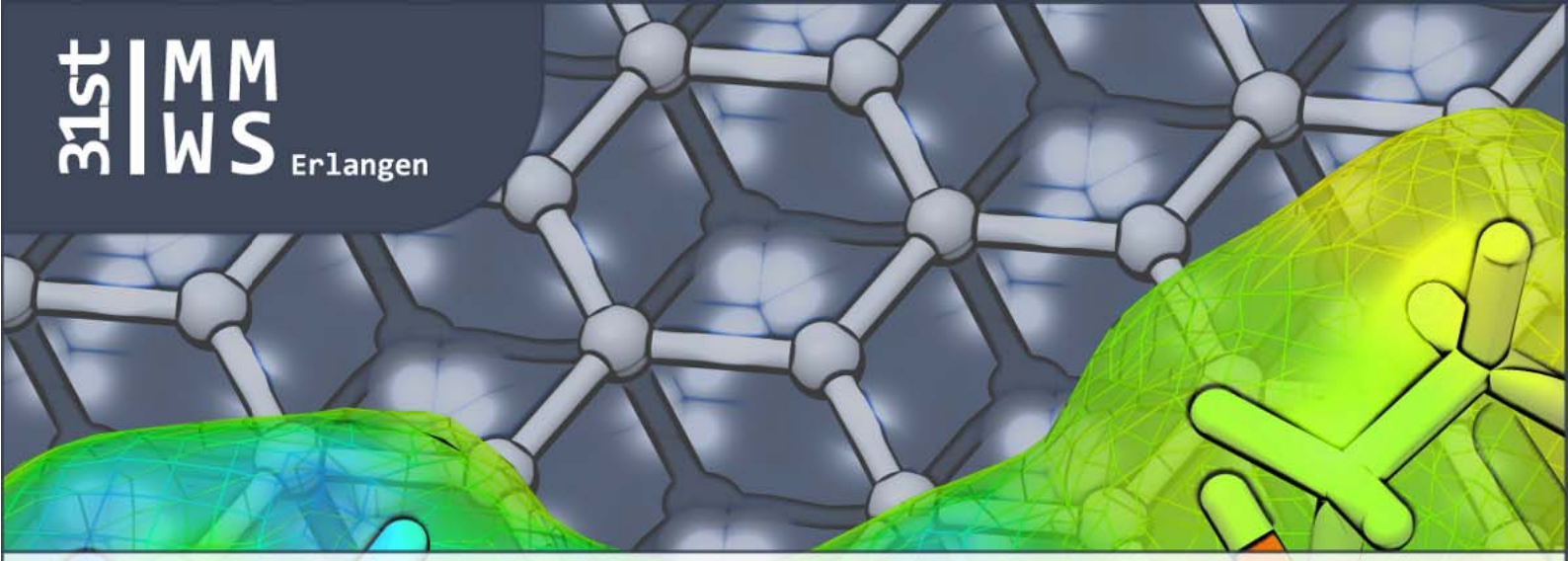
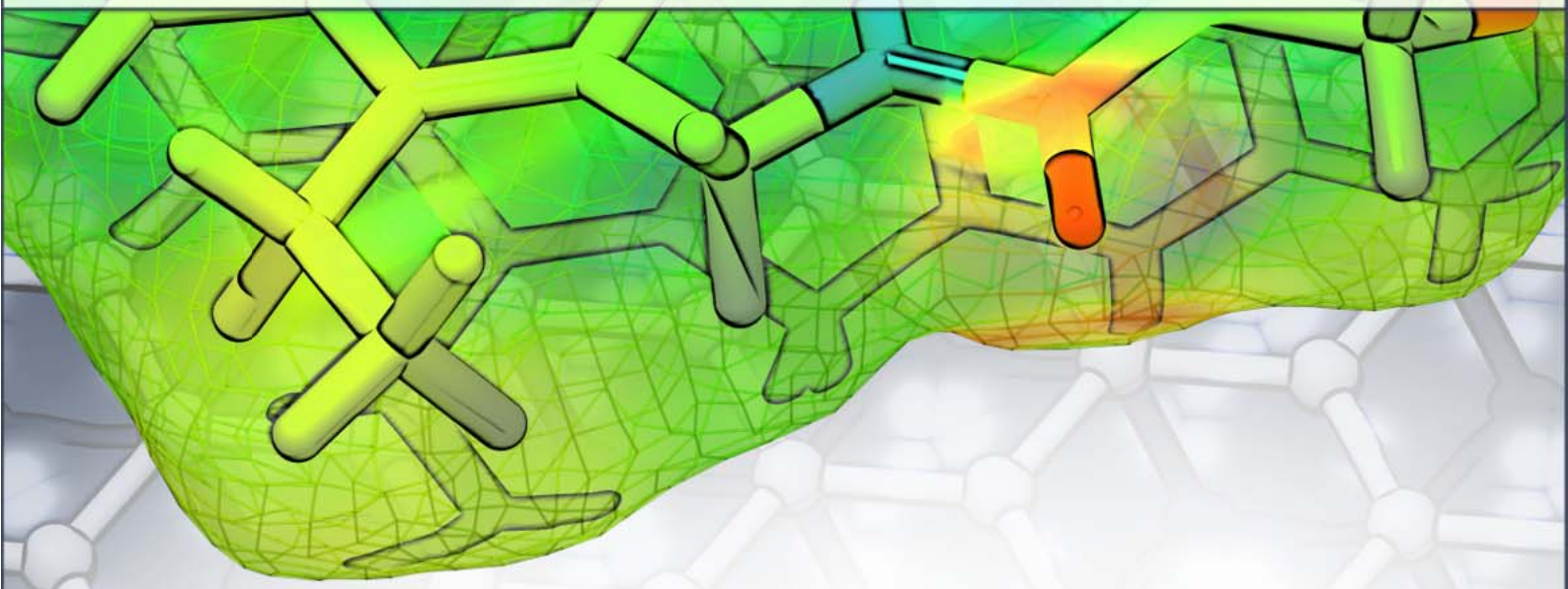
31st MM WS Erlangen



Molecular Modeling Workshop <2017>



Erlangen

March 27th-29th 2017

www.mgms-ds.de

molecular graphics & modelling society

FRIEDRICH-ALEXANDER UNIVERSITÄT ERLANGEN-NÜRNBERG

MOLECULAR MODELLING WORKSHOP 2017

Monday, March, 27th - Wednesday, March, 29th 2017

Welcome to the 31st Molecular Modelling Workshop (MMWS).

This is the 15th 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. However, this will be probably the last MMWS in Henkestraße as Organic, Medicinal and Pharmaceutical Chemistry in Erlangen will move into the first phase of the new Chemikum and the venue of the workshop will also move within Erlangen then.

This year's MMWS is the second for which the technical conference management of the Computer-Chemie-Centrum, CCC, is supported by the Bioinformatics group headed by Heinrich Sticht. The workshop's scientific program has been thoroughly compiled by Stefan Güssregen from Sanofi this time.

The MMWS can look back on a long history of giving graduate students and postdocs the opportunity to present their work. It predates the Young Modellers' forum, which is organized annually 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 modeling scene in Europe and that it continues to provide students and young researchers with a stage to present their work.

This time, we have three plenary speakers for our MMWS. We are happy to welcome Ivan Coluzza from the University of Vienna, Jordi Mestres from IMIM Barcelona, and Richard Lewis from Novartis as our plenary speakers this year for the focal topics of computational biochemistry, modelling in toxicology and polypharmacology, as well as molecular modelling in a pharma environment, respectively. By combining these three excellent plenary speakers, we hope to enable MMWS to keep pace with the rapidly changing face of modeling in Europe and the USA and to provide inspiration for young modelers.

So now, please enjoy the 31st Molecular Modelling Workshop.

Incidentally, if you are confused, "modeler/ing" is written with one "l" in US-English and with double "l" in British English. The proper names therefore use "modeller/ing" and the text "modeler/ing".

Scientific program

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DEAR COLLEGUES,

The 31st Molecular Modelling Workshop (March, 27th – 29th) 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):

PROF. IVAN COLUZZA

Universität Wien, Vienna, Austria
homepage.univie.ac.at/ivan.coluzza

DR. RICHARD LEWIS

Novartis, Switzerland
novartis.ch

PROF. JORDI MESTRES

IMIM, Barcelona
syspharm.imim.cat

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 mmws2017.mgms-ds.de

LOCATION

Conference location: All talks, coffee breaks, the poster sessions and the buffet dinner on Monday, March 27th will take place at the Institute for Organic Chemistry, Henkestraße 42, 91054 Erlangen.

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.

Prof. Ivan Coluzza

My research focuses on the applications of statistical mechanics to soft-matter and complex biological systems. During my research experience I developed a deep interest for many different fields, ranging from physics to biology. With computer simulations I study what allows proteins to use just about 20 building blocks to assemble the most variable and complex structures in nature. Proteins are also sophisticated molecular machines, that can walk push pull and even trap molecules and other proteins. An important goal of my work is to understand the function of specific proteins and design new molecular machines. Finally, I work on the construction of artificial chains of particles that can be designed and fold just like proteins, but are much simpler to control and synthesized.

I worked in worldwide leading groups in Biophysics and I created an extensive network of collaborations. I graduated in Physics at the University “La Sapienza” in Rome, got my PhD in Physics at the University of Amsterdam, and worked as a post-doctoral researcher at the University of Cambridge and at the National Institute of Medical research in London. Currently I hold a University Assistant position at the University of Vienna and in September 2017 I will start an Ikerbasque Tenure-track at the CIC biomaGUNE research center in San Sebastian (Spain).

Prof. Jordi Mestres

Jordi Mestres holds a PhD in Computational Chemistry from the University of Girona. After a post-doctoral stay at Pharmacia&Upjohn in Kalamazoo (Michigan, USA), in 1997 he joined the Molecular Design & Informatics department at N.V. Organon in Oss (The Netherlands) and in 2000 he was appointed Head of Computational Medicinal Chemistry at Organon Laboratories in Newhouse (Scotland, UK). In 2003, he took on his current position as Head of the Research Group on Systems Pharmacology, within the GRIB Research Program at the IMIM Hospital del Mar Research Institute in Barcelona. He is also Associate Professor at the University Pompeu Fabra (UPF). In 2006, he founded Chemotargets as a spin-off company of his group. He is also the recipient of the 2006 Corwin Hansch Award from the QSAR and Modelling Society and the 2007 Technology Transfer Award from the UPF. His current research interests focus on the development of systems approaches to precision medicine. He is the author of over 140 publications, 9 patents among them.

DR. RICHARD LEWIS

I started out as an organic chemist, making penicillins in Glaxo. However at university, I did a course in pharmacology, and started to become more and more interested in why molecules did what they did. That led to a PhD in drug design with Philip Dean, who was also in the dept of Pharmacology. After a few years as an itinerant PostDoc learning about docking and proteins, I joined Jon Mason's group at RPR, moving to Lilly to lead the European CADD team, before coming to Novartis in 2004. I have worked on kinases, proteases, transporters, ion channels, GPCRs, PPIs. I have also worked in diversity set selection, combinatorial library design, writing some of the first tools to handle problems in these areas. More recently, I have been working on toolkits for medicinal chemists, in particular around ADME. My current interests are using big data and decision making.

Research Experience
B.A.(Hons), Natural Sciences(Chemistry), Cambridge University
Ph.D., Pharmacology, Cambridge University
Fulbright Senior Scholar, Dept. of Pharmaceutical Chemistry, UCSF, USA with Tack Kuntz.
Royal Commission of 1851 Research Fellow, ICRF, UK with Mike Sternberg.
My Favorite Publications

- Meng E. & Lewis R.A. (1991) J Comput Chem, 12, 801-808.
- Good A.C. & Lewis R.A. (1997) J Med Chem, 40, 3926-3936
- Lewis R.A. (2005) J Med Chem, 48(5), 1638-1648.
- Ertl P. & Lewis R.A. (2012) J Computer-Aided Mol Des, 26(10): 1207-1215.
- King R., Muggleton S., Lewis R.A. & Sternberg M.J.E.S. (1992) PNAS, 89, 11322-11326.

Lectures Program

PROGRAM

Monday, March 27th 2017

11:30-14:00	**Registration**
14:00-14:15	**Welcome remarks / Agenda review**
14:15-15:15	**PLENARY LECTURE I: Richard Lewis** 25 years in Pharma: What has changed in the industry since 1991?
15:15-15:40	**L1: Thien Anh Le (Würzburg, Germany)** Rational design of covalent inhibitors
15:40-16:05	**L2: Susanne Hermans (Düsseldorf, Germany)** Virtual screening for ligands with predefined dynamic allosteric response
16:05-16:30	**L3: Oliver Lemke (Berlin, Germany)** One-step protein labeling with the tubulin tyrosine ligase – substrate scope explained by computational studies
16:30-16:50	**Coffee Break**
16:50-17:15	**L4: Dr. Simone Brogi (Siena, Italy)** Combination of in silico approaches to identify fluorescent probes preventing PrPSc replication in prion diseases
17:15-17:40	**L5: Birgit Waldner (Innsbruck, Austria)** Explaining electrostatic serine protease substrate readout similarity
17:45-18:45	**Annual Meeting of the MGMS-DS e.V.**
19:00	**Buffet - Dinner**

PROGRAM

Tuesday, March 28th 2017

08:30-08:55	**L6: Achim Sandmann (Erlangen, Germany)** Effects of protein side chain intercalation in DNA binding
08:55-09:20	**L7: Stevan Alesić (Berlin, Germany)** Structural basis for the recognition of the proline rich sequences by FBP-21 tandem-WW domains
09:20-09:45	**L8: Martin Urban (Dortmund, Germany)** Relation between K^+ channel gating and sequence specific helix distortions by a joint experimental and molecular dynamics simulation approach
09:45-10:10	**L9: Dr. Christoph Gertzen (Düsseldorf, Germany)** Dimerization interfaces of the GPCR TGR5 revealed by integrative modeling
10:10-10:35	**Conference Photo & Coffee Break**
10:35-11:00	**L10: Hanna Juhola (Tampere, Finland)** The role of the membrane in neurotransmitter interactions with their receptors
11:00-12:00	**PLENARY LECTURE II: Ivan Coluzza** Learning from natural molecular machines: the artificial chaperonin
12:00-13:30	**Lunch**
13:30-14:45	**POSTER SESSION I**
14:45-15:10	**L11: Dušan Petrović (Jülich, Germany)** Enzyme evolution and design with hamiltonian replica exchange molecular dynamics
15:10-15:35	**L12: Eric Schulze (Magdeburg, Germany)** Conformational dynamics of glycoproteins
15:35-16:00	**L13: Carl Mensch (Antwerpen, Belgium)** Towards a standardized characterization of solution phase protein structure using Raman optical activity
16:00-16:30	**Coffee Break**

PROGRAM

Tuesday, March 28th 2017

16:30-16:55	**L14: Dr. Christof Jäger (Nottingham, UK)** Towards engineering radical enzymes - thermodynamic reaction profiling and mechanistic insights into QueE
16:55-17:20	**L15: Dr. Johannes Margraf (Florida, USA)** Describing difficult singlet/triplet splitting problems with coupled cluster theory
17:20-17:45	**L16: Robert Stepic (Erlangen, Germany)** Water gas-shift reaction catalysis by ruthenium-based complexes
18:30	**Evening in the brewery *Steinbach Bräu***

Wednesday, March 29th 2017

08:30-08:55	**L17: Stefan Bauroth (Erlangen, Germany)** Molecular modelling and time resolved spectroscopy of electron transfer events in mid-sized molecular donor-acceptor-systems
08:55-09:20	**L18: Jonathan Bogaerts (Antwerpen, Netherlands)** Raman optical activity for drug discovery: Structural characterization of artemisinin derivatives in solution
09:20-09:45	**L19: Dr. Stephan Ehrlich (Schrödinger)** AutoTS: An automated transition state search tool
09:45-10:10	**L20: Lena Kalinowsky (Frankfurt, Germany)** A diverse benchmark data set for the validation of scoring functions based on 3D matched molecular pairs
10:10-10:40	**Coffee Break**
10:40-11:40	**POSTER SESSION II**
11:40-12:05	**L21: Dr. Gunther Stahl (OpenEye)** Conformational sampling of macrocycles: recent progress.
12:05-12:30	**L22: Dr. Abdella Ousaa (Thinghir, Morocco)** QSTR analysis and combining DFT of the toxicity of heterogeneous phenols
12:30-14:00	**Lunch**
14:00-15:00	**PLENARY LECTURE III: Jordi Mestres** Systems approaches to drug safety
15:00	**Poster & Lecture awards, Closing**

Poster Sessions

POSTER SESSION I

Tuesday, March 28^{8th} 2017 13:30-14:45

P01 **Stevan Alesić (Berlin, Germany)**
Structural basis fort he recognition of the proline rich sequences by FBP-21 tandem-WW domains

P02 **Ahmed T. Ardjani (Tlemcen, Algeria)**
Computational study of the antioxidant activity of 4-(5-choro-2-hydroxy-.phenylamino)-4-oxobut-2-enoic acid analogs using quantum-chemistry descriptors and molecular modeling

P03 **Frank Beierlein (Erlangen, Germany)**
DNA-dye-conjugates for detecting nucleic acids in live cells

P04 **Luka Bilić (Zagreb, Croatia)**
$P(TMG)_3$: elusive or synthetically accessible phosphane

P05 **Ebru Çetin (Istanbul, Turkey)**
Modeling and characterization of selective ligand for β-adrenoceptors

P06 **Giulia Chemi (Siena, Italy)**
Computational studies of NBDHEX as Giardia duodenalis thioredoxin reductase (gTrxR) inhibitor

P07 **Illija N. Cvijetić (Belgrade, Serbia)**
Target fishing docking studies of novel aryldiketo acids with promising antibacerial activity toward MDR strains

P08 **Christina de Bruyn Kops (Hamburg, Germany)**
Alignment-based method for the prediction of sites of metabolism of xenobiotics

P09 **Benedikt Diewald (Erlangen, Germany)**
Molecular dynamics study of the hapten-binding antibody B1-8

P10 **Lukas Eberlein (Dortmund, Germany)**
High pressure effects on spectroscopic and thermodynamic properties of small biomolecules

P11 **Stephan Ehrlich (Schrödinger, Germany)**
Virtual screening performance and core-hopping potential of common pharmacophore hypotheses derived from Phase's novel pharmacophore feature-based shape alignment

P12 **Daniela Eisenschmidt (Halle, Germany)**
Semiempirical calculations of Thlaspi arvense thiocyanate forming protein (TFP) product formation

Poster Session I

Tuesday, March 28th 2017 13:30-14:45

P13 **Duygu Emir (Balikesir, Turkey)**
A computational study on molecular structure and spectral properties of halogenated sumanene

P14 **John Ewalt (Hawai, USA)**
Water exchange at the beta-barrel ‚holes' of several far-red fluorescent proteins

P15 **Nils-Ole Friedrich (Hamburg, Germany)**
Benchmarking commercial conformer ensemble generators

P16 **Marko Hanževački (Zagreb, Croatia)**
The influence of chemical change on protein dynamics: a case study with pyruvate formate-lyase

Please remember to remove your posters on tuesday evening!

POSTER SESSION II

Wednesday, March 29th 2017 10:40-11:40

P01 **Nadine Homeyer (Dundee, UK)**
Finding the lock for a key – identification of the targets of screening hit molecules

P02 **Anselm H. C. Horn (Erlangen, Germany)**
Role of N-terminal residues for structural stability of triangular $A\beta_{40}$ fibrillar oligomers

P03 **Jan L. Riehm (Saarbrücken, Germany)**
All around CYP106A2: the many faces of molecular modelling

P04 **Hanna Juhola (Tampere, Finland)**
The role of the membrane in neurotransmitter interactions with their receptors

P05 **Lena Kalinowski (Frankfurt, Germany)**
A diverse benchmark data set for the validation of scoring functions based on 3D matched molecular pairs

P06 **Oliver Lemke (Berlin, Germany)**
One-step protein labeling with the tubulin tyrosine ligase – substrate scope explained by computational studies

P07 **Dominik Munz (Erlangen, Germany)**
What makes a palladium terminal oxo stable?

P08 **Abdellah Ousaa (Meknes, Morocco))**
QSTR analysis and combining DFT of the toxicity of heterogenous phenols

P09 **Achim Sandmann (Erlangen, Gemany)**
Effects of protein side chain intercalation in DNA binding

P10 **Dimitry I. Sharapa (Erlangen, Germany)**
Accurate intermolecular potential for the C_{60} dimer

P11 **Eileen Socher (Erlangen, Germany)**
Structural investigation of the *E. coli* proteins HdeA and YmgD by MD simulations

P12 **Christian A. Söldner (Erlangen, Germany)**
Binding of glycolipids to the macrophage surface receptor mincle

P13 **Nicolas Tielker (Dortmund, Germany)**
The SAMPL5 challenge for embedded-cluster integral equation theory: solvation free energies, aqueous pKa and cyclohexane-water logD

POSTER SESSION II

Wednesday, March 29th 2017 10:40-11:40

P14 **Karina van den Broek (Essen, Germany)**
Mesoscopic simulaton of the membrane disrupting activity of the cyclotide kalata B1

P15 **Dustin Vivod (Erlangen, Germany)**
Molecular dynamics studies on the pH-dependent mechanism of phosphonic acid adsorption of anatase (101)

P16 **Christian R. Wick (Zagreb, Croatia)**
Modelling the reactions catalysed by coenzyme B12-dependent enzymes: accuracy and cost-quality balance

All abstracts are available on the conference web site:
www.mmws2017.mgms-ds.de

25 years in Pharma: What has changed in the industry since 1991?

Richard Lewis

Novartis Pharma AG, Basel, Switzerland

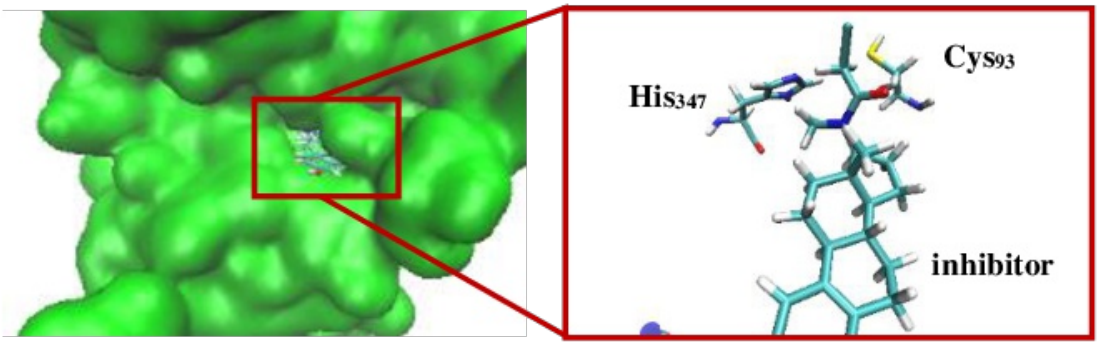
25 years is almost a full career for a scientist, but before looking to the future, we should ask what is really new in the last 25 years, i.e. since 1991? Surprisingly little! Most of techniques routinely today were introduced in the 1980s (many techniques have been re-invented since; the collective memory of the literature seems to be under 10 years and falling). The biggest revolution in computational chemistry was not new techniques, but computer power and data availability. We can now remove of the necessary short-cuts, refine our parameters, and validate using data sets of appropriate statistically power. We can now talk about our results with an estimate of error. If only we understood water and free energy!

The other paradigm shift has been in the holistic view of drug design. We are not here to improve, say, affinity, but also to factor in solubility, bioavaility, clearance, stability and many other issues that affect the success of a project. Although fundamental scientific progress has been slow, the opportunities for CADD scientists to really impact projects is at its highest.

Rational design of covalent inhibitors

Thien Anh Le, Bernd Engels

Institut für Physikalische und Theoretische Chemie, Universität Würzburg



Most drugs consist of ligands which interact with their target non-covalently. They have the advantage that they are so unreactive that unintended reactions with DNA or proteins do not take place. However, they have the drawback that generally their free energy of binding does not exceed 15 kcal/mol. Higher binding affinities can only be achieved with ligands which form a covalent bond with their target. Despite famous examples as Penicillin or Aspirin in the past the industry hesitated to develop new covalent drugs because they fear unintended side reactions resulting from the reactivity of ligands. [1] Since about 2005 covalent ligands undergo an intensive renaissance in academia and industry, because various very selective drugs were detected in the last few years. [2][3] This work presents a protocol for the rational design of covalent inhibitors starting from a non-covalent ligand.
The system investigated was FadA5 a thiolase of Mycobacterium tuberculosis. [4] Several synthesizable inhibitors have been designed and investigated in respect of their stability in protein via docking and molecular dynamic simulations. QM methods were used to investigate thermodynamic and kinetics of the inhibition reaction.

[1] J. Singh et al., *Nat. Reviews*, **2011**, *10*, 307-317.
[2] V. Hirsch, *BioDrugs*, **2015**, *29*, 167-183.
[3] T. Schirmeister et al, *JACS*, **2016**, *138*, 8332-8335.
[4] Schaefer et al., *Structure*, **2015**, *23*, 21-33

Virtual screening for ligands with predefined dynamic allosteric response

Susanne M. A. Hermans[1], Christopher Pfleger[1], Denis Schmidt[1], Markus Boehm[2], Alan M. Mathiowetz[2], Christopher L. McClendon[2], Kiyoyuki Omoto[2], Holger Gohlke[1]*

[1]*Department of Mathematics and Natural Sciences, Institute for Pharmaceutical and Medicinal Chemistry, Heinrich Heine University Düsseldorf, Düsseldorf, Germany*

[2]*Medicine Design, Pfizer Inc., 1 Portland Street, Cambridge, Massachusetts 02139, United States*

**Email: gohlke@uni-duesseldorf.de*

Allosteric regulation is the coupling between distant sites in biomolecules: An action at one site can affect the function at another site. Targeting allosteric regulation in biomolecules is a promising strategy in drug discovery, due to advantages over conventional orthosteric ligands. [1] However, the identification of novel allosteric pockets is complicated by the variety of allosteric mechanisms, differing by the extent of conformational change upon ligand binding. Particularly, dynamic allostery, which can occur in the absence of conformational change, [2] is difficult to detect from static crystal structures alone. Here, we present an efficient approach to probe dynamic allostery in biomolecules by constructing fuzzy ligands as surrogates for "true" ligands, with which an allosteric response is studied by deducing altered stability characteristics from rigidity analysis.

We probed the performance of the fuzzy ligand approach on the AsteX diverse set [3] containing 85 protein-ligand complexes, including 20 allosterically regulated proteins. For the *apo* states generated by removing the original ligand in Maestro, pockets were calculated using PocketAnalyzer^{PCA}. [4] Fuzzy ligands were generated by mapping the possible interactions of the binding pocket to build a rod-like structure that connects the interacting atoms placed in the pocket. Altered long-range stability characteristics upon binding of a ligand were computed by the Constraint Network Analysis (CNA) approach, which aims at characterizing biomolecular flexibility and rigidity for linking structure and function. [5] The fuzzy ligands were validated I) in terms of their influence on network rigidity compared to the "true" ligand and II) to what extent pharmacophore models based on them allow for a successful retrieval of binders in retrospective virtual screenings on DUD-E datasets. [6]

Altered per-residue stability characteristics from rigidity analysis of our fuzzy ligands are in agreement with those from "true" ligands. In 62% of all cases, the calculated per-residue energies correlate with $R^2 \geq 0.50$. The virtual screening results based on fuzzy ligands perform equally well or outperform, in 29% of the cases, the true ligands' results. In all, analyzing unexplored pockets with fuzzy ligands could thus be a promising step towards identifying novel allosteric drug targets and drugs.

[1] R. Nussinov, C.-J. Tsai, *Cell*, **2013**, *153*, 293-305
[2] A. Cooper, D.T. Dryden, *Eur. Biophys. J.*, **1984**, *11*, 103-109
[3] M.J. Hartshorn, M.L. Verdonk, G. Chessari, S.C. Brewerton, W.T.M. Mooij, P.N. Mortenson, C.W. Murray, *J. Med. Chem.*, **2007**, *50*, 726-741
[4] I.R. Craig, C. Pfleger, H. Gohlke, J.W. Essex, K. Spiegel, *J. Chem. Inf. Model.*, **2011**, *51*, 2666-2679
[5] C. Pfleger, P.C. Rathi, D.L. Klein, S. Radestock, H. Gohlke, *J. Chem. Inf. Model.*, **2013**, *53*, 1007-1015
[6] M.M. Mysinger, M. Carchia, J.J. Irwin, B.K. Shoichet, *J. Med. Chem.*, **2012**, *55*, 6582-6594

One-step protein labeling with the tubulin tyrosine ligase - Substrate scope explained by computational studies

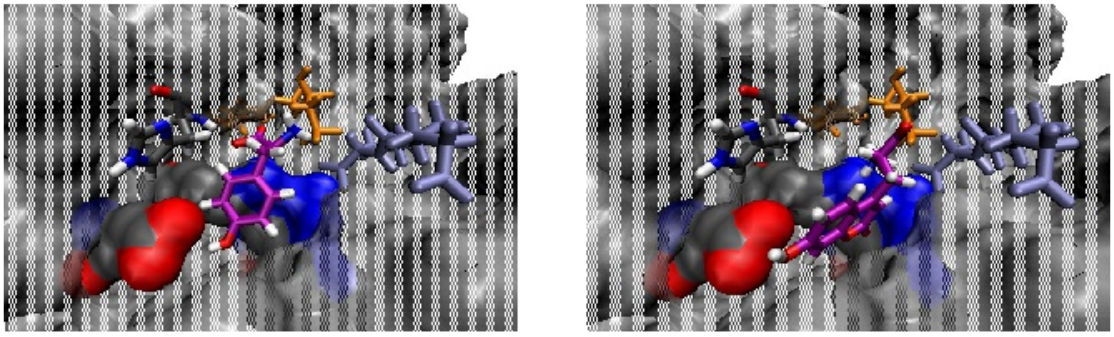
O. Lemke [▽], D. Schumacher [†,⊥], J. Helma [‡], H. Leonhardt [‡], C.P.R. Hackenberger [†,⊥], B.G. Keller [▽]

[▽] *Department of Chemistry and Biochemistry, Freie Universität Berlin, Takustr. 3, 14195 Berlin, Germany*

[†] *Department of Chemical-Biology, Leibniz-Institut für Molekulare Pharmakologie (FMP), Robert-Rössle-Str. 10, 13125 Berlin, Germany*

[⊥] *Department of Chemistry, Humboldt Universität zu Berlin, Brook-Taylor-Strasse 2, 12489 Berlin, Germany*

[‡] *Department of Biology II, Ludwig Maximilians Universität München and Center for Integrated Protein Science Munich, Großhadenerstr. 2, 82152 Martinsried, Germany*



Enzymatic catalysis provides a powerful tool for chemical synthesis. One example is the enzyme tubulin tyrosine ligase (TTL), which enables chemoenzymatic protein functionalization using tyrosine-derivatives [1]. Recent studies show that, the wild type TTL also accepts and ligates other unnatural amino acids, which can differ in size and structure, such as a coumarin-derivative, enabling one-step-fluorescence labeling.
To get insight into the broad substrate scope of TTL docking studies were performed. In these studies the binding behavior of the natural substrate tyrosine as well as other canonical and unnatural amino acids were investigated. Based on these information the important features of the binding pocket such as π-stacking interactions and hydrogen bond formation can be pointed out. Furthermore, molecular dynamic simulations were performed to predict the stability and flexibility of the substrates within the pocket [2].

[1] D. Schumacher, J. Helma, F.A. Mann, G. Pichler, F. Natale, E. Krause, M.C. Cardoso, C.P.R. Hackenberger, H. Leonhardt. Versatile and Efficient Site-Specific Protein Functionalization by Tubulin Tyrosine Ligase, *Angew. Chem. Int. Ed.*; **2015**, *54*, 1-6
[2] D. Schumacher, O. Lemke, J. Helma, L. Gerszonowicz, V. Waller, T. Stochek, P.A. Durkin, N. Budisa, H. Leonhardt, B.G. Keller, C.P.R. Hackenberger: Broad substrate tolerance of tubulin tyrosine ligase enables one step chemoenzymatic protein labeling, *submitted*

Combination of *in silico* Approaches to Identify Fluorescent Probes Preventing PrP^{Sc} Replication in Prion Diseases

Simone Brogi

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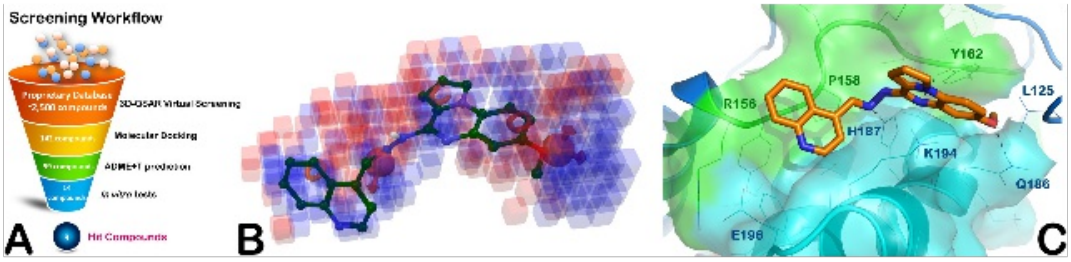
European Research Centre for Drug Discovery and Development (NatSynDrugs), Università degli Studi di Siena, via Aldo Moro 2, 53100 Siena, Italy

Prion diseases are neurodegenerative disorders caused by the accumulation of the misfolded protein PrP^{Sc} (pathological variant of the cellular protein PrP^{C}). Since, no treatments for these diseases are available, the discovery of diagnostic tools and specific therapeutics is urgently required. [1] It was established that molecules that bind PrP^{C} can prevent its misfolding, arresting the progression of disorders related to the abnormal PrP protein. So, *in silico* methods represent a valuable source to discover molecules with desired properties. Based on our knowledge in virtual screening, we designed a workflow to select molecules preventing PrP^{C} misfolding. Phase software (Schrödinger, LLC, New York, NY) was used to derive a 3D-QSAR model, using pharmacophore-based alignment, coupled to molecular docking and physico-chemical properties prediction for identifying molecules able to inhibit the misfolding of PrP^{C} (Fig. A).



The pharmacophore model (AARRR.20), built using 9 highly active compounds, was used as alignment rule for deriving a 3D-QSAR model (Fig. B) considering 58 molecules spanning five orders of magnitude (including 9 highly active compounds). These selected molecules, interacting with the same binding site (D-pocket), effectively inhibit the misfolding process. The model was firstly validated *in silico*, by a decoys set, evaluating the Güner and Henry score (*GH*) and the Enrichment Factor (*EF*), and by using the ROC curve analysis. Next, the 3D-QSAR model was experimentally validated. An *in silico* proprietary database screening (>2,500 compounds) was executed to discover new scaffolds with anti-prion properties. Subsequently, a docking study using Glide software (Schrödinger, LLC, New York, NY) against D-pocket was performed. Finally, the resulting hits were analyzed by means of QikProp (Schrödinger, LLC, New York, NY) and by FAFDrugs3.0 to avoid molecules which behave as Pan Assay Interference Compounds (PAINS). The selected hits (14 compounds) were biologically evaluated to confirm our *in silico* approach. Gratifyingly, 9 out of 14 retrieved hits, characterized by low toxicity, inhibited PrP^{Sc} accumulation in prion-infected neuroblastoma cells (ScN2a). Among them, the pyrroloquinoxalinehydrazone (Fig. C) showed higher potency (IC_{50}=1.6 μM). This molecule also binds to PrP^{Sc} aggregates in infected ScN2a cells with a fluorescence pattern similar to that found for Thioflavin-T. [2] By using the described protocol we identified theranostics preventing the pathological transition of PrP^{C} to PrP^{Sc}. The combination of the anti-prion profile with a fluorescence imaging behavior and the brain permeability suggests the hit as a prototypic tool for the development of diagnostic and therapeutic probes for prion diseases.

Acknowledgements

SB wishes to thank Prof Giuseppe Campiani, Prof Stefania Butini, Prof Sandra Gemma, Dr Margherita Brindisi, Dr Giulia Chemi, Prof Giuseppe Legname and Dr Ludovica Zaccagnini for the support during the development of the project.

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Explaining Electrostatic Serine Protease Substrate Readout Similarity

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Serine proteases are key players in numerous fundamental cellular reactions and are amongst the most important targets in drug design [1]. Despite having the same fold, serine proteases often show different substrate specificities, depending on the biological processes they are part of. Here, we investigate the role of enthalpy in electrostatic serine protease substrate readout similarity. We used GRID [2] to calculate binding site interaction potentials for nine serine proteases with chymotrypsin fold probing for different types of binding site interactions. We then determined similarities in binding site interaction potentials of all nine proteins and compared them to electrostatic substrate readout similarities. We were able to explain electrostatic substrate readout similarities for all cases. The results give a detailed view of the enthalpic interactions in serine protease subpockets driving electrostatic substrate readout similarity and can be exploited in selective drug design.

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Effects of Protein Side Chain Intercalation in DNA Binding

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Deformation of DNA by DNA-binding proteins is important for several crucial functions which include binding site recognition by shape readout, alignment of DNA-bound proteins with respect to each other, and compacting DNA to fit it into small compartments. One common way of strong DNA deformation is a localized kink between two successive base pairs, which is mainly visible in the roll angle. We conducted a search of the Protein Data Bank to find structures of protein-DNA complexes with kinked DNA. One widespread mechanism of inducing kinks is the intercalation of amino acid side chains between DNA base pairs; however, there exist also systems, which achieve kinking without intercalation.

By comparing the different X-ray structures of various protein-DNA complexes, we found that intercalated systems show narrow roll angle distributions while systems in which DNA is bent without intercalation show broad roll angle distributions.

We compared MD simulations of WT-proteins and mutants with alanines in place of the intercalating residues, to investigate the effect of intercalation. We used CcpA, Cren7, Sac7d, Sox-4, TBP and TFAM as model systems.

For Sac7d we found that if two residues intercalate, mutation of one to alanine made no difference. Upon mutation of all intercalating residues, the roll angle decreased, but did not completely vanish. These findings agree with previous mutational experiments [1]. The preliminary data of the simulations for the remaining systems suggest that the properties of these systems are affected by intercalation in a similar fashion.

We also compared systems with different DNA sequences and found that, while intercalating wt-protein-DNA complexes showed no sequence dependent roll angles, some of the non-intercalating mutants did bend different DNA sequences to varying degrees.

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Structural Basis for the Recognition of the Proline Rich Sequences by FBP-21 tandem-WW domains

Stevan Aleksić[1], Miriam Bertazzon[1], Jana Sticht[1], Christian Freund[1], Bettina G. Keller[1]

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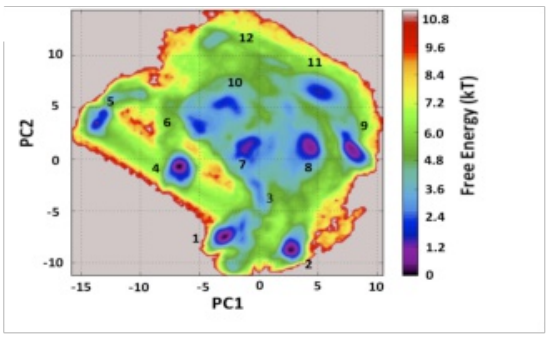

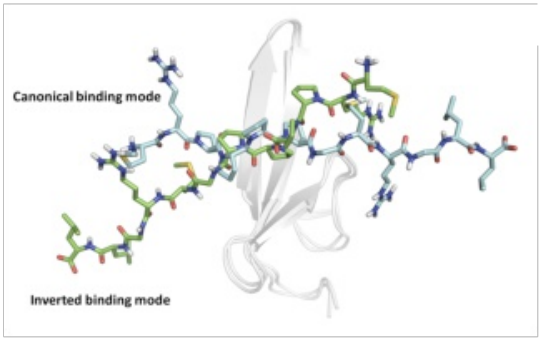

Formin-binding protein 21 (FBP-21) is a spliceosomal protein, which recognizes the proline-rich sequences (PRS) abundant in various splicing factors. The recruitment of PRS by tandem-WW domains (t-WW) of the FBP-21 is characterized by the low affinity, which in turn can be enhanced by the multivalent binding. Still the binding of the multivalent PRS to the t-WW is poorly understood. [1] In this study, we aim to elucidate the structural determinants of a such multivalent recognition by combining the nuclear magnetic resonance (NMR), isothermal titration calorimetry (ITC), molecular dynamics (MD) simulations, and protein-peptide docking.

NMR, and ITC measurements revealed that the monovalent PRS bind with higher affinity to a singular WW_1 construct compared to the t-WW domains. This finding raised a question, if there is a structure in the conformational ensemble of the apo t-WW domains, which favors binding to the WW_1 domain. We performed PCA analysis on the MD simulations of the apo t-WW domains, and showed that there is a structural preference for the higher WW_1 domain affinity. There are 12 long-lived structures in the conformational space of the apo t-WW domains, determined by the cluster-specific hydrogen bond network. Only in a single cluster, residues of the WW_1 domain binding groove are involved in the inter-domain interface formation. On contrary, in five clusters, the interface formation hinders the WW_2 domain binding groove residues from binding. Other six clusters are free to bind PRS in both binding grooves. However, further structural rearrangement is necessary, so that the relative orientation of the respective binding grooves is proper for the multivalent recognition.

As it was earlier confirmed by the spin labelling experiments [1], PRS can be docked to the t-WW domains in a canonical, or in an inverted binding mode. We ran the protein-peptide docking calculations, and found the same binding behavior. Both binding complexes were stable during the 20 ns MD runs, and serve as a basis for the modeling of the multivalent recognition by t-WW domains.

In conclusion, current efforts in our groups are towards proving a hypothesis, that multivalent recognition of the PRS by t-WW domains is governed by an allosteric mechanism. This mechanism comprises the initial recognition of the multivalent PRS by the WW_1 domain, triggering the structural rearrangement of the flexible linker, and bringing the WW_2 domain in the proper orientation to bind the second valance of the respective multivalent PRS.

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Relation between K^+ channel gating and sequence specific helix distortions by a joint experimental and molecular dynamics simulation approach

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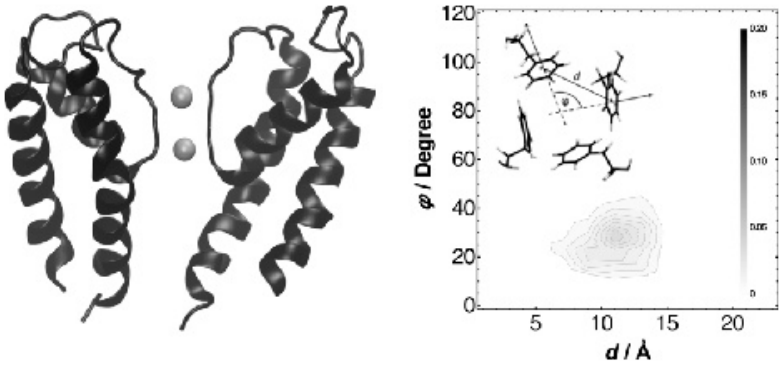
Ion channels fluctuate stochastically between "open" and "closed" states, which determine the ion flux through biological membranes, also known as "gating". This crucial feature of ion channels is necessary in cellular, biological systems to regulate the ion concentration level, which is essential for the processes of homeostasis or second messaging. Yet the origin of gating is not fully understood. A suitable ion channel model for investigations of gating is the tetrameric potassium-selective ion channel Kcv_{ATCV-1}. This minimalistic channel is found in *chlorella* viruses, and comprised of only 82 amino acids per monomer [1-3]. While electrophysiological experiments have already identified two gates in the wild-type channel, an additional 3rd gating state is found in the related channel Kcv_{ATCV}-"Smith" (Kcv_S). This 3rd gate leads to a predominantly closed channel (over 70%) in comparison with the wild-type Kcv_{ATCV-1} and the related Kcv_{ATCV}-"next to Smith" (Kcv_{NTS}) channel, which both lack this additional gate.



Site directed mutagenesis experiments revealed a significant dependency of this gate on the presence of phenylalanine at position 78 and serine at position 77. To investigate the characteristics of this 3rd gate by molecular dynamics (MD) simulations, initial homology models were created for Kcv_{ATCV-1} and for the two related channels Kcv_S and Kcv_{NTS}. For the description of the different behaviour in gating, potential π-π-interactions of the Phe78 residues were analysed in terms of angle/distance probabilities, considering also interactions between different monomers as well as probably interactions of the Ser77 which lead to a channel gating. The results allow for a microscopic interpretation of the gating states in Kcv_{ATCV} variants.

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Dimerization Interfaces of the GPCR TGR5 Revealed by Integrative Modeling

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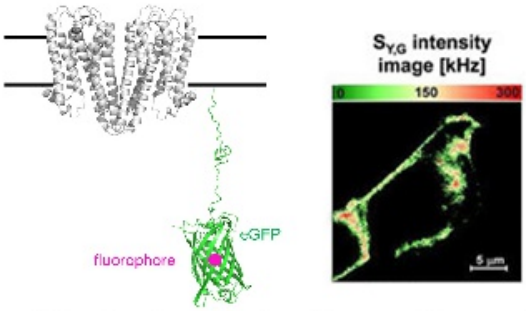
The bile acid sensing G-protein coupled receptor TGR5 is a very interesting drug target[1, 2]. Apart from regulating blood glucose levels, increasing metabolism, and reducing inflammation, it is known to foster the development of various types of cancer if overexpressed[3]. Hence, both enhancing and decreasing the signaling of TGR5 is highly interesting in the treatment of metabolic diseases and cancer, respectively. An emerging factor to influence the activity and signaling of GPCRs is targeting homo- and heterodimers and their formation[4]. Influencing dimers of GPCRs requires knowledge of their dimerization interfaces. However, the di- and oligomerization interfaces of TGR5 are unknown. Here, we present an integrative modeling study, which revealed the primary dimerization and putative oligomerization interfaces of TGR5 [5] based on known GPCR interfaces. We combined homology modeling, molecular dynamics (MD) simulations, and MM-PBSA calculations with live cell multi-parameter MFIS-FRET measurements to determine these interfaces. To measure distances between TGR5 protomers in live cells, the C-termini were labeled with different fluorophores, so that the apparent distance distribution could be used to identify dimerization interfaces. The structures for these interfaces were created via homology modeling of TGR5, based on three interfaces known from X-ray structures of other GPCRs. To calculate the expected FRET distance distributions to be compared to experiment, the TGR5 dimer structures were combined with MD simulations of the linker and fluorophore.



Subsequently, we calculated the effective energies of the snapshots combined with TGR5 dimers via MM-PBSA in an implicit membrane environment. To improve the calculation of the fluorescent dyes' probability distribution with respect to the TGR5 dimers, we estimated the entropic contribution of each snapshot in the ensemble and Boltzmann-weighted the distributions of the fluorophores. Relating the experimental measurements to the calculated distributions allowed us to detect, that the primary dimerization interface of TGR5 utilizes transmembrane helix (TM) 1 and helix 8. This knowledge can be exploited to synthesize bivalent ligands of TGR5 or to alter its dimerization state to influence its function.

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The Role of the Membrane in Neurotransmitter Interactions with Their Receptors

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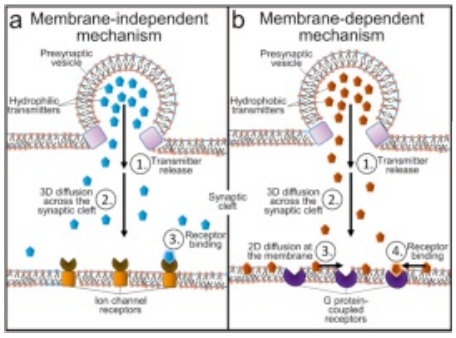
The interactions between neurotransmitters, their receptors, and cell membrane are not fully understood, although there is a growing awareness of the role of the membrane phospholipid composition in several neuropathologies, such as depression, schizophrenia, and Alzheimer's disease. Moreover, differences in the membrane composition are known to affect the functions of the receptors on the membrane and the interactions between neurotransmitters and membrane [1,2].

Traditionally, the neurotransmission is described as a process in which the neurotransmitters are released from presynaptic vesicle and neurotransmitters diffuse over the synaptic cleft towards the postsynaptic membrane. The process ends when the neurotransmitters are binding to their receptors and the postsynaptic neuron is activated. However, there are many macromolecules in the synaptic cleft, which can interact the neurotransmitters water-soluble domains in a non-specific way. These non-specific interactions might cause changes in the binding process.

In our recent study [3], we were able to categorize neurotransmitters in two groups based on the varying degrees of reversible membrane attachment. Membrane-binding neurotransmitters, such as dopamine, adenosine, and epinephrine, are binding to G-protein coupled receptors that have their binding pocket close to lipid bilayer. On the other hand, the membrane-nonbinding neurotransmitters, such as acetylcholine, glutamate, and glycine, are targeting ligand-gated ion channels whose binding pockets are located far from the membrane surface. After these observations, we postulated that there is a membrane-mediated mechanism for neurotransmission entry. In this mechanism, certain neurotransmitters first bind to the membrane and then laterally diffuse to the receptor's binding site.

To this end, we used atomistic molecular dynamic simulations, free energy calculations, and accelerated molecular dynamics simulations to confirm the most probable pathway of dopamine and adenosine entry in their receptors. Our study suggests the entry to take place via the membrane-water interface.



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Learning from natural molecular machines: the artificial chaperonin

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Incorrect folding of proteins in living cells may lead to malfunctioning of the cell machinery. To prevent such cellular disasters from happening, all cells contain molecular chaperones that assist nonnative proteins in folding into correct native structure. One of the most studied chaperone complexes is the GroEL-GroES. The GroEL part has a "double-barrel" structure, which consists of two cylindrical chamber joined at the bottom in a symmetrical fashion. The hydrophobic rim of one of the GroEL chambers captures nonnative proteins. The GroES part acts as a lid that temporarily closes the filled chamber during the folding process. Several capture-folding-release cycles are required before the nonnative protein reaches its native state. Here we report molecular simulations that suggest that translocation of the nonnative protein through the equatorial plane of the complex boosts the efficiency of the chaperonin action. If the target protein is correctly folded after translocation, it is released. However, if it is still nonnative, it is likely to remain trapped in the second chamber, which then closes to start a reverse translocation process. This shuttling model provides a natural explanation for the prevalence for double-barreled chaperonins. Moreover, we argue that internal folding is both more efficient and safer than a scenario where partially refolded proteins escape from the complex before being recaptured. Based on these results we propose a design for a device to help single protein refold and cluster break down.

Enzyme Evolution and Design with Hamiltonian Replica Exchange Molecular Dynamics

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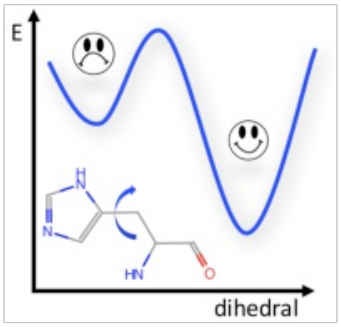
Molecular dynamics (MD) simulations are a powerful tool for computational enzymology.[1] However, classical MD is typically unable to cross high energy barriers and explore the complete conformational space at the commonly used nanosecond time scales.[2] Therefore, various enhanced sampling methods have been developed. Hamiltonian replica exchange (HREX) MD is a potent sampling method where *n* replicas of a system are simulated, with varying Hamiltonians, and are allowed to exchange the coordinates from time to time.[3] We studied how protein flexibility affects the catalytic activity over the directed laboratory evolution of glucose oxidase. The active site histidine can adopt two conformations: a catalytic and a non-catalytic one. While classical MD simulations were able to sample both, only one transition between the two conformations would typically happen during 100 ns simulation. This made it impossible to determine the relative populations of the two. On the other hand, even short HREX-MD runs were able to reproduce the experimental kinetic data for the glucose oxidase mutants. In another application, we used HREX-MD simulations to study the binding of a macrocycle to cytochrome P450. The substrate docking was not conclusive as many different binding poses were evaluated with similar scores. Due to the size and chemistry of the substrate, classical MD would not be an efficient method to explore ligand binding in this case. Therefore, we biased the substrate's Hamiltonian in the HREX simulations and, based on the identified low-energy binding modes, we performed enzyme design to manipulate the chemo-, regio-, and stereoselectivity of this enzyme.



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Conformational Dynamics of Glycoproteins

Eric Schulze, Matthias Stein

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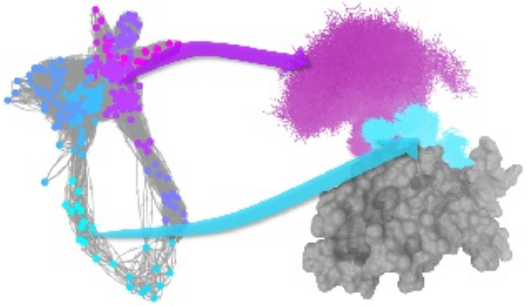

Site, number, type and the degree of branching of N-linked glycosylations modify biophysical attributes of glycoproteins in a hardly predictable manner. Structural studies can provide insight on fundamental protein-glycan interactions, but pose a challenge to crystallography due to the glycan's tremendous conformational flexibility. Molecular simulation techniques have proven their ability to accurately reproduce both free energy landscapes of glycosidic linkage torsion angles and intramolecular hydrogen bonds in a number of oligosaccharides [1].

In this research, we utilize molecular dynamics (MD) simulation to investigate structure and dynamics of various glyco-isoforms of human erythropoietin (EPO). In particular, sialylated, complex-type, biantennary N-glycans at positions ASN^{24}, ASN^{38} and/or ASN^{83} were modeled and simulated in explicit solvation for at least 100 ns each. Glycosidic linkage torsion angles were monitored and used for an initial conformational clustering into hundreds of microstates. Markov modelling involves computation of microstate transition probabilities and a spectral clustering via PCCA+ [2]. Finally, this allows us to reduce the conformational variance into a comprehensible number of distinct, kinetically relevant macrostates (see figure).

Extensive knowledge about conformational states allows us the identification of concealed patterns in noisy MD data and reduces the computational expense of calculating free energies, electrostatic potentials, hydrodynamic properties or protein-protein association rates. Additionally, Markov modelling serves as an enhanced sampling method in a way that kinetically unfavorable states are appropriate initial configurations for subsequent MD simulations to sample otherwise barely accessible states.

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Towards a standardized characterization of solution phase protein structure using Raman optical activity

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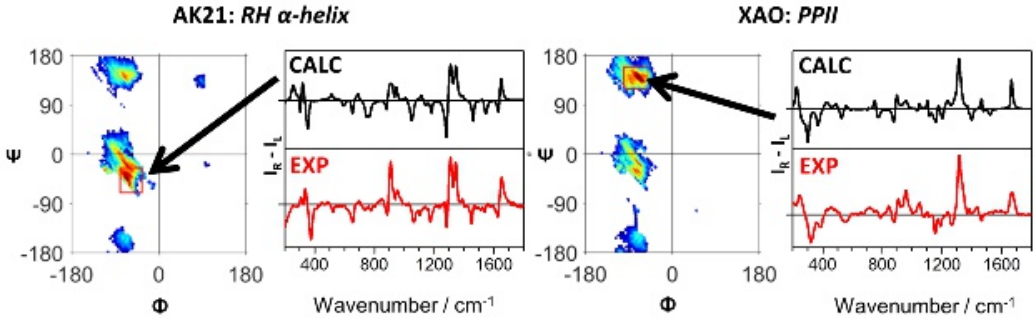
Over the past 20 years, Raman optical activity (ROA) has shown much promise as a strong technique to elucidate the structure and dynamics of proteins in solution. ROA is measured as the small difference in the right and left circularly polarised components in the Raman scattered light by chiral molecules. This technique is uniquely sensitive to local conformational propensities of peptides and proteins. While the ROA spectrum of a protein gives rich information on the secondary structure of a protein, the biggest and most urgent challenge is to understand the relation between the ROA patterns and the protein structure in detail. Because of important advances in computational chemistry and computer power, it is now possible to use quantum chemical calculations to simulate ROA spectra of peptides.

Here, we present the first large scale study on the relation between the ROA patterns and protein conformation.[1] By creating a large library of peptide models with systematically varying conformations and calculating the ROA signatures quantum mechanically, we are developing an approach to characterise the solution structure of peptides and proteins with unprecedented detail. By using similarity indices, experimental Raman and ROA spectra can be compared to the simulated spectra in the database, which allows an objective and detailed assignment of the experimental spectra.



Using this approach, the experimental spectra of different peptides with diverse but known conformational preferences were studied. The newly developed database correctly assigns the solution structure of these peptides. Furthermore, the results demonstrate the strong conformational sensitivity of ROA, as very slight changes in protein structure result in specific changes in the ROA patterns. The database characterises these differences in the spectra to structural differences.

While structural biology relies on the powerful techniques of NMR and crystallography, complementary methods are necessary to provide additional information on protein structure and dynamics where the former techniques fall short. ROA has a unique structural sensitivity to protein structure and the database developed in this work is a strong tool to assign preferential conformations and changes of proteins based on the ROA spectrum.

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Towards Engineering Radical Enzymes - Thermodynamic Reaction Profiling and Mechanistic Insights into QueE

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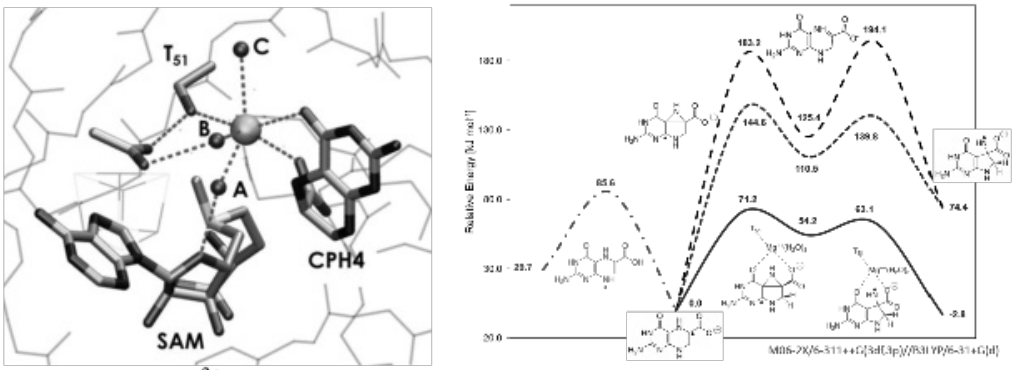
Radical S-adenosylmethionine (SAM) dependent enzymes[1] are a class of enzymes dealing with radical intermediates during catalysis. The enzymes harness these intermediates, which are hard control in classical synthesis, in a very controlled way for a wide range of challenging chemical processes leading to products of potential use in anti-viral, anti-cancer and antibiotic treatments. This makes them particularly attractive for enzyme engineering with its key goal to design enzymes for industrial biotechnological applications with improved or new properties which extend the chemistry of natural enzymes.

A thorough knowledge of the reaction mechanisms involved in the biocatalysis of these enzymes can lay the foundation for rational enzyme engineering. On the other hand this also shows one of the bottlenecks for a more rapid access to rational enzyme design. At best, all factors influencing the enzyme kinetics from substrate binding, the catalytic mechanism to effects by flexible protein dynamics are known in detail. Still, individual steps of the catalysis can be addressed by quicker methods, in order to get a first qualitative picture of how these steps can be influenced and manipulated which can feed into the enzyme design process.

Radical stabilization energies (RSEs)[2] for example, offer an attractive possibility to assess the overall thermodynamics of radical rearrangements as central steps in radical SAM enzyme catalysis. Through the example of the recently structurally resolved bacterial 7-carboxy-7-deazaguanine (CDG) synthase (QueE),[3] we will highlight key features and details of the biocatalytic reaction mechanism involved[4] and will investigate the potential of using radical stabilisation energies for of a rapid reaction profiling directly out of molecular-dynamics simulations of the enzyme substrate complex. Further, we will provide insights into other challenges of radical SAM enzymes addressed in the context of enzyme engineering.



Substrate and Mg^{2+} binding in the crystal structure of QueE (left) and reaction profile for radical rearrangement for model system (right).

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Description of Difficult Singlet/Triplet Splitting Problems with Coupled Cluster Theory

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Coupled-cluster (CC) theory is widely accepted as the most accurate and generally applicable approach in quantum chemistry. CC calculations are usually performed with single Slater-determinant references, e.g. canonical Hartree-Fock (HF) wavefunctions. On one hand, this is an attractive feature because typical CC calculations are simple to set up and there is no ambiguous user input required. On the other hand, there is some concern that CC results may be unreliable if the reference determinant provides a poor description of the system of interest. In this context, the prime suspects are systems that display static correlation effects, i.e. where the HF ground state has a relatively low weight in the full CI expansion. However, in many cases the reported "failures" of CC can be attributed to an unfortunate choice of reference determinant, rather than intrinsic shortcomings of CC itself. This is mainly connected to well known effects like spin-contamination, wavefunction instability and symmetry-breaking.

In this talk, a particularly difficult singlet/triplet splitting problem in two phenyldinitrene molecules is investigated, where single-reference CCSD(T) calculations were reported to give poor results. The reason for this is analyzed by using different reference determinants (e.g. restricted open-shell, RO, and symmetry-broken UHF) for CCSD(T), as well as performing higher level CCSDT calculations. We find that CCSD(T) does give qualitatively correct results for this problem, if the proper reference state is obtained. Quantitative accuracy can be obtained by using symmetry-broken reference determinants, at the expense of large spin-contamination.

Alternatively, doubly-electron attached equation-of-motion (DEA-EOM) approaches are a powerful tool for handling such systems. They are operationally single-determinant methods (i.e. simple to set up), while adequately taking the multi-reference nature of these molecules into account. Both the DEA-EOM and the similarity transformed DEA-STEOM-CCSD methods are found to be highly accurate. Our results indicate that CC is a powerful tool for describing systems with both static and dynamic correlation, although there are some pitfalls, mainly associated with the choice of the reference determinant.

Water Gas-Shift Reaction Catalysis by Ruthenium Based Complexes

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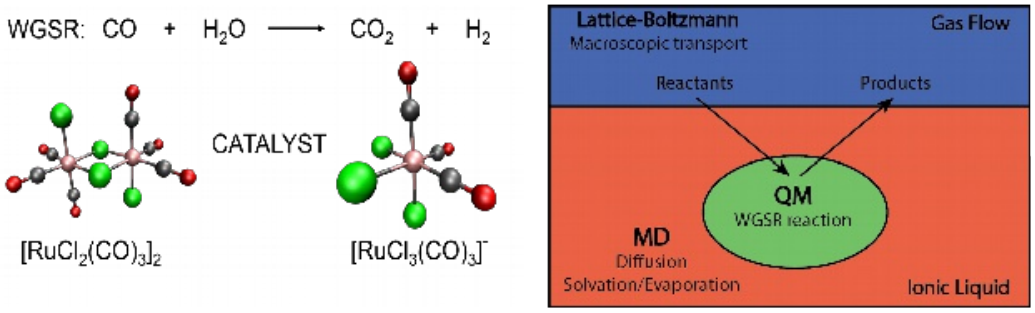

The Water Gas-Shift reaction (WGSR) is a process which results in the conversion of carbon monoxide and water into hydrogen and carbon dioxide, usually in presence of a catalytic material. The abundance of water, the toxicity of carbon monoxide and the importance of hydrogen as potential fuel of the future are some of the arguments that incite the interest of the industrial and scientific communities in this particular reaction [1].

In this study we take a closer look into the WGSR catalyzed by a Ruthenium based catalyst ($[RuCl_2(CO)_3]$) known for its high efficiency in the supported ionic liquid phase (SILP) [2, 3]. We tackle the problem of the unresolved mechanism for this specific catalyst and discuss monomer-dimer equilibrium and potential active species. To achieve this we use a plethora of well established quantum-chemical techniques ranging from optimizations and vibrational analysis to one-dimensional "coordinate driving" and multi-dimensional nudged elastic band searches. The theoretical framework for all of the calculations is density functional theory using the gradient corrected BP86 functional, which has proven to be successful for this class of transition metal complexes [4].

The final goal of this study is to identify the most likely mechanism involving this catalyst and to gain access to reaction rates which can then be refined using various approaches to account for the effect of the solvent. These rates, alongside the diffusion coefficients obtained in molecular dynamics simulations, can then be used in modeling macroscopic transport of the reactants and products. This would allow for prediction and optimization of input and output of modern SILP reactors.

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Molecular modelling and time resolved spectroscopy of electron transfer events in mid-sized molecular donor-acceptor-systems

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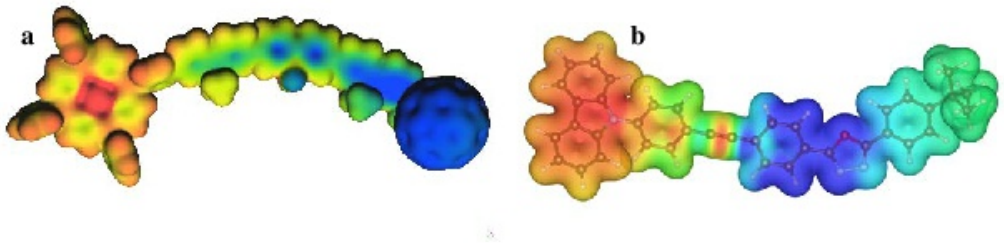
As electron transfer is one of the key steps in various fields, such as molecular electronics or solar energy conversion, a detailed understanding of electron-transfer mechanisms is one of the main aims in modern chemistry. Especially detailed structure-property-relations are barely understood yet, leading to many trial and error attempts in this field instead of distinct designs towards the desired properties. Therefore, one research field in our groups deals with the most simplified model system for intramolecular electron transfer – the donor-bridge-acceptor system.

In this talk, I will present two recent projects in which donor and acceptor units were kept unchanged, while the bridge properties were altered. In the first project (**a**) the influence of placing an electron-accepting dibenzothiophene-S,S-dioxide bridge-unit (**S**) at different positions within a fluorene bridge (**Fl**) was studied and compared to previous studies on pure fluorene linked zinc porphyrine-fullerene dyads.[1,2] Interestingly, the inclusion of the **S**-unit allows the mechanism to be tuned for charge separation by allowing either hole- or electron-transfer. This charge-gating behavior leads to unidirectional electron transfer, enabling the charge separation to be switched on and off by controlling the excitation wavelength.



In the second project (**b**) the simplest bridge geometry, a linear carbon polyyne-chain was altered by increasing the length from one to four bridge units, terminated by carbazole-donor and oxadiazole-acceptor moieties. Normally, increasing the distance between donor and acceptor leads to longer and therefore less efficient charge separation and recombination kinetics. In our model system, however, this trend is inverted, leading to faster charge separation and recombination kinetics for the longest dyad. Since this surprising finding, TD-DFT studies were performed to model the electronic properties of the excited states involved in order to elucidate the thermodynamic driving forces and reorganization energies.

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Raman optical activity for drug discovery: Structural characterization of artemisinin derivatives in solution

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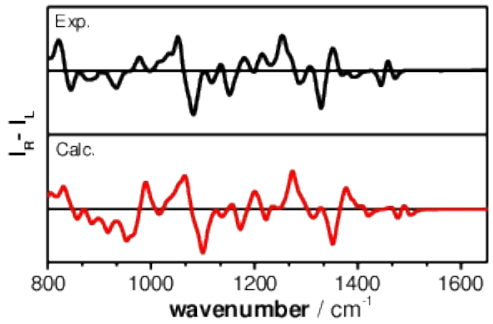
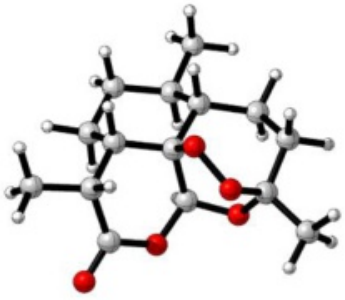
The natural compound artemisinin, which is currently employed in malaria treatment, is showing great potential as a candidate for such next generation cancer treatment.[1] One of the biggest challenges in drugs discovery research is the stereochemical characterization and the identification of conformational preferences in solution to have a better understanding of the molecular mechanism and the structure-activity relationship. Considering the limitations and side effects caused by conventional cancer treatments, new techniques for the structural characterization of drugs are strongly required, in order to obtain an accurate, site directed therapy.

The application of Raman opical acivity (ROA) to the structural characterization of natural products has increased significantly in the past years. [2, 3] ROA is based on inelastic (Raman) scattering of circular polarised light. When the experiment is combined with DFT calculations, ROA provides an unparalleled sensitivity towards solution phase conformation and stereochemistry of chiral molecules. Furthermore, ROA has emerged as a very strong tool in the structural analysis of proteins [4] making this method an ideal candidate for studying the structure of natural and synthetic lead compounds with potential pharmacological activity.





In this contribution, the performance of ROA applied on artemisinin, dihydroartemisinin and artesunate combined with quantum chemical calculations will be discussed. Furthermore, the effect of changing one stereocenter in the compound on the computed spectrum will be highlighted.

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AutoTS: An automated transition state search tool

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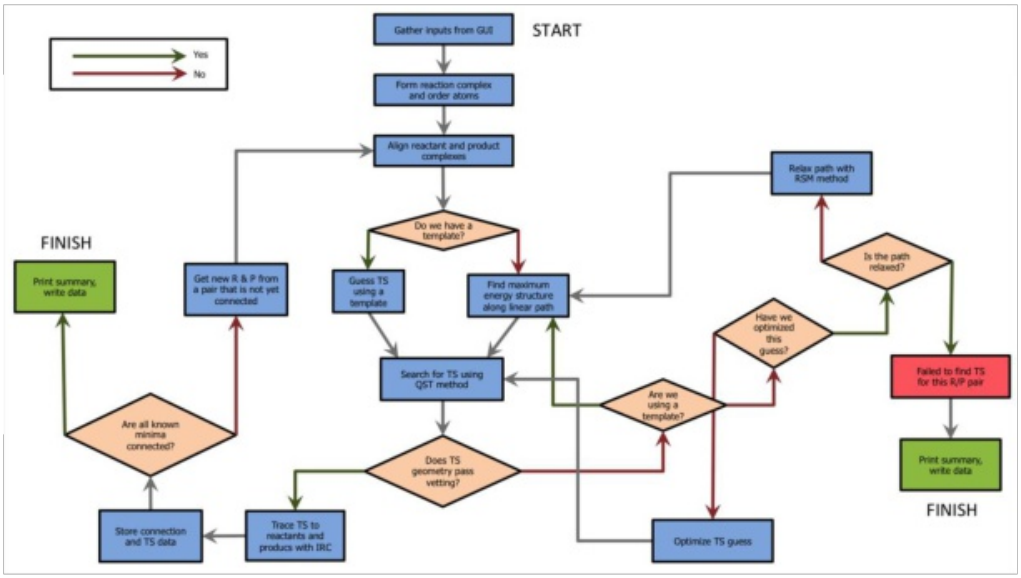
Transition state search is at the center of multiple types of computational chemical predictions related to mechanistic investigations, reactivity and regioselectivity predictions, and catalyst design. The process of finding transition states in practice is however a laborious multistep operation that requires significant user involvement.

We present a highly automated workflow designed to locate transition states for a given elementary reaction with a minimal setup overhead: The only essential inputs required from the user are the structures of the separated reactants and the products.

The workflow combines computational technologies from the fields of cheminformatics, molecular mechanics, and quantum chemistry. It automatically finds the most probable correspondence between the atoms in the reactants and the products, generates a transition state guess and launches the transition state search through a combined approach involving the relaxing string method and the quadratic synchronous transit. [1] Finally, it validates the transition state via the analysis of the reactive chemical bonds and imaginary vibrational frequencies as well as by the intrinsic reaction coordinate method. [2]

The approach is meant to be of general applicability for a wide variety of reaction types. It is highly flexible, permitting modifications such as a choice of accuracy, level of theory, basis set, or solvation treatment. Successfully located transition states can be used as templates for setting up transition state guesses in related reactions, saving computational time and increasing the probability of success.

The utility and performance of the method are demonstrated in applications to transition state searches in reactions typical for organic chemistry and medicinal chemistry.



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A Diverse Benchmark Data Set for the Validation of Scoring Functions based on 3D Matched Molecular Pairs

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Prediction of protein-ligand interactions and their corresponding binding free energy is a challenging task in structure-based drug design and related applications. Docking and scoring is a broadly used approximation of the latter. To demonstrate the predictive power and to investigate the strength and weaknesses of scoring functions several benchmark test sets have been developed in the past.[1]-[3] These data sets are characterized by high diversity in terms of protein families, ligand chemotypes and binding affinities. High diversity is well suited for the evaluation and comparison of the global performance of docking and scoring software. However, understanding the local behavior of a scoring function, how well it can differentiate between similar molecules is almost impossible with these data sets. Here, a novel benchmark data set based on Matched Molecular Pairs (MMPs) was developed to study the local behavior of scoring functions. MMPs are defined as molecules that differ in one well-defined transformation that is associated with a change in an arbitrary molecular property (transformation effect).[4] The assembled data set of 99 3D-MMP was used to investigate whether or not scoring functions can differentiate between chemically related compounds. Various scoring functions were used to score the data set, most of them are available within the commercially available software MOE 2014.09 [5] and GOLD Suite 5.2.2 [6]. The 3D-MMPs were scored in the respective crystal structures without any posing (i.e. the position of the small molecule was not changed) to focus on scoring and to exclude the influence of posing (i.e. the placement algorithm). Only three scoring functions (X-Score, Affinity dG and GoldScore) reached a prediction rate of more than 60% in the prediction of the trend of a transformation effect. Analyzing the relationship between molecular size and affinity led to the following results. In 51 3D-MMPs, the larger molecule was also the more active one. In only 20 3D-MMPs the smaller molecule was more active (the remaining molecules show no difference in bioactivity (n = 5) or the same number of heavy atoms (n = 23)). Hence, in 71.8% (51 out of 71) the larger molecule was also more active. This means that in this study the molecule's size would be the best scoring function.

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Conformational Sampling of Macrocycles: Recent Progress

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Macrocyclic molecules have been shown to be orally bioavailable ligands for targets such as GPCRs and protein-protein interfaces. Greater exploitation of macrocycles in drug discovery has been stymied by a lack of computational methods to investigate their properties, including their conformational space. Here we present extensive validation of a rapid, atom-based method for macrocycle conformational sampling, using datasets drawn from the CSD and the PDB. We compare the performance of the method to other approaches to the same problem to identify avenues for future improvement.

QSTR analysis and combining DFT of the toxicity of heterogeneous phenols

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Abstract
Quantitative structure–toxicity relationship (QSTR) models are useful to understand how chemical structure relates to the toxicity of natural and synthetic chemicals. The chemical structures of 70 heterogeneous phenols have been characterized by electronic and physic-chemical descriptors. Density functional theory (DFT) with Beck's three parameter hybrid functional using the LYP correlation functional (B3LYP/6-31G(d)) calculations have been carried out in order to get insights into the structure chemical and property information for the study compounds. The present study was performed using principal component analysis (PCA) method, multiple linear regression method (MLR), multiple non-linear regression (MNLR) and artificial neural network (ANN). The quantitative model of the toxicity of these compounds was accordingly proposed and interpreted based on the multivariate statistical analysis.
The statistical quality of the MLR and MNLR models was found to be efficient for the predicting of the toxicity, but when compared to the obtained results by ANN model, we realized that the predictions achieved by this latter one were more effective. This model provided statistically significant results and showed good internal stability and powerful predictability. The squared correlation coefficients were 0.801, 0.802 and 0.824 for MLR, MNLR and ANN models respectively. The obtained results suggested that the proposed descriptors could be useful to predict the toxicity of heterogeneous phenols to *Tetrahymena pyriformis*.

Keywords: QSTR model, DFT study, heterogeneous phenols, *Tetrahymena pyriformis*.

Systems Approaches to Drug Safety

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The recent explosion of data linking drugs, proteins, and pathways with safety events has promoted the development of integrative systems approaches to large-scale predictive drug safety. The added value of such approaches is that, beyond the traditional identification of potentially labile chemical fragments for selected toxicity endpoints, they have the potential to provide mechanistic insights for a much larger and diverse number of safety events in a statistically-sound non-supervised manner, based on the similarity to drug classes, the interaction with secondary targets and the interference with biological pathways. The combined identification of chemical and biological hazards enhances our ability to assess the safety risk of bioactive small molecules with higher confidence than using structural alerts only. We are still a very long way from reliably predicting drug safety but advances towards gaining a better understanding of the mechanisms leading to adverse outcomes represent a step forward in this direction.

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Structural Basis for the Recognition of the Proline Rich Sequences by FBP-21 tandem-WW domains

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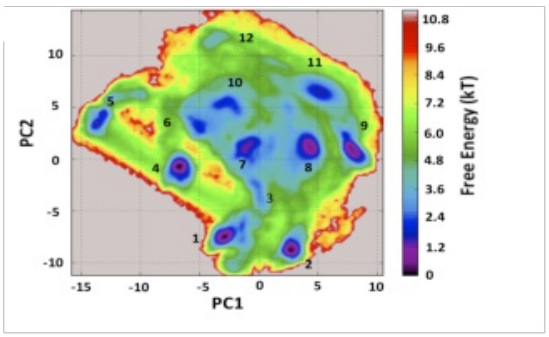

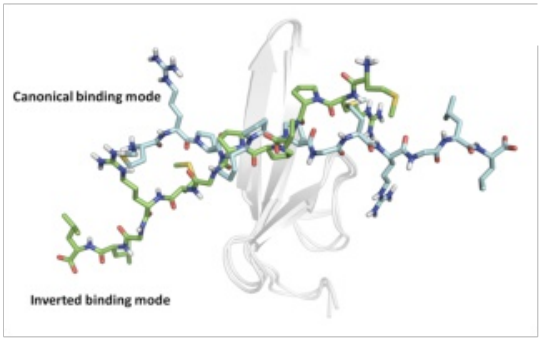

Formin-binding protein 21 (FBP-21) is a spliceosomal protein, which recognizes the proline-rich sequences (PRS) abundant in various splicing factors. The recruitment of PRS by tandem-WW domains (t-WW) of the FBP-21 is characterized by the low affinity, which in turn can be enhanced by the multivalent binding. Still the binding of the multivalent PRS to the t-WW is poorly understood. [1] In this study, we aim to elucidate the structural determinants of a such multivalent recognition by combining the nuclear magnetic resonance (NMR), isothermal titration calorimetry (ITC), molecular dynamics (MD) simulations, and protein-peptide docking.

NMR, and ITC measurements revealed that the monovalent PRS bind with higher affinity to a singular WW_1 construct compared to the t-WW domains. This finding raised a question, if there is a structure in the conformational ensemble of the apo t-WW domains, which favors binding to the WW_1 domain. We performed PCA analysis on the MD simulations of the apo t-WW domains, and showed that there is a structural preference for the higher WW_1 domain affinity. There are 12 long-lived structures in the conformational space of the apo t-WW domains, determined by the cluster-specific hydrogen bond network. Only in a single cluster, residues of the WW_1 domain binding groove are involved in the inter-domain interface formation. On contrary, in five clusters, the interface formation hinders the WW_2 domain binding groove residues from binding. Other six clusters are free to bind PRS in both binding grooves. However, further structural rearrangement is necessary, so that the relative orientation of the respective binding grooves is proper for the multivalent recognition.

As it was earlier confirmed by the spin labelling experiments [1], PRS can be docked to the t-WW domains in a canonical, or in an inverted binding mode. We ran the protein-peptide docking calculations, and found the same binding behavior. Both binding complexes were stable during the 20 ns MD runs, and serve as a basis for the modeling of the multivalent recognition by t-WW domains.

In conclusion, current efforts in our groups are towards proving a hypothesis, that multivalent recognition of the PRS by t-WW domains is governed by an allosteric mechanism. This mechanism comprises the initial recognition of the multivalent PRS by the WW_1 domain, triggering the structural rearrangement of the flexible linker, and bringing the WW_2 domain in the proper orientation to bind the second valance of the respective multivalent PRS.

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Computational Study of the antioxidant activity of 4-(5-chloro-2-hydroxy-phenylamino)-4-oxobut-2-enoic acid analogs using quantum-chemistry descriptors and molecular docking

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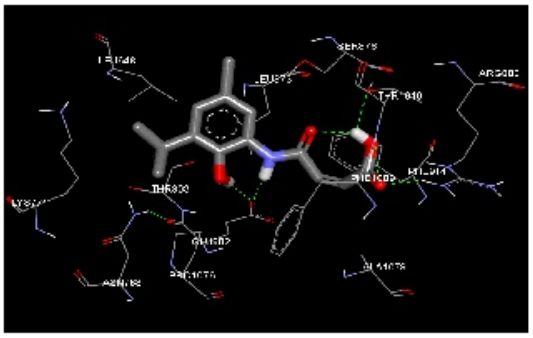
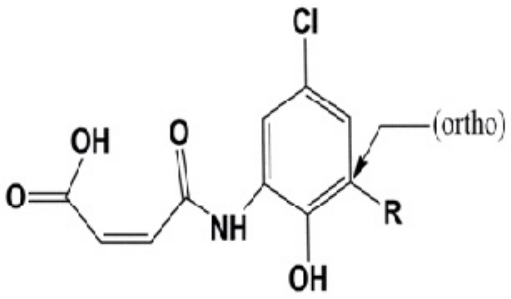
Antioxidants are chemicals that offer up their own electrons to free radicals and thus prevent cellular damage. In recent years, many efforts have been devoted to find new high order antioxidants for their potential applications to scavenge free radicals. Several strategies being executed and the most effective strategy appears to continually modify the existing classes of antioxidant agents to provide new analogues.





Recently [1], a novel compound, 4-(5-chloro-2- hydroxyphenylamino)-4-oxobut-2-enoic acid (compound A) was synthesized and screened for various biological activities like antitumor and antioxidant activities. Our first aim in the present work is to give a deeper insight about the high antioxidant activity of compound A and to suggest other derivatives which may have more antioxidant power than compound A and ascorbic acid. The substituent effect in the ortho position (see Fig.) on the antioxidant power is also analyzed. Our second goal is to study the main scavenging mechanisms (HAT/SPLET/SET-PT) in gas phase and in solvents (EtOH, DMSO, H_2O). For this purpose, we have calculated the more relevant quantum-chemistry antioxidant descriptors, namely, BDE, AIP, PDE, PA, and ETE. Aside from the antioxidant descriptors, we calculated other parameters, namely, the HOMO energy, the chemical hardness (η), the dipole moment and the atomic spin density (ASD). The antioxidant activity of compounds A-E against ROS has also been analyzed using the molecular docking technique. [2]

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DNA-Dye-Conjugates for Detecting Nucleic Acids in Live Cells

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Extensive molecular-dynamics (MD) simulations have been used to investigate DNA-dye and DNA-photosensitizer conjugates, which act as reactants in templated reactions leading to the generation of fluorescent products in the presence of specific desoxyribonucleic acid sequences (targets). Such reactions are potentially suitable for detecting target nucleic acids in live cells by fluorescence microscopy or flow cytometry. The simulations show how the attached dyes/photosensitizers influence DNA structure and reveal the relative orientations of the chromophores with respect to each other. Our results will help to optimize the reactants for the templated reactions, especially length and structure of the spacers used to link reporter dyes or photosensitizers to the oligonucleotides responsible for target recognition. Furthermore, we demonstrate that the structural ensembles obtained from the simulations can be used to calculate steady-state UV-vis absorption and emission spectra. We also show how important quantities describing the quenching of the reporter dye *via* fluorescence resonance energy transfer (FRET) can be calculated from the simulation data, and we compare these for different relative chromophore geometries.

F. R. Beierlein, M. Paradas Palomo, D. I. Sharapa, O. Zozulia, A. Mokhir, T. Clark, *PLoS ONE* **2016**, *11*, e0160229.

$P(TMG)_3$: Elusive or Synthetically Accessible Phosphane

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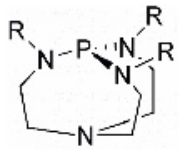

Figure 1. Verkade's base

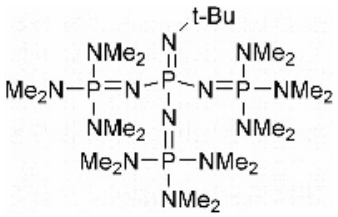

Figure 2. *t*-Bu-P4 phosphazene

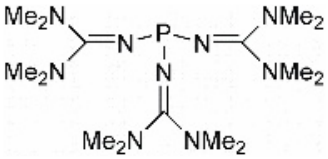

Figure 3. $P(TMG)_3$

Phosphanes are commonly used as ligands to form transition metal complexes whose importance is prominent in organic catalysis. Due to predominantly low basicity of known phosphanes they are rarely utilized as a Brønsted bases in base-catalysed reactions. Notable exceptions are proazaphosphatranes also known as Verkade's bases (Fig. 1.). Verkade's bases have been successfully applied in a variety of organic reactions where deprotonation of reactant is the initial step of chemical reaction.[1,2] Nevertheless, Verkade's bases with pKa = 33 in acetonitrile are substantially weaker than the strongest organic (Schwesinger) base *t*-Bu-P4 phosphazene with $pK_a = \sim 43$ (Fig. 2.).[1,2] Meanwhile, it was computationally demonstrated that substitution of PH_3 with strong electron donating substituents like dimethylamino (NMe_2) or tetramethylguanidino (TMG) groups significantly increases the basicity of resulting phosphanes, opening the door for strong phosphane Brønsted base design. Further, it appears that tris-(tetramethylguanidinyl) phosphane, $P(TMG)_3$ (Fig. 3.), could be much stronger base than proazaphosphatranes.[3] However, despite numerous synthetic attempts, the neutral $P(TMG)_3$ has never been prepared. Only protonated form $P(TMG)_3H^+$ was isolated as a stable salt. Deprotonation attempts resulted in either compounds decomposition or no reaction at all.[4] Using reliable DFT methods, we have investigated basicity, thermodynamics and kinetics of decomposition of $P(TMG)_3$ phosphane to guide synthetic chemists in future attempts of $P(TMG)_3$ preparation.

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Modeling and characterization of selective ligands for β-adrenoceptors

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G-protein coupled receptors covering one fourth of human genome is subjected to extensive interest of pharmaceutical industry. 30 to 40 percent of marketed drugs is targeted to GPCR family. [1] Yet, intrinsic flexibility of transmembrane proteins in signaling cascade makes GPCR proteins an area that needs more detail. β-adrenoceptors as a sub-class of GPCRs, is expressed in smooth muscle in lungs, heart and kidney.[2] Conformational flexibility of β-adrenoceptors and shared common motifs in signal transduction leads to adverse effects by activation/stabilization of non-targeted β-adrenoceptors. Thus, understanding of agonist/antagonist binding mechanism triggering functional activity is the utmost important topic in the area. Pursuant to the topic, in this study we have parametrized a human β2-adrenoceptor (hβ2-Ar) antagonist given as the Compound 4 of Reference [3]. The selectivity of this antagonist for hβ2-Ar compared to hβ1-Ar and hβ3-Ar is experimentally reported [3] which we have compared with our docking and steered molecular dynamics simulation results. [4]

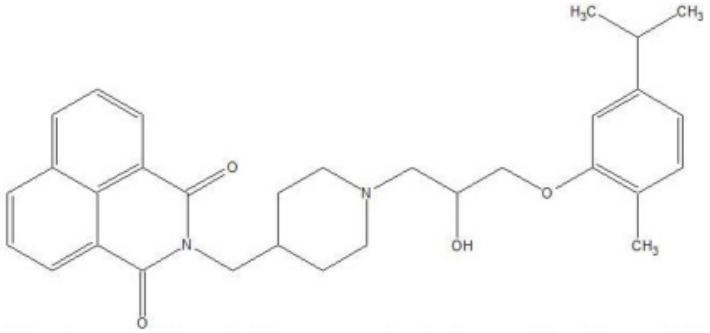

Figure 1. (*3-[(1-{2-hydroxy-3-[5-methyl-2-(propan-2-yl)phenoxy]butyl}pyrrolidin-3-yl)methyl]-3-azatricyclo[7.3.1.0^{5},^{13}]trideca-1(13),5,7,9,11-pentaene-2,4-dione*)

In order to predict the physiochemical properties of selective ligands for the β proteins, we performed a high affinity compound search of FDA Approved ZINC database for β-adrenoceptors through pharmacophore-based high-throughput virtual screening and docking, consisting of 3355 molecules using Molegro [5]. Docking results were complemented with steered molecular dynamics simulations. Compounds that are high affinity binders for hβ2-Ar, hβ1-Ar and hβ3-Ar are classified according to their ligand binding pocket interactions and compared with the experimentally known β2-selective compound.

Compound is formed in Chimera and initial minimization of generated file performed in Scrodinger Package. Initial mol2 and force field files is produced in Ante-chamber module with AM1-BCC charge model. Further parametrization of compound performed in Red [6]. Red program generates parameter files using RESP/ESP charges and Gaussian, Firefly and Gamess orientation algorithms. Gaussian orientation algorithm and RESP charge derivation is used in charge fitting. Atom charge values are fitted to reproduce the MEP (Molecular Electrostatic Potential) in a two stage fit. ESP charge derivation used in fitting to the reproduce the MEP to enable usage of acquired mol2 files in CHARMM, OPLS and AMBER force field simulations.

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Computational studies on NBDHEX as *Giardia duodenalis* thioredoxin reductase (*g*TrxR) inhibitor

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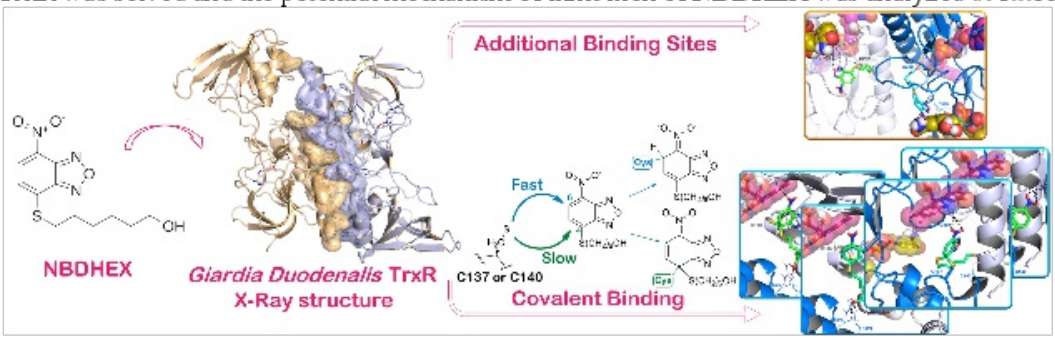
Giardia duodenalis is a microaerophilic parasite that colonizes the upper fractions of the humans' intestine. *Giardia* infection is a major responsible to diarrheal disease worldwide. [1] Nitroheterocycles (e.g. metronidazole) or benzimidazoles (e.g. albendazole) are the most commonly used therapeutic agents. Unfortunately, low compliance or resistance phenomena reduce their efficacy. We discovered that the antitumoral drug 6-(7-nitro-2,1,3-benzoxadiazol-4-ylthio)hexanol (NBDHEX) is active against *G. duodenalis* trophozoites. Administration of NBDHEX to parasite cells and *in vitro* led to the formation of covalent adducts with catalytic cysteines (C137 and C140) of thioredoxin reductase (*g*TrxR), a key component of *Giardia* redox system. Moreover, NBDHEX is modified by *g*TrxR *in vitro,* by nitroreduction. *g*TrxR provides to the parasite efficient defenses against reactive oxygen species (ROS) and it is a target of 5-nitroimidazole drugs contributing to their metabolism. However, the exact mechanism involved in the *g*TrxR inhibition mediated by these compounds is yet to be defined. The definition of the structural determinants of activity against gTrxR could be important for the identification of novel drugs endowed with an innovative mode of action. With this aim, the crystal structure of *g*TrxR was solved and the potential mechanism of inhibition of NBDHEX was analyzed *in silico*.



The crystallographic structures were employed in a comprehensive *in silico* analysis to gain insight into the mechanism governing the inhibitory activity of NBDHEX. Covalent docking was performed in Maestro suite 2015 adopting the Covalent Docking protocol (CovDock). [2] The binding mode of covalently bound NBDHEX was analyzed and the reaction SMARTS pattern was customized to obtain a reliable reaction for NBDHEX. Moreover, by means of Sitemap (SiteMap, version 3.4, Schrödinger, LLC, Release 2015), we identified an accessory binding site, supported by previous biochemical studies. Except for metronidazole, none of the drugs currently used against *Giardia* has *g*TrxR as the primary target. In this scenario, NBDHEX is an extremely interesting compound, being activated by *g*TrxR and, at the same time, inhibiting the enzyme itself. Our study paves the way for the rational design of optimized ligands with improved efficacy against *Giardia* infection and sharing the same mechanism of NBDHEX.

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Target fishing docking studies of novel aryldiketo acids with promising antibacterial activity toward MDR strains

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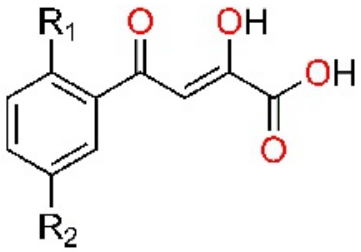
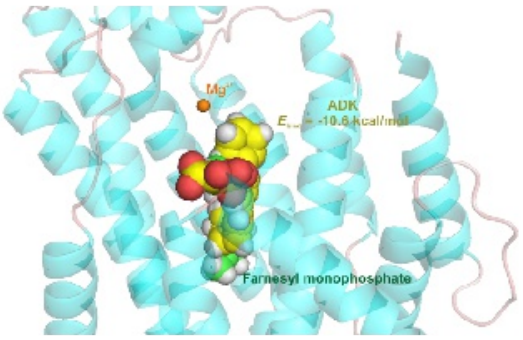
Antimicrobial resistance (AMR) is a major health problem worldwide, because of ability of bacteria, fungi and viruses to evade known therapeutic agents used in treatment of infections. Aryldiketo acids (ADK) exerted antimicrobial activity against several resistant strains of Gram-positive *S. aureus* bacteria. Our previous studies revealed that ADK analogues having bulky alkyl group in ortho position on a phenyl ring have up to ten times better activity than norfloxacin against the same strains [1].

In order to elucidate a mechanism of action for these potentially novel classes of antimicrobials, several bacterial enzymes were identified as possible targets according to literature data and pharmacophoric similarity searches for potent ADK analogues. Among the seven bacterial targets chosen, the strongest favorable binding interactions were observed between most active analogue and *S. aureus* dehydrosqualene synthase (CrtM, PDB entry: 4F6V), in the binding site of natural substrate farnesyl monophosphate.





Protein structures were prepared for docking by adding hydrogen atoms and removing steric clashes using the constrained MD simulation with the protein backbone and metal ions fixed in order to preserve the key features of experimental structures. The 10 ps molecular dynamics simulation at 300 K followed by conjugate gradient minimization was performed using NAMD 2.12 program [2] and CHARMM force field. The .sdf database consisting of 26 ADKs and five structural analogs lacking the diketo moiety was prepared using the best-ranking conformation generated with OMEGA 2.5.1.4. software [3], and further optimized using semiempirical PM7 method implemented in MOPAC 2016 [4]. AutoDock Vina software [5] was used for docking by setting exhaustiveness to 15, and only the most favorable binding mode was calculated for each molecule. Vega ZZ software was used as a GUI for majority of calculations [6].

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Alignment-Based Method for the Prediction of Sites of Metabolism of Xenobiotics

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Biotransformation of small organic molecules can produce metabolites with biological and physicochemical properties that differ substantially from those of the parent compound [1]. For example, an estimated 7% of all metabolites of drugs and drug-like molecules are toxic, while only about 3% of all metabolites maintain the desired target activity [2]. The ability to predict the atom positions in a molecule at which metabolic reactions are initiated (i.e. sites of metabolism) is of utmost importance to drug discovery, as the predictions can be used to guide lead optimization and avoid the formation of reactive products.

In 2008, Sykes et al. [3] published a pilot study in which they derived sites of metabolism (SoMs) based on molecular shape- and chemical feature-based alignment to molecules whose SoMs had been determined by experiment. This study suggested that alignment-based methods could have great potential for SoM prediction. We have therefore analyzed the breadth of applicability of alignment-based SoM prediction in detail. We transferred this approach from a structure-based to a ligand-based method and extended the applicability of the models from cytochrome P450 2C9 to all cytochrome P450 isozymes involved in drug metabolism. This approach results in good early enrichment comparable to that of reactivity models, which are generally considered to be the most accurate models for SoM prediction. However, the predictive capability of the alignment-based approach depends on the degree of molecular similarity to known ligands, yielding better predictions for more structurally similar molecules. As chemical reactivity is an important aspect of SoM determination that is not considered by the alignment-based approach, we additionally combined the alignment-focused method with a chemical reactivity model, leading to a further boost in accuracy.

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Molecular Dynamics Study of the Hapten-Binding Antibody B1-8

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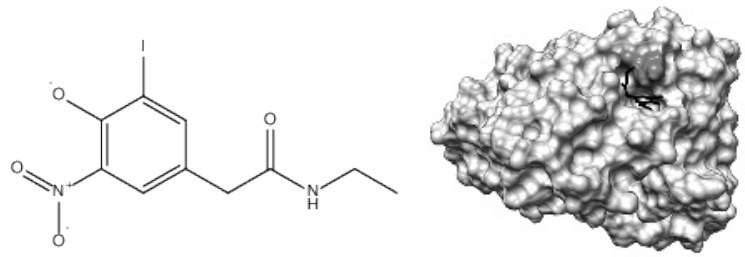

4-(2-(ethylamino)-2-oxoethyl)-2-iodo-6-nitrophenolate

Left: Structure of NIP. Right: B1-8 FV-Fragment (light grey) with NIP (black) and $Y101_H$ highlighted in dark grey.

Antibodies are vital to humoral immunity. With recurring exposures to the same antigen, the affinity of serum antibodies for this specific antigen will increase. This process is referred to as affinity maturation and can yield antibodies in a secondary response that have an affinity several orders of magnitude higher than in the primary response. The hapten-binding antibody B1-8 represents a model system to investigate affinity maturation. The mutation W33L in the heavy chain ($W33_HL$) is especially interesting since it always occurs in the secondary response and increases affinity approximately by one order of magnitude. This study uses MD-simulations of wildtype B1-8 and $W33_HL$ B1-8 in an unliganded state and bound to 4-(2-(ethylamino)-2-oxoethyl)-2-iodo-6-nitrophenolate (NIP) to assess the molecular basis for this increase in affinity. Initial results indicate that the $W33_HL$ mutation alters the dynamics of $Y101_H$, which in turn facilitates the access of ligands to the hapten binding pocket.

High pressure effects on spectroscopic and thermodynamic properties of small biomolecules

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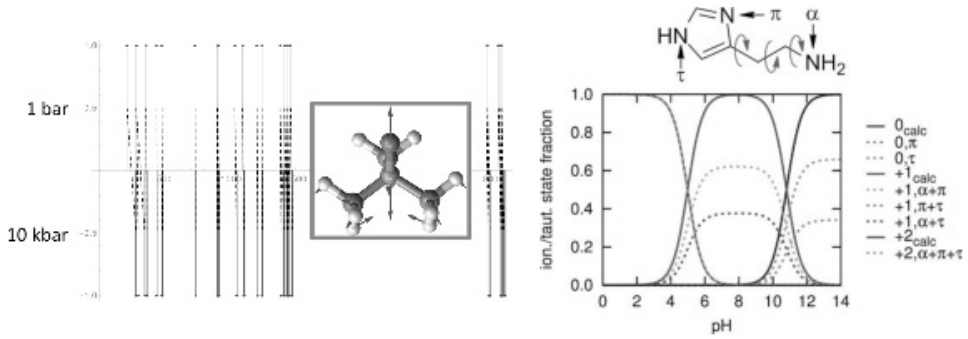
Biochemical processes of a vast number of lifeforms are accommodated to extreme conditions such as deep oceanic water. High pressure has substantial impact on the molecular basis of biological function. This poses a challenge to computational modelling approaches since the applicability of conventional empirical molecular force fields is questionable especially if chemical reactions are involved. As a step toward clarifying the situation, we need to account for high pressure in quantum-chemical (QC) calculations. A suitable methodology is provided by the "embedded cluster reference interaction site model" (EC-RISM) [1-3] that combines statistical-mechanical 3D RISM integral equation theory and QC calculations. In this context the impact of pressure is introduced by using solvent susceptibility functions containing all pressure dependent solvent properties. Besides a suitable technique for modelling the solvation features, we need to couple the method with an adequate sampling approach for molecules with acidic and basic sites or substantial conformational freedom, which can all be functions of applied pressure. Pressure therefore influences the intramolecular free energy surface which is also reflected in vibrational properties.

We investigated several of this processes for model systems such as the protein fold stabilizer trimethylamine-*N*-oxide (TMAO) [4,5] and the important neurotransmitter histamine. We illustrate the methodology in a pressure range of 1 bar up to 10 kbar to demonstrate the relevance of electronic polarization under extreme pressure conditions. The modulation of infrared bands of TMAO can be captured by pressure-dependent EC-RISM calculations [6], indicating the appropriate computational framework. Based on these benchmark data, the methodology is applied to histamine, revealing tremendous high pressure effects on partial molar volumes, populations, and pK_a, resulting in pressure and pH-dependent tautomer equilibria with potential impact on life-sustaining processes under extreme conditions.



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Virtual screening performance and core-hopping potential of common pharmacophore hypotheses derived from Phase's novel pharmacophore feature-based shape alignment

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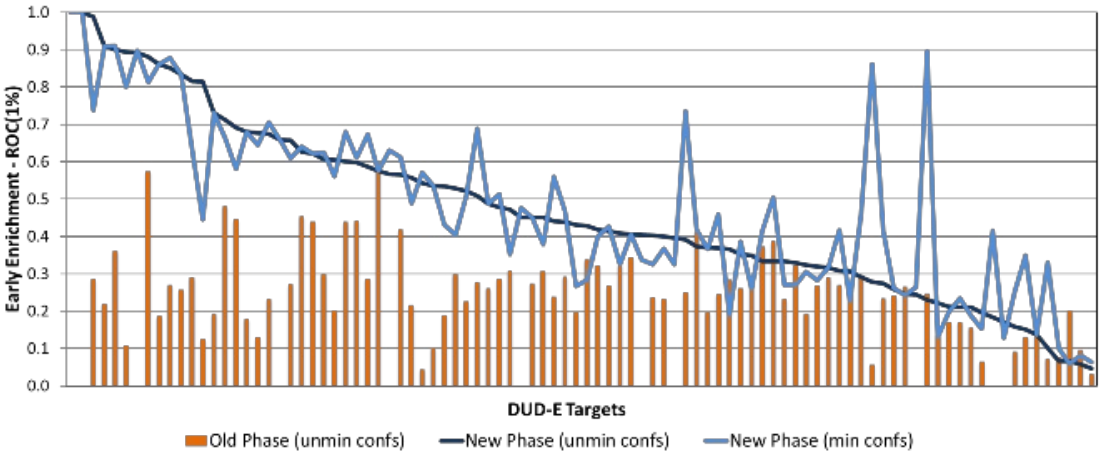
Motivated by very fast shape-alignment algorithms and the continuing need for pharmacophore modeling support in ligand- and structure-based discovery projects, we have developed a novel approach to generating common pharmacophore hypotheses by using feature-based shape alignments. We quantify the performance of this new method with a unique hypothesis-ranking metric in several retrospective virtual screening experiments. Using the DUD-E dataset, we examine the effect that the number and diversity of the active ligands employed in hypothesis creation have on the hypotheses' enrichment and core-hopping potential. We then compare the results to pharmacophore hypotheses that have been derived solely from protein-ligand complexes. Finally, using a dataset of aligned ligands taken from PDB complexes, we quantify the new common pharmacophore method's ability to generate interpretable hypotheses.



Semiempirical calculations of *Thlaspi arvense* Thiocyanate Forming Protein (TFP) product formation

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The crystal structure of *T. arvense* thiocyanate forming protein [1] is a representative of the so called specifier protein family which is involved in the glucosinolate degradation system in plants like mustard, horse radish, or broccoli. These specifier proteins exhibit a six bladed β-propeller structure with a closing blade which is formed by an N-terminal strand and three C-terminal strands. Extended loop structures are located on the bottom region of these proteins and form the active site. Based on the natural substrates allylglucosinolate aglucone and benzylglucosinolate aglucone, TaTFP forms thiocyanate, epithionitrile and nitrile, respectively.

The metal cofactor Fe^{2+} is octahedrally coordinated by amino acids of the highly conserved sequence motif EXXXDXXXH [2] and three water molecules. Protein ligand docking studies and semiempirical calculations of complexation energies indicate a substitution of one coordinating water with the negatively charged sulfur atom of the allylglucosinolate aglucone to form a stable low spin Fe^{2+} complex. Starting with this protein substrate interaction, a thermodynamically favored 3,4-epithiobutane nitrile formation was calculated with MOPAC [3]. An attack of the terminal double bond by the cleaved sulfur atom resulted in this three-membered ring structure. In the case of allylglucosinolate aglucone, the flexibility of TaTFP loop regions enables an additional metal substrate interaction with the terminal double bond of the allyl group. The electron pulling effect of the Fe^{2+} results in the thermodynamically favored formation of a stable allyl cation which subsequently can be attacked by the temporarily formed thiocyanate ion to form allylthiocyanate. Semiempirical calculations suggest that thiocyanate formation is only possible from this alternative substrate orientation.

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A Computational Study on Molecular Structure and Spectral Properties of Halogenated Sumanene

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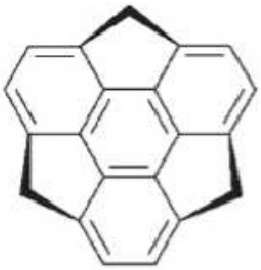
Bowl-shaped π-conjugated compounds have been attracting great interests because of their promising potential for electrical materials [1]. They are a group of key materials in the science of nonplanar π-conjugated carbon systems. Sumanene ($C_{21}H_{12}$) is a C_{3v} symmetric structure of fullerenes and a bowl-shaped π-conjugated aromatic compound with possessing interesting structural and physical properties, and it has been synthesized successfully by Sakurai, Daiko and Hirao [2]. Although there have been many experimental and theoretical studies on sumanene [3], the halogenated sumanenes have not been investigated computationally up to now. The use of DFT methods optimized geometries approximately reproduces the experimental values for the bowl-to-bowl inversion barrier of sumanene and its derivatives [4].



Benchmark studies usually analyze the difference between DFT and experiment statistically. The linear regression is performed by means of a least-squares fit, from which we obtain the slope as well as the scatter with respect to the regression line (SPSS program) to examine the performance of different implementations and functionals for the title compound at first. A computational study was conducted on fluorinated, chlorinated, and brominated sumanenes, which were subjected to the analysis of changes of the molecular electrostatic potential surfaces, spectral properties (Vibrational and NMR spectra) and bowl-to-bowl inversion barrier properties. The bowl shaped geometry and other properties were significantly affected by the substitution of halogens.

All calculations within DFT were performed using Gaussian 09 [5]. DFT calculations were performed by means of the hybrid, non-local exchange and correlation functional of Becke-Lee, Parr and Yang (B3LYP) [6] and [7].

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Water Exchange at the Beta-Barrel "Holes" of Several Far-Red Fluorescent Proteins

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There is a desire to improve several physical characteristics of far-red fluorescent proteins. One hypothesis is that the access of water to the fluorophore has some effect on these characteristics. Simulations of several temperatures as well as two water models have been performed on the Neptune, mCardinal, and mCrimsonT fluorescent proteins. Water exchange appears to be minimal below 320K. There also does not appear to be significant differences between the two water models used.

Benchmarking Commercial Conformer Ensemble Generators

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Recently we published a cheminformatics pipeline that allows the fully automated extraction of high-quality structures of protein-bound ligands from the PDB. [1] The criteria applied for the selection include the fit of the molecular structures to the electron density, the physicochemical and structural properties of the ligands, and many more. With this approach we compiled the Platinum Dataset, which with its 4626 structures is the most comprehensive collection of such structural data available.

In the initial publication, the Platinum Dataset was used for benchmarking seven freely available algorithms for conformer ensemble generation. In continuation of this work, we present an extended performance analysis of algorithms on a further refined version of the Platinum Dataset. The benchmarking study now also includes the most popular commercial algorithms for conformer ensemble generation: ConfGen [2], ConfGenX (Schrödinger), Cxcalc (ChemAxon), iCon (Inte:Ligand), OMEGA (OpenEye) [3] and three algorithms of the Molecular Operating Environment (MOE, Chemical Computing Group) [4].

We found the commercial tools to be much more similar in performance than the free tools and have more reliable success rates overall. Few commercial algorithms performed better than the best performing free tool RDKit. [5] ConfGenX and OMEGA reached nearly the same high accuracy, but OMEGA was faster and achieved a favorable balance of accuracy, ensemble size and runtime. We also analyzed the influence of different force fields on the performance of RDKit and ConfGenX.

The Platinum Dataset is available at http://www.zbh.uni-hamburg.de/platinum_dataset.

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The Influence of Chemical Change on Protein Dynamics: A Case Study with Pyruvate Formate-lyase

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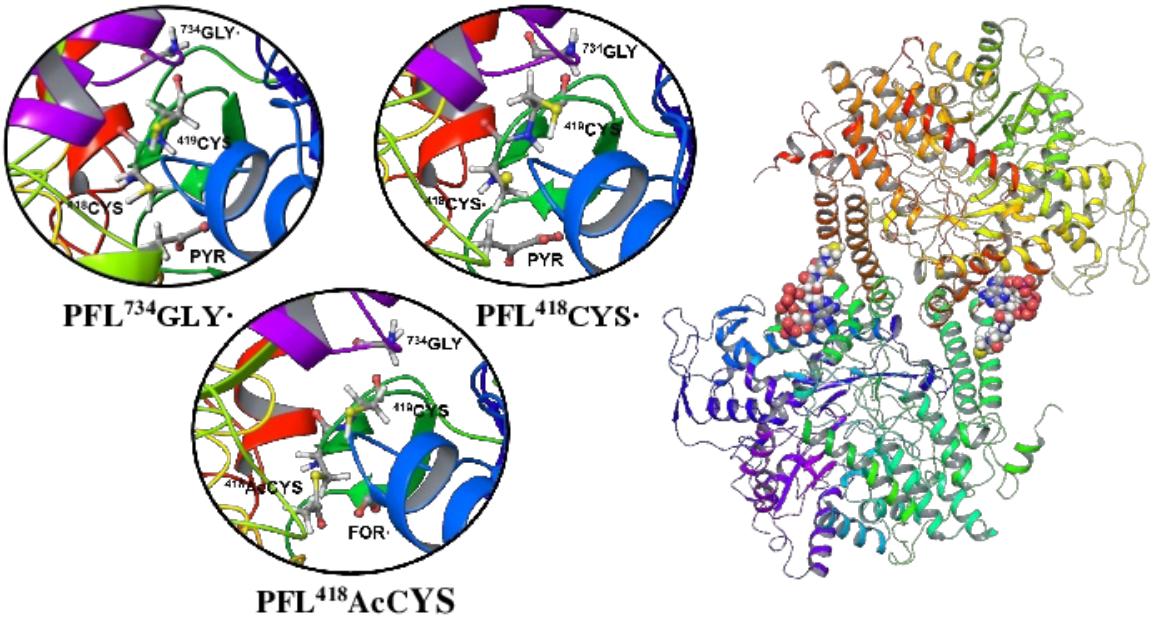

Pyruvate formate-lyase (PFL) catalyzes the break down of pyruvate into formate and the acetyl group upon the addition of a thiyl radical located at Cys418.[1] The radical is initially stored at Gly734 is shuttled to Cys418 via Cys419. The addition of radical Cys418-S· to pyruvate leads to C-C bond dissociation, resulting with formation of formyl radical and acetyl-Cys418. The latter species acts as a temporary acetyl carrier and a reactant in the subsequent half-reaction with the second substrate CoA to produce acetyl-CoA. Formation of Ac-CoA, the final product, closes the catalytic cycle of PFL.[2]

The investigated aspect of this mechanism concerns the process that allows CoA to enter the active site, which is a prerequisite for the second half-reaction. The problem with this step is that the binding site of CoA is located at the protein surface, while the active site is buried in the protein interior.[3] In search for possible solutions to this problem, the PFL system was subjected to long unrestrained molecular dynamics simulations.

The models representing the PFL system before and after the first half-reaction with pyruvate were used to examine the possible effect that acetylation of the enzyme has on the necessary conformational changes. The PFL protein comes in a homodimeric form and two sets of models were derived from the available crystal structure; one set of models was built using a single subunit (mPFL^{734}GLY·, mPFL^{418}CYS·, mPFL^{418}AcCYS), while the other contains the full dimer (dPFL^{734}GLY·, dPFL^{418}CYS·, dPFL^{418}AcCYS).

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Finding the lock for a key - Identification of the targets of screening hit molecules

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When molecules from phenotypic screens have been identified as hits the main question is: What are the targets of these hit molecules? Targets could be primary target molecules that are affected directly by the hit molecule or secondary targets associated with side effects or polypharmacology. Knowing the targets and potential binding sites of a hit molecule can provide the basis for further optimization of the initial hit, e. g. by structure-based design. But, how can targets and binding sites be identified?

We developed a target identification procedure that is based on hit molecule fragmentation and binding site analogy search using structures from the Protein Data Bank [1], the Credo Database [2], and models of *Mycobacterium tuberculosis* (Mtb) proteins from the Chopin Database [3]. The initial system was developed for Mtb, because tuberculosis is still a wide-spread disease today [4] and a number of drug design efforts have been initiated in recent years in order to fight this disease [5]. The target identification procedure was implemented into a database-based web platform that can be easily handled by medicinal chemists. Furthermore, the database of protein structures can be extended to proteins of other organisms, so that in the future target identification beyond *M. tuberculosis* proteins will be possible. We therefore believe that the developed platform will largely facilitate target identification for phenotypic screening hit molecules.

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

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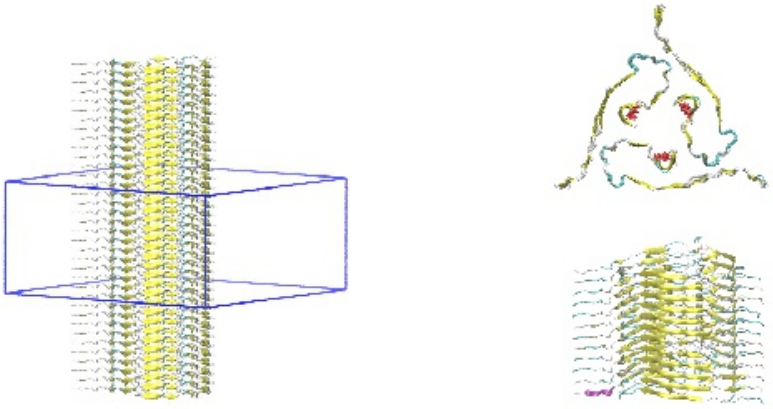
Alzheimer's Disease (AD) is the most prevalent neurodegenerative disorder and the main cause for dementia in industrial nations. One hallmark of AD is the development of senile plaque deposits in the brain that consist primarily of fibrillar amyloid β (Aβ) peptides. Aβ is a short peptide comprising 40 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.

Recently, Lu et al. published a solid state NMR structure of an Aβ_{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 Aβ_{1-42} fibril structures. Previously, we have investigated the stability of fibrillar Aβ_{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 Aβ_{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 Aβ_{40}.



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All around CYP106A2: The Many Faces of Molecular Modelling

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The application of Cytochrome P450 enzymes allows the selective hydroxylation of hydrocarbon skeletons that are otherwise difficult to synthesize. The necessary electron transport to the cytochrome can be achieved by a variety of ferrodoxins. Although 3D-structures and amino acid sequences are highly conserved between bacterial and mammalian ferredoxins, they give rise to different product distributions when used for the hydroxylation of progesterone by CYP106A2. [1, 2] Protein-Protein docking of bovine Adrenodoxine and the corresponding Electron transport protein 1 (Etp1) from yeast to CYP106A2 indicates that these differences are not only due to the lower redox potential of Etp1, but are also caused by subtle structural differences that lead to different binding modes of both redox enzymes. Moreover, molecular dynamic simulations of 15β-OH-progesterone in the binding pocket of CYP106A2 showed that reorientation occurs within 100ns, which suggests that the rate of electron transfer strongly influences the amount of polyhydroxylated products being formed. Likewise, rearrangement of intermediately formed radicals can influence the rate of turn-over: Despite dexamethasone exhibits a higher binding affinity compared to prednisone, it was found to be hydroxylated much slower. Semiempirical AM1 calculations of the conceivable radicals showed that migration to the more stable but unproductive radical in position 16 is responsible for the slow hydroxylation. [3]

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The Role of the Membrane in Neurotransmitter Interactions with Their Receptors

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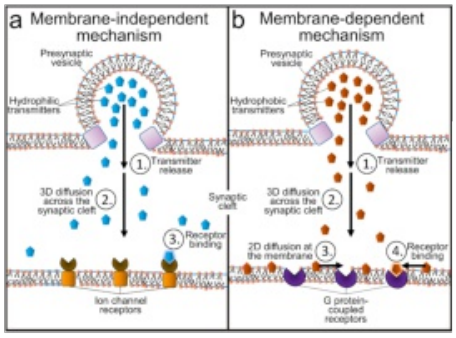
The interactions between neurotransmitters, their receptors, and cell membrane are not fully understood, although there is a growing awareness of the role of the membrane phospholipid composition in several neuropathologies, such as depression, schizophrenia, and Alzheimer's disease. Moreover, differences in the membrane composition are known to affect the functions of the receptors on the membrane and the interactions between neurotransmitters and membrane [1,2].

Traditionally, the neurotransmission is described as a process in which the neurotransmitters are released from presynaptic vesicle and neurotransmitters diffuse over the synaptic cleft towards the postsynaptic membrane. The process ends when the neurotransmitters are binding to their receptors and the postsynaptic neuron is activated. However, there are many macromolecules in the synaptic cleft, which can interact the neurotransmitters water-soluble domains in a non-specific way. These non-specific interactions might cause changes in the binding process.

In our recent study [3], we were able to categorize neurotransmitters in two groups based on the varying degrees of reversible membrane attachment. Membrane-binding neurotransmitters, such as dopamine, adenosine, and epinephrine, are binding to G-protein coupled receptors that have their binding pocket close to lipid bilayer. On the other hand, the membrane-nonbinding neurotransmitters, such as acetylcholine, glutamate, and glycine, are targeting ligand-gated ion channels whose binding pockets are located far from the membrane surface. After these observations, we postulated that there is a membrane-mediated mechanism for neurotransmission entry. In this mechanism, certain neurotransmitters first bind to the membrane and then laterally diffuse to the receptor's binding site.

To this end, we used atomistic molecular dynamic simulations, free energy calculations, and accelerated molecular dynamics simulations to confirm the most probable pathway of dopamine and adenosine entry in their receptors. Our study suggests the entry to take place via the membrane-water interface.



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A Diverse Benchmark Data Set for the Validation of Scoring Functions based on 3D Matched Molecular Pairs

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Prediction of protein-ligand interactions and their corresponding binding free energy is a challenging task in structure-based drug design and related applications. Docking and scoring is a broadly used approximation of the latter. To demonstrate the predictive power and to investigate the strength and weaknesses of scoring functions several benchmark test sets have been developed in the past.[1]-[3] These data sets are characterized by high diversity in terms of protein families, ligand chemotypes and binding affinities. High diversity is well suited for the evaluation and comparison of the global performance of docking and scoring software. However, understanding the local behavior of a scoring function, how well it can differentiate between similar molecules is almost impossible with these data sets. Here, a novel benchmark data set based on Matched Molecular Pairs (MMPs) was developed to study the local behavior of scoring functions. MMPs are defined as molecules that differ in one well-defined transformation that is associated with a change in an arbitrary molecular property (transformation effect).[4] The assembled data set of 99 3D-MMP was used to investigate whether or not scoring functions can differentiate between chemically related compounds. Various scoring functions were used to score the data set, most of them are available within the commercially available software MOE 2014.09 [5] and GOLD Suite 5.2.2 [6]. The 3D-MMPs were scored in the respective crystal structures without any posing (i.e. the position of the small molecule was not changed) to focus on scoring and to exclude the influence of posing (i.e. the placement algorithm). Only three scoring functions (X-Score, Affinity dG and GoldScore) reached a prediction rate of more than 60% in the prediction of the trend of a transformation effect. Analyzing the relationship between molecular size and affinity led to the following results. In 51 3D-MMPs, the larger molecule was also the more active one. In only 20 3D-MMPs the smaller molecule was more active (the remaining molecules show no difference in bioactivity (n = 5) or the same number of heavy atoms (n = 23)). Hence, in 71.8% (51 out of 71) the larger molecule was also more active. This means that in this study the molecule's size would be the best scoring function.

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One-step protein labeling with the tubulin tyrosine ligase - Substrate scope explained by computational studies

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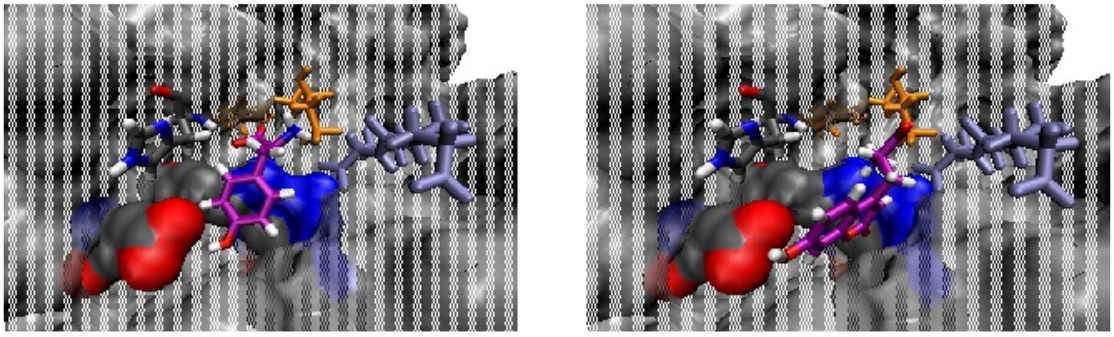

Enzymatic catalysis provides a powerful tool for chemical synthesis. One example is the enzyme tubulin tyrosine ligase (TTL), which enables chemoenzymatic protein functionalization using tyrosine-derivatives [1]. Recent studies show that, the wild type TTL also accepts and ligates other unnatural amino acids, which can differ in size and structure, such as a coumarin-derivative, enabling one-step-fluorescence labeling.
To get insight into the broad substrate scope of TTL docking studies were performed. In these studies the binding behavior of the natural substrate tyrosine as well as other canonical and unnatural amino acids were investigated. Based on these information the important features of the binding pocket such as π-stacking interactions and hydrogen bond formation can be pointed out. Furthermore, molecular dynamic simulations were performed to predict the stability and flexibility of the substrates within the pocket [2].

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What Makes a Palladium Terminal Oxo Stable?

Dominik Munz

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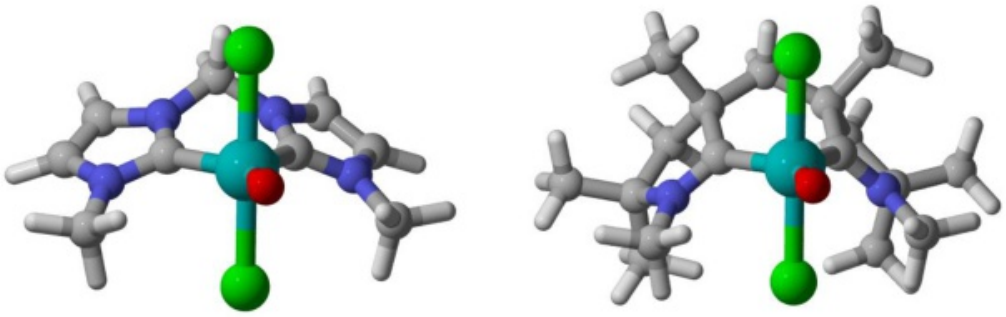

For decades, the isolation of late transition metal complexes featuring multiple bonds to pnictogen or chalcogen atoms like imido- or oxo-substituents has been a huge challenge. [1] Even more so, well characterized examples for the group 10 metals remain elusive. [2] Excitingly, such species have been proposed as intermediates for the catalytic activation of CH bonds or redox processes related to the conversion of small molecules as found for example in catalytic converters of cars.[3] Redox active cyclic (alkyl)(amino)carbene ligands (CAACs) have received considerable attention for the stabilization of reactive intermediates, radicals and low valent transition metals due to their strong π-acceptor properties, which exceed those of conventional NHC ligands considerably. [4] However, the stabilization of transition metal terminal oxo and imido compounds with such ligands has not yet been explored. Herein, I would like to report DFT (B2PLYP-D3(COSMO)/def2-TZVPP//B3LYP-D3/def2-TZVP) and CASSCF calculations, which predict that CAAC ligands will be very efficient for the thermodynamic stabilization of oxo and imido intermediates for palladium(II). [5] Importantly, the calculations rationalize in which way σ-donor and π-acceptor properties of a range of different carbene and related P or N donor ligands contribute to the electronic structure and spin state of Pd(II) or respectively Pd(IV) oxo complexes. Accordingly, the electronic properties of a huge variety of different ligands could be correlated to the expected thermodynamic stability of palladium oxo complexes.

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QSTR analysis and combining DFT of the toxicity of heterogeneous phenols

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Abstract
Quantitative structure–toxicity relationship (QSTR) models are useful to understand how chemical structure relates to the toxicity of natural and synthetic chemicals. The chemical structures of 70 heterogeneous phenols have been characterized by electronic and physic-chemical descriptors. Density functional theory (DFT) with Beck's three parameter hybrid functional using the LYP correlation functional (B3LYP/6-31G(d)) calculations have been carried out in order to get insights into the structure chemical and property information for the study compounds. The present study was performed using principal component analysis (PCA) method, multiple linear regression method (MLR), multiple non-linear regression (MNLR) and artificial neural network (ANN). The quantitative model of the toxicity of these compounds was accordingly proposed and interpreted based on the multivariate statistical analysis.
The statistical quality of the MLR and MNLR models was found to be efficient for the predicting of the toxicity, but when compared to the obtained results by ANN model, we realized that the predictions achieved by this latter one were more effective. This model provided statistically significant results and showed good internal stability and powerful predictability. The squared correlation coefficients were 0.801, 0.802 and 0.824 for MLR, MNLR and ANN models respectively. The obtained results suggested that the proposed descriptors could be useful to predict the toxicity of heterogeneous phenols to *Tetrahymena pyriformis*.

Keywords: QSTR model, DFT study, heterogeneous phenols, *Tetrahymena pyriformis*.

Effects of Protein Side Chain Intercalation in DNA Binding

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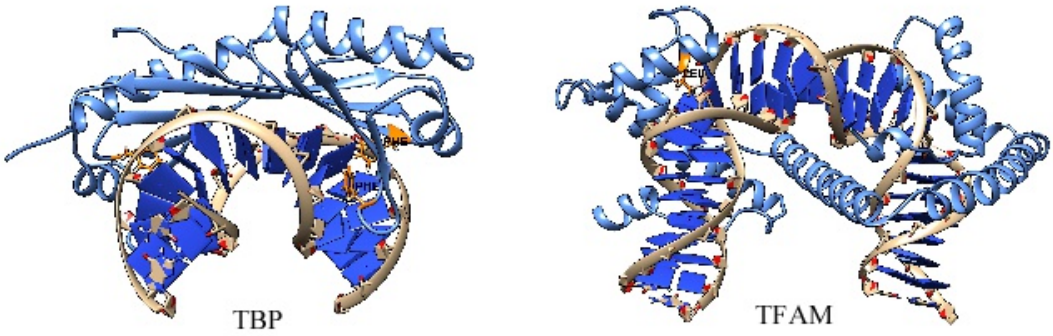

Several crucial functions including binding site recognition by shape readout, alignment of DNA-bound proteins with respect to each other, and compacting DNA to fit it into small compartments rely on deformation of DNA by DNA-binding proteins. One common way of strong DNA deformation is a localized kink between two successive base pairs, which is mainly visible in the roll angle.

We conducted a search of the Protein Data Bank to find structures of protein-DNA complexes with kinked DNA. One widespread mechanism of inducing kinks is the intercalation of amino acid side chains between DNA base pairs; however, there exist also systems, which achieve kinking without intercalation. By comparing the different X-ray structures of various protein-DNA complexes, we found that intercalated systems show narrow roll angle distributions while systems in which DNA is bent without intercalation show broad roll angle distributions.

Using MD simulations, we investigated the effect of intercalation by comparing WT-proteins and mutants with alanines in place of the intercalating residues. We used CcpA, Cren7, Sac7d, Sox-4, TBP and TFAM as model systems. For Sac7d we found that if two residues intercalate, mutation of one to alanine made no difference. Upon mutation of all intercalating residues, the roll angle decreased, but did not completely vanish. These findings agree with previous mutational experiments [1]. The preliminary data of the simulations for the remaining systems suggest that the properties of these systems are affected by intercalation in a similar fashion. We also compared systems with different DNA sequences and found that, while intercalating wt-protein-DNA complexes showed no sequence dependent roll angles, some of the non-intercalating mutants did bend different DNA sequences to varying degrees.

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Accurate Intermolecular Potential for the C_{60} Dimer

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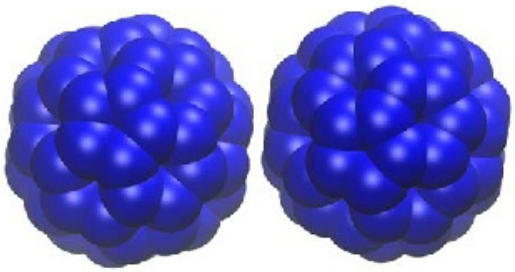
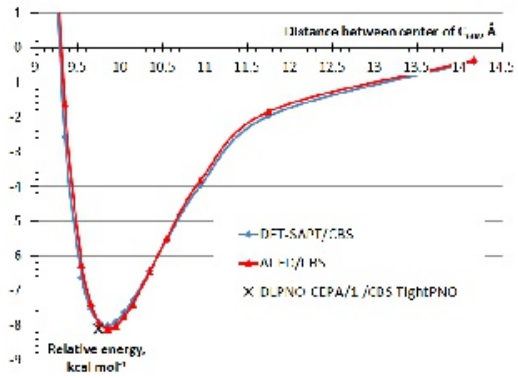




The self-assembly of molecular building blocks is a promising route to low-cost nanoelectronic devices. It would be very appealing to use computer-aided design to identify suitable molecules. However, molecular self-assembly is guided by weak interactions, such as dispersion, which have long been notoriously difficult to describe with quantum chemical methods. In recent years, several viable techniques have emerged, ranging from empirical dispersion corrections for DFT to fast perturbation and coupled-cluster theories. We test these methods for the dimer of the prototypical building block for nanoelectronics, C_{60}-fullerene.

Benchmark quality data is obtained from DFT-based symmetryadapted perturbation theory (SAPT), the adiabatic-connection fluctuation dissipation (ACFD) theorem using an adiabatic LDA kernel, and domain-based local pair natural orbital (DLPNO) coupled-pair and coupled-cluster methods. These benchmarks are used to evaluate economical dispersion-corrected DFT methods, double-hybrid DFT functionals, and second-order Møller–Plesset theory. Furthermore, we provide analytical fits to the benchmark interaction curves, which can be used for a coarse-grain description of fullerene self-assembly. These analytical expressions differ significantly from those reported previously based on bulk data.[1]

[1] D.I. Sharapa, J. T. Margraf, A. Hesselmann and T. Clark, *JCTC*, **2017**, *13*, 274-285.

Structural investigation of the *E. coli* proteins HdeA and YmgD by MD simulations

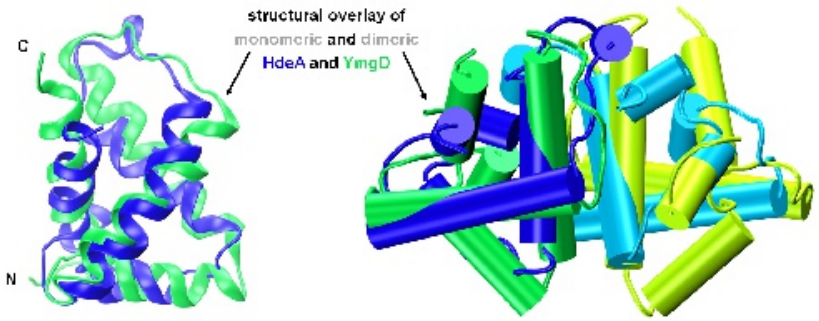
Eileen Socher, Heinrich Sticht

Bioinformatik, Institut für Biochemie,

Friedrich-Alexander-Universität Erlangen-Nürnberg, Germany

Enteropathogenic bacteria, which are for instance swallowed with food or water, need to survive the acid conditions in the host stomach before they can infect the intestine. For fulfilling this challenging task, different strategies have emerged. One mechanism for acid resistance in *Escherichia coli* is the expression of the periplasmic protein HdeA. HdeA has been shown to represent an acid-activated chaperone, which helps *E. coli* to tolerate very acidic environments, such as the mammalian stomach where the pH varies between 1 and 3.

YmgD is a structurally homologous protein to HdeA and it is also expressed in the periplasm of *E. coli*. In contrast to the function of HdeA, the function of YmgD has not yet been characterized. We performed pH-titrating molecular dynamics (pHtMD) simulations [1] to investigate the structural changes of both proteins and to assess whether YmgD may also exhibit an unfolding behavior similar to that of HdeA.



The unfolding pathway of HdeA includes partially unfolded dimer structures, which represent a prerequisite for subsequent dissociation. In contrast to the coupled unfolding and dissociation of HdeA, YmgD displays dissociation of the folded subunits, and the subunits do not undergo significant unfolding even at low pH values. The differences in subunit stability between HdeA and YmgD may be explained by the structural features of helix D, which represents the starting point of unfolding in HdeA. In summary, the present study suggests that YmgD either is not an acid-activated chaperone or, at least, does not require unfolding for activation. [2]

[1] E. Socher, H. Sticht, *Sci. Rep.*, **2016**, *6*, 22523.
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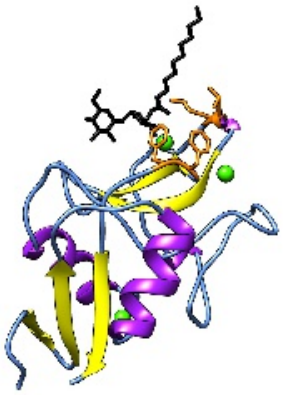
Binding of Glycolipids to the Macrophage Surface Receptor Mincle

Christian A. Söldner, Anselm H. C. Horn, Heinrich Sticht

Macrophage inducible Ca^{2+} dependent lectin (mincle) is a receptor expressed on macrophages that is involved in the recognition of the mycobacterial cord factor trehalose dimycolate thus leading to an immune response against *Mycobacterium tuberculosis*. Recent findings show that mincle is also activated by synthetic glycolipids such as trehalose acyl esters, which could be used as adjuvants for vaccination [1].

Complex structures of mincle and trehalose have been solved by X-ray crystallography and show that the sugar forms stable contacts with a conserved carbohydrate recognition domain and a Ca^{2+} ion [2, 3]. Hydrophobic residues on the surface of mincle form a groove that is likely to interact with the fatty acid of the trehalose acyl esters. However, the interaction between mincle and the acyl chains is difficult to characterize in detail: From an X-ray structure published for a complex of mincle and trehalose monobutyrate, only the first two carbon atoms of the fatty acid could be determined from the electron density map suggesting that the remainder might be flexible [3]. Although only linear acyl chains up to eight carbon atoms fit into the groove, esters with longer fatty acids have been shown to bind and activate mincle with even higher affinity [1, 3].



Trehalose acyl ester bound to mincle (black sticks: trehalose dodecyl ester, orange sticks: hydrophobic groove, green spheres: Ca^{2+} ions)

To investigate the interaction between fatty acids of different lengths and the protein, we performed all atom molecular dynamics (MD) simulations of trehalose acyl esters bound to mincle in explicit water. In our calculations, the acyl chains remain indeed very flexible and sample both linear and globular conformations during simulation. Frequent transient contacts occur predominantly with the hydrophobic residues of the protein groove. Longer acyl chains, however, contact also distant residues on the protein surface. Thus, the additional CH_2 groups confer an enhanced stabilization of the protein ligand complex due to an increased Van-der-Waals energy.

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The SAMPL5 challenge for embedded-cluster integral equation theory: solvation free energies, aqueous pK_a and cyclohexane-water log *D*

Nicolas Tielker,[1] Daniel Tomazic,[1] Jochen Heil,[1] Thomas Kloss,[2] Sebastian Ehrhart,[3] Stefan Güssregen,[4] K. Friedemann Schmidt,[4] Stefan M. Kast[1]

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[2]*IPhT, L'Orme des Merisiers, CEA-Saclay, Gif-sur-Yvette, France*
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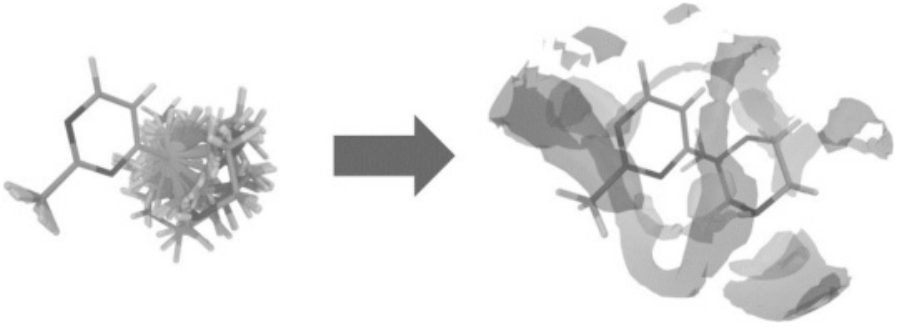
Reliable yet fast prediction of physicochemical properties of drug-like compounds requires proper theories, as for instance provided by the integral equation approach to fluid phase thermodynamics [1]. Such a method allows for efficient calculations of free energies of solvation or partition coefficients between immiscible or partly miscible phases like water and cyclohexane. To accurately model the solvation of small molecules we here combine such a statistical-mechanical description of the solvent with a quantum-level description of the solute in the form of the "embedded cluster reference interaction site model" (EC-RISM). This combination, optimized with respect to quantitative accuracy, takes both the electronic relaxation and the excess chemical potential governing the insertion into a solvent into account for predicting the free energy of solvation [2]. It is therefore possible to address challenging problems related to drug discovery.



The partition coefficients of drug-like molecules are difficult to predict since these species often contain functional groups and scaffolds that can result in more than one tautomeric and ionization state at physiological pH. Furthermore, the molecules' conformational ensembles must be considered for each solvent. To capture the state of such compounds in solution we exhaustively sample their conformational, tautomeric, and ionization states followed by calculating their free energies of solvation. This allows for the accurate prediction of both, partition coefficients (log *P*) and the pH-dependent distribution coefficients for ionizable compounds (log *D*), as demonstrated for the dataset of the SAMPL5 blind prediction challenge [3]. The compounds cover a wide range of chemistries, therefore offering a realistic testbed for a methodology that has not been parametrized using the target properties.

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Mesoscopic simulation of the membrane disrupting activity of the cyclotide Kalata B1

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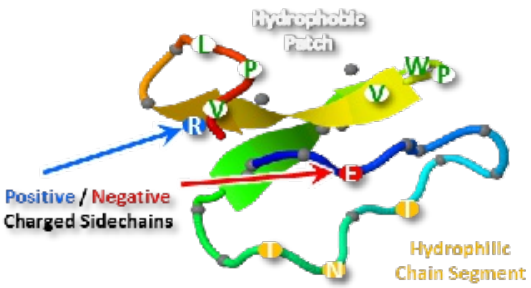
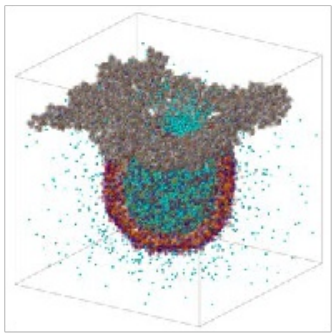
Dissipative Particle Dynamics (DPD) is an established simulation technique to study condensed matter systems on mesoscopic scales. Whereas its coarse-grained interacting units (beads) may not necessarily be identified with distinct chemical compounds at all, the DPD variant Molecular Fragment Dynamics (MFD) makes use of specific small molecules to represent all molecular species of interest. MFD has been successfully applied for studying surfactant systems at the water-air interface [1] and for phospholipid membranes, peptides and proteins [2].





Recent studies with the MFD technique demonstrate the membrane disrupting activity of different cyclotides like Kalata B1 (left figure), a 29 amino acid self-defense associated peptide expressed in plants [2]. This work aims at establishing better test systems for membrane pore formation due to cyclotide activity, like a 30 nm vesicle, its membrane composition resembling the naturally occurring lipid distribution cholesterol inclusive (right figure). The effects of single and multiple amino acid replacements within various cyclotides on membrane pore formation are compared to experimental results and may finally be utilized to predict the bioactivity profiles of specifically mutated cyclotids. These studies may support the understanding of pharmaceutical active peptides with cyclotide scaffold which are applied e.g. for anti-HIV treatment [3].

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Molecular dynamics studies on the pH-dependent mechanism of phosphonic acid adsorption on anatase (101)

Dustin Vivod[1,2], Dirk Zahn[1,2]

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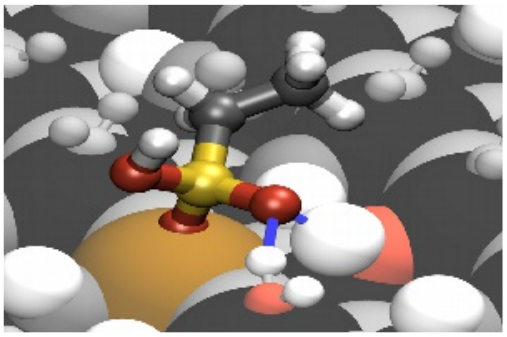
[2] *Chair of Theoretical Chemistry, Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU), Nägelsbachstraße 25, 91052 Erlangen, Germany*

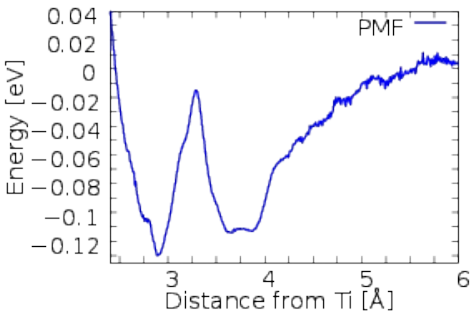
For dye-sensitized solar cells using titania nanotubes the mechanism behind the adsorption of phosphates onto a anatase surface is a vital process. By using molecular dynamics simulation the assosiation, adsorption, and desorption are investigated.

The adsorption of ethylphosphonic acid onto the anatase (101) surface under acidic conditions is investigated in a two step procedure. First the physisorption is evaluated by generating the potential of mean force, and in a second step a water exchange reaction is examined by comparing the difference in potential energy.

Multiple different configurations which may result from a deprotonation of the acid are considered. The energetics of the reactions on the surface are evaluated in comparison to the reaction in solution. It is shown that condensation reactions are energetically unfavored. Instead the configuration after a proton transfer to the solvent is the only one favored.

The desorption under neutral conditions is investigated by umbrella sampling.



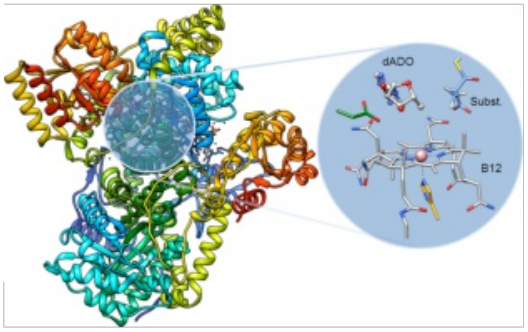


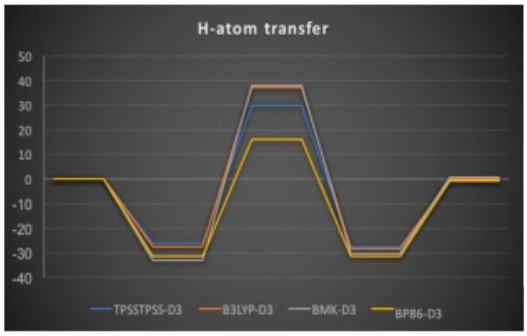
Modelling the reactions catalysed by coenzyme B_{12}-dependent enzymes: Accuracy and cost-quality balance

Christian R. Wick[1,2], David M. Smith[1,2]

[1] *Group for Computational Life Sciences, Division of Physical Chemistry, Ruđer Bošković Institute, Zagreb, Croatia*

[2] *PULS Group, Friedrich-Alexander-Universität, Erlangen, Germany*





Coenzyme B_{12} (5'-deoxyadenosylcob(III)alamin, dAdoCbl) is involved in vital enzymatic processes in nature, including humans. It constitutes one of the most prominent organometallic cofactors due to the presence of a carbon-cobalt (Co-C) bond between the central cobalt ion and the 5'-deoxyadenosyl ligand. The general formal mechanism for the initial reaction of coenzyme B_{12} dependent enzymes starts with homolytic cleavage of the Co-C bond, which leads to the formation of a 5'-deoxyadenosyl radical and a low-spin cob(II)alamin. In the (subsequent or concerted) second step, the 5'-deoxyadenosyl radical is involved in an H-atom transfer reaction, generating the substrate radical and 5'-deoxyadenosine. Interestingly, the rate of the enzymatically catalysed Co-C homolysis is increased by 12 orders of magnitude compared to the nonenzymatic reaction in solution, which demonstrates the astonishing catalytic power of these enzymes.

The reactions catalysed by coenzyme-B_{12}-dependent enzymes have been subject to many theoretical investigations, employing different levels of theory, model systems and methodologies. Recently, the Co-C cleavage was investigated with dispersion-corrected DFT and LPNO-CCSD calculations utilising the full coenzyme.[1] This and another study based on a slightly truncated model system[2] have elucidated the importance of the model system design and the inclusion of dispersion and solvent corrections for the first time. Concomitantly, the accurate description of the H-atom transfer reaction is known to be very sensitive to the level of theory applied.[3–5] Our goal is to find a level of theory that ensures an accurate 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.

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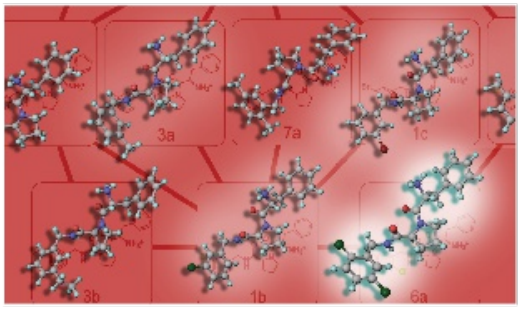

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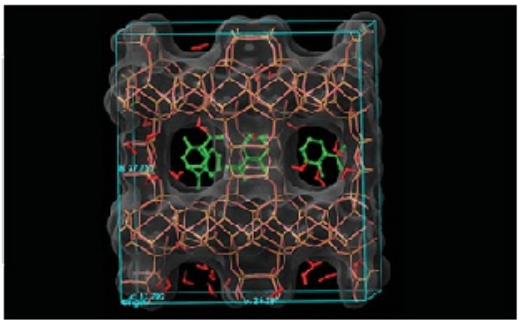

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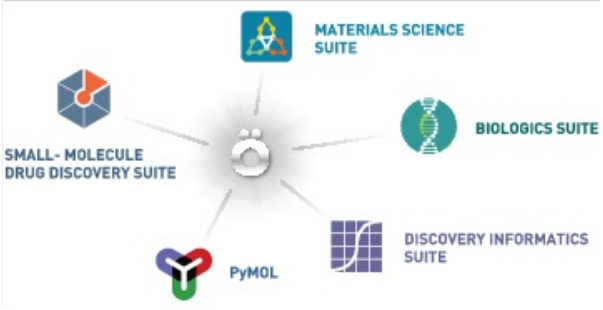

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How many double-digit integer numbers exist with the following property: if you add the number to the number you obtain by swapping the two digits, the result is a square number.

Challenge 2
A point *P(x;y)* lies on a circle around *M(2;2)* with the radius $r > 2$. Find the lowest value for x, if $y=r$ and r, x, and y are positive integer numbers.

Challenge 3
How many possibilites exist to obtain 100 as sum of two or more directly subsequent integer numbers?

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