evaluated with respect to their contribution to the formation of a protein-ligand complex, which then leads the next iteration round in the design process. This assignment is typically directed by pharmacophores, compound comparison and chemical intuition. We here complement the SBDD toolbox by presenting two novel physics-based approaches that allow for the localization of thermodynamic features in a host-guest binding system such as a protein-ligand complex which can aid the development of new drugs.

The three-dimensional (3D) reference interaction site model (RISM) integral equation theory can be formulated and applied in a way to address the problem of complex formation thermodynamics, accounting for solvation effects on an atomic level [2]. A particular advantage is the resulting definition of a free energy derivative (FED) with respect to interaction parameters developed by us. When applied to the complex formation problem, the FEDs allow for a rigorous spatially-resolved mapping of thermodynamics onto local structural features, which can be viewed and interpreted from both a ligand and a protein perspective to shed light onto crucial local interaction features.



Another complementary perspective results from applying 3D RISM for predicting highly localized binding site water molecules along with their thermodynamic features that are relevant for rationalizing properties of ligands replacing them [3]. This methodology allows for predicting interaction characteristics of a potential ligand group that targets a solvent-occupied binding site region.

Together, both approaches yield an in-depth picture of the thermodynamic contributions of direct and solvent-mediated interactions that can be employed for drug design and scoring.

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A Multi-Technique Approach to DNA Structure Determination

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Modern spectroscopic and microscopic techniques are of immense importance for studying biological macromolecules. Important information can be obtained using "spectroscopic rulers", like fluorescence resonance energy transfer (FRET) or electron paramagnetic resonance (EPR) spectroscopy, which are used to measure distances between chromophores or spin labels.
We present extensive GPU-accelerated MD simulations of oligonucleotides with covalently conjugated spin labels. These simulations provide insight into the conformations of the labelled nucleosides and a possible influence on DNA structure. The simulations are essential for understanding the experimental distance distributions obtained from EPR (DEER/PELDOR) measurements, especially as X-ray- or NMR-structural data are not available for all oligonucleotide/spin-label combinations of interest.
We believe that such a close combination of experiment and simulation is a promising approach to elucidating structural and spectroscopic features of complex and flexible biomolecules like DNA- or RNA-conjugates.

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Computational approaches to identify small-molecule inhibitors for the N-domain of p97

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The AAA ATPase p97 is an essential protein involved in numerous cellular processes and plays a key role in multiple aspects of protein homeostasis. Its functional diversity is mediated through the interaction with a large number of distinct cofactors. Due to its role in regulating a variety of physiological processes, p97 has emerged as a potential therapeutic target. Inhibitors of the cofactor binding would be a promising tool to understand the specific molecular and cellular functions of the different cofactors interacting with the N-domain of p97 [1].

Based on crystal structures of p97-cofactor complexes [2,3], different computational approaches were used to identify hot spot regions within the binding interface and to detect possible binding pockets for small molecules. Virtual screening protocols were developed, using structure-based pharmacophore models and docking studies. MD simulations and MM-GBSA calculations were carried out to select potential compounds for in vitro tests. MD simulations were also used to understand the influence of water molecules within the selected pockets, and the results were incorporated into the virtual screening protocols.

Selected compounds will be tested for their activity using fluorescence-polarization and biolayer-interferometry assays. In addition, the crystallisation conditions for the N-domain of p97 were improved and will form the basis for the crystallographic analysis of the identified compounds. Experimentally validated hits will be used as starting point for further optimization towards cofactor-specific inhibitors.

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Relative stability of homo- and hetero-bimetallic Pd(II) and Pt(II) complexes compared to their mononuclear analogues

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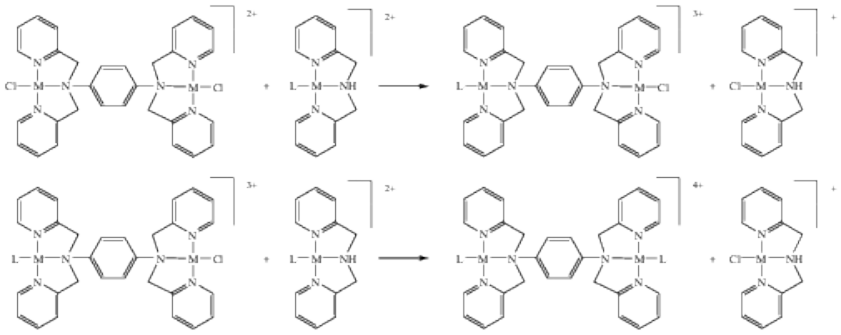
Notwithstanding the success story of cisplatin, there are number of problems that need to be considered during the treatment of cancer with cisplatin. As a result of these negative properties, research in recent years has focused more on non-classical multinuclear platinum and palladium complexes. [1]

In order to get insight in relative stability of bimetallic palladium(II) and platinum(II) complexes against their mononuclear analogues, we calculated the following model equation:



where M represent Pd(II) and Pt(II), and L stands for Tu, Gua, $S(CH_3)_2$, $HSCH_3$.

The B3LYP functional was used to optimize the geometries and to perform the frequency calculations of the examined systems. In all calculations, def2-SVP basis set was employed. The influence of solvent (water) was evaluated using CPCM formalism [2]. These calculations were performed using the Gaussian 09 program package [3].

Comparing the CPCM-energies of our model equation and considering the reliability of applied DFT method, we tend to consider our bimetallic Pd(II) and Pt(II) complexes and mononuclear analogues as equally stable.

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Design and optimization of mimetic peptide probes

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The design and generation of peptides capable of mimicking the binding sites of proteins represents a promising strategy for the exploration and modulation of protein interactions. Synthetic peptides have proven an excellent type of molecule for the mimicry of protein sites because such peptides can be generated as exact copies of protein fragments and can be subjected to further optimization.

We applied this approach to an oligomeric protein complex that is composed of hexameric protein rings and plays an important role for viral replication.
We investigated the different binding regions of the oligomer interface and designed mimetic peptides that contain the key interacting residues. The peptides were optimized for stronger binding to the interaction partner. For validation, the optimized and non-optimized peptides were compared with respect to their binding behavior using molecular dynamics simulations.

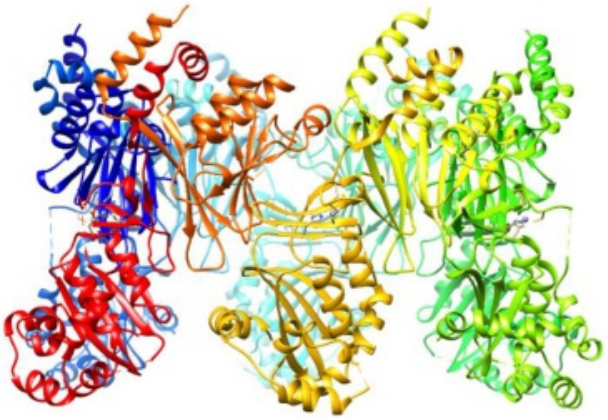

Figure: Hexameric protein ring

The computer-assisted analyses showed increases in binding stability for both suggested peptides with respect to the number of total contacts. The evaluation of the respective RMSDs supports this finding. While the total number of contacts in the optimized peptides were higher, the initial structural properties of the interactions were not preserved during the course of the simulation. This suggests that additional modifications may be required to increase the conformational stability of the suggested peptides.

Tautomerism of nucleic acid building blocks at ambient and extreme conditions

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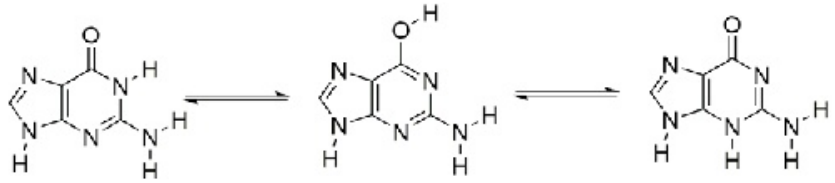
Extreme conditions such as high hydrostatic pressure or temperature as exhibited at deep sea hydrothermal vents, where water can exist either in liquid or in a supercritical form, influence structure and behavior of biologically active molecules. Knowledge of their environmentally modulated conformational, tautomeric and protonation state preferences is essential to understand their behavior in solution and mode of action in the organism. An accurate pH-, temperature- and pressure-dependent characterization of these properties in solution is of vital importance but poses a challenge to both experiment and theory even for well-studied compounds such as nucleic acid building blocks. Experimentally, rapid conformational changes and the fast proton transfer between multiple tautomeric forms make elucidating these equilibria cumbersome especially under extreme conditions, while the theoretical task is complicated due to the environmental effect on both electronic structure and solvent distributions.

We here predict tautomeric and conformational equilibria of natural and non-natural nucleobases in water under various environmental conditions by the methodology employed within the SAMPL blind prediction challenges for tautomers, distribution coefficients and acidity constants [1-3] of small molecules. Solvent effects on energetics and spectroscopic parameters in quantum-chemical calculations are considered using the "embedded cluster reference interaction site model" (EC-RISM) developed by us, which has been demonstrated to provide accurate estimates of thermodynamic quantities and spectroscopic features in solution even for high pressure solvents [4]. Refining the EC-RISM workflow with a coupled-cluster extrapolation, which allows treatment of electron correlation effects with high accuracy, is used to further improve the quality of tautomer predictions.



We obtain the contributions of all accessible states to the molecular ensemble as a function of pH, pressure and temperature as well as their respective relevance for understanding experimental NMR spectra. Preliminary results indicate remarkable tautomeric stability of natural nucleobases which could hint at tautomerism being an evolutionary relevant chemical optimization target.

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Comprehensive description of interactions of ionic liquid ions with *Bs*LipA

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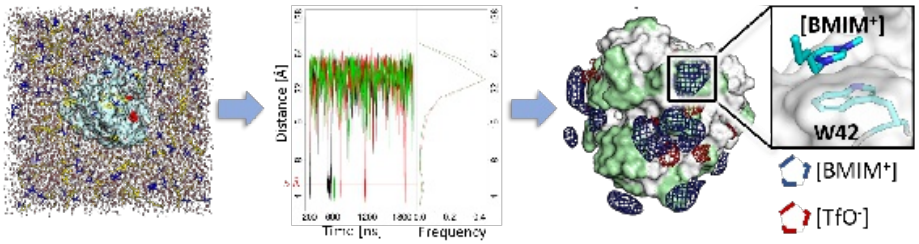

Ionic liquids (IL) and seawater are attractive (co-)solvents for biocatalysis due to their unique properties such as negligible vapor pressure respectively high abundance of seawater on earth [1,2] but, at the same time, influence activity and stability of enzymes in a complex manner [3]. However, this influence is not fully understood at the molecular level, and a general approach to guide protein engineering towards enzymes with improved IL and salt resistance has remained elusive. We aim at establishing a comprehensive description of the interactions of IL-/salt ions with the Lipase A from *Bacillus subtilis* (*Bs*LipA). Therefore, we employ molecular dynamics (MD) simulations to fundamentally understand the influences these solvents pose on proteins.
Our results reveal that MD simulations of *Bs*LipA in IL are feasible and successfully identify interaction sites of the IL ions with *Bs*LipA. We found multiple distinctive interaction sites of both the IL cation and the respective anion, which are in good accordance to recently published MD- and X-ray crystallography studies [4,5]. Interestingly, IL lead to only minor changes of the global protein structure but induce large changes in local intramolecular interactions of *Bs*LipA. This includes deep-reaching perturbations of the intramolecular H-bond network as well as changes in the ratio of active to inactive state conformations of the catalytic site, thus affecting both the catalytic site residues and the protein core. These results give new insights into the molecular effects of IL ions on *Bs*LipA activity in full atomic detail.
The knowledge derived from MD simulations will be applied to adapt a computationally highly efficient graph- and rigidity theory-based approach (Constraint Network Analysis) previously used successfully in the context of protein thermostability for the application with IL [6]. To experimentally validate and refine our model, a complete site-saturation mutagenesis library covering all possible single amino acid mutations of *Bs*LipA is available [7].

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A Dielectric Theory View of Biomolecular Charge Transfer

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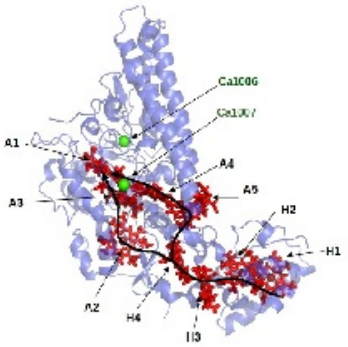

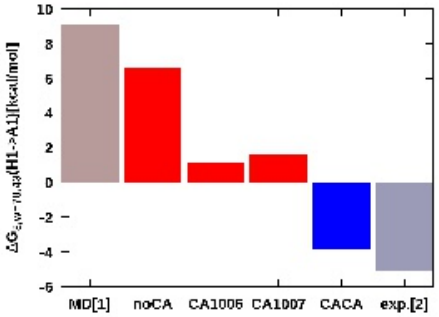

We show a calculation of thermodynamic driving forces, ΔG, for the electron transfer through subcomplex NrfHA of the cytochrome *c* nitrite reductase complex $NrfH_2A_4$ from *desulfovibrio vulgaris*. Molecular dynamics can be used to adjust dielectric constants for a numerical solution of Poisson's equation. Using the DelPhi program package [3] we show how the reorganization energy λ can be rationalized. As the binding pocket of Ca^{2+} ions in the protein structure of NrfA is conserved in many organisms [4], we investigate the influence of the presence of Ca^{2+} ions to the thermodynamic free energy landscape and show that the presence of two Ca^{2+} ions decrease the total free energy for the electron transfer over the entire electron transport chain towards an exergonic reaction.[5]

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Pharmacophore-based identification of chemical tool compounds inhibiting 17β-hydroxysteroid dehydrogenase 14 (17β-HSD14)

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Objective: Steroid-metabolizing enzymes are able to convert a multitude of diverse steroid hormones and other types of substrates (e.g. prostaglandins, fatty acids). Thus, they are also associated with a great variety of diseases in humans. [1] One pivotal enzyme class of steroid-metabolizing enzymes includes the hydroxysteroid dehydrogenases (HSDs). 17β-HSD14 is the latest identified 17β-HSD representing a tetrameric, cytosolic enzyme that catalyzes the inactivation of, for example, estradiol to estrone (due to oxidation in position 17). Although its physiological relevance is largely unknown, its high expression in (but not limited to) several steroidogenic tissues indicates a role in human sex steroid metabolism (e.g. breast cancer) and possibly also other metabolic pathways. [2,3] Except for some non-steroidal pyridine derivatives discovered by Bertoletti *et al.* and Braun *et al.*, no inhibitors on 17β-HSD14 have been reported to date. [4,5,6] Therefore, the aim of this study is to discover further structurally diverse inhibitors of 17β-HSD14 and thus enable a better characterization of the binding site and the enzyme's physiological function.

Methods: For the implementation of this issue, a pharmacophore-based virtual screening workflow was elaborated in LigandScout and the three best performing models were chosen for screening of 13 different chemical databases. The hits were docked into the X-ray crystal structure of 17β-HSD14 (PDB-entry 5ICM) with AutoDockVina implemented in LigandScout. [7,8] Based on the binding mode of the resulting docking poses, the final hit selection was carried out. In the end, the selected hits were biologically evaluated in a fluorimetric in vitro assay on human recombinant 17β-HSD14 at the University of Marburg. [4]

Results and Outlook: Out of 18 compounds, 2 turned out to be active in the low micromolar to nanomolar range, namely Specs compound AO-081/15245155 and nordihydroguaiaretic acid with a K_i of 0.65 μM and 1.30 μM, respectively. [9] Based on the outcome, the pharmacophore models will be refined and used again to screen several databases in order to discover further inhibitors with different scaffolds. Moreover, SAR studies will be carried out on compound AO-081/15245155, since several derivatives occurred in the hitlist.

Conclusions: There are probably several other scaffolds among natural products or synthetic chemicals that can inhibit the enzyme. The discovery of such inhibitors will contribute to a better understanding of 17β-HSD14 and it will guide to assessing the potential health risks associated to its inhibition through natural and/or synthetic sources.

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Elucidating Zinc Binding to the Voltage-Gated Proton Channel hHv1 Using Computer Simulations

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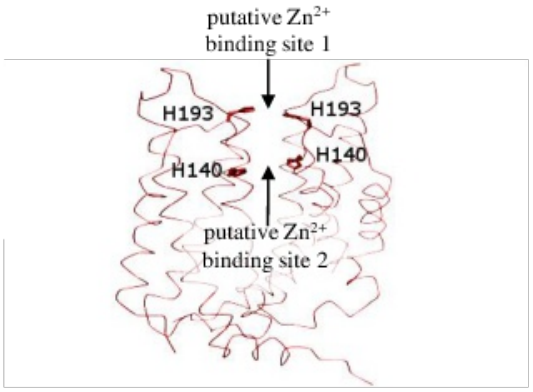
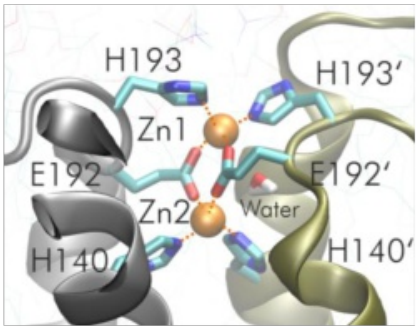
Institut für Physiologie, Klinikum Nürnberg Medical School, Paracelsus Medizinische Privatuniversität, Nürnberg, Germany





H_V1 voltage-gated proton channels are proton-specific ion channels with unique properties. For example, they are massively expressed in human sperm where they are necessary for maturation and motility, hence essential for conception.

Voltage-gated proton channels are strongly inhibited by Zn^{2+} and two histidine residues were found experimentally to be essential for Zn^{2+} binding. However, the two accessible histidine residues H140 and H193 are too far apart to coordinate simultaneously one Zn^{2+} in a structural model of the monomeric channel. It was thus hypothesized that two Zn^{2+} binding sites can be formed between pairs of equivalent histidine residues (H140–Zn–H140 and H193–Zn–H193) at the interface of a H_V1 homodimer. The consecutive experimental measurements were also in agreement with this hypothesis.

We tested this hypothesis and investigated the determinants of Zn^{2+} binding at the molecular level using computational approaches: molecular modeling, molecular docking, and molecular dynamics simulations.

Our results support the hypothesis enunciated above: The modeling and docking simulations show that the hH_V1 channels can form dimers that present an appropriate interface for two Zn^{2+} binding sites, each involving a pair of equivalent histidine residues from each monomer. The molecular dynamics simulations reveal that two Zn^{2+} can stably be accommodated in the proposed binding sites. The zinc ions are coordinated by the histidine and acidic residues. Essentially, the glutamate residues E192 play an essential role in Zn^{2+} binding. Comparison with another possible dimer conformation and with the monomeric form of the channel also reveals why the dimer conformation hypothesized above is more able to coordinate zinc ions.

Digital Biology for Better Antibody-Drug Conjugates – Modelling Cell-Level Pharmacokinetics

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Computational Chemistry & Biology[1], ADC Design and Characterization [2]
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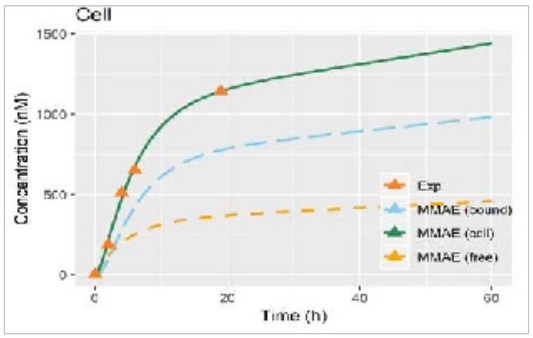
Antibody drug conjugates (ADCs) are therapeutic molecules that are aimed to deliver highly potent cytotoxic agents specifically to tumor cells with the help of a tumor-targeting monoclonal antibody that is linked to the payload drug. In a cell-level view, the ADCs bind to antigens expressed on the surface of the tumor cell. The ADC-antigen complexes get internalized, the linkers are cleaved, and the drug released. However, the ADC can already deconjugate outside the cell, depending on the properties of the linker and the drug. Free payload drug can also influx and efflux into and out of the cell. All these processes can be described mathematically with rate constants and differential equations. Accurate quantitative characterization of cellular ADC disposition could help in understanding and improving design of ADCs.



We used a model by Singh and Shah [1], built for trastuzumab-valine-citrulline-monomethyl auristatin E (Trastuzumab-vc-MMAE), to explore how different ADC constructs might behave in a cell-level system. Taking internal experimental data from an uptake assay of MMAE and from measuring the internalization of trastuzumab-vc-MMAE, we could fit the model to the ADCs used at Merck. Extending the model to also handle cell killing lead us to link ADC properties, like drug-antibody ratio and permeability, to predicted IC50 values.

The model was implemented with R Shiny library which gave it an easy-to-access browser interface and deployed on Docker container platform which enabled experimental scientists to use the tool from anywhere in the intranet. The project source code was managed in company's internal GitLab to aid collaborative development, and a one-button build-and-deploy pipeline enabled rapid prototyping with fast feedback from the users.

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Adsorption of organic molecules with high dipole moment on the Au(111) surface

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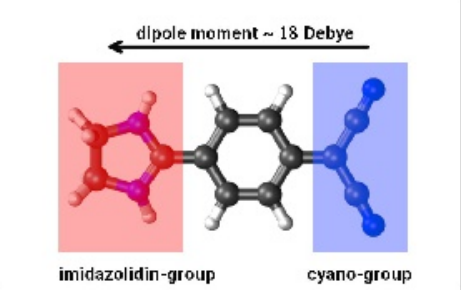
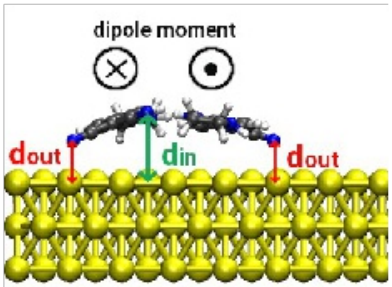
[1]Interdisciplinary Center for Molecular Materials and Computer-Chemistry-Center, FAU Erlangen-Nürnberg — [2]Institute for Chemistry and Biochemistry, FU Berlin





Molecules with high dipole moment exhibit promising electronic properties for possible single-molecule electronic devices [1]. Of particular interest is how they couple to conducting substrates and how this coupling changes electronic states and intramolecular charge distribution. To obtain first insights into the behavior of such high dipole molecules on a metallic substrate we have studied the adsorption of N2-Ethan-Tetracyanoquinodimethan and N2-Benz-Tetracyano-quinodimethan on a Au(111) surface using density functional theory (DFT). We have identified the preferred adsorption sites and molecular orientations on the surface and we determined possible periodic arrangements for dipolar stripes. Calculated scanning tunneling microscopy (STM) and local contact potential difference (LCPD) images will be presented and changes in the electronic structure of the molecules within the dipolar stripes will be discussed.

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Computational analysis of human heavy chain CDR3 repertoires

The paradox of tyrosine rich antibodies in memory B cell repertoires

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Next generation sequencing analysis of distinctive B cell subsets from leukapheresis products of hematopoietic stem cells from healthy donors [1] proved to be a powerful tool to characterize the human antibody repertoire. The antibodies produced by human naïve and memory B cells show significant differences in their heavy chain CDR3 repertoires. We prove that human heavy chain CDR3 loops are shorter in their memory repertoire compared to the naïve repertoire of the same donor and show a shift in the usage of an important J gene responsible for the creation of long CDR3 (J6) [2].

In addition, the quantification of specific amino acid motifs observed among all healthy donors hint that positive and negative selection shape the antibody memory CDR3 repertoire as opposing principles very specifically. These effects are highlighted by the observation of the paradox role of tyrosine repeats introduced by J gene 6. The usage of J6 is decreased in memory repertoire of healthy donors compared to the naïve repertoire of the same donor.

For the CDR regions Tyr is described by previous studies to be beneficial for antigen recognition and is expected to be positively selected [3]. In contrast, we show the decrease of Tyr motifs and Tyr rich J genes (J6) in all analyzed memory repertoires. Previous and current studies describe the prevalence of antibodies containing J6 in patients with autoimmune disease and the usage of J6 in antibodies against neo antigens in cancer patients [4,5]. We therefore suggest that tyrosine rich antibodies with long CDR3 are negatively selected and are an important future research subject in understanding autoimmunity.

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Keywords: Next generation sequencing, CDR3, J6, Tyrosine

Analysis of gating behavior and microscopic water structure in small viral K^+-ion channels

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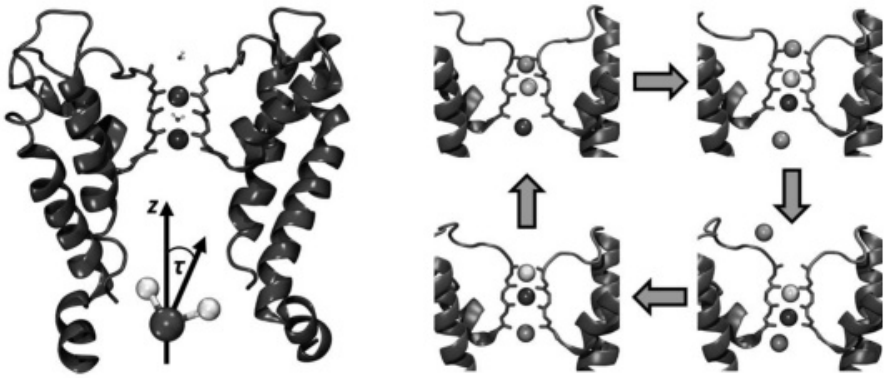
Ion channels fluctuate stochastically between "open" and "closed" states, which determine the ion flux through biological membranes, also known as "gating". This crucial feature of ion channels is necessary in cellular, biological systems to regulate the ion concentration level, which is essential for the processes of homeostasis or second messaging. Yet the origin of gating is not fully understood. The structure of a channel in its various gating states, which is controlled by its amino acid sequence, also plays a vital role for ion selectivity. We here focus on tetrameric potassium channels, for which very short, miniature systems exist. These ideal model systems, Kcv_{PBCV-1} and Kcv_{ATCV-1} that are found in *chlorella* viruses are comprised of only 94 and 82 amino acids per monomer [1-4] and play an important role for determining elementary structure-function relations. Although these channels are comparably small, they show all essential features like gating and selectivity.



A commonly used method for investigation of ion channels in a membrane domain is molecular dynamics (MD) simulation. Modern computer hardware allows for simulations up to microsecond timescales, in which multiple ion transitions are observable. To quantify the transition process relevant descriptors need to be developed. Ion transitions could correlate with structured ion and water distributions inside the channel cavity, dominated by confinement effects and water-ion interactions. To gain insight into these interactions we present a computational approach based on WaterDynamics [5] to determine the orientation of water molecules with respect to the channel axis for different trajectories showing various conduction characteristics. To analyze the orientation of intra-cavity solvent molecules the local solvent densities are calculated and combined with the probability density of water orientations and positions. The approach is applied to long MD trajectories and analyzed for different phases of the transitions composed of resting and rapid conductance states.

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Intermolecular interactions between dopamine and promazine using computational methods

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Dopamine (3, 4-dihydroxyphenylethylamine, DAH2), an important neurotransmitter, is existing in the mammalian central nervous system [1-3]. Its improper regulation is associated with neurological diseases such as Parkinsonism, where dopamine levels are reduced and schizophrenia, which can be related to excess activity of dopamine. Promazine (PZ) is a pyschotropic drug which is used extensively in mental disorders and anticancer activities. Its interactions in metabolism with the serotonin are important in terms of its biological activity. Biologically important aromatic molecules like basic nucleotides, aromatic amino acids, some drugs have π-electron systems. In this study, intermolecular interactions between photophysically excited promazine and naturally occurring hormone (dopamine) in the human body at ground-state will be investigated using computational tools. Conformational analyses have been performed to determine the initial structures for promazine and hormone (serotonin) using Spartan 08 [4]. Ground state geometry optimizations are first performed with Gaussian 09 [5] at the ω-B97XD/6-31G(d,p) level of DFT theory without symmetry constraint in gas phase and water phase, solvation calculations were performed by Tomasi's Polarizable Continuum Model (PCM) [6,7]. The electronic transitions were calculated by the time-dependent density functional theory (TD-DFT) with CAM-B3LYP, B3LYP and ω-B97XD methods using 6-311++G(d,p) basis set in gas phase and in water. Molecular orbitals, energy differences of frontier orbitals and electrostatic potentials for studied molecules were investigated. Intermolecular charge transfer between HOMO-LUMO orbitals of DA-PZ complex was observed in both media.

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Investigation of the Tacrine-Saccharin Complex: A Combined Computational and Experimental Study

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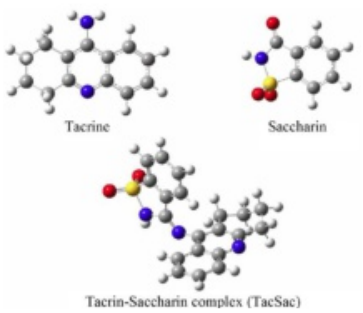
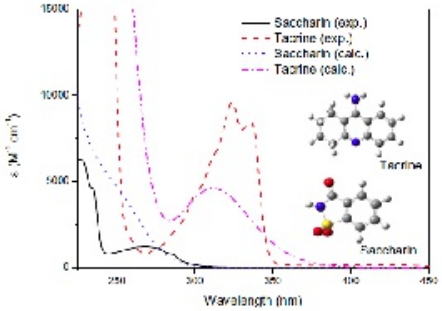
Ege University, Faculty of Scienc,e Biochemistry Department Bornova/Izmir, Turkey
Ondokuz Mayıs University, Faculty of Arts and Science, Chemistry Department Samsun, Turkey

Tacrine is a drug used in the treatment of different diseases including Alzheimer's disease. It is also of great interest to researchers due to its unusual interaction properties. Saccharin is a sweetener used as a sugar substitute in commercial products. There are many studies reported on tacrine and saccharin; but neither experimental nor computational studies are reported on the tacrine-saccharin complex formed by the reaction of tacrine and saccharin to form an amidine (TacSac) except our recent studies [1,2]. We investigated the spectroscopic properties of TacSac using computational and experimental tools.





Geometry optimizations, and frequency calculations were performed with Gaussian 09 Revision-C.01 [3]. Optimization were carried out with B3LYP, M06-2X, M06L, and ωB97XD functionals in addition to MP2. Pople type 6-311++G(d,p) basis set was used in all calculations. Frequency calculations followed geometry optimizations and all calculated frequencies were positive. The most stable conformer for each system was used in further calculations. Excited state calculations were carried out with CIS and TD-DFT (B3LYP, CAM-B3LYP) methods to obtain UV-Vis spectra. The polarizable continuum model (PCM) was used with default options in Gaussian 09 to evaluate the solvent effect. Calculations were repeated with the SMD (solvation model based on density) approximation to observe the contributions of nonelectrostatic solute–solvent interactions. Atomic Polar Tensor (APT) approach was used for charge analysis.
Similar geometries for TacSac was obtained in gas phase and in H_2O both with PCM and SMD models using MP2 in contrast to DFT results. Since the discrepancy was observed in PCM calculations in DFT, it may be concluded that the electrostatic interactions were overestimated in DFT-PCM calculations causing significant deviations in the geometry. The MP2 results also revealed that the formed amidine is stable. This conclusion is also significantly different than DFT results which showed that the formation reaction of TacSac between tacrine and saccharin has highly positive complexation energy values and free energy differences. The MP2 results indicate that the TacSac system can be easily synthesized with a condensation reaction, and the amidine product is a potential candidate for photochemical charge-transfer systems.

Some of the calculations were performed on TUBITAK-ULAKBIM TRUBA resources.

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A novel methodology for encoding hydrophobic interactions in atomistic graphs constructed from biomolecular structures

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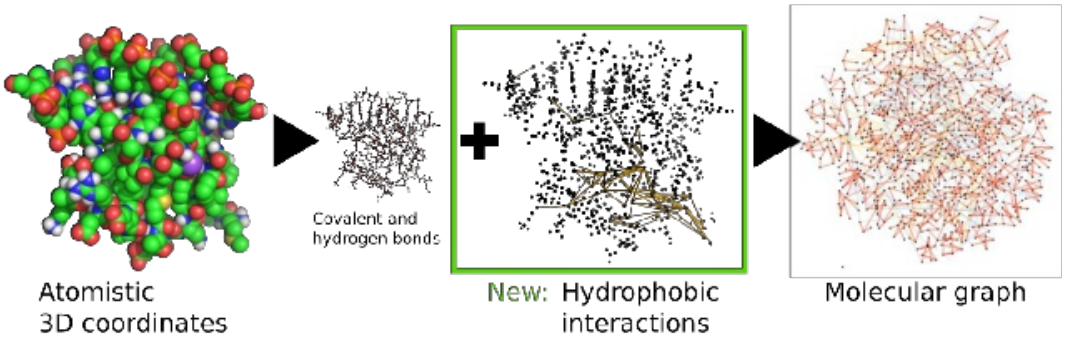
[3] *Institute of Chemical Biology, Imperial College London, London SW7 2AZ, UK*



Studying protein structures at the atomistic level through the lens of mathematical graph theory has been successful in modelling, exploring and explaining a wide range of protein properties, such as flexibility [1], multi-scale organisation [2] and allostery [3], whilst remaining computationally feasible even for large system sizes.

Stronger types of bonding, particularly covalent bonds and hydrogen bonds can be clearly defined as the interaction between two atoms and thus fit well into the paradigm of molecular graphs. However, hydrophobic interactions are equally as crucial to protein shape and stability [4]. Yet, expressing them in computational models of protein structures is poorly understood, in parts due to their many-body property [5]. In this work, we introduce a novel methodology for incorporating both local and global aspects of hydrophobicity in biomolecular graphs. From a set of "candidate" interactions found through geometric and other constraints, a Relaxed Minimum Spanning Tree (RMST) [6] is computed to produce a sparsified set of accepted hydrophobic interactions. The universality of this procedure allows the consideration of both standard and non-standard residues as well as hydrophobic interactions between protein and ligand.

Despite no *a priori* information about the hydrophobicity of certain residues, we found that this approach successfully identifies hydrophobic connectivity in the buried interior of the protein, whilst capturing the many-body effect by creating regions of high connectivity consisting of many individual links. Together with existing methodology for constructing atomistic, biomolecular graphs from covalent and hydrogen bonds, we are able to encode detailed physico-chemical structural information in a concise, yet more realistic mathematical representation of protein structure.

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Role of N-Terminal Residues for Structural Stability of Triangular Aβ_{40} Fibrillar Oligomers

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Alzheimer's Disease (AD) is the most prevalent neurodegenerative disorder and the main cause for dementia in industrial nations. One hallmark of AD is the development of senile plaque deposits in the brain that consist primarily of fibrillar amyloid-β (Aβ) peptides. Aβ is a short peptide comprising 40 to 42 residues, but nevertheless exhibits a vast conformational variability and a plethora of oligomeric states, which makes experimental studies about its structure and aggregation rather challenging.

Lu et al. published a solid state NMR structure of an $A\beta_{1-40}$ fibril isolated from an AD patient (PDB code 2M4J)[1]. The structure shows three-fold symmetry around the fibril axis with a central water channel and is thus markedly different from $A\beta_{1-42}$ fibril structures. Previously, we have investigated the stability of fibrillar $A\beta_{42}$ oligomers of different size by means of molecular dynamics (MD) simulations leading to a model for longitudinal and lateral fibril growth [2, 3].

Here, we present all-atom MD simulations in explicit water based on the patient-derived $A\beta_{40}$ fibril to elucidate how its conformational stability depends on the oligomer size. An infinite Aβ fibril was investigated as well to study the boundary effects of the finite oligomers.

Moreover, it is known from experiment that several Aβ species of different N-terminal length exist in vivo affecting the peptide's aggregation behaviour. We thus investigated the influence of the first eight Aβ residues upon the structure and dynamics of the fibrillar oligomers and the infinite fibril of $A\beta_{40}$.[4]

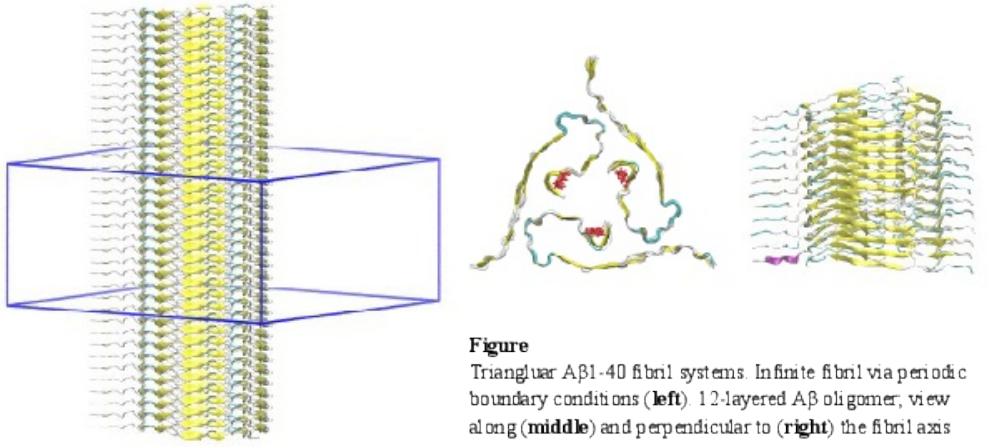

Figure
Triangluar Aβ1-40 fibril systems. Infinite fibril via periodic boundary conditions (**left**). 12-layered Aβ oligomer, view along (**middle**) and perpendicular to (**right**) the fibril axis

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Using accelerated molecular dynamics to retrieve conformational ensemble of Alamethicin

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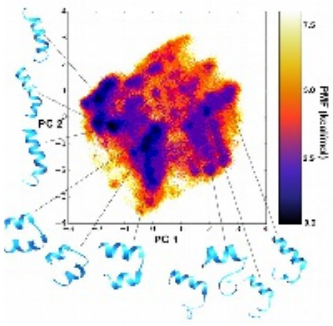
The use of enhanced sampling molecular dynamics simulations to facilitate the folding of peptides and proteins is a relatively new approach which has quickly gained momentum in recent years. One such technique, namely accelerated molecular dynamics introduced by Hamelberg et al. [1], can make accessible different intermediate states visited during peptide folding by lowering the energy barrier between them. In other words, the dynamic path from the unfolded state to all intermediates and finally to the near-native state is "flattened" by introducing a non-negative boost to the potential. This approach has been applied by Miao et al., [2] to elucidate the native structures of fast-folding small peptides from their unfolded states.



The molecule, Alamethicin, chosen in this study belongs to the class of peptaibols that are 7-20 residue long, non-ribosomally synthesized amphipathic molecules showing interesting membrane perturbing activity. It is important to elucidate the structure and dynamics of such peptaibols due to their potential antimicrobial effects and future application. However, all peptaibols including Alamethicin, consist of non-proteinogenic amino acids like aminoisobutyric acid (Aib), D-isovaline (Div), hydroxy-proline (Hyp) and C-terminal alcohol residues like phenylalaninol (Pheol), valinol, etc. which are not readily available within the residue libraries of most simulation software. In this study, we parameterized Aib and Pheol and constructed the unfolded structure of alamethicin to be simulated using accelerated MD simulation for its comparison with the native form available from the Protein Data Bank. We performed three consecutive 1 micro seconds (μs) long simulations. N-terminal folding was observed within the first 100 nano seconds (ns) while the C-terminal folding could only be achieved almost after 800 ns. It took 1 μs to attain the near-native conformation which usually may take several micro seconds worth of classical MD to produce the same results. Another important observation is the significant time spent by the peptide existing as a highly curved helical conformation (resembling a hairpin motif as shown in the figure). The figure describes free energy landscape of alamethicin calculated using principal component analysis based on torsional angles in stead of Cartesian coordinates. The curved conformation is an energetically stable state and would require an energy "boost" of roughly 2.5 kcal mol^{-1} to attain backbone linearity which is the native state. This technique has proven beneficial in order to obtain the complete conformational ensemble of such dynamic peptides. It can be concluded that accelerated MD simulation techniques are suitable for the elucidation of peptaibol structures and understanding their folding dynamics.

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Comparison of the Pharmacophore Features of Agonists and Antagonists in β3-Adrenergic Receptors

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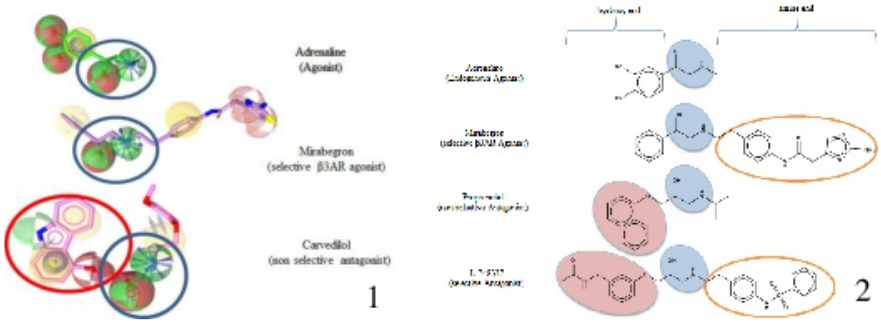
β3-Adrenergic receptors (β3-ARs), as well as β1-ARs and β2-ARs, belong to the G-protein coupled receptors (GPCRs) characterized by seven transmembranes (TM). The β3-ARs are expressed in several tissues and are considered as a drug target for the treatment of several pathologies such as obesity, type 2 diabetes, and overactive bladder [1]. Since β3-AR agonists evoked lipolysis and thermogenesis in rodents, the number of research publications related to these receptors increased dramatically [3]. However, the development of new β3-ARs antagonists is still limited, while the activation of these receptors is still the desired effect. Two compounds, L-748328 and L-748337 were reported as selective antagonists [2]. However, to support better improvement in discovery ligands of β3-ARs, the comparison of structure agonists and antagonist are still needed to be explored.

A set of β3-ARs ligands consisting of 2 endogenous agonists, 7 known β3-ARs agonists, and 7 antagonists was used for this study. The conformations of ligands were generated with LigandScout v3.12 using Omega v2.3.3. The pharmacophore features were extracted through ligand-based pharmacophore model calculations.

The endogenous agonists, the β3-ARs agonists, and the antagonists resulted in 10, 9, 11 pharmacophore features, respectively (fig. 1). The common pharmacophore features were HBD (Hydrogen Bond Donor), HBA (Hydrogen Bond Acceptor), PI (Positive Ionizable Area) located in the center of the molecules (ethanolamine moiety) indicated as the main pharmacophore of β3-AR ligands.



The significant difference between agonist and antagonist were located on the hydroxy end (fig.2). In antagonist, in this part has extended hydrophobic contacts with the receptor. Interestingly, on the amine end of the selective β3-ARs antagonists contains large substituents which are typical in selective β3-ARs agonists (fig.2). The RHS gave more hydrophobic interactions indicating the possibility of the selectivity of the β3-ARs relies on this side. β3-AR should have a larger hydrophobic pocket than the other two β-ARs since its sequence possesses only 50–70% to the other two β-ARs [3], suggesting that the development of both of selective agonist and selective antagonist for β3-ARs is still achievable provided.

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Basal Histamine H_4 Receptor Activation: Ligand Mimicry by the Diphenylalanine Motif

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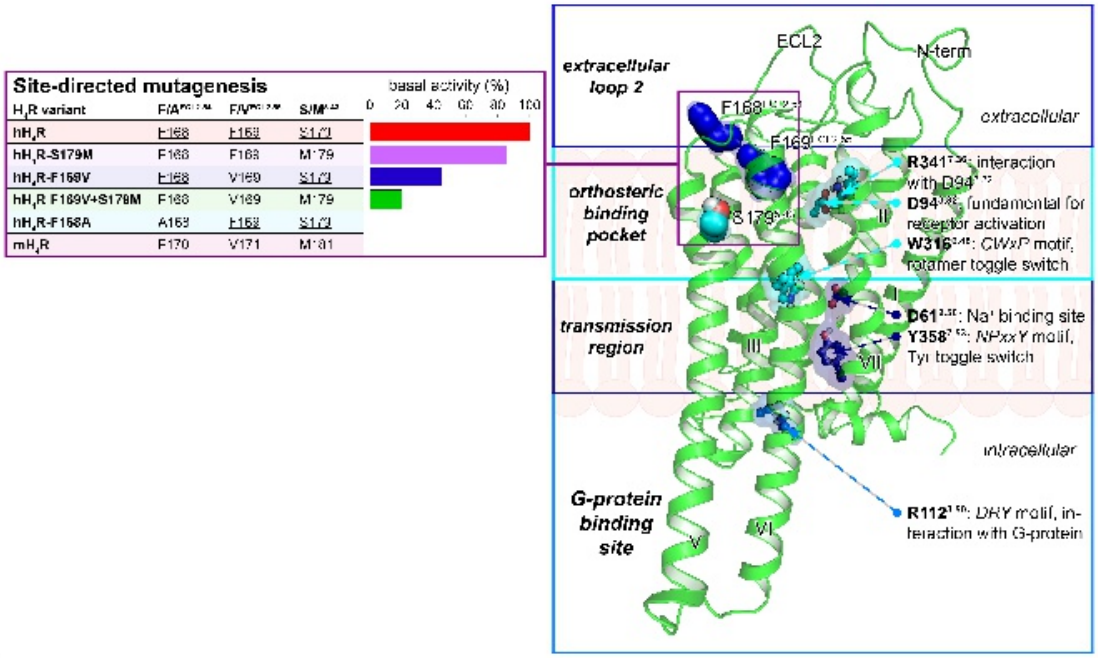
Histamine H_4 receptor (H_4R) orthologs exhibit species-dependent basal (constitutive) activity: In contrast to mouse H_4R (mH_4R), human H_4R (hH_4R) shows a high degree of basal activity. In a previous molecular-pharmacological study, the mutation F169V significantly decreased the high constitutive activity of hH_4R, and the basal activities of the hH_4R-F168A and hH_4R-F169V+S179M mutants were even comparable to that of mH_4R [1,2]. In contrast, the constitutive activity of hH_4R was maintained in the S179M mutation. Driven by such promising results, we aimed at further investigating the molecular mechanism of basal H_4R activation by performing 2 µs molecular-dynamics simulations of six H_4R variants (hH_4R, hH_4R mutants S179M, F169V, F169V+S179M, F168A, and mH_4R), each revealing a different degree of constitutive activity. Most interestingly, during the MD simulations, $F169^{ECL2.55}$ dips into the orthosteric binding pocket only in the case of hH_4R, thus adopting the role of an agonist and contributing to the stabilization of the active state. Strikingly, the overall distances between the C_α atoms of $D94^{3.32}$ and $Q347^{7.42}$, a measure of binding-pocket contraction, increased from hH_4R to the S179M, F169V, F169V+S179M, F168A mutants, and were highest for mH_4R. Remarkably, the overall C_α-C_α distances between $R112^{3.50}$ and $A298^{6.30}$, a measure of TM6 outward movement and GPCR activation, decreased in this order. Hence, these results, along with both information about additional motifs fundamental for GPCR activation and from rigidity analysis provide a molecular explanation for differential constitutive activities of H_4R variants. Moreover, this study has provided novel insights into molecular mechanisms of basal H_4R activation that are also of importance for other GPCRs.



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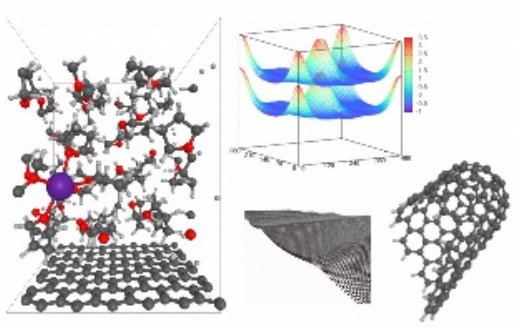
Atomistic simulations of chemical graphene exfoliation and carbon nanotube synthesis and of extended defects in bilayer graphene

Florian Wullschläger, Robert Maidl, Konstantin Weber, and Bernd Meyer

Interdisciplinary Center for Molecular Materials and Computer-Chemistry-Center, FAU Erlangen-Nürnberg



Results of three recent molecular dynamics (MD) and density functional theory (DFT) studies on graphene and carbon nanotubes (CNTs) will be presented. Reductive graphite intercalation with alkali metals and subsequent dispersion in tetrahydrofuran (THF) leads to an almost complete exfoliation of graphite into graphene monolayers. The properties of the exfoliation product in liquid THF have been investigated by force-field MD simulations and first insights into role of different alkali metals in the exfoliation process will be given. Second, with force field and DFT calculations we identified the crucial reaction step in the on-surface synthesis of CNTs with controllable and defined chirality by rolling-up appropriate precursor molecules via cyclodehydrogenation reactions. Finally, by using a specifically adapted registry-dependent interlayer potential we show that the properties of dislocations in quasi-2D crystals, i.e. bilayer graphene, differ significantly from their 3D counterparts [1]. In addition to an in-depth structural characterization of 2D dislocations, first results on the dislocation structure in twisted graphene bilayers will be given.

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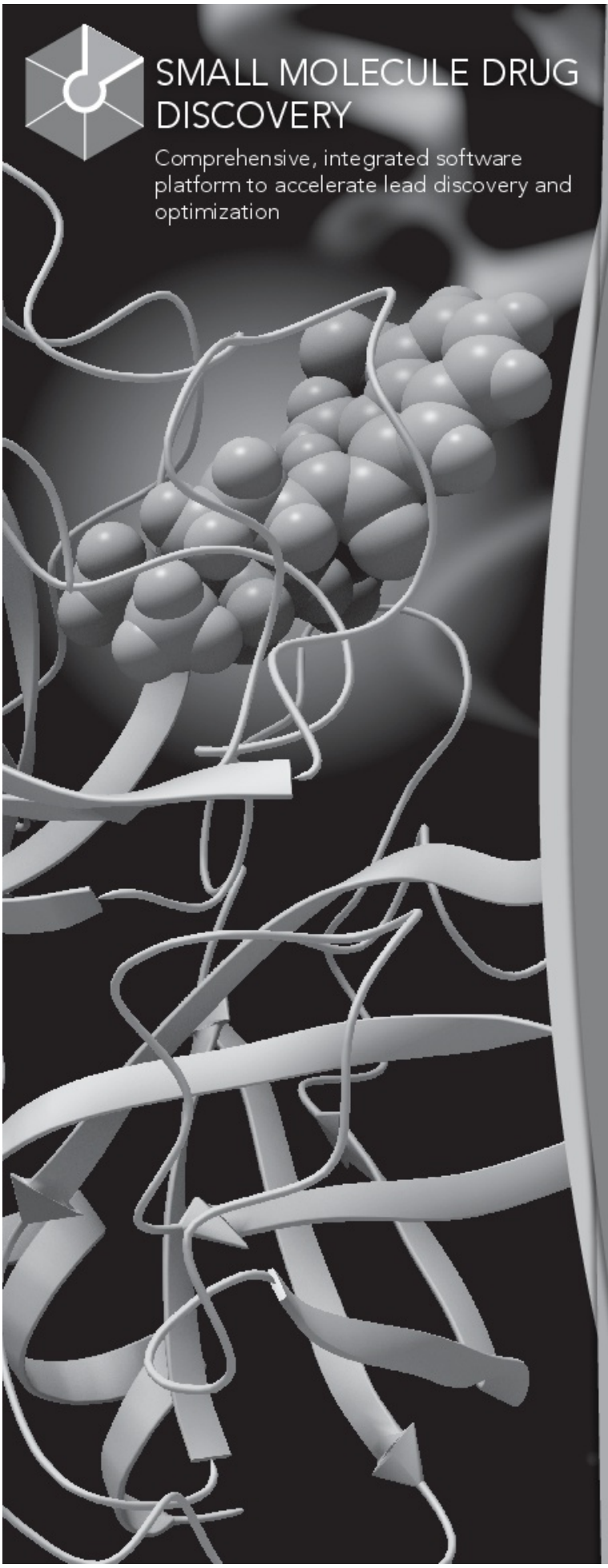

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2. Determine all solutions $x \in \mathbb{R}$ of the equation

$$||4^x - 3| - 2| = 1.$$

3. Consider all parabolas $f(x) = x^2 + px + q$ which have three intersections P_1, P_2 and P_3 with the coordinate axes. If a circle is constructed through these three points, this circle has besides P_1, P_2 and P_3 an additional fourth intersection P_4 with the parabola. Determine the coordinates of this point.

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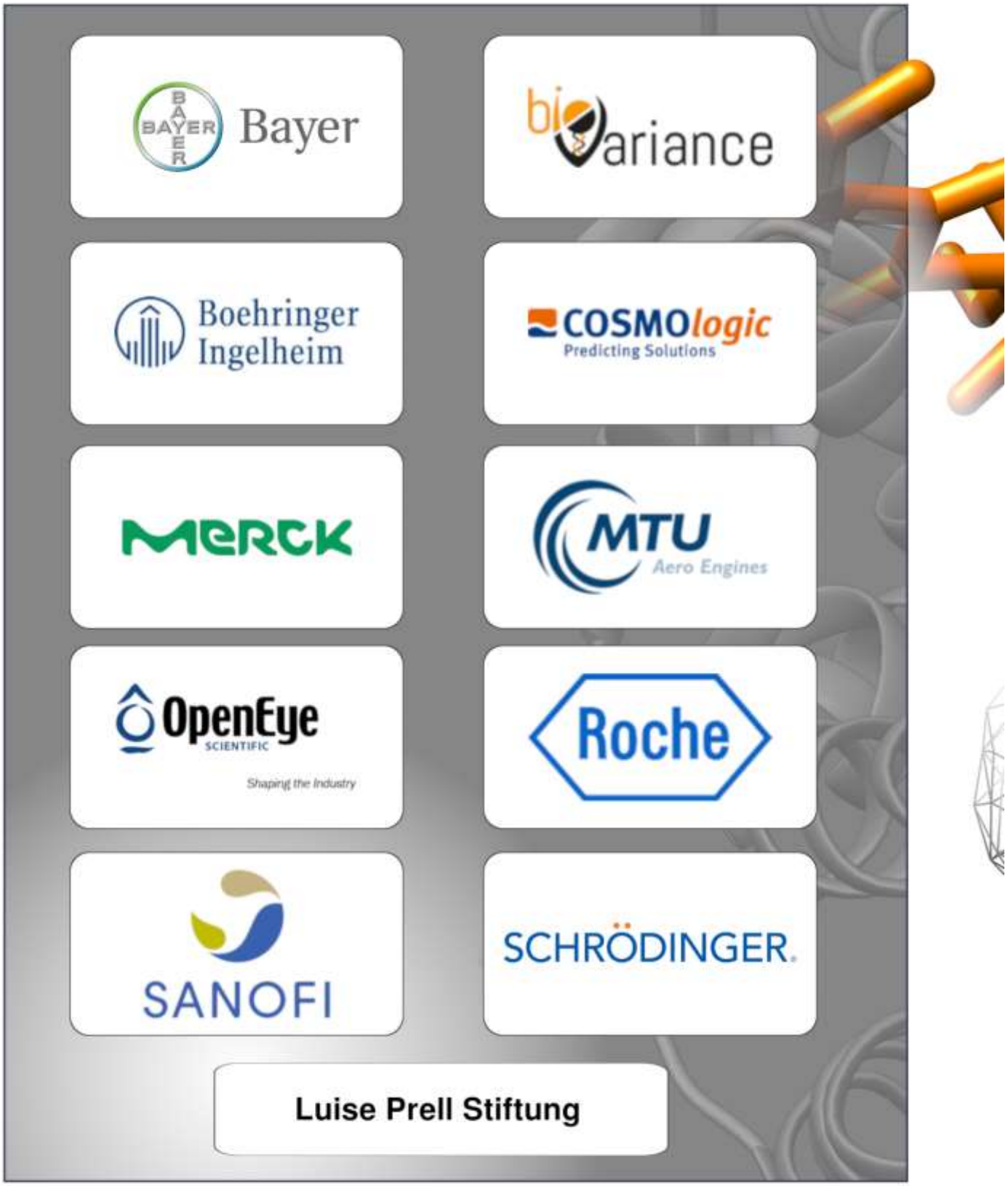

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